Issue 4, 2016
July – September 2016

SINGAPORE

A*STAR Research

HUMAN FRIENDLY ROBOTS

'Colleagues' who never let you down could be the future of industrial remanufacturing

A BIOTRANSFORMATIVE EXPERIENCE

A new taskforce aims to modify microorganisms to produce fragrance and flavor for industry

SMART DATA, SMART CITY

Data-exchange platform creates a dashboard to drive Singapore

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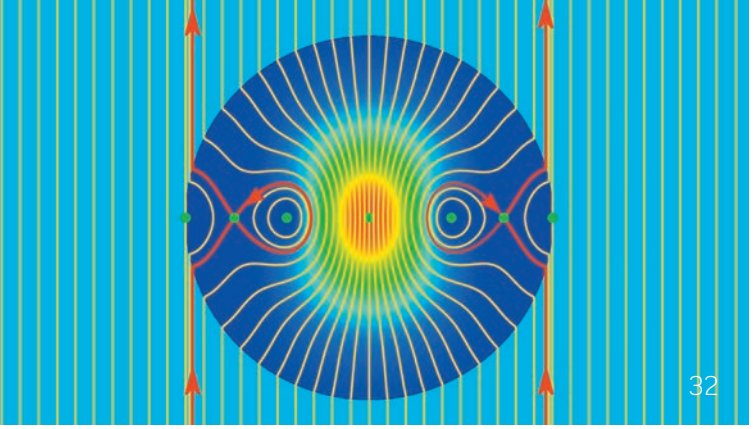
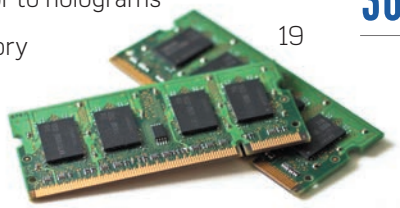
[TABLE OF CONTENTS]

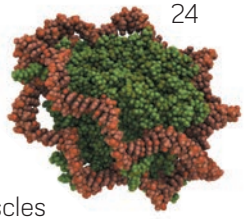

32

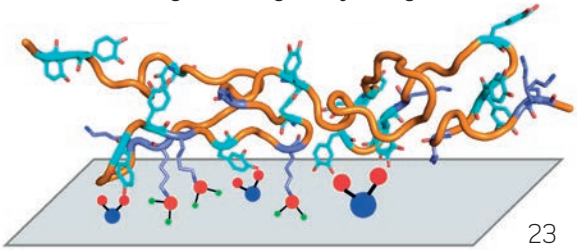
15 RESEARCH HIGHLIGHTS


19

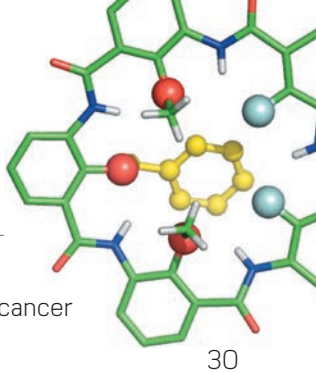
20 PICTURE STORY

21 RESEARCH HIGHLIGHTS

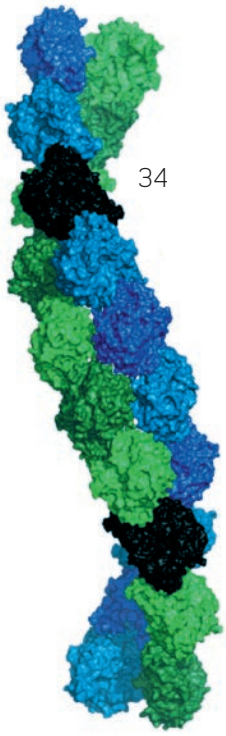

24


23

26 FEATURES & INNOVATIONS


30

28 RESEARCH HIGHLIGHTS

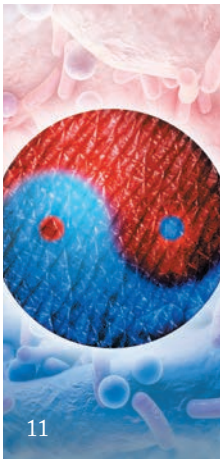

34

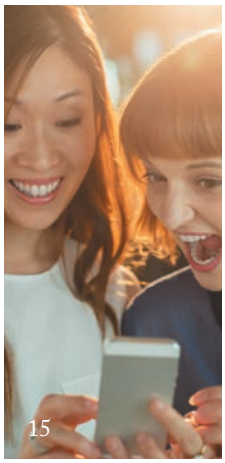
36 FEATURES & INNOVATIONS

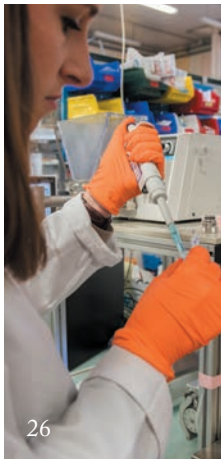
39 RESEARCH HIGHLIGHTS

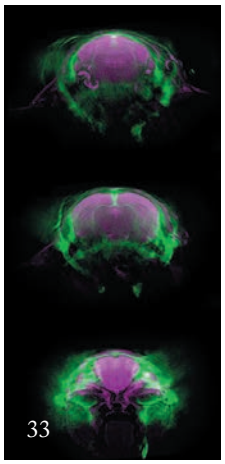
48 VOICES FROM A*STAR / NEXT ISSUE


26









[NOTES FROM THE EDITORS]

Managing editor, Lia Paola Zambetti

Welcome to the fourth edition of the new, slimmer format of *A*STAR Research*. This issue contains articles published between July and September 2016 and, as usual, covers the full breadth of research conducted at A*STAR to inform and enlighten you.

On page 26, we will introduce the Biotransformation Innovation Platform (BioTrans), which was officially opened on the 1st of August. Biotrans is a new entity in A*STAR tasked with harnessing microorganisms to transform cheap carbon sources into compounds useful for the biotech industry.

On the engineering side, Nancy Chen and her colleagues at the Institute for Infocomm Research (I^2R) devised a versatile, cheap and personalized system to correct mispronounced words — a language coach specific to each user that can, in principle, be used for any language (page 15).

On page 18 you can read about the Institute of Materials Research and Engineering's Dong Zhaogang and Joel Yang who developed a hologram that works throughout the visible spectrum using silicon structures — although we can't yet use our droids to send holographic videos to Jedi masters we are now one step closer.

The life sciences are making impressive strides, too: Malini Olivo and her colleagues from the Singapore Bioimaging Consortium developed a new, high-resolution and non-invasive approach to visualize brain tumors, a notoriously difficult target. Combining photoacoustic and magnetic resonance imaging led to clear images of blood flow and oxygenation in the cancerous tissue — in a clinical setting, this would be a very useful tool for evaluating whether a therapy is effective (page 33).

Finally, John Common and colleagues from the Institute of Medical Biology studied the skin microbiome of eczema sufferers and non sufferers, finding significant differences between the groups. They speculate that ammonia-oxidizing bacterial groups, absent in eczema patients but present in others, may be a cause (page 11).

This is just a taste of the research you are about to discover in our new issue of *A*STAR Research*. We hope you will enjoy reading it!

COVER IMAGE

A new class of collaborative robots may be the future of industrial remanufacturing [p36]
© suprun/Getty

A*STAR researchers have shown that a toxic peptide is a promising candidate for developing new cancer therapeutics.

Cancer:

TARGETED KILLING OF CANCER CELLS

TOXIC PEPTIDE PAYLOAD CAN BE DELIVERED EXCLUSIVELY TO AFFECTED CELLS

A drug that can kill cancer cells while leaving normal cells unharmed may be within our grasp thanks to research from A*STAR, although the approach is still several years away from clinical trials[1].

The discovery began when Sheng-Hao Chao's team at the A*STAR Bioprocessing Technology Institute realized that a segment of the hexamethylene bisacetamide-inducible protein 1 (HEXIM1) they were studying, known as the basic region (BR) peptide, was similar to a key region of the tumor-suppressing protein p53. Activation of p53 in damaged cells either leads to recovery of the cell via DNA repair or initiation of a cell-death process known as apoptosis. Since HEXIM1 was known to interact with p53 and other cancer-related proteins, the researchers speculated that BR might be involved in the p53 pathway.

To test this, the team engineered a new protein by connecting a cell-penetrating peptide to the BR peptide. While the BR peptide could not enter cells alone, the combined protein was readily taken up and proved toxic to the cells. By attaching a signal to target breast cancer cells, the team ensured that BR was delivered exclusively to these cells. The BR complex efficiently eliminated breast cancer cells but left normal cells unharmed. "Our peptide acts like a 'professional killer,' taking only the targeted cancer cells," says Chao. "This makes it a safer choice as a toxic payload for targeted therapies against cancerous cells."

The BR peptide can also be combined with different molecules, such as antibodies,

to target other cancer cell types. Its ability to selectively kill cells is a major improvement over existing toxic peptides, which can enter cells without assistance and therefore cause unwanted side-effects by killing normal cells.

Cancers sometimes overcome p53's suppressive action by regulating apoptosis or even p53 itself, but this will not be possible with BR. The team found that treatment with BR killed breast cancer cells within minutes, meaning that they weren't undergoing apoptosis, which takes hours. Cells lacking p53 were also killed, and further experiments demonstrated that BR acts not via the p53 pathway but through another protein, nucleophosmin, which is essential for cell growth and survival.

"That was totally unexpected," says Chao. "The combination of a unique safety feature and unique killing mechanism could make the BR peptide very attractive for developing new therapeutics against cancers. That's what we really hope."

Chao's team is currently engineering peptides with BR connected to other cancer-targeting molecules, as well as testing the peptide in mice.

1. Neo, S. H., Lew, Q. J., Koh, S. M., Zheng, L., Bi, X. & Chao, S.-H. Use of a novel cytotoxic HEXIM1 peptide in the directed breast cancer therapy. *Oncotarget* **7,** 5483–5494 (2015).

Data security:

TAKING CONTROL BACK FROM THE CLOUD

A USER-CONTROLLED FILE SECURITY SCHEME MAKES IT POSSIBLE TO INSTANTLY REVOKE ACCESS TO FILES HOSTED ON INTERNET CLOUD SERVERS

By securing data files with a 'need-to-know' decryption key, A*STAR researchers have developed a way to control access to cloud-hosted data in real-time, adding an extra layer of security for data-sharing via the Internet[1].

Cloud-based file storage has rapidly become one of the most popular uses of the Internet, allowing files to be safely saved in a virtual 'drive' that is often replicated on numerous servers around the world. Cloud storage theoretically provides near-seamless backup and data redundancy, preventing data loss and also enabling files to be shared among users almost anywhere. However, proper treatment of sensitive or confidential information stored on the cloud cannot be taken for granted — the security of the cloud environment is not immune to hacker attacks or misuse by a cloud provider.

> " CLOUD STORAGE SERVICES MAKE DATA STORAGE AND SHARING MORE EFFICIENT AND COST EFFECTIVE, BUT THEIR USE REQUIRES TRUST IN THE CLOUD'S SECURITY"

"Cloud services make data storage and sharing more efficient and cost effective, but their use requires trust in]security," says Jianying Zhou from the A*STAR Institute for Infocomm Research. "We wanted to find a way to ease security concerns by creating a system that does not require the data owner to trust the cloud service or assume perfect protection against hacking."

The scheme Zhou and his team developed allows access to an individual file hosted on a cloud service to be issued or revoked in real-time, and eliminates the possibility that files can be taken offline and accessed without authorization.

"We achieved this by depositing what we call a proxy key for each authorized user on the cloud," says Zhou. "This is a partial key that requires another revocable private key lodged with the cloud service provider to safeguard against collusion at provider level. By requiring files to be decrypted using the two keys every time they are accessed, we can revoke a user's access instantly by deleting the proxy key from the cloud."

A new data security scheme could extend user-level real-time file access control to the cloud.

The scheme allows the data owner to retain control over file access while making use of all the other benefits of cloud hosting. Importantly, it is applicable at the per-file and per-user level, and has 'lightweight' user decryption, meaning that files can be opened quickly even on mobile devices such as smart phones.

"Our technology could be used to provide scalable and fine-grained access control to various bodies of data collected by different organizations and shared via the cloud, with natural applications in areas such as healthcare, finance, and data-centric cloud applications," says Zhou.

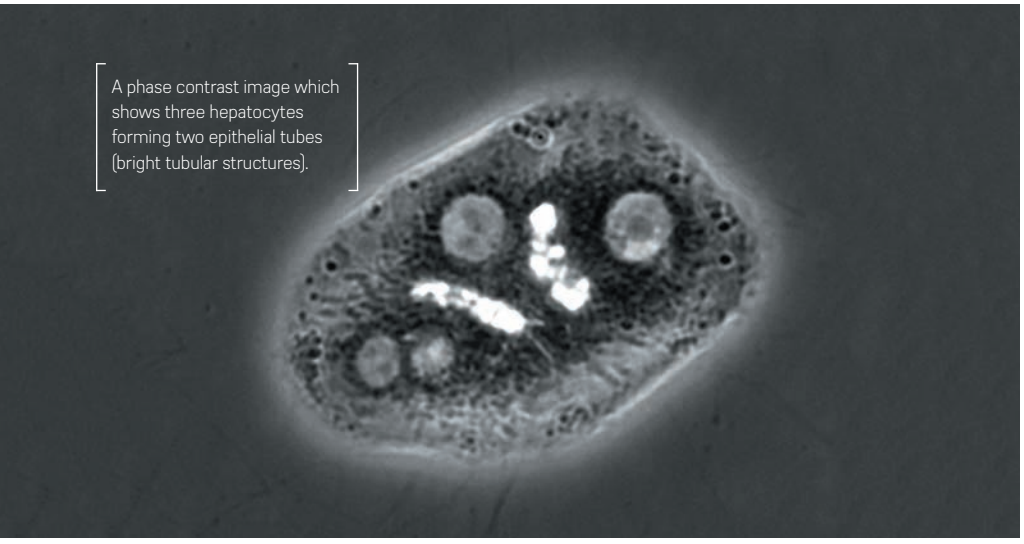
1. Yang, Y., Liu, J. K., Liang, K., Choo, K.-K. R. & Zhou, J. Extended proxy-assisted approach: Achieving revocable fine-grained encryption of cloud data, Computer Security ESORICS 2015, in *Lecture Notes in Computer Science* **9327**, 146–166 (2015).

Mechanobiology:

HOW THE BODY MAKES PIPES

SUPPORTING CELLS HAVE BEEN SHOWN TO GIVE RISE TO THE ELONGATED STRUCTURES OF EPITHELIAL TUBES

Researchers from Singapore and France have demonstrated, for the first time, that the mechanical forces generated by surrounding 'scaffolding' help to shape some types of epithelial tubes[1].



A phase contrast image which shows three hepatocytes forming two epithelial tubes (bright tubular structures).

Epithelial tubes form much of the plumbing of our bodies. These tubes are found in all the major organs and allow the flow of fluids that sustain life. For example, the liver contains an extensive network of epithelial tubes that distribute bile acids — compounds that enable the digestion and absorption of fats in the small intestine. Defects in the formation of these tubes can lead to diseases such as cholestasis, in which the flow of bile is impeded or stopped.

One aspect that has mystified biologists is how such long, elongated tubes form when most developmental processes operate equally in all directions to produce symmetric structures, rather than the asymmetric tubular structures of epithelial tubes.

Now, a team led by Virgile Viasnoff at the National University of Singapore and CNRS (France) and Hanry Yu at the A*STAR Institute of Bioengineering and Nanotechnology has shown that forces produced by supporting cells — generated by the asymmetric interaction with the extracellular matrix — give rise to the long cellular architectures of some epithelial tubes.

> " THIS IS AN EXCITING DISCOVERY SINCE IT MEANS WE CAN OBTAIN EPITHELIAL TUBES OF DIFFERENT SHAPES AND SIZES BY MANIPULATING THE MICROENVIRONMENT OF THESE CELLS. "

"This is an exciting discovery since it means we can obtain epithelial tubes of different shapes and sizes by manipulating the microenvironment of these cells," says Yu.

With a minimalist approach, the team experimented by culturing just two liver cells in tissue culture. When these cells were grown between walls coated with extracellular matrix, the three-dimensional arrangement of the extracellular matrix affected the shape of the lumens (the 'holes' in the cells that form the epithelial tubes). In particular, the lumens tended to move away from the extracellular matrix and toward the cell–cell interface, giving rise to the tubular structure.

The researchers modeled the situation mathematically and found that this elongation was driven by forces generated by the

asymmetric interaction between cells and the extracellular matrix.

"Our study has revealed for the first time the exact nature of this mechanism and how it works," says Yu. "It will contribute to a deeper understanding of the principles underlining epithelial tube formation as well as offer opportunities to develop better therapies for related diseases.

The team is keen to explore the medical implications of their discovery. "My group is focusing on translating our findings to different applications," says Yu. "Specifically, we are studying the mechanism of tube dynamics and developing assays to screen for cholestasis."

1. Li, Q., Zhang, Y., Pluchon, P., Robens, J., Herr, K. *et al.* Extracellular matrix scaffolding guides lumen elongation by inducing anisotropic intercellular mechanical tension. *Nature Cell Biology* **18,** 311–318 (2016).

Nutrition:

CHEW SLOWLY AND CHOMP LESS

CHEWING HABITS DETERMINE BLOOD SUGAR LEVELS AFTER A CARBOHYDRATE-RICH MEAL

How we chew a spoonful of rice could affect our risk of developing diabetes.

Taking slower and fewer bites of a spoonful of rice releases less glucose into the bloodstream than quick and continuous chewing, show A*STAR researchers[1]. Surges in blood sugar levels, known as the glycemic response, can increase a person's risk of developing obesity, heart disease and type 2 diabetes, which is of particular concern in Asia, a region accounting for 60 per cent of the global diabetic population.

"The old wives' advice to chew and chew and chew like a cow is actually counterproductive when it comes to glycemic response," says Christiani Jeyakumar Henry, who led the study, together with colleague Yung Seng Lee at the A*STAR Singapore Institute for Clinical Sciences, and Verena Tan. "These results are gratifying because chewing time and frequency are behaviors that we can consciously change," adds Lee.

The glycemic response to food varies considerably between individuals. Henry and Lee wanted to identify non-invasive ways for people to moderate this response. In a previous study on the mastication behavior of 11 Singaporeans, Henry found that smaller balls of white rice are chewed less before swallowing, when using chopsticks instead of a spoon, which significantly reduces blood sugar levels[2].

In the current study, the researchers looked at the glycemic response of 75 healthy men served a bowl of basmati or jasmine rice. They compared chewing parameters of frequency and duration per mouthful, saliva content, and the time taken for food to clear the stomach.

