The international journal of science / 26 August 2021

nature

outlook
Sickle-cell disease

PROTEIN POWER

AI network predicts highly accurate 3D structures for the human proteome

Troubled waters
The race to save the Great Barrier Reef from climate change

Coronavirus
Time is running out to find the origins of SARS-CoV-2

Storage hunting
Quantifying carbon held in Africa's montane forests

Nature.2021.08.28

[Sat, 28 Aug 2021]

This Week

- **Control methane to slow global warming — fast** [25 August 2021]
  Editorial • Carbon dioxide reductions are key, but the IPCC's latest report highlights the benefits of making cuts to other greenhouse gases, too.
- **Too many scientists still say Caucasian** [24 August 2021]
  World View • Racist ideas of categories for human identity continue to warp research and medicine.
- **Can Chinese diners embrace potatoes? The answer could affect Earth's climate** [18 August 2021]
  Research Highlight • A switch to spuds in a country where rice is prominent could cut greenhouse-gas emissions.
- **The animal that doesn't forget has tentacles, not a trunk** [17 August 2021]
  Research Highlight • Cuttlefish, an octopus relative, retain their cognitive powers as they grow older.
- **A tough prosthetic hand obeys the muscles' commands** [18 August 2021]
  Research Highlight • The inexpensive and lightweight prosthesis also provides feedback akin to a sense of touch.
- **What's the mystery source of two potent greenhouse gases? The trail leads to Asia** [18 August 2021]
  Research Highlight • Atmospheric levels of two powerful heat-trapping gases are rising quickly — and are higher than official emissions records suggest.
- **A staggering store of water is revealed in Earth's crust** [17 August 2021]
  Research Highlight • Modelling work shows that crustal groundwater accounts for more water than the world's ice caps and glaciers.
- **Are 20 seconds of handwashing really necessary? Physics says yes** [20 August 2021]
  Research Highlight • A simple model suggests that there's no fast way to rid hands of virus-sized particles.

- **Clever orangutans invent nutcrackers from scratch** [18 August 2021]
  Research Highlight • Chimpanzees are not the only great apes to develop tools without tutoring.

| Next section | Main menu |

- EDITORIAL
- 25 August 2021

Control methane to slow global warming — fast

Carbon dioxide reductions are key, but the IPCC's latest report highlights the benefits of making cuts to other greenhouse gases, too.

Oil and gas operations — such as Inglewood Oil Field in Los Angeles, California — are a key source of methane.Credit: Citizens of the Planet/Education Images/Universal Images Group/Getty

There's no substitute for eliminating fossil fuels and halting the release of carbon dioxide into the atmosphere to avoid the painful and disruptive effects of global warming. The latest report from the Intergovernmental

Panel on Climate Change (IPCC) leaves no doubt about this. But CO_2 is not the only greenhouse gas. The climate panel also highlights the problem — and opportunity — posed by methane, which has contributed as much as 0.5 °C of warming since pre-industrial times, second only to CO_2.

Methane is the main component of natural gas, whose popularity as a relatively clean source of fossil energy has soared by more than 50% over the past two decades. In the United States, cheap and plentiful natural gas supplies — obtained from controversial hydraulic fracking — have helped to displace coal. But there has also been a cost to the climate: fossil fuels have helped to boost atmospheric methane concentrations,which have more than doubled since pre-industrial times, from around 700 parts per billion by volume to nearly 1,900 p.p.b. in 2020.

Methane is of concern because it has an outsized impact on the climate. The gas makes up a tiny fraction of our atmosphere — CO_2 levels are more than 200 times higher. But in the first 20 years after release, methane is around 80 times more powerful than CO_2 at trapping heat in Earth's atmosphere. It also breaks down much more quickly than CO_2, with an average lifetime of around a decade, compared with centuries for CO_2. This means that curbing methane emissions could provide short-term relief while governments and businesses negotiate the more difficult transition from fossil fuels to clean energy.

IPCC climate report: Earth is warmer than it's been in 125,000 years

In an effort to reduce methane emissions, scientists have been investigating two linked questions. First, what are the major sources of methane? Second, where are the worst offenders? Livestock is the largest source, responsible for 31% of the global total, according to Ilissa Ocko at the non-profit Environmental Defense Fund (EDF) in New York City and her colleagues[1]. Oil and gas operations rank a close second, releasing 26%. Other sources include landfills, coal mines, rice paddies and water-treatment plants.

Reducing methane from livestock represents a particular challenge. People could eat less meat, but persuading people to change their diet is rarely straightforward. Moreover, meat consumption is rising in low- and middle-income countries — in line with rising incomes. It should be easier to curb emissions from other sectors. In many cases, doing so wouldn't cost anything — and it could even be profitable.

Global methane emissions could be cut by 57% by 2030 using existing technologies, Ocko and her colleagues report. And almost one-quarter of the global methane total could be eliminated at no net cost. The oil and gas industry could make the biggest difference here, having both the infrastructure and the incentive to minimize methane losses: more methane in their pipelines means more revenue. In other sectors, the operators of landfills, coal mines and wastewater-treatment plants could capture the gas and use it to generate electricity. And rice producers could minimize emissions with better irrigation and soil-management practices. If these measures were implemented worldwide, projected increases in global warming could be reduced by 0.25°C by 2050, and 0.5°C by 2100, the study finds. Those are significant numbers considering that the world has already warmed by 1.1°C, and global leaders have committed to limiting the total to 1.5–2°C.

The hard truths of climate change — by the numbers

The main problem is pinpointing precisely where methane emissions are coming from. More than a decade ago, researchers monitored methane from aircraft surveys using infrared sensors that can detect gases in sunlight reflected back from Earth[2]. Today, satellites are part of this monitoring effort. Research shows that a relatively small number of 'super-emitters' are responsible for a significant share of methane emissions, particularly in the oil and gas industry[3].

The ability to identify major methane sources is poised to advance in the next two years. In 2022, the EDF will launch a satellite designed to identify emissions across large swathes of land. Carbon Mapper, a non-profit partnership that includes NASA's Jet Propulsion Laboratory and the San Francisco-based company Planet, will follow up in 2023 with two prototype satellites designed to track methane and CO_2 at the scale of individual facilities.

In March, the United Nations Environment Programme and the European Commission launched the International Methane Emissions Observatory to help coordinate these efforts and help policymakers and companies take action. The observatory will also have access to estimated emissions inventories from governments and industry. Around 70 oil and gas producers, including giants such as Shell and BP, have committed to setting

clear emissions-reductions targets and reporting emissions under an initiative led by the Climate & Clean Air Coalition, an international initiative involving governments, non-profit organizations, businesses and others. This work will also help to inform new methane-reduction commitments due to be made at the UN climate conference in Glasgow, UK, in November.

The world will continue to warm as long as CO_2 is being pumped into the atmosphere. But curbing emissions of methane and other powerful greenhouse gases might reduce the sting. That is why governments and businesses should seize the opportunity, buying humanity a bit more time to do what needs to be done.

Nature **596**, 461 (2021)

doi: https://doi.org/10.1038/d41586-021-02287-y

References

1. 1.

   Ocko, I. B. *et al. Environ. Res. Lett.* **16**, 054042 (2021).

2. 2.

   Pétron, G. *et al. J. Geophys. Res.* **117**, D04304 (2012).

3. 3.

   Cusworth, D. H. *et al. Environ. Sci. Technol. Lett.* **8**, 567–573 (2021).

- WORLD VIEW
- 24 August 2021

Too many scientists still say Caucasian

Racist ideas of categories for human identity continue to warp research and medicine.

- Alice B. Popejoy [0]

Of the ten clinical genetics labs in the United States that share the most data with the research community, seven include ‘Caucasian’ as a multiple-choice category for patients’ racial or ethnic identity, despite the term having no scientific basis. Nearly 5,000 biomedical papers since 2010 have used ‘Caucasian’ to describe European populations. This suggests that too many scientists apply the term, either unbothered by or unaware of its roots in racist taxonomies used to justify slavery — or worse, adding to pseudoscientific claims of white biological superiority.

I work at the intersection of statistics, evolutionary genomics and bioethics. Since 2017, I have co-led a diverse, multidisciplinary working group funded by the US National Institutes of Health to investigate diversity measures in clinical genetics and genomics (go.nature.com/3su2t8n).

Many working in genomics do have a nuanced understanding of the issues and want to get things right. Still, I have been dismayed by how often the academics and clinicians I've encountered shy away from examining, or even acknowledging, how racism warps science. Decades of analyses have shown that 'racial groups' are defined by societies, not by genetics. Only the privileged have the luxury of opining that this is not a problem. As a white woman, I too have blind spots that need constant examination.

Don't ignore genetic data from minority populations

Pioneering works in social science such as Dorothy Roberts' *Fatal Invention* (2012), Kim Tallbear's *Native American DNA* (2013) and *The Social Life of DNA* (2016) by Alondra Nelson, have eloquently pointed out many of the flawed assumptions and approaches that plague human genomics.

A common theme of this scholarship is that groupings depend more on dominant culture than on ancestry. In Singapore, the government mandates that individuals are identified explicitly as Chinese, Malay, Indian or Other,

which affects where they can live and study. In the United States, people with ancestry from the world's two most populous countries, India and China, along with every other country on the continent, are collapsed into a single racial category called 'Asian'. Similarly, the term 'Hispanic' erases a multitude of cultural and ancestral identities, especially among Indigenous peoples of the Americas.

Erroneous ideas about genetic 'races' live on in the broad, ambiguous 'continental ancestry' groups such as 'Black, African' or 'African American', that are used in the US Census and are ubiquitous in biomedical research. These collapse incredible amounts of diversity and erase cultural and ancestral identities. Study participants deemed not to fit within such crude buckets are often excluded from analyses, despite the fact that fewer and fewer individuals identify with a single population of origin.

One practical way forwards is to move away from having people identify themselves using only checkboxes. I am not calling for an end to the study of genetic ancestry or socio-cultural categories such as self-identified race and ethnicity. These are useful for tracking and studying equity in justice, health care, education and more. The goal is to stop conflating the two, which leads scientists and clinicians to attribute differences in health to innate biology rather than to poverty and social inequality.

Facing up to injustice in genome science

We need to acknowledge that systemic racism, not genetics, is dominant in creating health disparities. It shouldn't have taken the inequitable ravages of a pandemic to highlight that. Furthermore, every researcher and physician should be aware of the racial bias that abounds in medical practice: some pulse oximeters give more accurate readings for light-skinned people than for those with dark skin; Black Americans are undertreated for pain; and historical biases in data used to train algorithms to make medical decisions can lead to worse outcomes for vulnerable groups. Hence the ongoing revisions to the subsection on race and ethnicity in the American Medical Association's *Manual of Style*, and why medical schools are examining how their curricula reinforce harmful misconceptions about race.

Thankfully, more researchers are collecting self-reported data on geographical family origins, languages spoken at home and cultural affiliations. I'd like to see data-collection forms with open-ended questions, rather than those that force fixed choices or reduce identity to a box labelled 'other'. These self-reported indicators could be combined with genetic data to improve on current approaches to mapping the dimensions of diversity in our populations.

Approaches to genetic ancestry based on known reference populations are inadequate, in part because so much global diversity is missing from our data. I am working with the Human Pangenome Reference Consortium, which aims to generate a more accurate and inclusive resource for global genomic diversity. It will include communities, especially Indigenous peoples, in developing protocols for data collection, storage and use. This respects Indigenous data sovereignty, and makes for more accurate and inclusive studies.

The more precisely we can measure genetic and non-genetic contributors to health and disease, the less researchers will rely on biologically meaningless designations that reinforce faulty assumptions and cause harm. The use of sequence data in clinical care could, for instance, facilitate recommendations for drug dosage that are genotype-based, rather than race-based.

Simply picking another word to replace 'Caucasian' won't be enough to root out racism in research and medicine. But all should be aware of the

harms the word represents.

Nature **596**, 463 (2021)

doi: https://doi.org/10.1038/d41586-021-02288-x

Rice planting in China releases the potent greenhouse gas methane. Those emissions contribute to making rice grown in China a generally less climate-friendly crop per calorie than potato. Credit: Costfoto/Barcroft Media/Getty

Sustainability

18 August 2021

Can Chinese diners embrace potatoes? The answer could affect Earth's climate

A switch to spuds in a country where rice is prominent could cut greenhouse-gas emissions.

China's ambitious plan to make the potato a staple crop could slash greenhouse-gas emissions — if the country's diners sacrifice some of their rice consumption.

Rice cultivation requires heavy use of water and fertilizer, and gradually degrades the soil. Seeking a sustainable and nutritious way to feed China's ballooning population, the government implemented a policy in 2015 to double potato yields and add potatoes to the Chinese diet.

Jun Bi at Nanjing University in China and his colleagues examined the policy's environmental implications and found that potatoes grown in China have lower greenhouse-gas emissions and water demand per calorie than do other crops, such as maize. Extrapolating from historical data, the researchers estimate that, from 2015 to 2030, greenhouse-gas emissions from Chinese farming of staple crops could fall nearly 9% if the government meets its potato goals and plants the crop in the most suitable places.

But if potato fields displace rice paddies and the population doesn't shift to a more potato-heavy diet, rice imports could increase. That would mean higher environmental costs because of transportation emissions, the authors warn.

Nature Food (2021)

- Sustainability

Age does not wither the mental powers of the common cuttlefish. Credit: Reinhard Dirscherl/Alamy

Neuroscience

17 August 2021

The animal that doesn’t forget has tentacles, not a trunk

Cuttlefish, an octopus relative, retain their cognitive powers as they grow older.

Even in old age, cuttlefish remain as mentally sharp as ever.

Ageing mammals — especially humans — gradually lose their ability to remember specific events. To find out whether the same is true of molluscs, an invertebrate group that includes clams, snails and octopuses, Alexandra Schnell at Cambridge University, UK, and her colleagues taught six older common cuttlefish (*Sepia officinalis*) that a seafood snack in their tanks changed location depending on the time of day. The old cuttlefish learnt to associate the time and location just as well as six young cuttlefish did.

Next, the researchers tested how well the molluscs could recall a specific memory about where and when they had eaten a specific snack for breakfast and use that memory to search for the food. Older cuttlefish were slightly better than young animals at this task, leading the researchers to conclude that they are the first known animal to not undergo mental decline with age.

It's still unclear which unique features of the cuttlefish brain anatomy and physiology lead to this phenomenon.

Proc. R. Soc. B (2021)

- Neuroscience

This soft prosthetic hand allows the wearer to grasp delicate objects such as cakes and berries. Credit: G. Gu *et al./Nature Biomed. Eng.*

Engineering

18 August 2021

A tough prosthetic hand obeys the muscles' commands

The inexpensive and lightweight prosthesis also provides feedback akin to a sense of touch.

A lightweight prosthetic hand can grasp strawberries without crushing them and still works after being hit with a hammer or run over by a 1.5-tonne

vehicle.

Xiangyang Zhu at Shanghai Jiao Tong University in China and his colleagues developed the resilient prosthesis for people with amputations below the elbow. The device boasts a 3D-printed palm and five jointed digits containing silicone tubes that are moved with pressurized air. Electrical signals from forearm muscles control the hand, which has five configurations.

Other prosthetic hands controlled through nervous-system signals can cost more than US$10,000. The components used in the team's version cost less than $500. The hand is also considerably more lightweight than its competitors, thanks to a bag worn at the waist that contains the battery and the electronics used to turn the arm's signals into movement instructions. The bag also carries the pumps and valves used to supply air.

Study participants needed just 15 minutes to learn how to control the prosthesis, which provides feedback using signals sent from pressure-sensitive sensors on the fingertips to electrodes on the upper arm.

Nature Biomed. Eng. (2021)

- Engineering

An aluminium smelter in Zouping, China. Two greenhouse gases whose atmospheric levels have soared in recent years have been traced to such smelters and to semiconductor factories in Japan and South Korea. Credit: Brent Lewin/Bloomberg/Getty

Atmospheric science

18 August 2021

What's the mystery source of two potent greenhouse gases? The trail leads to Asia

Atmospheric levels of two powerful heat-trapping gases are rising quickly — and are higher than official emissions records suggest.

The powerful greenhouse gases tetrafluoromethane and hexafluoroethane have been building up in the atmosphere from unknown sources. Now, modelling suggests that China's aluminium industry is a major culprit.

The gases are thousands of times more effective than carbon dioxide at warming the atmosphere. Official tallies of tetrafluoromethane and hexafluoroethane emissions from factories are too low to account for the levels in the air, which began to rise in 2015 after seven years of relative stability.

Seeking to pinpoint the sources of those emissions, Jooil Kim at the University of California, San Diego, and his colleagues analysed air samples collected roughly every 2 hours between November 2007 and December 2019 on South Korea's Jeju Island. The scientists also modelled the weather patterns that transported air across the island during that period, to track the gases' origins.

The results suggest that aluminium smelters in China account for a large proportion of these chemicals in the atmosphere. Semiconductor factories in South Korea and Japan are probably also to blame.

JGR Atmos. (2021)

- Atmospheric science

People gather at a pump in India to collect groundwater. Accessible, fresh water makes up only a fraction of the water in Earth’s crust. Credit: Jack Laurenson/Lnp/Shutterstock

Water resources

17 August 2021

A staggering store of water is revealed in Earth’s crust

Modelling work shows that crustal groundwater accounts for more water than the world’s ice caps and glaciers.

The depths of Earth's crust hold a huge volume of ancient, salty water that has been undetected until now.

Grant Ferguson at the University of Saskatchewan in Saskatoon, Canada, and his colleagues calculated how much of this underground water should exist. They analysed a global database of the types of rock that make up the uppermost 10 kilometres of the planet's continental crust. Nearly 88% is hard crystalline rock, and 12% is sedimentary rock, which has large spaces between its grains.

The scientists calculated how much water could exist between the grains of both of these rock types, and estimated that the uppermost 10 kilometres of Earth's crust holds nearly 44 million cubic kilometres of water. That's more than the amount frozen in glaciers and the ice sheets of Greenland and Antarctica.

Most of this vast reservoir lies at a depth of between 1 kilometre and 10 kilometres, beyond the reach of wells that could tap it. The groundwater used by many farmers for irrigation and by billions of people for drinking is at much shallower depths.

Geophys. Res. Lett. (2021)

- Water resources

No shortcuts, please: modelling supports the public-health directives to wash hands for 20 seconds. Credit: David Cliff/NurPhoto/Getty

Fluid dynamics

20 August 2021

Are 20 seconds of handwashing really necessary? Physics says yes

A simple model suggests that there's no fast way to rid hands of virus-sized particles.

Handwashing must be done at a minimum speed to dislodge viruses and bacteria, and it should last roughly 20 seconds, on par with the time that

public-health experts recommend, according to an analysis of the fluid dynamics of soaping up.

The simple act of handwashing masks some complex physics. Two rough surfaces — hands — slide past one another, separated by a thin layer of water and soap.

To illuminate the physical details, Paul Hammond, a consultant based in Bourn, UK, turned to a 135-year-old branch of fluid dynamics called lubrication theory, which excels at describing the physics of thin layers of fluids wedged between surfaces. Hammond used its formulas to devise a simple model that could be used to estimate how long it takes to dislodge any virus-sized particles.

The results confirmed that it does indeed require about 20 seconds of hand-rubbing to knock off pathogens. Although the analysis did not take the chemistry and biology of handwashing into account, the author says the results are an encouraging starting point for further study.

Phys. Fluids (2021)

- Fluid dynamics

A Sumatran orangutan named Padana raps nuts with a log ‘hammer’ atop a tree stump ‘anvil’, a technique she invented herself. Credit: Claudio Tennie

Animal behaviour

18 August 2021

Clever orangutans invent nutcrackers from scratch

Chimpanzees are not the only great apes to develop tools without tutoring.

Chimpanzees have long been thought to be the only non-human great apes to regularly smash nuts with stones or wooden hammers — one of the most complex forms of tool use observed in nature. Now, researchers have found

that orangutans, too, can use hammers to crack open nuts, and they learn to do so without copying others.

Elisa Bandini at the University of Tübingen in Germany and her colleagues observed 12 zoo-dwelling orangutans (*Pongo abelii* and *Pongo pygmaeus*) that were given hard nuts and small wooden logs as potential hammers. None of the animals had previously broken nuts open with tools.

Some of the apes never tried the potential tools. But most wielded the logs as hammers to crack open the nuts, and three used a tree stump or another object as an anvil to stabilize the nuts.

Four animals started to use the tools without observing more experienced individuals, which suggests that orangutans can spontaneously learn to use objects as efficient nutcrackers, the researchers say.

Am. J. Primatol. (2021)

- Animal behaviour

News in Focus

- **Babbling bats, autocorrected genes and COVID antibodies** [25 August 2021]
  News Round-Up • The latest science news, in brief.
- **African languages to get more bespoke scientific terms** [18 August 2021]
  News • Many words common to science have never been written in African languages. Now, researchers from across Africa are changing that.
- **Decades-old SARS virus infection triggers potent response to COVID vaccines** [18 August 2021]
  News • Dramatic antibody production in people infected during the 2002–04 outbreak furthers hopes of a vaccine against many coronaviruses.
- **The mutation that helps Delta spread like wildfire** [20 August 2021]
  News • A key amino-acid change might underlie the coronavirus variant's ferocious infectivity.
- **Brazilian road proposal threatens famed biodiversity hotspot** [17 August 2021]
  News • Scientists and environmentalists say the road, slated to pass through Iguaçu National Park, could harm research projects and precious ecosystems.
- **Iran hopes to defeat COVID with home-grown crop of vaccines** [17 August 2021]
  News Q&A • Nature talks to vaccine developer Kayhan Azadmanesh about efforts in Iran to develop ten or more COVID jabs, two of which have been approved for use.
- **Can artificially altered clouds save the Great Barrier Reef?** [25 August 2021]
  News Feature • Australian scientists are rushing to develop new technologies — such as ways to block sunlight — to help preserve corals in the face of climate change.
- **COVID vaccines and blood clots: what researchers know so far** [24 August 2021]
  News Feature • Scientists are trying to understand why a small number of people develop a mysterious clotting disorder after receiving a COVID jab.

