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A*STAR RESEARCH

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*A*STAR Research* is a publication of the Agency for Science, Technology and Research (A*STAR) — Singapore's lead government agency for fostering world-class scientific research.

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EDITORIAL

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The Agency for Science, Technology and Research (A*STAR) is Singapore's lead government agency dedicated to fostering world-class scientific research and talent for a vibrant knowledge-based economy.

A*STAR actively nurtures public-sector research and development in biomedical sciences, physical sciences and engineering, and spurs growth in Singapore's key economic clusters by providing human, intellectual and industrial capital to our partners in industry and the healthcare sector.

A*STAR currently oversees the following research institutes, consortia and horizontal technology program offices, and supports extramural research with universities, hospital research centers, and other local and international partners:

Advanced Remanufacturing and Technology Centre (ARTC)
Bioinformatics Institute (BII)
Bioprocessing Technology Institute (BTI)
Experimental Drug Development Centre (EDDC)
Genome Institute of Singapore (GIS)
Horizontal Technology Program Offices (HTPO):
- Artificial Intelligence, Analytics and Informatics (AI³)
- Urban and Green Technology (UGT)
- Social Sciences and Technology (SST)
- Robotics
- Agritech and Aquaculture (A2)
- Health and MedTech (HMT)
- Infectious Disease (ID)

Institute of Bioengineering and Nanotechnology (IBN)
Institute of Chemical and Engineering Sciences (ICES)
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Institute of Medical Biology (IMB)
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Institute of Materials Research and Engineering (IMRE)
National Metrology Centre (NMC)
Singapore Bioimaging Consortium (SBIC)
Singapore Immunology Network (SIgN)
Singapore Institute for Clinical Sciences (SICS)
Singapore Institute of Manufacturing Technology (SIMTech)
Singapore Institute of Food and Biotechnology Innovation (SIFBI)
Skin Research Institute of Singapore (SRIS)

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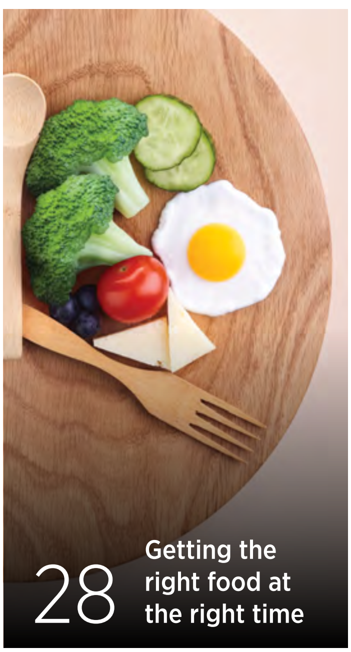

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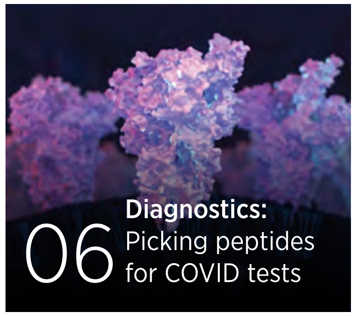
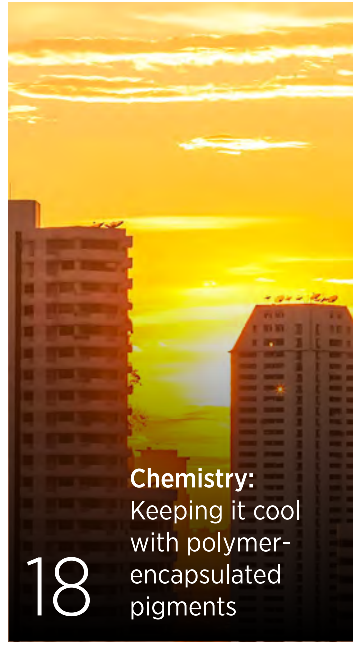
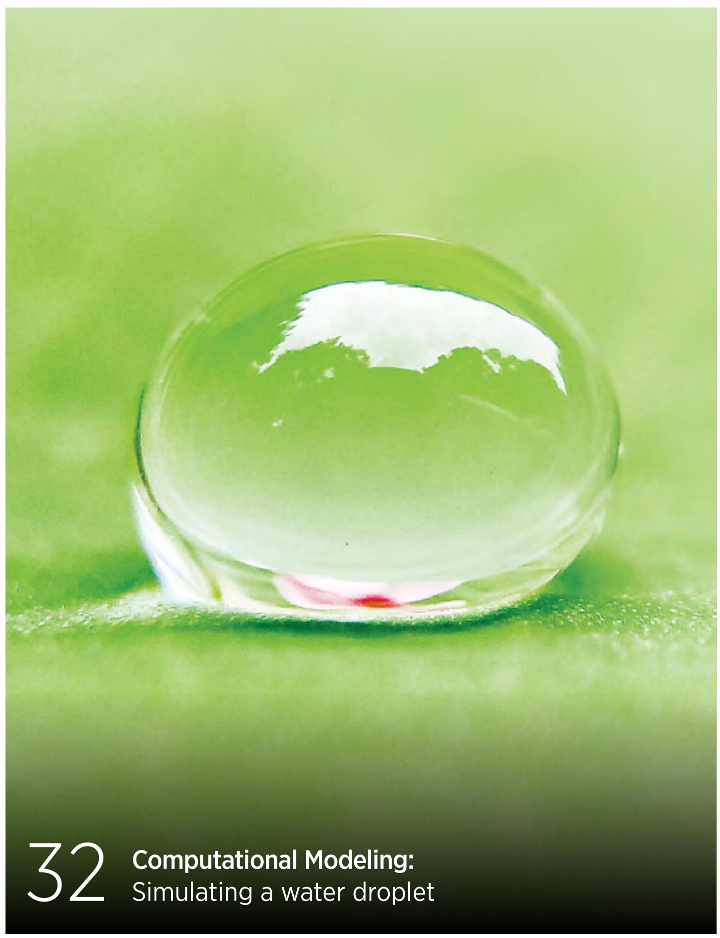






EDITORIAL NOTES

Despite the record rollout of COVID-19 vaccines globally, it's worth remembering that in the world of science, slow and steady wins the race. While Nobel Prize-winning technologies like lasers and CRISPR-Cas9 are now laboratory mainstays, their applications only became apparent years—if not decades—after their initial discovery.

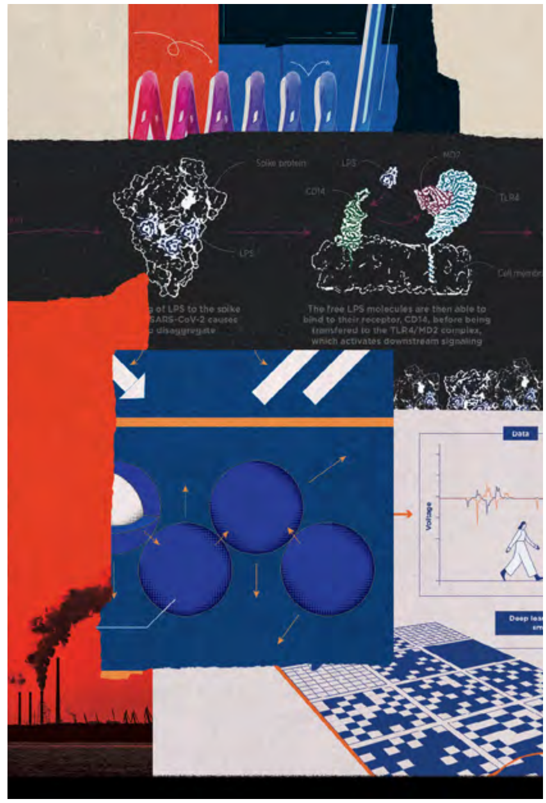
Such is the value of curiosity-driven science, also known as basic research. In contrast to applied research, which provides solutions to current problems, a subset known as use-inspired basic research (UIBR) seeks to answer science's most fundamental questions—fueling innovation and generating applications down the line. Find out how UIBR drives A*STAR to generate novel scientific knowledge addressing societal needs in our cover story, 'Basic research for breakthrough solutions,' on p. 08.

In particular, one distinguishing feature of UIBR is its cross-disciplinary nature. In 'Getting the right food at the right time (p. 28),' chronobiology and food science come together as Christiani Jeyakumar Henry of the Singapore Institute of Food and Biotechnology Innovation (SIFBI) and his team investigate how meal timing impacts metabolism and health.

Meanwhile, innovative thinkers like Min Hao Wong—a recipient of A*STAR's National Science Scholarship—are whipping up fresh solutions to age-old problems. In 'Reaping the fruits of nanotechnology (p. 20),' discover how embedded nanosensors could allow farmers to 'talk' to their crops and gather invaluable insights for better yields in a fraction of the time.

Beyond emerging fields like chronobiology and precision farming, A*STAR's efforts also extend from recent developments in COVID-19 research with 'How SARS-CoV-2 gets a bacterial boost (p. 04)' to sensors and machine learning with 'If floors could talk (p. 24).'

For more updates on the latest breakthroughs from A*STAR scientists, visit our website at **research.a-star.edu.sg** or follow us on Twitter at **@astar_research**, LinkedIn at **A*STAR Research**, and Telegram at **A*STAR Research**.



On the cover
Use-inspired basic research is about pursuing fundamental ideas while keeping potential applications in mind.

For the latest on A*STAR's COVID-19 research, please scan the QR code or visit: https://research.a-star.edu.sg/tag/covid-19/

IMMUNOLOGY

How SARS-CoV-2 gets a bacterial boost

In a classic case of double trouble, the binding of SARS-CoV-2's spike protein to bacterial lipopolysaccharide supercharges inflammation in COVID-19 patients.

While getting COVID-19 may already be daunting, the situation is even more complicated for infected individuals with pre-existing conditions. Case in point: COVID-19 patients with metabolic syndrome—a set of disorders including insulin resistance, obesity and hypertension—are more likely to take a turn for the worse and develop hyperinflammation. Still, scientists remain stumped by how exactly metabolic syndrome can aggravate SARS-CoV-2 infection.

New research suggests the answer may lie in bacterial molecules called lipopolysaccharides (LPS). Found in the membranes of Gram-negative bacteria, LPS can sometimes escape the gut and enter the bloodstream—with serious consequences. In acute respiratory distress syndrome—a common manifestation of severe COVID-19—LPS can activate immune cells and induce a massive cytokine storm. Intriguingly, elevated LPS levels in the blood are also a hallmark of metabolic syndrome, hinting at a connection to the two illnesses.

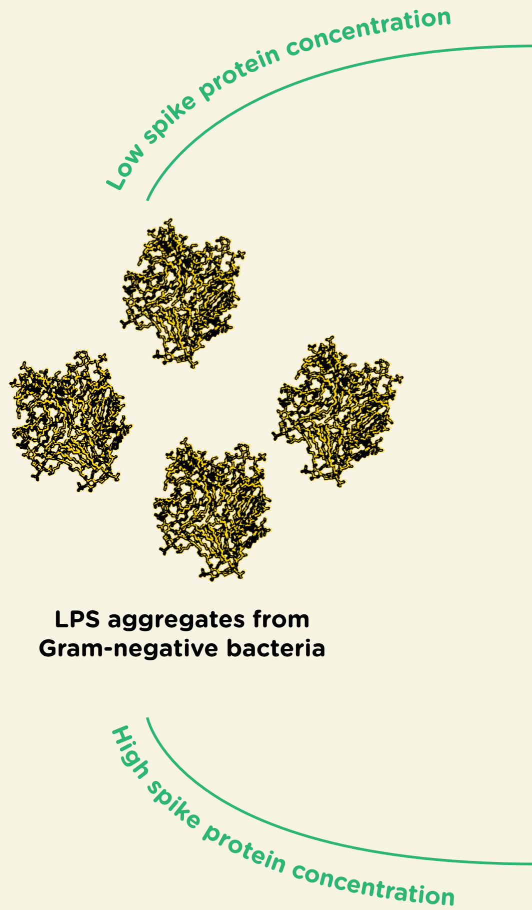
Seeking to tease out the relationship between LPS and SARS-CoV-2, researchers led by Peter Bond, a Senior Principal Investigator at A*STAR's Bioinformatics Institute (BII), joined forces with long-time collaborator Artur Schmidtchen of Lund University, Sweden. While Schmidtchen's group focused on *in vitro* and *in vivo* experiments, Bond and BII Research Fellow Firdaus Samsudin used computational modeling to identify potential binding sites between LPS and SARS-CoV-2.

To confirm an interaction between LPS and the virus, the research team performed native gel electrophoresis to show that the virus' spike protein became heavier with increasing doses of LPS.

Computational analysis and all-atom molecular dynamics simulations performed by Bond and Samsudin not only confirmed this binding but also identified a potential site of interaction. Their models showed that LPS most likely slots into a groove right beside the cleavage site linking the two subunits of the spike protein. Interestingly, LPS' interaction with the spike protein resembles the way it binds to and activates certain host immune cell receptors like CD14 and TLR4.

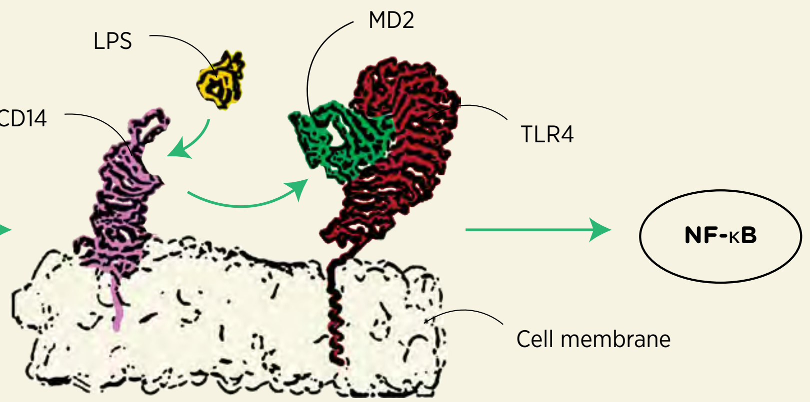
> **"This can potentially trigger the cytokine storm observed in severe COVID-19 patients, and may thus be a target for drugs that seek to prevent severe symptoms."**

True enough, the team found that in cell-culture and mouse models, the binding between LPS and the spike protein activated the transcription factor NF-κB to elicit a strong and prolonged inflammatory response. This response was much more pronounced than when induced by LPS or the spike protein alone—indicating synergy between the two molecules.

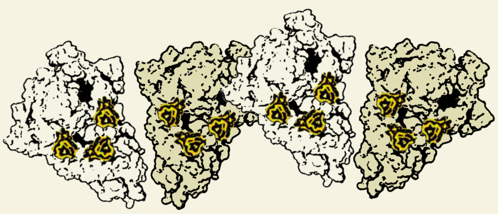


LPS aggregates from Gram-negative bacteria

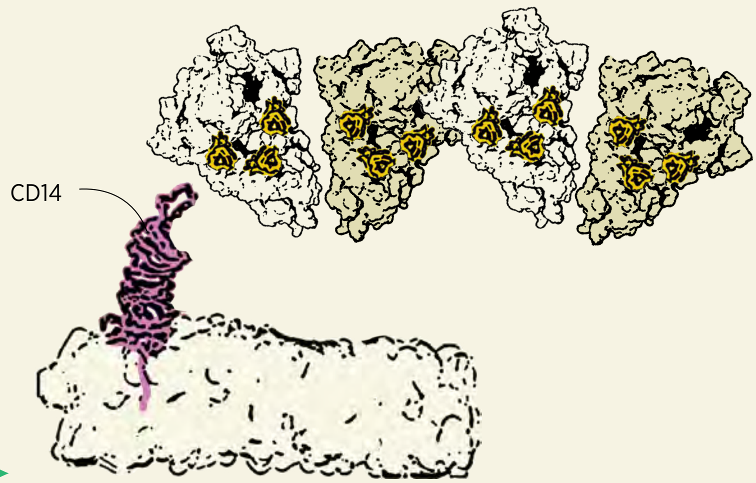
The binding of LPS to the spike protein of SARS-CoV-2 causes LPS to disaggregate



The free LPS molecules are then able to bind to their receptor, CD14, before being transfered to the TLR4/MD2 complex, which activates downstream signaling



At high spike protein concentration, most of the LPS is bound to the spike protein



This forms large aggregates which may provoke an immune response

"One potential mechanism is that the binding [of LPS and the spike protein] increases the number of free LPS molecules in the blood that can bind to CD14," explained Bond. "This can potentially trigger the cytokine storm observed in severe COVID-19 patients, and may thus be a target for drugs that seek to prevent severe symptoms." Testing for raised LPS levels could therefore also help to identify patients with a higher risk of developing severe COVID-19, he concluded. ★

ABOVE
Proposed model by which bacterial molecules like lipopolysaccharides (LPS) can bind to the spike protein of SARS-CoV-2 and trigger a stronger immune response.

