Naturalists

BIOSPHERE

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PC: Geeth Sameer

Editorial

"Nothing in science has any value to society if it is not communicated."
-Anne Roe, 1925

Very few other words spoken may dare claim to be truer. Indeed, communicating science and its inner workings is as important as attempting to understand and develop it. We at the editorial panel solemnly latch onto the faith that our unending passion for and fascination of this living world and its mysterious ways are best channelised in our endeavours to share it with an equally enthusiastic audience. Having said thus, Naturalists, behold the third issue of Biosphere, a manifestation of our attempt to present to you fragments of the enchanting world of biology and the community engaged in its study. Join us as we restage the origin of life as we know it, sneak a peek at the history and invaluable contributions of the Central Animal Facility, review our understanding of condensates as drivers of organisation and draw some insights about research in the life sciences from conversations with a theoretical biologist and a UG alumnus. Unfurl your sails and set forth with us on this expedition to understand and appreciate the natural world a wee bit more. We hope you have as enjoyable an experience in flipping through these pages as we did in producing them!

Manya Ganapathy
Editor

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"Whence Comest Thou?" Or The State Of Investigations Unto The Origins Of Life

- Parth Kalani

In 1859, Darwin published his crowning work 'On the Origin of Species'.
[1]As the theory of evolution grew bigger, all our questions about how each 'species' originated had answers - except for one, the first one. If bipeds came from quadrupeds, quadrupeds from animals that crawled, crawling animals from animals that swam, and these from unicellular organisms, and those from their archaic predecessors and so on and so on, where did it all start? How did the first living thing appear?

Owing to an unfortunate absence of magicians, time-travellers and aliens, we were forced to place our bets on abiogenesis – the creation of life from un- life, from non-living matter. Presented here is a very short (and by no means exhaustive) account of the various possibilities that have been considered, the various conclusions they've led us to, and the questions that have remained.

It all started in 1953, with the popular Miller-Urey experiments[2] that demonstrated the possibility of production of amino acids from the simplest of inorganic substrates and a lot of doors flung open. In 1961, Joan Oro[3] synthesized the nucleobases adenine and guanine using only simple inorganic molecules like HCN and ammonia, likely to be found in a reducing atmosphere. Formamide, a chemical produced by the reaction of water and HCN, can in fact be shown to give rise to all four of the nucleobases![4–6]

The '60s and '70s were marked by multiple researchers analysing meteorites and finding nucleobases aboard, a popular example being the Murchison meteorite, discovered in 1969. As of 2022, all five nucleobases along with multiple sugars and amino acids were known to be found in extraterrestrial material.[7] Thus, there is no doubt that nucleobases and sugars, at least, could befound on Earth, at least in some pockets. Even then, they are nucleobases, sugars, amino acids- they do not qualify as life.

What is life? This question is quite interesting and deserves separate consideration, but here we take a shortcut. NASA defines life as 'self-sustaining chemical system capable of Darwinian evolution'.[8] Thus, for us to say, 'we know now for sure that life can come into existence from non-living matter', we must say, 'We can show that there is a system of non-living matter which can be auto-arranged in prebiotic conditions and is able to replicate itself.'

We know now that our most beloved nucleobases can most certainly come into existence in prebiotic conditions, so can basic amino acids and sugars, but they don't replicate. Replication is reserved for nucleic acids, mostly DNA but sometimes RNA as well (owing to the actions of the RNA-dependent RNA polymerase) but neither of them replicate without proteins, and no proteins were known to exist without having been synthesized through code from an RNA. RNA, translation machinery and the appropriate code for protein synthesis couldn't possibly have evolved at once. It's now a chicken-and-egg problem. What came first, the code or the protein?

In 1982, Thomas Cech and Sidney Altman's laboratories independently discovered the solution to this puzzle, the ribozyme- an RNA that functions as an enzyme.[9, 10] In coming years, developments in *in vitro* evolution enabled us to figure out more and more and more ribozymes, eventually leading to a ribozyme that catalysed the activity of the RNA-dependent RNA polymerisation in 2001.[11] In 2009, the self-sustained replication of an RNA enzyme was demonstrated *in vitro*. RNA assumed the centre of this debate.[12]

This story alludes to the 'RNA World' hypothesis. Broadly, the hypothesis states that RNA preceded both DNA and proteins, i.e., life could exist with RNA.[11] If you look closely, we've skipped quite a few steps here. At best, production of nucleobases has been demonstrated in prebiotic conditions. At the very least, we need an elaborate chain of nucleotides and then an environment where they may stay, 'sustain' to form a functional 'living being'. This is the hard part.

It has been suggested that polymers *like* RNA actually preceded it (since their formation is more plausible in prebiotic conditions) and eventually incorporated more and more of RNA due to Darwinian selection.[13, 14] Multiple routes for the synthesis of RNA monomers have also been devised through elaborate experimentation.[15-18] Following the same spirit, multiple routes for the polymerization of said monomers have also been devised.[19-21]

This is something that's still going on, methods and routes are always showing up. However, seeing that much isn't certain beyond this, we present the reader with a small proposed 'timeline'[11] and divert attention to another matter of importance- even if RNA *can* replicate, how are they co-evolving with proteins and other such biomolecules, and how even do they stay stable while doing that?

Contemporary biology to the rescue again, the answer must be in membranes.

TABLE 1. Proposed timeline of events during the OoL

Stage	Order	Suborder	Potential event
Pre-RNA World	1	A	Pre-RNA monomer formation
		B	Ribonucleotide formation
		C	Deoxyribonucleotide formation
		D	Lipid formation
		E	Amino acid formation
	2	A	Montmorillonite polymerization
		B	Eutectic ice polymerization
		C	Fatty acid vesicle formation
	3	A	Fatty acid vesicle growth and division
		B	Pre-RNA hybrid polymers
		C	RNA/pre-RNA hybrid polymers

Modern cell-membranes are made from phospholipids that naturally form bilayers when in water. Phospholipids weren't there on prebiotic Earth, and thus there must have been other amphiphilic molecules that would have taken this work up. Amphiphilic fatty acids must have formed the first few vesicles that ended up incorporating phospholipids later for stability. RNA must have first been compartmentalized through these vesicles and that's how it would've begun.[22]

Through a very beautiful series of experiments, it is now established that vesicles do undergo Darwinian evolution, that they often spontaneously split into two, and that they can form what is called a 'hypercycle'- a positive feedback composed of two mutual catalysts represented by a membrane site and a specific compound trapped in the vesicle. Such site/compound pairs are transmissible to the daughter vesicles, leading to the emergence of distinct lineages of vesicles, subject to natural selection.

Lo and behold, life!

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Determined - A Science of Life Without Free Will

A Small Meditation on Robert Sapolsky's Revolutionary Magnum Opus

- Parth Kalani

The year is 1932- Sixteen years since the First World War and eight years to the Second. Arjun stands alone in the stark centre of Kurukshsetra, unable to fight his brethren and wanting to flee the battlefield once and for all. "What decision is correct? Which path, righteous?" he asks the Lord. Albert Einstein recorded a speech that year, on requests and by order of The German League of Human Rights, titled 'My Credo'. 'Credo' comes from the more popular word creed- a statement of faith, a set of fundamental beliefs.

"All actions are performed by the modes of material nature. The deluded self thinks, 'I am the doer'", Krishna said unto Parth. Einstein's 'Credo' expressed a similar idea. Paraphrasing Arthur Schopenhauer, he said, "Man can do what he wills; but he cannot will what he wills." This question, of whether humans choose to do things, or are forced to do them by the natural laws of causality, has been, historically, a very significant factor in building civilization, so much so that it can be seen as the primary cause of thousands of years of warfare on the lands of China alone.

This question is what neuroendocrinologist Robert Sapolsky boldly endeavours to answer through science in his book *Determined: A Science of Life Without Free Will*. Step by step, very slowly and smoothly, he explains his argument for the inexistence of free will, in a style very reminiscent of Darwin, who eased the reader into natural selection by first explaining the more familiar arena of artificial dog breeding programs. The book starts off with a very simple reading of Biology. You find more or less surface-level discussions on neuroscience, endocrinology, behavioural evolution, etc., but the beauty of the book is in the sheer connectedness of it all.

