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KERNEL

Editorial

Coal gets a bad rap because it is the single largest contributor to climate change. Could its environmental impact be reduced using innovative technologies? A new centre at IISc seeks to address this monumental problem.

In this issue of *Kernel*, also read about the limitations of antivenom treatment in the country for deadly snakebites, artificial enzymes that can stop HIV from reactivating, and the diverse pursuits of an electrophysiology lab that is working on untangling how cells in the brain communicate with each other.

MAKING COAL CLEANER



Supercritical carbon dioxide test loop at IISc (Photo courtesy: ICER)

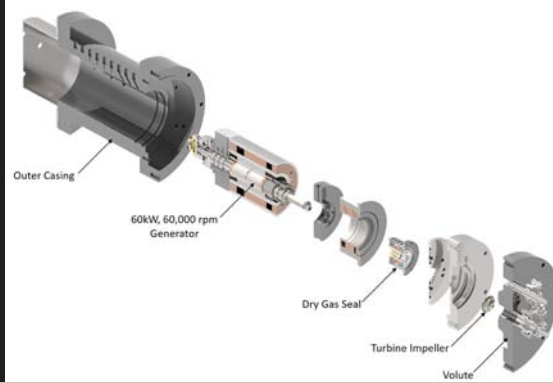
The climate change crisis has put the spotlight on fossil fuels, particularly coal, as a major source of environmental pollution. Coal is the **most polluting fuel**, but it continues to be widely used – it is India's primary energy source – due to the large amount of power it can generate, its abundance and low cost.

The need of the hour is to make its use cleaner and more environment friendly. The National Centre for Clean Coal Research and Development (NCCCRD) at the Interdisciplinary Centre for Energy Research (ICER), IISc, established in 2019,

aims to do just that. Funded by the Department of Science and Technology and led by IISc, it is a consortium of research groups from various institutions.

NCCCRD aims to develop technologies that increase the efficiency and reduce the environmental impact of coal as an industrial energy source, especially by reducing the carbon footprint of coal-based thermal power plants.

Thermal power plants burn fuels like coal to produce heat. This heat is carried by steam to turbines which rotate rapidly



and produce electricity through a generator. Researchers at NCCCRD are exploring ultra-supercritical steam and supercritical carbon dioxide as alternatives to steam. Supercritical CO_2 is a fluid state of CO_2 above its critical temperature of 37°C and critical pressure of 72.8 atm. It has the properties of both liquid and gaseous states – it can expand to fill compartments like a gas, but is also dense like a liquid. Similarly, ultra-supercritical steam is the state of steam above its critical temperature and pressure, where it has the properties of both water and water vapour.

Both Advanced Ultra-Supercritical (AUSC) steam and supercritical CO_2 plants would work at higher temperatures and pressures, which leads to a higher energy conversion efficiency. Therefore, more electricity will be produced for a smaller amount of fuel, reducing coal consumption.

Pradip Dutta, Professor at the Department of Mechanical Engineering and the Principal Investigator (PI) of NCCCRD, says, “We had previously set up a laboratory-scale supercritical CO_2 Brayton test loop facility as a part of an Indo-US collaboration for solar thermal power plants in 2012, but it was limited to research at the systems level. Currently, we are developing components like special heat exchangers and turbomachinery that can operate at high temperatures and pressures for the supercritical CO_2 based power plants.”

Designing compact turbomachinery – the moving parts involved in energy transfer – comes with a host of challenges, due to the high speeds of rotation ranging from 40,000 to 1,00,000 rpm. To ensure safe and continuous operation, researchers led by Pramod Kumar, Associate Professor, Department of Mechanical Engineering, are working on optimising the dimensions and structure of the components. Some of the components, like impellers, could be as small as a Rs 10 coin. The researchers are also developing Printed Circuit Heat Exchangers (PCHE) which offer very high cooling capacities at higher temperatures and pressures.

