Biologists use computers to study bacterial cell division

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A group of computational biologists at Virginia Tech have created a mathematical model of the process that regulates cell division in a common bacterium, confirming hypotheses, providing new insights, identifying gaps in what is understood so far, and demonstrating the role of computation in biology.

The research, published in the January issue of *PLoS Computational Biology*, looks at the molecular machinery that governs replication of DNA and cell division in Caulobacter crescentus, an easily studied bacterium that is closely related to the bacteria that fix nitrogen in legumes and to the bacteria that cause brucellosis in cattle and Rocky Mountain spotted fever in humans.

“All share the same characteristic of asymmetric division; the daughter cells are different than the mother cell in some fashion,” explains John Tyson, University Distinguished Professor of Biology at Virginia Tech and corresponding author of the PLoS article. “In C. crescentus, the mother cell attaches to a rock by a sticky stalk. If there is good eating, she divides and creates a daughter that can swim away. The stalked cell remains attached to the rock and the daughter—with a flagellum instead of a stalk—swims away, so that it does not compete with mama. After about 35 to 40 minutes, the daughter loses the flagellum, grows a stalk, and settles down to become a mother.”

The Virginia Tech researchers are interested in the molecular machinery that governs replication of DNA and division of a cell into two different

cell types. “A lot is known about genes that control this process. Much of the work was done in Lucy Shapiro’s laboratory at Stanford,” said Tyson.

“The mechanism is very complicated, involving dozens of genes and even more proteins. From experimental observations it is possible to construct a hypothetical ‘wiring diagram’ of how these genes and proteins interact.”

But it is difficult to predict how cells will control their replication-division cycles from such a complicated hypothesis, he said. “Our goal is to convert the wiring diagram into mathematical equations that can be solved on a computer so that we can say with more confidence how the mechanism will govern cell growth, division, and differentiation.”

The team’s goal is also to demonstrate the role of computation in understanding biology. “We want to convert intuitive expectations into mathematical equations that can be tested more rigorously,” Tyson said.

For example, models can be used to make testable predictions. A basic experiment is to create a mutant bacterium by knocking out a gene – thus learning the role of the gene. This mutation can be simulated in the mathematical model to confirm the role of the gene in the wiring diagram. The mathematical model must agree with the observed behavior of all known mutants, and it can be used to compute the expected properties of mutants never before created in a lab, Tyson said. “If the prediction is confirmed by experiment, it promotes more confidence in the model. And sometimes you find that the model cannot reproduce the behavior of mutant bacteria, which suggests that the wiring diagram is incomplete and helps focus research on an improved understanding of the cell-division process.”

In fact, there are known Caulobacter mutants that are not explained by the model described in the PLoS article, entitled “A Quantitative Study

of the Division Cycle of Caulobacter crescentus Stalked Cells." "We knew our model was incomplete," Tyson said, "but we decided to publish at this stage because the model is good enough to illustrate the advantages of a computational approach. We have a new version of the model that fixes the problem and that accounts for the differentiation and development of swarmer cells as well as stalked cells."

So stay tuned.

"Computational biology is not much different from experimental biology – you learn, publish, and keep working. There is always room for improvements. We would like to extend the model to the nitrogen-fixing and disease-causing cousins of C. crescentus," Tyson said.

Co-author Bruno Sobral, professor and executive and scientific director of the Virginia Bioinformatics Institute, remarked: "C. crescentus is a member of the alpha-proteobacteria, a group of diverse organisms whose members have successfully adopted different lifestyle and energy-yielding strategies in the course of evolution. It will be interesting to see if the molecular mechanism described in this study for control of the cell division cycle in C. crescentus is applicable to other species of this biologically important group of bacterial organisms."

Source: Virginia Tech