A*STAR RESEARCH

Issue 24 | July – August 2021

ADVANCING SYNTHETIC BIOLOGY ACROSS ALL FRONTS

Wielding the tools of synthetic biology to improve our lives in surprising ways

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UNRAVELING THE COMPLEXITY OF IMMUNE CELLS

Novel analytical technologies help us understand why immune responses vary among individuals

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FUELING THE FUTURE

Nuclear fusion could provide Singapore—and the rest of the world—with a safe and clean source of energy

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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:

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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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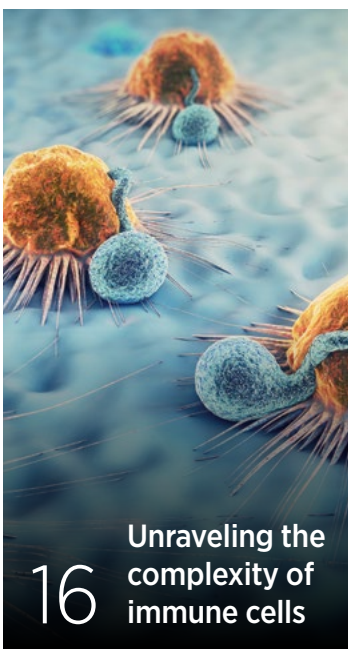

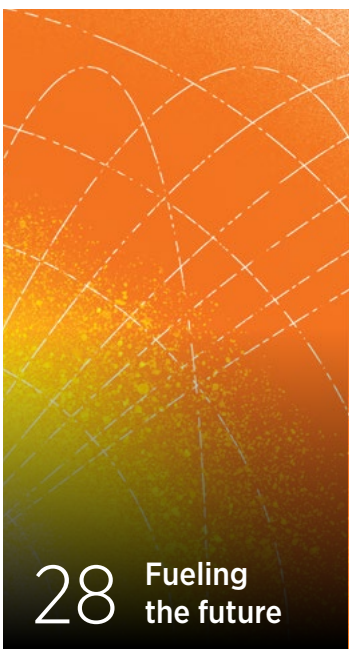

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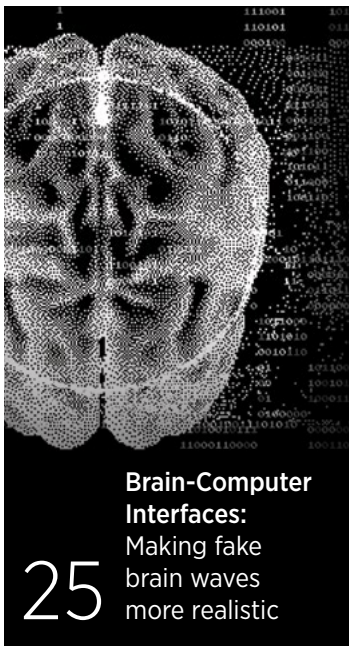

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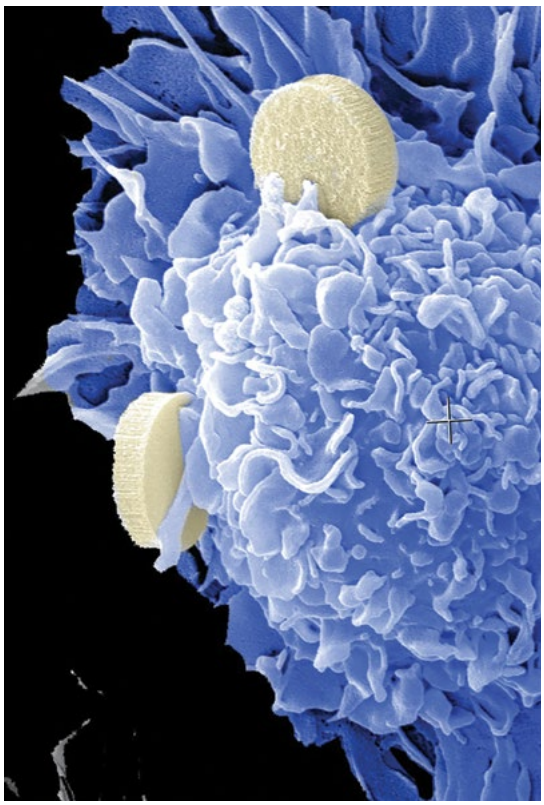


In their efforts to explain the world around them, trailblazing scientists in the 20th century discovered the fundamental building blocks of matter and life. From neutrons to nucleic acids and cells to carbohydrates, researchers today have a profound understanding of these building blocks and are wielding new technologies to harness them in innovative ways.

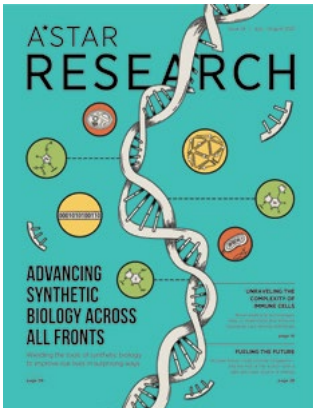
Consider the case of synthetic biology, an emerging discipline at A*STAR. Through Nobel Prize-winning tools like CRISPR/Cas9 and directed evolution, our scientists are adding new letters to the genetic alphabet and transforming microorganisms into efficient cellular factories producing high-value molecules. Dive into the depths of A*STAR's synthetic biology research focus in our cover story on p. 06.

Similarly, find out how Jinmiao Chen of the Singapore Immunology Network (SIgN) is combining artificial intelligence with state-of-the-art techniques for studying single cells in the feature 'Unraveling the complexity of immune cells (p. 16).' By exploring subtle variations in these individual cells, Chen hopes to understand the full spectrum of immune responses in patients.

Further proving that the whole is indeed greater than the sum of its parts is A*STAR scholar Valerian Hall-Chen. Currently a doctoral student, Hall-Chen is developing theoretical tools to advance an alternative source of power called nuclear fusion, where lighter elements combine and release large amounts of energy. In 'Fueling the future (p. 28),' discover how Hall-Chen intends to help Singapore someday reap the benefits of fusion power.

On top of exciting fields like synthetic biology and nuclear physics, A*STAR's research efforts also touch upon regenerative medicine with 'A recipe for mini livers (p. 13)' and plant-based dairy products with 'Taking the 'moo' out of yogurt (p. 20).'

As always, keep track of the latest advances from A*STAR scientists by visiting our website at **research.a-star.edu.sg** or following us on Twitter at **@astar_research** and LinkedIn at **A*STAR Research.** Please also subscribe to our new Telegram channel at **A*STAR Research!**



On the cover
Alternative nucleotides and genome editing tools are giving scientists the unprecedented ability to shape the building blocks of life.

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/

POLYMERS

The protective possibilities of polymers

From forming protective physical barriers to stabilizing mRNA vaccines, polymers provide endless solutions to the threat of coronaviruses and other current and impending diseases.

Of the many innovations spurred by the COVID-19 pandemic, polymer-based technologies used to make personal protective equipment like masks have undoubtedly been the most pervasive. But you may be surprised to learn that polymers have much wider applications—like in antiviral drugs and vaccines. Biotech companies Pfizer, BioNTech and Moderna, for example, have used a polymer called polyethylene glycol to improve the stability of mRNA in their COVID-19 vaccines now being deployed worldwide.

The expansive role that polymers are playing in the battle against coronavirus infections is the topic of a new review by researchers from A*STAR's Institute of Materials Research and Engineering (IMRE) and their collaborators. "The advantages of polymer-based technologies over current conventional treatments are inestimable," says Xian Jun Loh, Executive Director at IMRE and co-author on the review.

"Due to the unique material features in chemical structure flexibility, biocompatibility, easy functionalization and even biodegradability, polymers are the largest and most versatile class of biomaterials being extensively applied for therapeutic applications," said Zibiao Li, a Senior Research Scientist at IMRE and co-author on the review.

A key advantage of polymer-based technologies, Li noted, is the ability to synthesize large quantities quickly. This has been valuable for meeting the enormous uptick in demand for personal protective equipment after COVID-19 was found to spread through droplets or contact.

Apart from forming breathable barriers to prevent virus entry, polymers can also work inside the body. Synthetic polymers with electrostatic charge can interact with the infamous coronavirus spike protein or the negatively charged membrane of target cells to directly disrupt the virus-cell interaction that leads to infection. Natural polymers, too, have antiviral properties, with the added advantage of being more biocompatible than their synthetic counterparts.

Alternatively, polymers can act as drug delivery systems or prodrugs that enhance the overall therapeutic effects of antiviral drugs or vaccines. "Recently, a polymer-based, self-injection and sustained-release device for subcutaneous injection of Remdesivir (SelfExRem) for the treatment of COVID-19 was developed to reduce the frequency of administration and achieve stable drug release," Li said.

No one material, however, is perfect. For polymers, lingering toxicity issues mean that products require extensive testing before clinical use. Finding optimal sterilization methods, Li noted, is another challenge.

Nevertheless, the therapeutic potential of polymers extends beyond COVID-19, whether it be to enhance targeted drug delivery in precision medicine, or to arm us with the best possible defense against the dreaded "Disease X"—an anticipated deadly disease that many expect will cause an even more dangerous future pandemic. ★

Researcher
Xian Jun Loh, IMRE

ABOVE
Polymers are helping fend off viruses in many ways, including by enabling self-administered treatments like SelfExRem, a polymer-based device for the subcutaneous delivery of the anti-COVID drug Remdesivir.

1. Jian, X., Li, Z., Young, D.J., Liu, M., Wu, C., *et al.* Toward the prevention of coronavirus infection: what role can polymers play? *Materials Today Advances* **10**, 100140 (2021).

Photo credit: Myriam B / Shutterstock

COVID-19

How long do COVID-19 antibodies last?

The amount of neutralizing antibodies produced by COVID-19 patients—and the length of time they remain detectable—can vary wildly, a study suggests.

Although the scientific community has made tremendous progress in our understanding of SARS-CoV-2, the virus that causes COVID-19, there are still many unanswered questions. Of these, one of the most urgent unknowns to address is: Does natural infection confer protection against subsequent infection and how long might this protection last?

One key measurement used to indicate a protective response is the levels of neutralizing antibodies (NAbs), which work by binding to the virus and preventing it from entering cells. However, antibodies could also theoretically worsen symptoms through a pathway called antibody-dependent enhancement, as seen in the case of diseases such as dengue.

To better understand the antibody responses in COVID-19 patients, researchers in Singapore examined 164 patients for 180 days following the onset of symptoms, measuring the amount and binding strength of the antibodies they produced. Then, using a machine learning algorithm, they classified the antibody responses into five groups and predicted how long NAbs would last for each group.

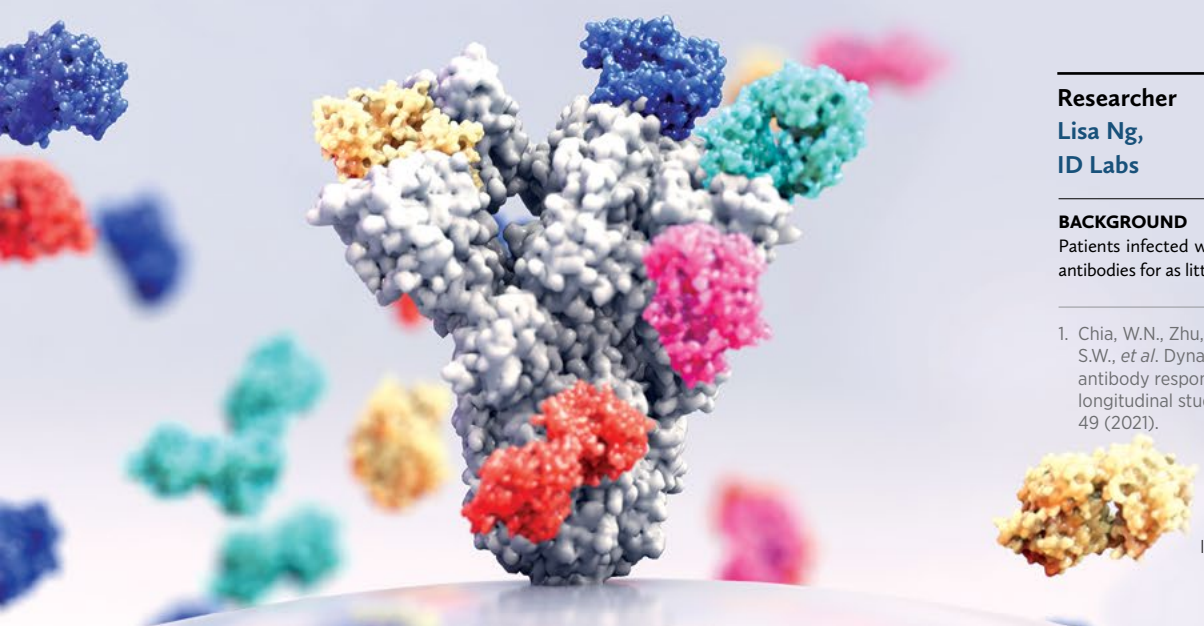
Patients who exhibited mild to no COVID-19 symptoms did not seem to have sustained immunity against the virus, with undetectable NAb levels by 180 days post-infection. On the other hand, those who suffered from moderate to severe symptoms tended to show persistent high levels of NAbs. This pattern is similar to the immune response of patients who had severe symptoms of the SARS virus in the early 2000s, said study co-author Lisa F.P. Ng, Executive Director at A*STAR's Infectious Diseases Labs (ID Labs).

"Neutralizing antibody levels were also predictive of immune protection from re-infection or symptomatic SARS-CoV-2 infection," she said, adding that low titers of NAbs are associated with symptomatic COVID-19 infection and subsequent re-infection.

NAb waning patterns varied widely depending on factors such as age, the presence of co-morbidities and clinical outcomes, with levels dropping off within 96 days on average for the rapid waning group compared to 1.5 years in the persistent group. "It is thus important to monitor NAbs strategically, stratifying by age, ethnicity and other factors, to determine optimal vaccine dosing strategies and improve vaccine design," Ng said.

On the other hand, a different branch of immunity—conferred by T cells rather than antibody-producing B cells—appeared to be the same in all patients regardless of disease severity and NAb levels. "This shows that individuals may still be protected if they have a robust T cell immunity when the neutralizing antibody level is low," Ng explained.

The team, including study corresponding authors David Lye at the National Centre for Infectious Diseases and Linfa Wang from Duke-NUS Medical School, are now studying the antibody responses in vaccinated individuals to understand the longevity of immunity provided by vaccination. ★



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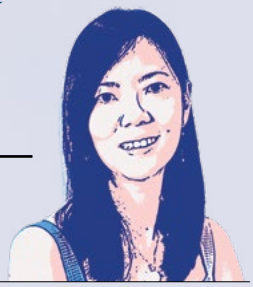
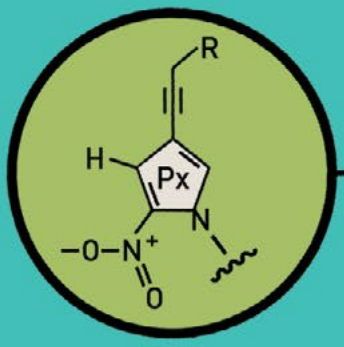


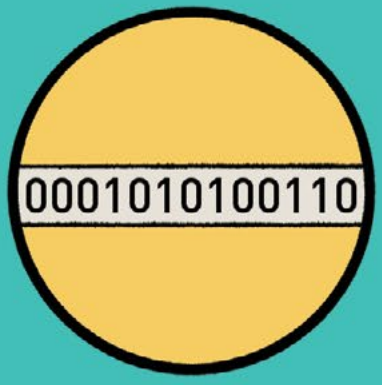
Researcher
Lisa Ng,
ID Labs

BACKGROUND
Patients infected with SARS-CoV-2 produce neutralizing antibodies for as little as 96 days or as long as 1.5 years.

