

TRANSLATING TIME: THE EYE

A Dissertation Submitted
to the Graduate School
University of Arkansas at Little Rock

in partial fulfillment of requirements
for the degree of

DOCTOR OF PHILOSOPHY

in Bioinformatics

in the Bioinformatics Graduate Program of the
University of Arkansas at Little Rock
in conjunction with the
University of Arkansas for Medical Sciences

May 2015

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ABSTRACT

The goal of the Translating Time: Eye Development research project is to increase understanding of unknown times of prenatal eye development events in mammals, especially in humans, based on the limited set of known timing of such events. The primary mammalian models included nine eutherian mammals: *Felis domestica* (cat), *Mustela putorius furo* (ferret), *Mesocricetus auratus* (hamster), *Macaca mulatta* (monkey), *Homo sapiens* (humans), *Mus musculus* (mouse), *Oryctolagus cuniculus* (rabbit), *Rattus norvegicus* (rat), and *Acomys cahirinus* (spiny mouse). The main subgoals of this research were to: mine the literature to identify a data set of eye development events for the selected placental mammals; determine the Gene Ontology annotations associated with the data set of the mined eye development events; predict unknown events in eye development for the selected organisms; and develop an internet-based resource for sharing the data and the methods that were developed for predicting eye development events. Since the *Danio rerio* (zebrafish) is considered a model organism for research in eye development, it was also investigated to determine whether or not it fits the model.

DEDICATION

I dedicate my dissertation work to my daughter, Alexis, who supported me throughout this process. She has been my biggest cheerleader throughout the entire doctoral process. You inspire me to strive to be the best that I can be so that you can have a hero and role model that you can touch. I thank God for you.

I also dedicate this dissertation to my family and friends for your many words of encouragement through the years. For your thoughts and prayers, the countless phone calls to check on the status of my dissertation work along the way. To my brother Marcus who encouraged and supported me, I will always be grateful for your friendship. This dissertation is also dedicated to my mom, Janie, and my dad, Robert, for all of their love and support.

A special dedication to my Lord and Savior, Jesus Christ because this would not have been possible without you. I have found strength in you through it all. From Hebrews 4:16, “Let us therefore come boldly unto the throne of grace, that we may obtain mercy, and find grace to help in time of need.” –Amen

ACKNOWLEDGEMENTS

I would like to thank my committee members for their guidance, and my family and friends for their encouragement and support. I would like to thank my dissertation advisor, Dr. Daniel Berleant for believing in me. Thank you for all of the reading and corrections to my dissertation as well as code analysis. You were inspirational in my understanding of the Translating Time Project. I would like to thank Dr. Benes for her expertise in biology. I would like to thank Dr. Chacko for his expertise in eye development and for guiding my understanding of the process. I would like to thank Dr. Milanova for her expertise in computer science. I would like to thank Dr. Tang for his guidance in the research. I would like to thank Dr. Isopheki for his support and expertise in biology and computer science. I am especially grateful to Dr. William Baltosser for his assistance and advice in reading between the lines in interpreting the quantitative data from the earlier work that forms a foundation for the present research. Lastly, thank you to my Lord and Savior Jesus Christ.

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Chapter 1

1.1 Overview

The overall objective of this dissertation is to gain an understanding of the timing of human and animal ocular development events. This is expected to eventually enable improvements in diagnostic and intervention capabilities for human diseases involving the eye. It is useful to understand eye development in animals because the conservation of pathways and genetic material in the development process allow us to compare human development with those of the model organisms. Thus, the knowledge obtained through the study of these organisms can help us better understand humans. This knowledge can lead to research and ultimately medical decisions that will increase the ability to treat and prevent much human illness. Use of model organisms thus makes it possible to do research that would be ethically unacceptable in humans.

Specific research that forms the foundation upon which the present research builds developed a mathematical model of neurodevelopment – a translation of time theory (Clancy et al., 2007a) based on nine eutherian mammals: *Felis domestica* (cat), *Mustela putorius furo* (ferret), *Mesocricetus auratus* (hamster), *Macaca mulatta* (monkey), *Homo sapiens* (human), *Mus musculus* (mouse), *Oryctolagus cuniculus* (rabbit), *Rattus norvegicus* (rat), and *Acomys cahirinus* (spiny mouse). The original intent of the mathematical model was to create, on the one hand, a scale showing a sequence of neurodevelopmental events and mapping them to numerical values, and on the other hand, a scale of species along which species that develop quickly are mapped to lower numbers and species that develop slowly are mapped to higher numbers. This permitted the two values, developmental event and species scores, to be combined to infer the time

of an unscored event in a specified species. This helps in the understanding of humans because it provides the foundation from which we can *extrapolate* the times of neurodevelopmental events in humans by looking at when the corresponding neurodevelopmental events occur in animals. This is important because detailed timing of neurodevelopmental events in humans is often obscure.

1.2 Purpose

The purpose of this research is to acquire knowledge to address whether or not time can be translated across species as it relates to eye development. Previous research shows that time has successfully been translated across species in other neurodevelopment events (Clancy et al., 2007); however, it has not been accomplished in other organs including the eye. Since the eye is structurally in close vicinity to the brain and in some research is categorized as a part of the brain, it is perhaps the most reasonable second organ on which to begin testing the translation of time theory. This theory holds that it is possible to translate time across species in neural development with large and small variations in event timings based on data obtained from the literature. The present research intends to provide a better understanding of the timings of human ocular developmental events from known times of those events in animals. It provides a proof of concept for expanding the translating time approach to additional organs such as the heart or lungs. Potential benefits include improvements to diagnostic and intervention capabilities related to certain health problems in humans such as birth defects of the eye.

A mathematical model proposed by the theory estimates the day for a specified developmental event in any of the nine species according to data from the others. This can be useful when empirical data are missing for a particular species. Error in the

mathematical model could stem from a need for adjustment factors besides those already determined for primate neurodevelopment events. This statistical model accounts for certain primate neurodevelopmental events that take place at different times than otherwise predicted by the model by modifying a constant k for primate cortical events and modifying k with a different value for primate limbic events. Cortical events are events that occur in the cortex of the brain while limbic events are those that occur in the portion of the brain located on each sides of the thalamus. When there is a comparison between primate and non-primate development, these events can reflect a minor shift in timing associated with limbic and cortical areas of the brain. The model can be enhanced through continued data collection by interested parties in the scientific and industrial communities (Clancy et al., 2000, 2001, 2010; Nagarajan et al., 2010).

1.3 Statement of the Problem

Work has been done to investigate developmental events concerning rods, cones, and optic nerve axons in the mouse visual system as well as peripheral eye structures (Sadler, 2006; Finlay & Clancy, 2008; Finlay, 2008; Finlay et al., 2008; Kaskan et al., 2005, Wallace, 2007; Harada et al., 2007; Niessen, 2006; Luo et al., 2006). The visual system is a component of the central nervous system which is responsible for sending, receiving, and interpreting light information. The visual system has two main elements, the eye and the brain. The eye detects and does basic interpretation of visible light input as it enters, while neurons transfer this data to the brain for further processing (Schiller, 1986; Marr et al., 2010). In the absence of light, the eye cannot identify objects. When light waves are present, they first enter the cornea, which is the clear dome part at the

front of the eye. Afterwards, the light progresses through the pupil, which is the circular opening at the center of the iris, which itself is the colored portion of the eye that controls the diameter and size of the pupil. The pupil also controls the amount of light that enters the retina. The retina is the portion of the eye that transduces light and generates nerve impulses, sending signals to the brain through the optic nerve (Montgomery, 1998; Koch et al., 2006). The retina is a part of the brain which has developed into part of the eye, and detects and initially processes neural signals in the presence of light. Neurons that are sensitive to light are called photoreceptors. Rods and cones are two primary types of photoreceptors. A rod functions in low light and is responsible for night vision in black and white while a cone functions in bright light and is responsible for color vision (Shepherd, 2004; Romer & Parsons, 1977; Patton et al., 2006; Tso & Jampol, 1982).

The structure and development of the human eye will be described in more detail in Chapter 2. However, research to date has not comprehensively addressed the novel idea of translating time across multiple species for a broad range of eye structures. The translating time statistical model predicts the time of a particular event in a specified species based on other event times and other species. The investigation of the timing of events, cellular differentiation into germ layers for example, is significant because of their critical roles in embryonic development. As part of this doctoral research project, I conducted a semi-automated literature review of cross-species eye development, building on keyword searches via the ScienceDirect, <http://www.sciencedirect.com/>, and PubMed, <http://www.ncbi.nlm.nih.gov/pubmed>, search engines. The search queries included use of the scientific names of the nine eutherian mammals and one fish investigated, combined with the words “eye development” and “pc” (referring to postconception). Since

postconception is the earliest time point in embryonic development, these were deemed useful keywords to search for in the literature. The searches included journals, books, and other works expected to be authoritative sources of knowledge because they comprise the scientific literature.

Based on event times known from the literature, I predicted unknown event times across species for structural components of the eye such as the lens, retina, and cornea with the goal of not only translating them among laboratory species but also eventually to humans. I also incorporated gene expression information for eye development events into the Website that I created for this project because developmental stages and events are controlled by genes. Comprehension of how these genes work is important because it reveals information about the control and processes of development. For example, genes tell cells to produce proteins. These proteins tell our bodies how to grow and survive. Identification of these proteins helps to better understand how the body works as well as what is transpiring when it does not work. Scientists and doctors are optimistic that genetic information can potentially help diagnose, treat, prevent and cure illnesses.

The Website I developed has a user interface as the front end for user interaction with a database at the back end used to store the data. My project documents historical data related to the research as well as predicts new data points for which experimental results may not be available. My research thus allows extension of the specific literature, which is currently modest, on the translation of time in eye development across species.

1.4 Specific Aims (Objectives)

Specific Aim (Objective) I: Construct a data set of eye development events for the zebrafish and selected placental mammals. Zebrafish was chosen as a 10th species to

include in this research because research has shown it to be a model organism for eye development (Schilling, 2002).

Main Task: Construct a computational pipeline to extract from the PubMed and ScienceDirect literature databases a combination of common and unique data points on eye development for nine placental mammals (including the human, ferret, cat, macaque, rat, mouse, guinea pig and rabbit) and one non-mammalian vertebrate (the zebrafish). The zebrafish was chosen because it is the model organism for eye development. PubMed and ScienceDirect are the two leading online research databases. ScienceDirect, <http://www.sciencedirect.com>, has over 2,500 peer-reviewed journals and more than 11,000 books. PubMed, <http://www.ncbi.nlm.nih.gov/pubmed>, has over 22 million citations for biomedical literature from life science journals, online books, and other articles, including MEDLINE.

Task 2: Develop a catalogued record of the queries as well as details about their observed effectiveness, wherein I am able to delineate which queries return the best results. During the research, sometimes it was necessary to base this effectiveness on my own observations and judgments.

Specific Aim (Objective) II: Determine the Gene Ontology annotations associated with the constructed data set of eye development events.

Main Task: Use Bioconductor to search for gene ontology data. Bioconductor is a software tool that is used for the analysis of genomic data. Bioconductor is an open source application that is based on the R programming language. It offers tools to analyze

genomic data (Bioconductor, 2003). Bioconductor was chosen because of its capability to assemble and process data from database like GenBank, the Gene Ontology Cortium, and LocusLink. Other options considered include Illumina, GO, KEGG, and TRANSFAC. Bioconductor had the best features and capabilities by pulling in data from several widely utilized gene databases.

Specific Aim (Objective) III: Predict unknown events in eye development for the selected organisms.

Main Task: Utilize the extracted common and unique data points to make predictions about missing data. This will be achieved by submitting the extracted data points to the Translating Time Across Mammalian Brains website for inclusion because the model can be improved by adding more data points. Current researchers are looking to expand species and data points.

Specific Aim (Objective) IV: Develop an Internet-based resource for sharing the data and methods that were developed for predicting eye development events.

Main Task: Provide the information necessary to replicate the work on another suitable computing environment such as UNIX or a Mac.

1.5 Limitations

There is a time constraint, defined to avoid our crawler from overloading servers at ScienceDirect, which is imposed on the software that implements a computational pipeline to extract from ScienceDirect literature databases a combination of common and

unique data points on eye development. A crawler in this context is an automated software application that used to query and download material from ScienceDirect, PubMed and PubMed Central. This constraint consists of a 10-second wait time, for each abstract that is downloaded from the website, such that a bottleneck is not created that causes a potential for the website to be adversely affected due to an overwhelming number of queries. Additionally, the user must be inside the UALR firewall to use this software because UALR has a ScienceDirect subscription, which is necessary for access. The Gene Ontology annotations related to the data set on eye development events will be only as complete as the annotations available in Bioconductor.

Chapter 2

2.1 Literature Review: Overview

The topics to be covered in this literature review include mammalian development, development of the eye, and translating time across the developing mammalian brain. We will see that there is research yet to be conducted which addresses translating time across species with a concentration on structural elements of the eye. Thus the work reported here is innovative and contributes to the translating time body of research. The purpose of this review is to identify a gap in the translating time project such that unique data points can be added to the original project and inferences can be made concerning the eye.

The methods utilized for this review include an electronic search of PubMed and ScienceDirect, which are two of the most widely used online journal search engines. The search also included hardcopy and electronic books from the University of Arkansas at Little Rock and the University of Arkansas for Medical Sciences as well as books in electronic format from other college libraries via Illiad, the interlibrary loan system. The key queries applied in the literature search included: “Human Development,” “Human Embryonic Development,” “Translating Time Across Species,” “Mammalian Development,” and “Human Eye Development.”

The rest of this chapter is divided into three sections, including the Introduction. Section A is a background on mammalian development. Section B provides key points about embryonic development of the eye. Section C presents background on the translation of time across mammalian species project.

2.1.1 Background: Early Mammalian Development

2.1.1.1 Precursors

Development of the reproductive system begins when primordial germ cells (PGCs) travel to the area where the gonads develop. “In their normal environment, PGCs do not at any time exist as an independent tissue, but are always closely associated with other cells from which they may derive nutrients as well as developmental signals” (DeFelici, 2001). As the progenitors of gametes (Raz, 2004; DeFilici et al., 2004), PGCs become germ cells which in turn generate the gametes of organisms that reproduce sexually. The gonads in prenatal development are the organs where gametes are generated. In females the gonads are ovaries, whereas the gonads in males are the testes. Gonads give rise to eggs and sperm plus somatic cells that are critical to the support and development of these germ cells. It takes over a decade in humans before gametes function to create the next generation (Alberts et al., 2002; Satoh, 1991; Twyman, 2001, Cinalli et al., 2008).

During the early nineteenth century, scientists discovered the biological processes involved in human fertilization (Matzuk et al., 2002). Frequently, the cells that give rise to an organ are a significant distance from where the organ actually develops (Garrison, 1921). The amalgamating or fusion of the egg and sperm constitutes fertilization, bringing about the first step in human and other animal development. After fertilization, chromosomes from the male and female join to produce a zygote. This zygote contains the complete genetic material of an organism. The result of this union is a single diploid nucleus. This is the onset of embryonic development (Gilbert, 2003; Boklage, 2010a).

The zygote swiftly divides, producing a multicellular embryo in a cycle of cell divisions called cleavages. The cleavage process subdivides the zygote such that it doubles the number of cells after each division. After embryogenesis begins, the cells are no longer referred to as a zygote. For example, the first division of the zygote produces a 2-cell embryo, the second division produces a 4-cell embryo, and when the embryo reaches the 16-cell stage, it is called a morula. Cleavage segregates the multicellular embryo into developmental areas. As cleavage continues, a fluid-filled center cavity, the blastocoel, forms and by day 6 of human development, the embryo is a hollow ball of cells called a blastocyst containing over 100 cells. The cleavage process takes place during week one of human development. The cells will now begin the process of differentiation in which they become specialized and divide based on their prospective functions (Schoenwolf et al., 2008a; Campbell et al., 2008; Boklage, 2010b). A graphical representation of human fertilization is shown in Figure 2-1. It depicts human development illustrating the ovaries, the point of fertilization, the cell division process, and implantation (the penetration of the uterus by the new embryo) on around day 9 after conception.

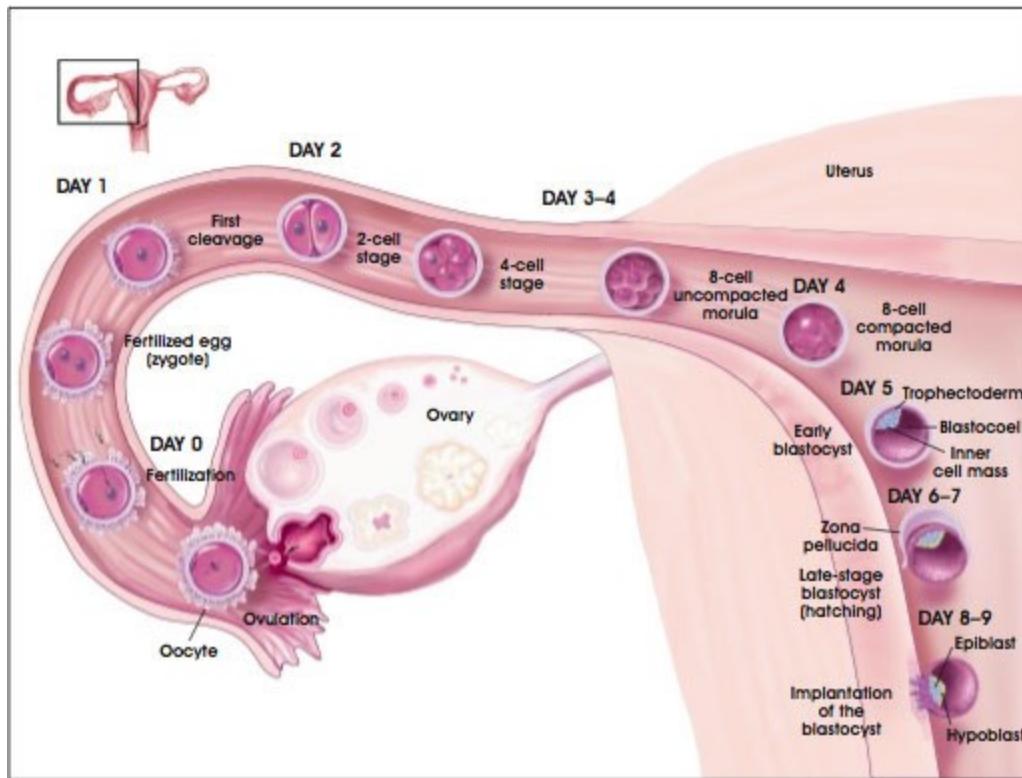


Figure 2-1: Human Fertilization (From Winslow, 1999)

According to Chiras (2012), “Human development consists of three stages: pre-embryonic, embryonic, and fetal. Pre-embryonic development begins at fertilization and ends just after implantation.” The onset of the embryonic period is marked by the completion of implantation. During the embryonic period, structural development as well as growth lasts until approximately 2 months from the time of conception. While in the embryonic period, two critical processes occur concurrently: 1) the inner cells of the embryonic disc differentiate into the embryo; and 2) the cells that constitute the outer layer generate the structures and tissues required to accommodate, nurture, and safeguard the fetus as it develops for the rest of the prenatal period (Sherman, 1977; Jirásek, 2001; Fukuda & Sugihara, 2012; Jirásek, 1978; Grobstein, 1985; Shea, 1985).

2.1.1.2 Formation of the Trilaminar Embryo

During week two of human development, the embryo divides into two layers, the epiblast and the hypoblast. This two-layered plate, formed through cell proliferation, is commonly referred to as the bilaminar embryonic disc (Moore & Persaud, 2003; Hartwig, 2008). The embryo is now considered a bilaminar embryo. The epiblast, the original inner cell mass cluster, is the top layer of the germ disc from which all tissues of the embryo are derived. The hypoblast, the bottom layer of the bilaminar germ disc, does not contribute to the tissues of the embryo but contributes to the formation of the yolk sac, which will generate blood cells in addition to the extraembryonic mesoderm. The formation of these two layers through cell proliferation develops the bilaminar germ disc (Moore & Persaud, 2003; Hartwig, 2008).

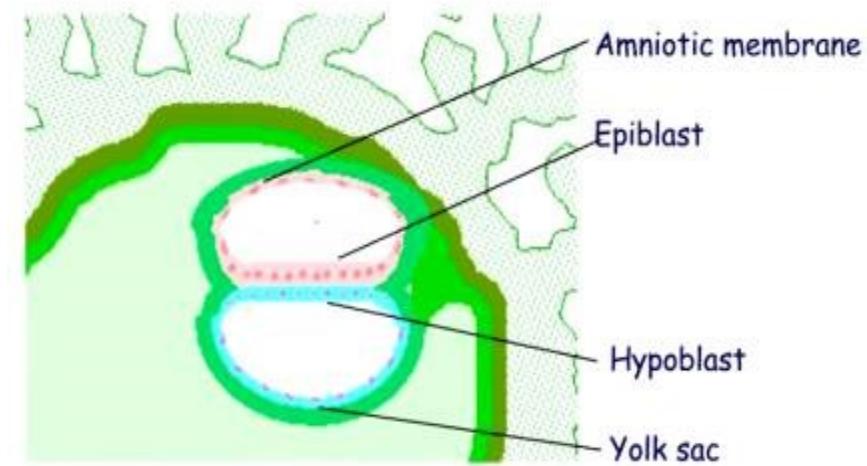


Figure 2-2: Bilaminar Embryo Disc (From Cushier, 2012)

As shown in Figure 2-2, the two-layered disc is separated into parts. The amniotic cavity lined with the amniotic membrane is one part and the yolk cavity with the yolk sac is another. The bottom of the amniotic cavity is formed by the epiblast while the top of

the yolk sac is formed by the hypoblast. Later, the mesoderm will become a product of the invagination of these cells. Additionally, the endoderm will become a product of many of the hypoblast cells. A third germ layer called the ectoderm will also arise from the epiblast.

In the third week of human embryonic development, programmed cell fate and regulated cell movement by blastomeres give rise to the three core germ layers: the ectoderm, mesoderm, and endoderm. In this process, called gastrulation, the bilaminar embryo is altered and becomes a trilaminar embryo. This structure is also known as the gastrula, wherein the blastula folds inward and enlarges. Upon the completion of gastrulation, the three germ layers are in position. After this, the epiblast is called the ectoderm, and the progenitor mesoendoderm now constitutes the mesoderm and the endoderm. These germ layers are the building blocks for primary body and organ development (Tuchmann-Duplessis, David, & Haegel, 1982; Muller, 1997; Gilbert, 2000). These cells give rise to the embryonic structure and stage identified as the gastrula, which is a trilaminar or three-layered structure. This phase in early development is called gastrulation. The trilaminar structure constitutes the three germ layers recognized as the ectoderm, mesoderm and endoderm (Forgács & Newman, 2005; Mundlos, 2009; Craig, 1999).

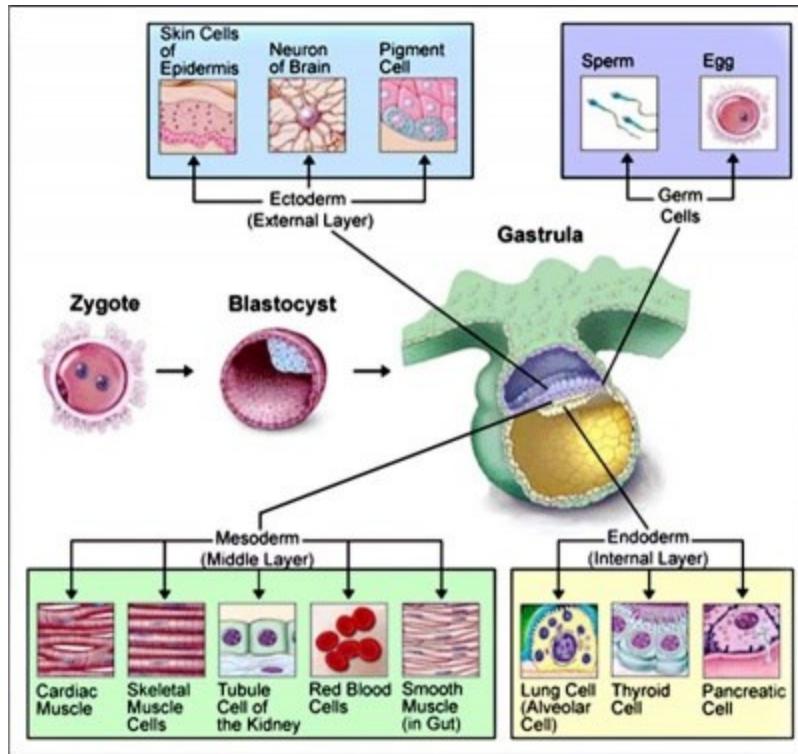


Figure 2-3: Trilaminar Embryo Disc (From Winslow, 2001)

As shown in Figure 2-3, the endoderm is the inner-most layer of the embryo, which later gives rise to the epithelial lining of the digestive tract as well as its associated glands, parts of the reproductive system, the urinary bladder, thymus, epithelial lining of the respiratory system, liver, pancreas, and thymus. The mesoderm is positioned between the endoderm and ectoderm. It gives rise to the skeletal, muscular, body cavity lining, and circulatory systems. Of these layers, the ectoderm is the first to emerge. It is the outermost layer and gives rise to the epidermis of the skin, sense receptors in the epidermis, cornea and lens of the eye. Additionally, the nervous system is a major derivative of the ectoderm. This particular differentiation of the ectoderm represents neurulation. The germ layers will later differentiate to produce the embryo's major organ systems (Evans & Hinrichsen, 1974; Nishimura et al., 1987; Weijer, 2009).

When the germ layers fold, the body of the vertebrate begins to emerge. In concert, formation of the primitive streak begins at the site of gastrulation, which is where the three germ layers form. Development requires the activation and inactivation of specific genes at particular times. Highly integrated cell-cell interactions occur along with interactions between cells and their non-cellular environment (Heisenberg & Solnica-Krezel, 2008; Schoenwolf et al., 2008b; Gilbert-Barnes & Debich-Spicer, 2004; Harrison & Jeffcoate, 1953).

The embryonic period begins during week 2 and lasts until week 8 of development. During this time the bilaminar disk as well as the trilaminar disk forms and the 3 germ layers give rise to major tissues and organs. This is the reason that the embryonic period is commonly known as the stage of organogenesis. By the end of this period, the embryo will resemble a human (Brauer, 2003; Harrison et al., 1966; Lewis & Harrison, 1966).

2.1.2 Development of the Eye – Selected Highlights

The eye is the foundation of the visual system in humans. Its main purpose is to detect and analyze light. The eye connects via the optic nerve to the brain. The cornea and the sclera form the outer layer of the eye. The iris, ciliary body, and choroid form the middle layer. The retina forms the inner layer. This is a summary of the major structural components of the eye (Bear et al., 2000). As with numerous other organs, the eye develops as a product of complex interactions of primitive cells during embryogenesis (Barishak, 2001). On day 22 of embryogenesis (day E22) the developing eyes emerge as a pair of willow grooves, the optic sulci, on each side of the forebrain as the neural tube closes. The neural tube is a tube that is formed in mammalian embryos by the closure of

ectoderm tissue, which is the precursor to the central nervous system that develops into the brain and the spinal cord. These willow grooves form the optic vesicles, and come in contact with surface ectoderm, which is essential for lens formation. Then the lens vesicles form, followed by the choroid, sclera, and cornea. The formation of the eye begins around week 3 and has ceased by week 8. The eyes become functional between months 5 and 7 of fetal development (Gross et al., 2008; Nguyen & Arnhieter, 2000).

The vertebrate eye consists of tissues from distinctive embryonic origins. For example, the lens and the cornea are derived from the surface ectoderm while the retina and the epithelial layers of the iris as well as the ciliary body are derived from the anterior neural plate or neuroectoderm. The different eye components are formed as a consequence of well-timed actions of transcription factors and inductive signals (Schoenwolf et al., 2008c; Sadler, 2006; Graw, 2010). The structural components of the eye are illustrated in the human eye diagram shown in Figure 2-4. According to Segal (2012), “When all of the components of the eye function properly, light is converted to impulses and conveyed to the brain where an image is perceived.” Each component serves a distinct purpose, for example, the macula is a part of the retina. Its main purpose is central vision. The retina contains photoreceptor cells that react to the presence and intensity of light by sending impulses to the brain where the image is assimilated.

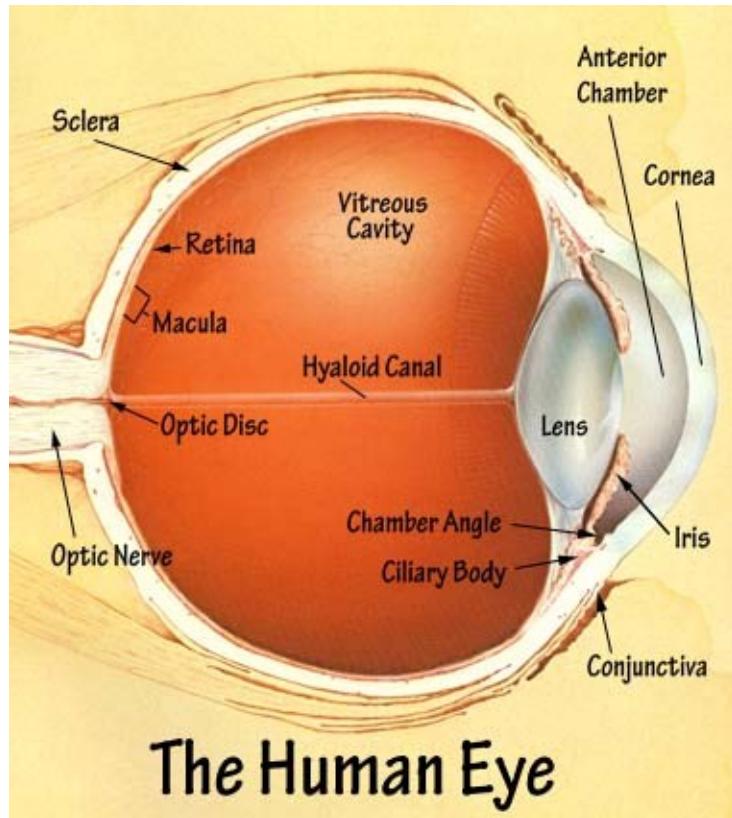


Figure 2-4: The Human Eye (From Segal, 2012)

Model organisms and the eye

Over 100 years ago the chicken emerged as a model organism in embryonic developmental biology (Burt, 2007; Cogburn et al., 2007). The use of the chicken as a model experimental species led to many fundamental discoveries in developmental biology (Burt, 2007). Reinforcement of this choice occurred with the sequencing of the chicken genome. This is fitting in a sense because the chicken has been incorporated into human culture for more than 8,000 years as a domesticated livestock species (Cogburn et al., 2007). Approximately 100 million years ago, the chicken and the zebrafish lineages diverged. With the sequencing of its genome, the zebrafish has emerged as the second significant model for understanding brain and eye development (Brown, 2003).

Since the Human Genome Project, the zebrafish's complete genome has also been sequenced, helping to make it even more important as a vertebrate model organism for scientific research (Anderson & Ingham, 2003). Although the zebrafish is less closely related to humans genetically than the chicken, its sizeable number of offspring, the transparency of the embryos during the course of the developmental period, and its quick embryonic development have made the zebrafish a favorite model organism for scientists studying eye development (Fadool & Dowling, 2008; Sprague et al., 2006). The zebrafish reaches sexual maturity in 4 months, with its optically transparent embryos developing externally. The latter helps make it a valuable choice as a model organism because neither the mouse nor *Drosophila melanogaster* permit direct observation of the vertebrate organs or tissues (Dodd et al., 2000). Its transparency during embryonic development establishes the zebrafish as the prime organism for microscopic examination of organs (Glass & Glass, 2004).

2.1.3 Translating Time Across Mammalian Species

The overall objective of the translating time project has been to gain understanding of human neurodevelopmental events such that improvements could be made to diagnostic and intervention capabilities (DeFelici, 2001). The original generic mammalian model included nine eutherian mammals: *Felis domestica* (cat), *Mustela putorius furo* (ferret), *Mesocricetus auratus* (hamster), *Macaca mulatta* (monkey), *Homo sapiens* (humans), *Mus musculus* (mouse), *Oryctolagus cuniculus* (rabbit), *Rattus norvegicus* (rat), and *Acomys cahirinus* (spiny mouse). The original intent of the statistical model (Raz, 2004) was to create, on the one hand, a scale of developmental events such that early events score low and later events score high, and on the other hand, an additional scale of

species where fast-developing species score low and slow-developing species score high. The rationale for scoring the species was to rank them linearly in regard to the neural development duration. The development events were also ranked. The sum of the species and events scores is a modified logarithm of postconception dates; therefore, the higher the postconception date the higher must be that sum. Therefore the two scores, of event and of species, could be combined to infer the time of an event in a specified species based on other event times and other species.

Neural developmental events are associated with data comprised of onsets, peaks, and tails of neurogenesis related to neuronal structures, which include but are not limited to associated neuronal death and components of process maturation. A constant k in the mathematical model accounts for events such as implantation, blastulation, and differentiation of the primitive germ layers that have been found to be consistent across tested mammals. A value of 5.37 was found for constant k , as shown below in Equation 1.

$$\text{Equation (1)} \quad Y = \ln (day - k)$$

where Y is the species score plus the event score plus the primate factor. Because primate brains develop slightly different than other mammals, the primate factor was used in early versions of the model to account for species that are primates by providing a correction for systemically different rates of development of the limbic and cortical systems of these species. This equates to a log transform of postconceptional days adjustable by k ; day is thus the postconceptional (pc) day. This nonlinear model can be solved for day such that an estimate of the day of a given developmental event in any of the nine species can be predicted based on the overall species score, overall event score, and whether it is a

primate. The model thus predicts species-event dates when empirical data are missing.

The statistical model accounts for certain primate neurodevelopmental events which occur at different times than otherwise predicted, by adjusting k by adding 0.248683 for primate cortical events and subtracting 0.079280 for primate limbic events. The primate factors were computed using standard regression methods (Clancy et al., 2007a; Clancy et al., 2007b).

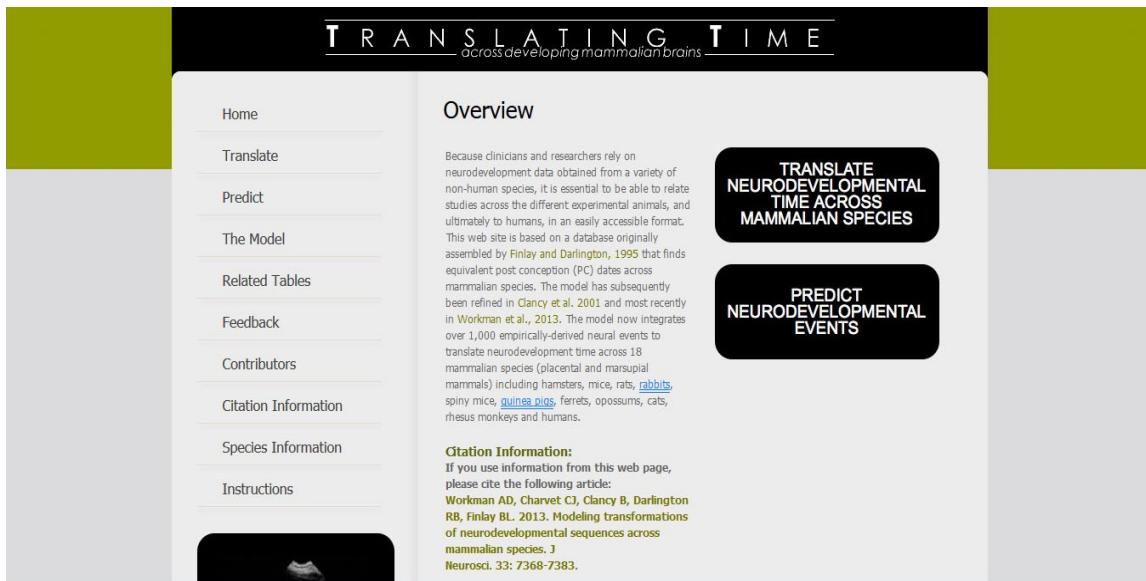


Figure 2-5: Translating Time Website (From <http://www.translatingtime.net/>)

As shown in Figure 2-5, this research evolved into a Web-based tool with a user-friendly front-end interface for researchers and clinicians to utilize and submit new data points (<http://www.translatingtime.net>). The back end is a MySQL database of data points. The user can predict times of neurodevelopmental events by “translating” them from other mammalian species. The translation is in postconceptional (pc) and postnatal

(pn) time, where the first 24-hour period after conception is often denoted as pc1, and pn0 denotes the first 24-hour period after birth.

Ocular Development

For over 400 million years, the functional and structural features of the vertebrate retina have remained the same. Over the past 20 years, researchers at Cornell University have utilized developmental and evolutionary approaches to study the structure and function of the vertebrate nervous system. One specific concentration has been the visual system (Franco et al., 2001; Kaskan et al., 2005; Chalfin et al., 2007; Finlay, 2008; Finlay et al., 2008; Dyer et al., 2009; Lameirao et al., 2009; Finlay, 2011). “Every existent animal is the descendant of animals going back to the beginning of evolutionary time, the successful survivor of multiple mass extinctions, climate shifts, niche invasions, diseases, disasters, and mishaps” (Finlay et al., 2005). Particular attention has been paid to New World primates in the development of size and conformation of the eye, including the retina, and the number and topography of rods, cones, and optic nerve axons. Individual level variations within species are extremely important in identification of normal development and its pathologies. For example, the number of rods and cones may vary within 100 of the maximum observed for one animal in a species to another animal in the same species (Finlay & Clancy, 2008; Cahalance et al., 2012; Charvet & Finlay, 2012; Wallace, 2007).

In addition, work has been done to investigate developmental events concerning rods, cones, and optic nerve axons in the mouse visual system as well as peripheral structures. Variations in the timing as well as the duration of gene expression are key

aspects in which the vertebrate eye differs amongst species. However, the cell types are conserved across species. A noteworthy difference is the eye size, its arrangement of cells and the ratio of numbers of cell types. This suggests timing of gene expression is a primary source of evolutionary variation (Harada et al., 2007; Niessen, 2006; Luo et al., 2006).

2.1.4 Assessment of the Literature and Placement of this Research

Mammalian embryonic development is a topic that has been researched for more than 100 years. Observing human embryonic development via experimentation in the uterus is unethical. Fortunately, researchers have established that we can rely on mammalian and non-mammalian models to help understand human development. Mouse genetics helped to revolutionize our understanding of mammalian development in general. Because the developmental processes are fundamentally similar, a variety of model organisms each can be utilized in building the foundation for understanding how we develop as humans. Since the Human Genome Project (which also included analysis of the laboratory mouse genome), large amounts of genetic information have been derived from these two organisms. The derivative data has proven valuable for the analysis of human embryonic development, genetic diseases and disorders, and evolutionary processes. Each model organism has advantages for the study of certain mammalian biological processes. The literature has clearly shown that, as noted earlier, our reliance on model organisms has helped us understand how *Homo sapiens* as a species forms during the early stages of development.

The literature to date has barely begun to address the novel idea of translating time across species with a focus on the broader range of all eye structural components. Animal

eyes are anatomically and functionally diverse; currently, there is active research on many different facets of the eye. Therefore, a dataset for each species will share common elements as well as have unique characteristics. The extraction of a combination of common and unique data points will enable the translating time process and thus the prediction of ocular event times across mammalian species. The use of a non-mammalian vertebrate, the zebrafish, in my analysis will provide an interesting opportunity for the research community to understand whether a very different species can work within the current model. This inclusion is another novel aspect of the research. It is expected that this research may be useful in the study and ultimately the reduction of congenital eye defects and eye abnormalities.

Chapter 3

3.1. Semi-Automated Literature Review

The aim of this portion of the project is to design, implement, utilize, and validate a tool and an approach to accomplishing semi-automated acquisition of data from the literature regarding eye-related developmental events. The *Danio rerio* (zebrafish) is included because it is considered a model organism for research in eye development. WebCrawler is the name coined for the software tool, which allows researchers to search online journals with keywords and/or phrases related to eye development. With this tool the user has the capability, for example, to view the keyword(s) in a context of 3 lines prior to and three lines after the designated word(s). This allows the researcher to decipher whether or not the article should be downloaded for further review.

This process can be more generally referred to as a type of text mining wherein a tool looks for patterns within a corpus of natural language text. Parsing separates the keywords or phrases in the document analysis, and it can cut the time it would take to actually download each document and read it without semi-automated assistance. This exemplifies the general intent for literature searches to take less human effort, resulting in shorter times in finding articles and their relevant passages applicable to research on a given topic.

3.1.1. Materials

A personal computer (PC) running the Windows 7 Professional Operating System version 6.1, 32-Bit Edition was used to develop the WebCrawler software application. Its processor is an Intel Pentium Dual CPU (Central Processing Unit) E6750 running at 2.66

GHz (Gigahertz) with 2 GB (Gigabytes) of RAM (Random Access Memory). The WebCrawler's Graphical User Interface (GUI) was written in Java via the NetBeans Integrated Development Environment (IDE) version 6.9.1 (Build 201007282301). Java is an object-oriented programming language that facilitates programs to be run on multiple platforms. It is derived as an improvement over C and C++, and was originally developed by Sun Microsystems, which later merged with the Oracle Corporation to become Oracle America. NetBeans version 7.0 was written in the Java programming language version 1.6.0_22 and released on April 19, 2011. The NetBeans IDE as well as the NetBeans Platform is dual licensed under the Common Development and Distribution License and the GNU General Public License version 2. Both are freeware that can be downloaded from www.netbeans.org.

The NetBeans IDE offers support for several languages such as PHP, JavaFX, C/C++, and JavaScript. Sun Microsystems made NetBeans open source in 2000 and in 2010 when Sun Microsystems merged with Oracle, it continued to sponsor the project. Both the NetBeans IDE as well as the NetBeans Platform is freely available through the Internet. The NetBeans IDE is platform independent, which means that it is not intended to be run on any one processor or operating system. It is designed to be installed on various systems such as Windows, Linux, and Apple. The key component here is the Java Virtual Machine (JVM), which executes Java bytecode programs that run identically regardless of the operating system or hardware under which the program runs. Although portability is a key feature of Java's bytecode, these interpreted programs tend to run slower than a program compiled to an executable.

The Web Crawler System

The WebCrawler Project contains 17 java files, which are divided into Source Packages. These files include approximately 3,609 lines of executable code and comments. The code for the WebCrawler Application is in Appendix A. In addition, it is available for download at <http://www.eyetranslatetime.net>. The Project is organized in 4 Source Packages: All_Purpose, Threads, Frames, and WebCrawling.

The All_Purpose Package consists of 4 files: FileChooser.java, HoweFileReader.java, HoweFileWriter.java, and URLTester.java. The files in this package handle the bulk of the generic I/O (input/output) functionality such as reading data to and from a file, file selection, and testing the URL string. The file chooser, FileChooser.java, contains 83 lines. The purpose of this class is to provide the user with the mechanism, a two column view dialog box, to choose a file from the file system. In this case, the Windows File System is utilized wherein the user's home directory is the starting point. The file reader, HoweFileReader.java, contains 99 lines of code. The purpose of this class is to read the content of the .html source files that have been downloaded. This is accomplished via the BufferedReader class by reading the lines into a vector. The file writer, HoweFileWriter, contains 125 lines of code. The purpose of this class is to write the content of the .html files that have been downloaded using an index based on the number of items that were downloaded from the search. The file URL tester, URLTester.java, contains 58 lines of code. The purpose of this class is to test and validate the URL that was passed as a parameter.

The Threads Package has 5 files: OverviewThread.java, PubMedCentralThread.java, ScienceDirectComplete.java, and ScienceDirectThread.java. A thread is an independent path of execution through the program. Multiple threads can

exist in the same process, for example, a user opens a document in Microsoft Word and then opens another document to write to. Essentially, there are two tasks executing concurrently inside a single program. In the case of WebCrawler, there are 5 threads running concurrently. The multipurpose Thread, OverviewThread.java, has 125 lines of code. The purpose of this class is to run the overall search and to determine the selection(s) for crawling the web. The Thread for the PubMedCentral (PMC) search, PubMedCentralThread.java, is 103 lines of code. The purpose of this Thread is to run the PubMedCentral search and obtain the PMC ID (identification) number. The PMC ID is the number assigned to a manuscript upon acceptance by NIH. The Thread for the PubMed search, PubMedThread.java, has 96 lines of code. The purpose of this Thread is to run the PubMed search as well as reading through the results to get the unique identifier, PMID (PubMed Identification), of the citation in the NCBI PubMed database. The Thread for the complete search of ScienceDirect, ScienceDirectComplete.java, is 531 lines of code. The purpose of this class is to run the complete ScienceDirect search. This class will download every journal from the search in ScienceDirect that UALR has access to. The software works for the corpus for which it is designed, but can be modified to search other journals. The Thread ScienceDirectThread.java that runs an abbreviated search of ScienceDirect is 207 lines of code. The purpose of this class is to run a Science Direct search with the exception of a "Long" or "Complete" search.

The Frames Package contains all of the major GUIs through which the user will interact. A frame is a window that can have a border, a title, and components such as buttons. There are 6 files in the Frames Package: Interface.java, InterfaceProgress.java, Questionnaire.java, SD_Minimums.java, SD_OptionSelecter.java, and

ScienceDirectStatus.java. The main GUI, Interface.java, is initiated upon running the WebCrawler Application. The purpose of this class is to provide an interface that allows the user the option to select the site(s), PubMed, PubMedCentral, and/or ScienceDirect to be searched, the term and/or phrases they want to search and the directory they wish to save to. The user can specify wait time between pages as well as a special wait time for documents downloaded from ScienceDirect. The user can also indicate how the search is to be completed when using ScienceDirect. A secondary purpose of this class is to start up all the threads that the program will use and start up additional GUIs. The interface, Interface.java, file is 561 lines of code. The purpose of this class is to display the program's progress to the user. The user will get data on the number of files found, the number of files downloaded, estimated time left and a status bar of progress based on the number of files downloaded in relation to the total number of files to be downloaded. The query form, Questionnaire.java, allows the user to add downloaded items to a folder that has already been created. This file contains 270 lines of code. The purpose of this class is to display the directory for the keyword list. It also tells whether or not there are a minimum number of files to be downloaded from a journal. The ScienceDirect minimum, SD_Minimumus.java, allows the user to specify a minimum number of documents that can be downloaded per journal. This file contains 121 lines of code. The ScienceDirect option selector, SD_OptionSelecter.java, contains 370 lines of code. The purpose of this class is provide the user the option to save files to the same directory as where previously saved files are stored. If selected, the user can select the directory from a Windows Dialog box. Additionally, this class queries the user as to whether or not there will be the minimum number of documents downloaded per journal. The ScienceDirect download

status file, ScienceDirectStatus.java, contains 256 lines of code. The purpose of this class is to provide the user with information on the Science Direct download status for articles that have completed the download process.

Additionally, there are Main and InformationModule java files. The Main.java file contains the main() method, which is where the program execution begins. It is in charge of the high level organization of the program's functionality. In the event that an application accepts command arguments to begin execution of the program, this is where those arguments would initially be accepted. The main() method is imperative for the application to run because it then invokes all of the other methods and functions required to run the application. The Libraries that are included in this project are .jar files from the JDK 1.6: resources, rt, jsse, jce, charsets, dnsns, localedata, sunjce_provider, sunmscapi, and sunpkcs11. They are automatically loaded based on the classes that are utilized during development. A library is a collection of functions or behaviors and functionality that is imbedded in the software, which allows the application to run properly at run-time. Libraries are imperative in the program linking process and are loaded dynamically. Because Java is platform independent, the programs or applications that are developed with Java do not rely on libraries that are native to the operating system. It does however have a set of standard class libraries that contain functions that are common to nearly all current operating systems. Libraries are typically loaded as .jar files. The Test Libraries include JUnit 3.8.2 – junit-3.8.2.jar and JUnit 4.8.2 – junit-4.8.2.jar. A JAR (Java Archive) is an archive file format that is similar to a .zip file format, however, the JAR file extension is .jar.

Christoper Biedenbender provided a starting point for the Web Crawling software. Christopher is a UALR graduate in the Information Science Department. His prototype was used for crawling the Web to search for journal articles related to protein content of corn. I modified the code for utilization in my translating time research.

Development Environment

The decision to utilize Java as well as NetBeans to develop the WebCrawler Application was an easy choice because of its platform independence and the wide array of libraries. Also, the Java programming language has been around since 1994. It is also a programming language ubiquitous in running applications on desktops, mobile devices, enterprise systems, and web servers. Java and NetBeans are both freely available under a free software license, the GNU General Public License, which means that they can be run, studied, redistributed and improved upon.

ScienceDirect and PubMed are two of the top ranking online search engines containing journals and electronic books. Therefore, both were search engines utilized for the WebCrawler journal search. ScienceDirect is operated by the Dutch company Elsevier. It contains more than 11 million articles from more than 2,500 journals and more than 6,000 electronic books. The abstracts for most of these articles are available free of charge and are offered in PDF (Portable Document Format from Adobe Acrobat) and HTML (HyperText Markup Language) formats; however, the full texts of most articles are available with a subscription to ScienceDirect or on a pay-per-view basis. The articles are categorized into 4 sections: Physical Sciences and Engineering, Life Sciences, Health Sciences, and Social Science and Humanities. ScienceDirect can be accessed via www.sciencedirect.com.

PubMed is a free online portal to MEDLINE (Medical Literature Analysis and Retrieval System), which contains 22 million records of citations as well as abstracts for the biomedical and life sciences topics. It articles include categories such as medicine, pharmacy, nursing, health care, dentistry, and veterinary medicine. It is operated by the United States National Library of Medicine (NLM) at the National Institutes of Health. The first release of PubMed was in January 1996. As with ScienceDirect, the abstracts for most of these articles are available free of charge and are offered in PDF and HTML formats; however, the full texts of articles are available only for recent years. PubMed can be accessed via the Internet at www.ncbi.nlm.nih.gov/pubmed/.

The HTMLAsText version 1.11 software was used to convert HTML documents to text files wherein all HTML tags are removed from the file. The HTMLAsText is an executable utility that converts HTML documents to text files. This is accomplished by removing all HTML tags. Additionally, the user can configure formatting of the converted text through user defined preferences from the GUI. HTMLAsText automatically removes all of the HTML tags and scripts from the document. The text that stays after the removal process is formatted based on the number of characters per line that the user selects. HTML entities such as the symbols " also known as (AKA) “ or double quote, and & AKA & or ampersand, are translated into the equivalent ASCII character(s). Moreover, paragraphs that are aligned with anything other than left-justification have space characters inserted to the left of the line(s).

Table data are delimited by comma, spaces, and tabs as a means of separating the data elements. Text blocks that are preformatted with the <pre> tag are output without additional formatting to the text. An extremely important and time saving feature of the

HTMLAsText utility is the capability to convert multiple files within the same folder, which was the option utilized for this project. If the “scan subfolders” option is selected, the utility will scan all subfolders within the specified folder. It is important to note that this option is only available when converting multiple files. A requirement of the multiple file conversion option is to use the wildcard (*) for the HTML file that will be converted, with the full path, for example, C:\Desktop\HTML*.html. Additionally, the wildcard (*) option is required for the text file that the user wants to save, for example, C:\Desktop\text*.txt. Single file conversion is also available. The HTMLAsText utility is freely available from NirSoft at www.nirsoft.net/utils/htmlastext.html. It is portable and does not require an installation. The utility has been available as freeware from NirSoft since 2004.

A Virtual Private Network (VPN) was used to access and run the WebCrawler Application remotely. The VPN expands the network and resources at UALR across the Internet. It is a means that I used to access UALR’s internal network over the Internet in a secure manner. When I was off campus or outside the UALR firewall, the VPN provided me with secure access to the resources inside the network. It permitted my home computer to send and receive data across the UALR network as if were private network to which I was connected with the functionality, security and management policies of an actual private network. It is accomplished through the creation of a virtual point-to-point connection through a combination of dedicated connections and encryption. The name “virtual private network” implies that the VPN connection via the Internet is essentially a wide area network (WAN) tied to a site; however, it appears to the user that there is a private connection. Therefore, the VPNs require that remote access be authenticated and

encryption methods used to ensure that disclosure of private information is prevented.

The capability to make a VPN connection comes standard with each operating system. It can be setup through any Windows Operating System using the *Network Connection Wizard*. Therefore, no additional software is required to set up a VPN.

Ares, a workstation that interfaces with UALR's High Performance Computing Cluster was utilized to perform the pattern matching in the Linux Environment because it has numerous text-editing utilities. It is a Dell PowerEdge 6950, running 4 Dual-Core AMD Opteron Processor 8220s with 32GB of RAM. It runs Rocks Cluster release 4.3, which incorporates CentOS (Community Enterprise Operating System) version 5.5, 64-Bit Edition. Rocks Cluster is a free software version of Linux. The intended goal of Rocks Cluster is for utilization of high performance computer clusters. It was originally partially funded by a grant through the National Science Foundation (NSF) for the National Partnership for Advanced Computational Infrastructure and the San Diego Supercomputer Center at the University of California at San Diego in 2000. It is presently funded by a follow-on NSF grant. In its initial form, Rocks was founded on the Red Hat Linux distribution; however, the latest versions of Rocks are now based CentOS with a customized Anaconda installer, which makes installation simpler. Both Rocks and CentOS are open source software. Rocks is available at www.rockscluster.org while CentOS is available at www.centos.org.

PuTTY was made use of to access Ares and to run the commands in the Linux environment. PuTTY is another freely available open source software application. It is a terminal emulator application that acts as a client for SSH, Telnet, and serial console, which use the secure shell protocol to connect to a remote computer. Although PuTTY

was originally written for Microsoft Windows, it has been ported to other operating systems. PuTTY is available at www.putty.org.

FileZilla is a cross-platform application used as a SFTP (Secure File Transfer Protocol) Client. It is able to handle transfer of files larger than 4 GB (Gigabytes). It is an open source client that is freely available from www.filezilla-project.org under the terms of GNU. Additionally, FileZilla supports application layer protocol SSL (Secure Sockets Layer), which is a protocol for encrypting information over the Internet. It also supports drag and drop, filename filters, and directory comparison.

3.1.2. Methods

The semi-automated literature review began with keyword searches via ScienceDirect's search engine interface and was later extended to PubMed and PubMedCentral. I initiated the searches using the scientific names of the nine eutherian mammals: *Felis domestica* (cat), *Mustela putorius furo* (ferret), *Mesocricetus auratus* (hamster), *Macaca mulatta* (monkey), *Homo sapiens* (humans), *Mus musculus* (mouse), *Oryctolagus cuniculus* (rabbit), *Rattus norvegicus* (rat), and *Acomys cahirinus* (spiny mouse), combined with the word “eye.” Secondly, I used the scientific names of the nine eutherian mammals combined with a word that is synonymous with the word “eye,” that word being “ocular.” Later, I moved on the more refined combinations of words such as “eye development” and “pc”, which is an abbreviation for postconception. Additionally, I used the keywords associated with the structural components of the eyes as it relates to the anatomy of the eye. Additionally, a search utilizing the zebrafish, a vertebrate model organism for eye development, was conducted using its scientific name, *Danio rerio*, joined with the keywords “eye development” and “pf”, which is an abbreviation for

postfertilization. Since the zebrafish hatches approximately 36 hours after fertilization, the keyword “hpf”, which stands for hours post fertilization was used also. A complete catalog of the keyword searches is shown below in Table 1.

