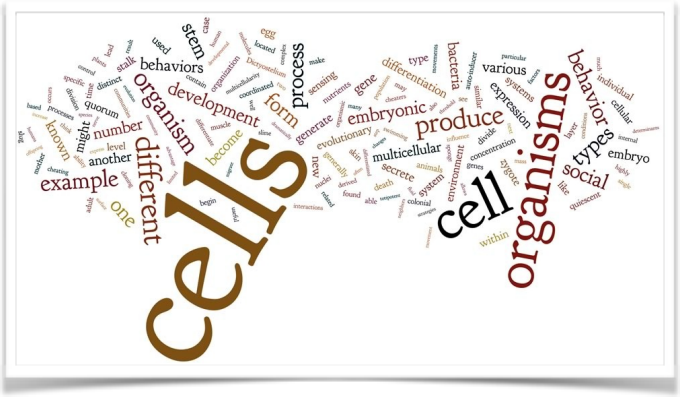
10. Social systems:

We end up by considering the dynamics of social systems, from bacterial quorum sensing to the development of an embryo.



Thinking about biology, we have to adopt a systems perspective. At each level of biological organization we can identify the objects that interact, how they interact, and the outcomes of their interactions. At the molecular level it is common to focus on the interactions between proteins and DNA (genes) that control gene expression (such as we have discussed in the context of the lac operon). These molecular level interactions play an important role in determining how cells behave. Interactions between cells influence the behaviors of the interacting cell, as well as the overall behavior(s) of biological communities and multicellular organisms. Interactions between organisms, ranging from mutual dependencies to host-pathogen and predator-prey interactions, underlie social and ecological systems. Interaction systems are complex. For example, interactions between cells will influence both lower (molecular level) and higher (organismic and social) systems. Moreover systems change over time and will respond to environmental perturbations in various, often unexpected ways. Systems thinking provides an analytical context to consider biological systems at all levels, from the gene to the ecosystem.

Microbial communities

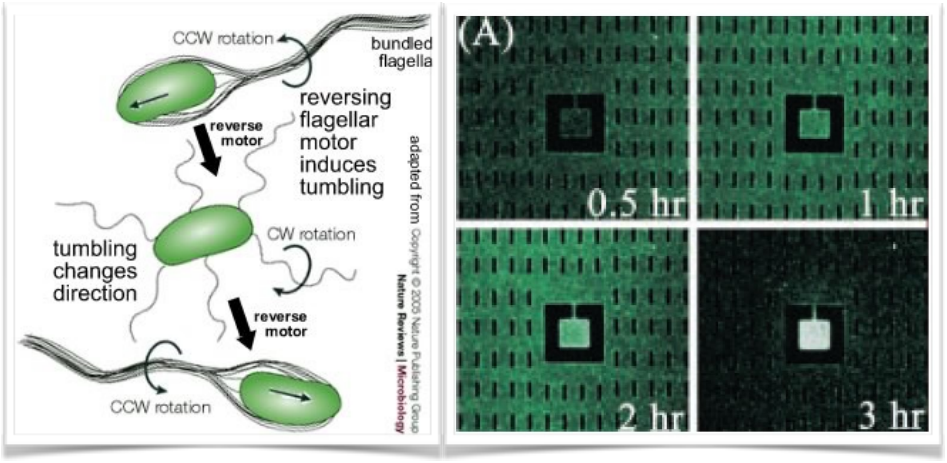
The organisms within a particular community are often critically dependent upon one another. Some organisms will secrete nutrients that are needed by others for their survival. Our own need for vitamins obtained from our diet reflects this interdependence. Some organisms secrete toxins to control the growth of others. Some will secrete molecules that influence the behaviors of other organisms (including themselves). There are complex molecular level conversations going on between the organisms in a ecosystem and the cells within an organism. Organisms are not independent, their behaviors are altered by their environment and they in turn, alter their environment.

