Naturalists

BIOSPHERE

August 2024

Editorial

Greetings Naturalists!

We humans have always gazed upon life and its origin with awe - a phenomenon so astonishing that, for centuries, it was attributed to forces far greater than ourselves. In a world governed by absolute laws and predictable patterns, life injects invigorating energy and unpredictabilty. The ubiquitous existence of life on Earth is nothing short of remarkable. From the searing heat of hydrothermal vents to the icy depths of freezing lakes, life always finds a way, defying the odds that nature presents. "BIOSPHERE" is our celebration of this vitality - a tribute to the wonders that the living world offers.

This debut issue was envisioned and executed by our predecessors, Chethana, Dhruba, and Shreshth, last year. Within its pages, you'll discover engaging interviews with researchers and instructors at IISc, as well as informative articles covering novel and impactful research across various fields of biology. This issue also features a wonderful piece by a UG alumna reminiscing about her semester abroad, along with an insightful lab visit to SAInI's laboratory at DBG.

Happy reading!

Shloak Vatsal
Editor

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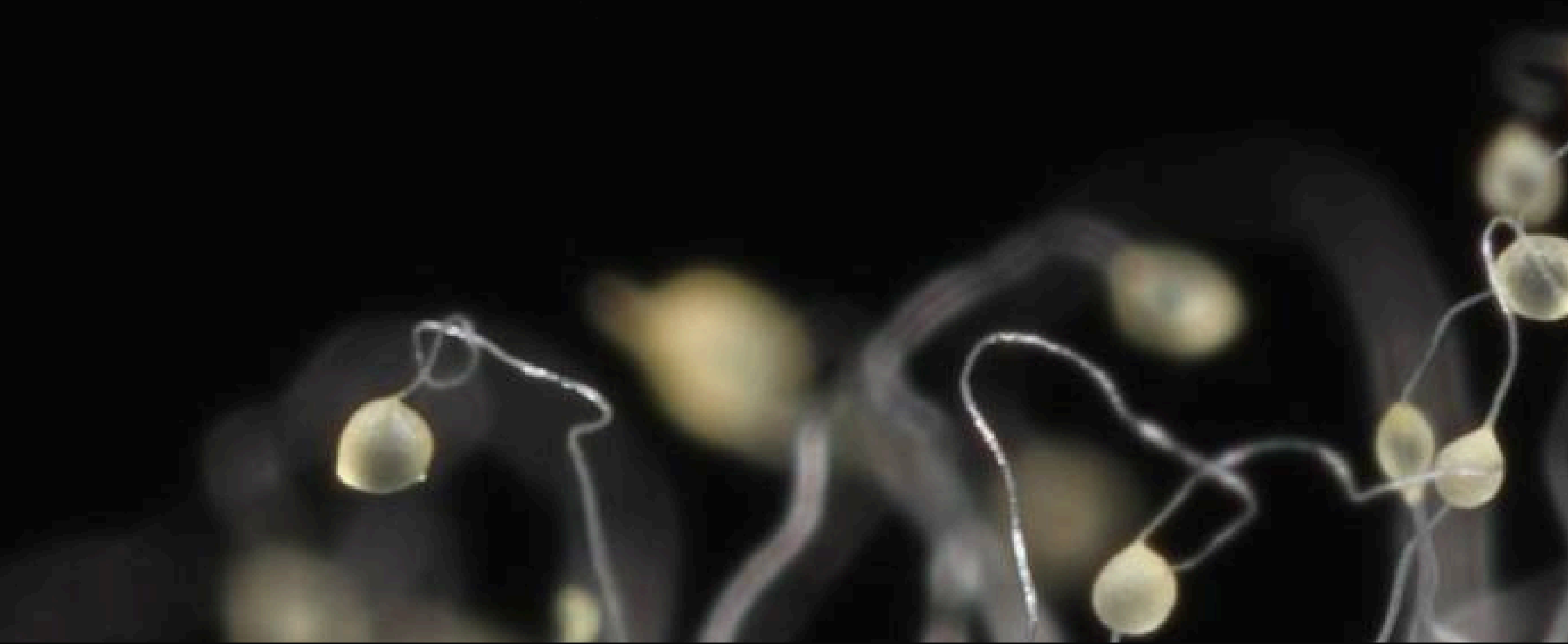

A Journey into Ageing

- Divija N., Shinjini M., Shreshth J., Chethana N., Dhruba D.

The era of modern biology grapples with a multitude of complex and fascinating phenomena, of which ageing is one of the most challenging problems. An epitome of the research vigour characteristic of IISc is the SAInI lab at the department of Developmental Biology and Genetics (DBG). It is a nexus of study into Aging, Inflammation, and Infection with a keen focus on G protein-coupled receptors (GPCRs). Not just content with studying these receptors, the team's groundbreaking research extends to exploring the 'cross-talk' between GPCRs and other receptor classes in relation to age-related cellular responses.

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The naturalist convenors interacted with Professor Deepak Kumar Saini to gain insights into his scientific journey and the study of fascinating, intricate pathways underpinning the very fabric of life.

Prof. Deepak, could you walk us through your academic journey and how it has influenced your current research focus?

Deepak Saini (DS): After completing my bachelors in biology and chemistry at Delhi University, I pursued a masters in biotechnology, followed by a PhD in biotechnology, with a focus on clinical microbiology and molecular biology, at AIIMS, New Delhi. My academic journey then took a turn, with postdoctoral work in neurobiology and microscopy at Washington University in St. Louis, USA. This shift led me to the fascinating world of signalling systems, while also stoking my interest in aging. This combined interest eventually brought me to IISc in 2010 as faculty.

