Naturalists

BIOSPHERE

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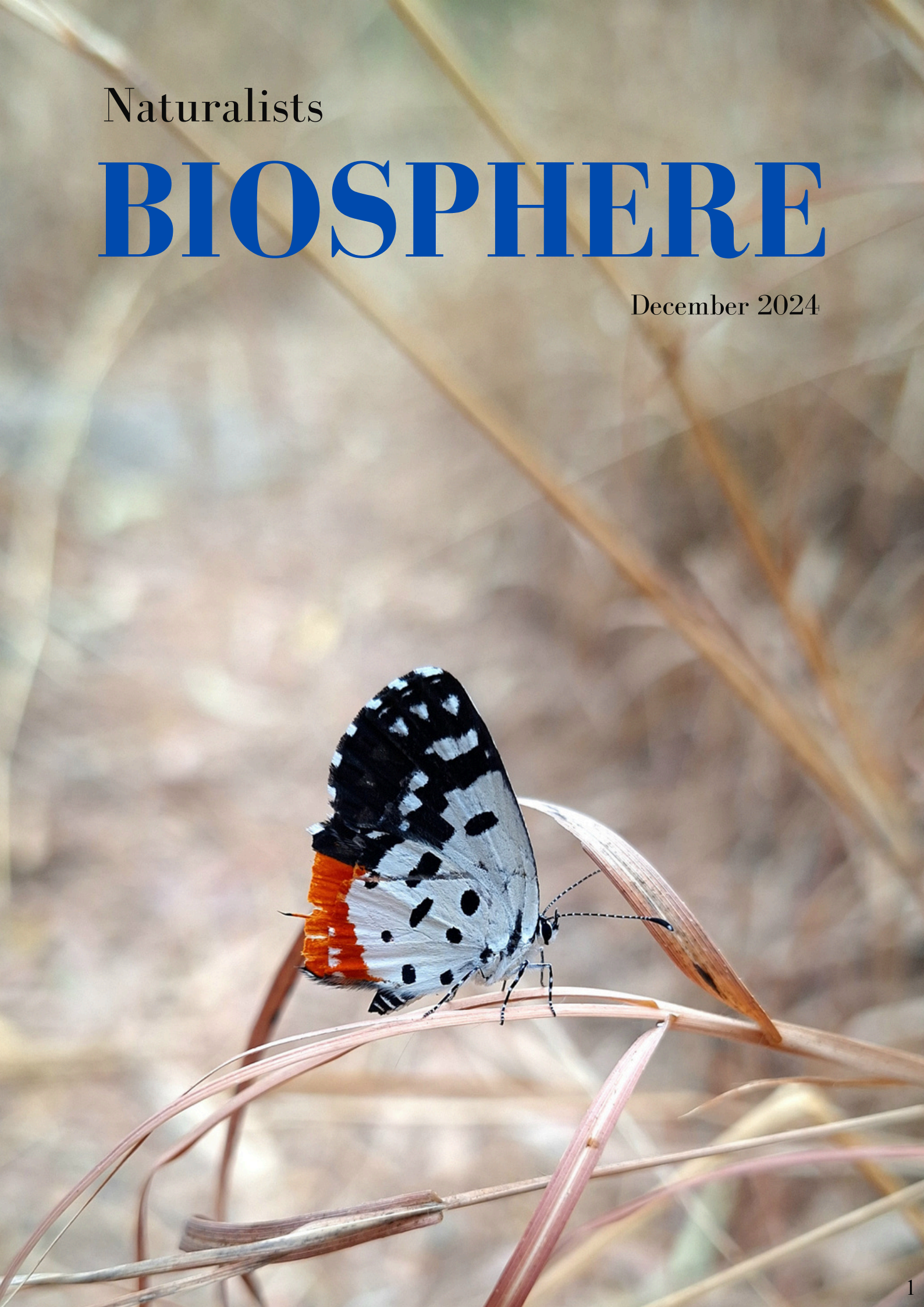

Editorial

Dear fellow Naturalists,

Welcome to the December issue of BioSphere, where we continue our journey of exploring and illuminating the countless wonders of the living world, involving more people and covering a wide array of topics. This issue not only aims to inform and engage the current UG biology community, but also marks an exciting evolution of BioSphere to serve as an archive of our times at the institute. We try to capture our community's thoughts, discussions, and aspirations, providing future readers with a rich tapestry of our experiences, insights into the people who shaped them, and the ideas that inspired us.

Within this issue, you'll find interviews and discussions about various academic and non-academic aspects of research, a sneak peek into the lives and labs of the IISc biology community. As our tenure as convenors draws to a close, we also reminisce about the diverse initiatives and memorable events we engaged in this year. Additionally, you will discover a series of articles that explore new frontiers in biology.

Wishing you a wonderful new year and happy reading!

Shloak Vatsal
Editor

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Cover Image: Hemanya Radadia

Cognitive Crossroads

- Shouvik Datta

The field of neuroscience is vast and ever-evolving, encompassing a wide range of studies from cellular mechanisms to complex behaviours. Shouvik interviewed Dr Ashesh K Dhawale, Assistant Professor at the Centre for Neuroscience, about what attracted him towards neuroscience, his interesting research on motor learning and decision-making, and unanswered questions in the field. They also talked about the challenges he faced initially setting up his lab, handling administrative duties with his research and his views on mentorship and collaborations.

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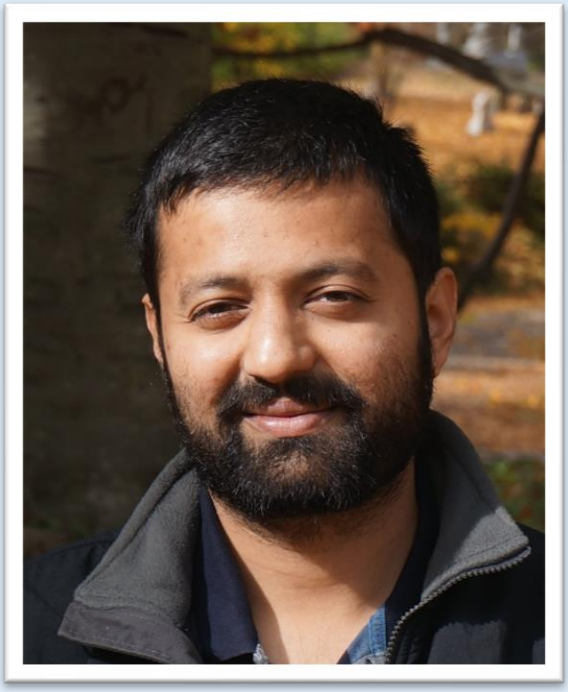
Could you please walk us through your academic life, from your bachelor's in Mumbai to becoming a researcher at IISc Bangalore?

Sure. I did my bachelor's in life sciences from St. Xavier's College in Mumbai. This was before we had any specialised institutes offering undergraduate programs for science. So, these colleges were the main option, and I was there for three years. The teachers were great and had ties to TIFR. We often went there to attend lectures and even took some courses over there. There was flexibility, and our college's location was quite close to TIFR, which was convenient.

I then applied to several PhD and integrated PhD programs and eventually went to NCBS, where I was keen on developmental biology. However, since there was no department structure, we could take rotations in any lab. I happened to take a course in neuroscience by Upi Bhalla, which was an eye-opener in terms of understanding the computation done by biological systems, in this case, the brain. I realised that my interest lay in computation. Even in developmental biology, I was interested in how cells know where to go, how they get together to create an organism, and what rules govern this process. The rules must be simple at the level of individual cells, and from these simple rules, you can build very complex systems. The same understanding can be applied to the nervous system, where neurons are complicated but less so than the brain. Putting neurons together, you get interesting emergent properties, leading to sensation, thought, perception, and action. This really interested me.

When I joined Upi Bhalla's lab to work on olfaction, I built a microscope as a rotation project. We had three-month rotations in different labs where he said, "Why don't you build a two-photon microscope using



the parts lying around?" It was great fun putting together optical components, using lasers and scanners, and understanding the principles of a microscope. Unlike a wide-field microscope, you must program it to orient the laser to focus on a particular part of the focal plane, gather information, count the number of fluorescence photons emitted, and then reconstruct the image pixel-by-pixel by scanning the laser beam across the image. Traditionally, people used electrophysiology to record neural activity in the brain. But here was an opportunity to use a microscope to look at neurons directly and put dyes inside them that would respond to changes in calcium and fluorescence, allowing us to record many neurons simultaneously, attaching labels to them.

To build this microscope, I enrolled in an amazing course at Cold Spring Harbor Labs called Imaging Structure and Function in the Nervous System. I met a student who would start his own position at Cold Spring Harbor Labs later that year. He had an interesting mouse engineered to express a new optogenetic tool, Chandler-Dobson, which offered the opportunity to use light to activate olfactory neurons to bypass odour stimulation. Odour space is very

complicated, varying along many physical and chemical dimensions. It's not clear how the olfactory system makes sense of odour space. Unlike vision, where we know that spatial location, intensity, and colour of light are important variables, for odours, the only known variable at the time was intensity. Even a simple odour activates many input channels to the olfactory system, binding to many olfactory receptor neurons and activating many neurons simultaneously.

Much pioneering work in other sensory systems, such as vision, was done by isolating and stimulating just one input at a time. This allowed the discovery of principles like centre-surround processing. But this can't be done with odours. There have been proposals that the olfactory system also does centre-surround processing, but how it does it is unclear. The ability to shine light on the exposed olfactory bulb, the first stage of odour processing, and use light to stimulate different receptor neurons was remarkable. He had made a transgenic mouse that allowed this. I talked to my advisor, and we set up a collaboration. I went to Cold Spring Harbor Labs for a couple of years, where I did the bulk of my PhD work. We built a small optical system that allowed us to take projectors used in classrooms and shine patterns of light on the exposed olfactory bulb surface to study the input of an olfactory neuron in terms of spatial locations on the bulb surface rather than what kind of odours it responds to. We published some papers on that.

I returned to Upi's lab and worked a bit on the hippocampal code, recording from the hippocampus in awake, behaving animals learning a task. We watched hippocampal neurons activate with activity patterns in large populations using two-photon microscopy and calcium imaging. After my PhD, I went to the U.S. for my postdoc in Bence Olvetsky's lab at Harvard University. I was always interested in the problem of movement. Working on the sensory system side of things, you see patterns of activity encoding something about the outside world. There's an encoding of the outside world in these activity patterns. But we don't know how these activity patterns are being used by downstream circuits. So, I was interested in the other end of the brain, which is the part that controls movement. The reason I went to Bence Olvetsky's lab is that his lab had developed a system to automate behavioural training in large numbers of rats. In fact, this is precisely what we do now in our lab as well. It's like an operant conditioning system, where you train animals to do things for a reward.