There are also other challenges. Due to the extreme conditions in the AUSC power plants, the materials that make up the components need to be strong enough to withstand them over a long time. “The materials can undergo environmental degradation and oxidation due to high temperatures, and corrosion due to steam at that temperature and pressure,” explains Satyam Suwas, Professor and Chair of the Department of Materials Engineering and co-PI of the project. “Additionally, since the components like pipes and turbines are manufactured in parts and welded together, the material should be weldable as well as retain its strength after welding.” Numerous research groups at the NCCCRD are working to develop and validate indigenous materials for these power plants. One such class of materials is a range of nickel superalloys. At high temperatures, most metals may lose their shape and strength, but these superalloys do not.

Researchers like Praveen Kumar, Associate Professor at the Department of Materials Engineering, are also working on understanding how the materials behave. “We plan to simulate the AUSC power plant conditions by conducting experiments at high temperatures to study the structural integrity of the materials – to see if the high pressure and temperature cause any deformations and damage in the material beyond what is permissible,” he explains. All materials may undergo fatigue and other time-dependent deformation processes. This requires regular monitoring to assess the remaining lifespan of the components and to check if the materials need to be replaced. So another aim of his group’s work is to develop predictive models that will let engineers understand how the material will behave over time so that they know when to inspect and replace the parts.

Another core area of research is the development of gasification

techniques for solid coal with high ash content. Gasification is the process of converting solid carbon-based fuel into its gaseous form, which is less harmful for the environment than burning solid coal. “While gasification is a well-known technology, it has been used mainly for coal with a low or medium level of ash content. However, the coal in India has 35-40% ash content, which is much higher than that of imported coal and could cause problems in the industrial processes,” says S Dasappa, Professor at the Centre for Sustainable Technologies.

At high temperatures over a long period of time, the ash content in the coal often forms sediments – a process called ash fusion – which can hinder the functioning of machinery. Dasappa explains, “We are using a concept called cyclone gasification, which could help address the issue.”

The researchers are also looking to use products from gasification, like carbon monoxide, hydrogen and methane, to produce hydrogen-rich fuels, methanol and fertilizers.

Gasification also comes into play in reducing carbon emissions by capturing the CO_2 generated. “In gasification, we do not allow the entire amount of coal to be converted to combustible gases, which allows us to separate CO_2 for possible usage. We can then capture and remove the carbon dioxide from these gaseous species so that the process is greener than a typical coal-driven Integrated Gasification and Combined Cycle (IGCC) power station,” says Dasappa.

Technologies that reduce the environmental footprint of fossil fuels like coal are critical to supplement India’s renewable energy efforts, because as Dutta puts it, “We cannot do away with fossil fuels in the near term.”

- Anoushka Dasgupta



DIFFERENCES IN SNAKE VENOM COMPOSITION RAISE QUESTIONS ABOUT TREATMENT

In India, snakebites kill around 58,000 people annually and disable many more, and a majority of these snakebites are attributed to the 'big four' – the Russell's viper (one of the deadliest snake species in the world), the spectacled cobra, the common krait and the saw-scaled viper. Its treatment involves the administration of commercial antivenom. However this treatment does not always prove effective, and so far, few efforts have been made to understand why this is so.

In a [recent study](#), researchers at the Centre for Ecological Sciences (CES) and collaborators have demonstrated that the venom of Russell's vipers shows dramatic differences in composition and toxicity based on geographical location. They also found that the commercial antivenom treatment for Russell's viper venom works as marketed for most populations of this snake, except the North Indian populations. This is in contrast to a [previous study](#) on cobras, which showed similar variation in venom based on location, but the commercial antivenom treatment was not effective against most populations.

Antivenoms are cocktails of antibodies that bind to the toxins in the venom and neutralise them. But even when this binding is seen in lab-based experiments, it is not sufficient to predict whether this will happen inside the human body, points out Kartik Sunagar, Assistant Professor at

CES and the corresponding author of the study. Commercial antivenoms are often deployed in the market without preclinical assessments (using animals) or clinical studies involving humans.

