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KERNEL

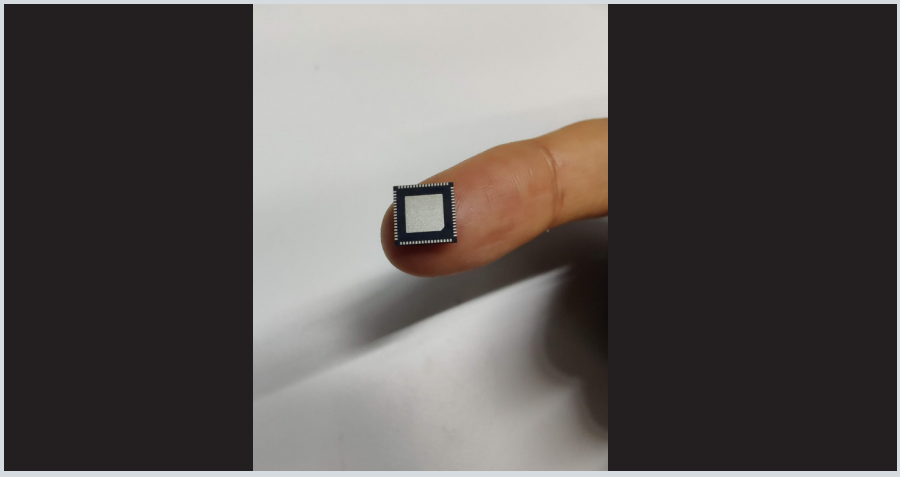
Editorial

Building devices that mimic the human brain is the 'holy grail' of computing. In this issue of *Kernel,* learn more about how IISc researchers are working on developing brain-inspired systems that can lead to smarter and faster computers.

This issue also spotlights research on a key protein that helps HIV fuse with the host cell, and hitchhiking worms that live in fig trees.

We also feature the work of an IISc researcher who is working towards the ambitious goal of making biology more predictive.

CAN A COMPUTER THINK LIKE A BRAIN?



An integrated chip designed at the NeurRonICS lab to implement a neuromorphic circuit for edge computing (Photo: NeuRonICS lab)

INSPIRED BY THE HUMAN BRAIN, RESEARCHERS AT IISc AND ELSEWHERE ARE TRYING TO MAKE SMARTER AND FASTER COMPUTING DEVICES

Consider a child playing on a swing, while licking on a candy, waving to her mom, and joining the other kids in a song from their favourite cartoon show. It may not seem extraordinary, but look closely and you will see that a four-year old is carrying out complex coordinated body movements, visual search, social engagement and memory recall, all at the same time. The best of our robots, in contrast, can only do a half-decent job at one of these tasks. Our brains clearly outsmart computers. Heck, even chicken brains outsmart our best computers. The realisation of such limits has led to the rise of 'neuromorphic' computing. At its core lies inspiration from biological systems because the "nervous system is the most sophisticated system that engineers can learn from, which is … developed over billions of years of evolutionary process," says Chetan

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Neurons growing on the multi-electrode array. Black dots are electrodes that pick up signals from neurons and carry to trace pads for recording (Photo: Grace Mathew Abraham)

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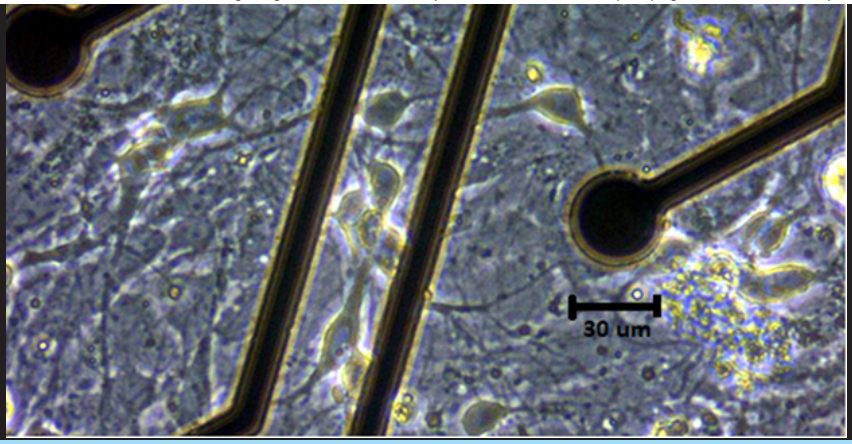


Singh Thakur, Assistant Professor at IISc's Department of Electronic Systems Engineering (DESE). The features that make our brains super-efficient, he explains, are the 'PPA' – power, performance and area metrics – a term routinely used by circuit designers.

