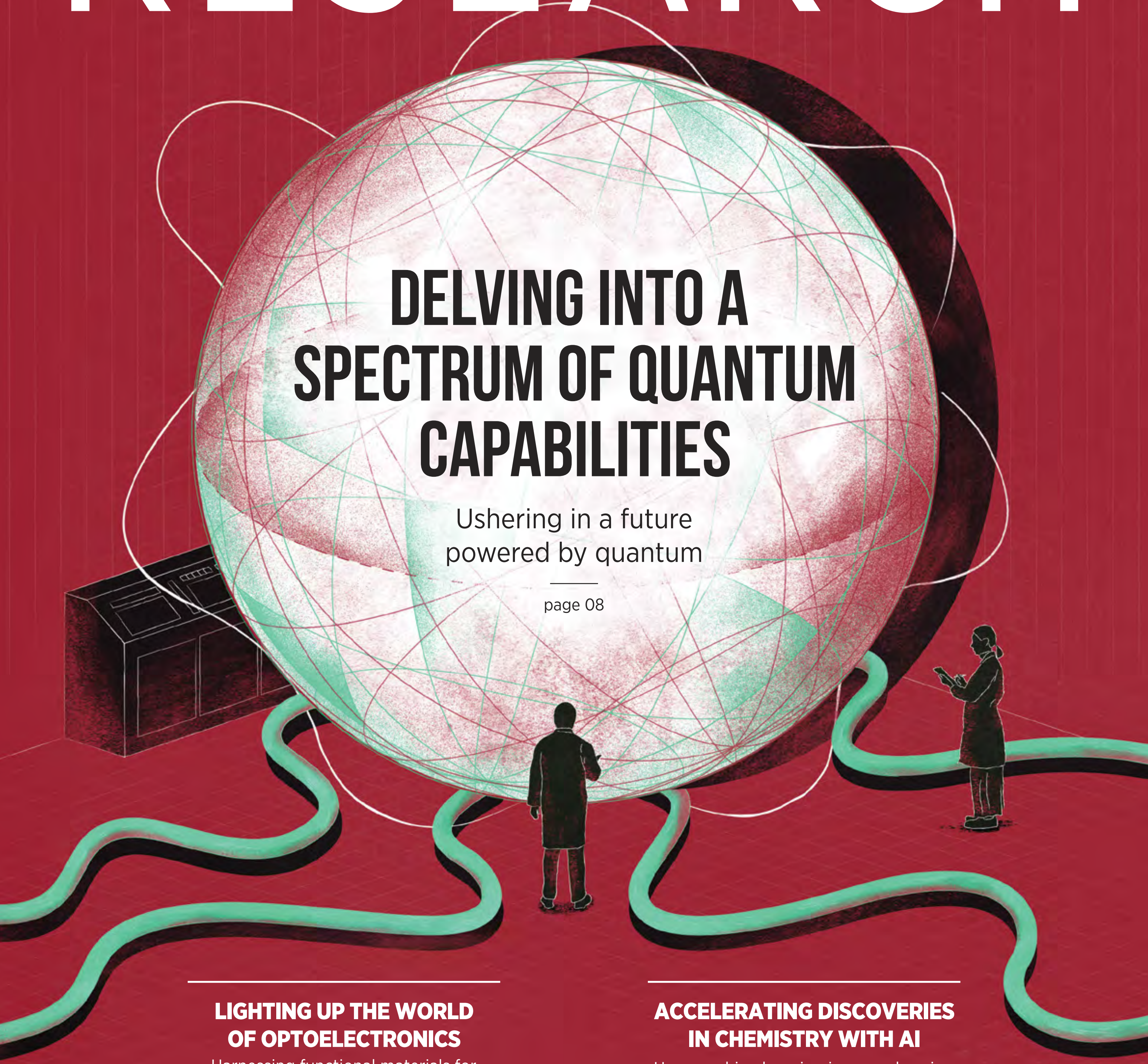
Issue 25 | September – October 2021

A*STAR RESEARCH



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A*STAR RESEARCH

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

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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.

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- Bioinformatics Institute (BII)
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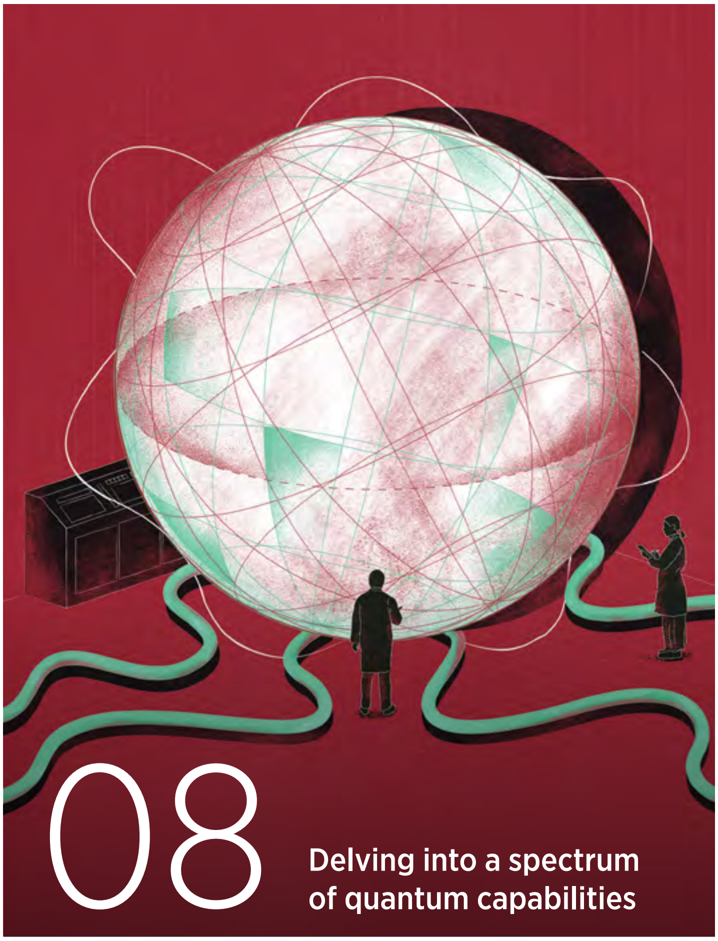

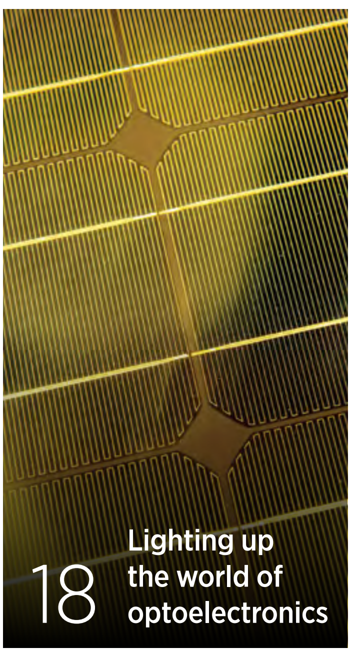

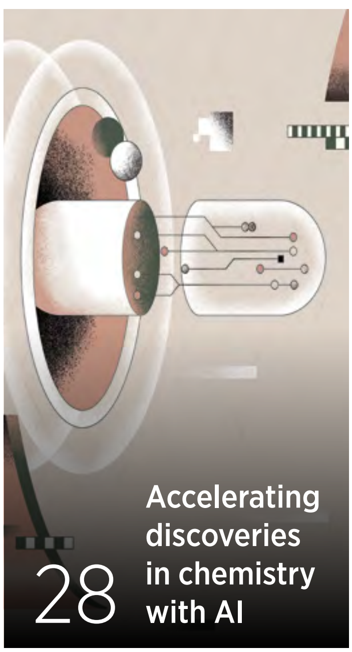

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EDITORIAL NOTES

With new technologies bursting onto the scene, finding ways for the general public to benefit from these innovations is key. Take the case of artificial intelligence (AI). Once a frontier technology, AI is now ubiquitous as scientists have learned how to create more powerful algorithms that make everything from laboratory research to our daily activities more efficient.

Today, another emerging technology—quantum—is nearing its tipping point. For quantum to someday become as widespread as AI, an in-depth understanding of its properties is needed to create useful applications. Across the board, A*STAR scientists are making important advances in the control of quantum phenomena. From materials design to biomedical sensing, explore fundamental and application-inspired quantum research efforts in our cover story on p. 08.

Meanwhile, Le Yang and colleagues at the Institute of Materials Research and Engineering (IMRE) are on a mission to build better devices that combine both light and electrical energy. To develop high-performance wearable sensors and solar cells, Yang's team aims to enhance the stability and efficiency of these materials in 'Lighting up the world of optoelectronics (p. 18).'

Building capabilities goes well beyond A*STAR's labs, with budding scientists like National Science Scholar Jacqueline Tan pursuing postdoctoral studies at the Massachusetts Institute of Technology (MIT). In 'Accelerating discoveries in chemistry with AI (p. 28),' discover how Tan is harnessing the computing power of AI to accelerate greener chemical reactions, in hopes of creating a better world for future generations.

Apart from exciting applications in manufacturing and sustainability, A*STAR scientists have also made headway in regenerating muscle tissue with 'Unboxing the muscle repair toolkit (p. 15)' and creating antimicrobial nanostructures with 'Self-cleaning surfaces inspired by insects (p. 22).'

To stay updated on the exciting research taking place at A*STAR, visit our website at **research.a-star.edu.sg** and follow us on Twitter at **@astar_research** and LinkedIn at **A*STAR Research**. Do remember to subscribe to our Telegram channel as well at **A*STAR Research**!

On the cover
As we approach a quantum revolution, A*STAR scientists are harnessing the technology behind super sensors, advanced algorithms and more.

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

IMMUNOLOGY

Not all antibodies are created equal

Some neutralizing antibodies against SARS-CoV-2 may heighten lung tissue damage from COVID-19, an A*STAR study finds.

As part of the body's frontline defense against microbial enemies, neutralizing antibodies have been thrust in the spotlight for their potential to treat COVID-19. Now, research led by Cheng-I Wang, a Principal Investigator at A*STAR's Singapore Immunology Network (SIgN), has uncovered a darker side to some of these immune heroes.

Previously, Wang and colleagues demonstrated that most neutralizing antibodies block the SARS-CoV-2 spike protein's receptor-binding domain (RBD) from interacting with ACE2 receptors on host cells. However, the influence of these antibodies on the generation of syncytia—cell fusions associated with severe COVID-19 symptoms—has remained a gray area.

"The formation of syncytia has been linked to lung tissue damage observed in severe COVID-19 cases when cell-cell fusion occurs inside the patient's airways," explained Wang, adding that clearer guidelines for selecting neutralizing antibodies as treatments for COVID-19 patients with severe lung damage are urgently needed.

In a study published in *Cell*, Wang teamed up with collaborators to analyze a panel of six antibodies for factors that may impact SARS-CoV-2 neutralization potency and syncytia formation. These include properties such as how strongly the antibody binds to its target and where the antibody binds to on the spike protein.

As predicted, all six antibodies blocked interactions between the SARS-CoV-2 spike protein and ACE2 receptors, but unexpectedly displayed a range of responses to syncytia formation.

"The formation of syncytia has been linked to lung tissue damage observed in severe COVID-19 cases when cell-cell fusion occurs inside the patient's airways."

An antibody called 3D11, for instance, displayed the strongest binding to the spike protein's RBD—which by current standards, would suggest potential therapeutic value. Interestingly, however, 3D11 attaches to the

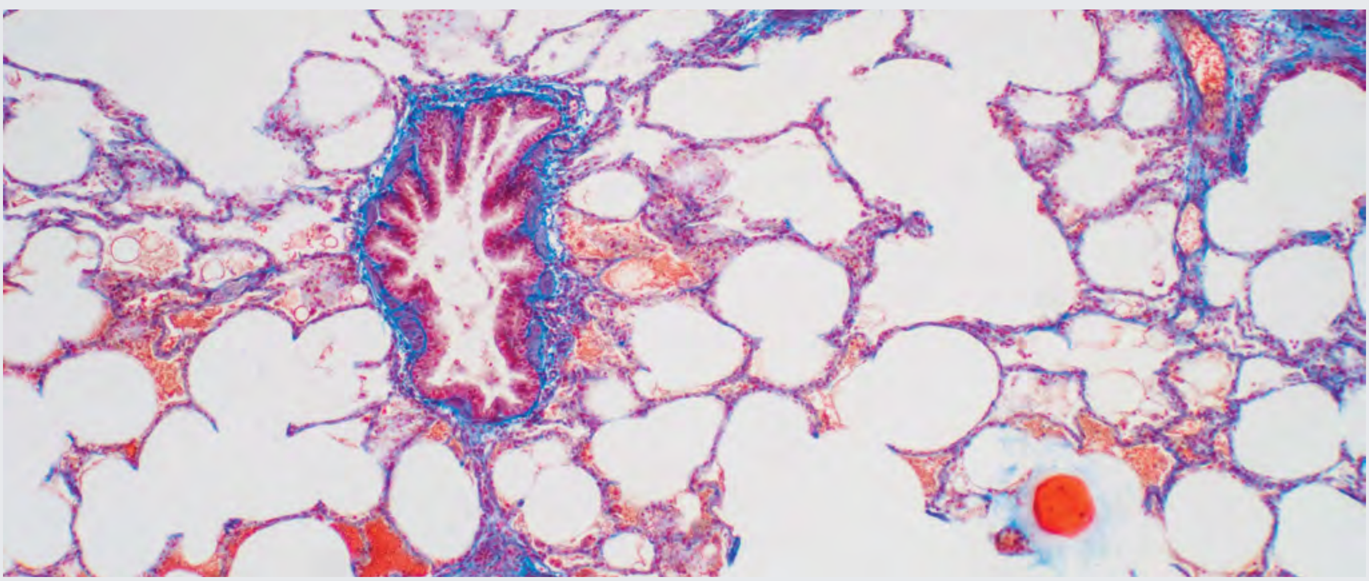
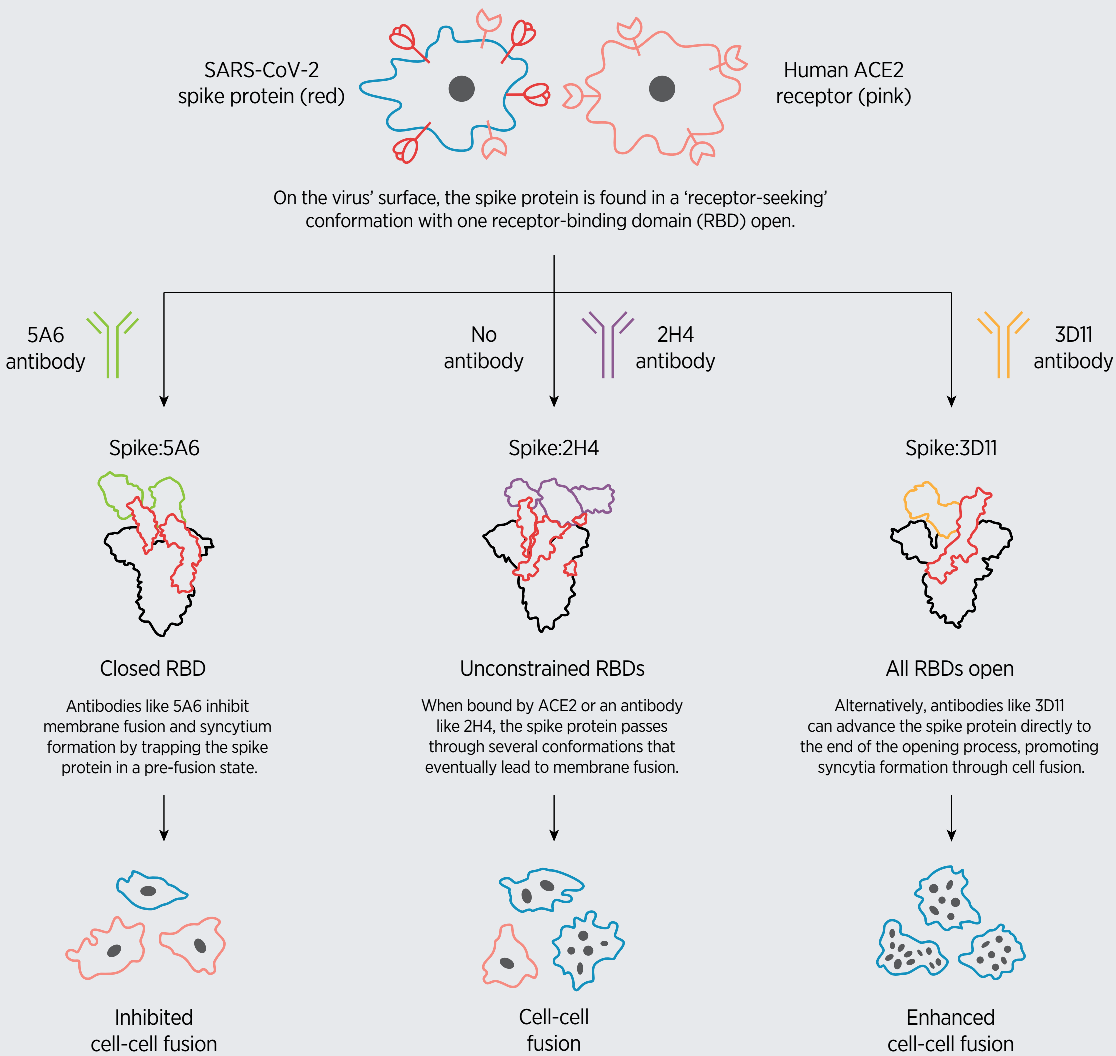


Photo credit: Choksawatdikorn / Shutterstock



How SARS-CoV-2 neutralizing antibodies modulate the formation of syncytia.