It seems you've taken a considerable leap from microbiology to signalling and then eventually aging research. How did this transition come about?

DS: As a PhD student, I explored cell-cell signalling, and later during my postdoctoral training, I focused on GPCR (G-protein-coupled receptors) signalling. The idea was to get exposure to more diverse areas from microbes to mammalian systems where we can do signalling studies. Interestingly, I did not like cell signalling during my masters - I always used to get intimidated by so many arrows going everywhere. However, I felt signalling was the challenge that I must tackle.

Our fundamental interest is in signal transduction. My group applies signalling studies in context of aging and how bacterium senses its world. This then leads to problems in interdisciplinary fields where one can look at biomaterials and aging. But, at its heart, we study how something reacts to stimulus. The focus on aging research emerged later, but it's essentially rooted in studying how organisms react to various signals.

After coming to IISc in 2010, how did you start the entire lab? How were the initial days?

DS: It's interesting, I joined in the old Biological Sciences Building. This building (the new DBS dept.)

was still under construction, even during my interview. I was hoping that by the time I joined it should be ready. It was not. So, I joined the old MRDG, which was what DBG was called previously. That time I took up some space in the lab of another faculty who was going to retire soon. It took us almost one and a half year to get the whole lab started in its full glory. Most of my equipment pretty much spent their warranty period in the boxes in the old department. Since we were hoping for our lab to shift, we were the first ones to relocate.

When you initiated the lab, did you start with aging or with cell signalling?

DS: Signalling, yes. When you start a new lab after your postdoc, you generally tend to lean on the projects with which you can hit the ground and start running so that there is a minimum lag time. When I started the lab, even though I had an interest in both aging and signalling, I had never worked on aging. And so, we started projects on signalling – the first two of my students took up bacterial signalling (a two-component signalling) and GPCR respectively. But there was no work on aging as such until the next year, when my third student joined, who showed interest in starting a project on ageing.

Who was the first person to have joined the lab?

DS: I joined in February 2010 and by August 2010 there were two students, and both were named Ruchi. We had to let go of their first names and used their surnames. One was Agarwal and the other was Jain, so it became A and J.

It sounds like students played a significant role in shaping the lab's research trajectory.

DS: Absolutely, the students had a crucial role. They helped in defining the domains we still work on, even after the initial three have gone for their post-docs.

How have your projects changed in today's context since you started?

DS: Initially, the projects I was involved with were primarily fundamental in nature. Now we think more about the practicality and translational impact of our projects. For instance, a project that I undertook revolved around studying GPCRs and their influence on downstream signalling within cells, using microscopy as a tool. Projects of those types have been shelved because they were not aligning with the aging problem that we started to work on. As a result, the majority of our projects in eukaryotic signalling now exclusively concentrate on various aspects of aging. All the problems which we are working on revolve around various aspects of aging -its drivers, its effects, modulators, drug screening, and the investigation into genes that regulate various dimensions of aging.

As for bacterial signalling, our work continues with two-component systems. These projects still uphold the essence of our initial discoveries, which were quite unanticipated and intriguingly deviated from conventional findings. Our continued interest in these problems stems from the captivating nature of the issues they present.

Can you describe the ideation process for a new project in the lab? How much influence do you and the students working on it have in this process?

DS: Typically, when students join the lab, we provide them with the autonomy to choose which of the two domains they wish to work on. More often than not, they have already formulated an idea of their preferred research direction. The conception of a project usually arises from mutual discussions. For instance, with the first few students, I outlined the problems we would like to investigate. However, subsequent students tend to formulate their research questions based on peripheral ideas or observations made by their senior peers, which they find intriguing. The issue at hand might expand into a bigger research question or might reach a conclusion - we let it evolve naturally, embracing the journey as it unfolds.

You talked about having collaborations with other labs. Can you elaborate on the collaborations that have happened? In what domains have they occurred?

DS: My lab collaborates extensively. My belief is that modern science is so broad and diverse that it is practically impossible for one person to possess all the necessary skills. Furthermore, if someone else has a skillset that I lack, I don't see the need for me to invest time in learning it when we can partner with those who can execute these experiments more quickly.

For instance, in my bacterial signalling work, I collaborate with Narendra Dixit from the chemical engineering department, who contributes significantly to our mathematical modelling. When it comes to protein-protein interaction modelling, I work with Nagasuma Chandra. For signalling studies requiring MD (molecular dynamics) analysis of receptors in altered signalling scenarios, we collaborate with Ganapathy Ayappa. We've also worked with many chemists who develop new probes and drug entities for our molecules, which prove useful in the context of aging.

Currently, we're collaborating with Kaushik Chatterjee, a materials engineer. Together, we're working to develop an aged lung model to comprehend how an aged lung might have a predisposition to fibrosis.

We're also working with Shantanu Shukla to examine the microbiome aspect of aging and with Ramray Bhatt, a specialist in cancer biology, to understand how aging increases the predisposition to cancer. The studies are diversifying, with more and more people getting interested in ageing. And I intend to keep it that way.

Are there any unexplored areas where you'd like to extend the lab's research domain?

DS: We're intrigued by numerous fascinating topics within the realms of ageing and tuberculosis signalling. However, the direction of our expansion should be in line with the current trends in the field. We're particularly interested in studying aspects of ageing vis-a-vis human cohorts. As of now, we conduct a lot of molecular and animal studies, but we're eager to branch out into human population studies. This necessitates a shift in mindset, the formation of new collaborations, and the utilization of different tools rather than just traditional microscopy that we're accustomed to.

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Students are at the heart of the projects undertaken in the lab. Naturalists had the opportunity to interact with some senior members who warmly shared their journeys of scientific endeavour and experiences in the lab. We present to you some excerpts of the engaging conversations.