An example of how even the simplest organisms can cooperate is an effect known as quorum sensing (which we have mentioned previously.) A bacterium of a particular species can secrete factors that are useful, for example, in the digestion of food into soluble nutrient molecules that it can ingest. But when growing in sparse situations (few organisms per unit volume or area), such a strategy is not efficient. For example if organisms are at low density, expensive to produce secreted molecules are more likely to diffuse away, and so be useless to the organism that produced them. However if there are large numbers of the organisms present, then the process becomes more efficient, the concentration of the secreted molecules will increase dramatically, reaching useful levels. By cooperating with their neighbors to produce a mutually beneficial behavior, each individual benefits.

How might this type of cooperation work? In bacteria a common strategy is for individuals to produce and secrete small (energetically inexpensive) molecules known as auto-inducers. They also

produce a cellular receptor for this same auto-inducer molecule. The auto-inducer-receptor pair enables organisms of the same type to recognize each other. The system works because the level of auto-inducer produced by a single bacterium is not sufficient to activate its receptors; only when the density of auto-inducer-secreting bacteria reaches a threshold level does the concentration of auto-inducer rise to a level high enough to activate the receptors. Activation of the auto-inducer-receptor generates a signal that in turn influences the bacterium's behavior (and generally gene expression).[254] One obvious behavior could be the secretion of digestive enzymes, but there are a number of others. For example, some types of bacteria (including *E. coli*) use quorum sensing to control cell migration. Over time individual cells migrate using their swimming system. One such system relies on flagellar (rotary) motors (driven by electrochemical gradients) to move the cell forward. In the absence of such a gradient, the motor reverses, this causes the cell to tumble and change direction. When moving up a gradient of attractant (or down a gradient of repulsant) tumbling is suppressed; the end result is directed movement.

This type of behavior has been illustrated dramatically by using *E. coli* that contain a plasmid that encodes the Green Fluorescent Protein (GFP). When illuminated with blue light, a cell expressing GFP enables glows green![255] When GFP-expressing *E. coli* are cultured in a maze-like environment with a central "chamber" with a single opening, the secreted attractant will accumulate to high concentrations within this space. Over a three hour period the bacteria will swim in a directed manner up the attractant concentration gradient into the chamber.[256] At this point quorum sensing behaviors will be activated. For example in situations where nutrients become scarce, a quorum sensing controlled behavior can lead some of the cells in the population to die, a process known as programmed cell death, releasing their nutrients for their neighbors to use. This can be seen as a type of altruism, since it helps the neighbors, who are likely to be relatives of the sacrificing cell.[257] Another type of behavior occurs under condition of stress, a subpopulation of cells will form slow or non-growing cells, known as quiescent or "persister" cells, while the rest of the population continues to grow.[258] If the environment turns seriously hostile, the persisters have a much higher probability of survival than do the actively growing cells. If conditions



[254] Bacterial quorum-sensing network architectures: http://www.ncbi.nlm.nih.gov/pubmed/19686078

[255] The original green fluorescent protein evolved in jelly fish Aequorea victoria, it is one of a multigene family of fluorescent proteins: see GFP-like Proteins as Ubiquitous Metazoan Superfamily: Evolution of Functional Features and Structural Complexity: http://www.ncbi.nlm.nih.gov/pubmed/14963095.

[256] Motion to Form a Quorum: http://www.ncbi.nlm.nih.gov/pubmed/12855801

[257] Programmed cell death in bacteria and implications for antibiotic therapy: http://www.ncbi.nlm.nih.gov/pubmed/23684151

[258] "Persisters": Survival at the Cellular Level: http://www.ncbi.nlm.nih.gov/pubmed/21829345

improve the persisters can reverse their behavior and reestablish an actively growing population. On the other hand, if the conditions never get hostile, the growing cells have an evolutionary advantage over cells that go quiescent. This implies the presence of a system can produce persisters when they might be useful. The ability of an organism to produce quiescent persister state helps insure the survival of the population within a wider range of environments than would be expected in a population that cannot produce persisters. This is a example of group selection. A similar behavior has been found to occur within populations of cancer cells.[259] Persister cells can survive therapeutic treatments and re-emerge later. We have already seen, in the context of the *lac* operon, how an initially uniform population of organisms can produce distinct phenotypes through stochastic processes; similar random events play an important role in the determination of cell fates in many social situations.

