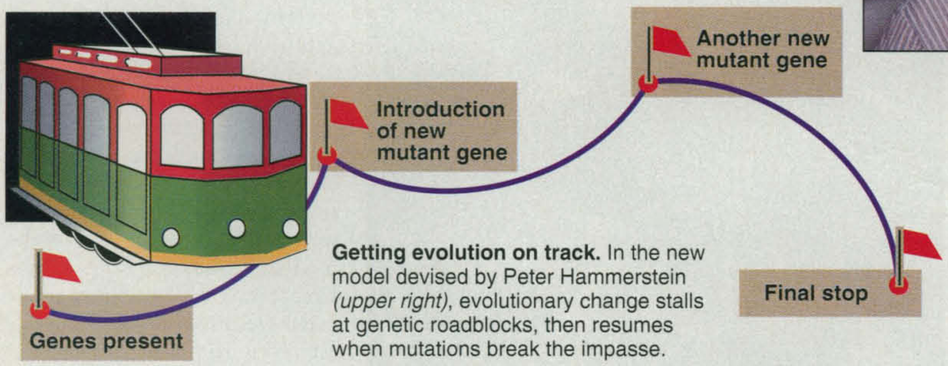
THEORETICAL BIOLOGY

Streetcar Carries Evolution Modelers Around Roadblocks

When Charles Darwin put forward his theory of evolution, he had no idea that an organism's physical attributes, and some of its behavior, are encoded by chemical entities called genes. Nowadays, the genetic view of biology is pervasive, defining everything from eye color through inherited diseases to, more controversially, certain types of human behavior, such as aggression, depression, and schizophrenia. But one thing geneticists have not fully come to grips with so far is how to model evolution itself: How can a set of genes adapt over time to create more successful organisms?

Two attempts to answer the question try to replicate evolution with mathematical models. On the one hand, population geneticists have tried to mimic how genes might evolve over time to increase their "fitness"—a measure of evolutionary adaptation. On the other are researchers who have taken an entirely different tack: They have tried to model how certain behaviors could have succeeded over the course of evolution. The models they use are based on game theory, a set of mathematical tools for understanding economic behavior, and in recent years their predictions have been shown to match quite closely the behavior of particular species in the field.



Getting evolution on track. In the new model devised by Peter Hammerstein *(upper right)*, evolutionary change stalls at genetic roadblocks, then resumes when mutations break the impasse.

ILLUSTRATION: K. SUTLIFF

Both approaches have serious shortcomings, however. Genetic models often get stuck in an evolutionary dead end, settling into an equilibrium without having adapted to new environments. And in spite of the success of game-theory approaches, theoretical biologists worry that these models may not be biologically realistic. Game models were originally developed to analyze the behavior of people, not animals, whose behavior is to a larger extent prescribed by their genes. "Are we doing something that is really [genetically] questionable?" asks game theorist Olle Leimar of the University of Stockholm in Sweden.

But new work by Peter Hammerstein, a theoretical biologist at the Max Planck Institute for Physiology and Behavior in Seewiesen, Germany, may help bring games and genes together, overcoming the shortcomings of both approaches. What Hammerstein has done is to develop a form of game theory in which each trait is governed by several different genes—something that population geneticists, whose models tend to link each trait to a gene at a single locus, have had difficulty doing. "It's a synthesis between hard-nosed population genetics and evolutionary game theory," says theoretical biologist Eörs Szathmáry of the Institute for Advanced Study in Budapest, Hungary.

The model, due to be published this spring in the *Journal of Mathematical Biology*, gets around the evolutionary dead ends that have dogged the population geneticists and offers some reassuring news for game theorists: Their models can stand up to the reality of genes. It also predicts a stop-and-start pattern of evolutionary change, which Hammerstein dubs the "streetcar theory," that is already finding some support in biological data. "It's a very exciting advance, and I think in a couple of decades' time people will look back and see how important this was," says theoretical biologist Geoffrey Parker of the University of Liverpool in the United Kingdom.