Researcher
Peter Bond, BII

1. Petruk, G., Puthia, M., Petrlova, J., Samsudin, F., Strömdahl, A.C., *et al.* SARS-CoV-2 Spike protein binds to bacterial lipopolysaccharide and boosts proinflammatory activity. *Journal of Molecular Cell Biology* **12** (12), 916–932 (2020).

DIAGNOSTICS

Picking peptides for COVID tests

Four newly discovered SARS-CoV-2 peptides not only promise to make COVID-19 tests cheaper and more specific, but may also reveal disease severity.

Though COVID-19 vaccination efforts may be gaining momentum across the globe, the emergence of novel variants has fueled a worldwide surge in new cases and deaths. Rapid and accurate testing, therefore, remains key to containing SARS-CoV-2's spread.

Among the different types of COVID-19 tests, serology assays stand out for their quick turnaround time and convenience, offering results in a matter of minutes instead of hours or days. Such tests work by detecting antibodies to specific viral proteins in our blood, providing an easy way to identify people who may have had recent or even past SARS-CoV-2 infection.

However, as SARS-CoV-2 is highly similar to other coronaviruses, false positives may result. Moreover, serology assays that rely on recombinant proteins can be costly, limiting their use in disadvantaged areas that may need them the most.

To pave the way for more accurate and cost-effective serology assays, researchers led by Lisa Ng, a Senior Principal Investigator at A*STAR's Infectious Diseases Labs (ID Labs) identified four specific epitopes—sections of SARS-CoV-2's proteins—that were highly recognized by antibodies in COVID-19 patients' plasma.

Ng and her team pinned down the four linear epitopes by constructing a library of pooled SARS-CoV-2 peptides covering the virus's various proteins. Taking plasma from patients with COVID-19, recovered SARS and seasonal cold patients, as well as healthy donors, the researchers used an enzyme-linked immunosorbent assay (ELISA) to screen for any antibody reactions against the peptide pools.

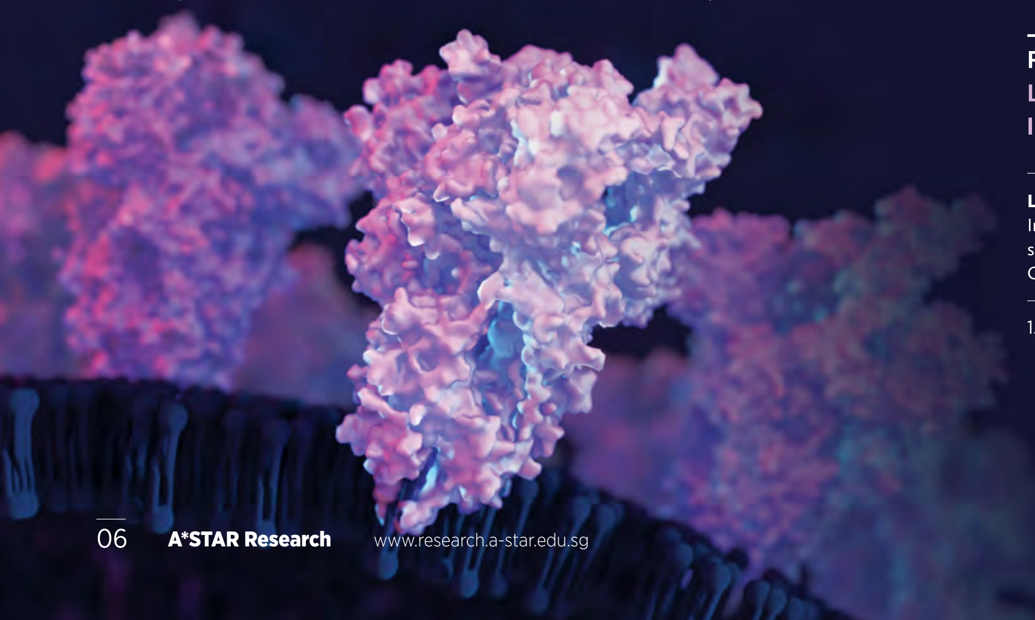
According to the team, the peptides S14P5, S20P2, S21P2 and N4P5 were highly recognized by antibodies within the plasma of COVID-19 patients. Neither recovered SARS patients, seasonal cold patients nor healthy donors had significant amounts of antibodies that recognized these peptides, demonstrating the specificity of the epitopes for SARS-CoV-2.

Incredibly, should these epitopes be applied in serology assays, a combination of all four peptides could result in a test with 100 percent specificity and specificity—at a fraction of the current cost.

"Unlike whole proteins, peptide epitopes are cost-effective and can be manufactured easily and quickly," explained Ng. "When detecting specific epitopes compared to whole recombinant proteins, issues of cross-reactivity are [also] minimized."

Aside from detecting past exposure to SARS-CoV-2, the peptides can also be used to indicate the progression of COVID-19 severity. For instance, the researchers found that high antibody levels against the epitopes were characteristic of severe COVID-19 patients admitted to the ICU or those with pneumonia.

"Given that COVID-19 has lasted for a little over a year, many researchers are striving to uncover more on the long-lasting responses of the disease," Ng said. With these newly discovered epitopes, more reliable point-of-care serology tests may soon be on the horizon—boosting immunosurveillance and our understanding of COVID-19 as we work to limit the scourge of SARS-CoV-2 on the world. ★



Researcher
Lisa Ng,
ID Labs

LEFT
Instead of using the whole spike protein, focusing on smaller fragments could make antibody tests for SARS-CoV-2 more accurate and cost-effective.

1. Amrun, S.N., Lee, C.Y., Lee, B., Fong, S., Young, B. E., *et al.* Linear B-cell epitopes in the spike and nucleocapsid proteins as markers of SARS-CoV-2 exposure and disease severity. *EBioMedicine* **58**, 102911 (2020).

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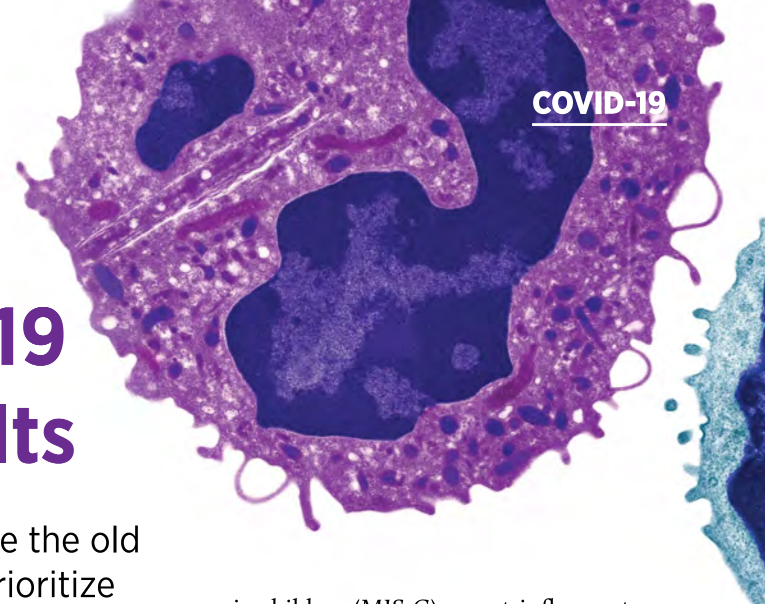


INFECTIOUS DISEASE

Comparing COVID-19 in children and adults

Understanding why COVID-19 tends to strike the old but spare the young could inform how to prioritize limited COVID-19 vaccines.

When COVID-19 swept the globe at the beginning of 2020, it soon became clear that the disease hit some much harder than others. Early on in the pandemic, it became apparent that age was a major factor influencing the severity of disease, with the oldest adults most at risk of serious complications and death. At the other extreme, children seem to be largely unaffected by SARS-CoV-2 infection, with most experiencing only mild symptoms or none at all.

Figuring out the mystery of why COVID-19 strikes the old but spares the young could help us identify at-risk individuals, inform the prioritization of vaccination programs and even give us a sense of how long a protective response might last, explained Elizabeth Tham, a Principal Investigator at A*STAR's Singapore Institute of Clinical Sciences (SICS). Tham is also a Consultant Pediatrician and Head of the Allergy, Immunology and Rheumatology division at the Department of Pediatrics, National University Hospital (NUH).

"This understanding could lay the groundwork for future therapeutics such as convalescent plasma infusions, monoclonal antibodies and vaccine development. It will also impact clinical decision making and healthcare policy including decisions on screening, quarantine, and the closure of schools and workplaces," Tham said.

"The innate immune response in children is also different from adults, with increased activation of neutrophils and decreased circulating monocytes, dendritic cells and natural killer cells."

In a review of the proposed mechanisms behind the age-related differences in responses to SARS-CoV-2, Tham and her colleagues from A*STAR and NUH found that the relatively immature immune systems of children offered them some protection against the disease.

Children's regulatory T cells exert stronger effects than those found in adults, she said, and their limited pro-inflammatory responses also mean that they are less likely to overproduce cytokines, a feature that is associated with severe lung damage in adults. "The innate immune response in children is also different from adults, with increased activation of neutrophils and decreased circulating monocytes, dendritic cells and natural killer cells," Tham added.

However, when children develop symptoms of COVID-19, they can be life-threatening. One such condition is a multisystem inflammatory syndrome in children (MIS-C), a post-inflammatory or autoimmune process where the initial infection triggers a systemic immune response. Although the mechanism behind MIS-C is still unclear, the emerging data suggest a possible genetic predisposition as it appears to strike children from certain ethnic groups more frequently than others.

While our understanding of COVID-19 and how it impacts children have come a long way since the pandemic was first recognized, more studies are required for a fuller understanding of the immune response in different age groups, Tham said. To that end, Tham is collaborating with researchers at NUH, the National University of Singapore, and Duke-NUS Medical School to evaluate the role of cross-reactive neutralizing antibodies from seasonal coronaviruses in modulating responses to SARS-CoV-2 in both children and adults, and also to study the longevity of antibody responses in previously COVID-19-infected children. ★

Researcher
Elizabeth Tham, SICS

ABOVE
Unlike adults, children have a stronger neutrophil response, which might explain why they respond differently to SARS-CoV-2 infection.

1. Wong, L.S.Y., Loo, E.X.L., Kang, A.Y.H., Lau, X.H., Tambyah, P.A., *et al.* Age related differences in immunological responses to SARS-CoV-2. *The Journal of Allergy and Clinical Immunology: In Practice* **8** (10) 3251-3258 (2020).

Photo credit: Steve Gschmeissner / Science Photo Library

BASIC RESEARCH FOR BREAKTHROUGH SOLUTIONS

By addressing technological and societal needs while advancing basic research, scientists can make a profound impact on Singapore and beyond, says A*STAR Deputy Chief Executive (Research), Andy Hor.

The next time you enjoy a cold glass of milk, consider the person who made it possible: a French scientist named Louis Pasteur. But apart from inventing—and lending his name to—the process of pasteurization, Pasteur also made profound contributions to other scientific disciplines. He developed fermentation techniques and a vaccine against anthrax, and even contributed to the birth of the discipline of stereochemistry.

While searching for a way to reduce crystal formation in wine, for example, Pasteur noticed that there were two forms of crystals: a left-handed version and a right-handed version. Intrigued by what he saw under the microscope, Pasteur painstakingly purified both forms of the crystals. His discovery that the crystals rotated light in opposite directions despite having identical chemical compositions led to a fundamentally new understanding of the optical properties of molecules.

Pasteur's style of research is better known as use-inspired basic research (UIBR), explained A*STAR Deputy Chief Executive (Research), Andy Hor. As its name suggests, UIBR is characterized by its vision: Drawing inspiration from grand challenges while answering the most fundamental questions in science. The end goal is to generate scientific knowledge that paves the way to address societal or economic needs. Because of its emphasis on solving complex, real-world problems, UIBR is a key focus for A*STAR to ensure more robust innovation pipelines for the future. Investments in such projects directly feed into the agency's goal of driving mission-oriented research that advances scientific discovery and technological innovation, he said.

*A*STAR Research* recently caught up with Hor to understand how UIBR directly benefits the research community and how it can cement Singapore's position as a global research and development (R&D) powerhouse.

Q: WHAT IS YOUR DEFINITION OF USE-INSPIRED BASIC RESEARCH AND HOW IS IT DIFFERENT FROM BOTH APPLIED AND BASIC RESEARCH?

Use-inspired basic research (UIBR) is by definition a subset of basic research, a fundamental approach aimed at better understanding a research subject or phenomenon. It should be novel—whether it's an original concept or an inventive new methodology—and it should be significant. Many things are novel, but may not be significant. In chemistry, for example, there are millions of molecules; by changing a molecule slightly we can make a new one. But simply making new compounds may not be significant if the fundamental architecture of the original molecule has not changed, or its main properties remain unaltered.

For UIBR, we need to know what the potential applications are. The potential need not be demonstrated today, but over time—perhaps five, ten or even 15 years down the road—it should become clearer. That is why some corners of the community dismiss the artificial line between basic and applied research; the question is just of quality and the application timeline.

Notwithstanding, we should not underestimate the value of research targeted at providing solutions to current problems—one may call this applied and translational research (ATR). These projects deliver tangible results in a much shorter timeframe, using current knowledge, approaches or technology with innovative adaptations. In A*STAR, we have the capacity to embark on a balanced range of research areas. Our ultimate consideration is quality, outcome and impact.

Q: WHY IS UIBR ONE OF THE PRIORITIES FOR A*STAR?

ATR remains the main thrust for A*STAR to deliver technological outcomes and socio-economic impact, whereas UIBR is the engine for new knowledge that fuels the innovation pipeline. We must provide solutions—both in the present and future—for industries and communities in areas that are important to our research.

UIBR projects in A*STAR are aligned with the Research, Innovation and Enterprise 2025 (RIE2025) plan, which has allocated at least one-third of the overall five-year RIE budget of S$25 billion to basic research. Such research promotes ideation, generates new knowledge, fosters investigator-led research, cultivates collaborations and develops talent. While we advance novel fundamental research, we must not lose sight of the big challenges that often are sources of inspiration for many researchers. These include problems of national or global significance, such as developing new technologies for digital health, advanced therapies for prevalent diseases, reducing carbon emissions or new logistic solutions.

As a science and technology organization, A*STAR is a talent hub for young people to hone their skills in conducting independent research, under the guidance of seasoned researchers in exploring ideas and tackling challenges. Numerous funding schemes are available in A*STAR and the ecosystem is designed to support such endeavors. For example, the A*STAR Central Research Fund award promotes investigator-led science and supports researchers in a full range of research activities. Talent is one of the keys to success in this knowledge-based and innovation-driven economy. It is also best developed in an environment that breeds novelty and values innovation.

Q: COULD YOU SHARE SOME EXAMPLES OF WELL-EXECUTED UIBR PROJECTS?

There are many good examples, one of which is Vitreogel Innovations, started by Xinyi Su of the Institute of Molecular and Cell Biology (IMCB) and Xian Jun Loh of the Institute of Materials Research and Engineering (IMRE). Xian Jun is a basic polymer scientist who, over time, developed a passion for gels, which are a form of dynamic polymers. He started with basic science, but always kept the applications of that science in mind. He and Xinyi—who is a clinical scientist and an ophthalmologist—came together to solve a problem she faced; namely, finding a suitable substance to replace the vitreous liquid in patients' eyes after a particular type of surgery. By working together, and via collaborations with colleagues at the National University of Singapore and Singapore Eye Research Institute, they came up with a safe, stable and biodegradable gel that serves as a vitreous substitute.

