THE AUTHOR FILE

Jennifer Phillips-Cremins

To better explore how genomes fold takes disparate fields and a love of math.

University of Pennsylvania Bioengineering

Jennifer Phillips-Cremins

It struck them at the same time: Jennifer Phillips-Cremins of the University of Pennsylvania's bioengineering department and her graduate student Heidi Norton were listening to a Penn colleague, network scientist Danielle Bassett, talk about identifying modules of neural connectivity in functional magnetic resonance imaging data. As Phillips-Cremins recalls, she and Norton said, almost in unison, "Her data looks just like nested TADs and subTADs." It gave them the idea for 3DNetMod, their new computational method to analyze 3D genome-folding. Topologically associating domains (TADs) are chromosomal compartments within which other TADs can be nested. It's a TAD-tangle. When and why chromosomes move, touch, overlap are still poorly understood. 3DNetMod applies principles in graph theory and network science to find nested, partially overlapping TADs and subTADs in data from chromosome conformation capture experiments such as Hi-C.

Before imaging advances and Hi-C techniques, genome-folding was not terribly visible. Like the evolution of television, says Phillips-Cremins, genome-folding maps have gone from hazy to high-definition. But it's still been hard to 'call' TADs, especially subTADs, from Hi-C data. "They're nested, they're partially overlapping, they have very, very complicated patterns," she says. Identifying these patterns can shed light on the genome's spatiotemporal gene expression patterns and how these patterns change, for example, in development or disease. She hopes to use 3DNetMod for studying the brain. She has noted how genome-folding changes as stem cells turn into neural progenitor cells. Perhaps genome-folding is part of what goes awry in neurodegeneration.

3DNetMod draws on principles used to study connectedness in the brain or in social networks. A network of neurons, friends or TADs can include loosely and densely connected communities. The method maximizes so-called network modularity and parses the network to find structures within these communities. "My interest is in tackling really hard problems using many angles," says Phillips-Cremins. As a child, she loved math. "I remember drawing a parabola on graph paper and the joy in the moment when the intuition between the equation and plot hit in the lightbulb moment." In high school, she enjoyed algebra and calculus and is grateful to the teachers who encouraged her even though being good at math wasn't cool among her peers. Then, when she was an undergraduate, math led her to chemical engineering with a math minor until she realized she wanted to work on biological problems.

After getting her bachelor's degree, Phillips-Cremins worked in industry for two years and then returned to university. When she began graduate school, it had been a while since high school biology, but she completed a PhD program in bioengineering run jointly by Georgia Institute of Technology and Emory University School of Medicine. "I look back on graduate school as a magical time of learning and discovery; it was like a whole new world was opened up to me—molecular biology, cell biology, anatomy, physiology," she says. "I was just like a sponge; I threw myself into it," she says.

She went on to more duality as a postdoctoral fellow with Job Dekker at University of Massachusetts Medical School and Victor Corces at Emory University. She traveled between the two labs and "although it sounds a bit nuts on paper," she found it exciting. "Looking back, I'm in shock and grateful for how much freedom Job and Victor gave me—it really prepared me for all the aspects of being a PI." She joined the faculty at the University of Pennsylvania in 2014. "Jennifer is a force!" says Dekker. The energy and creativity she brought to his lab have propelled her own lab and she has quickly established herself at the forefront of the rapidly growing 3D genome field, he says. "This field is already moving fast, but Jennifer is making it move even faster." In her lab, Phillips-Cremins fosters an interdisciplinary culture—"that is something I am very passionate about"—and she is proud of the 3DNetMod team's collaboration. The lab has statisticians, computational scientists, molecular and cell biologists, and people she calls integrators—students seeking wet-lab and dry-lab experience. She wants to train scientists to have depth in statistics, computational and experimental techniques so they can find patterns meaningful for the biology and "not patterns for patterns' sake," she says. Lab meetings involve many types of presentations, which gives the group depth and breadth and helps them to grow as a team. "Group meetings are really fun," she says.

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Vivien Marx

Norton, H. *et al.* Detecting hierarchical genome-folding domains with network modularity maximization. *Nat. Methods* **15**, 119–122 (2018).