An important evolutionary question involves what to do with the emergence of social cheaters? First, what exactly do we mean by a social cheater? In the context of quorum sensing, suppose an individual does not make the auto-inducer, but continues to make its receptor. It gains the benefits of communicating with other bacteria, but minimizes its contribution. It might well gain an advantage in that the energy used to make the auto-inducer could instead be used for growth and reproduction. There are limits to cheating, however. If enough members become cheaters the quorum sensing system will fail because not enough members of the community secrete the auto-inducer. There are other more pro-active strategies that can be used to suppress cheaters. It may be that the production of the auto-inducer is a by-product of an essential reaction. In this case, loss of the ability to produce the auto-inducer could itself lead to death. A second approach is more pro-active. For example, many bacterial species synthesize toxins to which they themselves are immune, but which kill cells of related species. It could be that toxin immunity could be coupled to auto-inducer expression. Social cooperation between cells can provide benefits, but also opens up the system to selfish cheaters.[260] Cancer, and the mechanisms to suppress it, is a particularly prominent example of cheater and anti-cheater behaviors.

Making metazoans

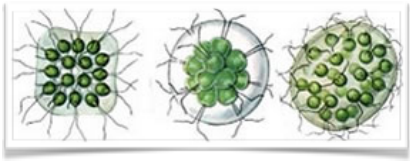
As we think about biological communities we begin our movement from biofilms and other ecologies to discrete systems, that is, what we think of as organisms. First, let us make it clear, a biofilm or microbial mat is not an organism, it is more correctly termed an ecological system or community, composed of distinct organisms, each of which gives rise to organisms genetically related to their parent(s). While horizontal gene transfer between organisms may occur to various extents, the idea of distinct organisms is still valid.

The next obvious level of organization is what we will call a colony. In colonial organisms individual cells are attached to one another, generally through the extracellular materials they secrete. They gain advantages associated with larger size (for example, they may be able to swim faster or being too big to swallow) but these advantages are constrained by the fact that the individual cells

[259] Evolution of cooperation among tumor cells: http://www.ncbi.nlm.nih.gov/pubmed/16938860

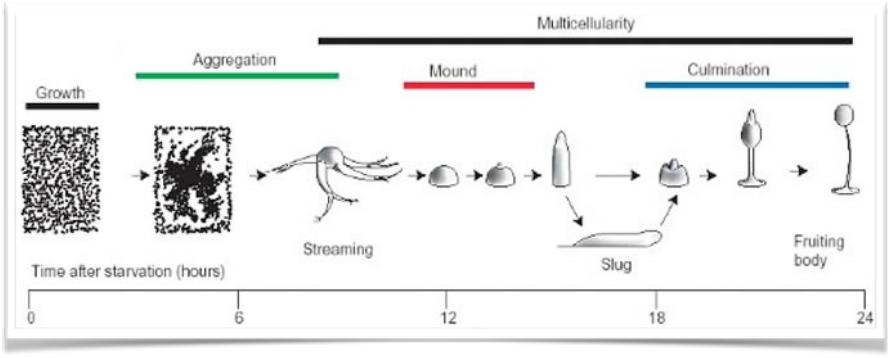
[260] Safeguards for cell cooperation in mouse embryogenesis shown by genome-wide cheater screen:http://www.ncbi.nlm.nih.gov/pubmed/24030493

retain their individuality. For example in colonial forms of algae there is no central coordination between the beating of neighboring cells. Moreover, in a pure colonial organism, each cell within the colony retains its ability to reproduce independently, either sexually or asexually. Previously we introduced the terms soma for the cells of the body that reproduce asexually and are responsible for the growth and repair of the organism, and the germ line, that is, the cells that are responsible for producing the next generation of organisms. In a purely colonial organism, all cells are potential germ cells. There is no central system for coordinating behavior.



So we might ask, what is the path from individual cells to integrated multicellular organisms? In general we think that the earliest step is likely to have been colonial organization. Some organisms can be used as part of a modern bestiary to illustrate various behaviors on the way to multicellular organisms.[261] This is not to claim that any represent real ancestors, all are modern organisms, well adapted to their current environment and the result of their own evolutionary history. Never the less, they have dealt with various aspects of multicellular coordination and differentiation in interesting ways.