Other examples include work by Florent Ginhoux of the Singapore Immunology Network (SIgN) on macrophages and dendritic cells, which could provide insights for therapeutic targets and intervention strategies. Also notable is research by Kui Yao of IMRE on piezoelectric materials as a basis for next-generation ultrasonic sensors and transducers. Many of these researchers publish in top journals, but what sets them apart is that they are always looking for problems to solve.

Q: HOW WILL THE OUTPUT OF UIBR PROJECTS BE MEASURED?

We need to make sure that the science that we do is competitive. The quality of UIBR research is typically reflected by their publication in prestigious journals such as *Science*, *Nature* and *Cell*. However, some of them are also seen in more specialized journals such as *Physical Review* Letters, *Advanced Materials* and the *Journal of the American Chemical Society*.

Many UIBR researchers also produce patents and different forms of non-academic outputs, such as designs, licenses and technical reports. One distinguishing feature is that UIBR researchers often collaborate with those outside their disciplines, and take a holistic and longer-term view of their research impact. They are therefore more inclined to move their research to its next step and keep challenging themselves with the question of "So what?". Much of our work with the industry today, from multinational companies like Applied Materials to small- and medium-sized enterprises like MiRXES, can be traced to such UIBR projects.

We, therefore, use a basket of measures to judge their research, including but not limited to journal publications. Focusing on non-academic outputs also helps us gauge the value of the UIBR research to the wider society and economy. Some UIBR projects can quickly generate intellectual property, partnerships, testbeds and prototypes in the course of developing cheaper, newer or better products, but others might stay at the basic arena for a longer gestation period. This is understandable and highly project-dependent. We will ask fundamental questions, like:

Professor Andy Hor
A*STAR Deputy Chief Executive (Research)

Where is the new knowledge? What is the novelty? Who will find this useful? What are the collaborative opportunities? Where is the translational potential? How does it change the world? The answers to these questions will often give us a good sense if the work is worth doing.

We understand the dynamics of UIBR—its uncertainty, the inherent risks and the long gestation period. A project could change course along the way, but what should be clear is that every project must be based on good science and aim to create new and important knowledge. Proposals must demonstrate their aspirations and detail how the work can shape how we think, live, work and play. What we don't want is research for the sake of research, or aimless research.

Q: APART FROM ACADEMIC OUTPUTS, HOW WOULD YOU MEASURE THE SUCCESS OF UIBR?

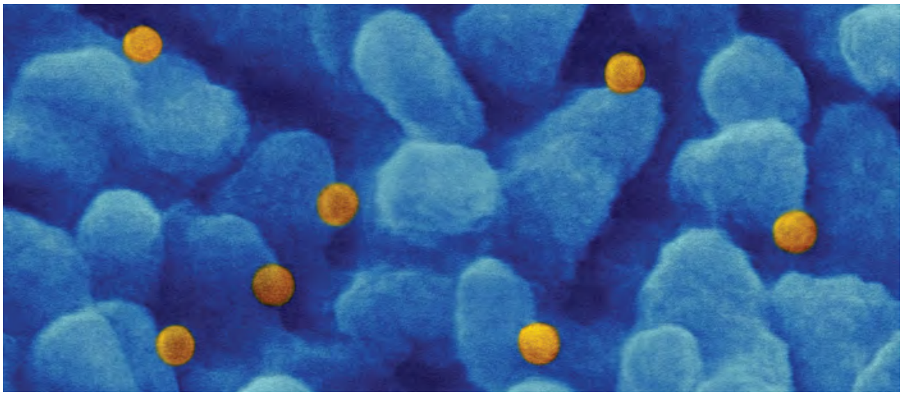
Some researchers, especially those in basic research, tend to think of publications as the culmination of their research efforts. This may be natural, whether at A*STAR or at other organizations. But I see publications as the starting point, not the destination or target. We must be clever in turning outputs into outcomes, and curating the impact from those outcomes. This can be accomplished if we consistently look beyond papers, patents and licenses, and not be contented with meeting or even exceeding key performance indicators.

My advice would be to seek qualitative assessments of every project we take on, asking how the results help shape the next chapter of the project and what is the impact of the project on people outside the research team. What is particularly exciting in the work? Why would people be interested in our papers and patents? How would that change their lives? Does the published work make a better world for all of us? Returning to UIBR, what exactly is the 'use,' and will we be a step closer to that use by the end of the project? This is our goal: To build a culture of novelty, innovation and impact at A*STAR.

Q: HOW WOULD THIS CULTURE OF NOVELTY, INNOVATION AND IMPACT DIRECTLY BENEFIT THE RESEARCH COMMUNITY IN PARTICULAR, AND SINGAPORE AS A WHOLE?

We intend to establish a structure and culture where people have a deep interest in creativity, discovery and invention. With that, we can attract the best people, give them the room to roam, and provide them the guidance to succeed. This means understanding the aspirations of individuals and giving them the opportunities to research in areas of their strengths and interest. Every individual must play a role in shaping the research landscape, as well as contribute to organizational advancement and nation building. This is not just about UIBR or ATR, but research across the entire value spectrum. Research doesn't exist in isolation, for its impact may lie elsewhere. In the vast land of research and innovation, creativity and inventiveness are the centerpieces and where UIBR belongs.

For A*STAR to serve its role well, it needs a good balance of basic and applied research, an effective platform to foster collaboration and translation, as well as a strong research environment and culture for people to create, innovate and realize their aspirations. It is in this context that we support UIBR. ★



IMMUNOLOGY

NLRP1: How the body senses the common cold virus

The mysterious trigger of the NLRP1 inflammasome sensor has finally been identified: a protease found in the common cold-causing human rhinovirus tells our body that it has been invaded.

Whether in business, military combat, or the body's immune response, all good defense strategies deploy multiple lines of defense. With the main goal of identifying risks, the body's first line of defense—the innate immune system—uses special protein sensors to detect pathogens that have breached the body's physical barriers, which activates the next level of immune response.

One class of sensors, known as Nodlike receptor (NLR) proteins, play an important role in inflammation. They cause the assembly of multiprotein structures called inflammasomes that stimulate the secretion of inflammatory signals and cell death. To date, several different NLR proteins and their triggers have been identified, showing that NLRs play an important role in the detection of threats ranging from bacteria to viruses and even stress like metabolic dysregulation. However, although it was the first NLR to be discovered in humans, the specific trigger of NLRP1 had remained elusive.

Noting that mutations in NLRP1 tend to cause inflammation in the skin and airways, a team of researchers from A*STAR, the National University of Singapore, and Nanyang Technological University (NTU) hypothesized that pathogens commonly found in those areas might activate NLRP1. They zeroed in on human rhinovirus, a virus responsible for the common cold. As the most frequent human disease, rhinoviruses are estimated to result in up to 75–100 million physician visits annually in the US alone.

Through a series of genetic and cell culture experiments, the researchers found that a rhinovirus enzyme called 3C protease activates NLRP1 by cutting the protein at a single site. This cleavage produces a fragment that is recognized by a protein complex called cullin$^{ZER1/ZYG11B}$, ultimately marking the fragment for degradation. The degradation in turn leads to the full assembly and activation of the NLRP1 inflammasome.

"NLRP1 can be said to serve as a tripwire trigger, sensing pathogen proteases that are infecting the human body," explained Bruno Reversade, a Research Director at A*STAR's Institute of Molecular and Cellular Biology (IMCB) and Genome Institute of Singapore (GIS), and lead author of the study with co-corresponding author Franklin Zhong of NTU and the Skin Research Institute of Singapore (SRIS). "Our findings challenge the paradigm that viral proteases are predominantly present for disabling the host immune response, showing that this protease actually triggers NLRP1 as well."

The study also highlights the important differences between human and mouse immune systems, as the equivalent of NLRP1 in mice is not activated by viral proteases. "This is a reminder that mouse models may not always properly recapitulate human diseases," Reversade added.

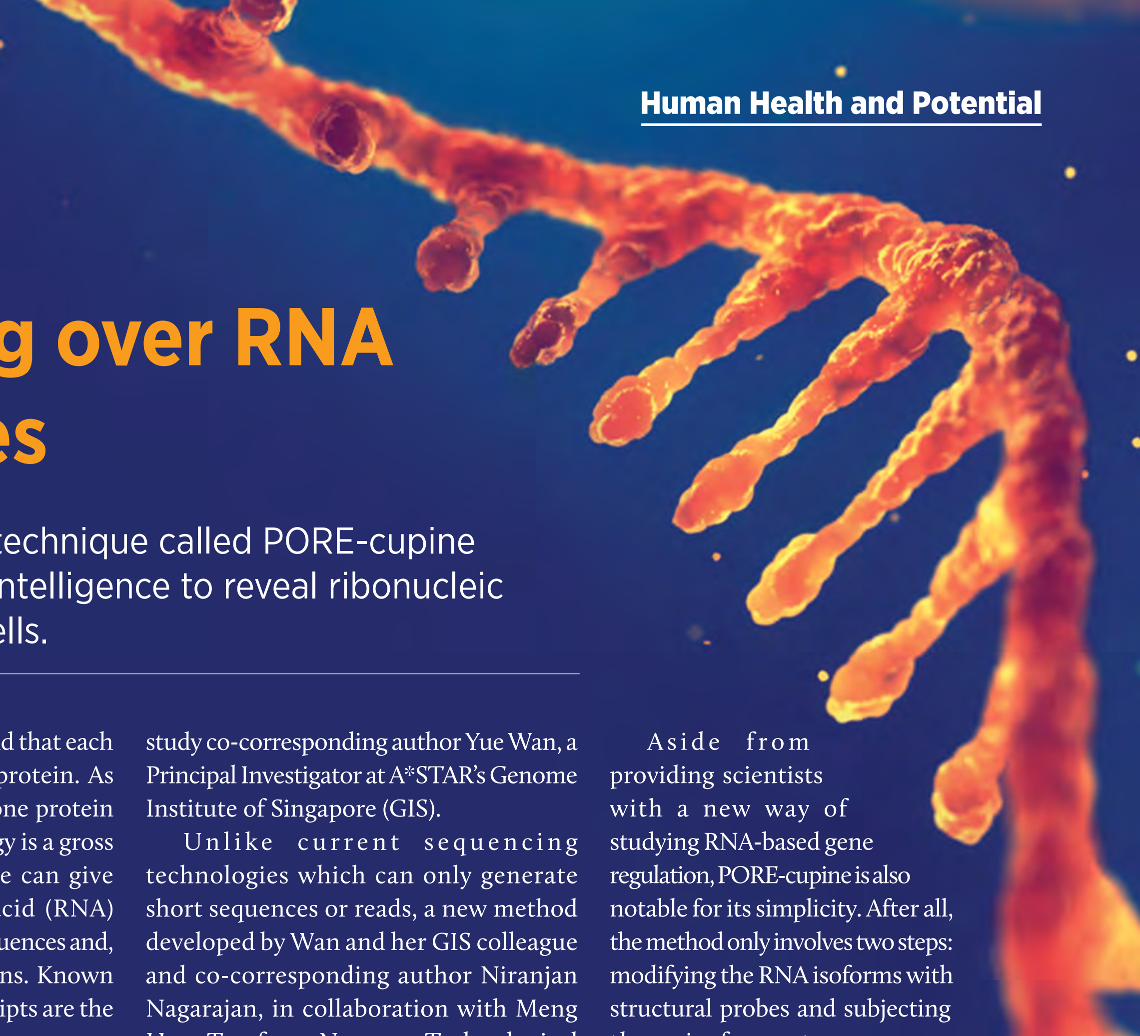
The researchers aim to develop a drug to block NLRP1 activity, as it has been implicated in several inflammatory diseases. ★

Researcher
Bruno Reversade, IMCB and GIS

ABOVE
Colored scanning electron micrograph of rhinoviruses (yellow) on nasal epithelial cells (blue). Researchers have now identified NLRP1 as the body's rhinovirus sensor.

1. Robinson, K.S., Teo, D.E.T., Tan, K.S., Toh, G.A., Ong, H.H., *et al*. Enteroviral 3C protease activates the human NLRP1 inflammasome in airway epithelia. *Science* **370**, eaay2002 (2020).

Photo credit: Dennis Kunkel Microscopy / Science Photo Library



GENOMICS

PORE-ing over RNA structures

A new sequencing technique called PORE-cupine combines artificial intelligence to reveal ribonucleic acid structures in cells.

Conventional wisdom once held that each gene produced only a single protein. As we now know, the one gene-one protein hypothesis in molecular biology is a gross oversimplification. One gene can give rise to several ribonucleic acid (RNA) transcripts that have similar sequences and, occasionally, different functions. Known as RNA isoforms, these transcripts are the equivalent of molecular siblings.

It turns out that although RNA isoforms arise from the same gene, they are regulated in a variety of ways. For instance, they can decay at different speeds. What governs the differences in regulation, however, is still largely unknown, and a clue may lie within their three-dimensional structures.

"Traditionally, mapping RNA structures of each isoform is difficult because different isoforms from the same gene still look very similar at the sequence-level," said study co-corresponding author Yue Wan, a Principal Investigator at A*STAR's Genome Institute of Singapore (GIS).

"Traditionally, mapping RNA structures of each isoform is difficult because different isoforms from the same gene still look very similar at the sequence-level."

Photo credit: nobeastsofierce / Shutterstock

Unlike current sequencing technologies which can only generate short sequences or reads, a new method developed by Wan and her GIS colleague and co-corresponding author Niranjan Nagarajan, in collaboration with Meng How Tan from Nanyang Technological University, could revolutionize the study of RNA-based gene regulation.

Their technique, dubbed by the researchers as PORE-cupine, owes its unique name to nanopore sequencing. Because it can generate long reads, it is much easier to map out which RNA isoform the reads belong to.

"In nanopore sequencing, current flows through biological pores when an RNA molecule threads through," explained Wan. "By detecting current changes through the pores, we are able to determine which base along the RNA molecule has been modified by chemical compounds, and hence whether it is double- or single-stranded."

Testing PORE-cupine on human embryonic stem cells, the team showed that structural differences among the RNA isoforms could alter the amount of proteins made within cells. They also found that shared sequences in different RNA isoforms of the same gene can fold into different structures.

Aside from providing scientists with a new way of studying RNA-based gene regulation, PORE-cupine is also notable for its simplicity. After all, the method only involves two steps: modifying the RNA isoforms with structural probes and subjecting these isoforms to nanopore sequencing, with no amplification step required.

Moving forward, the team aims to further refine the technique's machine learning algorithms. "We aim to test more structure-modifying compounds and additional types of machine learning strategies to figure out if there are other compounds or methods that can perform even better," said Wan. ★

Researcher
Yue Wan,
GIS

ABOVE
By combining nanopore sequencing with artificial intelligence, PORE-cupine helps researchers distinguish different isoforms of RNA.

1. Aw, J.G.A., Lim, S.W., Wang, J.X., Lambert, F.R.P., Tan, W.T., *et al.* Determination of isoform-specific RNA structure with nanopore long reads. *Nature Biotechnology* **39**, 336–346 (2021).

CANCER BIOLOGY

Tumors hide by mimicking fetal characteristics

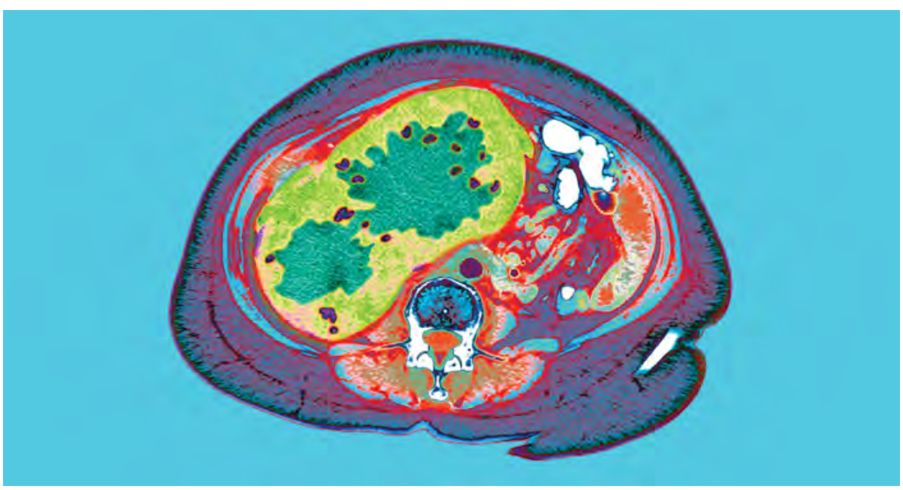
Liver tumors gain immune tolerance by activating cellular mechanisms involved in fetal development.

