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Why Is Life So Complex?

If nature favors simple solutions, why does the lowly marine mussel use an elaborate network of chemical courier to carry message through its cells?

For nearly seven hundred years, philosophers and scientists have been guided by Occam's razor — a 14th century caution against unnecessary complexity. *Entia non sunt multiplicanda praeter necessitatem*, William of Occam warned. *Entities are not to be multiplied beyond what is necessary.* Best to begin by considering the simplest theory that explains all the facts.

When they think about the world, 20th century scientists reach for the medieval philosopher's razor almost reflexively. Biologists employ Occam's principle of parsimony with particular confidence, because their discipline is rooted in evolution and evolution favors the efficient. Animals designed like Rube Goldberg machines — with unnecessarily elaborate systems for carrying out simple tasks — such animals fare poorly in nature. Clumsy designs pass quickly out of existence. And biologists go about their business with full confidence that it is just Dr. Occam — but life itself — that favors uncluttered designs.

But if this is true, if nature really does favor simple solutions, why is life so complex?

Why, for instance, is the biochemistry of life so stunningly complicated? Consider your own DNA, those strings of molecules that carry the information your cells need to build you and keep you running. Your genetic inheritance, which is packed inside virtually every cell in your body, consists of some 3 billion base pairs, or couplings, of four basic nucleotides (adenine, guanine, cytosine, and thymine, referred to as AGC and T).

Three billion base pairs. You could work a forty hour week, glancing at one base pair per second, and it would take you more than four centuries to

read the instructions for building a human being. Yet in the human body this incredibly detailed document is stored inside each cell, with plenty of room left for the other structures the cell builds to carry out its main tasks.

You could argue that the biochemistry of genetics is more a matter of miniaturization than complexity. The variety of information, after all, is limited: everything is either A,G,C, or T. A desk with three billion drawers is not necessarily a complex desk; it may be just a very large desk with very small drawers.

And you could argue that complex designs are necessary to build an organism as complicated as human beings. We speak, after all. We make plans. We build cities. We create art. Physically, we're a nice blend of strength and speed, endurance and longevity. We're adaptable enough to live in almost any environment on our planet and smart enough to explore the space around it. For all this, you might expect to find a certain complexity built into the animal.

But consider the lowly marine mussel, *Mytilus edulis*. Look at *Mytilus*: a handful of blue-black shells lying like rocks on the bottom of a plastic tub in a biologist's laboratory.

Life for *Mytilus* is not exactly strenuous. A filter feeder, *Mytilus* eats by straining seawater to extract plankton — the minute plants and animals that happen to float by. Observe *Mytilus* at mealtime. The shell is barely open; the animal inside — if you can see it at all — is a pale lozenge that looks about as lively as the remains of a bar of soap. Nearby, a delicate sea anemone waves gently in the current. From the impassive *Mytilus* — nothing. The stillness, the silence, the very name "filter feeder" suggest that the mussel is about as complicated as a spaghetti strainer.

But the fact is, inside the inscrutable mussel, remarkably complicated systems are at work.

A Biochemical Conversation

The filtering for this filter feeder actually takes place in the gills, where microscopic cilia wave back and forth in a synchronized beat that draws water through the gill. Other cilia on the same cells act as sieves, filtering out food particles. Still other cilia act as a conveyor belt, moving the food particles along a food groove toward the mussel's mouth. If a food particle escapes the sorting cilia, then the lateral cilia — those synchronized beaters that create the feeding current — serve as a backup filter. Sensitive to touch,

the lateral cilia stop beating when particles brush against them. Freezing in a position opposite to their normal beating, these cilia eject the food particle backward out of the gill and into the food groove.

With the microscopic morsel sent on its way, the lateral cilia resume their beating. This process — the mechanism by which the little locomotors beat — is one of many ciliary mysteries that interests Ray Stephens, a cell biologist who works at the Marine Biological Laboratory in Woods Hole.

The cilia, Stephens explains, begin beating when the animal begins to feed. The signal to beat comes from a neighboring nerve cell, or neuron. A wave of ions sweeps along the neuron's membrane. When the wave reaches the end of the neuron, a molecular messenger is released. The messenger (a neurotransmitter called serotonin) moves across the space between the cells (called the synapse) and binds to the membrane of the gill cell.

The neurotransmitter can't penetrate the membrane, but the message it has carried across the synapse (Go!) is not left lying on the gill cell's doorstep. When serotonin binds to molecules on the outside of the membrane, a second messenger (cyclic AMP) inside the cell responds, kicking off an intracellular chemical conversation:

The cyclic AMP binds to an enzyme called protein kinase.