- NEWS ROUND-UP
- 25 August 2021

Babbling bats, autocorrected genes and COVID antibodies

The latest science news, in brief.

A greater sac-winged bat (*Saccopteryx bilineata*) pup babbling. Researchers think the young bats make these sounds to practise their vocal skills.Credit: Michael Stifter

Baby bats babble like human infants

Pups of the greater sac-winged bat (*Saccopteryx bilineata*) develop their vocal skills by babbling in a similar way to human babies, a study shows. The research is the first to identify baby babble produced by a mammal that isn't a primate (A. Fernandez *et al. Science* **373**, 923–926; 2021).

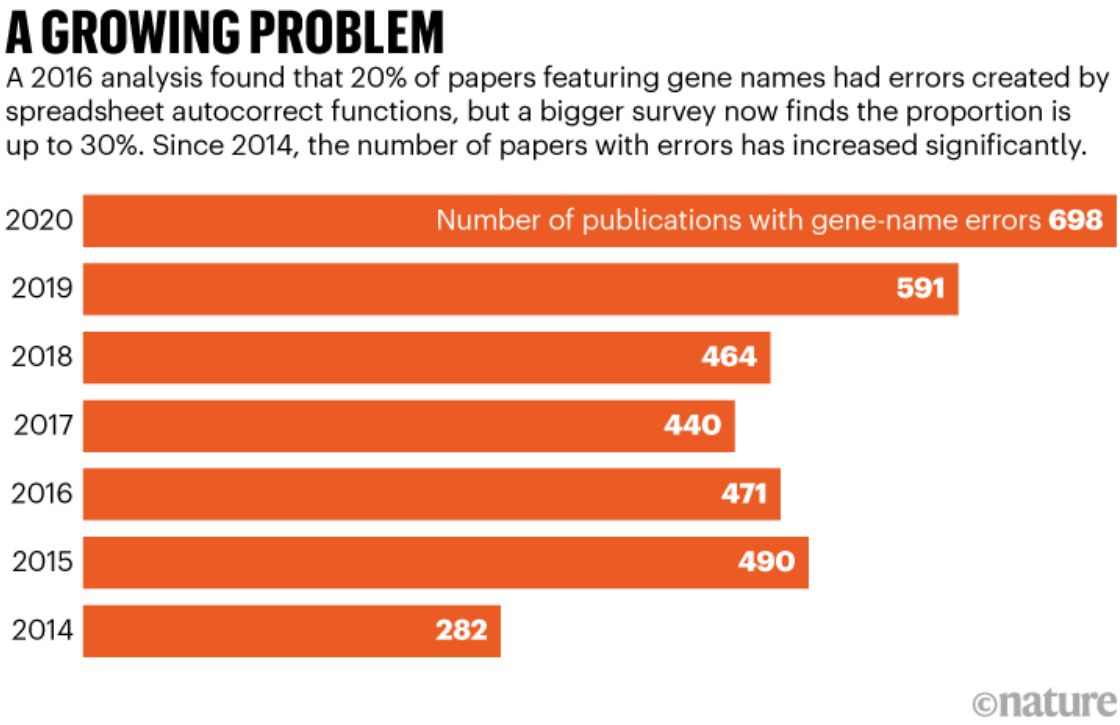
Researchers recorded 216 babbling bouts in 20 wild bat pups in Costa Rica and Panama. They used ultrasonic sound equipment to capture the individual 'syllables' of the pups' high-pitched squeals, and identified most of the 25 syllables produced by adult bats.

The team converted these audio snippets into images that show the pitch and intensity of the sound over time. This allowed them to search for eight key features that characterize babbling in human babies, including repetition of syllables and rhythm in the sounds. The bats' babble had all of these features.

"Even though there are millions of years of different evolutionary pathways between bats and humans, it's astonishing to see such a similar vocal-practice behaviour leading to the same result — acquiring a large vocal repertoire," says study co-author Ahana Fernandez, an animal behavioural ecologist at the Berlin Museum of Natural History.

Excel autocorrect errors still creating genomics headache

Five years after a study showed that autocorrect problems were widespread in the genetics literature, error-riddled spreadsheets persist, according to an analysis of published gene lists.



Source: Abeysooriya, M., Soria, M., Kasu, M. S. & Ziemann, M. *PLoS Comput. Biol*. **17**, e1008984 (2021).

The issue often occurs when the abbreviated form of a gene's name — or symbol — is incorrectly recognized as a date and autocorrected as such by Excel or Google Sheets. For example, *SEPT4* and *MARCH1* will be automatically changed to *4-Sep* and *1-Mar*. "It can have a significant impact," says biologist Auriol Purdie at the University of Sydney in Australia, who works with gene-microarray and gene-transcription data sets.

The problem was first documented in 2004, and in 2016 Mark Ziemann and his colleagues at the Baker IDI Heart and Diabetes Institute in Melbourne, Australia, quantified it (M. Ziemann *et al. Genome Biol.* **17**, 177; 2016). They found that 20% of papers in leading genomics journals contained conversion errors in Excel spreadsheets in supplementary data. These data sets are frequently used by other geneticists, so errors can be perpetuated and distort further analyses.

However, despite the issue being flagged with researchers — and steps being taken to fix it — the problem is still rife, according to a larger analysis

led by Ziemann, now at Deakin University in Geelong, Australia (M. Abeysooriya *et al. PLoS Comput. Biol.* **17**; e1008984; 2021). His team found errors in almost one-third of 11,000 articles published between 2014 and 2020.

A garment worker in Gazipur, Bangladesh, receives a dose of the Moderna vaccine against COVID-19.Credit: Ahmed Salahuddin/NurPhoto/Getty

Antibodies predict protection by Moderna COVID jab

Antibody levels in blood can predict the level of protection provided by Moderna's COVID-19 vaccine. After receiving the vaccine, people with relatively low levels of antibodies were more likely to develop symptomatic infections than were those who mounted a stronger antibody response, according to an analysis of such 'breakthrough' infections during the vaccine's efficacy trial (P. B. Gilbert *et al*. Preprint at medRxiv https://doi.org/grz3; 2021).

The study, posted as a preprint earlier this month, adds to the growing evidence that ‘neutralizing’ antibodies, which can block viral infection of cells, are a marker of vulnerability to COVID-19. A team including David Benkeser, a biostatistician at Emory University in Atlanta, Georgia, compared levels of these antibodies in the nearly 50 vaccinated trial participants who developed breakthrough infections with levels in matched controls who were not diagnosed with COVID-19.

The authors’ modelling found that people with undetectable levels of neutralizing antibodies were 10 times more likely to develop COVID-19 than were individuals whose antibody levels placed them in the 90th percentile of all study participants. The findings have not been peer reviewed.

Nature **596**, 467 (2021)

doi: https://doi.org/10.1038/d41586-021-02289-w

- NEWS
- 18 August 2021

African languages to get more bespoke scientific terms

Many words common to science have never been written in African languages. Now, researchers from across Africa are changing that.

- Sarah Wild

Researchers want to expand scientific terms in African languages including Luganda, which is spoken in East Africa. Pictured: student-teachers in Kampala.Credit: Eye Ubiquitous/Alamy

There's no original isiZulu word for dinosaur. Germs are called *amagciwane*, but there are no separate words for viruses or bacteria. A quark is *ikhwakhi* (pronounced kwa-ki); there is no term for red shift. And researchers and science communicators using the language, which is spoken by more than 14 million people in southern Africa, struggle to agree on words for evolution.

IsiZulu is one of approximately 2,000 languages spoken in Africa. Modern science has ignored the overwhelming majority of these languages, but now a team of researchers from Africa wants to change that.

[What's the isiZulu for dinosaur? How science neglected African languages]

A research project called Decolonise Science plans to translate 180 scientific papers from the AfricArXiv preprint server into 6 African languages: isiZulu and Northern Sotho from southern Africa; Hausa and Yoruba from West Africa; and Luganda and Amharic from East Africa.

These languages are collectively spoken by around 98 million people. Earlier this month, AfricArXiv called for submissions from authors interested in having their papers considered for translation. The deadline is 20 August.

The translated papers will span many disciplines of science, technology, engineering and mathematics. The project is being supported by the Lacuna Fund, a data-science funder for researchers in low- and middle-income countries. It was launched a year ago by philanthropic and government funders from Europe and North America, and Google.

Languages left behind

The lack of scientific terms in African languages has real-world consequences, particularly in education. In South Africa, for example, less than 10% of citizens speak English as their home language, but it is the main teaching language in schools — something that scholars say is an obstacle to learning science and mathematics.

African languages are being left behind in the online revolution, says Kathleen Siminyu, a specialist in machine learning and natural language processing for African languages based in Kenya. “African languages are seen as something you speak at home, not in the classroom, not showing up in the business setting. It is the same thing for science,” she says.

Siminyu is part of Masakhane, a grass-roots organization of researchers interested in natural language processing in African languages. Masakhane, which means ‘we build together’ in isiZulu, has more than 400 members from about 30 countries on the continent. They have been working together for three years.

The Decolonise Science project is one of many initiatives that the group is undertaking; others include detecting hate speech in Nigeria and teaching machine-learning algorithms to recognize African names and places.

Eventually, Decolonise Science aims to create freely available online glossaries of scientific terms in the six languages, and use them to train machine-learning algorithms for translation. The researchers hope to complete this project by the beginning of 2022. But there’s a wider ambition: to reduce the risk of these languages becoming obsolete by giving them a stronger foothold online.

Terminology creation

Decolonise Science will employ translators to work on papers from AfricArXiv for which the first author is African, says principal investigator Jade Abbott, a machine-learning specialist based in Johannesburg, South Africa. Words that do not have an equivalent in the target language will be flagged so that terminology specialists and science communicators can develop new terms. “It is not like translating a book, where the words might exist,” Abbott says. “This is a terminology-creating exercise.”

But “we don’t want to come up with a new word completely”, adds Sibusiso Biyela, a writer at ScienceLink, a science-communication company based in Johannesburg that is a partner in the project. “We want the person who reads that article or term to understand what it means the first time they see it.”

Biyela, who writes about science in isiZulu, often derives new terms by looking at the Greek or Latin roots of existing scientific words in English. Planet, for example, comes from the ancient Greek *planētēs*, meaning ‘wanderer’, because planets were perceived to move through the night sky. In isiZulu, this becomes *umhambi*, which also means wanderer. Another word for planet, used in school dictionaries, is *umhlaba*, which means ‘Earth’ or ‘world’. Other terms are descriptive: for ‘fossil’, for example, Biyela coined the phrase *amathambo amadala atholakala emhlabathini*, or ‘old bones found in the ground’.

In some scientific fields, such as biodiversity research, researchers trying to find the right terms will need to tap into spoken sources. Lolie Makhubu-Badenhorst, acting director of the Language Planning and Development Office at the University of KwaZulu-Natal in Durban, says that the absence of a scientific word from written data sets does not mean that it does not exist. “You’re written-centred, I’m oral centred. The knowledge is there, but it is not well-documented,” says Makhubu-Badenhorst, who is not part of the Decolonise Science project.

Decolonise Science’s terminology specialists will come up with a framework for developing isiZulu scientific terms, says Biyela. Once that’s complete, they will apply it to the other languages.

The team will offer its glossaries as free tools for journalists and science communicators, as well as national language boards, universities and technology companies, which are increasingly providing automated translation. “If you create a term and it isn’t being used by others, it isn’t going to permeate into the language,” says Biyela.

Google is calling for help to improve the quality of its African language translations.Credit: Cristina Aldehuela/AFP via Getty

Big tech: 'we need your help'

Masakhane’s researchers say that global technology companies have historically ignored African languages, but in recent years, they have begun funding research in the field.

“We’re aware that the many thousands of African languages are currently under-represented in translation software,” a Google spokesperson told *Nature.* The tech giant wants to expand Google Translate to include more African languages, including Twi, Ewe, Baoulé, Bambara, Fula, Kanuri,

Krio, Isoko, Luganda, Sango, Tiv and Urhobo, they added. However, it needs “speakers of those languages to help us improve the quality of our translations” so they can be integrated into the service.

“The big idea is cultural ownership of science,” Biyela explains. Both he and Abbott say it is crucial to decolonize science by allowing people to do research and speak about science in their own languages. At the moment, it is possible to use African languages to talk about politics and sport, but not science, says Biyela.

Similarly, English is the dominant language of environmental stewardship and conservation — but unless people understand the meaning of specific terms and concepts and can talk about them in their home languages, they can feel disconnected from government efforts to preserve ecosystems and species, says Bheka Nxele, a programme manager for restoration ecology, environmental planning and climate protection in the eThekwini municipality of South Africa.

The researchers are concerned that if African languages are not included in online algorithms, they could, eventually, become obsolete and forgotten. “These are languages [people] speak. These are languages they use every day, and they live with and see the reality that in *x* number of years, their language might be dead because there is no digital footprint,” says Siminyu.

Nature **596**, 469-470 (2021)

doi: https://doi.org/10.1038/d41586-021-02218-x

- NEWS
- 18 August 2021

Decades-old SARS virus infection triggers potent response to COVID vaccines

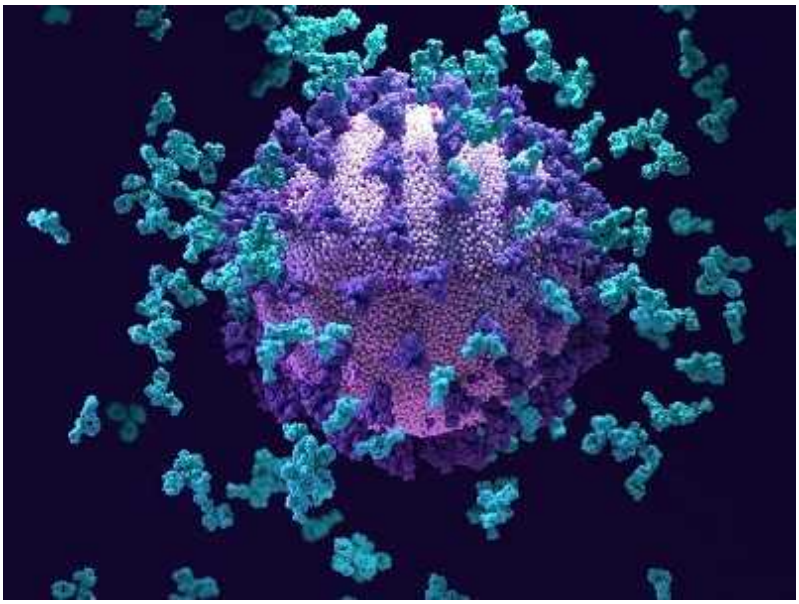
Dramatic antibody production in people infected during the 2002–04 outbreak furthers hopes of a vaccine against many coronaviruses.

- Smriti Mallapaty

A person is treated in hospital in Singapore during the 2003 outbreak of severe acute respiratory syndrome.Credit: Paula Bronstein/Getty

People who were infected almost two decades ago with the virus that causes severe acute respiratory syndrome (SARS) generate a powerful antibody response after being vaccinated against COVID-19. Their immune systems can fight off multiple SARS-CoV-2 variants, as well as related coronaviruses found in bats and pangolins.

The Singapore-based authors of a small study published today in *The New England Journal of Medicine*[1] say the results offer hope that vaccines can be developed to protect against all new SARS-CoV-2 variants, as well as other coronaviruses that have the potential to cause future pandemics.



This ‘super antibody’ for COVID fights off multiple coronaviruses

The study is a “proof of concept that a pan-coronavirus vaccine in humans is possible”, says David Martinez, a viral immunologist at the University of North Carolina at Chapel Hill. “It’s a really unique and cool study, with the caveat that it didn’t include many patients.”

SARS-CoV-2 belongs to the sarbecovirus group of coronaviruses, which includes the virus that caused SARS (called SARS-CoV), as well as closely related bat and pangolin coronaviruses.

Sarbecoviruses use what are known as spike proteins to bind to ACE2 receptors in the membranes of host cells and enter them. They can jump

from animals to humans, as they did before in both the current pandemic and the 2002–04 outbreak of SARS, which spread to 29 countries. “The fact that this has happened twice in the last two decades is strong rationale that this is a group of viruses that we really need to pay attention to,” says Martinez.

Neutralizing antibodies

Last year, Linfa Wang, a virologist at Duke–NUS Medical School in Singapore who led the latest study, went looking for people who had survived SARS to see whether they offered any clues about how to develop vaccines and drugs for COVID-19. He detected ‘neutralizing’ antibodies in their blood that blocked the original SARS virus from entering cells, but did not affect SARS-CoV-2 — which he found surprising, because the viruses are closely related.

But when Singapore rolled out the Pfizer–BioNTech COVID-19 vaccine this year, Wang decided to interrogate how the SARS infection affected responses to the vaccine. What he discovered was striking. Eight vaccinated study participants, who had recovered from SARS almost two decades ago, produced very high levels of neutralizing antibodies against both viruses, even after just one dose of the vaccine.

Variant-proof vaccines — invest now for the next pandemic

They also produced a broad spectrum of neutralizing antibodies against three SARS-CoV-2 variants of concern in the current pandemic — Alpha, Beta and Delta — and five bat and pangolin sarbecoviruses. No such potent and wide-ranging antibody response was observed in blood samples taken from fully vaccinated individuals, even those who had also had COVID-19.

The researchers suggest that such broad protection could arise because the vaccine jogs the immune system's 'memory' of regions of the SARS virus that are also present in SARS-CoV-2, and possibly many other sarbecoviruses.

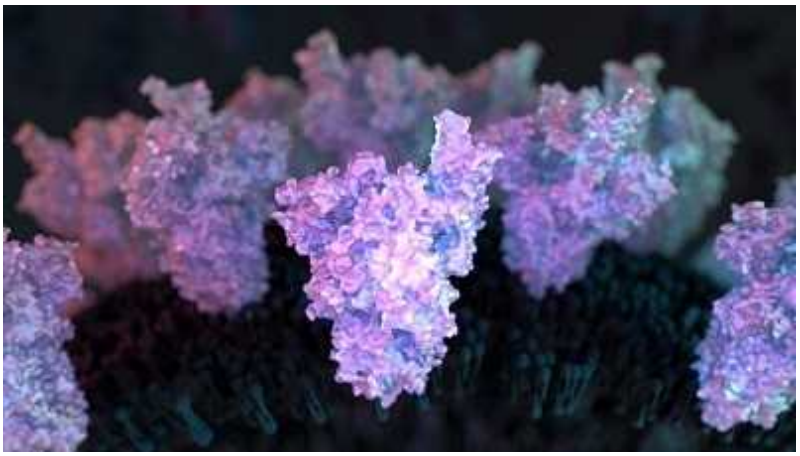
Coronaviruses found in bats have the potential to cause future pandemics, so the fact that a broad spectrum of neutralizing antibodies is generated that protects against some of them "is encouraging", says Daniel Lingwood, an immunologist at the Ragon Institute of MGH, MIT and Harvard in Boston, Massachusetts. But researchers say it is not clear how long this protection lasts.

A vaccine that is widely effective against sarbecoviruses could be administered to the general population in high-risk areas close to animals that harbour them, limiting the potential spread of these viruses in people, adds Christopher Barnes, a structural biologist at Stanford University in California.

Which part of the virus

Barton Haynes, an immunologist at Duke University School of Medicine in Durham, North Carolina, says the study raises the question of whether a similar response could be generated if people vaccinated against COVID-19 were given a booster shot that targeted the original SARS virus. This might protect them against new variants of SARS-CoV-2 and other sarbecoviruses. Wang says preliminary studies in mice suggest that is possible.

But the latest study doesn't identify exactly which sections of the viruses induce the broad immune response, something that would be needed to develop vaccines. That's the "biggest question", says Martinez. If it is a region of the virus that is present not just in sarbecoviruses, but in the entire group of coronaviruses, there is potential for creating a vaccine against all of them, he says.



Rare COVID reactions might hold key to variant-proof vaccines

Several research groups have identified specific antibodies that prevent SARS-CoV-2 and other sarbecoviruses from spreading in cells. Others are already working on pan-coronavirus vaccines, and have synthesized components that induce strong protection in monkeys and mice.

Haynes and his colleagues, for example, have developed[2] a protein nanoparticle studded with 24 pieces of a section of the SARS-CoV-2 spike protein called the receptor binding domain, a key target of antibodies. They

found that in monkeys, the nanoparticle induced much higher levels of antibodies against SARS-CoV-2 than did the Pfizer vaccine. It also induced cross-reactive antibodies against the original SARS virus and bat and pangolin sarbecoviruses.

Martinez and his colleagues have induced these widely reactive antibodies in mice, using a vaccine made from a combination of spike proteins from different coronaviruses[3]. But Martinez says the latest study suggests that this complex spike chimaera might not be necessary; a similar protective response could be induced simply by the original SARS virus's spike protein.

Wang says he is already working on potential vaccines that target multiple sarbecoviruses, and he now hopes to find additional survivors of the 2002–04 SARS outbreak to conduct a much larger study, including testing their responses to other COVID-19 vaccines.

Nature **596**, 471-472 (2021)

doi: https://doi.org/10.1038/d41586-021-02260-9

References

1. 1.

   Tan, C.-W. *et al. N. Engl. J. Med*. https://doi.org/10.1056/NEJMoa2108453 (2021).

2. 2.

   Saunders, K. O. *et al. Nature* **594**, 553–559 (2021).

3. 3.

