Molecular Biology Through Discovery (Fall 2012)
Strategies of Life

Outline:

A. Genes and organisms

B. Self-assembly of cell membranes

C. Metabolism: monomers, polymers, central metabolism

D. Summary

A. Genes and organisms

Perhaps the central questions in molecular biology is how information passes from one generation to the next and how that information acts to direct the formation of cells and organisms. A treatise on molecular biology will therefore dwell on informational molecules – DNA and RNA – how they are related to protein and how protein are responsible for the structure and functioning cells. You might be presented with a picture such as that shown in **Fig. 1**. You might be offered the metaphor of DNA as the blueprint for the cell.

But DNA is not a blueprint, i.e. a diagrammatic representation. Examine DNA as closely as you like, you will not find there a picture of a cell or anything else. If DNA were a blueprint, it would be useless, because a blueprint requires someone with intelligence to read it and devise the steps to make the abstraction a reality.

Perhaps you can salvage the metaphor by postulating that DNA gives directions that are so specific as to not require intelligence. Now we have not a blueprint but more like a computer program. The program might specify the size of the beams of the house, the type of nail, precisely where the nail should be pounded into the beam, and so forth. But that's just the beginning. It would also have to specify how to build the nail pounder and the conveyer to bring the beam to that machine, and then the machines to build the nail pounder and the conveyer, and the machines to build THOSE machines,… this is all adding up to a very complicated program, far more complicated than could fit into life-sized DNA!

So let's try a different direction. Suppose DNA doesn't know how to specify a three-dimensional house but does know how to specify something simpler. **Fig. 2** shows how specifying a two-dimensional unfolded box could lead to the spontaneous appearance of a three-dimensional box, relying on specific types of glue and a source of energy.

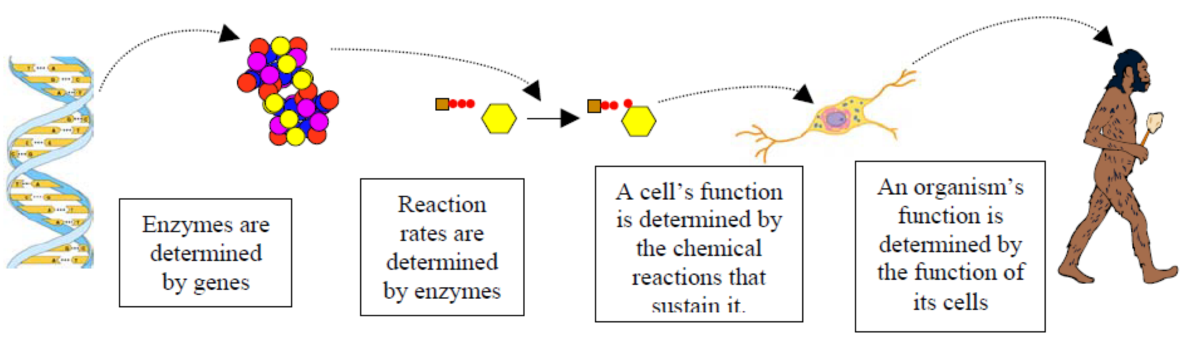


Fig. 1. Cartoon view of how genes determine organismal function.

Now imagine this unfolded box with doors and windows, pipes for the plumbing, electrical wiring… and all of it is positioned so that when the wind blows the walls around, the parts come together to make a functioning house. Imagine further that with more wind, the houses aggregate according to different types of glue to form neighborhoods, and the neighborhoods aggregate to form cities.

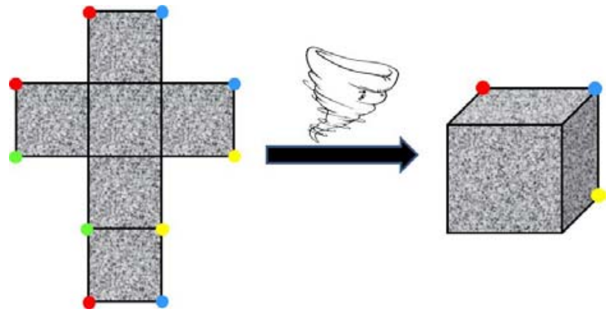


Fig. 2: Self-folding box. Unfolded box at left spontaneously folds into box at right (aided by a stiff wind). Red glue sticks only to itself, as does blue, green, and yellow glue, all leading to the final structure.

