



Phase Space Invaders' podcast episode with Tamar Schlick: a trajectory from mathematics to biology

Miłosz Wieczór^{1,2} · Tamar Schlick^{3,4,5,6}

Received: 3 January 2025 / Accepted: 10 January 2025

© International Union for Pure and Applied Biophysics (IUPAB) and Springer-Verlag GmbH Germany, part of Springer Nature 2025

Abstract

We present a transcript of the Phase Space Invaders podcast interview, with Tamar Schlick interviewed by Miłosz Wieczór. The conversation covers topics in computational biophysics and beyond: DNA and RNA research from genome organization to viral RNA frameshifting, transitioning from applied math to biology, developing algorithms and their utility in molecular dynamics and complex multiscale systems, the role of computers in biophysical research, writing reviews and books, collaborating in science, and using long-distance running as a template for building supportive communities.

Introduction: the Phase Space Invaders is born

Scientists are a rather traditional bunch. We write formal papers, present didactic scientific talks at conferences, and tend to mix very little with the public. But those who entered the field in the Internet era are increasingly active on social media, whether it is promoting and discussing their work or sharing broader thoughts about the scientific process.

So when MW decided to start a podcast series, he sought to provide a new forum for scientific interactions. He paired a cool name—the Phase Space Invaders—with a sassy

design, and worked out the technical details to deliver professional and engaging conversations to the growing crowd of podcast consumers (Fig. 1).

In 2024, during the podcast's first year, MW posted about two dozen discussions with scientists working on cutting-edge topics in computational biology and biophysics. In each conversation, the Phase Space Invaders podcast seeks to uncover the exciting, the serious, the overlooked, and the personal aspects of a biophysicist's journey. It tries to address the need for inspiring and integrating discussions across disciplines, to voice concerns and observations that do not fit into traditional formats, and to bring informed opinions and recommendations to newcomers in the field. In this vein, the podcast intends to be an educational resource for computational biophysicists at the graduate level, showcasing the diversity of problems, approaches, mindsets, past struggles, and future paths relevant to the community.

The idea of the podcast was born out of a feeling we all get when participating in the many hallway chats at small conferences: there is so much more to science than what gets published, and yet almost by definition, this experience is only available to a small group of people. At its core, science is a social endeavor, though it often does not feel like one from the lab bench or the computer desk. We get inspired by each others' stories and visions, but we often do not even hear them until many years into our careers. And there seems to be something deeply humanizing about hearing someone else's voice in its casual and unpolished form. It opens us up to bringing up topics otherwise considered “unacademic” and yet deeply meaningful to who we are as scientists. Many of us had great mentors who taught us the

✉ Miłosz Wieczór
miłosz.wieczor@irbbarcelona.org

- ¹ Molecular Modeling and Bioinformatics, Institute for Research in Biomedicine (IRB) Barcelona, 08028 Barcelona, Spain
- ² Department of Physical Chemistry, Gdansk University of Technology, 80-233 Gdańsk, Poland
- ³ Department of Chemistry, New York University, 100 Washington Square East, Silver Building, New York, NY 10003, USA
- ⁴ Courant Institute of Mathematical Sciences, New York University, 251 Mercer St., New York, NY 10012, USA
- ⁵ Simons Center for Computational Physical Chemistry, New York University, 24 Waverly Place, Silver Building, New York, NY 10003, USA
- ⁶ New York University-East China Normal University Center for Computational Chemistry, New York University Shanghai, Shanghai 200122, China



Fig. 1 Phase Space Invaders aims to inspire interdisciplinary work and foster collaboration across domains central to computational biophysics, with Tamar Schlick's scientific career being a prime example of such a barrier-defying mindset

realities of our respective fields, and it is inspiring to think how many young people could benefit from having these conversations accessible to them.

The interview below is a transcript of a podcast episode featuring Tamar Schlick, slightly edited for clarity. As stated in the podcast introduction by MW, Tamar is a Professor of Chemistry, Mathematics, and Computer Science at New York University, who brought countless contributions to computational biophysics from multiple directions: large-scale modeling of chromatin structure and function, development of algorithms for molecular dynamics, designing free energy methods in connection with enhanced sampling, and applying graph theory to understanding RNA function, most recently to viral frameshifting. Trained as an applied mathematician, she used her tenacious trans-disciplinary curiosity to work on the most fascinating questions of the past decades and, in the conversation below, explains both where her passion for biology came from and where it might take us if applied with integrity and scientific rigor.

The conversation

Miłosz Wieczór: Tamar, do you think there's a difference in how you perceive biomolecules compared to people with an explicit physics background?

Tamar Schlick: I think we all approach problems differently based on our training. Having a mathematics

background—both my first degree and Ph.D. degree were in applied math—gave me a really different perspective, not just to appreciate concepts in mathematics, but the way a mathematician thinks or approaches a problem. As an applied mathematician, you want to collect a lot of information, think deeply about a problem, but also approach it in a very practical way. We have a saying that “pure mathematicians solve ideal problems exactly, while applied mathematicians solve real problems approximately”. So the fun is in the approximation. In order to solve real problems, you have to make approximations, simplify a lot of issues, introduce parameters for inspection, but the key is to find the right variables that will really allow you to get to the heart of the problem in biophysics. So while coming at problems in biophysics from a math angle certainly gave me some disadvantages, such as not being as familiar with all the biology that people from that field knew by heart, at the same time it gave me a different perspective and a community of people familiar with the algorithms and the latest mathematical research. That was very advantageous when I started to work on algorithms. Fast forward to today, now our field of computational biophysics is highly multidisciplinary, and there are people from all fields, mathematics, computer science—certainly as AI becomes more prominent—and chemistry, biology, physics, and even bioengineering. I've had many postdocs that came from bioengineering and they were among the most resourceful in terms of developing methods and pursuing novel applications. So there's great synergy now, and I think it's very common to see computational biology labs with an amalgam of people from all kinds of backgrounds. That makes science more fun and, I think, more productive.