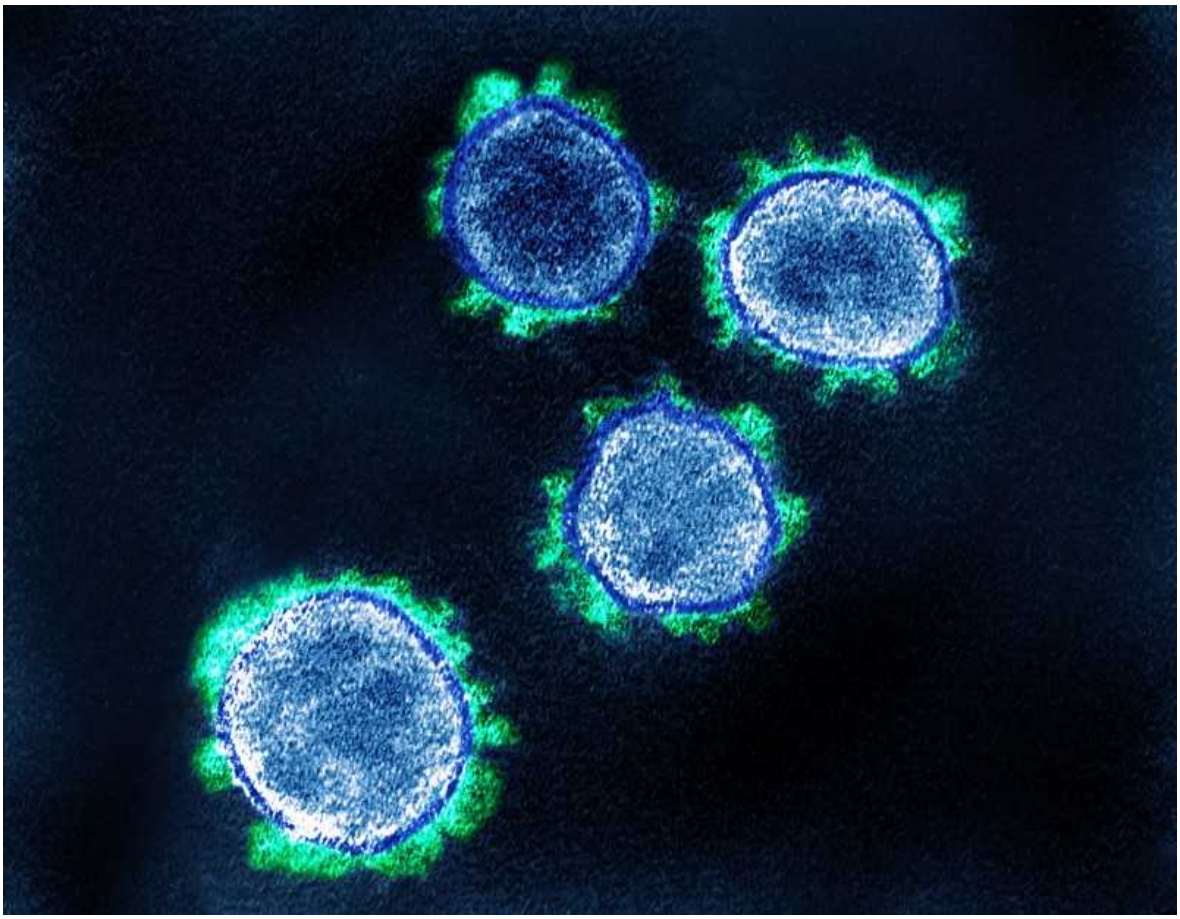
   Martinez, D. R. *et al. Science* https://doi.org/10.1126/science.abi4506 (2021).

- NEWS
- 20 August 2021

The mutation that helps Delta spread like wildfire

A key amino-acid change might underlie the coronavirus variant's ferocious infectivity.

- Ewen Callaway



SARS-CoV-2 coronavirus particles isolated from a US case of COVID-19. Scientists are trying to understand why the Delta variant spreads so quickly.Credit: National Institutes of Health/Science Photo Library

As the world grapples with the hyper-infectious Delta coronavirus variant, scientists are racing to understand the biological basis for its behaviour.

A slew of studies has highlighted an amino-acid change present in Delta that might contribute to its swift spread. Delta is at least 40% more transmissible than is the Alpha variant identified in the United Kingdom in late 2020, epidemiological studies suggest.

“The key hallmark of Delta is that transmissibility seems to be ramping up to the next notch,” says Pei-Yong Shi, a virologist at the University of Texas Medical Branch in Galveston. “We thought Alpha was pretty bad, very good at spreading. This one seems to be even more.”

How do vaccinated people spread Delta? What the science says

Shi’s team and other groups have zeroed in on a mutation that alters a single amino acid in the SARS-CoV-2 spike protein — the viral molecule responsible for recognizing and invading cells. The change, which is called P681R and transforms a proline residue into an arginine, falls within an intensely studied region of the spike protein called the furin cleavage site.

The presence of this short string of amino acids set off alarm bells when SARS-CoV-2 was first identified in China, because it is associated with heightened infectivity in other viruses such as influenza, but had not previously been found in sarbecoviruses, the family of coronaviruses to which SARS-CoV-2 belongs. “This little insert sticks out and hits you in the face,” says Gary Whittaker, a virologist at Cornell University in Ithaca, New York.

Pre-activated virus

To penetrate cells, the SARS-CoV-2 spike protein must be cut twice by host proteins. In the SARS-CoV-1 virus that causes severe acute respiratory syndrome (SARS), both incisions occur after the virus has locked on to a cell. But with SARS-CoV-2, the presence of the furin cleavage site means that host enzymes (including one called furin) can make the first cut as newly formed viral particles emerge from an infected cell. These pre-activated viral particles can then go on to infect cells more efficiently than do particles requiring two cuts, says Whittaker.

Delta wasn’t the first SARS-CoV-2 variant to gain a mutation that alters the furin cleavage site. The Alpha variant has a different amino-acid change at the same location as Delta. But the available evidence suggests that the mutation’s effect has been especially profound in Delta.

In a study reported as a preprint on 13 August[1], Shi’s team found that the spike protein is cut much more efficiently in Delta-variant particles than in Alpha particles, echoing results reported in May by virologist Wendy Barclay at Imperial College London and her team, who compared Delta with an earlier strain[2]. Follow-up experiments by both groups showed that the P681R change was largely responsible for spike being clipped so much more efficiently. “This really nailed it, in terms of the mechanism,” says Shi.

COVID vaccines slash viral spread – but Delta is an unknown

Researchers are also beginning to join the dots between P681R and Delta's ferocious infectivity. Shi's team found that, in cultured human-airway epithelial cells infected with equal numbers of Delta and Alpha viral particles, Delta rapidly outcompeted the Alpha variant, mimicking epidemiological patterns that have played out globally. But Delta's advantage disappeared when the researchers eliminated the P681R change.

The mutation might also speed up the spread of SARS-CoV-2 from cell to cell. A team led by Kei Sato, a virologist at the University of Tokyo, found that spike proteins bearing the P681R change fuse with the plasma membranes of uninfected cells — a key step in infection — almost three times faster than do spike proteins lacking the change[3].

"I think the virus is succeeding on volume and speed," says Whittaker. "It's become a much more efficient virus. It's going through people and going through cells a lot quicker."

More than one mutation

Although evidence is building that the P681R change is a crucial feature of Delta, researchers emphasize that it is unlikely to be the only mutation responsible for the variant's fast spread. Delta carries numerous other mutations to the spike protein, as well as to other less well-studied proteins,

that might be important. “It’s very simplistic to say it’s just this 681 change. I think it’s a sum of everything,” says Teresa Aydillo-Gomez, a virologist at Icahn School of Medicine at Mount Sinai in New York City.

The epidemiological and genetic context of the mutation is also important to Delta’s rise, say scientists. One of Delta’s siblings, a variant called Kappa that, like Delta, was first identified in India, carries many of the same mutations, including P681R, but its effects haven't been as devastating as Delta’s. In a preprint posted on 17 August, a team led by structural biologist Bing Chen at Harvard Medical School in Boston, Massachusetts, reports that Kappa’s spike protein is cleaved less frequently and fuses to cell membranes much less efficiently than does Delta’s[4]. The researchers say this finding raises questions over the role of P681R.

[How the Delta variant achieves its ultrafast spread]

Researchers in Uganda identified the P681R change in a variant that spread widely in the country in early 2021, but that never took off as Delta did, even though it displays many of the same properties in cell-based lab studies. Whittaker’s team inserted the P681R change into a spike protein from the coronavirus that was circulating in Wuhan, China, at the beginning of the pandemic, and found no increase in its infectivity[5]. “It takes more than one mutation to make a difference,” he adds.

Regardless of its role in Delta's dominance, Whittaker and other scientists say, the mutation has underscored the importance of understanding changes in the coronavirus's furin cleavage site. Whittaker doesn't expect P681R to be the last furin cleavage site mutation to cause concern. "I'm waiting to see what happens next."

Nature **596**, 472-473 (2021)

doi: https://doi.org/10.1038/d41586-021-02275-2

References

1. 1.

   Liu, Y. *et al.* Preprint at bioRxiv https://www.biorxiv.org/content/10.1101/2021.08.12.456173v1 (2021).

2. 2.

   Peacock, T. P. *et al.* Preprint at bioRxiv https://www.biorxiv.org/content/10.1101/2021.05.28.446163v1 (2021).

3. 3.

   Saito, A. *et al.* Preprint at bioRxiv https://www.biorxiv.org/content/10.1101/2021.06.17.448820v2 (2021).

4. 4.

   Zhang, J. *et al.* Preprint at bioRxiv https://www.biorxiv.org/content/10.1101/2021.08.17.456689v1 (2021).

5. 5.

   Lubinski, B. *et al.* Preprint at bioRxiv https://www.biorxiv.org/content/10.1101/2021.06.30.450632v3 (2021).

- NEWS
- 17 August 2021

Brazilian road proposal threatens famed biodiversity hotspot

Scientists and environmentalists say the road, slated to pass through Iguaçu National Park, could harm research projects and precious ecosystems.

- Meghie Rodrigues

Protesters oppose the Caminho do Colono at Iguaçu Falls.Credit: Marcos Labanca

Brazil's National Congress could soon vote on a bill proposing to construct a road through the country's Iguaçu National Park. If the proposal moves ahead, researchers fear that it will threaten the park's lush forest, a biodiversity hotspot that is home to almost 1,600 animal species, including endangered animals such as the purple-winged ground dove.

Environmentalists and researchers have fought off construction of the 17.5-kilometre road for years, arguing that it will bring not only pollution to the park, but also poachers, who would threaten animals such as jaguars and tapirs. Even research in the park could be affected. In a portion of the park that dips into Argentina, for example, "poachers often steal our cameras", says Julia Pardo, a mammal conservation and ecology researcher at the Subtropical Biology Institute in Misiones, Argentina.

'Apocalyptic' fires are ravaging the world's largest tropical wetland

Under the leadership of President Jair Bolsonaro, Brazil's government has weakened protection of the country's forests in favour of industries such as mining, logging and ranching. The lower house of Brazil's Congress, the Chamber of Deputies, put the bill on a fast track in June, allowing it to skip regular debate among its committees and head straight for a vote — a move that has researchers worried.

If passed, the legislation would establish a dangerous precedent that could weaken environmental law in Brazil, says Sylvia Torrecilha, a biologist at the Secretariat of Environment, Economic Development, Production and Family Agriculture in the state of Mato Grosso do Sul. In addition to cutting Iguaçu Park in two with a road that will connect towns to its north and south (see 'Contested route'), the bill seeks to create a new type of protected area — the *estrada-parque*, or park road — in Brazil's System of Natural Conservation Units, which regulates environmentally protected areas. Approving the construction of the 'Caminho do Colono' (the Settler's Road) in Iguaçu could literally pave the way for creating through-ways in other parks and conservation areas in Brazil, says Torrecilha.

Normally, the idea of a park road is to preserve the green areas along an already-existing scenic route, she says, not to bring commercial or economic advancement to a state — the argument lawmakers have made in favour of the road. The proposal, from its very beginning, is "inappropriate", she adds.

A historical route

Established in 1939, Iguaçu National Park is famous for the waterfall — one of the world's largest — on the border with Argentina along its southwestern tip. But it is also notable because it contains the largest remaining patch of Atlantic Forest in southern Brazil. Although less well-known than the Amazon rainforest, the Atlantic Forest is rich in plant and animal species, and originally stretched along the coast of southeastern Brazil and down to Argentina and Paraguay. However, the forest is rapidly disappearing: it has lost almost 90% of its tree cover, accelerated by deforestation from urbanization, and agricultural and industrial activities in the twentieth century.

Because of these attributes, the park was designated as a World Heritage site by the United Nations cultural organization UNESCO in 1986.

If the legislation is successful, it will actually enable the creation of the Caminho do Colono for the second time. The government of Paraná, the state where Iguaçu National Park is located, transformed an existing walking path into an unpaved version of the road during the 1950s. “Nobody cared much at the time because there wasn’t much difference between the inside and the outside of the park, as the Atlantic Forest stretched all over the place,” says former park chief Ivan Baptiston. “With all the deforestation of the last decades, nowadays, the scenario is a lot different.”

In 1986 — the same year the park received its UNESCO World Heritage Site designation — Brazil’s Federal Prosecutor’s Office filed a civil suit to close the road, and the following year, a federal judge officially closed it. Since then, vegetation has overtaken the route, and some local residents

have tried and failed to force it back open, claiming economic hardships associated with not being able to travel efficiently through the area.

‘We are being ignored’: Brazil’s researchers blame anti-science government for devastating COVID surge

The new bill states that re-establishing the road would offer a “solution to a logistical problem in Paraná state”. Sponsored by Nelsi Coguetto Maria, a member of the Chamber of Deputies, the proposal also says it “answers a decades-old outcry of Paraná inhabitants, salvaging the region’s history and its socioeconomic, environmental and tourism relations”.

Environmentalists have criticized Coguetto Maria for backing the bill. And local media outlets have reported that his family potentially stands to gain from the Caminho do Colono: two of his sons are partners in construction companies that could pave the road. Coguetto Maria’s office did not respond to *Nature*’s queries about this, or about researchers’ concerns over the road. When the Chamber of Deputies approved fast-tracking the bill, he argued that the Brazil of today is “responsible”, and has the “competence and capacity to build an ecologically correct road”, pointing out that the road existed as a walking path before the park was even created.

Research interrupted

For many conservationists and researchers, the economic argument for opening the road doesn't hold water. The damage caused to the park's highly valued Atlantic Forest would far outweigh the potential economic gains for the surrounding towns[1], they say. Furthermore, the species protected by the park are irreplaceable, they add. Iguaçu is the only location in the world where the jaguar population is increasing instead of declining. If the road opens, says Pardo, pressure on the animals will skyrocket. "Easy access is the main enabler for poachers," she says.

Iguaçu Falls is located along the border of Argentina and Brazil, on the Iguaçu River.Credit: Thiago Trevisan/Alamy

Cars using the road will also cause air, soil, water and even sound pollution, says Victor Prasniewski, a conservation biologist at the Federal University of Mato Grosso in Brazil. Sound pollution, in particular, changes communication patterns among a number of species. "Birds that attract females by singing will be forced to sing louder or longer to get noticed," says Prasniewski, who published a paper last year[2] listing the potential negative impacts of the Caminho do Colono.

“These changes can affect the reproduction and even the evolution of some birds,” says Carlos Araújo, a bioacoustics ecologist at Argentina’s Subtropical Biology Institute. “The building of a road would be catastrophic to research in my field,” he says.

He works on a large-scale monitoring project looking for the purple-winged ground-dove (*Paraclaravis geoffroyi*), the last confirmed sighting of which was more than three decades ago. “It’s a rare animal, and we leave recorders spread over the forest to try and catch her singing. We often capture helicopter noise, which disturbs our work.” Cars and trucks on the road would create similar low-frequency noise, he says. “It will be a lot harder to find birds like this dove.”

Brazil’s lawmakers renew push to weaken environmental rules

For some, the argument that the road will enhance tourism in Paraná doesn’t make sense either. Reopening the road, says Carmel Croukamp Davies, chief executive of Parque das Aves, a private bird sanctuary and shelter near the park, could threaten Iguaçu’s UNESCO World Heritage title if it damages the park’s biodiversity and severs the Atlantic Forest. Visitors come because they want to experience nature, she adds: “Whoever doesn’t understand the impact of a proposal like this doesn’t understand an inch of tourism nor biodiversity.”

With Brazil's Congress having returned from holiday earlier this month, the bill could soon be put to a vote. And when it is, environmentalists worry it will be passed, given how many representatives in the Chamber of Deputies currently align with Bolsonaro. Then it would face the Senate, and finally, Bolsonaro, who is ultimately expected to approve it.

Nature **596**, 473-474 (2021)

doi: https://doi.org/10.1038/d41586-021-02199-x

References

1. 1.

   Ortiz, R. A. *Ambientalia* **1**, 141–160 (2009).

2. 2.

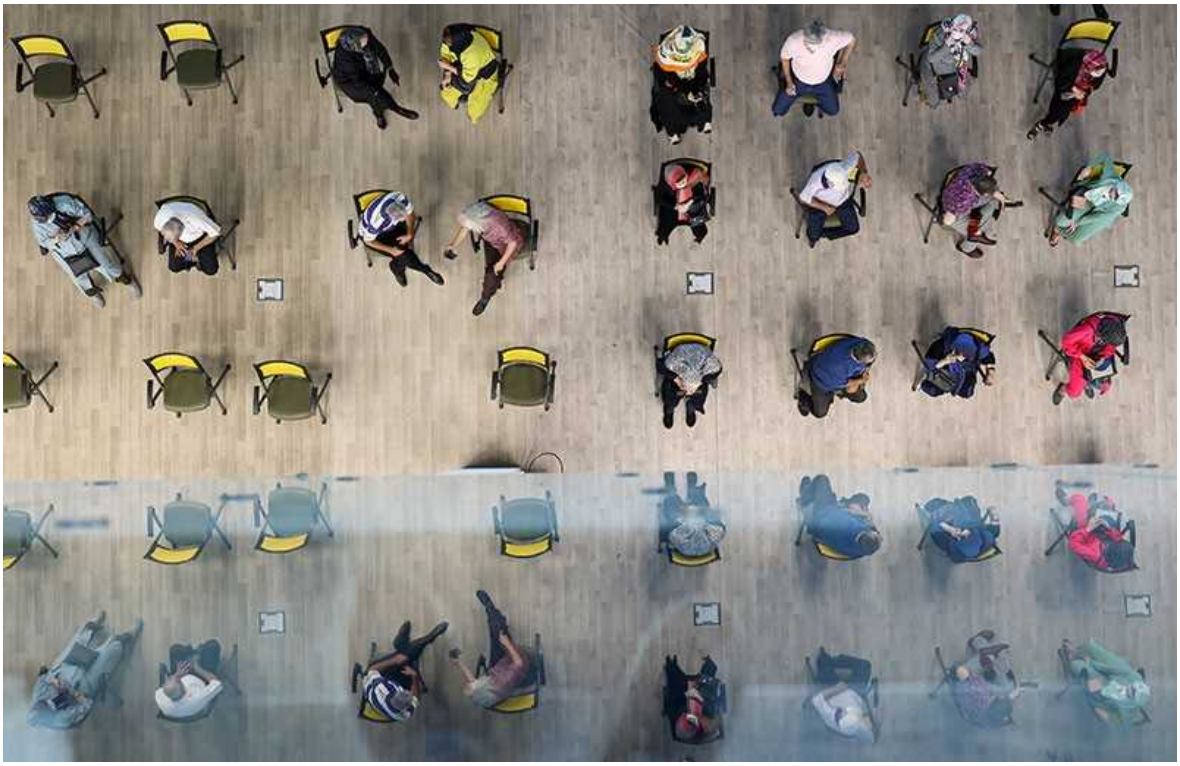
   Prasniewski, V. M. *et al. Ambio* **49**, 2061–2067 (2020).

- NEWS Q&A
- 17 August 2021

Iran hopes to defeat COVID with home-grown crop of vaccines

Nature talks to vaccine developer Kayhan Azadmanesh about efforts in Iran to develop ten or more COVID jabs, two of which have been approved for use.

- Smriti Mallapaty



Iranians wait to be inoculated at a mass vaccination centre in Tehran.Credit: Majid Asgaripour/WANA via Reuters

Iran was among the first countries to be hit with an outbreak of COVID-19 in early 2020. It is currently battling its fifth wave, probably driven by the Delta variant. Official figures suggest that more than 4.3 million people have been infected and 97,000 have died since the pandemic began, but the true toll is potentially much higher.

Scientists say Iran is one of few Middle Eastern nations with the capacity to develop vaccines. It has been doing so in earnest: around ten are under development and one is already bolstering its vaccination drive, but little is known about these vaccines outside Iran.

Nature speaks to Kayhan Azadmanesh, a medical doctor and biotechnologist who is head of the virology research division at the Pasteur Institute of Iran in Tehran, about the nation's vaccine landscape. Azadmanesh also advises the Iranian government and is developing two viral-vector vaccines through his spin-off company Humimmune Biotech.

How badly has the pandemic affected Iran?

Since January 2020, we've had five separates waves. We're currently experiencing the highest number of new cases reported so far, with around 40,000 a day, and the most common variant we detect is Delta. But many more cases are likely going unreported. The outbreak is putting pressure on hospitals and the situation is not looking good.

Which COVID-19 vaccines are available in Iran?

So far, 18 million or so doses have been administered: some 12 million were China's Sinopharm vaccine; 4 million were the Oxford–AstraZeneca vaccine; and one million were COVIran Barekat, developed by the Iranian state-owned Shifa Pharmed Industrial Group in Tehran. The remainder include doses of Russia's Sputnik V and India's Covaxin. More than half a million doses are being administered a day, and some 17% of Iran's population of 85 million have received their first dose of a COVID-19 vaccine.

Could you tell us about COVIran Barekat?

It is an inactivated vaccine and is still undergoing phase III trials, but it received emergency-use authorization in June. It was approved on the basis of the levels of antibodies it induces, including those that can ‘neutralize’ SARS-CoV-2, or block it from entering cells. In early trials, the researchers found that more than 93% of vaccinated people produced neutralizing antibodies. We don’t know how long this protection will last, but I assume that it will be similar to that provided by other inactivated vaccines — such as CoronaVac, produced by the Chinese firm Sinovac Life Sciences — for which antibody levels have been shown to drop after six months[1], suggesting that boosters are likely to be required.

Kayhan Azadmanesh holding rapid-antibody tests that show a negative result before, and a positive result after, he received a COVID-19 vaccination.Credit: Kayhan Azadmanesh

What other vaccines are being developed in Iran?