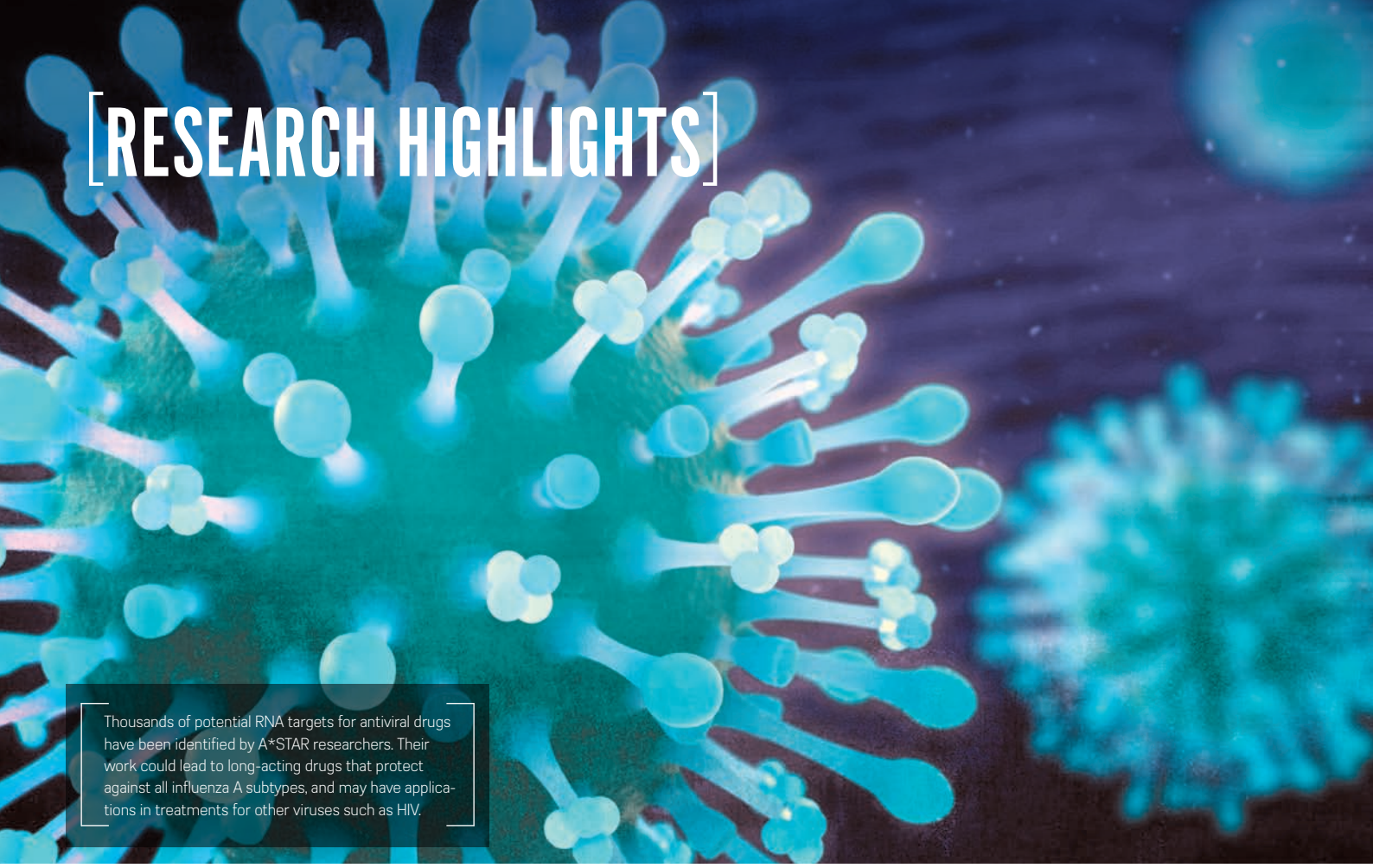
Blood samples and saliva swabs were taken from the study participants before and after every meal. Their jaw movements were monitored via surface electrodes and stomach activity measured using an ultrasound machine.

For both types of rice, fewer bites per mouthful, at a slower chewing rate, were associated with lower blood sugar levels. Lee insists, however, that further intervention studies are needed to confirm the link between chewing and glycemic response. Both the speed of stomach emptying and activity of salivary enzymes responsible for breaking down starch into smaller chains of glucose were not associated with changes in blood sugar levels.

Lee is currently also assessing stool samples of the participants for gut bacteria. "We want to identify the gut bacterial patterns that are associated with a higher or lower glycemic response."

Henry is keen to find more ways of manipulating blood sugar levels, for example by tricking people into chewing less and swallowing larger particles of rice by mixing the staple with peas, pistachios or nuts. "Food is the new medicine, that is our mantra," he says.

1. Tan, V. M. H., Ooi, D. S. Q., Kapur, J., Wu, T., Chan, Y. H., Henry, C. J. & Lee, Y. S. The role of digestive factors in determining glycemic response in a multiethnic Asian population. *European Journal of Nutrition* **55,** 1573–1581 (2015).
2. Sun, L., Ranawana, D. V., Tan, W. J. K., Quek, Y. C. R. & Henry, C. J. The impact of eating methods on eating rate and glycemic response in healthy adults. *Physiology & Behavior* **139,** 505–510 (2015).



Thousands of potential RNA targets for antiviral drugs have been identified by A*STAR researchers. Their work could lead to long-acting drugs that protect against all influenza A subtypes, and may have applications in treatments for other viruses such as HIV.

Computational biology:

COMBINING FORCES AGAINST INFLUENZA A

EFFECTIVE ANTIVIRAL DRUGS FOR MULTIPLE INFLUENZA A STRAINS COULD WORK BY ATTACKING COMBINED RNA TARGETS

Influenza A is one of the most prolific and diverse viruses on Earth; its ability to rapidly mutate to resist treatment challenges the management of future pandemics. Now, A*STAR researchers have identified thousands of segments of RNA that could act as potential new antiviral drug targets, and provide protection against all strains of influenza A[1].

During a pandemic, which could take only two months to spread across the world, the creation of a new vaccine to target a specific strain of influenza A could take up to six months. A new avenue being explored includes antiviral drugs created using so-called antisense oligonucleotides (AONs) — synthetic polymers that can block disease progression by altering viral RNA activity.

"The next influenza A pandemic is inevitable, given how easy it is for an animal-based subtype to mutate and infect humans," says Keng Boon Wee at the A*STAR Institute of High Performance Computing, who worked on the project with scientists across Singapore. "To make use of AONs, we need to identify specific RNA target sites found across all viral subtypes and strains. In the case of influenza A this means searching through almost 36,000 strains. We used computer simulations to hunt for RNA target sites in all current influenza A subtypes."

At first, the team thought they might find one target site that would protect against all subtypes. It became apparent, however, that this was simply impossible, because no single site is shared by all RNA sequences. Instead, the researchers realized they should

search for 'pairs' of sites that, if targeted simultaneously by AONs, could provide multi-subtype protection.

"Our initial search uncovered thousands of potential pairs," says Wee. "While we were pleasantly surprised that only two target sites are sufficient to address all strains from all subtypes simultaneously, we were very excited at the enormous potential to combine these pairs to create even more targets."

The team discovered that carefully selected pair combinations could significantly increase a new drug cocktail's 'hedge factor' — the time it takes for a virus to become drug resistant. By targeting pair combinations, antiviral drugs based on AONs could be developed that can provide long-term protection against all influenza A subtypes and strains.

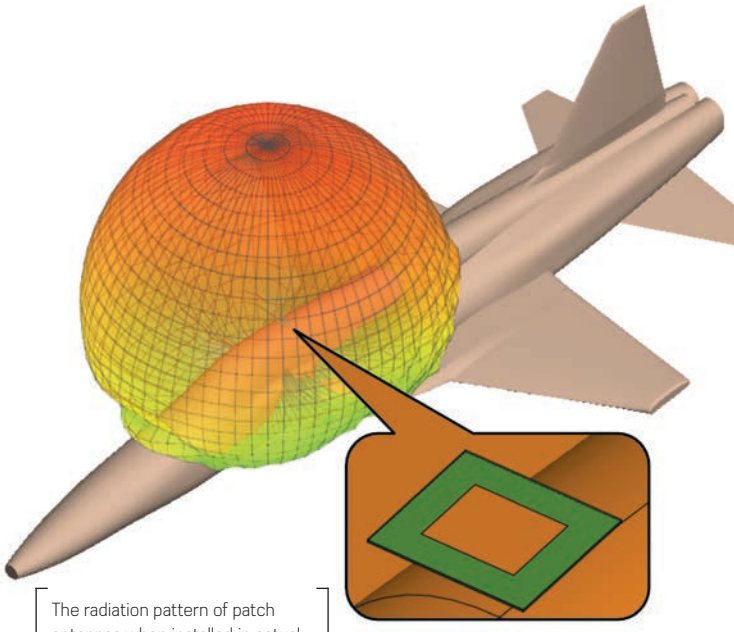
"Even when we remove targets that cannot be used due to unwanted effects, the potential target space is huge," says Wee. "Our technique is also applicable to other viruses, including HIV. We hope to work with experimental virologists to validate our combinatorial pairs and develop corresponding RNA therapeutics."

1. Wee, K. B., Lee, R. T. C., Lin, J., Pramono, Z. A. D., & Maurer-Stroh, S. Discovery of influenza A virus sequence pairs and their combinations for simultaneous heterosubtypic targeting that hedge against antiviral resistance. *PLoS Computational Biology* **12**, e1004663 (2016).

Antennas:

PREDICTING THE PATTERN

A MODEL THAT PREDICTS THE RADIATION PATTERN FROM PATCH ANTENNAS IN REAL INSTALLATIONS COULD TAKE THE GUESSWORK OUT OF COMMUNICATION DEVICE DEVELOPMENT



The radiation pattern of patch antennas when installed in actual equipment can now be predicted using a parametric model.

Patch antennas can now be integrated into mobile devices more efficiently using a model that predicts the signal radiation patterns of installed antennas, developed by A*STAR researchers[1]. The model solves one of the major obstacles faced by communications engineers — predicting how the radiation pattern of a patch antenna will change when it is installed in a device.

Patch antennas, composed of metallic strips, are designed to provide efficient communication in the smallest and flattest arrangement possible. Due to their small installation footprint, patch antennas are used in many applications where saving space is paramount, such as mobile phones, wearable devices, and aircraft. The problem is, the signal pattern emitted by the patch antenna can be affected by the way it is installed and the materials around it, which adds a layer of complexity to device development.

"The radiation pattern is a key performance indicator of an antenna," explains Si-Ping Gao from the A*STAR Institute of High Performance Computing, who led the study. "The typical radiation pattern from a patch antenna looks like a mushroom pointed in the direction of maximum radiation, but when installed, the radiation pattern can be totally different. We wanted to develop a method to predict the best position to mount the patch antenna in order to get the desired radiation pattern before actually mounting it."

Although radiation pattern simulation methods exist, all require detailed geometric information about the patch antenna, which is rarely available for off-the-shelf antennas. Even with an accurate geometric representation of the patch antenna, the simulations are computationally intensive.

"Instead of using detailed geometric information, we developed an equivalent model described using a handful of design parameters based on the radiation mechanism of the patch antenna," says Gao. "We then added the platform to the model and computed the installed radiation pattern. This allowed us to simulate the installed antenna radiation pattern

without geometric information and avoided direct modeling of antenna structures, which greatly sped up the simulation process."

The team demonstrated that the equivalent model simulation accurately reproduces the installed radiation pattern, making the integration of patch antennas into real devices easier and faster.

"This method can also be easily extended to other types of antennas or sensors by constructing equivalent models based on the radiation mechanism. These equivalent models could be collected in a database to facilitate efficient simulation of the installed radiation pattern of many different antennas and devices."

1. Gao, S.-P., Wang, B., Zhao, H., Zhao, W.-J. & Png, C. E. Installed radiation pattern of patch antennas: prediction based on a novel equivalent model. *IEEE Antennas and Propagation Magazine* **57,** 81–94 (2015).

Autoimmunity:

IMMUNE CELLS UPSET THE KIDNEY

INFILTRATING SELF-DEFENSE CELLS PROVOKE KIDNEY FAILURE IN A CHRONIC AUTOIMMUNE DISEASE

The crucial role of dendritic cells in a fatal renal condition of systemic lupus erythematosus (SLE) has been exposed by A*STAR researchers[1]. "Our studies show that these cells switch mild autoimmune phenotypes to severe kidney disease," says Anna-Marie Fairhurst at the A*STAR Singapore Immunology Network, who led the study.

SLE is a complex autoimmune disorder that predominantly affects women of child-bearing age. The disease is characterized by a range of gradually worsening symptoms, including joint pain, heart inflammation, and a butterfly-shaped rash across the nose and cheeks. A third of patients will develop life-threatening kidney disease, which Fairhurst has been trying to trace back to its pathological origins.

The immune cells of healthy individuals express a protein called Toll-like receptor 7 (TLR7) that helps them recognize foreign pathogens. When hyper-expressed in mouse models of SLE, however, TLR7 directs kidneys to their death. Fairhurst wondered which specific immune cells helped precipitate this decline. In an earlier study, she had eliminated the role of B cells[2], so her next suspect was the antigen-presenting dendritic cells.

Fairhurst and her colleagues doubled TLR7 expression levels in a mouse model of SLE and then selectively eliminated the surplus receptors from individual cell populations. When they deleted TLR7 in B cells, the disease continued to progress. But, this time, when they deleted TLR7 in dendritic cells, the disease stopped and they observed no inflammation in the kidneys (see image).

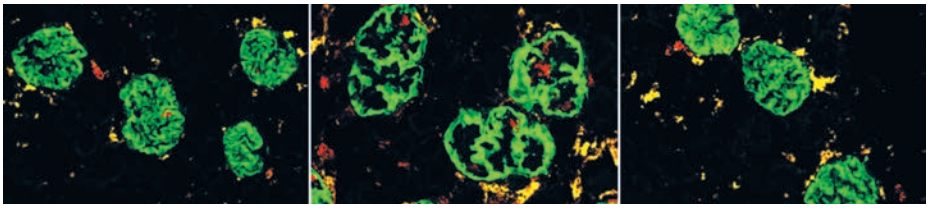
Further analysis revealed that a specific type of dendritic cell, known as conventional CD11b+, was primarily responsible for infiltrating the kidneys and causing the disease.

The problem with these findings was that the same dendritic cells in humans typically do not express TLR7. This raised a troubling question for Fairhurst about their role in human disease.

To test their relevance, she isolated dendritic cells from blood samples of healthy individuals and prodded them into expressing TLR7 using heat inactivated or live flu viruses, and a protein known to stimulate an immune response called interferon-alpha. Surprisingly, live influenza and interferon-alpha increased TLR7 expression in the dendritic cells.

Fairhurst plans to analyse blood samples from human patients of SLE to chart TLR7 expression levels for different manifestations of autoimmunity. Doctors recommend annual flu vaccines for SLE patients, but Fairhurst wants to investigate different vaccination strategies to determine which are the most beneficial.

"More than two-thirds of SLE patients 'in remission' still suffer and take daily medication," says Fairhurst. "We hope to make some changes in this process."



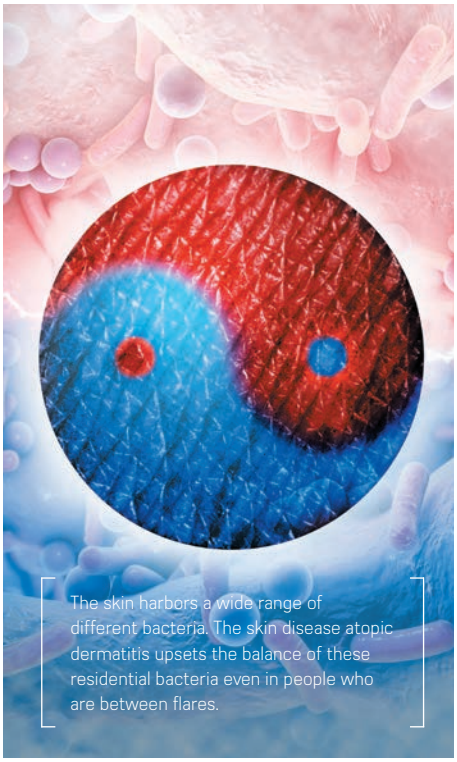
In mouse models of systemic lupus erythematosus that express high levels of Toll-like receptor 7 (TLR7) (center), dendritic cells (red) infiltrate the kidney's blood vessels and cause them to become large and inflamed. Normalizing TLR7 expression in all of the immune cells (left) or in the dendritic cell population alone (right), prevents the progression of kidney disease.

1. Celhar, T., Hopkins, R., Thornhill, S. I., De Magalhaes, R., Hwang, S.-H. *et al.* RNA sensing by conventional dendritic cells is central to the development of lupus nephritis. *Proceedings of the National Academy of Sciences USA* **45,** E6195–E6204 (2015).
2. Hwang, S.-H., Lee, H., Yamamoto, M., Jones, L. A., Dayalan, J. *et al.* B cell TLR7 expression drives anti-RNA autoantibody production and exacerbates disease in systemic lupus erythematosus–prone mice. *The Journal of Immunology* **189,** 5786–5796 (2012).

Skin microbiome:

LINK DISCOVERED BETWEEN SKIN DISEASE AND RESIDENT BACTERIA

EVEN WHEN NOT SUFFERING FROM FLARE-UPS, PEOPLE SUSCEPTIBLE TO ATOPIC DERMATITIS HAVE DIFFERENT MICROBES LIVING ON THEIR SKIN THAN NON-SUFFERERS



The skin harbors a wide range of different bacteria. The skin disease atopic dermatitis upsets the balance of these residential bacteria even in people who are between flares.

Microbial communities living on the skin of people susceptible to the skin disease atopic dermatitis differ from those of healthy individuals. This finding by A*STAR researchers provides insight into the roles that resident bacteria play in the disease and is promising for the early detection of susceptibility and potential interventional therapies[1].

Our skin hosts many bacteria and other microorganisms that are known collectively as the skin microbiome. Atopic dermatitis causes dry, itchy, inflammatory skin and is estimated to affect up to one in five people in developed countries. Periodically the dermatitis clears, only to flare up in recurrent episodes. The relapsing nature of the disease led John Common of the A*STAR Institute of Medical Biology and co-workers to wonder whether the makeup of the skin microbes of an atopic dermatitis sufferer differs from that of a healthy individual even between episodes, as such differences might explain what triggers flares.

As a test, the team developed an analysis technique to profile the metagenomes (the communities of bacteria, viruses and fungi) of 40 skin microbiome samples from people with recurrent atopic dermatitis. When they compared the results with those from another 40 individuals who had never had atopic dermatitis, they found significant variations between the two groups.

"We identified a clearly different skin microbiome signature for patients in remission from atopic dermatitis," explains Common. "This suggests that even when atopic skin looks relatively healthy and normal, there is an underlying shift in the skin microbiome. This altered microbiome may contribute to the cyclical nature of the disease flares."

The results also point to potential ways to treat atopic dermatitis. "Our study suggests that probiotic or microbe transplants could help restore the microbial balance providing long-term treatment alternatives," notes Niranjan Nagarajan from the A*STAR Genome Institute of Singapore.

The findings suggest a possible explanation for the increase in the global prevalence of atopic dermatitis — modern soaps that eradicate certain bacteria that oxidize ammonia. These bacteria were absent in the microbiomes of atopic dermatitis sufferers in the study. Thus, these ammonia-oxidizing bacteria may be important in staving off the disease.

The results have implications for other skin conditions. "This link between microbiome profile and skin health could apply to other skin diseases and subclinical conditions," notes Common.

The team is examining the development of microbiomes of infants that are at high risk of atopic dermatitis and is exploring the relevance of various strains of microbes identified in the study.

1. Chng, K. R., Tay, A. S. L., Li, C., Ng, A. H. Q., Wang, J. *et al.* Whole metagenome profiling reveals skin microbiome-dependent susceptibility to atopic dermatitis flare. *Nature Microbiology* **1**, 16106 (2016).

SMART DATA, SMART CITY

A*STAR researchers are designing a data-exchange platform that can act as a city's dashboard

We live in a sea of information. Every day, 2.5 billion gigabytes of data are produced by our smartphones, sensors and satellites, among other sources. Much of this data has no use beyond its initial purpose, but what if the disparate bits of meaningful data incidentally produced during the day-to-day operations of a city could be brought together and analyzed as an integrated whole to make the lives of urban dwellers flow more smoothly?

Singapore's Smart Nation initiative aims to do exactly this. A big part of the challenge is designing systems that are capable of handling huge amounts of data in vastly different, often unstructured, forms and assembling it to extract usable information on everything from traffic congestion to land usage. The A*STAR Urban Systems Initiative (USI) is perfecting the art of big-data consolidation in the cityscape.

A DATA MARKETPLACE

Launched by the A*STAR Institute for Infocomm Research (I^2R) in 2012, USI consists of five programs: Complex Systems, Urban Logistics, Integrated City Planning and Sense & Sense-abilities. But the initiative's backbone is formed by the A*STAR Data Analytics Exchange Platform, or A*DAX.

When Ng See-Kiong took over leadership of USI in November 2012, he realized that being able to combine data sets from multiple data owners would be the key to its success. "The city really is a complex system of systems," says Ng. "To understand transportation, for example, you can't just look at transportation; you also need to look at demography, job distribution, weather and other issues." This is where A*DAX comes

A*STAR's Urban Systems Initiative pulls together disparate data sets to transform Singapore into a truly 'smart nation'.

into play — an open-standards, cross-domain platform for data linking, sharing and analytics across Singapore's public and private sectors.