Note that all of this depends on the initial structure of the unfolded box and the judicious placement of spots of specific types of glue. All the magic relies in the initial structure, none in the construction itself. That's what DNA does, and even more remarkably than the unfolded house, it does it in one dimension. The precisely placed hooks and catches on the one-dimensional structure are enough to lead to a three-dimensional structure that can interact in specific ways with other three-dimensional structures and can provide the functions necessary to build a cell.

Flying boxes assembling in mid-air… it all sounds so magical.

SQ1. How do you think genes exert control over a cell?

B. Self assembly of cell membranes

Let me try to make flying boxes more tangible, by presenting to you an experiment that is imaginary, but one that I think you could readily see could be brought into the real world. Go to the calendar or to the Overview of Molecular Biology page and open the tour called **Self-Assembly**.

Run through it (I'll wait).

SQ2. Consider the first experiment in the Self-Assembly tour. How do you think the beads would behave if you filled the Petri dish not with water but with oil?

SQ3. The last few slides of the tour seem to suggest that proteins are composed of multiple types of subunits (which is true) and that the large number of types might contribute to more complicated three-dimensional shapes (which is at best half true). If the multitude of types of subunits are not necessary to direct the three dimensional structure of proteins, then why might they exist?

Those of us who find it difficult to assemble a swing set appreciate the enormity of the task of assembling an entire cell. How can genes, lacking a diagram or customer service center, direct the construction of the complex structures found within cells? Fortunately, cellular structures for the most part assemble themselves. Let's start with cell membranes.

A cell and many of its internal components are defined by their membranes. Membranes serve many functions. One basic function is to keep the innards of a cell or organelle inside, and in this

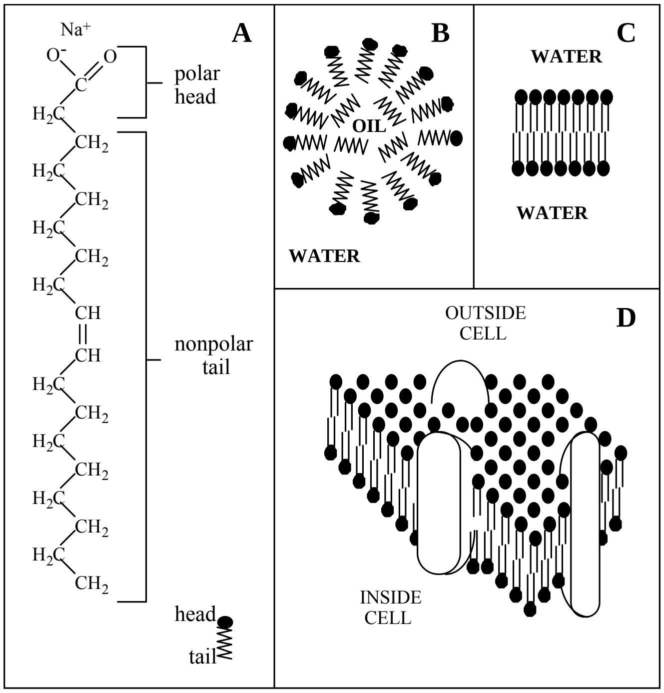


Figure 3. Amphipathic lipids

(A) Chemical representation and cartoon of sodium oleate, a fatty acid.

(B) Oil droplet composed of fatty acids surrounding oil.

(C) Phospholipid membrane composed of two layers of phospholipids, hydrophobic tail to hydrophobic tail, with the hydrophilic head groups exposed to water.

(D) Biological membrane, composed of proteins swimming in a matrix of phospholipids.

view one might think of cells as soap bubbles in water. But biological membranes are much more than mere walls. Much of what the cell does takes place on or in membranes. For example, most of the ATP used to power the cell is made through structures on membranes.

Just as life to a great extent is the play of membranes, so are membranes largely the play of lipids. Lipids (literally, fats) are oily substances that can't dissolve in water. There are a wide variety of them in cells -- fat and cholesterol are two -- but the ones that form the structure of membranes are of a special class: *amphipathic* lipids. These are lipids that are *hydrophobic* (water hating) on one end of the molecule and *hydrophilic* (water loving) on the other. Pure hydrophobic molecules, like oil, separate from water, while purely hydrophilic molecules, like salt, freely dissolve. A class of amphipathic lipids that we see every day (or should!) is soap, one of which is oleic acid (**Figure 3A**). This fatty acid has a long, hydrophobic chain and an acidic, hydrophilic head group. Oleic acid is also a common component of phospholipids, the primary material of biological membranes. Note that fatty acids and amphipathic lipids are often portrayed in cartoon fashion as hydrophilic balloons over a hydrophobic lines or squiggles.