The protein kinase releases a subunit.

The subunit activates a control protein.

The control protein switches on a yet another protein (ATPase dynein).

In a matter of milliseconds, the chemical couriers have swiftly completed their appointed rounds, and the rest is a mechanical contrivance. Little ratchet arms are activated on the filaments (microtubules) that form the skeleton of the cilia. Some of the ratchet arms snare neighboring microtubules, causing one microtubule to slide along another. The sliding makes the tips of the cilia bend, and the bending, repeated 20 times per second, sets up the feeding current.

This description of how lateral cilia beat is a hypothesis developed by Stephens and Elijah Stommel, his senior research assistant. Some of the specifics are not yet worked out — the role of the protein between the catalytic subunit and the switched-on dynein is uncertain, for example. But if some of the details are cloudy, the complexity is clear: The simple beating of the cilia is the result of a labyrinthine series of chemical reactions.

Observing such an intricate design for so straightforward a task, you might fairly ask whether some of the systems that sustain life aren't a bit more complex than they need to be.

Why Second Messengers

Biologists refer to Mytilus' intermediate messengers as a *second messenger system.* First proposed as models of how hormones act on the cell without entering it, second messenger systems have now been found performing a variety of tasks for a variety of organisms. NIH neurobiologist Dan Alkon has explored a second messenger system that is involved with learning and memory in the brains of snails and rabbits. On another front, Howard University embryologist Bill Eckberg and MBL scientist Ete Szuts have identified a second messenger system at work during fertilization of surf clams. Clearly, if second messenger systems are Rube Goldberg machines, if they do contain unnecessary parts or superfluous steps, then nature periodically opts for (or at least tolerates) inefficient solutions.

Look again at the mussels silently feeding in the tubs in Ray Stephens' lab. Why did *Mytilus* evolve with a relay system for passing information from nerve cell to cilia? Do the intermediate messengers do anything that a single swift courier couldn't do just as well by itself?

To answer that question — and *Mytilus* does provide a neat answer — you have to remember what the cilia are doing in the gills. Remember that the lateral cilia have more than one function. They beat like oars to set up feeding currents, and they also arrest in a backward position to flip invading particles out of the gill. But if the lateral cilia to are going to flip backward and momentarily freeze, the signal (Go! Beat!) must be either turned off or overridden. It is here, in the control of ciliary beating, that the second messenger system offers several advantages over a more direct, single messenger system.

For one thing, a system with multiple messengers offers multiple opportunities for tuning the message. Where the serotonin talks to the cAMP, where the cAMP binds to protein kinase, where protein kinase's subunit activates the control protein — at each joint in the system, the message can be adjusted.

Note, the content of the message cannot be changed; neuronal messages are binary messages. Some neurons say Go! or they they say nothing; others

say Stop! or they say nothing. But while the content of the message can't be changed, the message *can* be turned up or turned down or even snuffed out as it moves through the cell toward the cilia.

Not only does a system with multiple messengers offers multiple sites for tuning, it also offers the possibility of fine-tuning, if the cell is clever enough to make simultaneous adjustments at different sites. In the gill cells of *Mytilus*, calcium acts at three sites to regulate the beating of lateral cilia. Released into the cell when a food particle strikes the lateral cilia, a flood of calcium acts as an instantaneous brake on the ratcheting action. The same flood of calcium slows down the control protein and also stimulates a breakdown of cAMP (the concentration of cAMP ultimately controls the speed of the ratcheting action).

(Oddly enough, while calcium applies the brakes to lateral cilia, it removes the brake on abfrontal cilia. Thus, the same chemical acts as a brake and as a booster on different types of cilia in the same gill — but that's another story.)

In addition to allowing for fine tuning, second messenger systems make it possible for cells to amplify messages. The message passing through mussel gill cells is actually amplified three times. The biochemical conversation does not really consist of one molecule telling another molecule to tell yet another molecule to activate a ratchet. In fact, each molecule of serotonin activates many molecules of cAMP. At the next step, the message is passed on without amplification: each cAMP molecule releases just one catalytic subunit. The subunits, however, reamplify the message, since each subunit is able to activate many molecules of control protein. The dynein molecules provide the third amplification, when each is responsible for many cycles of ratchet action.

The advantage of a system that allows amplification (or in this case three separate amplifications) is obvious: each serotonin molecule can stimulate many ratchets. If every neurotransmitter molecule had to carry its own message, unamplified, through the cytoplasm to the site of ratcheting, the interior of the cell soon would be jammed with messenger molecules.