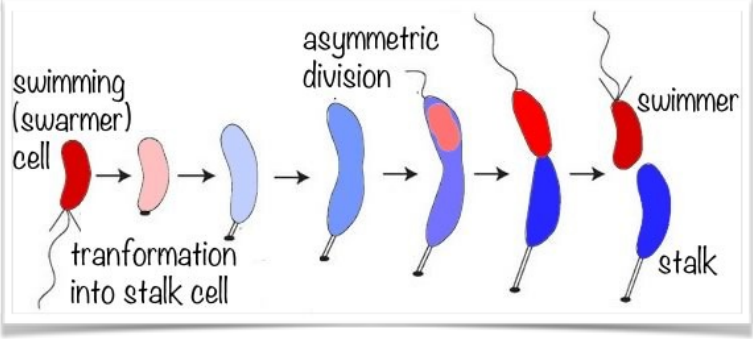
Consider the eukaryotic slime mold *Dictyostelium discoideum*. Cellular slime molds live in soil and eat bacteria - they are unicellular predators. Most of the time they are small, amoeba-like, haploid cells. Upon starvation they can undergo a dramatic aggregation process. Aggregation is triggered by the release, from individual cells, of pulses of cyclic adenosine monophosphate (cAMP); a process analogous to quorum sensing in bacteria (see above). The result is that individual cells begin to migrate up the cAMP concentration gradient, where they interact with and adhere to one another. Groups of cells produce more cAMP, and the end result are cellular aggregates, known as slugs, that contain between 10,000 to 100,000 discrete cells. Slugs migrate in a coordinated manner. Eventually the slug will stop its migration and begin a process of differentiation. Some of the cells of the slug differentiate to form stalk cells; the coordinated elongation of these stalk cells lifts the rest of the slug "body" into the air. The non-stalk cells differentiate to form spores, cells like the quiescent persisters we mentioned above. When released into the air, the spores are widely dispersed and, if they land in an appropriate environment, can go on to form single celled amoebae.



By now you may be able to generate a plausible scenario to explain exactly how the self-sacrificing behavior of stalk cells is possible. The answer lies in inclusive fitness. The purpose of the slug and stalk are to enable *Dictyostelium* cells to escape a hostile environment and colonize new, more hospitable environments. In fact, in a number of cases the spores carry with them bacteria that inoculate their new environments; these are bacteria that the amoeba can eat. The slime mold could be

[261] The medieval bestiary: http://bestiary.ca

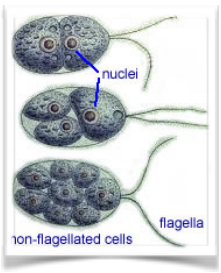
considered migrating bacterial farmers.[262] Since individual *Dictyostelium* amoeboid cells can not migrate far, most of the cells in any particular region, that is the cells that combine to form a slug, are likely to be closely related to one another - they are part of a clone. The sacrifice of the stalk cells is more than made up for by the increased chance that the spore cells will survive and produce lots of offspring. Of course there is a danger that some cells will diverge (through mutation) and cheat the system. That is, they will avoid becoming stalk cells. Such cheating has been observed in wild type *Dictyostelium* and cheating is a challenged faced by all multicellular systems. There are a number of strategies that are used to suppress cheaters, generally they are similar to those exploited in the context of quorum sensing.[263]



An organism that displays a distinct type of differentiation behavior is the bacterium *Caulobacter crescentus*. Under certain conditions it will produce stalk cells. These cells attach to a surface and divide to produce swimming cells that can migrate away and colonize new surfaces. The stalk cell can continue to produce swimming cells, and the swimming cells can settle down and transform into stalk cells. *C. crecentus* has established two different cell types designed to exploit two distinct environments.

