Math model accurately mimics cell division in carbon-cycling bacterium

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Scientists from the Department of Biological Sciences and the Virginia Bioinformatics Institute (VBI) at Virginia Tech have developed a quantitative, mathematical model of DNA replication and cell division for the bacterium *Caulobacter crescentus*. *C. crescentus*, an alpha-proteobacterium that inhabits freshwater, seawater and soils, is an ideal organism for genetic and computational biology studies due to the wealth of molecular information that has been accumulated by researchers. It also plays a key role in global carbon cycling in its natural environment.

The researchers work will appear in the August 14 edition of *PLoS Computational Biology*.* The article "Temporal controls of the asymmetric cell division cycle in Caulobacter crescentus" is by Genetics, Bioinformatics, and Computational Biology graduate student Shenghua Li, research scientist Paul Brazhnik, Professor and Director of VBI's Cyberinfrastructure Group Bruno Sobral, and University Distinguished Professor of Biological Sciences John Tyson.

The mathematical model described in the paper allows researchers to study and analyze the systems-level dynamics of the Caulobacter cell cycle, test hypotheses and suggest crucial new experiments. "By careful examination of the large amount of experimental information available about the genes, proteins and biochemical reactions involved in regulating the cell division of *C. crescentus*, we have developed a good understanding of the mechanism of cell division in this organism and a realistic, quantitative mathematical model of the molecular machinery that oversees Caulobacter's cell division cycle," said John Tyson.

Caulobacter normally undergoes a cell cycle that produces two different types of offspring: a motile "swarmer cell" with a flagellum, a slender thread-like structure that allows the bacterium to swim, and an immobile "sessile stalked cell" that lacks a flagellum. The two cell types undergo different development programs but share the same core molecular regulatory system that controls whether the cell commits to a new round of DNA synthesis and to the cell division process. This regulatory core comprises three key proteins - DnaA, GcrA, and CtrA - that act as control points or master switches for DNA replication and cell division. The new math model allows scientists to investigate how these proteins vary with time and their link to physiological events in both stalked and swarmer cells.

"Cells have some similarities to computers in the sense that they engage in information processing", said Tyson. "However, prokaryotic cells like Caulobacter have been somewhat neglected as information systems in studies by scientists. While computers are precise, digital processors, cells are analog systems that operate for the most part in sloppy, watery environments. Conveying instructions for DNA replication and cell division has profound consequences for a cell and needs to be done with considerable accuracy and precision and that's one of the reasons why we want to be able to model the process." Tyson added: "We have been able to establish a wiring diagram that maps the essential regulatory steps for DNA replication and cell division in Caulobacter in a way that is similar to how you would define a computer process. The model provides a rigorous account of the consequences of our hypotheses, which can be compared to experimental observations to test the model."

With the model in place, the researchers confirmed that it correctly represents the sequence of physiological events that take place during cell division. They were able to show in simulations that the model accurately describes how the different proteins change in quantity during the cell division cycle. Taking this one step further, they were also able

to simulate the impact of specific known mutations on cell function.

Mutant cells provide valuable information about how individual components of the cell cycle control system affect the features (phenotype) of cells. Commented Tyson: "Our model allows you to perform quantitative predictions for novel mutants. We have performed simulations of some novel mutants that to our knowledge have not been described in the scientific literature. For example, the math model predicts that if the master regulator CtrA cannot be properly phosphorylated, which is a key step in the activation of CtrA, then the cell replicates its DNA but cannot divide. It will grow very long and eventually die. Specific predictions like this can test the reliability of the model. A validated model can then be used to design new experiments by in silico simulations."

The researchers have built a math model that allows for the study of how the protein components change with time. Future versions of the model will also take into account the spatial localization of the proteins. Said Bruno Sobral: "Caulobacter crescentus is a member of the alpha-proteobacteria, a group of diverse organisms whose members have successfully adopted different lifestyle and energy-yielding strategies over the course of evolution. Caulobacter was also recently detected as a human pathogen, which makes its study directly relevant to human health. Since many genes and mechanisms discovered in Caulobacter are evolutionarily conserved among the alpha-proteobacteria our computational model of cell replication may be applicable to other family members, in particular the causative agents of brucellosis in cattle and Rocky Mountain spotted fever in humans."

More information: Shenghua Li, Paul Brazhnik, Bruno Sobral, John J. Tyson (2009) Temporal controls of the asymmetric cell division cycle in Caulobacter crescentus. *PLoS Computational Biology* 5(8): e1000463. doi: 10.1371/journal.pcbi.1000463

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