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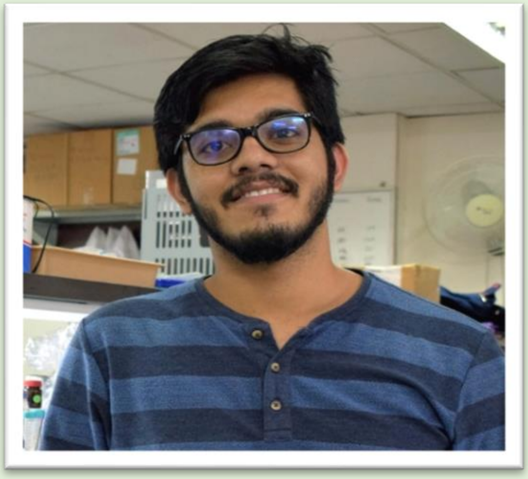
Abraham Mathew joined the PhD program in August 2018. He specializes in biotechnology and has completed his bachelor’s degree at Fergusson in Pune, and master’s degree from the Pune University. He works on various dynamics of cellular senescence.



Why did you choose Dr. Saini's lab?

Abraham Mathew (AM): Prior to my PhD, I had experience working on the mammalian system and eukaryotic cell lines. I did not want to shift to an alien field line proteins or prokaryotes. When I was deciding where to continue my research, I observed that most labs across India focus on cancer. However, Dr. Saini's lab stood out as it emphasized aging, which is associated with several lifestyle disorders such as cancer, diabetes, heart diseases, neurodegenerative disorders, and more. The understanding that controlling aging could potentially manage these disorders up to some extent motivated me to join Dr. Saini's lab, which is one of the few labs focusing on aging.

Can you describe the lab culture in the Saini lab?

AM: The lab culture in Saini lab is quite vibrant. I enjoy coming to the lab every day, even if there's no specific work. We have a congenial environment where everyone is supportive and willing to help. Dr Saini is encouraging and open to interesting ideas for experiments. I made a lot of friends, even with past members of the lab who are in touch with me. The lab has helped me grow both personally and scientifically with colleagues who, I believe, are all smarter than me and consistently offer great ideas and suggestions.

Have you mentored any interns in your lab? Can you tell us about your experience?

AM: Yes, I have had the opportunity to mentor a few interns. I've found the experience of mentoring quite rewarding. One of the interns I mentored was an MBBS student from CMC. I helped him understand histopathology, which was relevant to his work. I also mentored Nahid from Delhi University, who did her bachelor's and is now pursuing her master's. I'm also currently mentoring a final-year UG student, Souvik, who is doing his thesis work with me.

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Devandra Pratap Singh is a 6th year PhD student who joined back in July of 2017.He studies the two-component signalling in Mycobacterium Tuberculosis. He pursued his undergraduate and master's studies from a college associated with Dr. Ramanavalli, under Awadhi University, Failor.

What are the uses of studying two-component signalling in Mycobacterium?

Devendra Pratap Singh (DPS): Well, the two-component signalling system is quite primitive. Currently, our approach to studying the system is based on two proteins, the sensor kinase, and the response regulator. The sensor kinase senses signals and transfers the information to the response regulator, its downstream partner. This regulator ultimately gives the outcome, such as changes at the gene expression level or inhibiting some protein activity.

We study this signal transfer which occurs in the form of phosphorylation of these proteins. In our biochemistry experiments, we verify these proteins and incubate them with ATP, causing the sensor kinase to get phosphorylated. Then we incubate this phosphorylated kinase with the response regulator. This process is akin to phosphate hopping from the sensor kinase to the response regulator, effectively transferring the signal information.

In terms of biophysics, we purify the sensor kinase and response regulator. We can utilize techniques such as isothermal calorimetry, surface plasmon resonance, or biolayer interferometry to study their interaction. We typically use microscale thermophoresis for these studies, which allows us to monitor changes in the interaction based on the movement of the labelled molecule.

Have the projects in the lab changed over the years?

DPS: Projects in our lab tend to evolve over time. For instance, when I first joined, our crosstalk study was focused on in vitro studies and mapping out systems involved in the crosstalk. We then collaborated extensively both inside and outside the IISc campus and expanded our study areas significantly. We even ventured into crystallography and computational studies.

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Dr. Amrita Nepalia is a postdoctoral researcher, and her work is centred on understanding the ageing process, specifically the signalling pathways involved in cellular senescence and the factors that trigger it. She completed her PhD at the University of Rajasthan, Jaipur.

Could you share some details about your current projects?

Amrita Nepalia (AN): During my tenure under the Kothari fellowship in the lab, I embarked on a significant exploration into cellular senescence, specifically the roles of kinases and phosphatases.

In Dr. Deepak Saini's lab, we conducted extensive studies using an shRNA library. We began by knocking out different kinases and phosphatases, subsequently monitoring senescence parameters such as cell proliferation, SA-beta galactosidase, and inflammation.

We singled out specific hits from this investigation for further mechanistic study to comprehend their role in senescence. Interestingly, we uncovered a mitochondrial protein that acts as an independent driver of cellular senescence. When the levels of this protein were modified, senescence patterns also changed. Indeed, even without inducing damage, cells turned senescent when we suppressed this protein. This discovery marked a significant milestone in my Kothari project. In my ongoing work with Dr. Saini, we're collaboratively examining the use of bio-dendrimers as drug-delivery systems for substances like resveratrol and various phytochemicals. Additionally, we're striving to create a 3D model for lung fibrosis. Dr Saini continually inspires me to draft grants and project proposals, encouraging an independent line of thinking and fostering a spirit of inquiry.