RBD at a site that locks the spike protein in an 'open' pre-binding position, effectively accelerating interactions between the spike protein and ACE2, as well as promoting syncytia formation.

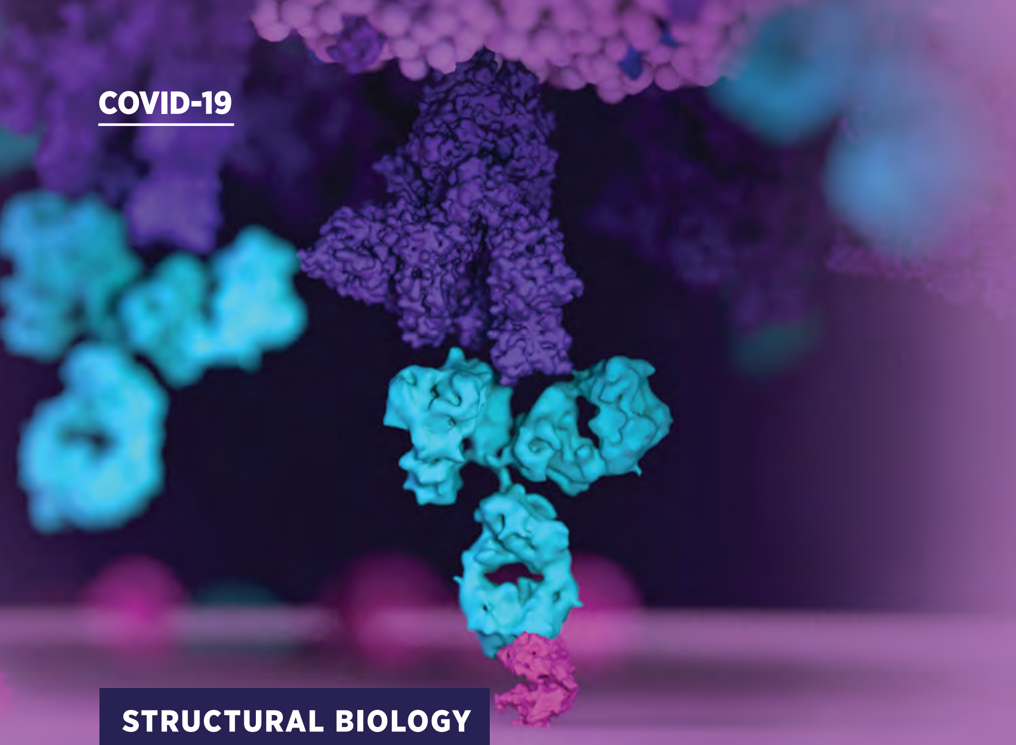
Conversely, the 5A6 antibody bound less strongly to the spike protein, but was far more potent, latching onto the RBD and strongly inhibiting syncytia development. A closer look at the structural dynamics of 5A6 binding to the RBD revealed that the antibody recognized an exposed loop near the tip of the RBD, trapping the spike protein in its 'closed' position, thereby hindering ACE2 binding.

"These findings suggest that the potential effectiveness of a neutralizing antibody is influenced by several possibly countervailing factors, highlighting a complex basis for viral neutralization potency," Wang concluded. The team is now looking for industry collaborators to commercialize the 5A6 antibody as a viable candidate for COVID-19 treatment. ★

Researcher
Cheng-I Wang, SIgN

LEFT
Ironically, certain neutralizing antibodies may accelerate interactions between the SARS-CoV-2 spike protein and human ACE2 receptor as well as promote the formation of cell fusions associated with severe COVID-19 symptoms in the lung.

1. Asarnow, D., Wang, B., Lee, W.H., Hu, Y., Huang, C.W., *et al*. Structural insight into SARS-CoV-2 neutralizing antibodies and modulation of syncytia. *Cell* **184**, 3192–3204.e16 (2021).



STRUCTURAL BIOLOGY

Secrets of the spike protein, revealed

Tracking how SARS-CoV-2 interacts with host cell receptors during infections may give us new ideas for COVID-19 drug targets.

Since the emergence of COVID-19 nearly two years ago, researchers have raced to discover the coronavirus' modus operandi. Similar to a choreographed dance, SARS-CoV-2 infections involve an intricate series of dynamic molecular events beginning with the virus binding to a host receptor called ACE2, aided by club-shaped 'spikes' that dot the pathogen's surface.

Until now, scientists have only captured snapshots of this molecular dance, such as the cleaving of the spike (S) protein into subunits called S1 and S2 after latching onto ACE2. To help design better clinical strategies for resisting COVID-19, experts are now seeking a more comprehensive, high-resolution view of how these early events mobilize viral entry into cells.

Bridging this knowledge gap is Peter Bond, a Senior Principal Investigator at A*STAR's Bioinformatics Institute (BII). Along with his collaborators, Bond leveraged a powerful combination of two complementary technologies to map structural changes occurring in the S protein during initial infection.

"Amide hydrogen/deuterium exchange mass spectrometry enabled characterization of the changing dynamics of the S protein upon ACE2 binding, while our molecular dynamics simulations elucidated corresponding atomic-level motions," explained Bond.

The team's study yielded some unexpected findings. For example, the attachment of ACE2 to the S protein triggered distinct structural changes in two 'hotspots' located some distance away from the binding site. They also observed more intense activity in the regions around the S1/S2 cleavage site, which Bond suggests could be a priming step before enzymes enter to proteolyze the S protein at remaining uncleaved sites, including the nearby S2 site. Meanwhile, the coronavirus' stalk region—a structure that anchors the spike to the viral envelope—stiffened and stabilized after ACE2 binding.

Collectively, these observations indicate that interactions between the S protein and ACE2 aren't simply a means for the coronavirus to recognize which cells to infect. These interactions may also have a far-reaching influence on other downstream processes critical to viral entry and infection, including the cleavage and fusion of the S protein.

"In addition, the proteolytic sites in the S protein are both known to be parts to which some neutralizing antibodies bind," commented Bond, making these hotspots prime targets for potential therapeutic development.

The newly-identified infection dynamics may also help expand our understanding of SARS-CoV-2 variants, with Bond noting that the Alpha and Delta variants harbor mutations near the S1/S2 cleavage site. In follow-up studies, the researchers plan to use a similar approach to uncover how mutations in these hotspots make some variants more of a threat. ★

Researcher
Peter Bond,
BII

ABOVE
Interactions between the spike protein and ACE2 don't just allow the virus to recognize which cells to infect. Instead, these interactions may also affect other processes crucial to viral entry and infection.

1. Raghuvamsi, P.V., Tulsian, N.K., Samsudin, F., Qian, X., Purushotorman, K., *et al*. SARS-CoV-2 S protein: ACE2 interaction reveals novel allosteric targets. *eLife* **10**, e63646 (2021).

Photo credit: Design_Cells / Shutterstock

IMMUNOLOGY

SARS-CoV-2 antibodies hold out against variants

Data shows that antibodies produced as part of the COVID-19 immune response can neutralize a more transmissible variant of SARS-CoV-2.

Take a look at certain parts of the world and it's almost like the pandemic never happened. From crowded venues to unmasked people out and about, widespread vaccination rollouts have allowed certain countries to enjoy some semblance of normalcy—at least, for a brief period. Though the light at the end of the tunnel seems tantalizingly close, the accumulation of mutations in SARS-CoV-2 has given rise to more contagious variants capable of causing severe infection, spurring governments to reinstate public health measures.

Among these is the highly transmissible G614 variant which quickly became the dominant SARS-CoV-2 strain worldwide in May 2020. G614 gets its powers from a point mutation in the gene encoding the spike (S) protein, a projection on the virus' surface which enables it to infect host cells.

According to Lisa Ng, Executive Director of A*STAR's Biomedical Research Council (BMRC) and Infectious Diseases Labs (ID Labs), this mutation increases the likelihood that G614 will be able to evade antibodies against wildtype SARS-CoV-2, potentially rendering our collective advances in COVID-19 diagnostics, therapeutics and vaccines ineffective.

To address these concerns, Ng and a team of collaborators studied the immune responses of 57 COVID-19 patients from Singapore infected with either the original D614 isolate or the G614 variant. Using flow cytometry, they found that levels of initial IgM antibodies in all patients dipped over time, while the subsequent IgG antibody titers against SARS-CoV-2 remained elevated even months after infection.

Still, one question remained: could antibodies induced against D614 neutralize G614, and vice versa? To determine the answer, the researchers performed an antibody neutralization assay, incubating patient plasma samples with so-called pseudoviruses modified to express the S protein of the D614 and G614 strains. Accordingly, IgM and IgG antibodies from the convalescent patients of either strain neutralized both SARS-CoV-2 variants similarly.

"Neutralizing antibodies elicited against the wildtype SARS-CoV-2 can neutralize the variant G614 strain to the same degree, thus suggesting that the G614 mutation will not hinder ongoing vaccination efforts," said Ng.

While this is good news, Ng cautioned that further studies are required to assess other variants of concern, such as the Delta variant, to ensure that vaccines and antibody-based therapeutics remain effective against the ever-changing coronavirus.

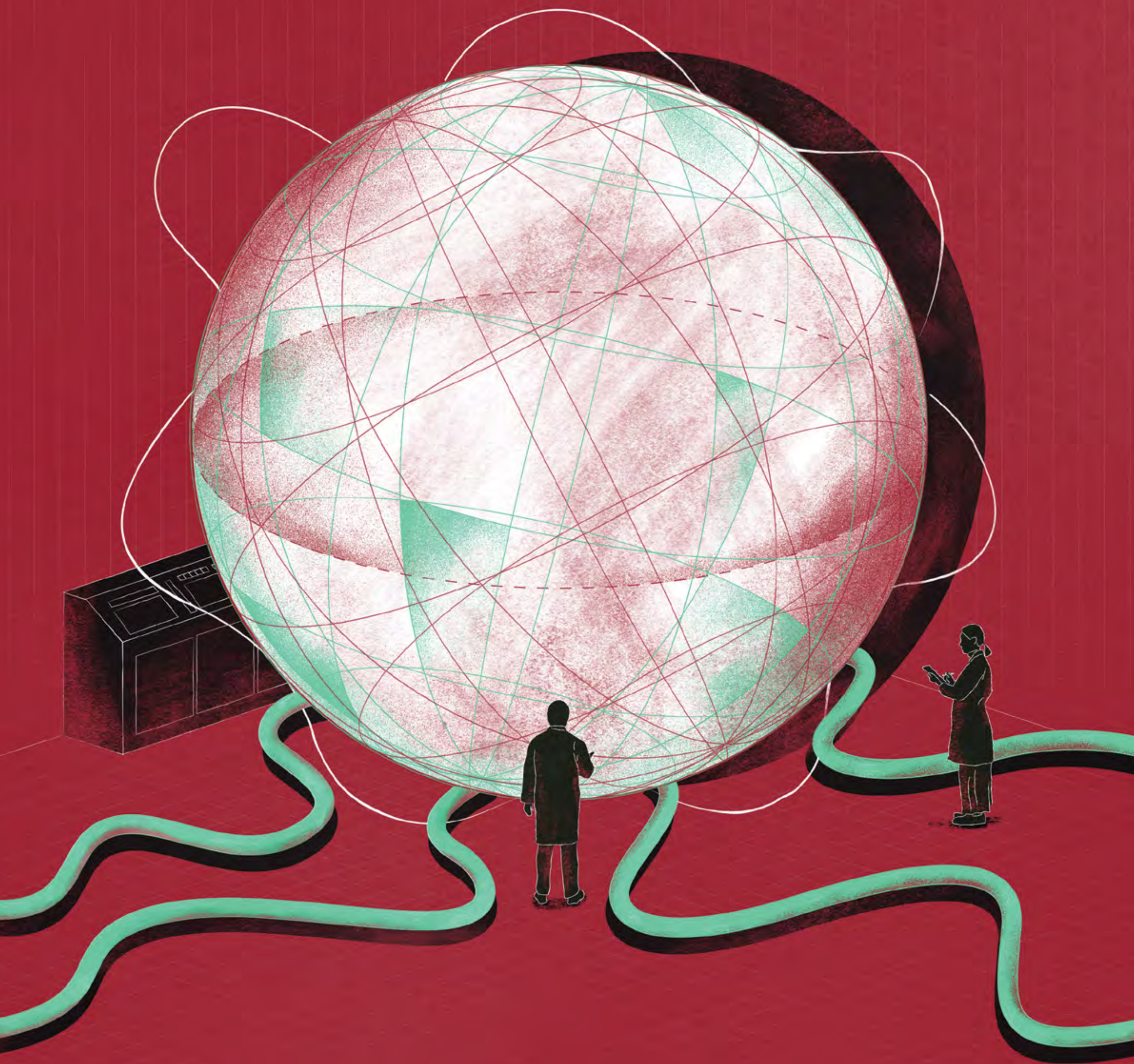
"SARS-CoV-2 is continuously mutating and evolving as part of its viral evasion mechanism," she added. "It is now critical to determine the extent of humoral protection that is being conferred upon vaccination against emerging and new variants." ★

Researcher
Lisa Ng,
ID Labs

ABOVE
Antibodies from convalescent patients infected with wildtype SARS-CoV-2 were capable of neutralizing the G614 variant and vice versa, suggesting that the G614 mutation will not hinder the ongoing vaccination rollout.

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).

Photo credit: Lightspring / Shutterstock



DELVING INTO A SPECTRUM OF QUANTUM CAPABILITIES

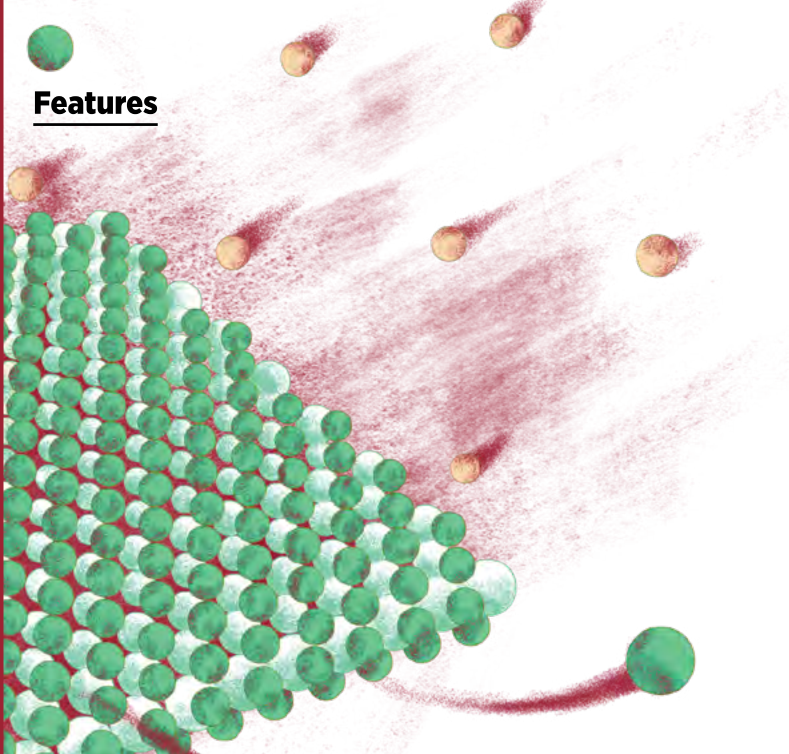
From advanced materials to atomic super sensors, A*STAR scientists are harnessing the power of quantum to the fullest, ushering in the next generation of trailblazing technologies.