Pasteurcovac is a recombinant-protein vaccine developed in a collaboration between Cuba's Finlay Institute of Vaccines in Havana and the Pasteur Institute of Iran. The vaccine is known as Soberana 02 in Cuba. It also received emergency-use approval in Iran in June, despite still being in phase III trials. There are several other inactivated vaccines and recombinant-protein vaccines in clinical trials, and there is at least one mRNA vaccine, two adenovirus-vector vaccines and one measles-virus-vector vaccine in earlier stages of development. Vaccines developed outside Iran are also currently in clinical trials and being produced locally.

Tell me about the vaccines you are designing?

My company, Humimmune Biotech, has been working on two vaccine candidates. One uses the measles virus as a backbone to introduce a gene that encodes either the SARS-CoV-2 spike protein, which the virus uses to enter cells, or the nucleocapsid protein that it requires to replicate. That vaccine is being produced by the Iranian firm BioSun Pharmed in Tehran.

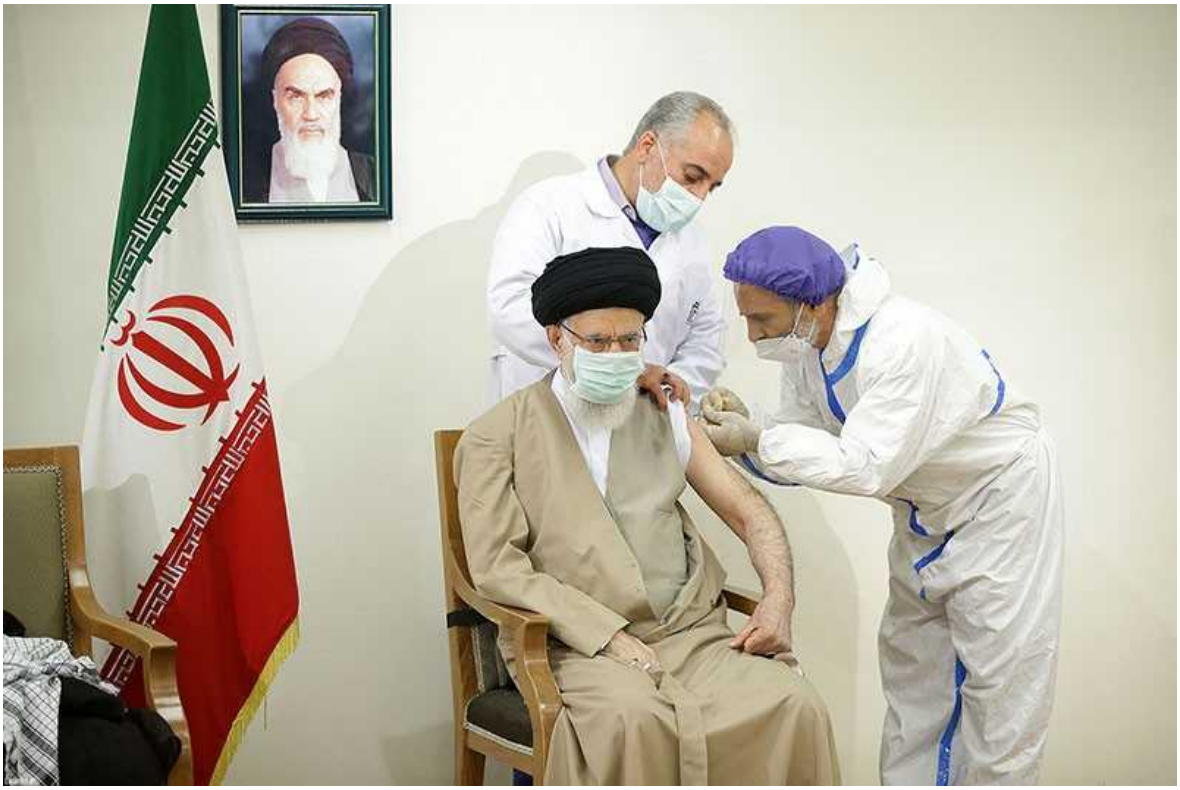
The other vaccine, which might be more promising, uses an adenovirus 5 backbone to deliver part of the sequence for the spike protein — a similar backbone to that used in the second dose of Sputnik V. We hope to start clinical trials early next year. Most of the COVID-19 vaccines used in Iran so far have been inactivated vaccines, which I expect will mean people will need booster shots next year. Our vaccine could be used as a booster, and a mix-and-match approach might even offer better protection. The technology can also be easily modified against new variants — we have already begun developing a version for Delta.

Why are Iranian scientists creating so many vaccines?

We have a long history of vaccine production in Iran. The Pasteur Institute of Iran was established in 1920, and has produced vaccines against

tuberculosis and rabies. Vaccines have also been developed in Iran against measles, mumps and human papilloma virus.

We can’t rely on help from the international community with the pandemic. We are living under sanctions imposed by the United States; in our opinion, these are unjustified. The United States says that sanctions don’t affect humanitarian activities, but when your ability to transfer money is restricted, it is difficult to buy drugs and medicines. And we have the technology to produce vaccines, so why not use it? To ensure the safety of Iranians, it makes sense to develop a variety of vaccines using different research and development strategies, as China has done.



Iran’s Supreme Leader Ayatollah Ali Khamenei receives a dose of the locally made COVIran Barekat vaccine in June.Credit: Iranian Supreme Leader's Office/ZUMA/Shutterstock

Why are Iranian researchers reluctant to publicize their work internationally?

This could be another side effect of the sanctions. Researchers in Iran might not want to draw too much attention to their work in case they put potential partnerships in jeopardy before they have achieved a final product, or they run the risk of losing access to raw materials and technologies they need for vaccines.

Researchers are also extremely busy, helping in the effort to fight the pandemic in Iran. They might not have time to publish results in international journals. But some have started to share results. In June, the researchers developing COVIran Barekat published a preprint of their preclinical results[2], and they will share clinical results very soon. We also plan to share the results of our adenovirus-vector vaccine soon.

What have been the biggest challenges in developing COVID-19 vaccines?

The sanctions have caused a lot of difficulty, because they make it hard for us to buy materials and equipment. For example, chromatography resins we need to purify vaccines are mostly produced by multinational companies that are major suppliers to the United States, so they might be afraid of selling to us. The United States says that we can apply for exemptions, but, in our experience, that hasn't worked. But somehow, we find a way. We modify our methods, find other providers, or look for local solutions. We search for the best we can get, but sometimes quality and efficiency are affected.

Also, one of the biggest challenges globally is scale. Prior to the pandemic, Iran primarily had to produce vaccines for children, with a production requirement for each vaccine of around three million doses a year. Now we need about 170 million doses to fully vaccinate the whole population.

What does the future hold for vaccine development in Iran?

The initial target for COVIran Barekat was to produce up to 30 million doses a month by September, which would have been enough to vaccinate the adult population. But they have not been able to achieve that, so we have

had to import millions of doses of other vaccines. As many people have said, this will not be the last coronavirus pandemic that we face. I expect the vaccine production capacity will be used for years to come to develop new vaccines and drugs, for both coronaviruses and other diseases.

Nature **596**, 475 (2021)

doi: https://doi.org/10.1038/d41586-021-02216-z

This interview has been edited for length and clarity.

References

1. 1.

   Li, M. *et al.* Preprint at medRxiv https://doi.org/10.1101/2021.08.03.21261544 (2021).

2. 2.

   Abdoli, A. *et al.* Preprint at bioRxiv https://doi.org/10.1101/2021.06.10.447951 (2021).

- NEWS FEATURE
- 25 August 2021

Can artificially altered clouds save the Great Barrier Reef?

Australian scientists are rushing to develop new technologies — such as ways to block sunlight — to help preserve corals in the face of climate change.

- Jeff Tollefson


A boat using the sea-spraying cloud brightening system over the Great Barrier Reef in Australia during a 2021 trial.

During a field trial, a turbine generates plumes of seawater droplets that rise into the sky. Credit: Brendan Kelaher/SCU

In place of its normal load of cars and vans, the repurposed ferry boat sported a mobile science laboratory and a large fan on its deck as it left Townsville, Australia, in March. Researchers dropped anchor in a coral lagoon some 100 kilometres offshore and then fired up the cone-shaped turbine, which blew a mist of seawater off the back of the boat. What happened next came as a welcome surprise: after briefly drifting along the ocean surface, the plume ascended into the sky.

Looking a bit like a jet engine, this mist machine is at the centre of an experiment that, if successful, could help to determine the future of the Great Barrier Reef. Three-hundred and twenty nozzles spewed a cloud of nano-sized droplets engineered to brighten clouds and block sunlight — providing a bit of cooling shade for the coral colonies below. Scientists used sensors aboard the ferry, drones and a second boat to monitor the plume as it migrated skyward.

The experiment wasn't big enough to significantly alter the clouds. But preliminary results from the field tests — which were shared exclusively with *Nature* — suggest that the technology might perform even better than computer models suggested it would, says Daniel Harrison, an oceanographer and engineer at Southern Cross University in Coffs Harbour, Australia, who is heading up the research. "We are now very confident that we can get the particles up into the clouds," Harrison says. "But we still need to figure out how the clouds will respond."

Harrison's project is the world's first field trial of marine cloud brightening, one of several controversial geoengineering technologies that scientists have studied in the laboratory for decades. The research has been driven by fear that humans might one day be forced to deliberately manipulate the Earth's climate and weather systems to blunt the most severe impacts of global warming.

For many Australians, that day arrived in 2017, when a marine heat wave spurred massive coral bleaching and death across much of the 2,300-kilometre Great Barrier Reef. That crisis hit just a year after another bleaching event along the reef, which supports more than 600 species of coral and an estimated 64,000 jobs in industries such as tourism and fishing. Research suggests that the reef lost more than half of its coral between 1995 and 2017, as a result of warming waters, tropical storms and predatory starfish (A. Dietzel *et al*. *Proc. R. Soc. B*. **287**, 20201432; 2020).

These corals could survive climate change — and help save the world's reefs

The project has raised concerns among some scientists abroad, in part because the Australian group has published little about its work. Environmentalists outside Australia objected to the project last year after news of the first trial broke, and there could be similar criticism when details of the 2021 trial emerge.

Harrison stresses that the cloud-brightening project is about local adaptation to climate change, not global geoengineering, because its application would be limited in both space and time. It's also just one part of a larger Aus$300 million (US$220 million) Reef Restoration and Adaptation Program (RRAP) launched last year by Australia to investigate and develop techniques and technologies to save the country's reefs. Many of the proposals, from cloud brightening to breeding heat-tolerant corals, would represent unprecedented human interventions in the natural reef system.

Ecological modelling suggests that a large-scale intervention involving multiple strategies — including a fleet of mist machines — could prolong the life of the reef while governments work to eliminate greenhouse-gas emissions. The goal now is to work out what's achievable in the real world, says Cedric Robillot, executive director of the RRAP.

"You need to consider every angle, from the fundamental science to the very pointy end of engineering, if you want to succeed," Robillot says. "It's not enough to just prove you could do it. You need to explain how you would do it."

Into the clouds

Harrison conducted his first field test in March 2020: a three-day proof-of-concept expedition on a small car ferry with four scientists, one representative from a local Indigenous group, and two shipping containers for equipment and sleeping quarters. The team had a minimal Aus$400,000 budget and limited scientific instrumentation to monitor the mist, but it was enough to document that the plume flowing out of their mist machine rode a draught of warm air high into the sky.

It was the first time they had witnessed this phenomenon. Their models had suggested that evaporation of the brine droplets would cool the plume, which would then float across the surface of the ocean, only slowly mixing upwards into the low-lying marine clouds. The models also indicated a risk that the tiny droplets might merge and drop out of the air. Instead, brine droplets floated along the surface of the ocean for half a kilometre without coalescing, gradually losing water and weight to evaporation along the way. And then they shot upwards.

A marine heat wave in 2017 caused coral bleaching along much of Australia's Great Barrier Reef.Credit: Juergen Freund/Nature Picture Library

"We didn't expect that at all," Harrison says, "but it turned out we were doing this experiment in the middle of a rising air mass."

The scientists feared it was a fluke. Although years of research and development have gone into the nozzles, initially led by a separate American team, this was the first time anybody had ever deployed them in the field with fresh seawater. The team also didn't know what to expect from clouds

and aerosols in that region, because research on the reef has focused almost exclusively on what happens below the water, not the conditions above.

For Harrison, the 2020 experiment was more than enough to justify moving forward with another, larger trial in March 2021. But it did raise eyebrows among some scientists and observers abroad, where geoengineering research has met strong opposition and struggled to attract funding.

IPCC climate report: Earth is warmer than it's been in 125,000 years

Most of the concern has centred on a form of solar geoengineering that involves injecting reflective material into the stratosphere to block sunlight at a global scale. But cloud brightening has also been studied as a potential global intervention, and it has attracted criticism from some environmental groups who argue that it carries inevitable ecological risks and detracts from efforts to limit greenhouse gases.

Some scientists, as well as environmental advocates who follow geoengineering research, told *Nature* that they were surprised to see the experiment move forward without more scrutiny — or without published research to justify such an investment.

Critics also worry that Australia is setting the wrong kind of precedent by rebranding a solar-geoengineering experiment that could have regional

impacts as a local adaptation project. “One could say that there should have been some level of consultation with the outside world,” says Janos Pasztor, who heads the Carnegie Climate Governance Initiative, an advocacy group in New York City that has been pushing for a global debate over geoengineering governance in the United Nations.

Harrison says scientists in the programme have consulted with regulatory authorities, as well as with the general public and Indigenous groups that have historic claims on the reef. He also readily acknowledges trying to avoid getting embroiled in a debate about solar geoengineering, arguing that the project would be more akin to cloud-seeding operations that are designed to promote rain and that are not considered to be geoengineering. One of the next modelling efforts, however, will be to explore any potential regional and global implications, he says.

A plume of seawater droplets rises up into the sky during a field trial in March 2021.Credit: Brendan Kelaher/SCU

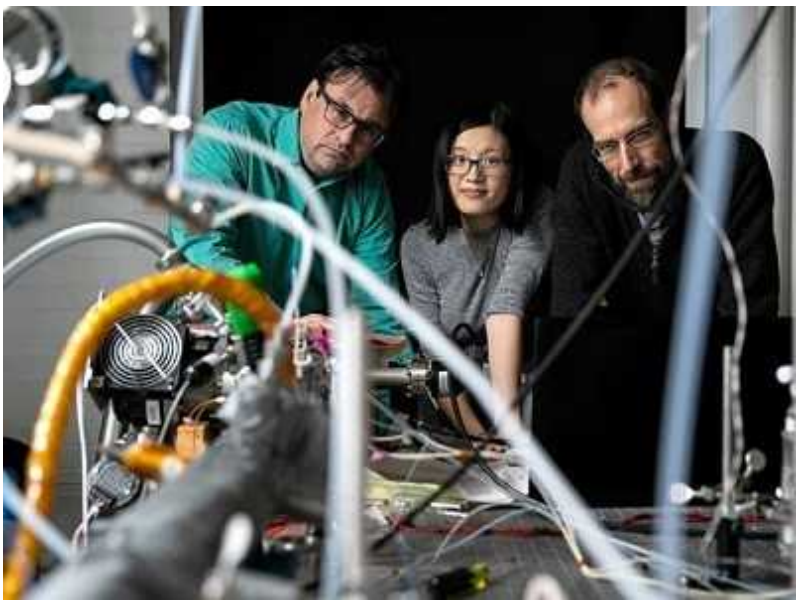
Others question the Australian government’s motivations in funding such work. Under the conservative prime minister Scott Morrison, the government has yet to strengthen its climate pledge under the 2015 Paris agreement, as many nations have done in the past year. Morrison has personally ruled out committing to net-zero emissions. Pushing for a

technological fix to global warming without moving to aggressively curb greenhouse gases is “sheer lunacy”, says Peter Frumhoff, chief climate scientist for the Union of Concerned Scientists, an advocacy group in Cambridge, Massachusetts.

Some researchers, however, are pleased to see marine cloud brightening move from theory to the field, including US scientists working on a similar project that has been struggling to get into the field for nearly a decade. “This is an early example of how climate disruption can drive interest in these things,” says Sarah Doherty, an atmospheric physicist who manages the Marine Cloud Brightening Project at the University of Washington in Seattle. Members of the team provided the initial nozzle design and have been tracking the Australian group’s progress.

Coral crisis

The first time that scientists observed a major bleaching event along the Great Barrier Reef was in 1998, and the second event followed four years later. In both cases, corals expelled the algae that live within them and that provide colour and energy through photosynthesis. Most of the corals eventually recovered. But in 2016 and 2017, many corals bleached and then died across two-thirds of the reef.



First sun-dimming experiment will test a way to cool Earth

“It was absolutely horrifying,” says David Wachenfeld, chief scientist at the Great Barrier Reef Marine Park Authority, which manages the reef. The clear message from those events was that the traditional approach to managing corals and coral reefs would not be enough, he adds. “Our hand was forced.”

In 2018, the Australian government allocated Aus$6 million to a consortium of universities and government research institutes for a feasibility study focused on potentially radical strategies that could be applied across the reef. Researchers reviewed some 160 ideas, including putting live corals on ice for long-term preservation and synthetically engineeering new varieties that can tolerate the warmer waters. Many approaches proved too costly and energy intensive, but 43 interventions were singled out for further study. Marine cloud brightening drew support in part because it theoretically provides direct relief precisely when and where corals need it most.

Much of the emphasis of the programme is on helping corals to adapt and repopulate the reef, including efforts to improve coral aquaculture operations so that they can produce millions of corals per year rather than thousands. For Madeleine van Oppen, a coral geneticist at the Australian Institute of Marine Science near Townsville, the RRAP programme helps to integrate her team’s work on assisting coral evolution to make them more heat tolerant.

Thanks to the RRAP, she says, data from those projects are now being fed directly into models that enable researchers to assess the potential benefits — as well as the risks — of releasing new strains of coral and microalga into the wild. The programme is also raising ecological questions, such as whether the introduction of new coral species can propagate disease, or whether a new variety of more heat-tolerant corals might displace corals struggling to survive.

Researchers are testing specialized nozzles that create jets of seawater mist.Credit: Alejandro Tagliafico/SCU

“It sort of speeds up the whole path from research to implementation in the field,” says van Oppen.

In the long run, the models indicate that without interventions, the extent of coral on the reef could shrink by well over 60% by 2070 compared with 2020 levels (S. A. Condie *et al. R. Soc. Open Sci.* **8**, 201296; 2021). But simulations suggest that Australia could cut those losses in half with a three-pronged approach focused on propagating heat-tolerant corals, controlling outbreaks of the predatory crown-of-thorns starfish and brightening clouds to take the edge off of heat waves. Crucially, the latest modelling also suggests that without the cooling provided by Harrison’s cloud brightening project, the other interventions might not amount to much.

Testing the wind

When Harrison’s group returned to the field this year, they had more-powerful drones as well as other aerosol sensors on a second boat. As in the previous year’s experiment, each time they created a plume, it rose into the sky after the droplets lost around 90% of their water to evaporation. The

likely explanation, Harrison says, is that the reef is creating its own weather as warm water along the shallow corals heats the air above.

Many more droplets are making it into the clouds than the scientists had initially calculated, but Harrison says their mist machine might need to be scaled up by a factor of 10 — from 320 to around 3,000 nozzles — to produce enough particles to brighten nearby clouds by around 30%. His team's modelling suggests that this could in turn reduce the incoming solar radiation on the reef locally by around 6.5%. Even then, the operation would require 800–1,000 stations to cover the length of the Great Barrier Reef.

Fevers are plaguing the oceans — and climate change is making them worse

But it's unclear whether that spray of salty droplets will have the desired effect, says Lynn Russell, an atmospheric chemist at the Scripps Institution of Oceanography in La Jolla, California, who has studied cloud brightening. Russell has not seen the latest — and as-yet unpublished — results, but questions whether there are enough of the low layered clouds considered suitable for cloud brightening.

Harrison acknowledges such concerns and says that his team sees more of these clouds on the southern part of the reef. His team's modelling suggests the technology will also work on the clouds that are common across the rest of the reef in summer. Even then, he says, it remains unclear how much

coverage a full-scale cloud-brightening operation could provide across the entirety of the reef. More measurements, and detailed modelling, are needed to provide answers.

For now, Harrison has secured funding for another two years, and he needs to demonstrate progress. The RRAP is testing all 43 approaches and will redistribute resources to projects that show potential, Robillot says. But he stresses that no amount of science and engineering will preserve the reef in its current form. “Even if we do all of this, the system that you’ll end up with is not going to be the Great Barrier Reef that we know today,” Robillot says. “You might, however, retain a very functional ecosystem.”

That’s enough to keep Harrison going, and his team is already preparing for a trip into the field in 2022. The scientists plan to run the mist machine at higher pressure, which should produce a sixfold increase in the number of particles, and they will use new instrumentation to determine how particles alter clouds. They are also investigating an entirely different nozzle technology that could reduce the number of nozzles needed by a factor of 1,000.

Harrison is more confident today than he was even a year ago that cloud brightening might work over the reef, but he is also realistic about the future if governments fail to limit carbon emissions. “There are only so many clouds available, and there is only so much you can brighten them,” he says. “Eventually, climate change just overwhelms things.”

Nature **596**, 476-478 (2021)

doi: https://doi.org/10.1038/d41586-021-02290-3

- NEWS FEATURE
- 24 August 2021

COVID vaccines and blood clots: what researchers know so far

Scientists are trying to understand why a small number of people develop a mysterious clotting disorder after receiving a COVID jab.

- Heidi Ledford

A health worker administers the Oxford–AstraZeneca COVID-19 vaccine in Mexico City. Some countries have restricted its use.Credit: Leonardo Montecillo/Agencia Press South/Getty

It was when the second person with unusual clots came in that Phillip Nicolson knew something was wrong. Blood clots are uncommon in young people, and it's even rarer to see a combination of blood clots and alarmingly low levels of platelets — cell fragments that help to form clots.

