Positive Division

Dr. Jaan Mannik, Graduate Student Matthew Bailey and Their Colleagues Discover How Attraction Creates Daughter Cells in *E. Coli*

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Like other living creatures, bacteria guarantee their future by passing down DNA to their children. *Escherichia coli* (*E. coli*, for short) are tremendously gifted at this, typically splitting down the middle into two daughter cells and providing each with a full set of chromosomes in favorable conditions as fast as every 20 minutes. Research has shown that exclusion plays a big role in this division process by limiting where necessary division proteins can gather in the parent cell. Assistant Professor Jaan Mannik, graduate student Matthew Bailey and their colleagues have identified a new positioning system for cell division proteins in *E. coli*: one that attracts these proteins rather than excluding them. Their findings were published August 7 in the journal *PLOS Genetics*.

Co-Authors Matthew Bailey (Physics Graduate Student), Boyd T. Warren (B.S., Microbiology, 2013), and Assistant Professor Jaan Mannik.

The Hydrogen Atom of Biology

Mannik explained that all cells are created by the division process. In our bodies cells have divided more than 10 trillion times, not accounting for the bacteria that we carry with us. He pointed out that we actually carry more bacteria cells than we do our own cells. *E. coli* can be a bit misunderstood in the general public, especially when stories appear about food outbreaks. While a few strains can cause problems, most *E. coli* are harmless and live quite tranquilly in healthy people.

"They are a natural part of us," Mannik said. "There are the pathogenic ones which cause concern, but we do have a lot of non-pathogenic *E. coli* in our bodies. We shouldn't kill them; then some bad bacteria will take over this niche, and that's not really desirable."

What *is* desirable to scientists like Mannik is studying bacteria to understand the physics of biological systems. He explained that *E. coli* are sort of the biological equivalent of the hydrogen atom in physics, which, with one proton and one electron, is a simple and elegant system. And when it comes to cell division, he explained, "*E. coli* are remarkably proficient at this: they divide in the middle of their rod-shaped bodies and pretty much always divide into two daughter cells with a full set of chromosomes."

Cellular Scaffolding

Mannik explained that cell division in *E. coli* is organized by FtsZ proteins, which organize into a ring-like structure called the Z-ring.

“They form a scaffold for other proteins which carry on the cell division,” he said; “enzymes which synthesize a new cell wall between the daughter cells to help segregate the chromosomes.”

How these division proteins are positioned is not quite clear yet. Previous studies have identified two models—the Min system and nucleoid occlusion—that regulate proteins by inhibiting their localization in certain regions of the cell.

“The Min is actually a very nice system and most physicists like it a lot,” Mannik said. There are two proteins in this system and “these proteins go back and forth from one pole of the rod-shaped cell to the other.”

The average distribution of those proteins maximizes at the poles and minimizes in the middle, he explained, thereby inhibiting cell division at the poles but allowing it in the cell’s center.

In nucleoid occlusion, he said, “cell division proteins are in general excluded from the nucleoid of the bacteria,” which is the region where the genetic material is located. In *E. coli*, the protein SlmA mediates the process.