In late 2019, Google researchers lit the quantum community abuzz. For the first time, they achieved an elusive milestone in the field: quantum supremacy. Up against the best of classical computing, the tech giant's Sycamore quantum computer finally leapfrogged the competition—carrying out a calculation that would have taken their classical counterparts 10,000 years to solve.

In another case of doing the impossible, researchers using Sycamore demonstrated a time crystal in early August this year. Sounding like something straight out of a Marvel movie, time crystals are veritable paradoxes—constantly changing yet stable, undergoing repeated cycles of change without burning energy. These milestones not only belie the excitement around quantum but also showcase the bizarre, law-defying ways of quantum phenomena.

High-speed computing is just one area where quantum systems are expected to outperform current systems. After all, units of quantum information called qubits can exist as multiple states simultaneously until they are measured, unlike traditional computer bits that only exist as zero or one. While these properties sound futuristic, the particles exhibiting these quantum effects are already all around us.

For example, charges that power electronic devices can exist in both spin up or spin down states when placed in a magnetic field. Meanwhile, photons or light particles are frequently entangled in optical networks and imaging applications. These linked units mirror each



other's properties, allowing measurements at a distance without ever directly observing the pair's opposite component.

As intriguing as these phenomena may be, bringing quantum from abstract theory and experimental observations to mainstream relevance poses another mountain to climb. The key to next-generation quantum technologies lies in inducing these quantum effects in a well-controlled and scalable way.

In the race to harness quantum properties for practical applications, A*STAR's researchers are part of a global community driving the quantum revolution across domains like telecommunications and bioimaging.

CRACKING THE QUANTUM CODE

While quantum computing promises supremacy over high-performance classical models, this advantage remains limited to the research and development stage. As full-scale quantum computers have yet to be realized, many opt for hybrid models combining quantum with classical algorithms. This allows developers to run simulations and explore the frontiers of quantum, executing algorithms on noisy intermediate-scale quantum (NISQ) devices—so called because they are still error-prone.

However, hybrid algorithms often demand a high number of measurements, driving up costs and slowing down performance. Meanwhile, current fixes to reduce these costs have yet to make a dent in solving larger problems that typically require adding more qubits as well as better fault tolerance. Given the limits of NISQ in correcting errors, these algorithms are often rendered unusable for commercially relevant applications.

To realize the quantum advantage, researchers from A*STAR's Institute of High Performance Computing (IHPC) like Dax Koh are devising novel techniques to scale up quantum algorithms and solve practical problems.

Supported by A*STAR's National Science Scholarship, Koh previously worked on an algorithm called the variational quantum eigensolver, alongside collaborators at Zapata Computing[1]. Like many other quantum models, this algorithm involves sampling and estimation, running through numerous possible outputs to find the best answer for a given problem.

The larger the problem, however, the longer the runtime needed to determine the solution—time that quantum systems may not be able to provide. Due to their fragility, a system can only maintain its quantum states for so long before collapsing, a phenomenon called quantum decoherence.

To speed up the algorithm, Koh's team developed a framework called the engineered likelihood function (ELF) that carries out statistical calculations known as Bayesian inference. During the inference phase, several possibilities are checked to determine the relationship between variables or to estimate the value of a certain parameter. By maximizing the information gained per run-through of this algorithm, ELF allowed the model to find the solution faster while reducing measurement costs.

"The ELF framework takes into account the depth and coherence of the quantum device implementing the quantum algorithm," Koh explained. Besides crucially running on NISQ devices, ELF is also adaptable, adjusting the algorithms' parameters when transitioning to more fault-tolerant machinery.

At IHPC, Koh continues to refine quantum algorithms to make them friendlier for NISQ devices, establishing in-depth insights into the power and limitations of quantum computers. For example, he and his team have studied how factors like qubit counts and noise affect the computational power of machine learning (ML) models, a subfield of artificial intelligence that emulates the human brain and makes predictions about new datasets based on training inputs.

With a keen understanding of quantum's limitations, scientists can devise innovative ways to overcome these barriers to create quantum-enhanced ML, further advancing the field.

Case in point: a quantum advantage could supercharge disciplines like materials design. As Koh optimizes quantum algorithms, his colleague Jun Ye—a Senior Scientist at IHPC—sees quantum-enhanced ML as a gateway to enhancing polymer innovation.

Given its potential to perform massive parallel sampling, quantum computing can accelerate materials design—predicting polymer properties and identifying tweaks to the structure and interactions of their subparts. Since electronic devices are made of numerous interacting particles, characterizing the quantum dynamics of these many-body systems is key to achieving desired properties like charge transport.

This vision draws from Ye's experience in designing semiconductors with enhanced electrical transport[2]. As an electron is in itself a quantum object, quantum mechanics govern properties like the movement of charge carriers from one molecule to another and coupling interactions between neighboring molecules.

While quantum dynamics has clear implications for manufacturing electronic devices, Ye explained that these fundamental laws are similarly applicable to quantum computing itself.

"Quantum computer operations and quantum circuit executions can be viewed as the time-evolution of a many-body quantum system composed of coupled qubits," he said. "One key area of research is to understand the role of various noises in affecting the dynamics of a quantum system."

"One key area of research is to understand the role of various noises in affecting the dynamics of a quantum system."

— Jun Ye, Senior Scientist at A*STAR's Institute of High Performance Computing (IHPC)

By determining how to mitigate the effects of noise, Ye seeks to improve error correction in these machines, overcoming a critical stumbling block for scalable quantum computing.

MATERIALIZING BREAKTHROUGHS IN QUANTUM DEVICES

In the computing arena, the significance of scalability is nothing new. From the first computers using vacuum tubes, classical technologies have advanced leaps and bounds by packing more power into tinier circuits on silicon chips. Behind these historic changes are breakthroughs in materials, spurring widespread adoption for real-world applications.

To catalyze a similar revolution in quantum devices, highly stable platforms are needed to support an increasing number of qubits while maintaining low error rates. After all, the uniquely high sensitivity of qubits to external changes makes them prone to errors. As these particles are susceptible to environmental conditions like heat, quantum computers generally need to be maintained and operated at sub-zero temperatures.

Facing this dilemma, the Quantum Materials and Devices group at A*STAR's Institute of Materials Research and Engineering (IMRE) is developing high-quality materials to build a scalable architecture for quantum devices.

Transition metal chalcogenides (TMDC), for example, are attracting interest as ultrathin semiconductors to support spin-based qubits. Carrying two different metal atoms in their crystal structure, these two-dimensional (2D) TMDCs have unique inversion asymmetry and time-reversal symmetry properties—resulting in the coupling of the spin and valley components of electrons[3].

"Spin-valley coupling provides a more stable type of quantum state which requires two keys to unlock, akin to two-factor authentication, via the 'spin-key' and 'valley-key,'" explained Johnson Goh, Principal Scientist and Head of the Quantum Technologies for Engineering Department at IMRE. This stability could make qubits more robust and potentially operable as quantum processor chips.

While faster qubit operation usually comes at the cost of faster decoherence, IMRE Scientist Aaron Lau explained that the unique spin-valley coupling in 2D semiconductors can protect against decoherence. By enabling both fast operations and long coherence lifetimes, such materials could already meet some of the major needs for scalable quantum devices.

Still, the viability of these semiconductors relies on their ability to withstand the cryogenic temperatures needed to preserve the fragile quantum states.

"Even if we can create the most exceptional quantum materials, without contacts that can work at extremely low temperatures, there will be no way to electrically probe and study their exotic properties," Lau said.

Typically, contact engineering approaches like physical vapor deposition tend to damage 2D materials. According to Lau, the process is akin to throwing darts.

Traveling from a source, metallic atoms of the contacts land on conventional bulk semiconductors where they may cause some surface damage with minimal impact on device performance. But in atomically thin 2D TMDCs, such surface defects can be catastrophic. It's the difference between throwing darts at a concrete wall (bulk semiconductors) versus tissue paper (2D TMDCs).

Goh, Lau and collaborators found that using indium alloys could limit the damage sustained by tungsten disulfide (WS_2) TMDCs at cryogenic temperatures[4]. By carefully depositing the indium alloy, the team reduced contact resistance in these materials, enabling more efficient charge transport.

But scientists also recognize that completely defect-free materials are practically impossible to manufacture over larger scales. "Instead of seeing this as a problem, we investigated whether different densities of defects called S-vacancies could provide an interesting range of electrical properties," said Goh, adding that S-vacancies are widely present in sulfur-based TMDCs.

S-vacancies, they found, hindered the mobility of negative charges, becoming more severe as defects accumulated[5]. However, S-vacancies did not significantly limit transport in hole-based TMDCs, injecting positive charges across the material. By showing that low-resistance contacts may be more promising for hole-based TMDCs, the study revealed valuable insights for developing electronic devices using 2D semiconductors.

Meanwhile, Goh, Lau and colleagues recently delved into a technique called chemical vapor deposition (CVD) that allows the scalable large-area synthesis of TMDCs. In an engineering feat, theirs was the first CVD device to show quantum confinement, where electrostatic fields spatially confine and alter the carriers in the material.

"Understanding low-temperature transport mechanisms is key to designing increasingly complex 2D semiconductor-based quantum devices," Lau said.

From basic research into TMDC properties to devising novel manufacturing methods, these efforts all contribute to a grand vision of mastering materials development for producing quantum devices at scale.

SUPER SENSORS ON COMPACT PLATFORMS

Besides manufacturing materials, translating fundamental knowledge into application-oriented research is a common vision across A*STAR, including in the fields of optics and sensing. For instance, light particles or photons can travel far and fast—making them ideal information carriers. By using photons as 'flying qubits,' as Jason Png, Director of the Electronics and Photonics Department at IHPC calls them, information transfer could be accelerated even further.

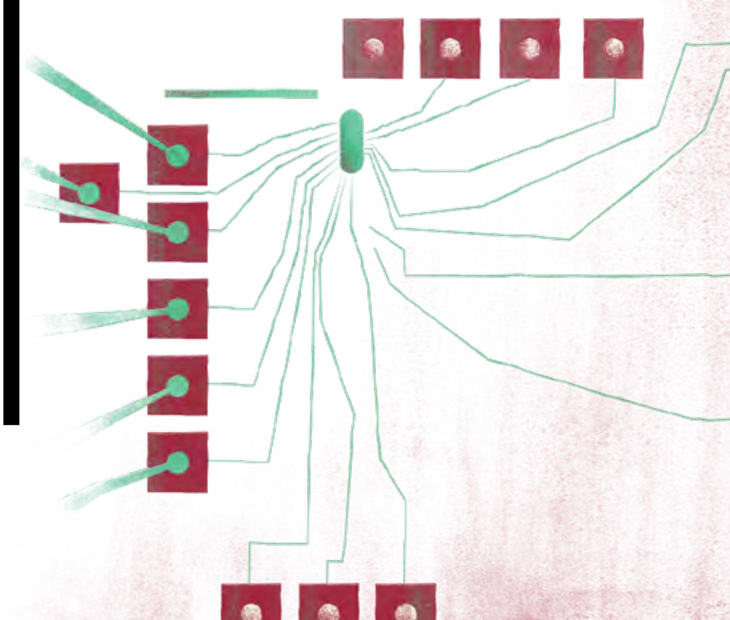
According to Png's IHPC colleague Lin Wu, photons can act as qubits even at room temperature, potentially paving the way for large-scale quantum computers. In particular, Wu's team studies cavity quantum electrodynamics, or the interaction between light confined in a reflective cavity and atoms or other particles under conditions where the quantum nature of photons is significant.

Through these cavities, the atoms or other particles can be manipulated in a scalable manner. One area where their work has since been applied is quantum sensing. Together with Png, Wu and her colleagues are exploring energized particles called plasmons in detecting antigens as markers of infection—giving biosensing a quantum twist[6,7]. By confining electromagnetic fields into tiny spatial regions, plasmonic nanocavities enable strong light-matter interactions even at the single-molecule level, measuring weak analyte signals that otherwise might have been mistaken as background noise.

"Conventional plasmonic sensors detect biological molecules in the weak coupling regime, with the detected molecules appearing as a shift in the spectral peak," said Wu. "In our quantum plasmonic immunoassay, detection appears as a split in the spectral peak due to the strong coupling between the quantum-emitter label attached to the target molecule and the plasmonic cavity. This makes our sensor much more sensitive."

"The plasmonic systems also bring the strong light-matter coupling from cryogenic temperature to room temperature, which largely relaxes the experimental requirements for practical implementation and miniaturization of the sensors," Png added.

In a collaborative effort between IHPC's Electronics and Photonics department and IMRE's Quantum Technologies for Engineering group, Png and IMRE Principal Scientist Leonid Krivitsky led the development of the first-ever



> ***"Understanding low-temperature transport mechanisms is key to designing increasingly complex 2D semiconductor-based quantum devices."***
>
> — Aaron Lau, Scientist at A*STAR's Institute of Materials Research and Engineering (IMRE)

integrated avalanche photodetector (APD) for the visible light range[8], making it more energy- and cost-efficient than detectors operating at infrared wavelengths.

The team's device uses a doped silicon waveguide coupled to a silicon nitride waveguide for highly efficient detection, restricting the area for light transmission while packing the system onto a compact chip. Png shared that they are now exploring design variations to stabilize the device, reduce noise and further optimize detection performance.

Already considered a mature technology, APDs operate at near-room temperature and on-chip designs are a promising frontier for scalability, Krivitsky noted. While still in the research stages, these devices could potentially be integrated with various sensing systems, including light detection and ranging (LIDAR) for remote, high-resolution environmental mapping. For a deeper dive into the team's APD, check out our research highlight on p. 26!

While APDs detect light, quantum sensors can also measure other properties such as magnetic fields, which could enhance applications like magnetic resonance imaging for brain scans.

IMRE Scientist Junyi Lee is leading the development of alkali atomic magnetometers, exploiting quantum effects to forgo the use of large and expensive magnets. "By directly measuring the energy shifts of alkali atoms with a laser, they can measure magnetic fields to better than a part per billion," Lee highlighted.

This means that not only would measuring instruments become more compact, the environmental footprint of quantum-powered innovations would also shrink significantly. As alkali magnetometers function even without cryogenic cooling, they require much less power to operate than other quantum sensors, providing significant cost savings.

Besides biomedical imaging, these sensors could pave the way for precise chemical analysis in food safety testing and in geomagnetic surveys to scope out the planet's underground structure and tectonic activity.

IGNITING A QUANTUM REVOLUTION

Today, scientists are gearing up for a new wave of technological transformations ushered by quantum. For the field to prosper, scalability is the key to transforming basic research into real-world applications. To reach this pivotal point, researchers around the world are establishing quantum's computational supremacy as well as uncovering the best ways to control quantum properties for electronics and metrology.

A*STAR researchers are among those pursuing such endeavors, whether by integrating quantum phenomena into existing systems or by building new devices to support quantum effects. These efforts are just the tip of the iceberg as the agency strives to build a smarter nation with tech-enabled applications, creating impact in areas like healthcare and sustainability.