Simply making the data freely accessible was not an option since a lot of it was proprietary and subject to privacy considerations. A*DAX's solution was to provide a platform capable of bringing data owners together and allowing them to exchange and integrate information on a 'peer-to-peer' basis. "The platform itself is a controlled environment with strict user access controls — if you are the data owner or service provider you can give access to other users," explains Ng. In layman's terms, "you can think of it kind of like a data marketplace, where people come together and agree to exchange information in a safe and controlled environment."

Once the data buyers and sellers had agreed to do business, the platform designers then needed to ensure that the different types of data — structured, semi-structured and unstructured — could be combined and extracted at the same time. In response, Ng's team created the A*DAX Fusion middleware, which allows a user to issue a single 'query' to any combination of multiple data sets of different data types based on a framework familiar to web service designers called RESTful APIs (representational state transfer application program interfaces).

USER FRIENDLY

Having access to reams of data is one thing, being able to interpret and make use of it is another. In a pivotal exchange between the team and some early adopters, the A*DAX team quickly learned that they also needed to develop the platform's analytic capabilities.

USI program director Ng See-Kiong (far right) and the A*STAR Data Analytics Exchange Platform team.

> **“WE FOUND THE USERS DIDN’T WANT MORE DATA — THEY WANTED MORE ANSWERS.”**

“We found that the users didn’t want more data — they wanted more answers,” Ng recalls. Generally, this meant helping users to find data, even when they couldn’t articulate exactly what they were looking for. “The user typically has lots of data, knows they want to make use of it but doesn’t know exactly what they can use it for,” says Ng. “Oftentimes we would have to put ourselves in the shoes of the user and try to create some visual analytics routines to produce insights that they might want to see from the data. This would act as inspiration for users to tell us what they wanted. It’s an iterative process — we have to enter this discovery journey together.”

The team eventually homed in on the strategy. “We decided not to give away the raw data and instead provide people with a way to query it for less specific information, but more valuable insights such as aggregates or predictions.” This had the added benefit of preserving a higher level of data security, while ensuring the data was still ‘usable’ — a very difficult balance to strike.

Christopher Monterola, senior scientist at the A*STAR Institute of High Performance Computing, heads the USI’s Complex Systems’ arm.

A SMART CITY ‘TESTBED’

One of the greatest joys for a researcher is seeing an idea they have conceptualized come to fruition. For Ng, A*DAX first came to life in the Jurong Lake District (JLD), Singapore’s first smart city ‘testbed’. A shared sensor and camera network was set up in the JLD, with A*DAX as the core data management system. Participating developers from different sectors have been able to use A*DAX’s capabilities to enhance their own applications and trials within JLD. Examples include a web-based service that integrates environmental information to help urban planners monitor and measure microclimates, as well as an automated system that is capable of detecting people sneaking a cigarette into non-smoking zones.

PREDICTING THE UNEXPECTED

A*DAX is designed to make predictions based on existing data, such as from public transport smart cards, taxi global positioning systems and mobile phone locations. But not all human behavior is well documented, or easily foreseen. “In real life, there are many situations where there’s no historical path for you to base your predictions on,” says Ng. “This is where complex systems come in — to use modeling and simulations to help people prepare for the unexpected.”

Christopher Monterola from the A*STAR Institute of High Performance Computing heads up the USI’s Complex Systems arm. “We provide the modeling and simulation framework and perspective on how to understand the interactions and mechanisms of the various constituents that make up urban systems — it’s a natural fit for the USI.”

Specifically, the team contributes mechanism-based models to complement the data, visualization and analytics from the other USI programs. Monterola and his team have previously designed sophisticated ‘agent-based’ mathematical models that predict diverse urban-mobility parameters, from land-use patterns for urban planning, through to train delays and traffic congestion — essential capabilities for a ‘smart city’. Combining the team’s predictive models with A*DAX’s data capabilities opens exciting possibilities for urban planners. These include being able to compare and contrast overlapping land use and travel infrastructure in different city designs, as well as handling traffic congestion due to a sudden surge of commuters in a given locality, and managing the ‘pulse’ of people in a city — their spending patterns, energy consumption and travel preferences, says Monterola.

MOVING FORWARD

Employing A*DAX as a ‘city dashboard’ is a logical move in a tech-savvy country like Singapore. But, A*DAX has the potential to be applied in other sectors as well, such as finance. Ng and the team are exploring ‘smart finance’ applications, specifically the use of A*DAX to bring together financial models and natural cartography for the calculation of more accurate insurance risk models. “We’re also hearing a lot about the Internet of Things, industry 4.0, autonomous vehicles, the sharing economy — a lot of these will require data analytics exchange platforms similar to A*DAX,” says Ng.

Now at the end of their initial five-year mandate, the USI team is set to continue making Singapore a ‘smarter’ nation. “We’re definitely not closing shop — we’ve only just started!” says Ng.

Software apps can teach language learners how to pronounce foreign words.

Speech recognition:

TAILOR-MADE LANGUAGE COACH IN YOUR POCKET

SELF-LEARNING COMPUTER SOFTWARE CAN DETECT AND DIAGNOSE ERRORS IN PRONUNCIATION

An inexpensive, versatile and personalized system for recognizing and correcting mispronounced words could improve language learning. The A*STAR-devised system gradually picks up the most common speech mistakes made by an individual, and potentially could be applied to any language[1].

"The majority of research in this field focuses on one language, or one type of native-language speaker," explains Nancy Chen at the A*STAR Institute for Infocomm Research, who led the effort along with Ann Lee at the Massachusetts Institute of Technology. "We wanted our system to be more general."

Computers typically 'learn' by recognizing patterns hidden in large data sets, such as the tendency of native Mandarin Chinese speakers to express '*v*' sounds in English as '*b*'. Most current speech recognition software learns these rules from training data — compiled recordings of language beginners that have been marked by a linguistics expert for phonetic mistakes. "But the process of having humans transcribe how sounds are mispronounced is time-consuming and labor-intensive, and doesn't scale well from language to language," says Chen. Instead the researchers developed an unsupervised learning system that could train itself.

Lee had previously created a rudimentary model that groups phonemes into distinct acoustic units — '*a*'s, '*e*'s, and '*i*'s — by measuring the differences between the speech sounds. The model then sifts mistakes and stores them as mispronunciation patterns to seek out.

To improve the model's ability to recognize mispronounced phrases, the A*STAR–MIT team introduced two techniques. First, instead of storing every possible error, the system only considers the most likely errors when assessing sound bites. "Unsupervised learning is a noisy process, so it helps to only consider estimated guesses that you are more confident with," explains Chen.

The second technique involves checking errors not just against a standard native speaker's voice, but also against the learner's own voice. By accounting for the learner's unique vocal characteristics, the system avoids detecting errors where they do not exist. "Smartphone apps can collect a lot of data specific to a user, which allows us to build a compact speech recognizer tailored to an individual," Chen elaborates.

The researchers tested their upgraded system on native English learners of Mandarin, and found that it halved the number of unlikely errors identified by the earlier model and reduced the number of undetected errors to levels comparable with a trained learning system.

Chen's team is currently advancing supervised and unsupervised learning techniques to also assess melody in speech, which affects the meaning of words in tonal languages like Mandarin.

1. Lee, A., Chen, N. F. & Glass, J. Personalized mispronunciation detection and diagnosis based on unsupervised error pattern discovery *2016 IEEE International Conference on Acoustics, Speech and Signal Processing (ICASSP)*, 6145–6149 (2016).

Materials science:

CHARGING AHEAD WITH MAGNESIUM BATTERIES

TIRED OF RUNNING OUT OF CHARGE ON YOUR SMARTPHONE? THE HUNT IS ON FOR A LONGER-LASTING BATTERY

Molybdenum selenide nanowire cathodes could be the missing ingredient needed to make long-lasting, high performance Magnesium-ion batteries a reality.

A battery for laptops and smart phones that is long-lasting, safe and affordable is a step closer thanks to work by A*STAR researchers[1].

Portable electronic devices need smaller batteries with high energy capacities. Now, Man-Fai Ng and colleague Pei Shan Emmeline Yeo, from the A*STAR Institute of High Performance Computing, have investigated a possible cathode material for a magnesium-ion battery to overcome some problems of the common power source, lithium-ion (Li-ion) batteries.

Constraints of Li-ion batteries include low power and limited battery life, which can be significantly improved if lithium is used as the negative electrode or 'anode'.

However, this creates safety issues as during charging and discharging of the battery, microscopic lithium fibers — known as dendrites — can form on the metal anode's surface.

If these dendrites reach the cathode, or positive electrode, the battery can short-circuit and catch fire. "Commercial Li-ion batteries use graphite as the anode to prevent this problem," says Ng. "But the trade-off is that graphite is of lower energy density."

Magnesium metal, on the other hand, does not form dendrites and, in addition to having a higher volumetric energy density than lithium

metal, is much more abundant — reducing the cost of raw materials.

Magnesium-ion (Mg-ion) batteries therefore hold promise as next-generation batteries because they would be low cost, safe and have high energy density, explains Ng. One particular challenge associated with Mg-ion batteries, however, is finding suitable cathode materials.

"Typical Li-ion cathode materials are not compatible with Mg-ion batteries due to their sluggish kinetics of insertion–desertion of magnesium ions in the cathode materials. Therefore, the performance of the Mg-ion batteries is low and of no practical use."

Ng and Yeo used supercomputer modeling to scan for a potential cathode material and identified one-dimensional molybdenum chalcogenide halide nanowires as a promising candidate.

"Among the nanowires studied, the molybdenum selenide nanowire with molecular formula (Mo_6Se_6) exhibits the best battery performance for its fast ion insertion kinetics and moderately good charge capacity," Ng says.

The team plans to collaborate with experimental groups to verify this theoretical prediction, and continue searching for potential cathode materials for Mg-ion batteries using first-principles modeling techniques.

Ng says first-principles modeling is a powerful tool for battery research as it can accurately study the structural and electronic properties of electrode and electrolyte materials; and the interactions between different materials.

More importantly, he says, it can be used for fast screening of materials with desired properties to speed up the search for useful materials to make Mg-ion batteries a reality sooner.

1. Yeo, P. S. E. & Ng, M.-F. First-principles study of molybdenum chalcogenide halide nanowires for Mg-ion battery cathode application. *Chemistry of Materials* **27,** 5878–5885 (2015).

Stem cells:

EVEN AT REST, HAIR STEM CELLS KEEP ACTIVE

UNDERSTANDING HOW HAIR FOLLICLE STEM CELLS MAINTAIN THEMSELVES COULD LEAD TO NEW THERAPIES FOR BALDNESS

Growth, destruction, rest, repeat — so goes the cycle of hair production, a process that is driven by a specialized group of stem cells living in a bulge located about mid-way along the sheath that surrounds the hair root. A*STAR researchers have discovered how these stem cells maintain their regenerative capacity during the long periods of dormancy in the hair cycle, a finding that could lead to new treatments for hair loss[1].

The stem cells that reside in the hair follicle bulge can remain dormant for weeks or even months. But when the timing is right, these cells emerge for growth, activated in part through a critical developmental cue: the Wnt signaling pathway.

Scientists had widely thought that the Wnt machinery turns off when the stem cells are resting. But a team led by Xinhong Lim, a stem cell scientist at the A*STAR Institute of Medical Biology, proved this assumption incorrect.

Lim and his colleagues discovered that a Wnt pathway gene called *Axin2* is expressed throughout the resting phase in the dormant hair follicle stem cells of mice. When they turned off Wnt activity and production in these *Axin2*-expressing stem cells, the hair follicles displayed abnormalities during the resting phase and subsequently couldn't grow properly.

What's more, these stem cells were found to produce their own Wnt signaling proteins: some that promote self-renewal of the stem cells, and others that inhibit Wnt, driving hair

A*STAR research could lead to new treatments for hair loss.

cell differentiation in other cells. This is unlike what happens with stem cells in most other parts of the body, where external signals in the microenvironment control their fate.

The findings show that, contrary to conventional wisdom, "active Wnt signaling is a constant feature of the hair follicle stem cell niche," says Lim.

"We revised the paradigm by suggesting that instead of an absence of Wnt during the resting phase and activity during the transition to the growth phase, we actually see the presence of a low level of Wnt signaling even during the resting phase, and a ramping up of Wnt signaling during the transition to growth."

A more complete understanding of how this works — including what level of Wnt signaling is needed to facilitate hair growth and what level maintains stem cell function — could enable drug companies to develop future therapies for baldness and other hair growth disorders. "Tweaking Wnt signaling may help us to more effectively culture hair stem cells for transplantation and drug screens to treat hair loss," Lim says.

1. Lim, X., Tan, S. H., Yu, K. L., Lim, S. B. H. & Nusse, R. *Axin2* marks quiescent hair follicle bulge stem cells that are maintained by autocrine Wnt/β-catenin signaling. *Proceedings of the National Academy of Sciences USA* **113,** E1498–E1505 (2016).

Materials:

SILICON BRINGS MORE COLOR TO HOLOGRAMS

SILICON HOLOGRAMS HARNESS THE FULL VISIBLE SPECTRUM TO BRING HOLOGRAPHIC PROJECTIONS ONE STEP CLOSER

We can't yet send holographic videos to Obi-Wan Kenobi on our droid, but A*STAR researchers have got us a little bit closer by creating holograms from an array of silicon structures that work throughout the visible spectrum[1].

Many recent advances in hologram technology use reflected light to form an image; however the hologram made by Dong Zhaogang and Joel Yang from the A*STAR Institute of Materials Research and Engineering uses transmitted light. This means the image is not muddled up with the light source.

The team demonstrated the hologram of three flat images at wavelengths ranging from blue (480 nanometers) to red (680 nanometers). The images appeared in planes 50 microns apart for red and higher spacings for shorter wavelengths.

"In principle, it can be tuned to any wavelength," says Yang.

Holograms can record three-dimensional images, which mean they can store large amounts of information in increasingly thin layers.

Recently, holograms that are mere hundredths of the thickness of a human hair have been made from metal deposited onto materials such as silicon. The holograms are created by nanoscale patterns of metal that generate electromagnetic waves that travel at the metal–silicon interface; a field called plasmonics.

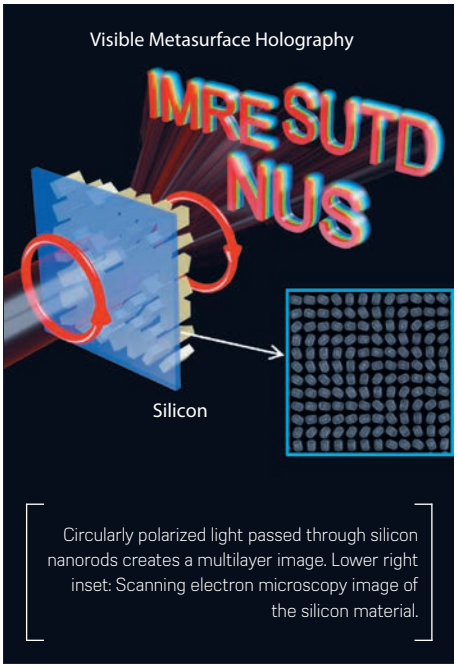
Silicon holograms are slightly thicker than the metal-based ones, but have the advantage of being broadband. Plasmonic holograms only operate in the red wavelengths because they undergo strong absorption at blue wavelengths.

A disadvantage of the silicon holograms is their poor efficiency at only three per cent; however Dong estimates this could easily be tripled.

"The losses can be lowered by optimizing the growth method to grow polycrystalline silicon instead of amorphous silicon," he says.

The hologram is an array of tiny silicon skyscrapers, 370 nanometers tall with footprints 190 nanometers by 100 nanometers. Unlike a city grid, however, the tiny towers are not laid out in neat squares but at varying angles.

The hologram operates with circularly polarized light, and the information is encoded on to the light beam by the varied angles of the skyscrapers. These alter the phase of the transmitted light through the 'Pancharatnam–Berry effect'.



Circularly polarized light passed through silicon nanorods creates a multilayer image. Lower right inset: Scanning electron microscopy image of the silicon material.

"What's interesting about this hologram is that it controls only the

phase of the light by varying the orientation of the silicon nanostructures. The amplitude is the same everywhere; in principle you can get a lot of light transmitted," says Yang.

The A*STAR researchers focused on nanofabrication and measurements and collaborated with Cheng-Wei Qiu from National University of Singapore, whose team specializes in hologram design.

1. Huang, K., Dong, Z., Mei, S., Zhang, L., Liu, Y. *et al.* Silicon multi-meta-holograms for the broadband visible light. *Laser & Photonics Reviews* **10,** 500–509 (2016).

Data storage:

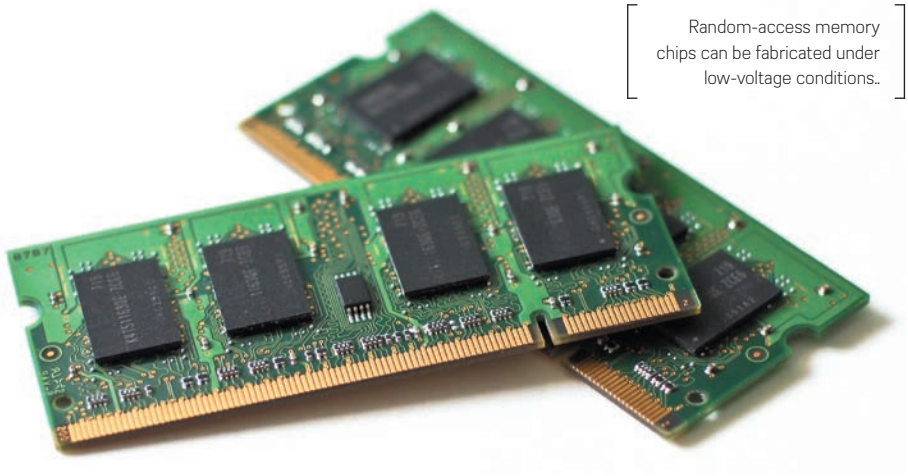
PERFECTLY FORMED MEMORY

RESISTIVE RANDOM-ACCESS MEMORY THAT AVOIDS AN INITIAL FORMING PROCESS IMPROVES FABRICATION METHODS AND RELIABILITY

An enhanced design for a promising computer memory technology has been developed by A*STAR researchers. Victor Zhuo and colleagues developed resistive random-access memory (RRAM) that, during fabrication, does not require a harmful high-voltage forming process[1].

"We demonstrate a forming-free RRAM cell with low operation voltages, a large resistance window and excellent thermal stability," says Zhuo.

RRAM is the most promising nonvolatile memory system as it shows similar functionality to present solid-state memory drives, but has a higher storage density and longevity. RRAM devices can be scaled down to smaller than 14 nanometers. They also offer a straightforward operation mechanism where the memory state of the material that corresponds to the bits used by computers is determined merely by the electrical resistance of the device. This resistance can be 'switched' by orders of magnitude, just by using electrical voltage pulses applied to the RRAM device.



Random-access memory chips can be fabricated under low-voltage conditions..

© Andrew Macdonald AKA My TYC/Moment Open/Getty

The rudimentary operation mechanism of RRAM means the chips have a simple fabrication method. However, a drawback of RRAM fabrication is that the memory device is not in one of the two electrical resistance states needed for operation. A high forming current is required to set the memory into the right state: this complicates fabrication and requires further monitoring for damages.

Researchers from the A*STAR Data Storage Institute and the A*STAR Institute of Microelectronics have developed a design for the device that delivers memory in the desired state and avoids the use of forming currents.

On the microscopic level, the resistance switching of RRAM occurs through the migration of oxygen atoms. As RRAM materials are made from a combination of metal and oxygen atoms; removing oxygen causes an oxygen shortage in the material. This lowers the material's electrical resistance, allowing electrical current to flow. Introducing oxygen back into the material increases its electrical resistance and makes it an insulator.