Oil or water... what's an amphipathic lipid to do? Soaps illustrate the solution. The hydrophobic tails aggregate together and surround oily dirt, permitting the dirt to be dispersed in water (**Figure 3B**). When you rinse off the soap, the dirt goes with it. No one has to teach soap how to form oil droplets or bubbles: because of the interaction between water molecules, bubbles form themselves. The geometry of tiny bubbles is determined by the geometry of the soap. The size of the hydrophilic headgroup (the balloon) of soap determines how curved the bubble can be.

The amphipathic lipids of membranes differ from soaps in part because of their geometry. Fatty acids like oleic acid have bulky head groups relative to their thin tails, so if you put them side by side, you get a curved surface, just as assembling wedged-shaped pieces would form a circular pie. However, most of the lipids of membranes are *phospholipids*, containing two hydrophobic chains along with the polar headgroup (**Figure 3C**). These lipids are more or less cylindrical, that is, the headgroup has about the same cross-sectional area as the two chains, so when you put them side-by-side you get not a curved surface but a plane. To prevent exposure of the hydrophobic chains to water, the plane is of two layers, a bilayer. The bilayer forms because of the amphipathic properties and geometry of its components. There is no need for some molecular machine to insert each component in place.

A cell membrane, then, is a vast bilayer composed in large part of amphipathic lipids (**Figure 3D**). The bilayer serves to exclude hydrophilic molecules from passing the membrane -- they can't get past the hydrophobic zone. It is thus possible to maintain a concentrated salt solution on one side of the membrane and a very dilute solution on the other, and this is precisely what the cell does.

The membrane is not pure lipid, however. If it were, the cell would be in virtual isolation from the outside world and would starve to death. It contains also protein that sit on the surface or span the membrane. These proteins serve a multitude of purposes. Many are involved in facilitating transport of hydrophilic molecules that the cell wants to be able to traverse the membrane (food, for example). Some proteins are involved in anchoring cell components to the membrane. As we shall see later, proteins find their way to the membranes in large part due to the same hydrophobic properties that govern the structure of the lipid bilayer.

SQ4. Picture in your mind the steps by which soap at a microscopic level helps get dirt off your skin.

SQ5. What are membranes? What are their functions?

SQ6. What is an example of something you have encountered that is hydrophobic? Amphipathic?

SQ7. Biological membranes contain proteins. Identify the protein in Figure 3D.

C. Metabolism: monomers, polymers, central metabolism

Complex soap bubbles within even more complex soap bubbles -- that is a simple view of what a cell looks like frozen in time. In real life, however, a cell is a high-powered organic chemistry factory, busily converting materials from its environment to its own uses. Take us, for example. We eat a meal (**Figure 4**), in so doing consuming the various components that make up the plants and animals on the table. We eat thousands of different kinds of protein -- it really doesn't matter too much which they are -- but in the end they're turned into our own.

How do we do it? The trick is to take the *polymers* we eat -- carbohydrate, protein, lipid, and nucleic acids and break them down into their component *monomers*. While the polymers are different from organism to organism, we all use the same monomers -- simple sugars to make carbohydrate, amino acids to make protein, and so forth (**Table 1**). We eat a huge variety of proteins and other polymers, break them down to amino acids and other monomers, interconvert them through central metabolic pathways (although humans are partially defective in this regard) to create the proportion of monomers suitable to our needs, then synthesize a huge variety of our own polymers. It is like cars converging from hundreds of surface streets to a few entrance points to the turnpike, leaving at a few exit points to go to hundreds of other surface streets in another city. Very logical, but something needs to control the flow of traffic.