Species	Keywords
<i>Felis domestica</i>	eye embryogenesis, embryonic day
<i>Mustela putorius furo</i>	eye embryogenesis, embryonic day
<i>Mesocricetus auratus</i>	eye embryogenesis, embryonic day
<i>Macaca mulatta</i>	eye embryogenesis, embryonic day
<i>Homo sapiens</i>	eye embryogenesis, embryonic day
<i>Mus musculus</i>	eye embryogenesis, embryonic day
<i>Oryctolagus cuniculus</i>	eye embryogenesis, embryonic day
<i>Rattus norvegicus</i>	eye embryogenesis, embryonic day
<i>Acomys cahirinus</i>	eye embryogenesis, embryonic day
<i>Danio rerio</i>	eye embryogenesis, embryonic day
<i>Felis domestica</i>	ocular embryogenesis, embryonic day
<i>Mustela putorius furo</i>	ocular embryogenesis, embryonic day
<i>Mesocricetus auratus</i>	
<i>Macaca mulatta</i>	ocular embryogenesis, embryonic day
<i>Homo sapiens</i>	ocular embryogenesis, embryonic day
<i>Mus musculus</i>	ocular embryogenesis, embryonic day
<i>Oryctolagus cuniculus</i>	ocular embryogenesis, embryonic day
<i>Rattus norvegicus</i>	ocular embryogenesis, embryonic day
<i>Acomys cahirinus</i>	ocular embryogenesis, embryonic day
<i>Danio rerio</i>	ocular embryogenesis, embryonic day
<i>Felis domestica</i>	eye
<i>Mustela putorius furo</i>	eye
<i>Mesocricetus auratus</i>	eye
<i>Macaca mulatta</i>	eye
<i>Homo sapiens</i>	eye
<i>Mus musculus</i>	eye
<i>Oryctolagus cuniculus</i>	eye
<i>Rattus norvegicus</i>	eye
<i>Acomys cahirinus</i>	eye
<i>Danio rerio</i>	eye

<i>Felis domestica</i>	ocular
<i>Mustela putorius furo</i>	ocular
<i>Mesocricetus auratus</i>	ocular
<i>Macaca mulatta</i>	ocular
<i>Homo sapiens</i>	ocular
<i>Mus musculus</i>	ocular
<i>Oryctolagus cuniculus</i>	ocular
<i>Rattus norvegicus</i>	ocular
<i>Acomys cahirinus</i>	ocular
<i>Danio rerio</i>	ocular
<i>Felis domestica</i>	eye development
<i>Mustela putorius furo</i>	eye development
<i>Mesocricetus auratus</i>	eye development
<i>Macaca mulatta</i>	eye development
<i>Homo sapiens</i>	eye development
<i>Mus musculus</i>	eye development
<i>Oryctolagus cuniculus</i>	eye development
<i>Rattus norvegicus</i>	eye development
<i>Acomys cahirinus</i>	eye development
<i>Danio rerio</i>	eye development
<i>Felis domestica</i>	ocular development
<i>Mustela putorius furo</i>	ocular development
<i>Mesocricetus auratus</i>	ocular development
<i>Macaca mulatta</i>	ocular development
<i>Homo sapiens</i>	ocular development
<i>Mus musculus</i>	ocular development
<i>Oryctolagus cuniculus</i>	ocular development
<i>Rattus norvegicus</i>	ocular development
<i>Acomys cahirinus</i>	ocular development
<i>Danio rerio</i>	ocular development
<i>Felis domestica</i>	eye development, pc
<i>Mustela putorius furo</i>	eye development, pc
<i>Mesocricetus auratus</i>	eye development, pc
<i>Macaca mulatta</i>	eye development, pc
<i>Homo sapiens</i>	eye development, pc
<i>Mus musculus</i>	eye development, pc
<i>Oryctolagus cuniculus</i>	eye development, pc
<i>Rattus norvegicus</i>	eye development, pc
<i>Acomys cahirinus</i>	eye development, pc
<i>Danio rerio</i>	eye development, pf
<i>Danio rerio</i>	eye development, hpf
<i>Felis domestica</i>	ocular development, pc

<i>Mustela putorius furo</i>	ocular development, pc
<i>Mesocricetus auratus</i>	ocular development, pc
<i>Macaca mulatta</i>	ocular development, pc
<i>Homo sapiens</i>	ocular development, pc
<i>Mus musculus</i>	ocular development, pc
<i>Oryctolagus cuniculus</i>	ocular development, pc
<i>Rattus norvegicus</i>	ocular development, pc
<i>Acomys cahirinus</i>	ocular development, pc
<i>Danio rerio</i>	ocular development, pf
<i>Danio rerio</i>	ocular development, hpf

<i>Felis domestica</i>	choroid retina vitreous humor optic nerve inferior muscle conjunctiva upper eyelid iris cornea lens aqueous humor lower eyelid suspensory ligaments pupil
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<i>Mustela putorius furo</i>	choroid retina vitreous humor optic nerve inferior muscle conjunctiva upper eyelid iris cornea lens aqueous humor lower eyelid suspensory ligaments pupil
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<i>Macaca mulatta</i>	choroid retina vitreous humor optic nerve inferior muscle conjunctiva upper eyelid iris cornea lens aqueous humor lower eyelid suspensory ligaments pupil
<i>Mus musculus</i>	choroid retina vitreous humor optic nerve inferior muscle conjunctiva upper eyelid iris cornea lens aqueous humor lower eyelid suspensory ligaments pupil
<i>Oryctolagus cuniculus</i>	choroid retina vitreous humor optic nerve inferior muscle conjunctiva upper eyelid iris cornea lens aqueous humor lower eyelid suspensory ligaments pupil

<i>Rattus norvegicus</i>	choroid retina vitreous humor optic nerve inferior muscle conjunctiva upper eyelid iris cornea lens aqueous humor lower eyelid suspensory ligaments pupil
<i>Acomys cahirinus</i>	choroid retina vitreous humor optic nerve inferior muscle conjunctiva upper eyelid iris cornea lens aqueous humor lower eyelid suspensory ligaments pupil
<i>Mesocricetus auratus</i>	choroid retina vitreous humor optic nerve inferior muscle conjunctiva upper eyelid iris cornea lens aqueous humor lower eyelid suspensory ligaments pupil

<i>Homo sapiens</i>	sclera iris pupil lens cornea anterior chamber posterior chamber optic disk vitreous body ciliary body choroid retina macula lutea fovea centralis
<i>Danio rerio</i>	sclera choroid retina iris cornea aqueous humor lens vitreous humor pupil
<i>Felis domestica</i>	eye development, event, pc
<i>Mustela putorius furo</i>	eye development, event, pc
<i>Mesocricetus auratus</i>	eye development, event, pc
<i>Macaca mulatta</i>	eye development, event, pc
<i>Homo sapiens</i>	eye development, event, pc
<i>Mus musculus</i>	eye development, event, pc
<i>Oryctolagus cuniculus</i>	eye development, event, pc
<i>Rattus norvegicus</i>	eye development, event, pc
<i>Acomys cahirinus</i>	eye development, event, pc
<i>Danio rerio</i>	eye development, event, pf
<i>Danio rerio</i>	eye development, event, hpf
<i>Felis domestica</i>	ocular development, event, pc
<i>Mustela putorius furo</i>	ocular development, event, pc
<i>Mesocricetus auratus</i>	ocular development, event, pc
<i>Macaca mulatta</i>	ocular development, event, pc
<i>Homo sapiens</i>	ocular development, event, pc
<i>Mus musculus</i>	ocular development, event, pc
<i>Oryctolagus cuniculus</i>	ocular development, event, pc
<i>Rattus norvegicus</i>	ocular development, event, pc
<i>Acomys cahirinus</i>	ocular development, event, pc
<i>Danio rerio</i>	ocular development, event, pf

<i>Danio rerio</i>	ocular development, event, hpf
<i>Felis domestica</i>	eye development, event, postconception
<i>Mustela putorius furo</i>	eye development, event, postconception
<i>Mesocricetus auratus</i>	eye development, event, postconception
<i>Macaca mulatta</i>	eye development, event, postconception
<i>Homo sapiens</i>	eye development, event, postconception
<i>Mus musculus</i>	eye development, event, postconception
<i>Oryctolagus cuniculus</i>	eye development, event, postconception
<i>Rattus norvegicus</i>	eye development, event, postconception
<i>Acomys cahirinus</i>	eye development, event, postconception
<i>Danio rerio</i>	eye development, event, post fertilization
<i>Felis domestica</i>	ocular development, event, postconception
<i>Mustela putorius furo</i>	ocular development, event, postconception
<i>Mesocricetus auratus</i>	ocular development, event, postconception
<i>Macaca mulatta</i>	ocular development, event, postconception
<i>Homo sapiens</i>	ocular development, event, postconception
<i>Mus musculus</i>	ocular development, event, postconception
<i>Oryctolagus cuniculus</i>	ocular development, event, postconception
<i>Rattus norvegicus</i>	ocular development, event, postconception
<i>Acomys cahirinus</i>	ocular development, event, postconception
<i>Danio rerio</i>	ocular development, event, post fertilization

Table 3-1: Search Strings with Keywords and Species Name

The citations only were exported in plain text format and run through the WebCrawler. By means of the WebCrawler, the entire work referenced by the citation was downloaded from ScienceDirect when it was available in HTML format. A supplementary search was conducted through the WebCrawler, as shown in Figure 3-1, to narrow the number of results based on a specified word or phrase.

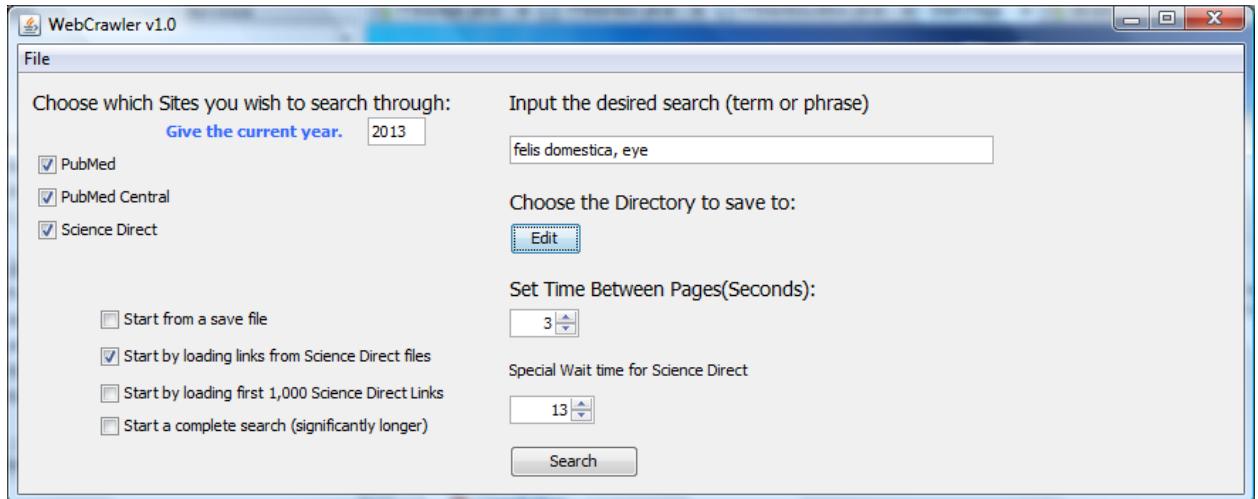


Figure 3-1: WebCrawler v1.0

Once those results were returned, multiple files were run through the HTMLAsText version 1.11 converter. This tool converts HTML documents to text files by eliminating the HTML tags. This step is done in preparation for cleaning the HTML tags from the file to make the pattern matching easier such that none of the valuable textual content is lost.

An external connection through a VPN was used for the connection to the UALR computer network. While on campus, only a local network connection is required. The network is encrypted such that only authorized users are allowed access. The VPN connection allowed for remote communications to on-campus network, which provided the portal to the pattern matching features of Linux. Instructions for the VPN setup to the UALR network can be found at <http://ualr.edu/computingservices/networks/vpn/>, which was last accessed on April 20, 2011.

In this case, PuTTY was chosen as the free open source client. SSH is a network protocol that utilizes encryption as a means of security for data transfer over an unsecure network like the Internet. PuTTY runs on the Windows machine as a client application through which the user tells it to connect to a Unix machine. Then, the user can work as

though he/she were actually sitting at the Unix terminal from a remote location. Once a connection to the network was made all of the files to the Linux machine for pattern matching. The files were placed in a folder and zipped prior to the file transfer. This process was repeated once the pattern matching was completed so that the files could be transferred back to my computer for further analysis.

I set up a file directory structure with meaningful names which pertained to the search. This allowed me to easily recognize the folder that pertained to a particular search. Once the file transfer was complete, I used PuTTY to login to the Ares, the host machine on the Linux server. From this point I could begin the file manipulation and pattern matching process. Since the files were transferred over to Ares were compressed in a zip archive, the follow command was used to unzip the files. This command, *unzip filename.zip*, extracts the contents of the zip file into its own directory and it produces subdirectories as needed. Likewise, upon completion the following command was used to create the archive and place all the files in the current directory in it in a compressed form: *zip filename **.

The ‘grep’ command line utility was used to search the files for a string pattern(s) in the text files that were transferred to Ares. The basic syntax of the ‘grep’ command is:

```
grep [-options] pattern [filename]
```

Much of the skill involved in pattern matching comes from choosing the pattern to search for, particularly when using the ‘grep’ command.

An example of the ‘grep’ options used for this literature review is:

- `grep -i -n -C 5 "postconception" *.txt > postconception.pdf`

The `-i` option ignores case distinctions in both the pattern and the input files. The `-n` option prefixes each line of output with the line number within its input file. Therefore, the filename is followed by the line number. The `-C` option prints the specified number of lines (N lines, with N being 5 in this case) before the match in the output context. Additionally, I wanted the match to appear with the lines from both before and after the match. Essentially, 5 lines before and after the pattern “postconception” were printed. The command shown above searches for the given string/pattern case insensitively. In this example, it looks for occurrences of strings like “postconception”, “POSTCONCEPTION” and “Postconception” case insensitively as shown below. This is an abbreviated version of the example showing only the search for the pattern, and not the 5 lines prior to and after the match.

- *Offspring reared by mothers exposed to filtered air both prior to and postconception.*
- *OFFSPRING REARED BY MOTHERS EXPOSED TO FILTERED AIR BOTH PRIOR TO AND POSTCONCEPTION.*
- *Offspring reared by mothers exposed to filtered air both prior to and Postconception.*

This pattern will be matched in the all of the files, where the asterisk (*) signifies the wildcard, in the current directory. The asterisk in the command says to do the job as often as the field allows. Also, in this example, I used redirection (>) to save the output of the grep in a file. The data will be written to a file call postconception.pdf. I chose to write to a file with a different file extension, .pdf, so that it would be easy to distinguish this file from others that I had already downloaded. Portable Document Format (PDF) was chosen

because it is a file format that is used to symbolize documents in an independent manner regardless of the operating system, hardware, or application software.

After the pattern matching was complete, the output files were moved into one folder and compressed into a zip file so that they could be transferred back from Ares to my personal computer (PC) for further analysis. The analysis included inspecting the output files for the context of the matched pattern. The name of the input file, for example, postconception1.txt, contained text so that when I read the 5 lines before and the 5 lines after the pattern, I had a clear context to decide whether or not the journal article needed to be downloaded for further inspection. If there was enough information to warrant that the complete document be downloaded, I used the original download as a cross-reference to obtain the ID from PubMed, PubMedCentral, or ScienceDirect so the article could be downloaded. After downloading and reading the article I was able to make a determination as to whether or not the article contained valuable events as well as the day or hour that the event occurred.

3.1.3. Results

An observation of the researchers with the original Translating Time Project was that locating neurodevelopmental events was a very time consuming task. Therefore, creating a semi-automated tool to conduct these searches turned out to be extremely useful. The tool along with additional processes developed made it easier to learn the “right” keywords to use during the search and to preview the context of the keyword or pattern prior to downloading the entire journal article. I began my literature review with the zebrafish because it is a model organism for eye development research. Knowing this, I felt that it would be the prime species to begin with.

As a result of my search with the initial species, I located 19 eye-related developmental events in the zebrafish cited in the literature. Seventeen of the 19 events were unique while the retina and the eye cup were events that referenced the same time of occurrence from different authors. Originally, my keyword searches yielded only results for the zebrafish and found no eye-related development events in the other nine species. Apparently the search was too specific or the keywords too narrow in scope, for example, “mus musculus, eye development” or “mus musculus, ocular.” This is likely in part because the WebCrawler version 1.0 only searches text for the keywords. Therefore, a user would have to rely on other methods to search for such data encoded in images in the ScienceDirect, PubMed, and PubMedCentral references.

There were 21 unique event timings that occurred in the literature associated with the cat. The literature review returned 20 unique events in eye development relating to the rat. There were 19 unique events discovered in the monkey literature review. The mouse literature review yielded 13 unique eye related events. The ferret literature search discerned 12 unique events. The literature review of the hamster detected 10 unique data points related to the eye development. The spiny mouse search yielded 3 results and the human came in last with only 1 eye related development event. Table 2, shown below, provides a list of the species name, the embryonic day or day postconception that the event occurred and in the case of the zebrafish, the postfertilization time in hours as well as the author(s) and year of the journal article.

The more general intended result is for literature searches to take less human effort, resulting in shorter times in finding information applicable to research on a given topic. The data for the translating time across mammalian species model is anticipated to

expand. This literature review and its focus on eye-related developmental events in particular will allow this data to be readily incorporated into an analysis to understand whether or not it fits the current model. This will in turn expand the current model to a second organ, the eye. Expanding this project to other organs through the integration of technological advances could assist researchers in understanding developmental events and the translation of time across species as it relates to those organs. Therefore, a researcher looking at the embryonic time that the retina develops in a ferret can translate time to another species, for example, the hamster, where the event occurs at an unknown time. Moreover, one could study the molecular makeup of the gene expression in the developing retina along with gene expression patterns.

Danio Rerio (Zebrafish)	Hours Post Fertilization	Reference
flat optic vesicle	16 hpf	Li et al. 2000
hemispheric eye	72 hpf	
eye cup	24 hpf	
Pupil	24 hpf	
choroid fissure	20-24 hpf	
pigmented epithelium	24 hpf	
optic stalk	24 hpf	
Lens	24 hpf	
lens placode	18 hpf	
optic primordium	14 hpf	
Retina	24 hpf	
optic placode	16 hpf	Moorman 2001
spherical eye cup	16 to 24 hpf	
optic lobe	12 hpf	
neural retina	15 hpf	
Retina	24-28 hpf	Hu et al. 1999
Retina	28 hpf	Easter et al. 1996
Cornea	24 hpf	Greililng and Clark 2009
choroid fissure	30 hpf	Kurita et al. 2004

Felis Domestica (Cat)	Embryonic Day	Reference
optic stalk	E19-E23	Willams et al. 1986
Retina	E28	Bernis et al. 1980
optic cup	E21-E23	Knospe 2002
Eyelids	E25-E28	
Cornea	E23-E25	
Iris	E32-E38	
Lens	E16-18	
retinal ganglion cells generation - start of neurogenesis	E19.5	Robinson and Dreher 1990
axons in optic stalk	E19	Dunlop et al. 1997
retinal horizontal cells - peak of neurogenesis	E30	Finlay and Darlington 1995
retinal ganglion cells generation - peak of neurogenesis	E30	
optic axons reach dLGN	E31.5	Robinson and Dreher 1990
optic axons invade visual centers	E32	Dunlop et al. 1997
retinal bipolar cells - peak of neurogenesis	E65	Finlay and Darlington 1995
rapid axon generation in optic nerve - start of neurogenesis	E27.5	Ashwell et al. 1996
retinal amacrine cells - peak of neurogenesis	E45	Finlay and Darlington 1995
retinal ganglion cell generation - end of neurogenesis	E35.5	Robinson and Dreher 1990
optic nerve axon number - peak of neurogenesis	E38.5	
onset of retinal wavers	E52	Meister et al. 1991
rapid axon loss in optic nerve ends	E53	Robinson and Dreher 1990
eye-opening	E72	
Mustela Putorius Furo (Ferret)	Embryonic Day	Reference
retinal axons	E24	Johnson et al. 1993
retinogeniculate axon	E27	
geniculocortical axon	E27	
corticogeniculate axons	E27	
Retina	E23	Etzrodt et al. 2009
retinal ganglion cell generation - start of neurogenesis	E21	Robinson and Dreher 1990

axon in optic stalk	E24	Dunlop et al. 1997	
optic axon at chiasm of optic tract	E24	Dunlop et al. 1997	
optic axon s reach dLGN	E28.5	Robinson and Dreher 1990	
optic axons invade visual centers	E26	Dunlop et al. 1997	
onset of retinal waves	E47	Meister et al. 1991	
eye-opening	E72	Robinson and Dreher 1990	
Macaca Mulatta (Monkey)			
optic stalk	E39	Williams et al. 1985	
optic vesicle	E27 ±1	Hendrickx et al. 1997	
lens disc	E29 ±1		
lens pit	E30 ±1		
optic cup	E30 ±1		
lens vesicle	E31 ±1		
eyelid folds begin	E37 ±1		
eyelids	E45 ±1		
retinal pigment	E33 ±1		
retinal ganglion cells generation - start of neurogenesis	E30	Robinson and Dreher 1990	
optic axons at chiasm of optic tract	E36	Dunlop et al. 1997	
retinal horizontal cells - peak of neurogenesis	E40	Finlay and Darlington 1995	
retinal ganglion cells generation - peak of neurogenesis	E43		
retinal amacrine cells - peak of neurogenesis	E56		
retinal ganglion cells generation - end of neurogenesis	E57		
optic nerve axon - peak of neurogenesis	E69	Robinson and Dreher 1990	
retinal bipolar cells - peak of neurogenesis	E85	Finlay and Darlington 1995	
rapid axon loss in optic nerve ends	E110	Robinson and Dreher 1990	
eye-opening	E123		
Mus Musculus (Mouse)			
Retina	E13	Yu et al. 2002	
ocular muscles begin	E11	Raymond et al.	

		1995
optic nerve	E11.5	Denier et al. 1997
optic disc	E12.5	
retinal ganglion cell generation - start of neurogenesis	E10.5	Robinson and Dreher 1990 Dunlop et al. 1997
axon in optic stalk	E12.3	
optic axon at chiasm of optic tract	E13	
retinal ganglion cells - peak of neurogenesis	E13	Finlay and Darlington 1995
optic axons reach dLGN	E14.5	Robinson and Dreher 1990 Dunlop et al. 1997
optic axons invade visual centers	E15.5	Finlay and Darlington 1995
retinal amacrine cells - peak of neurogenesis	E15.5	Robinson and Dreher 1990
retinal ganglion cell generation - end of neurogenesis	E18.5	
eye-opening	E30	

Oryctolagus Cuniculus (Rabbit)	Embryonic Day	Reference
optic cup	E16	Greiner 1982
retinal ganglion cell generation - start of neurogenesis	E13	Robinson and Dreher 1990
rapid axon generation in optic nerve - start of neurogenesis	E15.5	
optic nerve axon number - peak of neurogenesis	E23.5	
visual cortical axons	E34.5	
onset of retinal waves	E31.5	Zhou 1998
rapid axon loss in optic nerve ends	E32.5	Robinson and Dreher 1990 Dunlop et al. 1997
eye-opening	E43	

Rattus Norvegicus (Rat)	Embryonic Day	Reference
neural retina	E19	Rath et al. 2007
retinal pigmented epithelium	E21	
Retina	E14	Weber et al. 1983
posterior lens fibers	E13	Kim et al. 1999
anterior lens epithelial cells	E13	
iris	E15	Vidovic et al. 1995
lens	E16	Gao et al. 1998

retinal ganglion cell generation - start of neurogenesis	E11.5	Robinson and Dreher 1990
rapid axon generation in optic nerve - start of neurogenesis	E15	
optic axons reach dLGN	E15.5	
retinal ganglion cell generation - end of neurogenesis	E18.5	
optic nerve axon number - peak of neurogenesis	E19.5	
visual cortical axons	E28.5	
rapid axon loss in optic nerve ends	E29	
eye-opening	E36	
axons in optic stalk	E14.5	Dunlop et al. 1997
optic axons at chiasm of optic tract	E15	
optic axons invade visual centers	E16.5	
retinal ganglion cells - peak of neurogenesis	E16	Finlay and Darlington 1995
retinal amacrine cells - peak of neurogenesis	E16	

Acomys Cahirinus (Spiny Mouse)	Embryonic Day	Reference
optic nerve	E15	Weinert 2005
optic chiasm	E16	
primary optic tract	E17	

Mesocricetus Auratus (Hamster)	Embryonic Day	Reference
axons emerge from retina	E9-E10	Jhaveri et al. 1991
front of retinal axons crosses the chiasm	E13	
retinal ganglion cell generation - start of neurogenesis	E9.5	Robinson and Dreher 1990
retinal ganglion cells - peak of neurogenesis	E12	Finlay and Darlington 1995
optic axons invade visual centers	E16	Dunlop et al. 1997
retinal amacrine cells - peak of neurogenesis	E14	Finlay and Darlington 1995
retinal ganglion cell generation - end of neurogenesis	E14	Robinson and Dreher 1990
optic nerve axon number - peak of neurogenesis	E18	
rapid axon loss in optic nerve ends	E31.5	
eye-opening	E31.5	

Homo Sapiens (Humans)

eye-opening	E157.5	Kurjak et al. 2004; Clancy et al. 2007
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Table 3-2: Eye-related development event references**3.1.4. Discussion**

Animal eyes are anatomically and functionally diverse and researchers work on many different facets of the eye. Therefore, the dataset for each species will share common elements as well as have unique characteristics. The extraction of a combination of common and unique data points will permit the translation and thus the prediction of ocular developmental event times across mammalian species. The use of a non-mammalian vertebrate provides an exciting opportunity to understand whether a very different species can work within the current model. It is expected that this research may be useful in the study and ultimately the reduction of congenital eye defects and eye abnormalities, such as those that may be attributable to programmed cell fate problems during embryogenesis. We have shown that a semi-automated literature review permits the search of journals, books, and references to be accomplished by previewing the material using keywords that allow the user to observe whether or not the article contains information relevant to the search topic. This might indicate, for example, that we should read only 38 of the 269 articles which contain the keywords associated with a research area under consideration.

The literature search for the zebrafish performed as expected, returning the most number of eye development structural events amongst the 10 species. The search for other species returned eye development structural events along with events that give rise

to structures such as the eyelid, retina, and lens. Animals play a major role in our understanding of diseases as well as in the development of effective medical treatments. Research animals provide the scientist with complex living systems consisting of cells, tissues and organs. I am glad to say that no animals needed to be sacrificed for this research. Instead I used published literature to extract eye related development events. Due to the ethical, professional, and legal implications in the medical and scientific community there was only minimal expectation of finding events related to fetal eye development event timing in humans.

This part of the research has shown that a semi-automated literature review for eye-related development events is a viable strategy for extracting event times. Refining the search over time to find the “right” keywords yielded more significant results than the original searches and these results were used to apply the Translating Time model to eye development. The WebCrawler tool allowed us to search online journals using keywords and/or phrases related to eye development and to view the keyword(s) in the context of lines prior to and lines after the designated word(s). The more general result to show that literature searches can be partially automated, permitting the researchers to find specific information applicable to research on a given topic. More research was conducted using keywords such as “ocular development,” “embryonic day,” and “eye embryogenesis” in an effort to perform a more extensive literature review. However, these keywords yielded a large number of results of low interest. The keywords yielding the best results stemmed from using the scientific name for the species and an event name.

3.2. Gene Ontology

The aim of this portion of the project is to determine the Gene Ontology annotations associated with constructed data set on eye development events. Bioconductor was chosen as the software to search for gene ontology data because it was used in the earlier stages of my dissertation wherein a performance evaluation of the 'ttime' package across a cluster computing environment versus a comparative analysis in a serial computing environment in an effort to assess the computational performance. The 'ttime' package is an R package

I conducted a baseline performance evaluation of the 'ttime' package in two environments, one Windows-based and one Linux-based. I wanted to know if parallelization could be utilized as part of this research. This open source package uses R version 2.12.0 and the 'pvclust' package. The Windows machine operates Windows Vista 32-Bit Edition with Service Pack 2. The system is a Compaq Presario CQ60 Notebook PC (Personal Computer) manufactured by Hewlett-Packard. Its processor is an Intel Pentium Dual CPU (Central Processing Unit) T3400 at 2.16 and 2.17 GHz (Gigahertz) with 2 GB (Gigabytes) of RAM (Random Access Memory).

Ares, a workstation, was also utilized for this baseline. It is a Dell PowerEdge 6950, running a 4 Dual-Core AMD Opteron Processor 8220 with 32 GB of RAM. It runs Cluster Rocks release 4.3 that includes CentOS version 5.5, 64-Bit Edition. Cluster Rocks is a freeware version of Linux.

The high performance computing (HPC) cluster environment at the University of Arkansas at Little Rock Computer Science Department was also employed. It consists of three types of nodes: a front end node, a login node, and compute nodes. The front end

node, hpc1-cpsc.host.ualr.edu, contains the cluster setup and node definitions. It runs a torque resource manager and moab scheduler. It shares /home via NFS (Network File Server), and has approximately 3.3 terabytes (TB) available. The login node, hpc1-cpsc-login.host.ualr.edu, is where users login to compile programs and submit computing jobs. The /home is mounted from the front end node via NFS. The nodes compute 1-1 through compute 2-32 (2 racks, 32 nodes per rack). Each node has 2 CPU sockets, each with a quad core Intel Xeon 2.66 GHz CPU. Each node has 16 GB of RAM.

The HPC environment also utilizes three types of networks: a public network, a private 1000 Mb network, and a private Infiniband network. The public network is for front end and login node usage only. It has an eth1 interface, with the following Internet Protocol (IP) address: 144.167.99.0/24. The private network has a NFS and Message Passing Interface (MPI) ring assembly, accessed at IP address 192.168.1.0/24. The private Infiniband network is for MPI message passing. Its use is for higher speed and lower latency than a 1000 MB Ethernet. The nodes in the cluster communicate using the standard network protocol TCP/IP (Transmission Control Protocol and Internet Protocol) over high-speed 10 networks. The TCP/IP is accomplished via Internet Protocol Over Infiniband (IPoIB), which uses an ib0 interface with IP address 192.168.2.0/24, required by some applications. Native IB is faster than IPoIB, hence, is preferred for MPI applications. The compute nodes currently run on the Linux Operating System, which includes CentOS version 4.5.

By default, R utilizes a single processor. Thus, consumption of time with and without dual processors was measured to verify performance. The performance of the

‘ttime’ package was measured using the system clock by executing the following code from the console:

```
library(ttime);
data(event_data);
npsp <- 1;
system.time(pred_vals <- translate(event_data, npsp), gcFirst = TRUE)
system.time(phylo(pred_vals), gcFirst = TRUE)
```

where line 1 loads the ‘ttime’ library into the current workspace. In line 2, the event data for known and unknown neurodevelopmental events across species is passed as a parameter to the data function, which will later be returned by the translate function. There are 10 species, 8 of which are non-primates; therefore, in line 3 shown above, only 1 species is evaluated. However, for the compute times shown in Tables 1 and 2 (see page 41 and pages 50-54) the number of non-primate species (npsp) is incremented by 1 to 8 to accommodate, accordingly.

The system time to predict events is shown in line 4, which generates a scatter plot of the translated neurodevelopmental event timings across species. The second parameter ensures that garbage collection is performed prior to the evaluation of the expression in the first parameter. Line 5 generates a phylogenetic tree via hierarchical clustering. It also returns the system time to generate a dendrogram and performs garbage collection prior to the process.

Since data for the translating time across mammalian species model is anticipated to expand as more data about developmental events becomes available and incorporated into the analysis, it is important to explore the options related to parallelization of the ‘ttime’ package. An important gauge for users is the performance of a web-based

application, which is measured by the execution time. The ultimate goal is to ensure timely delivery of the requested information as the dataset grows.

The results showed that parallelization was an inefficient means to overcome the speed bottleneck of a single processor, hence our investigation of the implementation and use of parallel computers. Compute nodes can run on a single machine with a single or several processors, or on multiple machines connected through a communications network. However, because of the small dataset currently being utilized by Translating Time Project there is no need to include the implementation of a parallelized version of the '*ttime*' package. The aforementioned is important because the translating developmental event time across mammalian species research has evolved into a web-based tool for researchers and clinicians. This type of analysis is critical to the success of the project as more data about developmental events is identified and incorporated into the analysis.

3.2.1 Materials

Originally, Bioconductor was utilized to incorporate gene expression for eye development events. It makes available tools for the understanding and examination of high-throughput genomic data in an open source environment. To achieve such functionality, Bioconductor uses the R statistical programming language for Bioinformatics development. Bioconductor was developed for use with the R language and is publicly available through the CRAN R package repository. Bioconductor is open-source software that is freely available at <http://www.bioconductor.org/>. It contains readily available packages to access gene expression and ontology data. Gene Ontologies (GO), Chromosome Maps, KEGG Pathway Analysis, and Phylogenetic Analysis are a

few of the Bioconductor packages. Capabilities within the *GO* package include the ability to access the gene identification, the gene term, and ontology type from the Gene Ontology website or a local file. The Gene Ontology project maintains on its Website a standardized representation of gene and gene product attributes across species and databases. The map viewer utilizes a method to select an organism and manipulate an organism-specific global map. KEGG (Kyoto Encyclopedia of Genes and Genomes) is another bioinformatics online tool. It is comprised of online database resources supporting searches relating to genomes, biological chemicals and enzymatic pathways. Pathway development permits queries based on 3 distinct categories: systems, genomic, and chemical information.

R is an open-source integrated software suite, which was designed for data manipulation, computations, and graphical display associated with statistical computing. It runs on the Unix, Windows, and Mac families of operating systems, some of which are free of charge (such as Linux). The analyses were developed using both Windows and Linux versions of R version 2.12.0. R is freely available through a GNU license at www.r-project.org.

The online Gene database from National Center for Biotechnology (NCBI) website was utilized to search for genes related to the eye and the 10 species upon which this research is based. The Genes database is a searchable database of genes that allows for the examination of genes from genomes which have been completely sequenced and have active research community that contribute gene-specific data. This information includes but is not limited to gene products and their attributes such as protein

interactions, phenotypes, interactions, homologs, and external databases. Access to the Genes database is freely available at <http://www.ncbi.nlm.nih.gov/gene/>.

The Gene Ontology (GO) website was used to as the source to annotate gene and gene product attributes that resulted from the Genes database search. The GO project is a collaborative effort amongst the GO Consortium to focus on a unified representation and consistent descriptions of gene and gene products in different databases amongst species. The ontology has three areas: cellular component, molecular function, and biological process. The ontologies are structured such that each term has relationships defined with one or more other terms in the same domain and in some instances other domains. Additionally, the vocabulary in GO is species-neutral. There are also tools that are freely available to access and process the annotation data. The Gene Ontology Consortium is supported by a grant from the National Human Genome Research Institute (NHGRI). GO is available at <http://www.geneontology.org/>.

GeneCards is online database of human genes, which provides genomic, proteomic, transcriptomic, genetic and functional information about known and predicted genes. It uses standard terminology and approved gene symbols. GeneCards is developed and maintained at the Crown Human Genome Center by the Weizmann Institute of Science. Academicians and companies collaborate with GeneCards to ensure that the terminology and symbols and when there is an ID different than the GeneCards ID an External ID is provided that shows aliases and descriptions to eternal databases such as accessions from **HUGO Gene Nomenclature Committee** (HGNC), EntrezGene, UniProt, and Ensembl). GeneCards uses over 100 sources and links in an effort to standard nomenclature for the genes. It is freely available at <http://www.genecards.org/>.

3.2.2 Methods

Bioconductor components are distributed and manipulated through R packages, which are add-on modules for R. A search in the Bioconductor website for packages to perform the annotated search yielded packages for only 6 species as shown below in Table 3-3.

Species	Package Name
Homo sapiens	BSgenome.Hsapiens.UCSC.hg18
Mus musculus	BSgenome.Mmusculus.UCSC.mm10
Rattus norvegicus	BSgenome.Rnorvegicus.UCSC.rn5
Danio rerio	BSgenome.Drerio.UCSC.danRer7
Macaca mulatta	BSgenome.Mmulatta.UCSC.rheMac2
Oryctolagus cuniculus	biomaRt

Table 3-3: Species in Bioconductor

It is important to note that complete genome data is available for only 5 of the 6 species shown in Table 3-3. The Oryctolagus cuniculus has partial genome data. The genes that are available are accessible via the biomaRt package. From the start of this project, there was the notion that there would not be annotations available on many if any of the species. Therefore, I abandoned the idea of using Bioconductors in an effort to conduct a more thorough search by using online annotation websites such as GO and NCBI's Gene database. The analysis via Bioconductor would have been incomplete and created more work that was not uniform during the search process.

Since Bioconductor was never the source of the gene or gene product data, I decided to access the source, GO, directly. I was looking for the gene(s) name for each species related to eye development. From the NCBI home page, I clicked on the drop-down menu and selected the Gene database. I entered the scientific name of the species delimited by a comma along with the keywords, “eye development,” originally. For example, the query for human in the Gene database was “homo sapiens, eye development.” I did not want to refine my search in this case because I felt it best that the query return broad results and that I actually read through the results to decipher whether or not the query return a gene or a gene product data. Refining the search meant that there was a possibility that I could miss potential gene data had it not be categorized as a gene related to eye development. For example, the gene was associated with a particular eye disease such as cataract, which is a decrease in vision due to clouding of the lens. Therefore, I used the scientific name of the species for each of the 10 species in the research combined with the word “eye.” For example, the search for human, I typed “Homo sapiens, eye” in the text box and clicked Go. The database located the desired Gene record in the results and I clicked the symbol to open the record. Functional information is located in the Summary, Bibliography, and General gene information sections. Additionally, there are links for resources such as Conserved Domains and BioSystems. NCBI also provides the capability to search the gene name, symbol or sequence accession number.

3.2.3 Results

Table 2, shown below provides a listing of the high level results from the aforementioned queries as well as the number of results returned along with the gene

name(s), if any. The details of the gene results are shown in Appendix B. The details include the official symbol and name of the gene, aliases (if any), other designations, the chromosome on which the gene is located as well as the location on the chromosome, the annotation, MIM identification (ID) and an identification number. The MIM ID is information from Online Mendelian Inheritance in Man (Online Mendelian Inheritance in Man), a database created by Johns Hopkins University that includes genes and genetic disorders.

The results show that there are 13 genes in Homo sapiens that are related to eye development. Although all 13 genes are in some way related to eye development or disorders, the VSX2 gene (aka: CHX10, HOX10, MCOP2, MCOPCB3, RET1) is a visual system homeobox gene. A homeobox gene is a gene that is engaged in the bodily segmentation during embryonic development. During this segmentation, cells become specific organs or tissues and in this case, the VSX2 gene is an example of one of many genes that contributes to the development of the visual system.

Upon completing the search from the Genes database, I used the GeneCards website as means of validating whether or not the gene returned from Genes were related to eye development in humans. Abbreviated results from GeneCards are shown in Appendix C. The results show that each of the genes returned from the Gene database query are valid in such that they are related to eye related defect(s) or anomaly. Moreover, it specifies the structural eye component for which the defect is related.

	Human	Zebra-fish	Rat	Mouse	Monkey	Cat	Spiny Mouse	Rabbit	Hamster	Ferret
Keyword Number of query results	Homo sapiens	Danio rerio	Rattus norvegicus	Mus musculus	Macaca mulatta	Felis domestica	Acomys cahirinus	Oryctolagus cuniculus	Mesocricetus auratus	Mustela putorius furo
	666	273	309	449	7	10	0	10	0	0
Gene Names	GDF6	PAX2A	PAX6	PAX6						
	VSX2	RX3	PAX2	PAX2						
	RAX	PAX6A	PAX4	SOX2						
	SHH	PAX6B	VAX2	SOX9						
	SIX6	SOX2	STRA6	SOX11						
	PAX6	SOX9B	PRPH2	VAX2						
	SOX2			CRX						
	OTX2			SOX1						
	STRA6			SOX8						
	BCOR			STRA6						
	HCCS			RD3						
	BMP4									
	SMOC1									

Table 3-4: Eye database query results from NCBI

3.2.4 Discussion

Researchers spend a lot of wasted time and energy looking for available information centered on each concentrated area of research. Having online resources such as the Gene database has allowed me to search one location for genes related to the species utilized in my research because of common terminology that the research community has decided to use. There were no results found for the hamster, ferret, or spiny mouse. Although the query for the monkey, cat, and rabbit yielded results, further inspection of the small number of results showed there to be no genes related to eye development. The best results from the species search came from the human, mouse, rat, and zebrafish.

The Gene Ontology data associated with each gene from the queries in this portion of the research will be linked to the website in the next section of the dissertation. Additionally, links to articles in PubMed related to genes and their role in eye development or disorders are on the website for this research. For example, there are two known eye related defects associated with the VSX2 gene. The defects in the VSX2 gene are the cause of microphthalmia isolated type 2 (MCOP2), which causes a small eye and iris abnormalities. Additionally, defects in VSX2 are the cause of microphthalmia isolated with coloboma type 3 (MCOPCB3) also known as isolated colobomatous microphthalmia 3. The malformations resulting from ocular colobomas are from abnormal morphogenesis of the optic cup and stalk, and the fusion of the fetal fissure (optic fissure).

Going into this research, I thought it would be a great idea to have readily available the genes related to eye development and find out whether or not research had

shown structural components that these genes give rise to. Researchers can potentially spend a lot of time and effort locating this information within huge repositories but still do not have a method for viewing only the genes that are related to eye development as it relates to translation of time amongst species. The current translating time project does not reference genes for neurodevelopmental events; therefore, this portion of the research is unique in doing so. The identification of genes is important because their expression can determine the neurodevelopmental events. Since gene regulation provides the cell with control over structure and function, manipulation in timing, location, and the amount of gene expression can affect the actions of the gene. This is important for making improvements in diagnostics and intervention capabilities by regulating expression of these genes so that we can continue to understand human development because it improves our ability to treat and prevent illness and possibly these eye related defects.

3.3 Predicting unknown events

The main objective for this portion of my dissertation was to utilize the data points extracted from the literature in an effort to make predictions about missing data for the selected organisms. Additionally, I also expected to prove or disprove whether or not the Zebrafish, a model organism for eye development, develops in conformance to the model and thus is a viable species to add to the data for this research. Future researchers may wish to apply this method to other parts of organisms, other species, and other wet lab experimental data points. Making this data and methods publicly available can make it possible for scientists to further expand this research. In addition it can preserve valuable research time by lessening the need to learn to use software packages such as

Minitab, SAS, and SPSS, all of which perform multiple variable regression analysis.

Upon completion of the initial analysis, successful data prediction for missing data points was achieved. The data prediction analysis has been automated for ease of use and to cut back on errors caused by hand calculations.

3.3.1 Materials

This section details the major software tools utilized for this part of the research. These are Microsoft Excel and (Visual Basic for Applications) VBA. Additionally, Table 1: Database of Time of Events in Neural Development for Nine Eutherian and Six Metatherian Mammals, from Darlington, et al., 1999, was used in this portion of the research.

Microsoft Excel

Excel 2013 32-bit is part of Microsoft Office Professional 2013. Excel is a spreadsheet application, which is one of several applications made available by Microsoft through its Office Suite. It utilizes grids to offer data manipulation for financial, engineering, and statistical purposes along with offering graphing capability. Other features include the ability to create reports and slide shows by sharing current data with other applications in the suite (Frye, 2013).

Visual Basic for Applications

Excel VBA is the name of the Excel programming language. It was originally developed in 1993 by Microsoft. VBA was used to create macros, which is a set of instructions given Excel to automate a process, for example. It is a form of Visual

Basic, an event driven programming language designed by Microsoft. VBA allows the user to manipulate the spreadsheet and the data therein. The code for the macros was written using the Visual Basic Editor because of its ease of use. It is provided by clicking the Developer Tab and accessing the Macros feature (Jelen & Syrstad, 2013). Access to a window for writing code and the ability to run and debug code is another feature of VBA. In the example below, the code for a user-defined subroutine, runManyOptimizations, is pictured. Another option for writing macros is the Macro Recorder, which records the user's actions and generates the VBA code for the user.

Data Source

The data source for this portion of my research was Table 1: Database of Time of Events in Neural Development for Nine Eutherian and Six Metatherian Mammals, from the journal article “Commentary: Neural Development in Metatherian and Eutherian Mammals: Variation and Constraint” (Darlington et al., 1999). Since my research centered around nine eutherian mammals, *Felis domestica* (cat), *Mustela putorius furo* (ferret), *Mesocricetus auratus* (hamster), *Macaca mulatta* (monkey), *Homo sapiens* (human), *Mus musculus* (mouse), *Oryctolagus cuniculus* (rabbit), *Rattus norvegicus* (rat), and *Acomys cahirinus* (spiny mouse), the focus was only on the part of the table containing data for those species. It is with this data that I will show how to reverse engineer the algorithm they utilized to construct the table quoted in Table 3-5 to perform the current analysis.

TABLE 1. Database of Time of Events in Neural Development for Nine Eutherian and Six Metatherian Mammals

Event scale ¹	Placental mammals (Species scale value)										Marsupials (Species scale value)					
	0.565 Hamster	0.619 Mouse	0.821 Rat	1.013 Rabbit	1.153 Spiny mouse	1.650 Ferret	1.753 Cat	2.285 Macaque	2.500 Human	0.736 Short-tailed opossum	1.098 Dunnart	1.119 S. Amer. opossum	1.440 Brush-tailed possum	1.603 Quokka	1.756 Tammar wallaby	
0.789 Peak—cranial motor nuclei	—	9.0 ⁴	11.0 ⁴	—	—	—	—	—	—	—	—	—	—	—	—	—
0.952 Peak—locus coeruleus	—	—	11.0 ⁴	—	—	—	—	32.0 ⁴	—	—	—	—	—	—	—	—
0.971 Start—RCC generation	9.5 ³	10.5 ³	11.5 ³	13.0 ³	—	21.0 ³	19.5 ³	30.0 ³	—	—	—	—	—	—	—	—
0.992 Peak—inferior olfactory nucleus	—	10.0 ⁴	12.0 ⁴	—	—	—	—	—	—	—	—	—	—	—	—	—
0.995 Peak—magnocellular basal forebrain	—	—	12.0	—	—	—	—	30.0 ⁴	—	—	—	—	—	—	—	—
1.000 Start—superficial SC lamina	11.0 ³	10.5 ³	12.5 ³	—	—	—	—	30.0 ³	—	—	—	—	—	—	—	—
1.071 Peak—red nucleus	—	—	12.0 ⁴	—	—	—	—	—	—	—	—	—	—	—	—	—
1.090 Peak—vestibular nuclei	—	—	12.0 ⁴	—	—	—	—	—	—	—	—	—	—	—	—	—
1.096 Posterior commissure appears	13.0 ²	—	—	—	—	—	21.0 ²	35.0 ²	33.0 ²	—	—	—	—	—	—	30.0 ²
1.105 Start—LGNd generation	10.5 ³	10.5 ³	13.5 ³	—	—	21.5 ³	36.0 ³	—	—	—	—	—	—	—	—	—
1.139 Start—subcortical plate generation	11.5 ³	—	11.5 ³	—	20.5 ³	23.5 ³	39.5 ³	—	—	—	—	—	—	—	—	—
1.155 Peak—subplate	10.0 ⁴	11.0 ⁴	14.0 ⁴	—	14.0 ⁴	24.0 ⁴	43.0 ⁴	—	—	—	—	—	22.0 ⁴	—	—	—
1.155 Peak—raphe complex	—	13.5 ⁴	12.0 ⁴	—	—	—	30.0 ⁴	—	—	—	—	—	—	—	—	—
1.192 Peak—reticular nuclei	—	11.0 ⁴	13.0 ⁴	—	—	—	24.0 ⁴	—	—	—	—	—	—	—	—	—
1.193 Peak—Purkinje cells	—	10.5 ⁴	14.0 ⁴	—	—	—	39.0 ⁴	—	—	—	—	—	22.0 ⁴	—	—	—
1.198 Peak—medial geniculate nucleus	—	11.0 ⁴	13.0 ⁴	—	—	—	26.0 ⁴	—	—	—	—	—	26.0 ⁴	—	—	—
1.201 Mammillo-thalamic tract appears	—	—	14.0 ⁴	—	—	—	23.0 ⁴	—	44.0 ⁴	—	—	—	—	—	—	30.0 ⁴
1.206 Peak—deep cerebellar nuclei	—	—	13.0 ⁴	—	—	—	—	38.0 ⁴	—	—	—	—	—	—	—	—
1.208 Peak—preoptic nucleus	—	12.5 ⁴	12.0 ⁴	—	—	—	—	—	—	—	—	—	22.0 ⁴	—	—	—
1.222 Peak—globus pallidus	—	11.0 ⁴	14.0 ⁴	—	—	—	—	—	—	—	—	—	—	—	—	—
1.231 Medial forebrain bundle appears	14.0 ²	13.0 ²	13.0 ²	—	—	24.0 ³	19.0 ³	—	35.5 ²	33.0 ²	—	16.0 ³	—	—	—	28.0 ²
1.232 Axons in optic stalk	—	12.3 ³	14.5 ³	—	—	—	—	—	51.0 ³	—	—	—	—	—	—	—
1.241 Peak—ventrolateral geniculata nucleus	11.0 ⁶	11.5 ⁴	14.0 ⁴	—	—	—	26.0 ⁴	—	—	—	—	—	—	—	—	—
1.257 Start—cilia VI generation	11.5 ³	—	13.0 ³	14.5 ³	—	22.5 ³	26.5 ³	45.0 ³	—	—	—	—	—	—	—	—
1.268 Peak—LGNd	11.0 ⁶	12.0 ⁴	14.0 ⁴	—	—	—	27.0 ⁴	43.0 ⁴	—	—	—	—	26.0 ⁴	—	—	30.0 ²
1.291 Fasc. retroflexus appears	14.0 ²	14.0 ²	12.0 ²	—	—	—	21.0 ²	40.0 ²	—	—	—	—	31.0 ⁴	—	—	—
1.304 Peak—cochlear nuclei	—	12.0 ⁴	14.0 ⁴	—	—	—	—	—	—	—	—	—	—	—	—	—
1.305 Peak—suprachiasmatic nucleus	11.5 ⁴	13.0 ⁴	14.0 ⁴	—	—	24.0 ³	—	36.0 ⁵	—	18.0 ⁵	23.5 ³	—	22.0 ⁴	—	31.0 ⁵	—
1.317 Optic axons at chiasm/tract	—	13.0 ⁴	15.0 ⁴	—	—	—	25.0 ⁴	—	—	—	—	—	—	—	—	—
1.319 Stria medullaris thalami appears	—	—	14.0 ⁴	—	—	—	—	48.0 ²	44.0 ²	—	—	—	—	—	—	28.0 ²
1.325 Peak—amygdala	—	12.0 ⁴	15.0 ⁴	—	18.0 ⁴	—	—	38.0 ⁴	—	—	—	—	—	—	—	—
1.330 Peak—mitral cells	—	12.0 ⁴	14.0 ⁴	—	18.0 ⁴	—	—	39.0 ⁴	—	—	—	—	—	—	—	—
1.337 Peak—substantia nigra	—	—	15.0 ⁴	—	—	—	—	—	—	—	—	—	—	—	—	—
1.340 Peak—nucleus of lateral olfactory tract	—	12.5 ⁴	14.0 ⁴	—	—	—	—	—	—	—	—	—	—	—	—	—
1.349 Peak—VPL and VB	—	12.5 ⁴	14.0 ⁴	—	—	—	—	40.0 ²	56.0 ²	—	—	—	22.0	—	—	40.0 ²
1.342 External capsule appears	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
1.355 Peak—retinal horizontal collaterals	—	—	—	—	—	—	—	30.0 ⁴	40.0 ⁴	—	—	—	—	—	—	—
1.363 Rapid optic axon generation	—	—	15.0 ⁴	15.5 ⁴	—	—	27.5 ⁴	—	—	—	—	—	—	—	—	—
1.364 Peak—claustrum	—	12.5 ⁴	—	—	18.0 ⁴	—	—	—	—	—	—	—	22.0 ⁴	—	—	—
1.368 Peak—superior colliculus	12.0 ⁴	13.0 ⁴	15.0 ⁴	—	—	—	—	41.0 ⁴	—	—	—	—	29.0 ⁴	—	—	—
1.388 End—LGNd	11.5 ³	12.5 ³	15.5 ³	—	—	—	31.5 ³	43.0 ³	—	—	—	—	—	—	—	—
1.400 Peak—septal nuclei	—	13.0 ⁴	14.0 ⁴	—	19.0 ⁴	—	—	45.0 ⁴	—	—	—	—	—	—	—	—
1.402 Peak—anterior olfactory nucleus	—	13.5 ⁴	12.0 ⁴	—	22.0 ⁴	—	—	—	—	—	—	—	—	—	—	—
1.415 Peak—retinal ganglion cells	12.0 ⁴	13.0 ⁴	16.0 ⁴	—	—	30.0 ⁴	43.0 ⁴	—	—	—	—	—	—	—	—	—

Table 3-5: Database of Time of Events in Neural Development for Nine Eutherian and Six Metatherian Mammals (From Darlington et al., 1999b)

1.419 Internal capsule appears	—	—	15.0 ²	—	—	—	—	40.0 ²	63.0 ²	—	—	—	—	—	42.0 ²
1.436 Peak—entorhinal cortex	—	13.0 ¹	14.0 ¹	—	20.0 ¹	—	—	48.0 ¹	—	—	—	—	—	—	—
1.437 Start—LGnd generation	12.5 ³	—	—	—	27.5 ³	30.5 ³	45.5 ³	—	—	—	—	—	—	—	—
1.443 Peak—inferior colliculus	—	—	16.0 ⁴	—	—	—	—	43.0 ⁴	—	—	—	—	25.0 ⁴	—	—
1.457 Peak—cortical layer VI	12.0 ¹	12.5 ¹	16.0 ¹	—	18.0 ¹	—	33.0 ¹	53.0 ¹	—	—	—	—	38.0 ¹	—	—
1.466 Peak—AV, AM, and AD nuclei	—	—	13.5 ⁴	15.0 ⁴	—	—	—	—	—	—	—	—	—	—	—
1.471 Start—cortical lamina V	12.5 ³	—	13.5 ³	—	27.5 ³	32.5 ³	58.5 ³	—	—	—	—	—	20.0 ⁴	—	—
1.476 Peak—caudoputamen	—	14.0 ¹	15.0 ⁴	—	20.0 ¹	—	—	45.0 ¹	—	—	—	—	—	—	—
1.488 Peak—subiculum	—	13.0 ¹	16.0 ⁴	—	20.0 ⁴	—	—	48.0 ⁴	—	—	—	—	—	—	—
1.496 Peak—parasubiculum	—	13.5 ¹	16.0 ⁴	—	—	—	—	48.0 ¹	—	—	—	—	—	—	—
1.501 Fornix appears	—	14.0 ¹	15.0 ²	—	—	—	—	48.0 ¹	63.0 ²	—	—	—	—	—	36.0 ²
1.510 Peak—pontine nuclei	—	13.5 ⁴	16.0 ⁴	—	—	—	—	—	—	—	—	—	—	—	—
1.522 RGC axons reach LGnd and SC	—	14.5 ¹	15.5 ¹	—	—	28.5 ¹	31.5 ¹	—	—	—	—	—	—	—	—
1.526 Peak—presubiculum	—	13.5 ⁴	17.0 ⁴	—	—	—	—	48.0 ⁴	—	—	—	—	—	—	42.0 ⁴
1.534 Stria terminals appears	15.0 ²	13.5 ²	—	—	—	—	—	—	56.0 ²	—	—	—	—	—	—
1.544 End—superficial SC	12.0 ¹	14.0 ¹	17.5 ¹	—	—	—	—	56.0 ¹	—	—	—	—	—	—	—
1.549 Anterior commissure appears	13.0 ²	14.5 ²	—	—	—	—	—	48.0 ²	70.0 ²	19.0 ²	—	25.0	—	—	42.0 ²
1.556 Peak—dendrite gyrus	—	—	16.0 ⁴	—	22.0 ⁴	—	—	48.0 ⁴	—	—	—	—	—	—	—
1.582 Optic axons invade visual centers	16.0 ⁵	15.5 ⁵	16.5 ⁵	—	—	26.0 ⁵	32.0 ⁵	—	60.0 ⁵	20.0 ⁵	28.5 ⁵	—	—	38.0 ⁵	38.5 ⁵
1.590 Peak—CA 1–2	—	15.0 ¹	18.0 ¹	—	20.0 ¹	—	—	48.0 ¹	—	—	—	—	—	—	—
1.599 Peak—cortical layer V	14.0 ¹	13.0 ¹	16.0 ¹	—	20.0 ¹	—	35.0 ¹	70.0 ¹	—	—	—	—	45.0 ¹	—	—
1.615 Peak—cone	—	14.0 ¹	—	—	—	—	—	36.0 ⁴	56.0 ⁴	—	—	—	—	—	—
1.633 Start—lamina IV generation	12.5 ³	—	15.5 ³	20.0	—	32.5 ³	37.0 ³	70.0 ³	—	—	—	—	—	—	—
1.647 Peak—nucleus accumbens	—	16.0 ¹	19.0 ¹	—	22.0 ¹	—	—	45.0 ¹	—	—	—	—	—	—	—
1.667 End—lamina VI generation	13.5 ³	—	15.5 ³	—	—	36.5 ³	37.5 ³	65.0 ³	—	—	—	—	—	—	—
1.669 Peak—retinal arcnica cells	14.0 ¹	15.0 ¹	16.0 ⁴	—	—	45.0 ¹	56.0 ¹	—	—	—	—	—	—	—	—
1.676 Peak—tufted cells	—	16.0 ¹	17.0 ⁴	—	22.0 ⁴	—	—	—	—	—	—	—	—	—	—
1.680 Hippocampal commissure appears	—	—	15.0 ⁴	17.0 ²	—	—	37.0 ²	—	77.0 ²	—	—	—	—	—	63.0 ²
1.689 Peak—cortical layer IV	15.0 ¹	14.0 ¹	17.0 ¹	—	20.0 ¹	—	39.0 ¹	80.0 ¹	—	—	—	—	49.0 ¹	—	—
1.722 End—RGC generation	14.0 ¹	18.5 ¹	18.5 ²	—	—	—	35.5 ³	57.0 ³	—	—	—	—	—	—	—
1.745 Peak—isles of Calleja	—	16.0 ⁴	—	—	—	—	—	—	—	—	—	—	—	—	—
1.751 End—cortical lamina V generation	15.5 ³	—	16.5 ³	19.0	—	38.5 ³	39.5 ³	75.0 ³	—	—	—	—	—	—	—
1.792 Corpus callosum appears	15.0 ²	17.0 ²	18.5 ²	—	—	—	39.0 ²	—	87.5 ²	—	—	—	—	—	—
1.836 LGnd axons in the subcortical plate	—	—	17.5 ³	—	—	—	41.5 ³	78.0 ³	—	—	—	—	—	—	—
1.857 Peak—cortical layer II–III	16.0 ¹	15.0 ¹	18.0 ¹	—	22.0 ¹	—	—	56.0 ¹	80.0 ¹	—	—	—	67.0 ¹	—	—
1.869 Peak optic axon number	18.0 ¹	—	19.5 ³	23.5 ³	—	—	38.5 ³	69.0 ³	—	—	—	—	—	—	—
1.881 Cortical axons reach LGnd	—	—	19.5 ³	24.5 ³	—	—	—	67.0 ³	—	—	—	—	—	—	—
1.898 Peak—lamina IV	15.5 ³	—	17.5 ³	—	—	42.5 ³	42.5 ³	85.0 ³	—	—	—	—	—	—	—
2.031 Cortical axons innervate LGnd	—	—	21.5 ³	27.5 ³	—	—	—	81.5 ³	—	—	—	—	—	—	—
2.135 Start—superficial SC laminae	—	—	24.5 ³	29.5 ³	—	—	—	86.0 ³	—	—	—	—	—	—	—
2.140 Peak—rods	—	19.0 ⁴	—	—	—	65.0 ⁴	85.0 ⁴	—	—	—	—	—	—	—	—
2.188 Cortical innervation of LGnd adult-like	—	—	24.5 ³	30.5 ³	—	—	—	96.0 ³	—	—	—	—	—	—	—
2.198 LGnd axons in lamina IV	—	—	25.0 ¹	—	—	—	61.5 ¹	91.0 ¹	—	—	—	—	—	—	—
2.214 Peak—retinal bipolar cells	—	—	—	—	—	—	65.0 ¹	85.0 ¹	—	—	—	—	—	—	—
2.295 SC segregation	24.0 ⁵	24.0 ⁵	—	—	—	58.5 ⁵	—	175.0 ⁵	—	63.5 ⁵	53.5 ⁵	49.0 ⁵	78.0 ⁵	100.0 ⁵	
2.300 VC axons in the superficial layer of SC	—	—	28.5 ³	34.5 ³	—	—	—	96.0 ³	—	—	—	—	—	—	—
2.316 End/contra segregation	23.5 ²	25.5 ²	28.5 ³	32.0 ³	—	56.0	60.5 ³	87.0 ³	175.0	—	—	—	—	—	—
2.316 End—rapid axon loss	31.5 ²	—	29.0 ²	32.5 ²	—	—	53.0 ²	110.0 ²	—	—	—	—	—	—	—
2.579 Eye opening	31.0 ^{2.5}	30.0 ²	36.0 ^{2.5}	43.0 ²	—	72.0 ^{2.5}	72.0 ^{2.5}	123.0 ^{2.5}	182.0 ^{2.5}	44.0 ⁵	58.5 ⁵	80.0 ⁵	105.0 ⁵	138.0 ⁵	168.0 ⁵

Table 3-5 (cont.): Database of Time of Events in Neural Development for Nine Eutherian and Six Metatherian Mammals (From Darlington et al., 1999)

3.3.2 Methods

The original research that provided the foundation for the present work used the equation $Y = \ln(days - k)$ as the model. Days are postconception days and k is a constant that needed to be determined in order to find optimal species and event values that lead to the best possible predictions for data points for which wet lab experimental data is not yet available for eye development. If, as in Table 3-5, the species hamster has a species score of 0.565, and the event “Start – RGC Generation” (Start - Retinal Ganglion Cells Generation) has an event score of 0.971, then the sum of the event score

and the event score is 1.536. The table shows the corresponding day as 9.5. If that and $k = 5.37$ are plugged into the equation $Y = \ln(days - k)$, the resulting prediction for Y is 1.418. The error, or difference between this value and the value in the table which was determined to be the sum of the species and event, 1.536, is 0.118.

