

## Patterns in Genome Organization May Partially Explain How Microbial Cells Work

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The top and middle figures indicate nonrandom patterns of gene density along the length of the *Bacteroides thetaiotaomicron* (top) and *Escherichia coli* (middle) chromosomes. (The numbers along the horizontal axes represent chromosome position in kilobases, and the numbers on the vertical axes are the sizes of the nonrandom regions in kilobases. White regions are areas without patterns.) The bottom graph indicates the rank order of gene-density patterning found in 151 species studied, with *B. thetaiotaomicron* exhibiting the strongest nonrandom genome organization based on gene density, with *E. coli* ranked in the middle of the study group.

The location of a piece of real estate may be its most important feature to many Realtors, and bioengineering researchers at the University of California, San Diego (UCSD) and the University of Virginia have reported that the location of genes and other features distributed along the chromosomes of bacteria and simpler organisms also is fundamentally important to how microbial cells operate.

In a paper published Jan. 13 online in *PLoS Computational Biology*, the researchers reported large- and small-scale organizational patterns in the genomes of 135 bacteria ranging from those that cause typhoid fever and various other human infections to organisms that enrich the nitrogen content of soil. In addition, 16 more primitive microorganisms, including one that thrives in boiling hot springs, also exhibit patterns in their genomes that are highly nonrandom.

"This high degree of organization of prokaryotic [organisms that lack nuclei] genomes is a complete surprise, and this finding carried many implications that biologists might not have considered before," said Bernhard Palsson, a professor of bioengineering at UCSD's Jacobs School of Engineering and adjunct professor of medicine and co-author of the analysis. "These findings show that evolution of prokaryotes is constrained not just by variations in the content of genes, but also by the intricate ways in which those genes are arranged on chromosomes."

A bacterial cell usually operates with one copy of its genome. Until 2002, there had been no way to determine if a particular gene or area of the chromosome was segregated in any particular way inside individual bacterial cells. New techniques that attach fluorescent "reporter" markers to predetermined spots on chromosomes have indicated that many bacterial genes tend to be found at specific cellular locations. Nonrandom patterns are not obvious in the sequences of prokaryotic genomes, which led the team led by Palsson to use signal-processing methods to identify long-range spatial patterns in the arrangement of sequenced microbial genomes. They related the degree of organization in each genome they studied based on various characteristics.

"Bacterial chromosomes may have something like ZIP codes that fix groups of genes to certain locations within the cell where they are most needed," said Timothy E. Allen, a member of Palsson's team at UCSD who is currently an assistant professor of biomedical engineering at the University of Virginia. He said the surprising organization begs the question of what it means. The sequence order of bacterial genomes most likely affects the way in which the DNA is compressed, often more than 1,000-fold, to fit within the confines of the cell. "In some cases, it might suggest that a genome is arranged into relatively large physically distinct coils inside the cell, but nobody knows for certain," Allen said. "One of the take-home messages of our study is that we need to develop more ways to measure the location of specific genes within individual cells."

Palsson's team included Allen, recent Ph.D. graduate Nathan D. Price, and Ph.D. candidate Andrew R. Joyce. They downloaded the sequences of the 151 prokaryotic genomes from the CBS Genome Atlas Database and analyzed regions of each genome for the relative amount of four basic building blocks of DNA, the density of genes and expression level of those genes, and other factors.

To detect patterns in those features, they used wavelet analysis, a statistical technique that also has been used to identify patterns in geophysical data, such as warming of the surface of the ocean off South America that causes El Niño climatic events. The wavelet analysis of bacterial genomes yielded "scalograms," maps colored to elucidate the strength of a variety of periodicities associated with chromosome position. Just as the wavelet analysis has identified significant increases in sea surface temperatures in El Niño events, it also revealed nonrandom patterns in the genomes of most of the 151 microorganisms studied.

"The analysis generated diagrams of psychedelically colored islands of statistically significant patterns floating in a sea of insignificant patterns," said Palsson, author of *Systems Biology: Properties of Reconstructed Networks* (Cambridge University Press, 2006). "Basically, it demonstrated that most bacterial genomes are highly organized. Our results demonstrate that there are significant evolutionary constraints that act upon genomes organization as well as upon genome content. That interplay between organization and function can't be ignored if we want to gain a better fundamental understanding of how a microbial cell works."

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