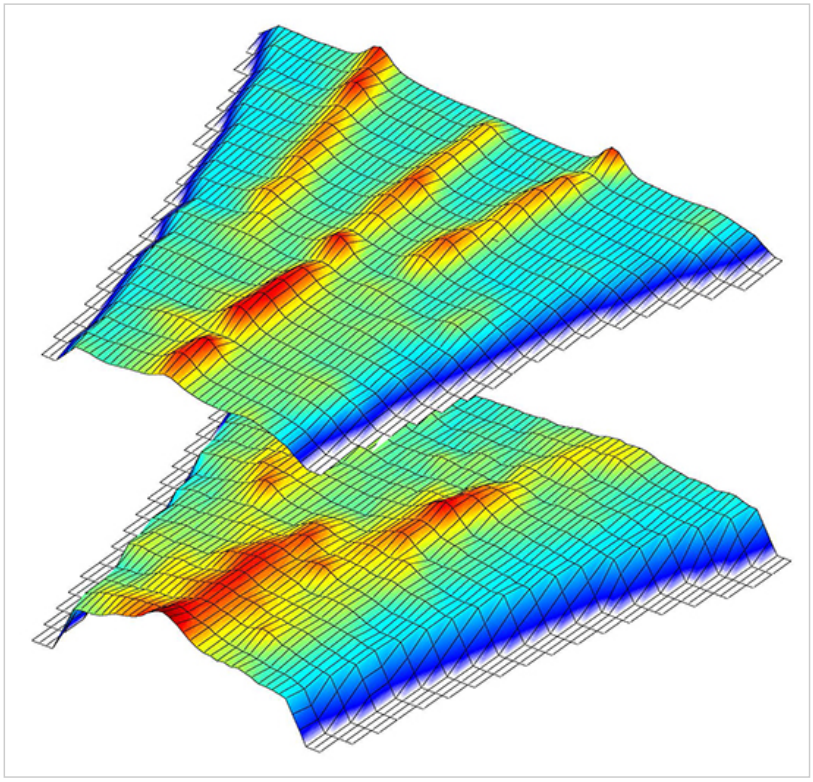
“That protein works in a very interesting way,” he said. “*E. coli* has a chromosome, and this chromosome is a circular piece of DNA (that’s) replicated from a single site called the origin. There are two replication forks which go in opposite directions from this origin. They meet on the other side of the circle and this is called the Ter (or terminus) region.”

The SlmA protein attaches to the chromosome in specific sites, but none of them are in the Ter region.

“The Ter region is important in cell division,” Mannik said, and it figures into the findings presented in “Evidence for Divisome Localization Mechanisms Independent of the Min System and SlmA in *Escherichia coli*,” which appeared in *PLOS Genetics*.

In 2012 Mannik and his colleagues published findings indicating that *E. coli* likely had systems beyond Min or occlusion influencing the position of division proteins. In this latest work, they bolstered this assertion by showing that even if the genes responsible for both the Min and occlusion systems were removed, *E. coli* cells were still capable of dividing accurately in the center. To find out how, they labeled cell division proteins with fluorescent tags and then tracked the tags with nanometer scale resolution.

They found that the Ter region of the chromosome moves to the middle of cell and acts as a positional landmark for the Z-ring. Thus, this chromosomal region *attracts* cell division proteins, in contrast to the other systems, which repel these proteins from certain regions of the cell. They call this new positioning system the Ter linkage. Mannik explained that this link has been hypothesized since the 1960s but never found. They also showed that certain proteins (MatP, ZapB, and ZapA) link the Ter region and the Z-ring.



In the Ter linkage model of cell division for *E. coli*, the Ter macrodomain of the chromosome moves to the center of the cell and the cell division proteins then assemble at this location. The top image is the ZipA-GFP protein (one of the division proteins) and the bottom is MatP-labeled Ter region of the chromosome.

The research team included Mannik, Bailey (who performed the measurements), Boyd T. Warren (who finished a bachelor's degree in microbiology in 2013) and Paola Bisicchia and David J. Sherratt of the University of Oxford (UK) Department of Biochemistry.

Mannik said there are further investigations ahead, including how exactly the Ter linkage functions. Studies have also indicated that even when the Min, nucleoid occlusion, and Ter linkage systems have been removed, *E. coli* cells can still divide, although inaccurately. It is not clear what positioning mechanisms are involved in these cells.

"We hope to find out answers to these remaining puzzles soon," he said.

More Information

- **"Evidence for Divisome Localization Mechanisms Independent of the Min System and SlmA in *Escherichia coli*" (http://www.plosgenetics.org/article/info%3Adoi%2F10.1371%2Fjournal.pgen.1004504)** in *PLOS Genetics*

- **Laboratory of Cellular Biophysics - the Mannik Lab (http://www.phys.utk.edu/jmannik/LCBHome.html)**