A*STAR
RESEARCH

SHAPING A SUSTAINABLE SINGAPORE

The multidisciplinary
A*STAR teams helping the nation
achieve its sustainability goals

page 08

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

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

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

A*STAR Infectious Diseases Labs (ID Labs)

A*STAR Skin Research Labs (A*SRL)

Advanced Remanufacturing and Technology Centre (ARTC)

Bioinformatics Institute (BII)

Bioprocessing Technology Institute (BTI)

Experimental Drug Development Centre (EDDC)

Genome Institute of Singapore (GIS)

Horizontal Technology Coordinating Offices (HTCO):

  Agritech and Aquaculture (A2)

  Artificial Intelligence, Analytics and Informatics (AI³)

  Health and Medical Technologies (HMT)

  Infectious Diseases (ID)

  Robotics

  Social Sciences and Technology (SST)

  Urban and Green Technology (UGT)

Institute of Bioengineering and Bioimaging (IBB)

Institute of Sustainability for Chemicals, Energy and Environment (ISCE²)

Institute of High Performance Computing (IHPC)

Institute for Infocomm Research (I²R)

Institute of Molecular and Cell Biology (IMCB)

Institute of Microelectronics (IME)

Institute of Materials Research and Engineering (IMRE)

National Metrology Centre (NMC)

Singapore Immunology Network (SIgN)

Singapore Institute for Clinical Sciences (SICS)

Singapore Institute of Manufacturing Technology (SIMTech)

Singapore Institute of Food and Biotechnology Innovation (SIFBI)

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EDITORIAL NOTES

I n a century where the way we live our lives has increasing repercussions on the world around us—in extreme weather events, supply chain disruptions, and environmental degradation—sustainability has moved from a feel-good watchword to a vital element for consideration in every aspect of our society. From how we grow our food to the way we dispose of our waste, today's scientists face monumental challenges to meet the needs of future generations without costing the earth.

This issue's cover story, 'Shaping a sustainable Singapore (p. 08)', takes a broad look at how A*STAR supports the country's sustainable development goals as its lead public sector research and development agency. Working in tandem with academia and industry, A*STAR researchers and research institutes are making strides in creating innovative, integrated solutions to decarbonise the nation, digitise and automate industries, and create a more liveable city for a growing population.

From this overview, take a deeper dive into our feature on metabolic engineering with Xixian Chen at A*STAR's Singapore Institute of Food and Biotechnology Innovation (SIFBI). In 'Streamlining operations of life's fundamental factories (p. 22)', Chen explains how A*STAR researchers are using microorganisms as biological factories, producing food and cosmetics from renewable carbon sources while using less energy, land and water than conventional methods.

With production also comes waste. An A*STAR scholar, Edward Neo, is keen to tackle the way we manage it. In our second feature, 'Closing the recycling loop with chemistry (p. 28)', he discusses how artificial intelligence and chemistry can reduce the amount of single-use plastics going to landfill.

This issue also highlights other A*STAR advances in fields ranging from molecular biology in 'Designing drugs on new principles (p. 04)' to materials science in 'A modern twist to ancient alloys (p. 32)'.

For more of the latest developments from A*STAR scientists, visit our website at **research.a-star.edu.sg**. You can also stay up-to-date by following us on Twitter at **@astar_research**, LinkedIn at **A*STAR Research** and Telegram at **A*STAR Research**.

On the cover
Green urban design, alternative energy, future foods and automation are among the myriad solutions scientists are exploring to meet sustainability targets.

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/

PROTEIN MODELLING

Designing drugs on new principles

A computational model developed at A*STAR provides insights on how molecular dynamics of proteins impact their function, unlocking new precision medicine opportunities.

We have vaccines, treatments and diagnostics to combat the spread of COVID-19, yet the coronavirus is always one step ahead. A parade of variants has emerged over the years, each harbouring mutations that help it to evade pandemic countermeasures. Now, an innovation that combines computer science and protein biology advances could help us regain control.

Igor Berezovsky, Senior Principal Investigator at A*STAR's Bioinformatics Institute (BII) leads a team interested in the relationship between a protein's structure and its function. They have been studying a mechanistic phenomenon called allostery, where changes on one protein site—such as the binding of a ligand—trigger changes at a distant site via the dynamics of the whole structure. Allostery is an incredibly complex and sophisticated tool that can help in the development of more durable and effective treatments for a range of conditions.

For over five years, Berezovsky's team has been building computational frameworks to crack the allostery code. The researchers developed a theoretical model called the Structure-Based Statistical Mechanical Model of Allostery (SBSMMA) that offers key advantages over previous phenomenological approaches.

"SBSMMA can calculate the energetics of allosteric signalling at the single amino acid level, giving users the ability to predict the intra-protein communication provided by protein dynamics with unprecedented precision," Berezovsky explained.

In their latest study, the team took SBSMMA to the next level, developing comprehensive protocols for analysing allosteric signalling and targeting new sites and effectors. They demonstrated the computational framework's utility in the design of allosteric drugs for tackling mutating targets in two disease models, COVID-19 and cancer.

The researchers mapped the mutational blueprints of these conditions by analysing the allosteric effects of both individual amino acid mutations and ligand binding. They compiled these data in the Allosteric Signalling Maps (ASMs) and Allosteric Probing Maps (APMs), computational tools that help predict how allostery and mutations can impact protein signalling.

According to Berezovsky, these tools can also be used to design new allosteric site-effector pairs, and can be particularly
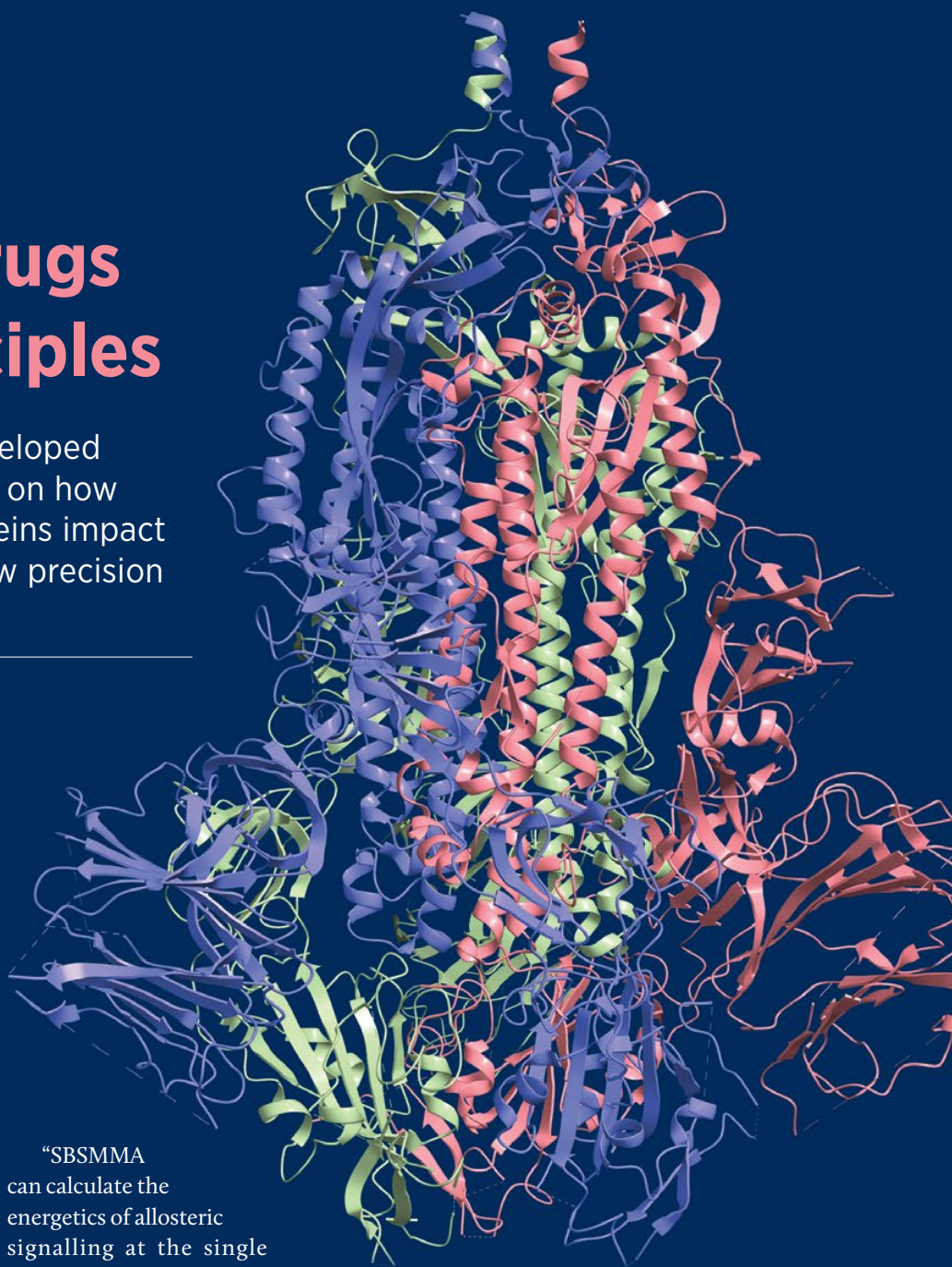
Photo credit: Volodymyr Dvornyk / Shutterstock
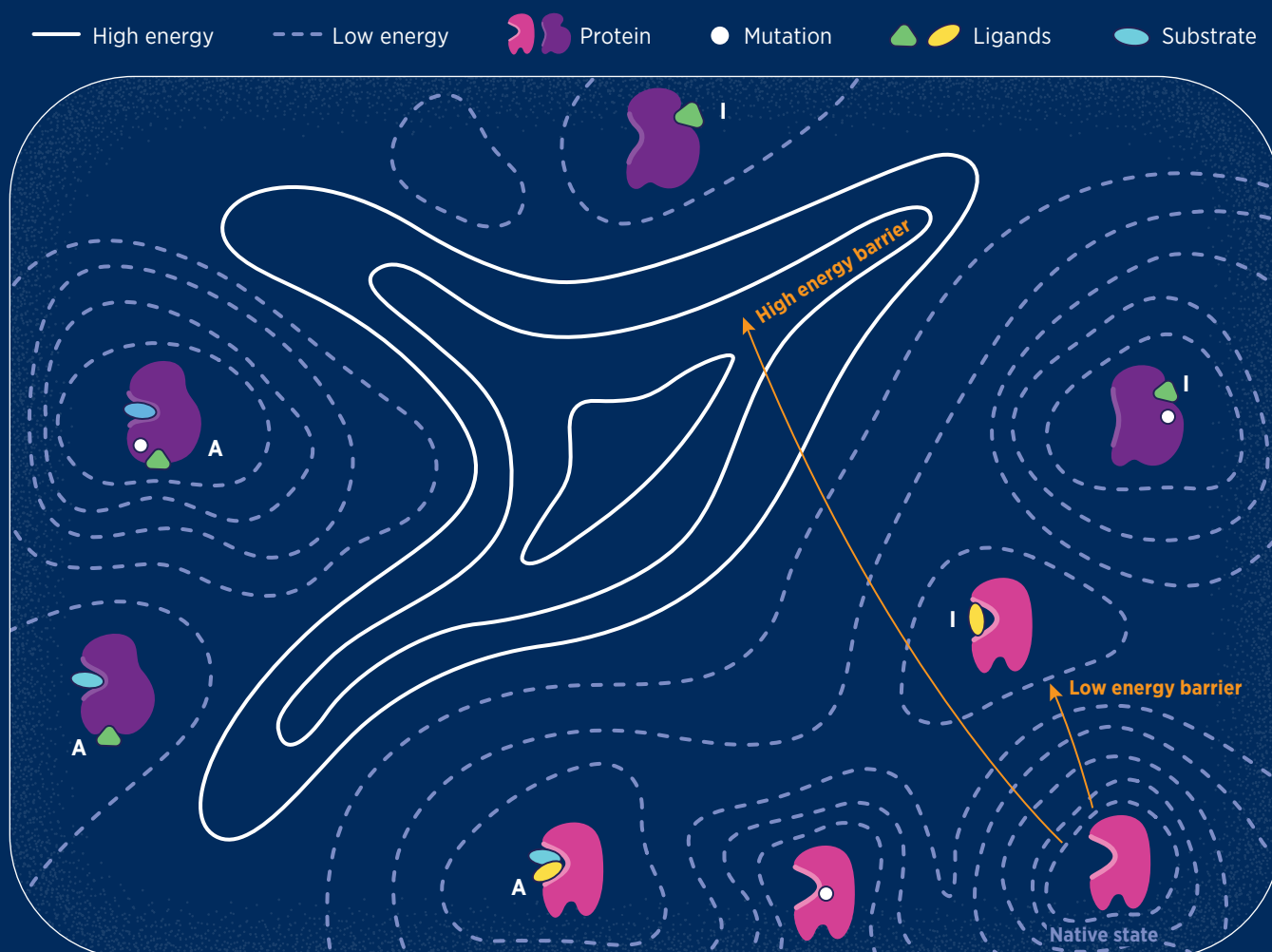
A hypothetical energy landscape containing orthosterically/allosterically regulated (pink/purple) protein structures can be explored with SBSMMA. Activated (A) or inhibited (I) protein states are separated from the native state by energy barriers which can be passed with the help of ligands and/or mutations.

"SBSMMA can calculate the energetics of allosteric signalling at the single amino acid level, giving users the ability to predict the intra-protein communication provided by protein dynamics with unprecedented precision."

useful when the allosteric sites of a given protein are still unknown. "The procedure can start from using available information or it can start from what we call agnostic analysis," he said.

Protein scientists have full access to these tools online through the AlloSigMA web server and the AlloMAPS database, which Berezovsky's team is continually refining. "We just updated AlloMAPS with exhaustive data on allosteric signalling in the SARS-CoV-2 spike protein," Berezovsky said, which allows researchers to pinpoint specific mutations that act as viral drivers and develop therapeutic strategies to make the virus less harmful. ★

**Researcher
Igor Berezovsky,
BII**

IN BRIEF
Changes on one site of a protein can result in changes in both morphology and function elsewhere, a phenomenon that may be leveraged for therapeutic purposes.

1. Tan, Z.W., Tee, W-V., Samsudin, F., Guarnera, E., Bond, P.J., Berezovsky, I.N. Allosteric perspective on the mutability and druggability of the SARS-CoV-2 Spike protein. *Structure* **30**, 590-607 (2022).
2. Tee, W-V., Tan, Z.W., Lee, K., Guarnera, E., Berezovsky, I.N. Exploring the Allosteric Territory of Protein Function. *The Journal of Physical Chemistry B* **125**, 3763–3780 (2021).

COVID-19

Why remdesivir works for some COVID-19 patients but not others

Remdesivir treatment is more likely to be successful in COVID-19 patients who are naturally able to mount a strong immune response against infections.