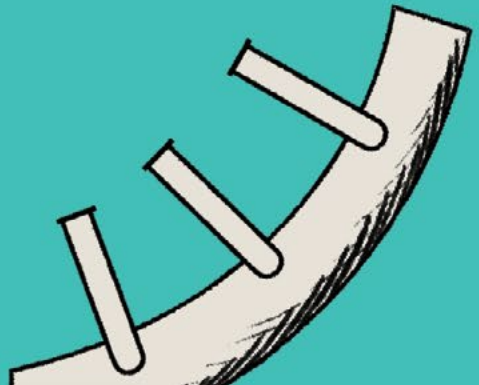
1. Chia, W.N., Zhu, F., Ong, S.W.X., Young, B.E., Fong, S.W., *et al*. Dynamics of SARS-CoV-2 neutralising antibody responses and duration of immunity: a longitudinal study. *The Lancet Microbe* **2** (6), e240-49 (2021).

ADVANCING SYNTHETIC BIOLOGY ACROSS ALL FRONTS





From expanding the genetic alphabet to uncovering antibiotics hidden in silent genes, A*STAR's researchers are wielding the tools of synthetic biology to improve our lives in surprising ways.

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In the early 20th century, pioneering molecular biologists sought to understand the intricacies of living systems by breaking them down into their most basic units—the building blocks of life that we now know as nucleic acids, proteins, lipids and carbohydrates.

Today, not only do scientists have a deep understanding of these building blocks, but with molecular biology tools like recombinant DNA, polymerase chain reaction (PCR), DNA synthesis and genome editing, they can redesign living systems to gain new or improved functions and even construct novel biological entities from scratch. Accordingly, applying engineering principles to biological systems has quickly become a full-fledged field of its own: synthetic biology.

As Nobel Prize-winning technologies like directed evolution and CRISPR/Cas9 make molecular biology techniques more powerful than ever, the synthetic biology approach and its applications are slowly permeating different aspects of society.

From using microbes to sustainably produce high-value molecules to cells engineered to fight their diseased counterparts, it's only a matter of time before such products become widespread in our daily lives. With the growing spotlight on synthetic biology, here's an overview of A*STAR's ongoing efforts in this developing field.

FROM A TO Z

One emerging tool in synthetic biology comes from a millennia-old war waged between bacteria and the viruses that infect them, known as bacteriophages or phages. To prevent bacterial enzymes from chopping up their DNA, phages have evolved to write their genomes using a chemical base called 2-aminoadenine or Z, instead of adenosine (A).

This unique version of genetic material, known as Z-DNA, was first discovered by Soviet scientists in 1977 in a phage called S-2L, which infects photosynthetic bacteria. Their experiments revealed that the phage replaced A with Z, which formed three hydrogen bonds with thymine (T) instead of the usual two.

"Because there is an extra hydrogen bond between the Z-T base pair than the canonical A-T base pair, Z-DNA is more stable at higher temperatures and more specific for sequence recognition," shared Huimin Zhao from the Singapore Institute of Food and Biotechnology Innovation (SIFBI). "Also, because A is replaced by Z, Z-DNA is resistant to degradation by nucleases that recognize and cut specific DNA sequences containing A."

However, four decades since this discovery, scientists still couldn't explain how the S-2L phage synthesized its Z-containing genome. But in a recent *Science* publication, an international team of researchers including Zhao and his SIFBI colleagues Ee Lui Ang and Yifeng Wei reported a breakthrough: the discovery of a multi-enzyme system responsible for the synthesis of the Z-containing phage genome [1].

As it turns out, these enzymes are widespread in nature, with dozens of other phages found to harbor them. In a phage known as *Acinetobacter* phage SH-Ab 15497, the team even verified the presence of Z-DNA.

Given its hardiness compared to conventional genetic material, Z-DNA is more than just a biological oddity. It could be the key to overcoming current limitations in emerging techniques that harness DNA's distinctive properties. Consider DNA data storage, which offers a density of up to 1,018 bytes per mm^3—far surpassing the capacity of today's hard drives and magnetic or optical data storage systems.

Thanks to the advent of sequencing, storing data as DNA is remarkably straightforward: digital information is first encoded into DNA sequences, which are synthesized into actual DNA molecules that are stored. To read the information, the DNA molecules are sequenced and converted back into digital data. Numerous copies can be simultaneously made from a simple PCR run.

When kept away from light, humidity and extreme temperatures, DNA can last up to millennia compared to the typical decades-long lifetime of archival storage media like tape and optical disks. By using Z-DNA, DNA data storage can be made stable and long-lasting even when exposed to higher temperatures.

Another technique that could benefit from Z-DNA is DNA origami, where long, single-stranded DNA molecules fold into two- or three-dimensional shapes through crossover base pairing. Therapeutic molecules can then be readily loaded into the

cavities and docking sites of DNA origami, turning the tiny nanomachines into formidable drug delivery systems.

Given Z-DNA's stability and binding strength, applying it to DNA origami could result in better-folded nanostructures that are more resistant to enzymatic degradation. Sure enough, certain DNA origami structures have been shown to successfully cross biological barriers like mature plant cell walls.

NEW CHARACTERS IN THE GENETIC CAST

Aside from the naturally-occurring Z base, synthetic biologists are also expanding the 'vocabulary' of the genetic alphabet by creating 'unnatural' base pairs. Since Watson and Crick first delineated the structure of DNA almost 70 years ago, conventional wisdom held that the complementary binding of bases A and T, as well as cytosine (C) and guanine (G) is fundamental to the flow of genetic information.

"However, the limited letters of the genetic alphabet restrict the further improvement of biomaterials and biosystems with increased functionalities," explained Ichiro Hirao, a Senior Group Leader at A*STAR's Institute of Bioengineering and Bioimaging (IBB). For instance, only 20 amino acids are possible with the current four-letter alphabet. By adding just two more letters, up to 216 different amino acids can be formed.

In 2009, Hirao and IBB Senior Research Scientist Michiko Kimoto did exactly that: creating two new genetic letters—Ds and Px—which combine to form a third, artificial base pair[2]. Along with collaborator Andreas Marx from the University of Konstanz in Germany, the A*STAR team determined that the tertiary structure of Ds-Px when complexed with DNA polymerase was strikingly similar to the A-T and G-C pairs[3]—allowing for high accuracy in DNA replication.

Beyond new amino acids, unnatural base pairs like Ds and Px can be used in myriad ways. For instance, functional groups of interest can be attached to unnatural bases, endowing nucleic acids with desired new functionalities.

The unnatural base pairs can be used as well to generate DNA aptamers—short, single-stranded nucleic acid molecules that selectively bind to targets ranging from simple inorganic molecules to large protein complexes. Introducing Ds bases to DNA aptamers also dramatically enhances their affinities[4].

While they operate much like antibodies, generating aptamers is significantly easier and cheaper. Moreover, aptamers are neither immunogenic nor toxic, making them ideal candidates for diagnostic and therapeutic applications, like purifying target molecules from complex mixtures or designing biosensors, among others.

However, generating DNA aptamers with unnatural bases requires a method that can reliably determine their sequence. Accordingly, the A*STAR team has been developing a modified Sanger sequencing method for DNA containing unnatural bases[5]—further simplifying this in 2019 by refining conventional deep sequencing methods[6].

In their 2019 update, the team used replacement PCR to replace unnatural bases with their natural counterparts, creating an expansive encyclopedia detailing natural base replacement patterns. By comparing the natural base composition in the actual and encyclopedic data, scientists could easily pinpoint the original positions of the unnatural bases.

Ultimately, their refined sequencing method paves the way for quicker and more efficient methods of generating aptamers. Since then, Hirao and his team have already used the improved method to create novel diagnostics for dengue infection, with more use cases sure to arise over the years.

SYNTHETIC BIOLOGY TECHNIQUES FOR NATURAL PRODUCTS

Despite its name, there's more to synthetic biology than exploring unnatural bases and products. At its core, the discipline seeks to take existing systems to the next level through frontier tools like the CRISPR/Cas9 genetic scissors, which won its inventors the Nobel Prize in Chemistry last year.

At A*STAR, Yee Hwee Lim at the Institute of Chemical and Engineering Sciences (ICES), Fong Tian Wong at the Molecular Engineering Lab (MEL), Institute of Cell and Molecular Biology (IMCB), and their colleagues harness CRISPR/Cas9 to better predict, design and build pathways for synthesizing beneficial natural products.

In 2017, for instance, their team—along with SIFBI's Zhao—unearthed a new antibiotic from a silent biosynthetic gene cluster found in *Streptomyces roseosporus*[7]. "50 percent of current commercial drugs are derivations or mimics of natural products," said Lim.

"For a long time, the discovery of new natural products has been hindered by our inability to activate silent gene clusters and produce the encoded molecules under lab conditions."

To work around this setback, the team leveraged CRISPR/Cas9 to replace native repressed promoters with strong constitutive ones in the bacterial genome—activating the expression of the whole biosynthetic gene cluster. Notably, the gene cluster was found to encode auroramycin, which has potent activity against Gram-positive bacteria, including the notorious superbug methicillin-resistant *Staphylococcus aureus*, as well as antifungal properties.

More recently, in 2020, Lim and Wong's team used CRISPR/Cas9 to accelerate the combinatorial engineering of auroramycin's native biosynthetic pathways[8]. In their study, they employed different engineering strategies to target different pathways, producing 12 strains of auroromycin with variations in methylation and hydroxylation, among others. By comparing the bioactivity profiles of various analogs, the team managed to pinpoint the key to auroramycin's antifungal activity: an additional methyl group in its 3,5-*epi*-lemonose outer sugar unit.

In the same vein, Fan Hao, a Senior Principal Investigator at A*STAR's Bioinformatics Institute (BII), is applying his experience in computational modeling and docking to accelerate the synthesis of natural products through enzyme engineering. In collaboration with the National University of Singapore, BII is developing enhanced enzymes that catalyze the synthesis of therapeutic agents like cannabinoids, which have potential antibacterial, anti-epileptic and anti-tumor effects[9].

"For a long time, the discovery of new natural products has been hindered by our inability to activate silent gene clusters and produce the encoded molecules under lab conditions."

The team does this by suggesting mutations in the enzyme active site through computational approaches. Through modeling and docking, they can then effectively screen *in silico* the binding of a series of chemically related substrates onto a large collection of mutated enzymes[10]. They are also improving their methods with the aid of machine learning models. All in all, with the help of synthetic biology techniques, researchers across A*STAR are unlocking a treasure trove of new, enhanced natural products.

TINY FACTORS WITH A BIG IMPACT

Even as scientists find novel antibiotics hidden in unassuming bacteria, other microbes like *Escherichia coli* and the baker's yeast *Saccharomyces cerevisiae* have emerged as two prominent workhorses in the field. By modifying specific synthesis pathways, researchers can transform the two microorganisms into cellular factories that generate useful products far more efficiently compared to traditional techniques.

Consider SiNOPSEE Therapeutics, an A*STAR spinoff company led by IMCB Research Director Uttam Surana that tackles unwanted blood vessel growth—a characteristic symptom associated with diseases like cancer and blindness—using small molecule drugs. Such drugs were produced based on the principles of synthetic biology, according to Surana.

First, the team developed 'humanized' S. *cerevisiae* strains by integrating human proteins and pathways into the yeast's genome through genetic engineering. This allowed them to use the yeast as a platform to design drug screening strategies that could rapidly identify inhibitors against disease-causing proteins or pathways—in other words, potential drug candidates. This platform is now being used to develop a pipeline of novel anti-cancer compounds.

But S. *cerevisiae* isn't the only yeast that's making a mark in synthetic biology. Also at the IMCB, Research Director, Yue Wang is studying *Candida albicans*—a common fungal pathogen in humans that causes life-threatening infections. As multi-drug resistant *Candida* strains emerge worldwide—threatening to

render existing antifungals obsolete—researchers like Wang are looking for novel ways to study these fungal foes.

Until recently, *C. albicans* was thought to be diploid, meaning that it had two sets of genes. However, its diploid nature made the fungus tricky to study within the laboratory. Producing *C. albicans* mutants resistant to antifungals like echinocandin, for instance, would take about 100 days on average as both copies of the target gene had to be inactivated.

To accelerate the process, Wang and his team created the first haploid strains of this pathogen—designing a one-step protocol to delete genes in haploid *C. albicans* strains that takes only 11 days, as well as another method to quickly construct mutant libraries of the haploid strains in a week[11,12].

The latter relies on introducing genetic elements called transposons, which are capable of "jumping" around the genome to cause mutations. Since then, the team has applied the new technologies to two other *Candida* species, including the superbug *C. auris*, discovering new drug resistance and antifungal mechanisms along the way[13,14].

SYNTHETIC BIOLOGY DAWNS AT A*STAR

Given the field's vast scope, A*STAR is now pioneering a synthetic biology program to successfully bring the various themes discussed together. Set to helm the program is none other than Shawn Hoon, Director of IMCB's MEL, who is known for his work on biomimetic materials inspired by nature.

According to Hoon, the program aims to develop end-to-end capabilities for biomanufacturing—integrating A*STAR's existing capabilities in synthetic biology, bioinformatics, artificial intelligence and automation for biosystems design across multiple levels. "The resulting platform will be based on the design-build-test-learn cycle, and aspires to be a fully automated, scalable and high-throughput platform, that goes from discovery to engineering to production," he explained.

Armed with this platform, the synthetic biology program is set to explore the possibilities offered in areas like the biomanufacturing of bioactive molecules, specialty chemicals, biologics and materials as well as food. Together, these areas are predicted to make up around 80 percent of synthetic biology's potential impact on society.

As they continue to tinker with these natural systems, A*STAR scientists are standing at the brink of the next biomedical revolution—pushing the boundaries of life as we know it to great effect. ★

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STEM CELLS

Making a mark on stem cell therapy

A novel genomic biomarker may help to meet the demand for donor mesenchymal stem cells in regenerative medicine.

The future of regenerative medicine has never looked brighter. Ongoing clinical trials for treatments using stem cells—cells that have the potential to develop into a variety of tissue types—are giving hope to patients with conditions ranging from autoimmune to neurodegenerative diseases.

Many clinically explored cell-based therapies use mesenchymal stem cells (MSCs) isolated from human donors, and these MSCs vary greatly in terms of quality and growth potential. To comply with clinical requirements, a time-consuming and expensive screening step is required after harvesting to assess their quality.

Seeking to find a biomarker that can identify high-quality MSCs more efficiently, Simon Cool, a Research Director at A*STAR's Institute of Molecular and Cell Biology (IMCB), and collaborators from A*STAR's Genome Institute of Singapore (GIS) compared the molecular profiles of donor MSCs placed in two groups: high- or low-growth potential.