Weighing just 1.5 kg, the human brain is compact, highly efficient and power-thrifty (the calories in a banana can keep it energised. Contrast that with a desktop computer which uses up to 250 watts – the equivalent of 2,000 bananas an hour). In addition, our brains are fault-tolerant, as they can adapt to neuron loss, and are self-learning. Neuromorphic engineering aims to marry these features, essentially etching brain architecture on to solid state devices.

Neuromorphic computing combines diverse disciplines – biology, electrophysiology, signal processing and circuit design, to name a few. In 2015, such interdisciplinary exchange at IISc led to the formation of the Brain, Computation and Data Science initiative, supported by the Pratiksha Trust. The group brings together labs from DESE, Centre for Neuroscience (CNS), Molecular Biophysics Unit (MBU), Electrical Communication Engineering (ECE) and other departments. An interdisciplinary PhD programme has been launched under its umbrella, along with three Distinguished Chair positions.

One of the groups under this initiative is the NeuRonICS lab, headed by Thakur, where research spans diverse levels. On one end, they work on algorithms for "event-based sensors", which are sensory devices modelled on biological systems. An example of this is a neuromorphic camera, which can be more data- and power-efficient than conventional cameras. Its speedy tracking makes it useful in applications such as recognising high-speed activity and detecting anomalies. The lab is also developing algorithms for a 'silicon cochlea', an FPGA-based model of the cochlear system that can act as an efficient pre-processing unit for speech-based machine learning applications (FPGA or Field-programmable gate array is an integrated circuit that can be programmed after manufacturing for different applications).

Moving up from such sensors, the lab has also successfully modelled a network of grid cells and place cells – types of neurons that help us track where we are. This recent work is a collaboration with Rishikesh Narayanan, Associate Professor at MBU. This spatial navigation model could be used by robots to move intelligently in novel environments. Such 'biomimetic' systems can be built on silicon chips, another area of focus in the NeuRonICS lab. Towards this goal, they have used novel devices to model neuronal interconnections (synapses).

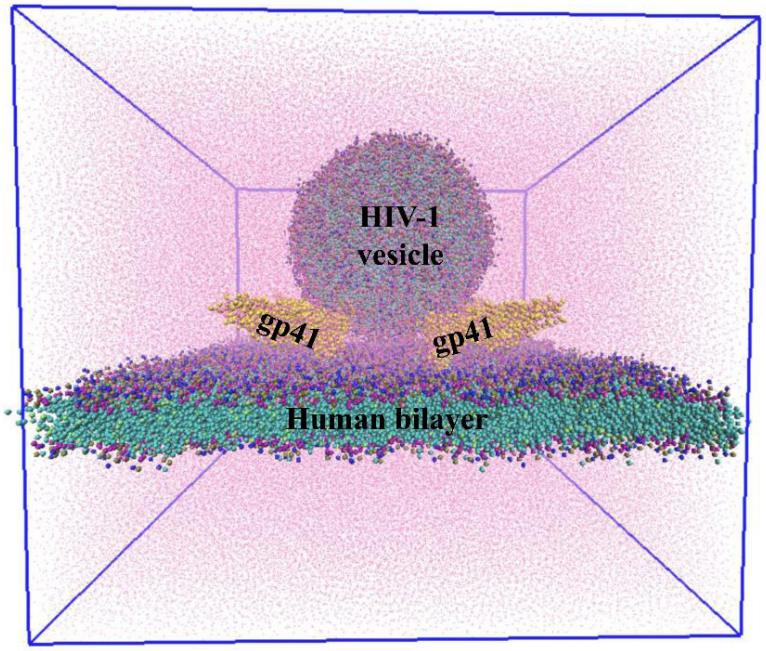
In contrast to Thakur's approach, Bharadwaj Amrutur, Chair of the Robert Bosch Centre for Cyber Physical Systems and Sujit K Sikdar, Professor at MBU, have been working on developing neuro-electric hybrid devices by using neurons grown in the lab rather than recreating them in silicon. This brain-in-a-dish approach harnesses the parallel computing capacity and power efficiency of neurons as well as the accessibility of well-developed hardware and software. In an earlier study, they connected input devices (sensors) to a live neuronal culture which was specially grown on metal contacts called electrodes. The electrodes conducted appropriate signals from sensors to neurons to compute a solution for an obstacle avoidance problem. The resulting activity of the neurons was used to control a navigating robot seamlessly in real time.