In October 2020, the US Food and Drug Administration (FDA) approved the emergency use of the antiviral drug remdesivir to treat COVID-19. Finally, after seven months of fear and uncertainty, there appeared to be hope against the disease that had brought the world to a standstill.

Remdesivir helps patients fight COVID-19 by preventing the virus from multiplying further, effectively putting a stop to its life cycle. However, there was a curious catch: it didn't work all the time. Many patients on oxygen support continued to deteriorate despite remdesivir treatment, suggesting that the drug was effective only in some patients. Why this was so, or what factors made these patients more responsive to remdesivir than others, remained mostly unknown.

To help answer this question, Lisa Ng, Executive Director at A*STAR Infectious Diseases Labs (ID Labs), led a research team in the search for key immune markers that could help doctors identify patients for whom remdesivir treatment would be successful.

With collaborators from the National Centre for Infectious Diseases, the researchers collected plasma samples from 28 severe COVID-19 patients who were treated with remdesivir. Those who did not

> **"Although the exact function of T_h2 in severe COVID-19 is unclear, it is known to have a vital role in the reduction of inflammation in other lung disorders."**

deteriorate enough to need oxygen support were deemed as treatment responders.

Remdesivir turned out to be effective in 21 patients. When Ng and her team measured the levels of immune response markers of this group before and after the treatment, they found that the responders had higher levels of type 2 helper cells (T_h2) than type 1 helper cells (T_h1). This finding suggested that the balance between T_h1 and T_h2 was a potential indicator of response to remdesivir.

"Although the exact function of T_h2 in severe COVID-19 is unclear, it is known to have a vital role in the reduction of inflammation in other lung disorders," Ng explained. "Responders had a higher T_h2 response, indicating that remdesivir

treatment is working and reducing their overactive inflammation."

Other T_h2-associated cytokines were also elevated in responders, further suggesting that T_h2 and its related pathways play an important role in the drug's effectiveness.

Meanwhile, non-responders were more likely to have overactive and uncontrollable inflammation that not even remdesivir could treat, suggesting that adding anti-inflammatory agents to remdesivir could be a promising treatment strategy. However, Ng and her team emphasised that more research is needed before definitive treatment guidelines can be drawn from these results.

"Our findings warrant further studies with larger cohorts to define the underlying immune response differences between responders and non-responders of remdesivir that could have prevented or limited the aggravation of COVID-19," said Ng. ★

Researcher
Lisa Ng,
ID Labs
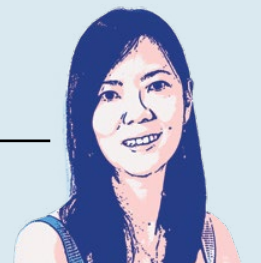
IN BRIEF
Remdesivir, the first antiviral drug approved to treat COVID-19, curiously does not work for all patients.

Photo credit: Myriam B / Shutterstock

1. Chan, Y.H., Young, B.E., Fong, S.W., Ding, Y., Goh, Y.S., et al. Differential cytokine responses in hospitalized COVID-19 patients limit efficacy of remdesivir. *Frontiers in Immunology* **12**, 680188 (2021).

STEM CELLS

Searching for good fat's origins

Researchers have identified a stem cell marker that influences fat cell development, unlocking exciting therapeutic opportunities for chronic diseases.

Due to its links to chronic disease, excess body fat has earned a bad reputation over the years. But not all fat cells, or adipocytes, are created equal. While the accumulation of 'bad' fat around internal organs isn't considered healthy, researchers believe that a distinct class of adipocytes located beneath the skin may help protect against chronic disease.

"These 'good' adipocytes protect against developing metabolic diseases like diabetes and cardiovascular diseases by storing excess calories and secreting metabolically beneficial bioactive molecules," said Shigeki Sugii, a Group Leader at A*STAR's Institute of Bioengineering and Bioimaging (IBB).

Adipocytes develop from a population of progenitor cells called adipose-derived stem cells (ASCs). However, many of the biological processes that govern this maturation are unclear, and researchers still don't know which ASCs end up becoming 'good' adipocytes.

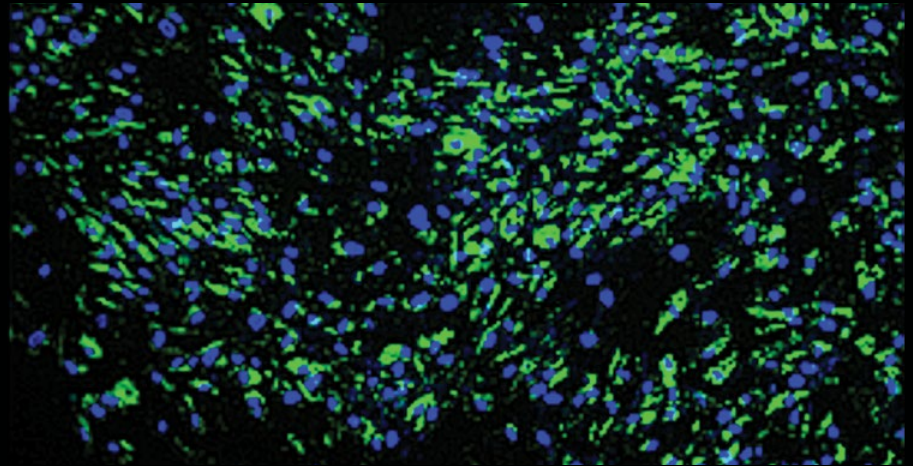Hoping to bridge this gap and unlock new therapeutic targets, Sugii and his team took a closer look at ASC differentiation. Previously, Sugii's group had identified that ASCs found under the skin's surface expressed a specific biomarker, a protein called CD10. Following up on these studies, the team hypothesised that the levels of CD10 could impact ASC's potential to mature into 'good' fat.

To test their theory, the team generated two genetically engineered ASC cell lines where the *CD10* gene was either turned off or switched to overdrive. They then stimulated these cell lines to differentiate using a cocktail of growth factors. Using lipid droplet formation to measure adipocyte maturation, the scientists measured how CD10 impacted fat formation.

The role of CD10 as an orchestrator of fat development was evident. ASCs that lacked CD10 produced fewer lipid droplets than the control cells. On the other hand, those with abundant CD10 levels had significantly more mature adipocytes than control cells at the same time point.

Furthermore, the team uncovered a new aspect of adipocyte maturation. "It was generally believed that the adipocyte differentiation almost always involves a master regulator called PPARγ," said Sugii. "But we showed that CD10 activates the formation of fat cells independent of PPARγ signaling pathways."

Together, these findings suggest that CD10 may someday be used as a stem cell biomarker for predicting the quality of mature adipocytes from ASCs—with potential applications for treating metabolic conditions like obesity and diabetes.

According to Sugii, ASC populations that strongly express *CD10* may be high-quality sources of 'good' adipocytes that could be transplanted in patients to reverse the adverse metabolic processes associated with the disease. Since their study, the team has patented their CD10 technology and is currently collaborating with industry partners to expand the clinical application boundaries of human ASC transplantation. ★

Researcher
Shigeki Sugii,
IBB

IN BRIEF
A protein called CD10 in adipose-derived stem cells activates the formation of 'good' fat cells, which can protect against metabolic diseases.

1. Chakraborty, S., Ong, W.K., Tau, W.W.Y., Zhou, Z., Bhanu Prakash, K.N., *et al*. CD10 marks non-canonical PPARγ-independent adipocyte maturation and browning potential of adipose-derived stem cells, *Stem Cell Research & Therapy* **12**, 109 (2021).

SHAPING A SUSTAINABLE SINGAPORE

Researchers at A*STAR are forming multidisciplinary teams to meet key sustainability targets in support of the Singapore Green Plan 2030.

I f all goes well, in just eight years from now, Singapore will be a global city of sustainability. Specifically, sustainable development, as defined in the seminal 1987 Brundtland report, must "meet the needs of the present without compromising the ability of future generations to meet their own needs". This lofty goal is a part of the country's Green Plan 2030, Singapore's commitment to the United Nations' 2030 Sustainable Development Agenda, and not an easy ask.

To ensure it grows sustainably, Singapore has put into place goals to guide the nation's growth without straining its environmental as well as human, social and economic resources. The five-year Research, Innovation and Enterprise (RIE) 2025 plan, for instance, dedicates two of its four domains to developing a sustainable nation. Similarly, other national initiatives like the aforementioned Singapore Green Plan and inaugural Zero Waste Masterplan provide clear targets to be met by 2030, such as reducing carbon emissions by 36 percent and waste by 30 percent.

"While innovations in research and development (R&D) are crucial to meeting these targets, the best approach is to tackle this collaboratively," said Lean Weng Yeoh, Chief Sustainability Officer of A*STAR. "The nature of sustainability is complex and cannot be resolved with individual scientific disciplines," he shared. "Such ambitious sustainability goals require different disciplines working closely together to deliver integrated solutions."

This is where A*STAR, as Singapore's lead public sector R&D agency, plays a key role. It functions as a convener of the entire ecosystem, creating private-public partnerships with academia and industry R&D centres to deploy sustainable technologies. A*STAR's own efforts encompass research and innovation to tackle sustainability challenges, from developing new materials to taking cutting-edge synthetic-biology approaches to food production.

A NEW INSTITUTE FOR SUSTAINABLE CHEMICALS, ENERGY AND ENVIRONMENT

Perhaps most telling of A*STAR's dedication to Singapore's sustainability vision is the reorganisation of its former Institute of Chemical and Engineering Sciences (ICES) into the new Institute of Sustainability for Chemicals, Energy and Environment (ISCE²). Launched in 2022, ISCE² aims to support Singapore's sustainability goals and initiatives by leveraging existing strong partnerships with the energy, chemical and pharmaceutical industries to deliver and deploy sustainable solutions.

"We have repositioned existing core competences and capabilities to address national imperatives and to advance R&D in low-carbon technologies, green processes, digitalisation and automation as well as sustainable materials," explained Yeoh. "This [new research institute] is timely given an increased global focus on climate change and sustainability."

Singapore, with its limited human and natural resources, faces serious threats posed by climate change. This small urban island state, like the rest of the world, is getting hotter. Between 1980 and 2020, the average temperature rose from 26.9 to 28.0 °C. This seemingly minute difference of just over 1 °C has much larger consequences—for Yeoh, climate change represents one of the greatest existential challenges in Singapore.

"Climate change will have an adverse impact on water supply stability, biodiversity and greenery, public health, urban heat island effects and food security," said Yeoh. "Because the impact of climate change is closely linked to greenhouse gas emissions, innovations in decarbonisation and energy transition will be crucial in mitigating the effects of greenhouse gases."

THE NEW GREEN MATERIALS

Just like carbon emissions and rising temperatures, plastic waste is another troubling by-product of modern human life. Despite the prevalence of recycling bins and public awareness campaigns, recycling plastic isn't as easy as one might think. Only an estimated four percent of the plastic waste in Singapore is actually recycled, with the rest ending up in landfills or incinerators.

To address the plastic waste problem, research at ISCE² focuses on developing green materials as plastic substitutes that can be easily recycled or biodegraded. The Sustainable Polymers (SP) Division at ISCE² spans a wide range of materials research areas that aim

> **"We have repositioned existing core competences and capabilities to address national imperatives and to advance R&D in low-carbon technologies, green processes, digitalisation and automation as well as sustainable materials."**
>
> — Lean Weng Yeoh, Chief Sustainability Officer of A*STAR

to reconfigure and reorient the plastic value chain towards a more sustainable state. One solution is to develop green materials and sustainable packaging technologies for use in the fast-moving consumer goods industry, such as in food packaging and other commercial items.

"If you look at the amount of plastic waste globally, close to half comes from the packaging industry, and most of them are single-use plastics," said Zibiao Li, Director of the Sustainable Polymer Division.

A key reason why plastic packaging is so hard to recycle has to do with how it is constructed: it isn't always just pure plastic. Current flexible plastic packaging is dominated by multilayer packaging materials, explained Li.

A single piece of flexible plastic packaging often includes layers of different materials, such as structural layer materials, aluminium and adhesives, to improve properties that could include barrier performance, resistance to mechanical stress, sealability and printability. But while this complex composition makes these plastics good for use as packaging, they pose a challenge to recycle.

To alleviate the plastic problem in the short term, the team at ISCE² is improving the properties of recyclable polyolefin materials, called mono-material packaging, for

use as packaging that performs just as well as conventional multilayer plastic. The team has already partnered with local enterprise Aegis Packaging to commercialise the recyclable plastic material.

In the long term, however, Li advocates for more sustainable alternatives that do not rely purely on recyclability. "We are looking at advanced packaging materials that can be degraded into small molecules, water or carbon dioxide," Li suggested.

MODELLING A MORE LIVEABLE CITY

A*STAR's success in the development of integrated, multidisciplinary solutions can be attributed in part to its seven Horizontal Technology Coordination Offices (HTCOs). HTCOs act as conveners and sit at the intersection of disciplines to coordinate research outcomes from A*STAR's many research institutes and programmes.

One successful example is the solution produced by the Urban and Green Technology HTCO in collaboration with the Housing and Development Board (HDB), Singapore to identify and tackle the challenges unique to densely populated urban residential areas.

Singapore is home to over five million people, and this high population density may result in the city not being the most comfortable place to live in. Studies have shown that urban areas are hotter as more concrete surfaces trap heat while increased urban and industrial activity results in increased noise levels.

While solutions for urban heat and noise exist, for a city to be truly sustainable as well as comfortable, these urban discomforts should be addressed in a way that does not tax the environment. One such solution is to cool cities naturally without relying on energy-intensive air conditioning systems.

In response, a team led by built environment specialist Hee Joo Poh, a Senior Scientist at A*STAR's Institute of High Performance Computing (IHPC), developed the Integrated Environmental Modeller (IEM), an award-winning digital modelling tool, in collaboration with A*STAR's Urban and Green Technology HTCO and HDB, and supported by the Ministry of National Development (MND) and National Research Foundation Singapore (NRF).

The IEM's simulation software draws upon multiple data sources to recreate and simulate microclimate scenarios in Singapore, thus allowing urban planners and architects to accurately model different design plans for comfortable and sustainable residential towns.

Through these in-depth simulations and models, the IEM helps to optimise land use and building layouts to promote natural ventilation and reduce heat, glare and noise levels. For example, it has demonstrated how the strategic placement of greenery in areas exposed to the sun can mitigate high ambient temperature.

"Conducting large scale urban microclimatic modelling during the town planning and urban design stage is important to establish feasible mitigation strategies and translate them into planning and urban design guidelines," said Poh, who worked on the IEM tool alongside Wee Shing Koh, a Senior Scientist at IHPC, and Fachmin Folianto, a Principal Research Engineer at A*STAR's Institute for Infocomm Research (I²R).