Steps to metazoans multicellular animals and plants

As we think about how organisms can increase in complexity, there are really only a few strategies available. One way is to generate very complex unicellular organisms. This strategy is limited, however, and organisms of this type are generally small, only a few hundred micrometers in length. The alternative path to complexity is through multicellularity, which appears to have occurred around 1 billion years ago. In true multicellular organisms (as opposed to colonial organisms), different cells become highly specialized. Most cells are relieved of the need to produce a new organism; that task is taken up by specialized cells in the germ line. As noted above, this allows for the formation of cells with very limited, but highly useful abilities.



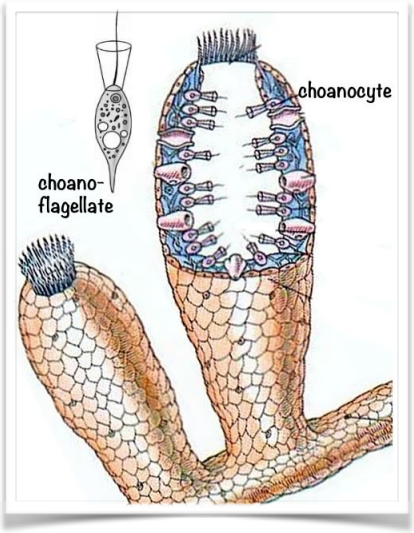
To get a better idea of the evolutionary history of multicellularity it is helpful to look in detail at the organization, both cellular and genomic, of current organisms. It has been estimated that multicellularity arose multiple times among the eukaryotes.[264] To begin to understand the steps in the process it is useful to consider those unicellular organisms most closely related to a particular metazoan lineage (known as a sister group). We can then speculate on the various steps between the unicellular and multicellular forms. In the case of the animals, it appears that their (our) unicellular

[262] **Small molecules mediate bacterial farming by social amoebae**. http://www.ncbi.nlm.nih.gov/pubmed/23975931

[263] Kin Recognition Protects Cooperators against Cheaters: http://www.ncbi.nlm.nih.gov/pubmed/23910661

[264] Multicellularity arose several times in the evolution of eukaryotes: http://www.ncbi.nlm.nih.gov/pubmed/23315654

sister group are the choanoflagellates.[265] Choanoflagellates have cells that are characterized by a single flagellum surrounded by a distinctive collar structure.[266] Choanoflagellates exist in both unicellular and simple colonial forms.



Sponges (porifera) are among the simplest of the metazoans. Fossils of extinct sponges, such as the Archaeocyathids, are found in Cambrian rock that is over 500 million years old. Earlier sponge-like organisms have been found in even older Precambrian rock. Sponges contain only a few different types of cells. These include the cells that form the outer layer of the organism (pinococytes) and the cells (porocytes) that form the pores in the organism's outer layer. The skeletal system of the sponge, the spicules, are produced by sclerocytes. A distinct type of cell (archaeocytes) function in digestion, gamete production, tissue repair and regeneration. Sponges also include cells, known as choanocytes, that move fluid through the body. It is the striking resemblance of these cells to the unicellular choanaflagellates (and subsequent genomic analyses) that led to the hypothesis that choanoflagellates and animals are sister groups.[267]

The next level of metazoan complexity is represented by hydra and related organisms, the hydrozoa, which include jellyfish. Some of these organisms alternate between a sessile and benthic, or floating, lifestyles.[268] The hydrozoa contain more distinct cell types than the porifera. The most dramatic difference is their ability to produce coordinated movements associated with swimming and predation. While sponges are passive sieves, the hydrozoa have a single distinct mouth, an internal stomach-like cavity, and motile arms specialized to capture prey. Their mouth also serves as their anus, through which wastes are released.

Hydrozoan movements are coordinated by a network of cells, known as a nerve net, that acts to regulate contractile muscle cells. Together the nerve net and muscles cells generate coordinated movements, even though there is no central brain (which in its simplest form is just a dense mass of nerve cells). A hydra can display movements complicated enough to capture and engulf small fish. Stinging cells, nematocysts, are located in the “arms". Triggered by touch, they explode outward, embedding themselves in prey and delivering a paralyzing poison.[269] Hydrozoans are complex enough to be true predators.