Miłosz Wieczór: Right. I think we still tend to think of those fields in a ladder-like way, or as “the tree of knowledge”—with mathematics as the foundation and other fields building on top of that. But here, the distance between mathematics and biology is quite sizable, and I have seen mathematicians making the complaint that in biology there are just so many empirical facts that one has to memorize—they would consider it so unpure. Have you ever dealt with such questions—how do I memorize so many accidental aspects of life on the molecular level, or why are the solutions so inelegant?

Tamar Schlick: Well, when I started my Ph.D. and wanted to develop a project, my advisor asked me: what would you like to work on?, and I said, I want to work on DNA. I've always been interested in it and I had just become fascinated by the simplicity and complexity in DNA, the hierarchical structure of DNA biology, with many levels of folding—from the simple, boring molecule that may appear in Bio 101 courses to epigenetic regulation, and chromatin-level effects in human disease. As I learned more about DNA, I thought that this was just a beautiful problem to work on—take DNA compaction, or how the DNA needs to

fit in a compartment that's many orders of magnitude smaller than the size of DNA when stretched out. Very relevant here are the mathematical fields of knotting and topology, and there are so many other exciting areas of mathematics that can be applied to this problem. So that's how I got started in the field: I learned everything that I could about DNA, not just from textbooks—textbooks and articles can only take you so far—but talking directly to my co-advisors, in the departments of biology, math, and computer science. And my advisor was very good at asking: who are the leading people in the field? Let's invite them for seminars at Courant Institute (the NYU Institute of Math). That's how we met Harold Scheraga and Martin Karplus, and later on, that got me to do my postdoc with Shneior Lifson at the Weizmann Institute in Israel. I remember Scheraga coming and telling us about the multiple minimum problem, and that was so fascinating to us. We brought in the computer scientists to Courant and I developed a fast truncated Newton method (Schlick and Overton 1987), which initially got me in the computational chemistry community.

So that's how I think a mathematician gets into the problems in biology. Once you get interested in a scientific problem, you go to conferences—I remember the Gordon Conference in Computational Chemistry was a great way to meet people working in the field in a very informal way, and I just asked tons of questions. Of course, I stayed in the field working on DNA, from modeling DNA to supercoiled DNA dynamics, which started later with Wilma Olson (Schlick and Olson 1992a, b), and then into chromatin and epigenetic control, which we're very focused on at this time.

Miłosz Wieczór: It's wonderful if we have this shared vocabulary with which we can translate biological problems straight into concepts that mathematicians recognize as problems they can work with. And these days, you now also include RNA in these big questions that fascinate you.

Tamar Schlick: Yes, and RNA has also provided a great opportunity for the application of mathematical tools. Already about 20 years ago we had this idea of applying graph theory to represent, enumerate, analyze, and classify RNAs (Gan et al. 2003, 2004). Other mathematicians started this in the 1970s, and biologists soon realized that RNA secondary structure could be represented as graphs, but it was mostly used to represent 2D structures (Waterman 1979). We wondered if we could go beyond representation and use graph enumeration, a result in graph theory, to enumerate the motif universe of RNAs (Fera et al. 2004). Imagine if we could do that for a protein; that is not possible because most proteins are globular. For RNA, however, you can actually enumerate the motif universe within a certain approximation, and learn many things, such as what fraction of that possible motif universe is indeed used by nature. That's how we developed the RNA-as-graphs, or RAG, approach (Gan et al. 2004). Later, it turned out that graph theory is very

useful not just to enumerate and describe these RNA structures, but also to analyze and design RNAs (Jain et al. 2018). This comes from clustering and other approaches that I don't want to go into in too much technical detail—that's all in our papers (Jain and Schlick 2017; Jain et al. 2020)—but just to highlight that this can be very useful when you're interested in specific RNAs. Now, when the pandemic hit, we had all these tools available. We had just been working on what we call *dual graphs*—ways to represent RNAs with pseudoknots, or intertwined base-paired segments (Jain et al. 2019, 2020). That turned out to be crucial for the frameshifting element of SARS-CoV-2, the RNA virus causing COVID-19 (Bhatt et al. 2021). With the support of a RAPID grant from the National Science Foundation, we launched this project (Schlick et al. 2021a) and we've been working on it for the past few years. It turns out to be a gold mine of opportunity for advancing the structural understanding of the mechanisms of frameshifting. We work with experimental collaborators on the mutants we proposed to interfere with the frameshifting mechanism, and they have indeed shown how effective our mutant designs are for nearly abolishing frameshifting (Schlick et al. 2021b; Yan et al. 2022, 2023; Yan and Schlick 2024). So I think this is a great way to advance viral RNA studies and open new therapeutic avenues.

Miłosz Wieczór: What would be the biggest strength of this approach—would you say it's in functional prediction, or maybe there's some necessary topology element that is evolutionarily preserved? What was the most surprising result to come out of this research so far?