Yet in the space of one week in March, two young people with this pairing of symptoms had arrived at the Queen Elizabeth Hospital in Birmingham, UK, where Nicolson works as a haematology specialist. And both had recently been given the Oxford–AstraZeneca COVID-19 vaccine.

Nicolson had been on call at the hospital all weekend, and had been looking forward to a rest on Monday. Instead, he found himself rushing around to get consent to collect samples to study in the laboratory. By the time he arrived at the second patient's bedside, a third had been admitted.

That week, Nicolson was among the first to witness what researchers now call vaccine-induced immune thrombotic thrombocytopenia (VITT), a life-threatening and mysterious condition that affects a very small number of people who have received the Oxford–AstraZeneca or Johnson & Johnson (J&J) COVID-19 vaccines. It is now estimated that VITT occurred in about 1 in 50,000 people aged under 50 who received the Oxford–AstraZeneca vaccine[1]. This and similar observations in other countries have led some officials to delay and then scale back the deployment of these vaccines.

Despite fervent work by researchers such as Nicolson, the mechanism that links the vaccines and VITT is still uncertain. Establishing a mechanism could reveal ways to prevent and treat the condition, and improve the design of future vaccines. Over the past few months, researchers have gathered clues and developed a host of hypotheses.

Working through these possibilities is a daunting task. "You can have your hypothesis, but how do you find which is the one that caused an event in maybe 1 in 100,000 people?" asks John Kelton, a haematologist at McMaster University in Hamilton, Canada. "It's really, really hard."

Clotting concepts

The unusual constellation of symptoms was immediately familiar to some haematologists, particularly those with experience of treating people with a rare reaction to the anti-clotting drug heparin. That syndrome, called HIT, is also characterized by low platelet counts and sometimes the presence of clots.

HIT is caused by heparin, a negatively charged molecule, binding to a positively charged protein called platelet factor 4 (PF4) that is produced by platelets to promote clotting. In some people, the immune system views this complex as foreign, and develops antibodies against it.

COVID vaccines and safety: what the research says

These antibodies can also bind to and activate platelets, priming them to clump together and trigger clotting. The clots can clog up important blood vessels, and the condition can be fatal, although some treatments improve the chances of survival.

Only a handful of labs around the world study HIT, and those that do scrambled to get samples from the few people who had been diagnosed with VITT. When researchers analysed the samples, it was clear that vaccine recipients who had this mysterious clotting reaction were also producing antibodies against their own PF4[2–4]. But it was anyone's guess as to what had triggered these antibodies. Kelton, who has been studying HIT for decades, had to wait to get precious specimens from people with VITT, and

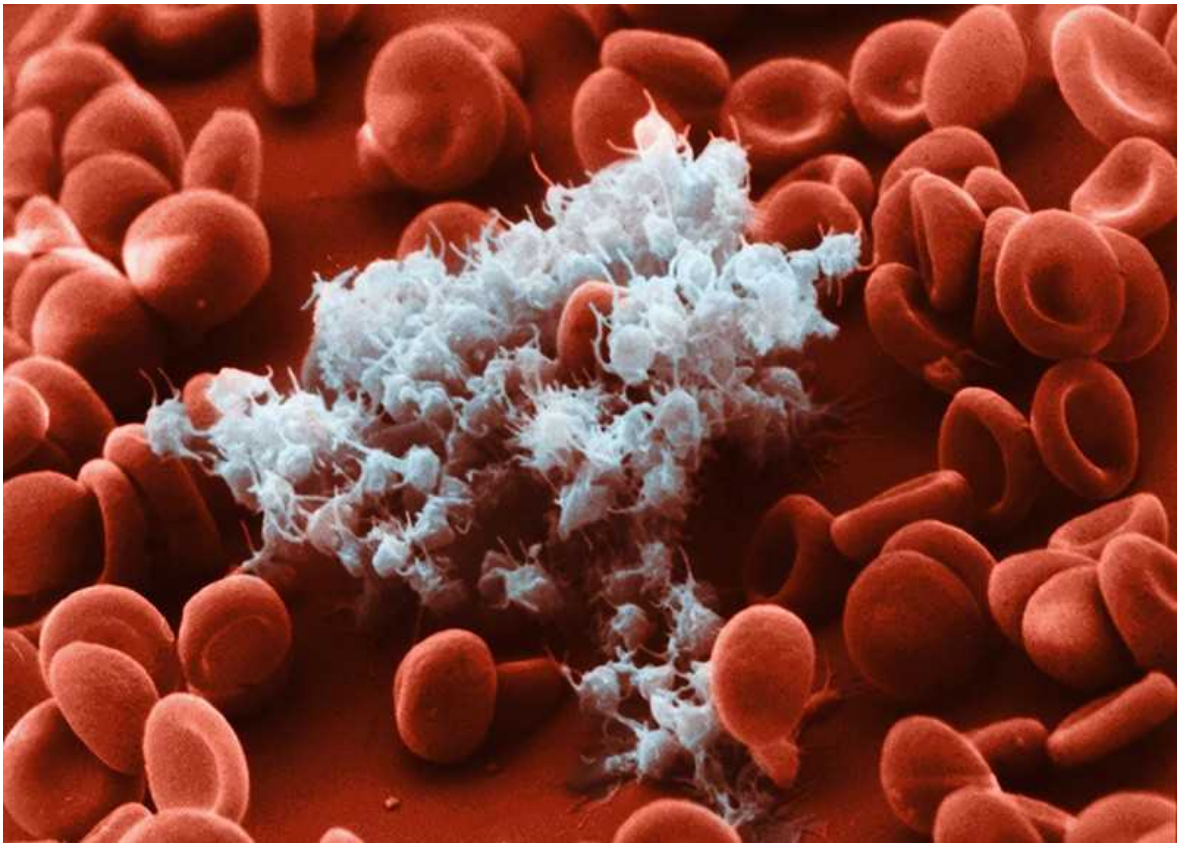
then his team had to wade through samples of varying quality. Some were contaminated by treatments the people with VITT had received. “Many, many samples were not what I would call pristine,” he says. “These people are as sick as can be, and the physicians throw the book at them. They have every kind of chemical in them.” And about two-thirds of the samples his team received lacked the PF4 antibodies altogether, suggesting that the patients did not have VITT, but instead had developed a clotting disorder that was probably unrelated to their vaccination, Kelton says.

Eventually, his team was able to get five samples taken from people before treatment for VITT. When researchers characterized antibodies in the samples, they found that some were binding to PF4 at the same site as the one used by heparin, and that they were also capable of activating platelets[5]. The results suggested that the mechanism behind the vaccine-linked syndrome was similar to that of HIT — but the trigger seemed to be the vaccine rather than heparin.

Suspect ingredients

Something in the vaccine or the body’s response to it must be binding to PF4 — but what? VITT has been linked to two COVID-19 vaccines, both of which use disabled adenoviruses as a ‘vector’ to shuttle a gene encoding a coronavirus protein, called spike, into human cells. Once there, the gene is expressed and the protein is made. The immune system detects spike and generates antibodies against it that are crucial for protection against coronavirus infection.

Some researchers have proposed that impurities in the vaccines left over from the manufacturing process — such as snippets of DNA floating around in the solution, or proteins in the broth used to grow the virus — are interacting with PF4 to generate the clumps that are then targeted by antibodies[6].



Platelets (white) are fragments of cells that encourage clots to form.Credit: Lennart Nillson, Boehringer Iingelheim International

Others think the culprit could be the adenovirus itself. Previous work has shown that adenoviruses can bind to platelets and trigger their depletion in mice[7]. It's conceivable that those mice might also have developed clots if they had been followed for longer, says Maha Othman, who studies blood clotting at Queen's University in Kingston, Canada, and was lead author of the study.

Before the COVID-19 pandemic, adenovirus-based vaccines were being developed against infections such as HIV and Ebola, but had not yet been used in large populations. There have been no reports that these vaccines produced a VITT-like condition; however, they were not tested in nearly as many people as have received the Oxford–AstraZeneca COVID-19 vaccine.

Haematologist Mitesh Borad at the Mayo Clinic in Phoenix, Arizona, and his colleagues have analysed the structure of the chimpanzee adenovirus

used in the Oxford–AstraZeneca vaccine and determined that it has a strong negative charge. Molecular simulations suggest that this charge, combined with aspects of the virus's shape, could allow it to bind to the positively charged PF4 protein[8]. If so, it could then set off a cascade much like the rare reaction to heparin, says Borad, although it remains to be seen whether this happens.

How could a COVID vaccine cause blood clots? Scientists race to investigate

Even if the adenovirus is to blame, Borad says he would not advocate that vaccine developers stop using adenoviruses in vaccines. Some adenoviruses could be engineered to reduce their negative charge, he says, and some are less negatively charged than others; the Ad26 adenovirus used in the J&J COVID-19 vaccine does not have as much of a charge as the chimpanzee virus, which might explain why VITT seems to be less common in recipients of the J&J vaccine. And so far, no link to VITT has been reported for the Sputnik V COVID-19 vaccine, which uses both Ad26 and another adenovirus called Ad5 that has still less negative charge, he adds.

Then there's the spike protein itself. One team of researchers wondered whether the antibodies that bind to PF4 in people with VITT are an unintended by-product of the body's immune response to spike. But they

found that the PF4 antibodies can't bind to it, suggesting that they are not part of the immune response to the viral protein[9].

But cancer researcher Rolf Marschalek at Goethe University Frankfurt in Germany and his colleagues have shown that the snippets of RNA that encode spike can be cut apart and stitched back together in different ways in human cells; some of these forms, called splice variants, can generate spike proteins that get into the blood and then bind to the surface of cells that line blood vessels[10]. There, they cause an inflammatory response that is also seen in some SARS-CoV-2 infections, which in severely affected people can lead to the formation of clots.

And the lower rate of clots in J&J's vaccine compared with Oxford–AstraZeneca's could be because the version of spike generated by the J&J vaccine was engineered to remove the sites that allow the RNA to be processed into splice variants, says Marschalek.

Marschalek thinks that if this idea is borne out, then the Oxford–AstraZeneca vaccine and other adenovirus-based vaccines could be rendered safer if their versions of spike were similarly engineered.

There are reports that the teams behind the Oxford–AstraZeneca and J&J vaccines are working to develop safer adenoviral vectors, and Marschalek says he would be surprised if companies abandoned adenoviral vectors altogether. Others agree. "I think they are very popular and will remain popular," says Othman, citing the ease with which the vaccines can be produced and manipulated, and the wealth of data suggesting that, for most people, the vaccines are safe. Instead of abandoning them, she says, "we should study more about the immune responses to them."

[Why is it so hard to investigate the rare side effects of COVID vaccines?]

One possible factor affecting the safety of adenoviral vaccines is how they are administered. The COVID-19 vaccines are given as injections into muscle, but if the needle happens to puncture a vein, the vaccine could enter the bloodstream directly. Leo Nicolai, a cardiologist at Ludwig Maximilian University of Munich, Germany, and his colleagues found in a mouse study that platelets clump together with adenovirus and become activated when the Oxford–AstraZeneca vaccine is injected into blood vessels, but not when it is injected into muscle[11].

It's possible, says Nicolai, that on rare occasions, a vaccine is inadvertently injected into a vein — as was done in the earlier mouse studies that found that adenovirus could bind to platelets. If so, many cases of VITT might be avoided by asking vaccinators to first draw a small amount of fluid from the injection site with the syringe to check for blood before they actually push the plunger to administer the vaccine. This is already standard practice in some countries, and Denmark has added it to its official guidelines for COVID-19 vaccine administration.

Improving treatments

Better treatments are still needed for VITT, which according to a UK study[1] killed 49 of the 220 people who were diagnosed with the condition between

March and June 2021. Currently, doctors treat VITT by giving anti-clotting treatments other than heparin, and administering high doses of naturally occurring antibodies from blood-plasma donors. The antibodies compete with the anti-PF4 antibodies for binding sites on platelets, and reduce the latter's ability to promote blood coagulation. "The hope is to try to confuse the body and hide the dangerous antibodies within a huge fog of normal antibodies," says Kelton. "That's a very, very blunt tool."

In Birmingham, Nicolson has been working to develop more-specific approaches. He has tested blood serum from people with VITT to see whether he can repurpose drugs developed for other conditions to treat it. In particular, he is focusing on treatments that interfere with a protein on platelets, to see whether any drugs can prevent platelet activation and the cascade of events that leads to clots in VITT.

But even if he were ready to launch a clinical trial of these therapies, there are few people in whom to test them. Since he saw the first cases in March, the United Kingdom has changed its vaccination policy, and now recommends the Oxford–AstraZeneca vaccine only for people over 40. VITT is more frequent in younger vaccine recipients, possibly because of their more-robust immune responses.

It is unclear whether other countries will have the same luxury of restricting Oxford–AstraZeneca vaccines to older people, given that it is relatively cheap and widely available compared with the mRNA vaccines, for example. Until now, VITT has primarily been reported in Europe and the United States, but researchers don't yet know whether this reflects regional differences in susceptibility to VITT, or differences in reporting systems that gather data on potential vaccine side effects. In Thailand, for instance, researchers reported in July that there had been no cases of VITT after 1.7 million doses of the Oxford–AstraZeneca vaccine were given[12].

Nicolson says the number of people referred to his hospital with VITT has declined drastically: "We're not seeing it any more, it's almost stopped happening."

Nature **596**, 479-481 (2021)

doi: https://doi.org/10.1038/d41586-021-02291-2

References

1. 1.

   Pavord, S. *et al. N. Engl. J. Med*. https://doi.org/10.1056/NEJMoa2109908 (2021).

2. 2.

   Schultz, N. H. *et al. N. Engl. J. Med* **384**, 2124–2130 (2021).

3. 3.

   Greinacher, A. *et al. N. Engl. J. Med.* **384**, 2092–2101 (2021).

4. 4.

   Scully, M. *et al. N. Engl. J. Med.* **384**, 2202–2211 (2021).

5. 5.

   Huynh, A., Kelton, J. G., Arnold, D. M., Daka, M. & Nazy, I. *Nature* https://doi.org/10.1038/s41586-021-03744-4 (2021).

6. 6.

   Greinacher, A. *et al.* Preprint at Research Square https://doi.org/10.21203/rs.3.rs-440461/v1 (2021).

7. 7.

   Othman, M., Labelle, A., Mazzetti, I., Elbatarny, H. S. & Lillicrap, D. *Blood* **109**, 2832–2839 (2007).

8. 8.

Baker, A. T. *et al.* Preprint at bioRxiv https://doi.org/10.1101/2021.05.19.444882 (2021).

9. 9.

Greinacher, A. *et al. Blood* https://doi.org/10.1182/blood.2021012938 (2021).

10. 10.

Kowarz, E. *et al.* Preprint at Research Square https://doi.org/10.21203/rs.3.rs-558954/v1 (2021).

11. 11.

Nicolai, L. *et al.* Preprint at bioRxiv https://doi.org/10.1101/2021.06.29.450356 (2021).

12. 12.

Noikongdee, P. *et al.* Preprint at medRxiv https://doi.org/10.1101/2021.07.15.21260622 (2021).

Opinion

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  Correspondence •
- **First authors: is co-equal genuinely equal?** [24 August 2021]
  Correspondence •
- **Could Europe become the first climate-neutral continent?** [24 August 2021]
  Correspondence •
- **Home laboratory: interactive science from the kitchen** [24 August 2021]
  Correspondence •

- COMMENT
- 25 August 2021

Origins of SARS-CoV-2: window is closing for key scientific studies

Authors of the March WHO report into how COVID-19 emerged warn that further delay makes crucial inquiry biologically difficult.

- Marion Koopmans [0],
- Peter Daszak [1],
- Vladimir G. Dedkov [2],
- Dominic E. Dwyer [3],
- Elmoubasher Farag [4],
- Thea K. Fischer [5],
- David T. S. Hayman [6],
- Fabian Leendertz [7],
- Ken Maeda [8],
- Hung Nguyen-Viet [9] &
- John Watson [10]

The World Health Organization assembled a team of staff and independent experts tasked with understanding the origins of SARS-CoV-2. Credit: Aly Song/Reuters/Alamy

Our group was convened by the World Health Organization (WHO) in October 2020. We have been the designated independent international members of a joint WHO–China team tasked with understanding the origins of SARS-CoV-2. Our report was published this March[1]. It was meant to be

the first step in a process that has stalled. Here we summarize the scientific process so far, and call for action to fast-track the follow-up scientific work required to identify how COVID-19 emerged, which we set out in this article.

The window of opportunity for conducting this crucial inquiry is closing fast: any delay will render some of the studies biologically impossible. Understanding the origins of a devastating pandemic is a global priority, grounded in science.

The mandate

We, all the members of the international expert team, each submitted detailed, confidential statements to the WHO on potential conflicts of interest, including funding, collaborative studies, public statements and other issues around the origins of COVID-19 that could be perceived as conflicts. After the WHO had reviewed these, team members were appointed in their individual capacity, not as representatives of their employers.

So far, our mission has been guided by terms of reference agreed between the WHO and China in 2020, before our involvement[1]. These terms tasked us with making a detailed reconstruction of the early phase of the pandemic, beginning in Wuhan, China, where the first known cases were reported. Our mandate was to conduct a collaborative study with leading scientists in China to review data they had generated on the basis of initial questions from the WHO. We refined the generic list of questions described in the mandate into a detailed workplan described in the mission report[1] (see also Annex A; go.nature.com/3k26jzx).

WHO report into COVID pandemic origins zeroes in on animal markets, not labs

The workplan specified eight items: specific retrospective studies detailing the profile of respiratory illness in the general community and hospitalized people in Wuhan and Hubei in the second half of 2019; a review of patient files for 76,000 cases in the same time period that had been notified by 233 Wuhan health centres; a review of death certificates and analysis of those data for possible clusters; and a detailed reconstruction of the investigation into the early outbreak, combining all data and findings from the various groups involved in human, animal and environmental studies (a One Health approach; see go.nature.com/3jy7ekh). The other four items were: extensive mapping and trace-back of the supply chain of products sold at the Huanan seafood market in Wuhan; testing of a wide range of livestock, wildlife, pets and zoo animals for evidence of infection with SARS-CoV-2; analysis of published and unpublished viral genomic data and linking them with metadata for reconstruction of initial clusters; and a review of relevant literature related to the origins mission.

The possibility of a laboratory origin for the virus's introduction into the local human population — what has come to be called the lab-leak hypothesis — was not part of the WHO's original terms of reference for the team.

The mission

This January, we undertook a 28-day mission to Wuhan to interview clinical, laboratory and public-health professionals and visit institutions involved in the early epidemic response and subsequent investigations. Our work was supported by a team of staff from the WHO China office and from WHO headquarters in Geneva, Switzerland; staff from the Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (OIE); and a WHO-appointed team leader[1]. The huge burden of preparatory work was shouldered by the team in China, including more than 1,000 health-care professionals who collected, analysed, presented and discussed data and study outcomes during our joint mission.

Scientific discussions between the international and Chinese teams during this mission were lively. Large amounts of information were exchanged on the basis of the work carried out. It took days of discussion to develop recommendations on essential further work and ongoing data sharing. We drafted a model of the potential ‘pathways of emergence’ to structure our thoughts. We listed current evidence for and against these pathways (see Fig. 1 of ref. 1).

We found the laboratory origin hypothesis too important to ignore, so brought it into the discussions with our Chinese counterparts. And we included it as one of the hypotheses for SARS-CoV-2 origin in our report.

Officials collect COVID-19 test samples in a fresh market in China's Shanxi province in January.Credit: Wei Liang/China News Service/Getty

We had limited time on the ground in Wuhan and a limited mandate. So we prioritized understanding the role of labs in the early days of the epidemic, the overall lab biosafety procedures and potential staff illness or absenteeism owing to respiratory disease in the late part of 2019. We spoke to the leadership and staff at the three Wuhan labs handling coronaviruses: the Wuhan Institute of Virology, the Chinese Center for Disease Control and Prevention (CDC) in Wuhan, and the Hubei provincial CDC. We reviewed published work from these labs to assess their scientific history of working with coronaviruses related to severe acute respiratory syndrome (SARS).

The Chinese team was and still is reluctant to share raw data (for instance, on the 174 cases identified in December 2019), citing concerns over patient confidentiality. Access to data on these cases was not specified in the mandate, although the WHO had demanded it during the investigation, and has done so since . The legal and possible other barriers could not be addressed in the short time frame of our visit. Also, by then, it was clear that

the 174 cases were not likely to be the earliest ones, so we considered them less urgent for understanding origins.

It was therefore agreed that a second phase of studies would address these concerns and review these data.

The report

In our joint report[1], members of both teams concluded unanimously that there was clear evidence of widespread SARS-CoV-2 circulation in Wuhan during December 2019. We reported evidence for earlier emergence but reached no resolution on when, where and how that occurred. We concluded that the Huanan seafood market had a significant role in the early part of the pandemic, and that there were credible links to wild-animal markets to follow up. We agreed that the earliest cases of COVID-19 had probably been missed, as is common for outbreaks of new diseases[2].

Divisive COVID ‘lab leak’ debate prompts dire warnings from researchers

Our joint report summarized the evidence base that was generated during this first phase of origin tracing. It concluded that there was no definitive proof for or against any of the four proposed pathways: direct zoonotic introduction (through a spillover from wild animals) and three indirect routes of introduction (see Fig. 1 of ref. 1). These three are: zoonotic infection from handling infected farmed animals; zoonotic introduction

through the consumption of contaminated food or food from infected animals; or introduction through escape from a laboratory working with animal viruses. The report noted that we considered direct introduction or indirect zoonotic introduction through an intermediate host the most plausible.

As laid out in our terms of reference, this initial study was not expected to provide definitive answers to the origin of SARS-CoV-2. Rather, phase 1 was always intended to form the foundation of a longer process of scientific investigation that could last for months or years. Therefore, the report put forward recommendations for phase 2 studies that would follow the evidence and trace back further along the most likely pathways. As a joint WHO–China study report, these recommendations were agreed on by members of both the international and the Chinese team. The report also stated that this assessment could be revised if new evidence became available.

