THE AUTHOR FILE

Mario Nicodemi

Polymer physics, comparing ways to assess chromatin structure and taking in tales at the Italian seaside.

Italy has been hard hit by COVID-19 and now faces a third wave, but that's not deterring his team, says Mario Nicodemi. As computationally oriented theoretical physicists, they find remote work easier to set up than wet-lab researchers do. The pandemic is motivating the team to work even harder to bring physics concepts to biology. Nicodemi is on the faculty of University of Naples Federico II, which was founded in 1224; he is a researcher at Italy's National Institute for Nuclear Physics (INFN); and he has a lab at the Max Delbrück Center for Molecular Medicine in Berlin. As a physicist, he can study "wonderful and intellectually super-exciting concepts," he says, but he sees biology as a field with regularly emerging new developments. A decade ago, INFN launched a national project that Nicodemi finds exciting and which he now coordinates. It's devoted to applying theoretical physics to biology. Now that biology is becoming more experimentally quantitative, the nexus of physics and biology is, in his view, the future of both disciplines.

Nicodemi enjoys the chromatin architecture field as "a natural place where physics meets biology," he says. In biology, unlike in physics, fundamental paradigms change every year or two. Yesteryear's 'junk DNA' has become today's gene regulatory regions. A linear DNA sequence can fold in many different ways, and each can have a biological implication. With chromosomal folding "you see the complexity of the encoding," he says. "We are really delving into the principles whereby life itself is working."

"Mario brings a physicist's rigor and insightfulness into the study of chromatin structure," says Bing Ren, a researcher at the University of California, San Diego, who has long collaborated with Nicodemi in the US National Institutes of Health 4D Nucleome program. "Using simulation, modeling and computational tools, he and his colleagues turn the static chromatin fibers into moving objects that can guide us to appreciate the fundamental forces that shape the chromatin structure."

In his latest work, Nicodemi and colleagues have compared the performance of three methods used for the high-throughput and genome-wide assessment of the intricately folded nuclear chromatin architecture. These are ways to find which position on a chromosome is in physical contact with another. Knowing who is encountering whom and getting a quantitative readout of these encounters matters biologically, says Nicodemi. The contacts regulate genes in different ways and can play a role in disease. The team produced in silico implementations of Hi-C, SPRITE and GAM, the last of which Nicodemi's team co-developed. "We wanted to explore them in a simplified but controlled framework," he says. The in silico approach let the group tweak many parameters and see how the technology behaves in ways that would be cost-prohibitive in a real-life lab setup.

Mario Nicodemi.

One technically involved step was creating 3D versions of chromosomes as bona fide representations of real chromatin, he says. They drew on microscopy data to do so. They also modeled regions of the genome, focusing on regions around the mouse *Sox9* and *Epha4* genes that have human homologs associated with disease-causing structural variants. Mutations can, for example, change folding patterns such that disease results. The scientists validated results with experimental data such as fluorescence in situ hybridization imaging.

The good news about the comparison: "It is reassuring that the three are all faithful to the fundamental real structure of chromatin, at least as seen by our computers," says Nicodemi. For bulk analysis, they all do equally well at representing the 3D conformations. "At the level of single-cell measurements, they all become very, very noisy." This reflects the typical heterogeneity of cells but leads to differences in the minimum numbers of cells needed to achieve comparable contact patterns and faithful representations of the actual structures. Among the results: SPRITE worked better with small numbers of cells than Hi-C and GAM. And GAM-based results showed less noise than the other methods when assessing contacts at longer distances between chromosomal contact points. Nicodemi hopes the paper can guide labs in selecting methods best suited to their experimental conditions. All three methods are based on sequencing. One day, microscopy-based methods might take over, he says, but such imaging-based methods are still technically challenging and likely not practicable for biomedical applications.

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As he completed his PhD research in theoretical physics at the University of Naples, the work took him to the École supérieure de physique et de chimie industrielles in Paris, where he became a postdoctoral fellow. He was next a fellow at Imperial College London, then joined the faculty in Naples. He did a stint the University of Warwick's Centre for Complexity Science in the UK and then returned to his alma mater. "I'm really grateful to all those countries," he says. He felt at home everywhere. Especially these days, it's important to him to open doors and bring people together. "Accepting people with their differences is the key for improving our society and improving science," he says. When he is not working on his research, says Nicodemi, "I tend to read a lot"—novels, essays, history, especially history of science. He and his family summer at the Italian seaside, where he enjoys interacting with locals. Not only is there fantastic food, "they have fantastic stories to tell," he says. "Every time I discover something exciting." ❐

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Reference
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