What are your future plans?

AN: Presently, I'm applying for extramural grants, notably a scheme specifically for women called BioCARe, offered by DBT. In case that doesn't pan out, I will look for other opportunities in academia where I can continue my research work.

Are you considering faculty positions in the future?

AN: Yes, I would be interested in pursuing faculty positions. However, I feel I need to acquire a few more skills on the bench before taking that step. My plan is to continue hands-on work for at least one or two more years.

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The current work in SAInI Lab reflects the dedication of the researchers to the field and the collective effort to understand mechanisms of ageing and disease. Looking to the future, we can expect to see several valuable contributions in the field of biogerontology made by this tenacious and inspiring team. We wish them the best in their endeavours and look forward to further illuminating discussions in the future. The world of science is undoubtedly more prosperous by their involvement, and we are grateful to the members of the lab for sharing their journey with us.

Prerna Sharma

Active Matter Biophysics

- Shravani Deoghare

Pursuing science is an endeavour with countless wonders as well as challenges. We have had the privilege of interviewing Dr. Prerna Sharma, with whom we explore multiple aspects of doing research in science. We also delve into her field of study which is within the exciting realm of biophysics. Prerna Sharma is an Associate Professor at the Department of Physical Sciences and a faculty member of BSSE (BioSystems Science and Engineering) at the Department of Biological Sciences, here at IISc. After completing her PhD in TIFR, Mumbai, and Post-Doc at Brandeis University, Massachusetts, she started her tenure as a faculty member at the age of 28. Dr. Prerna has had an illustrious career so far - her most notable works regarding micro-phase separation in membrane biophysics have been published in Nature.

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Could you share your personal journey as a researcher? What inspired you to pursue this field, and how has your journey been so far?

Prof. Prerna: Well, I was an undergraduate Physics honours student at St. Stephen's College. The first year was challenging, but by the second year, I had begun to grow comfortable with the course. Initially, I had different career paths in mind – becoming a civil servant, pursuing an MCA in computer science, or taking up an MBA. Alongside these, I contemplated continuing with physics.

The turning point came when a senior mentioned that he would be joining TIFR, Mumbai for a Ph.D. program, along with a fellowship. I liked physics and when I was assured of some salary to go with, there was nothing like it. It was the best of both worlds. After clearing the TIFR entrance exam and subsequent rounds of interviews, I joined the integrated Master's and PhD programme at TIFR, which I completed in six years. After that, there was no looking back. I pursued a postdoc before eventually joining as a faculty member here. Of course, I didn't anticipate delving into such a lengthy career. Financially, you have support during your PhD and postdoc, but there's no assurance of a job. So, you need to have a genuine passion for the subject and be resilient enough to handle the journey.

Regarding biophysics, during my PhD, I worked in an area called soft matter physics (and still do), which lies at the intersection of physics, chemistry, and biology. Although I was fascinated by biophysics during my undergraduate years, I wasn't sure if I was ready to delve into it seriously, and hence consciously chose soft matter physics.

After that phase, I felt a strong desire to explore biology and was confident in my ability to pursue this challenge. I was fortunate to be hired as a postdoc in a lab that didn't strictly focus on biophysics but rather bio-inspired physics - they used biological materials to investigate physics-related questions. While some aspects of my research align with core biophysics, for example, ciliary beating, I generally work on soft matter-related problems.

What would you consider to be the most challenging phase of your career?

Personally, I found my PhD to be the most challenging. It is a roller coaster ride where you're learning new things, making mistakes, and expected to produce something original, non-trivial, and highly creative. However, after settling in I began to enjoy it. Even after completing six years of my PhD, I was still excited, approaching labs with new ideas and seeking ways to conduct experiments.

Could you give a short description of what your PhD thesis is like?

Yes, I worked on interfacial physics. I focused on how colloidal particles adhere to glass substrates and developed a sensitive technique to measure the strength of adhesion. Normally, you can measure friction using either macroscopic instruments or highly precise nanoscopic instruments. We wanted to measure friction on the micron scale, which is in between. I developed a technique where optical tweezers were used to hold the particle and bring it into contact with the substrate in a well-defined manner, allowing us to measure the strength of adhesion.

Additionally, I studied problems related to fluid flow through porous media. We were interested in the interfaces between the solid and the fluid, particularly in how the morphology of the porous medium affects flow.

What inspired you to choose these problems? Could you explain the applications these questions have or the relevance of these questions to any modern-day applications?

Essentially, these were the problems chosen by my advisor for me. I was particularly interested in the porous media problem, and my advisor allowed me to pursue it on my own as a senior student. From an application standpoint say, in food additives or biofilms, you need to know how micron-sized constituents adhere to substrates. However, we wanted to focus on the simplest version of the problem, which is how micron-sized plastic particles stick to glass. This didn't have direct applications, but it is relevant to several applications as such.

Additionally, studying flow through porous media is significant because it relates to oil recovery. When you have oil trapped in rocks beneath the ocean, you push water through to extract it. I was studying fluid flow in that medium, which has direct relevance.

What sort of questions is your lab trying to address as of now?

Well, I find that to be the fun part! Consider the field of biological active matter - most biological matter is considered active matter because individual constituents consume energy and perform work or movement. In my lab, we study algae cells, specifically Chlamydomonas. We observe their phototaxis and motility, among other things. I want to investigate their collective behaviour. While there have been many studies on Chlamydomonas and single-cell behaviour, particularly in biology, most of them don't focus much on the effect of cell concentration or collective effects. I plan to spend some time examining these aspects.