The response

Before the report was released, formal statements to the WHO from some governments were circulated in February, with three contentions: that China had not shared data adequately; that we had paid insufficient attention to the lab-leak hypothesis; and that our scientific conclusions were influenced by China's political stance regarding transmission through the food chain.

Since its release, our report has received extensive coverage in the popular and scientific press and on social media. Much of this has focused on how we conducted the work, and has critiqued us, our methods and results. Five months on, criticisms of the WHO–China joint study continue to emerge.

When asked, our team has emphasized that much new information was shared by the Chinese team as a result of the agreed studies, and that even more was shared as part of the iterative process between the international and Chinese teams.

A woman pushes a cart at the closed wholesale seafood market in Wuhan, China, last January.Credit: Getty

Our critics have also suggested that the report dismisses the possibility of a lab leak. A laboratory origin hypothesis is presented in the pathway model in Figure 5 on page 119 of the report; we explicitly state in the report that it is possible. We held frank discussions with key scientists in the relevant Wuhan institutions — a line of inquiry that exceeded our original mandate. When we reviewed the responses to our questions on this issue, and all other available data, we found no evidence for leads to follow up; we reported this fact.

In our report, we state that if evidence supporting any of the hypotheses becomes known following publication, phase 2 studies should carefully examine this. For instance, we described that there was evidence of the presence of live animals in the market at the end of December 2019, but that the data presented to the team did not show definitive evidence of live mammals. This evidence came to light after publication[3] (as we discuss in more detail later in this article).

Another criticism was that the potential for introduction of SARS-CoV-2 through frozen food was included owing to pressure from China. The report addressed this hypothesis for three reasons: analysis showed that frozen food imported from all over the world was sold at the Wuhan market, including frozen wild-animal meat; foodborne viral-disease outbreaks are widely documented, including occasionally from frozen foods; and SARS-CoV-2 can remain infectious when frozen[4]. Therefore, the team felt it could not rule out introduction from undercooked meat from infected animals.

Some of the public discourse around the report probably originates from miscommunication and misunderstanding about the nature of the work. Although the published report correctly calls it a joint study to reflect what was laid out in the World Health Assembly resolution and terms of reference, it was publicly called an investigation by journalists, by representatives from some member states and, on occasion, by representatives of the WHO. This might have led to expectations that the report would provide watertight evidence based on formal audits of the institutes involved in the studies.

New data

There have been calls from scientists for further investigation of the lab-leak hypothesis[5]. And there has been a wave of media items that give equivalence to the weight of evidence for a lab leak and for emergence through an intermediate host — an equivalence that the currently available data do not support, in our view.

The COVID lab-leak hypothesis: what scientists do and don't know

The arguments and data for a zoonotic spillover event were summarized in a review published as a July preprint by a group of scientists who were not part of the international team[6]. That review includes new data released since the report, on SARS-CoV-2-related coronaviruses in bats in China's Yunnan province[7,8] and an inventory of live mammals for sale in Wuhan markets up until November 2019, some of which could have theoretically been able to harbour SARS-related coronaviruses[3]. This inventory, compiled by scientists from the United Kingdom, Canada and China, would have been welcomed by the team had it been available earlier; it needs to be taken up in the phase 2 studies.

In June, a preprint[9] was published analysing genomic data that had been deleted after March 2020 from the database of the US National Center for Biotechnology Information at the request of the scientists from China who generated the information (that team had published its findings based on the raw data in June 2020[10]). Our colleagues in China contacted the authors of the June 2020 paper, retrieved the data and added them to the SARS-CoV-2 genome phylogenetic data published in our report. The data were from people who had an onset of illness in January, so they did not contribute any new information to the origins question.

In the report, and since, we have publicly called for any data supporting the lab-leak hypothesis to be published and submitted to the WHO. None has, so far.

Six priorities

To keep up the momentum for phase 2 studies, our team has met weekly since the publication of the joint report. We have continued collaboration with our Chinese co-authors, including work on a list of corrections to the phase 1 report. Both the international team and the Chinese team have now put forward to the WHO priorities for phase 2 studies, developed from the recommendations in the joint report.

The international team listed the following priorities:

Further trace-back studies. On the basis of disease reporting, look for early COVID-19 cases in all regions inside and outside China that have the earliest evidence for SARS-CoV-2 circulation.

Antibody surveys. Use standardized methods in the regions that have the earliest evidence for SARS-CoV-2 circulation (inside and outside China) to identify any places where infections occurred that were not observed through disease reporting.

Trace-back and community surveys. These will need to be conducted at sites of wildlife farms that supplied animals to markets in Wuhan in the months before human cases were recognized (inside and outside China, depending on supply-chain analysis).

Risk-targeted surveys of possible hosts. Assess wild bats and other potential reservoirs or intermediate hosts in China and neighbouring countries, and selected high-risk farmed animals (including those farmed for fur), for evidence of exposure.

Detailed risk-factor analysis. Analyse pockets of earlier cases evidenced from the antibody surveys or other studies, and conduct an assessment of all possible exposures.

Follow-up. Investigate any credible new leads.

Time's up

The search for the origins of SARS-CoV-2 is at a critical juncture. There is willingness to move forward from both the WHO international team and the Chinese team.

Crucially, the window is rapidly closing on the biological feasibility of conducting the critical trace-back of people and animals inside and outside China. SARS-CoV-2 antibodies wane, so collecting further samples and testing people who might have been exposed before December 2019 will yield diminishing returns. Chinese wildlife farms employ millions of people (14 million, according to a 2016 census[11]) and supplied live mammals to cities across China, including Wuhan[3]. In response to the SARS-CoV-2 pandemic, many of these farms are now closed and the animals have been culled, making any evidence of early coronavirus spillover increasingly difficult to find.

In July, four months after the full report and five months after our debriefing, the WHO informed member states of plans to create a committee that will oversee future origins studies. We are pleased to see both this and its implication that outbreak investigations will be conducted routinely, rather than in an ad hoc manner that could be perceived as politically motivated or with potentially punitive goals.

However, applying this new process to the continuing SARS-CoV-2 origins mission runs the risk of adding several months of delay. Member-state representatives would need to negotiate detailed terms around the sensitive issue of investigating laboratory practices, then nominate and select team members, who would then have to develop a work plan.

Therefore, we call on the scientific community and country leaders to join forces to expedite the phase 2 studies detailed here, while there is still time.

Nature **596**, 482-485 (2021)

doi: https://doi.org/10.1038/d41586-021-02263-6

References

1. 1.

   World Health Organization. *WHO-Convened Global Study of Origins of SARS-CoV-2: China Part. Joint WHO–China Study* (WHO, 2021).

2. 2.

   Anderson, R. M. *et al. Phil. Trans. R. Soc. Lond. B* **359**, 1091–1105 (2004).

3. 3.

   Xiao, X., Newman, C., Buesching, C. D., Macdonald, D. W. & Zhou, Z.-M. *Sci. Rep.* **11**, 11898 (2021).

4. 4.

   Huang, S. Y. *et al. mSphere* **6**, e00104-21 (2021).

5. 5.

   Bloom, J. D. *et al. Science* **372**, 694–694 (2021).

6. 6.

   Holmes, E. C. *et al.* Preprint at Zenodo http://doi.org/10.5281/zenodo.5075888 (2021).

7. 7.

   Li, L.-L. *et al.* Preprint at bioRxiv https://doi.org/10.1101/2021.03.17.435823 (2021).

8. 8.

   Zhou, H. *et al. Cell* https://doi.org/10.1016/j.cell.2021.06.008 (2021).

9. 9.

Bloom, J. D. Preprint at bioRxiv https://doi.org/10.1101/2021.06.18.449051 (2021).

10. 10.

Wang, M. *et al. Small* **16**, 2002169 (2020).

11. 11.

Intergovernmental Science-Policy Platform on Biodiversity and Ecosystem Services. *IPBES Workshop on Biodiversity and Pandemics: Workshop Report*. (IPBES, 2020).

- CORRESPONDENCE
- 24 August 2021

Five principles for climate-resilient cities

- Christian Albert [0],
- Samuel Rufat [1] &
- Christian Kuhlicke [2]

The recent catastrophic floods in China, Belgium and Germany underscore the importance of building climate-resilient cities. We represent a consortium that has proposed a comprehensive climate-adaptation programme to help guide urban decision-making and governance to better prepare for future climate-related events (see go.nature.com/3ctpwau).

Such efforts hinge on five principles learnt from earlier disasters. The world must improve early-warning systems and strengthen flood barriers and civil protection, in particular for smaller watersheds; develop ‘sponge’ cities and landscapes that harness nature-based flood-risk mitigation; carry out climate-risk assessments of crucial infrastructure such as hospitals, transport and freshwater supply; climate-proof exposed buildings; and reinforce action with strong political cooperation and solidarity, particularly with the most vulnerable groups of people.

We have the scientific knowledge to develop climate-resilient cities (see, for example, X. Bai *et al. Nature* **555**, 23–25; 2018). However, political will and bold decisions will be essential for implementing the solutions and the necessary societal transformations.

Nature **596**, 486 (2021)

doi: https://doi.org/10.1038/d41586-021-02309-9

| Section menu | Main menu |

- CORRESPONDENCE
- 24 August 2021

First authors: is co-equal genuinely equal?

- Jonathan Kipnis [0]

‘Equal’ distribution of co-first authors on research papers should be a win–win concept — not just for those authors, but also for multi-disciplinary science. Yet some seek to reshuffle their respective positions on CVs for career purposes. How can we ensure that co-equal means genuinely equal?

Principal investigators and trainees must use the term responsibly, with endorsement by all of the project’s participants. Besides trainees who work side-by-side on a shared project, co-first authorship might be justified if one trainee supplies information that strengthens a crucial conclusion or spends months revising a paper abandoned by another trainee, for example.

My recent tweet (see go.nature.com/3sek93o) prompted suggestions for improving recognition of co-first authorship, such as by using an expanded citation format of ‘X, Y, Z *et al*.’, and by highlighting each as a first author with EndNotes in papers and on PubMed or Google Scholar. This would make it easier for faculty members to recognize participants’ equal contributions when evaluating them for promotion and tenure, irrespective of name order.

Nature **596**, 486 (2021)

doi: https://doi.org/10.1038/d41586-021-02310-2

- CORRESPONDENCE
- 24 August 2021

Could Europe become the first climate-neutral continent?

- Nebojsa Nakicenovic [0] &
- Peter D. Lund [1]

Two scientific reports released in June indicate what it would take for Europe to become the first climate-neutral continent. As the lead author of the Group of Chief Scientific Advisors to the European Commission and chair of the energy project of Science Advice for Policy by European Academies, respectively, we contributed to these reports, advising policymakers on how to accelerate the transition from fossil fuels to renewable energy (see go.nature.com/3k5f6i7 and go.nature.com/3yw4pjg).

Central to the transition is immediate adoption of innovative technologies that are backed by regulatory and market measures, along with social and behavioural changes to incentivize and support low-carbon energy choices. Investment must be stepped up to hasten development of flexible, efficient and resilient energy systems that rely on electrification and hydrogen.

A coordinated combination of policies, measures and instruments, including carbon pricing as a driving force, will shape an effective, consistent and just regulatory system. For example, this could extend current emissions-trading arrangements and introduce a border carbon-tax adjustment.

Nature **596**, 486 (2021)

doi: https://doi.org/10.1038/d41586-021-02311-1

- CORRESPONDENCE
- 24 August 2021

Home laboratory: interactive science from the kitchen

- Poorti Kathpalia [0] ,
- Arpita Konar [1] &
- Beena Pillai [2]

The COVID-19 pandemic has compromised laboratory training and scientists' access to the latest experimental tools. Digital technology has helped hugely, but it cannot offer the essential hands-on learning experience of a lab. This shortfall in experimental know-how is hindering scientists from generating and using new data, particularly in disadvantaged countries.

Our own training in the latest advances in RNA biology by international experts at a 2020 workshop was brought to a halt as India hurtled towards two successive COVID-19 waves. Our monthly outreach events for schoolchildren also stalled.

To provide these children with an immersive research experience, even though they were confined to their homes, we transformed our lab into a live online classroom. Teaching staff were masked up and safely distanced. The children watched on their digital devices as we isolated DNA, and they reproduced the protocol in their kitchens using reagents from a kit that we mailed to them in advance. They discussed the methods and scientific principles with our graduate students at the same time.

The challenges of these interactive classes offered these schoolchildren a stimulating and fulfilling learning experience.

Nature **596**, 486 (2021)

doi: https://doi.org/10.1038/d41586-021-02278-z

Work

- **Three questions to address rigour and reproducibility concerns in your grant proposal** [19 August 2021]
  Career Column • Addressing weaknesses and limitations in your science will reassure potential funders, say grant-writing coaches Jennifer L. Wilson and Crystal M. Botham.
- **Innovative tools take aim at antibiotic-resistant microbes** [23 August 2021]
  Technology Feature • Diagnostics that rely on bacterial movements, genomics and machine learning could help to address a global crisis.
- **Making sense of quantum-level chaos** [23 August 2021]
  Where I Work • Fabio Deelan Cunden draws inspiration for his studies of randomness from ancient books and artefacts in a mathematics museum.

- CAREER COLUMN
- 19 August 2021

Three questions to address rigour and reproducibility concerns in your grant proposal

Addressing weaknesses and limitations in your science will reassure potential funders, say grant-writing coaches Jennifer L. Wilson and Crystal M. Botham.

- Jennifer L. Wilson [0] &
- Crystal M. Botham [1]

Credit: Getty

Since 2018, the US National Institutes of Health (NIH) has required that research proposals explicitly describe scientific rigour. They want to know scientists' approaches to ensuring the fidelity of their data, minimizing bias and maximizing new knowledge. The NIH did this to address transparency and reproducibility challenges in research. Other funders have also signalled a long-term commitment to better practices in science. In 2020, for example, the European Commission's Directorate-General for Research and Innovation, the body responsible for the European Union's research and innovation policy, issued guidance to improve research reproducibility. Writing about rigorous choices can be simple. As grant coaches at the Grant Writing Academy at Stanford University in California, we work with scientists who have already thought carefully about the quality of their science and want to address rigour in their grants. Our process focuses on asking simple questions to help them sufficiently justify the rigour in their research proposals.

Collection: Careers toolkit

For example, one recent proposal included a sentence like this: "We will use the stroke mouse model and treat the mice with our novel compound daily, for three weeks."

As grant coaches without specific knowledge of the model, we probed the writer with questions looking for more detail, such as “Why this mouse model?” and “Why daily dosing?” As it turns out, the mouse model and dosing regimen were standard in that laboratory, and the lab had published a study that showed the model was relevant to the stroke outcome of interest.

We pushed the writer to be more specific in their writing, to communicate how their approaches minimize bias due to the choice of model organism: ‘We will use the stroke model mouse, a model system we and others have shown to be relevant to understanding stroke outcomes [references], to test the effect of novel therapeutic compounds.”

This sentence is more successful because it clearly shows how the writer’s choices are adequate for addressing their research question, and how this choice will help them to derive knowledge about the disease condition.

Three-question framework

Our three-question framework helps to frame scientific choices when writing research proposals. Our process guides writers to explain their experimental choices, by asking questions that address limitations in their proposal:

1. What are the essential weaknesses or limitations in your science? Every scientific method has limits. Often, these limits are methodological or field-specific.

2. Which methods will you use, or are you already using, to address these limitations? These may be standard methods in your research group, but it’s important to highlight them as such for a reviewer.

3. What makes these methods adequate? Justify your choices by confirming how the field has tested or accepted these methods for overcoming limitations.

Revisiting our mouse-model example, one limitation of the approach is whether testing the compounds in the stroke model sufficiently replicated human stroke progression (this addresses question 1). Using the stroke-

appropriate mouse model addressed this weakness (and answers question 2), and referencing peer-reviewed publications justified the writer's selection of this model (which answers question 3). The revision justifies the animal model's relevance to the proposed research and references published data that support that statement.

Through our grant coaching, we have found that addressing scientific rigour often requires careful and specific wording: instead of, "We will use our new method to anticipate drug effects," we would guide a writer to "We will calibrate our new method using a landmark dataset, a gold-standard comparison in our field, to benchmark against known effects before anticipating new drug effects." A new method could bias results, but benchmarking the method against a well-regarded dataset of known effects justifies the method's adequacy for understanding effects of a new drug.

Jennifer Wilson and Crystal Botham developed a framework for writing grant proposals.Credit: Jennifer Brophy

In another scenario, the sentence, “We will assess treatment effects by comparing wound healing of the untreated left leg and treated right leg,” needs an introductory clause: “We have previously shown that wound-healing rates are different between individual animals, making it difficult to compare between them [references]. Thus, we will generate two wounds on the same animal and apply treatment to only one wounded area.” This explanation helps a reviewer to appreciate the writer’s ability to assess the treatment’s effect, and to prevent the effect from bias due to differences in wound-healing ability of individual animals.

Addressing rigour in research proposals is often less about changing scientific choices or overall project design, and more about justifying how experimental-design choices address limitations that could prevent the researcher from answering their question or diminish the knowledge they derive from their experiment.

Collection: Funding

Justifying scientific choices requires deliberate practice to achieve strong, persuasive writing. The grant writer must be aware of and unafraid to share the limitations to their science. The selection of the mouse model is a decision that supports rigour, but someone not familiar with the lab’s research, such as a grant reviewer, might not understand this unless the writer specifically justifies it. In the case of the stroke model, the selection

of the mouse model is a decision that improves quality, but that might have been taken for granted by the grant writers because everyone in the lab in this example uses this model. Understanding why the lab uses this stroke model would have enabled this writer to better justify their choice to a reviewer who isn't familiar with the lab's best practices.

Often, it's difficult to decide which choices require justification. We recommend examining published work and talks to understand limitations and how they were addressed. It might feel daunting to address all possible limitations to a research approach, so start by investigating journal publication requirements for reproducibility and transparency. Many journals have specific requirements about the reporting of protocols, the use of biological samples, the availability of analysis code and other technical details. Journal requirements are designed to overcome field-specific challenges to reproducibility and transparency. Take note of how others justify their choices — you don't have to go as far as explaining whether an experiment needs a control (almost all good experiments have at least one control), but you will probably need to justify how a particular control is well-suited to your research question.

Gaining this awareness is not an overnight process. Learning the limitations of a scientific field is an ever-evolving process, and assessing how others justify their rigorous decisions will deepen your understanding of how to make them. Our framework provides one way to prioritize and address hurdles to reproducible and transparent science. We encourage writers to have peers outside their research group read their work and use the three-question framework. Often, an outsider can provide a fresh perspective on the choices that a writer has taken for granted or failed to explicitly address.

We feel that developing awareness of rigorous practices during the writing of research proposals will elevate rigorous thinking throughout the research enterprise.

Nature **596**, 609-610 (2021)

doi: https://doi.org/10.1038/d41586-021-02286-z

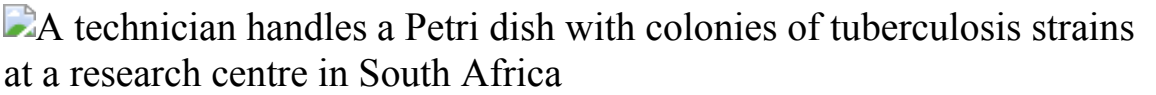
| Section menu | Main menu |

- TECHNOLOGY FEATURE
- 23 August 2021

Innovative tools take aim at antibiotic-resistant microbes

Diagnostics that rely on bacterial movements, genomics and machine learning could help to address a global crisis.

- Jyoti Madhusoodanan [0]


A technician handles a Petri dish with colonies of tuberculosis strains at a research centre in South Africa

Bacterial resistance to antibiotics is a major problem around the world. New solutions are hoping to change that. Credit: Joao Silva/NYT/Redux/eyevine

Maha Farhat spent months in 2007 tending to patients at a hospital in Durban, South Africa. Many were infected with HIV. But the infection that preyed on the then-medical-resident's mind, and her patients', was caused not by a virus, but by a bacterium: *Mycobacterium tuberculosis*, the pathogen that causes tuberculosis. In particular, she was concerned about strains that are resistant to common antibiotics.

Although immunocompromised individuals are especially susceptible to tuberculosis, the infection isn't unique to people with HIV: *M. tuberculosis* claimed 1.4 million lives worldwide in 2019, 208,000 of whom had HIV. "Tuberculosis was briefly superseded by COVID-19, but it's still the top infectious-disease killer globally," says Farhat, now a physician and bioinformatician at Harvard University in Boston, Massachusetts. Drug-resistant forms of tuberculosis are a major contributor to the problem.

Drug-resistant pathogens of all types have precipitated an antibiotic-resistance crisis that threatens public health, agriculture, animal husbandry

and more. But spotting these strains and identifying effective treatments is tricky. Labs equipped to handle especially infectious pathogens, such as *M. tuberculosis*, can be hard to come by in resource-limited countries, and instruments for testing for drug sensitivity can take days to return results. In many cases, physicians test for resistance only after one or more standard antibiotics fail. While waiting, patients might begin an unnecessary or ineffective course of antibiotics, or leave the clinic without treatment.

Farhat and other researchers are turning to tools such as atomic force microscopy, genomics and machine learning to create point-of-care diagnostic tests that they hope will provide results in minutes, minimizing the use of incorrect or unnecessary prescriptions. “An increase in rapidity is the most important advance needed,” says clinical microbiologist Evgeny Idelevich at the University Medical Center Greifswald in Germany.

Gauging growth

The gold-standard method for assessing drug susceptibility of microbes, known as a disk diffusion test, dates to 1889. Researchers culture bacteria on an agar plate, then place tiny paper disks loaded with drugs on the growing cells; zones around the disks become transparent if a drug kills bacteria or stalls their growth, indicating that the microbes are susceptible to the medication.

Companies have automated that same principle in antimicrobial sensitivity testing instruments, such as the BD Phoenix from BD Biosciences, headquartered in New Jersey, and the VITEK 2 from bioMérieux, based in Marcy-l’Étoile, France. These systems seed bacteria in liquid cultures with antibiotics and look for optical changes that indicate bacterial growth or death. The tests typically require somewhere between 4 and 8 hours, although results can take a day or more to arrive because clinicians must send samples to clinical microbiology labs[1].

