

## Modeling Early Evolution

The fittest organisms survive and produce offspring, according to the Darwinian theory of natural selection. And the changes that make an organism fit happen at the molecular level: when genes mutate they produce different proteins generating traits that may or may not benefit the organism. Yet the relationship between proteins and organism fitness is not well understood.

Now, for the first time, a computer model has attempted to connect the dots between organism evolution and the evolution of proteins.

“People understand that somehow the properties of proteins determine the evolution of populations, but this is only words,” says **Eugene L. Shakhnovich, PhD**, a professor of chemistry and chemical biology at Harvard University and lead author of the paper that appeared in *PLoS Computational Biology* in July 2007. “There’s no detailed microscopic picture of how these two biologies

ing a certain probability of occurring). The life expectancy of the organism is directly related to the stability of its proteins. The latter was determined using a “lattice” model that approximates a protein’s actual structure. It’s a useful approximation, however, because—for purposes of this model—a given amino acid sequence produces a specific measure of the stability of the native state of the protein, says Shakhnovich.

In about half of the 50 simulation runs, the organisms died off. But the successful organisms showed a characteristic pattern of protein evolution the researchers called “Big Bang” behavior. “At some point there is a discovery of a small number of advantageous protein structures and sequences that have evolvability properties,” says Shakhnovich. “These serve as a nucleus for expansion of the protein universe.”

Over time, the model reproduced other quantitative features of the existing protein universe, says Shakhnovich. “This makes us think that this model,

“[We] think that this model, while not the whole truth, captures essential aspects of early evolution,” says Eugene Shakhnovich.

talk to one another.”

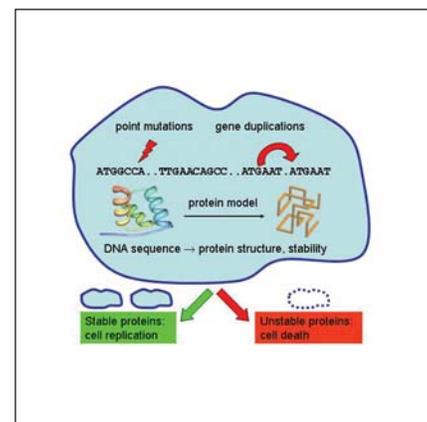
So Shakhnovich and his colleagues simulated an evolving set of proteins under selection pressure. “We developed a model, simpler than life, but still it’s microscopic with these two levels intimately connected,” he says. “So the properties of proteins in the model—like stability—are directly related to properties of model organisms that carry these proteins.”

The simulation starts with 100 organisms, each with the same single primordial gene in their genomes. At each time step, the organism can replicate, die, undergo a gene mutation or duplication, or do nothing (with each event hav-

while not the whole truth, captures essential aspects of early evolution.”

For example, in nature, one finds large and small protein families co-existing. This is inconsistent with a random process. “It has been a mystery as to why this type of distribution pops up in protein science and genetics,” says Shakhnovich. “Our model suggests the source of it is in the evolutionary dynamics of proteins.”

Next steps include adding more complexity: e.g., protein-protein interactions and immune responses. The researchers also hope to gain a better understanding of protein stability, possibly even using that information to develop more stable



*This schematic depicts a first-principles simulation of early evolution. One hundred organisms, each with the same single gene, begin to evolve. At each time step, the organism can replicate, die, undergo a gene mutation or duplication, or do nothing. The organism’s life expectancy depends on the stability of its proteins as determined by a protein lattice model. Courtesy of Eugene Shakhnovich.*

proteins, useful in drug discovery.

“This is the first paper where people have used a simple but realistic model of protein folding to simulate genomes containing multiple genes,” says **Claus Wilke, PhD**, assistant professor of integrative biology at the University of Texas Center for Computational Biology and Bioinformatics. “I think that’s an interesting approach, and I think that over time those kinds of simulations will lead to all kinds of interesting insights.”

—By **Katharine Miller**