"A biomarker that can accurately predict the quality and scalability of MSCs from donors prior to harvest would represent a major breakthrough in stem cell manufacturing."

"A biomarker that can accurately predict the quality and scalability of MSCs from donors before harvest would represent a major breakthrough in stem cell manufacturing," Cool said.

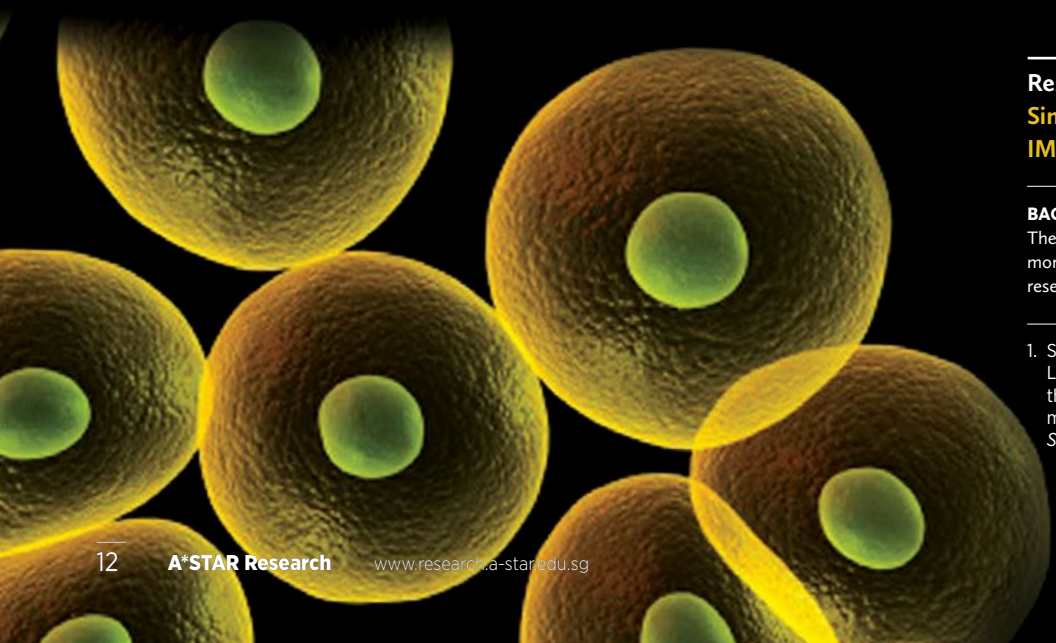
In microarray studies of donor MSCs, the researchers found a striking difference in the expression of the *GSTT1* gene, which codes for glutathione S-transferase theta 1, a member of a superfamily of metabolic enzymes. Most MSCs with high-growth potential did not express *GSTT1* due to a gene deletion.

Next, the researchers used RNA interference—a technique that uses RNA molecules to inhibit gene expression—to confirm that MSCs lacking *GSTT1* expression grew more rapidly, with enhanced clonogenicity and longer telomeres. Importantly, these MSCs did not lose their 'stemness.' The researchers have filed a patent based on these findings.

"We were surprised that what started as an unbiased molecular screen of MSCs with high- versus low-growth capacity resulted in the identification of a single but robust DNA biomarker," Cool said.

The critical next step is to assess the safety of rapidly growing cells. The researchers are in the process of determining whether the MSCs maintain an appropriate immune profile and retain stable genomic DNA.

Simultaneously, they are developing a diagnostic kit that can rapidly determine the genetic makeup of donors, which would support the banking of allogeneic stem cells for therapeutic use. They are also in the process of identifying additional biomarkers beyond *GSTT1*, which appears to be the most promising candidate so far. ★



Researcher
Simon Cool, IMCB

BACKGROUND
The lack of a single gene could make stem cells grow more rapidly and retain their regenerative properties, researchers say.

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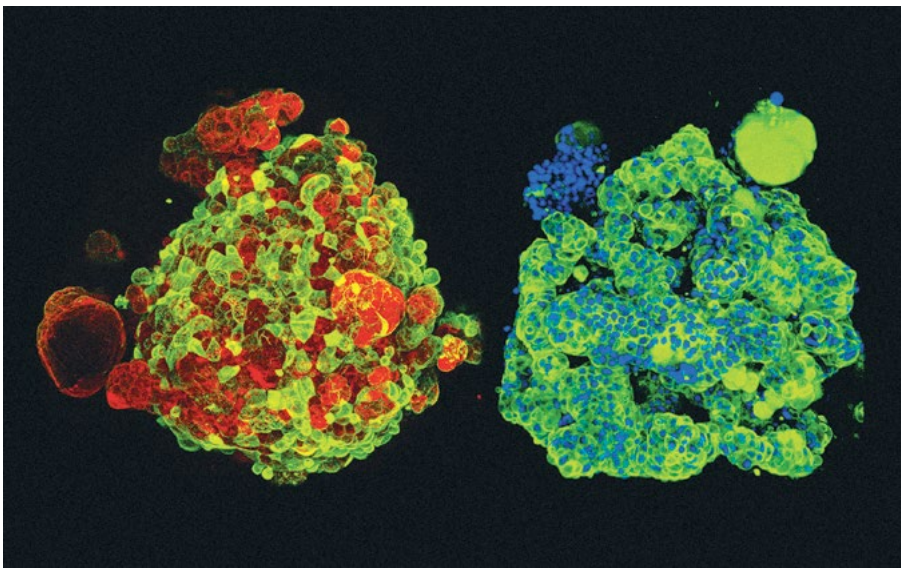
Photo credit: stemcelltreatment / Flickr

ORGANOIDS

A recipe for mini livers

For the first time, researchers have generated lab-grown livers that have functioning bile canaliculi, an important step towards modeling complex liver diseases.



Lab-grown livers that mimic the behavior of full organs could help to shed light on complex diseases like nonalcoholic steatohepatitis.

Photo credit: © A*STAR's Genome Institute of Singapore(GIS)

Liver disease is a significant healthcare issue—when the organ fails, besides joining a long waitlist for a transplant, patient options are limited. The liver is a complex organ, and managing conditions such as hepatitis remains a challenge given much is still unknown about the cellular basis of liver disease. Three-dimensional 'mini livers' derived from stem cells have the potential to bridge this gap. These tissue cultures known as organoids recapitulate the liver's complexity and can be a powerful tool for studying liver disease.

An A*STAR research team from the Genome Institute of Singapore (GIS), Institute of Medical Biology (IMB) and Skin Research Institute of Singapore (SRIS) has created the next generation of liver organoids that feature a network of canaliculi, the transport system for bile. This hepatic organoid, the first of its kind, captures a critical structural element of the liver, allowing researchers to investigate how pathologies impact liver function in a lab setting.

Under the right experimental conditions, stem cells can self-assemble into miniaturized liver tissues. "We have to mimic fetal liver development in a dish," explained study corresponding author Winston Chan, a Senior Program Manager at GIS. "This involves the timely introduction of signaling cues in a step-wise manner to direct the stem cells towards the endoderm lineage, form the posterior foregut, and to eventually differentiate into the liver organ."

Chan and the team first identified the precise biochemical cues required to induce the formation of specific structural components in liver organoids, such as the bile canaliculi system. They then validated the functionality of these structures by subjecting them to cholestasis-inducing drugs, which are known to disrupt bile function.

Additionally, they tested the utility of the organoids for studying liver disease by incubating the organoids with free fatty acids. Analyses revealed that the organoids' gene expression signatures mirrored those of cells derived from patients with nonalcoholic steatohepatitis (NASH).

This tissue engineering breakthrough highlights how hepatic organoids could revolutionize the development and testing of therapies for managing liver diseases such as NASH—conditions that involve an interplay between multiple liver cell populations and external factors.

Chan and colleagues continue to push the limits of what's possible with haptic organoids, with future studies focused on incorporating even more cell types into their organoid models. In particular, the researchers are looking at introducing immune cells and blood vessel endothelial cells, working towards eventually recreating the entire liver in a dish, said Chan. ★

Researcher
Winston Chan, GIS

1. Ramli, M.N.B., Lim, Y.S., Koe, C.T., Demircioglu, D., Tng, W., *et. al*. Human pluripotent stem cell-derived organoids as models of liver disease. *Gastroenterology* **159**, 4 (2020).

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.

In life, our goals are often clouded by conflicting motives, where wanting to do something pleasurable may clash with the pain or difficulty of the task. Conflicts between pain and essential behaviors like feeding can have dire consequences, like the loss of appetite, anxiety and depression seen in many people with chronic pain.

In the brain, the pain pathway connecting the parabrachial nucleus (PBN) to the central amygdala (CeA) has long been thought to suppress feeding. However, the PBN-CeA circuit has never explicitly been studied for its role in suppressing motivational drive for feeding, noted Yu Fu, a Principal Investigator at A*STAR's Singapore Bioimaging Consortium (SBIC). Apart from CeA, the PBN also relays pain signals to many other brain regions, but these circuits have not been rigorously studied because the pain-hunger connection was believed to have already been resolved, he added.

In a study published in *Science Advances*, Fu and his team report a new pathway important for regulating feeding: the PBN-lateral hypothalamus (LH) circuit. In contrast to the PBN-CeA circuit which seems to suppress feeding in response to the fear of pain, the PBN-LH circuit appears to suppress the motivation to feed in the first place.

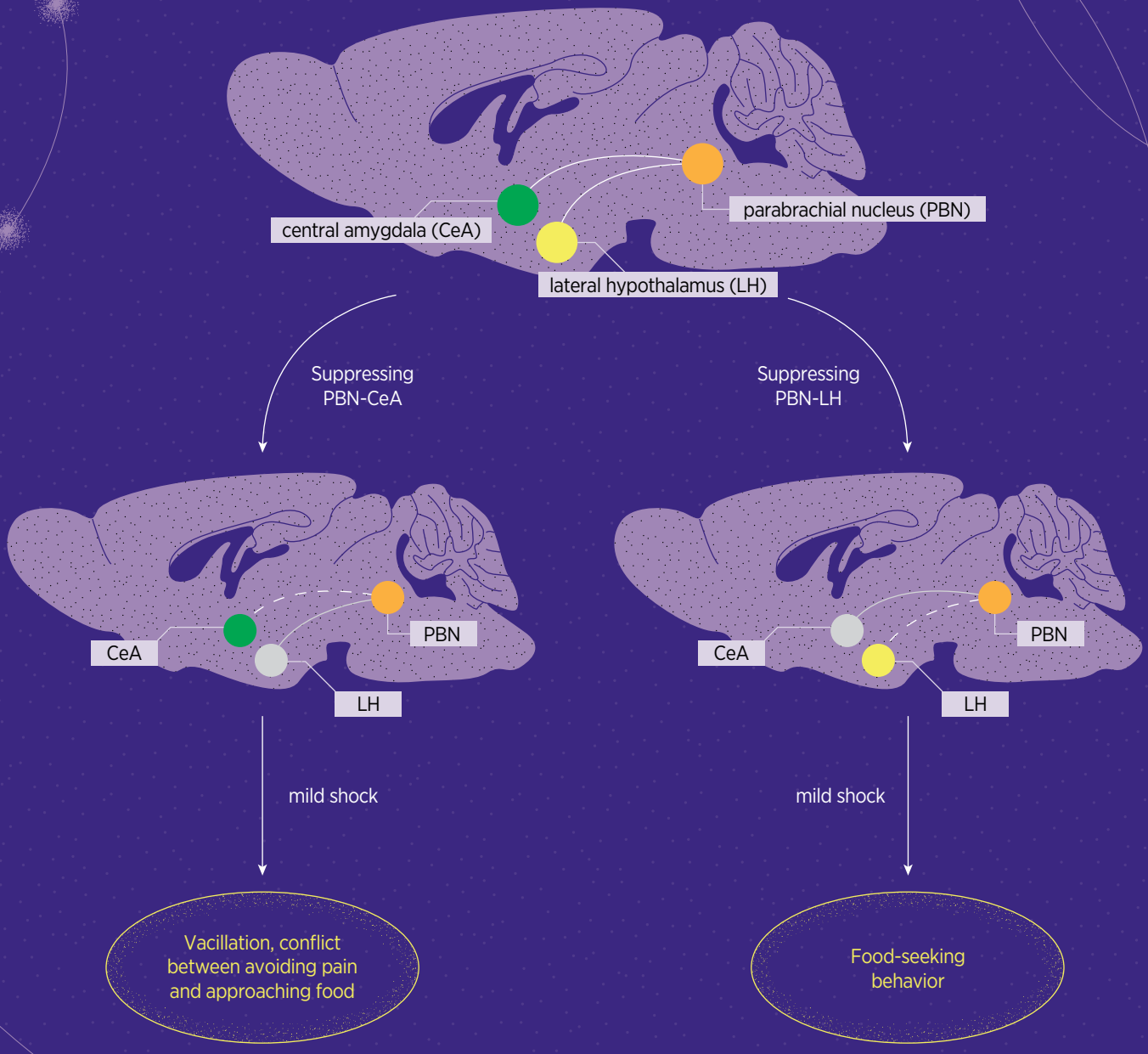
"Better medicines should be developed to target neural circuits involved in motivational loss, such as the PBN-LH circuit, for rescuing chronic pain patients from depressive disorders."

To tease apart this key difference, Siew Cheng Phua, an A*STAR scholar and the lead author of the paper, refined the 'approach-avoid' experiment, a decades-old paradigm designed to see how mice resolve the conflict between the pain of a foot shock and the desire to eat. While previous versions of this experiment looked at how much food the mice consumed at different levels of pain, Fu and the team instead focused on how much time the mice spent deciding between avoiding pain and approaching food, a behavior known as vacillation.

"Although both mild and strong pain almost completely abolished food intake, the mice displayed vacillation behavior under mild shocks, showing a clear motivational conflict between trying to obtain food and avoiding mild pain," Fu said. "However, animals facing strong shocks showed much less vacillation, probably due to intense fear driven by stronger pain."

Inactivating the PBN-LH circuit in mice suppressed their vacillation behavior under mild shock conditions and promoted food-seeking behavior, essentially resolving the motivational conflict between pain avoidance and reward approach. In contrast, disabling the PBN-CeA circuit did not have that effect and was instead linked to the escape behavior displayed in response to stronger shocks. "The PBN-CeA circuit is probably more involved in suppressing feeding by fear (strong shocks), which is qualitatively distinct from pain (mild shocks)," Fu explained.