In another project, they used similar neuronal cultures to demonstrate memory traces. They trained the network using a "barrage of inputs" so that specific connections developed between neurons. Despite these disturbances, the network did not go into overdrive, and remained stable – a condition called global homeostasis. This work might lead to better understanding of learning and memory, which require persistent input-driven changes in neuronal networks while maintaining stability. In collaboration with Thakur's lab, the group is also currently working on interfacing a neuromorphic cochlea with a live neuronal culture to understand how a neuronal network distinguishes sound signals.

Neuromorphic computing is a young but rapidly growing field, with huge challenges ahead. How one neuron can have thousands of synapses in a miniscule space is a 'routing' problem yet to be solved in silicon, as denser connections can lead to dissipated currents, wrecking the whole enterprise. Another challenging area is communication. Neurons compute on a gradation of inputs, but send a spike as output – hence banking on both continuous and discrete signals. Neuromorphic design too will have to incorporate mixed signal processing, to perform efficient communication along with computation. Better neuromorphic designs can lead to developing large-scale neural chips to simulate brain areas, and ask "better questions" about the brain – something Thakur looks forward to doing. He sees this as coming full circle with the two goals that early neuromorphic researchers had – the engineering goal of building neuro-inspired systems, and the scientific goal of using them to study brains. Successfully building a brain-like network in silicon could result in a computing resource for neuroscientists, enabling them to perform some experiments without having to use animals.
As we navigate these technical challenges, neuromorphic computing raises new questions in the fields of science policy, law and ethics. And at the other end of such challenges is Thakur's question: "Can we build something that is useful?"

- Sidrat Tasawoor Kanth

HIV-1 vesicle and human bilayer are tethered by gp41 trimer in the presence of explicit water models (pink dots) (Image: Biswajit Gorai)



MODELLING HIV FUSION

UNDERSTANDING HOW THE VIRUS FUSES WITH HOST CELLS CAN POINT SCIENTISTS TO BETTER ANTIVIRAL STRATEGIES

An interdisciplinary team of researchers at IISc has used robust computer simulations to understand how the Human Immunodeficiency Virus (HIV) – which causes AIDS – fuses with the host cell membrane. Published in the *Journal of Chemical Information and Modeling,* the study focuses on a process called gp41 mediated membrane fusion.

Gp41, a core component of the HIV envelope protein (Env), is essential for the viral membrane to fuse with the cell membrane of a type of immune cell in the host called T cell. This step is critical for HIV to invade and subsequently replicate within the host cell. "If gp41 fusion is blocked, then the whole invasion can be blocked there," explains Biswajit Gorai, a former postdoc at IISc and first author of the study. Therefore, understanding the membrane fusion process may help researchers in developing effective antiviral strategies.

Although a lot is known about the molecular details of viral entry, the optimal stoichiometry – the balance of components – required for infection has remained uncertain. "We wanted to see … how many gp41 units are required to achieve this process," explains Prabal K Maiti, Professor and Chair of the Department of Physics and the corresponding author.

The HIV envelope protein assembles into a three-part structure such that each unit comprises one gp41 protein. At the time of fusion, gp41 appears to fold into a six-helix bundle structure, which is thought to be necessary for membrane fusion. Maiti elaborates, "There were a lot of hints from experimental work which showed that gp41 forms a six helical bundle in the post-fusion step. That prompted us to test the hypothesis that gp41 could actually help in fusion, which can eventually help virus invasion."

The team first built computational models of HIV and host cell membranes, and then simulated the fusion process. "Initially we started with millions of atoms and it was very slow … but then we turned to a coarse-grained model, so now we can have microsecond simulations," explains Gorai. Starting with no gp41 on the HIV membrane as the baseline, the authors incrementally added gp41 units to their simulation. On doing so, they found that at least three gp41 units act cooperatively and are necessary for fusion.

In another first, the team built models of HIV and host membranes with lipid compositions nearly identical to biological membranes. Using different membrane models, the authors showed that only the membranes with such identical lipid composition fused successfully, while the rest did not, indicating that the lipid composition of the membranes is critical for fusion.

The researchers also analysed the nature of lipid transfer during fusion and found that the trio of gp41 units drives changes to the structure and arrangement of lipids at the site of fusion. Finally, using mathematical calculations, the team found that the presence of gp41 reduces the energy required for fusion by about four-fold, thereby making this process more favourable.

