From Flu to Lobsters to DNA

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This February, the Mathematical Sciences Research Institute launched a new public lecture series, designed to bring leading biologists to MSRI for a dialogue with mathematicians. The Simons Biology Colloquia, funded by Jim Simons, provided the speakers an opportunity to explain recent findings and issues in biology to mathematicians, and may in some cases foster an ongoing collaboration between the two sciences.

"Jim's philosophy is that it's hopeless to teach biologists mathematics, so we'll have to teach mathematicians some biology," said director David Eisenbud in his introduction to the first colloquium. Eisenbud also cited as inspiration the title of a 2004 article by Joel Cohen, head of the Laboratory of Populations at the Rockefeller Institute in New York: "Mathematics is biology's new microscope, only better; biology is mathematics' new physics, only better."

At the time of writing of this article, three speakers have visited MSRI to give Simons Biology Colloquia: Arnold Levine, the head of the new biology department at the Institute for Advanced Study in Princeton; Mimi Koehl, a biodynamics expert at the University of California at Berkeley; and Robert Schleif of Johns Hopkins University, who studies molecular dynamics. The fourth and final colloquium speaker for the spring semester will be Sydney Brenner, the winner of the 2002 Nobel Prize in Physiology or Medicine.

Smells Like a Lobster

You might not think that a sense of smell would be very useful underwater. The human nose, after all, has evolved to breathe air. One deep inhalation of seawater is likely to be your last. However, lobsters have evolved a very different method of olfaction: instead of "innies" (nostrils), they use "outies" (antennules) to smell their surroundings.

In her Simons Biology Colloquia, Mimi Koehl, a professor of integrative biology at Berkeley, discussed her work on sea creatures' complex olfactory environment. Several years ago, she and Angela Cheer, a mathematician at the University of California at Davis, studied how the odor-sensing hairs on an antennule interact with the surrounding fluid. The flow pattern changes significantly, depending on its Reynolds number. This is a dimensionless number that expresses whether an object moving through a fluid tends more to keep going through inertia or to slow down due to the fluid's viscosity. Smaller or slower-moving objects tend to have lower Reynolds numbers. The lobster can, of course, control how quickly it moves its antennules.

Koehl and Cheer discovered that at Reynolds numbers less than 1, water cannot flow between the hairs but only around them. But at Reynolds numbers above 1, water can pass between hairs, which makes it possible for the antennule to detect spatial differences in the concentration of odor molecules. Therefore the lobster flicks its antennules rapidly (high Reynolds number) to "sniff," and then relaxes them slowly (low Reynolds number) so the odors trapped
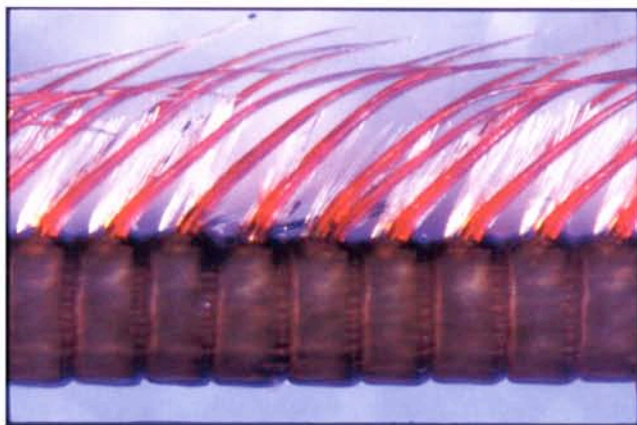
Lobster antennule with odor-sensing hairs.

in the brush of sensory hairs do not escape. "Each flick is like a snapshot of a 1-mm thick slice of water at one point in time," Koehl said.

But is there really information contained in the snapshot? In the past, biologists have assumed that odors diffuse in a cloud, which would make one slice the same as another. With laser imaging experiments using fluorescent dye as an analog for odor molecules, Koehl has shown that is not correct. In the turbulent water currents in a lobster's habitat, filaments of concentrated odor swirl around in a pattern that changes as a lobster nears the odor source. It remains to be seen how and whether lobsters use this detailed information. However, in her second lecture she described an even simpler organism that definitely uses it. Swimming larvae of a sea slug, which eats coral, use chemosensors to detect reefs that they can colonize. When exposed to coral odor, the larvae stop swimming and sink; when they leave an odor filament, they start swimming again. Computer simulations show that this simple behavior enables the larvae to land on wave-swept reefs.