Interestingly, the researchers also briefly looked at the effects of the common analgesic buprenorphine and found that it did not improve motivation to feed even under mild pain. "Better medicines should be developed to target neural circuits involved in motivation loss, such as the PBN-LH circuit, for rescuing chronic pain patients from depressive disorders," Fu concluded. ★

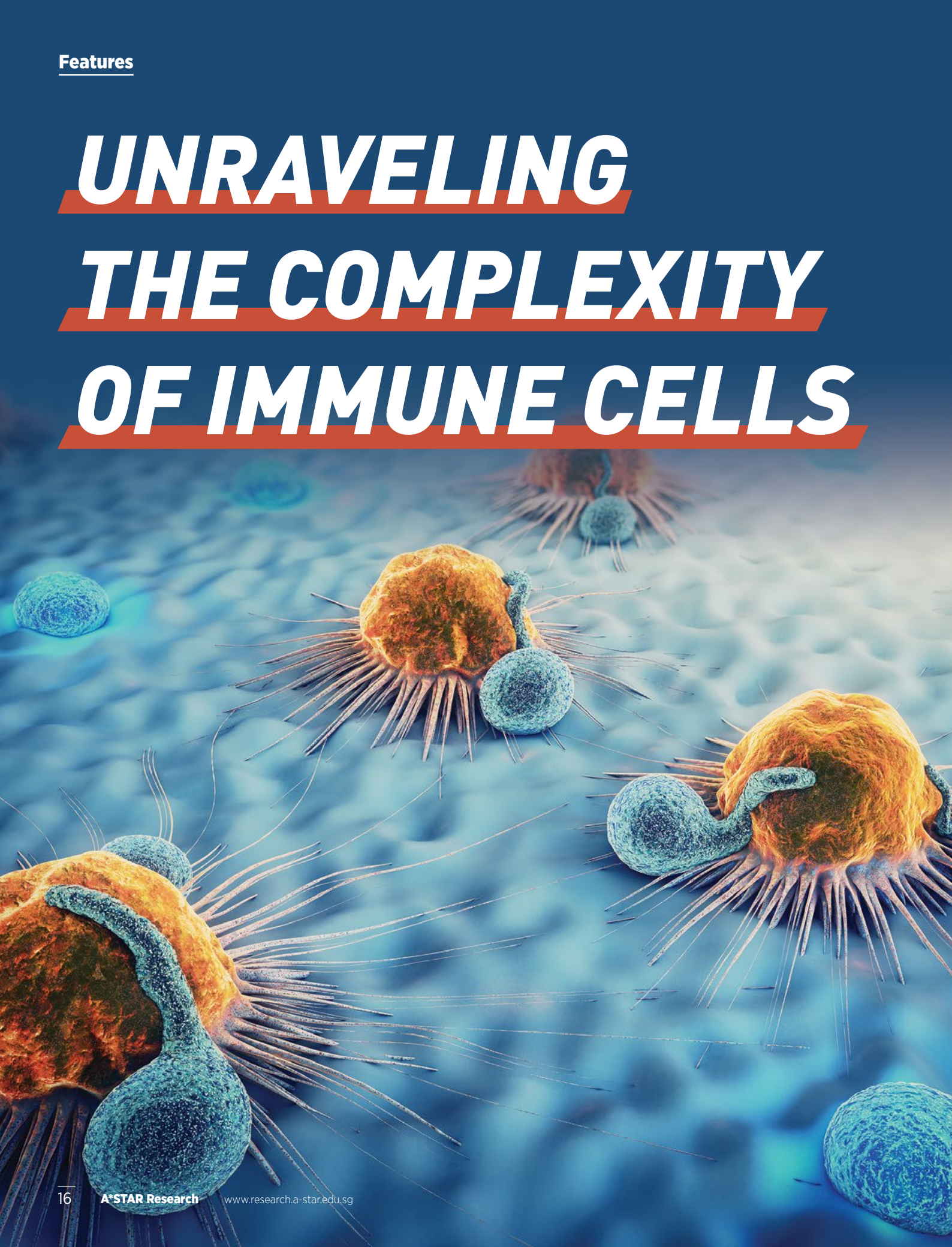


ABOVE
Neurons from the parabrachial nucleus (PBN) project into the central amygdala (CeA), lateral hypothalamus (LH) and other brain regions. While mild shocks normally lead to increased vacillation behavior, demonstrating a conflict between avoiding pain and approaching food, suppressing the LH-projecting neurons resolved the motivational conflict and increased food-seeking behavior.

Researcher
Yu Fu, SBIC

1. Phua, S.C., Tan, Y.L., Kok, M.Y.A., Senol, E., Chiam, J.H.C., *et al.* A distinct parabrachial to lateral hypothalamus circuit for motivational suppression of feeding by nociception. *Science Advances* **7** (19), eabe4323 (2021).

UNRAVELING THE COMPLEXITY OF IMMUNE CELLS



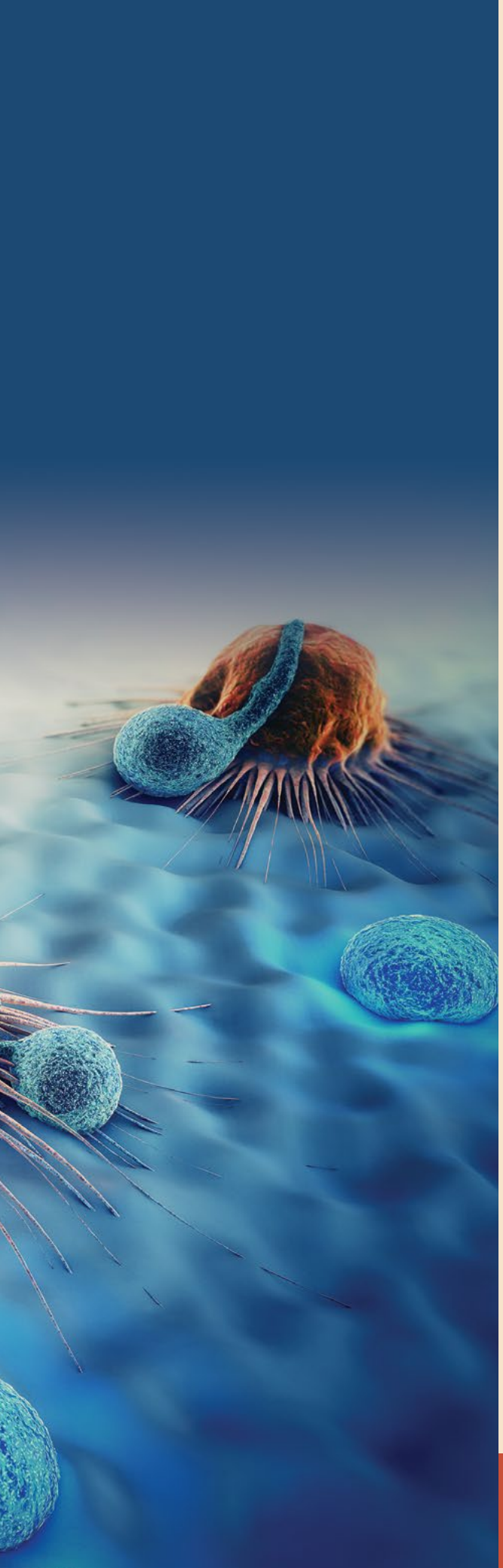


Photo credit: Christoph Burgstedt / Shutterstock

By tapping into the inner workings of cells, Jinmiao Chen uses novel analytical technologies to understand why immune responses vary greatly among individuals.

From bacteria eaters to cancer-cell destroyers, the immune system enlists a diverse army of cells to defend the body against illness. When fighting the same disease-causing agent, however, one individual might experience nothing more than a cough that disappears in a few days, while another may have more severe symptoms like breathing difficulties.

These differences at the individual level are rooted in subtle variations at the single-cell level—a tiny world, yet responsible for so much of biology's complexity. But how exactly these immune cells work together and what happens when they fail have remained unresolved questions.

Jinmiao Chen, a Principal Investigator at A*STAR's Singapore Immunology Network (SIgN), is harnessing single-cell technologies and artificial intelligence (AI) to characterize the medley of activities that immune cells are engaged in. By developing novel analytic methods, her group makes sense of cellular data such as genetic information and signals used in cell–cell communication, to understand how differences at the cellular level manifest as different responses to diseases and treatments.

In this interview with *A*STAR Research*, Chen dives deep into the complex world of immune cells and shares how her analytical work may serve as a springboard for advancing research on precision immunotherapies that are tailored to match patients' individual needs and immune system characteristics.

Q: WHAT ARE THE MAJOR CHALLENGES THAT YOU AIM TO SOLVE WITH YOUR RESEARCH?

Characterizing immune cells and cell–cell interactions is critical for understanding the mechanisms used by immune cells to promote disease progression and response to treatment. While diverse immune cell subsets have been characterized, much less is known about the interactions between subsets of immune cells, as well as the interactions of immune cells with non-immune cells like cancer tumor cells.

To examine these interactions, single-cell technology is generating large and complex datasets—creating atlases of immune cells. However, our ability to generate complex, high-dimensional data has far outstripped our ability to analyze and integrate it. Comparison between atlases has been difficult owing to the plethora of protocols used. Moreover, many studies have generated large volumes of overlapping data. There is thus an unmet need for unified analysis, integration and annotation of these datasets to reveal synergy between studies.

This provides opportunities for the development of data-driven and bio-inspired AI, especially with AI in the biological sciences, which previously lacked well-annotated big data. As such, we are working to build a bridge between AI and immunology.

Q: GIVEN YOUR BACKGROUND IN COMPUTER SCIENCE, WHAT LED YOU TO BIOINFORMATICS RESEARCH, AND IN PARTICULAR, SINGLE-CELL ANALYSIS TECHNOLOGIES?

During my PhD degree, I developed new AI techniques for data analysis, but my method was not widely used by biologists. I started to wonder how I could use my expertise to help biologists. When single-cell analysis first emerged, I was fascinated by its power and realized that this approach produces big and complex data, which is ideal for AI systems to process. Moreover, joining SIgN allowed me to work with different labs and learn about the beauty of immunology. Altogether, these inspired my research on combining single-cell technologies and AI for precision immunology.

Q: WHAT IS THE IMPACT OF THE SINGLE-CELL APPROACH, PARTICULARLY IN IMMUNOLOGY?

Understanding the interplay between the immune system and disease—and the huge variation in individual response due to fine-grained differences at the single-cell level—is a vital area of research. With single-cell 'omics technologies, we have analyzed immune cells at increasing scale and resolution.

Two newly emerging technologies called single-cell multi-omics and spatial 'omics have been transforming our understanding of the immune system. Multi-omics can identify subtle differences between cells, allowing us to dissect variable immune responses in cancer, autoimmune and infectious diseases. Spatial 'omics technologies, which simultaneously measure gene expression, protein production and cell location, enable the reconstruction of tissue structure and cell-cell interactions. This is critical for understanding the tumor microenvironment and characterizing interactions between tumor cells and immune cells.

Q: WHAT ARE SOME OF THE MOST INTERESTING RESEARCH PROJECTS THAT YOU ARE PURSUING RIGHT NOW?

By integrating existing public datasets into a comprehensive and unified atlas, our lab is generating well-annotated big data that will be useful for the development and training of AI models. Together with data-driven AI, Deep Integration of Single-Cell Omics (DISCO) provides immunologists with a reference Google map for studying the immune system in healthy and sick individuals. It currently carries data on six million cells across various tissues, from bones to the brain.

We also developed a spatial 'omics pipeline called the Unsupervised Spatially Embedded Deep Representation of Spatial Transcriptomics (SEDR) that combines genetic data with spatial relationships, accelerating follow-up analysis and integration tasks. This method was highly accurate in retracing the development of a brain region, identifying not only the genes expressed but also where they needed to be activated.

Meanwhile, in an ongoing study on gastric cancer, we discovered cell subsets that favor tumor growth, suppress the immune response and are resistant to chemotherapy. These were associated with poor clinical outcomes for patients.

Q: HOW WOULD YOUR WORK IN SINGLE-CELL ANALYTICS SUPPORT ADVANCES IN MEDICINE?

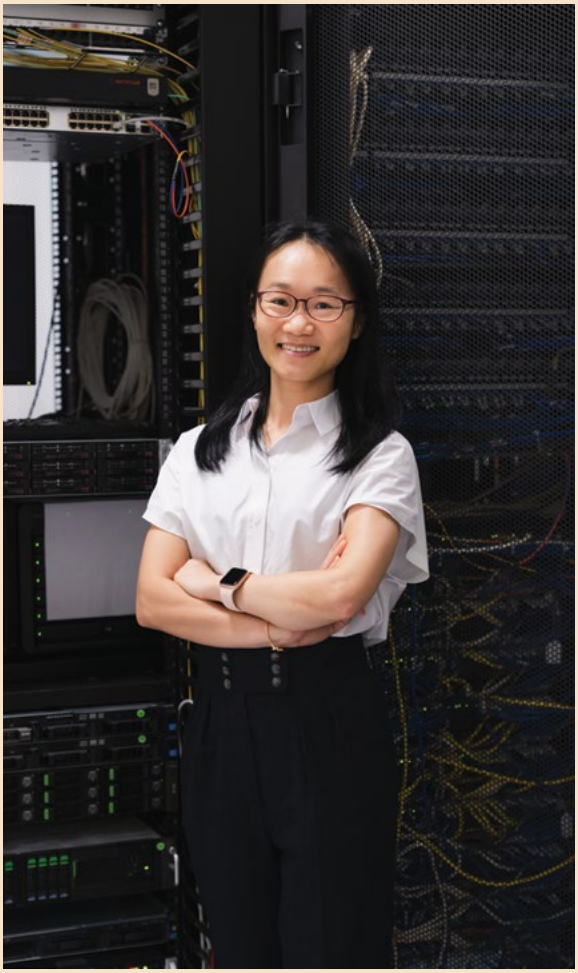
Soon, single-cell technologies will become more and more accessible, cost-effective and widely applied in translational research for a broad spectrum of diseases.

Our single-cell studies contribute directly to Singapore's national precision medicine research strategy. For example, the DISCO atlas characterizes all immune cells in healthy and diseased states, building a critical foundation for studying individual differences in immune responses. These atlases, combined with single-cell analysis of dysfunctional immune responses, will advance the development of personalized immunotherapies.

Q: HOW DO YOU PLAN TO TAKE YOUR RESEARCH FORWARD IN THE NEXT FEW YEARS?

Our lab will continue to build DISCO, including detailed, zoomed-in atlases on immune development from infants to the elderly, COVID-19 and other viral diseases, autoimmune diseases and various cancers. We will also use spatial 'omics and AI models to characterize tumor-immune cell-cell interactions in mouse breast cancer models before and after immunotherapy, as well as predict breast cancer patients' responses to immunotherapy. ★

"Single-cell technologies will become more and more accessible, cost-effective and widely applied in translational research for a broad spectrum of diseases."



Jinmiao Chen
Principal Investigator
A*STAR's Singapore Immunology Network (SIgN)

FOOD SCIENCE

Taking the 'moo' out of yogurt

By swopping fermentation for high pressure, plant-based yogurts may soon give dairy yogurts a run for their money.

It's never been easier to go vegan. From chicken to beef and seafood, plant-based alternatives can increasingly be found in restaurant menus and along supermarket aisles. As global demand for dairy increases, researchers have turned the spotlight on a market that is ripe for disruption: the yogurt industry.

Through decades of trial and error, fermentation has evolved into an industrialized process where dairy yogurt is given its flavor, texture and health benefits. But because plant-based kinds of milk naturally tend to be lower in sugar and protein content, they are less-than-ideal candidates for fermentation. Where dairy yogurts are rich and creamy, plant-based counterparts are either too starchy, watery or clumpy, making for an overall disappointing product.

In search of a plant-based alternative to dairy yogurt, a research team led by Christiani Jeyakumar Henry, Director of A*STAR's Clinical Nutrition Research Centre (CNRC), sought to develop a method that skipped the fermentation step entirely.