Currently, the team is working on identifying mutations that can be introduced in gp41 to block the fusion step. They are also hoping to develop antibodies that can prevent infection. "Together with my colleague, Narendra M Dixit [Professor, Department of Chemical Engineering], we are trying to pursue this line of a neutralising antibody system," says Maiti.

- Sukriti Kapoor

Pollinator wasp on a fig fruit (Photo: Nikhil More)

HOW HITCHHIKING WORMS CHOOSE THEIR VEHICLES

EVEN TINY ORGANISMS LIKE WORMS ARE CAPABLE OF MAKING COMPLEX DECISIONS, NEW STUDY FINDS

Tiny worms that live inside fig trees use the fig wasp as a "vehicle" to hitch rides from one tree to another, by crawling into the wasp's gut without harming it. This relationship has existed for millions of years. But how do these worms – called nematodes – choose their wasp vehicles? What cues do they use to check for co-passengers? A new study from the Centre for Ecological Sciences (CES) at IISc provides some answers.

It shows that the worms generally tend to choose wasps that have less crowded guts, and are already carrying other worms of their own species. Travelling with members of their own species can boost their chances of finding a mate when they reach their destination. Wasps carrying fewer worms also have a greater chance of reaching the destination safely.

"The main take-home message is that even very tiny organisms such as nematodes have complex decision-making processes," says Renee Borges, Professor at CES and senior author of the paper published in the *Journal of Animal Ecology*. "This kind of decision-making is exactly what we humans may do when we are making choices about which mode of transport we may use. We wouldn't want to get on to an overcrowded bus unless there was no other bus available."

The fig tree shares a win-win relationship with the fig wasp – the wasp helps in pollination and the tree provides food. The tree also hosts three different types of worms. These worms rely entirely on the wasps, which ferry young worms from one fig tree to another, where the worms then mature, mate and give birth.

In an earlier study, the researchers used controlled experiments to show that if there are too many worms boarding a wasp, they turn into parasites and affect not just the wasp but also the tree they reach. "But in a natural scenario, you will find that the nematode numbers will always be low," says Satyajeet Gupta, Research Associate at CES and first author of the study.

The new study shows that, to avoid overcrowding, the worms do tend to select wasps with fewer passengers. They check for this using chemical cues – they sniff out volatile compounds that the wasps emit by standing on their tails and waving their heads around. When the researchers offered the worms a choice between compounds emitted by a wasp carrying either fewer or more passengers, the worms selected the former.

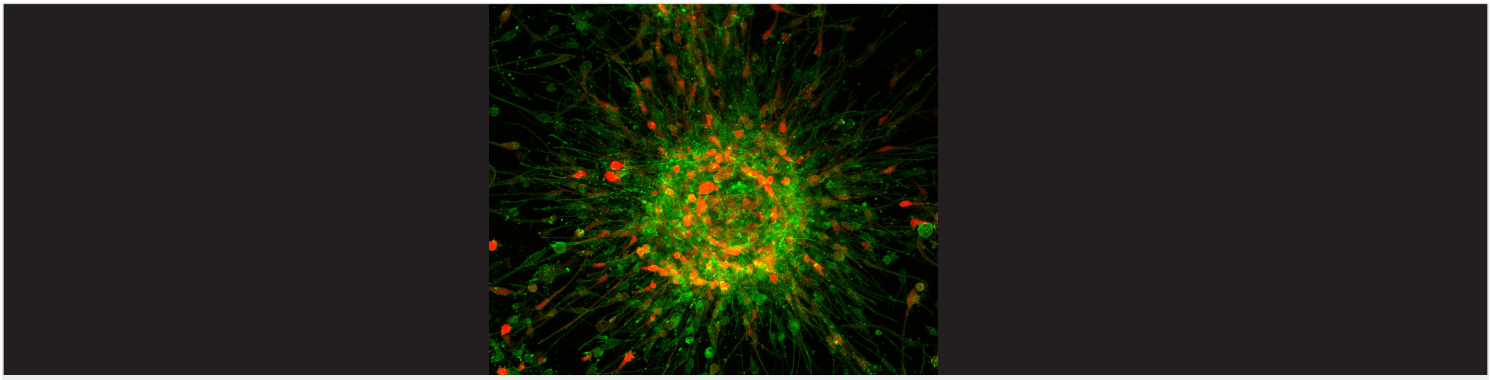
Although the worms could distinguish between wasps carrying different numbers of their own species, surprisingly, they could not recognise members of a different species, and treated those wasps carrying them as empty vehicles.