But researchers are also exploiting assays that are more commonly associated with the physical sciences than with microbiology labs.

In 2018, for instance, Idelevich devised a miniaturized version of the liquid culture test that relies on MALDI–TOF, a mass-spectrometry technique that uses laser-induced ionization and a long ‘flight tube’, through which ions travel, to identify molecules on the basis of their mass and charge. Idelevich and his colleagues placed microdroplets of cultures of two pathogens — *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* — directly on a solid support matrix used for MALDI–TOF and incubated each droplet with a different drug. They then processed the sample with a system specifically designed for bacterial identification: the MALDI Biotyper from Bruker Daltonik. Intensities of characteristic spectral peaks indicated whether the cultures were susceptible or resistant to the antibiotic[2].

Tuberculosis genomes track human history

In 2013, Giovanni Longo, at the National Research Council of Italy in Rome, and his colleagues found that when they bound pathogenic *Escherichia coli* to miniature diving-board-like structures called cantilevers and exposed them to antibiotics, the cantilever bobbed up and down because of small movements of attached, living bacteria. The movements ceased if the microbes were susceptible to the antibiotics. The movement was visible under an atomic force microscope within minutes — long before microbes replicated — meaning the test can identify live bacteria far faster than is possible with an assay that looks for bacterial growth[3].

Rachel McKendry, a nanotechnology researcher at University College London, and her then-graduate-student Isabel Bennett wanted to take that approach into the clinic. But attaching the bacteria to cantilevers that were 200 micrometres long in a Petri dish was easier said than done. “Only a fraction of the cantilevers would have bacteria attached, and sometimes they’d be either clumpy or too few attached,” Bennett says.

As she worked with Longo’s team to fine-tune the process, Bennett detected large differences in reflected light, which suggested that similar bacterial movements could be spotted even when the microbes were not tethered to the cantilevers. So, the team switched tactics: they altered the set-up to track bacteria as they floated across the structures’ surfaces. They made the cantilevers from a hard, reflective material, and developed software to analyse bacterial movement so that the readout was proportional to the number of bacteria in solution[4]. “This deceptively simple signal turned out to be really a nice way to detect resistance compared to current methods,” McKendry says.

Although not yet commercialized, the system could be adapted and scaled up for clinical use, Bennett suggests. The reflective surfaces could be turned into inserts placed in routinely used microtitre plates, and the atomic force microscope replaced with a DVD player’s optical reader to capture the signal. “It could potentially be a very easy, low-cost set-up,” she says.

Physicist Kamil Ekinci, at Boston University in Massachusetts, is pursuing another proxy for bacterial antibiotic resistance: electrical current. His team placed a urine sample spiked with *K. pneumoniae*, a common cause of urinary-tract infections, directly into a single channel of a microfluidic device with an antibiotic, and tracked electrical conductance through the channel[5]. “If the bacteria grow and clog the channel, they create more electrical resistance,” Ekinci says. “We’re basically transducing the bacterial growth into an electrical signal.”

The advantage, Ekinci adds, is that an electrical signal is easier to amplify and visualize than are microscopy images. “In principle, our technique can detect a single bacterial division,” he says — although he adds that the method might not work for all bacteria, particularly slow-growing pathogens such as *M. tuberculosis*.

Measuring molecular markers

Tests based on bacterial growth are easy, cheap and non-specific: a single test works across a wide range of pathogens. But because test results depend on growth conditions and using the right concentration of antibiotics, “everything else is a disadvantage”, says Susanne Häussler, who studies medical microbiology at Rigshospitalet in Copenhagen.

As an alternative, Häussler and others are turning to genomics for clues to drug resistance. This ‘culture-independent testing’ is the next big shift in the field, says epidemiologist Sophia Koo at Harvard University.

Relying on genes that are clearly linked to antibiotic-resistance mechanisms is an ideal route to a quicker diagnostic because it doesn’t require lengthy periods of bacterial incubation, says infectious-diseases researcher Gary Schoolnik at Stanford University in California. But it’s important to know which sequences in the bacterial genome are important for drug resistance, says Thomas Grys, a clinical microbiologist at Mayo Clinic in Phoenix, Arizona. “If you don’t, you could easily miss a new mechanism or detect a fragment of a gene that’s not actually conferring resistance.”

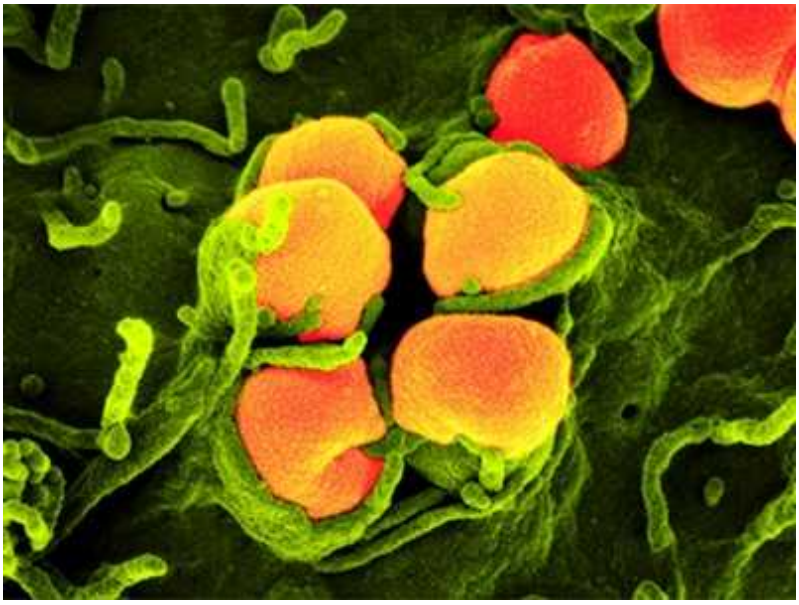
A disk diffusion test is a common way to uncover how effective an antibiotic is.Credit: Doncaster and Bassetlaw Hospitals/SPL

Schoolnik is also chief medical officer at Visby Medical, a California-based start-up that won US$19 million in 2020 as part of an Antimicrobial Resistance Diagnostic challenge sponsored by the US National Institutes of Health and the US Department of Health and Human Services' Biomedical Advanced Research and Development Authority.

The company's test is a single-use, point-of-care diagnostic, run using a simple hand-held device, to spot drug resistance in sexually transmitted pathogens such as *Neisseria gonorrhoeae*. The assay focuses on mutations that confer resistance to ciprofloxacin, a commonly used oral antibiotic for gonococcal infections. Mutations in the gene encoding the enzyme gyrase A spell the difference between *Neisseria* strains that are resistant or susceptible to ciprofloxacin.

PCR-based tests to detect such variants are of limited use in clinics because of the need for instruments, reagents and technicians who are trained to perform reactions. Visby's diagnostic bypasses these constraints by reducing

the assay to a simple colour change. Amplified fragments flow into a chamber on the device that contains capture probes for each variant of the gene. The binding results in a colour change that reflects whether a strain is sensitive or resistant to ciprofloxacin[6].



Untreatable gonorrhoea on the rise worldwide

Others continue to explore whole-genome sequencing to capture the spectrum of variants that confer resistance. But developing low-cost, speedy tests based on such information remains a challenge. “It’s not just about the presence of a resistance gene, but also its expression,” says Nicole Wheeler, a data scientist at the University of Birmingham, UK, who studies machine-learning approaches to genomics. “The more transcriptomic and proteomic data we collect, the more we stand a chance of improving our ability to predict resistance,” Wheeler says.

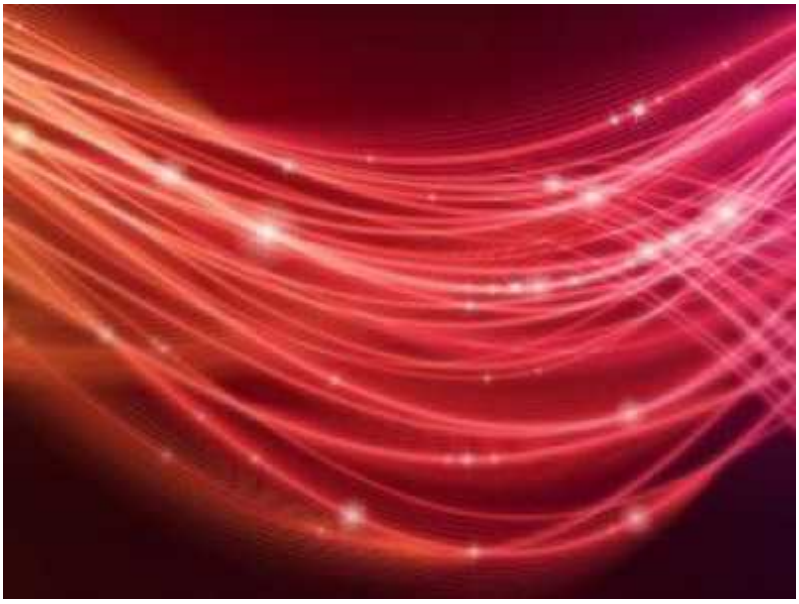
Techniques based solely on genome sequencing work well for some pathogens, such as *Salmonella enterica*, but mutations in multiple regulatory genes can alter gene-expression patterns (and thus resistance) in others, including *P. aeruginosa*. “In principle, all transcriptome data is in the genome,” Häussler says. “But it’s sometimes easier to look at the transcriptome instead of looking for all the possible mutations that alter gene expression.”

In 2014, for instance, Chikara Furusawa, a bioengineer at RIKEN in Osaka, Japan, studied lab strains of *E. coli* adapting to growth in the presence of different antibiotics, and found that he could use changes in gene expression to predict resistance more accurately than he could with genomic DNA sequences themselves[7]. “The correlation between gene expression and resistance was significantly higher than that between resistance and genomic markers,” Furusawa says.

Forecasting future resistance

In their work, Häussler and her colleagues honed in on a mix of genomic and transcriptomic markers as the best ‘signature’ to predict antibiotic resistance in *P. aeruginosa*[8].

But to improve their model, they turned to machine learning. Instead of simply identifying resistance-conferring mutations, they used their algorithms to identify a signature of DNA and RNA variations that predicted a strain’s resistance to antibiotics[8]. The algorithm helps to identify only key traits — it won’t be a part of an eventual diagnostic test, Häussler says. Still, such approaches can overcome the problem of capturing all ‘bug–drug’ combinations through the genome alone, Wheeler says.



Rather than simply informing clinicians of a pathogen's current resistance profile, these algorithms could also reveal which antibiotic-resistance mechanisms a strain might develop in response to treatments. Still, "deciding whether an algorithm should be trusted or not is challenging", Wheeler says. "They're black boxes. Even if you have all the code and all the data, you don't necessarily know what's driving the model to say sample A is resistant to azithromycin, for instance."

Another problem developers are working to overcome is overfitting, Wheeler says: an algorithm might "memorize a whole lot of unimportant features" in data, rather than learn to find true correlations. Because bacterial gene sequences can be very similar, machine-learning tools might oversimplify a problem and draw the wrong conclusions. Wheeler likens the problem to a flawed image search: an algorithm that is trained on many pictures of farm animals in fields might identify a photograph of an open space as a sheep. Bacteria frequently pass antibiotic-resistance genes around to each other on small circular chunks of DNA that aren't part of their genomes. "But because the rest of the genome is the same, the algorithm might say the strain is still sensitive," she says. "What we really want from these models is for them to learn the biology of resistance."

Given the constraints of studying and testing tuberculosis, Farhat adopted a machine-learning approach that uses whole genome sequences to make predictions. In April, she and her colleagues described a web-based tool called GenTB that can predict resistance to several tuberculosis drugs[9]. The tool's performance varies with the quality of input sequence data and the drug in question. Whereas one common mutation is responsible for up to 80% of resistance to the first-line drugs used for TB, several rare variants confer small boosts in resistance to second-line drugs, Farhat says. "Sometimes, you only see the resistance when several such mutations are present."

Work in progress

Whichever approach they use, researchers face the same fundamental challenge: to design a diagnostic that improves significantly on current devices. Current tests can already return results to clinicians in less than 24

hours for a dollar or two per test, Grys says. “The question is not whether a test is good,” he says. “The question is: is it better than what we have right now? It’s important to set a trajectory that helps us meet the goals.”

Some tests in development are restricted in the kinds of sample they can process, or the bacteria or antibiotics they can test. Visby’s diagnostic is currently limited to gonococcal infections, for instance, and Ekinci’s microfluidic device requires urine samples and cannot handle infections caused by more than one species of bacterium. Others that require advanced microscopes or spectrometry, such as cantilevers, will need to be adapted before they can be used by non-specialists working in resource-poor clinics around the world. Because many of these approaches test one or two microbes against a handful of drugs, they’ve conquered only “the tip of the iceberg”, says Alex van Belkum, director of microbiology research at bioMérieux. “There’s still a big lag between these technologies and the automated antibiotic susceptibility testing systems currently in laboratories.”

As in the COVID-19 pandemic — during which rapid tests have proved crucial to detecting and stopping the spread of the virus — low-cost, point-of-care diagnostics are essential in reducing the misuse of antibiotics, says McKendry. “Antimicrobial resistance is a very complex problem, and new tests are only one part of the solution.”

Nature **596**, 611-613 (2021)

doi: https://doi.org/10.1038/d41586-021-02292-1

References

1. 1.

   van Belkum, A. *et al. Nature Rev. Microbiol.* **18**, 299–311 (2020).

2. 2.

   Idelevich, E. A., Sparbier, K., Kostrzewa, M. & Becker, K. *Clin. Microbiol. Infect.* **24**, 738–743 (2018).

3. 3.

Longo, G. *et al. Nature Nanotechnol.* **8**, 522–526 (2013).

4. 4.

Bennett, I., Pyne, A. L. B. & McKendry, R. A. *ACS Sens.* **5**, 3133–3139 (2020).

5. 5.

Yang, Y., Gupta, K. & Ekinci, K. L. *Proc. Natl Acad. Sci. USA* **117**, 10639–10644 (2020).

6. 6.

Morris, S. R. *et al. Lancet Infect. Dis.* **21**, 668–676 (2021).

7. 7.

Suzuki, S., Horinouchi, T. & Furusawa, C. *Nature Commun.* **5**, 5792 (2014).

8. 8.

Khaledi, A. *et al. EMBO Mol. Med.* **12**, e10264 (2020).

9. 9.

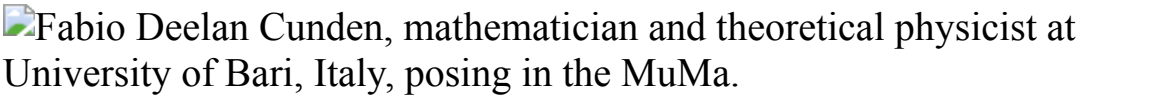
Gröschel, M. I. *et al.* Preprint at bioRxiv https://doi.org/10.1101/2021.03.27.437319 (2021).

- WHERE I WORK
- 23 August 2021

Making sense of quantum-level chaos

Fabio Deelan Cunden draws inspiration for his studies of randomness from ancient books and artefacts in a mathematics museum.

- Amber Dance [0]


Fabio Deelan Cunden, mathematician and theoretical physicist at University of Bari, Italy, posing in the MuMa.

Fabio Deelan Cunden is a mathematician and theoretical physicist at the University of Bari, Italy. Credit: Cosimo Sanitate for *Nature*

The blue ‘string art’ here is an example of a ruled surface, a complex shape that you can generate by moving a simple straight line. The white object is a Clebsch surface, another complex surface that is based on simple equations. On the lower left are red dice of different shapes, which I selected because they provide a primitive example of what I study at the University of Bari, Italy — probability and randomness.

Specifically, I’m interested in chaotic systems. With one of these, if you pick two points that are very close, they will diverge once the system evolves. To understand this, first think of a billiards table. This is a regular, nonchaotic system. If you hit two balls at similar angles from similar starting points, you can predict that they’ll end up near the same pocket. But if you add an obstacle in the middle, such as a pint glass, the system becomes chaotic and you can’t predict the balls’ paths.

I study chaos at the quantum level, where atoms and subatomic particles interact. At this scale, our ‘billiards table’ is called a quantum dot. Imagine it as a sort of box, where some electrons behave like the billiard balls. I seek to understand the chaotic motion of these electrons using random matrix theory, a type of mathematics. I’d also like to apply this approach to describe aspects of the folding of proteins and of a form of artificial intelligence called machine learning.

I often find I need some social interaction for inspiration, such as conferences or coffee with other researchers. The pandemic has made this impossible, but since I started here last December I’ve found an alternative in MuMa, the university’s Museum of Mathematics, where I’m sitting, just upstairs from my office. It’s filled with mathematical objects and ancient books by giants such as the astronomer and physicist Galileo Galilei. When I’m stuck, I head to MuMa and see others’ ideas. It makes me feel part of a chain going all the way back to Galileo.

Nature **596**, 616 (2021)

doi: https://doi.org/10.1038/d41586-021-02293-0

Research

- **Protein-structure prediction revolutionized** [23 August 2021]
  News & Views • The full might of a world-leading artificial-intelligence laboratory has been brought to bear on protein-structure prediction. The resulting method, AlphaFold2, promises to transform our understanding of proteins.
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  Article • Alanine-scanning mutagenesis is used to identify the PF4 epitope that is recognized by anti-PF4 antibodies in patients with vaccine-induced immune thrombotic thrombocytopaenia, revealing that the epitope corresponds to the heparin-binding site on PF4.
- **Tonic prime-boost of STING signalling mediates Niemann–Pick disease type C** [21 July 2021]
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- **Cycling cancer persister cells arise from lineages with distinct programs** [11 August 2021]
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- **Highly accurate protein structure prediction with AlphaFold** [15 July 2021]
  Article • AlphaFold predicts protein structures with an accuracy competitive with experimental structures in the majority of cases using a novel deep learning architecture.
- **Highly accurate protein structure prediction for the human proteome** [22 July 2021]
  Article • AlphaFold is used to predict the structures of almost all of the proteins in the human proteome—the availability of high-confidence predicted structures could enable new avenues of investigation from a structural perspective.
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  Matters Arising •

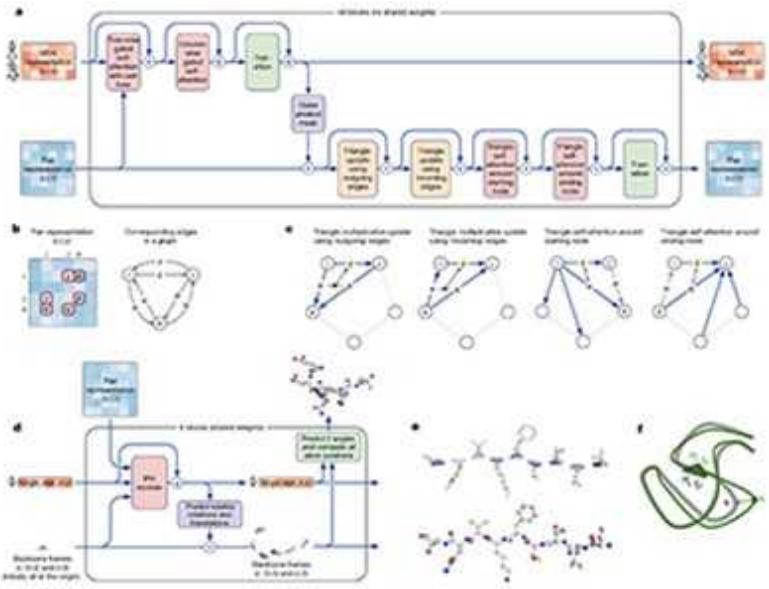
- NEWS AND VIEWS
- 23 August 2021

Protein-structure prediction revolutionized

The full might of a world-leading artificial-intelligence laboratory has been brought to bear on protein-structure prediction. The resulting method, AlphaFold2, promises to transform our understanding of proteins.

- Mohammed AlQuraishi [0]

Most proteins self-assemble into specific 3D structures that, together with other biological molecules, determine the function and behaviour of cells. Over the past five decades, biologists have experimentally determined the structures of more than 180,000 proteins and deposited them in the Protein Data Bank[1], a freely available online resource. Despite this painstaking effort, the structures of hundreds of millions of proteins remain unknown, including more than two-thirds of those in the human proteome — the full set of proteins produced by our genome.

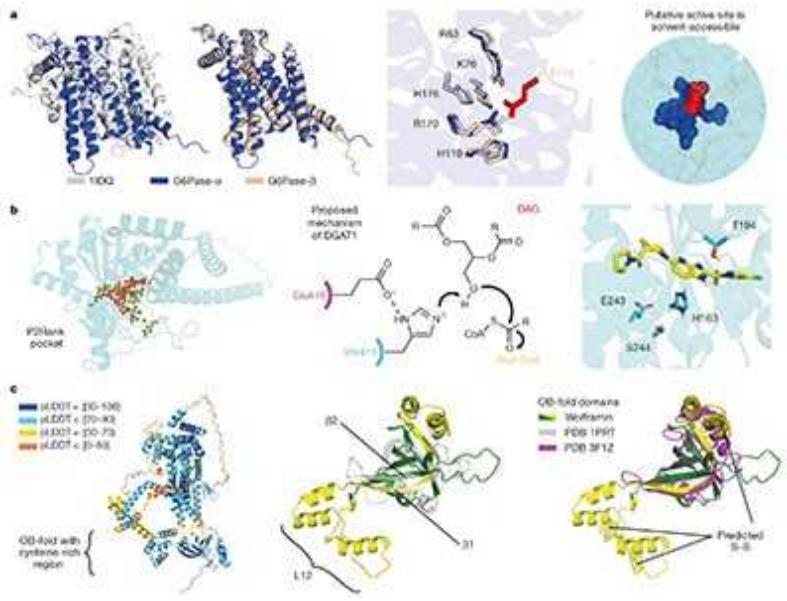


Read the paper: Highly accurate protein structure prediction with AlphaFold

In two papers in this issue, scientists at DeepMind, Google's London-based sister company, describe a machine-learning method, AlphaFold2, that predicts protein structures with near-experimental accuracy[2], and report its application to the human proteome[3]. DeepMind has also announced that it has applied AlphaFold2 to the proteomes of 20 model organisms (see go.nature.com/2w6zhus). AlphaFold2 is free for academics to use and, in collaboration with the European Bioinformatics Institute in Hinxton, UK, DeepMind will make the predicted structures of almost all known proteins freely available to all.