Cancer cells are strikingly different from healthy ones, leaving tell-tale signs that can be detected by immune cells. So how do these malignant tissues mask their true identities to avoid capture by the immune system? According to a study published in *Cell*, some liver cancer cells have an unusual way of surviving: By pretending to be growing fetal cells.

"The fetal immune system and fetoplacental-maternal interface are largely immunologically tolerant, allowing their co-existence within the mother until birth," explained Ramanuj DasGupta, a Senior Group Leader at A*STAR's Genome Institute of Singapore (GIS). "It has long been suggested that cancers may have similar mechanisms to avoid rejection by the body's own immune system."

Together with Pierce Chow of the National Cancer Centre Singapore; Jerry Chan of KK Women's and Children's Hospital; Florent Ginhoux of A*STAR's Singapore Immunology Network (SIgN); and the study's first author, Ankur Sharma, a postdoctoral fellow in his lab, DasGupta focused on a form of liver cancer called hepatocellular carcinoma (HCC), the second most common cause of cancer deaths globally.

The team analyzed gene expression profiles of around 200,000 single human liver cells isolated at different stages of both fetal and tumor development. The creation of this single-cell atlas was the key driver in discovering new aspects of tumor biology, particularly among rarer populations of HCC tumor cells, said DasGupta.



Colored axial computed tomography scan of a 45-year-old woman with a large hepatocellular carcinoma (dark green) within the liver. Such tumors can escape destruction by the immune system by pretending to be fetal cells.

Interestingly, the researchers found cells typically associated with the development of the fetal liver within HCC tumors. These cells, which include endothelial cells and macrophages, activate specific signaling pathways allowing tumors to thrive under the prying eyes of circulating immune cells. The tumor cells do so by altering their microenvironment in a way that promotes immune exhaustion or exclusion, or both. As a consequence, the cytotoxic immune cells can't infiltrate the tumor, or even if they do, are not activated to recognize and kill the tumor cells.

In particular, gene regulatory analysis showed that VEGF signaling between the HCC cells and endothelial cells can impart 'fetal-like' characteristics to the latter, which in turn activate the Notch-Delta pathway in blood monocytes and differentiate them into immune-suppressive macrophages.

"This study not only provides fundamental insights into the developmental origins of cancer and the specific processes that drive tumorigenesis, but may also usher in the development of new therapeutic strategies to re-activate the immune system in the fight against cancer," said DasGupta. With over 80 percent of HCC patients hailing from Asian countries, these developments could significantly impact the region.

Moving forward, the team is exploring the utility of their newly-discovered biomarkers as potential therapeutic targets, particularly when used in combination with existing immunotherapies. They are also investigating whether other solid tumors employ similar immune evasion tactics and how epigenetic factors influence these processes. ★

Researcher
Ramanuj DasGupta, GIS

1. Sharma, A., Seow, J.J.W., Dutertre, C.A., Pai, R., Blériot, C., *et al*. Onco-fetal reprogramming of endothelial cells drives immunosuppressive macrophages in hepatocellular carcinoma. *Cell* **183** (2), 377-394.e21 (2020).

Photo credit: Du Cane Medical Imaging Ltd / Science Photo Library

STEM CELLS

Sifting out rare stem cells

Single-cell techniques have helped to identify a key molecular switch controlling how adult cells can be turned back to a stem cell-like state.

We can't turn back time, but scientists have developed a method for 'rewinding' adult cells back to the stem cell-like states they were in during embryonic development. This process, known as reprogramming, carries immense potential in the field of regenerative medicine—patients could one day receive reprogrammed cells (of their own) to treat diseased tissues.

However, while cell reprogramming can be initiated, scientists have found it difficult to control the biological outcomes. Reprogrammed cells can take a multitude of possible routes on their way towards their final states, explained Jonathan Yuin-Han Loh, a Senior Principal Investigator at A*STAR's Institute of Molecular and Cell Biology (IMCB), and a co-corresponding author on the study. Ultimately, using current methodologies, only a few of these cells successfully become reprogrammed, significantly limiting the use of this technique for clinical applications.

In a step towards enhancing reprogramming efficiency, Loh and colleagues aimed to map the molecular mechanisms at play during this process. The scientists used advanced single-cell sequencing technologies to analyze individual human cells, sampled at various stages of their reprogramming journeys.

"Most of the previous studies are based on bulk measurement of a heterogeneous population, which mask the signals from rare, reprogrammed populations," said Loh, who added that conventional methods often miss the tiny fraction of successfully reprogrammed cells. "Single-cell approaches allow us to investigate molecular events occurring within every individual cell."

The team found three distinct subpopulations of cells that emerged early on during the reprogramming process, each of which had a different propensity for reverting to a stem cell-like state. Critically, they also identified specific molecular markers associated with each of these subpopulations, key features required for isolating cells with the greatest chances of becoming reprogrammed.

Additionally, the researchers uncovered a relationship between two molecular regulators of cell fate, FOSL1 and TEAD4. Activation of the transcription factor FOSL1 suppressed reprogramming. Conversely, turning off FOSL1 triggered the expression of TEAD4—the green light for cells to go down the reprogramming path. "A binary choice between FOSL1- and TEAD4-centric regulatory networks determines the outcome of a successful reprogramming," said study first author Qiaorui Xing, a researcher at IMCB.

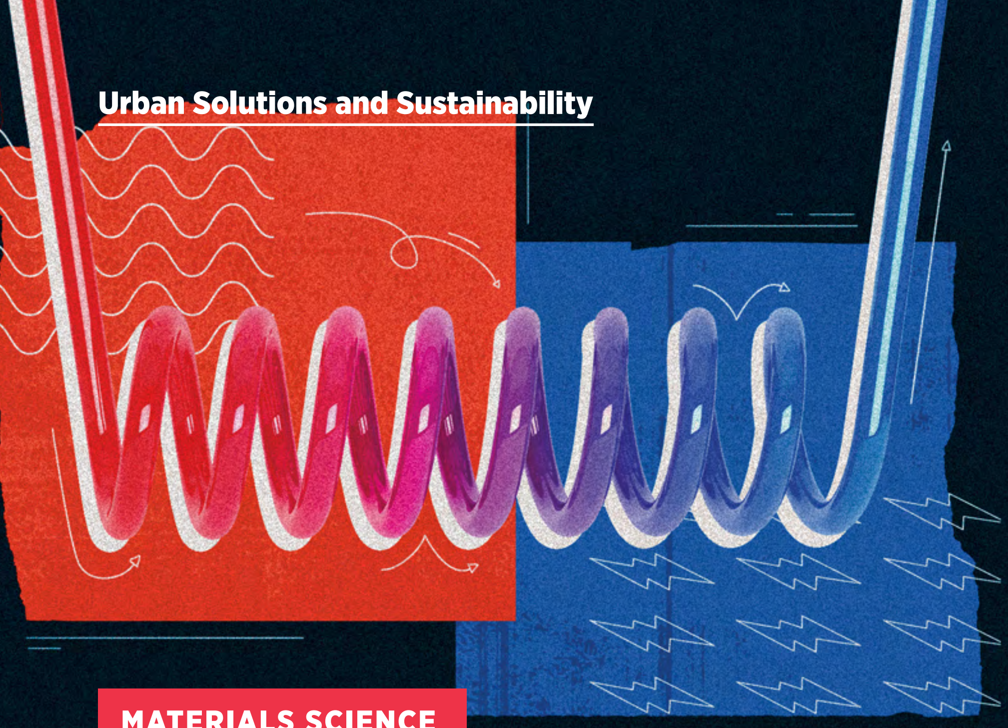
Together, these findings serve as a roadmap for tracking the trajectories of reprogrammed cells and could help propel stem cell therapies towards the clinic. In follow-up studies, Loh and colleagues plan to take a closer look at the role of transiently activated genes in reprogramming, to determine whether they could exploit these pathways to further boost reprogramming efficiencies. ★

Researcher
Jonathan Loh, IMCB

ABOVE
The switch between FOSL1 and TEAD4 pathways is an important step in the reprogramming of adult cells back into a stem cell-like state.

1. Xing, Q.R., El Farran, C.A., Gautam, P., Chuah, Y.S., Warrier, T., *et al*. Diversification of reprogramming trajectories revealed by parallel single-cell transcriptome and chromatin accessibility sequencing. *Science Advances* **6**, eaba1190 (2020).

Photo credit: pinkeyes / Shutterstock



MATERIALS SCIENCE

Alloys as electricity-generating allies

Mixing tin into germanium telluride creates a high-performance thermoelectric material that could make energy harvesting or cooling devices more effective.

Getting to distant planets for space exploration is only half the challenge—packing, transporting and generating energy for these missions requires highly specialized technologies. The 2015 film *The Martian*, for example, depicts the protagonist using a thermoelectric generator to fend off Mars' unforgiving cold.

Such machines require thermoelectric materials to convert differences in temperature into electricity, or vice versa. They are used in the real world to power fridges and air-conditioning units and as compact energy sources for space probes and planetary rovers.

"Whether a thermoelectric material is practically useful largely depends on its device efficiency, which is determined by the material's figure of merit, zT," explained Jianwei Xu, a Senior Researcher at A*STAR's Institute of Materials Research and Engineering (IMRE).

The utility of thermoelectric materials is influenced by their electrical and thermal conductivity. Additionally, some semiconductors undergo significant shifts in the organization of their molecules at different temperatures, a phenomenon that governs their thermoelectric potential.

Take germanium telluride (GeTe), which exists in two distinct phases: a rhombohedral phase at room temperature and a cubic phase at higher temperatures. The cubic phase is also associated with a lower thermal conductivity and therefore higher zT values. Together with study co-corresponding author Gang Zhang, a Senior Scientist at A*STAR's Institute of High Performance Computing (IHPC), Xu explored how chemical modifications could lock GeTe in the cubic phase, thus boosting its electricity generating capabilities.

The team mixed GeTe with precise amounts of elemental tin in a process known as alloying. Their new GeTe alloy was held at the pure cubic phase, which elevated its zT considerably. The idea of generating a GeTe alloy was sparked by combining thermoelectrics and ferroelectrics, materials that have reversible electrical poles.

"Having worked on ferroelectric materials, in which tuning phase transition temperature is important, we applied some of the knowledge from ferroelectric materials to tune the phase transition temperature in GeTe," said Ady Suwardi, a Scientist at A*STAR's Institute of Materials Research and Engineering (IMRE). This study, the first of its kind, demonstrates how cross-domain knowledge between thermoelectric and ferroelectric materials can drive scientific advancements, Suwardi shared.

Follow-up studies aim to further fine-tune GeTe, a brittle material that is prone to cracking after repeated use cycles in a generator. "We are now actively working to enhance the mechanical robustness of this material, which will be important before widespread commercial adoption," Xu said. Reducing manufacturing costs by identifying less expensive substitutes for Ge will also be a priority moving forward, he added. ★

Researcher
Jian Wei Xu, IMRE

ABOVE
Adding tin to germanium telluride greatly increases the material's ability to convert heat into electricity.

1. Suwardi, A., Cao, J., Hu, L., Wei, F., Wu, J., *et al.* Tailoring the phase transition temperature to achieve high-performance cubic GeTe-based thermoelectrics. *Journal of Materials Chemistry A*, 18880–18890 (2020).

Photo credit: doomu / Shutterstock

MATERIALS SCIENCE

Controlling defects to capture more CO_2

Defects are not necessarily bad; researchers have used them to improve the ability of molybdenum oxide thin films to capture CO_2.

The alarming rise in Earth's temperatures due to global warming is projected to have devastating effects on all life on the planet. The main culprit: the rise in carbon dioxide (CO_2), 36 billion tons of which were emitted in 2019 alone.

One way to mitigate or potentially even reverse the effects of climate change is to capture CO_2 from the air. Unfortunately, while burning fossil fuels is easy, re-capturing CO_2 released into the atmosphere is not. Despite the obvious increase in CO_2 levels, the gas still makes up only a small fraction of the air. On top of this, CO_2 is one of the most stable molecules in air, making it difficult to absorb chemically.

"While carbon capture technologies exist, they are costly and do not perform well at low concentrations of CO_2," said Sing Yang Chiam, Deputy Executive Director of A*STAR's Institute of Materials Research & Engineering (IMRE). "Capturing CO_2 directly under ambient conditions is even more difficult."

"While carbon capture technologies exist, they are costly and do not perform well at low concentrations of CO_2."

In the present study, first author Mohammad Tanhaei, a graduate student working at IMRE, turned to defect engineering to develop a material that can efficiently capture CO_2. Although defects are regarded as undesirable in most situations, intentionally added defects can improve a material's properties and performance. However, defects are often introduced using post-processing techniques, which are hard to control and require additional time and cost.

Instead, the researchers directly introduced defects while forming a thin film of molybdenum (Mo) oxide, a material with multiple stable oxidative states that can interact with the highly stable CO_2.

In doing so, the team boosted the material's ability to capture CO_2 to about 23 mmol/g under standard conditions, which, Chiam notes, is one of the best-reported performances to date. An additional benefit of using molybdenum oxide in a thin film format instead of a powder, as is usually the case for sorption applications, is that there will be lower toxicity and contamination risks, he added.

"We were pleasantly surprised that the material on a supporting substrate had superior sorption performance, which we attributed firstly to the lack of 'dead mass' that exists in powders and secondly to reactive meta-stable defects," Chiam said.

The researchers expect that the material can be developed to capture CO_2 in industrial settings or used as a coating on the walls of buildings and tunnels to remove CO_2 indoors. ★

Photo credit: Marek Piwnicki / Unsplash

Researcher
Sing Yang Chiam, IMRE

BACKGROUND
Defect engineering could help make carbon capture technologies more efficient and cost-effective.

1. Tanhaei, M., Ren, Y., Yang, M., Bussolotti, F., Cheng, J.J.W., *et al*. Direct control of defects in molybdenum oxide and understanding their high CO_2 sorption performance. *Journal of Materials Chemistry A* **8**, 12576–12587 (2020).

CHEMISTRY

Keeping it cool with polymer-encapsulated pigments

Encapsulating sun-blocking pigment particles within polymer shells can improve their ability to reflect light, leading to the enhanced cooling performance of coatings.

Your best bet against skin cancer is sunscreen, which works by absorbing ultraviolet light and reflecting visible and near-infrared (NIR) light to protect your skin cells from the damaging rays of the sun. As one of the safest and most effective sun-blocking pigments, titanium dioxide (TiO_2) is used in many brands of sunscreen—as well as in coatings designed to reflect sunlight off surfaces in a bid to lower cooling costs. Such coatings play an important role in keeping buildings cool in the face of climate change.

Although TiO_2 pigments can reflect visible light well, they may not be as effective in reflecting NIR light. However, NIR reflectance is a key factor in a coating's overall ability to reflect sunlight, or total solar reflectance (TSR), which is directly related to cooling performance.