The team also found that herbivorous and carnivorous worms – which are different species – used different factors to decide on their vehicle. The herbivores preferred empty vehicles but liked to board them in pairs so that they had a guaranteed mating partner when they reached their destination. The carnivores, on the other hand, preferred those vehicles that already carried a few members of their species.

"We've just scratched the surface," says Gupta. "This is a preliminary study towards [answering] the bigger question of how nematodes really make decisions when they are selecting a host … or a vehicle."

- Ranjini Raghunath

Image: Dharma Pally



DIFFERENCES IN SUGAR LEVELS DRIVE BREAST CANCER INVASION

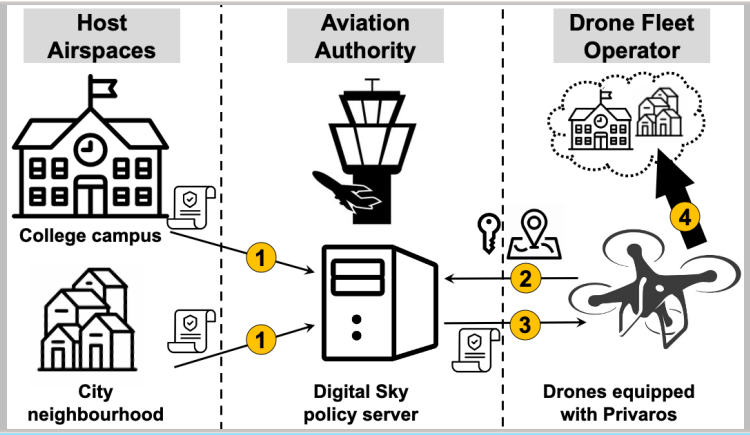
Malignant tumors are increasingly being understood as heterogenous – a patchwork of cells that look and behave differently, and cooperate or compete with each other as the cancer spreads.

A recent study led by Ramray Bhat in the Department of Molecular Reproduction, Development and Genetics shows that a specific sugar called 2,6-Sial is expressed to different levels on the surface of different breast cancer cells. Cells with higher levels of the sugar stick less strongly to their surroundings and are less likely to invade through them, while those with moderate levels stick strongly and invade more efficiently.

Using an in-house 3D culture technique, the researchers reconstructed the tumor microenvironment on a dish to film the tumoroid – cluster of cancer cells – as it grew. Then, they separated cells with differing 2,6-Sial levels, labeled and recombined them. Cells with higher 2,6-Sial levels moved slowly and formed the tumoroid's central bulk, while those with moderate levels moved fast and formed the invading front.

Using computer models, the team also showed that having a slow-moving central bulk boosts the efficiency with which fast moving cancer cells can 'unjam' and spread outwards in a circular fashion, thereby justifying the need for heterogeneity.

Image courtesy: Vinod Ganapathy lab



ENABLING PRIVACY-COMPLIANT DELIVERY DRONES

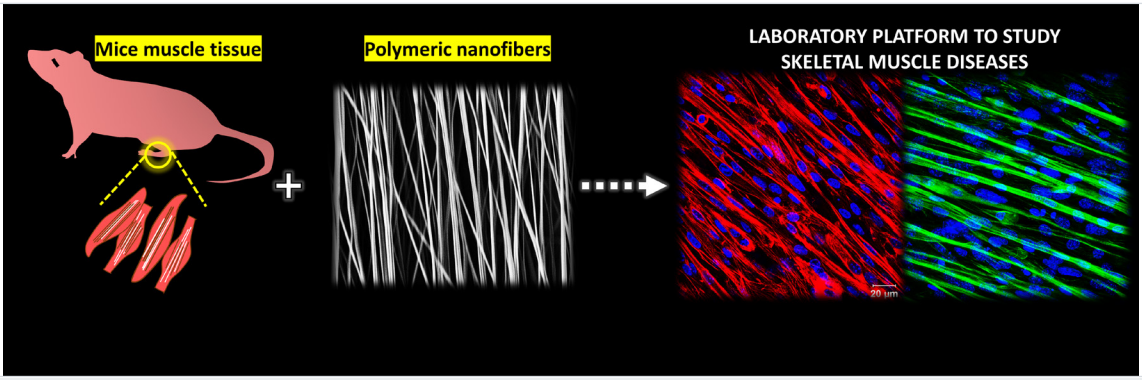
Delivery drones are typically equipped with various sensors such as cameras, microphones, GPS, and Lidar. A malicious drone fleet service operator could misuse these sensors to turn delivery drones into flying spies.