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[265] http://www.nytimes.com/2010/12/14/science/14creatures.html?_r=0

[266] Introduction to the Choanoflagellata: http://www.ucmp.berkeley.edu/protista/choanos.html

[267] The genome of the choanoflagellate *Monosiga brevicollis* and the origin of metazoans: http://www.ncbi.nlm.nih.gov/pubmed/18273011

[268] The live cycle of jellyfish: http://youtu.be/oHiVA9J_YIM

[269] How do jellyfish sting: http://youtu.be/HyIwa7W-ZV8

Questions to answer & ponder:

- What types of signals do human send and receive?
- How would changes in the affinity of an auto-inducer receptor influence the behavior of an organism?
- Why might an organism grow well in a biofilm but not in an isolated monoculture?
- In the case of a cellular slime mold, what is the advantage of multicellularity?
- Why do *Dictyostelium* stalk cells "sacrifice themselves" for fruiting body cells?
- Does coordinated movement require a brain?
- Does having a brain equal self-awareness?
- What types of evidence suggest that choanoflagellates and sponges are related?
- Why is the presence of highly specialized cells evidence for common ancestry?
- In terms of cell types and functions, how do a hydra and a sponge differ from one another?
- What kind of evidence, in modern organisms, might lead you to conclude that the last common ancestor of plants and animals had flagella?
- What are the advantages of a closed gut versus a sieve?

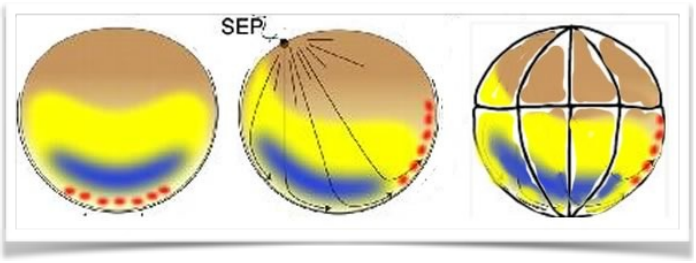
Differentiation

Complex organisms, from worms to humans, undergo a process known as embryonic development. This process begins with the fusion of a haploid sperm and a haploid egg (produced through meiosis) to form a new diploid organism. This cell then divides (by mitosis) to produce the embryo which develops into an adult. Cell division leads to embryonic cells that begin to behave differently from one another. For example, while the original diploid cell generated by fertilization (the zygote) is totipotent - that is, it can generate all of the cells found in the adult, the cells formed during development become more and more restricted with respect to the types of progeny that they can produce–they become committed to one or another specific fate. In part this is due to the fact that as cells divide, different ells come to have different neighbors and they experience different environments, leading to the expression of different genes. The question now becomes, what determines what types of cells does an embryonic cell produce in the adult?

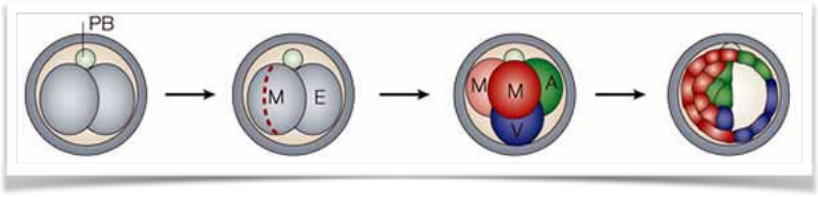
There are two basic, and interacting, processes that drive embryonic development. During the formation of the egg and following fertilization, cytoplasmic determinants (which may be proteins, RNAs, or metabolic products) can become localized to, or active in, specific regions of the egg, and later to specific regions of the embryo. The presence of these cytoplasmic determinants drives the cell that contains them in a specific developmental direction. This developmental direction is based on changes in gene expression. The second set of processes involved in embryonic development are the changing interactions between cells. These involve adhesive interactions and intercellular signals. They can direct a cell to adopt specific fates. There are many different types of embryonic development, since this stage of an organisms life cycle is as subject to the effects of evolutionary pressures as any other (although it is easy to concentrate our attentions on adult forms and behaviors). The study of these processes, known as embryology, is beyond our scope here, but we can outline a few common themes.