The RRAM devices studied by Zhuo's team uses tantalum oxide with electrical contacts made from either titanium nitride or tantalum. When using titanium nitride, which is chemically not very reactive, a forming voltage is required during production. However, when using the more chemically reactive tantalum, the device is ready to use right away. Tantalum has a natural affinity to react with the oxygen that helps to prepare the material in the right state.

The aim is to demonstrate this concept in advanced devices, adds Zhuo. "Our next step is to integrate RRAM memory devices with a selector for ultra-high-density nonvolatile memory applications."

1. Jiang, Y., Tan, C. C., Li, M. H., Fang, Z., Weng, B. B., He, W. & Zhuo, V. Y.-Q. Forming-free TaO_x based RRAM device with low operating voltage and high on/off characteristics. *ECS Journal of Solid State Science and Technology* **4,** N137–N140 (2015).

[PICTURE STORY]

The inaugural One-North Festival was held in Fusionopolis between 2 – 6 August 2016. The event celebrated how research, innovation, creativity and enterprise bring us new and exciting possibilities for the future and brought together scientists, industry exhibitors and the general public for five days of talks, science, discovery, and fun.

Solar panel technology has been dominated by silicon but now perovskite shows promise as a practical alternative.

Solar power:

PEROVSKITE CAN TAKE THE HEAT

MYTH-BUSTING RESEARCH INTO A NEW ALTERNATIVE SOLAR CELL MATERIAL COULD LEAD TO CHEAPER SOLAR CELLS

Solar cells that are cheaper and easier to manufacture could challenge the dominance of silicon, with new research showing an alternative material called perovskite is more efficient and adaptable than previously thought.

The challenge to developing efficient and cheap commercially available solar panels has, until now, been dominated by silicon, with emerging alternative solar cells considered minor players, says Wei Lin Leong from the A*STAR Institute of Materials Research and Engineering.

"Silicon is very labor-intensive and requires very high temperatures to process," Leong explains. "But with alternative cells there is inefficiency in capturing the energy from the Sun".

Perovskite is relatively easy to process, and therefore cheaper to manufacture, but also has an efficiency of 22 per cent, close to silicon cells' 25 per cent.

Yet, the dominance of commercial and research investment in silicon has made it difficult to convince researchers and commercial developers to adopt new technologies.

"This new class of solar cell is only around four years old, so although it has high performance, people don't understand the system and why it's doing so well," Leong says.

Her research has provided important insights into the basic physics of perovskite solar cells by measuring their efficiency at different temperatures and light intensities[1].

"Because it had only been tested at room temperatures, people were skeptical about

whether it would still work at the higher temperatures under direct sunlight on a rooftop, where it can go up to 60 degrees Celsius," Leong says.

For most conventional or silicon-based solar cell technologies, efficiency worsens as temperature rises.

Leong's study showed the perovskite cells still worked at higher temperatures, with performance peaking at around 330 Kelvin — or 57 degrees Celsius — and then declining slightly after that, meaning their performance will be high even on a relatively hot rooftop. It also showed that, contrary to arguments made by some critics, the material was highly efficient at collecting charge through electrodes.

Leong believes that perovskite will eventually challenge silicon commercially. "In terms of efficiency, perovskite is already close and it can be made much more cheaply," she says.

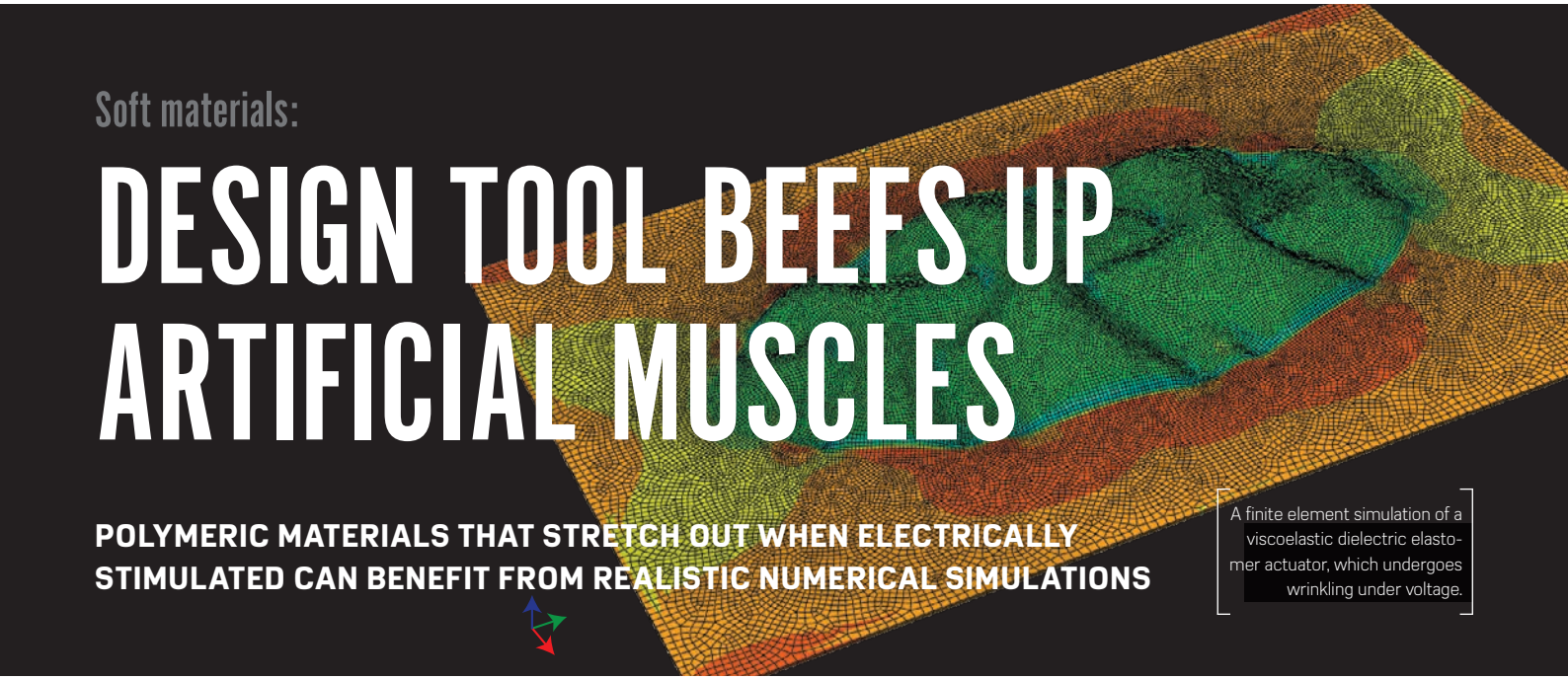
However, perovskite cells still contain lead, which means more research needs to be done to ensure the lead does not leak. "Another big challenge is to make cells big enough for commercial use, as right now all the research is on small cells," she says.

1. Leong, W. L., Ooi, Z., Sabba, D., Yi, C., Zakeeruddin, S. M., *et al.* Identifying fundamental limitations in halide perovskite solar cells. *Advanced Materials* **28**, 2439–2445 (2016).

Soft materials:

DESIGN TOOL BEEFS UP ARTIFICIAL MUSCLES

POLYMERIC MATERIALS THAT STRETCH OUT WHEN ELECTRICALLY STIMULATED CAN BENEFIT FROM REALISTIC NUMERICAL SIMULATIONS



A finite element simulation of a viscoelastic dielectric elastomer actuator, which undergoes wrinkling under voltage.

Robotic devices are usually composed of hard components such as aluminum and steel, in contrast to the soft tissues that power biological organisms. A study conducted by A*STAR researchers now makes it easier to turn squishy, electroactive polymers into artificial muscles and biomimetic energy harvesters through computer-aided design[1].

Dielectric elastomers are rubbery, insulating membranes that respond dramatically to electric fields — when sandwiched between two electrodes, they can expand by several hundred per cent in a two-dimensional plane. These special deformation properties have led to applications such as soft-body robotics and sensors. However, the shape-shifting membranes often develop changes in their electrically stimulated response over time, making them hard to optimize for long-term use.

Keith Choon Chiang Foo from the A*STAR Institute of High Performance Computing and his team realized that numerical simulations could help to improve dielectric elastomer devices. They turned to finite element analysis, a tool that predicts the performance of complex objects by modeling them as small interconnected geometric units, to reach this goal. But finding algorithms that replicate smart polymer behavior is not straightforward.

"Existing finite element software doesn't have the capability to simulate soft rubbery materials that respond to electricity and involve large deformations," says Foo. "Plus, most simulations of these polymers have been done using 'in-house' software, meaning source codes are not available to the scientific community."

The researchers solved these issues with a model that revealed how repeated movements affected the membrane's ability to respond to electricity and mechanical forces over time. Their algorithms coupled this property, known as viscoelasticity, to electrostatic charges in the device. They implemented this model into commercial finite element software. "We have made the subroutine freely available to aid other researchers," adds Foo.

The team's simulations highlighted examples where viscoelasticity has an impact on the performance of artificial muscle-like devices. For example, when an electrical pulse causes the membrane to stretch out, the elastomer takes a characteristic time to relax to the new

configuration. If the pulse cycles at a rate close to this relaxation time, mechanical actuation can be significantly affected.

Further tests showed the improved finite element analysis could quantify the critical time delay between the instant an electrical signal is applied and the maximum polymer actuation achieved. Because the computations agree well with previous experimental data, Foo is confident this technique can reduce trial-and-error approaches to biomimetic devices.

"This simulation tool may prove very capable," he remarks. "When we work with experimentalists, it helps guide our approach to soft machines."

1. Foo, C. C. & Zhang, Z.-Q. A finite element method for inhomogeneous deformation of viscoelastic dielectric elastomers. *International Journal of Applied Mechanics* **7**, 1550069 (2015).

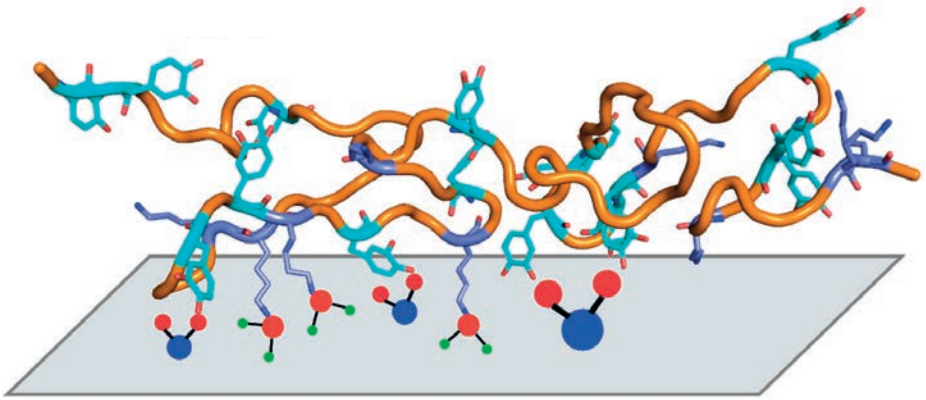
Marine studies:

GETTING A GRIP ON MUSSEL ADHESION

FIBROUS MUSSEL 'BEARDS' SECRETE STICKY PROTEIN PRIMERS TO CLING TO WET SURFACES

The Asian green mussel (*Perna viridis*) anchors itself underwater by timed secretion of adhesive proteins from threadlike foot extensions, a team of researchers in Singapore finds[1].

Lab experiments and computer simulations reveal that an especially long sticky protein acts as a primer — first catching the surface and repelling water molecules to make way for two proteins that form the final adhesive pad. The discovery could lead to new submersible glues or improved paints to prevent biofouling on ship hulls and drilling platforms.



The protein Pvfp-5 secreted in Asian green mussel 'beards' sticks strongly to wet surfaces and appears to suction out hydrated ions and water molecules.

> "BY GETTING A GLIMPSE OF WHAT EXISTS IN NATURE, WE CAN MIMIC AND MANIPULATE IT TOWARD SOMETHING USEFUL."

"Water is not a friendly media for sticking stuff together, but many marine creatures are able to do it," says Ali Miserez, who led the research at Nanyang Technological University, in collaboration with Chandra Verma at the A*STAR Bioinformatics Institute, with funding from the Maritime and Port Authority of Singapore and the Singapore Maritime Institute. "By getting a glimpse of what exists in nature, we can mimic and manipulate it toward something useful," adds Verma.

Mussels, within seconds of feeling out a rock with their foot, begin to produce long, stiff and durable threads, called byssus — usually described as the mussel 'beard'.

Miserez's laboratory had previously identified the byssus proteins — Pvfp-3, -5 and -6 — but wanted to know if they released in sequence or all at once. His team took a series of samples in rapid succession from Asian green mussels induced to secrete byssus onto a glass plate.

Mass spectrometry revealed that one protein, Pvfp-5, always comes out first. Further analysis, using methods called the quartz crystal microbalance and the surface force apparatus, showed that Pvfp-5 adheres most strongly to the surface, and infrared spectroscopy detected a gradual displacement of water molecules only around the area where Pvfp-5 lands.

To better understand the structure and function of Pvfp-5, Miserez collaborated with Verma, whose laboratory at A*STAR specializes in structural modeling. Verma's team built a three-dimensional atomic model of Pvfp-5 based on information gleaned from known structures of smaller protein fragments and then simulated its movement in water.

They found that Pvfp-5 was long and floppy, with a row of outward-facing dopa amino acids that form tight bonds on the surface. "Imagine a ball of cooked spaghetti — this flexibility allows the protein to adapt its shape to the surface," says Miserez.

Positively-charged lysine amino acids, in close proximity to Dopa amino acids, appear to act as suction pumps to remove hydrated ions and water from the surface (see image).

The researchers are keen to artificially reengineer the system to design materials that can bridge the liquid–solid divide, for application in surgical glues, catheters and antifouling paints. ■

1. Petrone, L., Kumar, A., Sutanto, C. N., Patil, N. J., Kannan, S. *et al.* Mussel adhesion is dictated by time-regulated secretion and molecular conformation of mussel adhesive proteins. *Nature Communications* **6,** 8737 (2015).

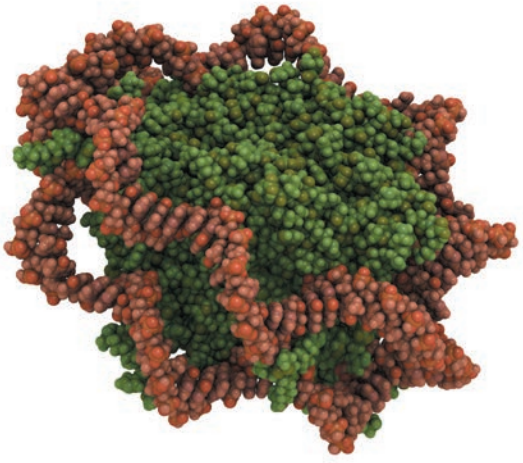
Genetics:

READING THE GENOME THROUGH A SHARPER LENS

A NEGLECTED HISTONE MODIFICATION HAS UNEXPECTED IMPLICATIONS FOR GENE ACTIVITY

A poorly understood histone modification has been shown to be a more sensitive predictor of gene expression switches than any other tested modification[1]. The finding, revealed by an A*STAR study, provides a new tool for studying gene regulation and could lay the groundwork for a better understanding of disease.

The two meters of DNA in the nucleus of every human cell is tightly wrapped around proteins called histones. If specific sites on these histones are chemically modified, for instance acetylated, these sites can mark interesting DNA regions, including enhancers that stimulate the expression of genes.



In cells, DNA is wrapped around bead-like complexes of histones. Chemical changes on these histones can result in changes to the expression of genes.

Scientists know of over 35 histone acetylation sites but have mostly focused on only two, called H3K27 and H3K9. Shyam Prabhakar from the A*STAR Genome Institute of Singapore calls this narrow focus a "historical accident". "Their importance was recognized in some seminal papers, but then most genomics researchers looked no further," he explains.

Prabhakar was not convinced these sites painted a complete picture for genome-wide expression studies, such as those conducted by the International Human Epigenome Consortium.

In this study, Prabhakar's team led by Vibhor Kumar performed 140 different assays on human immune cells, each of which tested the activity of a candidate enhancer. "We said: Let's be unbiased — which chemical modification is really telling us about enhancer activity?" Prabhakar recalls.

The scientists compared how well 40 different histone modifications associated with these active enhancers, as a test for how well they might predict unknown enhancers.

The result surprised Prabhakar's team: they discovered a previously little-known modification — H2BK20 acetylation — predicted enhancer activity better than any other site.

Prabhakar says this acetylation site could help reveal a new dimension of gene regulation specific to different cell states and could complement the information provided by other modifications. "We will be using it, and we hope others will use it, to find a larger set of enhancers and to identify interesting promoters," he says.

Prabhakar is also excited about the possibility that H2BK20 may be a more sensitive readout of the cellular processes underlying human disease. His team will now investigate this by comparing H2BK20 acetylation profiles of diseased and healthy tissue.

"We really need a mechanistic understanding of how all of these different histone acetylations change in disease and how that can be modulated with drugs to carry therapeutic effects," says Prabhakar.

As drugs that modulate acetylating enzymes are already used to treat diseases such as cancer, Prabhakar says he is quite confident that this will be a productive direction.

1. Kumar, V., Rayan, N. A., Muratani, M., Lim, S., Elanggovan, B. *et al.* Comprehensive benchmarking reveals H2BK20 acetylation as a distinctive signature of cell-state-specific enhancers and promoters. *Genome Research* **26,** 612–623 (2016).

Smart windows:

ADMITTING VISIBLE LIGHT, REJECTING INFRARED HEAT

A window coating that lets visible light through while blocking near-infrared radiation could cut energy consumption and reduce emissions.

A COATING THAT BLOCKS 90 PER CENT OF THE HEAT FROM SUNLIGHT COULD BE USED TO DEVELOP SMART WINDOWS

By fine-tuning the chemical composition of nanoparticles, A*STAR researchers have developed a coating that is promising for fabricating smart windows suitable for tropical countries[1]. Such windows block almost all the infrared heat from sun rays, while admitting most of the visible light.

The transparency of glass to visible light makes it the most common way to let light into a building. But because glass is also transparent to near-infrared radiation, windows also let in heat, giving rise to the well-known greenhouse effect. While this heating is welcomed in colder climates, it means that air conditioning has to work harder to maintain a comfortable temperature in tropical climes.

Developing smart windows that allow most of the sun's light in, while blocking near-infrared radiation, would cut energy costs and reduce carbon emissions.

> "IN TROPICAL SINGAPORE, WHERE AIR CONDITIONING IS THE LARGEST COMPONENT OF A BUILDING'S ENERGY REQUIREMENTS, EVEN A SMALL REDUCTION IN HEAT INTAKE CAN TRANSLATE INTO SIGNIFICANT SAVINGS."

"In tropical Singapore, where air conditioning is the largest component of a building's energy requirements, even a small reduction in heat intake can translate into significant savings," notes Hui Huang of the A*STAR Singapore Institute of Manufacturing Technology.

Huang and his co-workers have developed such windows by coating glass with tin oxide nanoparticles doped with small amounts of the element antimony. By varying the nanoparticles' antimony concentration, they could optimize their ability to absorb near-infrared radiation.

"Our infrared shielding coating, with 10-nanometer antimony-doped tin oxide nanoparticles, blocks more than 90 per cent of near-infrared radiation, while transmitting more than 80 per cent of visible light," says Huang. "These figures are much better than those of coatings obtained using commercial antimony-doped tin oxide nanopowders. In particular, the infrared shielding performance of our small antimony-doped tin oxide nanocrystals is twice that of larger commercial antimony-doped tin oxide powders."

The team produced the tiny nanoparticles using a synthesis technique known as the solvothermal method, in which precursors are heated under pressure in a special vessel, called an autoclave. The solvothermal method permits synthesis at relatively low temperatures. It also enables the nanoparticle size to be tightly controlled, which is important when trying to block some wavelengths of light while allowing others to pass through.