The Business of Living

Meditate on the biochemistry of mussel cilia, and you come away with several competing impressions. On the one hand, ciliary beating is a result of

a remarkably intricate molecular conversation. But if the system is intricate, it is also efficient. Is the system labyrinthine? Yes. But is it a Rube Goldberg machine? No. The whole point of a Rube Goldberg design is the unnecessary components. A possum could be eliminated here. A kangeroo could be removed there. The man could strike the match himself. Time and energy would be saved. Nothing would be lost.

But in *Mytilus*, the sytem can not be edited so easily. In *Mytilus*, the moths munching on flannel shirts are not gratuitous. Possums don't jump into baskets for no particular reason. In the gill cell, each molecular moth that carries the message through the cell serves a purpose. This second messenger system is elegant enough that you might want to rethink the question of complexity.

"*I* don't think it *is* complex," Stephens says, with a hint of surprise. "The control of lateral cilia is beautifully simple. In its use of amplification, specificity and feedback, balance and fine-tuning, it offers tremendous advantages over 'simple' and direct control."

The gill cells in *Mytilus*, then, are acquitted of the charge of superfluous complexity. But what of the other complicated systems buried everywhere in the cells and organs of plants and animals?

If you ask the people who know the systems best, those who spend their lives studying snail brains or barnacle eyes or cell division, you keep getting the same answer. Embryologists and neurobiologists, summer researchers and year-round scientists, principal investigators and post-docs, biologists by and large will tell you that the cells and organs they study are well-designed. Whether the microscopic intricacies of life are complicated or whether they are, in Stephens' words, "beautifully simple," the fact is those intricacies are paragons of efficiency.

This efficiency should not be surprising: the cells and organs that make life possible had better be well designed, because the job of living is formidable. Living beings —plants and animals, bacteria and slime molds and fungi — every animate entity faces a set of challenges that would give pause to the most inventive designer.

To begin as a microscopic dot, to sally out into the world, reorganizing the molecules out of which you are built, building new molecules that give rise to new cells, modifying some cells so they can gather and process information about the world, creating some cells that can repair rips

in the fabric and others that can repel invading molecules, to locate and ingest the raw materials necessary for further growth, to avoid becoming the raw material for someone else's growth — to carry out the business of life, a collection of ordinary chemicals had *better* be well organized.

Challenging as these basics are, the whole business of life becomes enormously more complicated when you consider that organisms also learn from their environment, and that learning too must be accomplished by the same collection of common chemicals.

Unraveled in part by Alkon's lab, the marine snail *Hermissenda*'s nervous system is a gloriously intricate pattern of connections, interconnections, and cross connections. But the snail's brain is a complex design because the snail has to learn, and learning is a complex task. In nature, *Hermissenda* clings tightly to the rocks when it is buffeted by waves. Alkon's group teaches *Hermissenda* to associate light with turbulence. *Hermissenda* — a minute collection of common chemicals — learns that in Alkon's lab, light means turbulence. Snails tutored by Alkon will hunker down in response to light alone.

Such learning sounds simple enough, but how can a few ounces of chemicals learn *any*thing? By what design can molecules and membranes remember? Suppose you wanted to design organs that can sense increases in light and in turbulence, and a brain that can note the ill effects of being tossed shell-over-pseudopod. Now how are you going to store all this information for future use? Initially, your system is wired in such a way that the incoming message from your balance organs ("surf's up") is paired with an outgoing message to the foot ("hang on"). Now you want to pair a message from your eye ("light's on") with the message to the foot. In order to learn this new behavior, you must rearrange the molecules in your brain, changing the synapses, or the nerve cell membranes, or the channels that allow ions to pass into and out of cells. And the learning — the new molecular arrangement — has to be rigid enough to last but elastic enough that it can be modified by new information. Obviously, you are going to have to come up with subtle designs if you are going to build something as smart as a snail out of a thimbleful of chemicals.

The biochemistry of life is complex not because nature allows superfluous possums into the loop; the biochemistry of life is complex because the business of living is complex — even for relatively simple marine animals.

Mytilus, after all, has to eat and grow and protect itself and reproduce. Because it lives, *Mytilus* has more in common with human beings than with the rocks it resembles at first glance.

So the mussel does need the second messengers. The lowly sea slug does need a neural network that looks like a street map of Manhattan. And the blueprint for building a human being does need to be startlingly long and unimaginably small. Life is complex for the straightforward reason that there is no simple way a collection of everyday chemicals can rise up and walk.