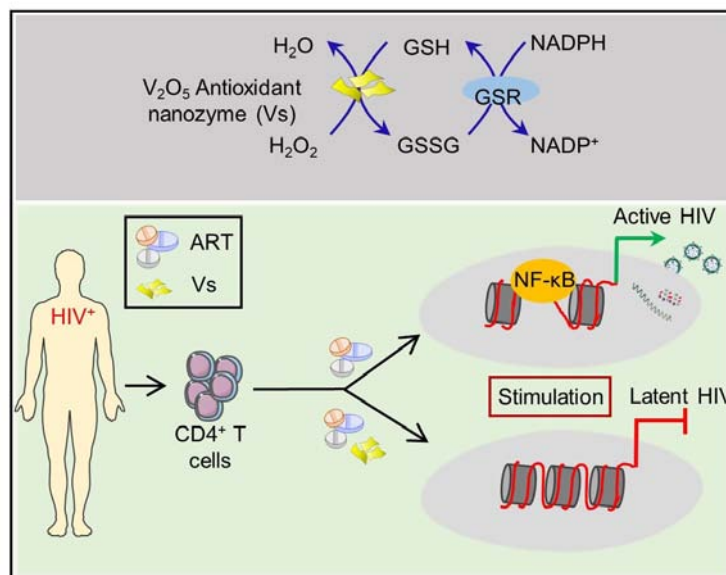
The researchers collected venom from 48 individual Russell's vipers in five biogeographical regions of India, and tested how well the antivenom neutralised them in mice. Snake venom is known to be an adaptive trait that can vary depending on the environment. The researchers used analytical techniques, including mass spectrometry, to reveal variations in composition and abundance of venom components. They also used assays in the lab to help identify the binding of the antivenom to the venom proteins outside the body, and performed experiments to check whether the antivenom could neutralise the toxic effects of venom injected into mice.

Surprisingly, despite the variations in venom composition, commercially available antivenom worked as marketed for most populations of this snake, except for those from the semi-arid region of Northern India. However, the experiments do not indicate whether the antivenom also offers protection against life-long injuries that accompany Russell's viper bites.

With the viper and cobra studies, says Sunagar, "we show that you cannot really predict the clinical or preclinical outcomes just by observing venom variation across populations. Instead, clinical and preclinical studies are the only methods to accurately test the effectiveness of commercial antivenoms." Alarming, the results of these studies along with an older study on the venom profiling of the 'big four' by the same team (which includes Romulus Whitaker, Gerard Martin, and Nicholas Casewell), show the preclinical ineffectiveness of commercial antivenoms in neutralising the venoms of the North Indian populations of three of the 'big four' snakes, he says.

The researchers highlight the urgent need for immediate production of region-specific antivenoms in snakebite hotspots of the country. As a long-term strategy, they also suggest developing an antivenom effective across India that would be evaluated by clinical trials. Sunagar also stresses the importance of developing recombinant antivenoms (which can be produced in cells on culture plates instead of the current method of using horse antibodies) for increased efficacy, specificity, and safety – another area that his lab is working on.

- Debraj Manna



NANOZYMES THAT CAN BLOCK HIV REACTIVATION

Researchers at IISc have developed artificial enzymes that can successfully block reactivation and replication of the Human Immunodeficiency Virus (HIV) in the host's immune cells.

Made from vanadium pentoxide nanosheets, these 'nanozymes' work by mimicking a natural enzyme called glutathione peroxidase that helps reduce oxidative stress levels in the host's cells, which is required to keep the virus in check.

The study, published in *EMBO Molecular Medicine*, was led by Amit Singh, Associate Professor and Wellcome Trust-DBT India Alliance Senior Fellow at the Department of Microbiology & Cell Biology and Centre for Infectious Diseases Research (CIDR), and Govindasamy Mugesh, Professor at the Department of Inorganic and Physical Chemistry.

"The advantage is that the nanozymes are stable inside biological systems and do not mediate any unwanted reactions inside the cells," says Mugesh. "They are also quite easy to prepare in the lab."