If fertilized eggs develop outside of the body of the mother and without parental protection, then these new organisms are highly vulnerable to predation. In such organisms, early embryonic development proceeds rapidly. The eggs are large and contain all of the nutrients required for development to proceed up to the point where the new organism can feed on its own. To facilitate such

rapid development, the egg is essentially pre-organized, that is, it is highly asymmetric, with specific factors that can influence gene expression, either directly or indirectly, positioned in various regions of the egg. Entry of the sperm (the male gamete), which itself is an inherently asymmetric process, can also lead to reorganization of the cytoplasm. Maternal and fertilization-driven asymmetries are stabilized by the rapid cycles of DNA replication and cell division, with growth being dependent upon the transformation of maternally supplied nutrients. As distinct cells are formed, they begin to become different from one another because i) they inherit different determinants, ii) the presence of these determinants leads to changes in gene expression, and iii) cells will secrete and respond to different factors, that further drive their differentiation into different cell types, with different behaviors based on differences in gene expression.



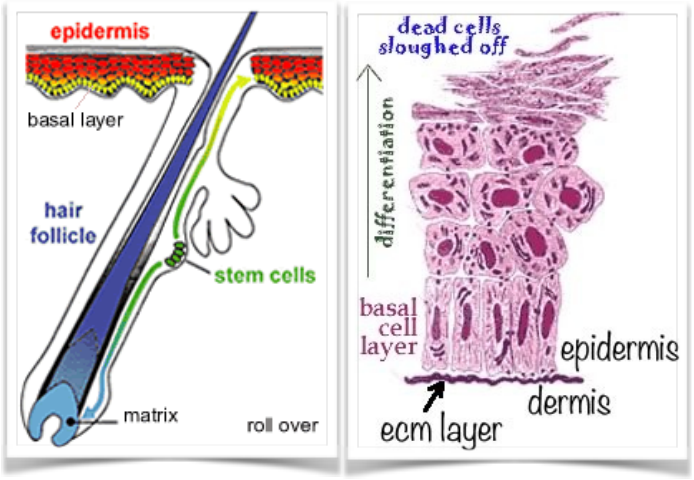
On the other hand, in a number of organisms, and specifically mammals, embryonic development occurs within the mother, so there is no compelling need to stockpile nutrients within the egg and the rate of development is dramatically slower. In such developmental systems, it is not the asymmetries associated with the oocyte and fertilized egg that are critical, but rather the geometries of the cells within the developing embryo. As the zygote divides, a major factor that drives the differentiation of cells is whether they lie on the surface of the embryo or within the interior. In mammals, the cells on the exterior form the trophectoderm, which goes on to form extraembryonic tissues, in particular the membranous tissues that surround the embryo and become part of the placenta, the interface between the embryo and the mother. Cells within the interior form the inner cell mass that produces to the embryo proper. Changes in gene expression will lead to changes in the ability to produce and respond to inductive signals, which will in turn influence cell behavior and gene expression. Through this process, the cells of the inner cell mass come to form the various tissues and organs of the organism; that is, skin, muscle, nerve, hair, bone, blood, etc. It is easy to tell a muscle cell from a neuron from a bone cell from a skin cell by the set of genes they express, the proteins they contain, their shapes (morphology), their internal organization, and their behaviors.



Stem cells

Stem cells are cells that continue to divide in the adult, but they divide in a very particular manner. At each division cycle, one daughter cell remains a stem cell, while the other goes on to differentiate. In part, this is due to the environment in which the stem cell finds itself, which is known as the stem cell niche. For example, in mammals, the stem cells that lead to the continuous regeneration of the skin and hair are located in a region of the hair follicle, known as the bulge. These cells divide rarely, with one daughter migrating away from the bulge and the other remaining in place. The migrating daughter cell will come to colonize the basal layer of the epidermis, where it continues to divide a number of times. Again, this is a stem cell-like division; the cells that remain attached to the

extracellular matrix layer remaining stem cell like, while those that leave the “basal cell layer” begin the process of differentiation that leads, eventually, to their death (you are constantly shedding dead skin cells.) In normal skin the process of cell birth and death is balanced. Hyperplasia occurs when cell birth occurs more frequently than cell death. Typically the non-stem cell products of a stem cell division are committed to differentiation and have a finite proliferative life span - they can divide only a limited number of times before they senesce (that is, stop dividing). Terminally differentiated cells no longer divide. The process of cellular senescence is thought to be an internal defense mechanism against cancer; often cancer cells accumulate mutations than enable them to circumvent the effects of senescence.