I'm also excited about projects related to membrane biophysics. We have a platform of colloidal membranes made up of rod-like viruses assembled in a 2-D monolayer geometry. I'm interested in studying how we can change the morphology of these sheets. The physical forces and mechanisms required to remodel cell membranes can be mimicked in the colloidal membrane system. We also have a system where we can study interactions between these membranes and other proteins or objects, making it more realistic since cell membranes are constantly interacting with the outside world.

Curvature instabilities on crystallised colloidal monolayers

How relevant is it that the membranes are made of viruses?

That's a very good question. We chose viruses mainly because they are highly monodispersed and have consistent dimensions. We are using non-pathogenic bacteriophages, which are single-stranded DNA coated with proteins. Nature produces them in identical forms, meaning that viruses of the same length have the same diameter.

It would be challenging to achieve such a level of monodispersity with synthetic rods. The goal is to self-assemble these viruses into fluid-like structures and create monolayers.

This model system shares key physical properties with cell membranes. For example, in both systems, the components are free to diffuse, and they exhibit two-dimensional behaviour. They also have similarities in terms of long-wavelength elasticity and bending rigidity. These shared physical properties allow us to establish a relevant analogue for membrane biophysics.

Apart from research themes in your own lab, are there any other subjects in soft matter physics that you're particularly excited about?

Yes, there are many fields that I find fascinating. One of them is DNA origami, which involves creating DNA structures with specific shapes and patterns. I'm also excited about DNA droplets which are created by designing the structures in a manner such that they coalesce into clusters. These fields interest me because it offers more flexibility, compared to using viruses. With DNA origami, I have greater control over the chemistry and physics involved. I can easily modify and functionalize these origami objects, which is not as straightforward with viruses.

Quite often, the scaffold DNA used in origami is derived from the same viruses I work with. Hence for my benefit, I read relevant papers relating to virology to gain useful technical knowledge.

What are some recent developments in biophysics, or soft matter physics, that upcoming researchers could focus on?

I may not be the best person to provide advice regarding biophysics because my focus is tangentially related to biological systems. However, in biology, there is an interesting trend where theoretical ideas from the field of active matter are being applied to core biophysics problems.

For instance, in motility assays involving molecular motors and actin filaments, fundamental biology has a good understanding of how individual motors work on filaments and the forces they exert. But when you have thousands of these motors and filaments interacting, complex patterns emerge that cannot be explained solely by understanding individual motor-filament interactions. Interdisciplinary collaboration is key as research on living systems and modified biomaterials would be needed to develop a theoretical framework for such phenomenon.

How does one build up the mental space for making the transition to doing research? This is in the context of us as undergrads wanting to pursue research but have been exposed to an education system comprised of rote learning.

When it comes to making the transition into exploring scientific questions and considering a long-term career in academia, my advice would be to focus on absorbing the material on your own terms. For me, the joy of academics came from immersing myself in the subject matter and taking my time with it, even if I didn't understand everything immediately.

If you can learn how to think critically about the material being taught, you will be well-prepared to pursue science. The key is to reflect on the knowledge rather than just respond to it during exams. By truly internalizing and owning the knowledge, you will be better equipped to generate creative and original ideas.

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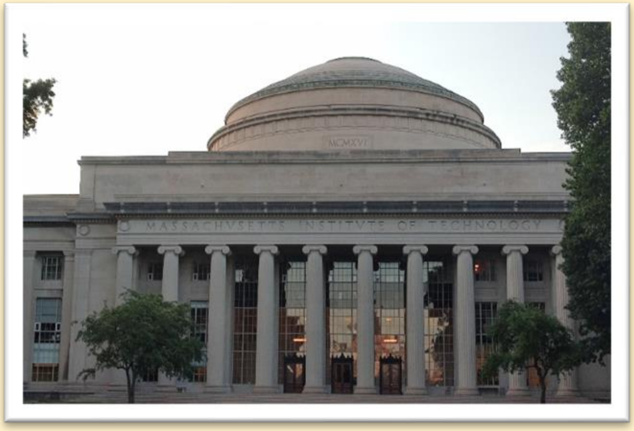
We were amazed by Dr. Prerna's journey and her valuable insights during our interview. Her strong passion, resilience, and interdisciplinary approach are truly inspiring and can be beneficial to aspiring researchers. Prof. Prerna's advice on critical thinking and reflection is noteworthy, and her technical knowledge provides valuable perspectives on relevant research topics in biophysics. We hope that this interview has left you excited to delve deeper into the fascinating world of soft matter and biophysics!

Lessons for Lab and Life

- Abheepsa Nanda

As my flight landed in Boston in July of last year, looking out over onto the glittering waters of the Boston Harbor, I felt anticipation and nervousness all at once. The surrealness of being in another country all by myself, without friends or family, hit me like a brick wall –Would I be able to live by myself, independent and alone?