"In the past, there was a lack of scientific modelling tools for urban planners to solve inter-linked multi-physics problems like wind, temperature and solar irradiance," Folianto said. "The team developed the IEM tool to unify and integrate these environmental factors."

Thanks to developments in high performance computing, IEM's simulations have also been scaled up for the whole of Singapore. The tool has also been adopted by HDB in the planning of the new residential Tengah Forest Town, the first time such an integrated technology has been used on a town-wide level.
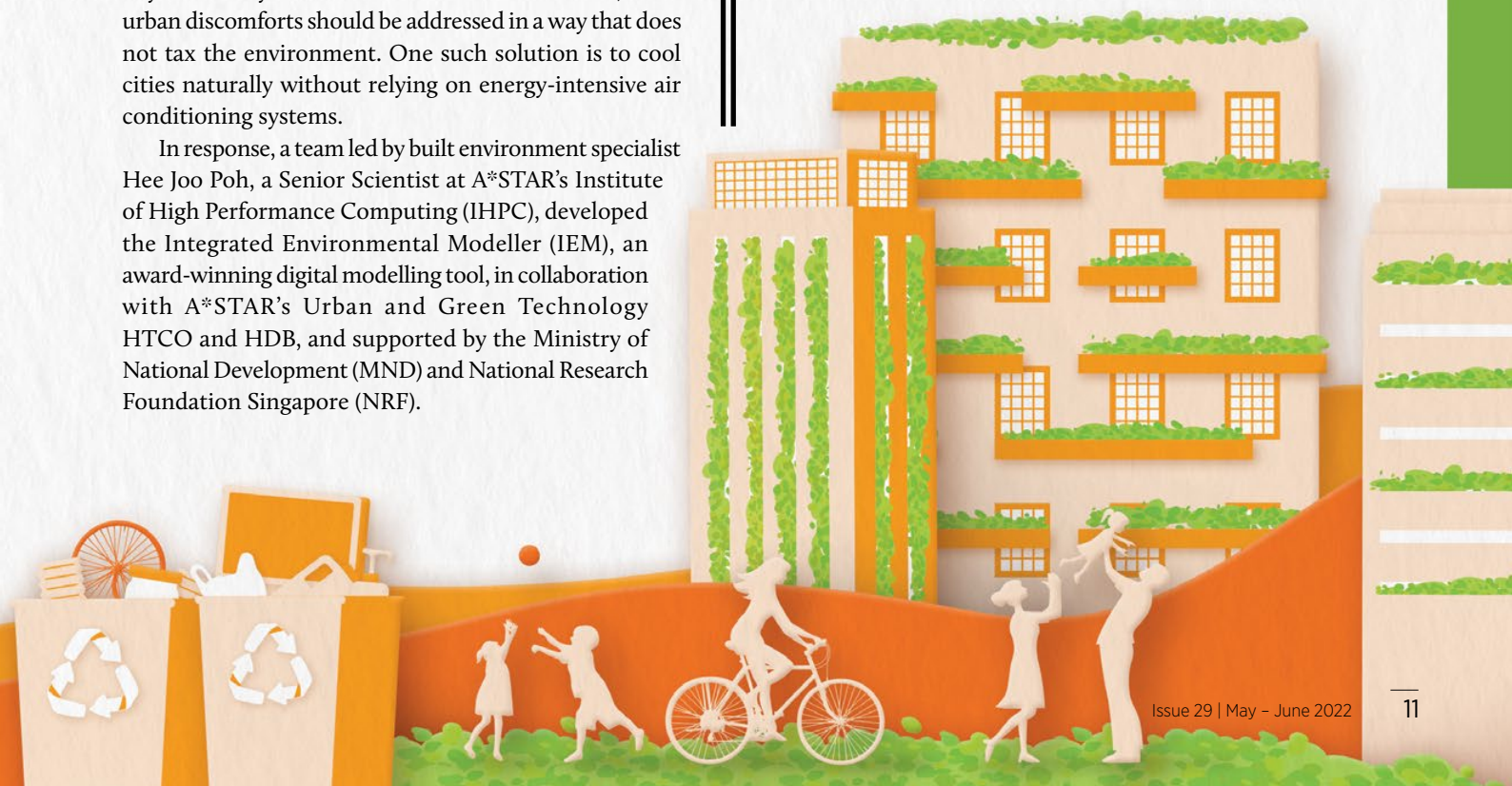
LENDING A ROBOTIC HAND

On the other end of Singapore's population challenge, A*STAR's Robotics HTCO hopes to tackle the problem of a limited and ageing workforce through smart robotic technologies, systems and solutions.

"Manpower and resources are finite, and so the optimised allocation of such resources is crucial for sustainable development," said Wei Wang, Lead of the Robotics HTCO.

Interestingly, Singapore's manufacturing sector has been able to maintain its contribution to the country's annual GDP at between 20 and 25 percent despite its limited manpower.

"One of the key enablers to this is robotics," said Wang, adding that robots increase productivity by performing repetitive and manual tasks, thus enabling staff to carry out higher value work. In fact, the International Federation of Robotics estimated in 2021 that Singapore has one of the highest densities of manufacturing robots in the world, with 605 robots per 10,000 human workers.

Wang points out that robots also can be deployed to tackle manpower challenges in sectors beyond manufacturing, leveraging on similar operation tasks like sanitation and material transportation in newer sectors such as healthcare and built environment.

In this landscape, A*STAR's Robotics HTCO has seed-funded 10 projects since November 2021, which include developing robotics technology for a myriad of purposes ranging from healthcare to precision agriculture and aquaculture solutions for sustainable food production. One project the HTCO is currently funding is an automation system to count and sort prawn larvae by size in vertical prawn farms, with the aim of optimising growth yield to resource.

FOOD FOR THE FUTURE

This issue of sustainable food security is particularly pertinent in the face of economic development and urbanisation. The United Nations projects approximately 68 percent of the global population will live in urbanised settlements by 2050, but this is nothing new for Singapore: the island nation has been a highly urbanised country since the 1950s, with a fully urban resident population. This shift away from agricultural settlements and towards urbanised residential and financial areas has led to decreased land availability for food production.

As a result, Singapore is currently highly reliant on food imports, with less than 10 percent of local food production contributing to the nation's total food supply. Besides limited land, there is also mounting pressure from supply chain disruptions and climate change to maintain access to food that meets the nutritional needs of Singapore's residents.

To mitigate the risks associated with the nation's future food supply, the Singapore Food Agency (SFA) aims to increase local agrifood capacity to produce 30 percent of Singapore's nutritional needs by 2030—dubbed 30 by 30.

But increasing food production with limited arable land for agriculture poses a unique challenge. In countries such as the US, urban farming—the practice of growing crops using smaller plots of available land in an urban setting—is used not only to promote a greener environment but also to address food deserts in urban areas, where lower income families may not be able to easily access fresh fruits and vegetables.

Here, A*STAR is taking a cutting-edge approach to tackle sustainable food production: synthetic biology.

Synthetic biology (Syn Bio) focuses on redesigning or reengineering existing organisms, usually microbes such as bacteria, yeast, fungi and microalgae, to design new, powerful ones for further use. A*STAR's Singapore Institute of Food and Biotechnology Innovation (SIFBI) is already harnessing the power of bacteria, yeast and fungi while planning to engineer microalgae to produce protein-rich foods for the nation.

"Compared to conventional sources of protein from meat and seafood, as well as plant-based alternatives like soy or wheat, our Syn Bio engineered microbe production will aim at having a much lower environmental footprint," said Melanie Weingarten, Director at Biotransformation, SIFBI.

As Weingarten explains, metabolic engineering of microbial strains requires significantly lower land usage as they are grown in bioreactors with higher productivity. More protein and nutrients can be grown in a shorter period of time which gives a higher space-time-yield.

Once grown via fermentation and harvested via downstream processing, the engineered microbes are usually obtained as a nutrient-rich powder containing as high as 70 percent protein by dry weight, starch, valuable lipids and high value bioactives. "We are working with various partners such as Temasek – Asia Sustainable Foods Platform and ADM, for support on upscaling fermentation and downstream processing. There, for example, we obtain protein-rich powder which is further formulated and processed, and finally put through a 3D printer to create food products," added Weingarten.

CHANGING HEARTS AND MINDS

Solving the production and supply of locally made foods may help to bring Singapore closer to its 30 by 30 goal. But while alternative proteins are a promising feature of a sustainable culture, not everyone may be willing to consume them. Some may view alternative protein sources with suspicion due to how they are produced, while others may believe that they cannot be as tasty or healthy as live-caught seafood or fresh meat.

Even beyond encouraging novel food sources, hesitation and lack of trust can prove to be a major problem in implementing and sustaining new behaviours and habits. In this vein, A*STAR's Social Science and Technology Horizontal Technology Coordinating Office (SST HTCO) aims to understand the role of behavioural change in implementing and supporting a sustainable culture.

"Ensuring greater sustainability is not always just about providing greener and more environmentally friendly options," said Joe Simons, Lead of the SST HTCO.

"It also entails understanding the factors driving people to make unsustainable choices and finding effective ways to support more sustainable lifestyles."

"A person's current behaviour is often locked in place by multiple factors which they may be unaware of," Simons shared. Some of these factors include preconceived generational beliefs, previously established habits, and personal or cultural biases when encountering something new.

Beyond understanding public perception of social issues and the challenges facing their adoption, the SST HTCO also develops solutions that combine these insights with technological innovations. One such project, led by Aimee Pink, a researcher at IHPC, is the development of a virtual interactive intervention to provide better information surrounding the manufacturing of alternative proteins.

HEALTHCARE IN AN AGEING CITY

Sustainable food and eating habits are one part of the picture: personal health is just as important in Singapore's goal of becoming a green and sustainable nation. This is particularly relevant given that Singapore is an ageing nation, with 17.6 percent of its residents aged 65 years and older in June 2021. As the cost of medical care increases and as the ageing population requires more medical care, there is an urgent need for more efficient and cost-effective measures.

The Health and Medical Technology Horizontal Technology Coordinating Office (HMT HTCO), led by Executive Director Malini Olivo and Deputy Director Maple Ye, is developing faster and more efficient point-of-care diagnostic devices and technologies that can assist clinicians in conducting diagnostic work on patients.

"Medical devices can be made more sustainable in many ways," Olivo noted. "The choice of materials, for example, has a big impact." However, Olivo added that sustainable alternatives must meet the same performance criteria as their original counterparts. They must also be tested for factors like biocompatibility, stability and ease of sterilisation, all of which involves time and costs.

Here, the use of artificial intelligence (AI) to assist doctors in clinical practice may speed things up and save on labour. For example, a tool created by A*STAR spin-off US2.ai can analyse and generate an echocardiogram report from patient scans in just two minutes, which saves up to 20 minutes of a clinician's time in making diagnoses.

By allowing technology to handle some of the more strenuous tasks of diagnostic work, healthcare workers are given the time and resources to provide better care

to patients. "Reducing cost, enhancing efficiency and improving accessibility to care are three key issues to tackle in the healthcare industry to achieve a more sustainable system," Ye said.

POWERING A BRIGHTER FUTURE

From the approximately 110,000 streetlights that line the roads to the air-conditioning keeping Singapore's many malls cool, our little red dot consumes a massive amount of energy. Over the years, Singapore has made great strides to implement alternative energy options—even going so far as to construct one of the world's largest floating solar farms across 45 hectares of open sea. However, the bulk of Singapore's energy generation, roughly 95 percent in 2021, continues to come from natural gas.

Despite being considered the 'cleanest' form of fossil fuel, natural gas still contributes heavily to air pollution, water pollution and ultimately, climate change. To fuel the switch to more sustainable energy generation, ISCE[2] is turning to green chemistry and renewable carbon research to support Singapore's sustainability goals.

In line with their goal to achieve net zero carbon emissions by 2050, ISCE[2] Team Leader Jie Bu explores the potential of carbon dioxide (CO_2) mineralisation. CO_2 mineralisation, which mimics the natural processes of the planet at a far quicker pace, is a promising candidate for secure and permanent carbon storage. Here, CO_2 is broken down and converted into a stable mineral product that can then be stored underground or even used in construction materials instead of being released back into the atmosphere.

Bu and his team at ISCE[2] are refining efficient CO_2 mineralisation methods that can be scaled up right here in Singapore. In one study, the team evaluated their patented method that utilises industrial wastes from Incinerator

Bottom Ash (IBA) and Recycled Concrete Aggregate (RCA), by combining them with CO_2 to make solid carbonate or Alternative Sand for land reclamation. They found that while the method is effective, it can be made 'greener' by recycling industrial wastes to create sustainable materials for the built environment and help close the carbon loop by permanently converting and storing CO_2 as concrete.

Similarly, CO_2 conversion can turn carbon emissions into fuels and valuable chemicals with the help of a catalyst. Synthetic natural gas can be produced as a source of renewable energy through methods like methanation and hydrogenation. In a recent publication, Luwei Chen, Deputy Director of the Catalysis and Reaction Engineering division at ISCE[2], worked with international partners to assess the potential of non-thermal plasma (NTP) technology for CO_2 conversion.

Typically, this conversion requires high temperatures, resulting in high energy consumption and low efficiency. The team found that with the right catalyst, however, NTP technology can power the process without needing to heat the entire reactor, making the conversion more efficient.

TAPPING INTO THE SUN'S RAYS

While industrial processes contribute to the largest share of greenhouse gas emissions, essentially any product or service we use leaves behind an environmental footprint. To ensure sustainability in the long term, it is important to understand the long-term impacts of the products, processes and services we utilise.

At the Singapore Institute of Manufacturing Technology (SIMTech), Coordinating Director of Research Jonathan Low assesses a variety of processes, from water supply to Industry 4.0 applications. When it comes to energy, a robust life-cycle assessment (LCA) that quantifies environmental impacts in a standardised manner can

> **"While we should utilise all resources, it is important to recognise that solar energy has the greatest potential to meet the scale of global demand."**
>
> — Kuo-Wei Huang, Director of Catalysis and Reaction Engineering at the Institute of Sustainability for Chemicals, Energy and Environment (ISCE²)

inform both public and industrial energy decisions, such as the implementation of new technologies or policies.

To this end, in 2018, Low and his team evaluated the life-cycle of photovoltaic electricity generation in Singapore, work that could inform the nation's solar cell choices. Such evaluations are especially important given the great potential of solar power as a source of clean energy.

"Global energy demand is huge and is likely to increase in 2050," explained Kuo-Wei Huang, Director of Catalysis and Reaction Engineering at ISCE². "While we should utilise all resources, it is important to recognise that solar energy has the greatest potential to meet the scale of global demand."

Huang's own team is interested in hydrogen carriers and sustainable fuels and has pioneered the development of electricity generating devices capable of converting formic acid into released hydrogen, removing the need for a hydrogen tank for fuel cell power.

