

## Evolutionary Thinking

By Deborah J. Ausman • Photography by Tommy LaVergne

**For most of us, the runny nose, sore throat, and hacking cough of the common cold are as much a part of the winter season as overplayed carols in grocery stores. As The Drifters might sing, “It comes this time each year.” And for that, we can thank—or blame— evolution.**

More than 200 viruses cause common cold symptoms. Each time one of them makes us sick, our body develops antibodies to protect us from future infection. In a static system, past encounters would render us less likely to get colds as we age, but the system isn't static. Changes can occur each time a virus replicates to make copies of itself. These changes, multiplied over the vast number of viruses involved in each infection, lead to the diversity and variation that enable the common cold to thwart the human immune system year after year.



Yousif Shamoo

The same evolutionary mechanisms that make the common cold so annoyingly predictable also power more devastating illnesses such as influenza and HIV. Combine mutational change with selective forces—immune system factors or the latest expensive antibiotic, for example—and you breed resistance, says Yousif Shamoo, associate professor of biochemistry and cell biology at Rice. The result is a deadly catch-22: Antibiotic resistance creates a growing need for new antibiotics, but no one wants to use the new ones because it's only a matter of time before they won't be useful anymore.

“We're never going to win this battle,” Shamoo says. “But if we stay one step of ahead of the bugs, we can find ways to stave off the inevitable.” Insights into evolution—how it works, when it works, and the impact it has on systems as it works—will be the primary weapons in this war. At Rice, evolution is studied not just by faculty in the department of ecology and evolutionary biology, but by researchers in statistics, bioengineering, biochemistry and cell biology, earth science, chemistry, anthropology, and even political science. Their goal is to harness evolutionary processes for predictive, practical purposes. For more than

100 years, evolutionary theory has provided profound insights into where humans might have come from. Now, at the beginning of the 21st century, Rice scientists expect evolution to provide similar insights into where humans may be going.

### Evolution Writ Small

The underlying principles of evolution proposed by Charles Darwin in 1859 are extraordinarily simple. Two factors power evolution: mutational change in an organism's DNA and natural selection, comprised of the internal and external pressures that determine which changes are successfully transferred to the next generation. According to Shamoo, evolution is not purposeful, driving an organism in a particular direction, but it's just as erroneous to label evolution a purely random process. That's because natural selection favors mutations that are beneficial. Under certain conditions, the mutations enable organisms to survive and reproduce; in other situations, the organism might die. Most often, minor mutations simply inhabit the organism's DNA, contributing to the natural genetic variation that keeps a species adaptable and successful.

From its beginnings with Darwin, evolution has been a descriptive discipline, providing insights on how different organisms might relate to each other. But the ability to map genomes, along with advanced statistical methods, sophisticated computational modeling, and high-throughput instrumentation, has transformed the field. Today, scientists like Shamoo and his colleagues at Rice are interested in exploring exactly how evolution proceeds. If evolution is reproducible, it could, theoretically, be harnessed to accomplish specific objectives of interest to humans, such as drug design and protein engineering.

Unfortunately, so many variables affect evolutionary processes that it is almost impossible to predict outcomes. “It's like forecasting the weather,” Shamoo says. Weather forecasters are smart people, but they can't say exactly where a hurricane will hit, or when, or at what force, because of all the variables involved. Evolution is similarly complex, and Shamoo's research aims to reduce the number of variables, enabling scientists to pinpoint ways in which evolution proceeds—or maybe even to direct the process intentionally.

In a collection of coffee pot-like vats, Shamoo creates a bacteria utopia. The temperature is around 55°C (130°F), the perfect temperature for the vat's inhabitants, *G. stearothermophilus*. Ordinarily, these bacteria live at temperatures up to 73°C, but Shamoo's variety has been genetically modified with a gene that produces a metabolic protein that breaks down at temperatures over 55°C. For one day, the bacteria enjoy an easy life—the temperature in the vat is perfect, and food is plentiful. The next day, however, Shamoo raises the temperature half a degree, and for the next month, he raises the temperature every other day while he and his fellow researchers observe how the microbes adapt.