There is currently no way to eliminate HIV from a patient's body completely. Anti-HIV drugs are only successful in suppressing the virus; they fail at eradicating HIV from infected cells. The virus hides inside the host's immune cells in a 'latent' state and stably maintains its reservoir. When the

levels of toxic molecules such as hydrogen peroxide increase in the host's cells, leading to a state of increased oxidative stress, the virus gets 'reactivated' – it emerges from hiding and begins replicating again.

A few years ago, Amit Singh's team developed a biosensor to measure oxidative stress levels in HIV-infected immune cells in real-time. "We found that to come out of latency and reactivate, HIV needs very little oxidative stress," he says. One way to prevent reactivation is to keep the oxidative stress constantly low, which would 'lock' the virus in a permanent state of latency. Enzymes such as glutathione peroxidase are essential for this process; they convert toxic hydrogen peroxide to water and oxygen. However, inducing the host cells to produce more quantities of these enzymes could disrupt the tightly regulated cellular redox machinery.

Around the same time, Mugesh's group published a study showing that nanowires made of vanadium pentoxide can efficiently mimic the activity of glutathione peroxidase. Singh's lab, therefore, decided to collaborate with them.

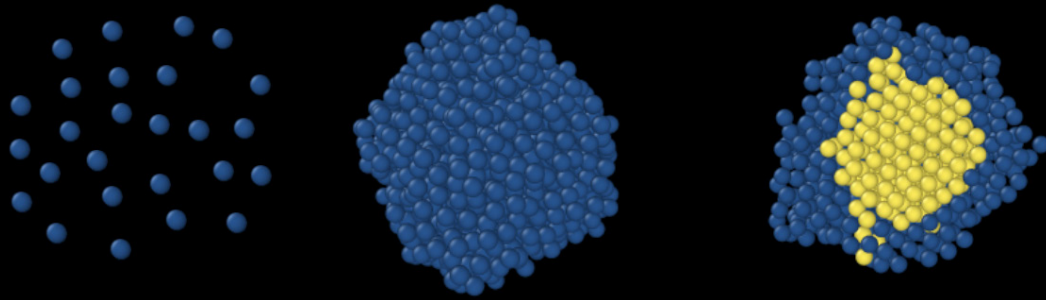
The researchers prepared ultra-thin nanosheets of vanadium pentoxide in the lab and treated HIV-infected cells with them. The sheets were found to reduce hydrogen peroxide just as effectively as the natural enzyme and prevent the virus

from reactivating. "We found that these nanosheets were having some sort of direct effect where the expression of the host genes essential for virus reactivation is reduced," explains Shalini Singh, first author and Research Associate at CIDR. When the team treated immune cells from HIV-infected patients undergoing antiretroviral therapy (ART) with the nanozymes, latency was induced faster and subsequent reactivation was suppressed when therapy was stopped, indicating that combining the two was more effective, she adds.

Combining ART with the nanozymes also has other advantages. Some ART drugs can cause oxidative stress as a side effect, which can damage heart or kidney cells, says Amit Singh. "Adding a nanozyme like this can help in reducing the side effects caused by such ART drugs." This can improve the quality of life of HIV patients undergoing treatment, he adds.

Although the nanozymes were found to be harmless to normal cells in lab tests, Mugesh points out that further studies are needed to understand if they can have other effects once they are introduced inside the body. "Where will they go? Which organs will they enter? How long will they stay in the body? We need to look at all these aspects," he explains.

- Ranjini Raghunath



HOW CRYSTALS NUCLEATE FROM DILUTE PHASES

Although seemingly simple, the nucleation of crystals from the fluid phase is a complex phenomenon. In spite of numerous computational and experimental studies, its mechanism is not completely understood. Recent studies have shown that, contrary to the century-old classical nucleation theory, crystal nucleation follows a two-step mechanism where the molecules initially come together to form an aggregate, followed by crystal nucleation within the aggregate. In chemical process

industries, an understanding of the nucleation mechanism is important for design and control of crystallisation processes. For example, in the pharmaceutical industry, polymorph control (control of crystal structure) during crystallisation is of vital technological and commercial importance.

