Model helps pinpoint cyanobacterial genes that capture the sun's energy

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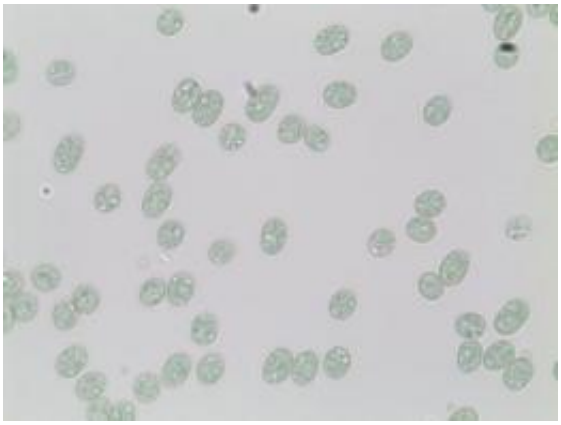


This is the single-celled marine cyanobacterium *Cyanothece* 51142 captured by a light microscope. Credit: Washington University in St. Louis

A new computer model of blue-green algae can predict which of the organism's genes are central to capturing energy from sunlight and other critical processes.

Described in a paper published in the journal *Molecular BioSystems*, the model could advance efforts to produce biofuel and other energy sources from blue-green algae, known as cyanobacteria. Researchers from the Department of Energy's Pacific Northwest National Laboratory, Washington University in St. Louis and Purdue University developed the model, which was made for the single-celled marine cyanobacterium *Cyanothece* 51142.

"Our model is the first of its kind for cyanobacteria," said the paper's lead author, PNNL computational biologist Jason McDermott. "Previous models have only zoomed in on specific aspects of cyanobacteria. Ours looks at the entire organism to find out what makes *Cyanothece* tick."

The research was funded by EMSL, the Department of Energy's Environmental Molecular Sciences Laboratory, a national user facility at PNNL, as part of EMSL's Membrane Biology Grand Challenge. The challenge encouraged scientists to take a systems biology approach to understand the network of genes and proteins that are responsible for photosynthesis and nitrogen fixation in cyanobacteria.

Cyanobacteria are noteworthy because they share qualities with both plants and microbes. They use the sun's energy to make sugar via photosynthesis like plants. And, like microbes, cyanobacteria also convert atmospheric nitrogen – an important nutrient for many organisms – into accessible forms, a process called nitrogen fixation.

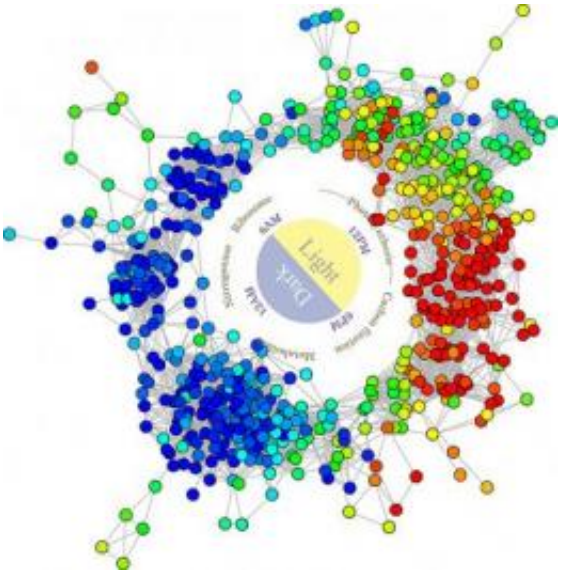
Working day and night

Many cyanobacteria physically separate their photosynthetic and nitrogen fixation activities in different cells. But *Cyanothece* is unusual because the same cell switches between these functions every 12 hours. It makes sugar when there's daylight and then spends the night breaking down that sugar to fix nitrogen and to produce other compounds.

"By understanding which genes trigger *Cyanothece* to start and stop photosynthesis and other important energy production functions, we may be able to better use cyanobacteria to make renewable energy," McDermott said. Genes serve as the blueprint for the creation of proteins, the cell's workers.