You pick up a pen to write. Why? The muscles and tendons in your wrist and fingers stretched or contracted in a precise order and manner such that the thumb opposed the index and the pen got pushed against gravity by friction. But why did your muscles do that? Your neurons ordered it to. Electrical impulses generated by neurons in your primary motor cortex travelled all the way through your corticospinal tract to excite them. But why did these neurons do that? They were ordered to do so by the basal ganglia, along with signals from the cerebellum, premotor cortex, SMA, etc. But why did they do that? Because you wanted to pick up the pen, right?

Well, these neurons only fire when they receive signals. They received a signal to fire from the prefrontal cortex, a latest addition in animal brains responsible for decision-making. Well, okay, you used the prefrontal cortex to take the decision, so what? The decision should still be yours, right? Nope. If you were to take a closer look, you would realize that like all other neurons in your body, neurons in the prefrontal cortex also fire only when signaled (surprise!), and what signals the neurons of the prefrontal cortex? Input neurons! From your entire body! Temperature, hormone levels, blood pressure, dizziness – every piece of data the body has is taketo the PFC at some point, where it is considered and decisions are made accordingly.

So then, why write? Perhaps you received a text from an old friend and got so engulfed by the sheer dopamine that you had to write back immediately. Hormone sensors in the body took this info to the PFC as a signal. Perhaps electricity was out, you were dying of heat. Temperature sensors conveyed this to the PFC and it decided it was time to complaint to the Board in writing. "Well, okay, but what about the fact that I get happy when I receive messages from a friend? I do that, right? I make friends, and I keep them friendships", you would think, but no. Turns out, it is simply evolutionarily favourable to make friends.
Chemical friendships like these are just tactics of self-preservation – even bacteria have them.

"Let's say most friendships are like that, chemically motivated, but that does not rule out the possibility of genuine friendships, you know", I thought to myself when I was three chapters in. But, guess what? There is a glaring hole there. What do we mean by 'genuine'? Friendships that we choose to keep without chemical motives? Sadly, there are no mechanisms in the human body to take inputs from any entity except chemical ones. A 2011 study published in PNAS provided empirical evidence for the following statement: "Chances that a judge grants parole to a criminal are around 65% after a meal, and drop to almost 0% just before one." This is because hunger is sensed by the brain. This sensation goes to the insula, the part of the brain that tells you that you are annoyed. The insular signals reach the PFC and the judge feels so annoyed that he cancels the bail.

This is not a singular exceptional experiment. There are quite a lot like this. A whole body of research shows how the dorsolateral PFC actually takes decisions and fires signals much before you perceive your decision. At that point, did you really take the decision? Where exactly is you, anyway? There is no point in this well-oiled machinery where you could stop a chemical process, interject, and say "No, I am a good man, I must not kill." You are a product of physical forces going on since the Big Bang and it is just these physical forces that do whatever is done. You have evolved to be a social animal, you get dopamine when you get attention, your brain signals you to gauge attention whenever it wants dopamine.

Action causes reaction causes reaction causes reaction. There's no space for you. In this whole scheme of things, there is no atom whose configuration you decide. Things change outside your body, your sensors sense them, your brain reads that, it fires. In their totality, biophysics, biochemistry, neuroscience, endocrinology and lastly behavioural evolution dictate the working of your body. Which of these is you? Yes, none.

This is what Sapolsky establishes through a series of very, very interesting experiments performed throughout the last century. He then considers a good amount of arguments against this argument, and shows how they are all very, very bad (namely the 'butterfly effect' and the infamous *'quantum consciousness'*). And lo and behold, it is solved. *Naiva Kinchitkaromi.*

In case you're still in doubt about whether to read this book- this was just the first half! The second continues this argument even further and hypothesizes how society would function once we accept this non-existence of free will. This is the single most dreadful and interesting thing I have read all year.

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Physics and Biology – A Stable Marriage?

- Milan Vijay

"This process of 'model building', essentially that of discarding all but the essentials and focusing on a model simple enough to do the job but not too hard to see all the way through, is possibly the least understood – and often the most dangerous – of all the functions of a theoretical physicist."

Philip Anderson

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Building a toy model, as intuitive as it sounds, might get ridiculously confounding when you're trying to match the behaviour of a dynamical system. With all the complexities involved, modelling of biological systems faces the very same challenge. Recent advancements have allowed researchers to derive more information from such a system than ever before.

But what to do with all this data? How do we effectively use this data to construct better models? We will be discussing these questions and more with Dr Akshit Goyal, Simons Young Researcher and Ramanujan Fellow, at the International Centre for Theoretical Sciences (ICTS). Before joining ICTS as a Faculty Member, Akshit completed a B.Sc (H) in Physics at St. Stephen's College, UoD, then his PhD at the National Centre for Biological Sciences (NCBS), followed by a Postdoctoral Fellowship at the Massachusetts Institute of Technology (MIT), USA. Akshit's work is primarily focused on understanding the collective dynamics of evolving ecosystems using concepts from dynamical systems, nonequilibrium statistical physics, data assimilation and information theory.

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Can you give us a brief introduction of yourselves for the people who are not familiar with you?

My name is Akshit. I am a faculty member at the ICTS, which is the International Centre for Theoretical Sciences. I am a part of the Biological Physics unit here, which consists of a bunch of people with backgrounds in physics who try to understand different aspects of biology, including biomechanics, fluid dynamics, cell biology, neuroscience, etc. I am not associated with the above fields. I work more on the ecology and evolution side, and so primarily my interests are in understanding how large collections of species come together and have intriguing dynamics. Some of these dynamics are of the kind that allow a lot of species to coexist, which is what we can see in our daily lives. My other interest is in understanding how these species evolve in the milieu where multiple species coexist as part of an ecosystem. We address these questions by applying methods from theoretical physics and collaborating with experimentalists to obtain datasets from various kinds of ecosystems.

Lovely! You did your bachelor's in physics, so did you always plan on doing the kind of research that you do right now, which is broadly modelling and theoretical biology? Or was there some event that influenced you?

This answer will sound very similar to the ones people in theoretical biology give to the same question. In my undergrad days, I did not know about the existence of theoretical biology. I decided to pursue physics because of my interest in astronomy and astrophysics. When I asked people what I should study to pursue these interests, physics

was mentioned more often, and that was my choice for the bachelor's degree.

I did my first summer project at the NCRA (National Centre for Radio Astrophysics). Everything changed in my second year, when I was ready to continue working on problems in astronomy and astrophysics. Still, my professor encouraged me to try something completely different for one summer. He was the one who asked me to give biology a shot. I was confused about this suggestion in the beginning, especially since I had not studied biology since the 10th standard. Still, this professor was someone whom I respected, so I took his advice. That is what brought me to NCBS, to do a project under Prof. Sandeep Krishna, who later became my PhD advisor.

That really changed my mind about what research was like and what research could be like. Because that summer I was free to try lots of random things, and it felt like I was creating a video game of sorts when I was constructing these theoretical biology models. This is what made me explore the field of theoretical biology and continue doing research in it.

That's a really unique trajectory! Moving on, how do we get the intuition that maybe this mathematical or physical tool might help in solving this complex biological problem?

I believe that there is a lot of scope for creativity and out-of-the-box thinking precisely because it's not obvious when you look at something in biology and get an intuition that you could visualise this problem in terms of a mathematical or physical problem. Similarly, it is not obvious when you are learning a mathematical/ physical concept that it can be applied to a biological problem. This is something that makes this profession sort of fun because you learn these concepts independently, and the adventure is in making connections between the biological problem and the mathematical/ physical concepts. Once you spend enough time in the field, you do realise that there are problems in biology that do not have good models for understanding them, and you can think of some mathematical concept that can clearly be applied.

Yes, it is often not obvious, but if you look at history, some fundamental discoveries have come from merging or marrying two disciplines, like Einstein's work in gravitation, which is based on differential geometry. So, combining ideas from independent disciplines happens very often in scientific research, but it is obvious in the case of theoretical biology.

That was very insightful! Since we are on the topic of the complexity of biological problems, I have another question for you. Working with two species of microbes in a petri dish can lead to varying results and is often hard. Would there be a time when we can experimentally test the simulations that leading researchers perform to understand complex microbial ecosystems? Can we achieve this by exploiting developments in sequencing technologies and other advances?