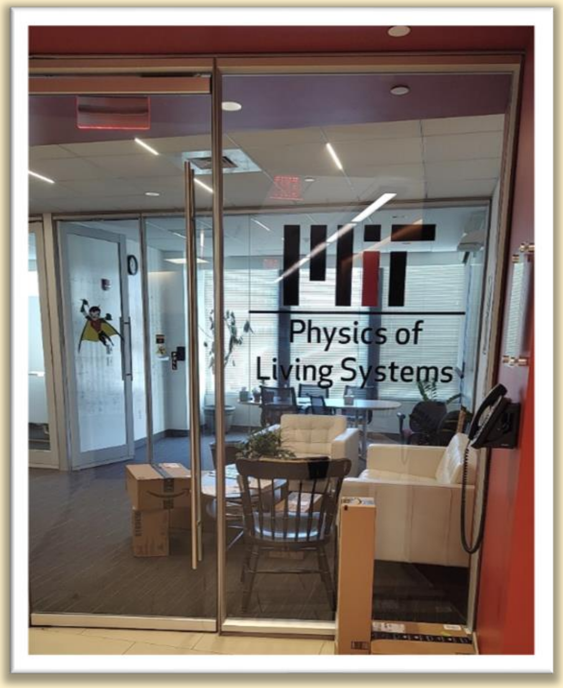
I spent seven months, from July to December of 2023, doing my thesis project in Cambridge at the Physics of Living Systems (PLS) department in the Massachusetts Institute of Technology. I interned in the Gore Lab, which works broadly on ecological systems biology, using microbial communities as tractable model systems to understand ecological and evolutionary dynamics. I had been following Professor Jeff Gore's work for a while and was overjoyed when he replied to my (embarrassingly persistent) cold mailing to accept me as an undergraduate intern in his lab! And after months of annoying visa troubles, housing hassles and a last-minute bout of COVID, I had finally managed to make my way to Cambridge.



As a part of Gore Lab, I worked mainly on understanding how carbon resource concentration and type determined the species diversity of bacterial communities. Since diversity determines stability as well as the functionality of microbial communities, which play an important role be it in biogeochemical cycles, human health or in industrial processes, the factors determining diversity are important. Gause's principle of competitive exclusion by extension suggests that the number of resources available in the environment determines the species diversity available. However, cross-feeding in bacteria, a phenomenon wherein certain bacteria metabolise a resource and share intermediate metabolites which other bacteria can then use and survive on, means that Gause's principle is violated in microbial communities. Hence, I used a combination of monoculture and community experiments as well as genomics and metabolic modelling to understand (or at least attempt to understand) resource-diversity relations in soil microbial communities.

Apart from work, I also explored MIT and Boston! Being present during the school year (as well as being fortunate enough to get on-campus housing) meant I could participate in plenty of MIT club activities and events – and I took full advantage. I tried sailing, surfing, rock climbing, became a regular member of the LARPing club, attended concerts and went to parties. When autumn tumbled around and trees turned vibrant hues of orange, red, yellow and violet, I went on a hike with the MIT Outing Club to Vermont to see the fall colours. I roamed around Boston, with friends or by myself, made easy by the local metro or the 'T'. I even managed to make a couple of trips to New York City and a trip to Washington DC! But living alone also came with a fair share of responsibilities. I also had to learn how to manage my own finances, meals and household chores. Cooking became a way for me to de-stress (read: procrastinate on my graduate school applications) after work and I experimented a lot with food in the early few months.

My semester abroad has heavily influenced my current approach to science and my education, even outside of working on my project. I met and interacted with many interesting academicians, be it through talks or



through their visits to our lab (including my personal hero, Dr. Manu Prakash, inventor of the Foldscope!). Gore Lab is highly interdisciplinary, and members came from all over the world and over lunches I heard a lot about how science was conducted in other countries. Hearing the perspectives and advice of such a broad range of people influenced my own view of what my academic journey should be. I talked to several exceedingly helpful people about the various graduate programmes I wanted to apply to and it was while talking to some of these people that I learned about and was recommended the masters programme I am going to join in a few months! I learned that it is okay to take your time with your academic journey, learned what is important when picking a lab and how to maintain a work-life balance. I also took a sneak peek at a life of full-time research (and decided I liked it!) and learned how to do more independent research. I found several mentor figures in the senior members of my lab who I hope to keep in contact with.

All in all, my seven months abroad ended up being one of the most important experiences of my undergraduate career and shaped a big part of who I am and what I want to do in the future. After this, I begin my Masters programme in ETH Zurich, which I hope will be a similarly transformative experience!

HS Vinod

A foray into UG biology labs

- Diya S., Tanisha K.

Anyone who is an undergraduate student of IISc and interested in biology won't need an introduction to him, but HS Vinod made our lives so much easier during the third and fourth semester biology labs. We went to meet Vinod one fine afternoon when he was busy helping out the iGEM team, and an interesting conversation that shone light on the many facets of biology followed.

T: What was your journey in the field of science like?

Until high school I was an average student, I would not say I was highly talented. During my bachelors, a few professors really inspired me regarding both teaching and research. I worked in a tissue culture lab and was taught to troubleshoot various problems at experiment checkpoints. Even though the facilities were less, at least when compared to IISc, they managed to teach us very efficiently.

We worked on an anti-cancerous drug producing plant. We proliferated multiple generations and they are still cryopreserved. The stock preserved by my batch is still being used, as we produced them in bulk. It can last them for at least 10 more years.

During my post-graduation, I worked on genetics. There, one of my teachers taught us to correlate science to daily life - say, for any disease faced by a family member, we can learn about the cause of the disease by studying the background of the same.

Since my masters, I was set to follow a career in research. The main purpose of taking up this job at IISc is to do research, but I like teaching as well.

D: What kept you motivated in this field of work?

I have worked here for almost 7 years, starting with the 3rd semester labs to the 2013 batch. From then on, I have seen the subsequent UG batches. For teaching UGs, even we have to prepare a lot, otherwise they will end up making memes.

Even if we do the same experiments each year, we have to keep up with the changes in the field of science. There is no hundred percent truth in science. The truth keeps changing with time.

T: New ways of conducting the same experiments are also coming up.

Exactly. So, it becomes quite challenging as we have to update our knowledge accordingly. Reading gives us more ideas about the same and it becomes interesting to work upon.

T: What is your work here as a lab instructor?

We prepare most of the experiments for labs.

It is challenging to reduce an entire paper to a 3-4 hour experiment, hence we end up doing a lot of homework. There are a lot of things we must take care of and ultimately, we should get results too.