When using this method throughout the table, the sum of the species score plus the event score for a known event can be compared to the output from the model equation shown above. Therefore, my goal was to write macros that would generate the optima for k , each species value, and each event value in my dataset. The intent was to generate these values such that the results would produce a total root mean square (RMS) that was a close as possible to 0. The RMS is the square root of the mean of the squared errors in the dataset. It is the same statistical measure used in the previous research when computing PC date predictions for unknown data.

In order to achieve this goal, I needed to find a value of k that would minimize the RMS error because k is otherwise undetermined. Optimal values for k , species values, and event values would lead to the best available predictions for when corresponding events occur in species for which these events have not been observed experimentally. Therefore, selecting the optimal value of k by testing values of k over a sufficiently wide range (we used 0 to 10 in increments of .01) is a critical step in the process. Upon performing this process, I discovered that any value of k greater than 8.49 would throw an error because it would result in a negative argument in the $Y = \ln(days - k)$. The natural logarithm of a negative number is undefined. Since the original research used 2 decimal digits of precision for the k value, I did the same in the present analysis. Additionally, 3 decimal digits of precision were used for the species

and event scores in the earlier work; thus, 3 decimal digits were used here for those scores as well.

In order to implement the calculations in a spreadsheet, I created a workbook that contained 5 worksheets: *Event + Species Values*, *E-Values*, $y=LN(E-k)$, *Error Figures*, and *Error Squared Figures*. The *Events + Species Values* sheet shows the nine eutherian mammals from the fastest to the slowest developing species in columns from left to right, respectively. Additionally, this spreadsheet shows the 46 ocular development events for which data for these organisms was extracted from the scientific literature during the data extraction process. These are listed at the left of each row. The *Event + Species Value* worksheet, shown in Table 3-6, shows each species with an assigned species value and each event with an assigned event value. For each worksheet thereafter, the column and row headers are replicated. This worksheet is where the macro code for the analysis to predict k , value for each species, as well the value for each event, is run by clicking the *run many optimizations* button. Further details on the algorithm for the macro are described later in this section.

Event Name	Event Value	Mesocricetus Auratus (Hamster)	Mus Musculus (Mouse)	Rattus Norvegicus (Rat)	Oryctolagus Cuniculus (Rabbit)	Acomys Cahirinus (Spiny Mouse)	Mustela Putorius Furo (Ferret)	Felis Domestica (Cat)	Macaca Mulatta (Monkey)	Homo Sapiens (Humans)
	Species Value	896	0.960	1.105	1.239	1.311	1.692	1.755	2.256	2.569
retinal ganglion cells generation - start of neurogenesis	1.147	2.043	2.107	2.252	2.386	2.582	2.902	3.403		
axons emerge from retina	1.116	2.012								
ocular muscles begin	1.235		2.195							
optic nerve	1.271		2.231							
axons in optic stalk	1.289		2.249	2.394				3.044		
optic disc	1.389		2.349							
retinal ganglion cells generation - peak of neurogenesis	1.481	2.377	2.441	2.586				3.236	3.737	
posterior lens fibers	1.291			2.396						
anterior lens epithelial cells	1.291			2.396						
optic axon at chiasm of optic tract	1.431		2.391	2.536			3.123			
optic axons reach dLGN	1.568		2.528	2.673			3.260	3.323		
retina	1.504		2.464	2.609			3.196	3.259		
iris	1.600			2.705				3.355		
lens disc	1.039								3.295	
lens pit	1.07								3.331	
lens vesicle	1.111								3.367	
eyelid folds begin	1.299								3.555	
retinal pigment	1.177								3.433	
optic axons at chiasm of optic tract	1.270								3.526	
retinal pigmented epithelium	1.838			2.943			2.638			
optic chiasm	1.327						2.707			
primary optic tract	1.396							3.308	3.371	
optic axons invade visual centers	1.616	2.512	2.576	2.721						

Event Score

Event Score + Species Score

Event Score + Species Score

Event Name		<i>Mesocricetus Auratus</i> (Hamster)	<i>Mus Musculus</i> (Mouse)	<i>Rattus Norvegicus</i> (Rat)	<i>Oryctolagus Cuniculus</i> (Rabbit)	<i>Acomys Cahirinus</i> (Spiny Mouse)	<i>Mustela Putorius Furo</i> (Ferret)	<i>Felis Domestica</i> (Cat)	<i>Macaca Mulatta</i> (Monkey)	<i>Homo Sapiens</i> (Humans)
		0.896	0.960	1.105	1.239	1.311	1.692	1.755	2.256	2.569
lens	1.242			2.347				2.997		
optic nerve axon number - peak of neurogenesis	1.850	2.746		2.955	3.089			3.605	4.106	
eye/optic cup	1.238				2.477			2.993	3.494	
optic stalk	1.271							3.026	3.527	
optic vesicle	0.962								3.218	
retinal axons	1.398						3.090			
retinal horizontal cells - peak of neurogenesis	1.479							3.234	3.735	
visual cortical axons	2.207			3.312	3.446					
cornea	1.335							3.090		
axon in optic stalk	1.238						2.930	2.993		
retinogeniculate axon	1.526						3.218			
geniculocortical axon	1.526						3.218			
corticogeniculate axons	1.526						3.218			
eyelids	1.474							3.229	3.730	
onset of retinal waves	2.139				3.378		3.831	3.894		
rapid axon generation in optic nerve - start of neurogenesis	1.435			2.540	2.674			3.190		
retinal amacrine cells - peak of neurogenesis	1.700		2.660	2.805				3.455	3.956	
retinal ganglion cell generation - end of neurogenesis	1.727	2.623	2.687	2.832				3.482	3.983	
neural retina	1.727			2.832						
retinal bipolar cells - peak of neurogenesis	2.275							4.030	4.531	
rapid axon loss in optic nerve ends	2.292	3.188		3.397	3.531			4.047	4.548	
eye opening	2.478	3.374	3.438	3.583	3.717		4.170	4.233	4.734	5.047

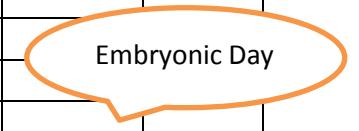
Event Name		Mesocricetus Auratus (Hamster)	Mus Musculus (Mouse)	Rattus Norvegicus (Rat)	Oryctolagus Cuniculus (Rabbit)	Acomys Cahirinus (Spiny Mouse)	Mustela Putorius Furo (Ferret)	Felis Domestica (Cat)	Macaca Mulatta (Monkey)	Homo Sapiens (Humans)
		0.896	0.960	1.105	1.239	1.311	1.692	1.755	2.256	2.569
front of retinal axons crosses the chiasm		1.500	2.396							

# of known events	10	13	20	8	3	12	22	19	1
# of events to predict	57	54	47	59	64	55	45	48	66
	67	67	67	67	67	67	67	67	67

Table 3-6: Event + Species Worksheet

In the *E-Values* worksheet shown in Table 3-7, the known values, extracted from the scientific literature, are shown for various species and events for which the information could be found. For example as shown in the table for the *Mus Musculus* species, the event *ocular muscles begin* is reported in the literature to occur on postconception day 11. Each blank space in the sheet is an unknown value that the analysis will later predict. There were 108 known events mined from the literature for the given species, and 495 event time cells that were not found in the literature but are predicted by the algorithm. This is a total of 603 event times in all.

Event Name		Mesocricetus Auratus (Hamster)	Mus Musculus (Mouse)	Rattus Norvegicus (Rat)	Oryctolagus Cuniculus (Rabbit)	Acomys Cahirinus (Spiny Mouse)	Mustela Putorius Furo (Ferret)	Felis Domestica (Cat)	Macaca Mulatta (Monkey)	Homo Sapiens (Humans)
		0.896	0.960	1.105	1.239	1.311	1.692	1.755	2.256	2.569
retinal ganglion cells generation - start of neurogenesis		1.147	9.5	10.5	11.5	13		21	19.5	
axons emerge from retina		1.116	9.5						30	
ocular muscles begin		1.235		11						
optic nerve		1.271		11.5			15			
axons in optic stalk		1.289		12.3	14.5				19	
optic disc		1.389		12.5						
retinal ganglion cells generation - peak of neurogenesis		1.481	12	13	16				30	43
posterior lens fibers		1.291			13					
anterior lens epithelial cells		1.291			13					
optic axon at chiasm of optic tract		1.431		13	15			24		
optic axons reach dLGN		1.568		14.5	15.5			28.5	31.5	
retina		1.504		13	19			23	28	
iris		1.600			15				35	
lens disc		1.039								29
lens pit		1.075								30
lens vesicle		1.111								31
eyelid folds begin		1.299								37
retinal pigment		1.177								33
optic axons at chiasm of optic tract		1.270								36
retinal pigmented epithelium		1.838			21					
optic chiasm		1.327					16			



Embryonic Day

Event Name		Mesocricetus Auratus (Hamster)	Mus Musculus (Mouse)	Rattus Norvegicus (Rat)	Oryctolagus Cuniculus (Rabbit)	Acomys Cahirinus (Spiny Mouse)	Mustela Putorius Furo (Ferret)	Felis Domestica (Cat)	Macaca Mulatta (Monkey)	Homo Sapiens (Humans)
		0.896	0.960	1.105	1.239	1.311	1.692	1.755	2.256	2.569
primary optic tract	1.396					17				
optic axons invade visual centers	1.616	16	15.5	16.5			26	32		
lens	1.242			16				17		
optic nerve axon number - peak of neurogenesis	1.850	18		19.5	23.5			38.5	69	
eye/optic cup	1.238				16			22	30	
optic stalk	1.271							21	39	
optic vesicle	0.962								27	
retinal axons	1.398						24			
retinal horizontal cells - peak of neurogenesis	1.479							30	40	
visual cortical axons	2.207			28.5	34.5					
cornea	1.335							24		
axon in optic stalk	1.238						24	19		
retinogeniculate axon	1.526						27			
geniculocortical axon	1.526						27			
corticogeniculate axons	1.526						27			
eyelids	1.474							26.5	45	
onset of retinal waves	2.139				31.5		47	52		
rapid axon generation in optic nerve - start of neurogenesis	1.435			15	15.5			27.5		
retinal amacrine cells - peak of neurogenesis	1.700	14	15.5	16				45	56	
retinal ganglion cell generation - end of neurogenesis	1.727	14	18.5	18.5				35.5	57	

Event Name		Mesocricetus Auratus (Hamster)	Mus Musculus (Mouse)	Rattus Norvegicus (Rat)	Oryctolagus Cuniculus (Rabbit)	Acomys Cahirinus (Spiny Mouse)	Mustela Putorius Furo (Ferret)	Felis Domestica (Cat)	Macaca Mulatta (Monkey)	Homo Sapiens (Humans)
		0.896	0.960	1.105	1.239	1.311	1.692	1.755	2.256	2.569
neural retina	1.727			19						
retinal bipolar cells - peak of neurogenesis	2.275							65	85	
rapid axon loss in optic nerve ends	2.292	31.5		29	32.5			53	110	
eye opening	2.478	31.5	30	36	43		72	72	123	157.5
front of retinal axons crosses the chiasm	1.586	13								

Table 3-7: E-Values Worksheet

In the $y = LN(E - k)$ worksheet, shown in Table 3-8, k is subtracted from the known values of the times of developmental events that are in the corresponding cells of the *E-Values* worksheet. It is important to note that the equation here is the one originally used by the Translating Time for Neurodevelopment project, where E equates to the day. The natural log of this value is computed, which produced the results in each cell of this worksheet. The species values and events values are not fully constrained because it is their sums that are used in worksheet *Event + Species*. Thus the research would produce essentially the same results if all the species values were increased (decreased) by some number c and all the event values were decreased (increased) by the same amount. We chose to resolve that ambiguity with species values within a range of .5 to 3.5 and event values within the range .5 to 2.5. It is expected from the model that the faster developing species would end up with lower species value scores and the slower developing species would end up with higher species value scores.

Event Name		Mesocricetus Auratus (Hamster)	Mus Musculus (Mouse)	Rattus Norvegicus (Rat)	Oryctolagus Cuniculus (Rabbit)	Acomys Cahirinus (Spiny Mouse)	Mustela Putorius Furo (Ferret)	Felis Domestica (Cat)	Macaca Mulatta (Monkey)	Homo Sapiens (Humans)
		0.896	0.960	1.105	1.239	1.311	1.692	1.755	2.256	2.569
retinal ganglion cells generation - start of neurogenesis	1.147	2.012	2.138	2.249	2.396		2.943	2.861	3.331	
axons emerge from retina	1.116	2.012								
ocular muscles begin	1.235		2.195							
optic nerve	1.271		2.249			2.563				
axons in optic stalk	1.289		2.330	2.524				2.832		
optic disc	1.389		2.349							
retinal ganglion cells generation - peak of neurogenesis	1.481	2.301	2.396	2.638				3.331	3.713	
posterior lens fibers	1.291			2.396						
anterior lens epithelial cells	1.291			2.396						
optic axon at chiasm of optic tract	1.431		2.396	2.563			3.090			
optic axons reach dLGN	1.568		2.524	2.601			3.276	3.384		
retina	1.504		2.396	2.832			3.044	3.257		
iris	1.600			2.563				3.496		
lens disc	1.039								3.295	
lens pit	1.075								3.331	
lens vesicle	1.111								3.367	
eyelid folds begin	1.299								3.555	
retinal pigment	1.177								3.433	
optic axons at chiasm of optic tract	1.270								3.526	
retinal pigmented epithelium	1.838			2.943						
optic chiasm	1.327					2.638				

$$y = \ln(E - k)$$

$$y = \ln(16 - 2.02)$$

Event Name		Mesocricetus Auratus (Hamster)	Mus Musculus (Mouse)	Rattus Norvegicus (Rat)	Oryctolagus Cuniculus (Rabbit)	Acomys Cahirinus (Spiny Mouse)	Mustela Putorius Furo (Ferret)	Felis Domestica (Cat)	Macaca Mulatta (Monkey)	Homo Sapiens (Humans)
		0.896	0.960	1.105	1.239	1.311	1.692	1.755	2.256	2.569
primary optic tract	1.396					2.707				
optic axons invade visual centers	1.616	2.638	2.601	2.673			3.177	3.401		
lens	1.242			2.638				2.707		
optic nerve axon number - peak of neurogenesis	1.850	2.771		2.861	3.067			3.597	4.204	
eye/optic cup	1.238				2.638			2.995	3.331	
optic stalk	1.271							2.943	3.610	
optic vesicle	0.962								3.218	
retinal axons	1.398						3.090			
retinal horizontal cells - peak of neurogenesis	1.479							3.331	3.637	
visual cortical axons	2.207			3.276	3.481					
cornea	1.335							3.090		
axon in optic stalk	1.238						3.090	2.832		
retinogeniculate axon	1.526						3.218			
geniculocortical axon	1.526						3.218			
corticogeniculate axons	1.526						3.218			
eyelids	1.474							3.198	3.761	
onset of retinal waves	2.139				3.384		3.806	3.912		
rapid axon generation in optic nerve - start of neurogenesis	1.435			2.563	2.601			3.238		
retinal amacrine cells - peak of neurogenesis	1.700	2.483	2.601	2.638				3.761	3.989	
retinal ganglion cell generation - end of neurogenesis	1.727	2.483	2.802	2.802				3.511	4.007	
neural retina	1.727			2.832						

Event Name		Mesocricetus Auratus (Hamster)	Mus Musculus (Mouse)	Rattus Norvegicus (Rat)	Oryctolagus Cuniculus (Rabbit)	Acomys Cahirinus (Spiny Mouse)	Mustela Putorius Furo (Ferret)	Felis Domestica (Cat)	Macaca Mulatta (Monkey)	Homo Sapiens (Humans)
		0.896	0.960	1.105	1.239	1.311	1.692	1.755	2.256	2.569
retinal bipolar cells - peak of neurogenesis	2.275							4.143	4.419	
rapid axon loss in optic nerve ends	2.292	3.384		3.295	3.417			3.931	4.682	
eye opening	2.478	3.384	3.331	3.526	3.713		4.248	4.248	4.796	5.047
front of retinal axons crosses the chiasm	1.500	2.396								

Table 3-8: $y = \ln(E-k)$ Worksheet

The *Error Figures* worksheet, shown in Table 3-9, is used to compute the error value for each cell for which there is a known event time extracted from the literature. The formula used to compute the value in each cell was the corresponding cell value from the $y=\ln(E-k)$ worksheet minus the corresponding cell value from the *Event + Species Values* worksheet. For example, the cell that corresponds to the species Rat and event “retinal ganglion cells generation - start of neurogenesis” is assigned the value of 2.249–2.252, or –0.003. This error value is the difference between the value predicted by the model based on fitting it to all available data extracted from the literature, and the value reported in the literature for the worksheet cell’s corresponding species and developmental event, from observations of actual animal subjects. As in this example, some cells have negative error values; therefore, I went a step further by creating another spreadsheet wherein the error value is squared; these squares were then used to compute a RMS over all such errors, giving a summary measure of how well the model fits the data. Different values of k result in different RMSs, and the appropriate value of k must be determined by numerical experimentation. The best value of k is the one that leads to the lowest RMS value for the known event times.

Event Name		<i>Mesocricetus Auratus</i> (Hamster)	<i>Mus Musculus</i> (Mouse)	<i>Rattus Norvegicus</i> (Rat)	<i>Oryctolagus Cuniculus</i> (Rabbit)	<i>Acomys Cahirinus</i> (Spiny Mouse)	<i>Mustela Putorius Furo</i> (Ferret)	<i>Felis Domestica</i> (Cat)	<i>Macaca Mulatta</i> (Monkey)	<i>Homo Sapiens</i> (Humans)
		0.896	0.960	1.105	1.239	1.311	1.692	1.755	2.100	2.569
retinal ganglion cells generation - start of neurogenesis		1.147	-0.031	0.031	-0.003	0.010		0.104	-0.041	-0.072
axons emerge from retina		1.116	0.000							
ocular muscles begin		1.235		0.000						
optic nerve		1.271		0.018			-0.019			
axons in optic stalk		1.289		0.081	0.130					
optic disc		1.389		0.000						
retinal ganglion cells generation - peak of neurogenesis		1.481	-0.076	-0.045	0.052				0.095	-0.024
posterior lens fibers		1.291			0.000					
anterior lens epithelial cells		1.291			0.000					
optic axon at chiasm of optic tract		1.431		0.005	0.027			-0.033		
optic axons reach dLGN		1.568		-0.004	-0.072			0.016	0.061	
retina		1.504		-0.068	0.223			-0.152	-0.002	
iris		1.600			-0.142				0.141	
lens disc		1.039								0.000
lens pit		1.075								0.000
lens vesicle		1.111								0.000
eyelid folds begin		1.299								0.000
retinal pigment		1.177								0.000
optic axons at chiasm of optic tract		1.270								0.000
retinal pigmented epithelium		1.838			0.000					
optic chiasm		1.327				0.000				

$\text{LN}(E - k) -$
(Species+Event
Value)

Event Name		Mesocricetus Auratus (Hamster)	Mus Musculus (Mouse)	Rattus Norvegicus (Rat)	Oryctolagus Cuniculus (Rabbit)	Acomys Cahirinus (Spiny Mouse)	Mustela Putorius Furo (Ferret)	Felis Domestica (Cat)	Macaca Mulatta (Monkey)	Homo Sapiens (Humans)
		0.896	0.960	1.105	1.239	1.311	1.692	1.755	2.100	2.569
primary optic tract	1.396					0.000				
optic axons invade visual centers	1.616	0.126	0.025	-0.048			-0.131	0.030		
lens	1.242			0.291				-0.290		
optic nerve axon number - peak of neurogenesis	1.850	0.025		-0.094	-0.022			-0.008	0.098	
eye/optic cup	1.238				0.161			0.002	-0.163	
optic stalk	1.271							-0.083	0.083	
optic vesicle	0.962								0.000	
retinal axons	1.398						0.000			
retinal horizontal cells - peak of neurogenesis	1.479							0.097	-0.098	
visual cortical axons	2.207			-0.036	0.035					
cornea	1.335							0.000		
axon in optic stalk	1.238						0.160	-0.161		
retinogeniculate axon	1.526						0.000			
geniculocortical axon	1.526						0.000			
corticogeniculate axons	1.526						0.000			
eyelids	1.474							-0.031	0.031	
onset of retinal waves	2.139				0.006		-0.025	0.018		
rapid axon generation in optic nerve - start of neurogenesis	1.435			0.023	-0.073			0.048		
retinal amacrine cells - peak of neurogenesis	1.700	-0.113	-0.059	-0.167				0.306	0.033	
retinal ganglion cell generation - end of neurogenesis	1.727	-0.140	0.115	-0.030				0.029	0.024	
neural retina	1.727			0.000						

Event Name		Mesocricetus Auratus (Hamster)	Mus Musculus (Mouse)	Rattus Norvegicus (Rat)	Oryctolagus Cuniculus (Rabbit)	Acomys Cahirinus (Spiny Mouse)	Mustela Putorius Furo (Ferret)	Felis Domestica (Cat)	Macaca Mulatta (Monkey)	Homo Sapiens (Humans)
		0.896	0.960	1.105	1.239	1.311	1.692	1.755	2.100	2.569
retinal bipolar cells - peak of neurogenesis	2.275							0.113	-0.112	
rapid axon loss in optic nerve ends	2.292	0.196		-0.102	-0.114			-0.116	0.134	
eye opening	2.478	0.010	-0.107	-0.057	-0.004		0.078	0.015	0.062	0.000
front of retinal axons crosses the chiasm	1.500	0.000								

Table 3-9: Error Figures Worksheet

The last worksheet in the workbook is the aforementioned *Error Squared Figures* as shown in Table 3-10. Each cell value corresponds to a cell in the previous worksheet which is squared. For example, the Species Cat, event “axons in optic stalk” from the *Error Figures* worksheet is -0.212 squared to produce a value of 0.045 in the current (*Error Squared Figures*) worksheet. The RMS formula was used to compute an overall error metric for the table. In doing so, I took the square root of the mean of the squares of all of the errors. The k enabling the smallest RMS value is the best value of k .

Event Name		<i>Mesocricetus Auratus (Hamster)</i>	<i>Mus Musculus (Mouse)</i>	<i>Rattus Norvegicus (Rat)</i>	<i>Oryctolagus Cuniculus (Rabbit)</i>	<i>Acomys Cahirinus (Spiny Mouse)</i>	<i>Mustela Putorius Furo (Ferret)</i>	<i>Felis Domestica (Cat)</i>	<i>Macaca Mulatta (Monkey)</i>	<i>Homo Sapiens (Humans)</i>
		0.896	0.960	1.105	1.29	1.311	1.692	1.755	2.256	2.569
retinal ganglion cells generation - start of neurogenesis	1.147	0.001	0.001				0.011	0.002	0.005	
axons emerge from retina	1.116	0.000								
ocular muscles begin	1.235		0.000							
optic nerve	1.271		0.000			0.000				
axons in optic stalk	1.289		0.007	0.017				0.045		
optic disc	1.389		0.000							
retinal ganglion cells generation - peak of neurogenesis	1.481	0.006	0.002	0.003				0.009	0.001	
posterior lens fibers	1.291			0.000						
anterior lens epithelial cells	1.291			0.000						
optic axon at chiasm of optic tract	1.431		0.000	0.001			0.001			
optic axons reach dLGN	1.568		0.000	0.005			0.000	0.004		
retina	1.504		0.005	0.050			0.023	0.000		
iris	1.600			0.020				0.020		
lens disc	1.039								0.000	
lens pit	1.075								0.000	
lens vesicle	1.111								0.000	
eyelid folds begin	1.299								0.000	
retinal pigment	1.177								0.000	
optic axons at chiasm of optic tract	1.270								0.000	
retinal pigmented epithelium	1.838			0.000						

Error
Figure
Squared

Event Name		Mesocricetus Auratus (Hamster)	Mus Musculus (Mouse)	Rattus Norvegicus (Rat)	Oryctolagus Cuniculus (Rabbit)	Acomys Cahirinus (Spiny Mouse)	Mustela Putorius Furo (Ferret)	Felis Domestica (Cat)	Macaca Mulatta (Monkey)	Homo Sapiens (Humans)
		0.896	0.960	1.105	1.239	1.311	1.692	1.755	2.256	2.569
optic chiasm	1.327					0.000				
primary optic tract	1.396					0.000				
optic axons invade visual centers	1.616	0.016	0.001	0.002			0.017	0.001		
lens	1.242			0.084				0.084		
optic nerve axon number - peak of neurogenesis	1.850	0.001		0.009	0.000			0.000	0.010	
eye/optic cup	1.238				0.026			0.000	0.026	
optic stalk	1.271							0.007	0.007	
optic vesicle	0.962								0.000	
retinal axons	1.398						0.000			
retinal horizontal cells - peak of neurogenesis	1.479							0.010	0.010	
visual cortical axons	2.207			0.001	0.001					
cornea	1.335							0.000		
axon in optic stalk	1.238						0.026	0.026		
retinogeniculate axon	1.526						0.000			
geniculocortical axon	1.526						0.000			
corticogeniculate axons	1.526						0.000			
eyelids	1.474							0.001	0.001	
onset of retinal waves	2.139				0.000		0.001	0.000		
rapid axon generation in optic nerve - start of neurogenesis	1.435			0.001	0.005			0.002		
retinal amacrine cells - peak of neurogenesis	1.700	0.013	0.003	0.028				0.093	0.001	
retinal ganglion cell generation - end of neurogenesis	1.727	0.020	0.013	0.001				0.001	0.001	

Event Name		Mesocricetus Auratus (Hamster)	Mus Musculus (Mouse)	Rattus Norvegicus (Rat)	Oryctolagus Cuniculus (Rabbit)	Acomys Cahirinus (Spiny Mouse)	Mustela Putorius Furo (Ferret)	Felis Domestica (Cat)	Macaca Mulatta (Monkey)	Homo Sapiens (Humans)
		0.896	0.960	1.105	1.239	1.311	1.692	1.755	2.256	2.569
neural retina	1.727			0.000						
retinal bipolar cells - peak of neurogenesis	2.275							0.013	0.013	
rapid axon loss in optic nerve ends	2.292	0.038		0.010	0.013			0.013	0.018	
eye opening	2.478	0.000	0.011	0.003	0.000		0.006	0.000	0.004	0.000
front of retinal axons crosses the chiasm	1.500	0.000								

Table 3-10: Error Figures Squared Worksheet

I began the analysis with a k value of 8.49 and chose arbitrary species and events values up to 2.500 with 3 digit precision. A k value of 8.49 was chosen because a preliminary desk check showed that a value greater than 8.49 would yield invalid value in the $y=\ln(E-k)$ equation. Once it was learned that a low RMS value could be obtained, it was apparent that this model worked for eye development events in the nine eutherian species. The process was automated and the computer completed the analysis. Using an original value of 8.49 for k , I tested species and event values to find an optimal set of species and event values. Since optimizing the event values will in general change the optimum species values, and vice versa, this optimization process must be iterated over a loop of optimizing species values and then event values, until the species and event values settle down to a stable state. As a proxy for this I looked at how much the output RMS value changed from one iteration to the next. It was necessary to determine how many iterations were needed before little to no change in the output RMS value was observed. As a desk check, I used the buttons from the macros to optimize the species values, apply the best species values, optimize the event values, then apply the best species value, which was considered one iteration through the optimization process. Through this method, I learned that running the optimization analysis more than six times produced little to no change in the RMS value. Therefore, the loop was run six times to test each value of k from 0 - 8 in increments of 1.0. Storing the k value that yielded the lowest RMS, the surrounding region of $k+/- 1$ was then checked in increments of .01, to find the best value of k . The pseudocode algorithm for optimization of k using 6 cycles is as follows:

For each value of k

For cycles 1 through 6

OptimizeSpeciesValues

OptimizeEventValues

Through each iteration the species values and event values are optimized such that the changes in the RMS lessens until there is no significant change. To put this in context, here is high level pseudocode for the overall algorithm architecture.

For each plausible value of k (i.e. $0 < k < 8.5$)

Iterate 6 times

For each species S

 find optimal scaling value of S within its plausible range (i.e. $0 < S < 3.5$)

For each ocular development event E

 find optimal scaling value of E within its plausible range (i.e. $0 < E < 2.5$)

Store:

the table's RMS error for k , and

the species and event scale values optimized to k

Choose k associated with lowest table RMS error as optimum for k

Fill spreadsheet with predictions species and event scale values optimized to optimum k

The spreadsheet macros implement this algorithm. Detailed pseudocode for these macros appears next. The actual code itself is provided in Appendix E.

The Scaling Macros (RunManyOptimizations.xlsx)

The Scaling Macros comprise 10 subroutines that perform the analysis that I termed *scaling* in an effort to compute optimal k , species values, and event values. The

macros scale through a predetermined number of variables, which will be discussed later in this section. These subroutines consist of approximately 338 lines of executable code and comments. The code for the macros is located in Appendix E. In addition, they are available for download at <http://www.eyetranslatetime.net>. The *loopLNValues* subroutine is approximately 27 lines of code and comments. It takes as input the range of values in column M (13th col.) from the $y = \ln(E - k)$ sheet, and uses the adjacent cells in column N to store the output while the cells adjacent to that in column O are used to house the output of the computed RMS values averaged over the cells in the corresponding row of the table. The *rowsAndColumns* subroutine is approximately 63 lines of code. The value of k is set such that it will not exceed 8.49, so that the macro will never try to take the natural log of 0. For each k , it tests each species scale value from .5 to 3.5 and each event scale value from .5 to 2.5. Each value of k is considered a candidate value. However, only the k value that enables the smallest RMS value is considered the optimal k value. The macro compares the RMS value enabled by the current value of k as it step through each value of k while temporarily holding the k value associated with the smallest RMS until it has iterated through all the k values to be tested. It then stores the optimal value of k into the *Event + Species* spreadsheet.

The *OptimizeSpeciesValues* subroutine is short. The code calls the *OptimizeSpeciesValuesUsingK* subroutine. The *OptimizeSpeciesValuesUsingK* subroutine is approximately 32 lines of executable code and comments. Using the current value of k , the macro iterates from .5 to 2.5 in increments of .001 for each species, storing the species value that produces the lowest RMS for the current k value being tested. The *OptimizeEventValues* subroutine is short, and calls the *OptimizeEventValuesUsingK*

subroutine. The *OptimizeEventValuesUsingK* subroutine is approximately 32 lines of executable code and comments. Using the current value of k , the macro iterates from .5 to 2.5 in increments of .001 for each event, storing the event value that produces lowest RMS in conjunction with the current k value. The *resetSpeciesAndEventValues* subroutine is approximately 21 lines of code and comments. It resets the species and event values to the original values. The *applySpeciesValues* subroutine has approximately 11 lines of code. It takes the value for each species and copies it to the bottom of the *Event + Species Values* sheet in row 58. This allows it to be with other data that will be output. The *applyEventValues* subroutine is approximately 8 lines of code. It takes the best value for each event that has been temporarily stored in a range of cells from column P (16th col.) and places it to the right of the event. The *runManyOptimizations* subroutine is approximately 124 lines of code. This code runs on a click of the *run many optimizations* button in the *Event + Species Values* sheet. It is where the overarching analysis takes place. It scales k from 1 to 8, in increments of 1. Based on the best of these values for k , it then tests values within $k +/- 1$ in increments of .01 to optimize k . For each tested value of k , it optimizes species and event scale values to find the best set that produces the lowest RMS error. It runs 6 iterations of the regression loop, each loop including optimization of the event and species scale values, for each k , to get the best RMS.

Pseudocode, a high level description that describes the code algorithm, is used in this section to detail how the macro code works. The *runManyOptimizations* subroutine is where the program execution initiates. It is enabled when the user clicks the *run optimization cycles* button in the *Event + Species Value Sheet*. Once the program begins

processing, calls are made to the following subroutines: resetSpeciesAndEventValues, OptimizeSpeciesValuesUsingK(bestK), applySpeciesValues, optimizeEventValuesUsingK(bestK), and applyEventValues. This means the program flow of control is sent to each of these subroutines to be executed.

Initially, declare the following variables:

numCycles

kTimes1

actualK

bestK

bestRms

totalRmsCell

numCycles = 6

The variable numCycles is set to 6 because during preliminary testing I found that for each value of k , I needed to iterate 6 times through the event and species value optimization process to obtain the best RMS value.

Changes to the best RMS value were trivial after the 6th iteration through the loop, which is why the loop terminated after 6 iterations.

bestK = -1

The variable bestK is assigned a value of -1 because k iterates from 0 to 8. Through preliminary testing, I found that a value of k greater than 8.5 would cause the program to crash. Therefore, k has the potential to be 8.49, which will keep the program below the upper bound for k .

Take the values in the range from column O (15^{th} col.), which temporarily holds the best value for the current k for each species and event and store the totals in row 57 of the current Sheet. Store the sum of this range of values in the *totalRmsCell* variable.

As the program iterates, temporarily show the best species value for each species, given current best k in row 58. The pseudocode is given next.

Iterate from 1 to 8 for each whole number of k , kTimes1.

Store the current value of k in actualK.

Call *resetSpeciesAndEventValues*:

Reset the range of cells containing the species values, resetColSrc, to predefined values as shown below, respectively.

0.571 0.625 0.827 1.019 1.069 1.366 1.669 2.201 2.416

Reset the range of cells containing the event values, eventCell, to the original values that were on the Sheet.

For each cycle 1 to 6:

display k and value as well as the current *cycle* of the total number of cycles, such as “cycle 2 of 6,” in cell *b1*. Return the flow of control to the *runManyOptimizations* subroutine. For each species test from .500 to 3.500 and for each event test from .500 to 2.500 both in increments of .001, and compute the RMS for each candidate value.

If the RMS is better than

the current best then store it.

In detail:

Call OptimizeSpeciesValuesUsingK(k)

This subroutine takes the value of k as the parameter by which it will optimize the each species, which allows the program to hold the best value of k with the lowest RMS each cycle through.

Declare the following variables:

seCandidateValueCell

candidateRmsCell

bestRmsCell

bestSEValueCell

candidateValue

Initialize k to the value in Sheet y=ln(E-k), cell M2

Clear all of the values from the range of cells c57 to k58

For each species,

set the candidateRmsCell in row 56

set bestRmsCell in row 57

set bestSEValueCell in row 58

As the program is running this allows the user to see the temporary values that are being stored in the candidateRmsCell, which are the candidate RMS values for the current k .

Call applySpeciesValues

As the program runs, display the value for each species across row 58

Call optimizeEventValuesUsingK(actualK)

Take the actualK value in as a parameter

Declare the following variables:

seCandidateValueCell

candidateRmsCell

bestRmsCell

bestSEValueCell

candidateValue

Initialize k to the value in Sheet y=LN(E-k), cell M2

Clear the values in the range of cells O3 to P48

For each event in the range of cells B3 to B48

 Set (display) the candidateRmsCell values for the range in

 Column N

 Set (display) the bestRmsCell values for the range in Column

 O

 Set (display) the bestSEValueCell values for the range in

 Column P

For each candidateValue from .5 to 2.5 in increments of .001

 Calculate RMS, candidateRMSCell

 (temporarily holds to values in Column N)

Call applyEventValues

Declare the following variables:

colSrc

eventCell

For each eventCell in the range of B3 to B48, take the value and store it in the range of cells in Column P

If RMS is better than current best then store it

Next, focus on area of k around bestK, using increments of .1:

Further restrict k values to $.01 < k < 8.50$

Call resetSpeciesAndEventValues

Call OptimizeSpeciesValuesUsingK(bestK)

Call applySpeciesValues

Call optimizeEventValuesUsingK(bestK)

Call applyEventValues

Next, focus on smaller area around bestK, using increments of .01

Further restrict k values to $.01 < k < 8.50$

Call resetSpeciesAndEventValues

Call OptimizeSpeciesValuesUsingK(bestK)

Call applySpeciesValues

Call optimizeEventValuesUsingK(bestK)

Call applyEventValues

There are 5 other buttons on the *Event + Species* Spreadsheet wherein the user can invoke the individual subroutine that runs from the button. These buttons are: reset, optimize species value, apply best sp, optimize event values, and apply best ev. Although the pseduode for each of these buttons has already been

described, it is important to note the button that invokes the subroutine. The reset button invokes *resetSpeciesAndEventValues*, the optimize species button invokes *OptimizeSpeciesValuesUsingK*, the apply best species button invokes *applySpeciesValues*, the optimize event values button invokes *optimizeEventValuesUsingK*, and the apply best ev button invokes *applyEventValues*. Early on in the analysis, the optimize species value, apply best sp, optimize event values, and apply best ev buttons were used to determine how many cycles were needed to scale the species and event values before little to no change in the best RMS value would be observed as previously described.

There are two additional subroutines in the scaling macros; however, they are invoked from sheets other than the *Event + Species* Sheet. The *loopLNValues* subroutine is invoked from the *Errors Figured Squared* Sheet. This macro code is invoked only if the user clicks the *Calcluate* button on this sheet. The algorithm for the pseudocode is shown below. It allows the user to see the candidateRMS, bestK, and bestRMS as the program executes.

LoopLNValues subroutine

Declare the following variables:

inputCell

outputCell

rmsCell

Display the candidateRMS in cell M2

Display the bestK in cell N2

Display the bestRMS in cell O2

Display the range of values for the sum of event and species for candidateRMS in cells M

Display the range of values for the sum of event and species for bestK in cells N

Display the range of values for the sum of event and species for bestRMS in cells O

The other subroutine that can be invoked from the $y=LN(E-k)$ Sheet is the *rowsAndColumns* subroutine:

Declare the following variables:

inputCell

candidateRmsCell

bestRmsCell

bestKCell

k

kMax

kInt

rowI

colI

kMax

Hard-code or manually set the k value

Set kMax to 8.50 so that the program never take a ln of zero

Clear any existing ln values from the range of cells in column M

Clear any existing error sum values from the range of cells in column N

Clear any existing ln values from the range of cells in column O

Iterate k from 1 to 8.5

Set M2 to k value, copy k here just to make it easy to monitor progress

Set ln values for the range of cells in column M

Set error sum values for the range of cells in column N

Set the ln values for the range of cells in column O

For each row calculate new RMS and candidateRmsCell

If the value for bestRmsCell = null or value for the candidateRmsCell is less than the bestRmsCell.Value

Then assign the value of candidateRmsCell to the value of bestRmsCell

Set value equal to value of bestKCell

3.3.3 Results

The analysis was begun using a k value of 8.49 as an initial test. Through preliminary testing, I found that using a k value of higher than 8.49 caused the program to crash. Holding k at 8.49 yielded a RMS value of more than .722. This was obtained by manually iterating through the process of finding the best species scale and event scale values for that value of k . One iteration involved clicking first on the *optimize species values* button, then the *apply best sp* button, then *optimize event values*, and finally *apply best ev*. It was found that by running 6 iterations the optimal species scale and event scale values had settled close to a fixed point, in that the lowest RMS value did not change at the 3 decimal digit precision point when the 7th iteration was run. This resulted in the RMS = .480.

Having empirically identified six as a number of iterations providing a satisfactory tradeoff between accuracy and processing time, the process was automated. To do this, a macro was written which provided several buttons to help automate the

process. The buttons were *reset*, *optimize species values*, *apply best sp*, *optimize event values*, and *apply best ev*. The code that runs from these buttons was discussed in section 3.3.2 of this document.

Recall that the objective of processing is to find the optimal values for k , the species scale values, and the event scale values. In order to find the optimal value of k , the process was automated to first test integer values of k as noted earlier. Then, for the best integer value i , cycle through values of k for which $i-1 < k < i+1$ in increments of .1, then .01. The RMS for $k = 3.02$ was 0.23964, for $k=3.01$ was 0.23960, and for $k=3.00$ was 0.23948. Clearly there is a downward trend in RMS as k decreases. This trend was found to continue down to $k=2.02$, for which the RMS was 0.23168, slightly lower than for $k=2.03$ for which RMS=0.23183. At $k=2.01$ the RMS was 0.23168 to five digits of precision, the same RMS value as for $k=2.02$, however in fact it was slightly higher than for $k=2.01$ in the sixth decimal place. Therefore the optimal value for k was 2.02. However it is important to note that the RMS is affected only a very small amount for a significant range of k . It is interesting to note in this context that previous research states that k is an estimate (Darlington et al., 1999). Figure 3-2 depicts the spreadsheet page for the program that iterates k from 0-8 and performs the analysis. Here you can see the 6 button options available to run the program.

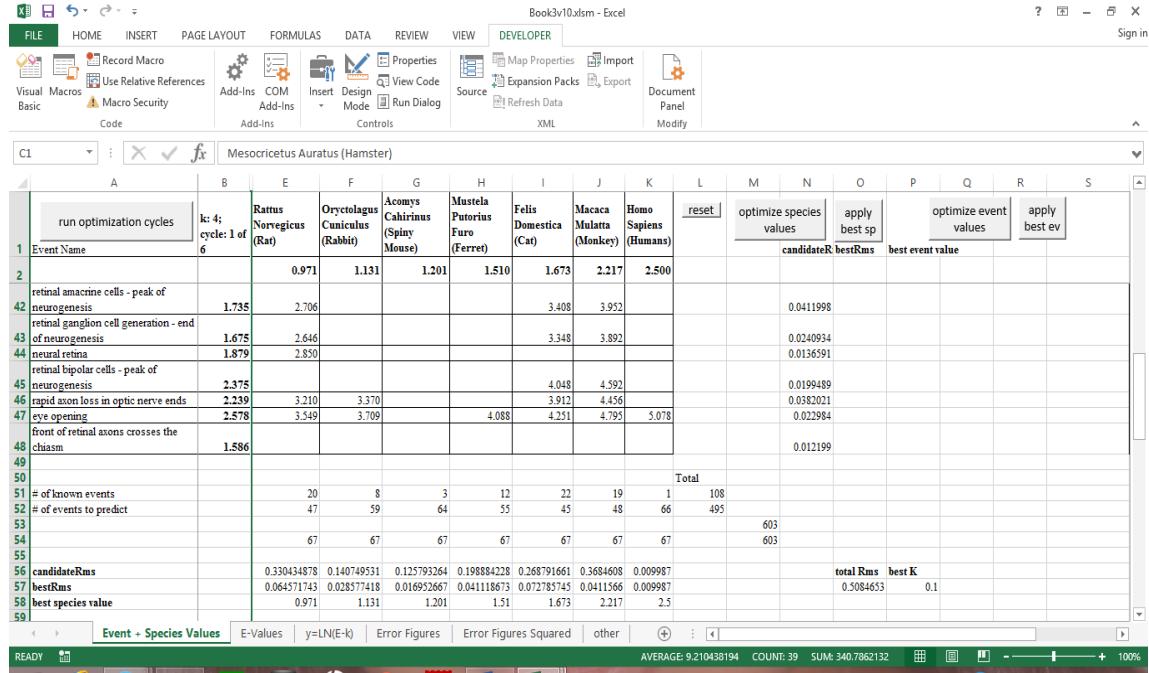


Figure 3-2: Run Optimization Cycles

Let us now move on to prediction analysis. Given the formula $y = \ln(E - k)$, we wish to solve for E to give a prediction for the embryonic day that an event occurs on. The steps used to solve the equation are:

- Step 1: $e^y = E - k$
- Step 2: $e^y + k = E$

To make the predictions for the 495 events for which experimental lab data were not found in the literature, I summed the predicted species and event for each cell with a missing value in the '*Event + Species Values*' Sheet. Afterwards, I used the formula referenced above to compute the predictions as shown below in Table 3-11.

Event Name		Mesocricetus Auratus (Hamster)	<i>empi</i> <i>r.</i>	Mus Musculus (Mouse)	<i>empi</i> <i>r.</i>	Rattus Norvegicus (Rat)	<i>empi</i> <i>r.</i>	Oryctolagus Cuniculus (Rabbit)	<i>empi</i> <i>r.</i>	Acomys Cahirinus (Spiny Mouse)	<i>empi</i> <i>r.</i>	Mustela Putorius Furo (Ferret)	<i>empi</i> <i>r.</i>	Felis Domestica (Cat)	<i>empi</i> <i>r.</i>	Macaca Mulatta (Monkey)	<i>empi</i> <i>r.</i>	Homosapiens (Humans)	<i>empir</i>
		0.896		0.960		1.105		1.239		1.311		1.692		1.755		2.256		2.569	
retinal ganglion cells generation - start of neurogenesis	1.147	9.7	9.5	10.2	10.5	11.5	11.5	12.9	13	13.7		19.1	21	20.2		32.1	30	43.1	
axons emerge from retina	1.116	9.5	9.5	10.0		11.2		12.6		13.3		18.6		19.7		31.1		41.8	
ocular muscles begin	1.235	10.4		11.0	11						14.8		20.7		21.9		34.8		46.9
optic nerve	1.271	10.8		11.3	11.5					15.2	15	21.4		22.6		36.0		48.5	
axons in optic stalk	1.289	10.9		11.5	12.3					15.5		21.7		23.0	19	36.6		49.4	
optic disc	1.389	11.8		12.5	12.5					16.9		23.8		25.2		40.3		54.4	
retinal ganglion cells generation - peak of neurogenesis	1.481	12.8	12	13.5	13	15.3	16	17.2		18.3		25.9			30			59.4	
posterior lens fibers	1.291	10.9		11.5		13.0	13	14.6		15.5		21.8						9.5	
anterior lens epithelial cells	1.291	10.9		11.5		13.0	13	14.6		15.5		21.8						1.5	
optic axon at chiasm of optic tract	1.431	12.3		12.9	13	14.6	15	16.5		17.5		24.7	24					56.6	
optic axons reach dLGN	1.568	13.8		14.5	14.5	16.5	15.5	18.6		19.8		28.1	28.5	29.8	29	47.8		64.6	
retina	1.504	13.0		13.8	13	15.6	19	17.5		18.7		26.4	23	28.0	28	45.0		60.7	
iris	1.600	14.2		15.0		17.0	15	19.1		20.4		28.9		30.7	35	49.3		66.6	
lens disc	1.039	8.9		9.4		10.6		11.8		12.5		17.4		18.4		29.0	29	38.9	

Predicted Date
vs Empirical Date
Slight Variation!

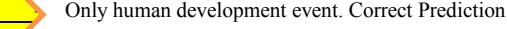
Predicted Date
vs Empirical Date
Prediction Correct!

Event Name		Mesocricetus auratus (Hamster) empi r.	Mus Musculus (Mouse) empi r.	Rattus Norvegicus (Rat) empi r.	Oryctolagus Cuniculus (Rabbit) empi r.	Acomys Cahirinus (Spiny Mouse) empi r.	Mustela Putorius Furo (Ferret) empi r.	Felis Domestica (Cat) empi r.	Macaca Mulatta (Monkey) empi r.	Homosapiens (Humans) empir.
		0.896	0.960	1.105	1.239	1.311	1.692	1.755	2.256	2.569
visual cortical axons	2.207	24.3	25.7	29.5	28.5	33.4	34.5	35.7	51.4	88.7
cornea	1.335	11.3	11.9	13.5	15.1	16.1	22.6	24.0	24	38.3
axon in optic stalk	1.238	10.5	11.0	12.4	13.9	14.8	20.7	24	22.0	34.9
retinogeniculate axon	1.526	13.3	14.0	15.9	17.9	19.1	27.0	27	28.6	45.9
geniculocal axon	1.526	13.3	14.0	15.9	17.9	19.1	27.0	27	28.6	45.9
corticogeniculate axons	1.526	13.3	14.0	15.9	17.9	19.1	27.0	27	28.6	45.9
eyelids	1.474	12.7	13.4	15.2	17.1	18.2	25.7	27.3	26.5	43.7
onset of retinal waves	2.139	22.8	24.2	27.6	31.3	31.5	33.5	48.1	47	51.1
rapid axon generation in optic nerve - start of neurogenesis	1.435	12.3	13.0	14.7	15	16.5	15.5	17.6	24.8	26.3
retinal amacrine cells - peak of neurogenesis	1.700	15.4	14	16.3	15.5	18.5	16	20.9	22.3	31.7
retinal ganglion cell generation - end of neurogenesis	1.727	15.8	14	16.7	18.5	19.0	18.5	21.4	22.9	32.5
neural retina	1.727	15.8		16.7		19.0	19	21.4	22.9	32.5
retinal bipolar cells - peak of neurogenesis	2.275	25.8		27.4	31.4	35.6	38.1	54.8	58.3	65
Event Name		Mesocricetus auratus empi r.	Mus Musculus (Mouse) empi r.	Rattus Norvegicus (Rat) empi r.	Oryctolagus Cuniculus (Rabbit) empi r.	Acomys Cahirinus (Spiny Mouse) empi r.	Mustela Putorius Furo (Ferret) empi r.	Felis Domestica (Cat) empi r.	Macaca Mulatta (Monkey) empi r.	Homosapiens (Humans) empir.

		tus (Hamster)	e)					Mouse)	Furo (Ferret)				(Monkey)		(Humans)	
		0.896	0.960	1.105		1.239		1.311	1.692		1.755		2.256		2.569	
rapid axon loss in optic nerve ends		2.292	26.3	31.5	27.9	31.9	29	36.2	32.5	38.7	55.7	59.2	53	96.4	110	131.1
eye opening		2.478	31.2	31.5	33.1	30	38.0	36	43.1	43	43.1	43	53	96.4	110	157.5
front of retinal axons crosses the chiasm		1.586	13.0	13	13.7	15.5		17.5	18.6	18.6	26.3	27.9	44.8	44.8	60.5	60.5

Table 3-11: Actual Event Dates and Predicted Dates by Species and Events

Only human development event. Correct Prediction!



The cells with a yellow shading represent each of the 495 predictions. I randomly chose 100 predicted values to validate our assumption that the sum of the species score plus the event score for an *already known* event time will on average produce an output from the model equation relatively consistent with the known experimental value (within the limits of the model's accuracy and the sources of noise). This held true for the predicted values in this research.

As shown below in Table 3-12, there is some slight variability between predicted event values in days postconception and the empirical data when available. The predicted dates are close to the observed empirical data for the majority of the known events. In some instances such as eye-opening in *Mus musculus*, the predicted postconception date from the model exactly matched that provided by the empirical data.

There are a few instances when the predicted date does not match well with the empirical data. For example, the prediction for the event “retinal horizontal cells - peak of neurogenesis” in *Macaca mulatta* is 43.9 while the empirical data show this event to occur on postconception day 40. In Clancy et al., 2001, the research saw the same type of variability in other events for species such as *Macaca mulatta* where the prediction for the event “subplate start” is 37.9 while the empirical data show that the event occurs on PC day 39.5. However, the variability amongst the other species in the research was much less. It is important to note that when the empirical data was extracted from the literature some events were given a range of dates and the average of that range was provided in the table. Another notable item is that Darlington et al., 1999, found that the eye-opening event in humans occurred on PC day 182; however, later Clancy et al.,

2007, revised this value to PC day 157.5. In this case, I did not average the two numbers as I did in other cases when there was variability with event values within species. I used the most current value provided in the literature. My prediction for eye opening in *Homo sapiens* is exact to that of the empirical data because it is the only event for *Homo sapiens* so the species value can be adjusted to produce zero error without affecting other predictions. Recall that according to Gross et al., 2008, as well as Nguyen & Arnhieter, 2000, eyes become functional during months 5 through 7 of fetal development; therefore, as more data becomes available on date of eye-opening this event value has the potential to change in the future.

The predictions for which $k = 2.02$ indicates that there is little to no difference in the predicted event values for $k = 2.02$ vs $k = 3.00$. For example, there are 10 predicted values for which empirical data is available. Of those 10 predictions, 3 predicted values are the same in both tables while 6 of the remaining predictions vary by only 0.1. Additionally, there is a 1.0 variation in the prediction for the eye-opening event in *Homo sapiens* across the two tables. This illustration shows that for the estimate of $k = 3.00$ there is little to no change in the predicted event values versus using the value of $k = 2.02$.

I also tested the model with the *Danio rerio* dataset, which contained 17 events mined from the literature. Since the data collected for the events for the zebrafish were in hours post fertilization, I converted units on all of the event times, using 24 hours as 1 day. Therefore, the event *hemispheric eye* occurring at 72 hours post fertilization received a converted time of 3. Additionally, *optic lobe* appeared at 12 hours post fertilization and so received a converted time of 0.5. Then, I utilized

the same methods used to predict the events values and the species score with the nine eutherian mammals for this research. When $k=3$ was used with the Zebrafish events based on hours post fertilization in the formula $y = \ln(E - k)$, an error was thrown because you cannot take the natural log of a negative value. Because k roughly models the time before species diverge in their event timing, the zebrafish seems to be behaving differently from the other species in the model right from the start. Thus the model does not work for the zebrafish in comparison to mammals. The negative results for the zebrafish show lack of compatibility between eutherian mammals and the zebrafish, indicating that the zebrafish does not fit the current model as a viable additional species for the translating time research as it relates to eye development.

3.3.4 Discussion

Adaptation of the algorithm utilized in previous research was used in previous research was the foundation for this work. This proved to be useful and workable. It was the process by which I was able to break down the problem in order to test whether or not the model worked with the same nine Eutherian Mammals but on a different dataset. The analysis used to deduce the original research design helped to better understand the interaction between k , the species scale values, and the event scale values. This enabled designing the pseudocode to use in building the code to compute k , the species scale values, and the event scale values. A dataset for eye development events was extracted from the literature using data mining so that this could be used in this research. In doing so, I was able to extend the earlier work on which the present work is based. That earlier work was in the domain of neurodevelopment, and the

present work shows that the same approach produced useful results in the domain of ocular development as well for eutherian mammals. The zebrafish event values were converted to PC days instead of hours post-conception to accommodate for the events occurring in days instead of hours post-fertilization in order to tell whether or not the zebrafish fit the model. However, zebrafish, did not match the model. We conjecture that this approach may prove useful for other organ systems as well, however investigating that remains a task for future research.

Creating spreadsheets that worked with the algorithm proved to be a useful method for solving the analysis problems related to values of k , species scale scores, and event scale scores. The macro code was an integral part that made the predictions a success. Other researchers may wish to use this spreadsheet based approach instead of the statistical package approach relied upon in the earlier work.

Figure 3-3, shown below, depicts the predicted PC days vs. the empirical days that an event occurs on. Since the events are eye development events, the date of occurrence is early in the development process. An example of an outlier is the “eye opening” event in humans, which occurs on day 157.5. There were 108 known events in the literature and this research produced, 27 events, 25% of the events correctly. Of the remaining 81 events, this research predicted 34 or 58 percent of the events within 1 day. Additionally, 19 of the events fall within 2 days, which may be due to variability within the species. There are 28 events where the predicted day falls outside of a 2 day timeframe.

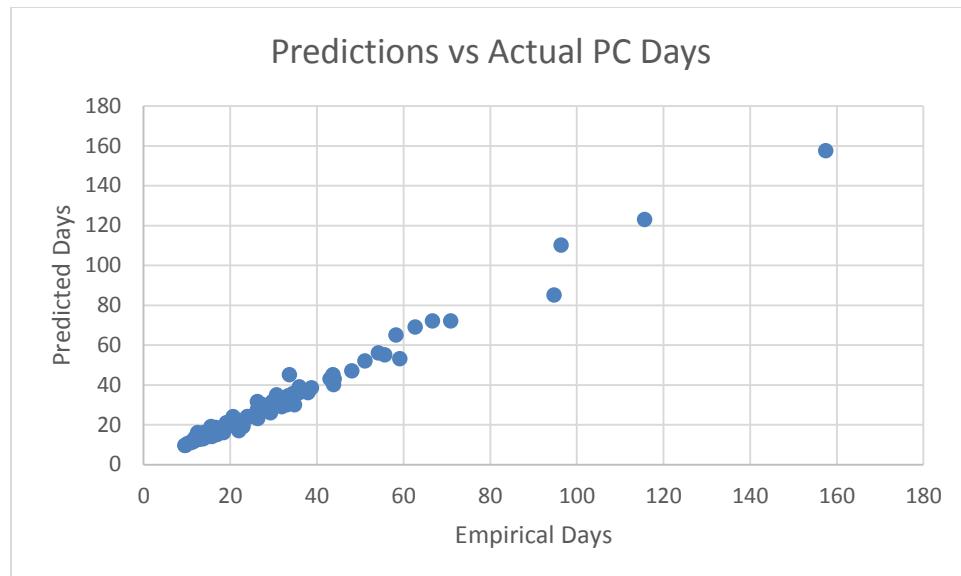


Figure 3-3: Scatter Plot Diagram of Predicted vs Empirical Days

This research shows that the analysis process can be achieved with ordinary spreadsheets as an alternative to specialized software such as SAS, Minitab or SPSS. To help with this, my code and the results are being made publically available. This research also showed that although the zebrafish is a model organism for eye development it does not fit this developmental model. This is perhaps not too surprising since the zebrafish is a fish, and mammals generally have more in common with each other than with fish. It is possible, however, that a model based approach could be developed to apply to fish, and perhaps a more generalized model that can accommodate groups as different as fish and mammals might someday be discovered.