You're right that it may prove to be difficult to manipulate even two species, especially if you're thinking about spatial organisation, growing the species together on the plate and keeping them happy is a challenging task from an experimental perspective. Given this, how can we extend this number from 2 to 200? I would like to make a few remarks about this.

People are already working or starting to work with communities that are highly diverse. This includes environmental samples; for instance, I have numerous collaborators who cultivate marine microbial communities or soil communities in labs, allowing them to grow and then isolate these species. For simple experiments like those in test tubes, these new methods should be sufficient, but the same might not apply for complex spatial studies. Experimentalists are currently trying to change some parameters in the microbe's environment, like temperature, nutrients and more, and study the results of it on the microbes. These results can also tell us about the dynamics of assembly in communities.

To make this possible, we need to make use of the advent of sequencing technologies. These sequencing technologies are not new per se, almost 10-15 years old or even more, but presently, they have become cheap enough to allow sequencing of many communities at once.

This is really what has changed in terms of the landscape of how sequencing technologies are utilised for understanding complex microbial systems.

The second thing that has changed is that now we can sequence at much greater depth with less error. We can also look at the evolutionary dynamics of communities by looking at mutations that arise and how the communities themselves are evolving.

These are essentially the major contributions that these sequencing technologies have made to the field's progress so far. Moreover, since the theories

we develop are statistical in nature, making predictions about any particular community is very challenging. So, we need the same kind of data, which is statistical in nature, to test these theories. You need an ensemble of different microbial communities to test anything.

Those are some very valuable inputs. Onto a more general and integral question in the field of mathematical modelling. Since there is no defined framework for addressing each and every problem, how do we get an intuition towards what parameters we should really consider and those which might be significant towards the question that we are asking?

Of course, this is a difficult question with no one-size-fits-all answer. Here are my takes on this.

One, when we make a model, we are not making it in abstraction; there will always be a purpose. For the same system, we can make very different models if we consider different purposes. So, the phenomenon you are considering as important while writing down the equations should depend on the phenomenon you're trying to address with the model for this system. For instance, when we consider the growth of a bacterial species, it might be very important to consider what nutrients are available and how these bacterial species take up the nutrients. These bacterial species will be subject to all sorts of forces and surface tension from other bacteria surrounding them. While these forces are also important in nature, it might not be so relevant if your goal is to explain the rate at which bacterial collectives grow. When this is your goal and your system is well-mixed, these forces can be neglected while making the model. On the other hand, if your bacteria are on a rigid surface like an agar plate, where they're far away from food and the only way to obtain the food is to push and pull at each other, a model that describes the growth of collectives should also include these forces.

Over time, you can gain a lot of experience and that kind of teaches you a lot about what will ultimately be the most important and least important factors when it comes to a particular system and purpose. It is sort of building an internal library about all the models you've built and all the approaches you've considered and what eventually worked out for the model.

Two, it also depends on the aesthetics, but as a physicist or as scientists in general and reductionists, we always find it aesthetically pleasing when something simple produces something complicated. So, we always kind of try to err on the side of the simplest possible model that is sufficient to explain the phenomena that we're interested in.

I'm definitely keeping these in mind, especially the second point. Now, onto the last question for this session. For someone who is interested in the idea of understanding biology or biological systems from a theoretical and mathematical perspective, are there any key resources that could be kept in mind? Are there any key papers or books that helped you, especially in the initial phases where you were just getting started in the field?

I have a completely opposite perspective on this. I believe theoretical biology is one of the rare disciplines in science where the best way to get a feeling for it and to get started is to just do something. And this is opposed to a lot of other fields of physics, where you would often need to read books, papers, and learn a lot of things to get started and get a feeling for what it is like to do something new and interesting and research-worthy. You can actually get started in theoretical biology tomorrow because there are thousands of problems out there. You can pick up any decent set of papers or talk to anyone doing theoretical biology, and they will present you with 10 or more problems. Further, you can read a few things about these problems and come up with ideas that should be tried. So, it's very simple and easy for you to get started on your own.

My strong recommendation to any student out there who wants to get started in theoretical biology is not to get stuck in the trap of reading. I think reading sort of paralyses and doing sort of catalyses. I feel that in theoretical biology, you should read after you do something. Because in the process, you get to know what your system is doing, how it's behaving, and then you try maybe something else. So, only after you do something should you read what other people have done. This can help you understand whether what you've done fits into already established models. This is what I did in my first summer project, so maybe that's why I'm biased, but I just played with some model of something, and I had a lot of fun doing it, and it was only after that that I started reading about the classic understanding of these kinds of phenomena. What I found was that a lot of the things that people were talking about in the literature, I had kind of already realised myself by playing around with the model for just a month or two. So again, a lot of these things are accessible. They're a lot of fun because they're creative.

What I often find is that students read first and that paralyzes them because it sets them into one

perspective or one framework of doing something and this is not the field where it's so rigid that all the frameworks are decided for you. You stand to make the biggest impact by actually not thinking like the way everyone thinks. If you think the way everyone thinks, you might become completely replaceable. But if you think about the problem from a different perspective, that's when you're going to be valuable and that's also when you're going to have fun because you're going to have your own take on thinking about something.

The more you know, you might also become burdened by facts. And those facts, again, paralyze you because they give you the feeling that we as a species understand all these things. But the fact is that we don't understand almost anything really, especially in biology. Many students think this is a bad thing. Especially, a lot of students in physics think that biology is bad because we don't understand anything. But I would say, if you were a researcher, this is a goldmine. If we don't understand anything now, we stand to understand so much. Also, when you're studying physics now, you would wish that you were born in the 1800s so that you could have discovered all these things. From the perspective of biology, we are in the 1800s. If you really feel like you should have been born at some other point where something new was happening and we were in the midst of not knowing anything about a set of things about the world around us, then biology is really like that.

So, my advice to people would be to read about problems, talk to people about problems but you should try and do something on your own. Even if it is wrong, even if it is simple, even if it is silly, I think it will give you a lot of confidence and a lot of intuition and you will never get that intuition from years of reading.

Lovely! You've given us a lot of intriguing points to think about. It has been a pleasure to discuss a wide range of topics and get answers for our questions, even if some might have been trivial, from a person who does active research and remains engaged in the field of theoretical biology. Thank you for this conversation!

ACKNOWLEDGEMENTS

Big thanks to Akshit for sharing his story. I also thank Fisher's Fishes for their contributions in this collaborative effort and for giving me the primary motivation to write this article. I thank the Naturalists convenors and the newsletter editor for their continuous support and patience in the writing process.

Curiosity and Cravings - IISc UGs catapulting to their future

- Shouvik Datta

Alan Varghese is a 5th year PhD candidate at NYU School of Medicine working on the labs of Prof Dan Littman and Prof Evgeny Nudler. He works at the intersection of metabolism and immunology. The first part of his PhD work on how restriction of amino acid cysteine drive rapid weight loss was just published (https://doi.org/10.1038/s41586-025-08996-y)

He was formerly an undergrad at IISc, finishing his BS in 2020 in Biology. He was a Khorana Scholar and worked primarily in Prof Dipankar Nandi's lab on multicellular behavior by Salmonella describing how and why Salmonella form a novel string like multi-cellular structure (https://doi.org/10.3389/fmicb.2020.613704).

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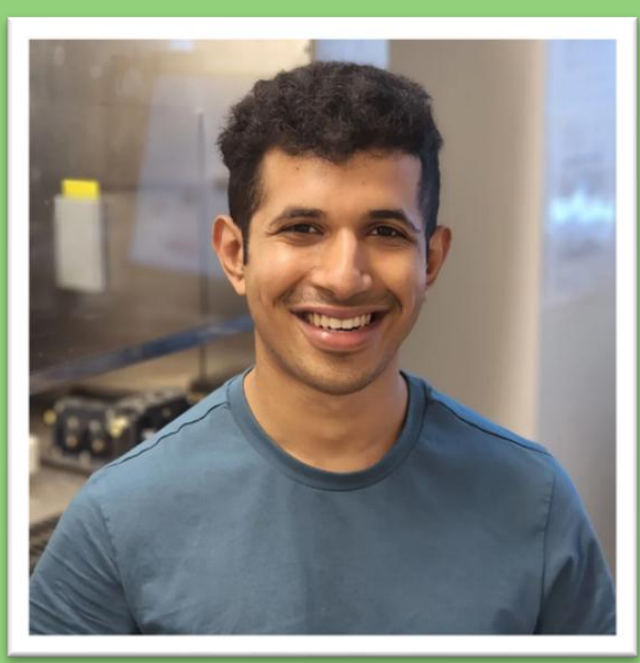
Could you give us a brief walkthrough of your academic life until now?