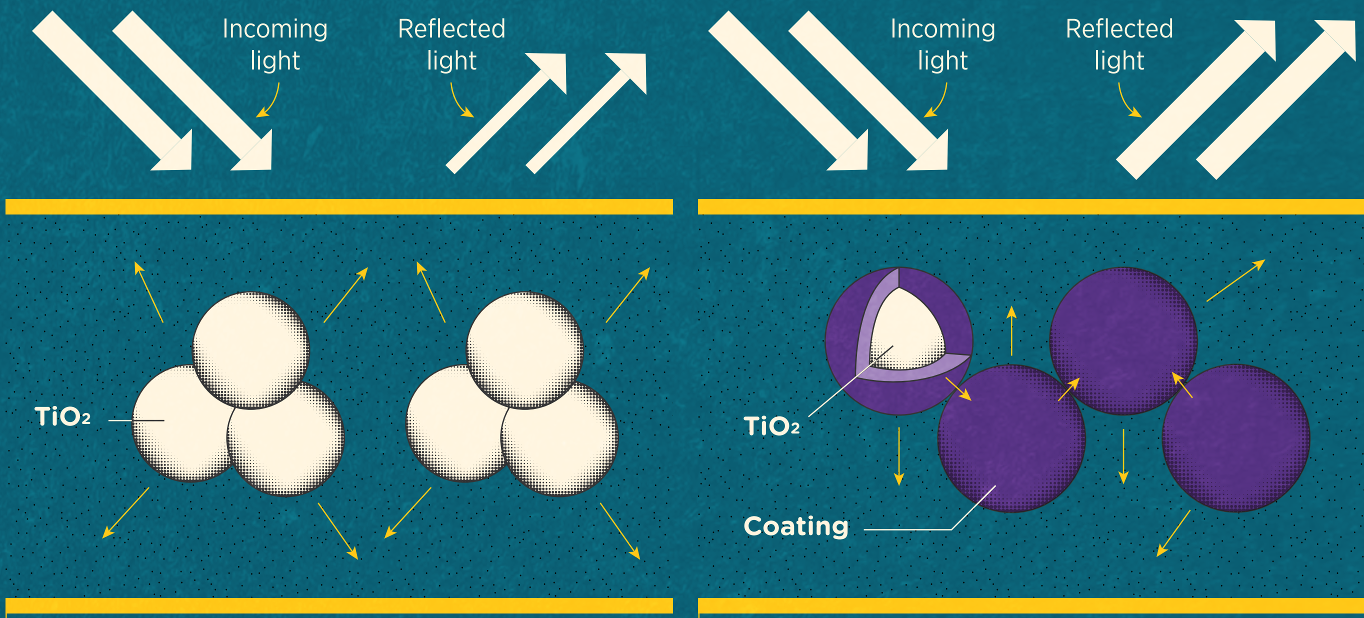
> **"For cool coatings, we have to take cost into account so we used relatively cheap materials like poly(methyl methacrylate) and polystyrene."**

One way to improve reflectance is by increasing the distance between TiO_2 particles, which tend to clump in a coating film, particularly at high concentrations. To physically separate the particles, a team of researchers from A*STAR's Institute of Chemical and Engineering Sciences (ICES) coated them with different shell materials and assessed their effectiveness.

"For cool coatings, we have to take cost into account so we used relatively cheap materials like poly(methyl methacrylate) and polystyrene to encapsulate TiO_2," explained study co-corresponding author Satyasankar Jana, a Senior Scientist at ICES.

When compared with bare TiO_2, encapsulated TiO_2 particles were more evenly spaced in the coating. Furthermore, just as light bends when it moves from air to water, the need for light to travel through materials with different refractive indexes improved the scattering of light, ultimately improving TSR by up to 7-10 percent and enhancing the cooling effect.

Photo credit: TWStock / Shutterstock



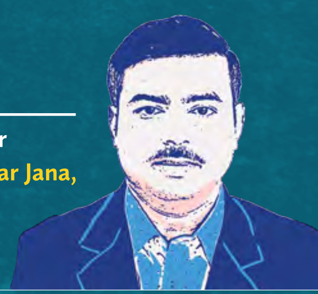
- Without encapsulation, some TiO_2 particles agglomerate, especially when TiO_2 levels are high.
- This causes overlapping, ultimately reducing the light-scattering ability of solar reflective coatings.

- Encapsulation increases the spacing between TiO_2 particles, preventing agglomeration and enhancing light sattering.
- The refractive index mismatch between the coating and the particles further increase light scattering.

"In the lab, we observed a difference of 8 °C under NIR irradiation. Under actual sunlight we observed a difference of close to 3 °C for a small test panel," said Alexander van Herk, a co-corresponding author on the study and a Principal Scientist at ICES. "This is considerable as we are comparing equal amounts of TiO_2 and other components in the two samples, so this temperature difference is simply due to the encapsulation."

Apart from coatings on urban surfaces, polymer-encapsulated TiO_2 could also be used in high-end applications such as automotive coatings, Jana added. Building on their findings, the researchers are now studying if their pigment encapsulation approach can be used to improve NIR reflectivity in road markings and car coatings for better visibility in autonomous driving environments. "We are currently investigating this line of research with a project supported by an Industry Alignment Fund grant," he said. ★

ABOVE
Encapsulating titanium dioxide nanoparticles in affordable shell materials can enhance their ability to reflect near-infrared light.



Researcher
Satyasankar Jana, ICES

1. Dong, S., Quek, J.Y., Van Herk, A.M., Jana, S. Polymer-encapsulated TiO_2 for the improvement of NIR reflectance and total solar reflectance of cool coatings. *Industrial & Engineering Chemistry Research* **59**, 17901-17910 (2020).

REAPING THE FRUITS OF NANOTECHNOLOGY

Nanosensors embedded in plants could allow farmers to 'talk' to their crops and gather valuable data for better yields, says Min Hao Wong.

Behind the success of every Formula 1 team is an array of high-tech sensors and extensive data analytics. Each car is equipped with over 200 sensors tracking everything from individual tire temperature to a driver's heart rate. While sensors can make the split-second difference between victory and loss in motor racing, they could potentially make an even bigger impact in an industry that is not traditionally thought of as tech-savvy: agriculture.

Set to grow into a US$2–3 billion market by 2026, agricultural sensors have transformed farming all over the world. The goal of precision farming is clear—maximize productivity while minimizing negative environmental effects. Towards this end, factors like weed mapping, salinity and yield are measured and analyzed to point farmers to the best course of action.

Taking the technology one step further, Min Hao Wong, currently a Strategy and Business Development Group Leader at A*STAR's Singapore Institute of Food and Biotechnology Innovation (SIFBI), developed nanosensors to gather meaningful data from within plants. Typically, to evaluate the effectiveness of new chemicals or pesticides, farmers would have to wait weeks to observe results—with or without agricultural sensors. Wong's technology reduces that time substantially.

Wong's tiny 'nanobionic' sensors are designed to interface directly with plant tissue, cells and organelles, and are capable of relaying accurate real-time information to farmers and researchers through infrared communication. Made of carbon nanotubes wrapped with amphiphilic polymers which have separate sections to both attract and repel water, the nanosensors can be delivered in a solution and absorbed through the leaves. The polymers on these nanosensors react to analytes like water and oxygen to determine a plant's needs—allowing plants to 'talk' to farmers and let them know what they need, when they need it.

To bring this technology to farmers, Wong co-founded Plantea, a company selling proprietary nanosensors and software for better plant growth and maximized food production. Through Plantea, Wong and his team aim to eventually develop self-controlled farming environments where sensors determine and automatically set ideal growth conditions like temperature and nutrient levels.

A recipient of A*STAR's National Science Scholarship, Wong was named one of Forbes' 30 Under 30 in 2018 as well as an MIT Technology Review Innovators under 35 honoree. In this interview with *A*STAR Research*, he shares what inspired his research on plant nanosensors and the impact he hopes his technology will have on the future of food in Singapore and beyond.

Q: HOW DID YOU FIRST BECOME INTERESTED IN DESIGNING AGRICULTURAL NANOSENSORS?

My interest in plants began at a very early age. While still in high school, I participated in a science research program organized by the department of plant biology at a local university, where I had the chance to learn more about the composition of fern and pollen spores in the air and how they can affect human health or cause allergies. I became fascinated with plants, and always wondered if there was a way to make plants communicate information to us.

Q: WHAT KEY AGRICULTURAL PROBLEM WILL YOUR RESEARCH ADDRESS?

While not everyone knows it, plants are very diverse. Living things are divided into five kingdoms, and plants occupy an entire kingdom of their own called Plantae, beneath which are hundreds of thousands of species.

The nanosensor technology my colleagues and I developed is a species-agnostic way of probing plant health. We aim to utilize biosensors to monitor biotic and abiotic stresses, plant hormonal signaling, as well as soil and crop health, using a minimally invasive technique. If the data obtained can be successfully translated into beneficial interventions during farming, one can potentially improve both the quantity and quality of crops.

Photo credit: Max Böttinger / Unsplash

Q: YOU STARTED YOUR OWN COMPANY, PLANTEA, AS A GRADUATE STUDENT AT MIT. WHAT CHALLENGES DID YOU FACE ALONG THE WAY, AND HOW DID YOU OVERCOME THEM?

When we started Plantea we managed to raise a substantial amount of non-dilutive funding through grants and accelerators, which I am deeply thankful for. The key challenge we faced was that urban farms, our beachhead market at the time, are often low-margin, risk-adverse businesses looking for turnkey solutions that yield benefits quickly. Urban farms are also very diverse in terms of technology levels, crop types, ownership models and other factors. The team quickly realized that to be successful we needed to return to the lab to do more product development and articulate our value proposition to target segments within urban farms.

Q: WHAT ARE SOME IMPLICATIONS OF YOUR WORK AND WHO WILL BENEFIT FROM THE TECHNOLOGY?

At a broader level, our work will hopefully help urban farms move the needle by improving the productivity and nutritional quality of their crops. By interfacing plants with nanoparticles, we hope to introduce non-native functions like soil or groundwater monitoring, communicating information to external devices.

Our work will also improve our understanding of how plants respond to environmental factors. For example, our technology will allow for real-time persistent monitoring of stomatal function to show exactly how stomata respond to factors like soil, water and light.

This will then benefit the broader society, in terms of growing more food with fewer resources. For a land-scarce and resource-constrained nation such as Singapore, this could be particularly relevant.

> **“The key challenge we faced was that urban farms, our beachhead market at the time, are often low-margin, risk-adverse businesses looking for turnkey solutions that yield benefits quickly.”**

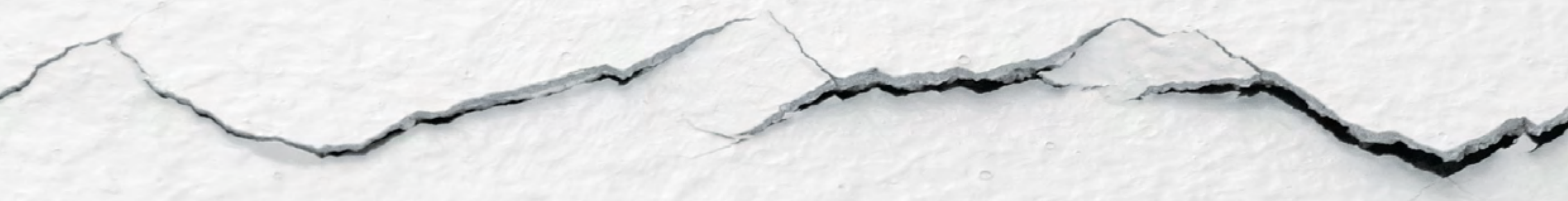
Q: HOW DO YOU SEE YOUR RESEARCH EVOLVING IN THE NEXT DECADE?

Ultimately, for sensors to be useful, the data obtained must be translated into beneficial interventions. One key area of research is better integrating this sensor-actuator cycle and quantifying its benefits. Further, with climate change, topics such as how plants react to heat stress, how the environment may undergo desertification and impact soil microbiomes, would also become more relevant.

An additional area that I find to be quite exciting is how nanotechnology may enable plants to be engineered with favorable traits. For instance, some in the nanotechnology community have started to look at how genes can be delivered into plant cells and organelles through rationally designed nanocarriers. My current work assesses whether it is feasible to implement this in practice, and what the benefits of successfully integrating nanotechnology into future farming practices could be for both traditional and urban agriculture. ★

ABOUT THE RESEARCHER:

Min Hao Wong is currently a Strategy and Business Development Group Leader at A*STAR’s Singapore Institute of Food and Biotechnology Innovation (SIFBI), specializing in food and biotechnology. Wong obtained his PhD degree in chemical engineering from the Massachusetts Institute of Technology where he worked with nanomaterials and designed sensors, as well as diagnostic devices for agriculture and healthcare. In 2018, Wong was named one of Forbes’ 30 under 30 (Asia) as well as one of MIT Tech Review’s Innovators under 35.



MACHINE LEARNING

Piecing the cracks together

A hybrid approach combining deep learning with Bayesian inference has enabled more accurate, efficient and automatic crack detection.

As you walk around your neighborhood, you will likely see cracks in the concrete under your feet, in beams and even along some buildings. These cracks can be a sign that the structure may become unsafe, which is why inspections in many industries—from infrastructure to aeronautics—commonly include crack detection.

Manual visual inspection is still the main method used to detect cracks today, an approach that requires specialist knowledge and is labor-intensive, expensive and time-consuming. In the past three decades or so, researchers have made considerable strides in developing ways to automatically detect cracks, first using image processing methods and more recently using machine learning-based approaches.

The challenge with automatic detection is that cracks vary widely in length, shape and orientation, and often have low signal-to-background ratios, making it difficult to train deep learning technologies accurately. In this study, first author Fen Fang, a Research Scientist at A*STAR's Institute for Infocomm Research (I²R) supervised by team leader Liyuan Li, describes a novel hybrid approach that combines deep learning with Bayesian analysis, a method of statistical inference, to more robustly and efficiently detect cracks from images.

The researchers first re-trained an existing algorithm to detect patches of cracks with sufficiently high signal-to-noise ratios, layering it information about real-world cracks that had been annotated for machine learning. To identify the true cracks, they next trained a deep learning model to estimate the orientation of the crack in each patch and developed a Bayesian algorithm to analyze the probability that the detected crack is real.

"Based on domain knowledge, true cracks are tiny, linked lines, while false positives are often isolated and separate patch detections," Fang explained. "Hence, we developed a Bayesian integration approach based on spatial proximity, orientation consistency and alignment consistency to connect the potentially true patch detections and suppress false detections."

The researchers tested their approach on a newly built dataset of 1,675 raw images of cracks found in over ten materials that were captured at different times of the day and under varying weather conditions. "Our dataset included not only concrete and asphalt road surfaces but also surfaces made of rock, terrazzo, marble, brick, tiles and so on. With this enhanced diversity, we achieved much better performance on real-world images," Fang said.

The patent-pending technology has been commercially licensed by a multinational corporation for use in construction and building inspections, in addition to being used by a government agency for airplane inspections, she added. ★

"Our dataset included not only concrete and asphalt road surfaces but also surfaces made of rock, terrazzo, marble, brick, tiles and so on."

Researcher
Fen Fang,
I²R

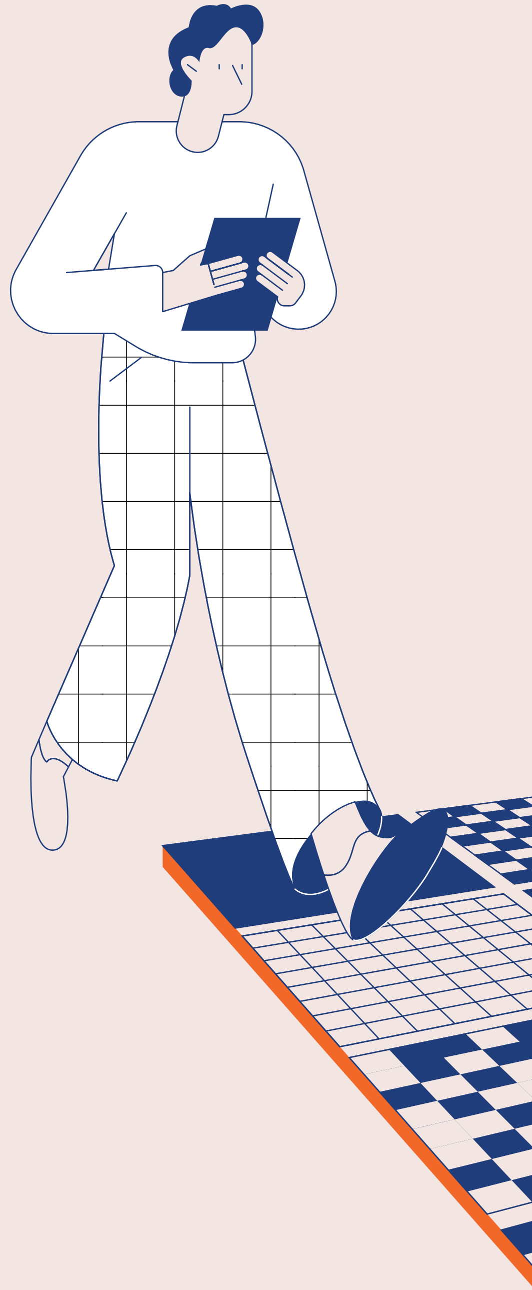
ABOVE
Bayesian analysis is helping algorithms distinguish true cracks from false positives, even on complex surfaces like terrazzo.