The work has already attracted the interest of industry. "A local glass company supporting this project is interested in licensing this smart window technology with infrared shielding," says Huang. Potentially, the coating techniques could be applied on-site to existing windows, he adds. ■

1. Huang, H., Ng, M., Wu, Y. & Kong, L. Solvothermal synthesis of Sb:SnO_2 nanoparticles and IR shielding coating for smart window. *Materials & Design* **88**, 384–389 (2015).

Researchers at the A*STAR Biotransformation Innovation Platform will develop microbes that can produce fragrant and flavorful chemical compounds at an industrial scale.

A BIOTRANSFORMATIVE EXPERIENCE

A new taskforce aims to modify microorganisms to produce fragrance and flavor for industry

A*STAR is set to launch its Biotransformation Innovation Platform (BioTrans), a multidisciplinary taskforce that will harness the power of microorganisms to transform cheap and sustainable carbon sources into chemical compounds of interest to the biotechnology industry.

Biotransformation occurs when anything from microorganisms to human beings transform a chemical substance by consuming it. An example of this is the industrial production of antibiotics using the natural capacity of filamentous fungi to convert simple sugars into life-saving drugs. Another example in line with BioTrans' activities can be seen in the use of genetically modified yeasts to produce the sugar substitute, Stevia. It tastes significantly more natural than the version on supermarket shelves, which is based on natural plant extracts. Scientists like Nic Lindley, director of BioTrans, are eager to investigate biotransformation as a production method for high-value chemical compounds required by the food and personal care sectors, which are difficult to synthesize through traditional methods.

THE SCENT OF SUCCESS

The food and personal care sector has seen positive growth in recent years, with the global market for fragrances and perfumes alone predicted to exceed US$40 billion by 2020. The sector relies heavily on plants and animals as raw material for their products, but changing land-use patterns are forcing companies to look for sustainable alternatives to chemical synthesis.

With the opening of BioTrans, A*STAR is well positioned to contribute to this emerging market opportunity. To produce bioalternatives, researchers must first tease out the genetic elements involved in the synthetic pathway of the target molecule and use that information to create — via metabolic engineering and synthetic biology — a 'cell factory' capable of producing economically viable concentrations of the target molecule. The snag in this process is ensuring that the cellular strains created in the laboratory are tough enough to perform under the harsh fermentation conditions typical in industrial processes. When cells succumb to the pressure, a common occurrence, the entire project is sent back to the drawing board. The approach is to build strain robustness into the design from the project outset. This model of early-stage innovation sets the platform apart, says Lindley, and will help to speed up passage through the pipeline.

BioTrans researchers will provide a much-needed link between research and industry. "We aim to bridge the gap between what can be done in our laboratories and bring it to commercial success, thereby contributing to reinforcing the Singapore economy in this important domain," explains Lindley.

GREATER THAN THE SUM OF ITS PARTS

Lindley was looking for a new challenge when Kenneth Lee, head of the Food Nutrition and Consumer Care cluster at the A*STAR Biomedical Research Council and the founding director of BioTrans, contacted him in May 2015. For the previous 12 years, Lindley had led a systems biology and engineering laboratory in France. The opportunity to lead a small, dynamic team at the junction between science and industry was too attractive to pass up.

In the year since his encounter with Lee, Lindley has prepared BioTrans for its official launch, enlisting staff and developing state-of-the-art technologies, including techniques for analyzing volatile compounds, an automated taste-screening platform, advanced fermentation processes and molecular tools for engineering proteins and metabolites. "While the technological toolbox in BioTrans is important, the real strength is the people willing to move into this complex environment and learn how to work with the disciplines," says Lindley, praising the enthusiastic group of 25 scientists who have joined the platform either as collaborators based in other A*STAR institutes or as full-time staff.

But BioTrans's strongest selling point is the collective intelligence approach adopted by the program, Lindley says. "We thrash out ideas before fixing on a coordinated project built up from the various skills which can be articulated to do something no individual scientist would imagine on their own." Some early projects the team has begun to work on involve generating stress-resistant microbial strains and testing the potential for creating new flavors and fragrances.

Closer collaborations with industrial partners will follow. Lindley is "even more enthusiastic for the project now than I was at the beginning."

Just some of the fast-growing team contributing to the 'collective intelligence' of BioTrans.

A study by A*STAR researchers finds that activated B cells (white and red) and T cells (green) cluster in close contact within liver cancer tissues. The higher the density of B cells, the better the patient's chances of survival.

Immunology:

B CELL CLUSTERS HELP CONTROL LIVER CANCER

IMMUNE SYSTEM B CELLS PLAY A ROLE IN TACKLING LIVER CANCER AND PROVIDE A MARKER FOR PATIENT PROGNOSIS

Immunotherapy — developing treatments by boosting natural immune system responses — holds great potential in the fight against serious diseases. Now, A*STAR researchers have determined how one group of immune cells called tumor-infiltrating B cells (TiBs) can fight liver cancer[1]. Their results could inform future treatments.

Tumor-infiltrating cells, including TiBs and T cells, are white blood cells that have left the bloodstream to enter cancerous tissue. Depending on their type and 'conditioning' they may either promote or control tumor growth. Previous studies have demonstrated a positive correlation between the density of T cells found inside a tumor and a patient's chances of survival. As such, tumor-infiltrating cells are of great interest to scientists developing immunotherapies for cancer.

"The presence of TiBs in tumors has always been controversial, with studies producing conflicting results on whether they play a positive or negative role during cancer," says Alessandra Nardin of the A*STAR Singapore Immunology Network, who worked on the project with an international team of scientists. "We wanted to determine the role of TiBs in liver cancer progression regardless of patients' ethnicities or individual disease triggers."

The team used tissue samples from 112 Asian and European patients with liver cancer. In Asia, there is a relatively high volume of cases of the disease, mainly due to the prevalence of Hepatitis B infection in the region. In Europe, the causes of liver cancer include alcohol consumption and Hepatitis C infection.

Nardin's team traced markers indicating the presence and activation of TiBs and T cells, and examined their distribution inside tumor samples (see image). They found that T cells and TiBs clustered inside tumors, and that those patients with a high density of TiBs had a better chance of survival, regardless of ethnicity or disease triggers. Further investigations using mice models showed that mice with depleted mature TiBs lacked T cell activation and exhibited poor control of tumors.

"The close proximity of TiBs and T cells suggests a functional interaction between them that enhances local immune activation," says Nardin. "TiBs are needed to help T cells control the growth of the tumor and slow cancer progression. We were pleased to discover that TiBs can also act as an independent indicator of improved disease prognosis."

Further work is needed to understand the mechanisms by which TiBs influence the responses and behavior of other immune cells inside tumors.

1. Garnelo, M., Tan, A., Her, Z., Yeong, J., Lim, C. J. *et al.* Interaction between tumour-infiltrating B cells and T cells controls the progression of hepatocellular carcinoma. *Gut*, advance online publication 15 December 2015 (doi: 10.1136/gutjnl-2015-310814).

Genomics:

EXPANDING THE POWER OF PORES

SMARTER SOFTWARE ALLOWS RESEARCHERS TO GENERATE HIGHER-QUALITY DATA FROM AN EXCITING NEW DNA SEQUENCING TECHNOLOGY

New DNA sequencing technologies allow researchers to pursue different strategies for exploring the genome, but only if they have software that accurately interprets the data. Researchers led by Niranjan Nagarajan at the A*STAR Genome Institute of Singapore have developed an algorithm that could help a cutting-edge sequencing platform achieve its potential[1].

Most clinical genomics data is produced by so-called 'short-read' instruments, which generate billions of small stretches of nucleotide sequence information (or 'reads'). These reads must be mapped back to the appropriate position in the genome — a complicated task, given that each read typically spans just 100–200 bases.

A new platform called the MinION takes a different approach, channeling individual DNA strands into protein nanopores and identifying each nucleotide as it passes through. This allows scientists to gather much longer reads that can, in principle, be mapped more concisely. Additionally, the platform is portable and relatively inexpensive, opening up new sequencing applications.

However, nanopore sequencing is more error-prone than short-read, and mapping has been further impeded by software problems. "When we heard about the MinION system, we were naturally excited and eager to explore applications," says Nagarajan. "But, when we started mapping MinION data with existing tools, we found they didn't perform very well." The disparity is because these algorithms were developed with established platforms in mind, and are not a good fit for this new type of data.

To fill the gap, Nagarajan's team developed new software called GraphMap that maps MinION data with remarkable speed and accuracy. Their system employs a 'funneling' approach to improve the efficiency of plotting each individual read's position. "This progressively eliminates incorrect alignment locations and refines alignments, ensuring that a large space of candidate alignments can be considered," he says.

GraphMap assigned locations for more than 90 per cent of the MinION reads collected over several experiments, overcoming the system's higher error rate and mapping many

The tiny MinION nanopore device from Oxford Nanopore Technologies could offer a valuable tool for DNA sequencing once researchers learn to make the most of the data it produces.

nucleotides that would have been neglected by other software tools. It also consistently achieved high accuracy rates, assigning correct base assignments for more than 98 per cent of the mapped sequences. "We were able to show that GraphMap alignments enable accurate variant calling even in complex and rearranged regions of the human genome," says Nagarajan.

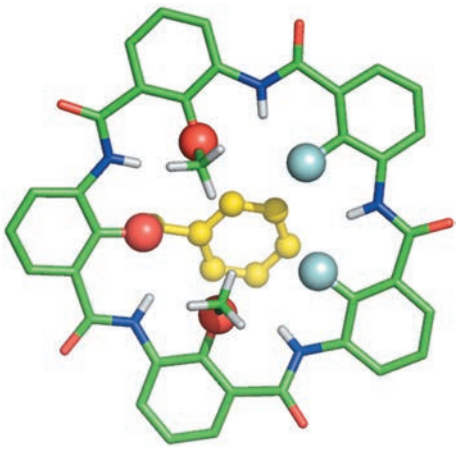
In addition to pinpointing disease-related genomic variations, Nagarajan is also enthusiastic about applying MinION to detect harmful microbes. "GraphMap alignments enabled accurate species and strain identification," says Nagarajan, "and we're continuing to develop protocols for better and faster pathogen identification."

1. Sović, I., Šikić, M., Wilm, A., Fenlon, S. N., Chen, S. & Nagarajan, N. Fast and sensitive mapping of nanopore sequencing reads with GraphMap. *Nature Communications* **7,** 11307 (2016).

Ion recognition:

RINGING THE CHANGES

SUBTLE VARIATIONS IN SIZE, SHAPE AND ELECTRONIC PROPERTIES OF RING-SHAPED MOLECULES, KNOWN AS MACROCYCLES, LEAD TO CHANGES IN ION-SELECTIVITY



Structure of one of a library of macrocycles. The core pentameric structure of the macrocycle is shown in green. Pale blue and red balls show the positions of oxygen and fluorine atoms that vary in different library members.

Selective ion transport is the foundation of water purification technology, as well as underpinning a range of biological effects — such as the function of nerves — and diagnostic technologies that use ion-sensitive electrodes to detect abnormalities in biological fluids. Now A*STAR researchers have invented a new synthetic-ion recognition system and found a way to fine-tune the selectivity of the system that will benefit many applications.

The ability to pick out one type among many metal ions is vital in many fields. Ring-shaped molecules — known as macrocycles — have long been used as synthetic-ion recognition systems. The ion binding properties of the macrocycles are defined by the size and shape of their internal cavity and how well this matches the desired metal ion.

Now, Huaqiang Zeng from the A*STAR Institute of Bioengineering and Nanotechnology, and colleagues from China, have designed a series of macrocycles assembled from five building blocks[1].

"Over the past eight years, we had studied the properties of pentamers of several different single building blocks," explains Zeng. "Hydrogen bonding between the units means that the macrocycles are formed with very little strain and flexibility, and this in turn means that we can exchange building blocks within the same framework to tune their ion binding properties."

Each of the five building blocks is decorated with a chemical group — fluorine, hydroxy and alkoxy groups — which are projected into the central cavity of the macrocycle. The subtle changes in the steric and electronic properties of these groups define the selectivity of ion binding.

A blending of approaches to constructing new macrocycles can produce a very large library of different macrocycles from relatively few different building blocks. For example, two different building blocks can be assembled in eight different ways, but five building blocks can potentially lead to 629 possible macrocycles.

Zeng and co-workers prepared a small selection of these possibilities and compared their ability to selectively extract specific metal ions from a mixture of 20.

> "WE PLAN TO EXPAND BOTH THE SET OF BUILDING BLOCKS AND THE NUMBER OF MACROCYCLES."

The team was able to identify macrocycles that were selective for the extraction of caesium, silver and potassium ions. "We plan to expand both the set of building blocks and the number of macrocycles," explains Zeng. "This will be the key to identifying macrocycles with higher selectivity and affinity.

Zeng says that, in the longer term, the team plans to use their new ion-binders to construct artificial ion channels for wider applications in diverse fields, including molecular sensing and water purification.

1. Liu, Y., Shen, J., Sun., C., Ren, C. & Zeng, H. Intramolecularly hydrogen-bonded aromatic pentamers as modularly tunable macrocyclic receptors for selective recognition of metal ions. *Journal of the American Chemical Society* **137,** 12055–12063 (2015).

Optics:

NANODISKS DRIVE A POLARIZING TRANSFORMATION

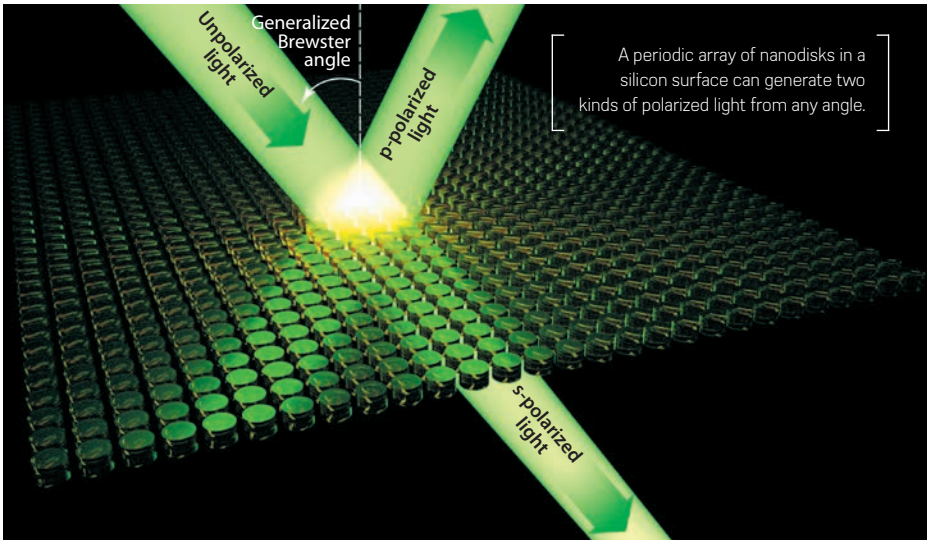
MANIPULATING MAGNETIC AND ELECTRIC DIPOLES INSIDE NANOSTRUCTURED INSULATORS ENABLES NEWFOUND CONTROL OF LIGHT POLARIZATION AT ANY ANGLE

Polarizing filters produce richer, less reflective images by limiting vibrating light waves to one specific orientation. However, these filters only work with light that is reflected from a certain angle. An A*STAR-led team now report that arrays of silicon nanodisks can polarize light at any angle, and into any desired orientation — a finding that opens the way to improved photonic control over ultra-thin optical devices[1].

When polarized light passes through air into an insulating dielectric crystal, it is partly reflected at the interface. But at one particular angle, known as Brewster's angle, incoming light travels through the dielectric with no reflection at all. Studies have shown that this trick arises when electric dipoles, induced by light in the dielectric, align with the reflection direction to inhibit optical reflection. However, this only happens naturally for a particular polarization of light.

Ramón Paniagua-Domínguez from the A*STAR Data Storage Institute and co-workers investigated ways to expand the Brewster effect beyond the restrictions of specific light polarizations and angles. To do so, they turned to metasurfaces — devices that use micro- and nanoscale surface patterns to manipulate electromagnetic radiation in ways not seen in nature.

The team realized that if magnetic dipoles could be excited at the same time as the electric dipoles, the subsequent interference patterns would produce other directions and polarizations where Brewster's effect would occur. Because natural materials have very weak magnetic dipoles at optical frequencies, Paniagua-Domínguez developed a theoretical model to engineer this kind of response from a metamaterial.

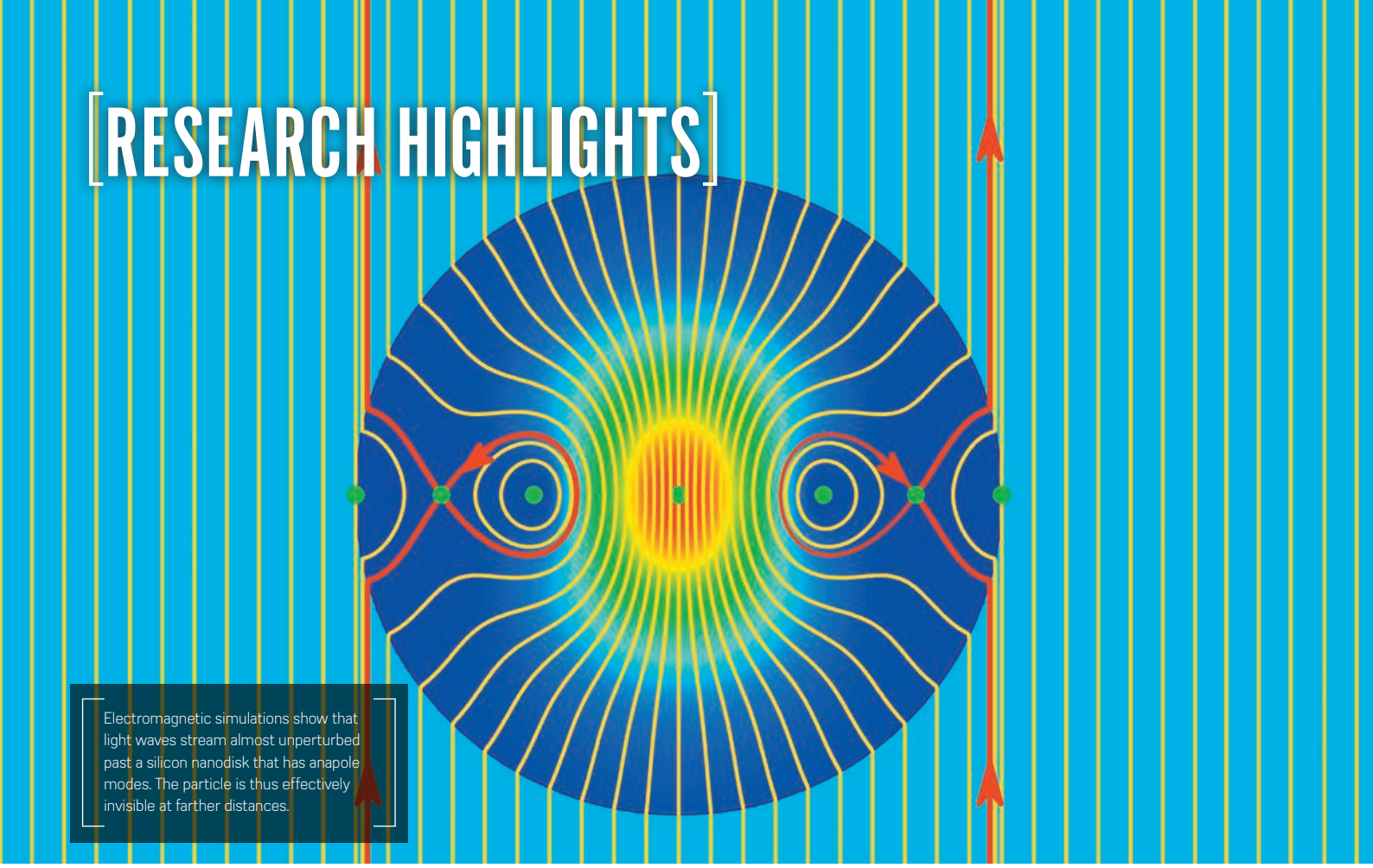


"Silicon has one of the largest refractive indices at optical frequencies, together with very low losses," he notes. "And when you shape it into nanospheres, with sizes smaller than the excitation wavelength, a high-quality magnetic-dipole response presents itself."