I like to start from late high school. When I was a kid, all I wanted to do was math. I used to look for patterns and try to find new formulae, and I spent most of my time doing math. By 11th standard, I knew that I wanted to go to IISc for my bachelor's degree, but at that point I was still more interested in math.

I wrote KVPY but did not qualify for the interview, and that was the point where I started questioning whether I should even do science. Still, math was my first love, so I decided to continue with it. That year, I qualified for RMO and wrote INMO, hoping to get into the math camp. However, I managed to solve only two out of six questions, while the cutoff was around two and a half or three, so I missed it. I was very disappointed.

At that time, I was still making a lot of immature decisions. Nobody in my family was really into science, so I did not have much guidance. I assumed that if I could not ace INMO, my math skills were not good enough to be a mathematician. In hindsight, that was a flawed assumption, but I did not know better then. Since I was reasonably good at chemistry, I switched focus and decided to try KVPY SX again. Since I did well in chemistry, I cleared SX the following year.

Around the same time, I also developed an interest in biology. I wrote both chemistry and biology Olympiads and cleared the first level in both. When I reached the second level, I realized that biology could actually be logical and reasoning-based. High school biology often focuses on memorization, but when I started reading Campbell Biology, I realized that biology could be approached using logic and problem-solving skills similar to math. That made me feel like I could actually be a decent biologist. When I cleared the second level of the Biology Olympiad, I felt confident enough to pursue biology further.



At that stage, I assumed that doing well in Olympiads would translate to doing well in a

scientific career, which I now know is not true. But at that time, I did not have enough information to think otherwise. Eventually, I joined IISc's UG program. When I arrived, I decided to pursue biology because that was where I seemed to perform best.

After joining IISc, I learnt about the Whitehead Fellowship at MIT, which allows you to start an independent lab right after your PhD. That became the first concrete "dream job" I had, even though there was no deep logic behind it. Once I decided that this was something I wanted, I realized that strong research output would be essential, so I began focusing heavily on research early on.

I completed all the compulsory coursework, but beyond that, I avoided taking very difficult courses unless they genuinely interested me. One of the toughest and most enjoyable courses I took was Game Theory by Prof. Narahari, a four-credit course that also involved a project. I worked on that project with Sharath K. Menon from my batch.

So, was that the one where you worked on developing a game theory model for quorum sensing?

Yes. It was a lot of fun because I was working on a bacterial system—specifically quorum sensing and multicellular behaviour in Salmonella. I was able to do experimental validation alongside the theoretical work, which made the project especially rewarding.

I did not try to take courses just because they were considered difficult. In biology, you often learn much more by actually doing experiments than by taking many courses. Courses that focus only on memorization, without teaching how to think, felt similar to high school biology and were not very useful. On the other hand, courses that involved reading and discussing classical papers were extremely valuable.

Some core courses were unavoidable, but for non-core courses, I avoided those that mainly required memorizing facts that would be forgotten after a semester. If a course was hard, I took it only if it genuinely excited me and taught me how to think. Otherwise, I preferred to focus more on research, especially in biomedicine.

From the end of my first semester, I was primarily focused on research—first with Prof. Raghavendra Gadagkar and Prof. S. P. Arun, then with Prof. Dipankar Nandi. During COVID, I spent seven months in the US, returned to complete my thesis, and graduated in 2020.

During my PhD, coursework has been minimal, and the focus has been almost entirely on research. In biology, people do not judge you based on GPA as much as on your publications. If you have strong papers, that is what matters. I have already published one major paper during my PhD, which is technically sufficient to graduate, but I plan to stay longer to better prepare for an independent fellowship position.

I am just curious, what eligibility is required for the position?

Since it is an independent fellowship where you essentially run your own lab, strong publications are crucial. Having a high-impact paper helps a lot but having more than one significantly improves your chances because it shows that your success was not just due to luck. That is why I want to wait and try to publish one more paper before applying.

So, you graduated in 2020, which was peak COVID-19. What was that period like?

I was still taking courses when COVID began around March. As cases started appearing in India, some of my friends and I stocked up on groceries, expecting a lockdown. Instead, we were suddenly asked to leave campus. There was no graduation ceremony or farewell—we were simply sent home.

After a two-month break, we resumed courses online and finished them by June or July. By then, I had already been admitted to a PhD program, but all embassies were shut, so I could not apply for a visa. I did not want to spend an extra year in India, especially since I already knew I wanted to work with my PhD advisors.

Thankfully, embassies reopened in September, and I was able to secure an appointment and join the program in January. I convinced the program to let me attend classes online initially, even though they were scheduled at New York time, which meant staying up late.

COVID was very difficult emotionally. What I missed the most was the IISc campus and the fact that we never got to say a proper goodbye. Most of my close friends are now in the US, and we meet often, but the lack of closure with the campus still makes me sad.

Was deciding to join IISc also an instinctive decision, like the Whitehead Fellowship?

Yes, in a way. As a kid, I did not like the idea of engineering because I associated it with sitting in front of a computer all day, which my father and cousins did. I preferred being outdoors, which is a very silly reason in hindsight.

I also did not want to be a doctor, even though my family encouraged it. So I made a deal with myself: if I got into IISc, I would join; if not, I would go to medical school. I was confident I could get into a good medical college in Kerala.

I remember reading about the IISc UG program in The Hindu and thinking that it would be an amazing place to do science, with access to resources and opportunities. I was a very curious child—I explored nature, dissected small animals, observed plants, and asked questions constantly. Once I realized that biology suited me best, pursuing science felt like the natural choice.

So how did you move across such different research areas?

I find science interesting in general, and I do not believe you need to restrict yourself too early. Often, when I started working on something, it led me in an unexpected direction. Over time, I learned to let the science guide me and focus on doing my best wherever it led.

Some projects were driven by curiosity, while others happened accidentally. For instance, while working on a gene function project in Prof. Nandi's lab, I stumbled upon an unusual multicellular behaviour in Salmonella. Since nobody understood it, I took it up as a challenge.

Later, during my PhD, my background in microbiology led me into host–pathogen and host–microbiota interactions, which eventually evolved into a metabolism-focused project. Throughout this process, talking to people, attending conferences, and learning continuously helped me adapt.

I believe it is beneficial to train in diverse areas. If someone works on the same problem for too long without progress, thinking from a different perspective can help. My immunology lab, for example, has postdocs from many different backgrounds, and it is a very successful lab. Many of the strongest applicants are not trained in immunology initially.

As an undergraduate, it is not necessary to lock yourself into one topic early. Exploration is important.

As a UG senior, what misconceptions did you have about PhD life?

Because I worked extensively in Prof. Nandi's lab, I was already treated somewhat like a PhD student, which helped prepare me. However, one misconception I had was that all PhD students in the US would be exceptionally strong academically. That turned out not to be true. Only a subset are outstanding, which is not very different from anywhere else.

Another realization was that IISc students are often better equipped to handle rigorous coursework. IISc does not have strong global name recognition, but the training is excellent. Many of my IISc classmates were stronger than several PhD students I encountered abroad, which was surprising at first.

Living abroad also comes with challenges—handling everything yourself, following strict visa rules, and being far from family. At the same time, you earn more and can travel extensively, which I enjoy. Once you reach a good graduate school, you can relax a bit and start enjoying the outcome of your hard work.

What would you say you learnt in a broader perspective from your life at IISc, or as you mentioned, the internship and the topics that you worked on?

The first and most important thing I learnt at IISc was something Prof. S.P. Arun taught me: you have to be the harshest critic of your own ideas and hypotheses. You have to actively try to disprove your own hypothesis. Many times, you may be able to convince reviewers or even your advisors to some extent, but you cannot fool yourself away from the truth.