We don't really have to bother about the result unless inferences on positive or negative results are to be drawn. It is more important for students to learn the techniques. However, students always want positive results, so we have to put in that effort as well.

I have also been working on my own research. I have some ideas on host-pathogen interactions. I have discussed with many professors regarding this, and they have guided me towards better solutions. I have proposed my hypothesis to many hospitals wherein people have agreed with it. However, it is not completely executed yet. If and when approved, a lot of people's health issues may get resolved.

D: What do you like the most about your job here?

I like the conversations with students. Especially, if they come up with "why this, why not that" questions. Sometimes, even we may not know the answer, but we are all here to find answers.

T: What do you like about the undergraduate program here?

In our college days, we did not have access to such sophisticated instruments – our knowledge was limited to theory. Handling the instrument, yourself and troubleshooting on the way will help you have a good grasp on the technique, which is something our labs can provide.

The advanced curriculum is also a plus. Here, students are exposed to topics in mathematics and physics too, apart from a major biology discipline. As a result, several UGs are good at computational biology as well as practical biology.

D: Any advice for the UG students?

I find that they are not utilising a hundred percent of the facilities here. Many are simply eager to leave and only a few focused students properly complete the experiments. During this age it is understandable to have such an attitude, but it will be help them if they learn the basics here so that they can learn more advanced techniques in the established labs.

Many students also keep switching from one lab to another. It is good, in a way, because they are learn new things, but the drawback is that nothing may work for them. I have seen students in both the categories.

The lifestyle of students is another issue. Even though they get freedom from their parents, proper food, sleep and a little bit of exercise helps with good physical and mental health. The curriculum puts them under pressure, but if they can still manage to find a few minutes for exercise, it will be good.

ARTICLE

Unstructural Biology and Drug Design

-Kedhar R

The function of a protein is heavily dependent on its three-dimensional structure, or so is what most (older) textbooks say. However, a class of proteins called 'Intrinsically Disordered Proteins' (IDPs) have, in the past 2 decades, been proven to have important functions within all biological systems.

In this article, we explore how this relatively new sidekick of molecular biology, 'unstructural' biology, has been making waves in the field; and we also talk about IDPs as potential drug targets.

More than a third of the eukaryotic proteome contains intrinsically disordered regions of over 30 amino acid residues. These proteins lack a unique 3D structure when they are isolated and exist in multiple interchangeable conformations. This lack of fixed structure can be advantageous in the cell, as one protein can interact with multiple other proteins due to larger recognition surface area and conformational flexibility. They are ideal for certain tasks within the cell such as regulatory and signalling functions. Proteins involved in these functions are enriched in intrinsically disordered regions.

However, there arise a few caveats with the presence of IDPs in cells. These proteins need to be carefully regulated within the cell, as excessive expression causes issues. Their interactions with other proteins in nature are largely linear motif mediated, and as related proteins often contain similar binding sequences for such motifs, an excess concentration of IDPs may cause them to bind to each others' targets, causing problems. Altered availability of IDPs is associated with cancers and neurodegenerative disorders. The regulation of these proteins within the cell occurs by various mechanisms, ranging from regulated transcript synthesis to post-translational modification and increased degradation levels.

Most drugs in use today target enzymes or cell-surface receptors. There are almost no commercially available drugs that specifically target intrinsically disordered regions in proteins. However, IDPs make good targets for many reasons. Primarily, these proteins, as stated above, are important in signalling and regulatory pathways, and are hence also associated with a wide range of diseases. Overexpression ofthe c-Myc protein, for instance, is found in human cancer cells.

Drugs that target these proteins can work in multiple ways. The interactions of IDPs with partner proteins can be an effective target mechanism, as shown below. Disordered regions can be predicted accurately by sequencing. Within these regions, there exist sequences called Molecular Recognition Features (MoRFs) that undergo binding interactions. Small molecules targeting these sequences can thus effectively inhibit protein function. Targeting of the post-translational modification mechanisms that are essential for the function of IDPs is also a viable option.

Now, we talk about a specific oncoprotein called C-Myc. This protein is essential in proliferation of mammalian cells. However, its deregulation and overexpression are features of cancerous cells. C-Myc is a regulatory protein, which binds to DNA and regulates expression of target genes. Its function is dependent on dimerisation with another protein, Max (I have not made this name up). Small molecules have been identified which target the MoRFs on C-Myc and inhibit C-Myc-Max association. In mice, it has been observed that many of these compounds inhibit tumor growth in vivo.

Another disordered protein, EWS-FLI1, is associated with Ewing's Sarcoma, a cancer affecting bones and surrounding tissue, prevalent in children and young adults. This cancer can cause pain and broken bones even in the absence of injury. The binding of EWS-FLI1 with RNA helicase A (RHA) is thought to be involved in development of the Sarcoma. Small molecules have been found which can reduce RHA–EWS-FL1 binding, inhibiting tumor growth. Since EWS-FLI1 expression is specific to cancer cells, it is a viable and effective drug target.

In conclusion, the study of intrinsic disorder in protein is an exciting field of active research and offers not only a better discernment of all biological systems but can also be exploited for effective drug design. Understanding IDPs is key to further research of cancers and neurodegenerative diseases, which are some of the most disastrous, yet mysterious diseases plaguing humankind. Identification and characterisation of IDPs has proved to be important in understanding various biological pathways, and modern advancements in technology will aid in more research in the field.

