

Building an Online Resource for Candida Tropicalis

Final Report for CS39440 Major Project

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Declaration of originality

I confirm that:

- This submission is my own work, except where clearly indicated.
- I understand that there are severe penalties for Unacceptable Academic Practice, which can lead to loss of marks or even the withholding of a degree.
- I have read the regulations on Unacceptable Academic Practice from the University's Academic Quality and Records Office (AQRO) and the relevant sections of the current Student Handbook of the Department of Computer Science.
- In submitting this work I understand and agree to abide by the University's regulations governing these issues.

Name

Date

Consent to share this work

By including my name below, I hereby agree to this dissertation being made available to other students and academic staff of the Aberystwyth Computer Science Department.

Name

Date

Acknowledgements

I am grateful to...

I'd like to thank...

Abstract

Include an abstract for your project. This should be no more than 300 words.

CONTENTS

1	Background & Objectives	1
1.1	Background	1
1.2	Existing Databases	2
1.3	Alignment Tools	2
1.4	Similar systems	3
1.5	Analysis	4
1.6	Research Method and Software Process	4
2	Experiment Methods	6
2.1	Provided data	6
3	Software Design, Implementation and Testing	8
3.1	Requirements	8
3.2	Database	8
3.3	Design	9
3.3.1	Overall Architecture	10
3.3.2	Some detailed design	10
3.3.3	User Interface	10
3.3.4	Other relevant sections	10
3.4	Implementation	10
3.5	Testing	11
3.5.1	Overall Approach to Testing	11
3.5.2	Automated Testing	11
3.5.3	Integration Testing	11
3.5.4	User Testing	11
4	Results and Conclusions	12
5	Evaluation	13
	Appendices	14
A	Third-Party Code and Libraries	15
B	Ethics Submission	16
C	Code Examples	17
3.1	Random Number Generator	17
	Annotated Bibliography	20

LIST OF FIGURES

LIST OF TABLES

Chapter 1

Background & Objectives

This section should discuss your preparation for the project, including background reading, your analysis of the problem and the process or method you have followed to help structure your work. It is likely that you will reuse part of your outline project specification, but at this point in the project you should have more to talk about.

Note:

- All of the sections and text in this example are for illustration purposes. The main Chapters are a good starting point, but the content and actual sections that you include are likely to be different.
- Look at the document on the Structure of the Final Report for additional guidance.

1.1 Background

Researchers at Aberystwyth University have been studying three species of yeast, *Candida tropicalis*, *Candida boidinii*, and *Candida shehatae*. To study the genetics of these species, they have each had their genomes sequenced by Illumina sequencing machines. From that point the sequences of DNA that have been read are then assembled into contigs (contiguous DNA fragments). This process produces an accurate representation of the species DNA, which then can then be aligned to other better understood DNA and annotated as such.

Arabinose and Xylose are five carbon sugars ubiquitously found in plants such as grass, which can be used as a feedstock for industrial biotechnology. *Candida tropicalis* is able to convert arabinose & xylose into arabitol and xylitol respectively. Xylitol is a commercially valuable anti-bacterial foodgrade sugar use in the manufacture of chewing gum. However arabitol and xylitol are stereoisomers and cannot be easily separated. *Candida boidinii* cannot metabolise arabinose, for an unknown reason, but does metabolise Xylose but at a much slower rate which is commercially in-viable.

Understanding at a genomic level why *Candida boidinii* is unable to utilise arabinose and genetically modifying *Candida tropicalis* to have the same phenotype, may enable *Candida tropicalis* to exclusively produce xylitol and not arabitol. This would mean a cheap and easy to produce

source of Xylitol, which can be used for many applications. One exciting possibility is using it as a low glycaemic index table sugar that can be used by diabetics.

1.2 Existing Databases

Before undertaking this project I had some experience working with genomic data, and had been sitting in on lectures for a functional genomics module. This helped me get a good understanding of the basics of genetics and get a foothold on the terminology that is used in the world of bioinformatics. As the core of the project focuses on having the data ingested into a database, the first action was to investigate the current database solutions that had been developed for genomic information.

The most well established was CHADO which was initially developed back in 2005 for the FlyBase project. It has since then grown to accommodate genomic information for eukaryotes, plants, and other complex multicell animals. It uses PostgreSQL to store its data and Perl to setup and maintain the database. Due to its monolithic approach of being a one size fits all solution, it has over 200 tables in a very complex schema. This makes working on it rather difficult, as you have to consider a huge amount of relations between your tables.