"Instead of fermentation, we used a technique called high-pressure processing (HPP) to form plant-based yogurts by pressure-induced protein gelation," Henry explained. "The products are packaged in a flexible container, and all food components are subjected to uniform pressure in a high-pressure chamber."

Starting with a variety of plant protein powders (mung bean, chickpea, pea, lentil and faba bean), Henry and study first author Shaun Sim tested how well the protein gels that were formed could mimic the texture and consistency of Greek dairy yogurts. To mimic whole milk yogurts, they added 5% by weight of sunflower oil to the protein gels. In the end, faba bean and chick pea (with sunflower oil) had the closest viscoelastic properties to the skim and whole milk yogurts, respectively.

Decoupling flavor generation (still a work in progress) from texture formation via HPP allows manufacturers to optimize flavor production without having to worry about texture, Henry noted. However, the high pressure may potentially be detrimental to gut-healthy probiotic bacteria cultures. More work in this area is needed, Henry added, before these high pressure-processed yogurts can be found on supermarket shelves.

"The products are packaged in a flexible container, and all food components are subjected to uniform pressure in a high-pressure chamber."

"Our proof-of-concept study showed that HPP can be used to generate plant-based yogurts with comparable texture to dairy yogurts, using minimal ingredients, and much more quickly compared to traditional fermentation methods," Henry said. His team is now exploring novel flavors not resembling dairy yogurt and collaborating with industry partners to commercialize the technology. ★

Researcher
Christiani Jeyakumar Henry, CNRC

ABOVE
High-pressure processing could help make dairy-free yogurt a reality.

1. Sim, S.Y.J., Hua, X.Y., Henry, C.J. A novel approach to structure plant-based yogurts using high pressure processing. *Foods* **9**, 1126 (2020).

Photo credit: DagnyWalter / Pixabay

INFECTIOUS DISEASE

Getting ahead of dengue outbreaks

This two-step outbreak detection framework could give early warnings of dengue outbreaks, improving Singapore's ability to control the disease.

While COVID-19 is currently at the forefront of public consciousness, it is far from the only infectious disease we need to worry about. For highly urbanized, tropical Singapore, dengue has been a perennial concern. 2020 saw a record high of over 38,000 cases, far surpassing the previous high of 22,318 cases in 2013.

Just as weather reports can help people plan their daily activities, disease forecasting models are helping public health officials prepare for potential dengue outbreaks. However, most existing dengue prediction models focus on predicting what the absolute number of cases will be in the next couple of weeks, rather than trying to detect a sharp, consecutive increase in cases that would suggest an impending outbreak.

"There are two problems with this approach," explained Xiuju Fu, a Senior Scientist at A*STAR's Institute of High Performance Computing (IHPC). "The first is that accuracy drops dramatically the farther ahead the model tries to see. Second, there is a lack of clear definition of the threshold, so such identification of dengue outbreaks can be quite subjective."

Instead, Fu and her team developed a model that can detect dengue outbreaks at an early stage, buying time for public health officials to launch interventions and prepare resources. The key to their success was that they focused on broader differences between outbreak and non-outbreak situations rather than simply the number of cases.

The researchers first sought to determine what 'normal' years and periods would look like, using weekly dengue data from 2006 to 2011, years where numbers were relatively low. To establish the best baseline possible, they deliberately left out periods when an outbreak was in full swing. The resulting model was able to generate accurate forecasts a week in advance.

Borrowing the 'control chart' concept from manufacturing quality control processes, the researchers then input the differences between the forecasted value and the actual number of cases observed. If the difference deviates from the normal pattern, the model signals that an outbreak might be imminent. "Moreover, by using the proposed framework adaptively, the dynamic threshold for detecting outbreaks can be automatically determined, which makes the model intelligent and adaptive in changing environments," Fu said.

Fu and her team are currently working on adding further detail such as spatiotemporal patterns to their predictions. This additional layer of information could help identify which areas are more prone to large-scale dengue outbreaks, helping officials launch more targeted—and thus less costly—proactive control measures. ★

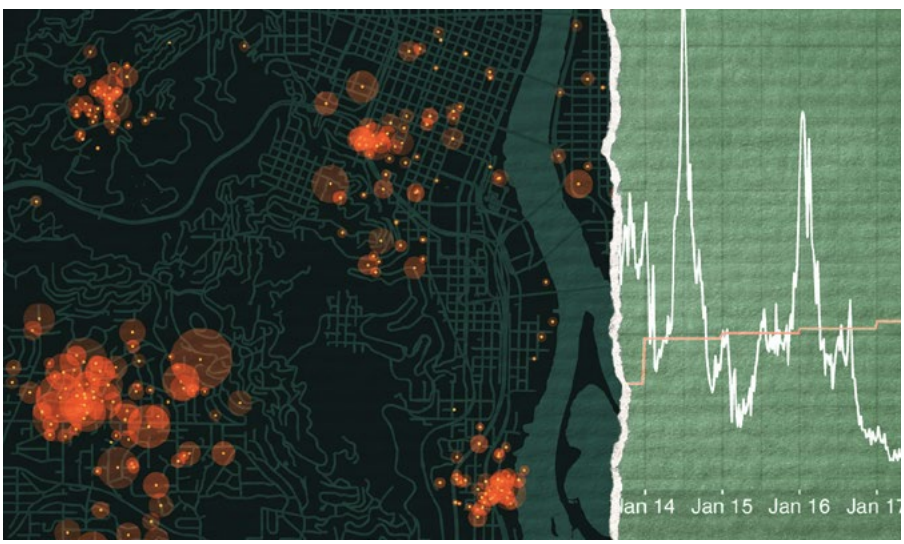


Photo credit: Astibuag / Shutterstock

Researcher
Xiuju Fu, IHPC

LEFT
Determining what 'normal' levels of dengue infection look like helped researchers quickly spot trends suggesting that an outbreak is imminent.

1. Chen, P., Fu, X., Ma, S., Xu, H.Y., Zhang, W., *et al*. Early dengue outbreak detection modeling based on dengue incidences in Singapore during 2012 to 2017. *Statistics in Medicine* **39**, 2101-2114 (2020).

URBAN SOLUTIONS

Mapping the pulse of Singapore's shared bikes

Quantifying where and when communities use dockless bike-share systems could help operators and urban planners design more biking-friendly cities.

While the first bicycle was invented over two hundred years ago, the two-wheeled mechanical wonder appears to be going through a renaissance. Compared to gas-guzzling cars, bikes are not only more environmentally friendly, but also offer benefits to human health. It's no wonder then, that in land-constrained countries like Singapore, bike-share systems have become popular as an alternative to vehicles and a complement to public transportation systems.

Bike-share systems can be either station-based or dockless. Compared to station-based systems, dockless systems lack defined origin and destination points, making their use unpredictable and difficult to study. This is one reason why most research on bike-share usage thus far has focused on station-based systems, said Jie Song, a Research Scientist at A*STAR's Institute of High Performance Computing (IHPC).

"The spatiotemporal analyses of shared bike trips is capable of identifying 'hotspot' regions where high numbers of bike trips occur, which period of the day such hotspots form, and the average length of these bike trips."

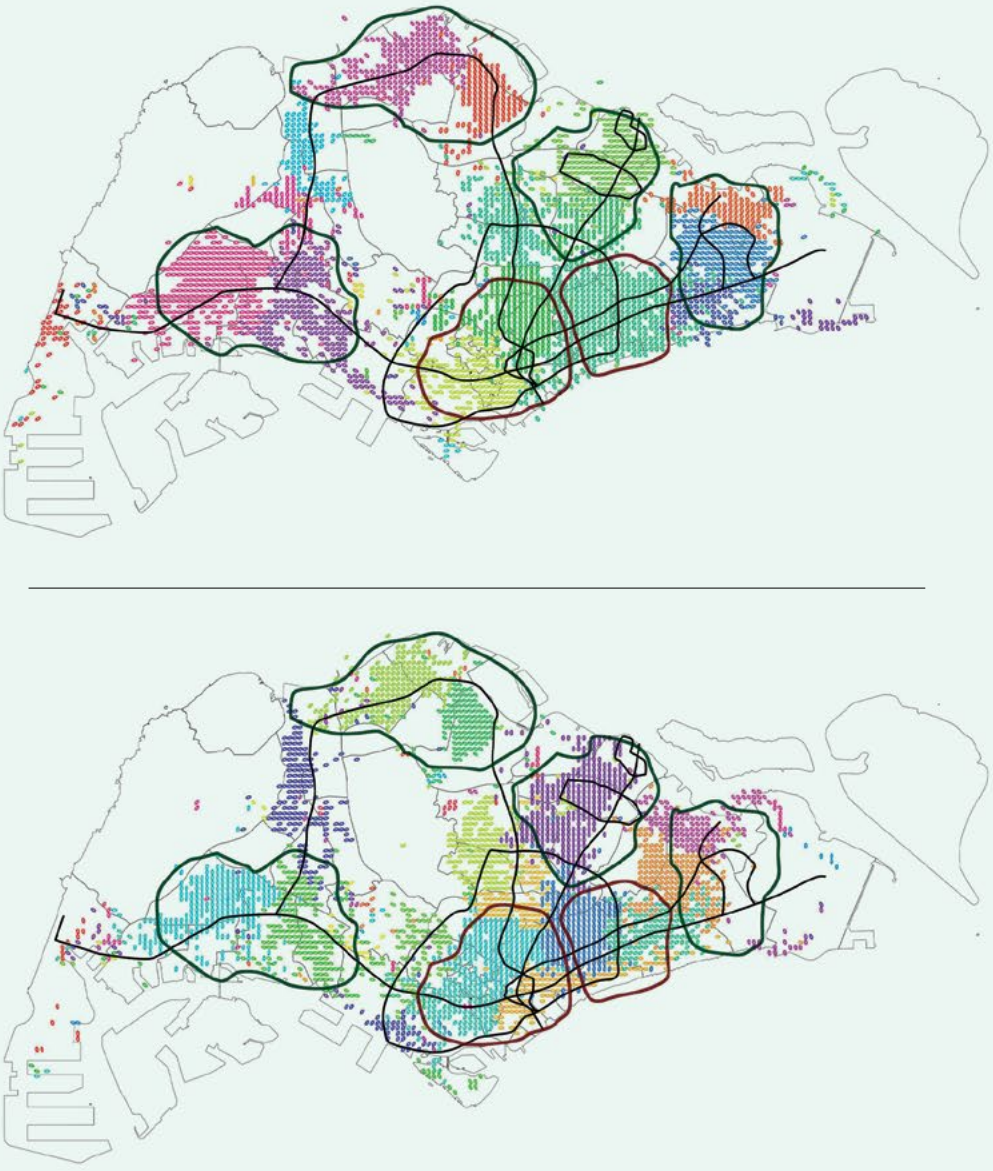
To fill this gap, Song and his colleagues developed an analytical approach to pinpoint when and where bike riders used dockless systems and applied it in Singapore. Their study forms part of a three-year ongoing project run by the Land Transport Authority of Singapore to simulate multiple modes of transport across the island using spatial autocorrelation and community modeling.

"The spatiotemporal analyses of shared-bike trips is capable of identifying 'hotspot' regions where high numbers of bike trips occur, which period of the day such hotspots form, and the average length of these bike trips," Song noted.

By taking GPS data from all active bike-share providers in Singapore across eight continuous days—including weekdays, weekends and a public holiday—the researchers identified six clear hotspots around subway line interchanges: four in residential heartland towns like Yishun and Jurong East, and two downtown. This suggests that local riders use bikes to address the first-and-last mile problem, otherwise known as the initial and final leg of a trip to and from public transport hubs.

Photo credit: Hathaibunn / Shutterstock

Weekday shared bike usage patterns in the morning between 6-9am (above) and in the evening between 5-7pm (below)



ABOVE
GPS data has revealed 'hotspots' where shared bicycles tend to be used, typically close to public transport hubs.

They also found larger "communities" on weekdays than weekends, indicating that Singaporeans may not simply use shared bikes for the first-and-last-mile problem; rather, end-to-end trips may be more common than expected. However, the researchers note that these interpretations are based on limited data and require validation.

Beyond Singapore, the team's analytical approach can also be applied to systems elsewhere. "Given a dockless bike-share dataset in other major cities, the analyst can easily apply the proposed approach to generate a series of insights about the spatiotemporal characteristics of bike-share usage," Song said.

Moving forward, their data-informed approach can be used to advise bike-share operators on the ideal location for bike-share facilities as well as urban planners on designing cycling-friendly towns, suggested Song and his co-authors. ★

Researcher
Jie Song, IHPC

1. Song, J., Zhang, L., Qin, Z., Ramli, M.A. A spatiotemporal dynamic analyses approach for dockless bike-share system. *Computers, Environment and Urban Systems* **85**, 101566 (2021).

MACHINE LEARNING

Helping robots feel their way around

A deep learning technique developed by A*STAR researchers uses WiFi data to help robots find their way around.

One of the things that humans do effortlessly but is unexpectedly challenging for robots is navigating new environments. While exploring a new area, we use visual cues to build up a mental map of the location—and our position within it. Similar camera-based systems are available to help robots 'see,' but they fall short in certain contexts, like when sensors do not have a clear line of sight or when backgrounds are blank and featureless.

Nonetheless, robots have other senses that are unavailable to humans and can be used to map out the environment. Taking advantage of the fact that WiFi is ubiquitous in most indoor spaces, a team led by Le Zhang of A*STAR's Institute for Infocomm Research (I²R) designed a novel non-visual system that helps robots orient themselves in new environments.

First, a mobile device is used to survey a location where WiFi access points have been installed beforehand. At specified reference spots, the device saves the unique WiFi received signal strength (RSS) from each access point, which is recorded in a map database. Afterward, when a robot or another device sends RSS details from anywhere within the surveyed space, information from the database could be used to estimate its exact location.

"Our model, called DeepFuzzy, is proposed to inherit the merits of decision trees and deep neural networks within an end-to-end trainable architecture."

What the team needed from here was a technique that could accurately turn RSS information into location coordinates. The algorithms used for these calculations are called fingerprinting-based algorithms; named after the fact that virtual 'fingerprints' are taken in an area that serves as *a priori* knowledge for robot localization or navigation.

"Our model, called DeepFuzzy, is proposed to inherit the merits of decision trees and deep neural networks within an end-to-end trainable architecture," Zhang said.

In DeepFuzzy, high-level features are first extracted from a sample by a deep network, after which they are routed into decision trees that use fuzzy logic to make predictions. These 'fuzzy trees' are better suited to dealing with ambiguous information and give more generalizable results. In performance comparisons against other models, deep learning techniques generally outperformed their counterparts, but DeepFuzzy gave the most accurate estimates of them all.

Zhang said DeepFuzzy can be used in tasks ranging from visual surveillance to image super-resolution. He and his team plan to take what they learned from this project to produce better deep learning techniques with useful applications. "We are always interested in developing effective and efficient deep learning techniques for real-life problems," he said. ★

Researcher
Le Zhang,
I²R

LEFT
DeepFuzzy is helping robots make use of WiFi for indoor navigation.

1. Zhang, L., Chen, Z., Cui, W., Li, B., Chen, C., *et al.* WiFi-based indoor robot positioning using deep fuzzy forests. *IEEE Internet of Things Journal* **7** (11), 10773–10781 (2020).