1. Fang, F., Li, L., Gu, Y., Zhu, H., Lim, J.H. A novel hybrid approach to crack detection. *Pattern Recognition* **107**, 107474 (2020).

MACHINE LEARNING

If floors could talk

Floor mats equipped with deep learning could take us one step closer to truly smart homes.



Mention the phrase 'smart home' and a host of appliances come to mind, from fridges and speakers to the intelligent microwave oven you never knew you needed. While all these objects offer convenience and new functions, the biggest—and possibly most useful—smart home feature might be right at your feet: the floor.

When used at home, smart floors could help to detect falls without the use of privacy-invading video cameras. In places like office buildings, smart floors can help reduce electricity consumption by automatically turning of lights and air conditioning in unoccupied rooms. But smart floors have yet to hit the mainstream due to two main challenges; firstly, finding an efficient way to power them and then making sense of the data generated.

By tapping on triboelectricity—the same phenomenon that causes static—a team from the SIMTech-NUS joint lab has developed a low-cost smart mat that uses a deep learning algorithm to transform triboelectric signals into accurate information about occupants of a room.

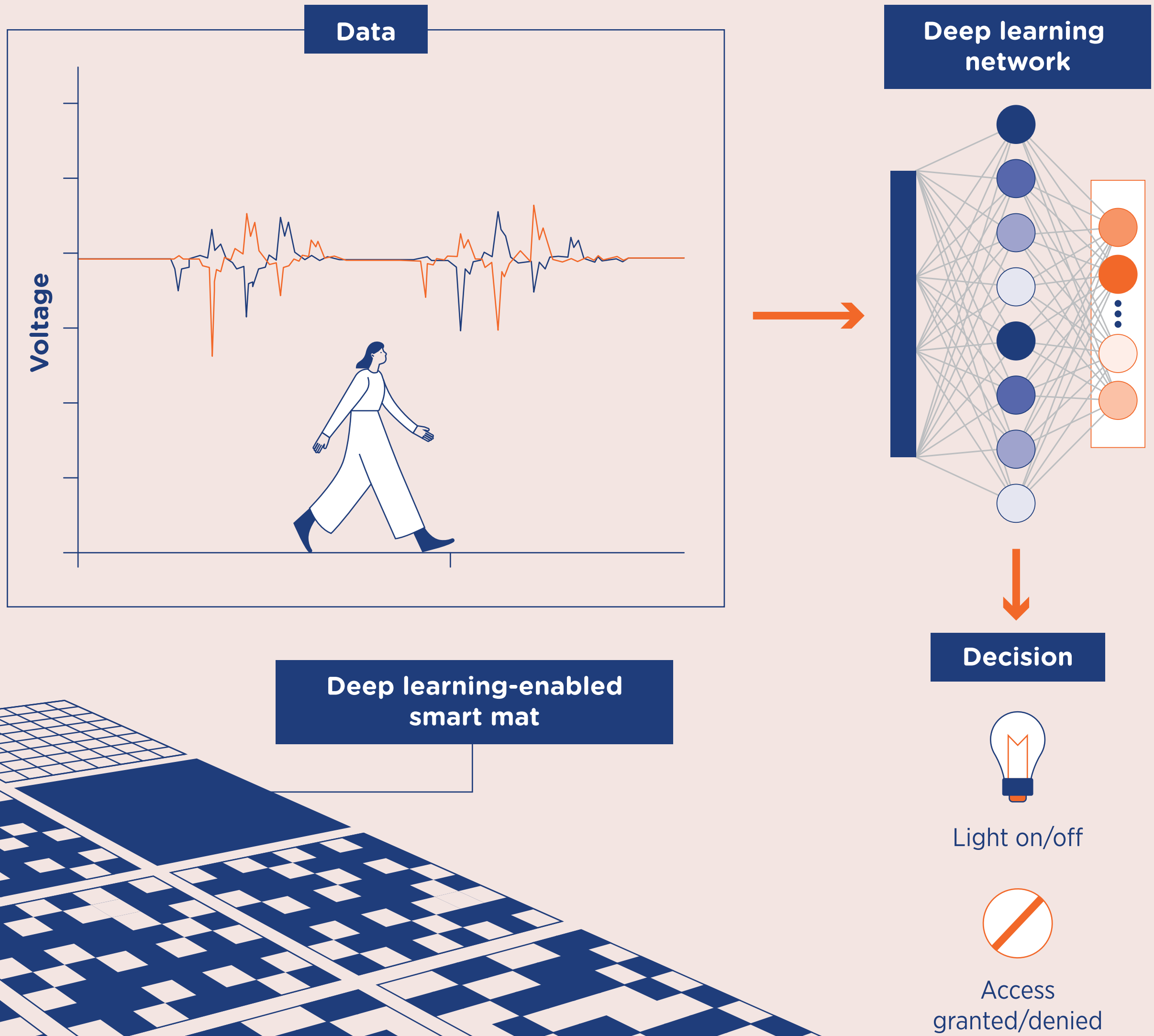
"The design concept was inspired by the QR code system," said study co-author Xuechuan Shan, a Senior Scientist at A*STAR's Singapore Institute of Manufacturing Technology (SIMTech), explaining the 3 x 4 array of mats with electrodes of different densities that are screen-printed onto a plastic film. "Employing these unique 'identity' electrode patterns enabled the parallel connection of numerous floor mats in an array configuration, minimizing the number of output terminals and system complexity."

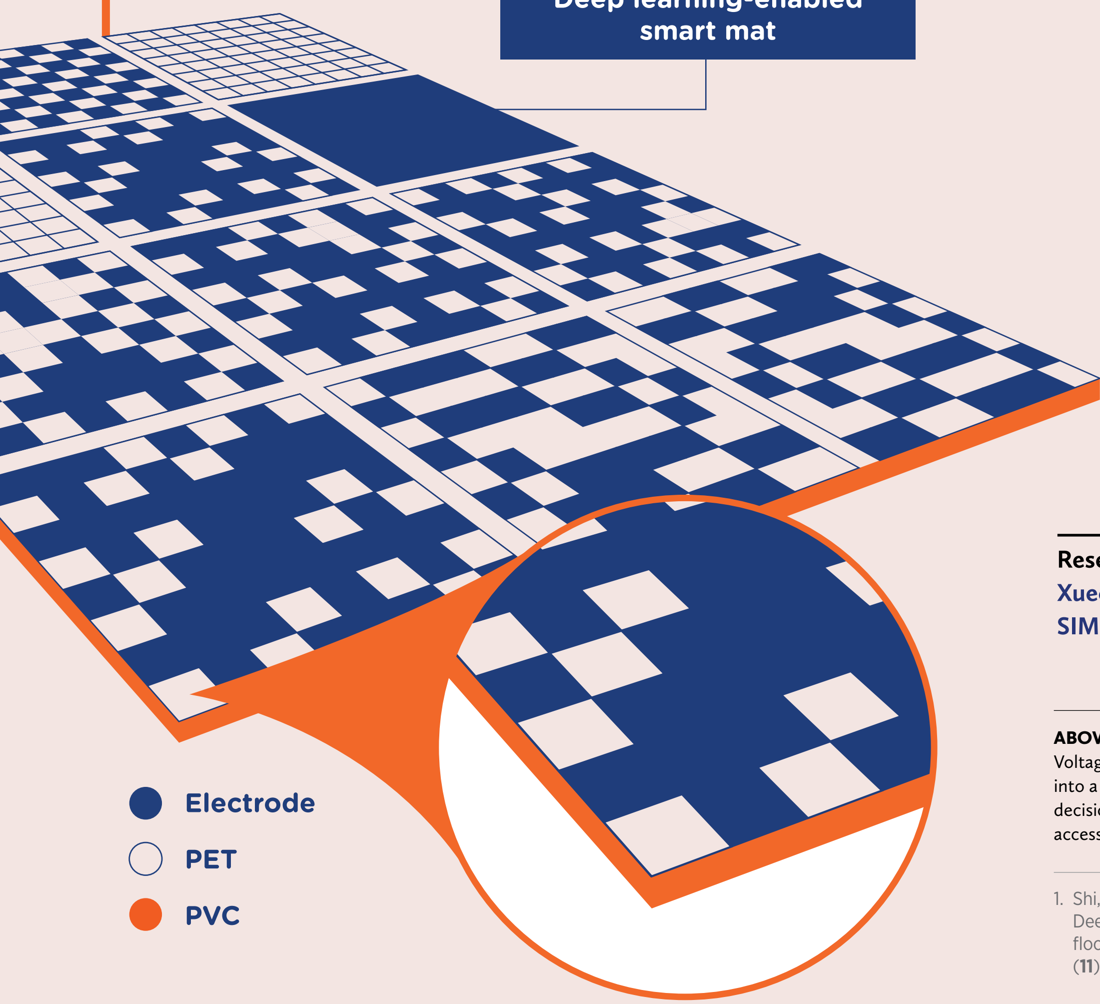
When a shoe comes into contact with the top layer of the mat, friction causes the sole to be negatively charged; and as it is pulled away, the mat is left positively charged, Shan explained. The positive charges attract negative charges from the ground through the printed electrodes, creating a flow of current that traces a person's footsteps while generating electricity at the same time.

While the phenomenon is well known, the sensor configuration is more critical and gait recognition is more computationally complex to analyze than other biometrics. To get around this problem, the researchers used a well-developed deep learning model to convert the signals into gait information.

"After optimizing the network structure and other high-level parameters, we were able to achieve an average prediction accuracy of 96 percent for a ten-person dataset, offering high accuracy in practical, real-time scenarios," Shan said.

Not satisfied with these promising initial results, Shan believes that they can push the envelope further. "We will further optimize the sensors to improve robustness, accuracy and functionality," he said. "We plan to expand the application beyond user identification to smart-home-based interactions like motion recognition and gesture prediction." ★





Researcher
Xuechuan Shan, SIMTech

ABOVE
Voltage data collected by the smart floor mats is fed into a deep learning network, which can then make decisions such as whether to turn the lights on or grant access to a room.

1. Shi, Q., Zhang, Z., He, T., Sun, Z., Wang, B., *et al.* Deep learning enabled smart mats as a scalable floor monitoring system. *Nature Communications* (**11**) 4609 (2020).

PHOTONICS

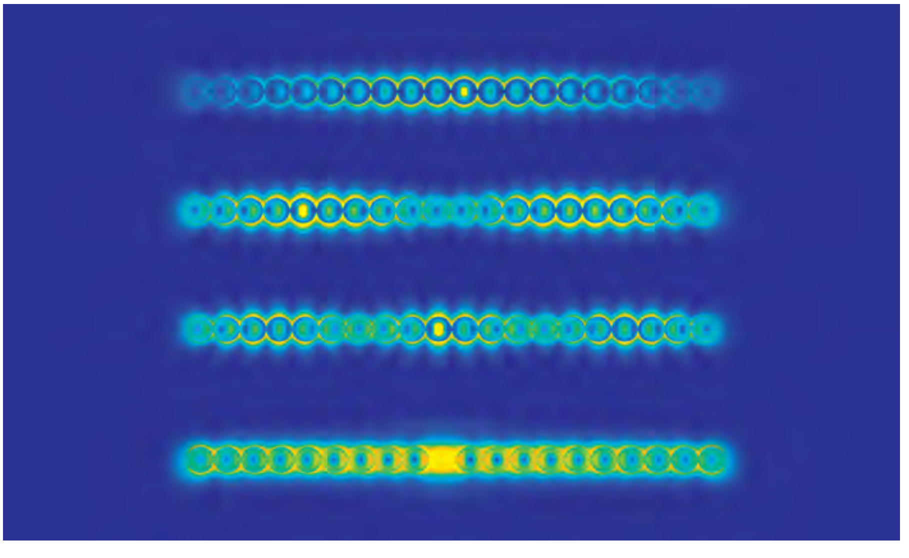
Shining a way forward for on-chip lasers

A*STAR researchers have developed a compact on-chip laser using a nanoantenna chain as an optical resonator.

Tiny computer microchips can hold immense computing power, thanks to the marvel of electronic integrated circuits which are printed down to the nanometer. But as these devices shrink, the physical constraints of supplying energy to and removing heat from chips become harder to overcome. As such, researchers around the world are looking to develop futuristic devices based on photonics, which manipulate light instead of electrons to perform computations.

However, the development of compact photonics to rival electronic microchips requires semiconductor lasers that can generate strong light while taking up little space. A group of scientists led by Arseniy Kuznetsov, a Principal Scientist at A*STAR's Institute of Materials Research and Engineering (IMRE), has invented a novel nanoantenna chain which fits in a small space and delivers laser light horizontally, making it perfect for developing photonic microchips.

"The 'nanoantennas' we work with are tiny etched cylinders, which interact resonantly with light because their size is comparable to the wavelength of light," explained Kuznetsov, whose team has successfully built lasers from two-dimensional arrays of nanoantennas. However, those designs emitted light vertically, away from the nanoantennas rather than along them, and so were less suited for photonics applications that require light to be manipulated along the surface of a microchip.



Instead, computational modeling by colleagues at A*STAR's Institute of High Performance Computing (IHPC) showed that light could resonate along a one-dimensional chain of nanoantennas and be emitted at either end. Kuznetsov and his team then built prototype 'nanochains,' each containing a hundred nanoantennas, using gallium arsenide, a common material for converting input energy into laser light output. They found that these nanochains indeed formed successful lasers when illuminated with pump light.

"Compared to a competing state-of-the-art nanowire laser, our nanochain laser only required one-tenth as much input energy to emit laser output, while occupying only one-quarter of the area," Kuznetsov said. Furthermore, Kuznetsov and his team discovered that they could control the direction of laser output, as off-center illumination caused laser emission from only the illuminated end of the nanochain, while illuminating the center of the nanochain resulted in lasing from both ends.

"We have successfully demonstrated the first on-chip nanoantenna chain laser and also showed that we can control the directionality of the emitted laser," Kuznetsov said. However, he noted that the current prototype has important limitations, such as only operating at cryogenic temperatures. He and his team are currently working to improve the efficiency of the nanochain laser so that it can eventually be powered by electrical excitation instead of light. ★

Researcher
Arseniy Kuznetsov, IMRE

LEFT
One-dimensional chains of nanoparticles (left) could pave the way for photonic microchips that perform computations using light instead of electrons.

1. Thanh, X.H., Ha, S.T., Pan, Z., Phua, W.K., Paniagua-Dominguez, R., *et al.* Collective Mie Resonances for Directional On-Chip Nanolasers. *Nano Letters* **20** (20), 5655-5661 (2020).

MACHINE LEARNING

Sharper sound classification with less data

A generative adversarial network has been used to develop audio classification technologies that require much less training data.

"Hey Siri, what's the weather forecast for today?" Ever wondered how devices such as smart speakers understand and respond to such requests? Apple's Siri and Amazon's Alexa are classic examples of audio classification technologies, devices powered by artificial intelligence (AI) that perform tasks according to voice commands.

As with most AI-driven systems, audio classification systems first need to go through a training regime. Here, their machine learning networks are fed large datasets of thousands of audio samples, to condition the software to interpret and perform tasks accurately.

However, compiling these massive audio datasets—such as the Google Speech Command Dataset—is both expensive and time-consuming. Moreover, due to their highly variable nature, audio inputs pose a unique challenge for machine learning processes.

"Sound propagation is very sensitive to the environment, which is constantly changing," explained speech technology expert Huy Dat Tran, a Senior Scientist from A*STAR's Institute for Infocomm Research (I^{2}R), adding that collecting audio data for all the possible sound variations of a specific command is virtually impossible.

Tran and the study's first author, fellow I^{2}R researcher Kah Kuan Teh, explored the potential of using data augmentation—a process of expanding datasets by adding slightly modified versions of existing data—to streamline and expedite the development of audio classification systems.

The researchers explored the use of two audio data augmentation methods, physical modeling and wavelet scattering transfer, as well as a machine learning framework called the generative adversarial network, or GAN.

Data augmentation techniques were applied to condensed versions of the Google Speech Command Dataset, using between 10 and 25 percent of the original data. Tran and Teh found that combining these two approaches and embedding them into GAN yielded a ground-breaking result: Their new model interpreted voice commands with 92 percent accuracy after being trained with just 10 percent of the Google dataset.

By dramatically lowering the amount of training data required, this new GAN has the potential to create powerful voice command technologies more quickly and cost-effectively than ever before, said Tran.