Tamar Schlick: What is very intriguing about these frameshifting elements is that they're very small RNAs, but they have many folds, depending on the length of the molecule. So as you change the relevant length—the length of the mRNA transcript, depending on where the ribosome is coming along—these alternative folds appear. Biologists have known about them for some time, but their roles in the frameshifting mechanism are not well understood. From the experimental side, we have cryo-EM structures, we have X-ray crystal structures of the frameshifting element of SARS-CoV-2, but it's mostly been found to be in this one pseudoknot structure, specifically a 3–6 pseudoknot in our dual-graph notation. But it turns out that some chemical experiments that reveal dynamic secondary RNA structure, DMS and SHAPE, show a variety of conformations, and using our graph approaches for mutational design (Jain et al. 2020), it was very easy to design mutants. Our idea was (Schlick et al. 2021a, b): what if we change that pseudoknot to something else, for example eliminating the ability of this RNA to fold into multiple folds or, in other words, blocking conformational transitions? So we designed three particular mutants that would lock the frameshifting element in one particular fold, and our experimental collaborators did

the testing. They showed nearly abolished frameshifting for those mutants, and this is now a paper in the RNA journal (Dey et al. 2024). So I think we're beginning to understand that these conformational transitions are very important for frameshifting. Now, with RNA editing techniques, or perhaps small molecules that bind to RNA, this discovery could lead to new therapeutic avenues. The interesting thing about working on viral RNA is that we're going to the heart of the infection, as opposed to working with viral proteins, which are more downstream products, so if we could stop the virus from entering or replicating, that could go a long way. And, of course, it's not just SARS-CoV-2 that uses these frameshifting mechanisms: they're present in other coronaviruses, the flu virus, HIV, and many others, so this is a very important general mechanism, also relevant to some human genes (Penn et al. 2020). This is an exciting area, and I'm sure we will learn a lot more as we continue this exploration.

Miłosz Wieczór: That sounds beautiful. I think the conformational heterogeneity of RNA will keep us busy and employed for some time. And it's great to have new better tools to describe or approach that problem, right? It's such a fertile field to explore.

Tamar Schlick: Yes, and DNA doesn't cease to amaze us too, with both genome structure and function. And there are so many interesting areas to explore using models at different resolutions. So we've been working on a nucleosome resolution model—on the kilobase level—to understand the effect of epigenetic marks on the folding of the chromatin fiber, and its effect on higher-order folding (Arya and Schlick 2009; Bascom et al. 2019; Beard and Schlick 2001; Collepardo-Guevara and Schlick 2012; Grigoryev et al. 2016; Li and Schlick 2024; Portillo-Ledesma and Schlick 2024; Portillo-Ledesma et al. 2021, 2022, 2024). In parallel, many in the community are working on different levels of coarse-grained models, from the base pair resolution to nucleosome resolution all the way to higher-order polymer models (Dans et al. 2016; Huertas et al. 2022; Portillo-Ledesma et al. 2023). Together with a wealth of experimental data from Hi-C and other experiments, it is really creating exciting rich opportunities for collaboration and advances in understanding how this epigenetic control of genomes plays a role in human diseases. And so what suddenly emerges from something very theoretical and abstract is this multiscale image of chromatin fiber folding on many levels. If we add all these contacts with proteins and RNAs, we get an exciting, rich, and dynamic environment that we've only scratched the surface of.

Miłosz Wieczór: I absolutely agree. We also have this wonderful new data coming from cryo-electron tomography that starts to reveal the path that the chromatin fiber traces in the nucleus (Hou et al. 2023). It's going to be a huge challenge to integrate these insights into what we know about

chromatin structure, including, as you say, local variation under different conditions. That's going to be a gold mine.

Tamar Schlick: Yes, and this is where I think modeling comes with an advantage: in experiments, you can only explore one condition at a time. The nice thing about models is that once you have one that's verifiable and reliable, you can explore, say, different densities of linker histones or salt concentrations (Arya and Schlick 2009; Portillo-Ledesma et al. 2022). That turns out to be very useful for specific applications.

Miłosz Wieczór: And alluding to your past work on algorithms, do you think this new era of integrative/large-scale modeling will have its own challenges when it comes to developing new algorithms? Are the problems we're facing significantly different there?

Tamar Schlick: AI algorithms will clearly need a lot of statistical guidance in application, reliability, and so on. I think the history of algorithmic developments presents an interesting case study—early on, many thought algorithms would solve all the problems. I remember in the 1980s, when I started working on algorithms, a lot of mathematicians worked on the time step problem in molecular dynamics (Board et al. 1994; 1996). And a common belief was that these symplectic integrators—in other words, integrators with favorable energy-conserving properties—would just solve this time step problem. Of course that wasn't the case, even though lots of great papers came out and we learned a lot about resonance and mode coupling, and we proposed many approaches to mitigate some of these effects (Barth and Schlick 1998; Barth et al. 1997; Schlick et al. 1998). It turned out that this symplectic and effective leapfrog method that people were using, which is velocity Verlet, is really the way to go when combined with a small time step (Skeel et al. 1997). However, I think that while algorithms have a very, very important role to play in the advance of computational biophysics, what is really important is the computation. That is, I think a lot of computation is what is going to help us solve real-life problems.