Cellular differentiation and genomic information

An important question that was asked by early developmental biologists was, is cellular differentiation due to the loss of genetic information. Is the genetic complement of a neuron different from a skin cell or a muscle cell? This question was first approached by Briggs and King in the 1950s through nuclear transfer experiments in frogs. These experiments were extended by Gurdon and McKinnell in the early 1960s. They were able to generate adult frogs via nuclear transfer using embryonic cells. The process was inefficient however - only a small percentage of transferred nuclei supported normal embryonic development. Nevertheless, these experiments suggested that it was the regulation rather than the loss of genetic information that was important in embryonic differentiation.

In 1996 Wilmut et al used a similar method to clone the first mammal, the sheep Dolly. Since then many different species of mammal have been cloned, and there is serious debate about the cloning of humans. In 2004, cloned mice were derived from the nuclei of olfactory neurons using a method similar to that used by Gurdon. These neurons came from a genetically engineered mouse that expressed GFP (see above). A hybrid gene contained the coding sequence for GFP and a regulatory sequence that led to its expression in most cell types of the mouse. Neuronal nuclei were transplanted into an oocyte from which the original nucleus had been removed (an enucleated oocyte). Blastula derived from these cells were then used to generate totipotent embryonic stem cells. It was the nuclei from these cells that were transplanted into enucleated eggs. The resulting embryos were able to develop into full grown and fluorescent mice, proving that neuronal nuclei retained all of the information required to generate a complete adult animal.

The process of cloning from somatic cells is inefficient – many attempts have to be performed, each using an egg, to generate an embryo that is apparently normal (most embryos produced this way were abnormal). At the same time, there are strong ethical concerns about the entire process of reproductive cloning. For example the types of cells used, embryonic stem cells, are derived from the

inner cell mass of mouse or human embryos. Embryonic stem cells can be cultured in vitro and under certain conditions can be induced to differentiate into various cell types. Since the generation of totipotent human embryonic stem cells involves the destruction of a human embryo, it raises a number of ethical issues.

Current research attempts to avoid these issues by focussing on optimizing the process by which somatic nuclei can be reprogrammed to support totipotent and pluripotent development. In this scenario, somatic cells from a patient are treated with genes (or more recently gene products) for a small number (typically) four molecules to induce differentiated somatic cells to become pluripotent cells. These “induced pluripotent stem” (iPS) cells behave much like embryonic stem cells. The hope is that a iPS cells derived from a patient could be used to generate tissues or even organs that could be transplanted back into the patient, and so reverse and repair disease-associated damage.

Questions to answer & to ponder:

- Are the advantage(s) of multicellularity the same for plants versus animals ?
- How might asymmetries be generated in the zygote?
- Why do differentiated cells express different genes than do undifferentiated cells?
- How could two cells that express the same set of transcription factors, express different genes?
- In terms of transcription factors and chromatin packing, why is it difficult to reverse differentiation?
- What is the primary characteristic of a stem cell?
- Why might the organism want to reduce the number of stem cells it contains?
- Based on your understanding of the control of gene expression, outline the steps required to reprogram a nucleus so that it might be able to support embryonic development.
- What is necessary for cells to become different from one another - for example how do muscle cells and skin cells come to be different from one another?
- What are the main objections to human cloning? What if the clone were designed to lack a brain, and destined to be used for "spare parts"?
- How would a clone be different from a twin?
- How do we "check" whether our reading of another's emotions are correct.?
- Would different types of social groups have different types of morality?
- Does social evolution explain morality?
- Is the next step in evolution the evolution of eusocial humans? speculate (please)