Looking ahead, Huang hopes to establish A*STAR as a global hub for catalysis and energy research, one that is capable of driving decision-making and industrial change with robust discoveries.

"It is important to conduct wide-ranging discussions, science-based techno-economic analysis and energy accounting to identify realistic solutions," Huang explained. "Climate policies can then be developed and executed accordingly."

A FUSION OF IDEAS

As A*STAR researchers move the needle closer to a sustainable future for Singapore, researchers must also consider frontier solutions that push the envelope.

Though it seems like something out of a science fiction novel, Singapore has entered the realm of fusion energy thanks to funding at the Nanyang Technological University, new national roadmaps to net zero emissions, and the contributions of A*STAR researchers.

Here, one young theoretical physicist hopes to play his part developing the field. A*STAR scholar Valerian Hall-Chen's work involves developing methods to measure the information released from fusion plasmas so that researchers can then better design ways to harness the energy for practical use.

Given that the core of fusion experiments regularly reaches temperatures several times hotter than the centre of the sun, indirect methods have to be used—like launching microwaves into the plasma and measuring what comes out. This is where Hall-Chen steps in: he interprets the complex data and physical phenomena observed with the help of the theoretical tools he developed.

"I find this research exciting because it bridges experiment, simulation and theory—paving the way for advancements that each alone would not have been able to achieve," Hall-Chen said.

With its new chemical and renewable energy arm, as well as continued research into sustainable living, alternative proteins and accessible healthcare, A*STAR is dedicated to charting a course towards Singapore's sustainability goals.

"We will focus on developing research capabilities at ISCE² and A*STAR, and translating technologies with industry partners for large-scale deployment. This will help Singapore become a global scientific leader, establish sustainability as an economic driver, and create a more sustainable future for its people," shared Yeoh, Chief Sustainability Officer at A*STAR. ★

Unravelling the ancestry of a unique community

By looking at Peranakan Chinese genomes, researchers confirm the community arose from genetic mixing between local Malay women and foreign Chinese traders in the past.

Have you ever felt curious about your family's history? Who are your ancestors? Where did they come from and when did they arrive in your community? For the Peranakan Chinese, who prize family mythology and community folklore, the answers to these questions have been hotly debated for generations.

Historians have traced the origins of Peranakan Chinese back to the 15th century when traders migrated from China and settled in Southeast Asia. As a result, a striking feature of Peranakan Chinese is their hybrid culture— traditional Chinese customs thoroughly blended with Malay influences.

However, whether the Peranakan Chinese also share mixed genetics in addition to their mixed culture has remained a point of debate and uncertainty. Some members of the community believe they descended solely from China, while others believe that intermarriages with the local Malay population must have occurred over the years.

To answer this question, Roger Foo, a Principal Investigator at A*STAR's Genome Institute of Singapore (GIS), and a team of researchers performed whole-genome sequencing on the blood samples from nearly 200 Peranakan Chinese in Singapore.

According to Chaolong Wang, the lead author of the study and a Principal Investigator at GIS at the time, the key advantage of whole-genome sequencing is its ability to produce a high volume of genetic and molecular information, which

Photo credit: GeorgeTan / Flickr

> ## "It was always suspected that there is Malay ancestry among self-declared Peranakans. With this cohort of Peranakans, we've proven it to be the case."

in turn allows a clearer, more detailed rendering of a population's genetic history.

"With whole-genome sequencing, we could assess the genetic history at a higher resolution," said Wang.

The researchers then compared this genetic history with the genomes of other Singaporean Chinese, obtained from the SG10K Project, a nationwide programme that seeks to establish a comprehensive genetic databank of Singapore's population.

Their analyses revealed that the two previously isolated Chinese and Malay ethnic groups had indeed intermarried, or admixed, with contemporary Peranakan Chinese inheriting around 5.62 percent Malay ancestry. In comparison, the genetic make-up of Singaporean Chinese is only approximately 1 percent Malay. Furthermore, the researchers pinned down two distinct points in history that are pivotal to the current genetic make-up of Singaporean and Peranakan Chinese.

The first happened some 1,600 to 1,700 years ago, when Han Chinese migrated from central to southern China, giving rise to the present-day Southern Chinese. At around the same time, Austronesian and early Malay populations encountered each other, eventually giving birth to current-day Malays.

The second event was more recent, occurring only around 190 years ago when intermarriages between local Malay
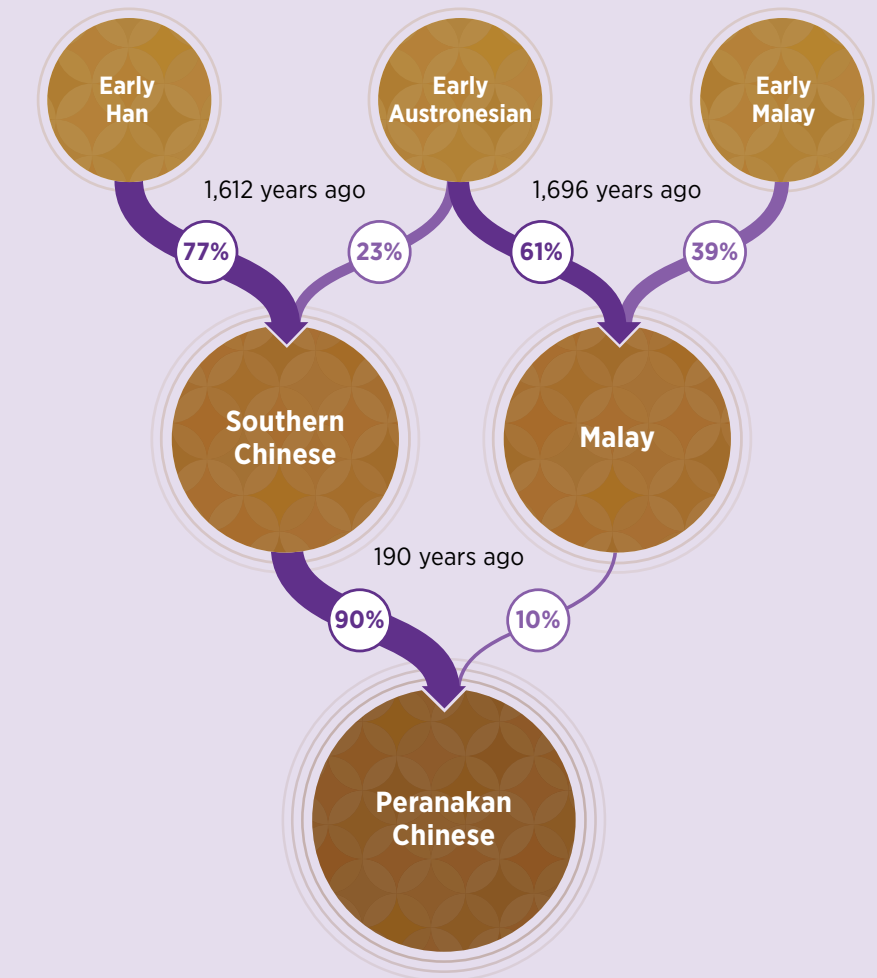
The researchers' analysis of Peranakan Chinese genomes shows relative contributions from ancestral sources and when the admixture events took place.

women and foreign Chinese traders could have taken place.

"It was always suspected that there is Malay ancestry among self-declared Peranakans. With this cohort of Peranakans, we've proven it to be the case," said Foo. "It is a revelation to the community and adds to our local knowledge of history."

Building on the team's findings, future research could look at other Peranakan Chinese communities in different countries across the region, ultimately forming a clear and accurate genetic history of this unique ethnic group. ★

Researcher
Roger Foo,
GIS

IN BRIEF
Researchers pinpointed two historical migration events which may have shaped the genetic landscape of today's Peranakan Chinese.

1. Wu, D., Li, P.Y., Pan, B., Tiang, Z., Dou, J., *et al.* Genetic Admixture in the Culturally Unique Peranakan Chinese Population in Southeast Asia. *Molecular Biology and Evolution* **38**, 4463-4474 (2021).

DIABETES

A closer look at metformin in maternal diabetes

New data suggest that metformin administered to pregnant mothers may have unintended effects on the fetus, prompting the need for further assessment of the drug's risk-benefit ratio.

When it comes to medically managing prenatal issues, clinicians must strike a delicate balance, weighing up the risks and benefits of drugs for treating maternal health complications. While health complications may adversely impact the pregnancy and the baby, the drugs used for treating health complications may also have unintended consequences.

In many cases, it remains unclear whether to continue prescribing a drug or to avoid it completely. Hence, clinicians and patients must discuss the risk and benefits of using a particular drug in pregnancy.

Currently, a drug called metformin is prescribed for certain cases of adult type 2 diabetes and gestational diabetes mellitus (GDM) in expectant mothers. GDM results from a combination of insufficient insulin production by the pancreas and increased insulin resistance, causing elevated blood sugar levels. Although GDM usually resolves after pregnancy, there is a high risk of later progression to type 2 diabetes.

While metformin has no obvious detrimental effects on babies exposed to the drug during pregnancy, there is evidence of metformin crossing the placenta to the unborn fetus. However, it had yet to be seen if metformin could potentially have more subtle effects on the developing baby and its organs like the pancreas—until now.

A team led by Adrian Teo, a Principal Investigator from A*STAR's Institute of Molecular and Cell Biology (IMCB), and Shiao-Yng Chan, Deputy Executive Director of A*STAR's Singapore Institute for Clinical Sciences (SICS), Associate Professor at the National University of Singapore and Senior Consultant at the National University Hospital, developed a technique for modelling the fetal pancreas using stem cells. The researchers aimed to use this platform to examine increased rates of diabetes in children born to mothers who had diabetes during their pregnancies.

First, the team used human embryonic stem cells and created specialised cell culture conditions to coax them into forming pancreatic beta-like cells—a type of cell that synthesises and secretes glucose-regulation hormones like insulin and amylin.

The researchers then added metformin to the cell culture media to mimic the drug passing through the placenta to the fetus. Finally, RNA sequencing and other cell-based assays were used to determine the genetic and functional changes caused by metformin exposure.

"We found that metformin exposure impairs the development of human pancreatic beta cells and their insulin secretion function *in vitro*," said Teo. "We also observed a dip in the expression of key pancreatic genes and abnormal cellular metabolism." Still, it remains to be determined if the same could also occur *in vivo*, or within the actual biological environment of a mother's womb.

Their study represents the first time human stem cells have been used to predict the impact of metformin exposure in fetal pancreatic tissues. However, experimental cell culture models cannot fully capture the complexity of drug dynamics in expectant mothers, as metformin may also be cleared by the mother's kidneys, allowing variable amounts to cross the placenta. To address these limitations, Teo's team plans to further the study in animal models of GDM.

Ironically, the actual detrimental effects of uncontrolled high glucose from the lack of anti-diabetic drug treatment may be worse than the impact of metformin itself. "A more in-depth understanding of the implications of metformin use in the management of diabetes during pregnancy is needed," said Teo. "Meanwhile, we caution against excessive metformin dosing during pregnancy." ★

Researcher
Adrian Teo,
IMCB

IN BRIEF
Exposure to metformin could impair the development of a fetus' insulin-producing cells if sufficient drug amounts cross the maternal placenta.

1. Nguyen, L., Lim, L.Y., Ding, S.S.L., Amirruddin, N.S., Hoon, S., *et al*. Metformin perturbs pancreatic differentiation from human embryonic stem cells. *Diabetes* **70** (8), 1689-1702 (2021).
2. Nguyen, L., Chan, S.Y., and Teo, A.K.K. Metformin from mother to unborn child–Are there unwarranted effects? *EBioMedicine* **35**, 394-404 (2018).

Photo credit: Yusuf Salleh / Shutterstock

MATERIALS SCIENCE

Ultrafast heating sparks high-performing catalysts

A*STAR researchers develop a new technique for manufacturing powerful and versatile synthetic catalysts.

It usually only takes a spark to get a fire going. In the case of chemical reactions for manufacturing processes, this spark is a catalyst—a substance added to galvanise reaction speeds to boost efficiency. Single-atom catalysts, or SACs, are a relatively new class of synthetic materials that's leading the pack: they are incredibly potent and exhibit unparalleled breadth, accelerating a wide range of chemical reactions.

SACs get their power from a highly reactive metal core that is supported by a molecular mesh of non-metal dopants. Getting the balance right, however, is a challenge: current manufacturing techniques often use an excess of dopants which causes impurities to impinge on the metallic active site, thereby weakening SACs' performance.

A team led by Xian Jun Loh and Enyi Ye, researchers from A*STAR's Institute of Materials Research and Engineering (IMRE), hypothesised that a 'heat-shock method' commonly used

> **"For example, researchers could apply our method to introduce non-metal dopants into their single-atom catalysts efficiently."**

in building synthetic materials could also serve as a viable solution for generating better SACs. In collaboration with Yujie Xiong from the University of Science and Technology of China (USTC), the researchers tested their theory using carbon-supported nickel SACs as a model.

The researchers developed a novel joule heating strategy for creating SACs. This ultrafast heating method causes the temperature to surge over 2,700 °C in just a few milliseconds, limiting opportunities for dopant impurities to form on SACs.

In turn, several trial manufacturing runs were performed using different ratios of SAC building blocks to determine the optimal conditions for high-performance SACs. The catalytic activity of these test SACs was then assessed using carbon dioxide reduction (CO_2RR), a reaction used in the fuel industry.

The team found that the heat shock method exceeded expectations. Traditional SACs typically achieve selectivity rates of around 90 percent within a small reaction voltage range. The next-generation SACs developed by the team surpassed 92 percent selectivity across a higher voltage window.

"We are breaking the voltage range limitation of high CO selectivity catalysts," said Ye, adding that this enables high efficiency reactions even with voltage fluctuations during manufacturing.

As part of their study, the researchers demonstrated the versatility of their new method, generating a library of other metal-based SACs including copper, zinc and iron. Ye notes that this work provides a blueprint for the next wave of high-performance SACs by mapping molecular structures with catalytic properties.

"It opens a new way of designing high-performance SACs," said Ye. "For example, researchers could apply our method to introduce non-metal dopants into their SACs efficiently." ★


Researchers
Xian Jun Loh and Enyi Ye, IMRE

IN BRIEF
The ultrafast heating method generates single-atom catalysts with fewer impurities, enhancing their ability to accelerate reactions.