I remember in 1989 I read this editorial by John Maddox, who was the editor of *Nature*, and he said: "One of these days someone will begin a paper with, here's the Hamiltonian of a DNA molecule, and will then—after a little algebra—tell us how the stop codons work"... and so on (Maddox 1989). I remember writing about this quote, and I said: I don't think it's going to be a little algebra. I think it's going to be a lot of computation. Looking back at the progress in molecular dynamics, that's exactly what turned out to be really crucial: not fancy algorithms, but just a lot of computer time and taking small reliable steps repeatedly (1996). Of course, you have to do things right. Algorithms have to be reliable. But computer time has made a huge difference, and computational biologists have exploited computational resources extremely well. In my perspective articles, I have

these charts showing how the field of computational biology compares to progress in other fields, or the fastest computers available (Schlick and Portillo-Ledesma 2021; Schlick et al. 2011; Schlick et al. 2021c). And the landmark simulations in our field are always near the top. Because of that, I think we have put a great effort into utilizing the best available resources out there. Algorithms have had an important role to play in guiding us and certainly gave us a lot of ideas—from enhanced sampling to integration or resonance, then to long-range interactions, integrating, say, PME with multiple time step methods (Qian and Schlick 2002). But ultimately, lots of computation is really key to solving important real problems.

Miłosz Wieczór: Maybe this comes back to this concept of computational irreducibility? This is Stephen Wolfram’s favorite idea that often you cannot know the answer to a problem until you actually go through the steps, iterate, and see the outcome (Wolfram 1985). Perhaps we’re suffering from the same issue there. And here’s this promise of AI, which is saying: maybe there are workarounds and advanced pattern-finding will somehow alleviate this problem. But as you say, there will likely always be a limit where this is not the case.

Tamar Schlick: I think we’re definitely in the hype phase, or at peak expectation curve, of the AI era. It feels just like biomolecular modeling and simulations were in the late 1980s: they thought it will be the solution to everything, to drug design and biology, but it wasn’t. Later scientists worked diligently on developing improved force fields and enhanced sampling methods, work we were happy to contribute to in connection to DNA polymerase mechanisms (Radhakrishnan and Schlick 2004a, b, 2005). And yet there’s no doubt that AI will continue to make astounding progress, but I’m sure there will be more downs before we go up again with these methods. And there remains so much to explore. Large language models are beginning to help us understand certain problems, including RNA structure and transitions, so I think AI and all these algorithms will be very important when coupled with lots of computation and guidance. In this way, they might take us forward to solving important problems.

Miłosz Wieczór: I agree we need to keep our feet on the ground there. I personally go through the cycles of hype and doubt as well, from “Oh, every interesting problem is now solved and we will be left jobless” to “Oh no, actually none of these new methods works at all”. And probably the reality is somewhere in the middle.

Tamar Schlick: Because it feels like for every idea that you have, you can find that someone’s written a paper about it, right? And it sometimes makes you think: well, what can I contribute if these people have already done that, and with such a level of detail? How can you possibly approach it? But I think that there are always opportunities

for new perspectives. That’s why I like to work with undergraduates the most. They don’t know anything and they’re so open to new ideas that they will say, well, why aren’t you doing it this way?, referencing some little thing they heard in a class. It’s refreshing, and sometimes that’s what you need. So even though it’s easy to feel overwhelmed by what exists in the literature, when you really get to the heart of the problem, you will always find some niche where you can contribute something that is either unexplored or not done in a very good way.

Miłosz Wieczór: And there’s also truth to the fact that even genius ideas are relatively cheap. There are so many genius ideas floating around but it’s often the *Sitzfleisch* or the act of sitting on an idea and perfecting it to some extent that actually matters.

Tamar Schlick: Yes. Ideas are very, very important in guiding us, but I think it’s even harder to execute them, and that’s where most of the work is. Yet still, without ideas, our field would go nowhere, so it’s always good to dream and to come up with new avenues for research. Ultimately, there’s lots of room for every new person who comes in and is intrigued by the problems in computational biophysics.

Miłosz Wieczór: Absolutely!, people are very welcome to come in and help.

To switch gears a little bit, I like to ask people who write a lot about writing. You had a book out, entitled “An Interdisciplinary Guide to Molecular Simulations” (Schlick 2010), and on top of that, you have written a lot of perspective articles (Li et al. 2023; Portillo-Ledesma et al. 2023; Schlick and Portillo-Ledesma 2021; Schlick et al. 2011; Schlick et al. 2021c). I also noticed in one of your commentaries that one of the major bits of advice for students was mastering good writing (Schlick 2020). How do you approach writing? What struck me was that your interdisciplinary guide was in fact very non-mathematical—in the sense that it didn’t contain a lot of maths compared to many other textbooks that would approach this subject. What is your recipe for good writing?

Tamar Schlick: I think I love writing because it helps me think and get my ideas down. I often talk to my students and they say, they love the science but they hate the writing part. And I respond to that: until you don’t start writing the paper, you won’t really think beyond just the results and the data. If you’re a good writer, you will find so much more to do once you put together the data. But I think it’s a little different with a textbook. Every new teacher wants to have the material available exactly for the course they want to teach and for the audience they have at their institution. When I started teaching molecular modeling, I had a very interdisciplinary audience—from math or computer science, who knew nothing about biology, to biologists and chemists who knew nothing about mathematics. That’s why my

goal in writing the book was just to get the mathematicians excited about biology. And when I entered the field, I knew the exciting thing was that problems were tangible. You could talk about nucleic acids or proteins, or the amino acid content and vitamins, that are actually relevant to nutrition. The folding problem is related to genetics and diseases, and proteins that make your body run. That's how I wanted to get those mathematics students excited upon entering the field.