Researchers in the Department of Computer Science and Automation led by Vinod Ganapathy have now developed "Privaros", a set of enhancements to the drone software stack, which allows "host airspaces" such as an apartment complex, a university campus, or a city municipality to ensure that "guest" delivery drones visiting the airspace are privacy-compliant. The host airspace decides what privacy policies it wishes to enforce. For example, an apartment complex could require that all images of residents appearing in the video feed captured by the drone be blurred out before the video feed leaves the drone. Or, a city municipality may require that a drone only moves along certain pre-specified drone lanes.

Privaros incorporates new mechanisms into the drone software stack that allow such host-specified policies on board the drone. Trusted hardware on board can be used to prove to the host airspace that the guest drone is in compliance with its policies.

This work also shows how Privaros can be integrated with upcoming policy frameworks, such as India's Digital Sky framework.

Image: Aditi Jain



NANOFIBER PLATFORM TO STUDY MUSCLE DISORDERS

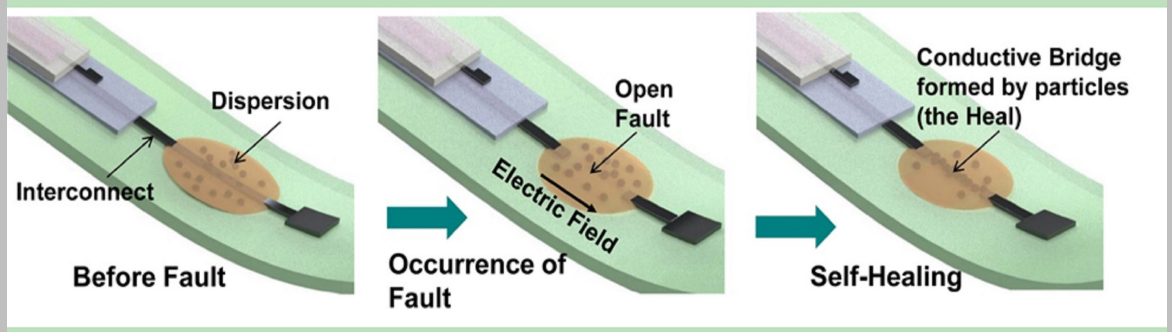
Skeletal muscles are formed by the fusion of parent muscle cells called myoblasts. These muscles are usually tethered to the bones by tendons. Skeletal muscle disorders accompany loss in muscle fibers, which often causes difficulty in movement, pain, and stiffness upon stress and aging.

Despite extensive research in the lab, current treatments for such disorders are often ineffective. This gap, in taking knowledge from the bench to the bedside, is mainly because of the lack of suitable lab-made muscle models that can replicate behaviour akin to that of skeletal muscles inside the body. Researchers at the Centre for BioSystems Science and Engineering, Department of Materials Engineering and Department of Microbiology and Cell Biology have recently addressed this issue. They used nanofibers of polycaprolactone (PCL), a biodegradable polyester, to create a mesh-like structure on which they cultured myoblasts in the lab and allowed the cells to grow into muscle fibers.

Experiments showed that the lab-grown muscle fibers retain their alignment when grown on such polymeric substrates and could reproduce critical properties of skeletal muscles, such as stress-induced muscle degeneration. The nanofiber mesh offers a robust platform to not only study muscle disorders, but also to test the effectiveness of drugs to treat them.

- Debraj Manna

Image courtesy: Sanjiv Sambandan



SELF-HEALING CIRCUITS

Flexible electronic devices such as foldable display screens, wearable sensors, and self-powered, portable energy devices are made up of millions of circuits composed of thin-film transistors (TFTs). These devices are prone to open-circuit failures due to mechanical stress from bending or stretching, electric stress from electrostatic discharge arising from human contact or corrosion from moisture or sweat. Could their durability be enhanced by employing self-healing TFT circuits?

Researchers from the Department of Instrumentation and Applied Physics, IISc, and the Department of Engineering, University of Cambridge, have collaborated to develop such circuits.

They packaged particles that can conduct electricity in the TFT circuit such that when gaps are generated, the open current induces the particles to align and form a conductive bridge, thereby completing the circuit and "healing" it. Such particles can only align in the presence of an open current, and otherwise remain dispersed and insulated in the circuit.