Generally, operant conditioning has been known for a long time, but the automation of it is a relatively recent phenomenon. Previously, you had to hand-train these animals, transfer them from a home cage to a training cage, and then back. This is very laborious and limiting for two reasons. One is that you can't do behavioural experiments in a high throughput manner. The second is that it's hard to train rodents to do very complex tasks because it takes a long time to train those tasks. Automation solves both of these problems. They developed a large facility where each animal lived in an experimental cage that was the same as its home cage. The entire training protocol, from the simplest to the more complicated stages of learning a new movement or skill, was entirely under computer control, which was really exciting. I joined the lab and worked on developing an electrophysiological recording system that allowed us to record in an automated manner around the clock. You could implant an animal with electrodes in your favourite part of the brain, usually the motor areas. We had to tether the animal because no wireless system has enough battery life to run for many days at a time. Over this cable, you could get electric signals from the brain, amplify them, digitise them, and send them to a computer. You keep the animal plugged in for weeks and months at a stretch. Using the system, we could isolate the activity of individual neurons. These extracellular recordings could track these neurons over weeks and sometimes even months. This has been a game changer in the field because if you want to understand any kind of neurological process that operates over long timescales, it's tough to do that without tracking the same neurons over these timescales. Neurons are so different in their response properties that you get much more signal power following the same neurons over time.

This is true not just for skill learning but also for studying diseases, development, degenerative disorders, and all kinds of phenomena that operate over long timescales. System neuroscience is not really geared towards understanding phenomena over long timescales, but with techniques like this, we can make a start. I used the system to record from areas like the basal ganglia and motor cortex in animals learning a new task or skill. We made several discoveries. We also used high throughput behavioural training to record vast data sets from individual animals as they solved a task. We could use the statistical power of these data sets, which are millions of trials, even hundreds of thousands of trials per animal, to infer the learning process at the level of individual trials. We study trial-and-error

learning, which is a somewhat noisy process with much variability. Only by averaging over many trials can you look at the signal within the noise. The signal is how they change their strategy in reaction to their actions and the outcomes of those actions.

During your shift from developmental to neurobiology, were there any factors other than the computational part that got you interested?

Yeah, computation is just one way of putting it. The other is to think about the collective phenomena, where interesting phenomena emerge from fairly simple components. This emerging complexity is something that is fundamentally interesting to me. It's something you can find in many fields. However, if I were to do this again, I think I might have randomly landed in a different field. It's not like there was any particular draw towards neuroscience, but it is a good place to study such phenomena, from circuits to behaviour.

Also, people make a big difference. You often choose a PhD lab because of the person who's heading it, because they have some skill set, or because they are fascinating people. You can learn a lot from them. I think that's also one of the reasons I chose neuroscience; it happened to be the field of people I liked working with.

How were the initial days after you came to IISc and started your lab? There must have been a shift from your academic and research life to include administrative work as well. How did the lab initially look?

It was an interesting transition because this was just post-COVID, and lockdowns were still in place. It was a somewhat difficult time to begin. There were issues like quarantine and not being able to move around freely. When I came by the lab, there was no space. There was a room, but it was full of junk, and I had to clear it out. Essentially, I had to build the lab from the ground up. We had to figure out, buy, and install every piece of furniture. It's not how I imagined my lab would begin. Most places set up a lab for you, or there's a lab that you inherit from somebody else. But here, I had to make one entirely from scratch. You also don't get the money right away. Even though I joined in July, I got my initial startup fund in November. I think the biggest issue is getting used to the bureaucracy inherent in most government institutions. But after a while, you learn the procedures and how to deal with them. It's not just scientific aspects; you have to learn admin aspects, dealing with the SAP system, which I'm sure you also struggle with. Then, getting stuff, learning how to place orders, and how to receive them. Many purchase rules exist, especially in India, with different procedures for different purchase values. Foreign equipment needs a totally different procedure. It takes a long time to get started here.

As an active researcher, not only do you need to do the administrative work but also keep up with the latest research. How do you manage your research studies, reading papers, and all of that, along with the massive load of administrative work?

I think the major admin load is at the beginning when you join because you're not used to the system, but it gets better over time. Of course, they give you more things to do, like being part of committees. Luckily, I'm not at that stage yet. Generally, we hire somebody who can do the admin work for you, who places orders, and who is essentially a secretarial assistant. However, every scientific environment has its own challenges. In India, for example, getting funding is not a significant challenge. Even though the quantum of funding is much less than you get in the West, getting a grant can be very difficult. You must write many grant applications before you get a successful one, forcing people to write grants most of the time. It's still a scientific activity, but you don't necessarily want to write five grants to get one. Every system finds a different way of taking away productive time. You just have to figure out a way to streamline it as much as possible, minimise distractions and focus on science. Sometimes, personal things get in the way, especially if you have a young family. It's a challenging process, but it gets easier with time.

Whenever a new member joins the lab, how do you proceed with that person to ideate what exactly they will be working on?

In my lab, I initially tried to mentor the master's students myself. But now I just don't have the time. When they join, they typically read the foundational papers for whatever problem they're interested in before being assigned a PhD or postdoc. For a PhD student, I let them be for a few months. Sometimes, they start experiments just to learn technical and motor skills, how to work with the automated training system, how to handle animals, how to perform surgeries, how to perform perfusions, etc. In terms of literature, they read broadly and widely. Eventually, they figure out some area that they're interested in. Then, I give them more targeted papers to read. We have weekly discussions about what they've done and what they want to do. Initially, I didn't have any such schedule because I used to be in

the lab constantly, meeting people daily. Now, with the lab growing, it's a little more challenging. So, there has to be a little more structure in the interactions. So yeah, it depends on the person joining, and we try to customise it for each in an informal way.

Are there any fields in neuroscience that you think are uncharted and have not been ventured into?

Yeah, this analogy describes what most work in science is like: people tend to look under the lamppost. That's how you write grants, too, wanting to make incremental advances. That's what you can justify doing, too, because it's guaranteed to work to some extent. But a shot in the dark has a very low probability of working.

There are many areas like that. One is that there's a lot known about how we learn from rewards. But in any kind of learning, reward is just one of the things we optimise. There are many other factors, especially costs, such as effort, punishment, and time delays, all of which must be optimised along with reward. You do a complete cost-benefit analysis when selecting or forego an action. There's almost nothing known about how the brain computes effort or cost. Another area that is less known is play. What is the role of play in development? Because many mammals play, not just humans. Rats, mice, and many animals play, yet its function remains mysterious. Rather, it has many functions, and we don't really know the reason for its evolution. There are also a lot of other mysteries, but these are the two that come to my mind. We also don't want a graduate or a PhD student to potentially waste many years of their research time following what could be a blind alley. These are the projects I give to undergrads or thesis students, which I think are more about effort rather than finding and are also more exciting for them.

After your postdoc, how did you decide what research field to set up your lab in?

Generally, people tend to work in a very similar area to what they worked on in their postdoc and don't tend to stray too far from it. At the same time, it's pretty rare for someone to do exactly what they did in their postdoc because you don't want to compete with your mentor on the same questions. So, you try to distinguish yourself for both your career and theirs.

In my postdoc, I was working on multiple projects, and there was one side project that I was engaged in. It looked at the role of variability in learning and how we control variability in our behaviour. When you're trying to throw a basketball, it's improbable that you'll get it every single time. You're going to vary in where it lands. Typically, variability is considered the outcome of noise in the nervous system or the muscles. However, there's an increasing appreciation that variability is potentially beneficial for learning because it allows the brain to explore different movement strategies and then select the ones that work better. Variability is good for learning but bad for performance, so it makes sense that the brain would regulate it in some way. To understand how we did a behavioural study where we trained animals on a motor task and looked at how they regulate variability. We found that they regulated based on the reward they received; they reduced

variability if they got a reward and increased it if they didn't. We could mathematically describe the regulation process and predict how they're going to change variability very reliably. That is something I took away from my postdoc, and my postdoc mentor is not working on it. Hence, this formed one of my core questions: how do we learn, and how do we use variability for learning?

Besides this, I also wanted to start something totally different, to expand into new directions. I tried to look at decision-making, which is thought to be formed by circuits distinct from motor circuits. I was wondering how animals make decisions when there are many options to choose from, as opposed to just the typical two options given in lab experiments.

So, these became the two core areas of the lab: decision-making and motor learning. Both are tied in with variability. In one case, it's choice variability; in the other, it's motor variability. We want to understand the circuits that underlie the ability to learn in more complex tasks than what we've studied so far.

During your doctoral studies, you mentioned closely working in a collaboration. Now, as a researcher, how do you come up with a particular collaborative work? Have there been any collaborations in your lab, and what were they on?

So, we've not had any formal collaborations yet, as I want to establish our own scientific base first. I think it's essential to publish a few studies yourself first to get established in the field and not have credit taken away from you because you're new in the area. But at the same time, we have interesting data sets already, so there are potential avenues for collaboration, especially with theorists. Collaboration with theorists or computational neuroscientists makes the most sense for us since the behavioural or neural results can be put into theoretical or computational frameworks to derive more meaning from them. There are people we've been talking to, but they're not formal collaborations yet. Different people have different approaches. Some like to collaborate from the get-go. Most of my work has been collaborative so far in PhD and postdoc, but I wanted to get something out from my lab individually first before we start.

To dedicate your PhD life, you need to have some faith that the question you're pursuing will give you something in return. After all, it's not only the effort but also the results that you need to come up with. How do you come up with such a question that gives you the required faith?

This is where your reading and planning come into play. That's why I give people enough time before starting the experiment. The idea is to have a very good understanding of what's being done in the field to identify gaps in our knowledge. What's an interesting question, not just to me but to the field as well. Otherwise, it won't get published in a decent journal, and nobody will appreciate it when it comes out. Finding the gap that people care about and you care about more importantly is important. Then, have a good plan to frame the question in a way that reaches the answer. Even with a negative result, how the experiment is done, or the approach is planned can be informative. It's about preparing a framework to interpret results, forecasting what results you could get, and what they mean for the theory. It's similar to writing a grant proposal where you want to convince someone that what you're doing is worth doing because the results are interesting regardless of what they are. You're exploring the question in a way that advances knowledge, not just confirming something someone has done before or getting stuck with results that are hard to interpret. Therefore, I like hypothesis-driven research much more than exploratory research, where you start doing something and then look at the results and develop an explanation post hoc. In such exploratory work, you often end up doing the wrong experiment and miss out on controls that would have been better done at the time. When you think in advance, you can plan everything out, including controls and additional experiments for alternative interpretations of the findings. Basically, planning is super important.