1. Xi, D., Li, J., Low, J., Mao, K., Long, R. *et al*. Limiting the Uncoordinated N Species in M–N$_x$ Single-Atom Catalysts toward Electrocatalytic CO$_2$ Reduction in Broad Voltage Range. *Advanced Materials* **34**, 2104090 (2021).
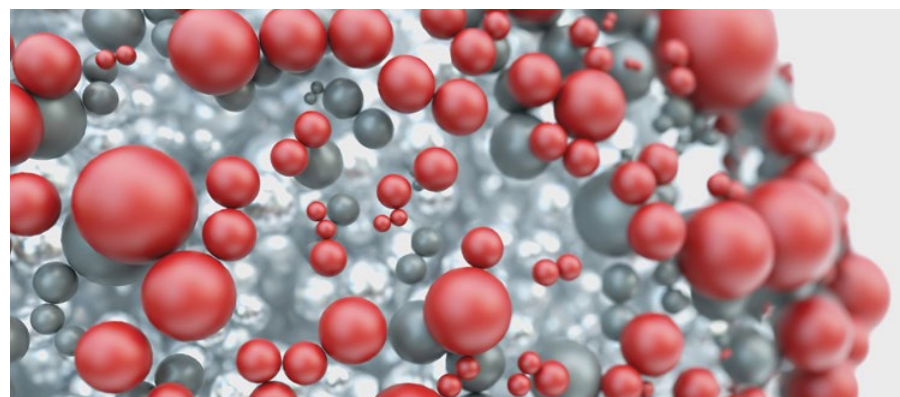
Bacteria turn nature's rainbow into therapeutics

A new bacterial platform makes plant-derived pigments more soluble, overcoming long-standing issues around their use in pharmaceuticals.

"Eat the rainbow"—a reminder to consume a diverse array of colourful fruits and vegetables to take advantage of their health-boosting pigments. Carotenoids, for example, give carrots their vivid orange colour and are also powerful antioxidants, properties that make them highly sought-after for use in pharmaceuticals and beverages.

Using plant-derived pigments for therapeutics, however, isn't easy, says Congqiang Zhang, a Junior Principal Investigator at A*STAR's Singapore Institute of Food and Biotechnology Innovation (SIFBI).

"For example, most carotenoids are insoluble in water, which limits their application in medicine and food where enhanced water dispensability is required to facilitate their effective uptake or use," explained Zhang.

Zhang and colleagues hypothesised a potential solution to this problem: leveraging a natural reaction used by plants
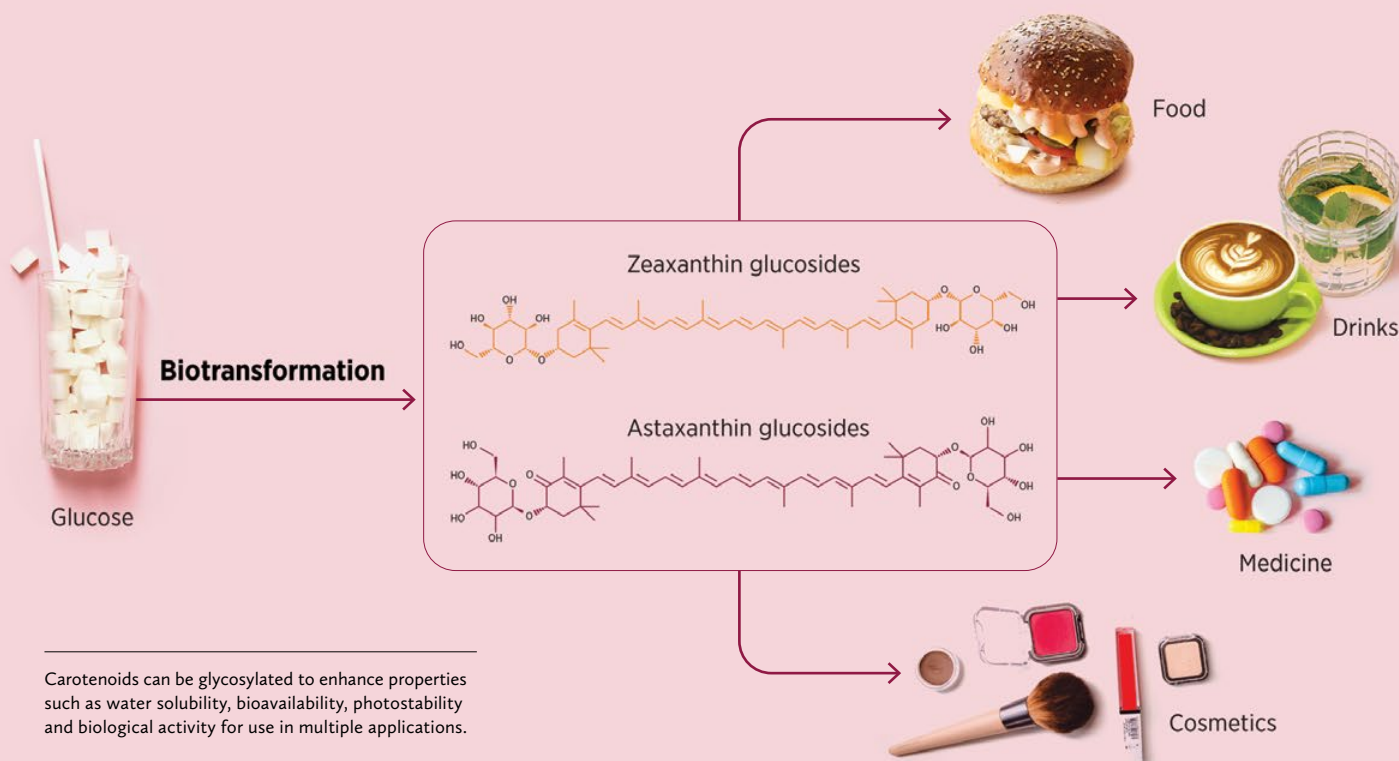
Carotenoids can be glycosylated to enhance properties such as water solubility, bioavailability, photostability and biological activity for use in multiple applications.

> **"Many glycosylated metabolites are produced in plants but they yield very low quantities and often have many unwanted isomers."**

and bacteria called glycosylation. Here, carbohydrate molecules such as glucose are attached to carotenoids, turning them into water-soluble compounds called carotenoid glycosides.

The researchers had previously developed an *E. coli*-based platform for testing the feasibility of using bacteria to create easy-to-dissolve carotenoids. According to Zhang, the benefit of their biosynthetic system is that the microorganisms produce 1,000 times more carotenoids than other natural sources such as plants. Moreover, bacterial growth conditions can be altered quickly and easily to optimise yields.

In their latest study, the researchers expanded the capabilities of their platform to produce two additional glucosides: zeaxanthin and astaxanthin glucoside. This involved genetically engineering and controlling over 15 gene encoding enzymes from bacteria and yeasts.

Balancing glucose levels, which act both as a reaction reagent and source of carbon, also proved to be important. "In addition to elegantly optimising carbon fluxes among different biosynthetic pathways, we had to identify the optimal culture conditions and carbon sources to maximise the yields of zeaxanthin glucosides and astaxanthin glucosides," Zhang noted.

The team's hard work paid off, with their fully optimised platform producing a promising maximum zeaxanthin glucoside yield of 78 percent. This work demonstrates how bacteria could overtake plants as commercial glycoside 'biofactories'.

Giving the example of the zero-calorie sweetener stevia as an example, Zhang said, "Many glycosylated metabolites are produced in plants but they yield very low quantities and often have many unwanted isomers."

By using synthetic biology to enhance natural reactions, the researchers have successfully created an innovative, patent-pending technique for producing glycosylated carotenoids. The team is now working on improving yields by modifying the bacteria to reduce cost, enhancing stability in large bioreactors, and priming the system for large-scale industrial production. ★
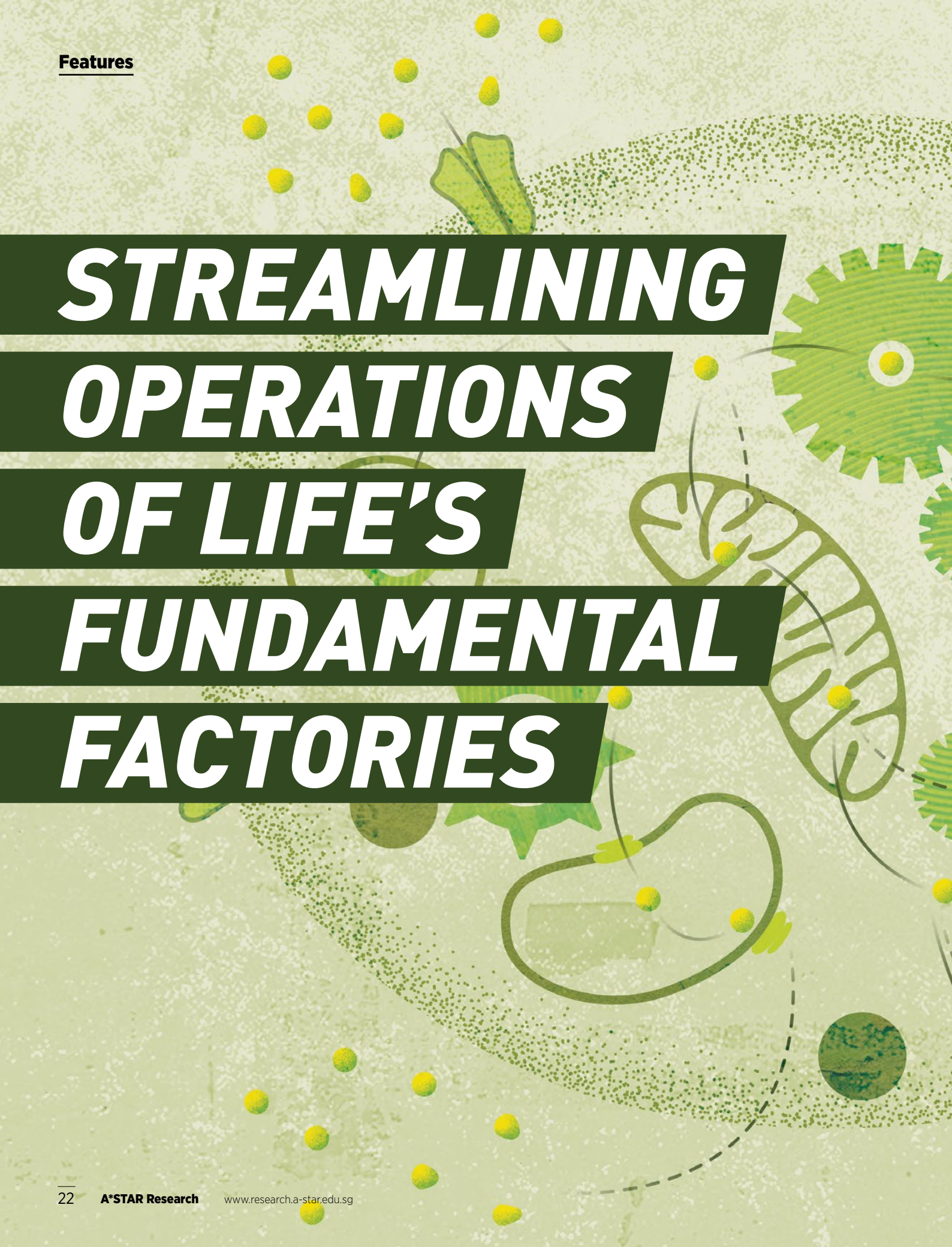
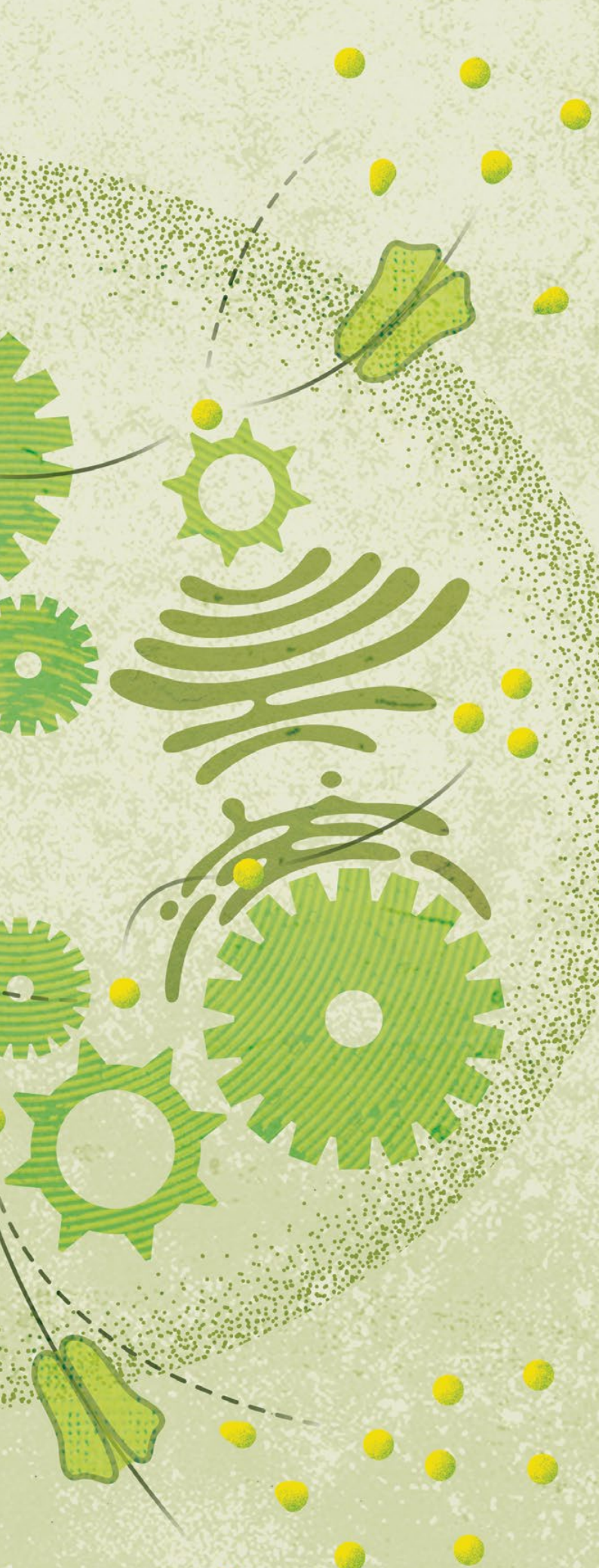**Researcher**
Congqiang Zhang, SIFBI

IN BRIEF
The researchers' new biosynthetic system yielded bacteria able to produce more carotenoids than natural sources.

1. Zhang, C., Seow, V.Y., Chen, X., Too, H.-P. Multidimensional heuristic process for high-yield production of astaxanthin and fragrance molecules in Escherichia coli. *Nature Communications* **9**, 1858 (2018).
2. Chen, X., Lim, X., Bouin, A, Lautier, T., Zhang, C. High-level de novo biosynthesis of glycosylated zeaxanthin and astaxanthin in Escherichia coli. *Bioresources and Bioprocessing* **8**, 67 (2021).