The results are remarkably consistent. Across 1,500 generations and millions of accumulated mutations, the surviving bacteria evolve one of six mutations in the gene to produce a high-temperature version of the metabolic protein. Subsequent experiments run under similar conditions produced surviving progeny containing one of this same set of six mutant genes. Crucially, the mutations don't always arise where researchers might expect, illustrating how dynamic and creative the force of natural selection is in solving tricky problems of life and death. "That's because the changes aren't trying to get someplace," says Shamoo. "The bacteria aren't thinking, 'How can I outwit this annoying scientist?' Mutations happen quite by chance and, as the bacteria interact with the environment, the survivors retain what works."

Shamoo notes that evolution can look random and unpredictable because researchers and observers frequently focus on a microcosm: individual organisms in a much larger population. "Mutations are rare," he says, "and it's even rarer that they confer a benefit to an organism." Across an entire population, though, "what works" will work, time after time, all conditions being equal.

Sometimes, researchers get lucky and discover that nature has put in place a set of constraints as rigorous as might be found in the lab. Janet Siefert, faculty fellow in statistics, studies a unique type of bacillus found only in the geothermal pools in the Cuatro Ciénegas basin in Mexico. Because the pools are low in phosphate, the bacillus—and only this bacillus—builds its membrane using sulfolipids rather than phospholipids. "We have analyzed this genome from the field using all the methods available to us," Siefert says, "and we have this amazing example of gene flow into this organism—it has recruited the genes that enabled it to adapt to the low-phosphate environment from another bacteria." The discovery provides a real-time look at horizontal gene transfer, a little-understood mechanism by which microbes can exchange DNA.



Janet Siefert

### Mutation vs. Recombination



Joff Silberg

"Nature has to have a variety of ways to facilitate change if it's going to win the numbers game," says Joff Silberg, assistant professor of biochemistry and cell biology. Proteins, which power all biomolecular processes, are built by combining any of the 20 amino acids found in nature. Given that bacterial proteins are around 300 amino acids long, some 20,300 possible combinations of amino acids can be made. For perspective, a pile of unique protein sequences with the same mass as the Earth would only contain 1050 proteins. Somehow, within this vast sequence space, nature must find functional proteins to catalyze reactions, transport materials, and build larger biomolecular structures. Evolutionary studies investigate how nature accomplishes this feat and, more importantly, how humans can co-opt these processes in the search for unique protein functions.

Mutation may be the most well-known method of generating new functionality, but it is not the most efficient. In laboratory studies, Silberg has quantified a mutational landscape for proteins that shows function sliding down an exponential cliff—the more mutations in a protein, the less likely that protein is to retain useful function. Mutation, says Silberg, is fine for making minor tweaks to a working system, either in an organism or in the lab, but bigger changes require larger, more drastic moves.

Enter horizontal gene transfer, such as that employed by the bacillus in Cuatro Ciénegas, and recombination. Silberg likens recombination to "taking the left front leg off an African elephant and swapping it with one off an Asian elephant—they are different beasts, but they do the same kind of business." While this type of wholesale change seems artificial, nature regularly employs it to recruit specific structural features for necessary tasks. Moreover, Silberg has found that libraries of proteins created by recombination provide more functional diversity than libraries produced by mutation.



Michael Deem

"If you have a changing environment and a population of individuals inhabiting it, that would select for individuals that evolve," says Michael Deem, John W. Cox Professor in Biochemical and Genetic Engineering. Deem models algorithms in protein evolution that Silberg's lab can then test. According to Deem, the ability to evolve manifests itself in proteins that recombine and mutate faster and more dramatically. Human immunodeficiency virus (HIV) demonstrates some of the most remarkable evolvability, thanks to ongoing competition with perhaps the most sophisticated evolved system: the human immune system.