Mapping a gene's purpose

Researchers – many of whom also worked on the model – sequenced *Cyanothece*'s genome in 2008. But knowing how many genes an organism has doesn't necessarily explain what those genes do. So scientists kept studying *Cyanothece* in the lab. By making a simple linear graph of when different genes were expressed over a 24-hour cycle, McDermott and his co-authors saw that many genes were expressed at similar levels and at similar times. The team hypothesized that such genes were involved in similar processes, such as photosynthesis or nitrogen fixation.



Researchers developed this wreath-like graph to visualize all the genes being expressed by the cyanobacterium *Cyanothece* over a 24-hour period. The graphic revealed the complex genetic network that enables *Cyanothece* to switch its cell between photosynthesis and nitrogen fixation as the day turns to night. Credit: Pacific Northwest National Laboratory

But there isn't always a straight line between one gene being turned on and a cellular process starting. Sometimes a series of genes have to be turned on or off before a process can begin. To better understand these complex relationships, McDermott crafted a circular graph that illustrates how genes are expressed around the clock. Each point on the graph represented a gene being expressed at a particular time. Lines connecting the dots demonstrated how some related genes are expressed one after another in a series.

Points of control

The wreath-like graph revealed a complicated, intertwined network of *Cyanothece* genes. In some cases, different series of related genes expressed one after another intersected at the same place, at an individual gene or a handful of genes. It appeared that the genes at these intersections serve as bottlenecks, or control points, for the subsequent expression of other genes down the road. The team predicted that if the bottleneck genes were removed, expression of the downstream genes would be affected. Amazingly, 11 of the 25 top bottlenecks identified were genes or proteins whose specific role in *Cyanothece* weren't previously known.

The next challenge was to figure out how each of these bottlenecks affects *Cyanothece*'s daily life. The team could have done experiments in the lab, removing each of these bottlenecks one at the time from the organism's genome to see what happened. But such experiments can be time-consuming. Seeking a simpler, more methodical solution, the authors built a computer model that would predict the roles of individual genes in *Cyanothece*.

Central players

They started with a previous whole-organism modeling approach called the Inferelator, which was developed at the Institute for Systems Biology in Seattle for a different microorganism. The team adapted the Inferelator's code to compute the cyclic nature of the connections between *Cyanothece*'s genes. They also added code to improve their ability to test the model's accuracy. When looking at low-oxygen conditions similar to those encountered by *Cyanothece* at night, the model predicted gene expression levels correctly the equivalent of about 75 percent of the time, in comparison to actual measurements.

The model predicted the roles that a number of bottleneck genes play for *Cyanothece*. For example, the model predicted that the patB gene is a bottleneck for the production of nitrogenase, the enzyme needed to fix nitrogen. If patB were removed from *Cyanothece*, the model predicted that nitrogenase production could decrease by as much as 80 percent. The model also identified an unnamed gene, currently labeled as gene cce_0678, as being key to the cyanobacterium's production of RuBisCO, a well-known enzyme that's important in photosynthesis. Without cce_0678, the model predicted RuBisCO production would decrease by about 60 percent.

Next, the research team will seek to further validate the model with lab experiments. They'll remove or increase the expression of specific genes predicted to be bottlenecks to test whether or not they impact *Cyanothece*'s energy production as the model predicted. The researchers will also use the model to examine the complex interactions between important processes in cyanobacteria, such as photosynthesis and nitrogen fixation.

"This model can serve as a first step toward a complete simulation of *Cyanothece*," McDermott said. "Knowing the detailed inner workings of cyanobacteria could be used to design efficient methods to make bioenergy and manage the carbon cycle, including the greenhouse gas

carbon dioxide."

More information: Jason E. McDermott, Christopher S. Oehmen, Lee Ann McCue, Eric Hill, Daniel M. Choi, Jana Stöckel, Michelle Liberton, Himadri B. Pakrasi and Louis A. Sherman, A model of cyclic transcriptomic behavior in the cyanobacterium Cyanothece sp. ATCC 51142, Molecular BioSystems, published online June 23, 2011, DOI: 10.1039/C1MB05006K

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