You need to try your best to figure out whether what you are saying is actually true and keep attempting to disprove it. Often, your advisor may not be able to tell you exactly what is wrong, but you should be able to see that the small things you are doing can be the reason for what you observe. If changing small details leads to changes in phenotype, you are the best person to recognise that—not your advisor or a reviewer.

Another important lesson, largely from Prof. Nandi, was the importance of having clear and simple experiments to answer questions. However, publishing is a different challenge. You have to present your work as a story that people can easily read and follow. Looking at your project and asking whether there is a clear narrative helps you understand whether you need to work more or clarify your direction.

One of the most important lessons Prof. Nandi taught me—something most PIs do not explicitly teach—is the importance of soft skills. As biologists, we often work in large groups and rely heavily on core facilities. Being able to get along with people, understand what they expect, and communicate effectively matters a lot. If people enjoy working with you, they are much more likely to help you. While this may sound utilitarian, I genuinely feel it is about being a good person. A happy work environment makes things easier, and people naturally want to help those who are respectful and considerate.

Phrasing is extremely important, especially when asking for something difficult, whether in person or over email. Even very strong people are sensitive. There are right and wrong ways to say things. Thinking carefully about how you communicate is a soft skill that becomes more important with experience.

So, like many of the PhDs, as a general outlook that we have—maybe in India especially—frustration is something that comes to mind. If you ever faced it in your five years until now, how were you able to bypass it?

Frustration does come at some point, and I definitely experienced it. One of the biggest moments of frustration was after a paper was essentially finished and we were about to submit it. In biology, the last author is the corresponding author, and I had two advisors. Since I designed the project myself, the responsibility of deciding who would be the last author was placed on me.

That was extremely difficult. One of the advisors told me directly that being the last author was very important for their career and grant renewals, which was a valid concern. At the same time, I felt the other advisor may have contributed more scientifically. Trying to make a decision that would keep both of them satisfied was far more stressful than finishing the project itself. It took nearly two weeks to figure out how to make one person the last author while ensuring the other was still comfortable with the decision. Both ended up as co-corresponding authors, but the last position still mattered.

There were also many frustrations arising from factors outside my control. In biology, you rely heavily on other people—animal facilities, reagent delivery, and shared resources. I have had instances where months of experiments were destroyed because of mistakes made by others.

For example, the special diet I was using for my mice were taken out and misplaced. I searched everywhere and was initially told they had been thrown away, even though they were unexpired. My mice would not survive the weekend without additional food, so I had to stop the experiment prematurely. Later, I received an email saying the diets had just been placed in another room. Situations like this are extremely frustrating.

There are also times when you do everything right and the experiment still fails.

One summer, we were waiting months for this batch of C. elegans strains to arrive in India. Due to a change in the transport route, they were exposed to excessive heat, and none survived. We had to start the experiment again from scratch.

These experiences are frustrating, but they are also part of research. You rely on other people and on luck, and sometimes things fail despite your best efforts.

So in your line of research right now, what do you think are the frontiers or uncharted areas that have not yet been explored?

From my current project, there are two major uncharted directions. The first concerns what happens during low CoA levels in an adult organism. How is CoA redistributed during starvation? Is it degraded or redistributed across tissues? Why does this redistribution occur, and how does it change when weight is regained?

This is particularly relevant now because of drugs like Ozempic, using which people lose weight rapidly due to reduced food intake. When weight is regained, fat often accumulates in unhealthy locations, which disrupts physiology. Understanding how CoA redistribution changes during weight regain is an important and previously unexplored question, and we now have the tools to study it.

The second uncharted area is behavioural. In our experiments, mice continue to reduce their food intake even as they lose weight. They could compensate by eating more and generating glucose or fat, but they choose not to. This behaviour

resembles aspects of anorexia, where individuals continue to avoid food despite being underweight.

This appears to be a regulated behavioural state rather than something they can simply snap out of. Understanding how this happens is still an open question, and we are currently developing neuroscience tools to investigate it. Studying how feeding behaviour is regulated could have implications for understanding anorexia, while studying CoA metabolism addresses a fundamental question in biology.

There are videos online showing "a day in the life" of different researchers. So what is a day in the life of an American PhD scholar like?

Every day is very different. You usually have flexibility in when you start your day, as long as it is reasonable. I typically work from around 9:30 or 10 in the morning until about 9:30 or 10 at night, with breaks for meals. On weekends, I work about four to five hours each day.

That said, there are days when I work much less and take time off to see a movie or travel. It depends on the day and what I want to do. Mentoring is also a big part of PhD life. In the summer, I work with high school students, and during the semester, I supervise undergraduates. My experience mentoring others at IISc helped prepare me for this role.

So what are your future plans, both for your PhD thesis and after that?

For my PhD thesis, I want to apply for the Whitehead Fellowship, which is an independent research fellowship. Ideally, I would like to publish one more paper before applying. I am also hoping to incorporate immunology into my thesis work. If that does not happen, my current project will likely form the core of my thesis.

If I do not get the fellowship, I will likely consider industry. I do not plan too far ahead, but I have spoken to enough people that I could transition quickly if needed.

As a closing question, what are some of the best memories you have from IISc, both academically and outside academics?

Some of my best memories involve spending time with classmates—playing badminton, biking around campus, going out to eat, and just hanging out together. The first three semesters were especially difficult, and we went through those hardships together. I think strong friendships are often forged during difficult times.

Academically, the courses were extremely stimulating and taught me resilience. Looking back, the difficulty of those courses made later research challenges feel more manageable. IISc was not easy, but it gave me lasting friendships, strong memories, and a solid foundation as a researcher.

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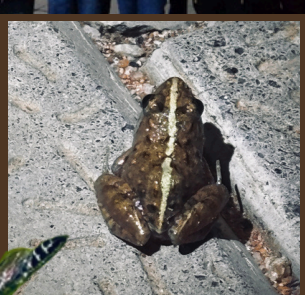
Into the Grasslands -
Memories of Challakere

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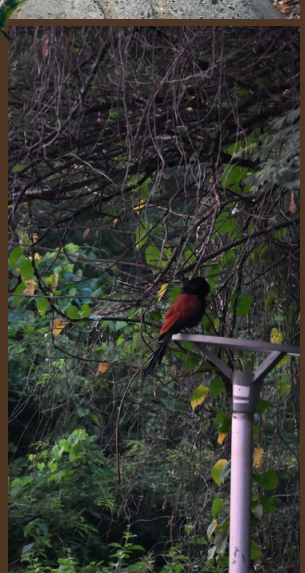



A scuffle with separation - A sneak peek into the phenomenon of LLPS

- Suvam Saswat Das

At the end of a stretch of long and exhausting days, you keep your purified protein safe on your workbench, go catch a sweet sleep, and reach lab early next morning, all excited to carry out those in vitro assays you had planned oh so long ago. But alas, fate has other plans in store for you. The solution of your protein, which was transparent the previous night, has now turned all turbid and milky-white in colour. Your protein, purified and quantified, is no longer usable for your experiments, and days of effort lay in vain. But do let me break unto you the faint silver lining of this dark cloud. Your protein is still normal and the change in the colour of its solution is actually an indication that the protein is functional. Weird, isn't it? This strange behaviour of your protein sample may be attributed to, for want of some technical jargon, the process of liquid-liquid phase separation. Let's dive in a little deeper to understand what transformed your protein.

Liquid –liquid phase separation may be described as a de-mixing process, whereby certain components of a homogenous solution separate out, resulting in a dense phase that is enriched for these components and a dilute phase that is depleted of them. In a cellular environment, this process leads to the formation of membrane-less compartments referred to as biomolecular condensates. Proteins form important constituents of several of these condensates along with nucleic acids, particularly RNA. A thermodynamic perspective reveals how certain types of proteins and RNA could contribute to condensate assembly. A de-mixing process proceeds with decreasing entropy and thus must be accompanied by a release of enthalpy to ensure a negative free energy and thus, spontaneity of the forward reaction. The negative enthalpy of phase separation is achieved by increased interactions of protein and RNA molecules with one another within the dense phase. These bindings may be between molecules of the same or different kind. In case of different molecules participating in phase separation, different compositions can yield different physical properties. A simple example is that of the Cacio e Pepe sauce, where different amounts of pasta water, cheese, starch, etc. can lead to different textures of sauce owing to different phase separating propensities, and a specific composition is necessary to make a perfect sauce like one made by an Italian Nonna. Biologically speaking, a large diversity of condensates differing in composition and biophysical properties may be formed, each having their own function and independent regulation. This variety is reflected in several classes of eukaryotic cells where condensates take the form of stress granules, P-bodies, P-granules, nuclear speckles, Cajal bodies and a collection of others.