When installing and populating CHADO, it was clear that the project wasn't very well maintained as during the installation several of the Perl modules that it depends on were failing their tests and not installing. This meant several modules had to be manually fixed just to get the application to install correctly. If it takes an experienced programmer and linux admin several hours to follow the default installation instructions, debugging issues at several steps, it isn't going to be appropriate to impose such a system on potentially less technically minded Biologists. This combined with the fact that Perl has now been superseded by more modern scripting languages such as Python and JavaScript, thanks to their superior package management, eco-systems and syntax, it was clear that a more modern approach would be more sustainable and maintainable for this project and for the future.

1.3 Alignment Tools

As the source of the data was uncertain, it was decided to investigate performing alignments in the event that more data, or different data was needed for the project than what was provided. The original alignment tool BLAST was developed in the 90's and is very widely accepted as the de facto standard for performing alignments. Alignment is when a DNA, or protein sequence is compared against a database of known protein sequences that have already been determined via previous research. This allows a researcher to match their sequences against known proteins and annotate them accordingly. These annotations aren't proof that the gene codes for that exact protein, but it is a strong indicator that it does. To prove it the researchers will test it in a lab experiment, however as there are many thousands of potential genes to test it is a lot more efficient to test genes that are predicted via an alignment. An alignment is a computationally intensive task there have been many efforts to improve the efficiency of the algorithm and make the most of developments made in computing since the 90's. One area that has been pursued is the use of GPU's to perform alignments in parallel utilising hundreds or thousands of cores of the GPU, compared to the tens of cores on a modern CPU.

Initially I tested Diamond [?] and was able to blast the data sets against the NCBI [?] non-redundant protein database, in about an hour and a quarter for each species, this was only using the CPU and may have been bottlenecked by the mechanical drives being used as storage. The hardware being used for this was an Intel i7-6700k @ 4.6Ghz, 16GB of RAM, a 7200rpm Hard Disk Drive, and a Nvidia GTX 980. As there was a high performance graphics card available it would be advantageous to make use a GPU accelerated alignment tool to make the most of the hardware available, and reduce the time that any future alignments may take.

The first attempt to use a GPU powered tool was BarraCUDA [?], which installed successfully and appeared to run fine, however it would attempt to read in the entire reference database into memory. This was an issue as the NCBI non-redundant database is around 66GB's in size, and the system that was being used only had 16GB's of RAM available.

Looking for other options I encountered CLAST [?], which unfortunately had compilation errors on the system. Debugging this was out of scope for my project as in this initial stage it didn't seem necessary. Next to try was Cudasw++ [?] this did install, but ran into the same issues as Barracuda, being limited by the system memory available.

In an attempt to get GPU acceleration working, the NCBI nr database was split up into 10GB chunks for use with these tools, however even after being reduced in size, BarraCUDA and Cudasw++ both had errors and failed to complete an alignment. It was decided that although the speed gains of a GPU accelerated alignment tool would be significant, the Diamond alignment was quick enough to not be a major bottleneck for the project, when compared with the extra time and effort that would have to be put into investigating how to get the GPU alignments to work.

1.4 Similar systems

From studying bioinformatics and researching the most common methods of manipulating and analysing the data gathered, a trend was found that indicated that unlike computer science, where tools are highly developed and have evolved to a very stable state where the best tools are known and highly specialised to suit their purpose, in bioinformatics a combination of factors including the relative youth of the field and the large number of competing projects that don't collaborate; there have been a wide array of tools created, often by biologists with no software engineering experience, none of which have been adopted and honed as the de facto standard. This means that for every task in the bioinformatics space there is often many different solutions offered, to what can be a very simple problem.

Gbrowse?

What was your motivation and interest in this project?

My interest in this project stems from my interest in genetics, something that has always fascinated me since I learned about how we evolved into being. As a computer scientist I relish the chance to apply the knowledge of my domain, to a real life application that can have a measurable positive impact on the world. Hopefully I will be able to use this experience to further my career into bioinformatics as well as helping contribute to the research being done.

1.5 Analysis

Taking into account the problem and what you learned from the background work, what was your analysis of the problem?

From researching the current solutions to the problem of annotating, storing and presenting genetic information, it was clear that a modern solution (describe that) wasn't currently in the public open source domain. Of the open source projects that were currently in use the majority appeared to be very old and monolithic, commonly written in Perl. Expand on all this etc.