While no quantum computer is ready yet to deliver useful work, quantum tech's list of potential benefits is growing longer each day. As quantum capabilities are built up across sectors, quantum can advance from nascency to the technology of the moment. ★

1. Wang, G., Koh, D.E., Johnson, P.D., and Cao, Y. Minimizing estimation runtime on noisy quantum computers. *PRX Quantum* **2**, 010346 (2021).
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IMMUNOLOGY

Memories of our first microbial encounters

Live bacterial strains present in fetal tissues may help lay the cornerstones of early and potentially life-long immunity.

Once a newborn leaves the safety of the womb, they enter a whole new environment teeming with microbial life. Many of these microorganisms will be friendly, such as those present in the mother's vaginal flora. But there will also be foes—potentially pathogenic microbes that pose a serious risk to vulnerable infants with naive immune systems.

Luckily, in a process called immune priming, babies' immune defenses get a head start even before the baby is born. Previous studies have demonstrated that as early as the second trimester in pregnancy, fetuses have surprisingly competent immune systems. Until now, however, the underlying mechanisms involved in immune priming have remained elusive.

In a first-of-its-kind study published in the journal *Cell*, a group of researchers co-led by Florent Ginhoux, a Senior Principal Investigator at A*STAR's Singapore Immunology Network (SIgN), made the unexpected discovery that early contact with microbes in the womb drives immune development in the growing fetus.

Ginhoux and collaborators, including Jerry Chan and Salvatore Albani at the KK Women's and Children's Hospital and SingHealth as well as Naomi McGovern from the University of Cambridge, analyzed gut, skin, lung, thymus, spleen and placental tissue samples from human fetal tissues using high-throughput 16S rRNA gene sequencing. To ensure accuracy, the researchers implemented a series of stringent controls to ensure that any bacterial genes detected in their results did not come from contaminants.

Fascinatingly, a diverse range of live microbes was found to be present in fetal organs, including several bacterial genera typically found in the adult gut such as *Gardnerella*, *Lactobacillus* and *Staphylococcus*. Tissue imaging and electron microscopy data helped piece together a map of microbial distribution, showing that bacteria were localized to particular areas of the gut tissues.

Next, the researchers designed an *in vitro* assay to measure fetal T cells' responses to microbial contact. The team reported a significant increase in total T cell count and the proliferation of $CD45RO^+$ and $CD69^+$ T cells. This indicated that fetal tissues had immune memory, or the ability to recognize previously encountered antigens and launch an appropriate immune response.

"Our study demonstrates for the first time that human fetal organs harbor microbes that may prime the fetal immune system, thereby putting early microbial memory in the context of fetal immune priming—a concept not explored before in fetal immunity," said Archita Mishra, a postdoctoral fellow at Ginhoux's lab and first author of the study.

Their work lays the foundation for a myriad of future studies, including understanding where fetal bacteria come from, how they colonize the fetus and how microbial diversity changes throughout gestation. In the future, the team plans to address some of these questions by diving deeper into the nature of microbe-immune priming in human fetal organs. ★

Researcher
Florent Ginhoux, SIgN

ABOVE
Live bacterial strains typically found in adults have been found in fetal organs, suggesting that these microbes may prime the fetal immune system and pave the way for early microbial memory.

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Photo credit: Liudmila Fadzeyeva / Shutterstock

REGENERATIVE MEDICINE

Unboxing the muscle repair toolkit

Scientists identify a key molecular marker of muscle stem cells, providing novel insights into the mechanisms around muscle regeneration.

Ever pulled a muscle or felt sore after a workout? That pain is the result of micro-tears to the muscle fibers, which can result from everyday physical activities, injury or certain conditions.

Muscle regeneration is an elaborate process involving a heterogenous population of specialized muscle stem cells that, once activated, divide and fuse with the torn fibers to help restore the muscle's integrity. Due to a lack of characterization, however, the stem cell-driven mechanisms behind muscle regeneration remain largely unknown, limiting our ability to harness the power of muscle stem cells therapeutically.

A team of researchers led by Nick Barker at A*STAR's Institute of Molecular and Cell Biology (IMCB) aimed to bridge this gap by studying the diverse molecular landscape of muscle stem cells. They hypothesized that Lgr5—a receptor previously identified as a stem cell marker in various epithelial cells—also delineates a population of skeletal muscle stem cells called muscular progenitor cells (MPCs), and may orchestrate cellular signaling pathways in regeneration and muscle stem cell pool replenishment.

"We have previously shown Lgr5 to be a marker of stem cells contributing to the epithelial maintenance of a range of tissues, including the small intestine, colon, skin, pyloric stomach and ovary," said Barker. "Lgr5 also marks the injury-activated stem cells responsible for tissue repair in the corpus (central) stomach and liver."

The team induced muscle injury in a transgenic mouse model that was genetically modified to enable the researchers to track the activity of Lgr5-expressing cells and their descendants. This technique, known as lineage tracing, follows a cell's journey through proliferation, differentiation and regeneration.

After an injury, the scientists observed that Lgr5 expression was upregulated, coinciding with stem cell activation and proliferation. They also found that the targeted elimination of Lgr5-expressing cells in injured muscle resulted in a decrease in muscle mass and myofibers, further supporting the hypothesis that Lgr5-expressing progenitor cells are essential for efficient muscle repair.

"In skeletal muscle, Lgr5 was absent in healthy animals, but was quickly upregulated in response to acute damage. We therefore hypothesized that the damage-inducible Lgr5 population could be a reserve stem cell population that helps to quickly repair the muscle," explained Barker.

Building upon this study, the team plans to explore the signals that regulate the formation of Lgr5-expressing MPCs. "The more we know about the progenitor cells and the underlying mechanisms driving muscle regeneration, the better chance we have to safely harness their regenerative medicine potential in the clinic," said Barker. "Hopefully, this will eventually lead to improvements in rehabilitation from sports injuries or breakthroughs in muscle-wasting disease management." ★

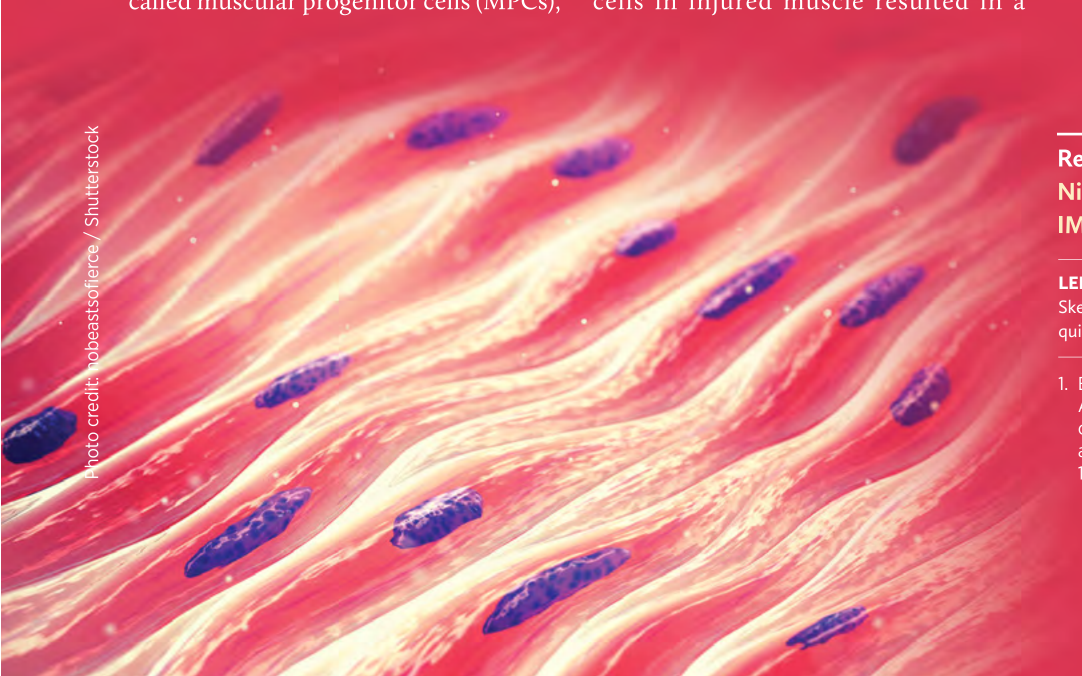


Photo credit: nobeastsofierce / Shutterstock

Researcher
Nick Barker, IMCB

LEFT
Skeletal muscle stem cells that express Lgr5 could help quickly generate muscle following damage.

1. Barker, N., Leung, C., Ahmad Murad, K.B., Tan, A.L.T., Yada, S., *et al.* Lgr5 marks adult progenitor cells contributing to skeletal muscle regeneration and sarcoma formation. *Cell Reports* **33** (12), 108535 (2020).

STEM CELLS

Opening the cellular gates to glucose

Low levels of sugar entering into pancreatic cells may be the culprit behind insulin secretion defects in early-onset diabetes.

Photo credit: © IMCB

After eating a bar of chocolate, you might down a glass of water to neutralize the sweet taste. Similarly, when blood glucose concentration runs high, our pancreas releases a hormone called insulin to bring sugar levels back to normal.

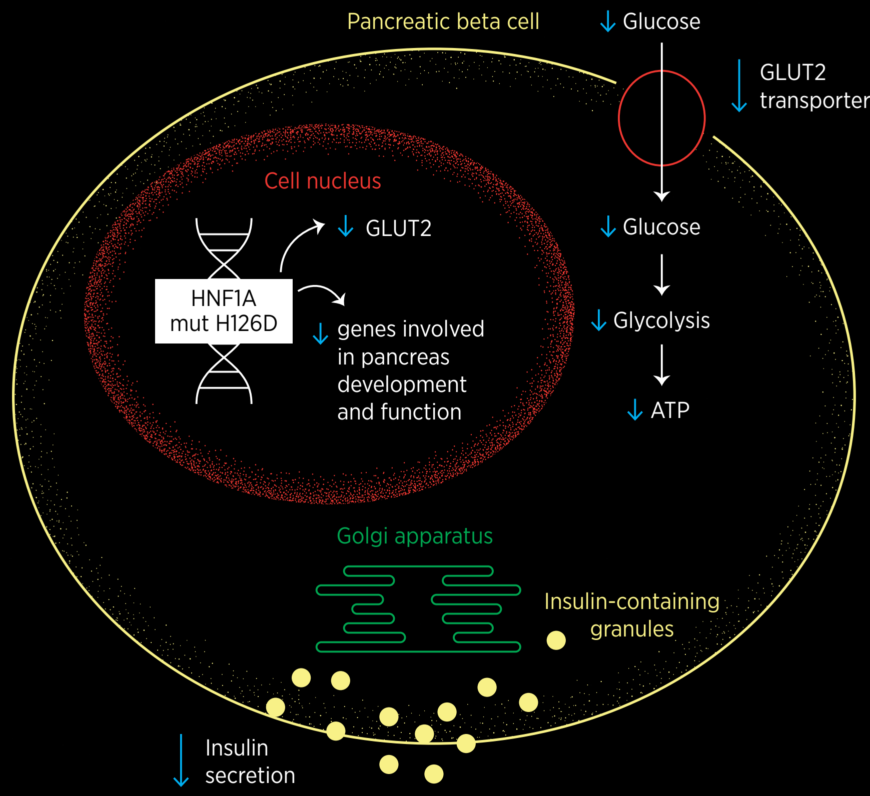
For diabetic patients, however, insulin function is impaired. In maturity onset diabetes of the young 3 (MODY3), a form of diabetes that typically manifests before the age of 25, pancreatic beta cells fail to secrete enough insulin to lower blood sugar levels.

These dysfunctional beta cells are traced to mutations in the HNF1A gene, but determining how insulin secretion defects arise in human cells had left scientists stumped. Now, researchers led by Adrian Teo, a Principal Investigator at A*STAR's Institute of Molecular and Cell Biology (IMCB), have modeled the effects of HNF1A mutations using human induced pluripotent stem cells (hiPSCs) from MODY3 patients.

Since stem cells can become any of the body's specialized cells, the team first triggered their differentiation into pancreatic beta cells. This approach overcame the limitations of rodent models, where heterozygous MODY3 mutations do not lead to any insulin secretion problems in mice, noted Teo.

"Rodent models may not be able to fully recapitulate MODY3 diabetes. Furthermore, rodent and human pancreas differ in terms of gene expression and morphology," he added.

To mimic the genetic profile of MODY3 patients, using hiPSCs was the



The H126D mutation in the gene HNF1A decreases the expression of the GLUT2 gene and protein, reducing glucose uptake and ATP production as well as lowering insulin secretion.

closest way to simulate the changes that occur in mutant beta cells.

Alongside a host of genes involved in pancreatic development, the results revealed a reduced expression of the GLUT2 gene, which codes for a protein that shuttles glucose molecules into beta cells. According to Teo, this was striking because other transporters—GLUT1 and GLUT3—are more abundant than GLUT2, yet were not affected by the mutation.

"The lower expression of GLUT2 has historically made its role seem relatively insignificant as compared to the other two glucose transporters. However, our findings have highlighted the importance of GLUT2 in human beta cells," he explained.

While only GLUT2 was reduced among the three transporters, the effects were drastic, as the researchers observed glucose uptake to drop by half. Without the influx of glucose molecules, the mutant pancreatic beta cells are no longer alerted to the elevated blood sugar levels. Moreover, they end up producing less ATP, the body's main energy molecule, hindering the release of insulin in MODY3 patients.

"The lower expression of GLUT2 has historically made its role seem relatively insignificant as compared to the other two glucose transporters. However, our findings have highlighted the importance of GLUT2 in human beta cells."

Given these results, the team is now looking into solutions for increasing glucose uptake in mutant beta cells, as well as investigating how these genetic changes may be involved in other types of diabetes. "Treatment methods that better facilitate glucose entry into the beta cells could help restore insulin secretion function in MODY3 patients," Teo said. ★

Researcher
Adrian Teo, IMCB

LEFT
Induced pluripotent stem cells (iPSC) from patients with maturity onset of diabetes of the young 3 (MODY3) have revealed the important role a receptor called GLUT2 plays in the disease. iPSC-derived human beta cells with nuclei (blue), PDX1 (red) and HNF1A (green).

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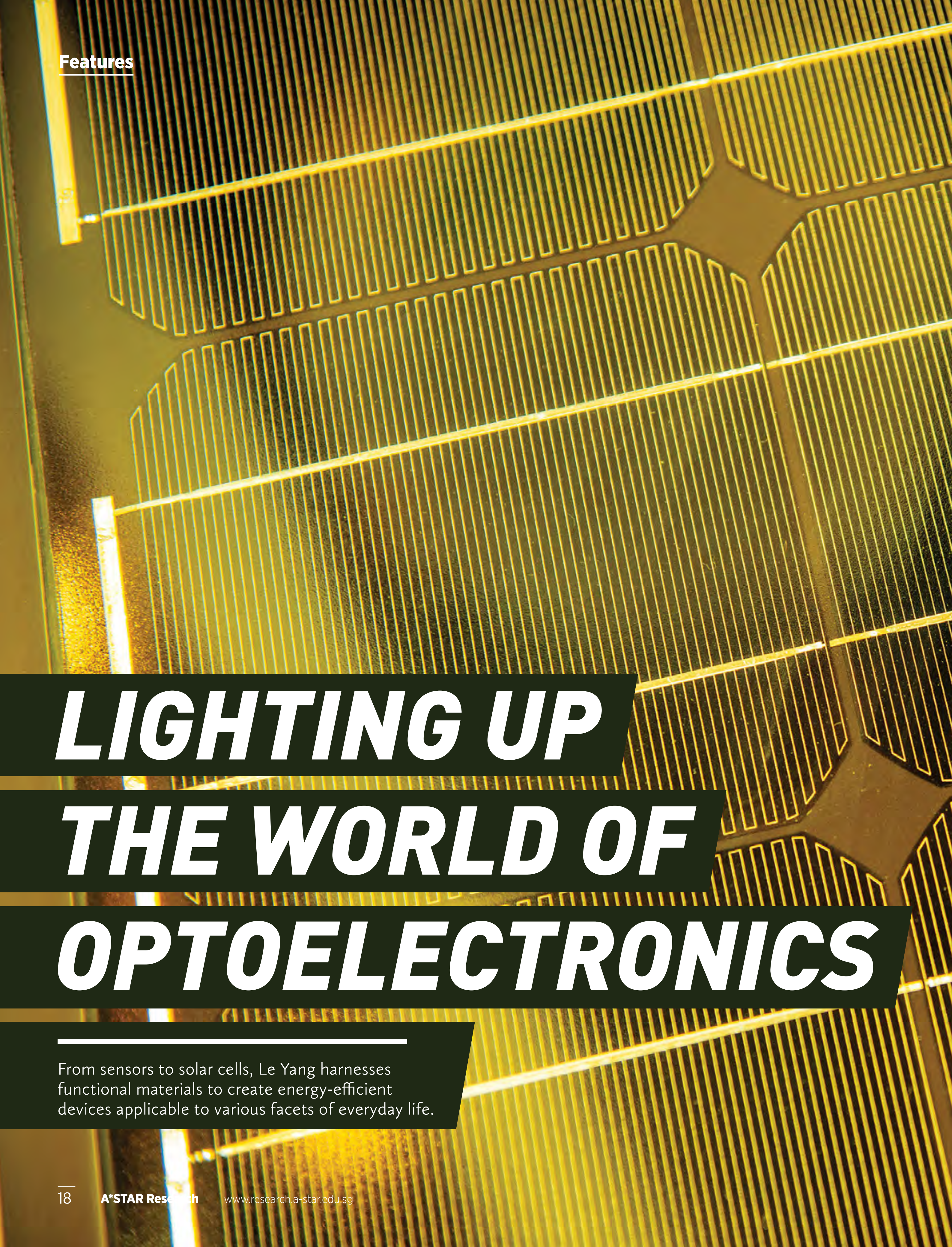


LIGHTING UP THE WORLD OF OPTOELECTRONICS

From sensors to solar cells, Le Yang harnesses functional materials to create energy-efficient devices applicable to various facets of everyday life.