When planning these experiments to validate or support our hypothesis, we design them with a fair amount of reductionism. Hence, multiple factors and parameters are not considered at the same time. However, when we think of biology as a subject in general, there is still some unpredictability associated with it. How is it that, when it comes to real-life situations where all these factors integrate together, we go on to integrate all of these things to consider every parameter?

Typically, different experiments have different goals, even if they're part of the same project. There are sub-questions of the larger question motivating each experiment. For example, if I'm going to lesion some area of the brain and then test its role in learning or behaviour, I'm asking if this area is required for that behaviour. The goal is to figure out which areas are necessary and understand what they might be doing by looking in more detail at the deficiency that results from the lack of this area. But if I'm recording,

I'm trying to understand how this area represents information in the outside world, whether it's movement, sensation, or something else. The questions tend to be independent and non-overlapping. You hope there's some consistency between the answers you get. For example, if an area has a very rich encoding of some behaviour, the expectation is that this area is required for the behaviour. However, it could be the case that neural activity can encode many variables important for solving this behaviour, but lesioning or inactivating this area has no impact on the animal's ability to solve the task. In that case, you would argue that this area has all these patterns but is not required. Maybe it's involved in some aspect of the behaviour you're not explicitly testing.

When results conflict, you look more closely at discrepancies and either do more experiments or build models to help understand them. It's an iterative process. When you do experiments, you get results and do another set. The technique also matters. There are different ways of silencing brain areas, some temporary, some permanent. Temporary techniques are reversible, like using muscimol, a GABA agonist that increases inhibitory tone in a circuit and shuts down spiking activity. Another way is to lesion the area, killing the neurons in that region. These have different effects because inactivation is more acute, while the lesion is more chronic. The brain has time to recover from the lesion, which can lead to different outcomes. Reconciling these effects can be challenging. For example, my postdoc lab found that the brain shows remarkable recovery in the function of downstream areas post-lesion, but there's no opportunity for that to happen with inactivation because the area comes back online soon. Temporary inactivations were popular, but my postdoc mentor decided to take a closer look at the variability in results. They found that you need to do both inactivations and lesions to understand the true role of an area in behaviour. This led to a Nature paper by paying attention to discrepant result.

Exploring the Journey of Scientific Research

- Isha A, Shravani D, Yukta S

In the world of scientific research, perseverance and curiosity drive groundbreaking discoveries. Yukta and Isha recently sat down with Chitra, a PhD student, and Riya, a research associate (RA), from the lab of Prof. Purusharth Rajyaguru at the Dept. of Biochemistry to explore their journey into research and the experiences they've gained along the way. Both have recently published a paper on modulators of protein translation, shedding light on the complexities of fundamental biology and the often challenging yet rewarding path of scientific inquiry.

Early Inspirations and Motivation

Chitra and Riya emphasised the excitement of exploration when asked what inspired them to pursue careers in science. For Riya, the thrill lies in conducting experiments and waiting for the outcome. "Even when things don't work out, it teaches you the importance of patience and perseverance," she explained. Chitra's journey began during her master's program at the Central University of Rajasthan. Her early exposure to research fuelled a passion that led her to pursue a PhD.

This excitement for discovery is what initially draws many into science. As Chitra highlighted, "It's not a routine job, and that's what makes it exciting."

Research Focus and Contributions

Currently, Chitra and Riya are involved in fundamental biology research, exploring how protein turnover is influenced by certain amino acids and how RGG motif proteins, which act as transcriptional repressors, can be modulated. Their lab's focus on low-complexity sequences (LCS), like

the RGG motif, allows them to delve into the intrinsic disorder in these sequences and their role in protein structure and function.

Riya added another fascinating layer to their work, mentioning their ongoing exploration of how yeast survives under Mars-like stress conditions. "It's still in the early stages, but it's quite exploratory," she said, demonstrating the versatility of their lab's approach to studying RNA granules and condensate formation under harsh conditions. Their research has implications for understanding life in extreme environments, making it both innovative and ambitious.

Images
Above, Chitra Togra, PhD student
Left, Riya Dhage, Research Assistant

Challenges in the Lab and the Role of the PI

When it comes to research, challenges are inevitable, and Chitra and Riya shared how crucial troubleshooting is in their daily work. Chitra explained, "Troubleshooting experiments take up most of the time. Each organism and system is unique, which makes the process more complex." This constant cycle of observation, hypothesis, and experimentation forms the backbone of their research efforts. Riya emphasised the importance of their Principal Investigator (PI) in this process. The PI, she explained, is a key figure who helps interpret data and decide on the future direction of their work.

The team faced additional challenges while publishing their paper. Riya explained that once data is collected, writing and revising the manuscript is an iterative process. "You often rearrange figures and experiments to tell the story better," she said, highlighting the importance of presenting data clearly and effectively. Although initially rejected, their paper was accepted with minor revisions after a year, a testament to their resilience and dedication to the research process.

Unexpected Results and Publishing Obstacles

Like most researchers, both Chitra and Riya encountered unexpected results during their experiments. Chitra remarked, "Often, the results are the opposite of what you expect, but that's science." They both agreed that handling these surprises requires an adaptable mindset. "You just have to figure it out as it happens," Chitra said.

Publishing their paper also presented its own hurdles. After addressing the reviewer's feedback, they were relieved to face only minor revisions, but they acknowledged that it's common for reviewers to request additional experiments. Riya reflected on this challenge, noting how they were fortunate to avoid further experimentation in this instance.

Balancing Life and Research

The conversation also touched on how Chitra and Riya balance their research with personal life. Chitra enjoys swimming and staying connected with her family to maintain balance. For Riya, resting on Sundays and occasionally indulging in painting helps her de-stress. They both agreed that keeping friendships outside the lab is vital to ensure a healthy work-life balance.

When asked for advice from aspiring scientists, Chitra emphasised the importance of mental resilience and commitment. "Science demands a lot of time and effort," she said. "If you're genuinely motivated, then it's the right path for you," Riya added, adding that patience is crucial, as experiments often take time to yield results. "Sometimes, it might take a year to get an experiment done. You have to be okay with that."

Memorable Moments and Future Plans

Looking back on their journey, both Chitra and Riya cited the publication of their paper as one of their most memorable academic experiences. Riya also expressed her gratitude for the supportive lab environment, where regular discussions and collaborations foster both personal and professional growth.

As for the future, Chitra plans to pursue a postdoctoral position, while Riya is focused on completing her PhD. Both are determined to continue exploring the world of science, contributing to the broader understanding of fundamental biology.

Chitra and Riya's experiences offer valuable insights into the world of scientific research, where persistence and curiosity often pave the way for breakthroughs. Their story highlights the importance of adaptability, teamwork, and patience in overcoming the many challenges researchers face. For anyone considering a career in science, their journey serves as an inspiring example of the rewards that come with dedication and passion.

Phage Therapy: Scary Good or Scary Bad

- Milan Vijay

Antibiotics need no introduction. The first one, Salvarsan, was discovered in 1910. Alexander Fleming's discovery of Penicillin in 1928 popularised their use. By the 1950s, the antibiotic market was up and booming, and for good reason. In addition to medical breakthroughs and disease treatment, antibiotics made many surgical procedures possible and helped develop the animal husbandry sector through general disease treatment and prophylaxis. It has been over a century since the first antibiotic was discovered, and sadly, antibiotics hold a bleak future ahead for us. Antimicrobial Resistance (AMR) has rapidly decreased the effectiveness of antibiotic treatment. So, we search for alternatives to combat these antibiotic-resistant infections.

Bacteriophages (or Phages in short) are viruses that invade bacterial cells. In the case of lytic phages, they disrupt the bacterial metabolism, causing lysis of these cells. The first bacteriophage was reported by Ernest Hankin when he observed the presence of marked antibacterial activity in the waters of the Ganges and Yamuna Rivers.

Phage therapy has been in use since the early 1920s. Further development and study of phage therapy was hindered by the fast-rising field of antibiotic discovery and treatment. Former Soviet Union countries, especially Georgia, have continued to develop and use phage therapy. At present, phage therapy is garnering more attention in the context of AMR.

To understand more about phage therapy, its advantages, its shortcomings, and the obstacles it currently faces, we will talk to Dr Rachit Agarwal, Associate Professor at the Department of Bioengineering, who is carrying out exciting research on bacteriophages at IISc, Bangalore. Dr Rachit's laboratory works on developing clinically viable therapeutic options for diseases like Tuberculosis and Osteoarthritis, and he is also carrying out exceptional research on bacteriophages.

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Prof. Rachit, could you tell us about the general bacteriophage work in your laboratory?

Most of what we do is centred around looking at treatment modalities that include various kinds of pathogens. The laboratory focuses on two pathogens: Mycobacterium tuberculosis (Mtb) and Pseudomonas aeruginosa (PA). For the last 5-6 years, we have been working on Mtb and got some decent results in vitro, but we still need to optimise the formulations to see how they can be made better translatable, first in animal models and then in human models. The work on PA is a more recent one and we have collaborations with groups from IIT Bombay and IISER Bhopal on this topic. We are trying to do some work in terms of using phage therapy for other pathogens like PA. Another project is on how the phages infect a non-replicating bacterium and studying whether the infected bacteria would survive for long durations. All these works would have

implications for phage therapy itself, especially inputs on bacteria fitness, but that's a long-term project. We are also looking at prevention methods, especially in the case of Mtb, where phages are trying to be used as prophylaxis, considering the

high burden of Mtb cases in India. Tuberculosis is very dangerous in densely populated countries like India, where the whole family is at risk of contracting TB if even one person gets the infection.

What made you interested in research involving these bacteriophages?

While doing my Postdoc, there was a project on phage therapy. It just happened to be that I had the skills and tools to be able to deliver various kinds of drugs, and they needed somebody to deliver these phages efficiently. Eventually, I worked on this project and enjoyed working with phages. They are a remarkable species with many intriguing features, which gives them high potential, in my opinion. Since then, I have been trying to carry on work related to phage therapy.

What are the significant limitations that phage therapy faces in the present scenario?