How did your analysis help to decompose the problem into the main tasks that you would undertake?

Looking at the data that I was provided with there was three clear stages to the development of my solution. The first would be to ensure that the data I had was valid and in the same format for each of the species that were being analysed. The next was to import that data into a database, and then from there develop a web front end to interact with the data in the database.

Were there alternative approaches?

An alternative approach to this project would have been to use one of the existing databases such as Intermine or CHADO, and then use a web front end compatible with those databases such as GBrowse or Jbrowse. This would like require slight changes to how the data was processed before going into these established systems, however it would mean that the data would be in a format that is well understood by bioinformaticians.

Why did you choose one approach compared to the alternatives?

As a computer scientist looking at this problem, there doesn't seem to be much need for a very complex solution. Once the data is generated, the hard bit, it just needs to be made into a database friendly format and then ingested to the database system. From there building a simple web front end to make the database accessible is a very simple task. There isn't any need to manipulate or modify the data, simply create and read it. Because of this it seemed that the current systems were greatly over complicating matters.

SQL vs MongoDB Discuss in many details Diamond or blast2go?

There should be a clear statement of the research questions, which you will evaluate at the end of the work.

In most cases, the agreed objectives or requirements will be the result of a compromise between what would ideally have been produced and what was felt to be possible in the time available. A discussion of the process of arriving at the final list is usually appropriate.

1.6 Research Method and Software Process

You need to describe briefly the life cycle model or research method that you used. You do not need to write about all of the different process models that you are aware of. Focus on the process model or research method that you have used. It is possible that you needed to adapt an existing method to suit your project; clearly identify what you used and how you adapted it for your needs.

For the research-oriented projects, there needs to be a suitable process for the construction of

the software elements that support your work.

Chapter 2

Experiment Methods

**** Not sure what we put for this section ****

This section should discuss the overall hypothesis being tested and justify the approach selected in the context of the research area. Describe the experiment design that has been selected and how measurements and comparisons of results are to be made.

You should concentrate on the more important aspects of the method. Present an overview before going into detail. As well as describing the methods adopted, discuss other approaches that were considered. You might also discuss areas that you had to revise after some investigation.

You should also identify any support tools that you used. You should discuss your choice of implementation tools or simulation tools. For any code that you have written, you can talk about languages and related tools. For any simulation and analysis tools, identify the tools and how they are used on the project.

For the parts of your project that need some engineering (hardware, software, firmware, or a mixture) to support the experiments, include details in your report about your design and implementation. You should discuss with your supervisor whether it is better to include a different top-level section to describe any engineering work. In this template, Chapter 3 is suggested as a place for that discussion.

2.1 Provided data

The data for this project was produced by a contracted researcher who had moved onto another project, because of this there was limited opportunity to talk with them about the data, how it was produced and what needed doing to it. Unfortunately, the data did not include any form of documentation, or annotation as to how it was produced, the only metadata available was the filenames.

This lead to a lot of confusion as it wasn't immediately obvious what each bit of data was and what it meant. Examining the data and learning about the biology behind it took several weeks for me to ascertain what bits of data were actually relevant to the project, and what other data needed producing. For each species there were three files that I would need to use. What was provided:

- Raw assembled contigs of DNA, these would be used to get a genes position in the genome,

and it's surrounding bases.

- Protein sequences annotated with Gene Ontology ID's, these had been extracted from an NCBI nr blast
- Coding sequences, these are the nucleotide sequences that coded for the proteins. Uncertain as to how they were produced.

Linking this data to the Candida Genome Database was a key bit of information that was missing. To do this the annotated proteins for *C. albicans* [?] were downloaded, then turned into a reference database with Diamond. With this the three species could then have their coding sequences aligned against *C. albicans* to produce accession ID's from the Candida Genome Database.

There was then several sets of data required to map these proteins to the Candida Genome Database, that would allow the researchers to easily compare the genes to well annotated species. First was a file of GO annotations for all the proteins stored in the Candida Genome Database. [?] This file conveniently also stores all the accession ID's for those proteins. This is what was used to map the alignment results to the Candida Genome Database.

In addition to this was a mapping file that mapped Candida Genome Database ID's to Uniprot ID's. With a small JavaScript script and some manual cleaning with a text editor, I was able to produce a complete mapping file in JSON, ready to be read in by the importation script.