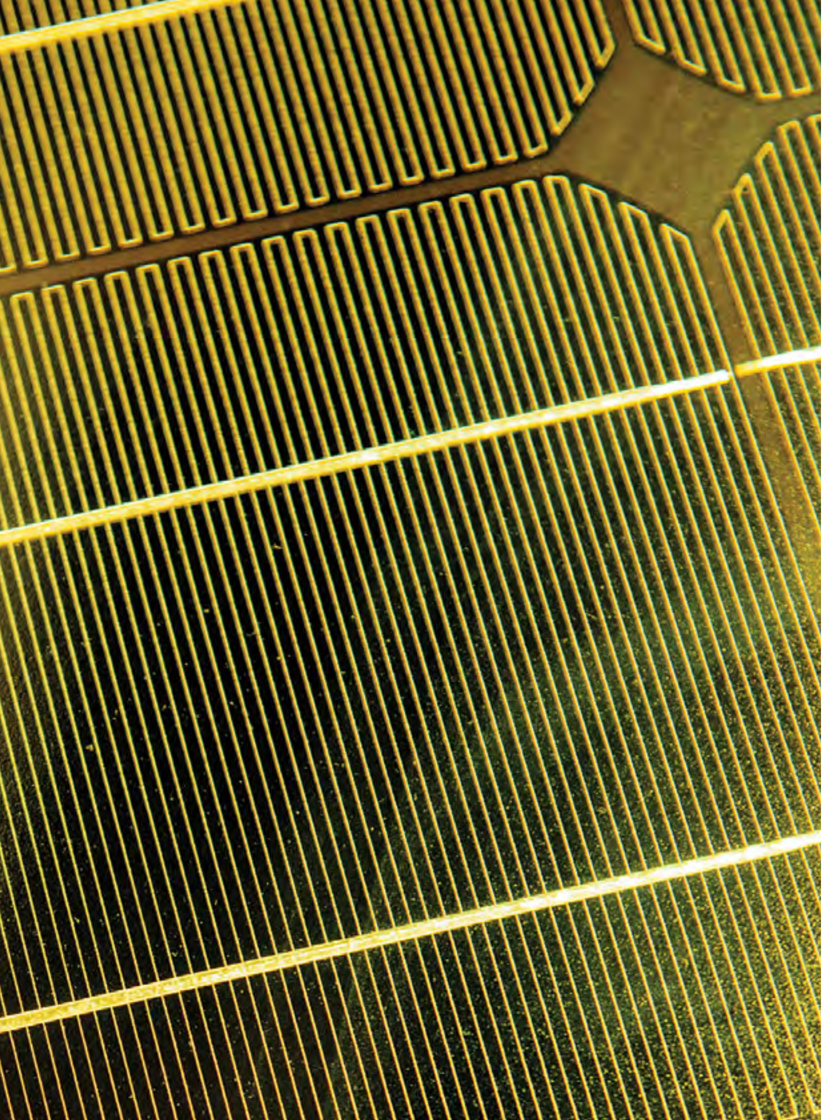


Photo credit: Hadrian / Shutterstock

What's one thing wearable sensors, LED TVs and solar cells have in common? Aside from being increasingly popular devices in our modern world, these seemingly disparate smart technologies are all enabled by polymer and organic electronics—a vibrant field that studies the applications of soft, flexible and conductive organic materials for electronic devices.

In recent years, organic optoelectronics based on the interplay between light and electrical energy, like organic light-emitting diodes (LEDs) and perovskite solar cells, have grown in prominence as electronic devices look to interact with the world around them. From X-rays to visible light, these devices can sense and control waves across the electromagnetic spectrum to great effect. But while organic optoelectronics-based gadgets are already commercially available, key challenges remain.

Consider the trade-off between stability and efficiency. Though optoelectronic devices made from organic materials promise to be more energy-efficient, these same materials can chemically degrade under light, resulting in short lifespans.

At A*STAR's Institute of Materials Research and Engineering (IMRE), scientists like Junior Group Leader Le Yang from the PRinted Organic Flexible Electronics & SenSors (PROFESS) group are seeking to achieve the elusive goal of both stability and efficiency in a single system.

In this interview with *A*STAR Research*, Yang talks about her initial foray into the exciting world of organic and polymer electronics as well as optoelectronics. She also discusses her efforts to take these devices to new heights—and new applications.

Q: GIVEN YOUR INITIAL TRAINING IN CHEMISTRY, WHAT SPARKED YOUR LATER INTEREST IN OPTOELECTRONICS?

In the early days of my learning journey, I had always been interested in the 'biology' side of science. This interest led me to pursue biological and medicinal chemistry during my undergraduate studies at Imperial College London.

However, I increasingly realized my dislike towards organic synthesis, a subject I thought I liked! Luckily, a summer project in polymers applicable to battery applications and a final-year project on semiconductor polymers sparked my interest in optoelectronics and energy-related research.

These experiences opened my eyes to an exciting multidisciplinary field that I had never considered before. This led to a one-year, pre-PhD attachment at IMRE, working on printable electronics and organic solar cells.

My interest blossomed even further during my postgraduate years at the University of Cambridge, where I read physics in organic optoelectronics. It's hard to explain exactly why I was so attracted to this research field, but understanding materials and their role in fabricating high-efficiency optoelectronics was certainly a key factor.

Today, I find building better devices, enhancing their performance and watching their performance improve to be an addictive experience. Knowing that my research is practical and use-inspired is also very compelling to me.

"Today, I find building better devices, enhancing their performance and watching their performance improve to be an addictive experience. Knowing that my research is practical and use-inspired is also very compelling to me."

— Le Yang, Junior Group Leader at A*STAR's Institute of Materials Research and Engineering (IMRE)

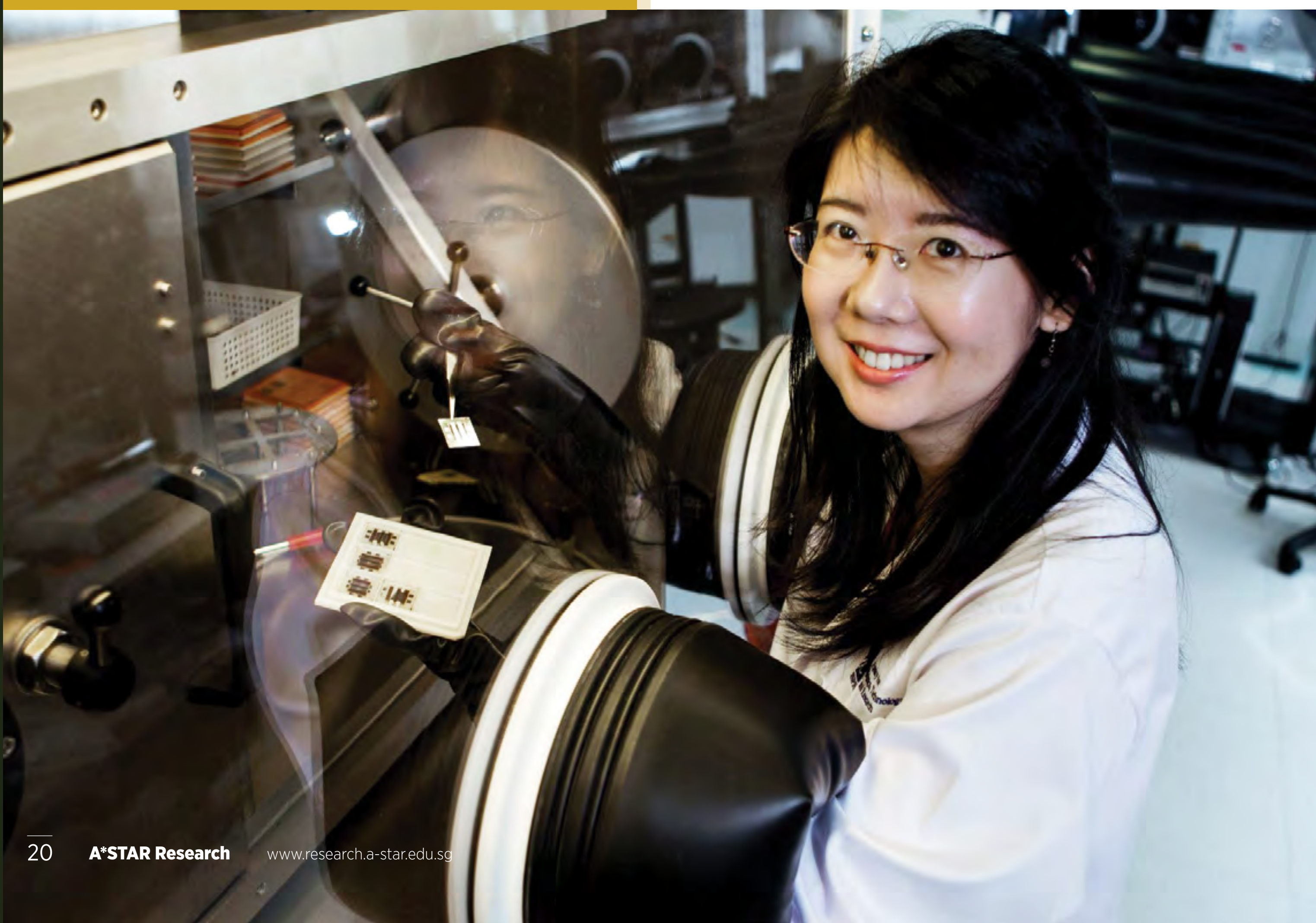
Q: AMONG YOUR RESEARCH PROJECTS, WHICH ARE YOU MOST PROUD OF? WHY?

Most of my completed work involves fabricating electronic devices like solar cells, LEDs and now sensors and other functional structures.

I felt great pride when our team discovered a novel emission pathway in a class of new emitters. In fact, I built solution-processed organic LEDs in the lab that broke the world efficiency record.

I remember when I achieved that unprecedented efficiency. I was so shocked that I dropped my phone the moment I saw the measurement. That drop smashed my phone screen and I had to fork out S$200 to fix it. True story, but a happy one nonetheless!

Apart from improving device efficiency, this discovery opens new routes to achieving printable high-efficiency organic LEDs for display tech.



Q: WHAT FUNDAMENTAL QUESTIONS DO YOU HOPE TO ADDRESS WITH YOUR RESEARCH?

Currently, with IMRE's support, I am embarking on two research fronts, with the first being developing wearable electronics and sensors.

I've been blessed with the opportunity to be involved in the Cyber Physiochemical Interfaces (CPI) program, led by Xiaodong Chen and supported by my colleagues at IMRE. We aim to bring integrated solutions to non-invasive and real-time wearable sweat sensing, applicable for healthtech, medtech, forensics and more.

This medtech endeavor has been new to me. Our team (Xinting Zheng, Yong Yu, Yuxin Liu, Changyun Jiang and Wei Peng Goh) came together because of this project, and I am humbled and honored to work alongside them.

My second research area aims to use organic materials in sustainably building functional structures and optoelectronic devices. We aim to study and fully utilize the photophysics of organic optoelectronic materials in constructing energy-efficient or energy-harvesting devices.

A fundamental challenge in organic luminescence is the lack of versatility in manipulating high-energy light. Despite this, high-energy light remains critical in many applications, from optogenetics to anti-counterfeiting. Yet, it could also be detrimental to our eyes and skin, our circadian rhythm and even to solar cells.

Therefore, converting to other colors in an energy-conserving way would be beneficial. These studies can serve applications such as display tech, agritech, solar tech, sensing and more. We also hope to address some of the biosensor challenges mentioned above with novel optoelectronic strategies.

Q: WHERE ELSE CAN RESEARCH INTO CYBER-PHYSIOCHEMICAL INTERFACES BE APPLIED?

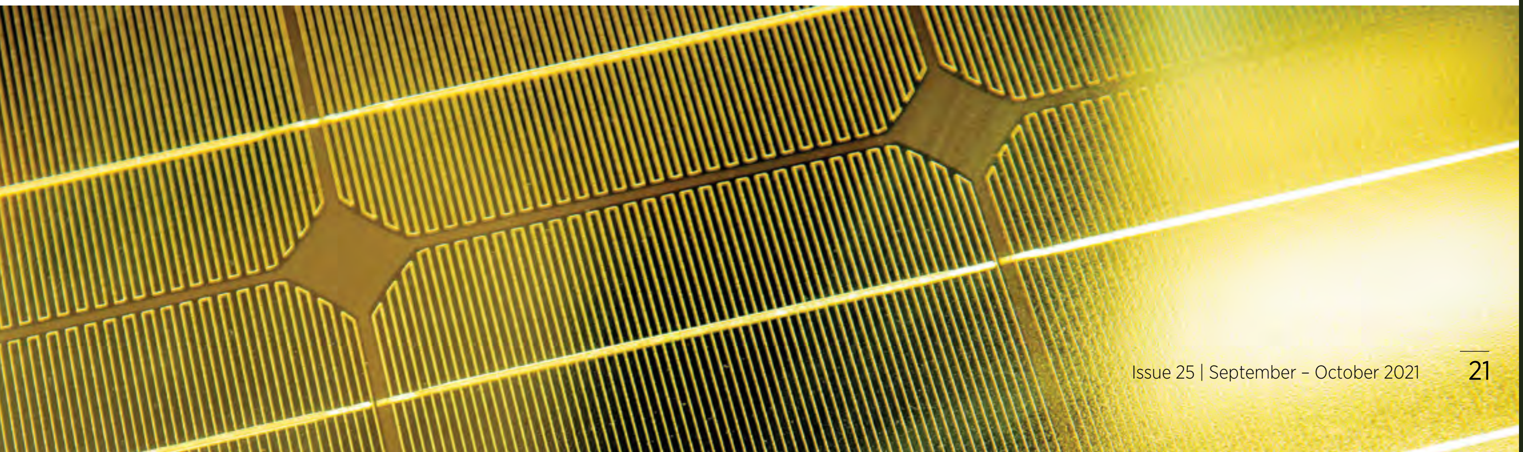
We hope that the capabilities we have built through the CPI program can be used as a platform technology for sensing. Currently, we are mainly targeting on-skin medtech and healthtech applications in the move towards digital healthcare, cloud-based and personalized medtech, as well as lifestyle monitoring. We are also gradually exploring sensing for forensic applications and other areas such as food or the environment.

Q: HOW CAN OPTOELECTRONIC DEVICES IMPROVE DISPLAY AND SOLAR ENERGY TECHNOLOGIES?