Mathematicians in the audience were not surprised to hear about the complex odor patterns. Using methods from dynamical systems, it may be possible to describe their structure theoretically, rather than empirically, and better explain how the sea slug's simple programming enables it to find and land on the coral. On a followup visit to MSRI in March, Koehl and her colleague Bob Full, who works on the locomotion of terrestrial organisms, explored the possibilities for collaboration with dynamical systems experts.

Lobster with a laser-lit plume of fluorescent dye.

One Flu Over the Chicken's Nest

Arnold Levine is best known among biologists for discovering the p53 tumor suppressor gene and understanding its function, but at Berkeley he gave lectures devoted to a new line of research that he has begun with three physicists at the Institute for Advanced Study: Michael Krasnitz, Raul Rabadan, and Harlan Robins. Using ideas from statistical physics, they have discovered a new way to distinguish between human and bird flu chromosomes. "What we did was to take a fresh approach, using mathematics that's not pioneering, to a problem that has never been treated that way," says Levine. "In the future we may need more pioneering methods."

The influenza virus, Levine explained, contains eight chromosomes, two of which code for the proteins hemagglutinin (H) and neuroaminidase (N) that dangle off the outside of the virus. These are the proteins that the human immune system sees. Therefore, from the immune system's point of view, a different subtype of H or N proteins corresponds to a different strain of flu virus. Among the earliest flu viruses isolated is the H1N1 type, which caused the pandemic of 1918. The Asian flu of 1957 was type H2N2, and the Hong Kong flu of 1968 was type H3N2. Public health officials are currently worried about the so-called bird flu, type H5N1, which has a high mortality rate among humans but does not seem able yet to pass from one human to another.

Levine's recent work showed that there is important information on the other six chromosomes, the ones that code for proteins our immune system doesn't see. Flu RNA, like human DNA, employs four different bases to code for the various proteins it makes; the letters representing them are A, C, G, and U. The code has a certain flexibility; two sequences of three letters or codons, such as GAA and GAG, can stimulate the insertion of the same amino acid into a protein. Thus the frequency of A's and G's in the genetic code can drift over time, without affecting the proteins or the organism. This happens about 80% of the time in a chromosome.

To their surprise, Levine and his colleagues found that the more generations a virus spends in human cells, the more its G's tend to be replaced by A's. He calls the phenomenon directed evolution. Human cells have an enzyme that changes G's to A's, and the mutations get passed on to later generations of virus. Interestingly, this directed or guided style of evolution happens only in the chromosomes that do not code for the H or N proteins. In the other two chromosomes, the substitution of A for G that occurs is then selected against by the human immune system. Therefore the proportion of G's does not decrease over time.

In bird flu viruses, the proportion of A's does not increase for a different reason: The bird immune system appears to lack the enzyme to convert G's to A's. Thus, Levine can tell the difference between a bird-flu chromosome and a human-flu chromosome. In the 1918 Spanish flu virus, at least six of the chromosomes came from bird flu viruses. This chromosome-swapping occurs when birds (such as chickens) and humans live in close proximity, and a bird becomes infected with both viruses. If the H5N1 virus changes to become a little bit more human-like, Levine believes, it may become capable of starting a new pandemic. At this point he cannot predict when that might happen, but the tools from statistical physics may allow him to track its progress.