In flexible TFTs, silver particles of a specific size, embedded in insulating silicone oil at an optimum density, were found to be ideal for healing gaps arising from electric failure or mechanical stretching.

The authors also describe a strategy for efficiently packaging these particles in TFT circuits for large-scale manufacturing. This could potentially widen the scope of applications of flexible electronic devices.

- Sukriti Kapoor

Photo courtesy: Satyaghosh Maurya

BIOLOGY THROUGH AN ENGINEER'S EYE

RAHUL ROY'S LAB AIMS TO ENGINEER NOVEL SOLUTIONS FOR BIOLOGICAL PROBLEMS

Nine years ago, when Rahul Roy was applying to IISc for a faculty position, he gave presentations at several departments, because he wasn't sure where he would fit in best. Although he was interested in both engineering and science, he didn't foresee working in an engineering department. Eventually, however, he joined the Department of Chemical Engineering as an Assistant Professor, where he has been pursuing diverse projects at the intersection of engineering and biology.

Rahul's lab, in his own words, is working towards the ambitious goal of making biology more "predictive". Biological systems are inherently complex and heterogeneous. Take for instance the human body. Scientists still don't know enough about how the different parts of our body work. This is because within each part, different cells behave differently. And within each cell, different molecules behave differently. This heterogeneity is a major problem in biology research; we cannot tell when a molecule will act differently.

This is also an issue when it comes to developing drugs and vaccines, which is now a painfully long process. Even after a molecule with therapeutic properties has been discovered, scientists need to test it first on cells in the lab, and then on animals, and finally perform clinical trials on humans to understand if they are safe and effective. But if researchers are able to better predict how our bodies would react to such treatments, it would be easier for them to bypass some of these steps and develop more effective and safer treatments in a shorter time.

Biologists with an engineering background like Rahul are using a combination of traditional biological techniques and new computational approaches to address such challenges. His lab is currently developing general "rules" that will help decrypt biological diversity at the molecular level and perhaps develop treatments without running clinical trials. "[While] we understand that there's still going to be a large heterogeneity, we'll still come up with rules which will explain the overall behaviour," he says.

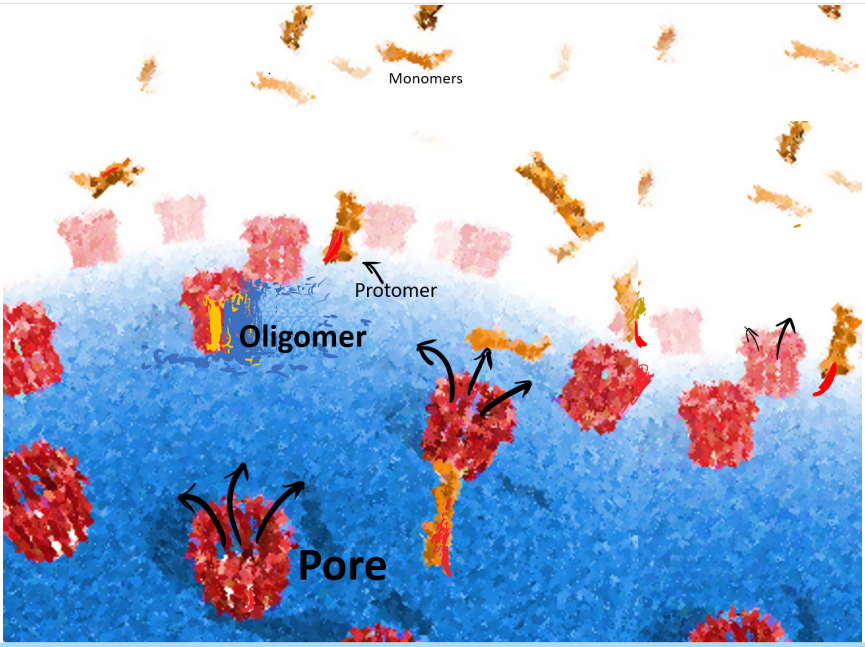
Towards this goal, Rahul's lab is interested in using single-molecule imaging to study how different copies of the same molecule carry out the same function differently. Take the rate at which an enzyme catalyses a biological reaction, for instance. The value that scientists assign to it is merely the average of the rates for multiple copies of the same enzyme. Even little modifications to the enzyme's structure can affect its catalytic activity drastically.