But I also included very detailed chapters on time step methods, long-range interactions, PME and fast multiple methods, and the potentials—just the basics. I thought that it's very important for students to understand the basics. I know I myself had a hard time organizing that knowledge when I was starting out because the papers I read were so focused on the results, and not so much on introducing the basics. To give you my main answer, then, I think that good textbooks teach you how to think or how to approach problems. And I think I was very inspired by Gilbert Strang, who had a very informal way of writing his linear algebra books (2006), which is in turn my favorite math subject. It's not stuffing people with information, facts, results, theorems. It's teaching you how to think. Why are things important? How are things related? How do you approach problems? Strang is magnificent at doing that, and linear algebra is a beautiful field. It really teaches you how to think abstractly and connect vector spaces with practical things, and that's very useful in our field from simulations to optimization.

Miłosz Wieczór: If someone hasn't seen him, I definitely recommend Gilbert Strang's lectures available on YouTube to everyone who ever struggled with linear algebra, this is a great resource. I haven't read the books myself, but his style makes learning so easy.

Tamar Schlick: Yes, it's really good. But another problem with books today is they become obsolete so fast once you're done with them. However, while the material itself may be out of date, I think the approach and the way they teach you how to think is always important. It's also the fact of putting a stamp on the field—the early book by McCammon and Harvey on molecular dynamics (1987) was important in establishing that this is a field that's going to grow in its importance. That's why I think there should be more appreciation for perspectives and reviews that are very important in helping people, especially young people, enter a field.

Miłosz Wieczór: I agree that if we want to be an interdisciplinary field, we need to have some sort of grounding in the basics. I hope this very conversation facilitates or encourages some transitions between fields, or going deeper into other subfields. At the same time, now in this era where people from AI or statistics come into biology in large numbers, I'm often worried that we need more resources like that to prevent people from reinventing the wheel.

Tamar Schlick: Sure, people don't have to write another molecular mechanics program or invent integrators from scratch, there are good resources out there. It's also important that before you work on a problem, you do your homework and before you invest years in a project make sure this time is not going to be wasted. But even though you do the homework, sometimes it does happen that what you discover is perhaps not as successful as you'd hoped for, yet you still learn a lot. Nothing is wasted in research and training, and we learn even from negative results, maybe even especially from negative results. It always goes somewhere, and we never know when we may need to use what we've done. That's why I think the main point is to work on something you're really passionate about, and this way you can never be sorry.

Miłosz Wieczór: Back to the question of providing perspectives and integrating knowledge, do you think the incentive structure is there for people to provide those resources? Do you think the academic system rewards those efforts well, or is it something that you have to reward yourself for internally?

Tamar Schlick: I think that it's not as appreciated as it might be. For example, there are a lot of special volumes in Biophysical Journal, and we always invite perspectives. But while some scientists like to write them, and take them very seriously and write very comprehensive pieces (those in Biophysical Journal are relatively short, while Annual Reviews or Current Opinion have different formats), often you have to follow certain guidelines, for example only cover the past couple of years of papers, so you end up somewhat limited in what you can bring to the table. I think there should be more appreciation for these kinds of reviews, and maybe a different way to rate or highlight them. That's because I know I've learned a lot from writing them myself, that is, putting together lots of results from a certain subfield and analyzing them in a certain way, yet I don't know if they are as widely read as they could be. Maybe we simply need to do more advertising on social media. I'm not there, I don't use them for science, but I think younger people are good at promoting their papers now on social networks and that solves this problem.

Miłosz Wieczór: I definitely have the personal impression that research papers spread more rapidly on social media than perspectives. There are much fewer recommendation of "Oh, have you read this perspective on that topic?". Maybe we should indeed do this more, and have more high-level discussions about what things mean rather than just what came out of the simulation.

And while we're at higher-level conversations—you have just completed the New York Marathon. We had this discussion before whether scientists, especially computational scientists, are more into running, but I couldn't find any data on this! What got you into running in the first place? Was it

a reaction to something, like a sedentary lifestyle, or some internal need?

Tamar Schlick: Oh, how much time do we have? Because my husband jokes that runners love to talk about running. Of course as scientists we sit a lot in front of computers, at least I do. I have extra energy that I need to expend in other ways, and running is a great way to get out there and be with nature, either running solo or with a group, and just think about things. I remember when I started running, a few years ago, with Adidas Runners NYC—it's a global runner group with branches all over the world, including in New York, Berlin, Tel Aviv, Shanghai—and I would go to their community runs, and ask myself: why am I here? These people are so different from my background. People from all kinds of professions, ages, political beliefs, you name it. Then I started talking to these people and I found that we have one thing in common: we're all these type-A personalities with goals and challenges; we like to set goals for ourselves and develop training plans for how to get there, such as a half or full marathon. And I learned to really enjoy these communities and talking to people not just about running, but about other things too. When you're out there running in July at 5 am—that's when we start our 16-week fall marathon training, in the oppressive heat and humidity in New York, we are done with long runs before most people get up—that takes dedication! So I really appreciate it that my fellow runners and me are making this commitment, week after week, and then meeting our goals together. At the same time, these communities are really model communities: they learned about inclusivity, equity and diversity way before it became an issue. I remember when I started running, we would have these tempo runs where you had to push yourself through very speedy segments. One time I was struggling and the pacer would push me: "you can do it, you can do it, I will run with you!", and we did it together. And then at the end, all these runners would be there when you finish the workout and would say: "great job, great job". And I think we need more of that in science. Science is so competitive, even though we tend to hide it pretty well. We're competitive about papers, grants, awards, conference participation. We don't tell each other often enough: "Good job! Great job!". But in runner communities, you compete only with yourself, to make yourself a better runner and achieve your goal distances and times. You don't compete with other members of your community, and there's something very attractive about that. And finally, as someone who goes to a lot of conferences around the world, running is very easy. You can get up, all you basically need is good running shoes, and you go out there, you explore, and it's a great way to meet people and just be out there with nature, get a perspective. And then you come back with lots of energy, ready to sit down the whole day and listen to lectures.