We can achieve this by working with organic materials that are light, flexible and sometimes stretchable. Furthermore, some organic molecules are more readily biodegradable.

Our goal is to build optoelectronic devices that are long-lasting, more stable and energy-efficient, while achieving high performance at the same time—be it for display, lighting or solar energy harvesting. One challenge working with organic optoelectronic devices is achieving both stability and efficiency simultaneously in one system. We certainly hope to design strategies to overcome that.

We are also designing and developing passive structures that do not need additional energy input for functional applications. For instance, we are excited about potential use cases in plant growth. Stay tuned! ★



MATERIALS SCIENCE

Self-cleaning surfaces inspired by insects

A*STAR scientists are developing the next generation of self-sanitizing surfaces by mimicking nanostructures on cicada wings.

The pandemic has heightened our anxiety about potentially pathogenic microorganisms lurking on shared surfaces in public areas. However, decontaminating everything may be doing more harm than good—the overuse of antibiotics and disinfecting agents is linked to the rise of anti-microbial resistance (AMR). Once acquired, AMR makes bacterial pathogens nearly invincible once they colonize surfaces, or worse, infect people.

To combat this emergent threat, researchers have begun looking to self-sanitizing surfaces in nature for inspiration. Insect wings are an excellent example: nanoscopic needle-like patterns on the surface of cicada and dragonfly wings destroy microbes physically instead of chemically, 'popping' microbes that land on them.

Scientists have been able to mimic these natural biocidal nanostructures using zinc, gold, titanium and silicon materials. However, these technologies aren't scalable as Yugen Zhang, a Group Leader at A*STAR's Institute of Bioengineering and Bioimaging (IBB), points out. "Most of the existing methods used for fabricating surface nanopatterns require special equipment, expensive starting materials and specific substrates," he said.

With funding support from the National Research Foundation's Competitive Research Program, Zhang and his team devised ways of lowering existing barriers around manufacturing self-sanitizing nanostructure surfaces. To achieve this, they chose iron as an elemental building block due to its low cost, high abundance and environmentally inert properties.

First, the researchers designed chemical reactions for creating needle-like iron nanopillars on surfaces such as glass and tin under high heat and pressure conditions. Raising the temperatures in the reactors was found to generate a second type of iron nanopillar array, both of which exhibited strong 'kill-by-structure' properties, puncturing microbial cell walls and membranes.

Promisingly, these novel surface modification techniques were not limited to specific starting surface materials. Zhang and colleagues developed a method to synthesize self-standing 'urchin-shaped' particles using the same iron compounds. These powders could then be applied as a coating to a wide range of materials, forming a protective biocidal outer layer. While coated surfaces were tough on bacteria, urchin-shaped nanoparticles were found to be non-toxic and gentle on mammalian cells.

This innovation could soon be a chemical-free solution for limiting the spread of microbes in public spaces. "This technology could lead to high-touch surfaces with long-term self-disinfection properties, either by creating surface nanostructures or by coating with urchin-shaped nanoparticles," said Zhang, who added that these particles could also simply be mixed into paint for direct application onto surfaces. The team now aims to prototype their discovery for commercialization. ★

Researcher
Yugen Zhang, IBB

ABOVE
Scientists have created insect-inspired iron nanopillars that can puncture microbial cell walls and membranes to lethal effect.

Photo credit: tresame24 / Shutterstock

1. Yi, G., Teong, S.P., Liu, S., Chng, S., Yang, Y.Y., *et al.* Iron-based nano-structured surfaces with antimicrobial properties. *Journal of Materials Chemistry B* **8**, 10146-10153 (2020).

SUSTAINABILITY

Unmasking environmentally friendly pandemic solutions

By knowing the environmental impact of reusable and single-use face masks, policymakers can make data-driven decisions on their use in Singapore.

Surgical face masks have become the ubiquitous symbol of the COVID-19 pandemic. While the debate on mask mandates rages on, there is a less talked about concern around protective face coverings: their environmental impact.

Numerous global reports have documented how an enormous surge in discarded face masks has overwhelmed waste management frameworks and threatened sensitive ecosystems.

"Single-use surgical face masks contain a large amount of polypropylene and can be considered as a plastic product," said Amos Lee, an A*STAR graduate scholar at the National University of Singapore (NUS) and former research engineer at A*STAR's Singapore Institute of Manufacturing Technology (SIMTech). "Thus, it shares a longevity similar to other plastic products and takes a long time to decompose after disposal."

In response, reusable face masks like the Singapore-developed embedded filtration layer (EFL) face mask have emerged as an eco-friendly alternative. However, there appear to be certain scenarios where single-use surgical masks can be more environmentally friendly compared to reusable options. This raises the question: are EFL face masks indeed greener than their disposable counterparts?

To address this unknown, Lee and colleagues at SIMTech examined and compared the emissions and waste generated by the two face mask formats.

The team conducted an exhaustive life cycle assessment which involved tracking pollutants emitted from the early stages of raw material extraction to their end-of-life disposal for each face mask.

Their results revealed that reusable EFL face masks produced fewer emissions and less waste than disposable ones. "Over 31 days, the use of the EFL reusable face mask will generate a 1.7 times lower carbon footprint and 10 times less solid waste compared to single-use surgical face masks in the context of Singapore," explained Lee.

The study provides valuable evidence to help policymakers make sustainable public health choices and craft public messaging. However, environmental impacts are often multi-faceted, making it challenging to determine the greenest option.

"When considering emissions relating to climate change, fossil fuel and metal depletion as well as freshwater and marine ecotoxicity, the more sustainable choice for Singapore is the EFL reusable face mask," said Lee, noting that surgical masks are superior in other sustainability metrics, such as water pollution and human toxicity.

Moving forward, Lee calls for more research and funding around creating more environmentally safe personal protective equipment, with a focus on alternative materials, better recycling capabilities and eco-friendly fabrication methods. ★

Photo credit: imtmphoto / Shutterstock

Researcher
Amos Lee, SIMTech

LEFT
Made-in-Singapore reusable masks with an embedded filtration layer were shown to be more environmentally friendly.

1. Lee, A.W.L., Neo, E.R.K., Khoo, Z.Y., Yeo, Z., Tan, Y.S., *et al*. Life cycle assessment of single-use surgical and embedded filtration layer (EFL) reusable face mask. *Resources, Conservation & Recycling* **170**, 105580 (2021).

Photo credit: Poravute Siriphiroon / Shutterstock

MATERIALS SCIENCE

Molecular blemishes boost batteries

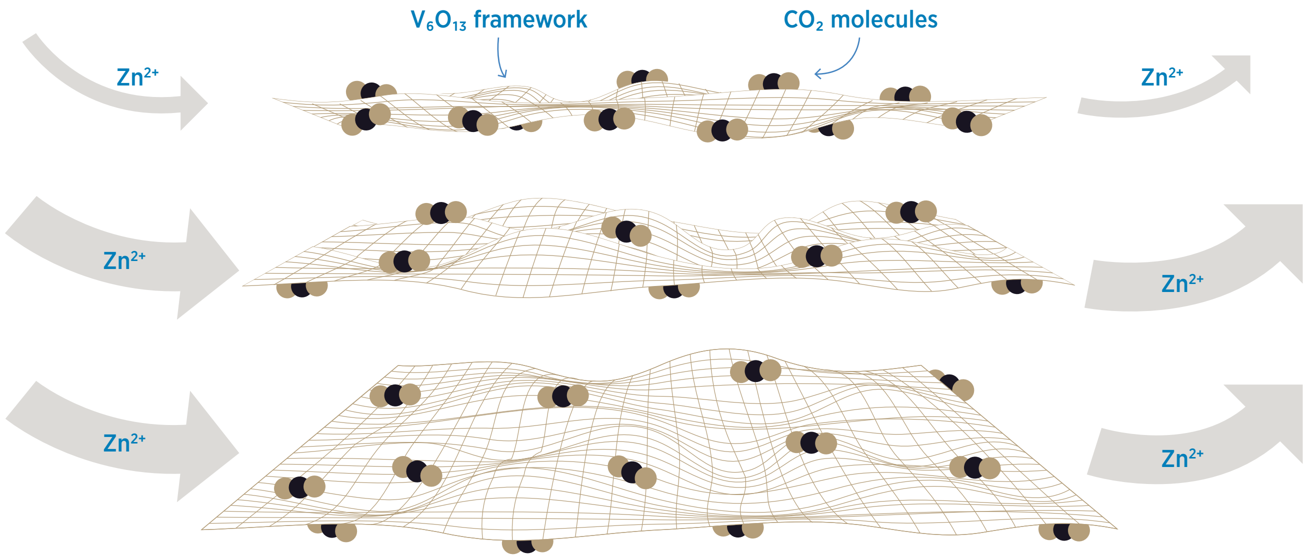
Embedding chemical impurities into zinc-ion batteries boosts their performance and prolongs battery life.

Ever noticed how the longer you own a smartphone, the more frequently you need to charge it? This is because the lithium rechargeable batteries that power many of today's technologies have fixed lifespans, with their capacity for storing electricity waning over time.

This phenomenon—known as cycle instability—along with issues like cost, hazards and the scarcity of raw materials for lithium batteries have spurred the search for alternative power sources. With their ready availability and safety, zinc-ion batteries (ZIBs) overcome many limitations of traditional lithium batteries. In ZIBs, positively charged zinc ions travel from the batteries' zinc metal anode to the vanadium oxide-based cathode.

Unfortunately, zinc-ion batteries still suffer from cycle instability. Strong interactions between embedded O^{2-} ions and the zinc charge carriers hinder the diffusion of zinc ions across the battery, gradually compromising recharging efficiency and weakening the battery capacity of ZIBs over time.

When the vanadium oxide framework is modified with CO_2, zinc ions can easily diffuse across the material, giving zinc-ion batteries a greater ability to store charge.



To unlock more durable, high-performing ZIBs, disrupting these molecular interactions could be key, explained Zhigen Yu, a Senior Research Scientist at A*STAR's Institute of High Performance Computing (IHPC). In a collaboration with Junmin Xue and Vincent Lee from the National University of Singapore's Department of Materials Science and Engineering, Yu and a team of researchers explored novel ZIB design approaches to achieve superior battery performance.

Tweaking the chemical composition of ZIBs can help these batteries achieve higher energy densities, making them a viable contender against other battery technologies on the market.

They hypothesized that introducing trace amounts of carbon dioxide (CO_2) to the vanadium oxide framework could reduce the zinc-ion diffusion barrier. Previously, water molecules had been used for this purpose, but the team speculated that CO_2 may provide ZIBs with an even greater functional boost.

"CO_2 is a small and abundant non-polar molecule consisting of one carbon and two oxygen atoms," said Yu. He explained that theoretically, the two oxygen atoms would 'pull' the zinc charge carriers along, ferrying them across the battery.

The study strongly supported their initial hypothesis, yielding spectacular results: the addition of CO_2 lowered the ZIB diffusion barrier over three-fold in one direction and by ten-fold in the other.

This in turn gave the newly designed ZIBs the ability to store over 40 percent more charge than their unmodified counterparts. Moreover, adding CO_2 allowed the ZIBs to handle significantly more charge/recharge cycles, retaining a whopping 80 percent of its capacity after 4,000 cycles. In contrast, first-generation ZIBs would wind down to 58 percent capacity after just 570 cycles.

According to Yu, their results demonstrate how tweaking the chemical composition of ZIBs can help these batteries achieve higher energy densities, making them a viable contender against other battery technologies on the market. In the future, the team plans to explore a similar approach to enhancing other types of metal-ion batteries. ★

Researcher
Zhigen Yu, IHPC

LEFT
Enhanced zinc-ion batteries developed by A*STAR researchers can store greater charge and handle more charge/recharge recycles.

1. Shi, W., Yin, B., Yang, Y., Sullivan, M.B., Wang, J., *et al*. Unravelling V_6O_{13} diffusion pathways via CO_2 modification for high-performance zinc-ion battery cathode, *ACS Nano* **15**, 1273-1281 (2021).

ENGINEERING

Bringing integrated avalanche detectors into the (visible) light

This first-of-its-kind integrated avalanche photodetector for visible light lays the foundation for next-generation innovations in imaging and communications.

From smartphone cameras to fiber-optic communications, many modern technologies are made possible by sensors that detect photons of light and convert them into energy. Called photodetectors, these sensors have grown in sophistication over the years. Avalanche photodetectors (APDs), for instance, can rapidly multiply weak stimuli like a few photons of light into larger, detectable signals. By integrating APDs into optically activated photonics circuits, many advances would be enabled by the faster speed, smaller device size and lower cost.

Still, photonics-integrated APDs remain restricted to capturing infrared wavelengths, likewise limiting their applications. Consequently, researchers are working to develop integrated APDs that can also detect visible light. With such devices, scientists could usher in the next generation of miniaturized bioimaging devices, high-speed communications tools and improved remote sensors.

For the longest time, however, such capabilities remained out of reach. According to Victor Leong, a Scientist at A*STAR's Institute of Materials Research and Engineering (IMRE), the problem boiled down to fundamental design differences between integrated APDs for infrared and visible light.

"The technique typically used to deliver input light from the photonics circuit to integrated infrared APDs—known as an interlayer transition—cannot be used for visible-light devices without significantly compromising on noise and speed performance," he explained.

In a breakthrough study, Leong and colleagues describe how they built the world's first visible-light APD, integrated on a photonic chip. To achieve this feat, the team applied an out-of-the-box design approach, fabricating the photodetector and input waveguide on the same layer in an 'end-fire' configuration, instead of the conventional interlayer transition where the input waveguide is placed either above or below the APD.

"By placing both the detector and input waveguide on the same device layer, the novel end-fire configuration avoids the drawbacks of the interlayer transition," Leong said. He added that this architecture was novel and difficult to fabricate, spurring the team to undergo a rigorous fabrication optimization process.

To determine the optimal device design, the researchers varied different parameters, including geometry and doping profile. While an interdigitated profile featuring alternating positively and negatively charged regions was more tolerant of fabrication errors, the trade-off was a loss of speed. Instead, the team found that a lateral doping profile with continuously aligned positive and negative regions was faster and more efficient.

Ultimately, the researchers' final design demonstrated a strong, balanced performance relative to state-of-the-art integrated infrared APDs. Their device not only strongly amplified input light signals with low levels of noise but was able to transmit this data with a high bit rate of 56 Gbps.

According to Leong, the team plans to raise the bar even higher, building upon their design to pursue the ultimate limit of single-photon detection sensitivity. Achieving this would pave the way for even more possibilities in quantum communications, optical computing and beyond. ★

Researcher
Victor Leong, IMRE

LEFT
By uniquely fabricating the photodetector and input waveguide on the same layer, scientists have created the world's first visible-light avalanche photodetector.

1. Yanikgonul, S., Leong, V., Ong, J.R., Hu, T., Siew, S.Y., *et al.* Integrated avalanche photodetectors for visible light. *Nature Communications* **12**, 1834 (2021).

Photo credit: luchschenF / Shutterstock

ENGINEERING

Lab assays on the go

A portable, low-cost spectrophotometer could free up scientists to perform routine experiments outside the lab.

Remember looking for the nearest payphone and scrambling for change, or having to wait by a landline phone when expecting an important call? With today's smartphones, such experiences are but distant memories. Now, we can effortlessly send and receive information anytime, anywhere. Given the transformative power of mobile technologies, imagine the possibilities if typically lab-based scientific equipment became portable too.

Take for instance the spectrophotometer, a quintessential piece of lab equipment used for measuring the concentration of substances like proteins and nucleic acids in solution. Spectrophotometers are bulky, expensive machines that need a constant power source, which restricts their use to a lab setting.

Freeing the spectrophotometer from the four walls of the lab opens up a whole new world of scientific prospects: testing for environmental contaminants in the field, mobile diagnostic units, food safety testing and more. To make this a reality, a team of researchers led by Samuel Gan, Principal Investigator at the Antibody and Product Development Lab of A*STAR's Experimental Drug Development Centre (EDDC) and Bioinformatics Institute (BII), sought to develop a fully portable smartphone-dependent spectrophotometer.