Photo credit: hellotechnology / Shutterstock

BRAIN-COMPUTER INTERFACES

Making fake brain waves more realistic

A new generative adversarial network-based framework generates artificial brain wave data that improves classification for better brain-computer interface performance.

From devices that help stroke victims regain function of their limbs to novelty cat ears you move with your mind, the promise and wonder of brain-computer interface (BCI) technology are quickly becoming a reality. Despite the rapid progress, however, the performance of BCI technology continues to be limited by the large amounts of high-quality brain wave data needed to train classification algorithms, which decode the real-world data into a format that computers can use.

One issue is that tasks employed to collect brain wave data—typically measured using electroencephalography (EEG)—are often unrealistic. "Many BCI experiments rely on controlled conditions in which subjects are instructed to fully focus on the main task," said Kai Keng Ang, a Senior Scientist at A*STAR's Institute for Infocomm Research (I²R). "However, this is different from what normally happens in real-life situations where various internal and external factors can make it difficult to stay focused on the task."

EEG data also vary from subject to subject and session to session, making it impractical to measure enough high-quality data from human subjects and difficult to generate artificial data using conventional models, Ang added.

In a new study, Ang collaborated with corresponding author Cuntai Guan of Nanyang Technological University to address these issues, designing a new framework to generate artificial EEG data that can be used to augment real training data for classification. Based on a type of neural network called deep convolutional generative adversarial network (DCGAN), the framework is trained on EEG data measured from subjects performing a task to detect movement intention, either while being completely focused (to simulate controlled conditions) or distracted (to resemble real-life scenarios).

In addition to real training data, the DCGAN-based framework also learns from subject-specific variables, which enables subject-specific artificial EEG data to be generated. "This will significantly reduce the calibration time when tailoring a BCI system to a new user," Ang explained.

The researchers, including study first author Fatemeh Fahimi, who was previously a postdoctoral researcher at I²R, also generated artificial EEG data using two benchmark methods for comparison. Compared to real EEG data alone, artificially augmented EEG data was able to produce more accurate classification results, especially under the real-life, distracted scenario.

"The improvement in accuracy suggests that with effective artificial EEG data generation, we can achieve high performance without undergoing a long calibration session to obtain more EEG data," Ang concluded. ★

Researcher
Kai Keng Ang, I²R

ABOVE
Artificially generated brain wave data is helping to make brain-computer interfaces more accurate.

1. Fahimi, F., Dosen, S., Ang, K.K., Mrachacz-Kersting, N., Guan, C. Generative adversarial networks-based data augmentation for brain-computer interface. *IEEE Transactions on Neural Networks and Learning Systems* 1-13 (2020).

Photo credit: local_doctor / Shutterstock

ROBOTICS

Teaching robots by example

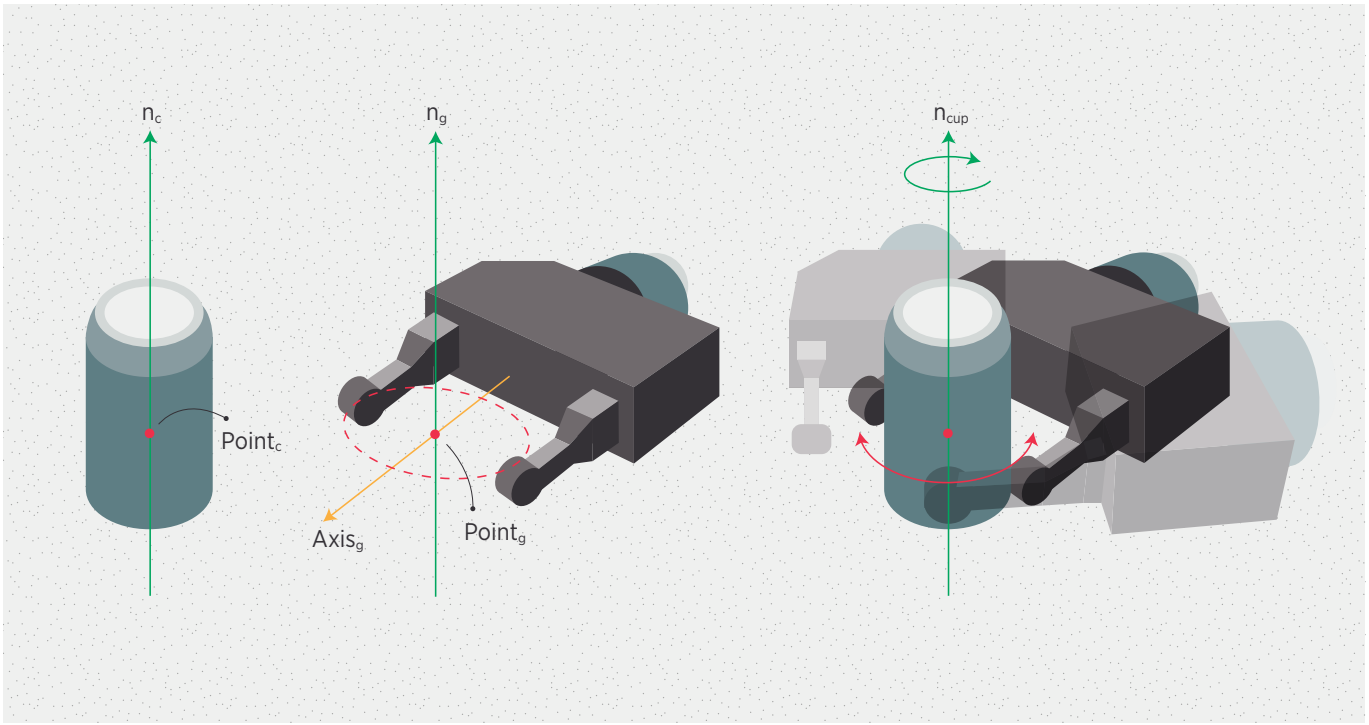
By breaking complex actions into their basic components, researchers have developed a versatile framework that enables robots to learn from human demonstrators.

Young children mimic everything they see and hear around them—sometimes to comic effect. While learning from observed behaviors comes naturally to children, it's a different story for robots. For a robot to learn to perform a task, one effective way is to define the geometric null space—the set of poses needed for the skill—and its constraints. Together, these form a mathematical representation of the skill that can be performed by any robot in any environment.

Take the simple example of grasping a bottle, said Yan Wu, Assistant Head of the Robotics and Autonomous Systems Department at A*STAR's Institute for Infocomm Research (I²R). "The hand pose is constrained to be at a certain distance and orientation with respect to the bottle. The geometric null space of this task is therefore a sort of cylinder with a radius and height depending on the dimensions of the grasped object," he said.

Current approaches rely on expert, handcrafted constraints, which are inefficient and laborious to create.

Photo credit: LightField Studios / Shutterstock



Reducing a task--such as grasping a cup--to a set of geometric constraints can help robots learn to perform actions by observing human demonstrators.

"But intuitively, if we segment it into pick, move and place skills, then the null spaces are apparent."

Instead, Wu and his collaborators Caixia Cai from I²R, Ying Siu Liang from A*STAR's Institute for High Performance Computing (IHPC) and Nikhil Somani from A*STAR's Advanced Remanufacturing and Technology Centre (ARTC) used human demonstrations. From these demonstrations, they developed a framework to teach robots the geometric null space and its constraints for six basic skills: grasp, place, move, pull, mix and pour.

While skills like grasping a cup are in themselves discrete actions, Wu and his team found that others had to be broken down into basic components. "For example when moving an object, demonstrating the entire pick and place action did not result in a usable geometric null space," Wu said. "But intuitively, if we segment it into pick, move and place skills, then the null spaces are apparent."

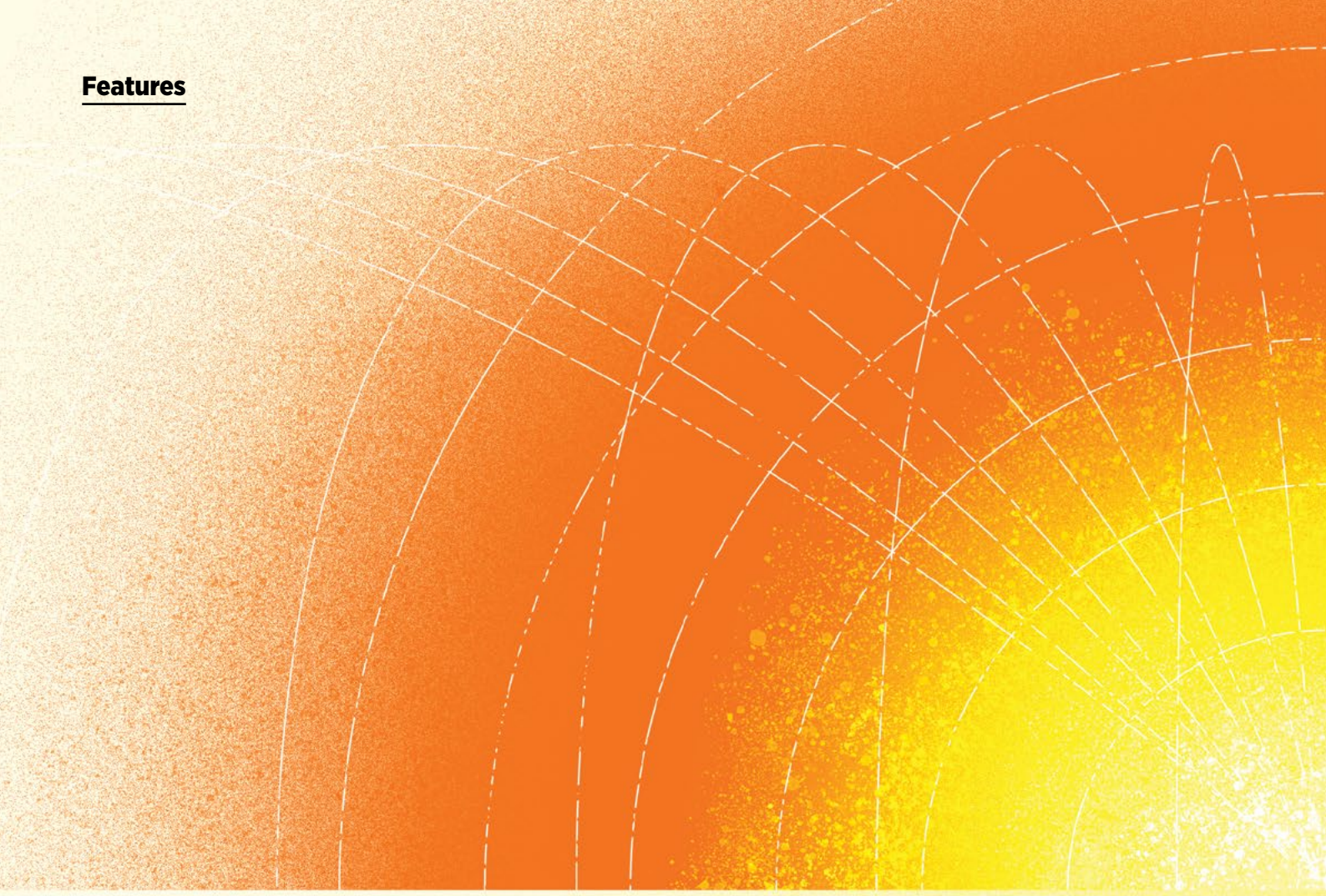
After identifying the basic skills that needed to be taught, the researchers collected position and orientation information from recorded human demonstrations, obtained a set of data points representative of the geometric null space for each skill, and estimated their parameters. The geometric constraints could then be inferred from the null space.

The researchers proved the effectiveness of their framework by successfully executing the six basic skills using a simple industrial robot and the open-source iCub humanoid robot. The same framework can be adapted to allow other types of robots to learn even basic skills that were not tested in the study—like twisting a lid—by simply tweaking the parameters, said Wu.

The researchers now plan to adapt their framework to learn more complex skills and incorporate deep learning methods throughout their pipeline. ★

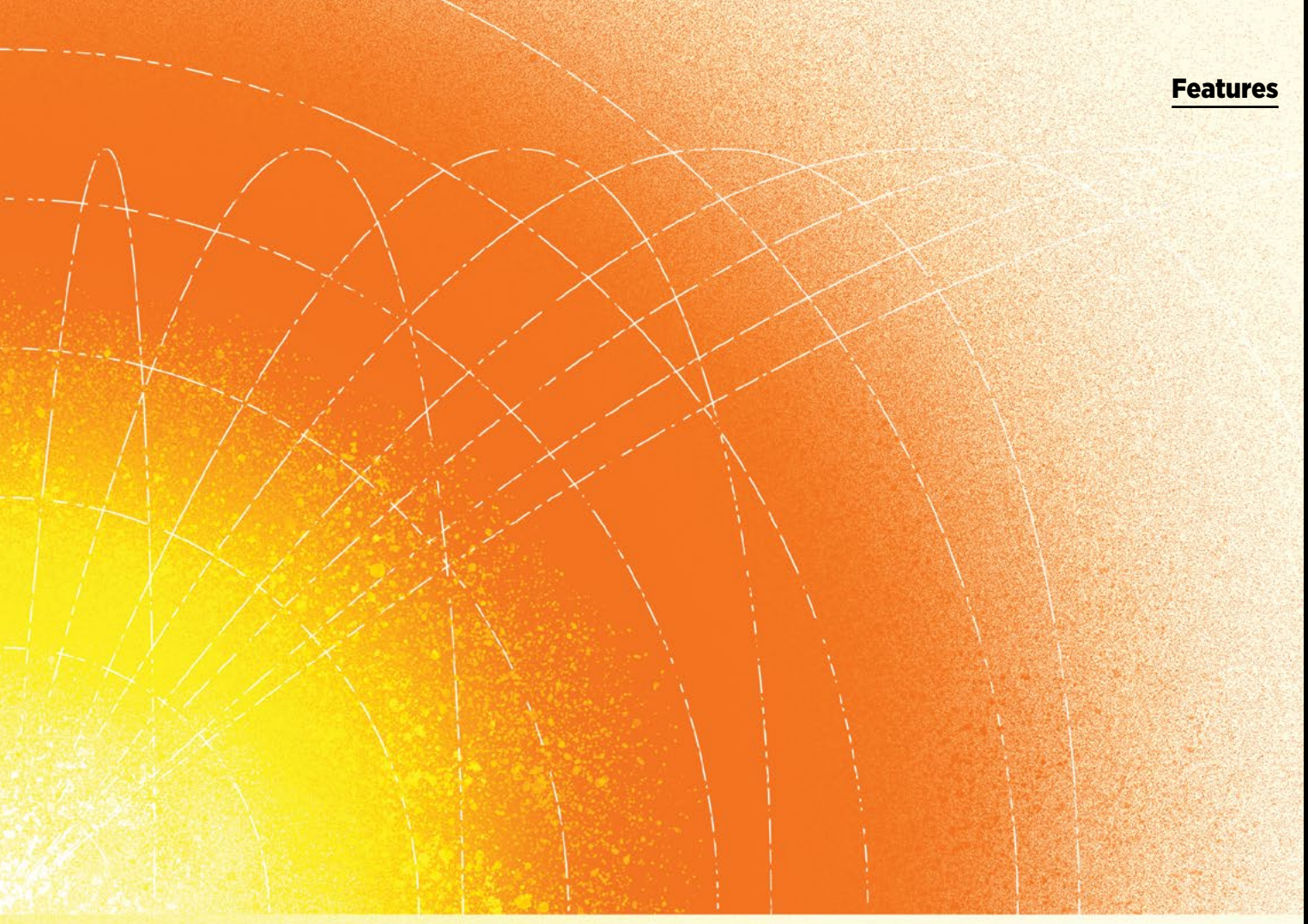
Researcher
Yan Wu, I²R

1. Cai, C., Liang, Y.S., Somani, N., Wu, Y. Inferring the geometric nullspace of robotic skills from human demonstrations. *2020 IEEE International Conference on Robotics and Automation (ICRA)* 7668–7675 (2020).