In such a scenario, Ravi Kumar Reddy Addula and [Sudeep N Punnathanam](#) from the Department of Chemical Engineering have [developed](#) a new molecular theory of crystal nucleation from dilute phases such

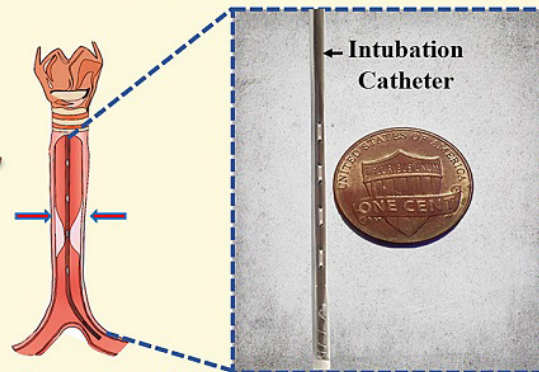
as vapours and dilute solutions. The molecular theory, with its basis in statistical mechanics, is able to provide the most complete description till date of the nucleation process and is expected to provide important insights into the mechanism of crystal nucleation from solutions. This should enable scientists and engineers to make improvements in process design and control of the crystallisation process.

- *Sudeep Punnathanam*

Flexible Multilayer Printed Circuit Board



Central Airway Obstruction Management Tool



CATHETER TO SENSE OBSTRUCTIONS IN AIRWAYS

Stenosis is a condition where the effective lumen (interior) area is reduced in the tracheal and bronchial segments of our respiratory tract or airway due to obstructions. This narrowing increases resistance to airflow; severe narrowing is often associated with morbidity and mortality.

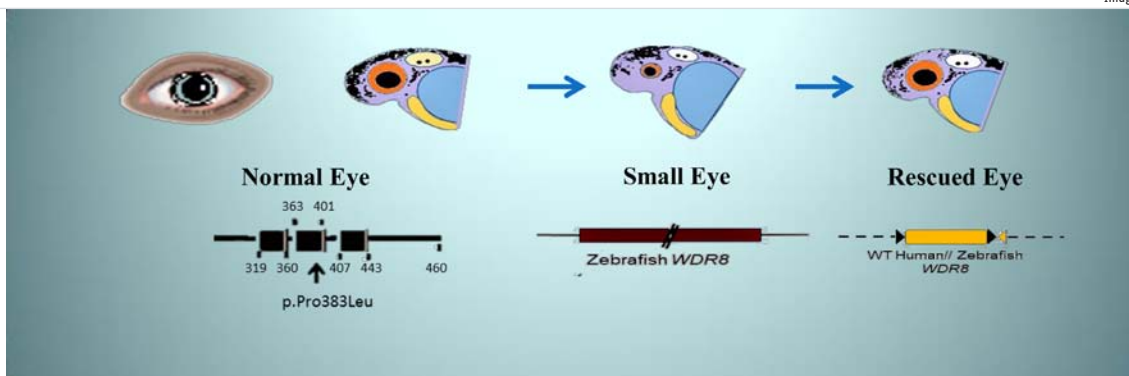
Characterising airflow patterns in the stenosed (obstructed) airway calls for newer diagnostic tools that can effectively quantify airflow changes at specific

obstructed sites. Researchers from the Department of Electronic Systems Engineering, Alekya B and [Hardik J Pandya](#), with collaborators Yeongjin Kim and Sanjay Rao, have [demonstrated](#) a manoeuvrable intubation catheter that can quantitatively measure air velocity across various segments of the tracheobronchial tree.

The catheter consists of a three-layer flexible printed circuit board integrated with thermal flow sensors based on micro-

electro-mechanical systems (MEMS) as well as a pair of sub-millimeter helical-shaped memory actuators. The researchers tested it by measuring air velocity in sheep trachea under normal and stenosed conditions. Even a 10% reduction in lumen area generated unique peaks corresponding to the obstruction site. Such a catheter can be used to identify stenosis at the preclinical stages.