"Once the DIY movement picks up, we envision such self-assembled devices to disrupt and free up the spatially bound nature of biomedical research."

Central to the team's design focus was affordability, to ensure that their innovation would be accessible even to low-resource communities. With this in mind, the researchers selected only off-the-shelf electronic parts, including wires, switches and batteries, to create their unit. Even the highly specialized LED lamps, components that directly influence the spectrophotometer's accuracy, were commercially sourced. Meanwhile, the device's inner workings were driven by an Arduino board that serves as the 'brain,' calculating concentration values based on input light signals.

The team then designed a 3D-printed outer shell, keeping in mind factors like the heat emitted during the machine's operation, wire paths and compatibility with commonly used containers housing the liquid samples. Finally, they developed an Android app to control the mobile spectrophotometer, allowing users to collect data and recalibrate the device with a smartphone—no desktop computers needed!

When put to the test, the portable device delivered slightly lower limits of protein measurements than its commercial counterpart, but showed superior higher ranges when quantifying nucleic acids. According to Gan, these performance differences underscore the need for future software optimization to boost the device's range. Nevertheless, the mobility and accessibility of the team's invention mark a significant milestone in the prospect of mobile lab platforms.

"Once the DIY movement picks up, we envision such self-assembled devices to disrupt and free up the spatially bound nature of biomedical research," said Gan, noting that portable spectrophotometers also have the potential to revolutionize point-of-care patient screening and diagnostics. ★

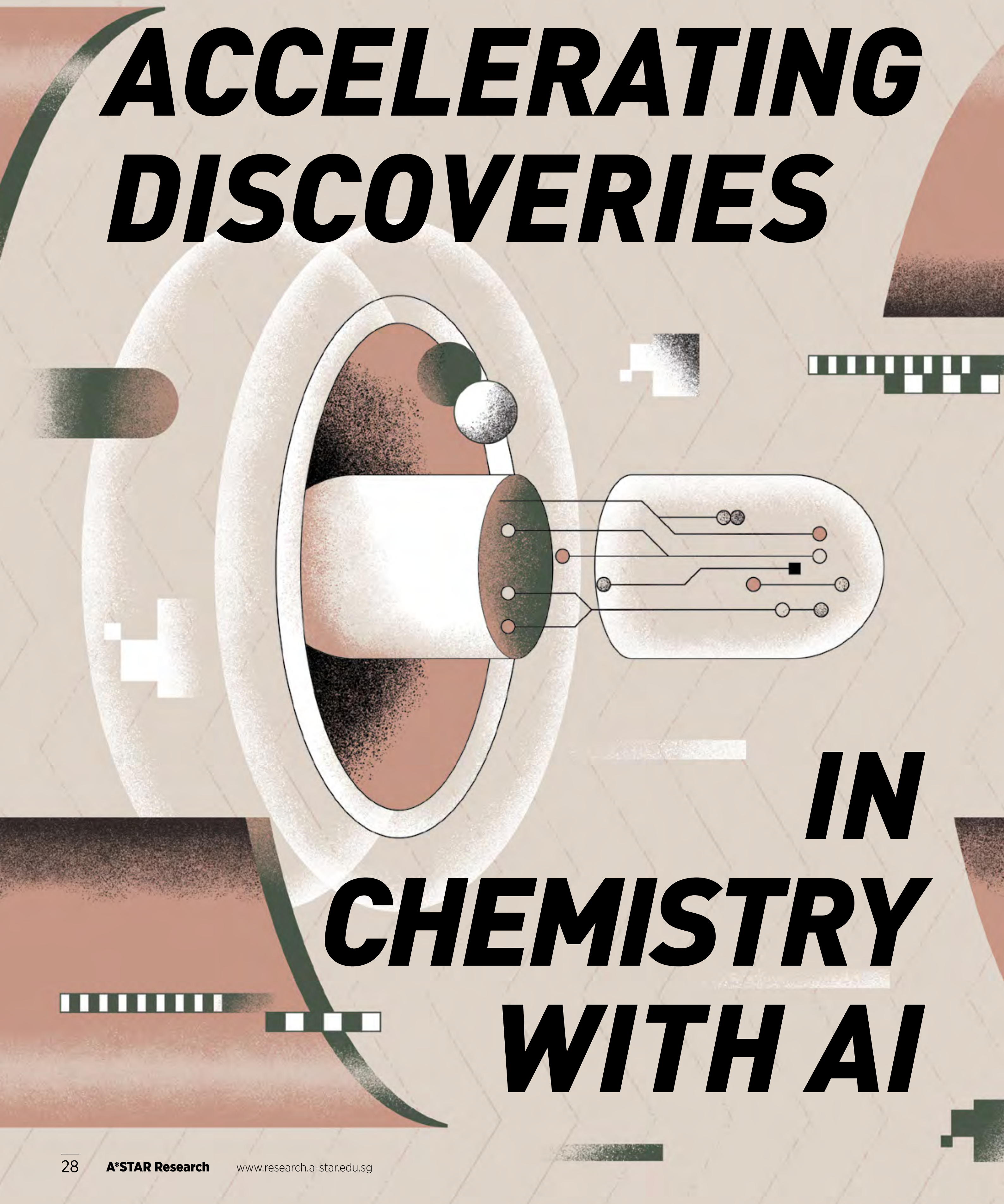
Researcher
Samuel Gan, BII

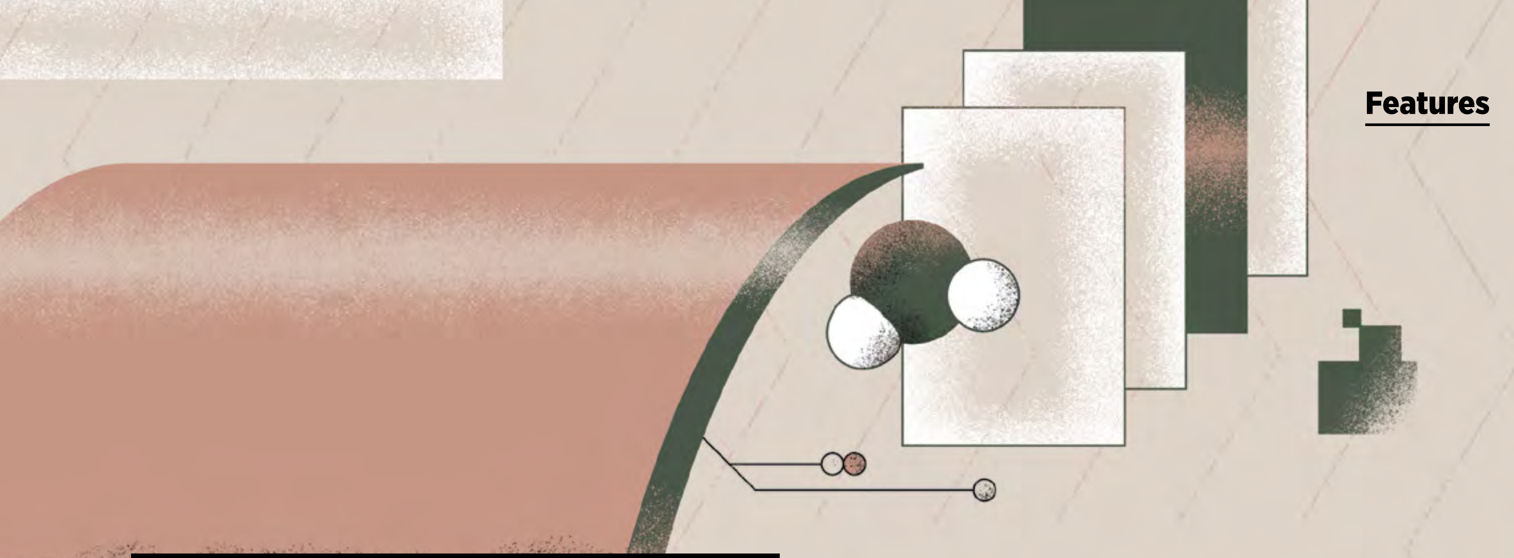
ABOVE
A portable spectrophotometer built from off-the-shelf electronic parts and controlled by an Android app could open the doors for biomedical research on the go.

1. Poh, J.J., Wu, W.L., Goh, N.W.J., Tan, S.M.X., Gan, S.K.E. Spectrophotometer on-the-go: The development of a 2-in-1 UV–Vis portable Arduino-based spectrophotometer. *Sensors and Actuators A: Physical* **325**, 112698 (2021).

Photo credit: Mykolastock / Shutterstock

ACCELERATING DISCOVERIES IN CHEMISTRY WITH AI





Machine learning and artificial intelligence have the power to transform chemical research, says A*STAR National Science Scholar Jacqueline Tan.

When it comes to boldly going where no man has gone before, we often think of frontier expeditions traversing the depths of outer space. But there's also much to be explored on Earth—specifically in the compounds that play crucial, if often unnoticed, roles in our daily lives.

From paint pigments to promising drug candidates, there appears to be a compound for just about every need, but scientists say that the number of compounds known today is far eclipsed by theoretical calculations. Given the seemingly infinite combinations of elements, the chemical space—or the set of all possible organic compounds—has been estimated to contain 10^{180} compounds, more than twice the number of atoms in the universe.

Given the sheer scale of compounds that remains to be discovered, it's no wonder researchers are looking to adopt quicker and more efficient methods to study and apply compounds and molecules. One such solution comes in the form of artificial intelligence (AI) and machine learning (ML)—a field that A*STAR National Science Scholar Jacqueline Tan hopes to harness to provide better ways for researchers to advance chemical research.

Supported by a strong belief that science is meant to improve the world for future generations, Tan's postdoctoral studies at the Massachusetts Institute of Technology (MIT) currently focus on ML methods in theoretical chemistry, as well as developing greener catalytic reactions.

In this interview with *A*STAR Research*, Tan shares the inspiration behind her work as well as the key findings setting the foundation for her future research.

Q: WHAT INSPIRED YOU TO BE A SCIENTIST AND WHY DID YOU APPLY FOR THE A*STAR NATIONAL SCIENCE SCHOLARSHIP?

In secondary school, my science teacher signed me up for a competition combining science and design. My team designed an customizable anti-spill hot water carrier that could prevent scalding and was crowned runner-up.

This experience made me realize how important educators are and convinced me that science was a way to improve the world. From then on, I believed that science and education go hand-in-hand—so applying for the A*STAR National Science Scholarship was not a difficult decision. Since then, the scholarship has helped me pursue my interest in science and given me the necessary skills to share with others what I've learned in turn.

Q: YOU STUDIED QUANTUM AND COMPUTATIONAL CHEMISTRY FOR YOUR PHD. WHY DID YOU LATER FOCUS ON MACHINE LEARNING AND THEORETICAL CHEMISTRY?

Once you step into the realm of computational chemistry, you find that you're dealing with data science, physics, engineering, math and, of course, chemistry. It truly becomes interdisciplinary and so it's not really a change—more of a transition into other areas of science that tie in closely with my current work. Science is really exciting, so you have to continuously learn and adapt to make the most of all these available tools.

Q: COULD YOU ELABORATE ON YOUR RESEARCH FINDINGS IN RADICAL CATION CHEMISTRY?

For one project, I worked with an experimental group at the University of Oxford to uncover how introducing intramolecular hydrogen bonding can significantly reduce the barrier to the rotation of non-biaryl atropisomers. These molecules are key in applications like medicinal chemistry and supramolecular chemistry.

In a project I worked on with Robert Paton, my supervisor at Oxford, we found that by taking out an electron for atropisomeric biaryls and creating radical cations, the resistance to racemization is reduced dramatically, so much so that some reactions can occur at room temperature—contrary to prior research. We also explored the mechanism of how these radical cation molecules operate. Our discoveries will have implications in pharmaceutical applications.

Q: COULD YOU TELL US MORE ABOUT THE MOST EXCITING PROJECT YOU ARE WORKING ON NOW?

Currently, I'm working on electrocatalysts, a class of catalysts that increases the reaction rate of electrochemical reactions. We are focusing on the oxygen reduction reaction (ORR), or the process of harvesting electricity from the conversion of O_2 and H_2 to form H_2O. So far, this process only recovers 25 percent of the total energy of the reaction.

To achieve a future renewable hydrogen economy, it is necessary to decrease the cost, improve the stability and increase the efficiency of hydrogen fuel cells. It is therefore interesting to explore the use of other metals rather than just state-of-the-art platinum alloys, which is one key aspect of our project right now.

Q: WHAT KEY PROBLEM DO YOU HOPE TO SOLVE THROUGH YOUR CURRENT RESEARCH WORK?

Broadly speaking, you can see many different fields of research trying to incorporate ML and AI into their projects. ML can help handle large amounts of data and a good working ML code can perpetuate important information as the code 'learns' from what it is doing—growing more sophisticated in the process.

“Science communication and science education are both important to me. I’ve always looked for opportunities to mentor others and share my research in a more palatable manner with the general public.”

— Jacqueline Tan, A*STAR National Science Scholar

Q: WHY DO YOU THINK SCIENCE COMMUNICATION IS IMPORTANT?

Science communication and science education are both important to me. I’ve always looked for opportunities to mentor others and share my research in a more palatable manner with the general public.

Before I left Singapore, I mentored fourth-year university students during their summer program. When I was at Oxford, I worked closely with a company producing scientific toys for children to inspire them about STEM research. While at MIT, I volunteered at the Cambridge Science Festival and at the MIT Museum to showcase amazing research to adults and children alike. Across the different universities and countries I’ve been to, the audiences I’ve engaged with have always had a strong interest in science communication.

I even incorporated science into my wedding! Over the years, the medium of communicating and promoting science has shifted online. But I believe that scientists will adapt to these changes as long as they are excited to share their findings with others. After all, excitement is contagious!

Q: HOW HAS MACHINE LEARNING CHANGED THE WAY WE UNDERSTAND CHEMISTRY?

The use of ML can accelerate chemical and drug discovery by exploring the combinatorial space of chemical motifs more effectively. Just to put it in perspective, there are an estimated 10^{60} possible small to medium-sized molecules to explore. Traditional methods cannot possibly tackle this astronomical number. ML, together with high-throughput virtual screening and experimentation, can at least help us approach this difficult task.

Back when I was doing my research internship at A*STAR’s Institute of High Performance Computing (IHPC), I worked in polymer research and made use of simulation tools to understand how the aromatic substitution of a surfactant molecule could help with encapsulating materials for drug discovery. We also investigated how the ring size of cyclic ketene acetals can help with polymer biodegradability, which in turn can help reduce negative environmental impacts.

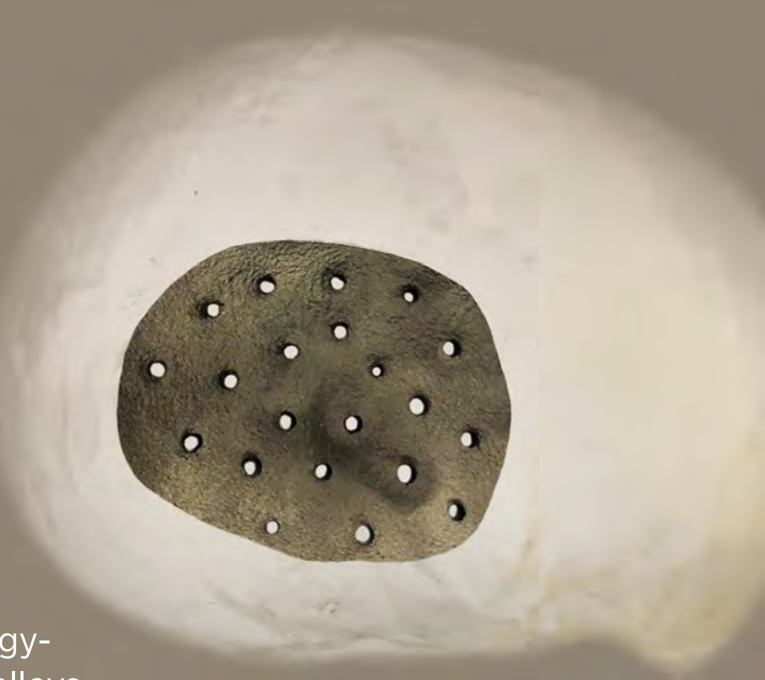
As our technical capabilities increase, can you imagine how much faster we can achieve these results, and how much deeper we can go in our scientific exploration?