The researchers are currently leveraging their innovation to enhance a range of audio detection applications, from security surveillance systems to senior care devices that listen out for falls. "More recently, in response to COVID-19, we have developed an audio cough detection system to monitor people in public areas," added Tran. ★

Researcher
Huy Dat Tran, I^{2}R

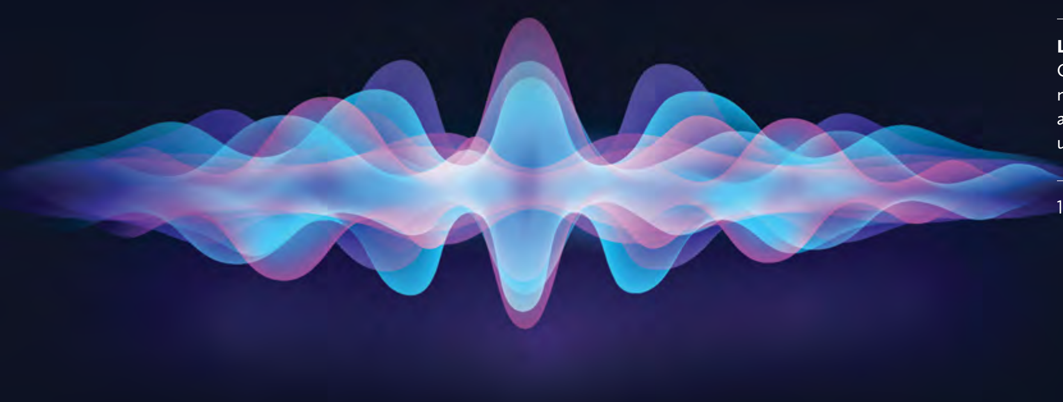


Photo credit: Chiken_brave / Shutterstock

LEFT
Combining data augmentation with a machine learning method known as generative adversarial networks helps algorithms make more accurate audio classifications using much less data.

1. Teh, K.K., Tran, H.D. Embedding physical augmentation and wavelet scattering transform to generative adversarial networks for audio classification with limited training resources. *ICASSP 2019 – 2019 IEEE International Conference on Acoustics, Speech and Signal Processing (ICASSP)*, 3262–3266 (2019).

GETTING THE RIGHT FOOD AT THE RIGHT TIME

Taking meal timing into account in dietary recommendations could radically alter our approach to food consumption, metabolism and health.

Photo credit: vetre / Shutterstock

While unhealthy diets and increasingly sedentary lifestyles have been blamed for the rising rates of obesity worldwide, these two factors alone cannot account for the alarming tripling of obesity rates in the four decades between 1975 and 2016. The evidence is mounting that obesity is not simply a matter of willpower, but a complex disease involving genetics, the environment and social factors like access to good nutrition.

A growing number of studies suggest that when you eat might turn out to be as important as what you eat, in terms of its impact on metabolism. Indeed, the emerging field of chronobiology—which studies the impact of timing on everything from sleep to sex—is upending the old assumption that the secret to losing weight is merely about changing the balance between calorie intake and expenditure.

MINDING THE GAP BETWEEN MEALS

What would happen, for instance, if the total amount of calories you consumed within a day remained the same but were consumed in just two meals instead of three? Fans of intermittent fasting, a practice of restricting meal times to certain hours of the day, swear that this not only helps with weight loss but can also improve metabolic factors like blood glucose control.

By creating an extended period of low blood sugar, fasting is believed to initiate the breakdown of stored carbohydrates and fats to produce glucose and restore blood sugar to normal levels, ultimately benefiting one's health. Though intermittent fasting might seem like the latest diet fad, the practice goes back centuries. "Ramadan fasting in Islamic culture, where believers abstain from food from dawn to dusk, has long provided a form of 'intermittent fasting,'" said Christiani Jeyakumar Henry, a Senior Advisor at A*STAR's Singapore Institute of Food and Biotechnology Innovations (SIFBI).

However, despite many studies around the world investigating the health impact of Ramadan fasting, the results so far have been mixed. Some studies reported that fasting led to a decrease in 'bad' cholesterol and lowering of blood pressure, while others found no change in body mass or even saw weight gain after the Ramadan month.

"A large variation in the results was observed across the globe due to cultural differences in dietary habits and variations in the duration of daily fasting time as a result of latitudinal differences," explained Henry. "Additional confounding factors include age, gender and socioeconomic status, as well as other health and lifestyle factors in various study populations."

Despite the inconsistencies, the team's analysis of the literature revealed that Ramadan fasting did have one notable health benefit: an improved blood lipid profile that lasted beyond the month of fasting. Fasting had only transitory or inconclusive impacts on other measures such as blood glucose levels. "In conclusion, the associated health benefits of fasting are largely dependent on the quality of foods selected by the devotees," Henry said, recommending that meals for breaking fasts should contain complex carbohydrates and plenty of fruits and vegetables.

"While we have known for some years that there are good and bad fats, good and bad carbohydrates, it is only very recently that we have recognized the importance of the timing of eating meals—what we call the chronobiology of eating," explained Henry.

THE SURPRISING BENEFITS OF A LIGHT DINNER

Just as the interval between meals is important during fasting, the timing of food consumption may also influence the metabolic activities of those following a regular schedule of three meals a day. To explore this idea, Henry and his team investigated the effects of meal timing and glycemic index (GI) on metabolic response.

The participants, all of Chinese ethnicity and aged 50–70 years old, each completed four separate interventions of low or high GI meals for dinner or breakfast, followed by subsequent standardized meals. Selecting this demographic also allowed the researchers to focus on slower metabolizers for whom meal timing could be especially relevant. Compared with Caucasians, Asians have a lower basal metabolic rate and are more predisposed to developing prediabetes and type 2 diabetes.

Analyzing the blood samples, the researchers found that dinner meals had significantly more detrimental effects on glucose metabolism than breakfast meals. Moreover, meals with high GI content led to a much greater glucose response after dinner, while the difference between high and low GI meals was not as apparent for breakfast.

Aside from higher blood glucose levels, insulin concentration also increased following dinner compared to breakfast meals. Insulin acts to lower blood glucose, but sometimes doesn't work as well as intended. Whether due to normal changes in metabolism or because of an illness, the body can become insensitive to the hormone, leading to difficulties regulating blood sugar.

To assess the insulin sensitivity of their study participants, Henry and the team measured plasma levels of free fatty acids (FFA), which are released as an energy source for glucose production but kept suppressed by insulin activity when the body already has adequate blood sugar. They found that despite the increased insulin levels, FFA concentrations were significantly lower after dinner than breakfast, suggesting reduced insulin sensitivity at night.

According to the researchers, poor glucose regulation was not only observed following the dinner test meals, but also carried over to subsequent meals. As the typical meal times were followed to better simulate the circadian timing of metabolic activities, these findings are even more astounding considering the longer interval between the dinner meal and the standardized breakfast, compared to the test breakfast followed by the standardized lunch. Placed under greater strain in the evening, the body takes much longer to clear out the excess glucose and return blood sugar levels to normal.

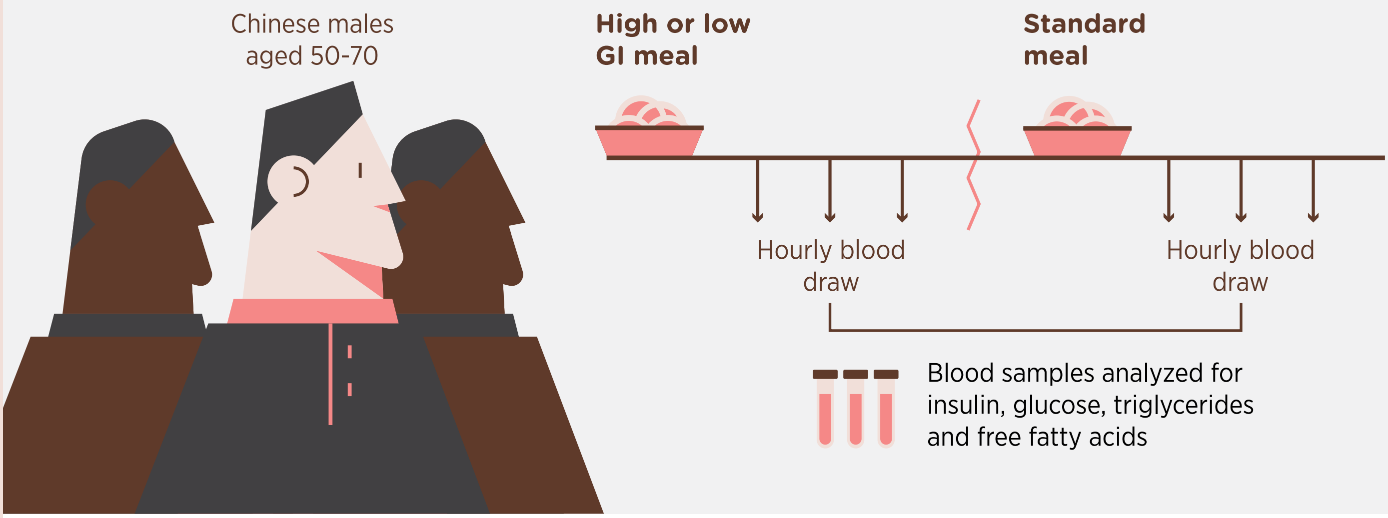
Because glucose metabolism plays a central part in the progression and management of chronic cardiometabolic disorders, these results have important implications when devising better dietary interventions for mitigating disease and improving health outcomes.

"Have dinner as early as possible and avoid eating a heavy, carbohydrate-rich dinner. Do not skip breakfast, but try to consume a low GI meal," advised Henry.

The team also envisions that the research will inform public health policies and be translated

"While we have known for some years that there are good and bad fats, good and bad carbohydrates, it is only very recently that we have recognized the importance of the timing of eating meals—what we call the chronobiology of eating."

Study design



into community-based actions. "We need to collaborate with other partners to disseminate these findings and make an impact on our community," Henry added.

SERVING UP STRONG EVIDENCE

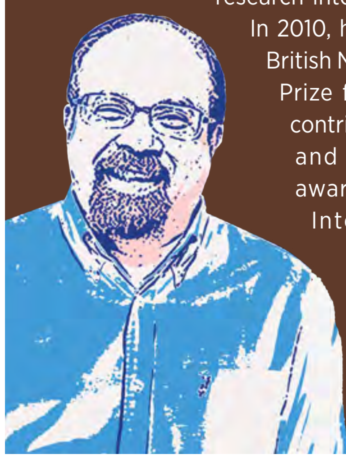
While these studies are just the tip of the iceberg, Henry and fellow researchers have shown that metabolic processes work best according to certain times and specific conditions. By highlighting the importance of meal timing and metabolic rate, the team is changing perceptions on the relationship between diet and health outcomes. For Henry, the long-held notions about food, including its use in traditional medicine, offer a wealth of yet untapped insights, beckoning for a closer look from the lens of science.

"In Asia, we have long considered food as medicine and medicine as food," he said. "It is against this backdrop that SIFBI has been conducting research to provide evidence-based science to corroborate with the concept of food as the new medicine."

Parallel to this focus on clinical nutrition, SIFBI is also dedicated to undertaking more Asian-centric research, especially as dietary patterns and metabolic risk factors have been shown to vary across demographics. This includes, for instance, an effort to establish a GI reference index of Asian cuisine and a study linking self-reported eating rate with cardiovascular risk among several Asian ethnic groups. Collectively, these endeavors are a step towards understanding health in a more personalized and context-specific way. ★

ABOUT THE RESEARCHER:

Christiani Jeyakumar Henry is a Senior Advisor at A*STAR's Singapore Institute of Food and Biotechnology Innovation (SIFBI) and Director of A*STAR's Clinical Nutrition Research Centre (CNRC). He obtained a PhD degree in nutrition from the London School of Hygiene and Tropical Medicine. Henry's research focuses on translating nutrition research into food applications. In 2010, he was awarded the British Nutrition Foundation Prize for his outstanding contributions to nutrition, and in 2019, he was awarded the Kellogg's International award for food research that led to a global impact.



1. Haldar, S., Egli, L., De Castro, C.A., Tay, S.L., Koh, M.X.N., *et al.* High or low glycemic index (GI) meals at dinner results in greater postprandial glycemia compared with breakfast: a randomized controlled trial. *BMJ Open Diabetes Research and Care* **8**, e001099 (2020).
2. Osman, F., Haldar, S., Henry, C.J. Effects of time-restricted feeding during Ramadan on dietary intake, body composition and metabolic outcomes. *Nutrients* **12**, 2478 (2020).

COMPUTATIONAL MODELING

Simulating a water droplet

An integrated simulation model provides a clearer picture of what happens when a water droplet comes in contact with a hydrophobic surface.

Most of us can recall the anguish of accidentally hitting over a cup of coffee and wetting the table. From a layman's perspective, this is a classic example of the wetting phenomena. But it belies the significance of wetting in industrial applications—the behavior of a liquid while maintaining contact with a solid surface is crucial in the design of coatings and surfactants, such as those used in shampoos or paints.

"In general, surfaces can be simplified as either hydrophobic or hydrophilic. The process of wetting, however, is much more complicated. The texture of the surface, for example, as well as its contact angle with an incoming droplet of water, are important factors to consider," explained Shuai Chen, a Research Scientist at A*STAR's Institute of High Performance Computing (IHPC) and the first author on a study that describes an integrated model of wetting.

Although computational scientists have long relied on a simulation method called molecular dynamics (MD) to predict the water contact angle of surfaces, MD is restricted to atoms and molecules at the nanoscale and fails to take into account the micro- and macrostructures of a surface. "Also, MD simulations can only be performed for short time scales and thus cannot be used to predict sliding and bouncing of water on surfaces," Chen added.

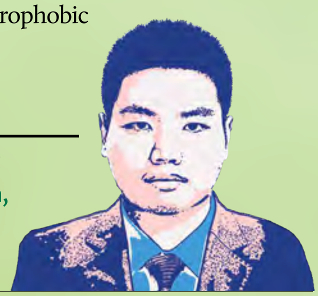
To overcome the limitations of MD simulations, Chen and colleagues employed a multiscale modeling strategy combining MD with computational flow dynamics (CFD), which effectively expands the model's field of view across space and time.

In MD simulations, they showed that the water contact angle of a water droplet on smooth polydimethylsiloxane (PDMS) surface could be widened by adding fluorocarbon chains on the surface. These simulation results were validated in experiments with C_8F_{17}-functionalized PDMS surfaces.

Experimental measurements also showed that altering the surface microstructure of PDMS by adding silica filler particles could maximize its hydrophobicity, obtaining the highest hydrophobicity with an optimum concentration of around 7.5 weight percent of silica.

To complete the picture of wetting at the microscale, the researchers used CFD simulations to show how a drop of water slides along an inclined surface. For the case of a surface with a small slope, the droplet slides along the surface, but when surface hydrophobicity is enhanced, the droplet bounces after it hits the surface. These findings were confirmed experimentally with PDMS surfaces.

"Fine-tuning the surface energy of coatings through experimental trial-and-error is tedious and time-consuming," Chen said. "Theoretical models provide useful guidelines for the virtual testing of an experimental formulation, and thus can accelerate the design of an optimal hydrophobic surface." ★



Researcher
Shuai Chen, IHPC

BACKGROUND
Simulations capturing how water droplets interact with surfaces could lead to the design of better water-repelling materials.

1. Chen, S., Yune, J.H.R., Zhang, Z., Liu, Z., Sridhar, N., *et al.* Multiscale modeling to predict the hydrophobicity of an experimentally designed coating. *The Journal of Physical Chemistry* **124**, 9866-9874 (2020).

Photo credit: Ravi Kant / Pexels

3D PRINTING

When two are stronger than one

New research shows that titanium alloys joined by 3D-printed curved interlayers are stronger and less likely to crack.

Whether you are flying 15,349 kilometers between Singapore and New York or just taking a short hop over to Kuala Lumpur, the journey of a thousand miles begins with a single turbine blade. Hidden in the jet engines tucked under the wing of every passenger plane, turbine blades are a marvel of modern engineering, designed to withstand the extreme heat and stress that enables flight. Leading industry players such as GE and Siemens have been exploring the use of 3D printing to make metal turbine blades, but finding the right alloy for the job can be challenging.

