Forced evolution: Can we mutate viruses to death?

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It sounds like a science fiction movie: A killer contagion threatens the Earth, but scientists save the day with a designer drug that forces the virus to mutate itself out of existence. The killer disease? Still a fiction. The drug? It could become a reality thanks to a new study by Rice University bioengineers.

The study, which is available online and slated for publication in the journal *Physical Review E*, offers the most comprehensive mathematical analysis to date of the mechanisms that drive evolution in viruses and bacteria. Rather than focusing solely on random genetic mutations, as past analyses have, the study predicts exactly how evolution is affected by the exchange of entire genes and sets of genes.

"We wanted to focus more attention on the roles that recombination and horizontal gene transfer play in the evolution of viruses and bacteria," said bioengineer Michael Deem, the study's lead researcher. "So, we incorporated both into the leading models that are used to describe bacterial and viral evolution, and we derived exact solutions to the models."

The upshot is a newer, composite formula that more accurately captures what happens in real world evolution. Deem's co-authors on the study include Rice graduate student Enrique Muñoz and longtime collaborator Jeong-Man Park, a physicist at the Catholic University of Korea in Bucheon.

In describing the new model, Deem drew an analogy to thermodynamics and discussed how a geneticist or drug designer could use the new formula in much the same way that an engineer might use thermodynamics formulas.

"Some of the properties that describe water are density, pressure and temperature," said Deem. "If you know any two of them, then you can predict any other one using thermodynamics.

"That's what we're doing here," he said. "If you know the recombination rate, mutation rate and fitness function, our formula can analytically predict the properties of the system. So, if you have recombination at a certain frequency, I can say exactly how much that helps or hurts the fitness of the population."

Deem, Rice's John W. Cox Professor in Biochemical and Genetic Engineering and professor of physics and astronomy, said the new model helps to better describe the evolutionary processes that occur in the real world, and it could be useful for doctors, drug designers and others who study how diseases evolve and how our immune systems react to that evolution.

One idea that was proposed about five years ago is "lethal mutagenesis." In a nutshell, the idea is to design drugs that speed up the mutation rates of viruses and push them beyond a threshold called a "phase transition." The thermodynamic analogy for this transition is the freezing or melting of water -- which amounts to a physical transition between water's liquid and solid phases.

"Water goes from a liquid to a solid at zero degrees Celsius under standard pressure, and you can represent that mathematically using thermodynamics," Deem said. "In our model, there's also a phase transition. If the mutation, recombination or horizontal gene transfer

rates are too high, the system delocalizes and gets spread all over sequence space."

Deem said the new results predict which parameter values will lead to this delocalization.

A competing theory is that a mutagenesis drug may eradicate a virus or bacterial population by reducing the fitness to negative values. The new mathematical results allow calculation of this mechanism when the fitness function and the mutation, recombination and horizontal gene transfer rates are known.

Without theoretical tools like the new model, drug designers looking to create pills to induce lethal mutagenesis couldn't say for certain under what parameter ranges the drugs really worked. Deem said the new formula should provide experimental drug testers with a clear picture of whether the drugs -- or something else -- causes mutagenesis.

Source: Rice University