The researchers fabricated an array of protruding disks, a few hundred nanometers in scale, onto a silicon surface. Reflection tests with several different wavelengths and angles revealed results strikingly different from conventional runs — light polarized both parallel and perpendicular to the interface produced zero-reflection points, while Brewster angles could be controlled by selecting appropriate light wavelengths. Paniagua-Domínguez then developed a dipole-based model to understand the observed phenomenon.

"The generalized Brewster's effect may add numerous new functionalities to those already achieved with metasurfaces," says Paniagua-Domínguez. "In particular, one could foresee devices that will perform particular operations, such as light-beam shaping, which will be controllable by the angle of incidence and polarization state of the incoming light."

1. Paniagua-Domínguez, R., Yu, Y. F., Miroshnichenko, A. E., Krivitsky, L. A., Fu, Y. H. *et al.* Generalized Brewster effect in dielectric metasurfaces. *Nature Communications* **7,** 10362 (2016).



Electromagnetic simulations show that light waves stream almost unperturbed past a silicon nanodisk that has anapole modes. The particle is thus effectively invisible at farther distances.

Electromagnetism:

INVISIBLE PARTICLES 'SEEN' FOR THE FIRST TIME

A MYSTERIOUS EFFECT IN WHICH PARTICLES DO NOT SCATTER LIGHT HAS BEEN OBSERVED AT OPTICAL WAVELENGTHS FOR THE FIRST TIME

A new optical effect in nanoscale disks of silicon, namely patterns of radiation that do not emit or scatter light, has been observed by A*STAR researchers and international collaborators[1]. These modes, which have never before been observed at visible wavelengths, could be used in tiny lasers that are not much bigger than viruses.

A fundamental principle of electromagnetism is that an accelerating electric charge will emit light, losing energy in the process. But, the possibility of creating special configurations of electrical current that do not radiate electromagnetic radiation has intrigued physicists for many decades. Such configurations may serve as possible models of stable atoms, which do not emit radiation despite having orbiting electrons.

A fascinating example of such a non-radiating source is known as an anapole — a distribution of charges and currents that does not radiate or interact with external electromagnetic fields. Elementary particles that exhibit anapole modes have been proposed as a potential source of the mysterious dark matter, which accounts for about 25 per cent of the mass and energy of the observable Universe, but is invisible to astronomers.

Now, a team working with Yefeng Yu of the A*STAR Data Storage Institute, along with overseas collaborators, have demonstrated the existence of anapole radiation modes in the lab. Specifically, they have created them at visible wavelengths in silicon nanodisks.

"Our collaborators in Australia and Germany theoretically predicted the existence of anapoles in nanoparticles, and we then confirmed it experimentally," says Yu. "For such modes, energy does not escape from the nanoparticle through radiation or scattering. And when the nanoparticle is excited by anapole light excitation, it does not scatter the light since it concentrates the energy at close distances and is invisible at long distances."

An anapole mode is a combination of two dipole moments — the electric dipole moment and a donut-like one, called a toroidal moment. At large distances from the nanoparticle, these two radiation fields cancel each other out and so appear invisible. The team demonstrated this effect in their experiments by observing that the silicon nanodisks were effectively invisible due to the cancelling of visible light scattering by the nanodisks (see image).

"Applications of this optical phenomenon have yet to be determined," says Yu. "At the moment, we think that it could be useful for the design of novel nanolasers." The team intends to experimentally explore the use of the anapole mode for nanolasers.

1. Miroshnichenko, A. E., Evlyukhin, A. B., Yu, Y. F., Bakker, R. M., Arkadi, C. *et al.* Nonradiating anapole modes in dielectric nanoparticles. *Nature Communications* **6**, 8069 (2015).

Bioimaging:

BRINGING BRAIN TUMORS INTO FOCUS

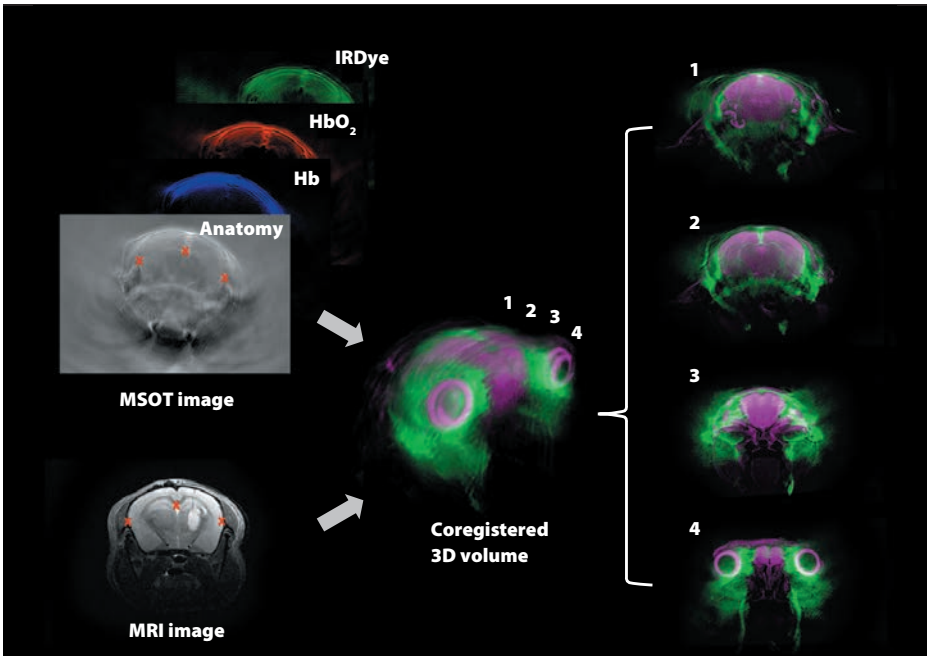
COUPLING OF PHOTOACOUSTIC AND MAGNETIC RESONANCE IMAGING GIVES CLEAR IMAGES OF BLOOD FLOW AND OXYGENATION STATUS IN BRAIN TUMOR TISSUE

Cancer diagnostics and therapy monitoring have moved into a new dimension through A*STAR research, which has developed a high-resolution and noninvasive approach to visualize brain tumors by combining photoacoustic with magnetic resonance imaging (MRI) techniques[1].

To be effective, anticancer therapies need early diagnosis and detection of malignant tumors, as well as a deep understanding of their metabolism. Current diagnosis uses *in vivo* imaging methods, coupling MRI and positron emission tomography (PET) at preclinical and clinical stages.

Within these methods, MRI produces detailed anatomical images of brain tumors while PET gives functional and metabolic information by detecting gamma-rays from a radioactive compound. However, PET presents a relatively low spatial resolution, and it cannot be used too long or frequently because of its radiative nature.

Now, Malini Olivo and co-workers from the Singapore Bioimaging Consortium have combined MRI with multispectral optoacoustic tomography (MSOT) instead



Co-registered three-dimensional volume resulting from magnetic resonance imaging (MRI) anatomical images (1–4) and their corresponding multispectral optoacoustic tomography (MSOT) functional images superimposed at reference landmarks (red crosses). MSOT images account for signals derived from the dye-labeled sugar analog (IRDye) as well as oxy- (HbO_2) and deoxy-hemoglobin (Hb).

of PET. In this non-radiative technique, laser light excites light-absorbing specimen components, causing tissues to expand thermoelastically. This generates acoustic waves, which propagate through the tissue and its surroundings before being detected and converted into ultrasound images by transducers.

"MSOT produces anatomical, functional and molecular data, while MRI offers good contrast for soft-tissue anatomy and various imaging sequences for different physiological properties," explains Olivo.

Because tumors exhibit abnormal glucose metabolism, the researchers monitored the uptake and behavior of a dye-labeled sugar analog acting as a probe in mice affected with brain cancer. They tracked the intravenously injected dye in the brain by separately acquiring MRI and MSOT images. Next, they superimposed both types of images using reference landmarks inside the brain to create a spatially correlated, or co-registered, three-dimensional volume (see image).

The dye accumulated in tumor and contralateral regions of the brain in the first hour after injection. Subsequently, it started to clear from the contralateral side but remained on the tumor side up to 48 hours post-injection. This provides a high tumor-to-normal contrast suitable for diagnostic imaging.

"This dye biodistribution can be coupled with other MRI and MSOT-derived information, such as oxygenation status and vasculature, to gain further insight into tumor physiology," says Olivo.

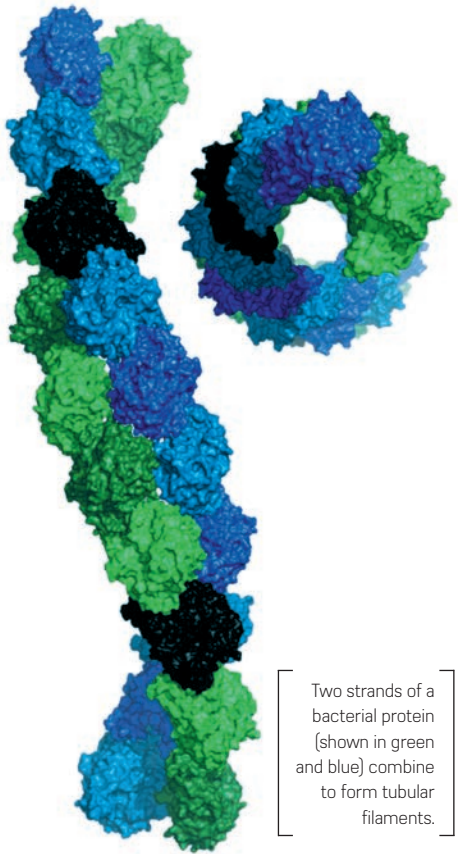
Olivo's team is further exploring potential applications of the multimodal approach to cancer diagnostics and therapy. "In a follow-up study, we can monitor blood vessel formation and oxygenation in tumors during their growth as well as changes in blood flow within tumors in response to anticancer drug treatments to evaluate drug efficacy," she adds.

1. Attia, A. B. E., Ho, C. J. H., Chandrasekharan, P., Balasundaram, G., Tay, H. C. *et al.* Multispectral optoacoustic and MRI coregistration for molecular imaging of orthotopic model of human glioblastoma. *Journal of Biophotonics* **9,** 701–708 (2016).

Cell biology:

MOVING DNA

PROTEINS THAT MOVE DNA AROUND IN A BACTERIUM ARE SURPRISINGLY SIMILAR TO THOSE IN OUR OWN CELLS



Two strands of a bacterial protein (shown in green and blue) combine to form tubular filaments.

Modified, with permission, from Ref. 1 © 2016 S. Jiang *et al.*

In both higher organisms and bacteria, DNA must be segregated when cells divide, ensuring that the requisite share of duplicated DNA goes into each new cell. While previous studies indicated that bacteria and higher organisms use quite different systems to perform this task, A*STAR researchers have now found a bacterium that uses filaments with key similarities to those in multicellular organisms, including humans[1].

Robert Robinson from the A*STAR Institute of Molecular and Cell Biology has a long-standing interest in what he calls the "biological machines" that move DNA around when cells divide. He and his co-workers had gleaned from gene sequencing analysis that there was something distinctive about the DNA-moving machinery in the bacterium *Bacillus thuringiensis*. Along with an international team of colleagues, the A*STAR researchers used electron microscopy and biochemical analysis to investigate the way small circular strands of DNA called plasmids moved in this bacterium. They identified a novel form of bacterial filament that combines to form tubules with some similarities to the microtubules observed in higher organisms.

Bacterial systems previously studied also use protein filaments to move DNA, but they do not share such obvious similarities to those of higher organisms. The new-found similarity in *B. thuringiensis* is of great interest from an evolutionary perspective as it suggests that evolution has furnished at least some bacteria and multicellular organisms with different machineries but similar methods to manipulate DNA.

There are practical possibilities for applying this knowledge, beyond its relevance to understanding bacteria. The finding specifically sheds light on the movement of plasmid DNA and genetic engineers use plasmids as vehicles to carry foreign genes into bacteria to modify them to perform useful new tasks. "Understanding

plasmid segregation can allow us to interfere with it," says Robinson. He explains that the research is revealing "new tools" that might be used to manipulate bacteria as well as being applied to synthetic biology — the attempt to construct new living systems from simple parts.

"We are keen to team up with scientists in Singapore who are working to build nanomachines and nanowires," Robinson adds. The concept of making molecular components and machines for use in manufacturing, medicine or computing is attracting the attention of many research teams worldwide. Thus the revelation found in *B. thuringiensis* may one day be used to manipulate DNA and other molecules within synthetic structures that extend the abilities of biological machinery into new applications.

1. Jiang, S., Narita, A., Popp, D., Ghoshdastider, U., Lee, L. J. *et al.* Novel actin filaments from *Bacillus thuringiensis* form nanotubules for plasmid DNA segregation. *Proceedings of the National Academy of Sciences USA* **113**, E1200–E1205 (2016).

Materials science:

SENSING A CHANGE

DISPOSABLE AND ULTRAFAST OPTICAL HUMIDITY SENSORS PROVIDE BETTER MOISTURE CONTROL FOR MANUFACTURING AND STORAGE

A*STAR researchers have designed a low-cost, stable and ultrafast responsive sensor that is easy to manufacture[1], overcoming the challenge of producing a simple, fast and highly sensitive version.

Fuke Wang and colleagues from the A*STAR Singapore Institute of Materials Research and Engineering have developed an optical humidity sensor that exploits the unique properties of ultrathin layers of graphene oxide (GO) films.

The humidity levels of ambient air can have a significant effect on human comfort and health; it can impact many manufacturing processes and is detrimental to the quality of stored goods. The ability to monitor and control humidity levels with accurate and reliable humidity sensors is essential for efficient manufacturing and storage practices as well as wellbeing.

"Our research shows for the first time that atomic-scale GO can be used for colorimetric humidity sensors," says Wang. "Due to the atomic properties of GO and their hygroscopic nature, the sensor is highly efficient and faster-responding compared with current sensor technologies."

Unlike most humidity sensors, which are electronic and require a power supply, GO-based colorimetric sensors respond to humidity levels by changing color, which can be easily observed (see image). For greater accuracy, the change in color can be quantitatively measured by analyzing the reflection spectra of the sensor. Because the GO sensor operates at the atomic level, it can rapidly respond to moisture changes.

Exploiting the atomic properties of GOs can only occur if films of uniform thickness can be fabricated; thickness influences the response time and uniformity determines the quality of the sensor.

The research team overcame this challenge by using a process, in which a substrate is dipped in and out of a solution at a constant speed.

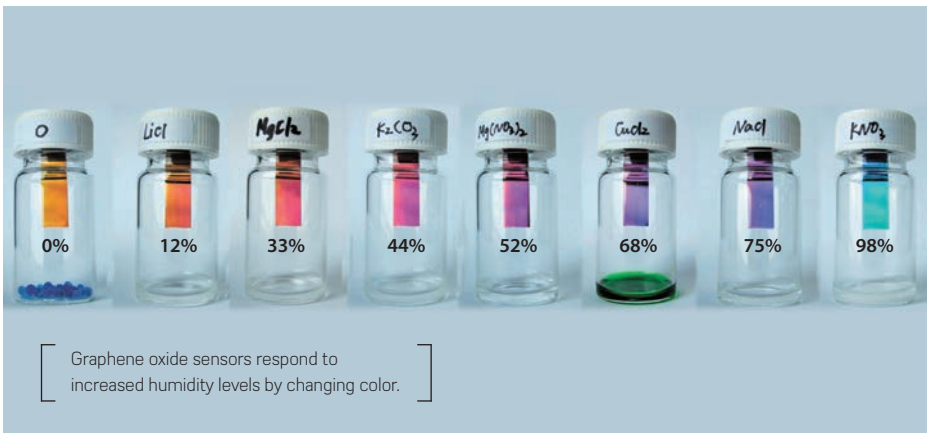
> "WE FOCUSED ON OPTIMIZING THE SOLUTION VISCOSITY, THE SUBSTRATE-SURFACE TREATMENT AND THE DIP-COATING CONDITIONS"

"We focused on optimizing the solution viscosity, the substrate-surface treatment and the dip-coating conditions," explains Wang, "this showed that we can now easily control the thickness of uniform films of GO with a process that is scalable and also generates zero waste."

The low-cost, nontoxicity and rapid response of GO sensors makes them ideal as disposable sensors. They can be incorporated into food packaging, where humidity levels need to be strictly controlled for storage, for medical instrumentation and semiconducting device manufacturing and storage, as well as environmental monitoring. Their disposal also has no environmental impact.

"We are now exploring further increases in efficiency and sensitivity, and the application to other vapors and gases," says Wang.

1. Chi, H., Liu, Y. J., Wang, F. & He, C. Highly sensitive and fast response colorimetric humidity sensors based on graphene oxides film. *ACS Applied Materials & Interfaces* **7**, 19882–19886 (2015).



Graphene oxide sensors respond to increased humidity levels by changing color.

'HUMAN-FRIENDLY' ROBOTS

A new class of collaborative robots may be the future of industrial remanufacturing

YuMi from ABB is a dual-arm collaborative robot that can assemble, pick and sort through small components.

By 2030, more than half of the world's jobs could be performed by machines. But, far from a dystopian vision of humans being forced from employment by the rise of the machines, Tijo Thayil, section manager for robotics development at the A*STAR Advanced Remanufacturing and Technology Centre (ARTC), believes this labor shift could be a positive development.

"There are some boring tasks that are done by a human operator — just assembling the same things every day, seven days a week," he says. These rote, repetitive tasks could be easily passed on to robots, freeing up human operators for more interesting duties.

Thayil emphasizes that there is still a role for humans in this automated future, and his work focuses on developing a new kind of collaborative approach between robots and humans for manufacturing tasks. The robots are described as "human friendly".

"The previous thinking was that in the future, when we are using a fully automated production line, humans will be replaced," says Thayil. "But now we are thinking of the robot acting more as an assistant."

His vision of the future sees man and machine working side by side, assisting each other in the tasks the other struggles to perform.

"We still need the intelligence and perception of the human to identify the appropriate tasks, and if the task is something that is repeated, it can be taken up by the robot."

Thayil says this new generation of robots can be programmed to perform new and varied tasks in a simple physical manner.

"You can teach a robot by demonstration. So the person has to show once how it has to be done and then after that the robot can repeat the task."

GOOD AS NEW

The biggest advantage of this collaborative class of robots, is that, unlike their dumber ancestors, the new generation can respond to stimuli and learn as they go. This is particularly important in remanufacturing, which the center specializes in.

With remanufacturing, a machine part — perhaps from an aircraft engine or mining truck engine — is restored as good as new through an industrial process, potentially using the kinds of robots that Thayil works on.

Andrew Soutar is the director of project management and research liaison at the ARTC. He says that although the concept of repair is as old as time, remanufacturing is a bright new direction for industry.

"The remanufacturing processing may involve first machining out damaged areas. Then an additive manufacturing process is carried out, so you would add material back to the component to bring it back to close to its optimum intended geometry. After that you need to carry out some final machining and then surface finishing processes to ensure that you have the required surface roughness," says Soutar.

Soutar says one of the selling points of remanufacturing is that a remanufactured engine is provided with an as-new warranty, whereas a repaired engine is not. There are also significant economic and environmental benefits.

> **"Flexibility and adaptability means that robots can now be put to work on smaller batches, opening up automation for smaller manufacturers."**

"If you're looking at the circular economy and sustainability then the cost of materials will be significantly lower for a

The KUKA LBR iiwa 7 R800 collaborative robot assists with quick shop-floor automation for the manufacturing industry.

remanufactured component than for a new component," notes Soutar. Since processing costs, such as energy and water, to repair a component are significantly lower than those required to make a new component from scratch, economic benefits can be passed on to the consumer.

ROBOTIC REPAIR

Thayil says the ability of the robots to respond specifically to each component is essential for automated remanufacturing.

"When you produce a new part, we have the Computer Aided Design or 'CAD' file and we know the shape exactly, everything is defined. You can move the tool according to the CAD file.