- *Alekya B and Hardik Jeetendra Pandya*



NEW GENE INVOLVED IN EYE DEVELOPMENT AND DISORDER

Microspherophakia is a rare genetic disorder characterised by a smaller-than-normal lens in the human eye, which can lead to glaucoma and sometimes blindness. Researchers led by [Upendra Nongthomba](#) and [Arun Kumar](#) at the Department of Molecular Reproduction, Development and Genetics have now [identified](#) a new gene responsible for this disorder.

In collaboration with the Prabha Eye Clinic and Research Centre, Bangalore,

the IISc team identified two families whose members had this abnormality. Advanced genetic analysis indicated that mutations in a particular gene (WRAP73/WDR8) were linked to the disorder.

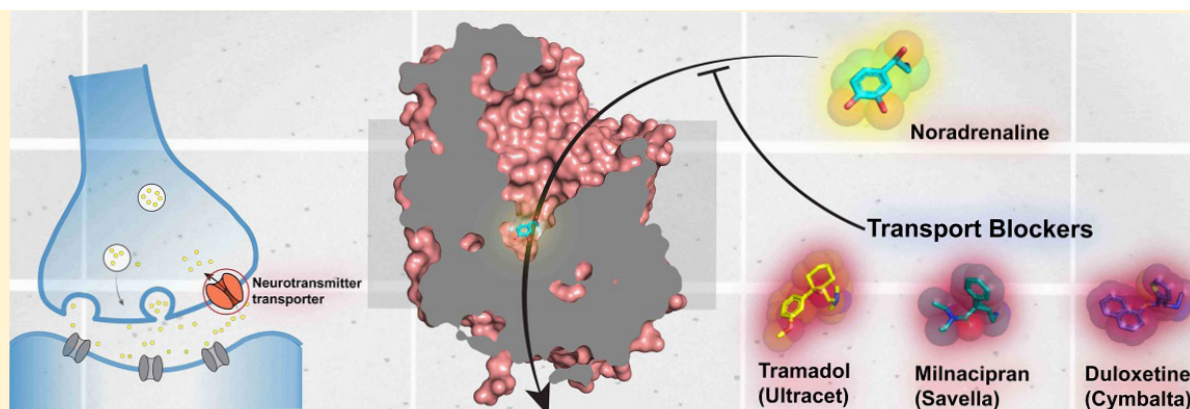
The team replicated the disorder conditions in zebrafish by removing the identified gene from its genome. They found that knocking out the gene prevents the stability of a protein required during cell division and arrests retinal cell development, resulting in a smaller eye size. When the

team re-inserted the corresponding human gene fragment into the affected fish, it reversed the symptoms of the disorder.

Though the exact mechanisms by which the WDR8 gene regulates early development of the eye are still unclear, these results may pave the way for early diagnosis and therapeutic remedies for Microspherophakia.

- *Sidrat Tasawoor Kanth*

Image: Aditya Mallela



HOW DOES CHRONIC PAIN MEDICATION BLOCK NEUROTRANSMITTER TRANSPORT?

Communication between neurons happens through the release of chemicals called neurotransmitters. One such neurotransmitter is noradrenaline. The release of this chemical in the spinal cord helps relieve chronic pain conditions like fibromyalgia and neuropathic pain.

Noradrenaline levels are regulated by membrane-embedded transporter proteins, which act like molecular 'vacuum cleaners', removing excess neurotransmitters. Drugs that are prescribed as chronic pain medications typically work to increase

the levels of noradrenaline in neuron junctions by blocking its transporter.

In a new study, researchers in the Molecular Biophysics Unit led by Aravind Penmatsa used X-ray crystallography to determine the structures of a neurotransmitter transporter to demonstrate how noradrenaline and dopamine – another neurotransmitter – display different types of interactions within the same transporter despite being chemically very similar. The distinct region within

the transporter with which noradrenaline interacts is also the site where certain pain-relief drugs bind and specifically block noradrenaline uptake.