The game of life. Game theory was created in the 1940s by the American mathematician John von Neumann in collaboration with economist Oskar Morgenstern as a tool for studying human economic behavior in situations where normal supply-and-demand analysis does not apply. The approach models economics as a game between players who may exploit various strategies that evolve through rounds of the game. In the early 1970s, British biologist John Maynard Smith of the University of Sussex saw the approach's potential for studying the evolution of behavior in terms of the costs and payoffs of specific adaptations.

Maynard Smith and his colleagues developed a number of game-theory models to discern whether strategies such as fighting or fleeing are more successful in winning payoffs such as food, social status, or a mate. They discovered that, over time, some strategies became dominant, and even when alternative, or "mutant," strategies were injected into the game, the dominant strategy soon defeated them, implying that a stable equilibrium had been reached. Such an equilibrium is called an evolutionarily stable strategy, and it has become a key concept in game-theory approaches to evolution.

Biologists were soon incorporating all sorts of animal behavior into game-theory models: aggression, cooperation, hunting, foraging. They have also started to test and refine their models by comparing them with observed behavior, ranging from spiders' competition for web sites to siblicide among baby egrets, social behavior among wasps and naked mole rats, and cooperation among guppies when faced with a predator (*Science*, 17 March 1995, p. 1591). "It's amazing how widely game theory has become a standard approach," says Parker.

But in spite of this empirical success, game theorists worried that real evolution, rooted in the genes, might not proceed the way their models predicted. "The games that appear to be most consistent with what you see happening, which involve changing strategies to match opponents' changing strategies, are the most difficult to tackle with genetics," says evolutionary biologist Joel Brown at the University of Illinois.

At the same time, efforts to model evolution at the level of genes were also falling short. The geneticists' models started out with mathematical "genomes," in which genes with different functions were assigned specific degrees of fitness. The researchers threw in some genomes with mutant genes and set evolution going. The overall fitness of a genome increased its success in "mating" with other genomes, after which recombination of the genomes took place, producing a new set of genomes for selection to act on. The average fitness of the population might be expected to increase over time in such a model. But researchers found that the models often became locked in an equilibrium that was far from the fittest possible combination of genes. "The models ... are [also] problematic when considering any trait encoded by more than one gene," adds Hammerstein.

The streetcar theory. In 1994, Hammerstein, in collaboration with Nobel economics laureate Reinhard Selten at the University of Bonn in Germany, decided to take a new tack toward breaking these impasses—and giving game theory some genetic plausibility at the same time. Hammerstein began with a classic game-theory model of the physical and behavioral, or "phenotypic," interactions between organisms, then linked the games to genes. Unlike the population-genetics models, however, his new approach does not draw a one-to-one connection between traits and genes. Instead, each strategy, which may be a single behavior or range of behaviors, is encoded by genes at two loci. The fitness of the genes is determined by the success of the associated strategies in the game.

When the model is running, genes compete with each other through their associated strategies, "mate" at random, and recombine. New offspring are created in proportion to each strategy's success. The new generation of genes and associated strategies then enters a further round of the game. Like the population geneticists, however, Hammerstein found that the model often ground prematurely to a halt. The genes seemed to get stuck at an equilibrium, even though the strategies they encoded were little better than they had been at the start of the game.

Hammerstein realized that these sticking points are the result of some kind of genetic constraint—a roadblock much like the one illustrated by a textbook example in genetics, sickle cell trait. Carriers of a single mutant gene for the trait have altered red blood cells that provide some resistance to attack by malaria parasites, enhancing fitness in areas where malaria is prevalent. But when a person inherits two copies of the mutant gene, one from each parent, the red blood cells are badly deformed, causing sickle cell disease. As a result, the resistance gene can't spread through the population, and evolution is stalled. "You can see it as the genetic recipe getting in the way of evolution," says Illinois's Brown.