"In repair and remanufacturing processes, however, the input part's shape or geometry is different each time. When it comes out of service we don't know how it will look. And now, with advancements in robotics, combined with the latest technologies such as vision modules and 3D scanning systems, robots can be tuned to respond according to the variations in input condition."

This flexibility and adaptability also means that robots can now be put to work on smaller batches, with high-mix, low-volume manufacturing, opening up automation for smaller manufacturers.

In an industry that spends millions tooling up the production line, collaborative robots offer the prospect of nimbler and more responsive manufacturing.

"If you develop an automation system for a dedicated application, it is only for that application. But if the robot is flexible, then tomorrow, if the components change, we can simply reprogram the robot to be used for the new component," says Thayil.

Soutar says the center has the particular ability to take good ideas and make them commercial reality. They focus on what is known as the mid technology readiness level range — classified as components that have been tested in the lab and relevant environments but not commercialized. "It's commonly called the Valley of Death."

"Many technologies come out of the universities, but, at the end of the day, not many of them get implemented in companies and that's often because of gaps in expertise in regards to developing the technologies, expertise in handling the process equipment, the availability of the process equipment and the other aspect may be the supply chain," says Soutar.

> **"You can use robots 24/7 — they don't need a lunch or coffee break. Humans, on the other hand, can get tired or bored, mainly because they're repeating a task that's easy for them."**

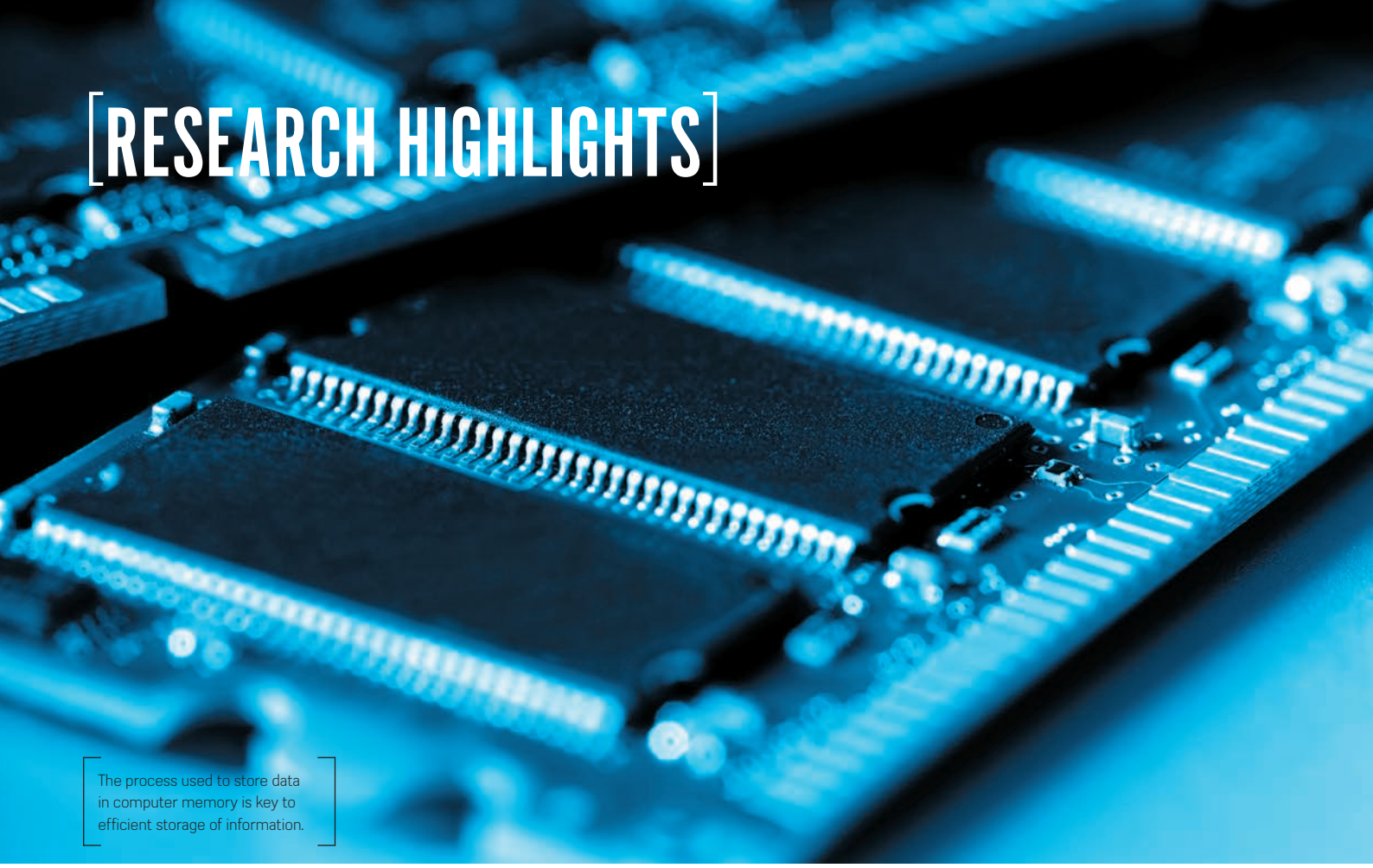
ARTC's industry partners, on the other hand, benefit from the center's significant experience in translating the results of R&D work to shop-floor application, and Thayil says partners are excited about the promise of robotized production.

"You can use robots 24/7 — they don't need a lunch or coffee break. Humans, on the other hand, can get tired or bored, mainly because they're repeating a task that's easy for them. Now the repetitious task can be taken up by the robot.

"For countries like Singapore it is not easy to get skilled labor. The younger generation want to do more value-added tasks. So if they are asked to use their intelligence and perception to add value to rote tasks performed by a robot, they will be happier."

Tijo Thayil

Andrew Soutar



The process used to store data in computer memory is key to efficient storage of information.

Data storage:

MEMORIES THAT LAST

A MORE EFFICIENT WAY TO WRITE DATA INTO NON-VOLATILE MEMORY DEVICES IMPROVES THEIR PERFORMANCE

A scheme to write data into next-generation memory chips has been developed by A*STAR Data Storage Institute researchers. The proposal by Jun Yang and colleagues requires considerably fewer resources to write data safely into memory — even during a system failure[1].

Non-volatile memory (NVM) technologies are the likely successor to current computer memory devices. A key advantage is their ability to keep data in the memory even when the computer is powered off, enabling virtually instant computer boots. NVM could even replace the computer hard drive, and thus unify the different memory types used by a computer in a single device.

One challenge when using NVM in computers is ensuring the accuracy of the data to be stored. NVM devices utilize different materials than existing silicon memory technology and so have different write processes and storage needs.

"Directly applying these existing approaches on byte-addressable NVM is inefficient," says Yang. Therefore, they require algorithms that are optimized for the unique properties of the new memory types but also remain compatible with the requirements of current computer processors. Another concern is memory operations. If they occur during a system failure, such as a computer system crash, there is a chance that the memory could become corrupt with wrong data.

The process used to store data — the sequence in which pieces of data are written into the memory — is key to the efficient storage of information. The data structure in the memory should be such that changes in one part of the data do not require extensive reorganization of the entire memory.

Tang's team adapted a version of the commonly used B+ tree architecture for organizing memory data. Then, following a systematic investigation into the performance of that structure for NVM systems, the team adapted it for use in NVM.

The data are separated into two groups, critical data and reconstructable data. Reconstructable data, in principle, can be derived from the critical data. Therefore, the

priority during the writing process is to ensure the consistency of the critical data, which are written into the memory first.

The new NV tree data structure can be up to 96 per cent more efficient in the operation of NVM, moving this technology closer to applications says Yang. "The new data structure makes it possible to build a more sophisticated storage system specifically optimized for NVM."

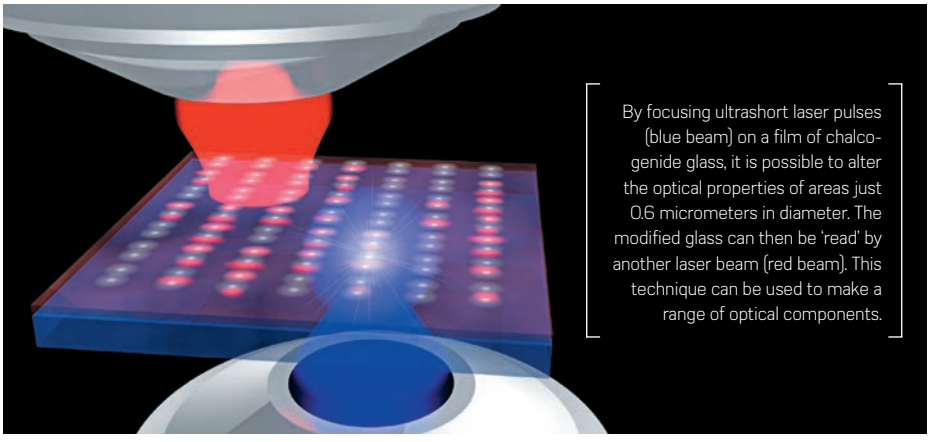
1. Yang, J., Wei, Q., Wang, C., Chen, C., Yong, K. L. & He, B. NV-Tree: A consistent and workload-adaptive tree structure for non-volatile memory. *IEEE Transactions on Computers* **65**, 2169—2183 (2016).

Photonics:

LIGHT-MODIFIED MATERIAL MODIFIES LIGHT

A MATERIAL WHOSE OPTICAL PROPERTIES CAN BE MODIFIED ON A SMALL SCALE BY LASER LIGHT PROMISES A WIDE RANGE OF APPLICATIONS

Properties of small areas of a versatile optical film can be tweaked by applying ultrashort pulses of laser light, A*STAR researchers show[1]. This tunability makes the material suitable for various light-based applications, from lenses to holograms.



By focusing ultrashort laser pulses (blue beam) on a film of chalcogenide glass, it is possible to alter the optical properties of areas just 0.6 micrometers in diameter. The modified glass can then be 'read' by another laser beam (red beam). This technique can be used to make a range of optical components.

When the shutter button on a camera is depressed, it focuses by electrically adjusting the positions of the constituent parts of the lens. Similarly, the parameters of optical components in many devices and scientific instruments are adjusted by moving their parts, or by stretching or heating them. Being able to use light to adjust optical components would offer many advantages, including fast response and easy integration into small and robust systems.

Now, such an optically adjustable system has been developed by Qian Wang of the A*STAR Institute of Materials Research and Engineering and co-workers, along with collaborators at the University of Southampton, UK, and the Nanyang Technological University, Singapore.

The team studied a material widely used in CD and DVD disks — chalcogenide glass. In rewritable CD and DVD data-storage devices, microsecond or nanosecond (10^{-9} second) laser pulses are used to switch the medium between two states — crystalline and disordered. In contrast, Wang and her team used a tightly controlled series of much shorter femtosecond (10^{-15} second) optical pulses to set the glass into incremental states between completely crystalline and completely disordered. By scanning the focused laser beam across the glass film, they could modify regions as small as about 0.6 micrometers (see image).

> "IT CAN EVEN BE USED TO WRITE COMPLEX STRUCTURES LIKE LENSES, DIFFRACTION GRATINGS, HOLOGRAMS AND ADVANCED RESONANT STRUCTURES KNOWN AS METAMATERIALS, DIRECTLY INTO A PHASE-CHANGE CHALCOGENIDE GLASS FILM."

"This technique allows us to build optical devices with smoothly varying properties across the surface, to erase them and then to rewrite a different structure, all on the same piece of optical canvas," notes team member, Edward Rogers, of the University of Southampton. "It can even be used to write complex structures like lenses, diffraction gratings, holograms and advanced resonant structures known as metamaterials, directly into a phase-change chalcogenide glass film."

The researchers used their system to make various optical components, including a hologram that had eight levels of gray shading.

Another advantage of the device is its compact size. "Compared to conventional bulk optical components, our optical devices are flat and much smaller, only tens of micrometers. This makes them easy to integrate into optical systems," explains Wang.

The method currently involves scanning a laser beam across the film, but in future it may be possible to use an optical-pattern generator, which would speed up writing of the film.

1. Wang, Q., Rogers, E. T. F., Gholipour, B., Wang, C.-M., Yuan, G., Teng, J. & Zheludev, N. I. Optically reconfigurable metasurfaces and photonic devices based on phase change materials. *Nature Photonics* **10**, 60–65 (2016).

Glaucoma genetics:

UNCOVERING CELLULAR MECHANISMS

NEW GENES ASSOCIATED WITH PRIMARY ANGLE CLOSURE GLAUCOMA SUGGEST WHICH STRUCTURAL CELL PROCESSES MIGHT CAUSE THE DISEASE

An A*STAR led team uncovered new genes associated with primary angle closure glaucoma.

A detailed search of the human genome has revealed five genetic locations linked to a form of glaucoma that causes many cases of blindness in Asia. Led by A*STAR, the large international team was able to access enough data on genetic markers to provide insights into the cellular processes that allow the disease to progress.

Chiea-Chuen Khor from the A*STAR Genome Institute of Singapore and co-workers focused on primary angle closure glaucoma (PACG), a form of the disease that is more prevalent in Asians than in people of other ethnicities and that has not been studied to the same extent as primary open angle glaucoma (POAG)[1]. The team has previously helped to expose genes linked to exfoliation syndrome, a common cause of POAG, particularly in Northern Europe and America.

"The main challenge of the study was to accumulate enough PACG patients and controls to be credible," says Khor. "We obtained such a large number of samples due to help from glaucoma surgeons, many of whom are close collaborators of our joint research leader, Professor Aung Tin from the Singapore National Eye Center."

Overall, the team amassed samples from more than 10,000 PACG patients and almost 30,000 controls, from 15 countries in Asia, Europe and South America. They performed a genome-wide association study, searching the entire genome to find genetic variants associated with PACG.

> "BECAUSE WE WERE ASSESSING MORE THAN A MILLION INDIVIDUAL GENETIC MARKERS, WE ADOPTED A VERY STRINGENT STATISTICAL THRESHOLD FOR DECLARING MARKERS TO BE SIGNIFICANTLY RELATED TO THE DISEASE."

"Because we were assessing more than a million individual genetic markers, we adopted a very stringent statistical threshold for declaring markers to be significantly related to the disease," explains Khor. "The markers that surpassed the threshold were

tested against other sample collections as a further 'replication' step, providing a very high degree of technical scrutiny for newly identified markers."

The study identified five new genetic loci associated with PACG, which include sequences linked to cell-to-cell adhesion and the metabolism of the structural protein, collagen. Both these processes are vital for healthy eyes, Khor explains.

"Even a subtle change in the finely balanced physiology of cell-cell adhesion and collagen metabolism in a space as small and tight as the anterior eye chamber could lead to cellular abnormalities, changing anatomical angles and triggering the development of glaucoma," Khor says.

The researchers aim to study the roles of the genes they identified in more detail, using PACG disease models such as mice and, eventually, human eye tissues.

"Our plan is to definitively identify the pathological genes for PACG before attempting biological investigations on scarce and valuable human tissues," says Khor.

1. Khor, C. C., Do, T., Jia, H., Nakano, M., George, R. *et al.* Genome-wide association study identifies five new susceptibility loci for primary angle closure glaucoma. *Nature Genetics* **48,** 556–562 (2016).

Chemistry:

A RECIPE FOR FILLING IN THE GAPS

A DECISION-MAKING TOOL HELPS PRODUCERS OF PHARMACEUTICAL AND OTHER VALUABLE CHEMICALS MAKE THE LEAP TO AN ENTIRELY NEW WAY OF MANUFACTURING

An understanding-based tool could help process development teams to decide whether switching from a batch reactor system to continuous product manufacturing makes techno-economic sense.

Historically, pharmaceutical industries have relied on novel medications to meet profit targets; however in today's competitive markets, the huge expenditures associated with drug development now challenge this approach. An international team led by A*STAR researchers show how manufacturers can make rapid decisions about switching to alternative drug manufacturing procedures with promising economic prospects[1].

High-value chemicals are traditionally made through 'batch processing', where inputs such as raw materials and energy are combined in a single reactor until the desired output is obtained. While this approach is simple, it can only be performed in a sequential manner. So if demand for a drug suddenly increases — to combat an emerging strain of influenza, for instance — such step-by-step operations cannot cope with the production scale-up required.

Soo Khean Teoh from the Institute of Chemical and Engineering Sciences at A*STAR and her co-workers have developed a methodology to assess the feasibility of switching from batch to 'continuous' processing, where all stages of chemical reactions occur simultaneously: flowable reagents are constantly fed into reactor, and likewise, products are extracted nonstop.

With continuous processing, operations are quicker, more energy-efficient, and use smaller installation facilities than batch techniques. Yet most chemical producers are hesitant to implement continuous systems, unless they see clear technical and economic benefits.

"The biggest challenge is that there is no 'one-size-fits-all' solution for changing from batch to continuous methods, because of the complex and varied chemistries involved," explains Teoh. "We had to devise a method that guides users to understanding the process in question, brainstorms about potential benefits, and helps them come to swift decisions."

The researchers' method initially screens chemical processes to uncover key business requirements and potential pitfalls, such as sticky reagents, with simple yes/no/maybe evaluations. Successful candidates are then

broken down into a flow chart analysis that identifies factors such as possible equipment, control schemes, and plant configurations. If the analysis makes economic sense, a final stage of process execution is put into place.

Liquid-phase reactions that proceed quickly and emit or absorb large quantities of energy proved to be particularly favorable for continuous processing. For example, the team demonstrated that the Reformatsky reaction — an organozinc-catalyzed reaction that frequently overheats with batch processing — could profit enormously from a continuous approach.

"Our methodology makes understanding the process much clearer, especially to the chemists and engineers dealing with the synthesis," says Teoh. "It makes it easier to decide to proceed or to kill the idea, minimizing wasted effort."

1. Teoh, S. K., Rathi, C. & Sharratt, P. Practical assessment methodology for converting fine chemicals processes from batch to continuous. *Organic Process Research & Development* **20,** 414–431 (2016).

Magnetic devices:

CONTROLLING ANISOTROPY

DEVICE ARCHITECTURE THAT CAN TUNE A MATERIAL'S MAGNETIC PROPERTIES COULD REDUCE THE POWER CONSUMPTION OF MEMORIES

The huge energy consumption of the world's data centers creates an urgent need to develop electronic devices that can process information with reduced power requirements. A device that harnesses the 'spin' of electrons offers a route toward this. A*STAR researchers show how the performance of these so-called spintronic memories can be optimized by careful control of its structure[1].

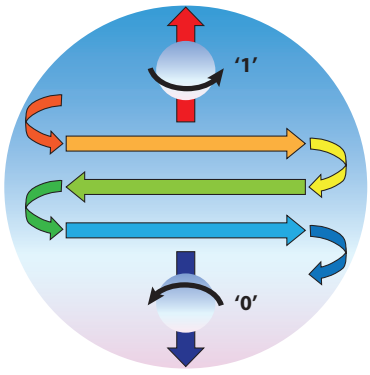
A spin-transfer torque magnetic random-access memory (STT-MRAM) comprises a stack of thin magnetic layers. One of these layers makes all the electrons in a current flowing through it have the same spin. This spin-polarized current can then change the magnetic properties of a second layer. This relies on the tendency of the electron spins in the material to align along one direction much more than it does another — a property called magnetic anisotropy.

"By having a high anisotropy, the magnet is stable and the memory is able to retain information," explains Sze Ter Lim from the A*STAR Data Storage Institute. "However, it also means that it is more difficult to switch to the opposite direction because of an effect called damping." Previous attempts to increase the anisotropy have also led to a proportional increase in damping.

Lim and his co-workers have now developed a STT-MRAM architecture in which the anisotropy can be increased without changing the damping. Their device has a central layer of tantalum. On either side of the central layer is a film of cobalt iron boron (CoFeB), which makes up the required magnetic layers. This in turn is sandwiched between magnesium oxide. The device is grown on a substrate and capped with another layer of tantalum.