STREAMLINING OPERATIONS OF LIFE'S FUNDAMENTAL FACTORIES

Harnessing the methods of metabolic engineering, Xixian Chen is blazing a trail toward sustainable production of industrially important compounds.

*O*ne of the first things we are told in biology class is that the cell is the most basic, fundamental unit of life. Not many people know, however, that cells can function as factories too, working overtime and at top efficiency to produce a wide variety of compounds—anything from biofuels to preservatives, from wine and cheese to life-saving drugs.

The process of turning cells into these production lines is called metabolic engineering. By tinkering with the cell's genetic material, metabolic engineers hope to optimise the many different cellular processes that yield the particular substance of interest. Single-celled microbes such as baker's yeast and *E. coli* bacteria are often used as they grow well on cheap food sources, making large-scale cultivation easier.

If the field wholly rises up to its promise, it can potentially transform many industries. Still, many roadblocks remain. For one, optimisation is a delicate balancing act. Rather than simply ramping up gene expression, metabolic engineers look for the ideal middle-ground between production volume and cellular viability.

Another barrier is that the biosynthesis routes involved in the production of many compounds of interest remain incompletely elucidated or completely unknown. Without mapping these out in full, efforts to optimise these cellular factories could prove futile.

At A*STAR's Singapore Institute of Food and Biotechnology Innovation (SIFBI), scientists like Junior Principal Investigator Xixian Chen are working around these limitations, developing completely new and sustainable pathways to help metabolic engineering meet its potential.

In this interview with *A*STAR Research*, Chen talks about her enduring fascination with metabolic engineering, her cutting-edge work at SIFBI, and how A*STAR helped her develop as a well-rounded scientist.

> *"Metabolic engineering enables the production of functional molecules using renewable carbon sources while taking up significantly less land and water."*
>
> — Xixian Chen, Junior Principal Investigator at A*STAR's Singapore Institute of Food and Biotechnology Innovation (SIFBI)

Q: WHAT DRIVES YOUR INTEREST IN TINKERING WITH CELLULAR AND MOLECULAR PROCESSES?

Metabolic engineering is a very exciting and interdisciplinary field that requires knowledge of engineering, biochemistry and microbiology, among others. More importantly, it can be used to produce compounds that are difficult to synthesise naturally or chemically.

I have a strong interest in organic chemistry, particularly in making organic compounds. Cells are the best organic chemists because they can make many complex compounds using only simple starting materials and even at mild reaction conditions. Instead of relying on heavy metals, cells use enzymes, the green catalysts that can transform a substrate into different products.

Q: HOW MIGHT METABOLIC ENGINEERING HELP OUR SEARCH FOR MORE SUSTAINABLE WAYS TO PRODUCE FOOD?

Metabolic engineering is the optimisation of pathways in host organisms, like baker's yeast, to achieve high TRY (titre, rate, yield) of target compounds. However, it is not as simple as just overexpressing a group of genes, but a complex engineering process to maximise the product output while causing minimal impact on the fitness of the host. This includes fine-tuning each enzyme's activity, balancing co-factors and preventing the accumulation of toxic or unstable intermediates. Some metabolically engineered hosts or microbes can be cultured in bioreactors and scaled up to more than 1,000 litres to produce desired compounds.

The food industry can greatly benefit from metabolic engineering. For instance, compounds used for food applications, such as flavourants, colouring agents or natural preservatives, are usually highly chiral; that is, only one form of the molecule is useful. Thus, these compounds tend to be difficult to produce through chemical means. Moreover, the starting materials for their chemical synthesis are usually derived from non-renewable and highly unsustainable petrochemicals. Another option is to extract these compounds from natural sources, but this requires agricultural land and water.

Metabolic engineering enables the production of functional molecules using renewable carbon sources while taking up significantly less land and water.

Q: AT A*STAR'S SIFBI, HOW HAVE YOU HARNESSED METABOLIC ENGINEERING TO SUSTAINABLY PRODUCE FOOD OR COSMETICS COMPOUNDS?

Our goal is always to achieve higher TRY for the molecules that we work on. We've achieved near-theoretical levels of yield for some natural products (that is, the maximum yield possible given the chemical reactions involved).

A prerequisite of metabolic engineering is that the target molecule's biosynthetic pathway is known. Unfortunately, many food and cosmetic molecules' pathways have yet to be elucidated. As a workaround, we are currently developing capabilities to design new-to-nature pathways based on chemical and biochemical rules. This will be our competitive edge in producing food and cosmetic molecules from renewable carbon sources using metabolic engineering strategies.

Aside from scientific advancement, A*STAR also helps us to commercialise our technology. Through their support, our patented technology has been licenced to the spinoff company Fermatics.

Q: COULD YOU EXPLAIN HOW FERMATICS' CORE TECHNOLOGY WORKS?

Multidimensional heuristic process, or MHP, is a platform technology by Fermatics that enables us to balance the activities of the multiple enzymes we have introduced into a host. By quickly identifying the highest-producing host strain, MHP reduces the number of trial-and-error attempts.

The idea behind it is simple: Instead of modulating individual enzymes, of which there are usually more than 10, MHP first groups several enzymes together, thereby reducing the overall number of combinations we have to test. This allows us to identify which group of enzymes is the bottleneck. We can then zoom into this group and focus our efforts there to enhance their efficiencies.

We spent the last 10 years building the molecular biology tools to make MHP work.

Q: HOW HAS A*STAR HELPED YOU TO GROW AS A RESEARCH SCIENTIST?

A*STAR provides a conducive and supportive environment for me to conduct industrially relevant research. Even during the very early stages of my career, my colleagues would include me in brainstorming sessions to tackle problems identified by industry colleagues.

SIFBI also allowed me to head a few industrial projects in partnership with multinational companies. All of these broadened my perspectives and made me more aware of industrial needs, as well as of the gaps that basic research needs to fill. ★

INTELLIGENT SYSTEMS

What is the best way to detect errors in intelligent systems?

A systematic comparison of different methods reveals best practices for anomaly detection and diagnosis in cyber-physical systems.

The self-driving car is one of the most iconic technological breakthroughs of the 21st century. By getting passengers to their destinations with minimal human input, self-driving cars have the potential to revolutionise urban transport, but they are not without risks.

Self-driving cars are a form of cyber-physical systems: computer algorithms that control and learn from mechanical components. Hence, system anomalies need to be continuously monitored, diagnosed and rectified in real-time to avoid component failures, or worse, crashes.

There are several proposed methods of anomaly detection; however, until now, researchers have yet to perform a systematic, head-to-head comparison of these various techniques. Consequently, identifying the best anomaly detection models for specific applications remains an uphill task.

Astha Garg, who was at A*STAR's Institute for Infocomm Research (I²R), led a team of researchers, which included Wenyu Zhang, currently a Research Scientist at the institute, to fill this gap. The researchers tested 45 unique anomaly detection methods using data inputs from seven publicly available datasets. They also performed anomaly diagnosis using 29 techniques on four datasets, representing the largest and most comprehensive review of anomaly assessment algorithms to date.

The team took a fresh approach to their analysis, breaking down the detection and diagnosis methods into three distinct modules. The first was a reconstruction model that predicts upcoming algorithmic errors. The next was a function that aggregates errors into an overall anomaly score, and finally, a thresholding function that determines a pass or a fail based on the score.

"By decomposing methods into the modular framework, we can investigate the effect of independent choices of each module," said Zhang, adding that this approach also allowed them to propose optimal design choices for anomaly detection and diagnosis.

Some modules proved to be more impactful than others. For example, in four of the seven tested datasets for anomaly detection, the scoring function had a bigger effect on detection performance than the reconstruction model. In particular, dynamic scoring functions, which continually adapt to unforeseen events, performed better than static ones.

The researchers found that a simple model, called the univariate fully connected autoencoder (UAE), had the best predictive performance overall, outperforming other models in five of the seven anomaly detection datasets.

"We find that existing evaluation metrics for event-wise anomaly detection can be misleading and propose a new metric that accounts for event-wise recall and point-wise precision," said Zhang, adding that their work sets the stage for the safe and reliable cyber-physical systems of tomorrow. ★

Researcher
Wenyu Zhang,
I²R

IN BRIEF
The new findings could make cyber-physical systems (such as self-driving cars) safer and more reliable by improving how they identify errors.

1. Garg, A., Zhang, W., Samaran, J., Savitha, R., and Foo, C.-S. An Evaluation of Anomaly Detection and Diagnosis in Multivariate Time Series. *IEEE Transactions on Neural Networks and Learning Systems* **33**, 2508-2517 (2022).

Copying the homework of machine learning algorithms

A new data selector may help more accurately train machine learning algorithms by recycling datasets from other applications.

Photo credit: nobeastsofierce / Shutterstock

Did you ever share revision notes with friends in school? If you've ever had to study at the last minute for an important exam, you'll know how useful it can be to share and compare notes with other students. As it turns out, the same is true for machine learning algorithms.

Effectively training a machine learning algorithm requires huge amounts of labelled data: raw data to be identified with meaningful labels to provide context for the algorithm. To ease the effort and cost of manually labelling data, computer scientists have developed a process called domain adaptation that allows machine learning algorithms to use existing labelled data from slightly different but still relevant data sets.

For example, a vehicle identification algorithm trained on labelled data from sunny Singapore could be used to train a vehicle identification algorithm to identify Icelandic vehicles despite the stark differences in the weather, vehicle types and road conditions.

Impressive though this is, current domain adaptation techniques are far from perfect. They often transfer irrelevant data that hinders or even negatively impacts learning. Now, however,

> **"In the next two to three years, we plan to achieve better performance in both partial domain adaptation and domain adaptation tasks."**

A*STAR researchers from the Institute for Infocomm Research (I²R), in collaboration with a team from Nanyang Technological University, have invented a new data selection software that automatically chooses the most relevant data from a well-labelled source and excludes irrelevant samples that might hinder learning.

"The most exciting thing is that the superiority of the proposed method becomes more noticeable when dealing with more complex datasets. Here, it continuously outperforms all the baseline methods on almost all tasks and improves the accuracy by a large margin," said Keyu Wu, first author of the research paper and Scientist at I²R.

Moreover, the researchers' data selector tool can also be used for partial domain adaptation (PDA) techniques, when the target domain doesn't need the entire data set from the source domain. This approach is more practical, as most real-world AI applications need only customised datasets to be trained. For example, a medical imaging dataset may cover five diseases, while training a customised real-world task may only require data from three of the five diseases.

While the data selector can currently be integrated into any existing domain adaptation or PDA model, the researchers still aim to improve their data selector further. "In the next two to three years, we plan to achieve better performance in both partial domain adaptation and domain adaptation tasks," Wu said. ★

Researchers
Keyu Wu and Zhenghua Chen, I²R

IN BRIEF
The data selection software helps machine learning algorithms perform tasks more accurately by removing irrelevant data from datasets used to train them.
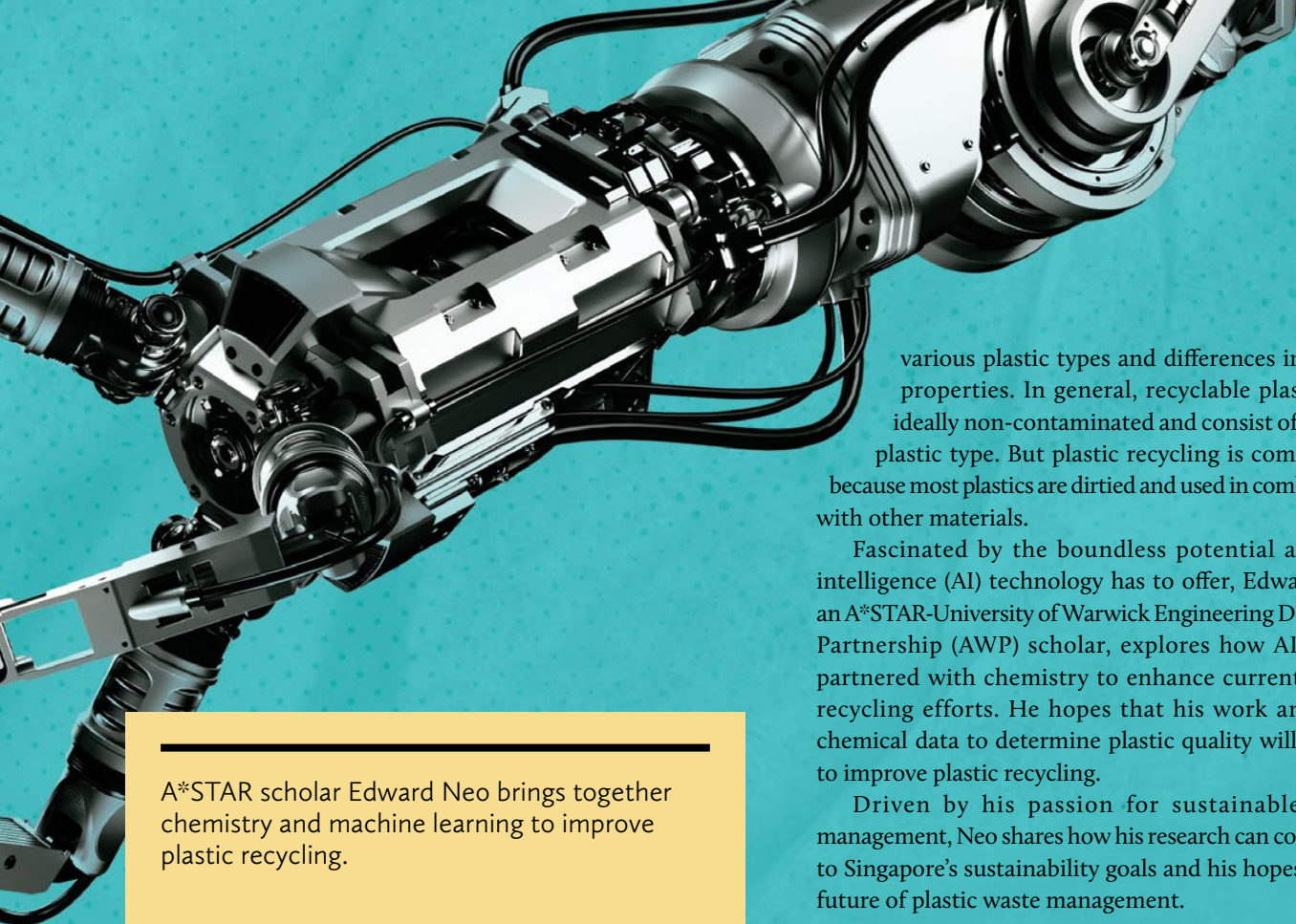
1. Wu, K., Wu, M., Yang, J., Chen, Z., Li, Z. *et al*. Deep Reinforcement Learning Boosted Partial Domain Adaptation. *Proceedings of the Thirtieth International Joint Conference on Artificial Intelligence* 3192-3199 (2021).
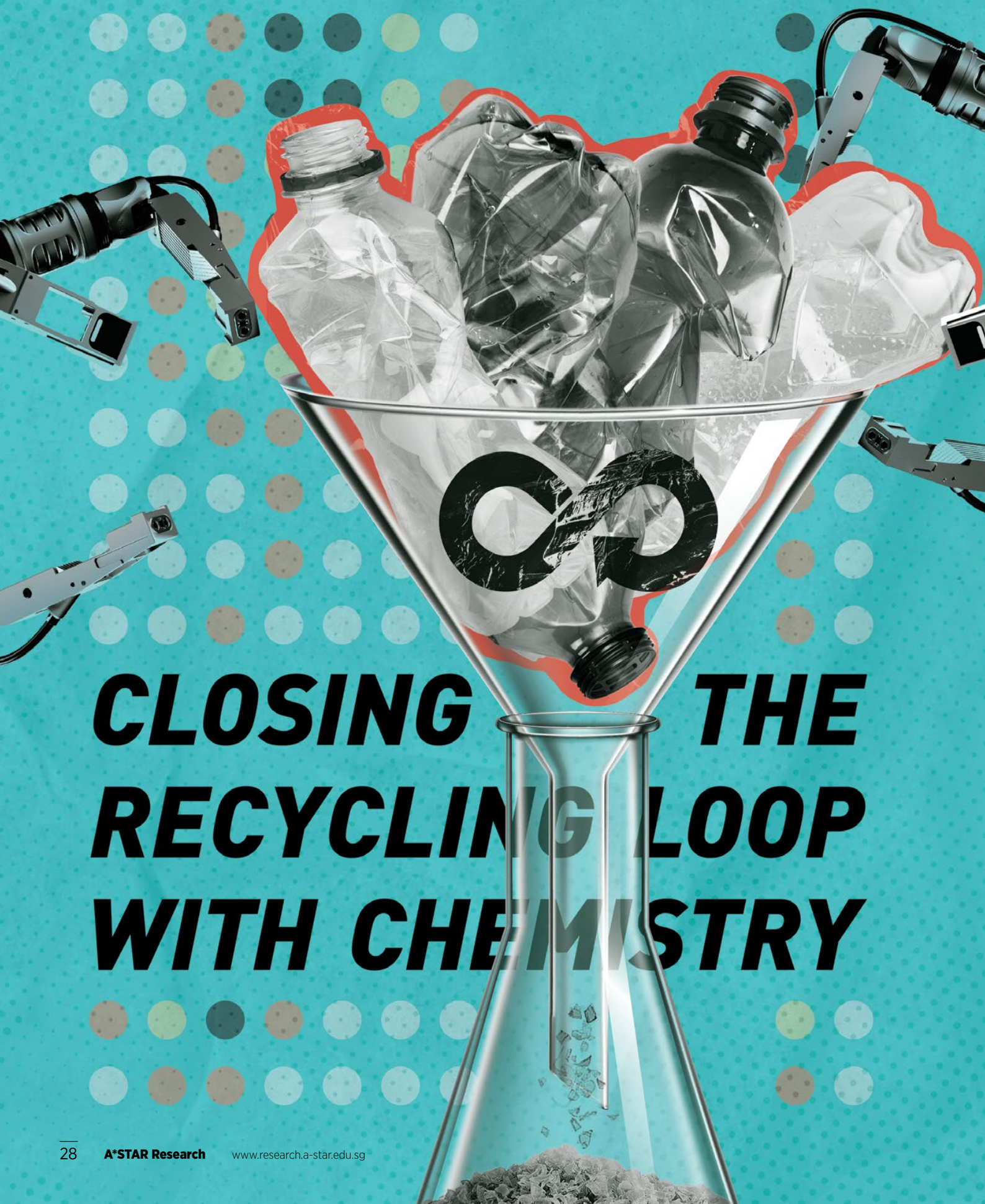
CLOSING THE RECYCLING LOOP WITH CHEMISTRY