Certain proteins alone, such as the one you painstakingly purified, possess the ability to undergo phase separation independently in a cellular environment. The ability and tendency of a protein to form condensates in solution depends both on its intrinsic properties and on extrinsic environmental variables. Several well characterised phase-separating proteins are endowed with the ability to form multiple multivalent interactions with one another. Each of these interactions are independently weak but the large number of such interactions established results in a highly negative enthalpy of phase separation. The types of interactions in the dense phase that contribute to condensate assembly include coulombic interactions, pi-cation interactions and pi-pi stacking interactions between peptide bonds and the side chains of amino acids. As a result, the propensity of a protein to undergo phase-separation may be predicted, to some extent, from its sequence. Notably, proteins with low complexity sequences- sequences that over-represent certain amino acids at the expense of others- and multiple charged residues are well known to be constituents of cellular condensates. Another class of proteins with a high propensity for phase separation is that of the intrinsically disordered proteins (IDPs). These proteins are defined by their inability to take up fixed structures in solution and thus often fluctuate

between different structural forms. Proteins may be identified as being intrinsically disordered or bearing intrinsically disordered regions (IDRs) based on amino acid compositions that are highly skewed in favour of charged and polar residues, with an underrepresentation of hydrophobic groups. Development of tools for prediction of these proteins has led to the revelation that nearly 33% of eukaryotic proteins bear intrinsically disordered regions. The amino acid composition of IDRs allows proteins that possess them to establish multivalent interactions with one another, thus contributing to phase separation.

Apart from properties embedded in the sequence and structure of proteins, environmental variables also influence phase-separation. Some of these extrinsic effectors include concentration of the protein, pH of the solvent, ionic strength of the buffer and temperature of the protein solution. Characterisation of how these factors affect condensation is crucial particularly when optimising protocols for purification of proteins with a high tendency to undergo phase separation. The effect of environmental variables on the assembly and disassembly of condensates also provides insights into their regulation in biological systems during both homeostasis, and departure from it.

Given the wide variety of factors that contribute to phase-separation and condensate formation, it is only natural that the process can be subjected to dysregulation by undesirable changes in any of the aforementioned variables. This dysregulation, that may arise due to mutations in the protein and subsequent changes in amino acid composition, mislocalisation and consequent shift in protein environment, and changes in local protein concentration, cellular pH and ionic strength in response to an unfavourable external environment, forms the basis of several disorders including neurodegenerative diseases, cancer and signalling aberrations. Many of these diseases are characterised by the conversion of liquid-like dynamic condensates into solid-like protein aggregates that are often immune to cellular clearance mechanisms. These liquid-to-solid transitions (LSTs) often impair essential condensate functions and, in certain conditions, also lead to toxic gain of function phenotypes, such as aberrant oncogenic transcription and toxic protein aggregation.

Owing to its widespread implications in prevalent medical conditions, condensate biology is gaining tremendous attention from researchers working in the fields of biochemistry, biophysics and medicine. The hope for discovery and design of therapeutic interventions against condensate driven disorders has sparked exceptional interest in the study of mechanisms and regulation of protein phase separation. Several labs worldwide are working endlessly towards realising the full potential of this knowledge in remedying pressing medical challenges. So, when faced with a turbid, colloidal solution of purified, phase-separated proteins, know that you are witnessing a phenomenon with grave clinical implications in the lives of many, and may that add more meaning to your work and fuel your motivation as you power through another round of purifying your phase-separating protein.

Knowing Your Priorities: Lessons from Stressed Cells

-Manya Ganapathy

During their lifetimes, cells are bound to encounter various types of environmental stresses. These could take the form of oxidative stress, nutrient deprivation, viral infections, metal ion toxicity and osmotic stress among others. To overcome such unfavourable conditions, it is necessary for cells to mount a suitable response that aids in both conservation of energy and ensures survival in situations of stress. Evolution has thus led to the selection of a response that achieves both these goals – the differential regulation of protein translation.

Translation of mRNA into proteins is an energy and resource-intensive process. Differential regulation of this process in conditions of stress is characterised by a near global downregulation of protein synthesis while ensuring the translation of select mRNAs, the products of which contribute to cell survival amidst adverse environmental conditions. Cells, both eukaryotic and prokaryotic, employ a fascinating variety of clever mechanisms to ensure such differential regulation during periods of stress.

Under normal circumstances, the primary mechanism of translation in a eukaryotic cell is the cap-dependent translation that relies upon binding of the 7-methyl guanosine cap at the 5' end of mRNA by the cap-binding protein, eIF4E. In the face of certain types of stresses, however, eIF4E protein is sequestered by eIF4E binding protein (eIF4EBP). This sequestration is regulated by the mammalian Target of Rapamycin Complex 1 (mTORC1) which, unlike under normal circumstances, fails to phosphorylate and reduce the affinity of eIF4EBP for eIF4E in conditions of stress. This reduced availability of free eIF4E results in lowered levels of cap-dependent translation. In this background, synthesis of proteins with pro-survival functions is ensured by cap-independent translation of select mRNAs. Very often, these mRNAs are characterised by the presences of secondary structures in their 5' untranslated regions (UTRs) known as internal ribosome entry sites (IRES) that act as ribosome landing pads for recruitment of ribosomes without the need of a cap binding protein.

Another mechanism for downregulation of translation in eukaryotic cells involves the phosphorylation of a translation initiation factor, eIF2, by one of several stress sensor kinases. eIF2 functions to form a ternary complex with the initiator tRNA (itRNA) and GTP, which is then recruited to the 40S ribosomal subunit, before the recruitment of the combined complex (known as the 43S pre-initiation complex) onto the mRNA. Phosphorylation of eIF2 reduces the level of recycling of the bound GTP after its hydrolysis, thereby lowering the level of available ternary complexes and thus, translation of transcripts. This condition, however, upregulates the synthesis of certain proteins, the translation of which, under normal conditions, is suppressed by upstream open reading frames (uORFs). An example of such a protein is the activated transcription factor 4 (ATF4) that functions to regulate genes involved in autophagy, mTOR regulation, metabolic enzymes and redox homeostasis. The ATF4 transcript consists of two ORFs upstream of the main ORF that codes for ATF4. Ribosomal scanning from the 5' end of the transcript causes the first uORF to be translated. At the end of this uORF, the ribosomes, instead of releasing the mRNA, reinitiate translation at the second uORF by recruitment of a new ternary complex. The translation of this second uORF inhibits the translation of the main ORF as these two ORFs are overlapping and not in frame. During stress, however, the lowered availability of the ternary complex leads to its delayed recruitment, thus favouring translation reinitiation at the downstream main ORF instead of at the second uORF, allowing for increased ATF4 translation during stress.

An additional mechanism for such translational regulation makes use of differential abundance of codons and tRNAs in conditions of normalcy and stress. In yeast, recent studies have shown that while transcripts coding for growth proteins use common codons, those encoding stress response proteins have a greater proportion of rare codons. Correspondingly, during stress, it has been found that the tRNA population is skewed towards greater abundance of tRNA for rare codons as compared to common codons. This allows for greater efficiency of translation of mRNA coding for stress-response genes in adverse conditions.

Ribosomal heterogeneity is another mechanism that is exploited to ensure translation of selective mRNAs during stress. Ribosomal heterogeneity refers to the variation among ribosomes brought about by differential modification of ribosomal proteins or ribosomal RNAs constituting the ribosomal machinery. Different ribosomal variants are known to exhibit differences in efficiency of translation of different mRNA transcripts. This feature allows for the selective mRNA transcription based on available ribosomes. An example of this mechanism has been very well characterized in prokaryotic systems. Translation in these primitive systems is initiated by recognition of a particular Shine-Dalgarno (SD) sequence at the 5' UTR of mRNA by a complementary anti Shine-Dalgarno (aSD) sequence near the 3' end of the 16S rRNA component of the small ribosomal subunit. In conditions of stress, bacteria activate a MazEF toxin-antitoxin system. This system is comprised of an endonuclease toxin MazF that is, under normal circumstances, neutralised by the antitoxin, MazE. Cleavage of MazE in conditions of stress, however, lead to the endonucleolytic cleavage by free MazF of certain transcripts at a recognition sequence at their 5' ends, thus producing leaderless mRNA without SD sequences. MazF also leads to cleavage at the 3' end of 16S rRNA, increasing the abundance of ribosomes which lack the aSD and selectively translate leaderless mRNA. This leads to upregulation of translation of leaderless transcripts.