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ARTICLE

Virovory

-Abhishek Kundu

Virovory, the consumption of viruses by other organisms, is emerging as a fascinating new field. It has already been established that viruses are a significant component of the natural food web, contributing to most mineral cycles and keeping various biomolecules in rotation. Many aquatic animals have enzymes that help degrade and digest viruses, providing a (previously hypothesised) negligible nutrient source to the organism. It had been experimentally observed that these organisms reduced viral abundance by up to 98% (in sponges). Hence, the theory of virovory in protists and metazoans has been introduced previously. However, what is new is the concept of an organism selectively feeding on a specific virus.

A recent paper published in late 2022 has produced conducive results that support the existence of virovory in the protist Halteria sp. The experimental setup involved growing two species of protists, Paramecium bursaria and Halteria, in two environments- one medium devoid of chloroviruses and the other medium with supplemental chloroviruses. This was to study the potential of virovory as a potential energy pathway. The researchers then fitted experimental data into bootstrapped classic trophic link models to determine if the protist-virus interaction can be categorised as one of the everyday ecological interactions.

Observations from the paper include that both protists can reduce the density of chlorovirus plaque-forming units by up to 2 degrees. Under supplemented conditions, Halteria shows robust growth, with minimal to no increase in control populations, with a 17% increase in growth efficiency. These findings have opened new avenues for speculation on the stature of viruses in the ecosystem since data projection implies the ingestion of 1014 - 1016 viruses daily in a pond ecosystem.

However, further research is necessary to gain a comprehensive understanding of virovory. Ongoing studies are currently being undertaken to explore the mechanisms of viral identification and virovory, which could have implications for immunology and ecology. The coevolution of mutations in prey-predator interactions is an area of particular interest, as it may shed light on the evolutionary pressure of predation on viral genomes.

The evolutionary implications of virovory also warrant investigation. While no perceptible evolution was observed in the small-scale experiment, ecological studies support the notion that predation can drive directional evolution. This could lead to more pathogenic viruses or viruses with "smoother" surfaces featuring fewer identifiable proteins on their coats.

The discovery of virovory in Halteria represents a ground-breaking and exciting area of research. It has the potential to provide valuable insights into the intricate interactions between microorganisms and their environments in aquatic ecosystems. By unravelling the mechanisms and consequences of virovory, scientists may uncover new layers of complexity in the natural world and deepen our understanding of viral dynamics, ecological processes, and the coevolutionary dynamics between viruses and their hosts. In summary, the recent paper on virovory in Halteria sp. highlights the importance of viruses in ecosystems and introduces a novel perspective on their ecological significance. The findings pave the way for further exploration, offering tantalising avenues for research into the mechanisms, evolutionary pressures, and broader ecological implications of virovory. As the field progresses, we can expect a deeper understanding of the complex relationships between microorganisms and their environments, ultimately enhancing our knowledge of aquatic ecosystems and their intricate dynamics.

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ARTICLE

Bacterial Biofilms: New Avenues

- Shloak Vatsal

Biofilms are communities of microorganisms that adhere to surfaces. They are encased in a matrix of extracellular polymeric substances (EPS), which the microorganisms produce themselves. These communities have been found to be ubiquitous in nature and are involved in various environmental and clinical processes.

The biofilm formation process is a multi-step one that involves reversible attachment of planktonic bacteria to a surface, followed by the secretion of adherence proteins for permanent attachment and EPS, and the maturation of the biofilm structure.

Quorum-sensing is a crucial mechanism of regulating biofilm formation, involving bacterial communication by diffusible signal molecules,. As the bacterial population grows and reaches a critical threshold, the concentration of these signal molecules increases, leading to changes in gene expression and behaviour. Quorum sensing plays a significant role in regulating the production of EPS, the differentiation of bacteria within the biofilm, and the maturation of the biofilm structure.

The EPS matrix is critical for developing antibiotic resistance within the biofilm community. It acts as a physical barrier, preventing antibiotics from reaching the bacteria within the biofilm and provides a platform for the exchange of genetic material, which can lead to the spread of antibiotic resistance genes within the biofilm community.

Biofilms pose a problem in various clinical and environmental settings. They can form on medical devices such as catheters and implants, causing chronic infections which are difficult to treat with antibiotics. They can also cover surfaces like pipes and tanks, leading to the build-up of biomass and reduced efficiency of industrial processes. Hence, various methods are being researched to inhibit and destroy them.

Quorum-sensing inhibition is a promising approach to biofilm inhibition. One approach to inhibiting quorum sensing is using small molecule inhibitors that interfere with the production or detection of quorum sensing signal molecules. For example, acyl homoserine lactone (AHL) molecules are commonly used in gram-negative bacteria as quorum-sensing signal molecules. The use of molecules that compete with AHLs for binding to the quorum-sensing receptor has been shown to inhibit biofilm formation and increase the susceptibility of bacteria to antibiotics. Another way is the use of enzymes that degrade the quorum-sensing signal molecules. For example, lactonases are enzymes that hydrolyse AHLs and have been shown to inhibit biofilm formation in various bacterial species.

Disrupting the EPS matrix is another promising approach to biofilm inhibition. One method to destroy the EPS matrix is using enzymes that degrade the polysaccharides and proteins that make up the matrix. For example, dispersin B is an enzyme that degrades the polysaccharide matrix of Pseudomonas aeruginosa biofilms and has been shown to inhibit biofilm formation and promote the dispersal of existing biofilms. Another approach is using physical and chemical treatments that break down the matrix. For example, high-frequency ultrasound has been shown to disrupt biofilms' EPS matrix and increase bacteria's susceptibility to antibiotics.

Our understanding of bacteria today, from pathogenicity to natural processes, has developed considering their planktonic form. As more research is being done on biofilms, we are learning about their role in the bacterial life cycle. This will surely change how we think of bacteria in the coming future.