A*STAR scholar Edward Neo brings together chemistry and machine learning to improve plastic recycling.

From containers and clothes to furniture and even public transport—plastic is seemingly irreplaceable in our lives. Invented less than 150 years ago, it has become so much a part of the modern era that some scientists have declared this period as 'The Plastic Age'.

Unfortunately, it is also because of its very omnipresence that plastic waste is piling up at an alarming rate. In fact, according to the Organization for Economic Cooperation and Development's (OECD) Global Plastics Outlook, worldwide plastic waste generation more than doubled from 2000 to 2019 to reach a whopping 353 million tonnes. Of that amount, just nine percent is recycled.

As the world looks to alleviate the dire consequences of plastic waste with ambitious international treaties and goals, governments and communities all over the world are ramping up plastic recycling efforts. This mission is echoed in Singapore too, with many initiatives, like litter clean-up campaigns and plastic recycling management, in place to tackle plastic waste sustainably.

While community programmes and well-placed recycling bins can contribute to the cause, a bigger issue lies in the difficulties of recycling plastic because of the various plastic types and differences in plastic properties. In general, recyclable plastics are ideally non-contaminated and consist of a single plastic type. But plastic recycling is complicated because most plastics are dirtied and used in combination with other materials.

Fascinated by the boundless potential artificial intelligence (AI) technology has to offer, Edward Neo, an A*STAR-University of Warwick Engineering Doctorate Partnership (AWP) scholar, explores how AI can be partnered with chemistry to enhance current plastic recycling efforts. He hopes that his work analysing chemical data to determine plastic quality will be able to improve plastic recycling.

Driven by his passion for sustainable waste management, Neo shares how his research can contribute to Singapore's sustainability goals and his hopes for the future of plastic waste management.

Q: WHAT SPARKED YOUR INTEREST IN CHEMOMETRICS?

As an undergraduate, I picked up programming and was deeply enthralled by the possibilities it has to offer. During my research attachment at A*STAR's Singapore Institute of Manufacturing Technology (SIMTech), I further honed my programming knowledge when I worked on developing automated waste-sorting bins. This project involved the use of AI image recognition technology to power the sorting process. While my job scope was more focused on software development, I had the chance to learn how to develop and implement an AI system. I was curious and wondered if the same AI technology could be applied to chemical data—this eventually led me to chemometrics.

Q: WHY DID YOU CHOOSE TO APPLY FOR THE AWP SCHOLARSHIP?

The AWP scholarship is a doctorate programme that develops leaders in an industrial setting. I applied for the programme as it was geared toward translational research and offered modules that help equip me with the soft skills required to potentially translate research into the market.

Q: COULD YOU SHARE WITH US ABOUT YOUR PASSION FOR PLASTIC RECYCLING?

As an eco-conscious person, one of my primary motivations is driving sustainability. Initially, I had no clear specific research topic of interest. Hence, I spent my undergraduate days exploring different sustainability-related projects.

Eventually, I realised that waste management was an environmental issue that I felt most strongly about. Even in social settings, I often encourage my friends to move away from single-use plastic products. Plastics also happen to be polymeric materials and working on plastic recycling ties in nicely with my chemistry background and interest.

Q: WHAT WAS YOUR GREATEST TAKEAWAY FROM YOUR MOST RECENT PROJECT?

Chemometrics is an interdisciplinary research topic that lies at the intersection of chemistry and machine learning. I am thankful to have supervisors from both domains who support my work. As such, I ensure that neither discipline ends up getting lost during research discussions. With that, my greatest takeaway is consistent scientific communication—conveying concepts to people who are not as familiar with the subject area.

EDWARD NEO

A*STAR scholar
A*STAR-University of Warwick
Engineering Doctorate Partnership (AWP)

"By 2030, Singapore aims to reduce waste sent to landfill by 30 percent, as outlined in the Singapore Green Plan. The effort is in hopes of extending the lifespan of our only offshore landfill—Pulau Semakau."

— Edward Neo, A*STAR-University of Warwick (AWP) Engineering Doctorate Partnership Scholar

Q: HOW HAS YOUR BACKGROUND IN CHEMISTRY SUPPORTED YOUR WORK IN PLASTIC RECYCLING?

As the popular saying goes, "A machine learning model is only as good as the data it is fed." Indeed, a large part of any AI-driven research is the data rather than the neural network model itself. Since my project primarily deals with chemical data, my background in chemistry has facilitated the collection of good quality chemical data using equipment I am trained to use, such as the infrared and Raman spectrometers. I am also better able to identify potential issues in the data that might be interfering with my AI models.

Additionally, with plastics being the main research subject, my background allows me to understand the properties of different types of plastic concerning their chemical structures and why certain recycling methods may or may not be suitable for different types of plastics.

Q: WHAT MOTIVATED YOUR RECENT PROJECT ON THE EMISSIONS FROM MASK PRODUCTION?

This research topic was relatively new at the time and as such, there were gaps in knowledge regarding mask emissions. I embarked on this project to quantify the environmental benefits of cloth masks over single-use masks in conjunction with A*STAR's involvement in producing pioneer batches of cloth masks with embedded filtration layers.

Q: COULD YOU DESCRIBE A CURRENT PROJECT YOU ARE WORKING ON?

I am currently studying how accelerated weathering can affect the spectra collected from plastic samples, and whether chemometrics can be used as a tool to distinguish such differences. The data I collect will hopefully provide useful information about the quality of plastic before recycling is done.

Q: HOW DOES YOUR RESEARCH ALIGN WITH SINGAPORE'S SUSTAINABILITY GOALS?

By 2030, Singapore aims to reduce waste sent to landfill by 30 percent, as outlined in the Singapore Green Plan. The effort is in hopes of extending the lifespan of our only offshore landfill—Pulau Semakau. One major contributor is plastic waste, with a six percent recycling rate in 2021. I believe improving the plastic recycling rate could help significantly reduce the amount of waste sent to the landfill. ★

MATERIALS SCIENCE

A modern twist to ancient alloys

Machine learning and computational platforms are helping develop robust protocols for manufacturing an emerging class of strong, super lightweight alloys.

Humans have been making alloys for millennia. Records as early as 3300 B.C. describe how bronze, an alloy that left its mark on civilisation, was created by mixing tin with copper. This traditional approach of adding a small amount of one element to a large quantity of another base element hasn't altered significantly and can limit the diversity of alloys that can be formed.

In the 1980s, materials scientists proposed a radically new method of alloy-making—blending five or more metals in near-equal proportions. The result was a novel class of materials known as high-entropy alloys (HEAs). What sets HEAs apart from other alloys is that they are exceptionally strong and pliable because more than five elements with almost equal amounts coexist in a single phase.

The significant challenge lies in how to build a phase selection rule to delineate the single-phase region in the vast temperature-compositions space of HEAs. Randomly combining metallic elements in the periodic table into a furnace is unlikely to produce HEAs because the high-fidelity phase selection rules are not established yet for materials scientists. Kewu Bai and Yong-Wei Zhang of A*STAR's Institute of High Performance Computing (IHPC) set out to break new ground in the field by developing a new 'recipe' for lightweight, high-strength, single-phase HEAs.

First, the team picked a panel of eight starting metals. They then defined their HEA manufacturing protocol by combining machine learning approaches with a computational tool called CALPHAD. CALPHAD is a staple in the materials scientists' toolkit, used to predict the phases in multi-element materials.

"The [CALPHAD predictions] can then be used as input for a machine learning model to derive high fidelity phase selection rules of single-phase HEAs," Bai explained.

The researchers extracted data on their metallic building blocks from a reliable thermodynamic database and used CALPHAD to predict their equilibrium phases. In total, they mapped the phase stabilities of 20 families of five-element HEAs, formed by varying the proportions of each component, across an array of temperatures.

Among the parameters with the highest predictive power for generating single-phase HEAs was equilibrium temperature. Interestingly, previous studies overlooked this parameter, which may explain why few single-phase HEAs were reported.

"The equilibrium temperature, which was neglected in the past, must be included in the machine learning descriptors," advised Bai.

The team also used their phase selection rules to construct the blueprints for 213 potential single-phase HEAs with the lightweight strength required for building planes and vehicles. In the future, the researchers plan to extend the HEA-design capabilities of their approach to develop increasingly complex HEAs to serve more manufacturing industries. ★

> **"The [CALPHAD predictions] can then be used as input for a machine learning model to derive high fidelity phase selection rules of single-phase HEAs."**

**Researchers
Kewu Bai and
Yong-Wei Zhang,
IHPC**

IN BRIEF
Combining five elements in a single phase results in high-entropy alloys that are strong and pliable.

1. Zeng, Y., Man, M., Bai, K., Zhang, Y.-W. Revealing high-fidelity phase selection rules for high entropy alloys: A combined CALPHAD and machine learning study. *Materials and Design* **202**, 109532 (2021).

COMPUTATIONAL IMAGING

Imaging with computational lenses

A modified image processing algorithm by A*STAR scientists is paving the way toward super-resolution imaging.

A picture paints a thousand words, and this is true of all forms of imaging, ranging from the X-rays that are used to capture signs of pneumonia in human lungs, to visible light used in lab microscopes, and even electron beams used to image viruses. However, some computer imaging experts say that today's imaging technologies have yet to reach their full potential.

At A*STAR's Singapore Institute of Manufacturing Technology (SIMTech), Joel Yeo and a team of researchers are working to take digital X-ray imaging to new heights with the help of computational lenses, specialised algorithms that process and boost the resolutions of laser images. Better imaging is a boon to many

industries from medicine to manufacturing, enhancing the speed and reliability of detection. Known as phase retrieval, this computer-aided imaging processing step has, however, proven challenging to optimise.

"Current applications of phase retrieval in research are still unable to recover the highest resolution possible," said Yeo, adding that high resolution image quality relies on the use of costly, energy-hungry supercomputers.

Yeo's team hypothesised that the key to achieving clearer and sharper laser images with minimal computational resources lay in a set of equations called the Fresnel propagator function. By incorporating these equations into existing phase retrieval

algorithms, the team was able to reconstruct captured images with pixel sizes a few times smaller than previously reported.

The team was also able to zoom into the captured images to reveal fine details without the need for expensive optical components such as lenses and mirrors. Furthermore, with the new algorithm, the resolution of captured images was no longer limited to the pixel size of the detector—they were instead able to obtain pixel sizes of around 1 μm, even with a camera that had large 13 μm pixel pitches.

"We tested our modified phase retrieval algorithm using simulated diffraction patterns, as well as on real-world data," Yeo explained. "We were pleasantly surprised by the high quality of the reconstructed image—a clear indication that the enhanced algorithm could accurately model the physics of image formation."

By reconstructing images with unprecedented clarity, this imaging innovation holds promising benefits for medical diagnostics, research and manufacturing. According to Yeo, the approach can also be used to improve applications that use laser imaging.