A significant limitation would be to get very reliable batches of phages. The phages tend to be heterogeneous. As a result, quite a bit of randomness is involved in each of the phage particles. The tolerance and the chances of mutations that could happen in different phages during the same formulation should be known. Another challenge is that we don't have all the information about these phages. There could be toxins within the phage genome that could affect the patient and the infection. There is a possibility of horizontal gene transfer; there are integrase genes and some other genes that could cause this. To an extent, this problem is overcome by using purely lytic phages that do not possess these genes, but there is always a risk that some unknown gene might function like that. I feel that more knowledge and understanding of the phages and the processes involved in phage therapy, as well as figuring out the formulation in the context of heterogeneity, would go a long way.

For a treatment method that has been documented since 1923, a lot of the side effects of phage therapy are yet to be studied. Ironically, phage therapy existed before antibiotics were made commercially available, and we have a long way to go in understanding the therapy. The discovery of antibiotics shifted the researchers' focus from phages to discovering and testing newer antibiotics. Would you like to comment on this?

Absolutely! Antibiotics are wonderful molecules. They have been at the forefront, along with vaccines, in helping humans become the dominant species and increasing the lifespan of an individual. Following the essential nature of evolution, the bacteria have started to evolve against antibiotics, so we fall back on our forgotten friend, the phages, to help in this battle.

We know that each bacteriophage is specific to a bacterium. Can the bacteria evolve resistance against the phages over time?

Absolutely! There have been many reports where the bacteria exhibited resistance against the phages. Most studies do report this. I think that the advantage that phages have over antibiotics

is the relative number of treatment options. There are certain classes of antibiotics. Whereas in the case of phages, there could be as many as a hundred times the number of phages than the number of bacteria out there. In that sense, the hope has always been that if one phage fails against a bacterium due to resistance exhibited by the bacteria, there would be more phages out there that can be used as a cocktail in this therapy.

Does the phage stay in the human body for a long time?

Phages have not been reported to stay long, especially if the pathogen has been cleared away. Our bodies have mechanisms to clear away any foreign object, whether protein, DNA, phage, or bacteria. Having said that, just like our gut microbiota and the commensal bacteria, a whole phageome is present in our body, which finds its way to exist for a long duration. But this tends to happen when the host is present, so they continue to amplify in numbers and exist. So far, I have not come across any study that suggests that the external phage tries to exist within the human phageome.

So, I think we require more human studies to determine whether the phages stay in the body for a long time and, if so, how long the phages stay.

From what I have read, the human body does produce immune responses against phages. Would such responses hinder phage therapy?

There are two ways to look at this. Lots of research has shown that phage pressure and immune pressure can work together to clear out the pathogen. On the other side, if the immune response is primarily directed against the phages, then it would reduce the efficacy of the therapy, and the bacteria would face less pressure. Reports suggest both these ideas. In some of the compassionate-use human trials, there was no detectable immune response, while in others, there was. There are instances where phage therapy worked even in the presence of this immune response. I feel that it's a complex problem at this stage. So, this would add to the challenges faced in implementing phage therapy on a broader scale.

Let's say that a patient underwent phage therapy, which was a success. Would there be any significant and noticeable side effects from an outsider's point of view?

Not really. The phages primarily infect the bacteria and not the mammalian cells. It is unlikely that there would be any significant long-term side effects

because of that. Still, gene transfer and other indirect effects pose a problem.

Historically, we isolated and concentrated certain chemical compounds from microbes. These came to be known as antibiotics. Some researchers are trying to isolate chemical compounds from phages called "lysins" and hoping to use them instead of whole phages. What do you think about this approach?

I think it's a valid approach and a very cool way to approach this problem. My only concern is that the protein delivery mechanisms in our body are not very well designed. So, as bioengineers, we must work a lot to deliver the protein to the site efficiently. Phages also face the same problem, but they have an advantage. Unlike lysins, phages and their dosages can be dynamic in some sense. Phages can amplify their numbers. So, when the phage finds the bacteria, the phage undergoes the lytic cycle, and the numbers reach hundreds, and from the hundreds, they can become millions and so on. Due to the ability of phages to amplify at the site, the dosage would be significantly lower than lysins. Overall, I think this is an interesting approach for topical applications where it's easy to deliver the lysins.

Let's take a situation where you or somebody you know has contracted an antibiotic-resistant infection. What do you think about using phage therapy on your own body?

I think that in terms of use in humans, that too in a streamlined fashion is yet to be achieved. There have been lots of cases where people have availed of phage therapy on a compassionate-use basis. The number of these is almost in the range of hundreds and thousands as of now. It is found that in most of these cases, phage therapy has been observed to be safe and very effective, producing good outcomes for the patient. From the regulatory standpoint, there are some challenges in delivering a species rather than the traditional method of delivering chemical molecules. To answer your question whether I would be open to using phage therapy, yes, if there is such a dire need for it when other treatments are not working.

Phage therapy is quite popular and has been in constant use in Former Soviet Union countries like Georgia, Poland and parts of Russia. As of now, Phage therapy is not approved in India. Generally, when people require the therapy, they travel to these regions where it is approved. Some companies facilitate the patient in availing phage therapy by travelling to these places.

Over time, with more research, more human trials, and more evidence favouring the effectiveness of phage therapy, do you think the common population will accept phage therapy just like antibiotic treatment methods?

I absolutely think so! There will always be people who remain against a particular product, such as vaccines. Then, there would be people who don't believe in pharmaceutical medicines and prefer traditional treatments like ayurveda. So, there will always be people for and against this. In general, I think that the population is growing more receptive to it. I have gone to conferences and talked to people, especially those who don't work with phages, and they are still interested in reading reports. I have received e-mails asking whether bacteriophages could be used to solve a problem. These are evidence suggesting that bacteriophages and their use is becoming more popular. Still, we have a long way to go.

To conclude, what are some other ways in which bacteriophages can be used at present?

People have used phages as a research tool for quite a long time. This includes trying to come up with ways to modify the bacteria. Phages can also be used as a diagnostic tool. Fluorophages and Luminescence-activated phages can be used to detect a particular pathogen in a mixture of bacterial populations. So, once the phage locates the pathogen, the event will trigger an increase in fluorescence or luminescence. Yeah! Phages are exciting beings.

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It is evident that despite the effectiveness and accuracy of phage therapy, it still has many obstacles to overcome. Slowly but surely, with more research and even more passionate people involved in phage therapy, it will gain more acceptance. Phage therapy is not the definite answer, but it buys us invaluable time for exploring more options to treat the diseases still at large.

Further Readings:

1. Dr Rachit's lab website: https://be.iisc.ac.in/~rachit/

2. Some YouTube videos

https://youtu.be/nWLRTFGpYuE?si=jiXtRP26JSJD5uQL

https://youtu.be/aVTOr7Nq2SM?si=_cbvin-H-waHS4uZ

3. Sulakvelidze, Alexander, Zemphira Alavidze, and J. Glenn Morris Jr. "Bacteriophage therapy." Antimicrobial agents and chemotherapy 45.3 (2001): 649-659

A Summer to Cherish

- Dhruba Dey

As I broke my "cab-fast" to get onto my Uber for the Montreal airport, my phone buzzed. It was a message from Shloak, asking me to write something about my "thesis abroad". I realised it had already been seven months since the day I was quietly waiting at the Berlin Airport for my "Deutschlandticket" to load on my wallet to get onto the subway. When I asked him what he wanted me to write about it, he asked for both "acads and fun". Now, I am sure this journal would have lots of exciting stuff about science, so me focusing more on fun is only fair. However, I would definitely throw in some science here and there just to not get rejected by my successors.

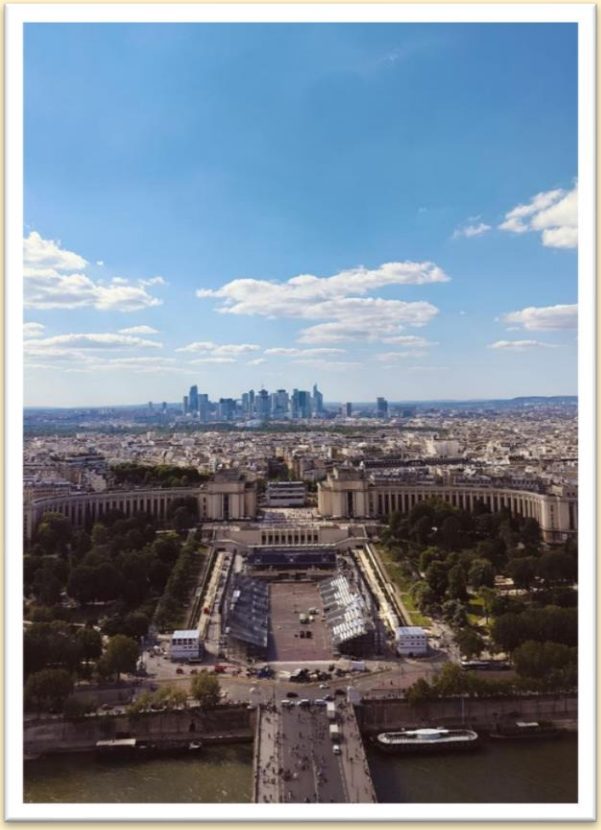
I joined the lab of Dr Sutapa Chakrabarti at Freie Universitat (FU) Berlin in the summer of 2024 for my DAAD WISE project on mRNA decay. Staufen mediated decay (SMD) is one of the many mRNA decay pathways by which proteins recognise and degrade mRNA molecules in the cell to regulate gene expression. My work involved trying to prepare crystals of two proteins, UPF1 and Staufen, with a synthetic RNA molecule so that one can discern the exact interacting partners. Preparing 16 litres of E. coli culture was probably the most mundane thing I did during those three months. Berlin's charm made the one-hour travel from my apartment to the lab quite interesting. I had to reach the subway station of Kottbuser Tor using the U8 every morning. A quick Reddit search can reveal how these places are known for their notoriety. From a co-passenger falling unconscious over me from a drug overdose to people taking out marches for the rarest of causes, it was the peculiarity that made Berlin stand out from the average European city. In addition to size-exclusion chromatography, bagging my groceries at the cashier swiftly by keeping them in an efficient order on the belt is undoubtedly a skill I mastered, so much so that getting help (though only once) was itself a culture shock.

Weekend trips to Paris and Switzerland will be the ones I will always cherish. The idea of "you won't get another chance to backpack across Europe in your early twenties" can, unfortunately, make you spend thousands on some French crepe or fancy train rides through the Alps. Paris remains one of the most "intense" cities I have ever visited. I witnessed a brawl on the first subway I took (the famous M6 line) stemming from a pickpocket. People cursing each other as the train crossed the Seine, overlooking the magnificent Eiffel Tower in the background was definitely laughable. The Swiss can be as expensive as possible, but they do have breathtaking peaks like Matterhorn and Stanserhorn to boast about. Solo travelling can be quite cumbersome, but Parisians

warning me to take care of my wallet and Swiss skiers lending me a hand are what I would keep in my memories.