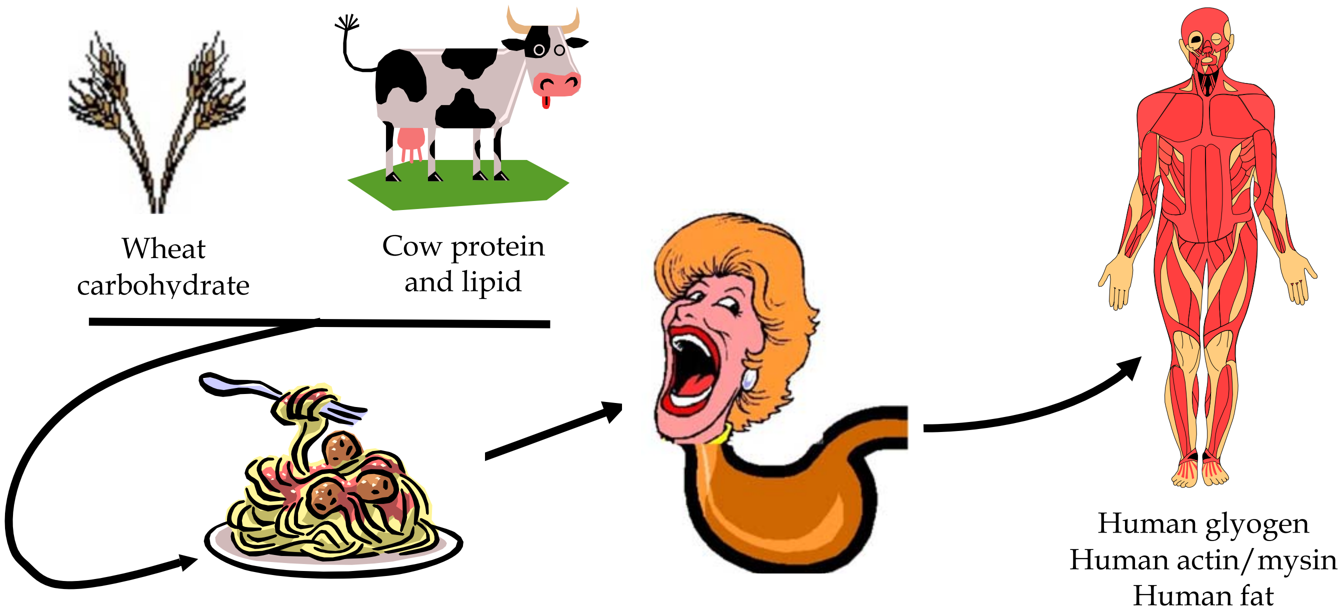


Figure 4. Polymers from food are broken down and reused as the polymers particular to our own needs.

What controls traffic are enzymes, proteins that act as catalysts in biochemical reactions. There are a limitless number of chemical reactions a compound can undergo, but at low temperatures, most biochemical reactions occur very slowly unless enzymes facilitate them. Enzymes provide the roads. At high temperature, a compound can jump the curb, plow through a few houses, and go wherever it likes, but with little control. At high temperatures we burn up. If you make the roads, if you control the enzymes, then you control the traffic. You can determine what compounds are made or not. And that means that you control the cell.

SQ8. Pick out from the list below those compounds that are polymers. Which are identical whether isolated from snails or whales?

A. phenylalanine
B. protein
C. starch
D. sugar
E. acetyl CoA
F. actin/myosin
G. nucleoside triphosphates
H. hydrophilic compounds

Table 1: Biological polymers and their monomeric subunits

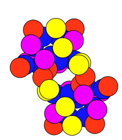
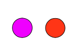
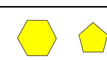
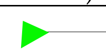
Polymer	 Nucleic acid (DNA, RNA)	 Proteins (e.g. myosin, ...)	 Complex carbohydrates (e.g. glycogen, cellulose)	 Fatty acid (e.g. stearic, oleic)
Monomer	 Nucleotides AMP, CMP, GMP, TMP	 Amino acids (e.g. tyr, phe, glu)	 Simple sugars (e.g. glucose, fructose)	 Acetyl CoA

Table 2: Differential expression of enzymes

Enzymes restricted to:	Example
Certain organisms	Mammals but not fish make lactose to consume milk sugar
Certain tissues	Skin but not neurons make enzymes to synthesize melanin from tyrosine
Certain developmental states	Fetal hemoglobin disappears as the organism matures
Certain environmental conditions	Heat induces production of enzymes to repair damage caused by heat

D. Summary

- DNA controls cell function by determining protein
- Cell membranes self-assemble, just as soap bubbles do (cells self-assemble in much the same way)
- Polymers from the outside are broken down to monomers.
- Monomers are built up into the organism's own polymers.
- Monomers can be interconverted.

So here is a recap, interspersed by a list of the tasks before us:

- The structural components of a cell largely self-assemble
- Metabolic pathways are responsible for making structural components (and for a host of other things)
- Pathways made possible by enzymes, which are proteins

→ ***We really need to understand what proteins are*** ←

- Proteins are determined by genes

→ ***We really need to understand what genes are*** ←

→ ***We really need to understand how genes determine proteins*** ←

- But, as we'll see, genes are constant in an organism while the need to respond to the environment is ever changing (see **Table 2** for examples)

→ ***We really need to understand how organisms control the expression of genes*** ←