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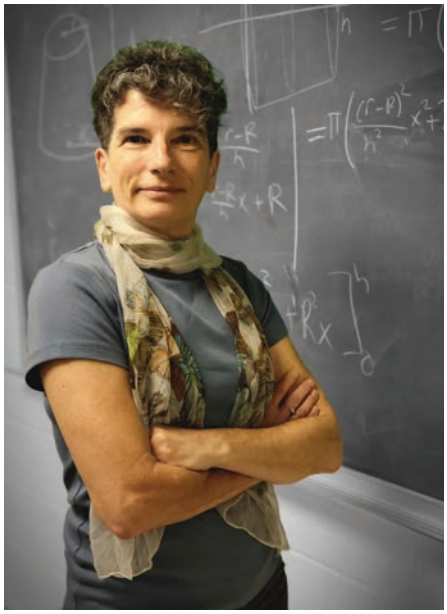
Interview Nataša Jonoska

Understanding biology from a mathematical perspective

Nataša Jonoska is a Distinguished Professor of mathematics, at the University of South Florida. She works on discrete models of bimolecular processes and biological computations, where she uses her background in symbolic dynamics to solve computational problems with molecules. This year, she was invited as plenary speaker at the Dutch Mathematical Congress (NMC). On that occasion Clara Stegehuis and Cor Kraaikamp talked with her about her research, and her journey toward doing interdisciplinary science.

When did you first become interested in mathematics?
"I never really knew myself that I wanted to be a mathematician. Still, my mother remembers that my first grade teacher told her that she was certain that I was going to become a mathematician. Mathematics was always easy for me, but I was bad at Latin and Greek. Because of this, I went to a high school that focused on mathematics instead of the gymnasium schools were you also had to study ancient languages. In this school, our mathematics courses were even taught by university professors, so they really exposed me to the field of mathematics."

And how did you decide to study mathematics?
"When I first came to the university, I came there with one of my friends, and we decided that we would like to choose the same major. When we had to hand in the paperwork stating our main field of study, we ran into a discussion. I wanted to become an architect, but my friend was not interested in that. So in the end we decided together to study mathematics, as that was something that we both knew through our high school education. Of course, looking back at this now, it was a very foolish way to determine my major field of study, but fortunately this rather random choice suited me well."


Nataša Jonoska

What questions do you like to solve in your research?
"The main questions that I am interested in are: how do molecules form? And how do they exchange information? For example, DNA molecules can exchange information by how they do or do not fit together. This formation of molecules can also help us in solving mathematical problems.

For example, we solved a three-coloring problem using DNA-based molecules. Basically, the DNA-molecule represents a graph in three-dimensional space. There are three types of molecules that can represent vertices: one molecule for each possible vertex color. From a computer science point of view, these different types of molecules try all possible colorings. We ensure that two similar colors will bind, whereas two different colors will form a bubble. We then use an enzyme that destroys all the bonds, so that only the different colors remain. If a target molecule of the size of the original graph then forms, that means that the graph is three-colorable. We experimentally showed on a specific example that this target molecule can indeed form and prove the three-colorability of the example graph. Showing that this target molecule forms is still not trivial. We cannot observe it directly, as these molecules are too small to observe. Therefore to show that the target molecule was built, we needed ideas from topological graph theory. Once the mol-



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ecules are built, there is a molecule that traverses all the edges of the graph. This is similar to an Eulerian tour, except that edges may be traversed twice. So when you fetch that molecule, and show that it contains all of the edges of your original graph, you have a proof of the three-colorability of the graph."

How did you get from being trained as a pure mathematician to doing real experiments with molecules?
"I was trained as a pure mathematician in symbolic dynamics. During my tenure track years, I was fascinated by a new paper that appeared in *Science* on using molecular biology to compute NP hard problems on graphs with DNA molecules. This paper focused on the Hamiltonian path problem. I then asked a colleague if they could explain the biology behind this, and we quickly decided that we could together also perform similar experiments for the road coloring problem. Unfortunately, this did not lead to our desired conclusion at that time, as the road coloring problem appeared to be much more difficult.

Still, this subject stayed in the back of my mind. Then I attended a conference talk by Nadrian Seeman, ~~about~~ a *Nature* paper by him reporting on forming a cube out of DNA. The fact that molecules could form an actual three-dimensional graph structure was fascinating to me. I then decided that I would like to work on these types of problems as well."

How did you teach yourself the biological background that you needed for this?
"It was a very steep learning curve. I spent a year in Ned's lab on a sabbatical to learn more about biology. He was very structural in his education on how to conduct experiments, and I followed this training as well. He assigned one of his PhD students to me, to make sure that I would not mess up any of the equipment.

After I made my first experimental design, he told me that I should first assemble the molecule myself by hand, using molecular building blocks. I spent a lot of time on building this molecule. When I finally showed it to him, he said 'This molecule hates itself', and quickly changed some of the building blocks to improve it. This made me realize how difficult it is to make a good sequence design, and how much I needed to learn. But after all of this, the improved molecule led to an experiment in which we represented a 3D graph by molecules. The paper we wrote was very well accepted, so then this learning curve paid off."

How could you convince your collaborators that mathematics can be useful to them?
"My first collaboration in this topic was with Ned. He was always open to all kinds of new ideas, so when I would approach him with some idea, he always encouraged me to investigate it. After our first collaboration, we collaborated for twenty more years. He recently passed away, and this is why I will also dedicate my talk at the NMC to him. But this first collaboration showed that the combination of mathematics and biology can be useful.

I think that I now understand biology from a mathematical perspective. I can use this approach for a careful and modular design of experiments. Biologists often collect large amounts of data, and would like to extract information from that. Still, if you want to know why or how something happened, you need to collect your data very carefully, otherwise this large amount of data still cannot give you the answer you are looking for. So in fact we often help to redesign the experiments, to obtain the right data that we need to answer these important questions."

What do you like most about your work?
"I really like learning new, fascinating science. There are always things that I had never thought of, and often my PhD students show me results that I had never imagined before. Recently, I started working on transcript RNA for example. As it turns out, it is still unclear what are all the types of interactions between DNA and transcript RNA during transcription, but we do know that they are extremely important. These interactions can for example help in double strand breaks of DNA repair. This is really a miracle: it would be similar to a mailman who also fixes all holes in the streets that they pass while delivering your mail.

I also enjoy going to conferences. They can give you creative, new research ideas. The very fact that I am now in this field of research is because I happened to attend a talk at a conference by Ned Seeman."

And what do you like least?
"I do not like applying for grants and funding. You spend a lot of time writing a proposal, and when it is not funded, this time was essentially wasted. Fortunately, I recently got some grants, which buys me some time until I have to apply for new ones."