As my cab pulled up at the airport, I couldn't help but remember one particular stranger. It was exactly four months ago when I was checking in for my flight to Montreal at the Berlin airport. Three months had passed, and it was time to start my thesis on cute little protists, the Diplonemids in Professor Gertraud Burger's lab, at the Universite de Montreal. My luggage was over by about eight kilos, and no amount of pleading and convincing the staff worked. As I opened my bags to get rid of some of my clothes and shoes, 6 German police officers surrounded me and towered over me. I had no choice but to trash everything, which added to the extra weight. I handed them to a Turkish janitor whom the police had called upon and proceeded to check in with whatever was left. Just before going to the security, I was interrupted by the same janitor. The Good Samaritan had waited for me so that he could return my clothes, which I could now carry with me as hand luggage. He had even changed the plastic of the trash can just when the police had called upon him. The person I was most grateful to throughout my stay in Europe was unironically a Turk.

As always, it was the people who made the strongest mark in the three months I was in Berlin. The public transport would come a close second. How different cultures perceive science and how a mix of them only enriches it was indeed a great experience and something to ponder for years.



GEMs of Synthetic Biology

- Aman Sahoo, Shloak Vatsal

Early on a Sunday morning, many undergraduates can be found, donned in their white coats, entering the Old Physics Building. Tucked away in a corner of the ground floor, the otherwise calm and peaceful UG Biology Lab is brimming with activity. The event was a lab tour organised by the iGEM IISc team, where the freshers, who have joined IISc recently, were shown around state-of-the-art machines and methods used in the lab. Bright-eyed and curious, these enthusiastic visitors bombard the team members with a flurry of questions. Patient and calm, they explain the nitty gritty of their labwork to their juniors while also answering our questions during the breaks.

International Genetically Engineered Machine (iGEM) is a competition that brings together more than 400 high school, undergraduate and graduate teams from across the world to solve real-world problems using synthetic biology – a field that applies engineering principles to biological systems, enabling the development of biotechnologies. Participating teams design, test and develop tools that work in harmony with nature and tackle global challenges.

IISc has participated in the competition for several years and has won gold medals six consecutive times. This year, the team is working on developing novel therapeutic strategies for proteinopathies, a class of diseases involving protein misfolding in the body. It includes many prevalent neurodegenerative conditions such as Alzheimer's, Parkinson's and Huntington's diseases. Their project, AptalXero, aims to treat Alzheimer's using aptamers, short single-stranded nucleic acid molecules with high specificity to particular targets. "We're not developing a complete cure for Alzheimer's but exploring the limits of this technology. Since aptamers can form confirmations that bind exactly to a specific folding of a protein, we thought to use this to distinguish between a normal protein and its misfolded form," explains Subhanan Banerjee, a second-year BSc (Research) student and the team leader.

The team is targeting multiple prizes this year. "Firstly, we have to fulfil several criteria to qualify for the medals. It includes a wiki with the documentation of our work, proof of concept, and details of the novel parts we have developed," says Subhanan. There are additional prizes for excellence in specific areas of the project, such as hardware, modelling, presentation and parts, encouraging teams to go above and beyond with their projects.

The members mainly consisted of second-year undergraduates in the BSc (Research) programme from different backgrounds and were motivated to join the project for various reasons. Recounting his

first exposure to iGEM, Parth Kumar says, "Though I am planning to major in chemistry, when our seniors told us about this excellent experience, I wanted to explore it and try to build on the legacy of the previous teams." Due to the novelty of problems, iGEM also gives them the freedom to plan and execute their experiments. "This was the first time we were designing experiments, and though it was not easy, I feel it was worthwhile learning," says Subhanan. Some were attracted to the project's far-reaching consequences. "I was fascinated by research on Alzheimer's even before I joined IISc. So the project presented a wonderful opportunity to learn more about and enter brain research," says Anurag Sarkar with a shine in his eyes.

However, science and research are not the only focus of the team. Parth says, "iGEM really emphasises communication and human practices. These involve talking to stakeholders, getting feedback and introducing people to this wonderful field." The team has organised a multitude of events that inculcate the spirit of science in people from various walks of life. From lab tours and paper reading sessions for the juniors to talks on synthetic biology for the public, the members seem to have all the bases covered. And that's not all. Through these efforts, the team is also laying down the foundation for the next bunch of budding researchers to build upon.

With all the research, coursework and events, the members have a tight daily schedule to follow. Each member has devised a personalised strategy to balance their academic and iGEM work. Anurag mentions sacrificing a bit of his academic rigour in exchange for the unique experience iGEM provides. Meanwhile Parth just treats it as additional coursework with a daily lab assignment. "Being a physics major and an iGEMer is hard, because I haven't been able to spare anytime on Physics", laments Subhanan. On the other hand, Avani has devised the most relatable solution: sacrificing sleep.

Apart from challenges in ideating and labwork, they also confessed to facing some problems with the administration. Being in a government institution comes with its pros and cons. While the financial support is enormous, the paperwork to obtain said support can often be mind-numbing.

"This one time, we ordered from IDT, a sponsor of iGEM who gives away items required for our project. However, the financial workflow of IISc requires every item being imported into the campus to be accompanied by a Purchase Order (PO). Now, a free item came with an invoice of 0 USD, which caused a mess with the Purchase section and the UG office. Now, we understand the importance of paperwork for audit purposes, and thankfully, the Dean of A&F cleared the issue, but the entire incident was stressful," Suvam laughs, recalling one such incident.

The group's efforts have not been in vain. Besides their success in the lab, they believe iGEM has provided an international platform for teams to collaborate and build upon each other's ideas. "A lot of the solutions posted by the undergrad teams are very simple but very efficient. Many people get inspired by previous iGEM ideas and grow up to be valuable members of academia working on niche problems", comments Anurag. Further, iGEM's focus on sustainable development and dual-use hazard has exposed the teams to the practical aspects of science, which many researchers do not focus on. "The restrictions of the competition shape the mind of the researchers to think about global challenges and to find unique ways to approach them", according to Anurag.

Genetic Jumbles

- Chandan G, K Sahapthan, Sacchit K

Genetics is a vast field deeply intertwined with many aspects of our lives, from physical traits to health and disease. In this interview, Chandan spoke with Dr Kavita Babu, Associate Professor at the Centre for Neuroscience, to get answers to puzzling questions in the field. They also talked about recent developments and the growing role of genetics in our daily lives.

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How do our genes influence traits like eye colour or height?

Multiple genes are required for such traits, which is why you have a range of heights instead of extremes. The same goes for eye colour. The influence of multiple sets of genes is essentially why you do not have Mendel's laws applicable, which say it's one gene for one phenotype.

Can our lifestyle choices impact how our genes work?

Yes, and one place where it's known well is epigenetics, where the DNA is the same, but you have changes in the output of the DNA. If you take a child and look at the epigenetic modifications and then check again 10-20 years later, you'll see changes across development, adulthood and ageing. If you were to do the same study on twins, and this has been done, these epigenetic changes are very different when the twins are in different environments or lifestyles. One of them might get cancer, and the other stays fine. One may be a smoker, and the other may not. One of them might have smoke-related diseases while the other does not. So, it's not just your genes that will determine whether you get any disease. External factors are also at play.

Are the genes of identical twins precisely the same, and do they always look alike?

Yes, the genetic material of identical twins is exactly the same, and they always look alike.

And do they have the same fingerprint as shown in crime thrillers?

No, I don't think any two people can have the same fingerprint. The way skin forms on tissues cannot be identical for two people. It's more of a physical manifestation.

How does understanding genetics help in developing new medicines?

Understanding genetics allows you to figure out the disease and its cause, and you need to know the cause of the disease to develop a medicine.

For instance, in Parkinson's disease, genetics can help you figure out that a lower amount of dopamine causes it, and the obvious treatment would be increasing dopamine. People have shown this in mice model systems. They also showed a lower amount of dopamine in human studies. Having said that, in Parkinson's, a single gene has not been implicated in this process, and you probably have multiple sets of genes that allow it to manifest. In fact, many people are now talking about it as Parkinsonianism. You might think it's just one gene that gives rise to lower dopamine, but that's not the case.

There are genetic model systems for other diseases as well, especially cancer. Mouse models have allowed the study of genes that regulate cell proliferation, and people have also been able to use different cocktails to reduce cancer.

What is personalised medication, and how does genetics play a role in it?

Personal medicine is essentially genome sequencing to find out what exactly the problem is, such as the point of deletion, duplication, etc. It works very well if you have non-identical twins, a large part of whose genomes are similar but with some differences. Identical twins don't work because both will have the problem.

If you sequence both of them along with the parents, you can get a good idea of what single nucleotide polymorphism (SNP) is, which is different and gives rise to the disease. And this has been used nicely in the US, where a kid was having a lot of problems manifesting as irritable bowel syndrome, but they found it was because of a gene that can be rectified by bone marrow transplantation. Once they figured it out, the child was immediately treated.

In another case, twins were having a cough and not feeling well, but the problem was mapped to a gene required for serotonin synthesis. They just treated the kids with serotonin, and that helped cure the case. This would help a lot, especially in the case of rare diseases, because you don't know what the cause is. If you were to do this sequence and compare it with people, normal individuals in the same family, you can get a lot of information.

Can our genes predict the risk for certain conditions like diabetes?

Yes, with mutations and necrotic factors. The best example is the trinucleotide repeats that give rise to Huntington's disease. There is a coding sequence with CAG repeats with which you can figure out whether a person has a propensity for Huntington's.

Can this understanding help in preventing diseases before they occur?

Let's say you can design a baby. If you know that a person has a propensity for Huntington's or something, you can cut off the extra trinucleotide repeats, which is actually simple to do. But the question arises: what would prevent you from doing it for anything else? You can demand blue eyes, smartness and such. On top of that, such a thing would also be costly, and only the rich could afford it. This raises a multitude of ethical questions.

What are GMOs, or genetically modified foods, and are they safe to eat?

Yes, I think they're safe to eat. It's basically changing the DNA of plants to withstand pests better or improve nutritional content, like reducing harmful fatty acids in soybeans. Many years ago, wheat was also developed to have more gluten that might not have been genetically modified in the sense that it's selected. In many cases throughout history, man-made selections have allowed us to get redder apples or fleshy bananas. GMOs are just a more targeted approach that will enable you to do the same.