Chapter 3

Software Design, Implementation and Testing

This could be one chapter or a few chapters. It should define and discuss the software that is developed to support the research that is being conducted. For example, if your research involves running experiments,

What software are you creating to support that work?

3.1 Requirements

There are two main components to the software being developed for this project. The first is the manipulation of the data into a database, and the second is a web front end for the data to be accessed via.

3.2 Database

The database has to store data for each gene that has been annotated in the dataset for each species. I decided upon this schema:

```
{ id: Schema.ObjectId
  , hitid: String
  , species: String
  , name: String
  , cgdid: String
  , uniprot: String
  , contig:
    { head: String
      , seq: String
    }
  , codingseq:
    { head: String
      , seq: String
    }
```

```

    }
  , protein :
    { head : String
    , seq : String
    , goids : [String]
    , desc : String
    }
  , codingRange :
    { start : Number
    , end : Number
    , fail : Boolean
    }
}

```

This will store the unique `_id` assigned by MongoDB to all documents, the ID of the hit that was found when the species coding sequences have been aligned with *C. albicans*, the species it came from, the gene name and ID from Candida Genome Database, the UniProt ID, the contig of raw DNA, the coding sequence of nucleotides, the protein sequence that the coding sequence codes for, along with the annotations from NCBI nr database to provide a description, an array of Gene Ontology [?] ID's and finally if it can be found the positions of the start and end of the coding sequence in the raw contig.

What design will be used?

What implementation issues are there and what testing is used?

Even though a research project is investigating specific research questions, it is still necessary for you to discuss the software that you develop. Research has a habit of generating bits of software that can exist for several years and need future modification. Therefore you need to be able to discuss the technical issues as well as the research approach.

3.3 Design

You should concentrate on the more important aspects of the design. It is essential that an overview is presented before going into detail. As well as describing the design adopted it must also explain what other designs were considered and why they were rejected.

The first stage in designing this system was to decide upon what database technology would be used for the data store. As discussed in the analysis a NoSQL database called MongoDB has been chosen to store the data. This choice was also influenced by the choice of server side language, which for this project will be NodeJS.

NodeJS was chosen because

- * Client and server side languages are the same
- * Integrates well with MongoDB as it uses BSON which works with native JSON
- * Provides easy package management via npm
- * ES6 syntax is very nice
- * I have a lot of experience with it and learning a new language is outside of the scope of the project

The website for this interface will be built off of nodestack??, a set of boilerplate code that uses several technologies including:

ES6 Webpack MongoDB Mongoose Travis CI Eslint Heroku Pug Stylus

<http://blog.owen.cymru/nodejs-es6-boiler-plate/>

The design should describe what you expected to do, and might also explain areas that you had to revise after some investigation.

Typically, for an object-oriented design, the discussion will focus on the choice of objects and classes and the allocation of methods to classes. The use made of reusable components should be described and their source referenced. Particularly important decisions concerning data structures usually affect the architecture of a system and so should be described here.

How much material you include on detailed design and implementation will depend very much on the nature of the project. It should not be padded out. Think about the significant aspects of your system. For example, describe the design of the user interface if it is a critical aspect of your system, or provide detail about methods and data structures that are not trivial. Do not spend time on long lists of trivial items and repetitive descriptions. If in doubt about what is appropriate, speak to your supervisor.

You should also identify any support tools that you used. You should discuss your choice of implementation tools - programming language, compilers, database management system, program development environment, etc.

Some example sub-sections may be as follows, but the specific sections are for you to define.

3.3.1 Overall Architecture

3.3.2 Some detailed design

3.3.2.1 Even more detail

3.3.3 User Interface

3.3.4 Other relevant sections

3.4 Implementation

This section should discuss issues you encountered as you tried to implement your experiments. What were the results of running the experiments? What conclusions can you draw from these results?

During the work, you might have found that elements of your experiments were unnecessary or overly complex; perhaps third party libraries were available that simplified some of the functions that you intended to implement. If things were easier in some areas, then how did you adapt your project to take account of your findings?

It is more likely that things were more complex than you first thought. In particular, were there any problems or difficulties that you found during implementation that you had to address? Did such problems simply delay you or were they more significant?

If you had multiple experiments to run, it may be sensible to discuss each experiment in

separate sections.