"We view the immune system as a real-time, evolving system," Deem says. This perspective has led his group to propose new vaccination strategies for influenza and HIV. The immune system, Deem says, has evolved to back winners: it produces the T-cells that demonstrate the most success in fighting particular infections. HIV, however, evolves fast enough that it can lay low through the immune system's initial counterattack and ultimately resurface as a different strain that's unaffected by the T-cells that fought that "successful" battle. To counter HIV's evolvability, Deem proposes injecting patients with different strains of HIV in different parts of the body, creating competition in different lymph nodes and generating a diverse arsenal of T-cells capable of fighting the various

types of HIV that could evolve in an infected individual.

Because proteins run the most rudimentary processes of life, insights into how they evolve have broad applicability. “There’s a huge effort to understand protein evolution because people want to retune proteins or create entirely new protein functions,” Silberg says. In addition, the tools developed and knowledge gleaned from these small-scale investigations benefit scientists studying how evolution proceeds in larger organisms and systems.

## Growth and Adaptation

Through a mix of traditional descriptive biology, modern statistical methods, and gene studies, Rice ecologists and evolutionary biologists are gleaning information about the growth and adaptation of living systems and individual organisms that would have been impossible to ascertain a few decades ago.

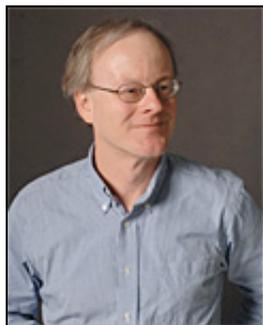


Michael Kohn

Michael Kohn, assistant professor of ecology and evolutionary biology, has pioneered a technique called natural selection mapping in his work with rats. Scientists have long sought the gene that makes some rats resistant to warfarin, the most common rat poison used globally. Kohn scanned the rat chromosome, looking for genetic material that has remained unchanged from generation to generation. He theorized that strong selection, such as that associated with poison, would reduce genetic variation in the area of the chromosome associated with the selection. The technique identified a small region of rat chromosome 1 that seemed the most likely place to find the gene or genes associated with resistance. “This is probably the first gene mapped in nature based solely on signals of natural selection,” Kohn says.

As in the protein studies conducted by Rice biochemists, Kohn’s work has shown that selection does not proceed with a goal in mind. Laboratory tests have identified the resistance gene as one associated with the vitamin K cycle. This is not surprising—warfarin works by inhibiting vitamin K production, and because vitamin K is a critical factor in stimulating blood coagulation, rats that ingest warfarin bleed to death from even minor injuries. Such knowledge about the nature of the mutation may change the way humans approach rat control not just in normal rats, but in those who are resistant to warfarin. Resistant rats have a mutation that prevents warfarin from binding to the protein produced by the abnormal gene—an action that also prevents that same protein from participating properly in the vitamin K cycle. As a result, rats with resistance to warfarin suffer from disorders related to vitamin K deficiency, which could mean that the best way to control warfarin-resistant rat populations is simply to wait for them to die out naturally.

Understanding the evolutionary dynamics of this system on a genetic level not only offers the possibility of a genetic test for warfarin resistance in rats but also has compelling applications in human disease. Warfarin, for instance, is commonly prescribed to heart attack and stroke patients to prevent blood clots from forming—a genetic test similar to the one developed for rats could help physicians monitor patients taking this medication. More importantly, many other proteins, including those involved in bone formation, depend on Vitamin K and could be adversely affected by warfarin in some people. Kohn’s group is currently investigating whether resistant rats suffer from higher calcification deposits in their arteries and lower calcium levels in their bones than their nonmutant peers. If the rats exhibit these symptoms, they could become a model for studying and treating osteoporosis and coronary disease. “The truth is,” Kohn says, “we would not even have come close to the gene or to knowing all that we do about this system without taking an evolutionary approach.”



David Queller

David Queller, the Harry C. and Olga K. Wiess Professor of Ecology and Evolutionary Biology, notes that genomics, perhaps more than anything else, has changed the way biologists approach their discipline. Once, biologists obtained most of their data from field observations. “Today, if you understand how to work with DNA, you can see the similarities and differences between organisms right there,” says Queller. “And what’s rewarding is how often the answers we get from DNA correspond to what we learned by just observing.”