Another direction of his lab's work is on the self-assembly of viruses and bacterial pore-forming toxins. Understanding how these toxins assemble can help scientists find ways to block the bacteria from entering our cells and causing infections. A toxin found in some bacteria, called Cytolysin A, forms a 12-sided ring-like structure. In one of their collaborative studies, the group found that subunits of this toxin assemble into the ring in any random sequence and that the assembly is reversible — when incomplete structures are formed, some previously built structures can break up and release bits that join and complete the partial structures.

A third area of interest is understanding how viruses like the novel coronavirus, SARS-CoV-2, mutate. In just the past few months, new SARS-CoV-2 variants have emerged. As the virus replicates, mutations arise and eventually accumulate in its genome. Errors during replication happen because RNA polymerase – the enzyme that creates copies of the virus – is inefficient. "Now, every time it [the virus] is making a copy of itself, it is actually creating a variant," Rahul explains. This leads to the accumulation of multiple variants of the same virus inside a host cell, which requires the use of antivirals that can simultaneously act on all of them.

Using a technique called single virus sequencing, Rahul's group has been able to discern the exact number of variants present in a blood sample. In another project, they have developed a method to count the number of RNA molecules that correspond to a particular gene in individual cells, by trapping a cell in a drop of a water-in-oil emulsion. This approach has helped them understand the exact concentration of a specific RNA

Artistic rendition of the pore-forming toxin action on cell membranes (Image courtesy: Satyaghosh Maurya)



molecule in each cell. Adding microfluidics to this approach allows them to study many cells simultaneously.

Yet another interest of Rahul's lab involves building tools for sensing and lab-on-chip devices. His team has recently developed a smartphone-based antibiotic sensing approach, where sensors made up of DNA molecules, called DNA aptamers, are used to detect the presence of an antibiotic. When the sensor detects the antibiotic, dyes attached to it exhibit a change in either the fluorescence colour or intensity that can be easily detected by a smartphone camera. Such sensors can be designed to detect other kinds of chemicals as well. Rahul believes that, in the future, pluggable adapters for smartphones might help convert them into point-of-care diagnostic devices.

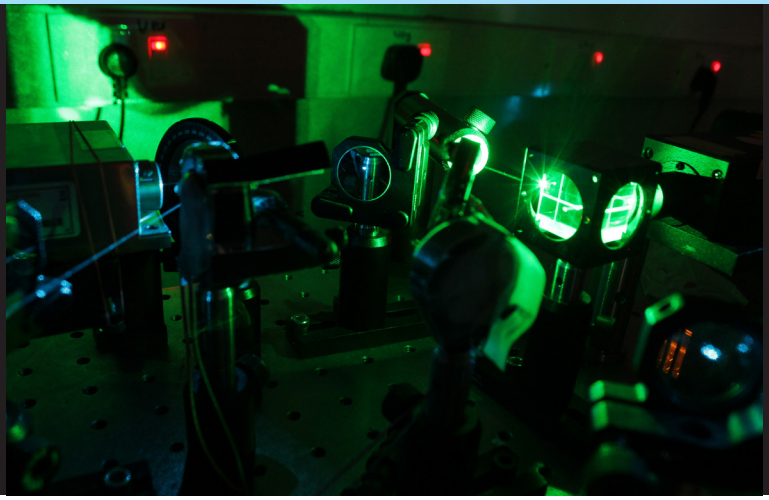
In recent months, Rahul's lab has also been working on projects related to COVID-19. They have developed a rapid antibody test for COVID-19. A home-based test kit is also in the making, which aims to use antibody fragments to enrich and detect the virus concentration in easily available biofluids like saliva. It can further intensify the signal using an isothermal amplification technique at 37°C. This kit can display results within 20 to 30 minutes and can be used without professional assistance by anyone who is not able to visit a pathology lab.

Exploring multiple projects can be hard. Rahul explains that the reason why he ended up pursuing so many diverse projects is that he designs these with major inputs from his students and postdocs, which has often resulted in him pursuing areas that he never anticipated he would be working on, like microfluidics.

He says that his motivation to pursue research comes from the sheer joy of finding out something for the first time. Seeing the eyes of budding young scientists light up with joy when they understand a new concept also keeps him going. Students, being "naive", often bring a unique perspective to a research problem because they do not carry the burden of preconceived notions, he says. "And that's why we always want not one person, but hundreds of people approaching the same problem from different angles."

- Debraj Manna

Snapshot of a section of the single-molecule imaging set up in the Nanobiology Lab (Photo courtesy: Satyaghosh Maurya)



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