Strong, lightweight and heat resistant, gamma titanium alloys like Ti–48Al–2Cr–2Nb are ideal for constructing high-temperature alloy components for aerospace applications—in theory. In practice, it is brittle and difficult to machine at room temperature due to its high aluminum content. On the other hand, a low aluminum content alloy called Ti–6Al–4V can be easily fabricated into any shape, but doesn't have all the desirable qualities of Ti–48Al–2Cr–2Nb.

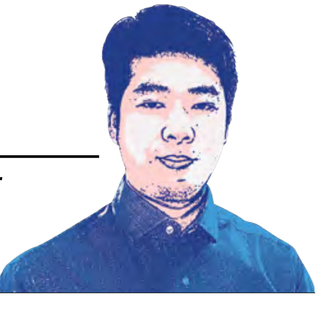
"We wanted to combine the advantages of the two alloys for the best of both worlds," said Pan Wang, a Scientist at A*STAR's Singapore Institute of Manufacturing Technology (SIMTech). To achieve this, the team started with a Ti–6Al–4V base, using a 3D-printing method called electron beam melting (EBM) to create a prototype turbine blade made of Ti–48Al–2Cr–2Nb on top. "We creatively produced a 3D-specific interlayer surface to enhance the bonding in an *in situ* way," he said.

By using different printing strategies, the team was able to create two different interfaces between Ti–48Al–2Cr–2Nb and Ti–6Al–4V, one straight and one curved in shape. To test the strength of the resulting bimetal components, the researchers pulled the joined pieces apart, recording the force needed and studying the resulting cracks. As predicted, the EBM-formed curved bimetal component was stronger than alloys joined using other methods, achieving a tensile strength of 389 MPa.

Studying the fracture patterns within the interlayer—an intermediate region between two different materials—further revealed that curved interlayers were thicker, had a larger surface area and contained higher levels of titanium solid solution, all of which enhanced strength. "The secret behind this strength is the design of 3D-specific interlayer," Wang said.

Interestingly, the researchers found that the curved interlayer blocked the propagation of primary cracks because they encountered the stronger Ti–6Al–4V. This either changes the crack direction or prevents it from propagating. "Consequently, extra tensile loading was needed to form the new cracks and thus the strength was increased," Wang explained.

The researchers are testing the mechanical performance of their novel bimetal component under high temperatures to qualify it for use in aerospace applications. To further improve the methodology, Wang said that future work could focus on accelerating the design of the interface by machine learning and suppressing the formation of a detrimental phase by calculated phase diagrams. ★



Researcher
Pan Wang,
SIMTech

ABOVE
Using 3D printing to combine parts made of two different alloys could make metal turbine blades stronger.

Photo credit: asharkyu / Shutterstock

1. Zhai, W.G., Wang, P., Ng, F.L., Zhou, W., Nai, S.M.L., *et al*. Hybrid manufacturing of γ-TiAl and Ti–6Al–4V bimetal component with enhanced strength using electron beam melting. *Composites Part B: Engineering* **207**, 108587 (2021).

ADDITIVE MANUFACTURING

A new angle on 3D-printed metal

Artificial neural networks are now being used to make 3D-printed metal structures more accurately—and stronger—than ever before.

Found in everything from the planes we fly in, to the ships moving goods across the ocean, 3D-printed parts are now commonplace. Although it is now possible to print increasingly complex shapes in a wide variety of materials, certain structures remain out of reach as we push design features beyond current process and equipment limits.

For example, while advances in an additive manufacturing process called powder bed fusion have enabled lightweight lattice structures to be printed in metal, such lattice structures often suffer from localized shape distortions, with the degree of distortion increasing with the angle of the overhang desired.

"For sub-millimeter lattices with large overhang angles, limitations arise related to laser spot size and the layer-by-layer printing thickness, which lead to systematic distortion of cross-sectional shapes and high surface roughness."

"For sub-millimeter lattices with large overhang angles, limitations arise related to laser spot size and the layer-by-layer printing thickness, which lead to systematic distortion of cross-sectional shapes and high surface roughness," explained Stefanie Feih, a Senior Scientist at A*STAR's Singapore Institute of Manufacturing Technology (SIMTech).

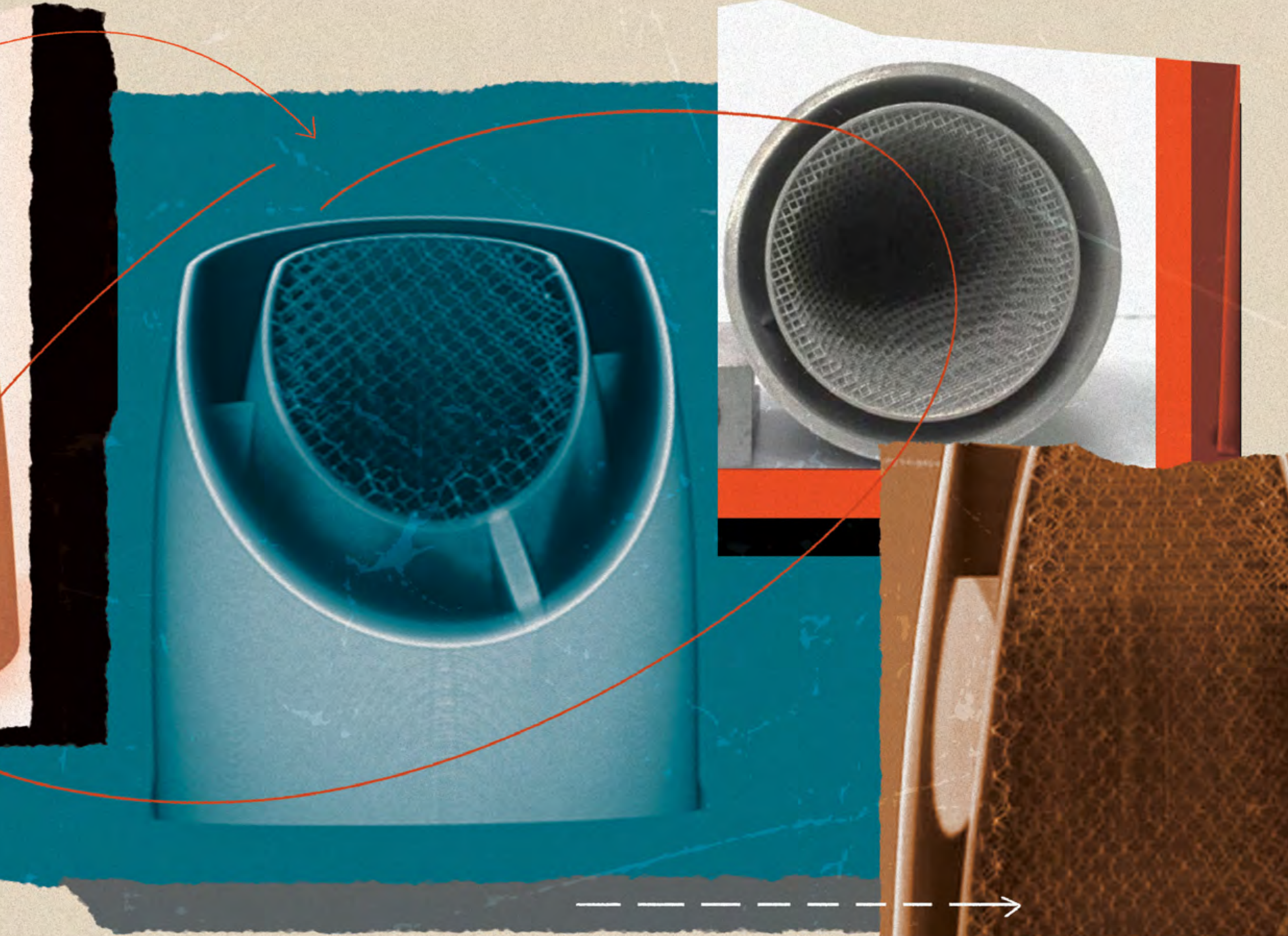
As a result, what you design and what is eventually printed can differ significantly, leading to reduced strength and stiffness. Geometric compensation is one method commonly used to minimize such discrepancies. However, current strategies are constrained by their use of pre-defined cross-section approximations—like circles, ellipses or polygons—of the original design shape.

Instead, Feih and collaborators at the National University of Singapore used an artificial neural network (ANN) model to generate lattice designs with free-form cross-sections, enhancing the accuracy of printing by using these cross-sections for improved compensation.

First, the team used 3D printing to create dome lattice structures of various diameters and overhanging angles. Next, they scanned the structures using high-resolution X-ray computed tomography to evaluate systematic deviations from the original design geometry. "This gave us 3D point cloud measurement data that was suitable for training the ANN model," Feih said. "We used the data without filtering to account for surface roughness, which is an important feature of the model."

When compared to an established geometric compensation method, the ANN compensation method produced a closer representation of the roundness of the printed cross-section, even for large overhanging angles of up to 60 degrees. The researchers attributed the improved structural accuracy to the ANN's ability to correct for highly localized imperfections caused by fused powder particles from the supporting powder bed.

Photo credit: Pan Wang / SIMTech



Feih said that the study is a “great achievement” for first author Ruochen Hong, a PhD student supervised by Wen Feng Lu at the National University of Singapore, who is working with the SIMTech team on improving the quality and reliability of 3D-printed lattices. Such a compensated design approach could replace costly process optimization studies, she added.

To further improve the technique, Feih noted that future work could focus on automating the process for generating training data for the neural network, given that the current data are material- and equipment-dependent. ★

Researcher
Stefanie Feih, SIMTech

1. Hong, R., Zhang, L., Lifton, J., Daynes, S., Wei, J., *et al.* Artificial neural network-based geometry compensation to improve the printing accuracy of selective laser melting fabricated sub-millimetre overhang trusses. *Additive Manufacturing* **37**, 101594 (2021).

ABOVE
Machine learning techniques are improving the quality and reliability of 3D-printed parts, such as these EBM-built components made with SIMTech’s “one-step-solution.”

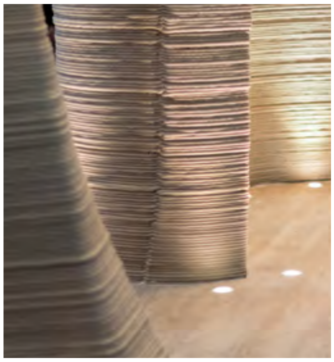
NEXT ISSUE

Here's a sneak peek of the material covered in the next issue of *A*STAR Research*

ROBOTICS

TEACHING ROBOTS BY EXAMPLE

By breaking down complex actions into their basic components, researchers have developed a versatile framework that enables robots to learn from human demonstrators.



3D PRINTING

FINDING FLAWS FAST

A new method of screening for defects on 3D-printed surfaces is paving the way for fully automated smart systems.

NEUROSCIENCE

TRACING THE PATH BETWEEN HUNGER AND PAIN

Researchers have identified a pain pathway that suppresses hunger, opening the door to understanding how pain quells other competing behaviors.

URBAN SOLUTIONS

WHERE ALL THE SHARED BIKES GO

An analytical approach that can quantify how populations use dockless bike-share systems over space and time may lead to improved services and facilities.

Agency for Science, Technology and Research
SINGAPORE

RE-ENVISION THE FUTURE

At A*STAR, you will be part of a vibrant and innovative team that advances science and develops innovative technologies to further economic growth and improve lives.

Spearhead groundbreaking research, lead teams and propel the industry forward with a career at A*STAR.

I AM AN ACCOMPLISHER

I aspire to translate research to enterprise, bringing research to real-world applications.

INDUSTRY COLLABORATOR

- Work with industry partners in business development and R&D
- Be an entrepreneur and create your own start-up

I AM AN EDUCATOR

I enjoy sharing knowledge as well as conducting my own research.

SCIENTIFIC EDUCATOR

- Be involved in academia and science education
- Conduct scientific research at A*STAR

I AM A THINKER

I have a curious mind and enjoy teamwork and communication.

SCIENTIFIC LEADER

- Become a Principal Investigator, Research Director or Project/Team Leader
- Lead a team of researchers to conduct research and collaborations

I AM AN INNOVATOR

I have novel ideas to translate research to solutions that would benefit the community.

RESEARCH EXPERT

- Conduct scientific research at A*STAR
- Develop scientific expertise

SCHOLARSHIPS AVAILABLE

- National Science Scholarship (NSS BS)
- National Science Scholarship (NSS PhD)
- A*STAR Graduate Scholarship (AGS)
- A*STAR Computing and Information Science (ACIS) Scholarship
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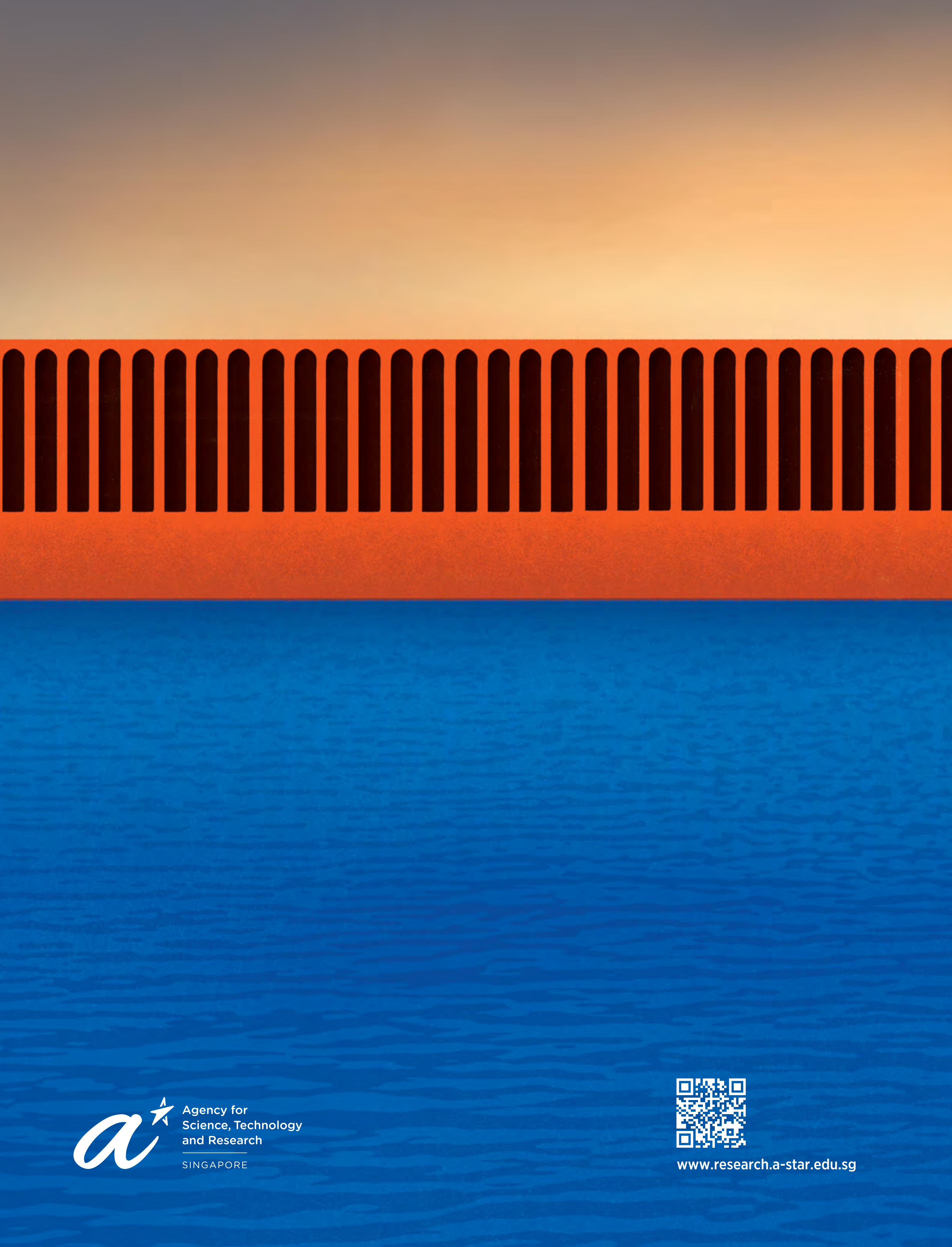

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