The plots tell the story
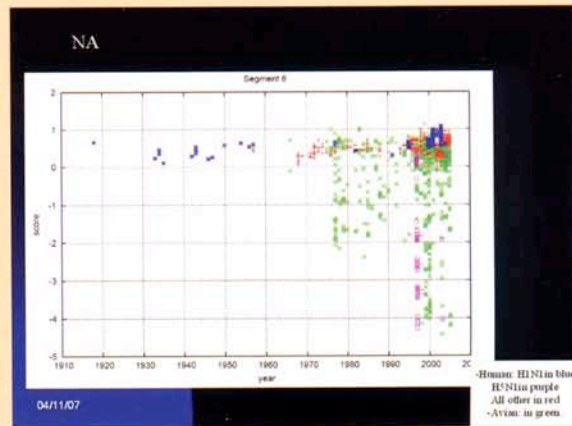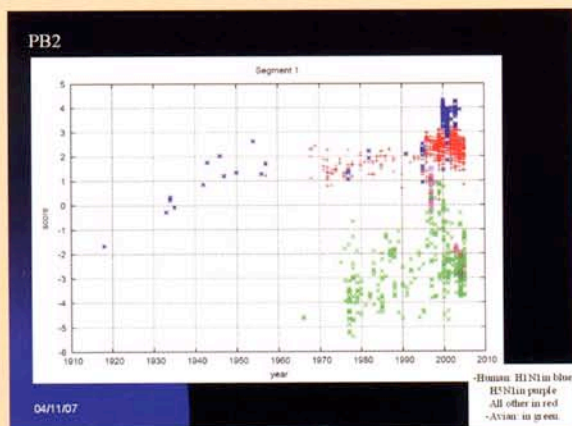
Left: Changes in the proportion of A's to G's (vertical scale) in samples of flu virus taken over time (horizontal scale, 1910–2010), restricted to a segment of RNA that does not code for external proteins that the human immune system can detect. In the blue H1N1 virus (a human flu) the ratio of A's to G's started out very birdlike, but has evolved over time to a higher score, a process that Levine calls "directed evolution." (The score is a measure of the entropy of the information contained on the chromosome, a concept derived from statistical physics.) Other human flus (red) have a high score. Avian flus (green) have a low score, and the H5N1 strain that is of current concern (purple) also has a low, birdlike score. **Right:** Same kind of data on a portion of the flu RNA that does affect the virus's ability to elude the human immune system. Here we see some difference between human flu viruses (blue, red) and avian (green), but we see no tendency for the score to change over time. Presumably this is because changing G's to A's in this part of the flu genome would adversely affect its ability to survive. H5N1 (purple) still looks quite different from human flu viruses.

Inside the DNA Toolshop

Imagine that you have a workshop, Robert Schleif asked his MSRI audience, and you want it to be totally self-contained. In other words, you want to be able to use the tools in the workshop to build new copies of every tool. How many tools would you need? "It's not a small number, but not an infinite number, either," he said.

This is exactly the problem that living cells solve every day. Their tools are genes, and the simplest cellular workshops known contain about 500 to 2000 tools. In his Simons Colloquia, Schleif took his mathematical audience on a guided tour of the cell's workshop.

In one lecture, Schleif described two of the machines in the cell's workshop, the copying machine and the clock. Then he explained how biologists have developed a third machine that doesn't exist in nature: a DNA sequencing machine, which translates the DNA code into letters that humans can understand.

The cell's copier, for instance, takes a double-helix strand of DNA, unzips it, and then creates a complementary copy of each of the two unzipped pieces (like a photographic positive made from a negative). It does this at an amazing speed: roughly 1000 pairs of amino acids are copied per second. Since each turn of the double helix takes about 10 to 11 base pairs, the entire molecule is spinning around at a rate of 100 revolutions per second at the same time that it is being unzipped and copied.

Under such circumstances, quality control is crucial, and Schleif described how the cell keeps the error rate under one per million. An incorrectly matched base pair creates a kink in the DNA, which the cellular machinery can sense and repair. But how does it know which strand of the DNA is the old, correct one, and which is the new, incorrectly copied one? The answer is methylation. Old DNA has methyl groups attached to it everywhere that the letters GATC appear; freshly made DNA does not.

The reason nature has chosen GATC has to do with symmetry. When you take the "photographic negative" of GATC, you get CTAG. And then when you read it backwards (because the cell's reading machinery reads the two strands in opposite directions), you get GATC again. Thus GATC should appear in the same place in both strands. GATC, Schleif said, is just one example of a recognition sequence, and most known recognition sequences obey the same symmetry principle.

According to Schleif, there are lots of mathematical principles like this to be discovered in biology. The toughest part is getting mathematicians over the linguistic hurdles created by terms like "methylation" and "recognition sequence." Schleif knows this from personal experience, as a physics major who studied molecular biology as a graduate student at Berkeley. "The first steps are really unpleasant, learning the 2000 or so compounds that are important in biochemistry," he says. "But as you learn more and begin to see the underlying principles, it becomes easier."

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