3.4. Web Site

The main goal of this part of my dissertation was to develop and demonstrate an Internet-based resource for sharing the data and methods I used for predicting eye

development events. The information necessary to replicate the work on another suitable computing environment is provided. Such a Web-based interface can be the primary means of interaction for anyone accessing the research findings. There is a database on the back end, which is the repository for all data points collected. The interface serves as the communication portal on the front end, mediating between the user and the data repository. It allows the user to query the repository, and return predictions of unknown event times across species. The interface has server-side code that allows computation on, as well as manipulation of, the data to be performed.

Sharing data and methods developed for predicting eye development events provides more efficient utilization of resources for translating time by making unnecessary the duplication of unique data. It can also conserve researchers' time by alleviating the need to duplicate the investigation of these data points that have been researched for a new organ on species. It is important to understand the value of this data because it has been investigated at a time when the current research is ripe for expansion.

3.4.1 Materials

This section explains the major software tools used in this part of the research. These are MySQL, Dreamweaver, PhotoShop, Bluehost, and SurveyMonkey.

MySQL

MySQL is a widely used open source database management system that is available from Oracle Systems (MySQL, 2013). MySQL was used as the storage and retrieval tool for data related to the translation of time for eye development. MySQL is

based on, a comprehensive language for defining data, data retrieval, and data manipulation with a database management system (DBMS). It is a tool with which we communicate with the DBMS, not an actual programming language such as C, C++, or Java. Originally named Structured English Query Language (SEQUEL) by IBM the name was later changed to Structured Query Language (SQL) after IBM found out that SEQUEL was already trademarked. An important feature of SQL is that it is vendor independent and portable amongst computer systems (Groff et al., 2010).

When data is requested from a database, SQL can be used to create the query. The DBMS processes the request, retrieves the data and returns the requested data. The code used to make the request from the database and return the results is called a database query, thus, the name Structured Query Language. SQL is a common language for database gateways in the context of Web development. Since there is an array of open source SQL like databases, SQL has become a low-risk and low-cost solution (Kofler, 2005).

MySQL is a clone of SQL that uses the GNU General Public License; however, a commercially licensed version is also available. The MySQL Workbench was used because it provides an integrated development environment (IDE) for database design, SQL development, database administration, and database migration. This software is a client/server system that supports a variety of application programming interfaces (APIs). MySQL is written in C and C++ (Pratt & Last, 2005). As of April 18, 2013 the latest stable version of MySQL Workbench is 5.2. The freeware version of MySQL can be downloaded from the MySQL Website, <http://dev.mysql.com/downloads/>. I downloaded the MSI, Windows installer file because it comes complete with a setup

wizard, which walks you through the installation process. Features of the IDE include the SQL Editor, which allows you to write, run, and debug SQL statements as well as compile and format them. The Object Explorer allows users to create, edit, and delete database objects and to perform actions on the database objects such as tables, views, and triggers. One can also import and export files and perform visual data modeling with this IDE.

Website development tools

Adobe Creative Suite (CS) Design Premium was utilized to design and develop the Website for my research. CS is a software suite developed by Adobe Systems. It is a collection of applications such as Photoshop, Acrobat, Flash, Fireworks, Illustrator, InDesign and Dreamweaver, which are used for web development, graphic design, and video editing. These applications are built on PDF and vector graphics. I used CS5.5, which was released on April 12, 2011, as a partial version update pending version CS6 (Bishop, 2013).

Adobe Dreamweaver CS5.5 was selected from this suite to develop the Website because of its ease of use for making and editing HTML Websites. It is used for creating Websites, publishing them, and site management after publication. The developer can work directly with the code and see the design (Padora et al., 2010). Dreamweaver allow the user the capability to develop and utilize cascading style sheets (CSS) and other scripting languages. CSS were designed by the World Wide Web Consortium (W3C) as a standard to describe the look and format of a web page written in a markup language such as HTML (HyperText Markup Language), XHTML (Extensible HyperText Markup Language), XML (Extensible Markup Language), or SVG (Scalable Vector Graphics) (Callihan, 2001). CSS are typically linked to the page

content from a separate document to describe the design definitions for the page presentation such as the color, font, and size (Schengili-Roberts, 2003). A feature of the Dreamweaver workspace is its drag and drop workflow (Shelly & Wells, 2010).

PHP is a scripting language that allows developers to create dynamic web pages. It was chosen to interact with MySQL for performing queries on the database. Dynamic web pages incorporate information from PHP, MySQL and CSS (Wellings, Thomson, 2008). Dreamweaver has the capability of creating Web pages with embedded PHP. An example of a dynamic web page is a display of a counter of visitors to a site. The connection between PHP and HTML is that PHP code runs in the middle of the requested page and is executed by the web server. Therefore, it augments and changes the basic HTML output. From the previous example, the site visitor is unaware of the PHP component of the page because the PHP code-generated counter text is actually embedded in the HTML source document which is provided by the server. PHP code is thus interpreted by the web server to generate the resulting web page. The PHP was designed to work with the MySQL API (Tatroe et al., 2013).

PHP was developed in 1994 by Rasmus Lerdorf. He developed a collection of open source Perl scripts for his personal usage, which were later rewritten in the C programming language and turned into PHP. Originally, PHP stood for Personal Home Page. Now it stands for Hypertext Preprocessor (McLaughlin, 2012). Although PHP comes packaged with the Dreamweaver IDE, online application programming interfaces (APIs) are freely available at <http://www.php.net>. PHP is a free software but it is not available under the GNU General Public License due to usage restrictions. It is available under the PHP License, which is an open source license (Beighley & Morrison, 2008).

Features of the Dreamweaver IDE include common features most software applications display across the top of the application, such as Windows based products with a title bar, standard toolbar, menu bar and insert bar one can customize this bar by adding commonly used buttons to make them readily available on this menu bar. The property inspector is located at the bottom on the application window. It allows you to view and change the property of a selected object. Another useful feature is a viewer, which allows you to see a combination of both the code and the design side-by-side, in a split view.

Photoshop was chosen as the image editing program because it allows one to work with pixel-based files. Photoshop allows working with files of many formats whether downloaded from the Internet, taken with a digital camera, or scanned from print (Galer & Andrews, 2010). It also provided the capability to create an image from scratch. Photoshop also permits creating and working with 3-D objects as well as with opacity, shininess, and glossiness of an image (Padova & Murdock, 2010).

Photoshop has an assortment of features for working with images. Its drawing tools such as the Pen, Type, and Rectangle are shown to the left of the screen. The Options bar allows one to create shape layers, fill pixels, and create custom shapes. One can also create Layers by stacking images on top of one another. You can create Channels, which are grayscale images. There are 56 possible channels and an image with RGB has a channel for each color (red, green, and blue) that can be used for editing the image.

Bluehost was chosen to host the Website for this research. It is a private web hosting company that was founded in 1996. In April 2013, Bluehost was ranked in the Top 10 Web hosting providers by Hosting-Review (hosting-review, 2013) making it a

suitable choice. It uses the latest server technology to minimize customer downtime and to ensure fast page access. In the Standard hosting package provided by Bluehost, the server software is ApacheHTTP Server version 2.2.23, and OpenSSL version 0.9.8e. Some important features of Bluehost are 24/7 US-based support, SimpleScripts 1-Click installs, and SSH Secure Shell Access. Additional standard hosting package features include: unlimited disk storage, unlimited domain hosting, free domain name for 1 year, MySQL databases, and unlimited e-mail accounts (Bluehost, 2013).

SurveyMonkey was selected to create a Web-based survey to test the usability of the Website. SurveyMonkey is a provider of free and paid web surveys. It allowed me as the developer to create a survey without doing any coding. Additionally, it allowed me to host the survey free of charge. It collects and analyzes the results based on rules that I set, which allowed me to filter, compare and show results to see trends and patterns. These results helped me to determine the effectiveness of the Website. Surveys are freely available from SurveyMonkey at <http://www.surveymonkey.com>. This cloud based company was founded in 1999 by Ryan Finley (Creswell, 2008).

3.4.2 Methods

I utilized a user-centered Web development approach to designing the Website. For this the Website is designed to meet user needs, including ease and content. In this case, the content requirement was to provide information about my research, “Translating Time: The Eye,” in electronic format. I used a traditional waterfall software development life cycle model, which consists of the following phases:

1. Requirements specification
2. Software design

3. Implementation and Integration
4. Testing
5. Deployment
6. Maintenance

I completed each phase prior to proceeding to the next. During the requirements specification phase, I determined the goal and conceptual design of the site as well as the type of user who would most benefit from access to the Website. I made a hand sketched draft design on paper of my perception of the Website layout as well as the layout for each page associated with the site. Additionally, I sketched the database schematics and the layout of the database tables. In phase 2, I collected the requirements for the targeted user type such as features that would cause them to want to return to the site. During implementation and integration, I made decisions in regard to the site's URL (uniform resource locator) also known as the web address who would host it, as well has how the Website would integrate with the database. I had previously used the CS suite; however, I had to familiarize myself with the current version of CS. After that, I commenced code design within Dreamweaver IDE.

In the testing phase, I checked each code to ensure that it was worked properly as well as ensuring that the newly registered domain name was fully functional and ensured that the URL format was correct. During the deployment phase, I moved all of the codes from my personal computer, which is where the development took place, to the Bluehost Website via FTP. The maintenance phase is the last in the waterfall model. During this phase, I periodically evaluated the Website. However, maintenance is a

continuous effort that can include accepting user feedback to determine if the site is meeting the users' needs and whether improvements should be made.

Event processing for access to this Website is as follows:

- The user's Web browser requests the Web page
- The user types in the address to the browser
- The browser sends a request to the Domain Name Server (DNS) to locate the IP address for the Website's server
- The DNS searches its list of hosts on the Internet to find a match to the domain and server the user typed
- Upon the location of a corresponding match the IP address is returned to the browser, which then sends a request, using that IP address, for the specific page
- The Web server sends the contents of the page to the browser
- The Web server is software that serve as an engine that runs a Website
- This takes place via a Web listener that accepts non-encrypted (HTTP) and encrypted (HTTPS) connections from browsers
- The server also invokes software that executes processes like database interactions, such as requests or inputs and, in return, generates the HTML file(s)
- The application server is a software framework that serves somewhat like middleware, or software that supplies services to the developer, such as input/out and interactions, that are unavailable from the operating system

- This software is in the middle between the operating system and external resources like the database management system, the internet services, and the user applications
- The application server sends requests to the database server that arise from either the front-end that runs on the user's computer that presents the data or the back-end that runs on the server and actually carries out the tasks to process requests like input/out, queries, and operations

Although not in the case of this research, on a larger scale a data warehouse database supports large scale databases that support complex processing, workload management, and data partitioning. These data warehouse databases are frequently updated through batch processing that typically occurs overnight. If the overall Translating Time Project grows, a data warehouse may become a viable data processing option. This process is commonly referred to using a client-server model. The browser begins reading the page, interpreting and/or parsing it and converting it to a displayed page, which is also known as rendering. If there is a stylesheet or an image linked from the page, the server sends a request to the browser to render or return that item also. The server creates the Web page, and, upon completion, the server sends the Web page back to the requestor. A depiction of this process flow is shown in Figure 3-4.

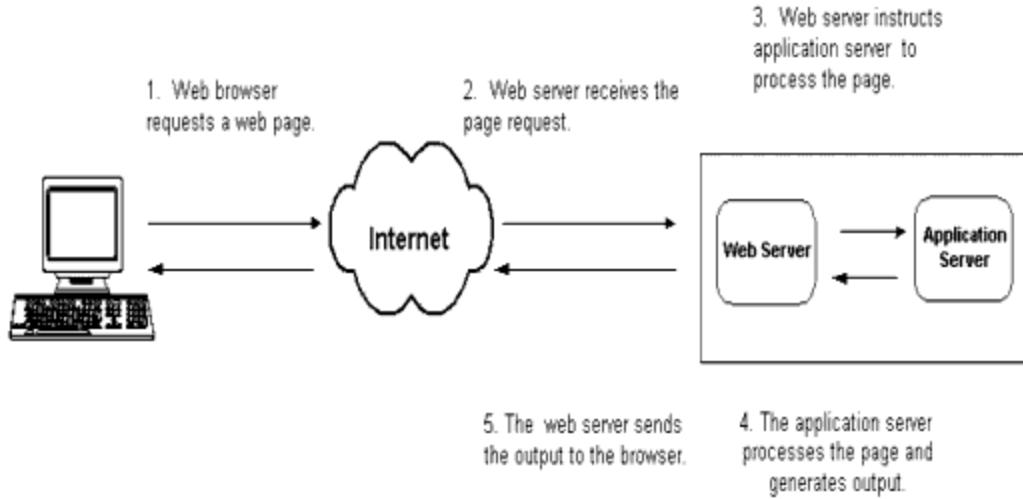


Figure 3-4: Web Server Processes

MySQL Setup

The MySQL Workbench had to be configured in order to make a new database connection. Click on New Connection to create a unique database connection for usage with the Website. Next, double click on the new connection to launch the SQL Editor, which is an “intellisense”-enabled database query tool. Click under Server Administration to manage the (new) instance of the server running on Bluehost. Provide a name of the server instance to manage and double click on the new server to begin managing the instance. Bluehost maintains SQL Server database engines, which have their own set of system and user databases that are not shared amongst instances. Web browsers process HTML, hence the operating system that a Web server runs on is irrelevant. In order to query a database, a connection to the database must be made and tested. After which one can build the SELECT statement(s) and perform the query. Once the query results are returned they can be displayed in the user’s Web page.

Deploying a Website Using Dreamweaver

When using the Dreamweaver IDE to deploy a Website, a local site to house all of the files for the Website must first be created. The local site resides in a local root folder that was on my computer's hard drive. Creating all of the files locally allowed me the opportunity to define and test the Web pages prior to uploading to the remote server at Bluehost. I accessed the Bluehost server remotely because it would host my Website on its servers although it is not directly connected to my computer which houses my local site. Upon gaining access to Bluehost, I set the Site Definitions under the Advanced tab of the dialog box by selecting the Remote Info category to define my remote site. Additionally, I selected the FTP option in the Access drop down box. This is where I set up the FTP host, host directory, and login information such as my ID and password. After that, I used the Put Files(s) button located in the Files panel to transfer the files to the Web via Bluehost. After a site is published to the Bluehost server, it is technically known as a remote site.

The capability through Dreamweaver is provided to do a Get File(s) operation, to transfer files from the remote server back to my local computer, to Check Out File(s), to Check In File(s), and to Synchronize the files. If this were a collaborative effort, the file check in command would be extremely important because a check out means "I am modifying this file so don't use." When a person checks a file out, that person's name appears on the Files panel next to a red check mark. If not checked out a green check mark is shown by the file's icon. Likewise, a file that has been checked in after editing is available for collaborators to check out and edit. However, when a file has been checked in after editing, the local version becomes read only and the lock

symbol shows beside it to prevent someone from making changes to what might no longer be the current common (remote) version. However, since I was the only person working on this site, the Put and Get commands were sufficient and I did not have the check files in or out. In Dreamweaver, the synchronization feature helped me keep the corresponding files on the server and the files on my local computer up to date and prevented me from accidentally updating out of date files. It is important to note Dreamweaver cannot make checked in or checked out files read-only on the remote server. When using an application other than Dreamweaver, checked out files might be overwritable on the server.

Adobe Photoshop was used to create the logo header image for the Website. During the planning phase, I determined the image size to be 960 x 90 pixels in width and height, respectively. I downloaded images from the internet for each of the 10 species utilized for this research except for the Homo Sapiens, for which, I used a photo of myself. I cropped the eyes from each image and imported it into Photoshop by creating a new layer for each component of the picture that I was constructing. This was important so that I could move and edit the images independently. Each time I imported a new image I added an ‘empty’ layer to my picture by clicking the Create New Layer button from the Layers dialog. I manipulated the layers until each image was placed precisely on the picture, then added layer styles and effects, which were applied to the content of the layers. I set the background layer of the picture as well as the text prior to saving. Upon completion, I added the custom logo to the Website layout via Dreamweaver as shown below in Figure 3-5.

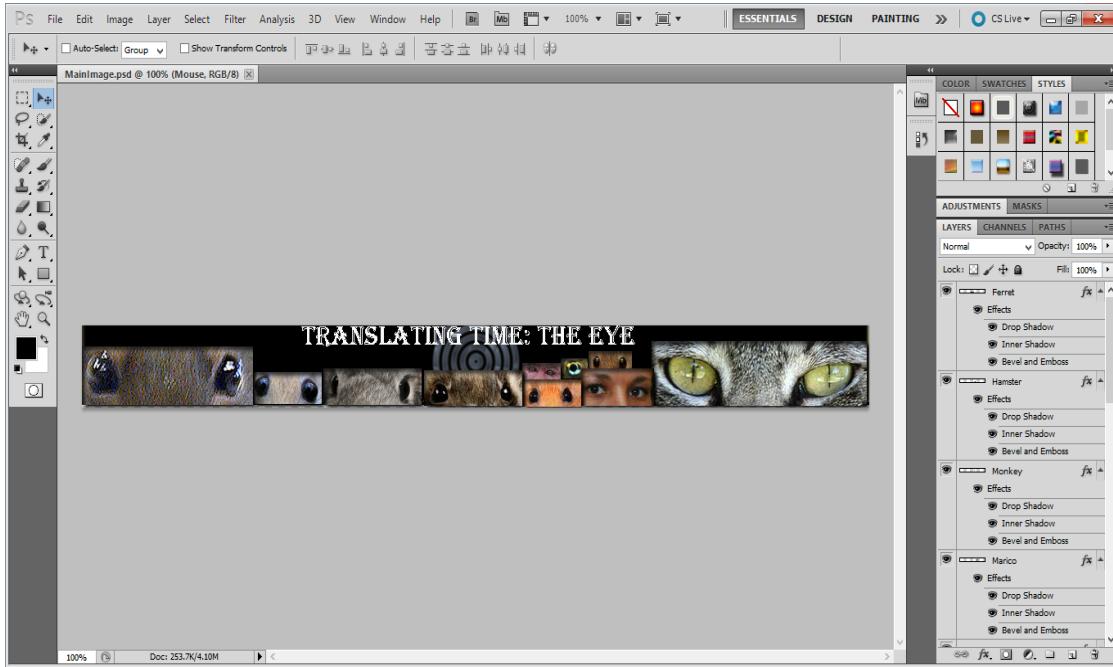


Figure 3-5: Web Site Logo created in Photoshop

The color schematics of this picture were tied into the color schematics and layout of the Website in my design phase.

3.4.3 Results

The Website has a top-down hierarchy whereby the homepage is at the top because it is the main entry point to the site. The site navigation status is displayed on each page so that users know their current location in the overall structure of the Website and where they can go from their current location in the Website. This is accomplished with textual navigation links displayed on the navigation bar to the left-hand side of each page. If the user wants to know which page(s) they have visited on the site, the site was designed such that the text of visited links is shown in blue while the color of active links, pages that have not been visited, is green with a gray background on the navigation bar and gray elsewhere in the page(s). This blue color allows the user to know they have already clicked on this link. Most browsers provide

built-in history features that allow users to see the page(s) which they have visited. If the user is viewing a certain page, the link to that page is not shown on the site navigation bar. This helps the user to know where they can go within the site from the current page. The user can navigate from any Web page shown below in Figure 3-6 with the exception of the Survey page, which allows navigation to SurveyMonkey, an external site and the BINF Program page, which links to the UAMS/UALR Joint Bioinformatics Program page. Because both of these pages are external to this site, the user must click the browser's Back button to navigate back to the Website. There are 8 pages in this Website, 7 of which are HTML files and 2 of which are PHP files. The html files included in this Website are index.html, ttacrossmammilianspecie.html, eye.html, aboutautho.html, survey.html, and references.html. The PHP files included in the Website are semiautomatedlitrev.php and geneontology.php.

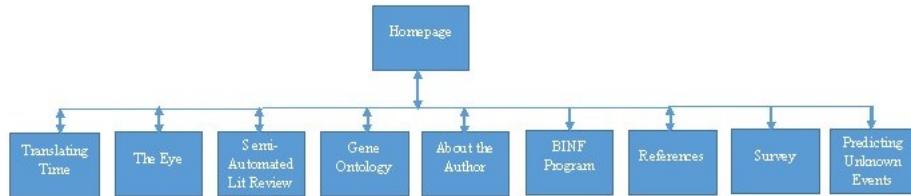


Figure 3-6: Web Site Page Layout

The HTML files are static, so the content does not change; however, the PHP files are dynamic and they are rendered based on the information returned from the database query. Static pages provide better control over page aesthetics. It allowed me to fix the width of the pages, for example, whereas dynamic pages are more fluid: The page content is subject to change based on the database request and the amount of data

that is returned by the query. With dynamic pages it is quite easy to distinguish the static page content from the content that forms the result of the query. The table showing the species name, development event, and author in the semiautomatedlitrev file is dynamic and all other information is static. The geneontology.html page links to the Genes Database from NCBI and GeneCards. In the event that I decide to revise any of this information in the future, I created this page as a PHP page. Therefore, future modification will not require much rework. The pages for this site are shown below in Figures 3-7 through 3-15 and the code is shown in Appendix D. The questionnaire for the online Website survey is shown in Figure 3-28. It is not functional and the visitor is not required to fill out the questionnaire. No data is stored from the questionnaire. The registered domain name for this Website is <http://www.translatingtimetheeye.net>.

TRANSLATING TIME: THE EYE

Overview

The overall objective of this dissertation is to gain an understanding of the timing of human and animal eye development events. This is expected to eventually enable improvements in diagnostic and intervention capabilities for human diseases involving the eye. It is useful to understand eye development in animals because, as model organisms, the knowledge obtained through the study of these organisms can help us better understand humans. The conservation of pathways and genetic material in the development process allow us to compare human development with those of the model organisms. We, as researchers, rely on knowledge gained from other organisms as well as organism from the same species. This knowledge leads to research and ultimately medical decisions that will increase the ability to treat and prevent much human illness. Use of model organisms makes it possible to do research that would be ethically unacceptable in humans.

Specific research, that forms the foundation upon which the present research builds, developed a mathematical model of neurodevelopment (Clancy et al., 2007) based on nine eutherian mammals: *Felis domestica* (cat), *Mustela putorius furo* (ferret), *Mesocricetus auratus* (hamster), *Macaca mulatta* (monkey), *Homo sapiens* (human), *Mus musculus* (mouse), *Oryctolagus cuniculus* (rabbit), *Rattus norvegicus* (rat), and *Acomys cahirinus* (spiny mouse). The original intent of the mathematical model was to create, on the one hand, a scale showing a sequence of neurodevelopmental events and mapping them to numbered values, and on the other hand, a scale of species along which species that develop quickly are mapped to low numbers and species that develop slowly are mapped to high numbers. This permitted the two values, developmental event and species scores, to be combined to infer the time of an unscored event in a specified species. This helps in the

Figure 3-7: Home Page



TRANSLATING TIME: THE EYE

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Development of the Eye – Selected Highlights

The eye is the foundation of the visual system in humans. Its main purpose is to detect and analyze light. The eye connects via the optic nerve to the brain. The cornea and the sclera form the outer layer of the eye. The iris and ciliary body form the middle layer. The retina forms the inner layer. This is a summary of the major structural components of the eye (Figure 4) (Bear, Connors, & Paradiso, 2000). As with numerous other organs, the eye develops as a product of complex interactions of primitive cells during embryogenesis (Barishak, 2001). On day 22 of embryogenesis (day E22) the developing eyes emerge as a pair of willow grooves, the optic sulci, on each side of the forebrain as the neural tube closes. The neural tube is a tube that is formed in mammalian embryos by the closure of ectoderm tissue, which is the precursor to the central nervous system that develops into the brain and the spinal cord. These willow grooves form the optic vesicles, and come in contact with surface ectoderm, which is essential for lens formation. Then the lens vesicles form, followed by the choroid, sclera, and cornea. The formation of the eye begins around week 3 and has ceased by week 8. The eyes are functional between months 5 and 7 of fetal development (Gross, Blechinger & Achtner, 2008; Nguyen & Arnhieter, 2000).

The vertebrate eye consists of tissues from distinctive embryonic origins. For example, the lens and the cornea are derived from the surface ectoderm while the retina and the epithelial layers of the iris as well as the ciliary body are derived from the anterior neural plate or neuroectoderm. The different eye components are formed as a consequence of well-timed actions of transcription factors and inductive signals (Schoenwolf et al. c, 2008;

Figure 3-8: The Eye Page



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Translating Time Across Mammalian Species

The overall objective of the translating time project has been to gain understanding of human neurodevelopmental events such that improvements could be made to diagnostic and intervention capabilities (DeFelici, 2001). The original generic mammalian model included nine eutherian mammals: *Felis domesticus* (cat), *Mustela putorius furo* (ferret), *Mesocricetus auratus* (hamster), *Macaca mulatta* (monkey), *Homo sapiens* (humans), *Mus musculus* (mouse), *Oryctolagus cuniculus* (rabbit), *Rattus norvegicus* (rat), and *Acomys cahirinus* (spiny mouse). The original intent of the statistical model (Raz, 2004) was to create, on the one hand, a scale of developmental events such that early events score low and later events score high, and on the other hand, an additional scale of species where fast-developing species score low and slow-developing species score high. Therefore the two scores, of event and of species, could be combined to infer the time of an event in a specified species based on other event times and other species.

Neural developmental events are associated with data comprised of onsets, peaks, and tails of neurogenesis related to neuronal structures, which include but are not limited to associated neuronal death and components of process maturation. A constant k in the mathematical model accounted for events such as implantation, blastulation, and differentiation of the primitive germ layers that were found to be consistent across tested mammals. A value of 5.37 was found for constant k , as shown below in Equation 1.

Equation (1)
$$Y = \ln (day - k)$$

Figure 3-9: Translating Time Page



TRANSLATING TIME: THE EYE

About the Author

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EDUCATION

M.S. Bioinformatics, University of Arkansas for Medical Sciences and University of Arkansas at Little Rock
M.S. Computer Science, Johns Hopkins University
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EXPERIENCE

2005-09 University of Arkansas at Little Rock, Little Rock, AR
Faculty, Department of Information Science (IFSC)

- Taught material from approved curriculum and developed daily lesson plans to include instructional aids
- Participated in school retention initiatives
- Motivated students to actively participate in all aspects of the educational process
- Participated in the ABET accreditation process
- Completed professional development and in-service activities in accordance with college standards
- Maintained expertise in subject area and recommends improvements in curriculum design
- Assisted in the department in obtaining ABET accredited, which will be effective through September 30, 2010
- Participated in core course academic support programs, certification programs, and

Figure 3-10: About the Author Page



TRANSLATING TIME: THE EYE

Semi-Automated Literature Review

The aim of this portion of the project is to design, implement, utilize, and validate a tool, which provides a semi-automated approach to literature review of eye-related developmental events. The *Danio rerio* (zebrafish) will be included in this evaluation of the literature because it is considered model organism for research in eye development. WebCrawler is the name coined for the tool, which allows researchers to search online journals with keywords and/or phrases related to eye development. Through this and other methods utilized the user has the capability and to view the keyword(s) in a context of 3 lines prior to and three lines after the designated word(s), for example. Therefore, allowing the researcher to ability to decipher whether or not the article should be downloaded for further review.

This document analysis provides method of grouping they keywords or phrases such that the 3 lines prior to and the three lines after the keywords can be view as a paragraph allowing the researcher to view the context of the words without the hassle of downloading the entire document only to learn that it is irrelevant to the research. This process can be more generally referred to as text mining wherein the tool looks for patterns across the entire document via a parsing method. Parsing separates the keywords or phrases in the document analysis can cut back on the time it would take to actually download each document and read them without knowing the context of the article. The more general intended result is for literature searches to take less human effort, resulting in shorter times in finding articles applicable to research on a given topic.



Figure 3-11: Semi-Automated Literature Review Page



Gene Ontology

The aim of this portion of the project is to determine the Gene Ontology annotations associated with constructed data set on eye development events. Originally, Bioconductor was utilized to incorporate gene expression for eye development events. It makes available tools for the understanding and examination of high-throughput genomic data in an open source environment. To achieve such functionality, Bioconductor uses the R statistical programming language for Bioinformatics development. Bioconductor was developed for use with the R language and is publicly available through the CRAN R package repository. Bioconductor is open-source software that is freely available at <http://www.bioconductor.org/>.

It contains readily available packages to access gene expression and ontology data. Gene Ontologies (GO), Chromosome Maps, KEGG Pathway Analysis, and Phylogenetic Analysis are a few of the Bioconductor packages. Capabilities within the GO package include the ability to access the gene identification, the gene term, and ontology type from the Gene Ontology web site or a local file. The Gene Ontology project maintains on its Web site a standardized representation of gene and gene product attributes across species and databases. The map viewer utilizes a method to select an organism and manipulate an organism-specific global map. KEGG (Kyoto Encyclopedia of Genes and Genomes) is another bioinformatics online tool. It is comprised of online database resources supporting searches relating to genomes, biological chemicals and enzymatic pathways. Pathway development permits queries based on 3 distinct categories: systems, genomic, and chemical information.

Figure 3-12: Gene Ontology Page



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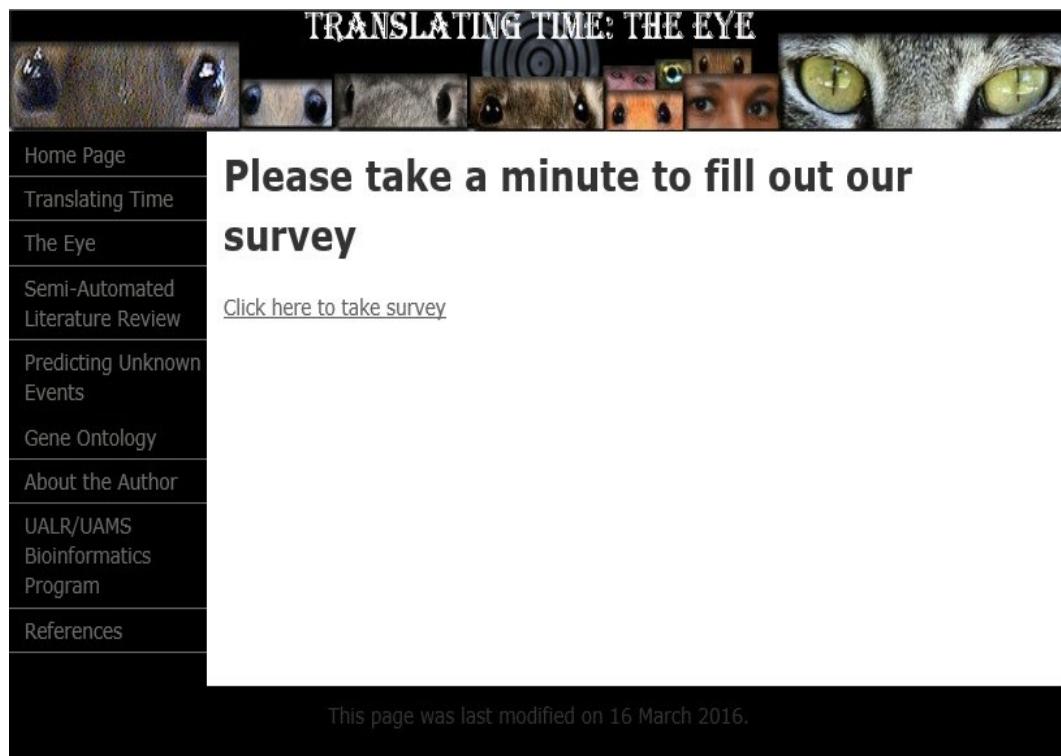


Figure 3-13: References Page

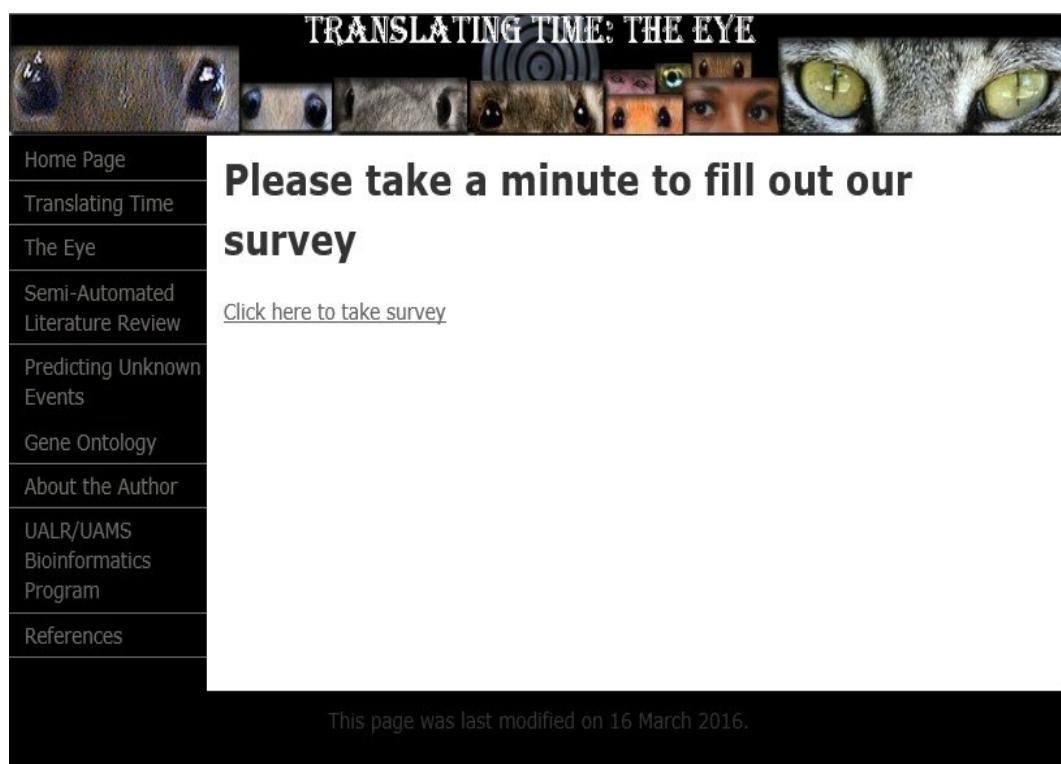


Figure 3-14: Survey Page



PREDICTING UNKNOWN EVENTS

Predicting Unknown Events

The main objective for this portion of my dissertation was to utilize the data points extracted from the literature in an effort to make predictions about missing data for the selected organisms. Additionally, I would also prove or disprove whether or not the Zebrafish, the "model organism for eye development," develops in conformance to the model and thus is a viable species to add to the data for this research. Future researchers may wish to apply this method to other parts of organisms, other species, and other wet lab experimental data points. Making this data and methods publically available can make it possible for scientist to further expand this research. In addition it can preserve valuable research time by lessening the need to learn to use software packages such as Minitab, SAS, and SPSS, all of which perform multiple variable regression analysis. Upon completion of the initial analysis, successful data prediction for missing data points was achieved. The data prediction analysis has been automated for ease of use and to cut back on errors caused by hand calculations.

The analysis was begun using a k value of 8.49 as an initial test. Holding k at 8.49 yielded a RMS value of more than .722. This was obtained by manually iterating through the process of finding the best species scale and event scale values for that value of k . One iteration involved clicking first on the *optimize species values* button, then the *apply best sp* button, then *optimize event values*, and finally *apply best ev*. It was found that by running 6 iterations the optimal species scale and event scale values had settled close to a fixed point, in that the lowest RMS value did not change at the 3 decimal digit precision point when the 7th iteration was run. This resulted in the RMS = .480.

Figure 3-15: Predicting Unknown Events Page

Translating Time: The Eye Website Survey

1. How often do you visit this site?

- Every day
- Several times a week
- About once a week
- Several times a month
- About once a month
- Less than once a month
- This is my first visit here

2. How likely are you to return to this Web site?

- Very Likely
- Very Likely
- Somewhat Likely
- Somewhat Unlikely
- Not At All Likely

3. How likely are you to recommend this Web site to others?

- Extremely likely
- Very likely
- Moderately likely
- Slightly likely
- Not at all likely

4. What features influenced your decision to continue using this website?

5. What is it about this site that you would most like to see improved?

6. What changes or additional features would you suggest for this website?

7. How did you first hear about this site?

- Search engine
- Another web site
- Friend or business associate
- Don't know/don't remember

Other (please specify)

Figure 3-16: Web Site Questionnaire

3.4.4 Discussion

The software design and development process worked as expected. I developed a Website for sharing the data and methods used for predicting eye development events for selected placental mammals. The Gene Ontology annotations associated with the data set on the eye development events is also available on the Website. Additionally, I have made available to users the necessary information to replicate the work on another suitable computing environment in this document. In doing so I explained the necessary steps and provided a compressed file of the code that I used to perform my research is also on the Website. Users will find the code for the WebCrawler of particular interest because this tool can be used for more general searches. Users can search online journals with the WebCrawler using keywords and/or phrases related to their desired research topics. The WebCrawler takes less time to search journals, books, and reference by previewing the material using keywords that allow the user can observe whether or not the article contains information relative to the search topic.

The Website has a user interface as the frontend for user interaction to a database on the backend, which serves as a repository to populate the user interface. Using existing Web development tools proved to be valuable because I was able to choose from the Website templates and use autogenerated code that came with the chosen template, while also using the code editor to make changes to the source code. Static and dynamic Web pages where generated during this section of my research because each type of page serves different purposes. Dynamic pages are not actually created until the Web page is requested. When the request is made, the web server makes a determination as to whether or not the page is static or dynamic based on the

file's extension, for example, .php or .html. I was developed the site locally and deployed it to the Web host so that it could be publicly available. I also made use of a domain name and a Web hosting provider for their hosting services such as access to MySQL Server. Since the eye is so closely related to the brain, the eye is sometimes considered to be a part of the brain. This project investigated eye development events as they relate to neurodevelopment as well as eye development events relating this research. I have concluded that this model is novel for eye development. It works to some degree but it is not perfect particularly for the model organism for eye development, the zebrafish. Researchers should continue to look at additional organs in an effort to understand which organs will or will not fit the model so that we can continue to expand our knowledge on translating time amongst species. Thus, providing medical professionals the necessary information to know when a procedure on organ can be performed in the womb.

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Appendix A: Web Crawler Source

FileChooser.java

```

/*
 * Marico Howe
 * File Name: FileChooser.java
 * Description: The purpose of this class is to provide the user with the mechanism
 * to choose a file. The user's home directory is starting point.
 */

package All_Purpose;

import java.io.File;
import javax.swing.JFileChooser;

public class FileChooser extends javax.swing.JFrame {

    /* Creates new form FileChooser */
    public FileChooser() {
        initComponents();
    }

    /* This method is called from within the constructor to
     * initialize the form.
     * WARNING: Do NOT modify this code. The content of this method is
     * always regenerated by the Form Editor.
     */
    @SuppressWarnings("unchecked")
    // <editor-fold defaultstate="collapsed" desc="Generated Code">
    private void initComponents() {

        jFileChooser1 = new javax.swing.JFileChooser();

        setDefaultCloseOperation(javax.swing.WindowConstants.EXIT_ON_CLOSE);

        jFileChooser1.addActionListener(new java.awt.event.ActionListener() {
            public void actionPerformed(java.awt.event.ActionEvent evt) {
                jFileChooser1ActionPerformed(evt);
            }
        });

        javax.swing.GroupLayout layout = new
        javax.swing.GroupLayout(getContentPane());
        getContentPane().setLayout(layout);
        layout.setHorizontalGroup(
            layout.createParallelGroup(javax.swing.GroupLayout.Alignment.LEADING)
            .addGroup(layout.createSequentialGroup()
                .addContainerGap()
                .addComponent(jFileChooser1, javax.swing.GroupLayout.DEFAULT_SIZE, javax.swing.GroupLayout.DEFAULT_SIZE, javax.swing.GroupLayout.PREFERRED_SIZE)
                .addContainerGap())
        );
        layout.setVerticalGroup(
            layout.createParallelGroup(javax.swing.GroupLayout.Alignment.LEADING)
            .addGroup(layout.createSequentialGroup()
                .addContainerGap()
                .addComponent(jFileChooser1, javax.swing.GroupLayout.DEFAULT_SIZE, javax.swing.GroupLayout.DEFAULT_SIZE, javax.swing.GroupLayout.PREFERRED_SIZE)
                .addContainerGap())
        );
    }
}

```

```

        layout.setHorizontalGroup(
            layout.createParallelGroup(javax.swing.GroupLayout.Alignment.LEADING)
                .addGroup(layout.createSequentialGroup()
                    .addContainerGap()
                    .addComponent(jFileChooser1,
                        javax.swing.GroupLayout.PREFERRED_SIZE, 582,
                        javax.swing.GroupLayout.PREFERRED_SIZE)
                    .addContainerGap(javax.swing.GroupLayout.DEFAULT_SIZE,
                        Short.MAX_VALUE))
            );
        layout.setVerticalGroup(
            layout.createParallelGroup(javax.swing.GroupLayout.Alignment.LEADING)
                .addGroup(javax.swing.GroupLayout.Alignment.TRAILING,
                    layout.createSequentialGroup()
                        .addComponent(jFileChooser1,
                            javax.swing.GroupLayout.PREFERRED_SIZE, 397,
                            javax.swing.GroupLayout.PREFERRED_SIZE)
                        .addContainerGap(javax.swing.GroupLayout.DEFAULT_SIZE,
                            Short.MAX_VALUE))
            );
    }

    pack();
}// </editor-fold>

```

```

private void jFileChooser1ActionPerformed(java.awt.event.ActionEvent evt) {

}

/*
 * @param args the command line arguments
 */
public static void main(String args[]) {
    java.awt.EventQueue.invokeLater(new Runnable() {
        public void run() {
            new FileChooser().setVisible(true);
        }
    });
}

// Variables declaration - do not modify
private javax.swing.JFileChooser jFileChooser1;
// End of variables declaration

}

```

HoweFileReader.java

```

/*
 * Marico Howe
 * File Name: HoweFileReader.java
 * Description: The purpose of this class is to read through the HTML source code
 * that was already downloaded
 */

package All_Purpose;

import java.io.*;
import java.util.Vector;

public class HoweFileReader {

    public int loopCounter = 0, tempCounter = 0, totalFilesFound = 0, overallCounter = 0,
    a = 0;
    public static Vector wholeDirectory = new Vector();

    public String fileLocation = null;
    public Integer overallFileCounter = 0;

    public Vector adjustedInformation = new Vector();
    public Vector fileLineData = new Vector();
    public static PrintWriter pw;
    public String singleString = " ";

    public Vector agricolaLinks = new Vector();
    public Vector searchResults = new Vector();
    public String[] tempTester = new String[52];

    /*
     * @param fileDirectory is the directory and file that will be read into the vector
     *
     * @see The file will be put line by line into a Vector
     */
    public void MyFileReader2(String fileDirectory){

        try{
            FileReader fread = null;
            BufferedReader bread = new BufferedReader(new FileReader(fileDirectory));

            String line;

```

```
        while((line=bread.readLine())!=null){
            fileLineData.add(line);
        }
        bread.close();
        fread.close();
    }

    catch(Exception e){
        System.out.println("Exception: " + e);
    }
}

/*
 * @see This method println's one vector
 */
public void printFileData(){

    for(int vectorIndex = 0; vectorIndex < fileLineData.size(); vectorIndex++){

        System.out.println( (String) fileLineData.elementAt(vectorIndex));

    }
}

/*
 * @see This makes the fileLineData vector into one large string
 */
public void saveToString(){

    for(int vectorCounter = 0; vectorCounter < fileLineData.size(); vectorCounter++){
        singleString += fileLineData.elementAt(vectorCounter).toString();

    }
}

public void lineCounter(){
    System.out.println(Integer.toString(fileLineData.size()));

}

}
```

HoweFileWriter.java

```

/*
 * Marico Howe
 * File Name: HoweFileWriter.java
 * Description: The purpose of this class is to store methods for the file writer
 */

package All_Purpose;

import java.io.FileWriter;
import java.io.IOException;
import java.io.PrintWriter;
import java.util.Vector;
import java.util.logging.Level;
import java.util.logging.Logger;
import webcrawlingrevised.InformationModule;

public class HoweFileWriter {

    public PrintWriter pw;

    public void writeSimpleSearchSaveFile(Vector unsearched, Vector searched, String saveDirectory){

        try{
            pw = new PrintWriter(new FileWriter(saveDirectory), true);

            pw.println("<html>");
            pw.println(" ");
            pw.println("<search term>");
            pw.println(InformationModule.searchQuery);
            pw.println("</search term>");
            pw.println(" ");
            pw.println("<unsearched list>");

            for(int i = 0; i < unsearched.size(); i++){

                pw.println(InformationModule.scienceDirectUnsearchedLinks.elementAt(i).toString());
            }

            pw.println("</unsearched list>");
            pw.println(" ");
            pw.println("<searched list>");

            for(int c = 0; c < searched.size(); c++){

```

```
pw.println(InformationModule.scienceDirectSearchedLinks.elementAt(c).toString());
    }

    pw.println("</searched list>");
    pw.println(" ");
    pw.println("</html>");

    pw.close();

}catch(Exception e){

}

Runtime.getRuntime().gc();
System.gc();
}

public void FileWriterString(String saveDirectory, String information){

try{

    pw = new PrintWriter(new FileWriter(saveDirectory), true);
    pw.println(information);

    pw.close();

}catch(IOException e){e.printStackTrace();}

}

public void FileWriterVector(String saveDirectory, Vector information){

try{

    pw = new PrintWriter(new FileWriter(saveDirectory), true);

    for(int index = 0; index < information.size(); index++){
        pw.println(information.elementAt(index));
    }

    pw.close();

}
```

```
 }catch(IOException e){e.printStackTrace();}

}

public void TransferMassNumberFiles(String saveDirectory, Vector information, int
count){

try{

pw = new PrintWriter(new FileWriter(saveDirectory), true);

for(int index = 0; index < information.size(); index++){
    if(information.elementAt(index).toString().contains("<File Name>")){
        pw.println(information.elementAt(index));
        pw.println(Integer.toString(count) + ".html");
        index++;
    }
    else{
        pw.println(information.elementAt(index));
    }
}

pw.close();

}catch(IOException e){e.printStackTrace();}

}

}
```

URLTester.java

```

/*
 * Marico Howe
 * File Name: URLTester.java
 * Description: The purpose of this classs is to take a URL string passed into
 * the method and a Directory to save the information to and it will save the
 * HTML source code to that directory.
 */

package All_Purpose;

import java.net.*;
import java.io.*;

public class URLTester{

    private static URL location;

    public void visitWebPage(String webPage, String saveDirectory){

        try {location = new URL(webPage);}
        catch(MalformedURLException e)
        {System.err.println ("Invalid URL: "+location);}

        InputStream myInput;
        BufferedReader dataInput;
        String lineOfText;
        PrintWriter pw;

        try {
            myInput = location.openStream();
            dataInput = new BufferedReader(new
                InputStreamReader(myInput));

            pw = new PrintWriter(new FileWriter((saveDirectory)), true);

            pw.println("This is the " + webPage + " file");

            pw.println(dataInput.readLine());

            while
                ((lineOfText = dataInput.readLine())
                != null) pw.println(lineOfText);

            pw.close();
        }
    }
}

```

```
    dataInput.close();
    myInput.close();
}

catch(IOException e){
    System.out.println("oops!!!!!");
    System.out.println("Exception: " + e.toString() );
}
}
```

OverviewThread.java

```

/*
 * Marico Howe
 * File Name: OverviewThread.java
 * Description: The purpose of this class is run the overall search and to
 * determine the selection(s) for crawling
 */
package Threads;

import java.util.logging.Level;
import java.util.logging.Logger;
import webcrawling.Interfaces.Interface;

public class OverviewThread extends Thread{

    /*
     * @serialField This lets the OverviewThread know that the search is complete and
     * constant change of the GUI is no longer needed.
     */
    public static boolean searchComplete = false;

    public void run(){

        Interface openingWindow = new Interface();

        openingWindow.jCBoxScienceDirectFirstThousand.setVisible(false);
        openingWindow.jCBoxScienceDirectLoad.setVisible(false);
        openingWindow.jCBoxScienceDirectSaveFile.setVisible(false);
        openingWindow.jCBoxScienceDirectComplete.setVisible(false);

        openingWindow.jScienceDirectSpinner.setVisible(false);
        openingWindow.jLblScienceDirectSpinner.setVisible(false);

        openingWindow.setVisible(true);

        do{

            this.ScienceDirectCheckboxes();

            try {
                this.sleep(1000);
            } catch (InterruptedException ex) {
                Logger.getLogger(OverviewThread.class.getName()).log(Level.SEVERE, null,
                ex);
            }
        }
    }
}

```

```

        }while(searchComplete == false);

    }

/*
 * @see This method changes all the check boxes in the GUI based on what is
currently selected.
*/
public void ScienceDirectCheckboxes(){

    if(Interface.jBoxScienceDirect.isSelected() != true){

        Interface.jCBoxScienceDirectFirstThousand.setVisible(false);
        Interface.jCBoxScienceDirectLoad.setVisible(false);
        Interface.jCBoxScienceDirectSaveFile.setVisible(false);
        Interface.jCBoxScienceDirectComplete.setVisible(false);

        Interface.jScienceDirectSpinner.setVisible(false);
        Interface.jLblScienceDirectSpinner.setVisible(false);

        Interface.jCBoxScienceDirectFirstThousand.setSelected(false);
        Interface.jCBoxScienceDirectLoad.setSelected(false);
        Interface.jCBoxScienceDirectSaveFile.setSelected(false);
        Interface.jCBoxScienceDirectComplete.setSelected(false);
    }
    else if(Interface.jBoxScienceDirect.isSelected() == true){

        Interface.jScienceDirectSpinner.setVisible(true);
        Interface.jLblScienceDirectSpinner.setVisible(true);
    }

    if(Interface.jBoxScienceDirect.isSelected() == true &&
       Interface.jCBoxScienceDirectComplete.isSelected() == false &&
       Interface.jCBoxScienceDirectFirstThousand.isSelected() == false
       && Interface.jCBoxScienceDirectLoad.isSelected() == false &&
       Interface.jCBoxScienceDirectSaveFile.isSelected() == false){

        Interface.jCBoxScienceDirectFirstThousand.setVisible(true);
        Interface.jCBoxScienceDirectLoad.setVisible(true);
        Interface.jCBoxScienceDirectSaveFile.setVisible(true);
        Interface.jCBoxScienceDirectComplete.setVisible(true);

        Interface.jCBoxScienceDirectFirstThousand.setSelected(false);
        Interface.jCBoxScienceDirectLoad.setSelected(false);
        Interface.jCBoxScienceDirectSaveFile.setSelected(false);
    }
}

```

```
    Interface.jCBoxScienceDirectComplete.setSelected(false);
}

if(Interface.jCBoxScienceDirectComplete.isSelected() == true){

    Interface.jCBoxScienceDirectLoad.setSelected(false);
    Interface.jCBoxScienceDirectSaveFile.setSelected(false);
    Interface.jCBoxScienceDirectFirstThousand.setSelected(false);

    Interface.jCBoxScienceDirectLoad.setEnabled(false);
    Interface.jCBoxScienceDirectSaveFile.setEnabled(false);
    Interface.jCBoxScienceDirectFirstThousand.setEnabled(false);
}

else if(Interface.jCBoxScienceDirectComplete.isSelected() != true){

    Interface.jCBoxScienceDirectLoad.setEnabled(true);
    Interface.jCBoxScienceDirectSaveFile.setEnabled(true);
    Interface.jCBoxScienceDirectFirstThousand.setEnabled(true);
}

}

}//End of ScienceDirectCheckboxes Method
```

PubMedCentralThread.java

```

/*
 * Marico Howe
 * File Name: PubMedCentralThread.java
 * Description: The purpose of this class is to run the PubMedCentral search
 * as well as reading through the results to get the IDs.
 */

package Threads;

import All_Purpose.HoweFileReader;
import All_Purpose.URLTester;
import java.util.Vector;
import java.util.logging.Level;
import java.util.logging.Logger;
import webcrawling.Interfaces.InterfaceProgress;
import webcrawlingrevised.InformationModule;

public class PubMedCentralThread extends Thread{

    public Vector idTags = new Vector();

    public void run(){

        System.out.println("The Pubmed Central Thread has started");

        //This next portion downloads the first file which gets the Id
        // Tags to download the rest of the files
        URLTester downloader = new URLTester();

        downloader.visitWebPage( InformationModule.pubMedCentral1 +
InformationModule.searchQuery +
                InformationModule.pubMedCentral2, InformationModule.pubMedCentralDir +
"\logfile.txt");

        try {
            this.sleep(1000);
        } catch (InterruptedException ex) {
            Logger.getLogger(PubMedCentralThread.class.getName()).log(Level.SEVERE,
null, ex);
        }
    }
}

```

```

HoweFileReader howeFR = new HoweFileReader();
howeFR.MyFileReader2(InformationModule.pubMedCentralDir + "\\logfile.txt");

boolean foundID = false;

//This reads through the search results and get the ID numbers
for(int a = 0; a < howeFR.fileLineData.size(); a++){
    if(howeFR.fileLineData.elementAt(a).toString().trim().contains("<Id>")){
        idTags.add(howeFR.fileLineData.elementAt(a).toString().substring(
            howeFR.fileLineData.elementAt(a).toString().indexOf(">") + 1,
            howeFR.fileLineData.elementAt(a).toString().lastIndexOf("</")));

        foundID = true;
    }
    else if(foundID == true &&
!howeFR.fileLineData.elementAt(a).toString().trim().contains("<Id>")){
        a = howeFR.fileLineData.size() + 50;
    }
}

howeFR.fileLineData.clear();

/* This is the portion that downloads the files and changes the interface
 * accordingly in real time
 */

InterfaceProgress.jLblOtherSitesFFound.setText(Integer.toString(idTags.size()));
InterfaceProgress.jOtherSitesBar.setMinimum(0);
InterfaceProgress.jOtherSitesBar.setMaximum(idTags.size());

for(int b = 0; b < idTags.size(); b++){
    downloader.visitWebPage(InformationModule.pubMedCentralLinks1 +
idTags.elementAt(b).toString().trim() +
    InformationModule.pubMedCentralLinks2,
InformationModule.pubMedCentralDir + "\\File Pool\\id_" +
idTags.elementAt(b).toString().trim() + ".html");

    InterfaceProgress.jLblOtherSitesFDownloaded.setText(Integer.toString(b + 1));
    InterfaceProgress.jOtherSitesBar.setValue(b + 1);
    InterfaceProgress.jLblOtherSitesAction.setText("Downloading File: " +
idTags.elementAt(b).toString().trim());
}

```

```
try {
    this.sleep(InformationModule.overallWaitTime);
} catch (InterruptedException ex) {
    Logger.getLogger(PubMedThread.class.getName()).log(Level.SEVERE, null,
ex);
}

}

}

}
```

PubMedThread.java

```

/*
 * Marico Howe
 * File Name: PubMedThread.java
 * Description: The purpose of this class is to run the PubMed search
 * as well as reading through the results to get the IDs.
 */

package Threads;

import All_Purpose.HoweFileReader;
import All_Purpose.URLTester;
import java.util.Vector;
import java.util.logging.Level;
import java.util.logging.Logger;
import webcrawling.Interfaces.InterfaceProgress;
import webcrawlingrevised.InformationModule;

public class PubMedThread extends Thread{

    public Vector idTags = new Vector();

    public void run(){

        System.out.println("The Pubmed Thread has started");

        //This next portion downloads the first file which gets the Id
        // Tags to download the rest of the files
        URLTester downloader = new URLTester();

        downloader.visitWebPage( InformationModule.pubMed1 +
InformationModule.searchQuery +
            InformationModule.pubMed2, InformationModule.pubMedDir +
"\\"logfile.txt");

        HoweFileReader howeFR = new HoweFileReader();
        howeFR.MyFileReader2(InformationModule.pubMedDir + "\\"logfile.txt");

        boolean foundID = false;

        //This reads through the search results and get the ID numbers
        for(int a = 0; a < howeFR.fileLineData.size(); a++){

            if(howeFR.fileLineData.elementAt(a).toString().trim().contains("<Id>")){

```

```

        idTags.add(howeFR.fileLineData.elementAt(a).toString().substring(
            howeFR.fileLineData.elementAt(a).toString().indexOf(">") + 1,
            howeFR.fileLineData.elementAt(a).toString().lastIndexOf("</")));

        foundID = true;
    }
    else if(foundID == true &&
    !howeFR.fileLineData.elementAt(a).toString().trim().contains("<Id>")){
        a = howeFR.fileLineData.size() + 50;
    }
}

howeFR.fileLineData.clear();

/* This is the portion that downloads the files and changes the interface
 * accordingly in real time
 */

InterfaceProgress.jLblPubMedFFound.setText(Integer.toString(idTags.size()));
InterfaceProgress.jPubMedBar.setMinimum(0);
InterfaceProgress.jPubMedBar.setMaximum(idTags.size());

for(int b = 0; b < idTags.size(); b++){
    downloader.visitWebPage(InformationModule.pubMedLinks1 +
    idTags.elementAt(b).toString().trim() +
    InformationModule.pubMedLinks2, InformationModule.pubMedDir +
    "\\\File Pool\\id_" + idTags.elementAt(b).toString().trim() + ".html");

    InterfaceProgress.jLblPubMedFDownloaded.setText(Integer.toString(b + 1));
    InterfaceProgress.jPubMedBar.setValue(b + 1);
    InterfaceProgress.jLblPubMedAction.setText("Downloading File: " +
    idTags.elementAt(b).toString().trim());

    try {
        this.sleep(InformationModule.overallWaitTime);
    } catch (InterruptedException ex) {
        Logger.getLogger(PubMedThread.class.getName()).log(Level.SEVERE, null,
ex);
    }
}