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

Based on what we can achieve now with ML and AI, and at the speed that we are going today, the future is full of possibilities. But at the end of the day, I do think sometimes we need to take a step back and remember that we are trying to improve the world for the next generation—something I realized for myself when I became a mother. I truly hope that my child will be able to thrive in the future that we are building for them. ★

MATERIALS SCIENCE

Magnesium alloy manufacturing goes green



Scientists have developed a faster, more energy-efficient method for 3D printing magnesium alloys, creating new opportunities for biomedical applications.

Popularly known as an important mineral for maintaining bone health, magnesium is also an attractive material for manufacturing everything from airplane parts to bone implants, thanks to its lightweight and biodegradable properties. However, the element is also highly reactive, making it difficult to fabricate related compounds using advanced technologies like additive manufacturing (AM) or 3D printing.

These challenges have led researchers to look for novel ways of applying AM protocols in the manufacturing of complex and customizable magnesium alloys. One such method is binder jet AM, which shapes powdered metals into their near-final form. Unlike fusion-based AM methods, binder jetting can be done at almost ambient temperatures. The downside, however, is that binder jetting is more time-consuming, hindering its widespread industrial adoption.

In their latest study, Mojtaba Salehi, Sharon Nai and colleagues at A*STAR's Singapore Institute of Manufacturing Technology (SIMTech) explored alternative AM methods that are more efficient. Specifically, the team sought to shorten a lengthy post-processing step called sintering, where powdered particles are fused into a solid material through heat or pressure.

Conventional sintering involves an external source generating heat that is transferred to the material, while in another technique called microwave sintering, the material absorbs microwave energy that is then converted into heat. The team's primary aim was to investigate if and how microwave heating shortened the sintering time of 3D printed magnesium parts, as compared to conventional sintering.

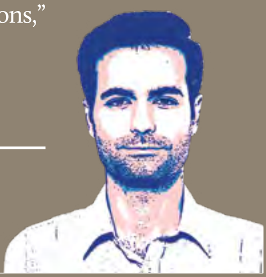
To this end, the researchers used the 3D printing method they established to manufacture magnesium alloys and then tested various sintering durations in both a conventional and a microwave furnace.

Comparing the physical, chemical and mechanical properties of the end products, the researchers found that microwave-sintered objects could be produced three times faster than their conventionally sintered counterparts, saving energy by nine-fold.

"Our comparative analyses of the properties and sintering mechanisms in the microwave and conventional furnaces revealed that the synergy between the post-print microwave heating and the binder-free method that we previously established to eliminate the lengthy binder removal step, could be the fastest and greenest approach for binder jet AM," Salehi said.

The researchers also explored the potential of using printed magnesium specimens as bone scaffolding. Intriguingly, magnesium parts sintered for 15 hours in a microwave furnace were found to have comparable interconnected pore structures and physical properties to the human cortical bone.

The team is now collaborating with research and industry partners in Singapore and Germany to develop digital manufacturing solutions for fabricating biodegradable magnesium implants. "Such an end-to-end manufacturing solution enables the fabrication of customized porous magnesium parts, revolutionizing the future of magnesium alloys for implant applications," Salehi said. ★



Researcher
Mojtaba Salehi, SIMTech

ABOVE
Researchers are using a greener variation of binder jet additive manufacturing to print magnesium parts for bone implants.

Photo credit: Mojtaba Salehi / SIMTech

1. Salehi, M., Seet, H.L., Gupta, M., Farnoush, H., Maleksaeedi, S., *et al.* Rapid densification of additive manufactured magnesium alloys via microwave sintering. *Additive Manufacturing* **37**, 101655 (2021).
2. Salehi, M., Maleksaeedi, S., Nai, S.M.L., Meenashisundaram, G.K., Goh, M H., *et al.* A paradigm shift towards compositionally zero-sum binderless 3D printing of magnesium alloys via capillary-mediated bridging. *Acta Materialia* **165**, 294-306 (2019).

ARTIFICIAL INTELLIGENCE

A death clock for machines

Deep learning algorithms for predicting machine failures in industrial settings can be compressed without compromising their performance, say A*STAR researchers.

Imagine running late for an important meeting but your car refuses to start, despite a full gas tank and no warning signs flashing on the dashboard. If only there had been a way to anticipate that the vehicle's engine was close to its end.

Artificial intelligence can make these predictions, at least in an industrial setting. Many companies use deep learning algorithms to estimate when machines are likely to start winding down, helping avoid emergencies due to unexpected failures. However, because these algorithms are so complex, they need to be run on advanced computing systems that are often housed off-site, thus limiting their use in real-time decision making.

A team of researchers led by Qing Xu, a Research Engineer at A*STAR's Institute for Infocomm Research (I²R), was interested in streamlining these computational platforms to make them more accessible for everyday, on-the-job use.

The experts turned to knowledge distillation, a method by which a larger, more complicated computing system called the 'teacher' transfers its knowledge to a smaller, more economical 'student' system. Upon distillation, the 'student' learns to copy the outputs of the 'teacher' using less disk space, allowing advanced calculations to be performed by regular computer hardware.

The problem is that this distillation process is not foolproof—compressing elaborate equations compromises the algorithm's predictive accuracy. To overcome this challenge, the team created a novel framework for knowledge distillation that they named KDnet-RUL.

Designed to be fast and take up minimal storage space, KDnet-RUL retains its teacher's accuracy through a specialized two-factor approach. First, a generative adversarial network facilitates the actual knowledge transfer from the original, highly complex prediction algorithm to a basic convolutional neural network. The 'student' then passes through several cycles of learning-during-teaching knowledge distillation to improve its accuracy at forecasting a machine's remaining lifespan.

For KDnet-RUL's test run, the researchers used C-MAPSS, a public dataset that simulates how turbofan engines degrade over time. They found that KDnet-RUL was just as effective as its 'teacher' network at estimating when these engines would fail. In some instances, the 'student' even had more accurate estimates than the 'teacher' and could deliver its lifespan predictions more rapidly.

"These findings provide a possible model compression solution that addresses an actual industry requirement of deploying a powerful but cumbersome network into resource-limited edge devices," Xu said.

"In the future, we will consider a more realistic and challenging scenario where the data for training and testing may come from different distributions," he added, stating that future iterations of KDnet-RUL may be able to apply a model derived from one machine to predict the lifespan of another. ★

Photo credit: YouraPechkin / Shutterstock

Researcher
Qing Xu,
I²R

LEFT
By distilling knowledge into smaller, more economical systems, deep learning algorithms could forecast machine breakdowns with improved accuracy and less disk space.

1. Xu, Q., Chen, Z., Wu, K., Wang, C., Wu, M., *et al.* KDnet-RUL: A knowledge distillation framework to compress deep neural networks for machine remaining useful life prediction, *IEEE Transactions on Industrial Electronics* (2021).

ROBOTICS

Safety first when man meets robot

A fresh design approach to high-performing variable stiffness rotating joints could enable humans to work safely alongside robots in industrial manufacturing environments.

Robotic automation offers pronounced advantages over human manpower in industrial settings. After all, robots can work tirelessly and perform difficult, repetitive tasks faster and more accurately. Nonetheless, it's unlikely that robots will ever completely replace humans. Instead, optimal productivity would require man and machine to work synergistically in shared workspaces.

For now, true human-robot collaborations remain out of reach, with safety being a major concern. In industrial robots, the key components for achieving high-velocity and high-payload performance are the motors called actuators that move their joints. However, these actuators are often rigid and unable to adapt to sudden environmental changes; one wrong step, and they could easily collide with or crush a human co-worker.

"As a result, humans and robots will be able to work together and share a workspace to improve the adaptability, flexibility and efficiency of adaptive manufacturing."

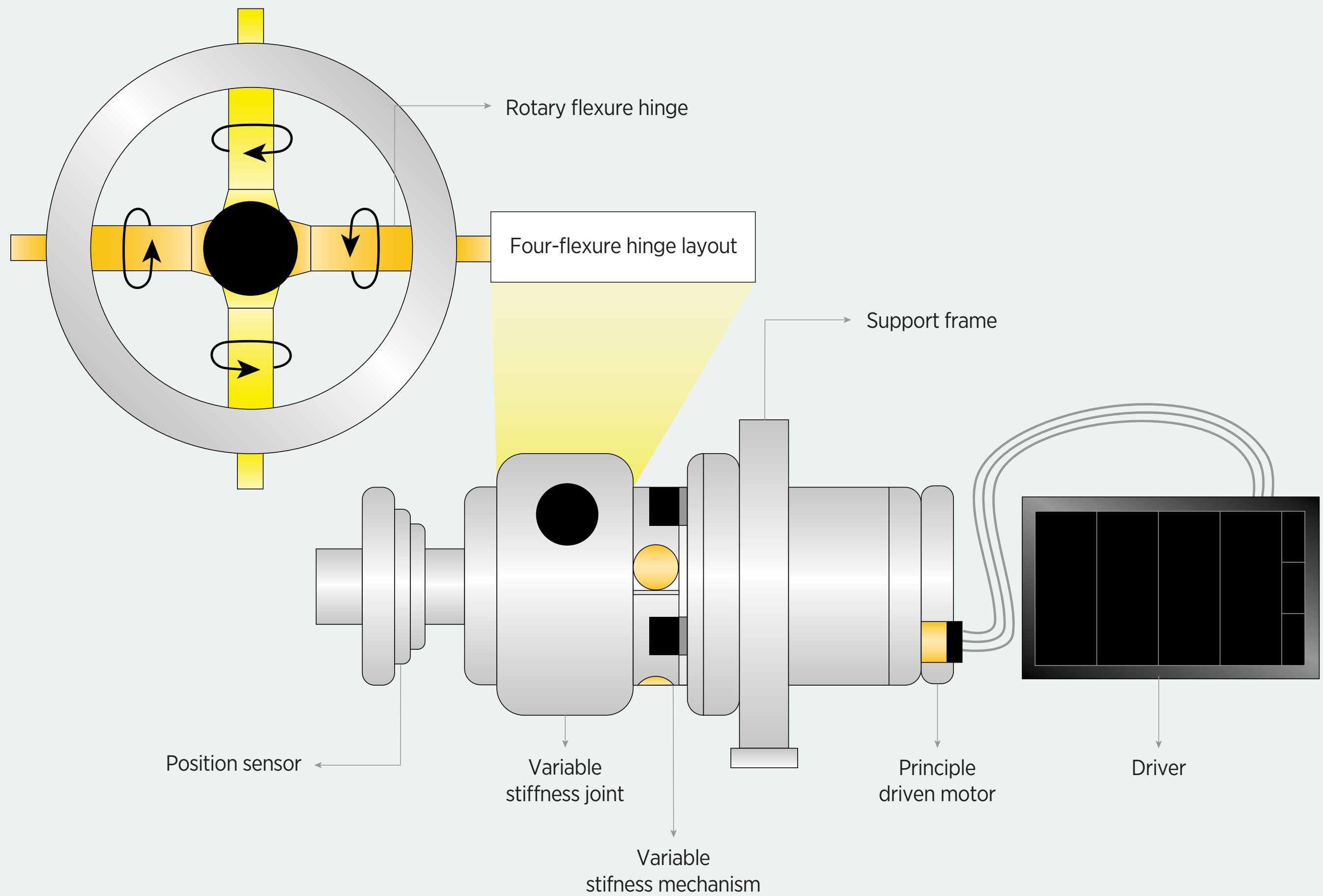
Variable stiffness actuators (VSAs) offer a potential solution to this safety concern. VSAs contain elastic elements that enable a robot to work in a 'safety mode' when alongside humans, and switch to higher stiffness modes when performing more demanding, robot-only applications.

"Without sacrificing payload and precision, VSAs can balance flexibility and rigidity to suit different application requirements," explained Wei Lin, a Senior Scientist at A*STAR's Singapore Institute of Manufacturing Technology (SIMTech). To push the limits of human-robot cooperation, Lin, his SIMTech colleague Haiyue Zhu and a team of robotics experts set out to create the next generation of VSA systems capable of more complex maneuvers and featuring enhanced safety profiles.

In their study, the team explored novel approaches to creating VSA-based robot joints that could twist and rotate, with the flexibility of working at different joint stiffness settings. They adopted an internal spring mechanism that uses thin, flexible parts called rotary flexure hinges to connect the input shaft—the central rod that delivers power to the device—to the output frame.

Until now, conventional single-spring mechanisms have been notoriously unreliable, with unbalanced twists between

Photo credit: TTHINK A / Shutterstock



With a variable stiffness mechanism based on four rotary flexure hinges at opposite orientations, the robotic joint's stiffness can be adjusted with low inertia and friction.

the input shaft and output frame during joint rotation leading to unpredictable positioning errors. To overcome this challenge in their new design, the researchers first modeled changes in actuator stiffness as the flexure hinge rotates. Based on these data, they compared the performance of six distinct flexure hinge configurations.

The optimal joint design, containing four flexure hinges at opposite orientations, could rotate freely about its axis without displaying any unwanted contortions. A prototype robot built by the team was found to be dynamic and adaptable, outperforming current VSAs by continually and rapidly modifying its joint stiffness. According to Zhu, their prototype managed to adjust from the lowest stiffness to the maximum stiffness in just 0.83 seconds, with a designable stiffness range that could easily be adapted to different industrial applications.

These results form a stepping stone in the researchers' pursuit of next-generation precision collaborative robots. Musing on a future where such man-machine partnerships become a reality, Zhu said: "As a result, humans and robots will be able to work together and share a workspace to improve the adaptability, flexibility and efficiency of adaptive manufacturing." ★

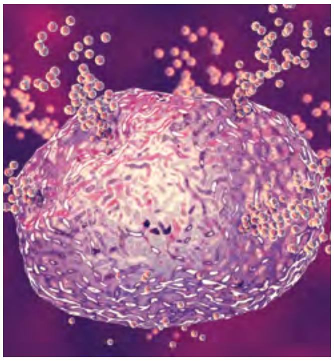
Researcher
Haiyue Zhu, SIMTech

LEFT
With their ability to twist, rotate and work at different joint stiffness settings, new variable stiffness actuators promise to bring man-robot collaborations into a safer reality.

1. Li, X., Zhu, H., Lin, W., Chen, W., and Low, K.H. Structure-controlled variable stiffness robotic joint based on multiple rotary flexure hinges. *IEEE Transactions on Industrial Electronics* (2021).

NEXT ISSUE

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



IMMUNOLOGY

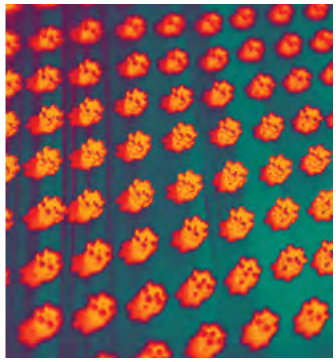
WHEN ALLERGIES PASS FROM MOTHER TO CHILD

Maternal antibodies can cross the placenta and pass on a mother's allergies to her unborn child, an A*STAR study found.

CARBON CAPTURE

CARBON-TRAPPING MINERALS PROMISE A GREENER TOMORROW

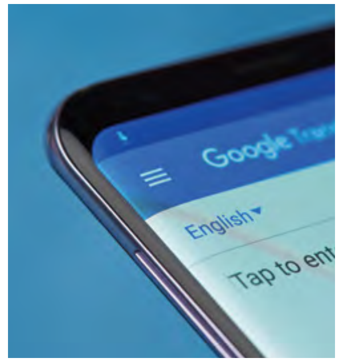
A technology for capturing waste carbon dioxide and turning it into sand could help Singapore reduce its carbon emissions.



PHOTONICS

SEEING BIOLOGICAL SPECIMENS IN A NEW LIGHT

Scientists have developed a technique for performing advanced infrared microscopy using off-the-shelf cameras built for visible light.



MACHINE LEARNING

BOOSTING MACHINE TRANSLATION BY DIVERSIFYING DATA

By generating diverse synthetic training data, machine translation can be made more efficient and effective.

A*STAR RESEARCH

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