3.5 Testing

Detailed descriptions of every test case are definitely not what is required here. What is important is to show that you adopted a sensible strategy that was, in principle, capable of testing the system adequately even if you did not have the time to test the system fully.

Provide information in the body of your report and the appendix to explain the testing that has been performed. How does this testing address the requirements and design for the project?

How comprehensive is the testing within the constraints of the project? Are you testing the normal working behaviour? Are you testing the exceptional behaviour, e.g. error conditions? Are you testing security issues if they are relevant for your project?

Have you tested your system on “real users”? For example, if your system is supposed to solve a problem for a business, then it would be appropriate to present your approach to involve the users in the testing process and to record the results that you obtained. Depending on the level of detail, it is likely that you would put any detailed results in an appendix.

The following sections indicate some areas you might include. Other sections may be more appropriate to your project.

3.5.1 Overall Approach to Testing

3.5.2 Automated Testing

3.5.2.1 Unit Tests

3.5.2.2 User Interface Testing

3.5.2.3 Stress Testing

3.5.2.4 Other types of testing

3.5.3 Integration Testing

3.5.4 User Testing

Chapter 4

Results and Conclusions

This section should discuss issues you encountered as you tried to implement your experiments. What were the results of running the experiments? What conclusions can you draw from these results?

During the work, you might have found that elements of your experiments were unnecessary or overly complex; perhaps third party libraries were available that simplified some of the functions that you intended to implement. If things were easier in some areas, then how did you adapt your project to take account of your findings?

It is more likely that things were more complex than you first thought. In particular, were there any problems or difficulties that you found during implementation that you had to address? Did such problems simply delay you or were they more significant?

If you had multiple experiments to run, it may be sensible to discuss each experiment in separate sections.

Chapter 5

Evaluation

Examiners expect to find in your dissertation a section addressing such questions as:

- Were the requirements correctly identified?
- Were the design decisions correct?
- Could a more suitable set of tools have been chosen?
- How well did the software meet the needs of those who were expecting to use it?
- How well were any other project aims achieved?
- If you were starting again, what would you do differently?

Other questions can be addressed as appropriate for a project.

Such material is regarded as an important part of the dissertation; it should demonstrate that you are capable not only of carrying out a piece of work but also of thinking critically about how you did it and how you might have done it better. This is seen as an important part of an honours degree.

There will be good things and room for improvement with any project. As you write this section, identify and discuss the parts of the work that went well and also consider ways in which the work could be improved.

In the latter stages of the module, we will discuss the evaluation. That will probably be around week 9, although that differs each year.

Appendices

The appendices are for additional content that is useful to support the discussion in the report. It is material that is not necessarily needed in the body of the report, but its inclusion in the appendices makes it easy to access.

For example, if you have developed a Design Specification document as part of a plan-driven approach for the project, then it would be appropriate to include that document as an appendix. In the body of your report you would highlight the most interesting aspects of the design, referring your reader to the full specification for further detail.

If you have taken an agile approach to developing the project, then you may be less likely to have developed a full requirements specification. Perhaps you use stories to keep track of the functionality and the 'future conversations'. It might not be relevant to include all of those in the body of your report. Instead, you might include those in an appendix.

There is a balance to be struck between what is relevant to include in the body of your report and whether additional supporting evidence is appropriate in the appendices. Speak to your supervisor or the module coordinator if you have questions about this.

Appendix A

Third-Party Code and Libraries

If you have made use of any third party code or software libraries, i.e. any code that you have not designed and written yourself, then you must include this appendix.

As has been said in lectures, it is acceptable and likely that you will make use of third-party code and software libraries. If third party code or libraries are used, your work will build on that to produce notable new work. The key requirement is that we understand what is your original work and what work is based on that of other people.

Therefore, you need to clearly state what you have used and where the original material can be found. Also, if you have made any changes to the original versions, you must explain what you have changed.

As an example, you might include a definition such as:

Apache POI library - The project has been used to read and write Microsoft Excel files (XLS) as part of the interaction with the client's existing system for processing data. Version 3.10-FINAL was used. The library is open source and it is available from the Apache Software Foundation [1]. The library is released using the Apache License [2]. This library was used without modification.

Appendix B

Ethics Submission

This appendix includes a copy of the ethics submission for the project. After you have completed your Ethics submission, you will receive a PDF with a summary of the comments. That document should be embedded in this report, either as images, an embedded PDF or as copied text. The content should also include the Ethics Application Number that you receive.