```

}

ScienceDirectCompleteThread.java

```

/*
 * Marico Howe
 * File Name: ScienceDirectCompleteThread.java
 * Description: The purpose of this class is to run the complete Science Direct
 * Search. Should download every single journal UALR has access to.
 */

package Threads;

import All_Purpose.HoweFileReader;
import All_Purpose.HoweFileWriter;
import All_Purpose.URLTester;
import java.io.File;
import java.util.Vector;
import java.util.logging.Level;
import java.util.logging.Logger;
import javax.swing.JFileChooser;
import javax.swing.JOptionPane;
import webcrawling.Interfaces.Interface;
import webcrawling.Interfaces.ScienceDirectStatus;
import webcrawlingrevised.InformationModule;

public class ScienceDirectComplete extends Thread{

    public void run(){

        treeBuild(InformationModule.masterLinkList,
        InformationModule.masterNameList);
        System.gc();
        Runtime.getRuntime().gc();

    }

    public void initialSearch(){
        HoweFileReader howeFR = new HoweFileReader();

        ScienceDirectStatus.jBarOverall.setValue(0);

        ScienceDirectStatus.jBarOverall.setMaximum(InformationModule.masterNameList.size());
    }

    for(int a = 0; a < InformationModule.masterNameList.size(); a++){

        ScienceDirectStatus.jBarOverall.setValue(a);
    }
}

```

```

    ScienceDirectStatus.jLblOverallAction.setText("Checking Relavency " +
Integer.toString(a) + " of " +
Integer.toString(InformationModule.masterNameList.size()));

    howeFR.MyFileReader2(InformationModule.baseSaveDirectory +
"\\"CompleteSearch\\Journal Save Files\\" +
InformationModule.masterNameList.elementAt(a).toString().trim() + ".html");

    this.uploadLinks(howeFR.fileLineData,
InformationModule.scienceDirectUnsearchedLinks,
InformationModule.scienceDirectSearchedLinks);

    InformationModule.totalSDFiles +=
InformationModule.scienceDirectUnsearchedLinks.size();
    ScienceDirectStatus.jLblOverallFilesFound.setText("Overall Files Found: " +
Integer.toString(InformationModule.totalSDFiles));

URLTester down = new URLTester();

ScienceDirectStatus.jBarLocal.setMaximum(InformationModule.minimumDownload);
ScienceDirectStatus.jBarLocal.setValue(0);

for(int b = 0; b < InformationModule.minimumDownload ||
InformationModule.scienceDirectUnsearchedLinks.size() < 3; b++){

    ScienceDirectStatus.jBarLocal.setValue(b);

ScienceDirectStatus.jLblLocalAction.setText(Integer.toString(InformationModule.scieenc
eDirectSearchedLinks.size()) +
" of " +
Integer.toString(InformationModule.scienceDirectUnsearchedLinks.size() +
InformationModule.scienceDirectSearchedLinks.size()));

    howeFR.fileLineData.clear();

down.visitWebPage(InformationModule.scienceDirectUnsearchedLinks.firstElement().to
String(),
    InformationModule.baseJournalDirectory + "\\" +
InformationModule.masterNameList.elementAt(a).toString().trim() +
"\\"+ InformationModule.totaldownedSDFiles + ".html");

    howeFR.MyFileReader2(InformationModule.baseJournalDirectory + "\\" +
InformationModule.masterNameList.elementAt(a).toString().trim() +
"\\"+ InformationModule.totaldownedSDFiles + ".html");

```

```

        for(int d = 0; d < howeFR.fileLineData.size(); d++){
            for(int e = 0; e < InformationModule.keywordList.size(); e++){
                if(howeFR.fileLineData.elementAt(d).toString().toLowerCase().contains(
                    InformationModule.keywordList.elementAt(e).toString().trim().toLowerCase() + ".") ||
                    howeFR.fileLineData.elementAt(d).toString().toLowerCase().contains(
                    InformationModule.keywordList.elementAt(e).toString().trim().toLowerCase() + " ") ||
                    howeFR.fileLineData.elementAt(d).toString().toLowerCase().contains(
                    InformationModule.keywordList.elementAt(e).toString().trim().toLowerCase() + "-")){
                    InformationModule.scienceDirectRelavency[a][1]++;
                }
            }
        }

        InformationModule.scienceDirectSearchedLinks.add(InformationModule.scienceDirectU
        nsearchedLinks.firstElement().toString());
        InformationModule.scienceDirectUnsearchedLinks.removeElementAt(0);

        InformationModule.totaldownedSDFiles++;
        ScienceDirectStatus.jLblOverallFilesDowned.setText("Overall Files
Downloaded: " +
        Integer.toString(InformationModule.totaldownedSDFiles));
    }

    if(InformationModule.scienceDirectUnsearchedLinks.size() < 5){
        InformationModule.scienceDirectStatus[a] = true;
    }

    howeFR.fileLineData.clear();
}

}

public void uploadLinks(Vector info, Vector unsearchedLinks, Vector searchedLinks){

    for(int i = 0; i < info.size(); i++){
        if(info.elementAt(i).toString().contains("<unsearched>")){
            for(int h = i + 1; h < info.size(); h++){
}

```

```

        if(info.elementAt(h).toString().contains("</unsearched>")){
            i = h;
            h = info.size() + 50;
        }
        else{
            unsearchedLinks.add(info.elementAt(h).toString());
        }
    }

    else if(info.elementAt(i).toString().contains("<searched>")){
        for(int h = i + 1; h < info.size(); h++){

            if(info.elementAt(h).toString().contains("</searched>")){
                i = info.size() + 50;
                h = info.size() + 50;
                System.out.println("uploaded all the links");
            }
            else{
                searchedLinks.add(info.elementAt(h).toString());
            }
        }
    }
}

public String pullHighestRelavency(Double[][] rating, Vector names){

    int tempPlace = 0;

    for(int a = 1; a < rating.length; a++){

        if(rating[tempPlace][0] < rating[a][0]){
            tempPlace = a;
        }
    }
    InformationModule.placeHolder = tempPlace;
    return names.elementAt(tempPlace).toString();
}

```



```

        firstLink = false;
    // }
    // else if(firstLink == false){
        firstLink = true;
    // }
}

temp = temp.substring(endIndex + 1);
endIndex = 0;
beginIndex = 0;
}
catch(Exception e){
    if(temp.length() > 100){
        temp.substring(90);
    }
}

}while(temp.contains("Volume"));

initial = false;
b = howeFR.fileLineData.size() + 50;

}
}

public void getIssues(Vector volumes, Vector issues){

ScienceDirectStatus.jLblLocalAction.setText("Constructing issue limbs");
ScienceDirectStatus.jBarLocal.setMaximum(volumes.size());
ScienceDirectStatus.jBarLocal.setMinimum(0);
ScienceDirectStatus.jBarLocal.setValue(0);

for(int c = 0; c < volumes.size(); c++){

ScienceDirectStatus.jBarLocal.setValue(c + 1);

URLTester downer = new URLTester();
downer.visitWebPage(volumes.elementAt(c).toString(),
    InformationModule.baseSaveDirectory + "\\CompleteSearch\\Tree Build\\" +
    Integer.toString(InformationModule.treebuilderCounter) + ".html");

InformationModule.treebuilderCounter++;

HoweFileReader howeFR = new HoweFileReader();
}
}

```

```

    howeFR.fileLineData.clear();
    howeFR.MyFileReader2(InformationModule.baseSaveDirectory +
"\\"CompleteSearch\\Tree Build\"+
        Integer.toString(InformationModule.treebuilderCounter - 1) + ".html");

    int beginIndex = 0;
    int endIndex = 0;
    String temp = null;
    String tempLink = null;
    boolean initial = false;

    for(int d = 0; d < howeFR.fileLineData.size(); d++){

        if(howeFR.fileLineData.elementAt(d).toString().contains("volumeIssueHeader") &&
           initial == false){

            initial = true;

        }
        else
        if(howeFR.fileLineData.elementAt(d).toString().contains("volumeIssueHeader") &&
           initial == true){

            temp = howeFR.fileLineData.elementAt(d).toString();

            boolean outIssues = false;
            do{

                try{
                    beginIndex = temp.indexOf("<A HREF=");
                    endIndex = temp.substring(beginIndex).indexOf("</A>") + beginIndex +
4;

                    tempLink = temp.substring(beginIndex, endIndex);
                    if(tempLink.substring(tempLink.indexOf(">"),
tempLink.indexOf("</")).contains(",") &&
                       tempLink.substring(tempLink.indexOf(">"),
tempLink.indexOf("</")).contains("Volume")){
                        issues.add("http://sciencedirect.com" +
tempLink.substring(tempLink.indexOf("") + 1, tempLink.lastIndexOf(""))));
                        System.out.println("Just added issue link: " +
issues.lastElement().toString());
                    }

                }
            }
        }
    }
}

```

```

temp = temp.substring(endIndex + 1);
endIndex = 0;
beginIndex = 0;
}catch(Exception e){
    System.out.println(" ");
    System.out.println("Small problem extracting an issue branch!");
    System.out.println(" ");
    // temp = temp.substring(265);
    if(temp.length() > 270){
        //temp = temp.substring(265);
        System.out.println("not taking chances, just stopping extraction of
Issue links");
        outIssues = true;
        temp = temp.substring(temp.length() - 1);
    }
    else{
        temp = temp.substring(temp.length() - 1);
        outIssues = true;
    }
}
}while(temp.contains("Volume") || outIssues != true);

initial = false;
d = howeFR.fileLineData.size() + 50;

}

try {
    this.sleep(InformationModule.scienceDirectWaitTime);
} catch (InterruptedException ex) {

Logger.getLogger(ScienceDirectComplete.class.getName()).log(Level.SEVERE, null,
ex);
}

}// End of For loops for that particular Volume

}

public void getAbstractLinks(Vector issues, Vector abstracts){

ScienceDirectStatus.jLblLocalAction.setText("Constructing abstract limbs");
ScienceDirectStatus.jBarLocal.setMaximum(issues.size());
ScienceDirectStatus.jBarLocal.setMinimum(0);

```

```

ScienceDirectStatus.jBarLocal.setValue(0);

for(int a = 0; a < issues.size(); a++){

    ScienceDirectStatus.jBarLocal.setValue(a + 1);

    URLTester downer = new URLTester();
    downer.visitWebPage(issues.elementAt(a).toString(),
        InformationModule.baseSaveDirectory + "\\CompleteSearch\\Tree Build\\"+
        Integer.toString(InformationModule.treebuilderCounter) + ".html");

    InformationModule.treebuilderCounter++;

    HoweFileReader howeFR = new HoweFileReader();
    howeFR.MyFileReader2(InformationModule.baseSaveDirectory +
    "\\CompleteSearch\\Tree Build\\"+
    Integer.toString(InformationModule.treebuilderCounter - 1) + ".html");

    int beginIndex = 0;
    int endIndex = 0;
    String temp = null;
    String tempLink = null;
    boolean initial = false;

    for(int b = 0; b < howeFR.fileLineData.size(); b++){

        try{
            if(howeFR.fileLineData.elementAt(b).toString().contains("You are
entitled to access the full text of this document") &&
            !howeFR.fileLineData.elementAt(b).toString().contains("volume issue
header")){
                temp = howeFR.fileLineData.elementAt(b).toString();

                beginIndex = temp.indexOf("<a href=");
                endIndex = temp.substring(beginIndex + 50).indexOf(">") + 50 +
beginIndex - 1;

                abstracts.add(temp.substring(temp.substring(beginIndex).indexOf("") +
1 + beginIndex, endIndex));
                //System.out.println(" ");
                System.out.println("Just added abstract: " + abstracts.lastElement());
            }
        }catch(Exception e){
    }
}

```

```

        }

    }

    try {
        this.sleep(InformationModule.scienceDirectWaitTime);
    } catch (InterruptedException ex) {

        Logger.getLogger(ScienceDirectComplete.class.getName()).log(Level.SEVERE, null,
        ex);
    }
}

public void treeBuild(Vector journalLinks, Vector journalNames){

    /*
     * This loop should download all volume links of the journal, then all
     * issue links and then gather all paperLinks..... Upon gathering all
     * then links it should save the links to a file and then pursue the
     * next journal.
    */
}

Vector volumes = new Vector();
Vector issues = new Vector();
Vector abstracts = new Vector();

ScienceDirectStatus.jBarOverall.setMaximum(journalLinks.size());
ScienceDirectStatus.jBarOverall.setMinimum(0);

for(int a = 0; a < journalLinks.size(); a++){

    boolean journalAlreadyConstructed = false;

    for(int h = 0; h < InformationModule.previouslySavedJournals.size(); h++){

        if(InformationModule.previouslySavedJournals.elementAt(h).toString().trim().equals(
            journalNames.elementAt(a).toString().trim())){

            // JOptionPane.showMessageDialog(ScienceDirectStatus.jBarOverall,
            // "Skipping " + journalNames.elementAt(a).toString().trim() + " b/c we
            already downloaded it!");
        }
    }
}

```

```

        journalAlreadyConstructed = true;
    }
}
if(journalAlreadyConstructed == false){

try{
    ScienceDirectStatus.jBarOverall.setValue(a + 1);
}catch(Exception e){
    ScienceDirectStatus.jBarOverall.setValue(a);
}
ScienceDirectStatus.jLblOverallAction.setText("Constructing Tree: " +
Integer.toString(a + 1) +
" of " + Integer.toString(journalNames.size()));

File ff = new File(InformationModule.baseJournalDirectory + "\\\" +
journalNames.elementAt(a).toString());
ff.mkdir();

URLTester downer = new URLTester();
downer.visitWebPage(journalLinks.elementAt(a).toString(),
InformationModule.baseSaveDirectory + "\\CompleteSearch\\Tree Build\\" +
Integer.toString(InformationModule.treebuilderCounter)+ ".html");

InformationModule.treebuilderCounter++;

this.getVolumes(journalLinks, volumes);
this.getIssues(volumes, issues);
this.getAbstractLinks(issues, abstracts);

/*
 * This for loop looks for abstracts with no http: in them which means
 * they do not need to be downloaded...
 */
for(int h = 0; h < abstracts.size(); h++){

if(!abstracts.elementAt(h).toString().contains("http")){

    abstracts.removeElementAt(h);
    h--;
}

}

InformationModule.totalSDFiles += abstracts.size();

```

```

abstracts.add(0, "<html>");
abstracts.add(1, "<unsearched>");
abstracts.add("</unsearched>");
abstracts.add("<searched>");
abstracts.add("</searched>");
abstracts.add("</html>");

    HoweFileWriter howeFW = new HoweFileWriter();
    howeFW.FileWriterVector(InformationModule.baseSaveDirectory +
    "\\\\" + CompleteSearch\\Journal Save Files\\\" +
    journalNames.elementAt(a).toString() + ".html", abstracts);

}

abstracts.clear();
issues.clear();
volumes.clear();

try {

    this.sleep(InformationModule.scienceDirectWaitTime);

} catch (InterruptedException ex) {

Logger.getLogger(ScienceDirectComplete.class.getName()).log(Level.SEVERE, null,
ex);
}

}

System.out.println(" ");
System.out.println(" ");
System.out.println("Finished creating search tree");

}//End of the loops for that particular journal

}

```

ScienceDirectThread.java

```

/*
 * Marico Howe
 * File Name: ScienceDirectThread.java
 * Description: The purpose of this class is to run Science Direct search with
 * the exception of a "Long" or "Complete" search.
 */
package Threads;

import All_Purpose.HoweFileReader;
import All_Purpose.HoweFileWriter;
import All_Purpose.URLTester;
import java.io.File;
import java.util.Vector;
import java.util.logging.Level;
import java.util.logging.Logger;
import webcrawling.Interfaces.ScienceDirectStatus;
import webcrawlingrevised.InformationModule;

public class ScienceDirectThread extends Thread{

    public static int saveFileCounter = 0;

    public void run(){

        URLTester downloader = new URLTester();

        /*
         * This loop will download each page in the Vector until download is complete
         */
        for(int downloadCount = 0; 0 <
InformationModule.scienceDirectUnsearchedLinks.size(); downloadCount++){
            System.out.println("About to download: " +
InformationModule.scienceDirectUnsearchedLinks.elementAt(0).toString());

            downloader.visitWebPage(InformationModule.scienceDirectUnsearchedLinks.elementAt(0).toString(),
                InformationModule.baseSaveDirectory + "\\" +
InformationModule.searchQuery + "\\Science Direct\\File Pool\\" +
Integer.toString(downloadCount) + ".html");

            InformationModule.scienceDirectSearchedLinks.add(InformationModule.scienceDirectU
nsearchedLinks.elementAt(0).toString());
        }
    }
}

```



```

        (info.elementAt(i).toString().toLowerCase().contains("cat" + " ") ||
        info.elementAt(i).toString().contains("cat" + ".") ||
        (info.elementAt(i).toString().toLowerCase().contains("homo sapiens" + "
        ") ||
        info.elementAt(i).toString().contains("homo sapiens" + "."))
    ){

        beginIndex = info.elementAt(i).toString().indexOf("title=" + "" + "You are
entitled to");

        beginIndex +=
        info.elementAt(i).toString().substring(beginIndex).indexOf("href=");
        beginIndex += 6;

        endIndex = ((info.elementAt(i).toString().substring(beginIndex).indexOf(""))
) + beginIndex;

        tempHyperlinks.add(info.elementAt(i).toString().substring(beginIndex,
endIndex));
    }
}

/*
 * The next 3 For loops just see if there are duplicates of the same URL and if there
 * are not any found then the links are added to the unsearched Vector
 */
for(int i = 0; i < InformationModule.scienceDirectSearchedLinks.size(); i++){

    for(int c = 0; c < tempHyperlinks.size(); c++){

        if(tempHyperlinks.elementAt(c).toString().trim().equals(
InformationModule.scienceDirectSearchedLinks.elementAt(i).toString().trim())){

            tempHyperlinks.removeElementAt(c);
            c--;
        }
        if(c < 0){
            c = 0;
        }
    }

}
for(int i = 0; i < InformationModule.scienceDirectUnsearchedLinks.size(); i++){

```

```

for(int c = 0; c < tempHyperlinks.size(); c++){

    if(c < 0){
        c = 0;
    }

    if(InformationModule.scienceDirectUnsearchedLinks.elementAt(i).toString().equals(
        tempHyperlinks.elementAt(c).toString())){

        //tempTitles.removeElementAt(c);
        tempHyperlinks.removeElementAt(c);
        c--;
    }
}

try{
    for(int cd = 0; cd < tempHyperlinks.size(); cd++){

        InformationModule.scienceDirectUnsearchedLinks.add(tempHyperlinks.elementAt(cd).t
oString());

        InformationModule.scienceDirectUnsearchedTitles.add(tempTitles.elementAt(cd).toStrin
g());
    }
} catch(Exception e){

}
InformationModule.scienceDirectUnsearchedTitles.clear();
}

}//End of ScienceDirectThread Class

```

Interface.java

```

/*
 * Marico Howe
 * File Name: Interface.java
 * Description: (1) The purpose of this class is to provide a GUI that allows the user
 * to select the sites they wish to search, the term they want to search and
 * the directory they wish to save to. (2) A secondary purpose is to start up
 * all the threads that the program will use and go to the second GUI.
 */

package webcrawling.Interfaces;

import All_Purpose.HoweFileReader;
import All_Purpose.HoweFileWriter;
import Threads.PubMedCentralThread;
import Threads.PubMedThread;
import Threads.ScienceDirectThread;
import webcrawling.*;
import java.io.File;
import java.util.Vector;
import javax.swing.JFileChooser;
import javax.swing.JOptionPane;
import webcrawlingrevised.InformationModule;

public class Interface extends javax.swing.JFrame {

    /* Creates new form Interface */
    public Interface() {
        initComponents();
    }

    /* This method is called from within the constructor to
     * initialize the form.
     * WARNING: Do NOT modify this code. The content of this method is
     * always regenerated by the Form Editor.
     */
    @SuppressWarnings("unchecked")
    // <editor-fold defaultstate="collapsed" desc="Generated Code">
    private void initComponents() {

        jBoxPubMed = new javax.swing.JCheckBox();
        jBoxPubMedCentral = new javax.swing.JCheckBox();
        jLabel1 = new javax.swing.JLabel();
        jBtnSearch = new javax.swing.JButton();
        jTxtSearchTerm = new javax.swing.JTextField();

```

```

jLabel2 = new javax.swing.JLabel();
jBoxScienceDirect = new javax.swing.JCheckBox();
jLabel6 = new javax.swing.JLabel();
jLabel7 = new javax.swing.JLabel();
jLblYear = new javax.swing.JLabel();
jTxtYear = new javax.swing.JTextField();
jCBoxScienceDirectSaveFile = new javax.swing.JCheckBox();
jCBoxScienceDirectLoad = new javax.swing.JCheckBox();
jCBoxScienceDirectFirstThousand = new javax.swing.JCheckBox();
jCBoxScienceDirectComplete = new javax.swing.JCheckBox();
jLblScienceDirectSpinner = new javax.swing.JLabel();
jScienceDirectSpinner = new javax.swing.JSpinner();
jOverallSpinner = new javax.swing.JSpinner();
jBtnSaveDirectory = new javax.swing.JButton();
jMenuBar1 = new javax.swing.JMenuBar();
jMenu1 = new javax.swing.JMenu();
jMnuClose = new javax.swing.JMenuItem();

setDefaultCloseOperation(javax.swing.WindowConstants.EXIT_ON_CLOSE);

jBoxPubMed.setText("PubMed");
jBoxPubMed.addActionListener(new java.awt.event.ActionListener() {
    public void actionPerformed(java.awt.event.ActionEvent evt) {
        jBoxPubMedActionPerformed(evt);
    }
});
jBoxPubMedCentral.setText("PubMed Central");

jLabel1.setFont(new java.awt.Font("Tahoma", 0, 14));
jLabel1.setText("Choose which Sites you wish to search through:");
jLabel1.addMouseListener(new java.awt.event.MouseAdapter() {
    public void mouseClicked(java.awt.event.MouseEvent evt) {
        jLabel1MouseClicked(evt);
    }
});
jBtnSearch.setText("Search");
jBtnSearch.addActionListener(new java.awt.event.ActionListener() {
    public void actionPerformed(java.awt.event.ActionEvent evt) {
        jBtnSearchActionPerformed(evt);
    }
});
jLabel2.setFont(new java.awt.Font("Tahoma", 0, 14));
jLabel2.setText("Input the desired search (term or phrase)");

```

```

jBoxScienceDirect.setText("Science Direct");

jLabel6.setFont(new java.awt.Font("Tahoma", 0, 14));
jLabel6.setText("Choose the Directory to save to:");

jLabel7.setFont(new java.awt.Font("Tahoma", 0, 14));
jLabel7.setText("Set Time Between Pages(Seconds):");

jLblYear.setFont(new java.awt.Font("Tahoma", 1, 11));
jLblYear.setForeground(new java.awt.Color(51, 102, 255));
jLblYear.setText("Give the current year.");

jCBoxScienceDirectSaveFile.setText("Start from a save file");

jCBoxScienceDirectLoad.setText("Start by loading links from Science Direct
files");

jCBoxScienceDirectFirstThousand.setText("Start by loading first 1,000 Science
Direct Links");
jCBoxScienceDirectFirstThousand.addActionListener(new
java.awt.event.ActionListener() {
    public void actionPerformed(java.awt.event.ActionEvent evt) {
        jCBoxScienceDirectFirstThousandActionPerformed(evt);
    }
});

jCBoxScienceDirectComplete.setText("Start a complete search (significantly
longer)");
jCBoxScienceDirectComplete.addActionListener(new
java.awt.event.ActionListener() {
    public void actionPerformed(java.awt.event.ActionEvent evt) {
        jCBoxScienceDirectCompleteActionPerformed(evt);
    }
});

jLblScienceDirectSpinner.setText("Special Wait time for Science Direct");

jBtnSaveDirectory.setText("Edit");
jBtnSaveDirectory.addActionListener(new java.awt.event.ActionListener() {
    public void actionPerformed(java.awt.event.ActionEvent evt) {
        jBtnSaveDirectoryActionPerformed(evt);
    }
});

jMenu1.setText("File");

```

```

jMnuClose.setText("Close");
jMnuClose.addActionListener(new java.awt.event.ActionListener() {
    public void actionPerformed(java.awt.event.ActionEvent evt) {
        jMnuCloseActionPerformed(evt);
    }
});
jMenu1.add(jMnuClose);

jMenuBar1.add(jMenu1);

setJMenuBar(jMenuBar1);

javax.swing.GroupLayout layout = new
javax.swing.GroupLayout(getContentPane());
getContentPane().setLayout(layout);
layout.setHorizontalGroup(
    layout.createParallelGroup(javax.swing.GroupLayout.Alignment.LEADING)
    .addGroup(layout.createSequentialGroup()
        .addGroup(layout.createParallelGroup(javax.swing.GroupLayout.Alignment.LEADING)
            .addGroup(layout.createSequentialGroup()
                .addComponent(jBoxPubMed)
                .addComponent(jBoxPubMedCentral)
                .addComponent(jBoxScienceDirect)
                .addGroup(layout.createSequentialGroup()
                    .addGap(94, 94, 94)
                    .addComponent(jLblYear)
                    .addGap(18, 18, 18)
                    .addComponent(jTxtYear,
                        javax.swing.GroupLayout.PREFERRED_SIZE, 41,
                        javax.swing.GroupLayout.PREFERRED_SIZE))
                .addComponent(jLabel1)))
            .addGroup(layout.createSequentialGroup()
                .addGap(54, 54, 54)
                .addGroup(layout.createParallelGroup(javax.swing.GroupLayout.Alignment.LEADING)
                    .addGroup(layout.createSequentialGroup()
                        .addComponent(jCBoxScienceDirectLoad)
                        .addComponent(jCBoxScienceDirectFirstThousand)
                        .addComponent(jCBoxScienceDirectComplete)
                        .addComponent(jCBoxScienceDirectSaveFile)))
                    .addGap(41, 41, 41)))
        .addGap(41, 41, 41)
    )
    .addGroup(layout.createParallelGroup(javax.swing.GroupLayout.Alignment.LEADING)
        .addGroup(layout.createSequentialGroup()
            .addGap(54, 54, 54)
            .addGroup(layout.createParallelGroup(javax.swing.GroupLayout.Alignment.LEADING)
                .addGroup(layout.createSequentialGroup()
                    .addComponent(jCBoxScienceDirectLoad)
                    .addComponent(jCBoxScienceDirectFirstThousand)
                    .addComponent(jCBoxScienceDirectComplete)
                    .addComponent(jCBoxScienceDirectSaveFile)))
                .addGap(41, 41, 41)))
        .addGap(54, 54, 54)
    )
)
);

```

```

.addGroup(layout.createParallelGroup(javax.swing.GroupLayout.Alignment.LEADING)
    .addGroup(layout.createSequentialGroup()
        .addComponent(jBtnSaveDirectory)
        .addContainerGap())
    .addGroup(layout.createParallelGroup(javax.swing.GroupLayout.Alignment.LEADING)
        .addGroup(layout.createSequentialGroup()
            .addComponent(jOverallSpinner,
                javax.swing.GroupLayout.PREFERRED_SIZE, 49,
                javax.swing.GroupLayout.PREFERRED_SIZE)
            .addContainerGap())
        .addGroup(layout.createParallelGroup(javax.swing.GroupLayout.Alignment.LEADING)
            .addGroup(layout.createSequentialGroup()
                .addComponent(jScienceDirectSpinner,
                    javax.swing.GroupLayout.PREFERRED_SIZE, 60,
                    javax.swing.GroupLayout.PREFERRED_SIZE)
                .addContainerGap())
            .addGroup(layout.createParallelGroup(javax.swing.GroupLayout.Alignment.LEADING)
                .addGroup(layout.createSequentialGroup()
                    .addComponent(jBtnSearch,
                        javax.swing.GroupLayout.PREFERRED_SIZE, 91,
                        javax.swing.GroupLayout.PREFERRED_SIZE)
                    .addContainerGap())
                .addGroup(layout.createSequentialGroup()
                    .addComponent(jLblScienceDirectSpinner,
                        javax.swing.GroupLayout.DEFAULT_SIZE, Short.MAX_VALUE)
                    .addComponent(jLabel6)
                    .addComponent(jLabel2)
                    .addComponent(jLabel7)
                    .addComponent(jTxtSearchTerm,
                        javax.swing.GroupLayout.DEFAULT_SIZE, Short.MAX_VALUE))
                    .addGap(176, 176, 176))))))
    );
layout.setVerticalGroup(
    layout.createParallelGroup(javax.swing.GroupLayout.Alignment.LEADING)
    .addGroup(layout.createSequentialGroup()
        .addComponent(jLabel2)
    .addGroup(layout.createParallelGroup(javax.swing.GroupLayout.Alignment.LEADING)
        .addGroup(layout.createSequentialGroup()
            .addComponent(jLabel2)

```

```

        .addGap(15, 15, 15)
        .addComponent(jTxtSearchTerm,
javax.swing.GroupLayout.PREFERRED_SIZE,
javax.swing.GroupLayout.DEFAULT_SIZE,
javax.swing.GroupLayout.PREFERRED_SIZE)
        .addGap(18, 18, 18)
        .addComponent(jLabel6)

.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.RELATED)
        .addComponent(jBtnSaveDirectory,
javax.swing.GroupLayout.PREFERRED_SIZE, 23,
javax.swing.GroupLayout.PREFERRED_SIZE)
        .addGap(15, 15, 15)
        .addComponent(jLabel7)

.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.RELATED)
        .addComponent(jOverallSpinner,
javax.swing.GroupLayout.PREFERRED_SIZE,
javax.swing.GroupLayout.DEFAULT_SIZE,
javax.swing.GroupLayout.PREFERRED_SIZE)
        .addGap(16, 16, 16)
        .addComponent(jLblScienceDirectSpinner)

.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.UNRELATED)
        .addComponent(jScienceDirectSpinner,
javax.swing.GroupLayout.PREFERRED_SIZE,
javax.swing.GroupLayout.DEFAULT_SIZE,
javax.swing.GroupLayout.PREFERRED_SIZE))
        .addGroup(layout.createSequentialGroup())
        .addComponent(jLabel1)
        .addGap(2, 2, 2)

.addGroup(layout.createParallelGroup(javax.swing.GroupLayout.Alignment.BASELINE)
)
        .addComponent(jLblYear)
        .addComponent(jTxtYear,
javax.swing.GroupLayout.PREFERRED_SIZE,
javax.swing.GroupLayout.DEFAULT_SIZE,
javax.swing.GroupLayout.PREFERRED_SIZE))

.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.RELATED)
        .addComponent(jBoxPubMed)

.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.RELATED)
        .addComponent(jBoxPubMedCentral)

```

```

.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.RELATED)
    .addComponent(jBoxScienceDirect)
    .addGap(40, 40, 40)
    .addComponent(jCBoxScienceDirectSaveFile)

.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.UNRELATED)
    .addComponent(jCBoxScienceDirectLoad)

.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.UNRELATED)
    .addComponent(jCBoxScienceDirectFirstThousand)

.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.RELATED)
    .addComponent(jCBoxScienceDirectComplete)))
.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.RELATED)
    .addComponent(jBtnSearch)
    .addContainerGap()
);

pack();
}// </editor-fold>

private void jMnuCloseActionPerformed(java.awt.event.ActionEvent evt) {
    // This is the close menu and closes the Program
    dispose();
}

public void createFile(String fileDirectory){

    File f = new File(fileDirectory);
    try{
        if(f.mkdir()){
            System.out.println("The " + fileDirectory + " directory was created");
        }
        else{
            System.out.println("Directory not created");
        }
    }catch(Exception e){
        e.printStackTrace();
    }
}

private void jBtnSearchActionPerformed(java.awt.event.ActionEvent evt) {

```



```

HoweFileReader benderFR = new HoweFileReader();
benderFR.MyFileReader2(files[a].getAbsolutePath());

this.pullFirstThousandScienceDirect(benderFR.fileLineData);

System.out.println("Pulling links from file: " + Integer.toString(a + 1) + " of
" +
Integer.toString(files.length));
}

}//End of If statement for first 1,000 Science Direct links

if(this.jCBoxScienceDirectLoad.isSelected() == true){

}

if(this.jCBoxScienceDirectSaveFile.isSelected() == true){

}

/*
 * So now that we have successfully pulled any links out of the literature at hand
 * the computer will actually start the Science Direct Search up if indeed it was
selected
 * to perform a Science Direct search
 */
if(this.jBoxScienceDirect.isSelected() == true ||
this.jCBoxScienceDirectFirstThousand.isSelected() == true ||
this.jCBoxScienceDirectLoad.isSelected() == true ||
this.jCBoxScienceDirectSaveFile.isSelected()){

ScienceDirectThread shortScienceDirect = new ScienceDirectThread();
shortScienceDirect.start();

}

//Basically if any of the three lesser sites are chosen then the InterfaceProgress class
// will be created and shown visible
if(this.jBoxPubMed.isSelected() == true ||
this.jBoxPubMedCentral.isSelected() == true){

InterfaceProgress progress = new InterfaceProgress();
progress.setVisible(true);
}

```

```

/*
 * The next series of If statements checks to see which websites are being searched
 * and in with what options and then starts doing what needs to be done
 * in order to do the search.
 */

if(this.jBoxPubMed.isSelected() == true){

    System.out.println("Going to start the pubMed thread");
    Thread pubMed = new PubMedThread();
    pubMed.start();

}

if(this.jBoxPubMedCentral.isSelected() == true){

    System.out.println("Going to start the pubMed Central thread");
    Thread pubMedCentral = new PubMedCentralThread();
    pubMedCentral.start();

}

// Closes and trashes this object
dispose();

}

}

public void pullFirstThousandScienceDirect(Vector info){

    int beginIndex = 0, endIndex = 0;

    for(int i = 0; i < info.size(); i++){

        if(info.elementAt(i).toString().contains("DOI:")){
            try{

                beginIndex = info.elementAt(i).toString().indexOf("DOI:") + 4;
                endIndex = info.elementAt(i).toString().lastIndexOf('.');

                i++;

                endIndex = info.elementAt(i).toString().lastIndexOf('!');

            }
        }
    }
}

```

```

InformationModule.scienceDirectUnsearchedLinks.add(info.elementAt(i).toString().substring(1, endIndex));

}catch(Exception e){
    //System.out.println("Just going to skip that citation");

}

}

}

private void jLabel1MouseClicked(java.awt.event.MouseEvent evt) {
    // TODO add your handling code here:

}

private void jBtnSaveDirectoryActionPerformed(java.awt.event.ActionEvent evt) {
    // This enables the user to select a base save directory

File[] files = null;

final JFileChooser fc = new JFileChooser();

fc.setMultiSelectionEnabled(false);
fc.setAcceptAllFileFilterUsed(true);
fc.setFileSelectionMode(JFileChooser.DIRECTORIES_ONLY);
fc.setApproveButtonText("Select Save Directory");

if(fc.showOpenDialog(this) == JFileChooser.APPROVE_OPTION) {
    files = fc.getSelectedFile().listFiles();
    InformationModule.baseSaveDirectory =
fc.getSelectedFile().getAbsolutePath();
    System.out.println("The save Directory is: " +
InformationModule.baseSaveDirectory);

}
else {
    System.out.println("Open command cancelled by user." );
}

InformationModule.searchQuery = Interface.jTxtSearchTerm.getText().trim();

```

```

createDirectory(InformationModule.baseSaveDirectory + "\\\" +
InformationModule.searchQuery);
createDirectory(InformationModule.baseSaveDirectory + "\\\" +
InformationModule.searchQuery + "\\Science Direct");
InformationModule.scienceDirectDir = InformationModule.baseSaveDirectory + "\\\" +
+ InformationModule.searchQuery + "\\Science Direct";

createDirectory(InformationModule.baseSaveDirectory + "\\\" +
InformationModule.searchQuery + "\\PubMed");
InformationModule.pubMedDir = InformationModule.baseSaveDirectory + "\\\" +
InformationModule.searchQuery + "\\PubMed";

createDirectory(InformationModule.baseSaveDirectory + "\\\" +
InformationModule.searchQuery + "\\PubMedCentral");
InformationModule.pubMedCentralDir = InformationModule.baseSaveDirectory + "\\\" +
"\\\" + InformationModule.searchQuery + "\\PubMedCentral";

createDirectory(InformationModule.baseSaveDirectory + "\\\" +
InformationModule.searchQuery + "\\Science Direct\\File Pool");

createDirectory(InformationModule.baseSaveDirectory + "\\\" +
InformationModule.searchQuery + "\\PubMed\\File Pool");
createDirectory(InformationModule.baseSaveDirectory + "\\\" +
InformationModule.searchQuery + "\\PubMedCentral\\File Pool");

}

/*
 * @param fileDirectory Creates the directory denoted by fileDirectory String
 */
public void createDirectory(String fileDirectory){

    File f = new File(fileDirectory);
    try{
        if(f.mkdir()){
            System.out.println("The " + fileDirectory + " directory was created");
        }
    }

    else{
        System.out.println("Directory not created");
    }
}

}catch(Exception e){
    e.printStackTrace();
}

```

```
}

/*
 * @param args the command line arguments
 */
public static void main(String args[]) {
    java.awt.EventQueue.invokeLater(new Runnable() {
        public void run() {
            new Interface().setVisible(true);
        }
    });
}

// Variables declaration - do not modify
public static javax.swing.JCheckBox jBoxPubMed;
public static javax.swing.JCheckBox jBoxPubMedCentral;
public static javax.swing.JCheckBox jBoxScienceDirect;
private javax.swing.JButton jBtnSaveDirectory;
private javax.swing.JButton jBtnSearch;
public static javax.swing.JCheckBox jCBoxScienceDirectComplete;
public static javax.swing.JCheckBox jCBoxScienceDirectFirstThousand;
public static javax.swing.JCheckBox jCBoxScienceDirectLoad;
public static javax.swing.JCheckBox jCBoxScienceDirectSaveFile;
private javax.swing.JLabel jLabel1;
private javax.swing.JLabel jLabel2;
private javax.swing.JLabel jLabel6;
private javax.swing.JLabel jLabel7;
public static javax.swing.JLabel jLblScienceDirectSpinner;
public static javax.swing.JLabel jLblYear;
private javax.swing.JMenu jMenu1;
private javax.swing.JMenuBar jMenuBar1;
private javax.swing.JMenuItem jMnuClose;
public static javax.swing.JSpinner jOverallSpinner;
public static javax.swing.JSpinner jScienceDirectSpinner;
public static javax.swing.JTextField jTxtSearchTerm;
public static javax.swing.JTextField jTxtYear;
// End of variables declaration

}
```


InterfaceProgress.java

```

/*
 * Marico Howe
 * File Name: InterfaceProgress.java
 * Description: The purpose of this class is to display the programs progress to
 * the user.
 */

package webcrawling.Interfaces;

public class InterfaceProgress extends javax.swing.JFrame {

    /* Creates new form InterfaceProgress */
    public InterfaceProgress() {
        initComponents();
    }

    /* This method is called from within the constructor to
     * initialize the form.
     * WARNING: Do NOT modify this code. The content of this method is
     * always regenerated by the Form Editor.
     */
    @SuppressWarnings("unchecked")
    // <editor-fold defaultstate="collapsed" desc="Generated Code">
    private void initComponents() {

        jLblPubMed = new javax.swing.JLabel();
        jLblPubMedFilesFound = new javax.swing.JLabel();
        jLblPubMedFilesDownloaded = new javax.swing.JLabel();
        jLblPubMedFDownloaded = new javax.swing.JLabel();
        jLblPubMedFFound = new javax.swing.JLabel();
        jPubMedBar = new javax.swing.JProgressBar();
        jLblScienceDirect = new javax.swing.JLabel();
        jLblScienceDirectFilesFound = new javax.swing.JLabel();
        jLblScienceDirectFilesDownloaded = new javax.swing.JLabel();
        jLblScienceDirectFDownloaded = new javax.swing.JLabel();
        jLblScienceDirectFFound = new javax.swing.JLabel();
        jScienceDirectBar = new javax.swing.JProgressBar();
        jLblOtherSites = new javax.swing.JLabel();
        jLblOtherSitesFilesFound = new javax.swing.JLabel();
        jLblOtherSitesFilesDownloaded = new javax.swing.JLabel();
        jLblOtherSitesFDownloaded = new javax.swing.JLabel();
        jLblOtherSitesFFound = new javax.swing.JLabel();
        jOtherSitesBar = new javax.swing.JProgressBar();
        jLblOverallProgress = new javax.swing.JLabel();
    }
}

```

```

jLblOverallFilesFound = new javax.swing.JLabel();
jLblOverallFilesDownloaded = new javax.swing.JLabel();
jLblOverallFDownloaded = new javax.swing.JLabel();
jLblOverallFFound = new javax.swing.JLabel();
jOverallBar = new javax.swing.JProgressBar();
jBtnCloseProgram = new javax.swing.JButton();
jLblSearchComplete = new javax.swing.JLabel();
jLblOverallFilesTimeLeft = new javax.swing.JLabel();
jLblOtherSitesTimeLeft = new javax.swing.JLabel();
jLblOtherSitesProgress = new javax.swing.JLabel();
jLblScienceDirectTimeLeft = new javax.swing.JLabel();
jScienceDirectProgress = new javax.swing.JLabel();
jLblPubMedTimeLeft = new javax.swing.JLabel();
jLblPubMedProgress = new javax.swing.JLabel();
jLblOtherSitesEta = new javax.swing.JLabel();
jLblPubMedEta = new javax.swing.JLabel();
jLblScienceDirectEta = new javax.swing.JLabel();
jLblOverallEta = new javax.swing.JLabel();
jLblOtherSitesAction = new javax.swing.JLabel();
jLblScienceDirectAction = new javax.swing.JLabel();
jLblPubMedAction = new javax.swing.JLabel();
jBtnScienceDirectDetails = new javax.swing.JButton();
jMenuBar1 = new javax.swing.JMenuBar();
jMenu1 = new javax.swing.JMenu();
jMnuClose = new javax.swing.JMenuItem();

setDefaultCloseOperation(javax.swing.WindowConstants.EXIT_ON_CLOSE);

jLblPubMed.setFont(new java.awt.Font("Tahoma", 1, 14));
jLblPubMed.setText("PubMed");

jLblPubMedFilesFound.setText("Files Found:");

jLblPubMedFilesDownloaded.setText("Files Downloaded:");

jLblPubMedFDownloaded.setText("1052");

jLblPubMedFFound.setText("1100");

jPubMedBar.setStringPainted(true);

jLblScienceDirect.setFont(new java.awt.Font("Tahoma", 1, 14));
jLblScienceDirect.setText("Science Direct");
jLblScienceDirect.addMouseListener(new java.awt.event.MouseAdapter() {
    public void mouseClicked(java.awt.event.MouseEvent evt) {
        jLblScienceDirectMouseClicked(evt);
    }
});

```

```
        }

});

jLblScienceDirectFilesFound.setText("Files Found:");

jLblScienceDirectFilesDownloaded.setText("Files Downloaded");

jLblScienceDirectFDownloaded.setText("1052");

jLblScienceDirectFFound.setText("1100");

jScienceDirectBar.setStringPainted(true);

jLblOtherSites.setFont(new java.awt.Font("Tahoma", 1, 14));
jLblOtherSites.setText("Other Sites");

jLblOtherSitesFilesFound.setText("Files Found:");

jLblOtherSitesFilesDownloaded.setText("Files Downloaded");

jLblOtherSitesFDownloaded.setText("1052");

jLblOtherSitesFFound.setText("1100");

jOtherSitesBar.setStringPainted(true);

jLblOverallProgress.setFont(new java.awt.Font("Tahoma", 1, 18));

jLblOverallProgress.setHorizontalAlignment(javax.swing.SwingConstants.CENTER);
jLblOverallProgress.setText("Overall Progress");

jLblOverallFilesFound.setText("Files Found:");

jLblOverallFilesDownloaded.setText("Files Downloaded");

jLblOverallFDownloaded.setText("1052");

jLblOverallFFound.setText("1100");

jOverallBar.setStringPainted(true);

jBtnCloseProgram.setText("Close Program");
jBtnCloseProgram.setEnabled(false);
jBtnCloseProgram.addActionListener(new java.awt.event.ActionListener() {
    public void actionPerformed(java.awt.event.ActionEvent evt) {
        jBtnCloseProgramActionPerformed(evt);
    }
});
```

```

        }

});

jLblSearchComplete.setFont(new java.awt.Font("Tahoma", 1, 11));
jLblSearchComplete.setText("Search Complete!");

jLblOverallFilesTimeLeft.setText("Estimated Time Left:");

jLblOtherSitesTimeLeft.setText("Estimated Time Left :");

jLblOtherSitesProgress.setText("Action in Progress:");

jLblScienceDirectTimeLeft.setText("Estimated Time Left:");

jScienceDirectProgress.setText("Action in Progress:");

jLblPubMedTimeLeft.setText("Estimated Time Left:");

jLblPubMedProgress.setText("Action in Progress:");

jLblOtherSitesEta.setText("1h 23m 34s");

jLblPubMedEta.setText("1h 23m 34s");

jLblScienceDirectEta.setText("1h 23m 34s");

jLblOverallEta.setText("1h 23m 34s");

jLblOtherSitesAction.setText("downloading file: 02287552");

jLblScienceDirectAction.setText("downloading file: 02287552");

jLblPubMedAction.setText("downloading file: 02287552");

jBtnScienceDirectDetails.setText("View Details");
jBtnScienceDirectDetails.addActionListener(new java.awt.event.ActionListener() {
    public void actionPerformed(java.awt.event.ActionEvent evt) {
        jBtnScienceDirectDetailsActionPerformed(evt);
    }
});

jMenu1.setText("File");

jMnuClose.setText("Close Program");
jMnuClose.addActionListener(new java.awt.event.ActionListener() {
    public void actionPerformed(java.awt.event.ActionEvent evt) {

```



```

        .addGroup(layout.createSequentialGroup()
                  .addComponent(jLblPubMedTimeLeft))

        .addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.RELATED)
                  .addComponent(jLblPubMedEta,
javax.swing.GroupLayout.DEFAULT_SIZE, 172, Short.MAX_VALUE)
                  .addGap(129, 129, 129)))
        .addGroup(layout.createSequentialGroup()
                  .addComponent(jLblPubMedProgress))

.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.RELATED)))
        .addGroup(layout.createSequentialGroup()
                  .addGap(42, 42, 42)
                  .addComponent(jLblPubMedAction,
javax.swing.GroupLayout.PREFERRED_SIZE, 311,
javax.swing.GroupLayout.PREFERRED_SIZE)

        .addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.RELATED)))
        .addGroup(layout.createSequentialGroup()
                  .addContainerGap()
                  .addComponent(jPubMedBar,
javax.swing.GroupLayout.PREFERRED_SIZE, 284,
javax.swing.GroupLayout.PREFERRED_SIZE)

        .addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.RELATED)))
        .addGroup(layout.createParallelGroup(javax.swing.GroupLayout.Alignment.LEADING)
                  .addGroup(layout.createSequentialGroup()

        .addGroup(layout.createParallelGroup(javax.swing.GroupLayout.Alignment.LEADING)
                  .addGroup(layout.createParallelGroup(javax.swing.GroupLayout.Alignment.LEADING)
                          .addGroup(layout.createSequentialGroup()
                          .addComponent(jScienceDirectBar,
javax.swing.GroupLayout.PREFERRED_SIZE, 284,
javax.swing.GroupLayout.PREFERRED_SIZE)

        .addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.RELATED)
                  .addComponent(jBtnScienceDirectDetails))
                  .addComponent(jLblOtherSites)
                  .addGroup(javax.swing.GroupLayout.Alignment.TRAILING,
layout.createSequentialGroup())
                  .addGroup(layout.createParallelGroup(javax.swing.GroupLayout.Alignment.LEADING)
                          .addComponent(jLblOtherSitesFilesDownloaded)
                          .addComponent(jLblOtherSitesFilesFound))

```

```

        .addComponent(jLblOtherSitesTimeLeft)
        .addComponent(jLblOtherSitesProgress))

.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.RELATED, 78,
Short.MAX_VALUE)

.addGroup(layout.createParallelGroup(javax.swing.GroupLayout.Alignment.LEADING)
            .addComponent(jLblOtherSitesEta,
javax.swing.GroupLayout.DEFAULT_SIZE, 200, Short.MAX_VALUE)
            .addComponent(jLblOtherSitesFDownloaded,
javax.swing.GroupLayout.DEFAULT_SIZE, 200, Short.MAX_VALUE)
            .addComponent(jLblOtherSitesFFound)))
        .addGroup(layout.createSequentialGroup()

.addGroup(layout.createParallelGroup(javax.swing.GroupLayout.Alignment.LEADING)
            .addComponent(jLblScienceDirect)
            .addComponent(jLblScienceDirectFilesDownloaded)
            .addComponent(jLblScienceDirectTimeLeft)
            .addComponent(jScienceDirectProgress))
        .addGap(14, 14, 14)

.addGroup(layout.createParallelGroup(javax.swing.GroupLayout.Alignment.LEADING)
            .addComponent(jLblScienceDirectEta,
javax.swing.GroupLayout.DEFAULT_SIZE, 267, Short.MAX_VALUE)
            .addComponent(jLblScienceDirectFDownloaded,
javax.swing.GroupLayout.PREFERRED_SIZE, 155,
javax.swing.GroupLayout.PREFERRED_SIZE)
            .addComponent(jLblScienceDirectFFound,
javax.swing.GroupLayout.DEFAULT_SIZE, 267, Short.MAX_VALUE)))
        .addGroup(javax.swing.GroupLayout.Alignment.TRAILING,
layout.createSequentialGroup()

.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.RELATED)
            .addComponent(jLblScienceDirectAction,
javax.swing.GroupLayout.PREFERRED_SIZE, 273,
javax.swing.GroupLayout.PREFERRED_SIZE))
        .addGroup(layout.createSequentialGroup()
            .addGroup(layout.createSequentialGroup()
                .addComponent(jLblOtherSitesAction,
javax.swing.GroupLayout.PREFERRED_SIZE, 268,
javax.swing.GroupLayout.PREFERRED_SIZE))
                .addComponent(jOtherSitesBar,
javax.swing.GroupLayout.PREFERRED_SIZE, 284,
javax.swing.GroupLayout.PREFERRED_SIZE))
            .addGroup(layout.createSequentialGroup()
                .addGap(11, 11, 11))
                .addComponent(jLblScienceDirectFilesFound)))

```

```

.addGroup(layout.createSequentialGroup()
    .addGap(220, 220, 220)

.addGroup(layout.createParallelGroup(javax.swing.GroupLayout.Alignment.LEADING)
    .addComponent(jLblOverallFilesTimeLeft)
    .addComponent(jLblOverallFilesDownloaded)
    .addComponent(jLblOverallFilesFound))
    .addGap(25, 25, 25)

.addGroup(layout.createParallelGroup(javax.swing.GroupLayout.Alignment.LEADING)
    .addComponent(jLblOverallFFound,
javax.swing.GroupLayout.DEFAULT_SIZE, 462, Short.MAX_VALUE)
    .addGroup(layout.createSequentialGroup()
        .addComponent(jLblOverallEta,
javax.swing.GroupLayout.PREFERRED_SIZE, 155,
javax.swing.GroupLayout.PREFERRED_SIZE)

.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.RELATED, 307,
Short.MAX_VALUE))
    .addComponent(jLblOverallFDownloaded,
javax.swing.GroupLayout.DEFAULT_SIZE, 462, Short.MAX_VALUE))))
    .addContainerGap()
    .addGroup(layout.createSequentialGroup()
        .addGap(463, 463, 463)

.addGroup(layout.createParallelGroup(javax.swing.GroupLayout.Alignment.LEADING)
    .addComponent(jLblSearchComplete)
    .addComponent(jBtnCloseProgram,
javax.swing.GroupLayout.PREFERRED_SIZE, 224,
javax.swing.GroupLayout.PREFERRED_SIZE))
    .addContainerGap(118, Short.MAX_VALUE))
    .addGroup(layout.createSequentialGroup()
        .addGap(26, 26, 26)
        .addComponent(jOverallBar, javax.swing.GroupLayout.DEFAULT_SIZE,
722, Short.MAX_VALUE)
        .addGap(57, 57, 57))
    .addGroup(layout.createSequentialGroup()
        .addContainerGap()
        .addComponent(jLblOverallProgress,
javax.swing.GroupLayout.DEFAULT_SIZE, 722, Short.MAX_VALUE)
        .addGap(73, 73, 73))
    );
    layout.setVerticalGroup(
        layout.createParallelGroup(javax.swing.GroupLayout.Alignment.LEADING)
        .addGroup(layout.createSequentialGroup()
            .addContainerGap()

```

```

.addGroup(layout.createParallelGroup(javax.swing.GroupLayout.Alignment.BASELINE)
)
    .addComponent(jLblScienceDirect)
    .addComponent(jLblPubMed))
.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.RELATED)

.addGroup(layout.createParallelGroup(javax.swing.GroupLayout.Alignment.BASELINE)
)
    .addComponent(jLblPubMedFilesFound)
    .addComponent(jLblPubMedFFound))

.addGroup(layout.createParallelGroup(javax.swing.GroupLayout.Alignment.LEADING)
    .addGroup(layout.createSequentialGroup()
        .addGap(11, 11, 11)

.addGroup(layout.createParallelGroup(javax.swing.GroupLayout.Alignment.BASELINE)
)
    .addComponent(jLblScienceDirectFilesDownloaded)
    .addComponent(jLblScienceDirectFDownloaded))

.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.RELATED)

.addGroup(layout.createParallelGroup(javax.swing.GroupLayout.Alignment.BASELINE)
)
    .addComponent(jLblScienceDirectTimeLeft)
    .addComponent(jLblScienceDirectEta))

.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.RELATED)
    .addComponent(jScienceDirectProgress)

.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.RELATED,
javax.swing.GroupLayout.DEFAULT_SIZE, Short.MAX_VALUE)

.addGroup(layout.createParallelGroup(javax.swing.GroupLayout.Alignment.BASELINE)
)
    .addComponent(jLblScienceDirectAction)
    .addComponent(jLblPubMedAction,
javax.swing.GroupLayout.PREFERRED_SIZE, 14,
javax.swing.GroupLayout.PREFERRED_SIZE))

.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.UNRELATED)

.addGroup(layout.createParallelGroup(javax.swing.GroupLayout.Alignment.BASELINE)
)

```

```

.addComponent(jScienceDirectBar,
javax.swing.GroupLayout.PREFERRED_SIZE, 33,
javax.swing.GroupLayout.PREFERRED_SIZE)
.addComponent(jBtnScienceDirectDetails)
.addComponent(jPubMedBar,
javax.swing.GroupLayout.PREFERRED_SIZE, 33,
javax.swing.GroupLayout.PREFERRED_SIZE))

.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.RELATED)
.addComponent(jLblOtherSites)
.addGap(8, 8, 8)

.addGroup(layout.createParallelGroup(javax.swing.GroupLayout.Alignment.BASELINE)
)
.addComponent(jLblOtherSitesFilesFound)
.addComponent(jLblOtherSitesFFound))

.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.RELATED)

.addGroup(layout.createParallelGroup(javax.swing.GroupLayout.Alignment.BASELINE)
)
.addComponent(jLblOtherSitesFilesDownloaded)
.addComponent(jLblOtherSitesFDownloaded)))
.addGroup(layout.createSequentialGroup()

.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.RELATED)

.addGroup(layout.createParallelGroup(javax.swing.GroupLayout.Alignment.BASELINE)
)
.addComponent(jLblPubMedFilesDownloaded)
.addComponent(jLblPubMedFDownloaded))

.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.RELATED)

.addGroup(layout.createParallelGroup(javax.swing.GroupLayout.Alignment.BASELINE)
)
.addComponent(jLblPubMedTimeLeft)
.addComponent(jLblPubMedEta))

.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.RELATED)
.addComponent(jLblPubMedProgress)))
.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.RELATED)

.addGroup(layout.createParallelGroup(javax.swing.GroupLayout.Alignment.BASELINE)
)
.addComponent(jLblOtherSitesTimeLeft)

```

```

.addComponent(jLblOtherSitesEta))
.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.RELATED)
.addComponent(jLblOtherSitesProgress)
.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.RELATED)
.addComponent(jLblOtherSitesAction)
.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.RELATED,
javax.swing.GroupLayout.DEFAULT_SIZE, Short.MAX_VALUE)
.addComponent(jOtherSitesBar,
javax.swing.GroupLayout.PREFERRED_SIZE, 33,
javax.swing.GroupLayout.PREFERRED_SIZE)
.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.RELATED)
.addComponent(jLblOverallProgress)
.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.RELATED)

.addGroup(layout.createParallelGroup(javax.swing.GroupLayout.Alignment.TRAILING)
.addComponent(jLblOverallFFound)

.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.RELATED)
.addComponent(jLblOverallFDownloaded)
.addGap(5, 5, 5))
.addGroup(layout.createSequentialGroup()
.addComponent(jLblOverallFilesFound)

.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.RELATED)
.addComponent(jLblOverallFilesDownloaded)

.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.RELATED)))
.addGroup(layout.createParallelGroup(javax.swing.GroupLayout.Alignment.BASELINE)
.addComponent(jLblOverallEta)
.addComponent(jLblOverallFilesTimeLeft))
.addGap(18, 18, 18)
.addComponent(jOverallBar, javax.swing.GroupLayout.PREFERRED_SIZE,
33, javax.swing.GroupLayout.PREFERRED_SIZE)

.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.UNRELATED)
.addComponent(jLblSearchComplete)

.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.UNRELATED)
.addComponent(jBtnCloseProgram,
javax.swing.GroupLayout.PREFERRED_SIZE, 32,
javax.swing.GroupLayout.PREFERRED_SIZE)
.addContainerGap(38, Short.MAX_VALUE))
.addGroup(layout.createSequentialGroup())