The team discovered that any alterations in this region severely compromise the drugs' ability to block noradrenaline uptake. The findings provide a paradigm for designing improved inhibitors of noradrenaline transport with limited side-effects, to mitigate chronic pain.

- *Shabareesh Pidathala*



DECODING THE BRAIN, ONE CELL AT A TIME

RISHIKESH NARAYANAN'S LAB PROBES WHAT GOES ON INSIDE CELLS IN THE BRAIN AND HOW THEY TALK TO EACH OTHER

Scientists who study the brain look at it at different levels: from behaviour to neural networks, all the way down to individual cells, molecules and genes. Decoding each of these will eventually help us piece together the puzzle of how our brain works.

Rishikesh Narayanan's lab at the Molecular Biophysics Unit in IISc works mainly at the cellular level, although they occasionally dabble in the molecular and network scales. Using computational and experimental techniques, they study how neurons and glia – the two main types of cells in our brain – function. They are particularly interested in investigating electrical activity in these cells, and the related mechanisms and functions, using a technique called electrophysiology. The group focuses on four different yet converging themes.

First, the lab investigates how neurons can produce the same functional outcome from different structural components, a phenomenon referred to as degeneracy in biology. Rishikesh and his students have shown how various molecules in the neurons, such as ion channels, can elicit the same functional outcome at the cellular level in different neuronal subtypes. They recently showed how, in a brain region called the hippocampus, different configurations of neurons and networks can produce the same kind of output or same coding efficiency.

Second, the lab is interested in figuring out how active dendrites work. Dendrites are small tree-like projections from neurons that passively receive information from other neurons – or at least researchers thought so till the early 1990s. But scientists later found that dendrites are “active” and contain “ion channels” – they do not just passively transmit the electrical signals across neurons but can generate them as well. Rishikesh explains that these dendrites can also actively filter incoming information before they reach the neuronal cell body.

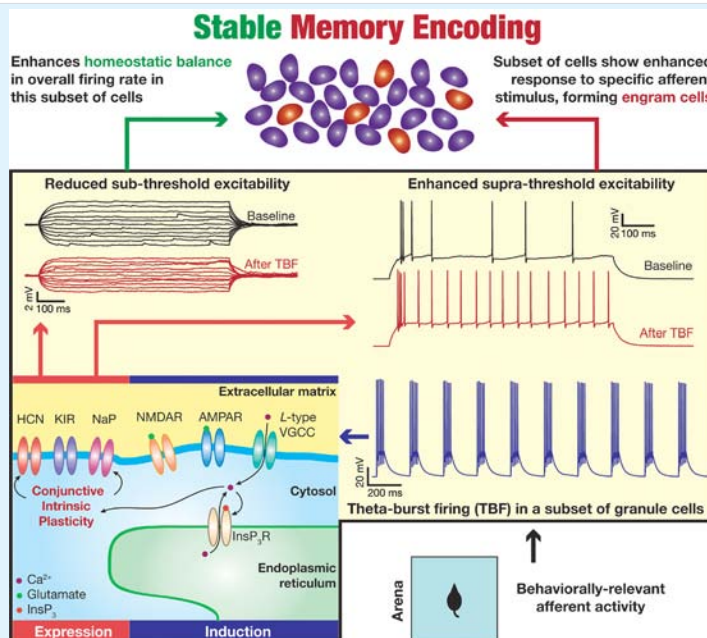
Building on this modern idea, Rishikesh's lab tries to understand how these active dendrites contribute to different properties of the neurons. Over the years, they have figured out some bits of the puzzle. For instance, the lab has shown that active dendrites change the extracellular electrical potentials in their vicinity, and that they regulate the manner in which different cells (neurons and glia) in the brain interact with each other.

Third, Rishikesh and his students investigate how neurons and their networks change with external stimuli. Specifically, they study how ion channels can participate in these changes – a phenomenon called intrinsic plasticity. Most researchers have placed the synapse – the connections between two neurons that allows messages

to pass – on a pedestal, as the sole agent that changes in response to stimuli ('synaptic plasticity') and, therefore, mediates cognitive functions like learning. But Rishikesh's lab, along with many others, has shown that synapses are not alone, and that changes in ion channels do this too.