Instead of altering the thickness of the magnetic layers, as previous studies have done, the researchers investigated the influence of the outer magnesium oxide. They showed that the anisotropy rises when the top layer thickness is increased from 1.3 nanometers to 2.5 nanometers. But the effect of this change on the damping is minimal.

Lim's team however does not believe that this change in anisotropy is directly related to the thickness of the magnesium oxide; indeed, similar changes to the thickness of the bottom magnesium oxide film had no effect. Instead, they suggest that the top tantalum atoms intermixed with the magnesium oxide during deposition, and this degrades the interface between the magnesium oxide and the CoFeB.



Spin-transfer torque magnetic random-access memories work by using magnetic thin films to control the 'spin' on an electron such that it can be used to store digital information.

"The next step is to integrate these optimized materials structures into practical devices and to evaluate its performance," says Lim.

1. Sabino, M. P. R., Lim, S. T., Wong, S. K., Ng, S. & Tran, M. Non-proportionality of magnetic anisotropy and damping in CoFeB/MgO-based systems. *Applied Physics Letters* **107**, 012405 (2015).

A*STAR researchers have used a zebrafish model to find a new way to fight cancer.

Cancer:

ZEBRAFISH MODEL LEADS TO NEW DRUG TARGET

BLOCKING A PROTEIN IN A CRITICAL SIGNALING PATHWAY COULD OFFER A NEW WAY TO COMBAT TUMORS

Cancer drugs that block a cell-signaling pathway called Hedgehog have shown promise in recent years in treating patients with skin cancer, leukemia and other types of tumors. But the available treatments mostly target the same protein in the Hedgehog pathway, and tumors often develop resistance to these drugs.

Researchers at the A*STAR Institute of Molecular and Cell Biology have now discovered an alternative potential drug target that, when disrupted, completely negates the ability of cells to respond to Hedgehog signaling[1].

Inhibiting this protein's activity "could provide an effective way of blocking Hedgehog activity in tumor cells," says Philip Ingham, a developmental geneticist at A*STAR and the Lee Kong Chian School of Medicine in Singapore, who led the work. Plus, he adds, "using a combination of drugs against different targets should reduce the probability" of resistance developing against any particular agent.

The Hedgehog pathway is vital for cell growth and differentiation in the developing embryo, but in adult tissues its activity can lead to cancer. The two drugs vismodegib and sonidegib — both of which target a protein called Smoothened, a key component of the Hedgehog pathway — are currently approved to treat a common kind of skin cancer called basal cell carcinoma. And, while drugs directed at other targets have been pursued, still more are needed. Especially sought are drugs that act downstream of Smoothened, undermining a tumor's resistance to Smoothened-directed agents.

Along with researchers at Stanford University, USA, Ingham and his team focused on one possible target; the G-protein-coupled receptor kinase 2, or GRK2. They generated zebrafish embryos lacking a functioning copy of GRK2 and observed a complete loss of responsiveness to Hedgehog or Smoothened activity.

Previously, scientists had only partially and transiently knocked down the activity of GRK2, revealing much more subtle effects on Hedgehog signaling. "Our study emphasizes the importance of making stable transmissible mutant alleles to study gene function," Ingham says.

Ingham says he is still "puzzled" by how exactly GRK2 regulates Hedgehog activity — it was previously thought to work by chemically modifying Smoothened through a process called phosphorylation, but Ingham's team showed this probably is not the case. Ingham now suspects that GRK2 works through some other protein intermediary.

Even without understanding of the mechanistic details, Ingham is optimistic about GRK2's chances as a potential drug target. Nonetheless, "GRK2 is not specific to the Hedgehog pathway," he cautions, "so blocking its activity could cause unwanted side-effects."

1. Zhao, Z., Lee, R. T., Pusapati, G. V., Iyu, A., Rohatgi, R. & Ingham, P. W. An essential role for Grk2 in Hedgehog signalling downstream of Smoothened. *EMBO Reports* **17,** 739–752 (2016).

Stem cells:

MUTATION HALTS EMBRYONIC PANCREAS DEVELOPMENT

A GENETIC MUTATION AND A FEW SHORT DAYS IN THE DEVELOPMENT OF AN EMBRYO COULD HOLD THE KEY TO A LIFETIME LIVING WITH DIABETES

Personalized treatment for people with diabetes could be a step closer after researchers discovered how a single gene mutation fundamentally alters pancreatic development[1].

The A*STAR researchers discovered that a point mutation in a gene known as *HNF1B* halts the embryonic development of the pancreas; it stops the growth of the vital beta cells, which produce the insulin that maintains a body's sugar balance.

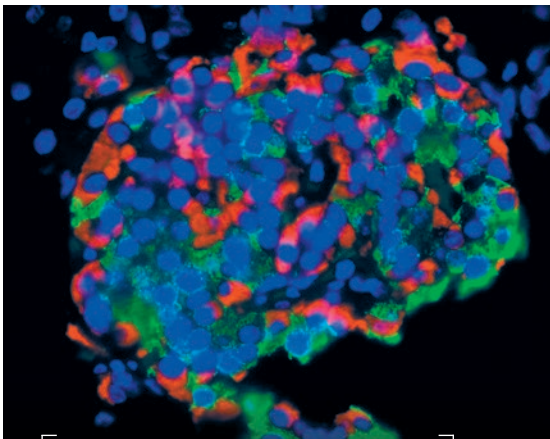
Improved understanding of beta cell development could lead to better-targeted diabetes treatments, explains study leader Adrian Teo, from the A*STAR Institute of Molecular and Cell Biology.

"By understanding the role of these beta cell genes, we can understand the mechanistic cause of diabetes," Teo says. "This may mean that eventually we could stratify our diabetic population into subgroups and treat them appropriately based on disease mechanism rather than just blood glucose levels."

The team used pluripotent stem cell lines from people with a rare form of inherited diabetes called maturity onset diabetes of the young, type 5 (MODY5), comparing them to cells grown from unaffected family members and healthy controls.

In MODY5, children who inherit the gene mutation from one parent grow a malformed and small pancreas, which means they develop diabetes usually before the age of 25.

"We used MODY5 patient-specific induced pluripotent stem cells to go back in time, mimicking human pancreas development in our cell culture dish," Teo explains. "Amazingly, we discovered that the *HNF1B* gene mutation actually affected the development of the human pancreas very early in life."



A*STAR researchers show that a mutation in the *HNF1B* gene affects the development of the pancreas in patients with a rare form of inherited diabetes, which means they develop diabetes by early adulthood. The image above depicts a human islet containing alpha and beta cells.

While there are a number of subtypes of MODY associated with a range of gene mutations, the team found *HNF1B* worked independently of all of those. In the early days of development the differentiating cells actually up-regulated other pancreatic development genes, in what may have been an attempt to compensate for the *HNF1B* mutation.

"We saw the same effects in numerous affected cell lines that were clearly distinct from the healthy family member and unrelated healthy control," Teo says.

"Together, these comparisons allowed us to study human diabetes mechanisms in an actual genetic background, which is different to other models that typically do not account for true human genetic background."

The team are now using a similar pluripotent stem cell method to examine the pancreatic defects involved in other forms of diabetes.

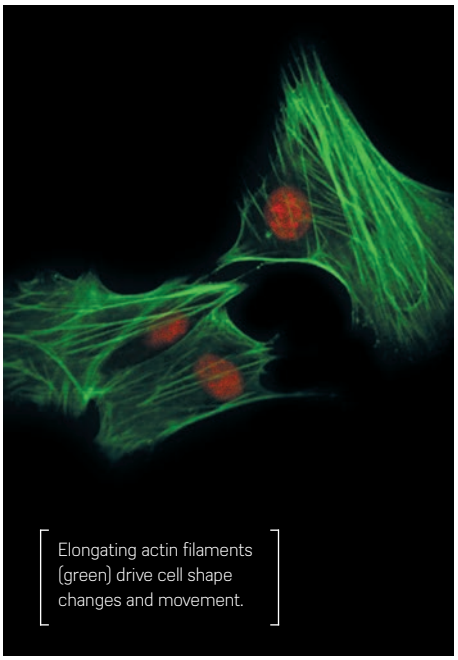
"Diabetes is a complex disease arising from a combination of genes and environment, but this model can help us understand the contribution that individual genes make to beta cell function," Teo explains.

1. Teo, A. K. K., Lau, H. H., Valdez, I. A., Dirice, E., Tjora, E. *et al.* Early developmental perturbations in a human stem cell model of MODY5/*HNF1B* pancreatic hypoplasia. *Stem Cell Reports* **6,** 357–367 (2016).

Cell biology:

EVOLUTIONARY THREAD UNDERLIES FILAMENT DIVERGENCE

GENETIC COMPARISONS PROVIDE INSIGHT INTO THE EVOLUTION OF A CRUCIAL FILAMENT PROTEIN IN ANIMALS, PLANTS AND BACTERIA



Elongating actin filaments (green) drive cell shape changes and movement.

Divergent evolutionary pathways in different domains of life have resulted in distinct filament systems that underlie cellular structure and polymerizing-protein motors, according to A*STAR researchers[1]. The work focuses on the protein actin, and proposes how divergent systems in animals, plants and bacteria arose.

Actin forms filaments that make up the cellular skeleton, provide a scaffold on which proteins can be locally assembled, and drive the movement of cells. While the structure of actin and its filaments is similar in all animals and plants, the structure of actin-like proteins in bacteria is markedly different. Robert Robinson, from the A*STAR Institute of Molecular and Cell Biology, and colleagues analyzed the genetic relationships between actin-like proteins in various organisms to understand these differences.

"By comparing the genomes from organisms that have diverged at different time points in evolution, we can chart the paths of how protein machines became more sophisticated," says Robinson. "We show that the filamentous force-generating machines from bacteria, plants and animals have followed different evolutionary paths."

The researchers determined that bacteria have a 'one-filament–one function' design, in which diverse actin-like proteins carry out distinct cellular functions. By contrast, plants and animals have developed a 'universal-pool-of-actin' system, in which a single type of actin is involved in many cellular processes.

Robinson and colleagues propose that the functional requirements of bacterial cells led to actin-like proteins evolving at different rates. For example, filaments required to ensure accurate bacterial cell division need to form at different times and locations to filaments involved in making the bacterial cell wall. Differences in function led to divergence

in structure, resulting in distinct forms of the protein.

The team suggests that the involvement of actin in various cellular processes in the common ancestor of animals and plants meant that any changes to the protein would compromise these functions, thereby restricting its evolutionary pathway. A big surprise though, says Robinson, is that a later drive toward extending filament variety within this restrictive framework led to different mechanisms for achieving filament diversity between plants and animals.

"We hope that the concepts we have defined will influence thinking in relation to filament systems," explains Robinson. However, he notes that little is known about actin filaments in the third domain of life: single-celled organisms called archaea. "We would like to see more archaea genomes sequenced to better understand the state of actin filaments at the time of their evolutionary split," he concludes. ■

1. Gunning, P. W., Ghoshdastider, U., Whitaker, S., Popp, D & Robinson, R. C. The evolution of compositionally and functionally distinct actin filaments. *Journal of Cell Science* **128**, 2009–2019 (2015).

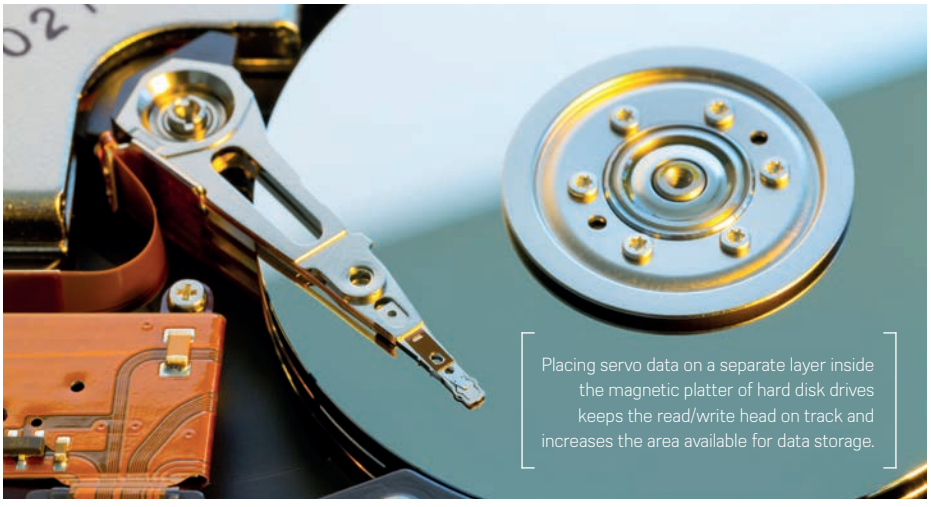
Data storage:

STAYING ON TRACK

A COMBINATION OF ADVANCED SIGNAL PROCESSING AND MAGNETIC LAYER STACKING PROMISES TO INCREASE HARD DRIVE CAPACITY AND RELIABILITY

The next generation of magnetic hard drives could be based on a new combination of technologies developed by A*STAR researchers aimed at increasing performance by stacking hard disk data and tracking bits in separate layers[1].

A conventional magnetic hard drive contains one or more thin magnetic platters that spin at very high speeds. Data is recorded on the platter in narrow circular tracks, and is read and written by a head that floats just nanometers above the magnetic surface. The head is kept on track by special magnetic 'servo' tracks that are arranged radially around the disk like the spokes on a bicycle wheel.



Placing servo data on a separate layer inside the magnetic platter of hard disk drives keeps the read/write head on track and increases the area available for data storage.

"As the head crosses the servo spokes, which for a typical disk happens up to 400 times per revolution, the servo information is used by the drive to push the head back to the center of the data track," says Kheong Sann Chan from the A*STAR Data Storage Institute.

The problem with existing servo systems is that due to the need to minimize the number of servo spokes on a disk, which take up disk space that could otherwise be used to store data, the head is only repositioned for a very small fraction of time. In-between servo spokes, the head is susceptible to disturbances like shock and vibration.

Chan, Yibin Ng and their colleagues have come up with a method to add a second magnetic layer on the disk entirely dedicated to holding servo information and keeping the head continuously on track while the disk spins at over 120 kilometers per hour beneath it.

"We developed a dedicated servo scheme consisting of two stacked magnetic layers: the top one for data and an underlayer to hold servo information," says Chan. "This means that servo information can be available all the time rather than just when the head is over the servo spokes. The scheme also frees up space on the data layer to hold more information."

Chan's team married the dedicated servo layer with a signal processing technique designed to separate the two sets of magnetic information read by the head. Signal processing has been a significant obstacle for this technology, but the researchers overcame it by matching the servo detector on the head to the specific pattern of servo data.

"This dedicated servo technology delivers an increase in overall system performance but will require some changes to how the servo patterns are written, which the hard drive industry is currently evaluating," says Chan. ■

1. Ng, Y., Cai, K., Chan, K. S., Elidrissi, M. R., Yu-Lin, M. *et al.* Signal processing for dedicated servo recording system. *IEEE Transactions on Magnetics* **51**, 3000905 (2015).

[VOICES FROM A*STAR]

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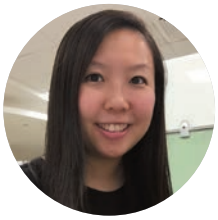
*Voices from A*STAR* is a monthly blog published on the A*STAR Research website. It features a personal account of the challenges and rewards of a life in science by A*STAR researchers from a range of disciplines. Staff interested in contributing to the *Voices from A*STAR* blog are encouraged to contact the managing editors.



Hweixian Penny

Research Fellow, SIgN

"We remember all the nameless scientists, who never donned suits or bowties for prize ceremonies — just their plain white coats. They, together as a community made the momentous discoveries upon which we built the armory for our current siege against [cancer]."

Qunya Ong

Scientist, IMRE

"Biomedical engineers are used to applying engineering principles to solve problems in biology and medicine. As a biomedical engineer by training, I find it interesting that the converse is also true — the world of biology can be a source of inspiration for engineering designs."

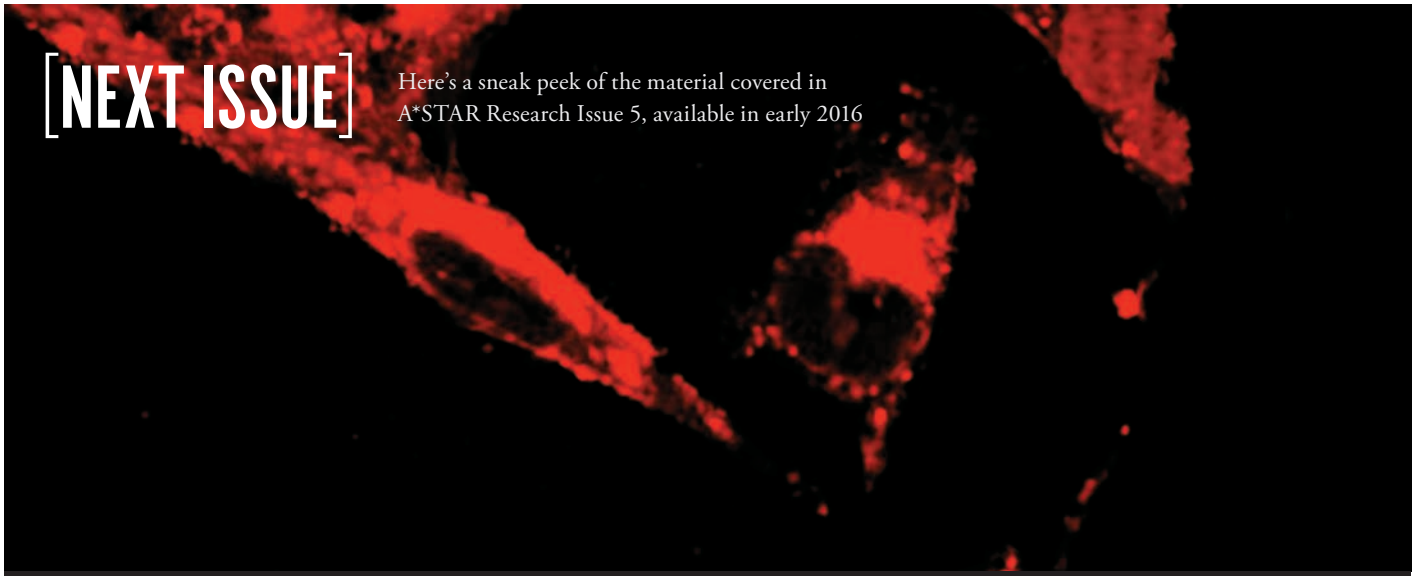
Pravin Kakar

Scientist, I^2R

"The phones we carry in our pockets, the credit cards we use, the EZ-Link cards that we tap on public transport and the Fitbits we wear are a treasure trove [of data] that can help [us] understand who we are."

[NEXT ISSUE]

Here's a sneak peek of the material covered in A*STAR Research Issue 5, available in early 2016



Biomedical materials:

SHARPSHOOTING NANOPARTICLES HIT THE TARGET

Multi stimuli-responsive nanocapsules selectively deliver drugs to exactly where they are needed.

Antimicrobial materials:

KILLING BACTERIA IN SECONDS

A synthetic material that kills common bacteria in seconds could have far-reaching applications in healthcare and domestic settings.

Plasmonics:

LIGHTING THE WAY TO MINIATURE DEVICES

Electromagnetic waves created on a layer of organic molecules could provide the perfect on-chip light source for future quantum communication systems.

Agency for
Science, Technology
and Research

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 centers and supports extramural research with universities, hospital research centers, and other local and international partners.

Bioinformatics Institute (BII)
Bioprocessing Technology Institute (BTI)
Clinical Imaging Research Centre (CIRC)
Data Storage Institute (DSI)
Experimental Therapeutics Centre (ETC)
Genome Institute of Singapore (GIS)
Institute of Bioengineering and Nanotechnology (IBN)
Institute of Chemical and Engineering Sciences (ICES)
Institute of High Performance Computing (IHPC)
Institute for Infocomm Research (I^2R)
Institute of Materials Research and Engineering (IMRE)
Institute of Medical Biology (IMB)
Institute of Microelectronics (IME)
Institute of Molecular and Cell Biology (IMCB)
National Metrology Centre (NMC)
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