```

```

.addGap(39, 39, 39)

.addGroup(layout.createParallelGroup(javax.swing.GroupLayout.Alignment.BASELINE)
)
    .addComponent(jLblScienceDirectFilesFound)
    .addComponent(jLblScienceDirectFFound))
    .addContainerGap(533, Short.MAX_VALUE))
);

pack();
}// </editor-fold>

private void jMnuCloseActionPerformed(java.awt.event.ActionEvent evt) {
    // This Shuts down Program

    dispose();
}

private void jBtnCloseProgramActionPerformed(java.awt.event.ActionEvent evt) {
    /* This Button activates when search is complete then allows you to close
     * program. It also makes the Global Boolean in InformationModule true so that the
     * program will end
    */
    dispose();
}

private void jLblScienceDirectMouseClicked(java.awt.event.MouseEvent evt) {
    // TODO add your handling code here:

    ScienceDirectStatus status = new ScienceDirectStatus();
    status.setVisible(true);
}

private void jBtnScienceDirectDetailsActionPerformed(java.awt.event.ActionEvent evt) {
    // TODO add your handling code here:
    ScienceDirectStatus status = new ScienceDirectStatus();
    status.setVisible(true);
}

/*
 * @param args the command line arguments

```

```
/*
public static void main(String args[]) {
    java.awt.EventQueue.invokeLater(new Runnable() {
        public void run() {
            new InterfaceProgress().setVisible(true);
        }
    });
}

// Variables declaration - do not modify
public static javax.swing.JButton jBtnCloseProgram;
private javax.swing.JButton jBtnScienceDirectDetails;
public static javax.swing.JLabel jLblOtherSites;
public static javax.swing.JLabel jLblOtherSitesAction;
public static javax.swing.JLabel jLblOtherSitesEta;
public static javax.swing.JLabel jLblOtherSitesFDownloaded;
public static javax.swing.JLabel jLblOtherSitesFFound;
public static javax.swing.JLabel jLblOtherSitesFilesDownloaded;
public static javax.swing.JLabel jLblOtherSitesFilesFound;
public static javax.swing.JLabel jLblOtherSitesProgress;
public static javax.swing.JLabel jLblOtherSitesTimeLeft;
public static javax.swing.JLabel jLblOverallEta;
public static javax.swing.JLabel jLblOverallFDownloaded;
public static javax.swing.JLabel jLblOverallFFound;
private javax.swing.JLabel jLblOverallFilesDownloaded;
private javax.swing.JLabel jLblOverallFilesFound;
public static javax.swing.JLabel jLblOverallFilesTimeLeft;
private javax.swing.JLabel jLblOverallProgress;
public static javax.swing.JLabel jLblPubMed;
public static javax.swing.JLabel jLblPubMedAction;
public static javax.swing.JLabel jLblPubMedEta;
public static javax.swing.JLabel jLblPubMedFDownloaded;
public static javax.swing.JLabel jLblPubMedFFound;
public static javax.swing.JLabel jLblPubMedFilesDownloaded;
public static javax.swing.JLabel jLblPubMedFilesFound;
public static javax.swing.JLabel jLblPubMedProgress;
public static javax.swing.JLabel jLblPubMedTimeLeft;
public static javax.swing.JLabel jLblScienceDirect;
public static javax.swing.JLabel jLblScienceDirectAction;
public static javax.swing.JLabel jLblScienceDirectEta;
public static javax.swing.JLabel jLblScienceDirectFDownloaded;
public static javax.swing.JLabel jLblScienceDirectFFound;
public static javax.swing.JLabel jLblScienceDirectFilesDownloaded;
public static javax.swing.JLabel jLblScienceDirectFilesFound;
public static javax.swing.JLabel jLblScienceDirectTimeLeft;
public static javax.swing.JLabel jLblSearchComplete;
```

```
private javax.swing.JMenu jMenu1;
private javax.swing.JMenuBar jMenuBar1;
private javax.swing.JMenuItem jMenuItem1;
public static javax.swing.JProgressBar jOtherSitesBar;
public static javax.swing.JProgressBar jOverallBar;
public static javax.swing.JProgressBar jPubMedBar;
public static javax.swing.JProgressBar jScienceDirectBar;
public static javax.swing.JLabel jScienceDirectProgress;
// End of variables declaration

}
```

Questionnaire.java

```

/*
 * Marico Howe
 * File Name: Questionnaire.java
 * Description: The purpose of this class is to display the directory for the
 * keyword list. It also tells whether or not there is a minimum number of files
 * to be downloaded.
 */

package webcrawling.Interfaces;

import Threads.ScienceDirectCompleteThread;
import java.io.File;
import javax.swing.JFileChooser;
import webcrawlingrevised.InformationModule;

public class Questionnaire extends javax.swing.JFrame {

    /* Creates new form Questionnaire */
    public Questionnaire() {
        initComponents();
    }

    /* This method is called from within the constructor to
     * initialize the form.
     * WARNING: Do NOT modify this code. The content of this method is
     * always regenerated by the Form Editor.
     */
    @SuppressWarnings("unchecked")
    // <editor-fold defaultstate="collapsed" desc="Generated Code">
    private void initComponents() {

        jPanel1 = new javax.swing.JPanel();
        jButton1 = new javax.swing.JButton();
        jLabel4 = new javax.swing.JLabel();
        jLabel5 = new javax.swing.JLabel();
        jLabel6 = new javax.swing.JLabel();
        jLblSaveFiles = new javax.swing.JLabel();
        jLblJournalList = new javax.swing.JLabel();
        jLblKeywordList = new javax.swing.JLabel();
        jLabel14 = new javax.swing.JLabel();
        jLblMinimumDowned = new javax.swing.JLabel();
        jButton4 = new javax.swing.JButton();
        jButton2 = new javax.swing.JButton();
    }
}

```

```

setDefaultCloseOperation(javax.swing.WindowConstants.EXIT_ON_CLOSE);

jButton1.setText("Submit");
jButton1.addActionListener(new java.awt.event.ActionListener() {
    public void actionPerformed(java.awt.event.ActionEvent evt) {
        jButton1ActionPerformed(evt);
    }
});

jLabel4.setFont(new java.awt.Font("Tahoma", 1, 11));
jLabel4.setText("Directory for previous save files:");

jLabel5.setFont(new java.awt.Font("Tahoma", 1, 11));
jLabel5.setText("File that contains journal list:");

jLabel6.setFont(new java.awt.Font("Tahoma", 1, 11));
jLabel6.setText("File that contains keyword list:");

jLblSaveFiles.setText("C:\\\\Users\\\\Marico Howe\\\\Documents");

jLblJournalList.setText("C:\\\\Users\\\\Marico Howe\\\\Documents");

jLblKeywordList.setText("C:\\\\Users\\\\Chris Biedenbender\\\\Documents");

jLabel14.setFont(new java.awt.Font("Tahoma", 1, 11));
jLabel14.setText("Required Minimum amount of documents to be downloaded per
journal:");

jLblMinimumDowned.setText("156");

jButton4.setText("SetSaveDirectory");
jButton4.addActionListener(new java.awt.event.ActionListener() {
    public void actionPerformed(java.awt.event.ActionEvent evt) {
        jButton4ActionPerformed(evt);
    }
});

javax.swing.GroupLayout jPanel1Layout = new javax.swing.GroupLayout(jPanel1);
jPanel1.setLayout(jPanel1Layout);
jPanel1Layout.setHorizontalGroup(
    jPanel1Layout.createParallelGroup(javax.swing.GroupLayout.Alignment.LEADING)
        .addGroup(jPanel1Layout.createSequentialGroup()
            .addGap(0, 0, Short.MAX_VALUE)
        )
);

.addGroup(jPanel1Layout.createParallelGroup(javax.swing.GroupLayout.Alignment.LEADING)
        .addGroup(jPanel1Layout.createSequentialGroup()
            .addGap(0, 0, Short.MAX_VALUE)
        )
);

```

```

.addGroup(jPanel1Layout.createSequentialGroup()
    .addContainerGap()

.addGroup(jPanel1Layout.createParallelGroup(javax.swing.GroupLayout.Alignment.LEADING)
    .addGroup(jPanel1Layout.createSequentialGroup()
        .addGap(10, 10, 10)
        .addComponent(jLblMinimumDowned,
            javax.swing.GroupLayout.PREFERRED_SIZE, 383,
            javax.swing.GroupLayout.PREFERRED_SIZE))
        .addGroup(jPanel1Layout.createSequentialGroup()
            .addGap(30, 30, 30)
            .addComponent(jLblSaveFiles,
                javax.swing.GroupLayout.DEFAULT_SIZE, 415, Short.MAX_VALUE))
            .addComponent(jLabel4)
            .addComponent(jLabel5)
            .addGroup(jPanel1Layout.createSequentialGroup()
                .addGap(22, 22, 22)
                .addComponent(jLblJournalList,
                    javax.swing.GroupLayout.DEFAULT_SIZE, 423, Short.MAX_VALUE))
                    .addComponent(jLabel6)
                    .addGroup(jPanel1Layout.createSequentialGroup()
                        .addGap(20, 20, 20)
                        .addComponent(jLblKeywordList,
                            javax.swing.GroupLayout.DEFAULT_SIZE, 425, Short.MAX_VALUE))
                            .addComponent(jLabel14)))
                .addGroup(jPanel1Layout.createSequentialGroup()
                    .addGap(206, 206, 206)
                    .addComponent(jButton1)
                    .addGap(39, 39, 39)
                    .addComponent(jButton4)))
                .addContainerGap())
            );
jPanel1Layout.setVerticalGroup(
    jPanel1Layout.createParallelGroup(javax.swing.GroupLayout.Alignment.LEADING)
        .addGroup(jPanel1Layout.createSequentialGroup()
            .addGap(25, 25, 25)
            .addComponent(jLabel4)

        .addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.UNRELATED)
            .addComponent(jLblSaveFiles)
            .addGap(18, 18, 18)
            .addComponent(jLabel5)

        .addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.UNRELATED)

```

```

.addComponent(jLblJournalList)
.addGap(18, 18, 18)
.addComponent(jLabel6)
.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.RELATED)
.addComponent(jLblKeywordList)
.addGap(11, 11, 11)
.addComponent(jLabel14)
.addGap(11, 11, 11)
.addComponent(jLblMinimumDowned)
.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.RELATED,
14, Short.MAX_VALUE)

.addGroup(jPanel1Layout.createParallelGroup(javax.swing.GroupLayout.Alignment.BASELINE)
.addComponent(jButton1)
.addComponent(jButton4))
.addGap(19, 19, 19))
);

jButton2.setText("Add Something");
jButton2.addActionListener(new java.awt.event.ActionListener() {
    public void actionPerformed(java.awt.event.ActionEvent evt) {
        jButton2ActionPerformed(evt);
    }
});

javax.swing.GroupLayout layout = new
javax.swing.GroupLayout(getContentPane());
getContentPane().setLayout(layout);
layout.setHorizontalGroup(
    layout.createParallelGroup(javax.swing.GroupLayout.Alignment.LEADING)
    .addGroup(layout.createSequentialGroup()
        .addGap(36, 36, 36)
        .addComponent(jButton2)
        .addGap(344, Short.MAX_VALUE)))
);

.layout.setHorizontalGroup(layout.createParallelGroup(javax.swing.GroupLayout.Alignment.LEADING)
    .addGroup(layout.createSequentialGroup()
        .addGap(36, 36, 36)
        .addComponent(jPanel1, javax.swing.GroupLayout.PREFERRED_SIZE,
        javax.swing.GroupLayout.DEFAULT_SIZE,
        javax.swing.GroupLayout.PREFERRED_SIZE)
        .addGap(344, Short.MAX_VALUE)))
);
.layout.setVerticalGroup(layout.createParallelGroup(javax.swing.GroupLayout.Alignment.LEADING)
    .addGroup(layout.createSequentialGroup()
        .addGap(36, 36, 36)
        .addComponent(jPanel1, javax.swing.GroupLayout.PREFERRED_SIZE,
        javax.swing.GroupLayout.DEFAULT_SIZE,
        javax.swing.GroupLayout.PREFERRED_SIZE)
        .addGap(344, Short.MAX_VALUE)))
);
.layout.setVerticalGroup(

```

```

        layout.createParallelGroup(javax.swing.GroupLayout.Alignment.LEADING)
        .addGroup(javax.swing.GroupLayout.Alignment.TRAILING,
layout.createSequentialGroup()
        .addContainerGap(306, Short.MAX_VALUE)
        .addComponent(jButton2)
        .addGap(31, 31, 31))

    .addGroup(layout.createParallelGroup(javax.swing.GroupLayout.Alignment.LEADING)
        .addGroup(layout.createSequentialGroup()
            .addGap(0, 0, 0)
            .addGroup(layout.createSequentialGroup()
                .addGap(0, 0, 0)
                .addComponent(jPanel1, javax.swing.GroupLayout.PREFERRED_SIZE,
                    javax.swing.GroupLayout.DEFAULT_SIZE,
                    javax.swing.GroupLayout.PREFERRED_SIZE)
                .addGap(0, 0, 0)
                .addGap(70, Short.MAX_VALUE)))
        );
    }

    pack();
}// </editor-fold>

private void jButton1ActionPerformed(java.awt.event.ActionEvent evt) {
    // TODO add your handling code here:
    ScienceDirectStatus status = new ScienceDirectStatus();
    status.setVisible(true);

    status.jLblMinimumFiles.setText(Integer.toString(InformationModule.minimumDownload));
    Thread complete = new ScienceDirectCompleteThread();
    complete.start();
    dispose();
}

private void jButton2ActionPerformed(java.awt.event.ActionEvent evt) {
    // This adds a component to the search.

    SD_OptionSelecter oSelecter = new SD_OptionSelecter();
    oSelecter.setVisible(true);
}

private void jButton4ActionPerformed(java.awt.event.ActionEvent evt) {
    // TODO add your handling code here:
    File file = null;

    final JFileChooser fc = new JFileChooser();

    fc.setMultiSelectionEnabled(false);
    fc.setAcceptAllFileFilterUsed(true);
}

```

```

fc.setFileSelectionMode(JFileChooser.DIRECTORIES_ONLY);
fc.setApproveButtonText("Select save Location");

if (fc.showOpenDialog(this) == JFileChooser.APPROVE_OPTION) {
    InformationModule.baseSaveDirectory =
fc.getSelectedFile().getAbsolutePath();

//Questionare2.jLblJournalList.setText(fc.getSelectedFile().getAbsolutePath().toString());

}

else {
    System.out.println("Open command cancelled by user." );
}

createFile(InformationModule.baseSaveDirectory + "\\CompleteSearch");
createFile(InformationModule.baseSaveDirectory + "\\CompleteSearch\\Journal
Save Files");
createFile(InformationModule.baseSaveDirectory + "\\CompleteSearch\\Tree
Build");
InformationModule.baseJournalSaveFiles =
InformationModule.baseSaveDirectory +
"\\"CompleteSearch\\Journal Save Files";

createFile(InformationModule.baseSaveDirectory + "\\CompleteSearch\\Journal
Repository");
InformationModule.baseJournalDirectory =
InformationModule.baseSaveDirectory +
"\\"CompleteSearch\\Journal Repository";
}

public void createFile(String fileDirectory){

File f = new File(fileDirectory);
try{
    if(f.mkdir()){
        System.out.println("The " + fileDirectory + " directory was created");
    }

    else{
        System.out.println("Directory not created");
    }

}catch(Exception e){
    e.printStackTrace();
}
}

```

```
/*
 * @param args the command line arguments
 */
public static void main(String args[]) {
    java.awt.EventQueue.invokeLater(new Runnable() {
        public void run() {
            new Questionnaire().setVisible(true);
        }
    });
}

// Variables declaration - do not modify
private javax.swing.JButton jButton1;
private javax.swing.JButton jButton2;
private javax.swing.JButton jButton4;
private javax.swing.JLabel jLabel14;
private javax.swing.JLabel jLabel4;
private javax.swing.JLabel jLabel5;
private javax.swing.JLabel jLabel6;
public static javax.swing.JLabel jLblJournalList;
public static javax.swing.JLabel jLblKeywordList;
public static javax.swing.JLabel jLblMinimumDowned;
public static javax.swing.JLabel jLblSaveFiles;
private javax.swing.JPanel jPanel1;
// End of variables declaration

}
```

SD_Minimums.java

```

/*
 * Marico Howe
 * File Name: SD_Minimums.java
 * Description: The purpose of this class is to display whether or not there is
 * a minimum amount of downloaded articles per journal.
 */
package webcrawling.Interfaces;

import webcrawlingrevised.InformationModule;

public class SD_Minimums extends javax.swing.JFrame {

    /* Creates new form SD_Minimums */
    public SD_Minimums() {
        initComponents();
    }

    /* This method is called from within the constructor to
     * initialize the form.
     * WARNING: Do NOT modify this code. The content of this method is
     * always regenerated by the Form Editor.
     */
    @SuppressWarnings("unchecked")
    // <editor-fold defaultstate="collapsed" desc="Generated Code">
    private void initComponents() {

        jLbl1 = new javax.swing.JLabel();
        jSpinner1 = new javax.swing.JSpinner();
        jLbl2 = new javax.swing.JLabel();
        jButton1 = new javax.swing.JButton();

        setDefaultCloseOperation(javax.swing.WindowConstants.EXIT_ON_CLOSE);

        jLbl1.setText("What will be the minimum amount of documents downloaded per
journal?");

        jLbl2.setFont(new java.awt.Font("Tahoma", 1, 11));
        jLbl2.setText("%");

        jButton1.setText("Submit");
        jButton1.addActionListener(new java.awt.event.ActionListener() {
            public void actionPerformed(java.awt.event.ActionEvent evt) {
                jButton1ActionPerformed(evt);
            }
        });

        
```

```

});

javax.swing.GroupLayout layout = new
javax.swing.GroupLayout(getContentPane());
getContentPane().setLayout(layout);
layout.setHorizontalGroup(
    layout.createParallelGroup(javax.swing.GroupLayout.Alignment.LEADING)
    .addGroup(layout.createSequentialGroup()
        .addContainerGap()

.addGroup(layout.createParallelGroup(javax.swing.GroupLayout.Alignment.LEADING)
    .addGroup(layout.createSequentialGroup()
        .addComponent(jSpinner1,
javax.swing.GroupLayout.PREFERRED_SIZE, 92,
javax.swing.GroupLayout.PREFERRED_SIZE)

.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.RELATED)
    .addComponent(jLbl2, javax.swing.GroupLayout.PREFERRED_SIZE,
22, javax.swing.GroupLayout.PREFERRED_SIZE))
    .addComponent(jLbl1))
    .addContainerGap(42, Short.MAX_VALUE))
    .addGroup(javax.swing.GroupLayout.Alignment.TRAILING,
layout.createSequentialGroup()
    .addComponent(jButton1)
    .addGap(63, 63, 63))
);
layout.setVerticalGroup(
    layout.createParallelGroup(javax.swing.GroupLayout.Alignment.LEADING)
    .addGroup(layout.createSequentialGroup()
        .addContainerGap()
        .addComponent(jLbl1)
        .addGap(23, 23, 23)

.addGroup(layout.createParallelGroup(javax.swing.GroupLayout.Alignment.BASELINE)
)
    .addComponent(jLbl2)
    .addComponent(jSpinner1, javax.swing.GroupLayout.PREFERRED_SIZE,
javax.swing.GroupLayout.DEFAULT_SIZE,
javax.swing.GroupLayout.PREFERRED_SIZE))
    .addGap(18, 18, 18)
    .addComponent(jButton1)
    .addContainerGap(javax.swing.GroupLayout.DEFAULT_SIZE,
Short.MAX_VALUE))
);

```

```

        pack();
    } // </editor-fold>

    private void jButton1ActionPerformed(java.awt.event.ActionEvent evt) {
        // When the user clicks submit

        // If the % sign in the GUI is invisible, meaning this is the form
        // for the minimum amount of downloaded articles per journal
        if(jLbl2.isVisible() == false){

            InformationModule.minimumDownload =
                Integer.valueOf(this.jSpinner1.getValue().toString());
            System.out.println("Minimum # of files to be downloaded : " +
                this.jSpinner1.getValue().toString());
            dispose();
        }
        // If the % sign in the GUI is visible, meaning this is the form
        // for the minimum % of articles that must be relavent to continue download of
        // specific journal
        else if(jLbl2.isVisible() == true){

        }
    }

    /*
     * @param args the command line arguments
     */
    public static void main(String args[]) {
        java.awt.EventQueue.invokeLater(new Runnable() {
            public void run() {
                new SD_Minimums().setVisible(true);
            }
        });
    }

    // Variables declaration - do not modify
    private javax.swing.JButton jButton1;
    public static javax.swing.JLabel jLbl1;
    public static javax.swing.JLabel jLbl2;
    private javax.swing.JSpinner jSpinner1;
    // End of variables declaration
}

```


SD_OptionSelecter.java

```

/*
 * Marico Howe
 * File Name: SD_OptionSelecter.java
 * Description: The purpose of this class is to allow the user the option to
 * select whether or not files were previously saved to a directory. If so,
 * the user can select the directory. Also, queries the user to whether or not
 * there will be the minimum amount of documents downloaded per journal.
 */

package webcrawling.Interfaces;

import All_Purpose.HoweFileReader;
import java.io.File;
import java.util.Vector;
import javax.swing.JFileChooser;
import webcrawlingrevised.InformationModule;

public class SD_OptionSelecter extends javax.swing.JFrame {

    /* Creates new form SD_OptionSelecter */
    public SD_OptionSelecter() {
        initComponents();
    }

    /* This method is called from within the constructor to
     * initialize the form.
     * WARNING: Do NOT modify this code. The content of this method is
     * always regenerated by the Form Editor.
     */
    @SuppressWarnings("unchecked")
    // <editor-fold defaultstate="collapsed" desc="Generated Code">
    private void initComponents() {

        jBtnSubmit = new javax.swing.JButton();
        jLabel1 = new javax.swing.JLabel();
        jCmbSetting = new javax.swing.JComboBox();

        setDefaultCloseOperation(javax.swing.WindowConstants.EXIT_ON_CLOSE);

        jBtnSubmit.setText("Submit");
        jBtnSubmit.addActionListener(new java.awt.event.ActionListener() {
            public void actionPerformed(java.awt.event.ActionEvent evt) {
                jBtnSubmitActionPerformed(evt);
            }
        });

        
```

```

});

jLabel1.setText("Which parameter do you wish to set?");

jCmbSetting.setModel(new javax.swing.DefaultComboBoxModel(new String[] {
"Directory for previously saved files", "File that contains journal list", "File that contains
keyword list", "Required minimum amount of documents to be downloaded per journal",
" " }));

javax.swing.GroupLayout layout = new
javax.swing.GroupLayout(getContentPane());
getContentPane().setLayout(layout);
layout.setHorizontalGroup(
    layout.createParallelGroup(javax.swing.GroupLayout.Alignment.LEADING)
    .addGroup(layout.createSequentialGroup()
        .addContainerGap()

.addGroup(layout.createParallelGroup(javax.swing.GroupLayout.Alignment.LEADING)
        .addComponent(jLabel1)
        .addComponent(jCmbSetting,
javax.swing.GroupLayout.PREFERRED_SIZE,
javax.swing.GroupLayout.DEFAULT_SIZE,
javax.swing.GroupLayout.PREFERRED_SIZE))
        .addContainerGap(35, Short.MAX_VALUE))
    .addGroup(javax.swing.GroupLayout.Alignment.TRAILING,
layout.createSequentialGroup()
        .addContainerGap(294, Short.MAX_VALUE)
        .addComponent(jBtnSubmit)
        .addGap(48, 48, 48))
);
layout.setVerticalGroup(
    layout.createParallelGroup(javax.swing.GroupLayout.Alignment.LEADING)
    .addGroup(layout.createSequentialGroup()
        .addContainerGap()
        .addComponent(jLabel1)
        .addGap(18, 18, 18)
        .addComponent(jCmbSetting, javax.swing.GroupLayout.PREFERRED_SIZE,
javax.swing.GroupLayout.DEFAULT_SIZE,
javax.swing.GroupLayout.PREFERRED_SIZE)
        .addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.RELATED,
62, Short.MAX_VALUE)
        .addComponent(jBtnSubmit)
        .addContainerGap())
);
pack();

```

```

} // </editor-fold>

private void jBtnSubmitActionPerformed(java.awt.event.ActionEvent evt) {
    // This is what happens when the user clicks submit

    if(this.jCmbSetting.getSelectedIndex() == 0){

        this.startFromSaveBeforeTreeConstructed(InformationModule.previouslySavedJournals);
        dispose();
    }
    if(this.jCmbSetting.getSelectedIndex() == 1){
        File file = null;

        final JFileChooser fc = new JFileChooser();

        fc.setMultiSelectionEnabled(false);
        fc.setAcceptAllFileFilterUsed(true);
        //fc.setFileSelectionMode(JFileChooser.DIRECTORIES_ONLY);
        fc.setApproveButtonText("Select Index file");

        if (fc.showOpenDialog(this) == JFileChooser.APPROVE_OPTION) {
            file = fc.getSelectedFile();

            Questionnaire.jLblJournalList.setText(fc.getSelectedFile().getAbsolutePath().toString());

        }
        else {
            System.out.println("Open command cancelled by user. ");
        }
        HoweFileReader howeFR = new HoweFileReader();
        howeFR.MyFileReader2(file.getAbsolutePath());

        this.getMasterIndex(howeFR.fileLineData,
InformationModule.scienceDirectMasterIndex);

        dispose();
    }
    else if(this.jCmbSetting.getSelectedIndex() == 2){
        File file = null;

        final JFileChooser fc = new JFileChooser();

        fc.setMultiSelectionEnabled(false);
        fc.setAcceptAllFileFilterUsed(true);
        //fc.setFileSelectionMode(JFileChooser.DIRECTORIES_ONLY);
    }
}

```

```

        fc.setApproveButtonText("Select Keyword(s) file");

        if (fc.showOpenDialog(this) == JFileChooser.APPROVE_OPTION) {
            file = fc.getSelectedFile();

            Questionnaire.jLblKeywordList.setText(fc.getSelectedFile().getAbsolutePath().toString()
            );

        }
        else {
            System.out.println("Open command cancelled by user." );
        }
        HoweFileReader howeFR = new HoweFileReader();
        howeFR.MyFileReader2(file.getAbsolutePath());

        this.getKeywords(howeFR.fileLineData, InformationModule.keywordList);

        dispose();
    }
    if(this.jCmbSetting.getSelectedIndex() == 3){
        SD_Minimums setting = new SD_Minimums();
        setting.jLbl1.setText("What will be the minimum amount of documents
downloaded per journal?");
        setting.jLbl2.setVisible(false);
        setting.setVisible(true);
        dispose();
    }
}

public void startFromSaveBeforeTreeConstructed(Vector info){

    File file = null;
    File[] f = null;

    final JFileChooser fc = new JFileChooser();

    fc.setMultiSelectionEnabled(false);
    fc.setAcceptAllFileFilterUsed(true);
    fc.setFileSelectionMode(JFileChooser.DIRECTORIES_ONLY);
    fc.setApproveButtonText("Select save Dir");

    for(int i = 0; i < f.length; i++){

        info.add(f[i].getName().toString().substring(0,
f[i].getName().toString().indexOf(".html")));
    }
}

```

```

        System.out.println("Just added " + info.lastElement().toString() + " to
constructed journal links");
    }
}

public void getKeywords(Vector start, Vector gatheredInfo){

    for(int a = 0; a < start.size(); a++){

        if(start.elementAt(a).toString().contains("<word>")){
            a++;
            gatheredInfo.add(start.elementAt(a).toString().trim());
            System.out.println("Just added " + start.elementAt(a).toString().trim() +
                " to list of keywords");

            for(int b = a; b < start.size(); b++){

                if(start.elementAt(b).toString().contains("<sm>")){
                    b++;
                    gatheredInfo.add(start.elementAt(b).toString().trim());
                    System.out.println("Just added " + start.elementAt(b).toString().trim() +
                        " to list of keywords");
                }
                else if(start.elementAt(b).toString().contains("</word>")){
                    a = b;
                    b = start.size() + 50;
                }
            }//End of For b loop

        }//End of If statement
    }
}

public void getMasterIndex(Vector startInfo, String[][] gatheredInfo){

    Vector names = new Vector();
    Vector links = new Vector();

    for(int i = 0; i < startInfo.size(); i++){

        if(startInfo.elementAt(i).toString().contains("<publicationType>Journal</publicationTyp
e>")){
            for(int h = i + 1; h < startInfo.size(); h++){

                String tempName = null;

```

```

String tempLink = null;

if(startInfo.elementAt(h).toString().contains("<publicationName>")){
    tempName =
startInfo.elementAt(h).toString().substring(startInfo.elementAt(h).toString().indexOf(">" )
) + 1,
        startInfo.elementAt(h).toString().indexOf("</>"));

for(int c = h; c < startInfo.size(); c++){
    if(startInfo.elementAt(c).toString().contains("<entitlementStatus>") &&
        !startInfo.elementAt(c).toString().contains("Non")){
        for(int d = c; d < startInfo.size(); d++){
            if(startInfo.elementAt(d).toString().contains("<homePageUrl>")){
                tempLink = startInfo.elementAt(d).toString().substring(
                    startInfo.elementAt(d).toString().indexOf(">") + 1,
                    startInfo.elementAt(d).toString().indexOf("</>"));

                links.add(tempLink);
                names.add(tempName);

                System.out.println("Added: " + tempName);
                System.out.println("Added: " + tempLink);
                if(links.size() == names.size()){
                    System.out.println("Everything is sized correctly.... Currently
at: " +
                    Integer.toString(links.size()));
                    System.out.println(" ");
                }
                else{
                    System.out.println("Sizing is off.....");
                    System.out.println("Names: " +
                    Integer.toString(names.size()));
                    System.out.println("Links: " + Integer.toString(links.size()));
                }
            }
            i = d;
            d = startInfo.size() + 50;
        }
    }
}

```

```

        c = startInfo.size() + 50;
    }
    else if(startInfo.elementAt(c).toString().contains("<entitlementStatus>")
&&
        startInfo.elementAt(c).toString().contains("Non")) {

            i = c;
            c = startInfo.size() + 50;

        }

        h = startInfo.size() + 50;
    }
}
}

/*
 * Now that everything is sized properly we will insert it into a String[][]]
 */

for(int c = 0; c < names.size() - 1; c++){
    for(int d = c + 1; d < names.size(); d++){

        if(names.elementAt(d).toString().trim().equals(names.elementAt(c).toString().trim())){

            System.out.println("The names are doubled up");
        }

        if(links.elementAt(d).toString().trim().equals(links.elementAt(c).toString().trim())){

            System.out.println("The links are doubled up");
        }
    }
}

if(links.size() == names.size()){

    gatheredInfo = new String[links.size()][2];
    InformationModule.scienceDirectRelavency = new Double[names.size()][4];
    InformationModule.scienceDirectStatus = new boolean[names.size()];

    for(int a = 0; a < links.size(); a++){

```

```

InformationModule.masterNameList.add(names.elementAt(a).toString());
InformationModule.masterLinkList.add(links.elementAt(a).toString());

InformationModule.scienceDirectRelavency[a][0] = 0.0;
InformationModule.scienceDirectRelavency[a][1] = 0.0;
InformationModule.scienceDirectRelavency[a][2] = 0.0;
InformationModule.scienceDirectRelavency[a][3] = 0.0;

InformationModule.scienceDirectStatus[a] = false;

}

System.out.println("Finished Extracting from index file");
links.clear();
names.clear();
}

/*
 * @param args the command line arguments
 */
public static void main(String args[]) {
    java.awt.EventQueue.invokeLater(new Runnable() {
        public void run() {
            new SD_OptionSelecter().setVisible(true);
        }
    });
}

// Variables declaration - do not modify
private javax.swing.JButton jButtonSubmit;
private javax.swing.JComboBox jComboBoxSetting;
private javax.swing.JLabel jLabel1;
// End of variables declaration
}

```

ScienceDirectStatus.java

```

/*
 * Marico Howe
 * File Name: ScienceDirectStatus.java
 * Description: The purpose of this class is to provides information on
 * the Science Direct download status for articles that have completed the
 * download process.
 */
package webcrawling.Interfaces;

public class ScienceDirectStatus extends javax.swing.JFrame {

    /* Creates new form ScienceDirect_Questionare */
    public ScienceDirectStatus() {
        initComponents();
    }

    /* This method is called from within the constructor to
     * initialize the form.
     * WARNING: Do NOT modify this code. The content of this method is
     * always regenerated by the Form Editor.
     */
    @SuppressWarnings("unchecked")
    // <editor-fold defaultstate="collapsed" desc="Generated Code">
    private void initComponents() {

        jLblOverallFilesDowned = new javax.swing.JLabel();
        jLblOverallFilesFound = new javax.swing.JLabel();
        jTabbedPane1 = new javax.swing.JTabbedPane();
        jScrollPane1 = new javax.swing.JScrollPane();
        jTblJournalStatus = new javax.swing.JTable();
        jScrollPane2 = new javax.swing.JScrollPane();
        jTblKeywordStatus = new javax.swing.JTable();
        jLabel3 = new javax.swing.JLabel();
        jLblOverallRelavency = new javax.swing.JLabel();
        jLabel8 = new javax.swing.JLabel();
        jLblMinimumFiles = new javax.swing.JLabel();
        jLabel9 = new javax.swing.JLabel();
        jBarLocal = new javax.swing.JProgressBar();
        jLblLocalAction = new javax.swing.JLabel();
        jBarOverall = new javax.swing.JProgressBar();
        jLblOverallAction = new javax.swing.JLabel();
        jLabel12 = new javax.swing.JLabel();

        setDefaultCloseOperation(javax.swing.WindowConstants.EXIT_ON_CLOSE);

```

```

jLblOverallFilesDowned.setText("Overall Files Downloaded: 55,215");

jLblOverallFilesFound.setText("Overall Files Found: 100,541");

jTblJournalStatus.setModel(new javax.swing.table.DefaultTableModel(
    new Object [][] {
        {null, null, null, null, null},
        {null, null, null, null, null}
    },
    new String [] {
        "Journal Name", "Files Found", "Files Downloaded", "% of relavent Files",
        "Status"
    }
));
jTblJournalStatus.getTableHeader().setReorderingAllowed(false);
jScrollPane1.setViewportView(jTblJournalStatus);
jTblJournalStatus.getColumnModel().getColumn(0).setResizable(false);
jTblJournalStatus.getColumnModel().getColumn(1).setMinWidth(105);
jTblJournalStatus.getColumnModel().getColumn(1).setPreferredWidth(105);
jTblJournalStatus.getColumnModel().getColumn(1).setMaxWidth(105);
jTblJournalStatus.getColumnModel().getColumn(2).setMinWidth(105);
jTblJournalStatus.getColumnModel().getColumn(2).setPreferredWidth(105);
jTblJournalStatus.getColumnModel().getColumn(2).setMaxWidth(105);
jTblJournalStatus.getColumnModel().getColumn(3).setMinWidth(105);
jTblJournalStatus.getColumnModel().getColumn(3).setPreferredWidth(50);
jTblJournalStatus.getColumnModel().getColumn(3).setMaxWidth(50);
jTblJournalStatus.getColumnModel().getColumn(4).setMinWidth(105);
jTblJournalStatus.getColumnModel().getColumn(4).setPreferredWidth(105);
jTblJournalStatus.getColumnModel().getColumn(4).setMaxWidth(105);

```

```
jTabbedPane1.addTab("Journal Information", jScrollPane1);

jTblKeywordStatus.setModel(new javax.swing.table.DefaultTableModel(
    new Object [][] {
        {null, null},
        {null, null}
    },
    new String [] {
        "Keyword (maybe a variation of the word)", "Downed # of articles for the keyword"
    }
));
jScrollPane2.setViewportView(jTblKeywordStatus);

jTabbedPane1.addTab("Keyword Information", jScrollPane2);

jLabel3.setText("Minimum # of Files downloaded per journal:");
```



```

.addComponent(jLblOverallAction,
javax.swing.GroupLayout.DEFAULT_SIZE, 245, Short.MAX_VALUE))
.addComponent(jLabel9,
javax.swing.GroupLayout.PREFERRED_SIZE, 51,
javax.swing.GroupLayout.PREFERRED_SIZE)
.addGroup(layout.createSequentialGroup()
.addGap(10, 10, 10)
.addComponent(jLblLocalAction,
javax.swing.GroupLayout.DEFAULT_SIZE, 245, Short.MAX_VALUE))
.addComponent(jLblOverallFilesDowned,
javax.swing.GroupLayout.DEFAULT_SIZE, 255, Short.MAX_VALUE)
.addComponent(jLblOverallFilesFound,
javax.swing.GroupLayout.DEFAULT_SIZE, 255, Short.MAX_VALUE)
.addComponent(jLblOverallRelavency,
javax.swing.GroupLayout.DEFAULT_SIZE, 255, Short.MAX_VALUE)
.addComponent(jLabel3,
javax.swing.GroupLayout.PREFERRED_SIZE, 220,
javax.swing.GroupLayout.PREFERRED_SIZE)
.addGroup(layout.createSequentialGroup()
.addGap(22, 22, 22)
.addComponent(jLblMinimumFiles,
javax.swing.GroupLayout.PREFERRED_SIZE, 60,
javax.swing.GroupLayout.PREFERRED_SIZE))
.addComponent(jLabel12,
javax.swing.GroupLayout.PREFERRED_SIZE, 51,
javax.swing.GroupLayout.PREFERRED_SIZE)
.addComponent(jBarLocal,
javax.swing.GroupLayout.PREFERRED_SIZE, 178,
javax.swing.GroupLayout.PREFERRED_SIZE)))
.addContainerGap())
);
layout.setVerticalGroup(
layout.createParallelGroup(javax.swing.GroupLayout.Alignment.LEADING)
.addGroup(javax.swing.GroupLayout.Alignment.TRAILING,
layout.createSequentialGroup()
.addContainerGap()
.addComponent(jLabel8, javax.swing.GroupLayout.PREFERRED_SIZE, 49,
javax.swing.GroupLayout.PREFERRED_SIZE)

.addGroup(layout.createParallelGroup(javax.swing.GroupLayout.Alignment.LEADING)
.addGroup(javax.swing.GroupLayout.Alignment.TRAILING,
layout.createSequentialGroup()
.addGap(39, 39, 39)
.addComponent(jLabel3)

.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.UNRELATED)

```

```

.addComponent(jLblMinimumFiles)

.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.RELATED, 103,
Short.MAX_VALUE)
.addComponent(jLblOverallFilesDowned)

.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.UNRELATED)
.addComponent(jLblOverallFilesFound)

.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.UNRELATED)
.addComponent(jLblOverallRelavency)

.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.RELATED)
.addComponent(jLabel9)

.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.RELATED)
.addComponent(jLblLocalAction,
javax.swing.GroupLayout.PREFERRED_SIZE, 14,
javax.swing.GroupLayout.PREFERRED_SIZE)

.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.RELATED)
.addComponent(jBarLocal,
javax.swing.GroupLayout.PREFERRED_SIZE, 27,
javax.swing.GroupLayout.PREFERRED_SIZE)

.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.UNRELATED)
.addComponent(jLabel12)

.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.RELATED)
.addComponent(jLblOverallAction,
javax.swing.GroupLayout.PREFERRED_SIZE, 14,
javax.swing.GroupLayout.PREFERRED_SIZE)
.addGap(14, 14, 14)
.addComponent(jBarOverall,
javax.swing.GroupLayout.PREFERRED_SIZE, 27,
javax.swing.GroupLayout.PREFERRED_SIZE))
.addGroup(layout.createSequentialGroup()

.addPreferredGap(javax.swing.LayoutStyle.ComponentPlacement.UNRELATED)
.addComponent(jTabbedPane1,
javax.swing.GroupLayout.DEFAULT_SIZE, 393, Short.MAX_VALUE)))
.addContainerGap()
);

pack();
} // </editor-fold>

```

```
/*
 * @param args the command line arguments
 */
public static void main(String args[]) {
    java.awt.EventQueue.invokeLater(new Runnable() {
        public void run() {
            new ScienceDirectStatus().setVisible(true);
        }
    });
}

// Variables declaration - do not modify
public static javax.swing.JProgressBar jBarLocal;
public static javax.swing.JProgressBar jBarOverall;
private javax.swing.JLabel jLabel12;
private javax.swing.JLabel jLabel3;
private javax.swing.JLabel jLabel8;
private javax.swing.JLabel jLabel9;
public static javax.swing.JLabel jLblLocalAction;
public static javax.swing.JLabel jLblMinimumFiles;
public static javax.swing.JLabel jLblOverallAction;
public static javax.swing.JLabel jLblOverallFilesDowned;
public static javax.swing.JLabel jLblOverallFilesFound;
public static javax.swing.JLabel jLblOverallRelavency;
private javax.swing.JScrollPane jScrollPane1;
private javax.swing.JScrollPane jScrollPane2;
private javax.swing.JTabbedPane jTabbedPane1;
public static javax.swing.JTable jTableJournalStatus;
public static javax.swing.JTable jTableKeywordStatus;
// End of variables declaration

}
```

InformationModule.java

```

/*
 * Marico Howe
 * File Name: InformationModule.java
 * Description: The purpose of this class is to store global variables.
 */

package webcrawlingrevised;
import java.util.Vector;

public class InformationModule {

    public static String searchQuery = null;
    public static String baseSaveDirectory = null;
    public static String baseJournalDirectory = null;
    public static String baseJournalSaveFiles = null;

    public static String[][] scienceDirectMasterIndex;
    public static Double[][] scienceDirectRelavency;
    public static boolean[] scienceDirectStatus;
    public static Vector keywordList = new Vector();

    public static Vector masterNameList = new Vector();
    public static Vector masterLinkList = new Vector();
    public static int treebuilderCounter = 0;
    public static int totalSDFiles = 0;
    public static int totaldownedSDFiles = 0;
    //Holds the array position that relates to the currently selected journal
    public static int placeHolder = 0;

    public static int overallWaitTime = 0;
    public static int scienceDirectWaitTime = 0;
    public static int minimumDownload = 0;

    public static Vector scienceDirectUnsearchedLinks = new Vector();
    public static Vector scienceDirectSearchedLinks = new Vector();
    public static Vector scienceDirectUnsearchedDoi = new Vector();
    public static Vector scienceDirectSearchedDoi = new Vector();
    public static Vector scienceDirectSearchedTitles = new Vector();
    public static Vector scienceDirectUnsearchedTitles = new Vector();

    public static Vector previouslySavedJournals = new Vector();
}

```

```
/*
 * The following are for downloading files from pubMed, PubMed Central, and
Agricola
 */

public static String pubMedCentral1 =
"http://eutils.ncbi.nlm.nih.gov/entrez/eutils/esearch.fcgi?db=pmc&term=";
public static String pubMedCentral2 = "&retmax=1000000";

public static String pubMedCentralLinks1 =
"http://www.ncbi.nlm.nih.gov/entrez/eutils/esearch.fcgi?db=pmc&term=";
public static String pubMedCentralLinks2 = "&retmax=1000000";

//This is the link that retrieves all the id tags
public static String pubMed1 =
"http://eutils.ncbi.nlm.nih.gov/entrez/eutils/esearch.fcgi?db=pubmed&term=";
public static String pubMed2 = "&retmax=1000000";

//This is the link that sends the browser to each individual abstract
public static String pubMedLinks1 = "http://www.ncbi.nlm.nih.gov/pubmed/";
public static String pubMedLinks2 =
"?ordinalpos=1&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_
DefaultReportPanel.Pubmed_RVDocSum";

//The following Strings represent the base directory for each web site
public static String pubMedDir = " ";
// public static String agricolaDir = " ";
public static String pubMedCentralDir = " ";
public static String scienceDirectDir = " ";

}// End of Class
```

Main.java

```
/*
 * Marico Howe
 * File Name: Main.java
 * Description: The purpose of this file is the Main class for the project.
 */

package webcrawlingrevised;

import Threads.OverviewThread;
import javax.swing.UIManager;

public class Main {

    /*
     * @param args the command line arguments
     */
    public static void main(String[] args) {
        // TODO code application logic here

        // TODO code application logic here
        try{

            UIManager.setLookAndFeel("com.sun.java.swing.plaf.windows.WindowsLookAndFeel");
        }

        catch (Exception e){
            System.out.println("Unable to load Windows look and feel");
        }

        OverviewThread oversight = new OverviewThread();
        oversight.start();

    }
}
```

Appendix B: Results by species from Gene database in NCBI

Homo sapiens

1. BMP4

Official Symbol: BMP4 and Name: bone morphogenetic protein 4[Homo sapiens]
 Other Aliases: BMP2B, BMP2B1, MCOPS6, OFC11, ZYME
 Other Designations: BMP-2B; BMP-4; bone morphogenetic protein 2B
 Chromosome: 14; Location: 14q22-q23
 Annotation: Chromosome 14NC_000014.8 (54416454..54423554, complement)
 MIM: 112262
 ID: 652

2. SOX2

Official Symbol: SOX2 and Name: SRY (sex determining region Y)-box 2[Homo sapiens]
 Other Aliases: ANOP3, MCOPS3
 Other Designations: SRY-related HMG-box gene 2; transcription factor SOX-2;
 transcription factor SOX2
 Chromosome: 3; Location: 3q26.3-q27
 Annotation: Chromosome 3NC_000003.11 (181429712..181432224)
 MIM: 184429
 ID: 6657

3. OTX2

Official Symbol: OTX2 and Name: orthodenticle homeobox 2[Homo sapiens]
 Other Aliases: CPHD6, MCOPS5
 Other Designations: homeobox protein OTX2; orthodenticle homolog 2
 Chromosome: 14; Location: 14q22.3
 Annotation: Chromosome 14NC_000014.8 (57267425..57277194, complement)
 MIM: 600037
 ID: 5015

4. STRA6

Official Symbol: STRA6 and Name: stimulated by retinoic acid 6[Homo sapiens]
 Other Aliases: PP14296, MCOPCB8, MCOPS9
 Other Designations: stimulated by retinoic acid 6 homolog; stimulated by retinoic acid
 gene 6 homolog; stimulated by retinoic acid gene 6 protein homolog
 Chromosome: 15; Location: 15q24.1
 Annotation: Chromosome 15NC_000015.9 (74471807..74502046, complement)
 MIM: 610745
 ID: 64220

5. BCOR

Official Symbol: BCOR and Name: BCL6 corepressor[Homo sapiens]
 Other Aliases: ANOP2, MAA2, MCOPS2
 Other Designations: BCL-6 corepressor; BCL-6 interacting corepressor
 Chromosome: X; Location: Xp11.4
 Annotation: Chromosome XNC_000023.10 (39910499..40036582, complement)
 MIM: 300485
 ID: 54880

6. HCCS

Official Symbol: HCCS and Name: holocytochrome c synthase[Homo sapiens]
 Other Aliases: CCHL, MCOPS7
 Other Designations: cytochrome c heme-lyase; cytochrome c-type heme lyase;
 holocytochrome c-type synthase
 Chromosome: X; Location: Xp22.3
 Annotation: Chromosome XNC_000023.10 (11129406..11141206)
 MIM: 300056
 ID: 3052

7. SMOC1

Official Symbol: SMOC1 and Name: SPARC related modular calcium binding 1[Homo sapiens]
 Other Aliases: OAS
 Other Designations: SPARC-related modular calcium-binding protein 1; secreted modular calcium-binding protein 1
 Chromosome: 14; Location: 14q24.2
 Annotation: Chromosome 14NC_000014.8 (70346114..70499083)
 MIM: 608488
 ID: 64093

8. GDF6

Official Symbol: GDF6 and Name: growth differentiation factor 6[Homo sapiens]
 Other Aliases: BMP13, CDMP2, KFM, KFS, KFS1, KFSL, MCOP4, MCOPCB6, SCDO4, SGM1
 Other Designations: GDF-6; Klip-Feil malformation; Klippel-Feil malformation; Klippel-Feil syndrome; growth/differentiation factor 16; growth/differentiation factor 6
 Chromosome: 8; Location: 8q22.1
 Annotation: Chromosome 8NC_000008.10 (97154558..97173020, complement)
 MIM: 601147
 ID: 392255

9. VSX2

Official Symbol: VSX2 and Name: visual system homeobox 2[Homo sapiens]
 Other Aliases: CHX10, HOX10, MCOP2, MCOPCB3, RET1
 Other Designations: ceh-10 homeo domain containing homolog; ceh-10 homeodomain-containing homolog; homeobox protein CHX10
 Chromosome: 14; Location: 14q24.3

Annotation: Chromosome 14NC_000014.8 (74706175..74729441)
MIM: 142993
ID: 338917

10. RAX

Official Symbol: RAX and Name: retina and anterior neural fold homeobox[Homo sapiens]
Other Aliases: MCOP3, RX
Other Designations: retina and anterior neural fold homeobox protein; retinal homeobox protein Rx
Chromosome: 18; Location: 18q21.32
Annotation: Chromosome 18NC_000018.9 (56934267..56940625, complement)
MIM: 601881
ID: 30062

11. SHH

Official Symbol: SHH and Name: sonic hedgehog[Homo sapiens]
Other Aliases: tcag7.582, HHG1, HLP3, HPE3, MCOPCB5, SMMCI, TPT, TPTPS
Other Designations: sonic hedgehog homolog; sonic hedgehog protein
Chromosome: 7; Location: 7q36
Annotation: Chromosome 7NC_000007.13 (155595558..155604967, complement)
MIM: 600725
ID: 6469

12. SIX6

Official Symbol: SIX6 and Name: SIX homeobox 6[Homo sapiens]
Other Aliases: MCOPCT2, OPTX2, Six9
Other Designations: homeobox protein SIX6; homeodomain protein OPTX2; optic homeobox 2; sine oculis homeobox homolog 6
Chromosome: 14; Location: 14q23.1
Annotation: Chromosome 14NC_000014.8 (60975938..60978525)
MIM: 606326
ID: 4990

13. PAX6

Official Symbol: PAX6 and Name: paired box 6[Homo sapiens]
Other Aliases: AN, AN2, D11S812E, MGDA, WAGR
Other Designations: aniridia type II protein; oculorhombin; paired box homeotic gene-6; paired box protein Pax-6
Chromosome: 11; Location: 11p13
Annotation: Chromosome 11NC_000011.9 (31806340..31839509, complement)
MIM: 607108
ID: 5080

Mus Musculus

1. Crx

Official Symbol: Crx and Name: cone-rod homeobox containing gene[Mus musculus]
 Other Aliases: Crx1
 Other Designations: cone-rod homeobox protein
 Chromosome: 7; Location: 7 8.6 cM
 Annotation: Chromosome 7NC_000073.6 (15865947..15879955, complement)
 ID: 12951

2. Sox1

Official Symbol: Sox1 and Name: SRY-box containing gene 1[Mus musculus]
 Other Aliases: BB176347, Sox-1
 Other Designations: transcription factor SOX-1
 Chromosome: 8; Location: 8 5.73 cM
 Annotation: Chromosome 8NC_000074.6 (12395519..12399555)
 ID: 20664

3. Sox8

Official Symbol: Sox8 and Name: SRY-box containing gene 8[Mus musculus]
 Other Designations: transcription factor SOX-8
 Chromosome: 17; Location: 17 12.69 cM
 Annotation: Chromosome 17NC_000083.6 (25565893..25570686, complement)
 ID: 20681

4. Rd3

Official Symbol: Rd3 and Name: retinal degeneration 3[Mus musculus]
 Other Aliases: 3322402L07Rik, rd-3, rd3
 Other Designations: protein RD3
 Chromosome: 1; Location: 1 97.09 cM
 Annotation: Chromosome 1NC_000067.6 (191977373..191988282)
 ID: 74023

5. Stra6

Official Symbol: Stra6 and Name: stimulated by retinoic acid gene 6[Mus musculus]
 Other Aliases: AI891933
 Other Designations: retinoic acid-responsive protein; stimulated by retinoic acid gene 6 protein
 Chromosome: 9; Location: 9 C
 Annotation: Chromosome 9NC_000075.6 (58129088..58153997)
 ID: 20897

6. Pax6

Official Symbol: Pax6 and Name: paired box gene 6[Mus musculus]
 Other Aliases: RP23-431C3.1, 1500038E17Rik, AEY11, Dey, Gsfaey11, Pax-6, Sey

Other Designations: Dickie's small eye; oculorhombin; paired box protein Pax-6; small eye

Chromosome: 2; Location: 2 55.31 cM

Annotation: Chromosome 2NC_000068.7 (105668896..105697364)

ID: 18508

7. Sox9

Official Symbol: Sox9 and Name: SRY-box containing gene 9[Mus musculus]

Other Aliases: RP23-36D5.1, 2010306G03Rik, AV220920, mKIAA4243

Other Designations: transcription factor SOX-9

Chromosome: 11; Location: 11 77.27 cM

Annotation: Chromosome 11NC_000077.6 (112782210..112787757)

ID: 20682

8. Pax2

Official Symbol: Pax2 and Name: paired box gene 2[Mus musculus]

Other Aliases: Opdc, Pax-2

Other Designations: optic disc coloboma; paired box protein Pax-2

Chromosome: 19; Location: 19 38.09 cM

Annotation: Chromosome 19NC_000085.6 (44757394..44837871)

ID: 18504

9. Sox2

Official Symbol: Sox2 and Name: SRY-box containing gene 2[Mus musculus]

Other Aliases: AL606746.1, Sox-2, lcc, ysb

Other Designations: transcription factor SOX-2

Chromosome: 3; Location: 3 16.93 cM

Annotation: Chromosome 3NC_000069.6 (34650005..34652461)

ID: 20674

10. Sox11

Official Symbol: Sox11 and Name: SRY-box containing gene 11[Mus musculus]

Other Aliases: 1110038H03Rik, 6230403H02Rik, AI836553, end1

Other Designations: transcription factor SOX-11

Chromosome: 12; Location: 12

Annotation: Chromosome 12NC_000078.6 (27334268..27342718, complement)

ID: 20666

11. Vax2

Official Symbol: Vax2 and Name: ventral anterior homeobox containing gene 2[Mus musculus]

Other Aliases: Dres93

Other Designations: ventral anterior homeobox 2; ventral retina homeodomain protein

Chromosome: 6; Location: 6 35.94 cM

Annotation: Chromosome 6NC_000072.6 (83711264..83738304)

ID: 24113

Rattus norvegicus

1. Pax6

Official Symbol: Pax6 and Name: paired box 6[Rattus norvegicus]
 Other Designations: oculorhombin; paired box gene 6; paired box homeotic gene 6;
 paired box protein Pax-6
 Chromosome: 3; Location: 3q32
 Annotation: Chromosome 3NC_005102.3 (102327226..102348223)
 ID: 25509

2. Pax4

Official Symbol: Pax4 and Name: paired box 4[Rattus norvegicus]
 Other Designations: paired box gene 4; paired box protein Pax-4
 Chromosome: 4; Location: 4q22
 Annotation: Chromosome 4NC_005103.3 (55483131..55488075, complement)
 ID: 83630

3. Pax2

Official Symbol: Pax2 and Name: paired box 2[Rattus norvegicus]
 Other Designations: paired box gene 2; paired box protein Pax-2
 Chromosome: 1; Location: 1q54
 Annotation: Chromosome 1NC_005100.3 (271947266..272025770)
 ID: 293992

4. Stra6

Official Symbol: Stra6 and Name: stimulated by retinoic acid 6[Rattus norvegicus]
 Other Aliases: RGD1307551
 Other Designations: stimulated by retinoic acid gene 6 homolog; stimulated by retinoic acid gene 6 protein homolog
 Chromosome: 8; Location: 8q24
 Annotation: Chromosome 8NC_005107.3 (62701454..62720528)
 ID: 363071

5. Prph2

Official Symbol: Prph2 and Name: peripherin 2[Rattus norvegicus]
 Other Aliases: RSRDS, Rds
 Other Designations: peripherin-2; retinal degeneration slow protein; retinal degeneration, slow
 Chromosome: 9; Location: 9q12
 Annotation: Chromosome 9NC_005108.3 (15002816..15006668, complement)
 ID: 25534

6. Vax2

Official Symbol: Vax2 and Name: ventral anterior homeobox 2[Rattus norvegicus]
 Other Designations: ventral anterior homeobox containing gene 2
 Chromosome: 4; Location: 4q34

Annotation: Chromosome 4NC_005103.3 (179975806..180001477)
ID: 64572

Danio rerio

1. pax2a

Official Symbol: pax2a and Name: paired box gene 2a[Danio rerio]
 Other Aliases: CH73-104D2.1, PAXZF-B, Pax-2, cb378, noi, pax-b, pax2.1, pax2a1, pax[zf-b], paxb
 Other Designations: no isthmus protein; paired box gene 2.1; paired box homeotic gene 2a; paired box protein Pax-2a
 Chromosome: 13
 Annotation: Chromosome 13NC_007124.5 (29994561..30027366)
 ID: 30425

2. pax6a

Official Symbol: pax6a and Name: paired box gene 6a[Danio rerio]
 Other Aliases: DKEYP-46C10.1, PAXZF-A, Pax6.1, cb280, fc20e07, pax-a, pax6, pax[zf-a], paxzfa, wu:fc20e07, zfpax-6a, zfpax-6b
 Other Designations: etID309716.25; paired box homeotic gene 6; paired box protein Pax-6; paired box protein Pax[Zf-a]; pax-6
 Chromosome: 25
 Annotation: Chromosome 25NC_007136.5 (15289723..15310396, complement)
 ID: 30567

3. sox2

Official Symbol: sox2 and Name: SRY-box containing gene 2[Danio rerio]
 Other Aliases: cb236, wu:fb83g04, wu:fc14d07, zgc:65860, zgc:77389
 Other Designations: soxp; transcription factor SOX2; transcription factor Sox-2
 Chromosome: 22
 Annotation: Chromosome 22NC_007133.5 (40333599..40335684, complement)
 ID: 378723

4. sox9b

Official Symbol: sox9b and Name: SRY-box containing gene 9b[Danio rerio]
 Other Aliases: fb18d01, wu:fb18d01
 Chromosome: 3
 Annotation: Chromosome 3NC_007114.5 (63179327..63184452, complement)
 ID: 60642

5. pax6b

Official Symbol: pax6b and Name: paired box gene 6b[Danio rerio]
 Other Aliases: DKEY-157G7.2, Pax6.2, cb566, fc09c10, id:ibd5095, wu:fc09c10, wu:fc33g08
 Other Designations: sri(l)
 Chromosome: 7
 Annotation: Chromosome 7NC_007118.5 (16636737..16662404)
 ID: 60639

6. rx3

Official Symbol: rx3 and Name: retinal homeobox gene 3[*Danio rerio*]

Other Designations: chk; chokh; eyes missing; eym; retinal homeobox protein Rx3

Chromosome: 21

Annotation: Chromosome 21NC_007132.5 (9291584..9294542)

ID: 30474

Appendix C: *Homo sapiens GeneCards Results with Gene related*

Defects

- Defects in **SOX2** are the cause of microphthalmia syndromic type 3 (MCOPS3). Microphthalmia is a clinically heterogeneous disorder of eye formation, ranging from small size of a single eye to complete bilateral absence of ocular tissues (anophthalmia). In many cases, microphthalmia/anophthalmia occurs in association with syndromes that include non-ocular abnormalities.
- Defects in **OTX2** are the cause of microphthalmia syndromic type 5 (MCOPS5). Up to 80% of cases of microphthalmia occur in association with syndromes that include non-ocular abnormalities. MCOPS5 patients manifest unilateral or bilateral microphthalmia/clinical anophthalmia and variable additional features including coloboma, microcornea, cataract, retinal dystrophy, hypoplasia or agenesis of the optic nerve, agenesis of the corpus callosum, developmental delay, joint laxity, hypotonia, and seizures.
- Defects in **STRA6** are the cause of microphthalmia syndromic type 9 (MCOPS9) also called Matthew-Wood syndrome or Spear syndrome. In many cases, microphthalmia/anophthalmia occurs in association with syndromes that include non-ocular abnormalities. Mutations in STRA6 may be a cause of isolated colobomatous microphthalmia, a disorder of the eye characterized by an abnormally small ocular globe
- Defects in **BCOR** are the cause of microphthalmia syndromic type 2 (MCOPS2). MCOPS2 is a very rare multiple congenital anomaly syndrome characterized by eye anomalies (congenital cataract, microphthalmia, or secondary glaucoma).
- Defects in **HCCS** are a cause of microphthalmia syndromic type 7 (MCOPS7) also known as microphthalmia with linear skin defects (MLS) or MIDAS syndrome.
- Defects in **BMP4** are the cause of microphthalmia syndromic type 6 (MCOPS6) also known as microphthalmia and pituitary anomalies or microphthalmia with brain and digit developmental anomalies.
- Defects in **SMOC1** are the cause of ophthalmoacromelic syndrome (OAS). A rare disorder presenting with anophthalmia or microphthalmia and limb anomalies. Most patients have bilateral anophthalmia/ microphthalmia, but unilateral abnormality is also noted. Other malformations are rare, but venous or vertebral anomaly was recognized each in single cases.
- Defects in **GDF6** are the cause of microphthalmia isolated type 4 (MCOP4).