“We study how ion channels change in response to certain activity patterns, how they interact with the changes in synapses and together produce stable learning,” Rishikesh explains. The lab has also developed computational rules that explain how this crosstalk happens between synaptic and intrinsic plasticity.

Fourth, the lab works on understanding the cellular neurophysiology of spatial navigation – how our brain maps out and remembers where we need to go. Two kinds of cells in the brain govern this activity: place cells – neurons that respond to a specific location – and grid cells – neurons that elicit action potentials (electrical impulses) at multiple locations that together form triangular grids. Originally, researchers in the field thought that the inputs must be clustered at the same dendrite for the neuron to produce a sharply tuned signal that maps out a particular place correctly. But Rishikesh's group showed that even dispersed signals converging on active



dendrites are sufficient to elicit sharp tuning in place cells.

Rishikesh's quest for understanding the brain began during his PhD at IISc. After his Bachelor's degree in electronics and communication engineering, he joined the Department of Electrical Engineering at IISc for his Master's under YV Venkatesh. He then stayed on to do his PhD in computational visual neuroscience as Venkatesh's interest in biological vision inspired him to pursue a neuroscience career.

After his PhD, Rishikesh pursued his postdoctoral research in Sumantra Chattarji's lab at the National Centre for Biological Sciences, Bangalore, and Daniel Johnston's lab at the University of Texas, Austin, focusing on experimental

neuroscience. He then returned to IISc in 2009 and set up his own lab to work at the interface of biology and engineering. In 2016, Rishikesh won the Shanti Swarup Bhatnagar Prize for his "contributions to the field of cellular neurobiology."

Setting up his own electrophysiology lab at IISc was not easy, he says. "At that time, the neuroscience community in the Institute and the country was really small." During those early years at IISc, Rishikesh received funding from a Human Frontier Science Program grant apart from the IISc startup grant. "But procuring the funds is only one part," Rishikesh says. "Converting them to equipment takes its own sweet time."

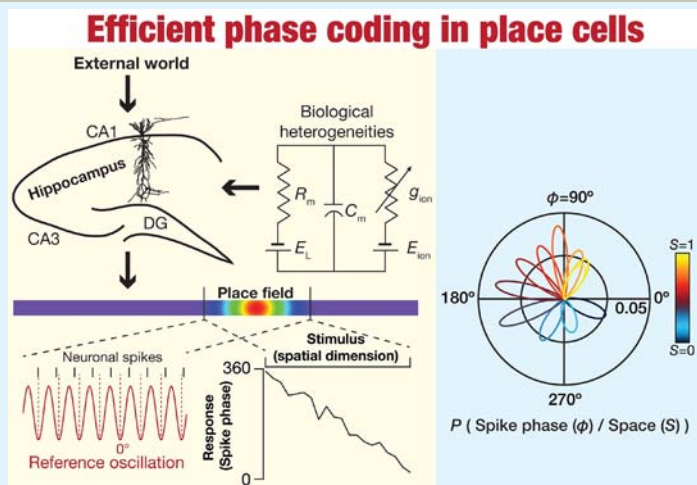
Rishikesh says that he prefers to procure different components from different places and assemble them in the lab. "It is an

interesting process, but it takes time," Rishikesh says. "I don't purchase everything from one place. I get the microscope from one company, the amplifier from another, the micromanipulator from a third guy, and I write code to interface them."

Having worked at the interface of biology and engineering, Rishikesh points out how neuroscience as a field is a melting pot of disciplines. "Students shouldn't be apprehensive about their academic backgrounds in entering neuroscience research," he explains. "A keen interest in learning new things, an attitude engrained in innovation and intellectual exploration, the recognition that there is no substitute for hard work, and the perseverance to rise from failures are at the heart of good science."

- Joel P Joseph

Degeneracy in efficient coding in place cells (Image/Research by Pavithra Seenivasan)



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