Miłosz Wieczór: As you say, there's a sort of like-mindedness of a good kind. It's not necessarily having the same views, but having the same mindset. And you're right that we could probably appreciate this intrinsic motivation in others more and more in science and recognize it more often.

Tamar Schlick: In a way we do it for our students, but we don't do it enough at other levels of academia. And people need it at all career levels; we all are insecure somewhere deep inside. Today it's hard not to feel like we haven't done enough, as there's so much great science everywhere. But we need to be more appreciative of what each person brings to the table rather than combative or competitive.

Miłosz Wieczór: It's a great conclusion to come from a conversation about running. One would think that it's a very distant connection, but it's actually spot-on, thank you for bringing this up! And then, I guess, that should come from the communities we build as scientists.

Tamar Schlick: Here I just wanted to emphasize the importance of working with people you like and whose ways of thinking you understand. As I started to work with different experimentalists, I met different kinds of them, and I realized some experimentalists see computational people as: "we'll just tell them what we want done, they will do it, and bring it to us complete, right?". Those are people who just don't understand what computational biophysics is, and you can't work with this kind of people. But then there are experimentalists who are really broad-minded, and who will say to you: "let me understand how you approach it through modeling" to start a real iterative process—"Okay, so you're doing it this way. Why can't you introduce this interaction". Those are the people I work with. Not the former kind. Because that's not a collaboration, that's an exploitation. It's important that you can learn from them and they can learn from you. I once heard a great definition of a good collaboration: that both parties feel that they're exploiting the other.

Miłosz Wieczór: That's a great goal to aspire to. Hearing the other side and doing the homework to understand what they mean by that is important. And I agree that many experimentalists approach computational science as a sort of magic or black box, or maybe just a visualization tool: "can we have a figure that shows this mechanism", and that's it.

Tamar Schlick: But overall, I think this is a very exciting field for young people. There are so many great problems to work on, and one should not get discouraged by the vast amount of literature on everything and anything. Keep in mind there's more than AI to our field, and there's lots of room for new methods, innovations and applications. The main thing is always: find a great problem to work on.

Miłosz Wieczór: I agree, I think one thing that physicists and mathematicians are always surprised by is how easy it is to have a conversation about a piece of biology and to come to the conclusion that we actually don't know

this! Because in mathematics or physics, especially fundamental physics, there's almost always an explanation going back to the 1930s or earlier.

Tamar Schlick: One of the early things I learned about biology is that if you ask, is it A or is it B?, it's always both. So that's been a very important realization.

Miłosz Wieczór: Couldn't agree more. Tamar Schlick, Thank you so much for your insights and for the conversation.

Tamar Schlick: Thank you so much. It's really great that you're doing this podcast, a great service to our community.

Acknowledgements MW acknowledges that his work is funded as part of the BioExcel CoE (www.bioexcel.eu), a project funded by the European Union contracts H2020-INFRAEDI-02-2018-823830, H2020-EINFRA-2015-1-675728, and is grateful to BioExcel for supporting the promotion and dissemination of the podcast. The numerous messages of support coming from the community of listeners, as well as the commitment of time, thought, and support of all podcast guests in the early days of this initiative are also particularly appreciated. TS acknowledges that none of the research described here would be possible without many wonderful mentors, students, postdoctoral fellows, and collaborators. Similarly, crucial was consistent support from the NYU IT High Performance Computing (HPC) group and interdisciplinary research support from the National Institutes of Health (NIH) and the National Science Foundation (NSF). Current support to T.S. from the NIH MIRA R35-GM122562 and NCI-34-1905-2281-104 (latter to J. Sweasy), NSF awards 2151777 and 2330628 from the Division of Mathematical Sciences, and NSF Award 2337391 from the Molecular Cellular Biosciences Core Programs is gratefully acknowledged. Finally, we thank Zilong Li for his help in preparing the figure.

Author contributions M.W. and T.S. wrote, edited, and reviewed the main manuscript text.

Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

References

- Arya G, Schlick T (2009) A tale of tails: how histone tails mediate chromatin compaction in different salt and linker histone environments. *J Phys Chem A* 113:4045–4059. <https://doi.org/10.1021/jp810375d>
- Barth E, Schlick T (1998) Overcoming stability limitations in biomolecular dynamics. I. Combining force splitting via extrapolation with Langevin dynamics in LN. *J Chem Phys* 109:1617–1632. <https://doi.org/10.1063/1.476736>
- Barth E, Mandziuk M, Schlick T (1997) A separating framework for increasing the timestep in molecular dynamics. *Comput Simul Biomol Syst* 97–121. https://doi.org/10.1007/978-94-017-1120-3_3
- Bascom GD, Myers CG, Schlick T (2019) Mesoscale modeling reveals formation of an epigenetically driven HOXC gene hub. *Proc Natl Acad Sci U S A* 116:4955–4962. <https://doi.org/10.1073/PNAS.1816424116>
- Beard DA, Schlick T (2001) Computational modeling predicts the structure and dynamics of chromatin fiber. *Structure* 9:105–114. [https://doi.org/10.1016/S0969-2126\(01\)00572-X](https://doi.org/10.1016/S0969-2126(01)00572-X)
- Bhatt PR et al (2021) Structural basis of ribosomal frameshifting during translation of the SARS-CoV-2 RNA genome. *Science* 1979(372):1306–1313. <https://doi.org/10.1126/science.abf3546>
- Board JA, Kalé LV, Schulten K, Skeel RD, Schlick T (1994) Modeling biomolecules: larger scales, longer durations. *IEEE Comput Sci Eng* 1:19–30. <https://doi.org/10.1109/99.338771>
- Collepardo-Guevara R, Schlick T (2012) Crucial role of dynamic linker histone binding and divalent ions for DNA accessibility and gene regulation revealed by mesoscale modeling of oligonucleosomes. *Nucleic Acids Res* 40:8803–8817. <https://doi.org/10.1093/nar/gks600>
- Dans PD, Walther J, Gómez H, Orozco M (2016) Multiscale simulation of DNA. *Curr Opin Struct Biol* 37:29–45. <https://doi.org/10.1016/J.SBI.2015.11.011>
- Dey A, Yan S, Schlick T, Laederach A (2024) Abolished frameshifting for predicted structure-stabilizing SARS-CoV-2 mutants: implications to alternative conformations and their statistical structural analyses. *RNA* 30:1437–1450. <https://doi.org/10.1261/rna.080035.124>
- Fera D et al (2004) RAG: RNA-As-graphs web resource. *BMC Bioinformatics* 5:1–9. <https://doi.org/10.1186/1471-2105-5-88>
- Gan HH, Pasquali S, Schlick T (2003) Exploring the repertoire of RNA secondary motifs using graph theory; implications for RNA design. *Nucleic Acids Res* 31:2926–2943. <https://doi.org/10.1093/nar/gkg365>
- Gan HH et al (2004) RAG: RNA-As-Graphs database—concepts, analysis, and features. *Bioinformatics* 20:1285–1291. <https://doi.org/10.1093/bioinformatics/bth084>
- Grigoryev SA et al (2016) Hierarchical looping of zigzag nucleosome chains in metaphase chromosomes. *Proc Natl Acad Sci U S A* 113:1238–1243. <https://doi.org/10.1073/PNAS.1518280113>
- Hou Z, Nightingale F, Zhu Y, MacGregor-Chatwin C, Zhang P (2023) Structure of native chromatin fibres revealed by Cryo-ET in situ. *Nat Commun* 14:6324. <https://doi.org/10.1038/s41467-023-42072-1>
- Huertas J, Woods EJ, Collepardo-Guevara R (2022) Multiscale modelling of chromatin organisation: resolving nucleosomes at near-atomic resolution inside genes. *Curr Opin Cell Biol* 75:102067. <https://doi.org/10.1016/J.CEB.2022.02.001>
- Jain S, Schlick T (2017) F-RAG: generating atomic coordinates from RNA graphs by fragment assembly. *J Mol Biol* 429:3587–3605. <https://doi.org/10.1016/J.JMB.2017.09.017>
- Jain S, Laederach A, Ramos SBV, Schlick T (2018) A pipeline for computational design of novel RNA-like topologies. *Nucleic Acids Res* 46:7040–7051. <https://doi.org/10.1093/nar/gky524>
- Jain S, Sajū S, Petingi L, Schlick T (2019) An extended dual graph library and partitioning algorithm applicable to pseudoknotted RNA structures. *Methods* 162–163:74–84. <https://doi.org/10.1016/J.YMETH.2019.03.022>
- Jain S, Tao Y, Schlick T (2020) Inverse folding with RNA-As-graphs produces a large pool of candidate sequences with target topologies. *J Struct Biol* 209:107438. <https://doi.org/10.1016/J.JSB.2019.107438>
- Li Z, Schlick T (2024) Hi-BDiSCO: folding 3D mesoscale genome structures from Hi-C data using Brownian dynamics. *Nucleic Acids Res* 52:583–599. <https://doi.org/10.1093/nar/gkad1121>
- Li Z, Portillo-Ledesma S, Schlick T (2023) Techniques for and challenges in reconstructing 3D genome structures from 2D chromosome conformation capture data. *Curr Opin Cell Biol* 83:102209. <https://doi.org/10.1016/j.ceb.2023.102209>