FUELING THE FUTURE

Nuclear fusion could provide Singapore—and the rest of the world—with a safe and clean source of energy, says A*STAR National Science Scholar Valerian Hall-Chen.



In 2015, history was made when the world's leaders met in Paris to discuss climate goals and how each country can help the world reach them. Together, the 197 participating countries agreed to reduce emissions in an attempt to limit this century's global temperature increase to just 1.5°C, beyond which climate change is expected to unleash catastrophic effects.

To achieve this ambitious goal, many countries including Singapore have turned to renewable energy sources like wind and solar. However, such sources of energy come with challenges as well—they can be expensive, harm wildlife, require large amounts of space and are dependent on the wind and the sun. To truly make a difference and reduce carbon emissions substantially, the world needs a clean and efficient source of energy.

According to A*STAR scholar Valerian Hall-Chen, the ability to harness nuclear fusion as an alternative source of power is the key to a sustainable future for Singapore and the rest of the world. Nuclear fusion works by heating light elements like isotopes of hydrogen, until they collide with enough energy to form heavier elements. With the right elements, this process creates a lot of energy without the use of fossil fuels or generating nuclear waste—a much feared risk when using older nuclear fission technology.

Despite initially working on photonics and plasmonics, Hall-Chen—currently a doctoral candidate at the University of Oxford and the Culham Centre for Fusion Energy, leveraged his background in theoretical physics to instead investigate methods to measure and interpret information from fusion plasmas. With efficient and effective techniques, Hall-Chen hopes to give researchers the tools to understand and eventually provide sustainable fusion power.

Committed to improving the lives of his fellow countrymen, Hall-Chen shares his hopes for Singapore's future in fusion power and how he intends to help the nation get there.

Q: WHEN DID YOU KNOW YOU WANTED TO BE A SCIENTIST AND WHY DID YOU CHOOSE TO APPLY FOR THE A*STAR NATIONAL SCIENCE SCHOLARSHIP?

In hindsight, I have always known that I wanted to be a scientist. I began pursuing this path seriously in secondary two, after chancing upon a popular science book on relativity in my school's library. I was left with far more questions than answers when I glimpsed the richness of physics and the natural world. It was also around this time that I learned of the A*STAR National Science Scholarship (NSS), but getting it seemed like a distant dream.

I had my first research attachment with A*STAR when I was in junior college. The joy the research work brought me reaffirmed my goal of becoming a scientist. For many of my peers, the NSS was a mark of prestige and a way to study at top overseas universities that one might not otherwise be able to afford. I acknowledge these reasons, and they have definitely rung true with me. However, for me, the NSS offered even more than that. The NSS has not only given me immense professional development, but also personal growth and independence.

Q: YOU WORKED ON PHOTONICS AND PLASMONICS BEFORE FOCUSING ON NUCLEAR FUSION FOR YOUR PHD. WHAT WERE THE FACTORS THAT INFLUENCED YOUR CURRENT RESEARCH FOCUS?

I find photonics and plasmonics to be interesting and useful fields. That being said, I noticed that there were many talented A*STAR scholars already in these fields or about to enter these fields. What is the value of yet another A*STAR scholar doing their PhD on these topics?

To put it bluntly, A*STAR scholarships are expensive, and I did not think I would be worth the taxpayers' money if I stayed in the same research area, especially since there were already so many more qualified scholars and staff already in it.

Ultimately, our role as scholars is to improve the lives of Singaporeans and to bring Singaporean innovations to the world stage. To this end, we must bring knowledge, and more importantly, vision, back to Singapore—particularly to areas in which Singapore does not already have them. Nuclear fusion is one such key area. I have sought to understand the developments in fusion, such that when the technology is sufficiently mature, there will be no time wasted in alerting Singapore to the opportunities it presents.

Q: WHAT IS A KEY PROBLEM YOU HOPE TO SOLVE WITH YOUR RESEARCH?

Energy—we do not have a source of energy that is clean, carbon-free, safe, reliable, able to provide the baseload, and not subject to the constraints of geography. As far as we know, nuclear fusion is the only candidate for such an energy source.

Q: WHAT IS THE MOST EXCITING PROJECT YOU ARE WORKING ON RIGHT NOW?

I am developing the theoretical tools required to understand measurements of plasma turbulence in fusion experiments. The core of such experiments regularly reaches temperatures several times hotter than the center of the sun. One cannot simply stick a probe in; indirect methods like launching microwaves into the plasma and measuring what comes out have to be used. Unfortunately, it is difficult to make sense of the data, so a thorough understanding of the physical phenomena involved is required. Our work will enable the fusion community to better understand the physics of plasma turbulence and design ways to reduce heat transport out of the core. I find this exciting because it bridges experiment, simulation, and theory—paving the way for advancements that each alone would not have been able to achieve.

Q: HOW SOON WILL WE SEE A WORKING FUSION REACTOR? WILL SINGAPORE ONE DAY BE POWERED BY FUSION ENERGY?

The most credible—at least in my opinion—fusion start-up is Commonwealth Fusion, which was spun off from MIT. Commonwealth Fusion has set a timeline of 10 years or so to a working fusion reactor. More conservatively, the EU-Japan collaboration on the DEMOnstration power plant (DEMO) is set to start operations in approximately 30 years. China's project, the China Fusion Engineering Test Reactor (CFETR), is expected to have timescales between the two. That being said, the time to a reactor is likely better measured in dollars, not years.

Large projects like this are often delayed—there are bound to be unexpected complexities. Such uncertainties are not surprising, especially in a new and rapidly evolving field like fusion energy. But after roughly half a century of development, I believe that commercial fusion energy is finally on the horizon. It is my vision that not only will Singapore be powered by fusion energy, but that Singapore will power the world with fusion energy. Capable of sustainably providing the grid's base load usage without the space requirements of solar power or the long-lived radioactive waste of today's fission power plants, fusion power will be an integral part of addressing climate change.

Q: HOW DO YOU SEE YOUR RESEARCH EVOLVING WHEN YOU COMPLETE YOUR PHD AND RETURN TO A*STAR?

As it is, I see that the time is not yet right for Singapore to start investing heavily in fusion research. Fortunately, I am unafraid of changing fields and my rigorous training in using theoretical physics to shed light on experimental data will serve me well in A*STAR. I have not yet decided for certain what I am going to do, but I have spoken with various researchers in A*STAR and there are many avenues I can take to contribute to Singapore in the next five years. I also intend to keep a metaphorical finger in the fusion pie, to prepare for the day when A*STAR will start a Fusion Energy Institute. ★

"It is my vision that not only will Singapore be powered by fusion energy, but that Singapore will power the world with fusion energy."

Valerian Hall-Chen
A*STAR National Science Scholar

MACHINE LEARNING

Teaching machines transferable skills

By giving algorithms the ability to generalize, researchers are expanding the range of problems that can be tackled with artificial intelligence.

With the ability to analyze large amounts of data and discern patterns that humans can't, artificial intelligence (AI) has taken the world by storm. While AI algorithms have advanced fields like computer vision and natural language processing, certain tasks remain the preserve of human experts, who can seamlessly transfer domain knowledge in one field to similar—though not identical—situations.

Can computers transfer learn in the same way that humans do? This question is at the heart of a subfield in machine learning aptly named transfer learning. In particular, an emerging technique known as transfer Bayesian optimization (TBO) can cut the time needed to solve computationally expensive decision problems from many days to a matter of hours, by building on the solution to a related problem instead of starting from scratch.

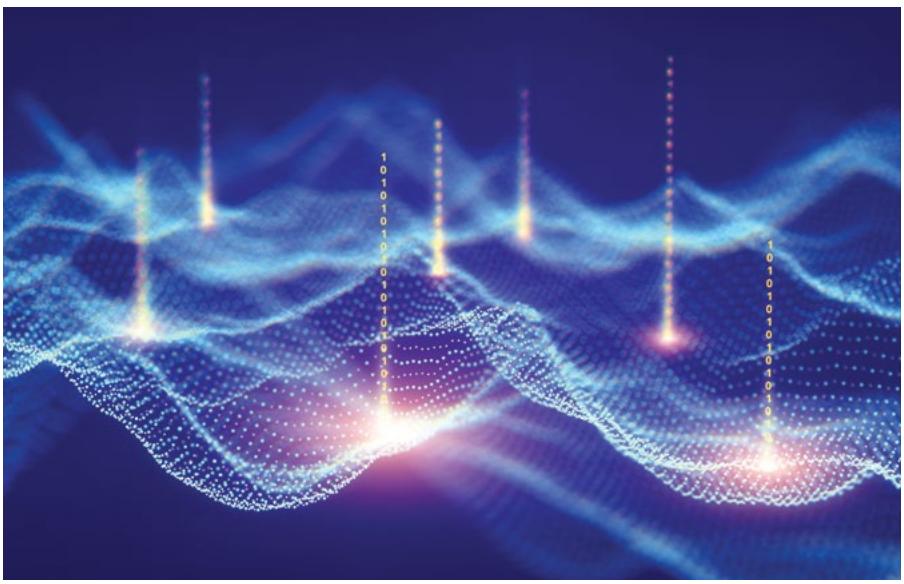
"TBO algorithms have exhibited human-like ability to leverage experiential priors to rapidly solve new problems," explained Abhishek Gupta, a Scientist at A*STAR's Singapore Institute of Manufacturing Technology (SIMTech). "However, the applicability of existing TBO algorithms was limited to scenarios where new problems bore exactly the same input features as the experiential priors."

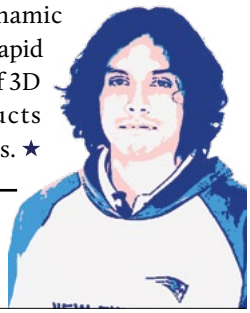
To extend the benefits of TBO algorithms to a wider range of decision problems, Gupta and his collaborators Yew-Soon Ong, A*STAR's Chief Artificial Intelligence Scientist, and Nanyang Technological University graduate student Alan Tan sought to generalize the algorithm to work across problems with dissimilar features. They used a feature transformation function in the form of a multi-layer neural network, which allowed features from previous examples to be automatically aligned to new problems without the need for human intervention.

The team tested their method on several case studies. In one, the algorithm was able to adapt knowledge from a turbojet engine to accurately learn the behavior of a turbofan engine with different features. Similarly, an algorithm trained to optimize a composite manufacturing process with four control parameters was able to quickly extend its results to a different process with six parameters.

"Our generalized TBO algorithm can learn from diverse experiential priors, thus boosting the productivity of optimization and decision-making processes," Gupta said. "In addition, TBO algorithms could offer a path towards greater AI democratization, mimicking an expert to build optimized AI models—such as deep neural networks—with limited computational resources."

Follow-up studies aim to increase the scalability and flexibility of the method to improve its ability to solve real-world problems, from the geometric design of aerodynamic structures to the rapid personalization of 3D printable products such as face masks. ★



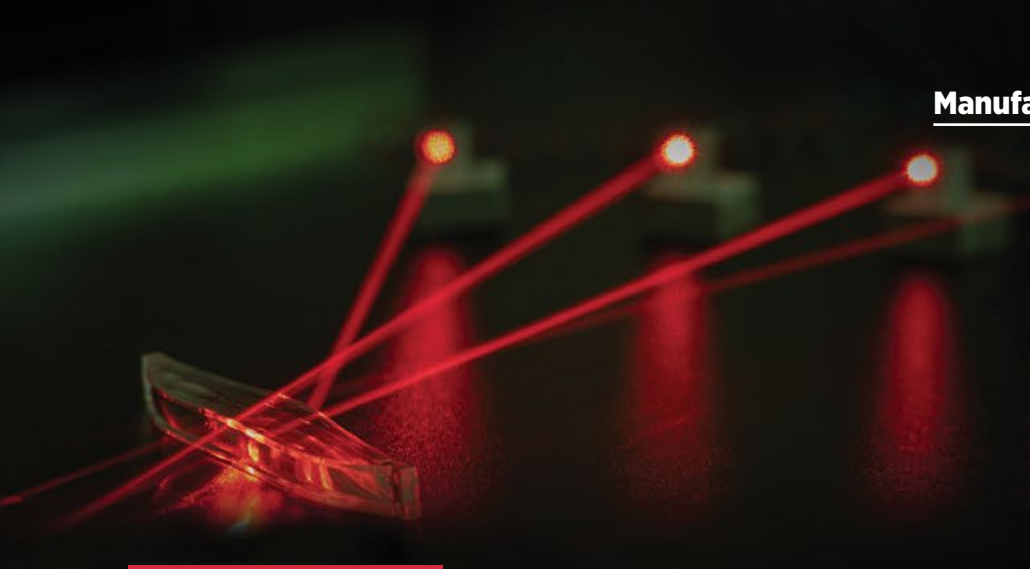


Researcher
Abishek Gupta, SIMTech

LEFT
Feature transformation is helping machines transfer learning in one context to other contexts, thereby democratizing artificial intelligence.

1. Tan, A.W.M, Gupta, A., Ong, Y.S. Generalizing transfer Bayesian optimization to source-target heterogeneity. *IEEE Transactions on Automation Science and Engineering*. (2020).

Photo credit: nobeastsofierce / Shutterstock



NANOPHOTONICS

Limiting light loss

Compact nanochain waveguides that can efficiently transmit infrared light and even slow light down to a fraction of its usual speed could take photonics mainstream.

From trendy gadgets to large industrial robots, minuscule electronic microchips power the many smart machines we use in our daily lives. Replacing electrons with light to create photonic circuits, however, could bring these chips to new heights.

Not only can high-speed, high-bandwidth photonic circuits lead to faster and more efficient optical computers, but they can also be used for other purposes like biosensing and quantum computing. Miniaturizing photonic circuits like traditional chips means shrinking a basic photonic component: waveguides, also known as the 'wires' of photonic circuitry that transmit light from one location to the next.

To replace the current bulky waveguides, researchers at A*STAR led by study first author Lu Ding, a Scientist at the Institute of Materials Research and Engineering (IMRE), designed a subwavelength nanochain waveguide capable of transmitting infrared light with low losses at a smaller footprint. Notably, while their nanochains are less bulky than conventional waveguides, they can still be manufactured using standard silicon fabrication techniques.

"A nanochain waveguide consists of a chain of identical silicon nanoparticles specially engineered to resonate at a particular frequency of light and guide the light," explained Thomas Ang, a Scientist at A*STAR's Institute of High Performance Computing (IHPC) who performed simulations for this study.