The mechanisms discussed thus far, and several others, are used by cells to prioritise their needs and selectively allocate limited energy and resources in periods of stress. Since diseases represent stress for cells, understanding these mechanisms gives us a better picture of disease pathology at the cellular level, thereby aiding in studies aimed at developing diagnostics and therapeutics. The potential roles of translational elongation and termination factors, modifications of mRNA, tRNA and ribosomal proteins and other such factors in selective translation during stress are active areas of research that promise to reveal plenty other lessons from stressed cells.

The Biological Lego Set: Building Structures with Integrative Modeling

- Trishna Kodamasingh

Proteins are often called the cell' s workhorses, but they seldom act alone. Instead, they interact with other proteins, nucleic acids, and biomolecules to form large structures called macromolecular assemblies. These structures perform vital functions in the cell, such as DNA replication, gene regulation, cellular signalling, and immune responses. Understanding their three- dimensional organisation is essential for grasping how life operates at the molecular level and for developing treatments for diseases caused by their malfunctions.

Determining these assemblies' structures is a major challenge in structural biology. Techniques like X-ray crystallography, cryo- electron microscopy, and nuclear magnetic resonance (NMR) have greatly advanced our knowledge of biomolecular structures. However, they often only provide partial insights when studying large, dynamic complexes. No single method can capture the complete picture.

This is where the Integrative Modeling Platform (IMP) comes into play. IMP is a computational system that combines various sources of information to create three- dimensional models of macromolecular assemblies. Data from NMR, cross-linking mass spectrometry, cryo- EM, biochemical tests, and computational predictions can all be merged into one workflow. Instead of relying on a single dataset, IMP integrates multiple independent pieces of evidence to produce models that best fit all available data.

The platform generates thousands of possible structures and assesses how well each model aligns with the data. Models that meet the experimental constraints are kept, while others are discarded. As more data is added, the accuracy and reliability of these structures improve. This method allows scientists to study systems that are too large, flexible, or complex for traditional approaches.

Conventional modelling often depends on methods like Markov Chain Monte Carlo sampling or molecular dynamics simulations, which can be computationally intensive for large assemblies. Exploring the vast number of possible structures remains a significant hurdle.

To address this challenge, our IISc Software IGEM team employed Distance Restraint and Energy Assisted Modeling (DREAM) with a bottom-up strategy. Rather than modelling the entire assembly simultaneously, this approach begins by constructing smaller, well-defined regions using existing restraints. These substructures are then assembled into a full model, which decreases computational workload while preserving accuracy. The use of parallelised model generation and refinement improves the scalability of integrative modelling, allowing the investigation of more complex biological systems.

As experimental data continue to grow richer and larger, frameworks like IMP are becoming vital tools in structural biology. By integrating information from multiple sources into cohesive structural models, they help scientists unravel the intricate molecular machinery that sustains life.

CAF — The Caffeine of Biological Research at IISc

-Aditya Kamath Ammembal

Animal experiments have long been integral to research at the Indian Institute of Science (IISc), playing a crucial role in advancing scientific understanding and therapeutic development. While in vitro systems like 2D and 3D tissue cultures offer valuable insights, they fall short of replicating the complexity of living organisms. To truly understand how therapeutic interventions will function in humans, in vivo testing remains essential. However, human trials are impractical and unethical due to our long lifespans and the ethical standards of modern research. Therefore, animal models such as mice and monkeys, which offer quicker and more feasible experimentation, have become indispensable. These models allow researchers to observe disease progression and therapeutic effects more effectively. At IISc, this work is made possible by the Central Animal Facility (CAF), a crucial asset to the institution's research infrastructure.

The history of animal experimentation at IISc dates back to 1951, when M. R. Sirsi, from the Department of Pharmacology, began using laboratory mice to study the use of chemotherapy for tuberculosis. By 1965, N. R. Moudgal, from the Department of Biochemistry, had established the Primate Research Lab (PRL) to study reproductive biology using bonnet macaques. By 1971, the institute was using both small animals, like rodents, and larger ones, such as goats and monkeys. The need for a dedicated animal facility led to the construction of the current facility, located in front of PRL, in 1990. A modern, state-of-the-art building is now being constructed adjacent to the existing one with the intention of further enhancing the scope of animal research at IISc.

CAF supports not only biological research but also interdisciplinary studies across engineering, chemistry and nanoscience. Over the last two decades, the number of animals used in research at IISc has surged from 336 to nearly 19,000, with the number of departments using them having increased from 4 to 20. Having a central facility like CAF, where animals are housed in a clean and controlled environment, is critical for maintaining high research standards.

CAF is responsible for providing genetically uniform animal models, ensuring consistency across experiments. For example, a strain of mice at CAF is likely to be genetically identical to the same strain found at top research institutions worldwide, such as Harvard. The facility has two units: the older one, established in 1971 to cater to academic and industrial needs, and the newer, 36,000-square-foot National Facility for Laboratory Animal Experimentation. The latter serves researchers at IISc, other institutions across India, and even private industries, while also establishing a Transgenic Core Facility for creating genetically modified mouse models and preserving valuable strains.

With rising awareness of animal ethics, strict regulations govern the use of animals in research. At IISc, all researchers must pass a rigorous Standard Operating Procedure (SOP) exam with a cutoff set at 90% before being allowed to work with animals. Trained veterinarians ensure humane treatment of animals, while the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), in conjunction with the Institutional Ethics Committee, reviews all projects every three to four months. These measures ensure that experiments on animals are conducted ethically while paving the way for those advances in research that cannot be achieved by in vitro models alone.

Cancer is getting on my nerves (literally!)

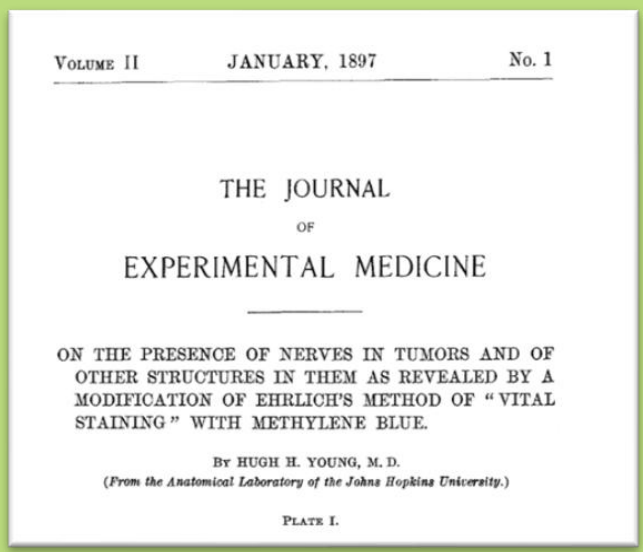
A sneak peek into cancer neuroscience

- Yukta Subramanian

Cancer has been a mind-boggling problem for clinicians and researchers. The more we study it, the more we realize its complexity. Occasionally, however, we come across revelations and ideas that fundamentally shift the way we view this disease. Take for example the somatic mutation theory or the discovery of cancer stem cells.

One such thread of investigations began in the 19th century. It was January 1897, and a young doctor named H.H. Young had set out to study tumours using the then-novel methylene blue staining procedure. Unlike in previous studies, which used other methods for cell visualisation, he could see bundles of nerve fibres creeping into many of his samples, almost half of them. This was something new! Unfortunately, Dr. Young couldn't pursue this work further. Most researchers paid little heed, assuming that since nerve innervation is found in almost all tissues, it is also naturally present in a tumour as a silent element surrounding the growing mass.