How do scientists use genetics to study human evolution?

All life evolved from a single cell, right? So, you can look at sequences across phyla and at similarities in sequences especially at the level of specific genes. You can determine how close humans are to mice or flies, allowing you to study evolution by looking at who evolved from whom step-by-step. And since much of it is known, it will enable you to make these evolutionary trees to get the evolution that has given rise to humans.

Is it possible to bring back extinct animals like the woolly mammoths using genetic technology?

Why not? If you have the entire DNA sequence, you can pre-program it. The challenge is that the whole of the genetic sequence is not there. Fossils can be a great source. The problem is that the earth's environment has changed and might not be conducive for them. But if you give the exact conditions it requires to survive and access the genetic material, then why not? You can get a new Jurassic Park!

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Naturalists in 2024: A Reflection

- Rahul Chavan, Shloak Vatsal

As we approach the end of our term, Naturalists reflect on a remarkable year of activities and learning. From the foundations of synthetic biology to the intricate mysteries of cancer, we tried covering a broad spectrum of topics this year, ensuring that there was something for everyone to engage with and learn from.

Our calendar of events began with a talk by the convenors on cell-free synthetic biology, an emerging field with immense potential for revolutionising biotechnology. The session introduced attendees to the principles of creating biological systems without living cells, highlighting ideas about its applications in medicine and engineering. The event also saw the launch of the new Naturalists logo, featuring a Slender Lorris in the colourful background of leaves inspired from the IISc logo.

Throughout the year, we also hosted a series of talks, bringing experts and alums from diverse fields to share their insights. One of the standout sessions was by our alumna, Dr Janhavi Kolhe, a scientific editor at Cell. In a casual chat at the DBS canteen, she opened up about her PhD struggles, exploration of various career paths, and a behind-the-scenes perspective on the often-overlooked profession of publishing.

Other notable talks included Kedhar's talk introducing the concept and applications of minimal cells and Dr Tanweer Hussain's exploration of structural biology, where he unravelled the many aspects of this field. In a similar vein, Prof Ramray Bhat challenged traditional perspectives with his thought-provoking discussion on the many definitions of cancer, encouraging us to rethink the disease beyond its clinical aspects. A session on ancient DNA research by Chethana Nair transported us to the distant past to uncover its implications for understanding evolution and human history, while Prof Annapoorni Rangarajan's session on stem cells and cancer biology pushed us to think about the future, exploring cutting-edge research that could redefine medicine and therapeutics.

To demystify the process of graduate applications, we invited Prof Arvind Rao from the University of Michigan, offering practical tips and advice tailored to aspiring researchers. Complementing this was an insightful session by UG alumni Karthik and Tapan, who shared personal anecdotes and strategies for selecting PIs, internships, and navigating the early stages of a research career.

While theoretical knowledge is vital, experiential learning is equally important. To this end, Naturalists organised hands-on workshops and field sessions that allowed students to apply what they learned in real-world contexts. The major highlight was the lab session on in vitro transcription (IVT) and basic microbiology techniques, where we tried providing hands-on experience with fundamental experimental methods. Fieldwork involved an outing to Lalbagh Botanical Garden, a haven of biodiversity

in Bengaluru. This trip wasn't just a stroll through nature—members were tasked with selecting a tree of their choice and investigating its soil microbiome. Back in the lab, they analysed their samples, gaining insights into the microbial ecosystems surrounding plant life.

Encouraging students to engage deeply with research and share their findings was another key focus of the year. Our paper presentation competition provided a platform for participants to delve into scientific literature, critically analyse research papers, and present their interpretations to an audience. This exercise honed their communication skills while fostering a deeper understanding of contemporary biology. The summer project expo was another highlight, showcasing the innovative projects undertaken by the UG Biology community during their breaks. We also organised mock thesis presentations for graduating seniors, providing them a supportive environment to refine their work and receive constructive feedback from peers. And like every year, Naturalists had a buzzing audience at our Open Day exhibits.

One of the most impactful initiatives this year was the creation of a lab database to provide insights into the working environments of various research groups on campus. This resource aims to help students make informed decisions when selecting labs for internships or projects, ensuring a better fit for their interests and aspirations. We also held a major selection meeting aimed at students deciding whether to take up biology as their primary field of study. By addressing their questions and concerns, we sought to ease the decision-making process and highlight the vast opportunities within the discipline.

2024 has been a year of growth, discovery, and connection for Naturalists. From hosting insightful talks and hands-on sessions to building resources and fostering a sense of community, we've strived to make biology accessible, engaging, and meaningful. None of this would have been possible without the enthusiasm of our members and the generosity of our speakers. As we look ahead to the coming year, we are confident our successors will continue exploring new frontiers, expanding our outreach, and strengthening our community. Here's to many more years of discovery with Naturalists!

Touring a Shrinking Green Fortress

- Hemanya Radadia

As evening falls on campus, the distinctive 'Chuhuawaarrrr...' of the Mottled Wood Owl can be heard from the trees on the road to the swimming pool. Sometimes, it flies from its nest in the Jubilee Gardens, and passersby are treated to the sight of this gigantic owl. After sunset, roaming around the main building, an observant person may find a couple of spotted owlets. And if one walks a decent distance on the campus, they are bound to hear the shrill, high-pitched voice of the slender loris, a small nocturnal primate that stays atop trees.

Even after hearing the shrill call of the loris, it is hard to locate it, for it keeps moving from branch to branch. But once a torchlight shines on it, its large round eyes shine back to reveal the beautiful creature. The primate is hunted for its use in black magic rituals. This does not concern the loris inside IISc, but the loss of trees does. A connected canopy is essential for them as they do not jump between branches or descend to the ground to move to the next tree. As the space between trees shrinks into smaller connected components, lorises find themselves isolated from potential mates, shelters, and food.

In the last two decades, the campus has lost nearly 13 hectares of tree cover, equivalent to 1,588 fallen trees, according to an internal report on land usage analysis. Construction has picked up pace, especially after COVID-19, with the building of new departments like TCS Smart X hub and new hostels for students. Many concerned students, faculty members and environmentalists in Bengaluru have protested, demanding transparency in the campus development plans and the engagement of stakeholders in the process. But the administration has prioritised constructing new infrastructure so far, ignoring all concerns raised against it.

The Indian Institute of Science continues to be a beautiful green island in a concrete jungle. There are several hundred trees and a similar number of non-tree species on the campus. Some are native to this land, and others are introductions from various parts of the world. Some of its trees are older than the Institute itself. The Avenue trees are eye-catching for their flowery canopies, their blooms cascading the roadside. They also constitute a large part of the campus vegetation (e.g., Mahogany Marg, Gulmohur Marg and Nilgiri Marg). Despite the many concrete structures that have come up on the campus, the greenery endured and treasured all the wealth of flowers, some rare and some abundant. Most of the trees on the campus are spring and summer flowering species (Jacaranda, Lagerstroemia, Cassia, Butea, Cochlospermum, Delonix, and Erythrina, for example), which create stunning sights from February through May.

Image
A rare instance of a slender loris coming down to the ground. Photo credit: Photography club

Earlier this year, a small, chicken-like bird called the slaty-legged crake was observed in the Jubilee Garden. This bird is a dense forest dweller native to south and south-east Asia. Slaty-legged crakes are territorial and quite secretive, hiding in bushes when disturbed. Birders from across Bengaluru visited the campus to get a glimpse of this rare bird. The nearest location where this bird is found is over 250 kilometres away in the Western Ghats. How it has survived on the campus for ages or how it came in the first place is a profound mystery. Another mystery is the occurrence of a smooth-coated otter in the Jubilee Garden's pond. Rare creatures like the Indian grey hornbill and the jungle cat also make appearances from time to time.

In winter, the campus hosts a panoply of colourful migratory birds that come to seek shelter in their freezingly cold homes. The orange-headed thrush can often be seen near the Jubilee Garden's pond. The nine-coloured Indian pittas, called Navrang in Hindi, can be seen hopping around on the ground in forested patches. Flycatchers with striking blue colours like the Verditer and Ultramarine flycatchers present themselves to a few lucky souls. In April, when they fly north to their homes, the ever-present Indian paradise flycatcher with its ethereal tail and majestic peacock calms the nerves of workaholic scientists.

Looking ahead, it is crucial to recognise the importance of preserving our campus biodiversity. By promoting sustainable practices and protecting natural habitats, we can ensure that species like the slaty-legged crake and slender loris continue to thrive while providing a calm and healthy learning environment for students and the IISc community.

Images
Above, An orange headed thrush. Photo credit: Hemanya Radadia
Left, A verditer flycatcher. Photo credit: Hemanya Radadia

Coacervates: Tiny Droplets, Big Impact

- Parth Kumar

When you think of a cell, the image that first pops into your head is likely the standard textbook image of a eukaryotic or bacterial cell – a resilient but fluid lipid membrane and a cytosol teeming with cell organelles and bustling with metabolic activity.

But, of course, that's not how things always were. We started with nothing but a bunch of molecules floating around in the boiling hot ocean, what we call the 'primordial soup' today.

Somewhere in between, there must have been a stage where molecules just started coming closer together – not forming anything as fancy as a membrane or an organelle, but also not as disordered as a random assortment of molecules sitting far apart. That's what a coacervate is – coming from the Latin 'co' (together) and 'acerv' (a heap), it's quite literally a heap of molecules clustered together in significantly higher concentrations than the surrounding medium. In a broad sense, it's just another colloid, a liquid dispersed in another liquid – but the way coacervation occurs is unlike other emulsions we know of.

Coacervation can be simple – a single kind of molecule (typically a polymer) spontaneously separating from the surrounding medium to form a droplet rich in that polymer. However, scientists are more interested in complex coacervation, which involves two (or more) different molecules. The fundamentals of chemistry dictate that things that have an affinity for each other will defy all odds and will come together, and it follows through with what happens in most instances of complex coacervation.

Say you have two clear solutions, one of a negatively charged polymer and another of a positively charged one. If you mix them together, the two molecules will attract each other electrostatically and choose to come together, separating from the surrounding liquid to form a new entity, a liquid droplet rich in the two molecules firmly held together. And voila – you know something's happened because you notice that the solution is turbid, a typical readout for the formation of coacervates, which are large enough to scatter light. This phenomenon is known as liquid-liquid phase separation (LLPS), and it lays the basis for any kind of coacervation. It's not just electrostatic interactions but also hydrogen bonding, hydrophobic interactions, and salt bridges concomitant with the partial exclusion of water molecules that make this process entropically and enthalpically favourable.