Despite their promise, the previous proof-of-concept nanochain waveguide tested by the group were inefficient light transmitters at wavelengths 960 nm and 720 nm, with propagation losses between 5.5 and 34 dB/mm due to large material losses, respectively. "To avoid material absorption in silicon, we redesigned the nanochains to operate using near infrared light at a wavelength of about 1550 nm, which silicon is more efficient at transmitting," Lu and Ang added.

When the team tested the new nanochain waveguide, they found that the propagation loss had been reduced to between 0.1 and 0.3 dB/mm—far lower than their previous prototypes, and comparable to conventional single mode silicon waveguides. The team also introduced raindrop-shaped optical couplers that shunt light into narrower nanoparticles, further reducing the losses associated with inserting or extracting light from the nanochain waveguide.

Moreover, the nanochain waveguides showed a 'slow light' effect—where light pulses pass through the waveguide at only three percent of light's speed in vacuum. "The slow light in a nanochain waveguide leads to strong light-matter interactions, which has potential applications for better light control in optical communications, quantum photonics or biosensing platforms," said Lu.

Having demonstrated the capabilities of silicon nanoparticle chains as efficient waveguides, the team hopes to expand their functionalities moving forward. Further modifying the structure and arrangement of the nanoparticles could enable the waveguides to control the polarization, propagation direction and other optical features of light signals, making them versatile and powerful components for integrated photonics. ★

Researcher
Lu Ding, IMRE (left)
Thomas Ang, IHPC (right)

BACKGROUND
Waveguides made of silicon nanoparticles are paving the way for a new generation of photonic circuits.

1. Ding, L., Yu, Y.F., Morits, D., Yu, M., Ang, T.Y.L., *et al*. Low loss waveguiding and slow light modes in coupled subwavelength silicon Mie resonators. *Nanoscale* **12**, 21713–21718. (2020).

Photo credit: luchschenF / Shutterstock

3D PRINTING

Finding flaws fast

A machine learning method that finds defects or dimensional deviation on 3D-printed surfaces 'on-the-fly' is paving the way for smart, fully automated systems.

As the new kid on the block, 3D printing is challenging traditional 'subtractive' manufacturing methods which remove, rather than add, material to produce an object. Although versatile and effective for building complex structures, 3D printing methods can sometimes lack robustness and repeatability, especially when used to make large metal parts.

Various aspects of the 3D printing process—like thermal stress, localized overheating and inconsistent machine speed—make it prone to producing surface defects or dimensional deviation, which, if not detected early, can be detrimental to the quality of the final piece.

"Vision-based surface topography measurement methods use cameras and computer vision algorithms to digitally reconstruct the 3D surface," explained Xiling Yao, a Research Scientist at A*STAR's Singapore Institute of Manufacturing Technology (SIMTech). "The surface reconstruction process is usually computationally heavy and limited in terms of precision and resolution."

Now, a research team including Yao, led by Guijun Bi, a Senior Scientist and Manager of the Joining & Machining Group at SIMTech, has developed a method that can detect defects 'on-the-fly' thanks to in-house designed software that simultaneously executes multiple point cloud processing functions and integrates the data into machine learning models.

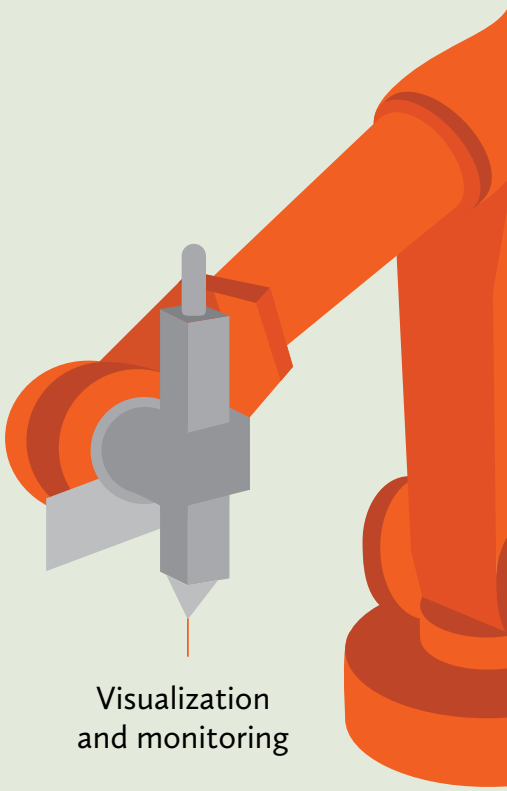
In the new system, a rapid and accurate sensor scans the surface of a printed object to obtain height data. Wasting no time, the multimodal software automatically processes this 3D spatial data into simple statistics for use by machine learning models, which then isolate and identify potential surface defects.

The researchers developed their rapid defect identification method for a robot-based laser-aided additive manufacturing (LAAM) system, a unique metal 3D printing process. They trained classifier algorithms to identify three main classes of surface non-conformance—bulge, dent and wavy defects—as well as defect-free surfaces using 73 LAAM-printed samples of varying size and shape. Compared to a state-of-the-art surface monitoring technique, the new method rapidly detected and classified defects even when there were multiple defect regions present in the same layer.

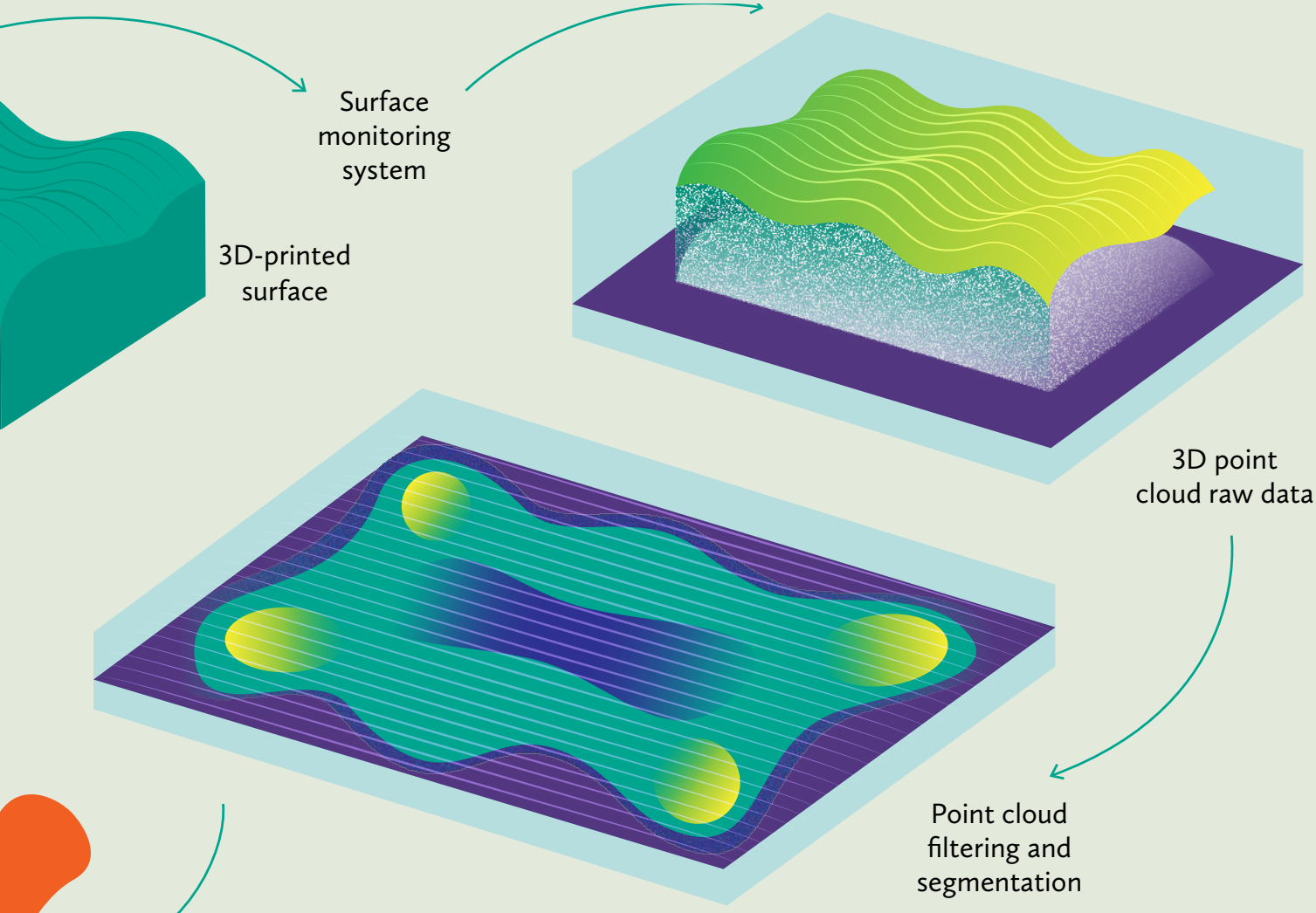
Despite being developed for LAAM, Yao said the technology can be used to monitor the surface conditions of other printed materials. Simply by developing a new set of training data, the framework can also easily be adapted for other processes.

"Our ultimate goal is to make LAAM technology smart and fully automatic, with self-learning and self-rectification capability, hence enhancing the printing quality and maximizing its productivity with minimal human intervention," Yao noted. "The next step, which we are working on now, is to develop a way for the machine to perform intelligent decision making and adaptive process planning and execution after errors are detected." ★

"Our ultimate goal is to make laser-aided additive manufacturing technology smart and fully automatic, with self-learning and self-rectification capability."



Visualization and monitoring



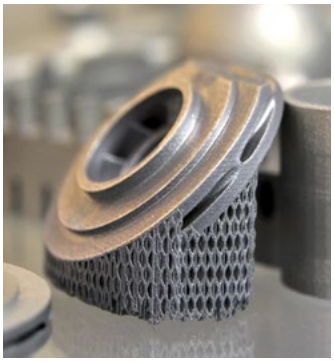
Researcher
Xiling Yao, SIMTech

ABOVE
In-situ design software that can execute multiple point cloud processing functions and integrate data into machine learning models.

1. Chen, L., Yao, X., Xu, P., Moon, S.K., Bi, G. Rapid surface defect identification for additive manufacturing with in-situ point cloud processing and machine learning. *Virtual and Physical Prototyping* **16** (1), 50–67 (2021).

NEXT ISSUE

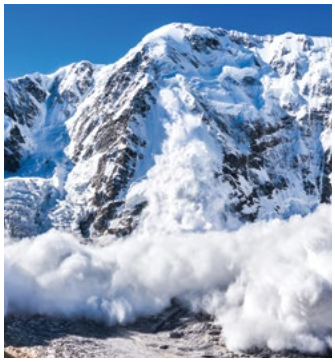
Here's a sneak peek of the material covered in the next issue of *A*STAR Research*



3D PRINTING

MICROWAVING 3D-PRINTED MAGNESIUM MAKES IT STRONGER

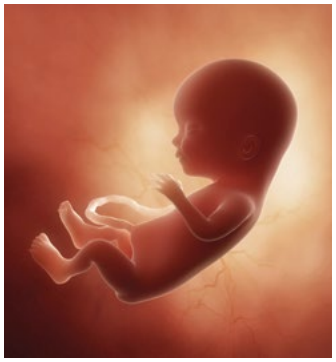
Using microwaves instead of traditional sintering methods makes processing 3D-printed magnesium three times faster and consumes nine times less energy.



PHOTONICS

BRINGING AN AVALANCHE OF APPLICATIONS INTO THE LIGHT

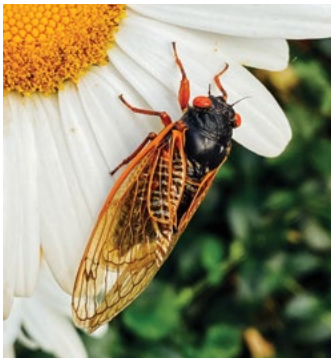
Silicon nitride has helped researchers develop an avalanche photodetector that can work with visible light, paving the way for next-generation photonics.



IMMUNOLOGY

MEMORIES OF OUR FIRST MICROBIAL ENCOUNTERS

Live bacterial strains found in fetal organs help lay the cornerstones of early and lifelong immunity.



MATERIALS SCIENCE

CICADA WINGS AND ANTIMICROBIAL WARFARE

Inspired by nanostructures on insect wings, A*STAR scientists created iron 'needle' arrays and particles for self-sanitizing surfaces.

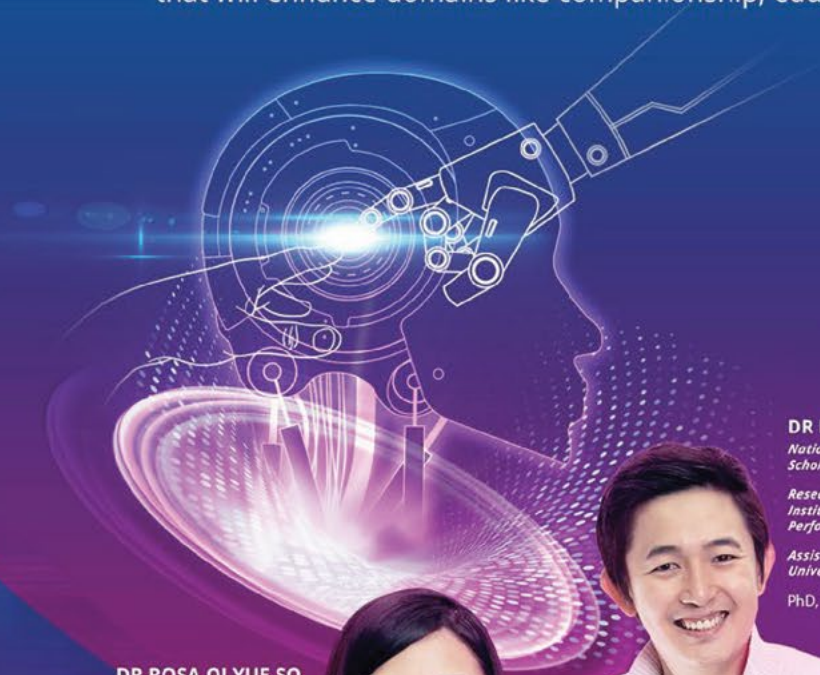
Agency for Science, Technology and Research
SINGAPORE

RE-ENVISION THE FUTURE

Artificial Intelligence (AI) continues to improve our lives. At A*STAR, we advance science and develop exciting cutting-edge technologies.

Join the frontlines of the scientific revolution and turn your dreams into reality. A*STAR scholars draw inspiration from the workings of the human brain to develop AI initiatives that will enhance domains like companionship, education and healthcare.

THE A*STAR SCHOLARSHIP IS KEY IN CRAFTING YOUR FUTURE!



DR CHESTON TAN
National Science Scholarship Recipient

Deputy Executive Director, AI, Analytics and Informatics Horizontal Technology Programme Office

Senior Scientist, Institute for Infocomm Research

PhD, Massachusetts Institute of Technology

DR DESMOND ONG
National Science Scholarship Recipient

Research Scientist, Institute of High Performance Computing

Assistant Professor, National University of Singapore

PhD, Stanford University

DR ROSA QI YUE SO
National Science Scholarship Recipient

Division Head of Healthcare and MedTech Division, Institute for Infocomm Research

PhD, Duke University

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