Next, Yeo and colleagues plan to apply their phase retrieval framework to enhance images captured via electron microscopy. "Being able to observe finer structures in proteins and molecules would greatly help researchers reveal the unknown and undiscovered properties of these nano-scaled objects," he shared. ★

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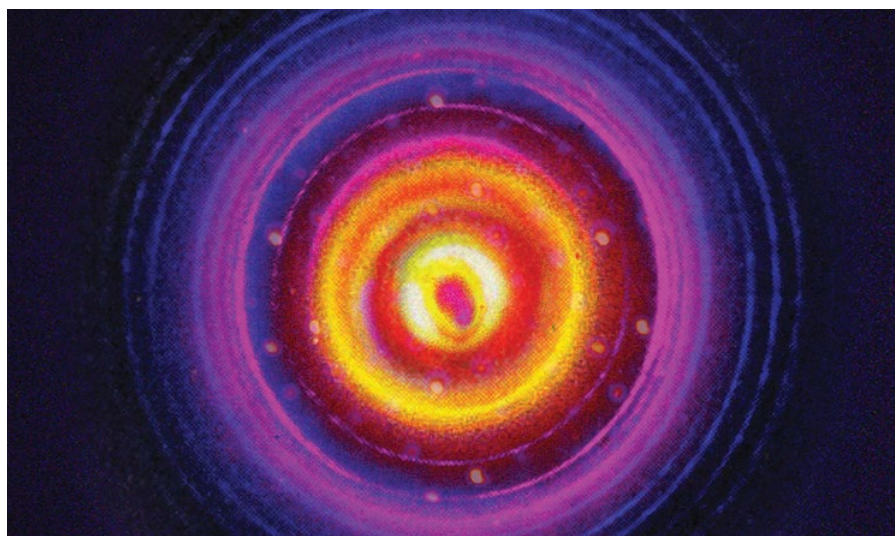
Researcher
Joel Yeo,
SIMTech

IN BRIEF
The algorithm performed well on both simulated patterns and real-world data, producing high-quality reconstructed images.

1. Yeo, J., Seck, H.L., and Zhang, Y. Super-resolution, multi-plane phase retrieval via amplitude flow variants. *Optics and Lasers in Engineering* **146**, 106715 (2021).

Holograms make better augmented reality

Scientists are creating advanced nanopatterned metasurfaces for projecting high-resolution 3D holograms in augmented reality headsets, thereby making the user experience more immersive.

Picture yourself on vacation, touring a new city on foot. At every turn, the augmented reality (AR) headset strapped to your face displays everything from information on historical landmarks to restaurant reviews superimposed on the buildings themselves. This scenario may not be too far off: AR has the potential to create such powerful, immersive experiences by blending real and online worlds, transforming how we learn, play and explore.

Although they've come a long way, experts say today's AR technologies still have notable limitations. Existing devices typically use two 2D display panels that show two slightly different perspectives of the same object, much like the glasses worn during 3D movies. Depth isn't projected accurately, and AR headsets are bulky with small, low-resolution viewing windows.

Arseniy Kuznetsov, a Principal Scientist at A*STAR's Institute of Materials Research and Engineering (IMRE), says that this suboptimal 3D viewing experience takes its toll on the wearer over time.

"Prolonged usage of this kind of AR device can cause eye fatigue, nausea and discomfort to the viewer," said Kuznetsov.

Kuznetsov's team, in collaboration with researchers from Nanyang Technological University's School of Electrical and Electronic Engineering, has been developing holograms as the "ultimate solution" for more realistic 3D displays. The researchers leveraged the unique properties of metasurfaces—specialised nanopatterned surfaces composed of nanostructures smaller
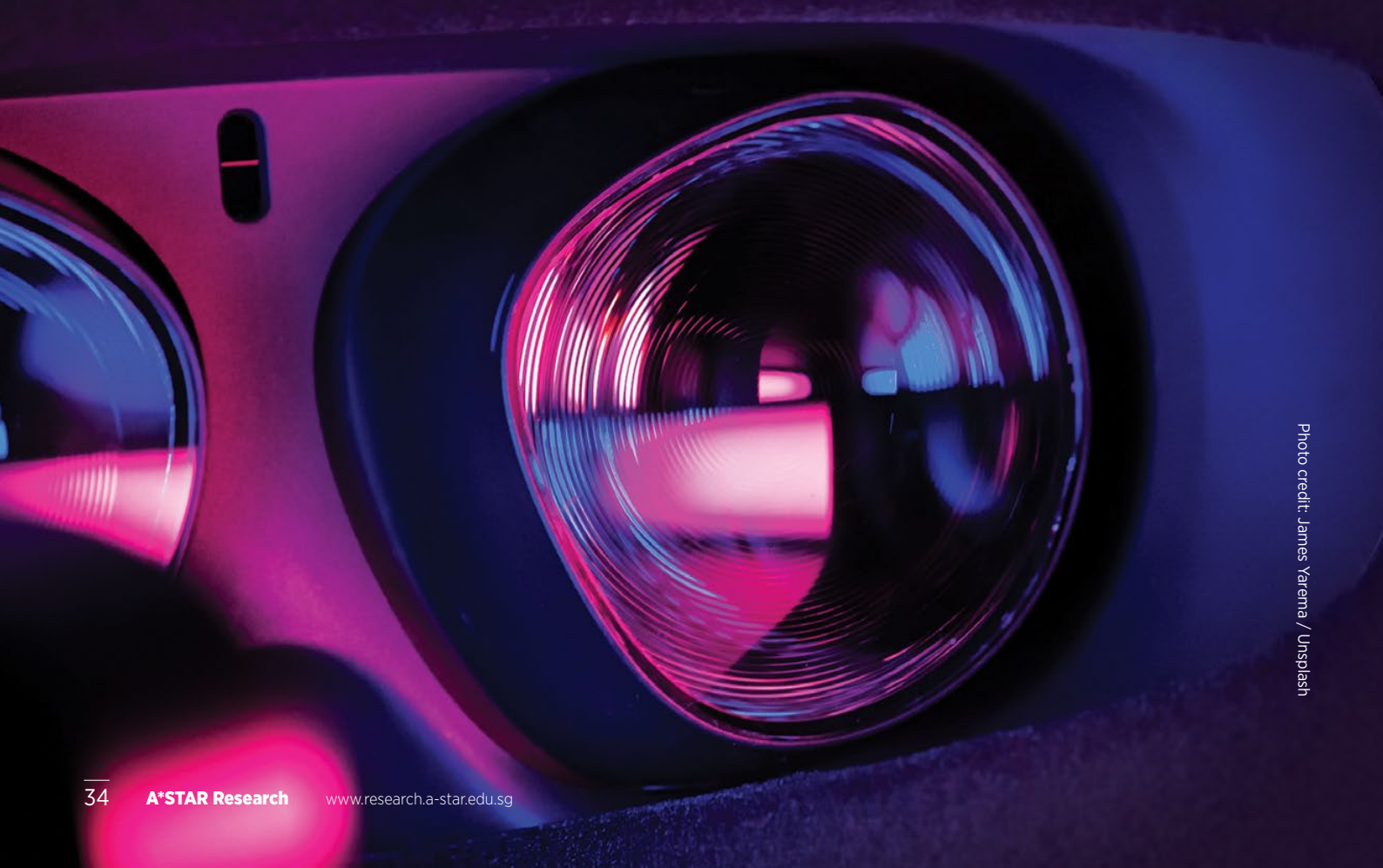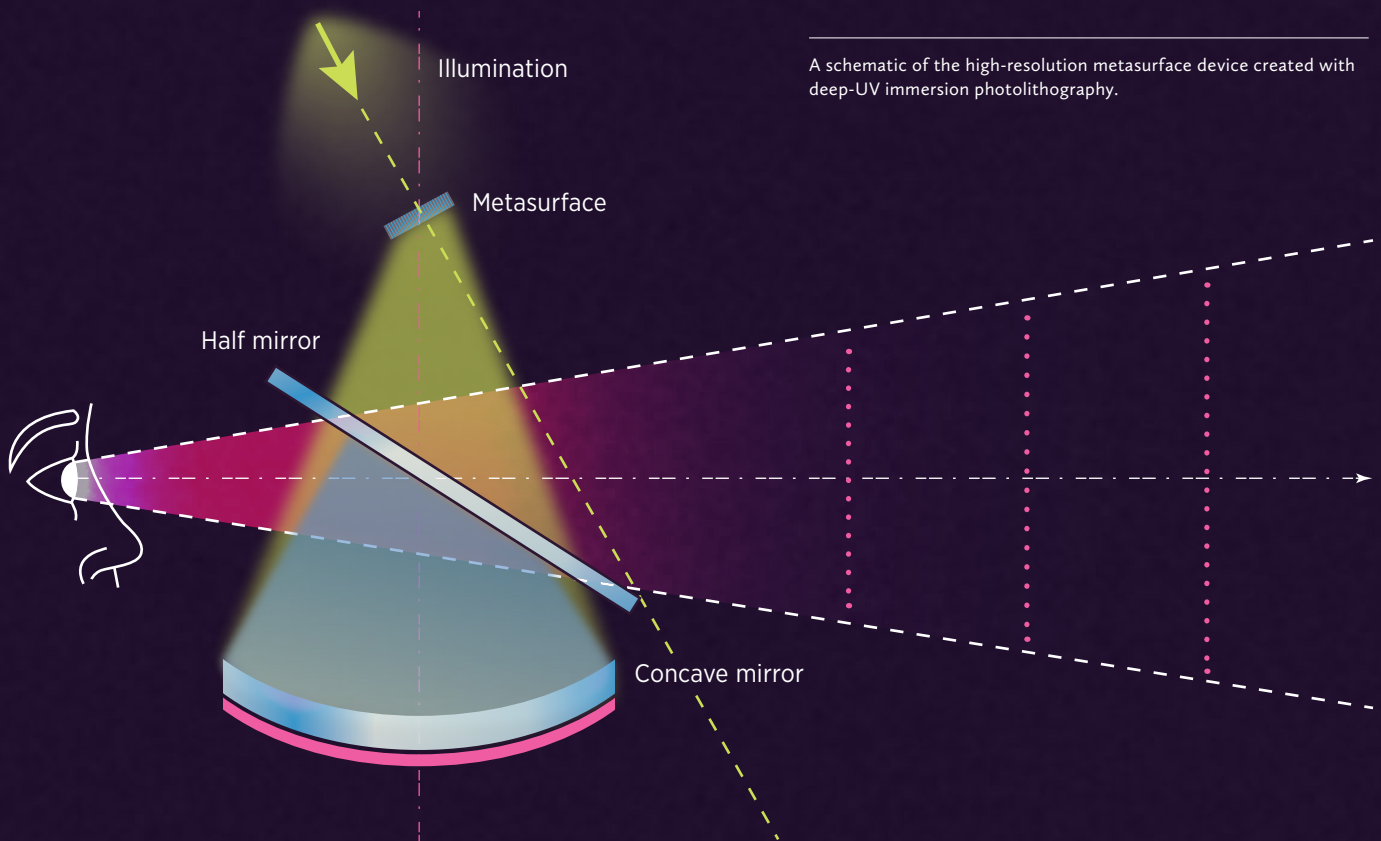
Photo credit: James Yarema / Unsplash

Illumination

Metasurface

Half mirror

Concave mirror

A schematic of the high-resolution metasurface device created with deep-UV immersion photolithography.

"Our technique allows high-resolution metasurface devices to be fabricated in a scalable manner, extending their application in optics beyond holography to flat lenses and complex beam generation."

than the wavelengths of light. These surfaces eliminate the need for traditional bulk optics, projecting ultra-sharp 3D holograms on compact, lightweight headsets with wide-angle views.

In their study, they described the generation of an advanced holographic near-eye metasurface display. They showed that the holograms could project high-quality virtual 3D scenes that overlay with the real world with more accurate depth depiction. In addition, they demonstrated how to make these metasurfaces using deep-ultraviolet immersion photolithography, a relatively low-cost manufacturing technique that uses standard semiconductor fabrication processes.

"Our technique allows high-resolution metasurface devices to be fabricated in a scalable manner, extending their application in optics beyond holography to flat lenses and complex beam generation," Kuznetsov said, adding that it could expand horizons for AR in education, entertainment and medicine.

The team has plans to make their metasurfaces dynamically tunable, paving the way for next-generation AR headsets that could finally allow their users to immerse themselves in an augmented reality. ★

Researcher
Arseniy Kuznetsov,
IMRE

IN BRIEF
The researchers' discovery brings us closer to next-generation 3D holograms that may improve on existing AR devices.

1. Song, W., Liang, X., Li, S., Li, D., Paniagua-Domínguez, R., *et al*. Large-Scale Huygens' Metasurfaces for Holographic 3D Near-Eye Displays. *Laser & Photonics Reviews* **15** (9), 2000538 (2021).
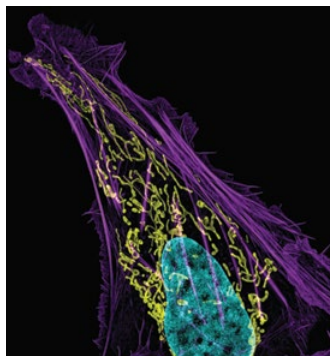
NEXT ISSUE

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

COVID-19
CAN'T SMELL? YOU'RE NOT WELL

A*STAR researchers develop a standardised, self-administered taste and smell test for detecting the early symptoms of COVID-19.
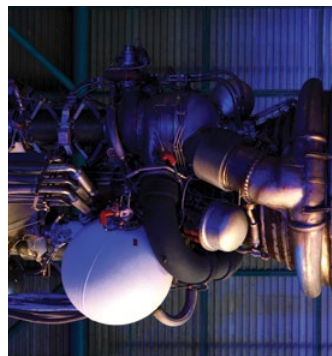
MOLECULAR BIOLOGY
CANCER CELL STAKE-OUT REVEALS NEW ASSOCIATIONS

A molecular tagging tool developed in Singapore identifies novel protein interactions on the surface of cancer cells.
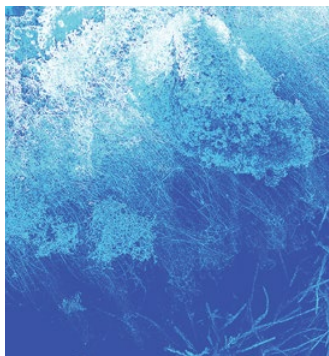
MATERIALS SCIENCE
MAGNETIC 'ABACUS BEADS' GIVE DEVICES AN EDGE

A*STAR scientists pave the way for mobile supercomputing using magnetic nanostructures.

METALS AND ALLOYS
MACHINE LEARNING HELPS ULTRASTRONG ALLOYS TAKE OFF

Materials science and computational techniques come together to advance new design schemes for aerospace alloys.

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