It's the simplicity of this phenomenon that makes it so exciting. Where amphipathic molecules like lipids form vesicles, many biopolymers like nucleic acids and polypeptides tend to be highly charged, as do small molecules like amino acids. This makes it entirely plausible that complex coacervation played a role in bringing them together to form the first primitive cells – as proposed by Alexander Oparin back in the 1920s. These ideas were only cemented when we discovered coacervate-like structures called biomolecular condensates within the cell, formed by LLPS – a notable example being the nucleolus.

Though coacervate research slowed down in the mid-20th century, they have recently returned to focus not because of their relevance in the origin of life but because we've realised that such systems hold immense potential for biomedical and soft material applications.

The idea is simple – the interactions that bring coacervates together (primarily electrostatic) are sensitive to stimuli like pH, temperature and even oxidation-reduction because these parameters tend to alter the net charge on molecules. Since losing charge means losing electrostatic forces, we can create stimulus-responsive coacervates, which would spontaneously assemble or disintegrate depending on whether the constituent molecules remain charged or not. Take the example of one of the most well-studied coacervates, constituted by adenosine triphosphate (ATP) as the negative moiety and polydiallyldimethylammonium chloride (PDDA) as the positively charged polymer. These were first reported by Stephen Mann and are known to be quite stable and remain assembled with time. If you use an enzyme like alkaline phosphatase (ALP) to break down the ATP, the coacervates dissociate. By using fuels like free inorganic phosphate and kinase enzymes, if you were to regenerate ATP, the coacervate would re-form. We thus have a system that opens and unloads its constituents in response to

a specific stimulus, making it an ideal cargo holder for drug delivery.

The cherry on top is that coacervates tend to sequester and encapsulate organic molecules, creating high concentrations within them. This is because the interior of coacervates consists of a dense organic phase, which provides favourable interactions for the uptake of dyes, proteins and enzymes. This sequestration property of coacervates is well-utilized in their application as microreactors – called so because these micron-sized liquid particles enhance reaction rates of common industrial reactions. They confine the substrates and enzymes in a small region, and the proximity drives the reaction. At times, the coacervate constituents may contain functional groups like free amines or imidazole moieties, which also help lower activation energies by providing strong interactions to stabilise the enzyme-substrate intermediates. In such a way, coacervates can also act as microzymes.

Stephen Mann is just one of many contemporary scientists actively researching coacervates as protocells and how we can exploit their behaviour. Scientists have been able to create stable membranes (often composed of polyoxometalates) around coacervates, making them more stable and robust enough for application. Recently, Mann demonstrated chemotaxis and motility in such protocells. Catalase is an enzyme that generates oxygen gas from H_2O_2, while glucose oxidase consumes glucose and oxygen as substrates. Mann placed the membrane-bound coacervates in a medium with gradients of glucose and H_2O_2 and used catalase to generate bubbles of oxygen within the protocells in the peroxide-rich (but glucose-poor) region. This made them buoyant, and the protocells migrated to a region with high glucose concentration, where the oxygen was consumed, and the buoyancy was lost, making the protocells descend back down to the peroxide-rich region, and the cycle could be repeated.

This biomimetic cascade is reminiscent not just of how cells have a tendency to migrate towards food but also of gas vacuoles in prokaryotes as primitive methods of locomotion and buoyancy. This programmed motility of coacervates can be well-exploited for directed and reusable drug delivery systems, as Mann also demonstrated.

Coacervate research is a crucial step towards understanding our past and how primitive life forms may have operated. Although we can only hypothesise, it doesn't change the fact that this research is yielding fruits in the form of promise for unique biomedical innovations. Perhaps we aren't that far off from creating artificial cells – and who knows where that would lead us!

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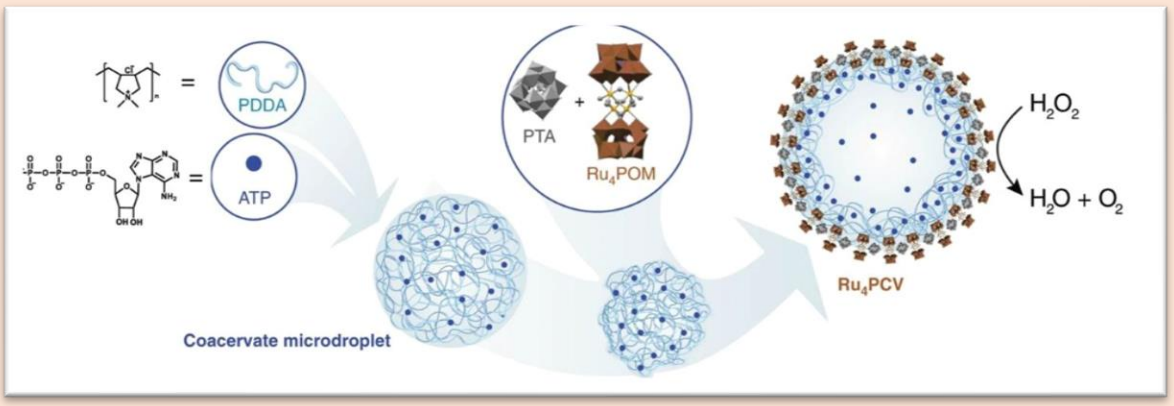


The Tick-Tock Within Us

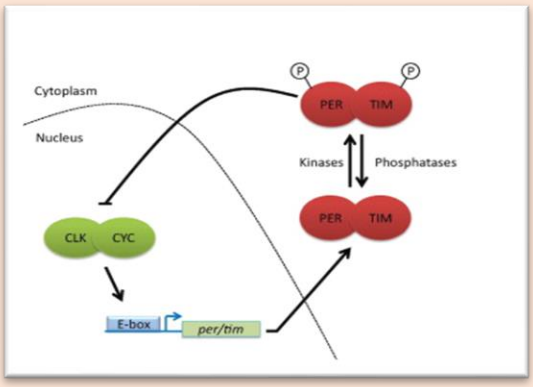
- Yukta Subramanian

On the International Space Station, where the concept of day and night disappears in the vastness of space, astronauts rely on artificial systems to maintain their body's rhythm. A sophisticated LED lighting system simulates the 24-hour light-dark cycle of the Earth by transitioning from blue-enriched bright light during the "morning" to dim red-enriched light before "evening." This careful simulation reflects a fundamental aspect of biology: the circadian rhythm.

In the 18th century, French scientist Jean-Jacques d'Ortous de Mairan first observed a biological clock. He found that the leaves of a mimosa plant continue to open and close rhythmically, even in constant darkness. This experiment hinted at an internal timekeeping mechanism independent of external cues like light. Today, we know that nearly all life forms—from tiny bacteria to plants, insects, and mammals—possess such circadian rhythms. These rhythms are endogenous, meaning they are generated internally, but they can be influenced by external cues called zeitgebers (German for "time-givers"). Light is the most potent zeitgeber, but temperature, food availability, and social interactions also play a role in synchronising these clocks.

At the core of circadian rhythms are molecular clocks, which rely on feedback loops involving specific genes and proteins. The first discovery in this direction was made in 1971 when Ron Konopka isolated mutant flies with alterations in their normal 24-hour cycle of activity. While this was a breakthrough, the journey to uncovering the mechanism of the rhythmic activity was arduous. As Michael Young, winner of the Nobel Prize in Physiology and Medicine for studying circadian rhythm, puts it in his Nobel lecture, "Ron Konopka had screened only 200 strains of mutagenised flies to find his first clock mutant (the gene was called period), and so we thought let's do some more genetic screening. We weren't as lucky as Ron. In fact, two postdocs had to screen 7000 strains of flies to find the second clock gene (timeless)." PER protein from the period gene and TIM protein from the timeless gene showed a periodic expression-level pattern. Further studies reveal the presence of a transcription-translation feedback loop. In this mechanism, the transcription of period and its partner gene timeless are repressed by their own gene products – the PER and TIM proteins, generating an autonomous oscillation.

Though initially studied in Drosophila melanogaster, the studies have shown that this mechanism is highly conserved across species. The hypothalamus's suprachiasmatic nucleus (SCN) acts as the central clock in mammals. The SCN is a small region of the brain located just above the optic chiasm that receives signals about light from the eyes. This information allows the SCN to adjust the body's rhythms to match the 24-hour day. Peripheral clocks in organs like the liver and heart take cues from the central clock to coordinate various functions across the body via humoral(blood) and neural communication. Disrupting the body clock over long periods is thought to be associated with many diseases, such as type II diabetes, cancer, and cardiovascular disease. As modern technology continues to push us away from natural cycles, understanding these rhythms becomes even more critical. Whether deep in space or here on Earth, a quiet clock ticks within us like all other living creatures.



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Molecular Scissors: Double Edged?

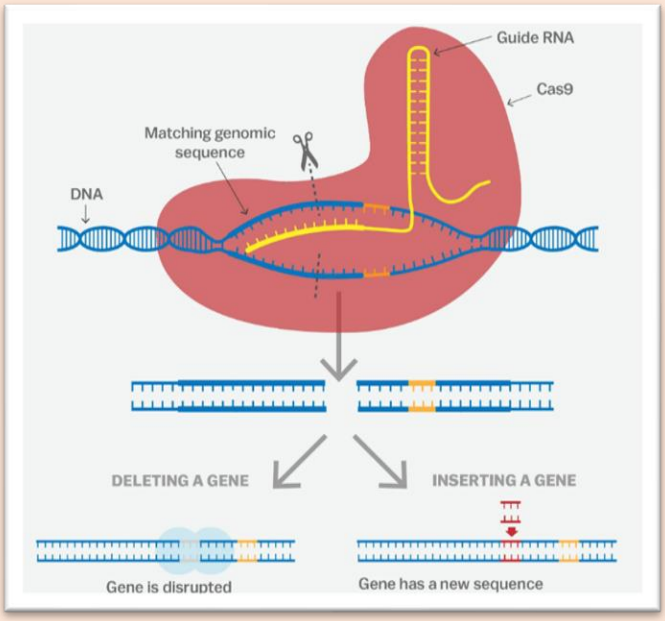
- Durga Naniwadekar

The development of CRISPR (Cas-9 system) as a gene editing tool has taken the field of biotechnology by storm. In the few years that have passed since its arrival on the scene, it has been deployed in a variety of fields, and its range of applications has been explored in detail. From the 2020 Nobel Prize in Chemistry being awarded to its pioneers to the first CRISPR-based gene therapy being approved in late 2023, it seems to assume the centre stage in any discussions on gene editing.