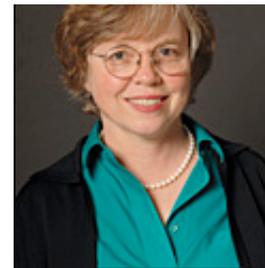
Genomics has added a critical dimension to Queller’s work with Joan Strassmann, the Harry C. and Olga K. Wiess Professor of Ecology and Evolutionary Biology. Queller and Strassmann are animal behaviorists studying the evolution of social behaviors, such as competition and cooperation. Some of the most perplexing questions in biology revolve around how behaviors like altruism evolve when, by definition, these traits put the individual demonstrating them at risk.

Queller and Strassmann study the social amoeba, a type of slime mold found commonly in soil. When food is scarce, individual amoebae band together as a modal slug that is better able to crawl around and find food. But if the food shortage continues, a subset of the collective opts to abandon its own reproductive aspirations for the sake of the group. This subset forms a sterile stalk, dying in the process but allowing the rest of the group to disperse as spores.

The dynamics of this social system are even more complex than those associated with the evolution of a physical trait. The modal slug often contains more than one genetic clone, which means that one clone can



cheat the rest of the group by sneakily contributing more material to spores than to the stalk. Cheating is a problem for all social systems, including those of humans. And while it's hard to believe that the manipulative strategies of a slime mold could have any relevance to human behavior, the social amoeba system provides a unique opportunity to study underlying cheater genes. "We already know a lot about the genetics and cell biology of this organism," Strassmann says. "Our work on the social games played by the various clones is making this the first social system that can be described genetically."



Joan Strassmann

## Synergies

Synergies between evolutionary biology and the social sciences are nothing new. Game theory and other models of cooperative and competitive strategies within populations have circulated between these fields since the 1970s. "We share a common language," says Rick Wilson, the Herbert S. Autrey Professor of Political Science, who notes that models proposed in evolutionary biology frequently have been put into play by economists and vice versa.

Wilson's recent work investigates reciprocal altruism, the strong tendency in humans to cooperate even when there's no incentive to do so. In one of his studies, a person is given 10 \$1 bills, 10 blank slips of paper the same size and weight as dollar bills, and two envelopes marked "Keep" and "Send." The person is told to put any combination of money or blank slips in the "Send" envelope and keep the rest. "What do you do?" Wilson asks. "Most people send about half. They don't know who is getting the money, there's no reason to do it, but they do it anyway, and they do it fairly consistently."

Wilson has found that 80 percent of participants send up to half of their money, regardless of ethnicity, economic status, or gender. Interestingly, one variable that can influence interactions is appearance. In a trust game where receivers and senders cooperated to divide a pot of money and saw pictures of their partners while playing, receivers expected attractive partners to share more money—and if their expectations weren't met, receivers often retaliated by keeping more of the pot for themselves.

"Why are we predisposed to pay attention to beauty, when we don't pay attention to a lot of other things?" Wilson asks. For Wilson and other social scientists, understanding the roots of these types of behaviors can provide important insights into how people interact within cultures and institutions. "It's not that we are predetermined by genes, but it's unlikely we'll escape them," he says. "There are obvious human constraints. I can't see the upper wavelengths of light. I can't grow wings and fly. There are just some things that I'm not going to be able to do. So we might as well admit what they are and spend a lot more time looking at them. Understanding how we are structured can help us design institutions that can overcome flaws or exploit strengths in our evolved nature."

For Rice scientists, evolution is as much a study of the future as it is a window into the past. "Bird flu. HIV/AIDS. Conservation. People are being exposed to evolutionary thinking all the time," Strassmann notes. Evolution always has been an interdisciplinary discipline, and that's certainly the case at Rice, where gene analyses are serving as test cases for algorithms in computer science and statistical and physical models are being used to calculate mutation rates or plot evolutionary dynamics in a variety of plant and animal species. Strassmann points out that, in many ways, Rice is the perfect place for this work to happen because it's a collective of "smart people finding the tools they need and the collaborations they need to run with their ideas."

Looking at the issues most crucial to humans today, Strassmann sees a definite trend that is supported by the research at Rice. "Everyone," she says, "has become an evolutionary biologist on some level."

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