- Maddox J (1989) Towards the calculation of DNA. *Nature* 339:577–577. <https://doi.org/10.1038/339577a0>
- McCammon JA, Harvey SC (1987) Dynamics of proteins and nucleic acids. (Cambridge University Press). <https://doi.org/10.1017/CBO9781139167864>
- Penn WD, Harrington HR, Schlebach JP, Mukhopadhyay S (2020) Regulators of viral frameshifting: more than RNA influences translation events. *Annu Rev Virol* 7:219. <https://doi.org/10.1146/ANNUREV-VIROLOGY-012120-101548>
- Portillo-Ledesma S, Schlick T (2024) Regulation of chromatin architecture by protein binding: insights from molecular modeling. *Biophys Rev* 16:331–343. <https://doi.org/10.1007/S12551-024-01195-5>
- Portillo-Ledesma S et al (2021) Nucleosome clutches are regulated by chromatin internal parameters. *J Mol Biol* 433:166701. <https://doi.org/10.1016/J.JMB.2020.11.001>
- Portillo-Ledesma S, Wagley M, Schlick T (2022) Chromatin transitions triggered by LH density as epigenetic regulators of the genome. *Nucleic Acids Res* 50:10328–10342. <https://doi.org/10.1093/NAR/GKAC757>
- Portillo-Ledesma S, Li Z, Schlick T (2023) Genome modeling: from chromatin fibers to genes. *Curr Opin Struct Biol* 78:102506. <https://doi.org/10.1016/j.sbi.2022.102506>
- Portillo-Ledesma S, Chung S, Hoffman J, Schlick T (2024) Regulation of chromatin architecture by transcription factor binding. *Elife* 13. <https://doi.org/10.7554/ELIFE.91320>
- Qian X, Schlick T (2002) Efficient multiple-time-step integrators with distance-based force splitting for particle-mesh-Ewald molecular dynamics simulations. *J Chem Phys* 116:5971–5983. <https://doi.org/10.1063/1.1458542>
- Radhakrishnan R, Schlick T (2004a) Orchestration of cooperative events in DNA synthesis and repair mechanism unraveled by transition path sampling of DNA polymerase β 's closing. *Proc Natl Acad Sci U S A* 101:5970–5975. <https://doi.org/10.1073/PNAS.0308585101>
- Radhakrishnan R, Schlick T (2004b) Biomolecular free energy profiles by a shooting/umbrella sampling protocol, “BOLAS.” *J Chem Phys* 121:2436–2444. <https://doi.org/10.1063/1.1766014>
- Radhakrishnan R, Schlick T (2005) Fidelity discrimination in DNA polymerase β : differing closing profiles for a mismatched (G:A) versus matched (G:C) base pair. *J Am Chem Soc* 127:13245–13252. <https://doi.org/10.1021/JA052623O>
- Schlick T (1996) Pursuing Laplace's vision on modern computers. 219–247. https://doi.org/10.1007/978-1-4612-4066-2_13
- Schlick T (2010) Molecular modeling and simulation: an interdisciplinary guide, vol 21. Springer New York, New York. <https://doi.org/10.1007/978-1-4419-6351-2>
- Schlick T (2020) Eight suggestions for future leaders of science and technology. *Biophysicist* 1:1–5. <https://doi.org/10.35459/tbp.2019.000123>
- Schlick T, Olson WK (1992a) Trefoil knotting revealed by molecular dynamics simulations of supercoiled DNA. *Science* 197(257):1110–1115. <https://doi.org/10.1126/science.257.5073.1110>
- Schlick T, Olson WK (1992b) Supercoiled DNA energetics and dynamics by computer simulation. *J Mol Biol* 223:1089–1119. [https://doi.org/10.1016/0022-2836\(92\)90263-J](https://doi.org/10.1016/0022-2836(92)90263-J)
- Schlick T, Overton M (1987) A powerful truncated Newton method for potential energy minimization. *J Comput Chem* 8:1025–1039. <https://doi.org/10.1002/jcc.540080711>
- Schlick T, Portillo-Ledesma S (2021) Biomolecular modeling thrives in the age of technology. *Nat Comput Sci* 1(5):321–331. <https://doi.org/10.1038/s43588-021-00060-9>
- Schlick T, Mandziuk M, Skeel RD, Srinivas K (1998) Nonlinear resonance artifacts in molecular dynamics simulations. *J Comput Phys* 140:1–29. <https://doi.org/10.1006/jcph.1998.5879>
- Schlick T, Colleparado-Guevara R, Halvorsen LA, Jung S, Xiao X (2011) Biomolecular modeling and simulation: a field coming of age. *Q Rev Biophys* 44:191–228. <https://doi.org/10.1017/S0033583510000284>
- Schlick T, Zhu Q, Jain S, Yan S (2021a) Structure-altering mutations of the SARS-CoV-2 frameshifting RNA element. *Biophys J* 120:1040–1053. <https://doi.org/10.1016/J.BPJ.2020.10.012>
- Schlick T et al (2021b) To knot or not to knot: multiple conformations of the SARS-CoV-2 frameshifting RNA element. *J Am Chem Soc* 143:11404–11422. <https://doi.org/10.1021/jacs.1c03003>
- Schlick T et al (2021c) Biomolecular modeling and simulation: a prospering multidisciplinary field. *Annu Rev Biophys* 50:267–301. <https://doi.org/10.1146/annurev-biophys-091720-102019>
- Skeel RD, Zhang G, Schlick T (1997) A family of symplectic integrators: stability, accuracy, and molecular dynamics applications. *SIAM J Sci Comput* 18:203–222. <https://doi.org/10.1137/S1064827595282350>
- Strang G (2006) *Linear algebra and its applications*. (Cengage Learning)
- Waterman MS (1979) Combinatorics of RNA hairpins and cloverleaves. *Stud Appl Math* 60:91–98. <https://doi.org/10.1002/SAPM197960291>
- Wolfram S (1985) Undecidability and intractability in theoretical physics. *Phys Rev Lett* 54:735–738. <https://doi.org/10.1103/PhysRevLett.54.735>
- Yan S, Zhu Q, Jain S, Schlick T (2022) Length-dependent motions of SARS-CoV-2 frameshifting RNA pseudoknot and alternative conformations suggest avenues for frameshifting suppression. *Nat Commun* 13:1–13. <https://doi.org/10.1038/s41467-022-31353-w>
- Yan S, Zhu Q, Hohl J, Dong A, Schlick T (2023) Evolution of coronavirus frameshifting elements: competing stem networks explain conservation and variability. *Proc Natl Acad Sci USA* 120:e2221324120. <https://doi.org/10.1073/pnas.2221324120>
- Yan S, Schlick T (2024) Heterogeneous and multiple conformational transition pathways between pseudo-knots of the SARS-CoV-2 frameshift element. *Proc Natl Acad Sci USA* In press

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.