Appendix C

Code Examples

For some projects, it might be relevant to include some code extracts in an appendix. You are not expected to put all of your code here - the correct place for all of your code is in the technical submission that is made in addition to the Final Report. However, if there are some notable aspects of the code that you discuss, including that in an appendix might be useful to make it easier for your readers to access.

As a general guide, if you are discussing short extracts of code then you are advised to include such code in the body of the report. If there is a longer extract that is relevant, then you might include it as shown in the following section.

Only include code in the appendix if that code is discussed and referred to in the body of the report.

3.1 Random Number Generator

The Bayes Durham Shuffle ensures that the psuedo random numbers used in the simulation are further shuffled, ensuring minimal correlation between subsequent random outputs [3].

```
#define IM1 2147483563
#define IM2 2147483399
#define AM (1.0/IM1)
#define IMM1 (IM1-1)
#define IA1 40014
#define IA2 40692
#define IQ1 53668
#define IQ2 52774
#define IR1 12211
#define IR2 3791
#define NTAB 32
#define NDIV (1+IMM1/NTAB)
#define EPS 1.2e-7
#define RNMX (1.0 - EPS)
```



```

double ran2(long *idum)
{
    /*-----*/
    /* Minimum Standard Random Number Generator      */
    /* Taken from Numerical recipies in C             */
    /* Based on Park and Miller with Bays Durham Shuffle */
    /* Coupled Schrage methods for extra periodicity   */
    /* Always call with negative number to initialise  */
    /*-----*/

    int j;
    long k;
    static long idum2=123456789;
    static long iy=0;
    static long iv[NTAB];
    double temp;

    if (*idum <=0)
    {
        if (-(*idum) < 1)
        {
            *idum = 1;
        }else
        {
            *idum = -(*idum);
        }
        idum2=(*idum);
        for (j=NTAB+7; j>=0; j--)
        {
            k = (*idum)/IQ1;
            *idum = IA1 *(*idum-k*IQ1) - IR1*k;
            if (*idum < 0)
            {
                *idum += IM1;
            }
            if (j < NTAB)
            {
                iv[j] = *idum;
            }
        }
        iy = iv[0];
    }
    k = (*idum)/IQ1;
    *idum = IA1*(*idum-k*IQ1) - IR1*k;
    if (*idum < 0)
    {
        *idum += IM1;
    }
}

```

```
k = (idum2)/IQ2;
idum2 = IA2*(idum2-k*IQ2) - IR2*k;
if (idum2 < 0)
{
    idum2 += IM2;
}
j = iy/NDIV;
iy=iv[j] - idum2;
iv[j] = *idum;
if (iy < 1)
{
    iy += IMM1;
}
if ((temp=AM*iy) > RNMX)
{
    return RNMX;
}else
{
    return temp;
}
}
```

Annotated Bibliography

- [1] Apache Software Foundation, “Apache POI - the Java API for Microsoft Documents,” <http://poi.apache.org>, 2014.

This is my annotation. I should add in a description here.

- [2] —, “Apache License, Version 2.0,” <http://www.apache.org/licenses/LICENSE-2.0>, 2004.

This is my annotation. I should add in a description here.

- [3] W. Press *et al.*, *Numerical recipes in C*. Cambridge University Press Cambridge, 1992, pp. 349–361.

This is my annotation. I can add in comments that are in **bold** and *italics and then other content*.

- [4] M. Neal, J. Feyereisl, R. Rascunà, and X. Wang, “Don’t touch me, I’m fine: Robot autonomy using an artificial innate immune system,” in *Proceedings of the 5th International Conference on Artificial Immune Systems*. Springer, 2006, pp. 349–361.

This paper...

- [5] H. M. Dee and D. C. Hogg, “Navigational strategies in behaviour modelling,” *Artificial Intelligence*, vol. 173(2), pp. 329–342, 2009.

This is my annotation. I should add in a description here.

- [6] Various, “Fail blog,” <http://www.failblog.org/>, Aug. 2011, accessed August 2011.

This is my annotation. I should add in a description here.

- [7] S. Duckworth, “A picture of a kitten at Hellifield Peel,” <http://www.geograph.org.uk/photo/640959>, 2007, copyright Sylvia Duckworth and licensed for reuse under a Creative Commons Attribution-Share Alike 2.0 Generic Licence. Accessed August 2011.

This is my annotation. I should add in a description here.