Almost a century later, a pathologist, Dr. Gustavo Ayala, regularly observed the growth of cancer cells around nerves in patients (medically referred to as perineural invasion) and learned that it correlated with an aggressive tumour and a lower probability of survival. He realized that no one knew *why* and *how* this happened. So, while awaiting his state medical license at Baylor College of Medicine, he decided to study it. He took a spinal nerve from a mouse and cultured it along with human prostate cancer cells in the same dish. And voila! Within 24 hours, neurons grew out long, thin filaments called neurites in the direction of the cancer cells. Cancer cells proliferated faster in the presence of these neurons. In fact, it is now established that denervating tumours leads to their shrinkage.



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ON THE PRESENCE OF NERVES IN TUMORS AND OF OTHER STRUCTURES IN THEM AS REVEALED BY A MODIFICATION OF EHRLICH'S METHOD OF "VITAL STAINING" WITH METHYLENE BLUE.

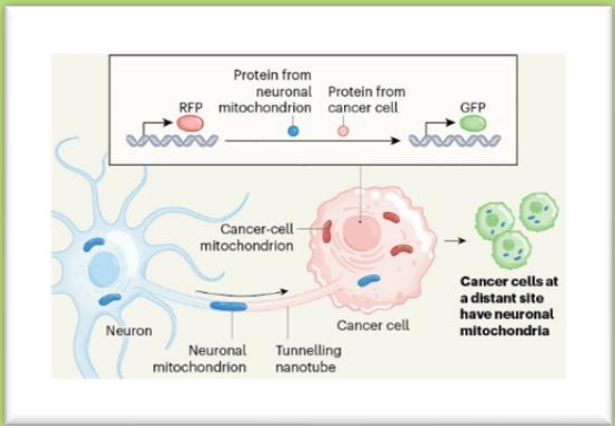
BY HUGH H. YOUNG, M. D.
(From the Anatomical Laboratory of the Johns Hopkins University.)

PLATE I.

PC: J Exp Med. H.H. Young's pioneering work on nerves in cancer.

More recent studies have proposed mechanisms for direct interaction between nerves and the tumour. Nerves not only promote the growth of cancer cells but also their spread to different parts of the body (called metastasis) by affecting either the properties of cancer cells or the surrounding milieu. For example, sympathetic nerves, which control the body's fight-or-flight response, can nudge immune cells called macrophages to digest tissue near tumours, thereby allowing cancer cells to invade against less resistance. Neurons can affect the state of the cancer cells, leaving them more prone to metastasize. A recent study published in *Nature* shows that nerves transfer their mitochondria, the cell's "powerhouses", to nearby cancer cells. Using a novel genetic tagging tool called MitoTRACER which labels only the cancer cells that receive neuronal mitochondria, the team observed these cell components moving across physical contacts (called the tunnelling nanotubes). The recipient cells showed higher mitochondrial respiration, better antioxidant balance, and greater

survival under the physical and oxidative stresses of metastasis.



PC: Nature. The transfer of organelles from neurons to tumour cells helps cancer spread. Hoover *et al.* used in vitro experiments and in vivo mouse models to examine whether energy-producing organelles called mitochondria are transferred from neurons to cancer cells. The authors developed a fluorescent labelling system called MitoTRACER that enabled them to identify and label tumour cells if neuronal mitochondria entered them.

These studies will eventually help us understand how the mind affects cancer progression; why chronic stress can negatively impact or a positive psychology may improve therapeutic outcomes. We may be able to repurpose bioelectric medicines and other neuromodulatory drugs that are FDA-approved for neurological diseases against cancer, taking us one step closer to fully understanding this truly nerve-racking problem.

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Further reading

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Condensing the chaos: How cells drive organisation.

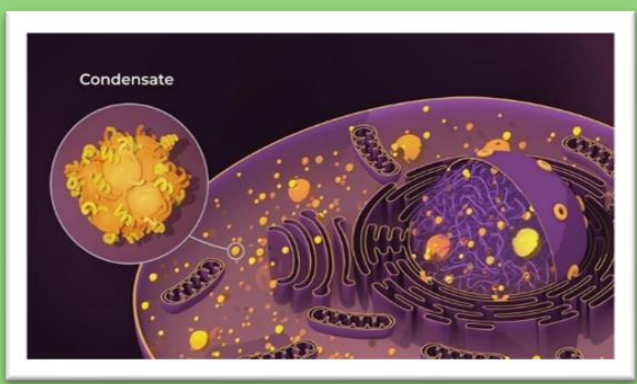
- Mayank Pandhari, Kedhar R Thyagarajan

Virtually every language has an equivalent of the phrase "looking for a needle in a haystack". Most Germanic languages use a direct translation of this phrase, pointing back to our agricultural roots, while South Koreans have a more contemporary take - "like finding Mr. Kim in Seoul". Locating minute entities in large spaces is a situation that we deal with often, and this is a problem across scales, from astronomists identifying stars through the radio waves they emanate, to protein molecules in cells finding their partners.

When one thinks of a cell, we generally imagine the insides to be a pool of floating molecules, often organized into membrane-bound compartments such as the nucleus. The cell, however, is a much more dynamic, dense and exciting environment, chalk full of millions (yes, millions) of large, varied proteins, nucleic acids and lipid molecules, bumping into each other constantly. However, this begs the question – in such a chaotic environment, how are the accurate and extremely specific reactions that are typical of cellular functioning carried out, while being regulated across space and time?

Over the last 15 years, we have made great strides towards answering this question, uncovering the various ways cells deal with this problem. Cells concentrate molecules in small, membrane-less structures known as condensates – little bubbles of biochemical reactions, suspended like olive oil in vinaigrette. They truly resemble liquid drops, being able to 'drip' off cellular surfaces and fuse with one another, thus giving the phenomenon the name 'liquid-liquid phase separation' - again reflecting how two immiscible liquids can separate themselves. These concentrated globules, however, can be precisely regulated by the cell, thus causing them to be assembled and dissolved as per their requirement.

The formation and regulation of these biomolecular condensates is the focus of Dr. Shovamayee Maharana's lab in the Department of Microbiology and Cell Biology, IISc. "Cells carry out thousands of biochemical reactions simultaneously; the ability of individual molecules to encounter their substrates and carry out these reactions in a hugely crowded and complex space has always been fascinating". The lab focuses on characterising the properties of molecules that allow them to form biomolecular condensates and explores their behaviour, especially in the context of cellular stress and inflammation. "Condensates allow cells to do pretty amazing things – recent research suggests that tardigrades may condense large parts of their cytoplasm in times when they need to endure harsh environmental conditions". Tardigrades are known to be able to survive in outer space without any protection. The fascinating biology of liquid-liquid phase separation and their manifestation in all sorts of cellular processes has led to multiple labs worldwide devoting their time to study this phenomenon and its implications.



Condensates come in many flavors, each type for a different function and at a different place in the cell. These are made by sequestering different proteins together, based on the need for their interaction. The fluid nature of these condensates allows them to exchange molecules with their surroundings, taking in substrates and giving out products. They are

present in the nucleus, as bodies that are involved in the repair of our genomes, and in the cytoplasm, for catalysing multiple important reactions. These globules interact not only with their surroundings but also with other condensates. As with other processes important to the cell, condensates are also known to be hijacked by viruses, shaped by evolutionary competition to disrupt host cell activity and promote their own proliferation.

The dynamic nature of condensates, however, is relevant beyond their function. The large number of mostly non-specific interactions between molecules that allow them to condense together also results in them being dysregulated in the cell in a myriad of diseases known as 'condensopathies'. In some of these disorders, condensates eventually change form, shifting from a dynamic liquid-like state to an aggregated solid state, thus preventing their dissolution and disrupting their function. Some of our gravest public health concerns, stemming from neurodegenerative diseases like amyotrophic lateral sclerosis (ALS) and Huntington's disease, as well as the broader disorders of multi-organ ailments and cancer, involve condensate malfunction. Understanding the mechanisms of condensate formation, dissolution and dysregulation would help open up an avenue of hope in the form of therapeutic discoveries that may result in resolving symptoms or even reversing diseases.

The excitement brought about in the biomedical field by the movement towards understanding these little droplets, and the potential to utilise this knowledge for therapeutic applications, has been unparalleled in recent years. This enthusiasm is mirrored by Dr. Shova, who is hopeful that her work and the work of other scientists in the field will open new avenues of knowledge and promote societal health and wellbeing.

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PC: Geeth Sameer