CRISPR, or Clustered Regularly Interspaced Short Palindromic Repeats, were first discovered in archaea and later in bacteria as a defence mechanism against viruses. When a virus enters the host, the bacterium inserts parts of its genetic material into its own genome, allowing for 'genetic memory'. It then creates a complementary 'guide RNA' sequence that helps the CRISPR-associated proteins recognise the viral intruder when it infects next and cut its DNA at specific places, deactivating it.

This efficiency and ease of directing and cutting specific spots immediately made it an excellent tool for gene editing. The scope of this technology is truly immense. It has allowed the development of potential cures for genetic diseases like beta-thalassemia and sickle cell anaemia by editing somatic cells. One such treatment, Casgevy, recently approved by the US FDA, entails extraction of the patient's blood stem cells and editing them to make them produce more fetal haemoglobin, causing the sickle haemoglobin to get diluted. Moreover, CRISPR can also be used to enhance the efficacy of cell-based therapies, including CAR-T cell therapy for cancer treatment. One can modify CRISPR-Cas components to fluoresce depending on whether it detects a specific target genetic sequence, allowing it to diagnose the presence of pathogenic DNA or genetic diseases. It can also be used for epigenome editing-methylating DNA and modifying histones-changing expression precisely. The field of synthetic biology, too, sees CRISPR bring a wave of change: it can be used to design and create synthetic circuits, networks, and organisms with specific functions. These may be bacteria or animal models to simulate human diseases. CRISPR can be used to develop more varieties of genetically modified crops- more easily tailored to suit growth, nutritional, and insecticidal needs.

CRISPR has also been proposed as a tool to revive extinct species, like the woolly mammoth, from fossilised DNA. In addition, CRISPR-made genetic elements that propagate at super-mendelian frequencies (>50%) can be introduced into disease vector populations to introduce sterility, potentially curbing the spread of malaria and other vector-borne diseases. Such 'gene drives' have also been proposed for use on invasive species.



Though studies of these in controlled lab environments have been promising, usage in gene drives may lead to rogue variants and cause ecological disasters and resistant organisms. Modifying invasive species may make them more invasive or harmful to the environment. The consequences of tinkering with populations can be irreversible and disastrous. It leads us to question how much liberty we give ourselves to modify our

planet's ecology further, either to bring back the extinct or to rid ourselves of species we consider detrimental.

Human genome editing takes other forms, too. While somatic gene editing discussed earlier introduces changes that cannot be passed on to future generations, germline gene editing can. It entails editing a fertilised zygote in the single-cell stage and then inserting it into the mother's body, making modifications inheritable. Compared to somatic editing, human germline editing is far more complex and unpredictable, with chances of off-target mutations, mosaicism, unknown side effects and complications. Unintended consequences of tinkering with even simple aspects of human populations may take time to reveal themselves. Human gene editing has opened up trillion-dollar commercial opportunities, and there is talk of increasing the human lifespan, preventing ageing, enhancing athletic performance and creating 'designer babies' with features decided by parents. Because it entails editing in the single-celled stage, it is impossible to obtain the consent of the unborn child. While gene-editing other species reduces them to consumable or modifiable objects, our human selves may also get objectified to meet parental ambitions or societal norms, undermining human identity and liberty. Moreover, human germline editing provides the possibility of gaining advantageous features over other groups.

The thought of dominating the world with a stronger, faster and more intelligent race has been a familiar fantasy of despots, who will be tempted to use CRISPR to practice eugenics.

Nations that fall behind rivals may consequently direct institutions studying CRISPR towards military use through controls and funding. It takes little racial, religious, and cultural difference for humans to consider other competing human groups as 'aliens' and 'vermin' and to use violence against them. It will be difficult to halt conflict when a race of genetically 'superior' people is created, and such a cascade can tear society apart.

Evidently, this growing field is full of possibilities and potential for great good. However, as with many promising new technologies, we must define where to draw the line while ensuring progress. It is a way of advancing power for individuals, firms, and nations. Some of the opportunities it creates are so economically lucrative that it becomes difficult to put the brakes. The ongoing patent struggle, even amongst the ones who developed it, is a testament to this.

Germline editing needs a caution-first approach. Its ethical dilemmas need conversation and open discourse among the scientific community, policymakers, other stakeholders, and, most importantly, diverse members of the public. Grassroots movements should be encouraged to create mass awareness and tap into the wisdom of diverse social, cultural, and ethical perspectives.

The interests of all affected stakeholders need to be protected, and benefits extended to the many, beyond just those who profit from these technologies. With appropriate checks and balances, governments, Lawmakers, and research institutions can step in to develop regulatory frameworks to restrict access to potentially dangerous technologies, ensure transparency, and make clear who is accountable.

While it is difficult to reach a consensus, it is vital to make a start so that we steer humanity in a direction it understands and assents to. The key to global solidarity is bringing this field to the public not only in a sensationalised way- but in a more nuanced way. This is where we, students and budding scientists, can make a difference!

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Tag, Target, Trash: A Nobel-Winning Tale

- Ritik Ravichandran, iGEM IISc '24

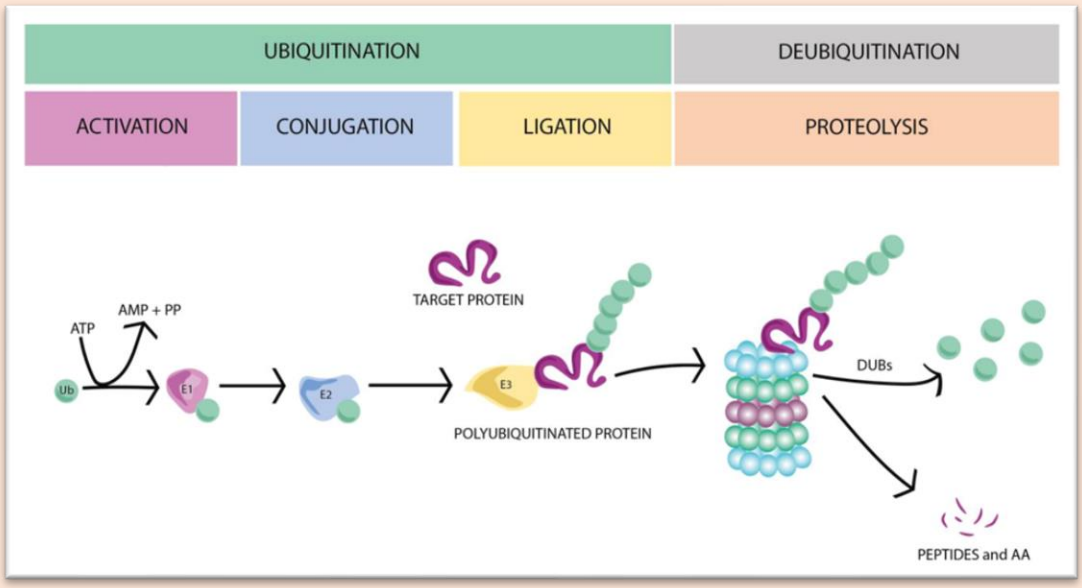
Everything in our body is run by proteins. They are the workhorses of life, driving nearly every biological process – from building structures to regulating metabolism and signalling pathways. That being said, every so often, it is possible that some of these proteins misfold, that is, they adopt an incorrect conformation. This results in them losing their function and frequently becoming harmful and potentially disease-causing.

Luckily, our body has developed checks for this sort of misfolding. One of these mechanisms is Targeted Protein Degradation or TPD for short. The way our body carries out this process is intriguing.

There are large, barrel-shaped molecules in our body known as proteasomes whose function is to break down proteins. But the question arises: if all our internal processes are facilitated by proteins, how do the proteasomes know which ones to break down and which ones to ignore? They do so by recognising a chemical molecule, which acts as a 'tag'. This moiety is called ubiquitin, a small protein (a rather ubiquitous one - hence the name) consisting of around 76 amino acids virtually indistinguishable across all life forms.

The actual process, however, is a tad more complicated, involving three enzymes. First, ubiquitin is activated by being attached to the ubiquitin-activating enzyme, E1. The ubiquitin is then transferred to a second enzyme, called ubiquitin-conjugating enzyme (E2). The final transfer of ubiquitin to the target protein is then mediated by a third enzyme called ubiquitin ligase or E3. It is after this that the proteasome recognises the protein and, hence, degrades. This is known as the Ubiquitin-Proteasome System (UPS), and the Nobel Prize in Chemistry in 2004 was awarded jointly to Aaron Ciechanover, Avram Hershko and Irwin Rose for the discovery of ubiquitin-mediated protein degradation.

But why was this discovery that important? To answer this, looking at the history of protein degradation research is essential. Several simple protein-degrading enzymes have been known for a long time. One such enzyme is trypsin, which breaks down the proteins in our food into amino acids in the small intestine. Likewise, the lysosome, the cell organelle in which proteins are absorbed from outside and broken down, has long been studied. Common to these processes is that they do not require energy to function.



Experiments as long ago as the 1950s showed, however, that the breakdown of the cell's own proteins does require energy. This had researchers stumped for decades, and it is precisely this paradox – or rather its explanation – that won the 2004 Nobel Prize in Chemistry: that is, the breakdown of proteins from within the cell (that is, endogenous proteins) requires energy, while foreign protein degradation takes place without added energy as illustrated earlier.

The discovery of the UPS system paved the way for a novel drug delivery system that goes by the name of PROTAC (Proteolysis Targeting Chimera). This is a synthetic molecule that not only quickens the transfer of ubiquitin to the target protein but also makes it more efficient. But how does this happen?

The PROTAC molecule is heterobifunctional, which is a fancy word to say that it has two sticky sites. One of these sites binds to the E3 enzyme and the other to the target protein. It then facilitates the ubiquitylation of the protein, and after the formation of the ubiquitin-protein complex, the PROTAC machinery is recycled to target another copy of the target protein, eventually leading to its destruction.

This discovery was groundbreaking in the field of pharmacology and medicine. Until its discovery, misfolded proteins in the body were destroyed by plugging the active sites of these proteins (the site in the protein that binds with other molecules) with a drug of a particular shape, thus rendering the misfolded protein incapable of harm. However, this meant that there would need to be a high concentration of the drug within the system for it to carry out its function. With PROTAC, there is a lesser amount of drug required as PROTACs can be used in multiple cycles of degradation. They can maintain activity without needing to be administered at high concentrations.

In short, PROTACs and the ubiquitin-proteasome system (UPS) make a powerful combination for targeted protein degradation. This approach can lead to more effective cancer treatments and exciting advances in personalised medicine!

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