- Defects in **VSX2** are the cause of microphthalmia isolated type 2 (MCOP2) also known as isolated clinical anophthalmia. Defects in VSX2 are the cause of microphthalmia with cataracts and iris abnormalities (MCOPCTI). Defects in VSX2 are the cause of microphthalmia isolated with coloboma type 3 (MCOPCB3) also known as isolated colobomatous microphthalmia 3. Ocular colobomas are a set of malformations resulting from abnormal morphogenesis of the optic cup and stalk, and the fusion of the fetal fissure (optic fissure).
- Defects in **RAX** are the cause of microphthalmia isolated type 3 (MCOP3).
- Defects in **SHH** are the cause of microphthalmia isolated with coloboma type 5 (MCOPCB5). Ocular colobomas are a set of malformations resulting from abnormal morphogenesis of the optic cup and stalk, and the fusion of the fetal fissure (optic fissure).
- Defects in **SIX6** are the cause of microphthalmia isolated with cataract type 2 (MCOPCT2).
- Defects in **PAX6** are the cause of aniridia (AN). A congenital, bilateral, panocular disorder characterized by complete absence of the iris or extreme iris hypoplasia. Aniridia is not just an isolated defect in iris development but it is associated with macular and optic nerve hypoplasia, cataract, corneal changes, nystagmus. Visual acuity is generally low but is unrelated to the degree of iris hypoplasia. Glaucoma is a secondary problem causing additional visual loss over time. Defects in PAX6 are a cause of Peters anomaly (PAN). Peters anomaly consists of a central corneal leukoma, absence of the posterior corneal stroma and Descemet membrane, and a variable degree of iris and lenticular attachments to the central aspect of the posterior cornea. Defects in PAX6 are a cause of foveal hypoplasia (FOVHYP). Foveal hypoplasia can be isolated or associated with presenile cataract. Defects in PAX6 are a cause of keratitis hereditary (KERH). An ocular disorder characterized by corneal opacification, recurrent stromal keratitis and vascularization. Defects in PAX6 are a cause of coloboma of iris choroid and retina (COI) also known as uveoretinal coloboma. Defects in PAX6 are a cause of coloboma of optic nerve (COLON). Defects in PAX6 are a cause of bilateral optic nerve hypoplasia (BONH) also known as bilateral optic nerve aplasia.

Appendix D: Translating Time: The Eye Web site Source Code

index.html

```
<!DOCTYPE html PUBLIC "-//W3C//DTD XHTML 1.0 Transitional//EN"
"http://www.w3.org/TR/xhtml1/DTD/xhtml1-transitional.dtd">

<html xmlns="http://www.w3.org/1999/xhtml">

<head>
<meta http-equiv="Content-Type" content="text/html; charset=utf-8" />
<title>Translating Time: The Eye Home Page</title>
<style type="text/css">
<!--
body {
    background: #42413C;
    margin: 0;
    padding: 0;
    color: #333;
    font-family: Verdana, Arial, Helvetica, sans-serif;
    font-size: 100%;
    line-height: 1.4;
}

/* ~~ Element/tag selectors ~~ */
ul, ol, dl { /* Due to variations between browsers, it's best practices to zero padding and
margin on lists. For consistency, you can either specify the amounts you want here, or on
the list items (LI, DT, DD) they contain. Remember that what you do here will cascade to
the .nav list unless you write a more specific selector. */
    padding: 0;
    margin: 0;
}

```

```

h1, h2, h3, h4, h5, h6, p {
    margin-top: 0; /* removing the top margin gets around an issue where margins
can escape from their containing div. The remaining bottom margin will hold it away
from any elements that follow. */
    padding-right: 15px;
    padding-left: 15px; /* adding the padding to the sides of the elements within the
divs, instead of the divs themselves, gets rid of any box model math. A nested div with
side padding can also be used as an alternate method. */
}

a img { /* this selector removes the default blue border displayed in some browsers
around an image when it is surrounded by a link */
    border: none;
}

/* ~~ Styling for your site's links must remain in this order - including the group of
selectors that create the hover effect. ~~ */
a:link {
    color: #666666;
    text-decoration: underline; /* unless you style your links to look extremely
unique, it's best to provide underlines for quick visual identification */
    background-color: #666;
}

a:visited {
    color: #6E6C64;
    text-decoration: underline;
}

a:hover, a:active, a:focus { /* this group of selectors will give a keyboard navigator the
same hover experience as the person using a mouse. */
    text-decoration: none;
}

```

```
/* ~~this fixed width container surrounds the other divs~~ */
.container {
    width: 960px;
    background: #FFF;
    margin: 0 auto; /* the auto value on the sides, coupled with the width, centers the layout */
}
```

/* ~~ the header is not given a width. It will extend the full width of your layout. It contains an image placeholder that should be replaced with your own linked logo ~~ */

```
.header {
    background: #ADB96E;
}
```

/* ~~ These are the columns for the layout. ~~

1) Padding is only placed on the top and/or bottom of the divs. The elements within these divs have padding on their sides. This saves you from any "box model math". Keep in mind, if you add any side padding or border to the div itself, it will be added to the width you define to create the *total* width. You may also choose to remove the padding on the element in the div and place a second div within it with no width and the padding necessary for your design. You may also choose to remove the padding on the element in the div and place a second div within it with no width and the padding necessary for your design.

2) No margin has been given to the columns since they are all floated. If you must add margin, avoid placing it on the side you're floating toward (for example: a right margin on a div set to float right). Many times, padding can be used instead. For divs where this rule must be broken, you should add a "display:inline" declaration to the div's rule to tame a bug where some versions of Internet Explorer double the margin.

3) Since classes can be used multiple times in a document (and an element can also have multiple classes applied), the columns have been assigned class names instead of IDs. For

example, two sidebar divs could be stacked if necessary. These can very easily be changed to IDs if that's your preference, as long as you'll only be using them once per document.

4) If you prefer your nav on the right instead of the left, simply float these columns the opposite direction (all right instead of all left) and they'll render in reverse order. There's no need to move the divs around in the HTML source.

```
/*
.mainsidebar {
    float: left;
    width: 180px;
    padding-bottom: 10px;
    background-color: #000000;
}

.content {
    padding: 10px 0;
    width: 780px;
    float: left;
}

/* ~~ This grouped selector gives the lists in the .content area space ~~ */
.content ul, .content ol {
    padding: 0 15px 15px 40px; /* this padding mirrors the right padding in the
headings and paragraph rule above. Padding was placed on the bottom for space between
other elements on the lists and on the left to create the indentation. These may be adjusted
as you wish. */
}
```

```

/* ~~ The navigation list styles (can be removed if you choose to use a premade flyout
menu like Spry) ~~ */

ul.nav {
    list-style: none; /* this removes the list marker */

    border-top: 1px solid #666; /* this creates the top border for the links - all others
are placed using a bottom border on the LI */

    margin-bottom: 15px; /* this creates the space between the navigation on the
content below */
}

ul.nav li {
    border-bottom: 1px solid #666; /* this creates the button separation */

}

ul.nav a, ul.nav a:visited { /* grouping these selectors makes sure that your links retain
their button look even after being visited */

    padding: 5px 5px 5px 15px;

    display: block; /* this gives the link block properties causing it to fill the whole LI
containing it. This causes the entire area to react to a mouse click. */

    width: 160px; /*this width makes the entire button clickable for IE6. If you don't
need to support IE6, it can be removed. Calculate the proper width by subtracting the
padding on this link from the width of your sidebar container. */

    text-decoration: none;

    background-color: #000000;
}

ul.nav a:hover, ul.nav a:active, ul.nav a:focus { /* this changes the background and text
color for both mouse and keyboard navigators */

    color: #690;

    background-color: #666666;
}

/* ~~ The footer ~~ */

.footer {

```

```

padding: 10px 0;
background: #CCC49F;
position: relative; /* this gives IE6 hasLayout to properly clear */
clear: both; /* this clear property forces the .container to understand where the
columns end and contain them */
background-color: #000000;
}

/* ~~ miscellaneous float/clear classes ~~ */

.fltrt { /* this class can be used to float an element right in your page. The floated
element must precede the element it should be next to on the page. */
float: right;
margin-left: 8px;
}

.flflft { /* this class can be used to float an element left in your page. The floated element
must precede the element it should be next to on the page. */
float: left;
margin-right: 8px;
}

.clearfloat { /* this class can be placed on a <br /> or empty div as the final element
following the last floated div (within the #container) if the #footer is removed or taken
out of the #container */
clear:both;
height:0;
font-size: 1px;
line-height: 0px;
}

-->

</style></head>

```

```

<body>

<div class="container">

    <div class="header"><a href="#"></a>

    <!-- end .header --></div>

    <div class="mainsidebar">

        <ul class="nav">

            <li><a href="ttacrosmammilianspecies.html" title="Translating Time">Translating Time</a></li>

            <li><a href="eye.html" title="The Eye">The Eye</a></li>

            <li><a href="semiautomatedlitrev.php" title="Semi-Automated Literature Review">Semi-Automated Literature Review</a></li>

            <li><a href="geneontology.html" title="Gene Ontology">Gene Ontology</a></li>

            <li><a href="aboutauthor.html" title="About the Author">About the Author</a></li>

            <li><a href="http://bioinformatics.ualr.edu/" title="UALR/UAMS Joint Bioinformatics Program">UALR/UAMS Bioinformatics Program</a></li>

            <li><a href="references.html" title="References">References</a></li>

            <li><a href="survey.html" title="Please take the time to take a survey">Survey</a></li>

        </ul>

    </div>

    <div class="content">

        <h1>Overview</h1>

        <p>The overall objective of this dissertation is to gain an understanding of the timing of human and animal eye development events. This is expected to eventually enable improvements in diagnostic and intervention capabilities for human diseases involving the eye. It is useful to understand eye development in animals because, as model organisms, the knowledge obtained through the study of these organisms can help us better understand humans. The conservation of pathways and genetic material in the


```

development process allow us to compare human development with those of the model organisms. We, as researchers, rely on knowledge gained from other organisms as well as organism from the same species. This knowledge leads to research and ultimately medical decisions that will increase the ability to treat and prevent much human illness. Use of model organisms makes it possible to do research that would be ethically unacceptable in humans. </p>

<p> Specific research, that forms the foundation upon which the present research builds, developed a mathematical model of neurodevelopment (Clancy et al., 2007) based on nine eutherian mammals: Felis domestica (cat), Mustela putorius furo (ferret), Mesocricetus auratus (hamster), Macaca mulatta (monkey), Homo sapiens (human), Mus musculus (mouse), Oryctolagus cuniculus (rabbit), Rattus norvegicus (rat), and Acomys cahirinus (spiny mouse). The original intent of the mathematical model was to create, on the one hand, a scale showing a sequence of neurodevelopmental events and mapping them to numbered values, and on the other hand, a scale of species along which species that develop quickly are mapped to low numbers and species that develop slowly are mapped to high numbers. This permitted the two values, developmental event and species scores, to be combined to infer the time of an unscored event in a specified species. This helps in the understanding of humans because it provides the foundation from which we can extrapolate the times of neurodevelopmental events in humans by looking at when the corresponding neurodevelopmental events occurred in animals. This is important because detailed timing of neurodevelopmental events in humans is often obscure. </p>

```

<p>&nbsp;</p>
</div>
<div class="footer">
<p align="center">This page was last modified on 6 May 2013.</p>
<!-- end .footer --></div>
<!-- end .container --></div>
</body>
</html>

```

ttacrosmammalspecies.html

```

<!DOCTYPE html PUBLIC "-//W3C//DTD XHTML 1.0 Transitional//EN"
"http://www.w3.org/TR/xhtml1/DTD/xhtml1-transitional.dtd">

<html xmlns="http://www.w3.org/1999/xhtml">

<head>
<meta http-equiv="Content-Type" content="text/html; charset=utf-8" />
<title>Translating Time Across Mammalian Species</title>
<style type="text/css">
<!--
body {
    background: #42413C;
    margin: 0;
    padding: 0;
    color: #333;
    font-family: Verdana, Arial, Helvetica, sans-serif;
    font-size: 100%;
    line-height: 1.4;
}

/* ~~ Element/tag selectors ~~ */
ul, ol, dl { /* Due to variations between browsers, it's best practices to zero padding and
margin on lists. For consistency, you can either specify the amounts you want here, or on
the list items (LI, DT, DD) they contain. Remember that what you do here will cascade to
the .nav list unless you write a more specific selector. */
    padding: 0;
    margin: 0;
}
h1, h2, h3, h4, h5, h6, p {

```

```
margin-top: 0; /* removing the top margin gets around an issue where margins
can escape from their containing div. The remaining bottom margin will hold it away
from any elements that follow. */
```

```
padding-right: 15px;
```

```
padding-left: 15px; /* adding the padding to the sides of the elements within the
divs, instead of the divs themselves, gets rid of any box model math. A nested div with
side padding can also be used as an alternate method. */
```

```
}
```

```
a img { /* this selector removes the default blue border displayed in some browsers
around an image when it is surrounded by a link */
```

```
border: none;
```

```
}
```

```
/* ~ Styling for your site's links must remain in this order - including the group of
selectors that create the hover effect. ~~ */
```

```
a:link {
```

```
color: #666666;
```

```
text-decoration: underline; /* unless you style your links to look extremely
unique, it's best to provide underlines for quick visual identification */
```

```
background-color: #666;
```

```
}
```

```
a:visited {
```

```
color: #6E6C64;
```

```
text-decoration: underline;
```

```
}
```

```
a:hover, a:active, a:focus { /* this group of selectors will give a keyboard navigator the
same hover experience as the person using a mouse. */
```

```
text-decoration: none;
```

```
}
```

```
/* ~this fixed width container surrounds the other divs~ */
```

```
.container {
    width: 960px;
    background: #FFF;
    margin: 0 auto; /* the auto value on the sides, coupled with the width, centers the layout */
}

/* ~~ the header is not given a width. It will extend the full width of your layout. It contains an image placeholder that should be replaced with your own linked logo ~~ */
.header {
    background: #ADB96E;
}

/* ~~ These are the columns for the layout. ~~
```

1) Padding is only placed on the top and/or bottom of the divs. The elements within these divs have padding on their sides. This saves you from any "box model math". Keep in mind, if you add any side padding or border to the div itself, it will be added to the width you define to create the *total* width. You may also choose to remove the padding on the element in the div and place a second div within it with no width and the padding necessary for your design. You may also choose to remove the padding on the element in the div and place a second div within it with no width and the padding necessary for your design.

2) No margin has been given to the columns since they are all floated. If you must add margin, avoid placing it on the side you're floating toward (for example: a right margin on a div set to float right). Many times, padding can be used instead. For divs where this rule must be broken, you should add a "display:inline" declaration to the div's rule to tame a bug where some versions of Internet Explorer double the margin.

3) Since classes can be used multiple times in a document (and an element can also have multiple classes applied), the columns have been assigned class names instead of IDs. For example, two sidebar divs could be stacked if necessary. These can very easily be

changed to IDs if that's your preference, as long as you'll only be using them once per document.

4) If you prefer your nav on the right instead of the left, simply float these columns the opposite direction (all right instead of all left) and they'll render in reverse order. There's no need to move the divs around in the HTML source.

```
*/
.mainsidebar {
    float: left;
    width: 180px;
    padding-bottom: 10px;
    background-color: #000000;
}

.content {
    padding: 10px 0;
    width: 780px;
    float: left;
}

/* ~~ This grouped selector gives the lists in the .content area space ~~ */
.content ul, .content ol {
    padding: 0 15px 15px 40px; /* this padding mirrors the right padding in the
headings and paragraph rule above. Padding was placed on the bottom for space between
other elements on the lists and on the left to create the indentation. These may be adjusted
as you wish. */
}
```

```

/* ~~ The navigation list styles (can be removed if you choose to use a premade flyout
menu like Spry) ~~ */

ul.nav {
    list-style: none; /* this removes the list marker */

    border-top: 1px solid #666; /* this creates the top border for the links - all others
are placed using a bottom border on the LI */

    margin-bottom: 15px; /* this creates the space between the navigation on the
content below */
}

ul.nav li {
    border-bottom: 1px solid #666; /* this creates the button separation */

}

ul.nav a, ul.nav a:visited { /* grouping these selectors makes sure that your links retain
their button look even after being visited */

    padding: 5px 5px 5px 15px;

    display: block; /* this gives the link block properties causing it to fill the whole LI
containing it. This causes the entire area to react to a mouse click. */

    width: 160px; /*this width makes the entire button clickable for IE6. If you don't
need to support IE6, it can be removed. Calculate the proper width by subtracting the
padding on this link from the width of your sidebar container. */

    text-decoration: none;

    background-color: #000000;
}

ul.nav a:hover, ul.nav a:active, ul.nav a:focus { /* this changes the background and text
color for both mouse and keyboard navigators */

    color: #690;

    background-color: #666666;
}

/* ~~ The footer ~~ */

.footer {

```

```

padding: 10px 0;
background: #CCC49F;
position: relative; /* this gives IE6 hasLayout to properly clear */
clear: both; /* this clear property forces the .container to understand where the
columns end and contain them */
background-color: #000000;
}

/* ~~ miscellaneous float/clear classes ~~ */

.fltrt { /* this class can be used to float an element right in your page. The floated
element must precede the element it should be next to on the page. */
float: right;
margin-left: 8px;
}

.flflft { /* this class can be used to float an element left in your page. The floated element
must precede the element it should be next to on the page. */
float: left;
margin-right: 8px;
}

.clearfloat { /* this class can be placed on a <br /> or empty div as the final element
following the last floated div (within the #container) if the #footer is removed or taken
out of the #container */
clear:both;
height:0;
font-size: 1px;
line-height: 0px;
}

-->

</style></head>

```

```

<body>

<div class="container">

    <div class="header"><a href="#"></a>
    <!-- end .header --></div>

    <div class="mainsidebar">
        <ul class="nav">
            <li><a href="index.html" title="Home Page">Home Page</a></li>
            <li><a href="eye.html" title="The Eye">The Eye</a></li>
            <li><a href="semiautomatedlitrev.php" title="Semi-Automated Literature Review">Semi-Automated Literature Review</a></li>
            <li><a href="geneontology.html" title="Gene Ontology">Gene Ontology</a></li>
            <li><a href="aboutauthor.html" title="About the Author">About the Author</a></li>
            <li><a href="http://bioinformatics.ualr.edu/" title="UALR/UAMS Joint Bioinformatics Program">UALR/UAMS Bioinformatics Program</a></li>
            <li><a href="references.html" title="References">References</a></li>
            <li><a href="survey.html" title="Please take the time to take a survey">Survey</a></li>
        </ul>
    </div>

    <div class="content">
        <h1><strong>Translating Time Across Mammalian Species</strong></h1>
        <p>The overall objective of the translating time project has been to gain understanding of human neurodevelopmental events such that improvements could be made to diagnostic and intervention capabilities (DeFelici, 2001). The original generic mammalian model included nine eutherian mammals: <em>Felis domestica</em> (cat), <em>Mustela putorius furo</em> (ferret), <em>Mesocricetus auratus</em> (hamster), <em>Macaca mulatta</em> (monkey), <em>Homo sapiens</em> (humans), <em>Mus musculus</em> (mouse), <em>Oryctolagus cuniculus</em> (rabbit), <em>Rattus
    
```

norvegicus (rat), and Acomys cahirinus (spiny mouse). The original intent of the statistical model (Raz, 2004) was to create, on the one hand, a scale of developmental events such that early events score low and later events score high, and on the other hand, an additional scale of species where fast-developing species score low and slow-developing species score high. Therefore the two scores, of event and of species, could be combined to infer the time of an event in a specified species based on other event times and other species. </p>

<p> Neural developmental events are associated with data comprised of onsets, peaks, and tails of neurogenesis related to neuronal structures, which include but are not limited to associated neuronal death and components of process maturation. A constant k in the mathematical model accounted for events such as implantation, blastulation, and differentiation of the primitive germ layers that were found to be consistent across tested mammals. A value of 5.37 was found for constant k, as shown below in Equation 1. </p>

$$\text{Equation (1)} \quad Y = \ln(\text{day} - k)$$

<p>

where Y is the species score plus the event score plus the primate interaction. This equates to a log transform of postconceptional days adjustable by k; day is thus the postconceptional (pc) day. This nonlinear model can be solved for day such that an estimate of the day of a given developmental event in any of the nine species can be predicted based on the data from the others. The model thus predicts species-event dates when empirical data are missing. The statistical model can account for certain primate neurodevelopmental events which occur at different times than otherwise predicted by adjusting k by adding 0.248683 for primate cortical events and subtracting 0.079280 for primate limbic events (Clancy et al b., 2007; Clancy et al c., 2007). </p>

<p align="center">

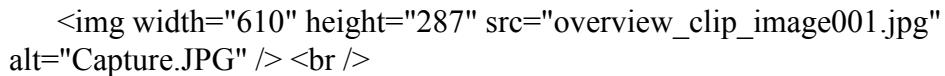


Figure 2: Translating Time: across developing mammalian brains Website (From Clancy, 2006)</p>

<p> As shown in Figure 2, this research has evolved into a Web-based tool with a user-friendly front-end interface for researchers and clinicians to utilize and submit new data points, (<http://www.translatingtime.net>). The back end is a MySQL database of data points. The user has the option to predict neurodevelopmental events by "translating" them across mammalian species. The translation is in postconceptional (PC) and postnatal (PN) time, where the first 24-hour period after conception is often denoted as PC1, and PN0 denotes the first 24-hour period after birth. </p>

<p>Ocular Development

Since over 400 million years ago, the functional and structural features of the vertebrate retina have remained the same. Over the past 20 years, researchers at Cornell University have utilized developmental and evolutionary approaches to study the structure and function of the vertebrate nervous system. One specific concentration has been on the visual system (Franco et al., 2001; Kaskan et al., 2005; Chalfin et al., 2007; Finlay, 2008; Finlay et al., 2008; Dyer et al., 2009; Lameirao et al., 2009; Finlay, 2011). “Every existent animal is the descendant of animals going back to the beginning of evolutionary time, the successful survivor of multiple mass extinctions, climate shifts, niche invasions, diseases, disasters, and mishaps (Finlay, Silveira, & Reichenbach, 2005).” Particular attention has been paid to New World Primates in the development of size and conformation of the eye, the developing retina, and the number and topography of rods, cones, and optic nerve axons in regard to retinal development. Individual level variations across species are extremely important in identification of normal development and its pathologies (Finlay & Clancy, 2008; Cahalance, Charvet, & Finlay, 2012; Charvet & Finlay, 2012; Wallace, 2007). </p>

<p> In addition, work has been done to investigate developmental events concerning rods, cones, and optic nerve axons in the mouse visual system as well as peripheral structures. Variations in the timing as well as the duration of gene expression are a key aspect in which the vertebrate eye differs amongst species. However, the cell types are conserved across species. The most noteworthy difference is the eye size, in its arrangement of cells and the ratio of number cell types. This implies that the primary source of variation to be an evolutionary factor (Harada, Harada, & Parada, 2007; Niessen, 2006; Luo et al., 2006). </p>

```

<div>
  <div> </div>
  <div> </div>
</div>
<p>&nbsp;</p>
</div>
<div class="footer">
  <p align="center">This page was last modified on 6 May 2013.</p>

```

```
<!-- end .footer --></div>  
<!-- end .container --></div>  
</body>  
</html>
```

eye.html

```

<!DOCTYPE html PUBLIC "-//W3C//DTD XHTML 1.0 Transitional//EN"
"http://www.w3.org/TR/xhtml1/DTD/xhtml1-transitional.dtd">

<html xmlns="http://www.w3.org/1999/xhtml">

<head>
<meta http-equiv="Content-Type" content="text/html; charset=utf-8" />
<title>Development of the Eye - Selected Highlights</title>
<style type="text/css">
<!--
body {
    background: #42413C;
    margin: 0;
    padding: 0;
    color: #333;
    font-family: Verdana, Arial, Helvetica, sans-serif;
    font-size: 100%;
    line-height: 1.4;
}

/* ~~ Element/tag selectors ~~ */
ul, ol, dl { /* Due to variations between browsers, it's best practices to zero padding and
margin on lists. For consistency, you can either specify the amounts you want here, or on
the list items (LI, DT, DD) they contain. Remember that what you do here will cascade to
the .nav list unless you write a more specific selector. */
    padding: 0;
    margin: 0;
}
h1, h2, h3, h4, h5, h6, p {

```

```
margin-top: 0; /* removing the top margin gets around an issue where margins
can escape from their containing div. The remaining bottom margin will hold it away
from any elements that follow. */
```

```
padding-right: 15px;
```

```
padding-left: 15px; /* adding the padding to the sides of the elements within the
divs, instead of the divs themselves, gets rid of any box model math. A nested div with
side padding can also be used as an alternate method. */
```

```
}
```

```
a img { /* this selector removes the default blue border displayed in some browsers
around an image when it is surrounded by a link */
```

```
border: none;
```

```
}
```

```
/* ~ Styling for your site's links must remain in this order - including the group of
selectors that create the hover effect. ~~ */
```

```
a:link {
```

```
color: #666666;
```

```
text-decoration: underline; /* unless you style your links to look extremely
unique, it's best to provide underlines for quick visual identification */
```

```
background-color: #666;
```

```
}
```

```
a:visited {
```

```
color: #6E6C64;
```

```
text-decoration: underline;
```

```
}
```

```
a:hover, a:active, a:focus { /* this group of selectors will give a keyboard navigator the
same hover experience as the person using a mouse. */
```

```
text-decoration: none;
```

```
}
```

```
/* ~this fixed width container surrounds the other divs~ */
```

```
.container {
    width: 960px;
    background: #FFF;
    margin: 0 auto; /* the auto value on the sides, coupled with the width, centers the layout */
}

/* ~~ the header is not given a width. It will extend the full width of your layout. It contains an image placeholder that should be replaced with your own linked logo ~~ */
.header {
    background: #ADB96E;
}

/* ~~ These are the columns for the layout. ~~
```

1) Padding is only placed on the top and/or bottom of the divs. The elements within these divs have padding on their sides. This saves you from any "box model math". Keep in mind, if you add any side padding or border to the div itself, it will be added to the width you define to create the *total* width. You may also choose to remove the padding on the element in the div and place a second div within it with no width and the padding necessary for your design. You may also choose to remove the padding on the element in the div and place a second div within it with no width and the padding necessary for your design.

2) No margin has been given to the columns since they are all floated. If you must add margin, avoid placing it on the side you're floating toward (for example: a right margin on a div set to float right). Many times, padding can be used instead. For divs where this rule must be broken, you should add a "display:inline" declaration to the div's rule to tame a bug where some versions of Internet Explorer double the margin.

3) Since classes can be used multiple times in a document (and an element can also have multiple classes applied), the columns have been assigned class names instead of IDs. For example, two sidebar divs could be stacked if necessary. These can very easily be

changed to IDs if that's your preference, as long as you'll only be using them once per document.

4) If you prefer your nav on the right instead of the left, simply float these columns the opposite direction (all right instead of all left) and they'll render in reverse order. There's no need to move the divs around in the HTML source.

```
*/
.mainsidebar {
    float: left;
    width: 180px;
    padding-bottom: 10px;
    background-color: #000000;
}

.content {
    padding: 10px 0;
    width: 780px;
    float: left;
}

/* ~~ This grouped selector gives the lists in the .content area space ~~ */
.content ul, .content ol {
    padding: 0 15px 15px 40px; /* this padding mirrors the right padding in the
headings and paragraph rule above. Padding was placed on the bottom for space between
other elements on the lists and on the left to create the indentation. These may be adjusted
as you wish. */
}
```

```

/* ~~ The navigation list styles (can be removed if you choose to use a premade flyout
menu like Spry) ~~ */

ul.nav {
    list-style: none; /* this removes the list marker */

    border-top: 1px solid #666; /* this creates the top border for the links - all others
are placed using a bottom border on the LI */

    margin-bottom: 15px; /* this creates the space between the navigation on the
content below */
}

ul.nav li {
    border-bottom: 1px solid #666; /* this creates the button separation */

}

ul.nav a, ul.nav a:visited { /* grouping these selectors makes sure that your links retain
their button look even after being visited */

    padding: 5px 5px 5px 15px;

    display: block; /* this gives the link block properties causing it to fill the whole LI
containing it. This causes the entire area to react to a mouse click. */

    width: 160px; /*this width makes the entire button clickable for IE6. If you don't
need to support IE6, it can be removed. Calculate the proper width by subtracting the
padding on this link from the width of your sidebar container. */

    text-decoration: none;

    background-color: #000000;
}

ul.nav a:hover, ul.nav a:active, ul.nav a:focus { /* this changes the background and text
color for both mouse and keyboard navigators */

    color: #690;

    background-color: #666666;
}

/* ~~ The footer ~~ */

.footer {

```

```

padding: 10px 0;
background: #CCC49F;
position: relative; /* this gives IE6 hasLayout to properly clear */
clear: both; /* this clear property forces the .container to understand where the
columns end and contain them */
background-color: #000000;
}

/* ~~ miscellaneous float/clear classes ~~ */

.fltrt { /* this class can be used to float an element right in your page. The floated
element must precede the element it should be next to on the page. */
float: right;
margin-left: 8px;
}

.flflft { /* this class can be used to float an element left in your page. The floated element
must precede the element it should be next to on the page. */
float: left;
margin-right: 8px;
}

.clearfloat { /* this class can be placed on a <br /> or empty div as the final element
following the last floated div (within the #container) if the #footer is removed or taken
out of the #container */
clear:both;
height:0;
font-size: 1px;
line-height: 0px;
}

.container .content p strong {
font-family: Arial Black, Gadget, sans-serif;
}

```

```

}

-->

</style></head>

<body>

<div class="container">

    <div class="header"><a href="#"></a>
        <!-- end .header --></div>

    <div class="mainsidebar">

        <ul class="nav">

            <li><a href="index.html" title="Home Page">Home Page</a></li>

            <li><a href="ttacrosmammilianspecies.html" title="Translating Time">Translating Time</a></li>

            <li><a href="semiautomatedlitrev.php" title="Semi-Automated Literature Review">Semi-Automated Literature Review</a></li>

            <li><a href="geneontology.html" title="Gene Ontology">Gene Ontology</a></li>

            <li><a href="aboutauthor.html" title="About the Author">About the Author</a></li>

            <li><a href="http://bioinformatics.ualr.edu/" title="UALR/UAMS Joint Bioinformatics Program">UALR/UAMS Bioinformatics Program</a></li>

            <li><a href="references.html" title="References">References</a></li>

            <li><a href="survey.html" title="Please take the time to take a survey">Survey</a></li>

        </ul>

    </div>

    <div class="content">

        <h1><strong>Development of the Eye – Selected Highlights</strong></h1>

```

<p>The eye is the foundation of the visual system in humans. Its main purpose is to detect and analyze light. The eye connects via the optic nerve to the brain. The cornea and the sclera form the outer layer of the eye. The iris and ciliary body form the middle layer. The retina forms the inner layer. This is a summary of the major structural components of the eye (Figure 4) (Bear, Connors, & Paradiso, 2000). As with numerous other organs, the eye develops as a product of complex interactions of primitive cells during embryogenesis (Barishak, 2001). On day 22 of embryogenesis (day E22) the developing eyes emerge as a pair of willow grooves, the optic sulci, on each side of the forebrain as the neural tube closes. The neural tube is a tube that is formed in mammalian embryos by the closure of ectoderm tissue, which is the precursor to the central nervous system that develops into the brain and the spinal cord. These willow grooves form the optic vesicles, and come in contact with surface ectoderm, which is essential for lens formation. Then the lens vesicles form, followed by the choroid, sclera, and cornea. The formation of the eye begins around week 3 and has ceased by week 8. The eyes are functional between months 5 and 7 of fetal development (Gross, Blechinger & Achtner, 2008; Nguyen & Arnhieder, 2000). </p>

<p> The vertebrate eye consists of tissues from distinctive embryonic origins. For example, the lens and the cornea are derived from the surface ectoderm while the retina and the epithelial layers of the iris as well as the ciliary body are derived from the anterior neural plate or neuroectoderm. The different eye components are formed as a consequence of well-timed actions of transcription factors and inductive signals (Schoenwolf et al. c, 2008; Sadler, 2006; Graw, 2010). The structural components of the eye are illustrated in the human eye diagram shown in Figure 1. "When all of the components of the eye function properly, light is converted to impulses and conveyed to the brain where an image is perceived." Each component serves a distinct purpose, for example, the macula in a part of the retina. Its main purpose is central vision for reading. The retina on the other hand contains photoreceptor cells that react to the presence and intensity of light by sending impulses to the brain where the image is assimilated.</p>

<p align="center">
</p>

<p align="center">Figure 1: The Human Eye (From Segal, 2012)</p>

<p align="left">Model organisms and the eye

Over 100 years ago the chicken emerged as a model organism in embryonic developmental biology (Burt, 2007; Cogburn et al., 2007).. The use of the chicken as a model experimental species lead to many fundamental discoveries for developmental biology (Burt, 2007). Reinforcement of this choice became evident with the chicken genome sequence. It is fitting in a sense because the chicken has been incorporated into human culture for more than 8 thousand years as a domesticated livestock species

(Gogburn et al., 2007). Approximately 100 million years ago, the chicken and the zebrafish lineages diverged. With the sequencing of its genome, the zebrafish has emerged as the second significant model for understanding brain and eye development (Brown, 2003). Communication in the zebrafish takes place during learned vocalizations, an ability absent in the chicken and only documented in humans and a small number of other animals Warren, 2010).</p>

<p align="left">Since the Human Genome Project, the zebrafish's complete genome has also been sequenced helping to make it an important vertebrate model organism for scientific research Anderson & Ingham, 2003). Although the zebrafish is less closely related to humans genetically than the chicken, due to the sizeable number of offspring, the transparency of the embryos during the course of the developmental period, and its quick embryonic development, the zebrafish has become a favorite model organism for scientists studying eye development (Fadool & Dowling, 2008; Sprague et al., 2006). The zebrafish reaches sexual maturity in 4 months, with the optically transparent embryos develop externally. The latter makes it a valuable choice as a model organism because neither the mouse nor the Drosophila melanogaster can provide direct observation of the vertebrate organs or tissues (Dodd et al., 2000). Its transparency during embryonic development establishes the zebrafish as the prime organism for microscopic examination of organs (Glass & Glass, 2004).</p>

<p align="left"> </p>

</div>

<div class="footer">

<p align="center">This page was last modified on 6 May 2013.</p>

<!-- end .footer --></div>

<!-- end .container --></div>

</body>

</html>

semiautomatedlitrev.php

```

<!DOCTYPE html PUBLIC "-//W3C//DTD XHTML 1.0 Transitional//EN"
"http://www.w3.org/TR/xhtml1/DTD/xhtml1-transitional.dtd">

<html xmlns="http://www.w3.org/1999/xhtml">

<head>

<meta http-equiv="Content-Type" content="text/html; charset=utf-8" />
<title>Semi-Automated Literature Review</title>

<style type="text/css">

<!--

body {

    background: #42413C;
    margin: 0;
    padding: 0;
    color: #333;
    font-family: Verdana, Arial, Helvetica, sans-serif;
    font-size: 100%;
    line-height: 1.4;
}

/* ~~ Element/tag selectors ~~ */

ul, ol, dl { /* Due to variations between browsers, it's best practices to zero padding and
margin on lists. For consistency, you can either specify the amounts you want here, or on
the list items (LI, DT, DD) they contain. Remember that what you do here will cascade to
the .nav list unless you write a more specific selector. */

    padding: 0;
    margin: 0;
}

h1, h2, h3, h4, h5, h6, p {

```

```
margin-top: 0; /* removing the top margin gets around an issue where margins
can escape from their containing div. The remaining bottom margin will hold it away
from any elements that follow. */
```

```
padding-right: 15px;
```

```
padding-left: 15px; /* adding the padding to the sides of the elements within the
divs, instead of the divs themselves, gets rid of any box model math. A nested div with
side padding can also be used as an alternate method. */
```

```
}
```

```
a img { /* this selector removes the default blue border displayed in some browsers
around an image when it is surrounded by a link */
```

```
border: none;
```

```
}
```

```
/* ~ Styling for your site's links must remain in this order - including the group of
selectors that create the hover effect. ~~ */
```

```
a:link {
```

```
color: #666666;
```

```
text-decoration: underline; /* unless you style your links to look extremely
unique, it's best to provide underlines for quick visual identification */
```

```
}
```

```
a:visited {
```

```
color: #6E6C64;
```

```
text-decoration: underline;
```

```
}
```

```
a:hover, a:active, a:focus { /* this group of selectors will give a keyboard navigator the
same hover experience as the person using a mouse. */
```

```
text-decoration: none;
```

```
}
```

```
/* ~this fixed width container surrounds the other divs~ */
```

```
.container {
    width: 960px;
    background: #FFF;
    margin: 0 auto; /* the auto value on the sides, coupled with the width, centers the layout */
}

/* ~~ the header is not given a width. It will extend the full width of your layout. It contains an image placeholder that should be replaced with your own linked logo ~~ */
.header {
    background: #ADB96E;
}

/* ~~ These are the columns for the layout. ~~
```

1) Padding is only placed on the top and/or bottom of the divs. The elements within these divs have padding on their sides. This saves you from any "box model math". Keep in mind, if you add any side padding or border to the div itself, it will be added to the width you define to create the *total* width. You may also choose to remove the padding on the element in the div and place a second div within it with no width and the padding necessary for your design. You may also choose to remove the padding on the element in the div and place a second div within it with no width and the padding necessary for your design.

2) No margin has been given to the columns since they are all floated. If you must add margin, avoid placing it on the side you're floating toward (for example: a right margin on a div set to float right). Many times, padding can be used instead. For divs where this rule must be broken, you should add a "display:inline" declaration to the div's rule to tame a bug where some versions of Internet Explorer double the margin.

3) Since classes can be used multiple times in a document (and an element can also have multiple classes applied), the columns have been assigned class names instead of IDs. For example, two sidebar divs could be stacked if necessary. These can very easily be

changed to IDs if that's your preference, as long as you'll only be using them once per document.

4) If you prefer your nav on the right instead of the left, simply float these columns the opposite direction (all right instead of all left) and they'll render in reverse order. There's no need to move the divs around in the HTML source.

```
*/
.mainsidebar {
    float: left;
    width: 180px;
    padding-bottom: 10px;
    background-color: #000000;
}

.content {
    padding: 10px 0;
    width: 780px;
    float: left;
}

/* ~~ This grouped selector gives the lists in the .content area space ~~ */
.content ul, .content ol {
    padding: 0 15px 15px 40px; /* this padding mirrors the right padding in the
headings and paragraph rule above. Padding was placed on the bottom for space between
other elements on the lists and on the left to create the indentation. These may be adjusted
as you wish. */
}
```

```

/* ~~ The navigation list styles (can be removed if you choose to use a premade flyout
menu like Spry) ~~ */

ul.nav {
    list-style: none; /* this removes the list marker */

    border-top: 1px solid #666; /* this creates the top border for the links - all others
are placed using a bottom border on the LI */

    margin-bottom: 15px; /* this creates the space between the navigation on the
content below */
}

ul.nav li {
    border-bottom: 1px solid #666; /* this creates the button separation */

}

ul.nav a, ul.nav a:visited { /* grouping these selectors makes sure that your links retain
their button look even after being visited */

    padding: 5px 5px 5px 15px;

    display: block; /* this gives the link block properties causing it to fill the whole LI
containing it. This causes the entire area to react to a mouse click. */

    width: 160px; /*this width makes the entire button clickable for IE6. If you don't
need to support IE6, it can be removed. Calculate the proper width by subtracting the
padding on this link from the width of your sidebar container. */

    text-decoration: none;

    background-color: #000000;
}

ul.nav a:hover, ul.nav a:active, ul.nav a:focus { /* this changes the background and text
color for both mouse and keyboard navigators */

    color: #690;

    background-color: #666666;
}

/* ~~ The footer ~~ */

.footer {

```

```

padding: 10px 0;
background: #CCC49F;
position: relative; /* this gives IE6 hasLayout to properly clear */
clear: both; /* this clear property forces the .container to understand where the
columns end and contain them */
background-color: #000000;
}

/* ~~ miscellaneous float/clear classes ~~ */

.fltrt { /* this class can be used to float an element right in your page. The floated
element must precede the element it should be next to on the page. */
float: right;
margin-left: 8px;
}

.flflft { /* this class can be used to float an element left in your page. The floated element
must precede the element it should be next to on the page. */
float: left;
margin-right: 8px;
}

.clearfloat { /* this class can be placed on a <br /> or empty div as the final element
following the last floated div (within the #container) if the #footer is removed or taken
out of the #container */
clear:both;
height:0;
font-size: 1px;
line-height: 0px;
}

-->

</style></head>

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    <div class="header"><a href="#"></a>

    <!-- end .header --></div>

    <div class="mainsidebar">

        <ul class="nav">

            <li><a href="index.html" title="Home Page">Home Page</a></li>

            <li><a href="ttacrosmammilianspecies.html" title="Translating Time">Translating Time</a></li>

            <li><a href="eye.html" title="The Eye">The Eye</a></li>

            <li><a href="geneontology.html" title="Gene Ontology">Gene Ontology</a></li>

            <li><a href="aboutauthor.html" title="About the Author">About the Author</a></li>

            <li><a href="http://bioinformatics.ualr.edu/" title="UALR/UAMS Joint Bioinformatics Program">UALR/UAMS Bioinformatics Program</a></li>

            <li><a href="references.html" title="References">References</a></li>

            <li><a href="survey.html" title="Please take the time to take a survey">Survey</a></li>

        </ul>

    </div>

    <div class="content">

        <h1><strong>Semi-Automated Literature Review</strong></h1>

        <p>The aim of this portion of the project is to design, implement, utilize, and validate a tool, which provides a semi-automated approach to literature review of eye-related developmental events. The <em>Danio rerio</em> (zebrafish) will be included in this evaluation of the literature because it is considered model organism for research in eye development. WebCrawler is the name coined for the tool, which allows researchers to search online journals with keywords and/or phrases related to eye development. Through this and other methods utilized the user has the capability and to view the
    
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keyword(s) in a context of 3 lines prior to and three lines after the designated word(s), for example. Therefore, allowing the researcher to ability to decipher whether or not the article should be downloaded for further review. </p>

<p>This document analysis provides method of grouping they keywords or phrases such that the 3 lines prior to and the three lines after the keywords can be view as a paragraph allowing the researcher to view the context of the words without the hassle of downloading the entire document only to learn that it is irrelevant to the research. This process can be more generally referred to as text mining wherein the tool looks for patterns across the entire document via a parsing method. Parsing separates the keywords or phrases in the document analysis can cut back on the time it would take to actually download each document and read them without knowing the context of the article. The more general intended result is for literature searches to take less human effort, resulting in shorter times in finding articles applicable to research on a given topic.</p>

<p align="center">

Figure 1: WebCrawler v1.0</p>

<p align="left">To download a copy of the WebCrawler code, click on the following link, WebCrawler v1.0.</p>

<p align="left">Results</p>

<p>An observation of the researchers with the original Translating Time Project was that locating neurodevelopmental events was a very time consuming task. Therefore, creating semi-automated tool to conduct this searches turned out to be a extremely useful. The tool along with additional processes developed made is easier to learn the “right” keywords to use during the search and to preview the context of the keyword or pattern prior to downloading the entire journal article. I began my literature review with the Zebrafish because it a model organism for eye development research. Knowing this, I felt that it would be the prime Species to begin with because there was no guarantee that I would find results for the other 9 species. </p>

<p> As a result of my search with the initial species, I located 19 eye-related developmental events in the Zebrafish cited in the literature. Seventeen of the 19 events were unique while the retina and the eye cup were events that referenced the same time of occurrence by different authors. Originally, my keyword searches yielded only results for the Zebrafish and found no eye-related development events in the other nine species. The assumption was that the search was too generic or the keyword was broad in scope, for example, “mus musculus, eye development”; or “mus musculus, ocular.” This is likely in part because the WebCrawler version 1.0 only searches text for the keywords. Therefore, a user would have to rely on other methods to search for such data encoded in images in the ScienceDirect, PubMed, and PubMedCentral references.</p>

<p> There were 21 unique event timings that occurred in the literature associated with the cat. The literature review returned 20 unique events in eye development relating to the rat. There were 19 unique events discovered in the monkey literature review. The mouse literature review followed closely yielding 13 unique eye related events. While the ferret literature discerned 12 unique events. The literature review of the hamster detected 10 unique data points related to the eye development. The spiny mouse search yielded 3 results and the human came in last with only 1 eye related development event. Table 1, shown below provides a list of the species name, the embryonic day or day postconception that the event occurred and in the case of the Zebrafish, the post fertilization time in hours as well as the author(s) and year of the journal article.

The more general intended result is for literature s;searches to take less human effort, resulting in s;shorter times in finding information applicable to research on a given topic. The data for the translating time across mammalian species model is anticipated to expand. This literature review and its focus on eye-related developmental events in particular will allow this data to be readily incorporated into an analysis to understand whether or not it fits the current model. This will in turn expand the current model to a second organ, the eye. Expanding this project to other organs through the integration of technological advances could assist researchers in understanding developmental events and the translation of time across species as it relates to those events. Therefore, a researcher looking at the embryonic time that the retina develops in a ferret can translate time across another species, for example, the hamster where the retina is an unknown event because the researcher may want to know what genes regulate retinal development. Moreover, one could study the molecular makeup of the gene expression in the developing retina along with gene expression patterns. </p>

<p>
</p> <p>Danio Rerio (Zebrafish)</p> <p>Hours Post Fertilization</p> <p>Reference</p>
<p>flat optic vesicle</p> <p>16 hpf</p> <p>Li et al. 2000</p>

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<p>cornea</p>	<p>24 hpf</p>	<p>Greililing and Clark 2009</p>
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<p>Felis Domestica (Cat)</p>	<p>Embryonic Day</p>	<p>Reference</p>
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<p>axons in optic stalk</p>	<p>E19</p>	<p>Dunlop et al. 1997</p>
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<p>retinal horizontal cells - peak of neurogenesis</p>	<p>E30</p>	<p>Finlay and Darlington 1995</p>
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<p>Mustela Putorius Furo (Ferret)</p>	<p>Embryonic Day</p>	<p>Reference</p>
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<p> retinogeniculate axon</p>	<p>E27</p>	</td>
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<p>optic vesicle</p>																																									

<p>E27 ±1</p>	<p>Hendrickx et al. 1997</p>
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<td width="171" valign="bottom"><p>Robinson and Dreher 1990</p></td>	
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<p>Robinson and Dreher 1990</p>	
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<p>posterior lens fibers</p>	<p>E13</p>
<p>Kim et al. 1999</p>	
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<p>anterior lens epithelial cells</p>	<p>&ampnbsp</p>
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<p>iris</p>	<p>E15</p>
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<p>Gao et al. 1998</p>	
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<p>retinal ganglion cell generation - start of neurogenesis</p>	
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<p>primary optic tract</p>	<p>E17</p>	<p>&nbsp;</p>
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<p><p>Mesocricetus Auratus (Hamster)</p></p>	<p></p>	<p></p>
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<p><p>Reference</p></p>		
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<p>axons emerge from retina</p>	<p></p>	<p></p>
<p><p>E9-E10</p></p>		
<p><p>Jhaveri et al. 1991</p></p>		
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E14	Robinson and Dreher 1990
optic nerve axon number - peak of neurogenesis	E18
rapid axon loss in optic nerve ends	E31.5
eye opening	E31.5
Homo Sapiens (Humans)	

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<p align="center"><strong>Table 1: Eye-related Development Events</strong></p>
</div>
<div class="footer">
  <p align="center">This page was last modified on 6 May 2013.</p>
  <!-- end .footer --></div>
<!-- end .container --></div>
</body>
</html>
```

geneontology.html

```

<!DOCTYPE html PUBLIC "-//W3C//DTD XHTML 1.0 Transitional//EN"
"http://www.w3.org/TR/xhtml1/DTD/xhtml1-transitional.dtd">

<html xmlns="http://www.w3.org/1999/xhtml">

<head>

<meta http-equiv="Content-Type" content="text/html; charset=utf-8" />
<title>Translating Time: The Eye Home Page</title>

<style type="text/css">

<!--

body {

    background: #42413C;
    margin: 0;
    padding: 0;
    color: #333;
    font-family: Verdana, Arial, Helvetica, sans-serif;
    font-size: 100%;
    line-height: 1.4;
}

/* ~~ Element/tag selectors ~~ */

ul, ol, dl { /* Due to variations between browsers, it's best practices to zero padding and
margin on lists. For consistency, you can either specify the amounts you want here, or on
the list items (LI, DT, DD) they contain. Remember that what you do here will cascade to
the .nav list unless you write a more specific selector. */

    padding: 0;
    margin: 0;
}

h1, h2, h3, h4, h5, h6, p {

```

```
margin-top: 0; /* removing the top margin gets around an issue where margins
can escape from their containing div. The remaining bottom margin will hold it away
from any elements that follow. */
```

```
padding-right: 15px;
```

```
padding-left: 15px; /* adding the padding to the sides of the elements within the
divs, instead of the divs themselves, gets rid of any box model math. A nested div with
side padding can also be used as an alternate method. */
```

```
}
```

```
a img { /* this selector removes the default blue border displayed in some browsers
around an image when it is surrounded by a link */
```

```
border: none;
```

```
}
```

```
/* ~ Styling for your site's links must remain in this order - including the group of
selectors that create the hover effect. ~~ */
```

```
a:link {
```

```
color: #666666;
```

```
text-decoration: underline; /* unless you style your links to look extremely
unique, it's best to provide underlines for quick visual identification */
```

```
}
```

```
a:visited {
```

```
color: #6E6C64;
```

```
text-decoration: underline;
```

```
}
```

```
a:hover, a:active, a:focus { /* this group of selectors will give a keyboard navigator the
same hover experience as the person using a mouse. */
```

```
text-decoration: none;
```

```
}
```

```
/* ~this fixed width container surrounds the other divs~ */
```

```
.container {
    width: 960px;
    background: #FFF;
    margin: 0 auto; /* the auto value on the sides, coupled with the width, centers the layout */
}

/* ~~ the header is not given a width. It will extend the full width of your layout. It contains an image placeholder that should be replaced with your own linked logo ~~ */
.header {
    background: #ADB96E;
}

/* ~~ These are the columns for the layout. ~~
```

1) Padding is only placed on the top and/or bottom of the divs. The elements within these divs have padding on their sides. This saves you from any "box model math". Keep in mind, if you add any side padding or border to the div itself, it will be added to the width you define to create the *total* width. You may also choose to remove the padding on the element in the div and place a second div within it with no width and the padding necessary for your design. You may also choose to remove the padding on the element in the div and place a second div within it with no width and the padding necessary for your design.

2) No margin has been given to the columns since they are all floated. If you must add margin, avoid placing it on the side you're floating toward (for example: a right margin on a div set to float right). Many times, padding can be used instead. For divs where this rule must be broken, you should add a "display:inline" declaration to the div's rule to tame a bug where some versions of Internet Explorer double the margin.

3) Since classes can be used multiple times in a document (and an element can also have multiple classes applied), the columns have been assigned class names instead of IDs. For example, two sidebar divs could be stacked if necessary. These can very easily be

changed to IDs if that's your preference, as long as you'll only be using them once per document.

4) If you prefer your nav on the right instead of the left, simply float these columns the opposite direction (all right instead of all left) and they'll render in reverse order. There's no need to move the divs around in the HTML source.

```
*/
.mainsidebar {
    float: left;
    width: 180px;
    padding-bottom: 10px;
    background-color: #000000;
}

.content {
    padding: 10px 0;
    width: 780px;
    float: left;
}

/* ~~ This grouped selector gives the lists in the .content area space ~~ */
.content ul, .content ol {
    padding: 0 15px 15px 40px; /* this padding mirrors the right padding in the
headings and paragraph rule above. Padding was placed on the bottom for space between
other elements on the lists and on the left to create the indentation. These may be adjusted
as you wish. */
}
```

```

/* ~~ The navigation list styles (can be removed if you choose to use a premade flyout
menu like Spry) ~~ */

ul.nav {
    list-style: none; /* this removes the list marker */

    border-top: 1px solid #666; /* this creates the top border for the links - all others
are placed using a bottom border on the LI */

    margin-bottom: 15px; /* this creates the space between the navigation on the
content below */
}

ul.nav li {
    border-bottom: 1px solid #666; /* this creates the button separation */

}

ul.nav a, ul.nav a:visited { /* grouping these selectors makes sure that your links retain
their button look even after being visited */

    padding: 5px 5px 5px 15px;

    display: block; /* this gives the link block properties causing it to fill the whole LI
containing it. This causes the entire area to react to a mouse click. */

    width: 160px; /*this width makes the entire button clickable for IE6. If you don't
need to support IE6, it can be removed. Calculate the proper width by subtracting the
padding on this link from the width of your sidebar container. */

    text-decoration: none;

    background-color: #000000;
}

ul.nav a:hover, ul.nav a:active, ul.nav a:focus { /* this changes the background and text
color for both mouse and keyboard navigators */

    color: #690;

    background-color: #666666;
}

/* ~~ The footer ~~ */

.footer {

```

```

padding: 10px 0;
background: #CCC49F;
position: relative; /* this gives IE6 hasLayout to properly clear */
clear: both; /* this clear property forces the .container to understand where the
columns end and contain them */
background-color: #000000;
}

/* ~~ miscellaneous float/clear classes ~~ */

.fltrt { /* this class can be used to float an element right in your page. The floated
element must precede the element it should be next to on the page. */
float: right;
margin-left: 8px;
}

.flflft { /* this class can be used to float an element left in your page. The floated element
must precede the element it should be next to on the page. */
float: left;
margin-right: 8px;
}

.clearfloat { /* this class can be placed on a <br /> or empty div as the final element
following the last floated div (within the #container) if the #footer is removed or taken
out of the #container */
clear:both;
height:0;
font-size: 1px;
line-height: 0px;
}

-->

</style></head>

```

```

<body>

<div class="container">

    <div class="header"><a href="#"></a>

    <!-- end .header --></div>

    <div class="mainsidebar">

        <ul class="nav">

            <li><a href="ttacrosmammalianspecies.html" title="Translating Time">Translating Time</a></li>

            <li><a href="eye.html" title="The Eye">The Eye</a></li>

            <li><a href="semiautomatedlitrev.php" title="Semi-Automated Literature Review">Semi-Automated Literature Review</a></li>

            <li><a href="geneontology.html" title="Gene Ontology">Gene Ontology</a></li>

            <li><a href="aboutauthor.html" title="About the Author">About the Author</a></li>

            <li><a href="http://bioinformatics.ualr.edu/" title="UALR/UAMS Joint Bioinformatics Program">UALR/UAMS Bioinformatics Program</a></li>

            <li><a href="references.html" title="References">References</a></li>

            <li><a href="survey.html" title="Please take the time to take a survey">Survey</a></li>

        </ul>

    </div>

    <div class="content">

        <h1>Gene Ontology</h1>

        <p>The aim of this portion of the project is to determine the Gene Ontology annotations associated with constructed data set on eye development events. Originally, Bioconductor was utilized to incorporate gene expression for eye development events. It makes available tools for the understanding and examination of high-throughput genomic data in an open source environment. To achieve such functionality, Bioconductor uses the R statistical programming language for Bioinformatics</p>

    </div>

```

development. Bioconductor was developed for use with the R language and is publicly available through the CRAN R package repository. Bioconductor is open-source software that is freely available at http://www.bioconductor.org/. </p>

<p>It contains readily available packages to access gene expression and ontology data. Gene Ontologies (GO), Chromosome Maps, KEGG Pathway Analysis, and Phylogenetic Analysis are a few of the Bioconductor packages. Capabilities within the GO package include the ability to access the gene identification, the gene term, and ontology type from the Gene Ontology web site or a local file. The Gene Ontology project maintains on its Web site a standardized representation of gene and gene product attributes across species and databases. The map viewer utilizes a method to select an organism and manipulate an organism-specific global map. KEGG (Kyoto Encyclopedia of Genes and Genomes) is another bioinformatics online tool. It is comprised of online database resources supporting searches relating to genomes, biological chemicals and enzymatic pathways. Pathway development permits queries based on 3 distinct categories: systems, genomic, and chemical information. </p>

```
<p>&nbsp;</p>
<p>&nbsp;</p>
</div>
<div class="footer">
<p align="center">This page was last modified on 6 May 2013.</p>
<!-- end .footer --></div>
<!-- end .container --></div>
</body>
</html>
```

aboutauthor.html

```

<!DOCTYPE html PUBLIC "-//W3C//DTD XHTML 1.0 Transitional//EN"
"http://www.w3.org/TR/xhtml1/DTD/xhtml1-transitional.dtd">

<html xmlns="http://www.w3.org/1999/xhtml">

<head>
<meta http-equiv="Content-Type" content="text/html; charset=utf-8" />
<title>About the Author</title>
<style type="text/css">
<!--
body {
background: #42413C;
margin: 0;
padding: 0;
color: #333;
font-family: Verdana, Arial, Helvetica, sans-serif;
font-size: 100%;
line-height: 1.4;
}

/* ~~ Element/tag selectors ~~ */
ul, ol, dl { /* Due to variations between browsers, it's best practices to zero padding and
margin on lists. For consistency, you can either specify the amounts you want here, or on
the list items (LI, DT, DD) they contain. Remember that what you do here will cascade to
the .nav list unless you write a more specific selector. */
padding: 0;
margin: 0;
}
h1, h2, h3, h4, h5, h6, p {

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margin-top: 0; /* removing the top margin gets around an issue where margins can
escape from their containing div. The remaining bottom margin will hold it away from
any elements that follow. */
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padding-right: 15px;
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padding-left: 15px; /* adding the padding to the sides of the elements within the divs,
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text-decoration: underline; /* unless you style your links to look extremely unique, it's
best to provide underlines for quick visual identification */
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background-color: #666;
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a:visited {
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color: #6E6C64;
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a:hover, a:active, a:focus { /* this group of selectors will give a keyboard navigator the
same hover experience as the person using a mouse. */
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text-decoration: none;
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```
/* ~this fixed width container surrounds the other divs~ */
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```
.container {
    width: 960px;
    background: #FFF;
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contains an image placeholder that should be replaced with your own linked logo ~~ */

.header {
    background: #ADB96E;
}

/* ~~ These are the columns for the layout. ~~
```

1) Padding is only placed on the top and/or bottom of the divs. The elements within these divs have padding on their sides. This saves you from any "box model math". Keep in mind, if you add any side padding or border to the div itself, it will be added to the width you define to create the *total* width. You may also choose to remove the padding on the element in the div and place a second div within it with no width and the padding necessary for your design. You may also choose to remove the padding on the element in the div and place a second div within it with no width and the padding necessary for your design.