To restart his model, Hammerstein had to break through such roadblocks. His tactic was to throw in a wide range of mutant genes. While many mutants had no effect, as the population geneticists had found when they tried a similar tactic, Hammerstein found to his delight that some mutations were able to kick-start the model. "The key difference between this approach and the population geneticists' is to consider a much wider set of possible mutations," he says.

Whereas genetic modelers tended to limit themselves to mutations within a given set of genetic constraints, Hammerstein also included mutations that could overcome the restrictions caused by phenomena such as recombination, which can tear apart a fitter genome. Take the case of the sickle cell gene: The fitter genome made up of one mutant copy and one normal copy, carried on separate chromosomes, gets split up during reproduction, and the two copies end up in separate sperm or eggs. Offspring thus face a lottery: They may end up with two normal genes, the fitter mixture, or—if both parents are carriers—the disease-causing pair of mutant genes. The lottery hampers the spread of the fit genome.

But Hammerstein says it is possible to think of a new, biologically plausible mutation that could restart evolution: a new gene that would confer resistance to all individuals who carry it without exacting a cost, or a duplication of the sickle cell gene locus, which would allow a single chromosome to carry copies of both the normal and mutant form of the gene. Either mutation could quickly spread. Thinking along these lines, Hammerstein was able to create theoretical mutant genes able to kick-start his models. "Putting mutants like this in the model destabilized the equilibrium and pushed the population to develop further to a new equilibrium state demonstrating enhanced adaptation," he says.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Holding its ground. Game theory successfully explains spiders' behavior in competition for web sites.

Eventually, after many temporary stops, the models came to a long-term stop when no further mutant was able to dislodge the genes from their equilibrium—a pattern Hammerstein has dubbed the "streetcar" theory of evolution. "Like a streetcar, the evolving population moves forward and evolves but then comes to a temporary stop when new genetic passengers join and the journey sets off again. After further stops and exchanges of genetic passengers, the streetcar eventually reaches a long-term stop," he says.

Because his model can overcome genetic constraints and keep the streetcar running toward a better strategy, Hammerstein believes it may be reflecting biological reality. Some population genetics studies support his view. Martin Kreitman, at the University of Chicago, who works on the fruit fly *Drosophila*, suggests there is evidence of "evolutionary sweeps" in some areas of its genome, in which a mutation appears to have spread rapidly through the population. "The similarity of some of these regions throughout the population points to a recent origin," says Kreitman. This fits with the view that the mutations may have overcome genetic constraints and, like the streetcar, started up again after a temporary stop.

The theory may also have practical applications. To explain the behavior of actual organisms, field biologists have to compare a behavior's fitness consequences with those of various alternative behaviors. "At present the choice of fitness measures in empirical studies is often arbitrary," says theoretical biologist Franjo Weissing at the University of Groningen. "In contrast, the streetcar theory suggests that the most adequate fitness measures are those which properly predict the invasion chances of rare mutants. This clarification of the meaning of fitness may turn out to be the most important spin-off of the streetcar approach," he adds.

While the start-stop aspect of the theory seems to agree with observed patterns of evolution, the nature of the long-term stop is particularly welcome to game theorists. When Hammerstein examined the attributes of the model at the last stop of the streetcar, the combination of genes specified a "fitter" strategy matching the one a pure game-theory model predicted. "The result provides a reconciliation between the population geneticists and the game theoreticians," says Weissing, and it's reassuring news for game theorists. "The results of this model suggest behavioral ecologists may not need to worry that their models may conflict with genetics, and they can continue looking at behavior with game-theoretic models," says biologist Alisdair Houston of the University of Bristol in the United Kingdom.

Hammerstein believes the model frees biologists trying to make sense of evolution to focus on phenotypes. "Whatever goes on amongst the genes, there are no long-term stops without economically well-behaved phenotypes," he says. In a way, says Hammerstein, the results are a further tribute to Darwin, who developed his theory of evolution by natural selection without knowledge of genetics. "I think Darwin might have been pleased."

–Nigel Williams