2) No margin has been given to the columns since they are all floated. If you must add margin, avoid placing it on the side you're floating toward (for example: a right margin on a div set to float right). Many times, padding can be used instead. For divs where this rule must be broken, you should add a "display:inline" declaration to the div's rule to tame a bug where some versions of Internet Explorer double the margin.

3) Since classes can be used multiple times in a document (and an element can also have multiple classes applied), the columns have been assigned class names instead of IDs. For example, two sidebar divs could be stacked if necessary. These can very easily be

changed to IDs if that's your preference, as long as you'll only be using them once per document.

4) If you prefer your nav on the right instead of the left, simply float these columns the opposite direction (all right instead of all left) and they'll render in reverse order. There's no need to move the divs around in the HTML source.

```
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    float: left;
    width: 180px;
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    background-color: #000000;
}

.content {
    padding: 10px 0;
    width: 780px;
    float: left;
}

/* ~~ This grouped selector gives the lists in the .content area space ~~ */
.content ul, .content ol {
    padding: 0 15px 15px 40px; /* this padding mirrors the right padding in the headings and
                                paragraph rule above. Padding was placed on the bottom for space between other
                                elements on the lists and on the left to create the indentation. These may be adjusted as you
                                wish. */
}
```

```

/* ~~ The navigation list styles (can be removed if you choose to use a premade flyout
menu like Spry) ~~ */

ul.nav {
    list-style: none; /* this removes the list marker */

    border-top: 1px solid #666; /* this creates the top border for the links - all others are
placed using a bottom border on the LI */

    margin-bottom: 15px; /* this creates the space between the navigation on the content
below */

}

ul.nav li {
    border-bottom: 1px solid #666; /* this creates the button separation */

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ul.nav a, ul.nav a:visited { /* grouping these selectors makes sure that your links retain
their button look even after being visited */

    padding: 5px 5px 5px 15px;

    display: block; /* this gives the link block properties causing it to fill the whole LI
containing it. This causes the entire area to react to a mouse click. */

    width: 160px; /*this width makes the entire button clickable for IE6. If you don't need to
support IE6, it can be removed. Calculate the proper width by subtracting the padding on
this link from the width of your sidebar container. */

    text-decoration: none;

    background-color: #000000;

}

ul.nav a:hover, ul.nav a:active, ul.nav a:focus { /* this changes the background and text
color for both mouse and keyboard navigators */

    color: #690;

    background-color: #666666;

}

/* ~~ The footer ~~ */

.footer {

```

```

padding: 10px 0;
background: #CCC49F;
position: relative; /* this gives IE6 hasLayout to properly clear */
clear: both; /* this clear property forces the .container to understand where the columns
end and contain them */
background-color: #000000;
}

```

/* ~~ miscellaneous float/clear classes ~~ */

```

.fltrt { /* this class can be used to float an element right in your page. The floated
element must precede the element it should be next to on the page. */
float: right;
margin-left: 8px;
}

```

```

.fltlft { /* this class can be used to float an element left in your page. The floated element
must precede the element it should be next to on the page. */
float: left;
margin-right: 8px;
}

```

```

.clearfloat { /* this class can be placed on a <br /> or empty div as the final element
following the last floated div (within the #container) if the #footer is removed or taken
out of the #container */
clear:both;
height:0;
font-size: 1px;
line-height: 0px;
}
-->
</style></head>
```

```
<body>

<div class="container">

<div class="header"><a href="#"></a>
<!-- end .header --></div>

<div class="mainsidebar">
<ul class="nav">
<li><a href="ttacrosmammalspecies.html" title="Translating Time">Translating Time</a></li>
<li><a href="eye.html" title="The Eye">The Eye</a></li>
<li><a href="semiautomatedlitrev.php" title="Semi-Automated Literature Review">Semi-Automated Literature Review</a></li>
<li><a href="geneontology.html" title="Gene Ontology">Gene Ontology</a></li>
<li><a href="aboutauthor.html" title="About the Author">About the Author</a></li>
<li><a href="http://bioinformatics.ualr.edu/" title="UALR/UAMS Joint Bioinformatics Program">UALR/UAMS Bioinformatics Program</a></li>
<li><a href="references.html" title="References">References</a></li>
<li><a href="survey.html" title="Please take the time to take a survey">Survey</a></li>
</ul>
</div>

<div class="content">
<h1>About the Author</h1>
<p>Marico Howe</p>
<p>EDUCATION</p>
<p>    M.S. Bioinformatics, University of Arkansas for Medical Sciences and University of Arkansas at Little Rock<br />
M.S. Computer Science, Johns Hopkins University<br />
```

B.S. Computer Science, Bowie State University

<!-- end .content -->

</p>

<p>EXPERIENCE</p>

<p> 2005-09 University of Arkansas at Little Rock, Little Rock, AR

Faculty, Department of Information Science (IFSC)

- Taught material from approved curriculum and developed daily lesson plans to include instructional aids

- Participated in school retention initiatives

- Motivated students to actively participate in all aspects of the educational process

- Participated in the ABET accreditation process

- Completed professional development and in-service activities in accordance with college standards

- Maintained expertise in subject area and recommends improvements in curriculum design

- Assisted in the department in obtaining ABET accredited, which will be effective through September 30, 2010

- Participated in core course academic support programs, certification programs, and student professional associations

2003-05 ITT Technical Institute, Little Rock, Arkansas

Program Chair, School of Business

- Assisted in leading the Little Rock campus from a two year technical institute into a four year college accredited by the Accrediting Council for Independent Colleges and certified by the Arkansas Higher Education Coordinating Board

- Increased and retained enrollment in access of one hundred students for the bachelor of science program

- Collaborated with headquarters Curriculum Managers and Academic Affairs Managers to implement new program curricula which enables graduates to be marketable locally as well as abroad

- Interviewed prospective faculty and provides recommendation for hire

- Observed instructor performance relating to curriculum expertise and writes evaluation report

 - Conducted Instructor conferences and professional development sessions

 - Kept abreast of education and technical methodology advancements in assigned programs

 - Assisted Dean with policy/procedure implementation and problem resolution

 - Conferred with headquarters Curriculum Managers and various professional organizations to obtain information and ensure program curriculum was successfully administered

 - Served as a technical expert on advisory committees

 - Maintained teaching assignments

-

2001-03 Johns Hopkins University/ Applied Physics Laboratory, Laurel, Maryland

Project Manager

- Managed and lead JHU/APL systems engineering and technical efforts in support of the Objective Defense Satellite Communications Control System (DSCS) Operations Control System (ODOCS)

- Worked with the ODOCS sponsor, PM-DCATS to understand sponsor needs, issues, risks and concerns and to identify and promote APL support opportunities

- Defined JHU/APL tasking and prepare statements of work

- Provided a weekly activity report to the sponsor

- Worked with sponsor to ensure proper and required resources are provided to APL for the ODOCS

- Worked internally within APL to ensure proper budget allocation and planning to ensure the project was appropriately staffed to achieve quality products on time and within budget

- Managed the day-to-day aspects of the project, ensuring quality work on time and within budget

- Worked with the Program Manager to establish roles and responsibilities for the project team members

- Mentored project team members

- Worked with PM-DCATS sponsors to explore additional methods to grow the ODOCS influence, while providing a means to expand APL's support within the ODOCS

- Responsibilities, also, included risk management, requirements management, interface management, and program planning

1999-00 Johns Hopkins University/ Applied Physics Laboratory, Laurel, Maryland

Software Engineer

- Provided software engineering expertise, technical advisory support, and engineering analysis to assist with development and/or acquisition of current and next generation decision support systems

- Interacted with the customer, users, and subject matter experts in extracting requirements, expertise, and/or knowledge for implementation in the decision support framework or rule base engine

- Analyzed and documented requirements for the implementation of generic decision support architectures

- Developed and unit tested prototypes of the implementation

- Presented advanced concepts materials to the sponsor, demonstrated prototype software/systems, lead requirements working group meetings, conducted COTS software evaluations, and field tested the software at the installation sites

- Provided database engineering expertise, technical advisory support, and engineering analysis to assist with development and acquisition of current and next generation collection, processing, analysis and dissemination systems in the Satellite Communications domain

- Designed, documented and implemented data collection, analysis, databases, and display applications in a worldwide distributed RDBMS Satellite Communications environment

- Participated in Information Systems Engineering working groups and transfer user requirements into the system (to include tasks such as requirements analysis, integration engineering, interface definition, concept development, and test & evaluation)

- Assisted the customers and users in the application of sound software and system engineering discipline and practices during the development and implementation of new systems and the extension of legacy systems for the desired architecture

SKILLS

- Experience in project management tools such as Microsoft Project, Microsoft Visio, and the Constructive Cost Model (COCOMO) Model

- Experience in computer software analysis and design using the UML and tools such as: Rational Rose and Artisan Real-Time Studio

- Experience with CORBA Technology, Microsoft IntallShield 6.2 and Aperture Technologies Computer Aided Facility Management Tool

- Experience with programming languages such as: .Net Technologies, JAVA, C++, C, COBOL, SQL, Visual Basic, and XML

- Experience with databases such as Oracle 8I, SQLNet, SQLServer 2005, and MS Access

- Experience on application servers such as: ColdFusion Server and Tomcat. In addition, experience on Internet programming: HTML, DHTML, ColdFusion, JavaScript, CGI, JSP, ASP, PHP, Servlets, and Cascading Style Sheets

- Experience and general background programming in operating systems such as: Unix (Solaris and C programming) and MS Windows

PUBLICATIONS

Howe, Marico and Tarasenko, Olga, Signal Transduction and Murine Macrophages Proteins: Data Mining and Phylogenetic Analysis, Proceedings of the 2nd Biology, Nanotechnology, Toxicology, and Applications Research Meeting, Little Rock, AR, April 26-27th, 2007.

Howe, Marico and Tarasenko, Olga, Bioinformatic Approach: Cell Signaling in Murine Macrophages, The Fifth Annual Conference of the MidSouth Computational Biology and Bioinformatics Society, Oklahoma City, OK, February 23-24th, 2008.

John Talburt, Chia-Chu Chiang, Marico Howe, Ningning Wu, Stephen Lucero, Abhinandan Katkuri, Cedric Konyaole, Miao Nie, Arijit Sarkar, Jonathan Loghry, David Nash, and Jeff Stires, A Semiotic Approach to File Layout Inference, 2008 Conference on Applied Research in Information Technology, Conway, AR, March 14, 2008. </p>

<p>M. C. Howe, D. Berleant and A. Everett, "The 'ttime' package: performance evaluation in a cluster computing environment", AIP Conference Proceedings 1326, American Institute of Physics, Nov. 4-5, 2010, Little Rock; in press. ISBN 978-0-7354-0906-4. </p>

<p>M. C. Howe, D. Berleant, C. Biendenbender and J. Chacko, "Toward a semi-automated literature review of eye development", 6th BioNanoTox (Biology, Nanotechnology, Toxicology) and Applications International Research Conference, AIP

Conference Proceedings, American Institute of Physics, Nov. 17-18, 2011, Little Rock, AR.</p>

<p> </p>

<p>AWARDS</p>

<p> Marico Howe, Elizabeth Pierce, Information Science Department: Assessment Overview, UALR Assessment Expo, Little Rock, AR, October 29th-31st, 2008, Winner.

GRANTS</p>

<p> National Summer Transportation Institute, Co-Director, Marico Howe, \$45,000, Director, Constance Meadors, Harding University, June – July 2008, Funding Agency – United States Department of Transportation, Federal Highway Administration

</p>

<p>SERVICE ACTIVITIES

</p>

<p>Chair, Recruitment Committee, Department of Information Science, 2006-2008

Member, Curriculum Committee, Department of Information Science, 2007-2008</p>

</div>

<div class="footer">

<p align="center">This page was last modified on 6 May 2013.</p>

<!-- end .footer --></div>

<!-- end .container --></div>

</body>

</html>

references.html

<!DOCTYPE html PUBLIC "-//W3C//DTD XHTML 1.0 Transitional//EN"
"http://www.w3.org/TR/xhtml1/DTD/xhtml1-transitional.dtd">

<html xmlns="http://www.w3.org/1999/xhtml">

```

<head>
<meta http-equiv="Content-Type" content="text/html; charset=utf-8" />
<title>Selected References</title>
<style type="text/css">
<!--
body {
    background: #42413C;
    margin: 0;
    padding: 0;
    color: #333;
    font-family: Verdana, Arial, Helvetica, sans-serif;
    font-size: 100%;
    line-height: 1.4;
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    margin-top: 0; /* removing the top margin gets around an issue where margins
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from any elements that follow. */
    padding-right: 15px;
}

```

}

a img { /* this selector removes the default blue border displayed in some browsers around an image when it is surrounded by a link */

border: none;

}

/* ~~ Styling for your site's links must remain in this order - including the group of selectors that create the hover effect. ~~ */

a:link {

color: #666666;

text-decoration: underline; /* unless you style your links to look extremely unique, it's best to provide underlines for quick visual identification */

background-color: #666;

}

a:visited {

color: #6E6C64;

text-decoration: underline;

}

a:hover, a:active, a:focus { /* this group of selectors will give a keyboard navigator the same hover experience as the person using a mouse. */

text-decoration: none;

}

/* ~~this fixed width container surrounds the other divs~~ */

.container {

width: 960px;

background: #FFF;

```

    margin: 0 auto; /* the auto value on the sides, coupled with the width, centers the
layout */

}

```

/* ~~ the header is not given a width. It will extend the full width of your layout. It contains an image placeholder that should be replaced with your own linked logo ~~ */

```

.header {
    background: #ADB96E;
}

```

/* ~~ These are the columns for the layout. ~~

1) Padding is only placed on the top and/or bottom of the divs. The elements within these divs have padding on their sides. This saves you from any "box model math". Keep in mind, if you add any side padding or border to the div itself, it will be added to the width you define to create the *total* width. You may also choose to remove the padding on the element in the div and place a second div within it with no width and the padding necessary for your design. You may also choose to remove the padding on the element in the div and place a second div within it with no width and the padding necessary for your design.

2) No margin has been given to the columns since they are all floated. If you must add margin, avoid placing it on the side you're floating toward (for example: a right margin on a div set to float right). Many times, padding can be used instead. For divs where this rule must be broken, you should add a "display:inline" declaration to the div's rule to tame a bug where some versions of Internet Explorer double the margin.

3) Since classes can be used multiple times in a document (and an element can also have multiple classes applied), the columns have been assigned class names instead of IDs. For example, two sidebar divs could be stacked if necessary. These can very easily be changed to IDs if that's your preference, as long as you'll only be using them once per document.

4) If you prefer your nav on the right instead of the left, simply float these columns the opposite direction (all right instead of all left) and they'll render in reverse order. There's no need to move the divs around in the HTML source.

```
*/
.mainsidebar {
    float: left;
    width: 180px;
    padding-bottom: 10px;
    background-color: #000000;
}

.content {
    padding: 10px 0;
    width: 780px;
    float: left;
}

/* ~~ This grouped selector gives the lists in the .content area space ~~ */
.content ul, .content ol {
    padding: 0 15px 15px 40px; /* this padding mirrors the right padding in the
headings and paragraph rule above. Padding was placed on the bottom for space between
other elements on the lists and on the left to create the indentation. These may be adjusted
as you wish. */
}

/* ~~ The navigation list styles (can be removed if you choose to use a premade flyout
menu like Spry) ~~ */
ul.nav {
    list-style: none; /* this removes the list marker */
```

```

    border-top: 1px solid #666; /* this creates the top border for the links - all others
are placed using a bottom border on the LI */

    margin-bottom: 15px; /* this creates the space between the navigation on the
content below */

}

ul.nav li {

    border-bottom: 1px solid #666; /* this creates the button separation */

}

ul.nav a, ul.nav a:visited { /* grouping these selectors makes sure that your links retain
their button look even after being visited */

    padding: 5px 5px 5px 15px;

    display: block; /* this gives the link block properties causing it to fill the whole LI
containing it. This causes the entire area to react to a mouse click. */

    width: 160px; /*this width makes the entire button clickable for IE6. If you don't
need to support IE6, it can be removed. Calculate the proper width by subtracting the
padding on this link from the width of your sidebar container. */

    text-decoration: none;

    background-color: #000000;

}

ul.nav a:hover, ul.nav a:active, ul.nav a:focus { /* this changes the background and text
color for both mouse and keyboard navigators */

    color: #690;

    background-color: #666666;

}

/* ~~ The footer ~~ */

.footer {

    padding: 10px 0;

    background: #CCC49F;

    position: relative; /* this gives IE6 hasLayout to properly clear */
}

```

```

    clear: both; /* this clear property forces the .container to understand where the
columns end and contain them */

    background-color: #000000;

}

/* ~~ miscellaneous float/clear classes ~~ */

.fltrt { /* this class can be used to float an element right in your page. The floated
element must precede the element it should be next to on the page. */

    float: right;

    margin-left: 8px;

}

.fltlft { /* this class can be used to float an element left in your page. The floated element
must precede the element it should be next to on the page. */

    float: left;

    margin-right: 8px;

}

.clearfloat { /* this class can be placed on a <br /> or empty div as the final element
following the last floated div (within the #container) if the #footer is removed or taken
out of the #container */

    clear:both;

    height:0;

    font-size: 1px;

    line-height: 0px;

}

-->

</style></head>

<body>

```

```

<div class="container">

    <div class="header"><a href="#"></a>

    <!-- end .header --></div>

    <div class="mainsidebar">

        <ul class="nav">

            <li><a href="index.html" title="Home Page">Home Page</a></li>

            <li><a href="ttacrosmammilianspecies.html" title="Translating Time">Translating Time</a></li>

            <li><a href="eye.html" title="The Eye">The Eye</a></li>

            <li><a href="semiautomatedlitrev.php" title="Semi-Automated Literature Review">Semi-Automated Literature Review</a></li>

            <li><a href="geneontology.html" title="Gene Ontology">Gene Ontology</a></li>

            <li><a href="aboutauthor.html" title="About the Author">About the Author</a></li>

            <li><a href="http://bioinformatics.ualr.edu/" title="UALR/UAMS Joint Bioinformatics Program">UALR/UAMS Bioinformatics Program</a></li>

            <li><a href="survey.html" title="Please take the time to take a survey">Survey</a></li>

        </ul>

    </div>

    <div class="content">

        <h1>Selected References</h1>

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    </div>

```

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<p>Luo, T., Sakai, Y., Wagner, E., & Dräger, U. (2006). "Retinoids, eye development, and maturation of visual function." Journal of Neurobiology 66(7): 677-686.</p>

<p> </p>

</div>

<div class="footer">

<p align="center">This page was last modified on 6 May 2013.</p>

<!-- end .footer --></div>

<!-- end .container --></div>

</body>

</html>

survey.html

```

<!DOCTYPE html PUBLIC "-//W3C//DTD XHTML 1.0 Transitional//EN"
"http://www.w3.org/TR/xhtml1/DTD/xhtml1-transitional.dtd">

<html xmlns="http://www.w3.org/1999/xhtml">

<head>

<meta http-equiv="Content-Type" content="text/html; charset=utf-8" />
<title>Site Survey</title>

<style type="text/css">

<!--

body {

    background: #42413C;
    margin: 0;
    padding: 0;
    color: #333;
    font-family: Verdana, Arial, Helvetica, sans-serif;
    font-size: 100%;
    line-height: 1.4;
}

/* ~~ Element/tag selectors ~~ */

ul, ol, dl { /* Due to variations between browsers, it's best practices to zero padding and
margin on lists. For consistency, you can either specify the amounts you want here, or on
the list items (LI, DT, DD) they contain. Remember that what you do here will cascade to
the .nav list unless you write a more specific selector. */

    padding: 0;
    margin: 0;
}

h1, h2, h3, h4, h5, h6, p {

```

```
margin-top: 0; /* removing the top margin gets around an issue where margins
can escape from their containing div. The remaining bottom margin will hold it away
from any elements that follow. */
```

```
padding-right: 15px;
```

```
padding-left: 15px; /* adding the padding to the sides of the elements within the
divs, instead of the divs themselves, gets rid of any box model math. A nested div with
side padding can also be used as an alternate method. */
```

```
}
```

```
a img { /* this selector removes the default blue border displayed in some browsers
around an image when it is surrounded by a link */
```

```
border: none;
```

```
}
```

```
/* ~ Styling for your site's links must remain in this order - including the group of
selectors that create the hover effect. ~~ */
```

```
a:link {
```

```
color: #666666;
```

```
text-decoration: underline; /* unless you style your links to look extremely
unique, it's best to provide underlines for quick visual identification */
```

```
}
```

```
a:visited {
```

```
color: #6E6C64;
```

```
text-decoration: underline;
```

```
}
```

```
a:hover, a:active, a:focus { /* this group of selectors will give a keyboard navigator the
same hover experience as the person using a mouse. */
```

```
text-decoration: none;
```

```
}
```

```
/* ~this fixed width container surrounds the other divs~ */
```

```
.container {
    width: 960px;
    background: #FFF;
    margin: 0 auto; /* the auto value on the sides, coupled with the width, centers the layout */
}

/* ~~ the header is not given a width. It will extend the full width of your layout. It contains an image placeholder that should be replaced with your own linked logo ~~ */
.header {
    background: #ADB96E;
}

/* ~~ These are the columns for the layout. ~~
```

1) Padding is only placed on the top and/or bottom of the divs. The elements within these divs have padding on their sides. This saves you from any "box model math". Keep in mind, if you add any side padding or border to the div itself, it will be added to the width you define to create the *total* width. You may also choose to remove the padding on the element in the div and place a second div within it with no width and the padding necessary for your design. You may also choose to remove the padding on the element in the div and place a second div within it with no width and the padding necessary for your design.

2) No margin has been given to the columns since they are all floated. If you must add margin, avoid placing it on the side you're floating toward (for example: a right margin on a div set to float right). Many times, padding can be used instead. For divs where this rule must be broken, you should add a "display:inline" declaration to the div's rule to tame a bug where some versions of Internet Explorer double the margin.

3) Since classes can be used multiple times in a document (and an element can also have multiple classes applied), the columns have been assigned class names instead of IDs. For example, two sidebar divs could be stacked if necessary. These can very easily be

changed to IDs if that's your preference, as long as you'll only be using them once per document.

4) If you prefer your nav on the right instead of the left, simply float these columns the opposite direction (all right instead of all left) and they'll render in reverse order. There's no need to move the divs around in the HTML source.

```
*/
.mainsidebar {
    float: left;
    width: 180px;
    padding-bottom: 10px;
    background-color: #000000;
}

.content {
    padding: 10px 0;
    width: 780px;
    float: left;
}

/* ~~ This grouped selector gives the lists in the .content area space ~~ */
.content ul, .content ol {
    padding: 0 15px 15px 40px; /* this padding mirrors the right padding in the
headings and paragraph rule above. Padding was placed on the bottom for space between
other elements on the lists and on the left to create the indentation. These may be adjusted
as you wish. */
}
```

```

/* ~~ The navigation list styles (can be removed if you choose to use a premade flyout
menu like Spry) ~~ */

ul.nav {
    list-style: none; /* this removes the list marker */

    border-top: 1px solid #666; /* this creates the top border for the links - all others
are placed using a bottom border on the LI */

    margin-bottom: 15px; /* this creates the space between the navigation on the
content below */
}

ul.nav li {
    border-bottom: 1px solid #666; /* this creates the button separation */

}

ul.nav a, ul.nav a:visited { /* grouping these selectors makes sure that your links retain
their button look even after being visited */

    padding: 5px 5px 5px 15px;

    display: block; /* this gives the link block properties causing it to fill the whole LI
containing it. This causes the entire area to react to a mouse click. */

    width: 160px; /*this width makes the entire button clickable for IE6. If you don't
need to support IE6, it can be removed. Calculate the proper width by subtracting the
padding on this link from the width of your sidebar container. */

    text-decoration: none;

    background-color: #000000;
}

ul.nav a:hover, ul.nav a:active, ul.nav a:focus { /* this changes the background and text
color for both mouse and keyboard navigators */

    color: #690;

    background-color: #666666;
}

/* ~~ The footer ~~ */

.footer {

```

```

padding: 10px 0;
background: #CCC49F;
position: relative; /* this gives IE6 hasLayout to properly clear */
clear: both; /* this clear property forces the .container to understand where the
columns end and contain them */
background-color: #000000;
}

/* ~~ miscellaneous float/clear classes ~~ */

.fltrt { /* this class can be used to float an element right in your page. The floated
element must precede the element it should be next to on the page. */
float: right;
margin-left: 8px;
}

.flflft { /* this class can be used to float an element left in your page. The floated element
must precede the element it should be next to on the page. */
float: left;
margin-right: 8px;
}

.clearfloat { /* this class can be placed on a <br /> or empty div as the final element
following the last floated div (within the #container) if the #footer is removed or taken
out of the #container */
clear:both;
height:0;
font-size: 1px;
line-height: 0px;
}

-->

</style></head>

```

```

<body>

<div class="container">

    <div class="header"><a href="#"></a>

    <!-- end .header --></div>

    <div class="mainsidebar">

        <ul class="nav">

            <li><a href="index.html" title="Home Page">Home Page</a></li>

            <li><a href="ttacrosmammilianspecies.html" title="Translating Time">Translating Time</a></li>

            <li><a href="eye.html" title="The Eye">The Eye</a></li>

            <li><a href="semiautomatedlitrev.php" title="Semi-Automated Literature Review">Semi-Automated Literature Review</a></li>

            <li><a href="geneontology.html" title="Gene Ontology">Gene Ontology</a></li>

            <li><a href="aboutauthor.html" title="About the Author">About the Author</a></li>

            <li><a href="http://bioinformatics.ualr.edu/" title="UALR/UAMS Joint Bioinformatics Program">UALR/UAMS Bioinformatics Program</a></li>

            <li><a href="references.html" title="References">References</a></li>

        </ul>

    </div>

    <div class="content">

        <h1>Please take a minute to fill out our survey</h1>

        <p><a href="http://www.surveymonkey.com/s/KFVY7SC">Click here to take survey</a>&nbsp;</p>

        <!-- end .content --></div>

    <div class="footer">

        <p align="center">This page was last modified on 6 May 2013.</p>

    
```

```
<!-- end .footer --></div>  
<!-- end .container --></div>  
</body>  
</html>
```

<http://www.surveymonkey.com/s/KFVY7SC>

```

<!DOCTYPE html PUBLIC "-//W3C//DTD XHTML 1.0 Transitional//EN"
"http://www.w3.org/TR/xhtml1/DTD/xhtml1-transitional.dtd">
<html xmlns="http://www.w3.org/1999/xhtml" class="Panda">
<head><title>Translating Time: The Eye Website Survey</title>
<link id="fav" href="/favicon1.ico" rel="shortcut icon"></link>
<meta http-equiv="Content-Type" content="text/html; charset=utf-8" />
<meta name="viewport" content="width=device-width, user-scalable=yes" />
<meta http-equiv="Content-Language" content="en" />

<link rel="stylesheet" type="text/css"
href="http://secure.surveymonkey.com/css/default_themes.css?rv=201307171202"
media="all" />

<script type="text/javascript"
src="http://secure.surveymonkey.com/js/SurveyV12.js?rv=201307171202"></script>
<link rel="stylesheet" type="text/css"
href="http://secure.surveymonkey.com/css/s_iphone.css?rv=201307171202"
media="only screen and (max-device-width: 480px)" />

<meta id="metadesc" name="description" content="Web survey powered by
SurveyMonkey.com. Create your own online survey now with SurveyMonkey's expert
certified FREE templates."></meta>
</head>
<body id="BodyTag" class="notranslate" onload="setup();">

<form name="frmS" method="post"
action="/s.aspx?sm=9ojL1xa12%2bmhoMWTQ4XR9Q%3d%3d" id="frmS">
<div>
<input type="hidden" name="__EVENTVALIDATION" id="__EVENTVALIDATION"
value="/wEDgL+raDpAgKq7M2aCgLL+IOiBwKg6PF5AqnO0tsHAvko7kIAvm3qN
4FAouckuUIArDpqQBAo3HvMQNAtCN/L0JApzRpLAOAsP2pbEKAtSemZcEs5lKc
1Rb2DhjpuYC6hUvzCiqct8=" />
<input type="hidden" name="__VIEWSTATE" id="__VIEWSTATE"
value="" />
</div>
<!--content area-->
```

```

<div id="PageContentDiv"><h1 class="sTitle sTitleCf"><div style="text-align:left;"><span class="notranslate">Translating Time: The Eye Website Survey</span></div></h1><div class="pTitle"><h2></h2>&nbsp;<br class="clear"></div><div class="pgHdr"><div id="q1" class="question" style="margin:0 0 0; width:auto;"><div class="qContent"><div class="qHeader"><abbr class="noborder" title="Question 1">1</abbr>. How often do you visit this site?</h3></div><div class="qBody"><table cellspacing="0" cellpadding="0" border="0" style="width:100%;"><tr><td valign="top" style="width:100%;"><div class="qOption hover AnswerOptionText"><input type="radio" class="rb" id="input_526291507_10_6117553181_0" name="input_526291507_10_0_0" value="6117553181_0" /><label for="input_526291507_10_6117553181_0" id="linput_526291507_10_6117553181_0" class="rb_off"><span class="qLabel AnswerOptionText"><span class="hlbl">How often do you visit this site? &nbsp;</span>Every day</span></label></div><div class="qOption hover AnswerOptionText"><input type="radio" class="rb" id="input_526291507_10_6117553182_0" name="input_526291507_10_0_0" value="6117553182_0" /><label for="input_526291507_10_6117553182_0" id="linput_526291507_10_6117553182_0" class="rb_off"><span class="qLabel AnswerOptionText">Several times a week</span></label></div><div class="qOption hover AnswerOptionText"><input type="radio" class="rb" id="input_526291507_10_6117553183_0" name="input_526291507_10_0_0" value="6117553183_0" /><label for="input_526291507_10_6117553183_0" id="linput_526291507_10_6117553183_0" class="rb_off"><span class="qLabel AnswerOptionText">About once a week</span></label></div><div class="qOption hover AnswerOptionText"><input type="radio" class="rb" id="input_526291507_10_6117553184_0" name="input_526291507_10_0_0" value="6117553184_0" /><label for="input_526291507_10_6117553184_0" id="linput_526291507_10_6117553184_0" class="rb_off"><span class="qLabel AnswerOptionText">Several times a month</span></label></div><div class="qOption hover AnswerOptionText"><input type="radio" class="rb" id="input_526291507_10_6117553185_0" name="input_526291507_10_0_0" value="6117553185_0" /><label for="input_526291507_10_6117553185_0" id="linput_526291507_10_6117553185_0" class="rb_off"><span class="qLabel AnswerOptionText">About once a month</span></label></div><div class="qOption hover AnswerOptionText"><input type="radio" class="rb" id="input_526291507_10_6117553186_0" name="input_526291507_10_0_0" value="6117553186_0" /><label for="input_526291507_10_6117553186_0" id="linput_526291507_10_6117553186_0" class="rb_off"><span class="qLabel AnswerOptionText">Less than once a month</span></label></div><div class="qOption hover AnswerOptionText"><input type="radio" class="rb" id="input_526291507_10_6117553187_0" name="input_526291507_10_0_0" value="6117553187_0" /><label for="input_526291507_10_6117553187_0" id="linput_526291507_10_6117553187_0" class="rb_off"><span class="qLabel AnswerOptionText">This is my first visit here</span></label></div></td></tr></table></div></div></div id="q2" class="question" style="margin:0 0 0 0; width:auto"><div class="qContent"><div class="qHeader"><abbr class="noborder" title="Question 2">2</abbr>. How likely are you to return to this Web site?</h3></div><div class="qBody"><table cellspacing="0" cellpadding="0" border="0" style="width:100%; "><tr><td valign="top" style="width:100%; "><div class="qOption hover AnswerOptionText"><input type="radio" class="rb" id="input\_526291701\_10\_6117555100\_0" name="input\_526291701\_10\_0\_0" value="6117555100\_0" /><label for="input\_526291701\_10\_6117555100\_0" id="linput\_526291701\_10\_6117555100\_0" class="rb\_off"><span class="qLabel AnswerOptionText"><span class="hbl">How likely are you to return to this Web site? &nbsp; </span>Very Likely</span></label></div><div class="qOption hover AnswerOptionText"><input type="radio" class="rb" id="input\_526291701\_10\_6117555101\_0" name="input\_526291701\_10\_0\_0" value="6117555101\_0" /><label for="input\_526291701\_10\_6117555101\_0" id="linput\_526291701\_10\_6117555101\_0" class="rb\_off"><span class="qLabel AnswerOptionText">Somewhat Likely</span></label></div><div class="qOption hover AnswerOptionText"><input type="radio" class="rb" id="input\_526291701\_10\_6117555102\_0" name="input\_526291701\_10\_0\_0" value="6117555102\_0" /><label for="input\_526291701\_10\_6117555102\_0" id="linput\_526291701\_10\_6117555102\_0" class="rb\_off"><span class="qLabel AnswerOptionText">Somewhat Unlikely</span></label></div><div class="qOption hover AnswerOptionText"><input type="radio" class="rb" id="input\_526291701\_10\_6117555103\_0" name="input\_526291701\_10\_0\_0" value="6117555103\_0" /><label for="input\_526291701\_10\_6117555103\_0" id="linput\_526291701\_10\_6117555103\_0" class="rb\_off"><span class="qLabel AnswerOptionText">Not At All Likely</span></label></div></td></tr></table></div></div></div id="q3" class="question" style="margin:0 0 0 0; width:auto"><div class="qContent"><div class="qHeader"><abbr class="noborder" title="Question 3">3</abbr>. How likely are you to recommend this Web site to others?</h3></div><div class="qBody"><table cellspacing="0" cellpadding="0" border="0" style="width:100%; "><tr><td valign="top" style="width:100%; "><div class="qOption hover AnswerOptionText"><input type="radio" class="rb" id="input\_526291798\_10\_6117556014\_0" name="input\_526291798\_10\_0\_0" value="6117556014\_0" /><label for="input\_526291798\_10\_6117556014\_0" id="linput\_526291798\_10\_6117556014\_0" class="rb\_off"><span class="qLabel AnswerOptionText"><span class="hbl">How likely are you to recommend this Web site to others? &nbsp; </span>Extremely likely</span></label></div><div class="qOption hover AnswerOptionText"><input type="radio" class="rb" id="input\_526291798\_10\_6117556015\_0" name="input\_526291798\_10\_0\_0" value="6117556015\_0" /><label for="input\_526291798\_10\_6117556015\_0" id="linput\_526291798\_10\_6117556015\_0" class="rb\_off"><span class="qLabel AnswerOptionText">Very

likely</span></label></div><div class="qOption hover AnswerOptionText"><input type="radio" class="rb" id="input\_526291798\_10\_6117556016\_0" name="input\_526291798\_10\_0\_0" value="6117556016\_0"/><label for="input\_526291798\_10\_6117556016\_0" id="linput\_526291798\_10\_6117556016\_0" class="rb\_off"><span class="qLabel AnswerOptionText">Moderately likely</span></label></div><div class="qOption hover AnswerOptionText"><input type="radio" class="rb" id="input\_526291798\_10\_6117556017\_0" name="input\_526291798\_10\_0\_0" value="6117556017\_0"/><label for="input\_526291798\_10\_6117556017\_0" id="linput\_526291798\_10\_6117556017\_0" class="rb\_off"><span class="qLabel AnswerOptionText">Slightly likely</span></label></div><div class="qOption hover AnswerOptionText"><input type="radio" class="rb" id="input\_526291798\_10\_6117556018\_0" name="input\_526291798\_10\_0\_0" value="6117556018\_0"/><label for="input\_526291798\_10\_6117556018\_0" id="linput\_526291798\_10\_6117556018\_0" class="rb\_off"><span class="qLabel AnswerOptionText">Not at all likely</span></label></div></td></tr></table></div></div><div id="q4" class="question" style="margin:0 0 0 0; width:auto"><div class="qContent"><div class="qHeader"><abbr class="noborder" title="Question 4">4</abbr>. What features had influenced your decision to continue using this website? </h3></div><div class="qBody"><span><input id="text\_526291904\_0" name="text\_526291904\_0" class="open" type="text" size="50" value="" /></span><div class="hlbl"><label for="text\_526291904\_0">What features had influenced your decision to continue using this website? </label></div></div></div><div id="q5" class="question" style="margin:0 0 0 0; width:auto"><div class="qContent"><div class="qHeader"><abbr class="noborder" title="Question 5">5</abbr>. What is it about this site that you would most like to see improved?</h3></div><div class="qBody"><span><input id="text\_526291971\_0" name="text\_526291971\_0" class="open" type="text" size="50" value="" /></span><div class="hlbl"><label for="text\_526291971\_0">What is it about this site that you would most like to see improved?</label></div></div></div><div id="q6" class="question" style="margin:0 0 0 0; width:auto"><div class="qContent"><div class="qHeader"><abbr class="noborder" title="Question 6">6</abbr>. What changes or additional features would you suggest for this website? </h3></div><div class="qBody"><span><input id="text\_526292024\_0" name="text\_526292024\_0" class="open" type="text" size="50" value="" /></span><div class="hlbl"><label for="text\_526292024\_0">What changes or additional features would you suggest for this website?</label></div></div></div><div id="q7" class="question" style="margin:0 0 0 0; width:auto"><div class="qContent"><div class="qHeader"><abbr class="noborder" title="Question 7">7</abbr>. How did you first hear about this site? </h3></div><div class="qBody"><table cellspacing="0" cellpadding="0" border="0" style="width:100%; "><tr><td valign="top" style="width:100%; "><div class="qOption hover AnswerOptionText"><input type="radio" class="rb" id="input\_526292213\_10\_6117560280\_0" name="input\_526292213\_10\_0\_0" value="6117560280\_0"/><label for="input\_526292213\_10\_6117560280\_0">

```

id="linput_526292213_10_6117560280_0" class="rb_off">>How did you first hear about this site? Search
engine</label></div><div class="qOption hover AnswerOptionText"><input
type="radio" class="rb" id="input_526292213_10_6117560281_0"
name="input_526292213_10_0_0" value="6117560281_0" /><label
for="input_526292213_10_6117560281_0" id="linput_526292213_10_6117560281_0"
class="rb_off"><span class="qLabel
AnswerOptionText">Another web site</label></div><div class="qOption hover
AnswerOptionText"><input type="radio" class="rb"
id="input_526292213_10_6117560282_0" name="input_526292213_10_0_0"
value="6117560282_0" /><label for="input_526292213_10_6117560282_0"
id="linput_526292213_10_6117560282_0" class="rb_off">Friend or business
associate</label></div><div class="qOption hover AnswerOptionText"><input
type="radio" class="rb" id="input_526292213_10_6117560283_0"
name="input_526292213_10_0_0" value="6117560283_0" /><label
for="input_526292213_10_6117560283_0" id="linput_526292213_10_6117560283_0"
class="rb_off"><span class="qLabel
AnswerOptionText">Don't know/don't
remember</label></div></td></tr><tr><td colspan="1"><div class="qOption
AnswerOptionText"><label for="text_526292213_6117560278">Other (please
specify)</label><input class="open" id="text_526292213_6117560278"
name="text_526292213_6117560278" type="text" size="50" title="Other (please
specify)" value="" /></div></td></tr></table></div></div></div></div>
<!--end content area-->
<div id="panButtonBar">

<div style="text-align:center;">

<input type="submit" name="NextButton" value="Done" onclick="onesubmit(this);"
id="NextButton" class="btn btntext grey" />
<!-->

</div>

</div>

<div class="pbf">
 Powered by SurveyMonkey

<div id="SampleSurveysFooter">

```

Check out our <a id="pbhl" title="Go to SurveyMonkey.com to create free online surveys" href="http://www.surveymonkey.com/mp/survey-templates/" target="\_blank">sample surveys</a>  
and create your own now!  
</div>  
</div>

```
<div class="pbf">
<a id="pbhli"
href="http://www.surveymonkey.com/?ut_source=survey_poweredby&utm_medium=vMaziSmw7qcBV%2bta5mwUXgpo9luaAxR%2b4yr%2b1fI0Di8%3d&utm_term=SurveyBasic&utm_campaign=TY1hhyaZ5Sp5JDx8jwK0Bw%3d%3d&utm_content=1" target="_blank">
</div>
```

```
<div class="spacer" style="height:100px;"> </div>
```

```
<input type="hidden" name="hid_smC0l1d" id="hid_smC0l1d"
value="nbP2MYyuijrh8Uj2x_2fMFxa_3d_3d" />
<input type="hidden" name="hid_smRsL1d" id="hid_smRsL1d" />
<input type="hidden" name="hid_smRs1d" id="hid_smRs1d"
value="E6uK1MhOcpBUysyKIC0vrg_3d_3d" />
<input type="hidden" name="hid_smCSV" id="hid_smCSV" />
<input type="hidden" name="hid_smS1d" id="hid_smS1d"
value="3hCTZsR8AB93OCpNMPrL_2fA_3d_3d" />
<input type="hidden" name="hid_smM0D" id="hid_smM0D"
value="E6uK1MhOcpBUysyKIC0vrg_3d_3d" />
<input type="hidden" name="hid_smV3Rsn" id="hid_smV3Rsn"
value="2bIsl_2fh5_2fh6OtfepyR5a_2fDw_3d_3d" />
<input type="hidden" name="hid_smS3CT1d" id="hid_smS3CT1d"
value="h6N82kJgRRH5LAMHOh3aWA_3d_3d" />
<input type="hidden" name="hid_DC" id="hid_DC"
value="9X2eC2dh9yNHdL8HbVRzUnIFXQXJ6zbqkdn7hyNvC_2fF9hexNnuHcQePrw
_2b6n9oGE" />
<input type="hidden" name="Hidden_CollectorToken" id="Hidden_CollectorToken" />

<input type="hidden" name="Hidden_Simple" id="Hidden_Simple" />
<input type="hidden" name="hid_l04dez" id="hid_l04dez"
value="513o0KgWwUkTujvNGV8a7SaYnR6v5glAFaZhN6MXZno_3d" />
```

```

<div>

</div></form>

<noscript><style type="text/css" media="all">form {display:none;} #jserror {text-align:center;margin-top:50px;}</style><div id="jserror" class="qHeader">Javascript is required for this site to function, please enable.</div></noscript>

<script type="text/javascript">
/* <![CDATA[*/
var _gaq = _gaq || [];
_gaq.push(['_setAccount', 'UA-56526-1']);
_gaq.push(['_setDomainName', '.surveymonkey.com']);
_gaq.push(['_addIgnoredRef', 'www.surveymonkey.com']);
var gaq_id = '1';
if (gaq_id != '1' && gaq_id != '0') {
 _gaq.push(['_setCustomVar', 4, 'Package Type', '0', 1]);
 _gaq.push(['_setCustomVar', 5, 'User ID', '1', 1]);
}
_gaq.push(['_setSessionCookieTimeout', 7200000]);
_gaq.push(['_setCampaignCookieTimeout', 2592000000]);
_gaq.push(['_trackPageview']);
_gaq.push(['_trackPageLoadTime']);
(function() {
 var ga = document.createElement('script'); ga.type = 'text/javascript'; ga.async = true;
 ga.src = ('https:' === document.location.protocol ? 'https://ssl' : 'http://www') +
 '.google-analytics.com/ga.js';
 var s = document.getElementsByTagName('script')[0];
 s.parentNode.insertBefore(ga, s);
})();
/*]]> */
</script>

<script type="text/javascript">
/* <![CDATA[*/
function nes(e){e=(e)?e:event;var c=(e.which)?e.which:e.keyCode;return(c!=13);}var
is=document.getElementsByTagName("input");for(var i=0;i<is.length;i++){var
_i=is[i];if(_i.type=="text")_i.onkeypress=function(e){ return nes(e); }};
/*]]> */
</script>

```

```
<!-- 16 -->
</body>
</html>
```

## Appendix E: Scaling Macros Code

```
Sub loopLNValues()
'
' loopLNValues Macro
'

 Dim inputCell As String
 inputCell = "M2"
 Dim outputCell As String
 outputCell = "N2"
 Dim rmsCell As String
 rmsCell = "O2"

 Dim i As Integer
 i = 4
 While Range("M" & CStr(i)).Value <> ""
 Range("M" & CStr(i)).Calculate
 Range(inputCell).Value = Range("M" & CStr(i)).Value
 Range(outputCell).Calculate

 Range("N" & CStr(i)).Value = Range(outputCell).Value
 Range("O" & CStr(i)).Value = Range(rmsCell).Value

 i = i + 1
 Wend
End Sub
```

```

Sub rowsAndColumns()
 Dim inputCell As Range
 Dim candidateRmsCell As Range
 Dim bestRmsCell As Range
 Dim bestKCell As Range

 Set inputCell = Sheets("y=LN(E-k)").Range("M2")

 Dim k As Double
 Dim kMax As Integer
 Dim kInt As Integer
 Dim rowI As Integer
 Dim colI As Integer

 kInt = 1
 kMax = 850 'set to this so that we never take a LN of zero

 'clear old values
 Range("n3", "o48").Value = ""
 Range("c51", "k52").Value = ""

 While kInt < kMax
 ' set M2 to K value
 k = kInt / 100
 inputCell.Value = k
 'copy k here just to make it easy to monitor progress
 Range("L2").Value = k

 'for each row calculate new rms
 rowI = 3
 While rowI < 49
 Set candidateRmsCell = Range("M" & rowI)
 Set bestRmsCell = Range("O" & rowI)
 Set bestKCell = Range("N" & rowI)

 candidateRmsCell.Calculate

 If bestRmsCell.Value = "" Or candidateRmsCell.Value < bestRmsCell.Value
 Then
 bestRmsCell.Value = candidateRmsCell.Value
 bestKCell.Value = k
 End If
 rowI = rowI + 1
 End While
 End While
End Sub

```

Wend

'for each col calculate new rms

colI = 3

While colI < 12

Set candidateRmsCell = Cells(50, colI)

Set bestRmsCell = Cells(52, colI)

Set bestKCell = Cells(51, colI)

candidateRmsCell.Calculate

If bestRmsCell.Value = "" Or candidateRmsCell.Value < bestRmsCell.Value

Then

bestRmsCell.Value = candidateRmsCell.Value

bestKCell.Value = k

End If

colI = colI + 1

Wend

kInt = kInt + 1

Wend

End Sub

Sub OptimizeSpeciesValues()

Call OptimizeSpeciesValuesUsingK(8.49)

End Sub

Sub OptimizeSpeciesValuesUsingK(k As Double)

Dim seCandidateValueCell As Range

Dim candidateRmsCell As Range

Dim bestRmsCell As Range

Dim bestSEValueCell As Range

Dim candidateValue As Integer

Sheets("y=LN(E-k)").Range("M2").Value = k

Range("c57:k58").Value = ""

'for each species instance c2:k2

For Each seCandidateValueCell In Range("c2", "k2")

Set candidateRmsCell = Cells(56, seCandidateValueCell.Column)

Set bestRmsCell = Cells(57, seCandidateValueCell.Column)

Set bestSEValueCell = Cells(58, seCandidateValueCell.Column)

'candidateValues are multiplied by 1000

For candidateValue = 500 To 3500

seCandidateValueCell.Value = candidateValue / 1000

```

'calculate RMS
candidateRmsCell.Calculate

'if RMS is better than current best then store it
If bestRmsCell.Value = "" Or candidateRmsCell.Value < bestRmsCell.Value
Then
 bestRmsCell.Value = candidateRmsCell.Value
 bestSEValueCell.Value = seCandidateValueCell.Value
End If

 Next candidateValue
 Next seCandidateValueCell
End Sub
Sub optimizeEventValues()
 Call optimizeEventValuesUsingK(8.49)
End Sub

Sub optimizeEventValuesUsingK(k As Double)

 Dim seCandidateValueCell As Range
 Dim candidateRmsCell As Range
 Dim bestRmsCell As Range
 Dim bestSEValueCell As Range
 Dim candidateValue As Integer

 Sheets("y=LN(E-k)").Range("M2").Value = k

 Range("o3:p48").Value = ""

 'for each event instance b3:b48
 For Each seCandidateValueCell In Range("b3:b48")
 Set candidateRmsCell = Cells(seCandidateValueCell.Row, Range("n:n").Column)
 Set bestRmsCell = Cells(seCandidateValueCell.Row, Range("o:o").Column)
 Set bestSEValueCell = Cells(seCandidateValueCell.Row, Range("p:p").Column)

 'candidateValues are multiplied by 1000
 For candidateValue = 500 To 2500
 seCandidateValueCell.Value = candidateValue / 1000
 'calculate RMS
 candidateRmsCell.Calculate

 'if RMS is better than current best then store it
 If bestRmsCell.Value = "" Or candidateRmsCell.Value < bestRmsCell.Value
 bestRmsCell.Value = candidateRmsCell.Value
 bestSEValueCell.Value = seCandidateValueCell.Value
 End If
 Next candidateValue
 Next seCandidateValueCell
End Sub

```

```

End If

 Next candidateValue
 Next seCandidateValueCell
End Sub

Sub resetSpeciesAndEventValues()
 Dim resetColSrc As Integer
 Dim eventCell As Range

 resetColSrc = Range("t:t").Column

 '0.571 0.625 0.827 1.019 1.069 1.366 1.669 2.201 2.416
 Range("Event + Species Values'!c2").Value = 0.571
 Range("Event + Species Values'!d2").Value = 0.625
 Range("Event + Species Values'!e2").Value = 0.827
 Range("Event + Species Values'!f2").Value = 1.019
 Range("Event + Species Values'!g2").Value = 1.069
 Range("Event + Species Values'!h2").Value = 1.366
 Range("Event + Species Values'!i2").Value = 1.669
 Range("Event + Species Values'!j2").Value = 2.201
 Range("Event + Species Values'!k2").Value = 2.416

 For Each eventCell In Range("b3", "b48")
 eventCell.Value = Cells(eventCell.Row, resetColSrc).Value
 Next eventCell

End Sub

Sub applySpeciesValues()
 Range("Event + Species Values'!c2").Value = Range("c58").Value
 Range("Event + Species Values'!d2").Value = Range("d58").Value
 Range("Event + Species Values'!e2").Value = Range("e58").Value
 Range("Event + Species Values'!f2").Value = Range("f58").Value
 Range("Event + Species Values'!g2").Value = Range("g58").Value
 Range("Event + Species Values'!h2").Value = Range("h58").Value
 Range("Event + Species Values'!i2").Value = Range("i58").Value
 Range("Event + Species Values'!j2").Value = Range("j58").Value
 Range("Event + Species Values'!k2").Value = Range("k58").Value

End Sub

Sub applyEventValues()
 Dim colSrc As Integer
 Dim eventCell As Range

```

```

colSrc = Range("p:p").Column

For Each eventCell In Range("b3", "b48")
 eventCell.Value = Cells(eventCell.Row, colSrc).Value
 Next eventCell
End Sub

Sub runManyOptimizations()
 Dim numCycles As Integer
 numCycles = 6

 Dim kRadius As Double
 Dim kTimes1 As Integer
 Dim kTimes10 As Integer
 Dim kTimes100 As Integer
 Dim actualK As Double
 Dim bestK As Double
 bestK = -1
 Dim bestRms As Double
 Dim totalRmsCell As Range
 Set totalRmsCell = Cells(57, Range("o:o").Column)
 Dim bestKCell As Range
 Set bestKCell = Cells(57, totalRmsCell.Column + 1)

 For kTimes1 = 1 To 8
 actualK = CDbl(kTimes1)
 Call resetSpeciesAndEventValues

 For cycle = 1 To numCycles
 Range("b1").Value = "k: " & actualK & "; cycle: " & cycle & " of " & numCycles
 Call OptimizeSpeciesValuesUsingK(actualK)
 Call applySpeciesValues
 Call optimizeEventValuesUsingK(actualK)
 Call applyEventValues
 Next cycle

 'if RMS is better than current best then store it
 If bestK = -1 Or totalRmsCell.Value < bestRms Then
 bestRms = totalRmsCell.Value
 bestK = actualK
 bestKCell.Value = bestK
 End If
 Next kTimes1

 'next focus on area around current bestK
 kRadius = 1

 'restrict k values to less than 8.50 to avoid LN(0) errors
 Dim maxKTimes10 As Integer

```

```

maxKTimes10 = ((bestK + kRadius) * 10) - 1 '-1 to skip value tried in first loop
If maxKTimes10 > 84 Then
 maxKTimes10 = 84
End If

'restrict k values to greater than .01
Dim minKTimes10 As Integer
minKTimes10 = ((bestK - kRadius) * 10) + 1 '+1 to skip value tried in first loop
If minKTimes10 < 1 Then
 minKTimes10 = 1
End If

'increment is effectively 1/10
For kTimes10 = minKTimes10 To maxKTimes10
 actualK = kTimes10 / 10
 Call resetSpeciesAndEventValues

 For cycle = 1 To numCycles
 Range("b1").Value = "k: " & actualK & "; cycle: " & cycle & " of " & numCycles
 Call OptimizeSpeciesValuesUsingK(actualK)
 Call applySpeciesValues
 Call optimizeEventValuesUsingK(actualK)
 Call applyEventValues
 Next cycle

 'if RMS is better than current best then store it
 If bestK = -1 Or totalRmsCell.Value < bestRms Then
 bestRms = totalRmsCell.Value
 bestK = actualK
 bestKCell.Value = bestK
 End If
 Next kTimes10

'bestK is now x.x (e.g 5.7). Now focus on next level of precision
kRadius = 1 / 10

'restrict k values to less than 8.50 to avoid LN(0) errors
'Dim maxKTimes100 As Integer
'maxKTimes100 = ((bestK + kRadius) * 100) - 1 '-1 to skip value tried in first loop
>If maxKTimes100 > 849 Then
 'maxKTimes100 = 849
'End If

'restrict k values to greater than .01
'Dim minKTimes100 As Integer
'minKTimes100 = ((bestK - kRadius) * 100) + 1 '+1 to skip value tried in first loop
>If minKTimes100 < 1 Then
 ' minKTimes100 = 1
'End If

'increment is effectively 1/100
For kTimes100 = minKTimes100 To maxKTimes100
 ' Call resetSpeciesAndEventValues

```

```

' actualK = kTimes100 / 100
' For cycle = 1 To numCycles
 ' Range("b1").Value = "k: " & actualK & "; cycle: " & cycle & " of " & numCycles
 ' Call OptimizeSpeciesValuesUsingK(actualK)
 ' Call applySpeciesValues
 ' Call optimizeEventValuesUsingK(actualK)
 ' Call applyEventValues
'Next cycle

'if RMS is better than current best then store it
'If bestK = -1 Or totalRmsCell.Value < bestRms Then
 ' bestRms = totalRmsCell.Value
 ' bestK = actualK
 ' bestKCell.Value = bestK
'End If
'Next kTimes100

'found bestK. Recalculate everything using that value
Call resetSpeciesAndEventValues
Call OptimizeSpeciesValuesUsingK(bestK)
Call applySpeciesValues
Call optimizeEventValuesUsingK(bestK)
Call applyEventValues
End Sub

```