AlphaFold2 — as the name implies — is the second iteration of a system that DeepMind introduced three years ago at the Thirteenth Critical Assessment of Structure Prediction (CASP13) competition. The first version of AlphaFold was technically impressive[4], and outperformed the other CASP13 entrants at the task of predicting protein structures from amino-acid sequences. However, it had a median accuracy of 6.6 ångströms for the most difficult set of proteins tested — that is, for the middle-ranked protein in the set, the atoms in the proposed structures were, on average, 6.6 Å away from their actual positions. This is much less accurate than experimental methods. Moreover, the original AlphaFold arguably represented only an incremental improvement over competing algorithms, in both design and performance.

AlphaFold2 fundamentally changes this. Its median accuracy at CASP14, which was held in 2020, was 1.5 Å — comparable to the width of an atom and approaching the accuracy of experimental methods. Moreover, its design has few parallels with existing algorithms.



Read the paper: Highly accurate protein structure prediction for the human proteome

The prediction of protein structures is difficult for many reasons: the number of plausible shapes for any given protein is huge, but an algorithm must pick just one; the number of known structures is (relatively) small, limiting the data available for training structure-predicting systems; the rules underlying protein biophysics are only approximately known, and are expensive to simulate; and the forces that determine a protein's structure result not only from local interactions between nearby chemical groups in the protein molecule, but also from long-range interactions spanning the whole protein. Jumper *et al.*[2] report a multitude of ideas to address these challenges in their design of AlphaFold2.

Central to this design is a machine-learning framework — known as an artificial neural network — that considers both local and long-range interactions in protein molecules. This differs from previous algorithms, which commonly considered only local interactions to reduce the computational burden of structure prediction. AlphaFold2 does not try to

capture long-range interactions through computational brute force, which would be hopeless even with the resources available at Google. Instead, the authors introduced computational operations that efficiently capture long-range interactions on the basis of fundamental aspects of protein geometry. For example, the operations account for the fact that the coordinates of any three atoms in a protein must satisfy the triangle inequality rule (in other words, the sum of the lengths of any two sides of the triangle defined by the coordinates must be greater than or equal to the length of the remaining side).

AlphaFold2 applies these operations repeatedly (about 200 times) to gradually refine a model of a protein into its final 3D structure. Such iterative refinement, used millions of times, rather than hundreds, is a central component of physics-based approaches to protein-structure prediction[5]. But it is rarely used in machine-learning approaches — which instead predict structures by recognizing patterns of mutation in evolutionarily related proteins to detect co-evolving, and therefore spatially proximal, amino-acid residues[6]. AlphaFold2 breaks the mould by combining these two strategies. Crucially, it does not impose known rules of protein biophysics or try to mimic the physical process of protein folding, as has previously been attempted[7,8]. Instead, it performs purely geometric refinements learnt from its repeated attempts to predict protein structures. In this sense, it exemplifies the learning-driven revolution that has swept the field of protein modelling[6,9].

In a companion paper, Tunyasuvunakool *et al.*[3] report the use of AlphaFold2 to predict the structures of almost all human proteins that independently acquire well-defined 3D shapes, for a total of 23,391 proteins. Predictions at this scale were previously possible, but three features of the new system provide a big leap forward.

First, the accuracy of the predictions is sufficiently high to generate biological insights and hypotheses that can be tested experimentally. Second, a calibrated self-assessment of each prediction provides a reliable estimate of correctness at the level of individual amino-acid residues (Fig. 1), enabling biologists to make inferences about confidently predicted regions. Third, AlphaFold2 is applicable to whole proteins, including large ones that

have multiple, independently self-assembling units — a common feature of mammalian proteins. The resulting resource ‘confidently’ predicts nearly 60% of all human-protein regions; most of the remaining regions might be unable to acquire well-defined structures, or be able to do so only in the presence of other biomolecules.

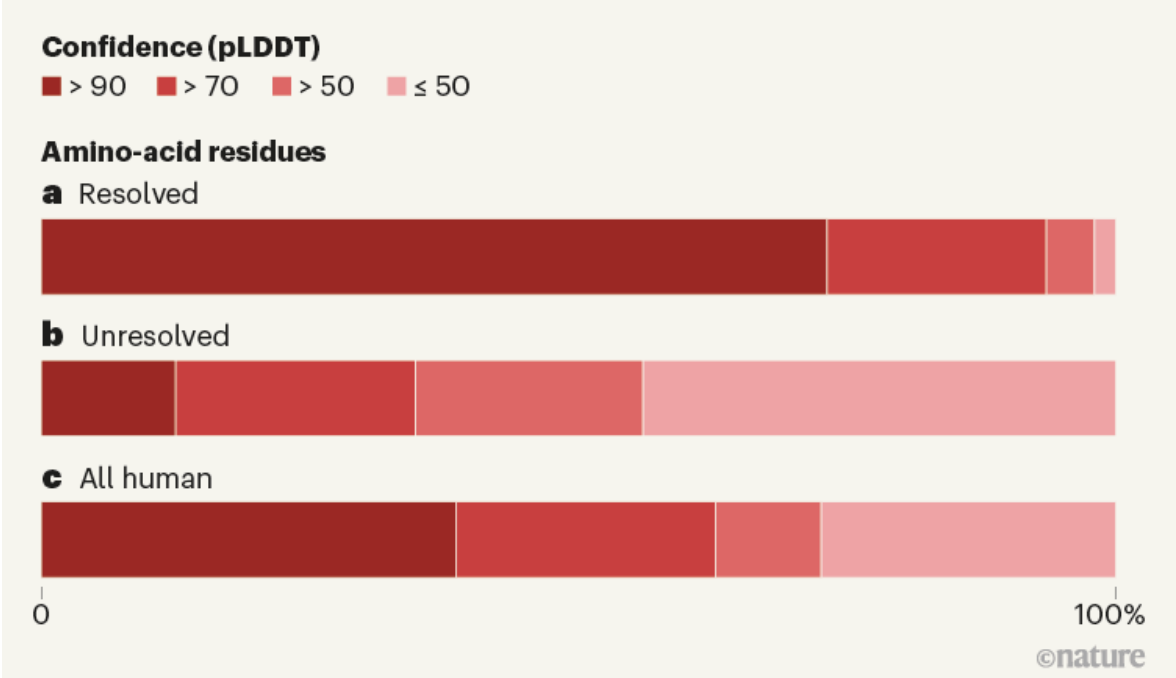


Figure 1 | The confidence of protein-structure predictions by AlphaFold2. Jumper *et al.*[2] report a machine-learning system, called AlphaFold2, that predicts the 3D structures of proteins from amino-acid sequences. Tunyasuvunakool *et al.*[3] used the same system to predict the structures of all human proteins that self-assemble into specific 3D structures. AlphaFold2 produces a confidence metric called the predicted local distance difference test (pLDDT) to estimate how well the predicted position of each amino-acid residue agrees with experimentally determined positions, on a scale of 1 to 100. The charts show the fractions of residues corresponding to different ranges of pLDDT for: **a**, residues that were previously resolved in structure-determination experiments (3,440,359 residues); **b**, residues that could not be resolved in experiments (589,079 residues); **c**, all of the residues in human proteins (10,537,122 residues). (Data from ref. 3.)

AlphaFold2 has already helped structural biologists to solve crystallographic protein structures[10] and refine ones derived from cryo-electron microscopy experiments. It provides biophysicists studying protein motion with starting (static) structures, and those studying protein interactions with hypotheses about how protein surfaces bind to each other. AlphaFold2 also presents opportunities to formulate new algorithms for bioinformatics based on protein structures, and might help systems biologists to understand the behaviour of cellular pathways and molecular machines on the basis of the structures that comprise them. And the study of evolution, which has long relied on genetic sequences, can now more readily be formulated in terms of the onset of new classes of protein structure (folds) and their relationship to cellular function and organismal fitness.

It is tempting to compare the scale of this advance to that of the Human Genome Project, but there are important differences. In contrast to the human genome sequence, the predicted structures have not been experimentally verified; it will take time for evidence of their correctness to emerge, so that scientists can gain confidence in the predictions. Of course, experimental measurements can also be affected by 'noise', bias and incompleteness — 20 years passed between the publication of the first draft of the human genome and the complete sequence[11] — and modern structure-determination techniques routinely involve some computational inference. As predictions improve, disagreements between protein models and experiments could become difficult to resolve, a situation familiar to physicists[12] but largely unprecedented in biology.

Disordered protein regions, which do not have well-defined shapes but often encode functionally crucial parts of proteins, present an ongoing and fundamental challenge to AlphaFold2 and, therefore, to our understanding of protein structure. Future methods must take this disorder into account and begin to reflect the flexibility inherent in most proteins.

Other differences between the Human Genome Project and the present advance are in AlphaFold2's favour. Structure predictions are (relatively) cheap and will soon be available for all proteins, whereas genetic-sequencing technology took years to deploy and mature. Computational methods evolve rapidly, and it might therefore soon be possible to predict the structures of multi-protein complexes, alternative conformations of a

protein (for proteins that adopt them) and the structures of designed proteins with a level of accuracy similar to that currently achieved by AlphaFold2. Finally, protein structures provide immediate biological insights, because they fit within established conceptual frameworks that relate a protein's structure to its function — unlike genetic sequences, which were largely inscrutable at the dawn of the genomics era. The fruits of this revolution might thus be more swiftly reaped.

Nature **596**, 487-488 (2021)

doi: https://doi.org/10.1038/d41586-021-02265-4

References

1. 1.

   Bernstein, F. C. *et al. J. Mol. Biol.* **112**, 535–542 (1977).

2. 2.

   Jumper, J. *et al. Nature* **596**, 583–589 (2021).

3. 3.

   Tunyasuvunakool, K. *et al. Nature* 596, 590–596 (2021).

4. 4.

   Senior, A. W. *et al. Nature* **577**, 706–710 (2020).

5. 5.

   Kuhlman, B. & Bradley, P. *Nature Rev. Mol. Cell Biol.* **20**, 681–697 (2019).

6. 6.

   AlQuraishi, M. *Curr. Opin. Chem. Biol.* **65**, 1–8 (2021).

7. 7.

Jumper, J. M., Faruk, N. F., Freed, K. F. & Sosnick, T. R. *PLoS Comput. Biol.* **14**, e1006578 (2018).

8. 8.

Ingraham, J., Riesselman, A., Sander, C. & Marks, D. *Int. Conf. Learning Representations* https://openreview.net/forum?id=Byg3y3C9Km (2019).

9. 9.

Wu, Z., Johnston, K. E., Arnold, F. H. & Yang, K. K. *Curr. Opin. Chem. Biol.* **65**, 18–27 (2021).

10. 10.

Millán, C. *et al.* Preprint at bioRxiv https://doi.org/10.1101/2021.06.21.449228 (2021).

11. 11.

Nurk, S. *et al.* Preprint at bioRxiv https://doi.org/10.1101/2021.05.26.445798 (2021).

12. 12.

Brumfiel, G. *Nature* https://doi.org/10.1038/nature.2012.10249 (2012).

- NEWS AND VIEWS
- 25 August 2021

African tropical montane forests store more carbon than was thought

The inaccessibility of African montane forests has hindered efforts to quantify the carbon stored by these ecosystems. A remarkable survey fills this knowledge gap, and highlights the need to preserve such forests.

- Nicolas Barbier [0]

In a paper in *Nature*, Cuni-Sanchez *et al*.[1] report the assembly of a large database of tree inventories for 226 mature montane-forest plots in 12 African countries. The authors analyse the data to determine the amount of aboveground biomass and carbon stored in these highly diverse and threatened ecosystems. Their results suggest that African montane forests store more carbon than was previously thought, and the findings should help to guide efforts to conserve these ecosystems.

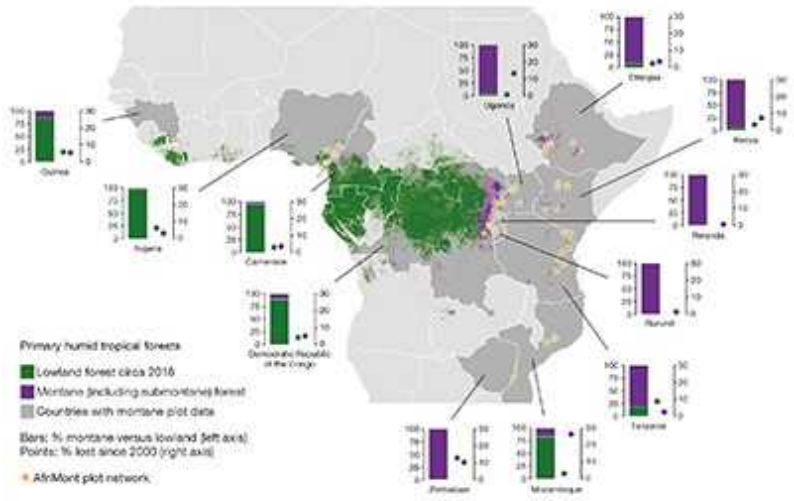
Cuni-Sanchez and colleagues measured trunk diameters and heights of the trees in plots, and identified the botanical species to deduce wood density — an approach that constitutes the gold standard for estimating the biomass, and thus the amount of carbon, contained per unit of forest area. This method involves the use of general statistical equations for describing tree form, called allometric models, and considers only the aboveground parts of trees. It therefore disregards several other pools of carbon, notably in the roots and soil. The overall approach might seem crude, but recognizing and measuring the many hundreds of tree species found on steep, cloud-shrouded slopes (Fig. 1), let alone the underground carbon, without visiting

the sites, will long remain difficult, even with the best drones and satellite systems.

Figure 1 | Montane forest in Boginda, Ethiopia. Cuni-Sanchez *et al.*[1] use data from a survey of montane tropical forests in Africa to quantify the amount of carbon stored above ground in these ecosystems.Credit: Bruno D'Amicis/Nature Picture Library

Anyone who has conducted field inventories in tropical mountains knows that measuring and identifying 72,336 trees, often just a few steps away from the void, is an amazing feat. For comparison, a previously reported study[2] based its estimates of the carbon stored in montane African forests on as few as seven plots. The study also brings together contributions from numerous researchers and institutions, including many in Africa, to greatly increase the size of the data set, which is also a remarkable achievement. Even so, the total area of forest studied is less than 150 hectares, whereas African montane forest covers about 100,000 times that area, inevitably raising questions about how representative the inventory is.

Statisticians might raise their eyebrows at the sampling design. As is usually the case in meta-analyses, the data set was neither homogeneous (for example, there is a roughly tenfold variation in the plot sizes), nor were the sites selected at random. However, the authors did their best to rule out possible biases induced by sampling artefacts.



[Read the paper: High aboveground carbon stock of African tropical montane forests]

Cuni-Sanchez *et al.* chose not to discuss one tricky aspect of surveys of this sort (extensively discussed elsewhere[2]): how should the land area of a steep slope be measured? The authors followed standard practice, which is to measure the extent of forest plots and of land-cover types in reference to horizontal, planimetric areas (that is, the areas that would be represented on a 2D map, as if seen from the air). This tends to overestimate aboveground carbon because the sloped surface area is greater than that of the planimetric area — which means that the tree density of the planimetric area is higher than it is on the slope. By contrast, the use of planimetric areas underestimates total montane-forest area (by about 40%; see ref. 2). These two biases should roughly cancel each other out when estimating carbon stocks, or changes to stocks, for a region or country. But care should be taken not to combine data acquired using planimetric and non-planimetric areas in future meta-analyses, because the resulting estimates could end up well off the mark.

One might expect that trees in mature African montane forests would be, on average, shorter — and therefore store less carbon — than their lowland counterparts, because of their lower environmental temperatures and shallow soils, frequent landslides and strong winds. However, this is not what Cuni-Sanchez *et al*. report. Instead, they find that average aboveground carbon stocks are not significantly different from those of mature lowland forests. This contrasts with the situation in the neotropics and southeast Asia, where montane forests store, on average, less carbon than do lowland forests.

However, the new results fit with the 2016 discovery that the tallest African trees (81.5 metres) grow on Mount Kilimanjaro[3], the highest mountain in Africa. African forests, in general, tend to contain fewer but larger-statured tree stands than does, for example, Amazonia[4]. The current study confirms that this peculiarity applies even at high altitudes.

The authors investigate several possible drivers for the variations in biomass observed at different sites in their study, including topography, climate, landslide hazard, and even the presence of elephants or certain conifers (Podocarpaceae), but were unable to identify any clear pattern. Many environmental, historical and biological effects probably interact, with each of these effects varying greatly in ways that are poorly captured by available data sets. These effects must therefore be disentangled before a predictive model of African montane carbon distribution can be developed.

Tropical carbon sinks are saturating at different times on different continents

Nevertheless, Cuni-Sanchez and colleagues' study underlines a crucial message: African montane forests are immensely valuable, and not only because they host the source of the River Nile, mountain gorillas and ecosystems such as mysterious lichen-covered forests. They also store vast amounts of carbon, and thereby have a key role in tackling climate change. Of course, this immense intrinsic value does not preclude intense human exploitation of these ecosystems, which can lead to rapid degradation and deforestation. For instance, on the basis of satellite monitoring, Cuni-Sanchez and colleagues report that Mozambique lost nearly one-third of its montane forests between 2000 and 2018.

There is, however, the faint hope that putting a financial value on carbon, and the establishment of economic incentives to avoid deforestation in tropical countries, might help to check the flood of damage[5]. The aim is to reward African countries — for which montane forest sometimes constitutes the last remaining forests — for their conservation endeavours, and for renouncing efforts to access the timber and ore in these ecosystems, even when such resources are otherwise desperately lacking. By gathering the best-available data to provide precise, country-level estimates of average aboveground carbon content in African montane forests, Cuni-Sanchez and colleagues' study will add weight to such efforts — not least because the new estimates are, on average, two-thirds higher than the values reported by the Intergovernmental Panel on Climate Change[6].

The next step should be to extend measurements in these forests, particularly by continuing to support national forest-inventory efforts. These inventories target all vegetation types, rather than just the most intact forests, and all carbon pools, using standardized protocols and systematic sampling methods. Remote sensors, both in the sky and in space, should also be used to fully map the detailed spatial variation of forest diversity, structure and dynamics. But there is no excuse for delaying policymaking — we already know enough to justify immediate decisive action to preserve yet another of Earth's threatened treasures.

Nature **596**, 488-490 (2021)

doi: https://doi.org/10.1038/d41586-021-02266-3

References

1. 1.

   Cuni-Sanchez, A. *et al. Nature* **596**, 536–542 (2021).

2. 2.

   Spracklen, D. V. & Righelato, R. *Biogeosciences* **11**, 2741–2754 (2014).

3. 3.

   Hemp, A. *et al. Biodivers. Conserv.* **26**, 103–113 (2017).

4. 4.

   Lewis, S. L. *et al. Phil. Trans. R. Soc. B* **368**, 20120295 (2013).

5. 5.

   Venter, O. *et al. Science* **326**, 1368 (2009).

6. 6.

   Domke, G. *et al.* in *2019 Refinement to the 2006 IPCC Guidelines for National Greenhouse Gas Inventories* Vol. 4 (eds Calvo Buendia, E. *et al.*) Ch. 4, 4.48 (IPCC, 2019).

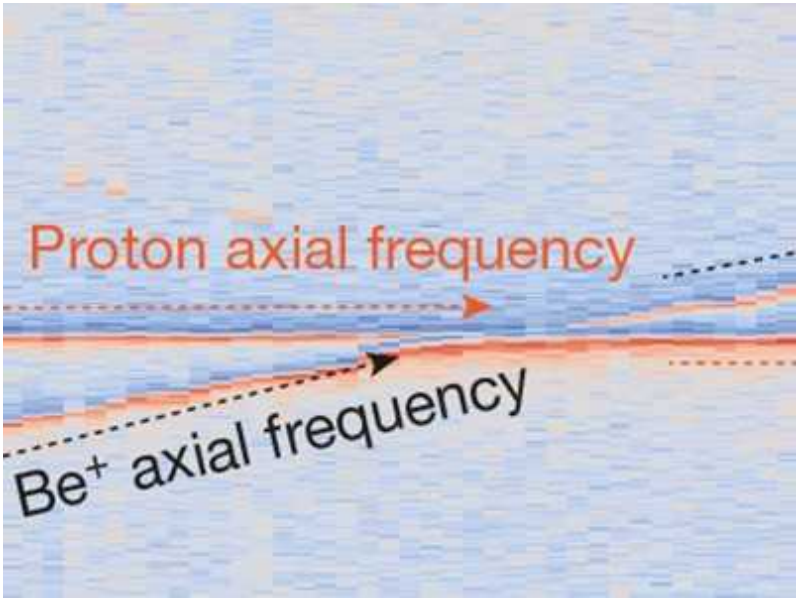
- NEWS AND VIEWS
- 25 August 2021

Single proton cooled by distant ions

Laser-cooled ions have been used to substantially lower the temperature of a proton located several centimetres away. This technique could be useful in ultraprecise measurements of the properties of antimatter particles.

- Manas Mukherjee [0]

In a paper in *Nature*, Bohman *et al*.[1] (the BASE Collaboration) report the cooling of a single proton by a cloud of laser-cooled beryllium ions. Remarkably, the ions were separated from the proton by a distance of about 9 centimetres — which is too far apart for the charges on the ions to have interacted with that of the proton. This means that the ions could not have exerted a direct cooling effect on the proton. Instead, the researchers used an indirect cooling process, mediated by an electric circuit that established an effective interaction. This approach has potential applications in studies of antimatter particles and in the field of quantum information.

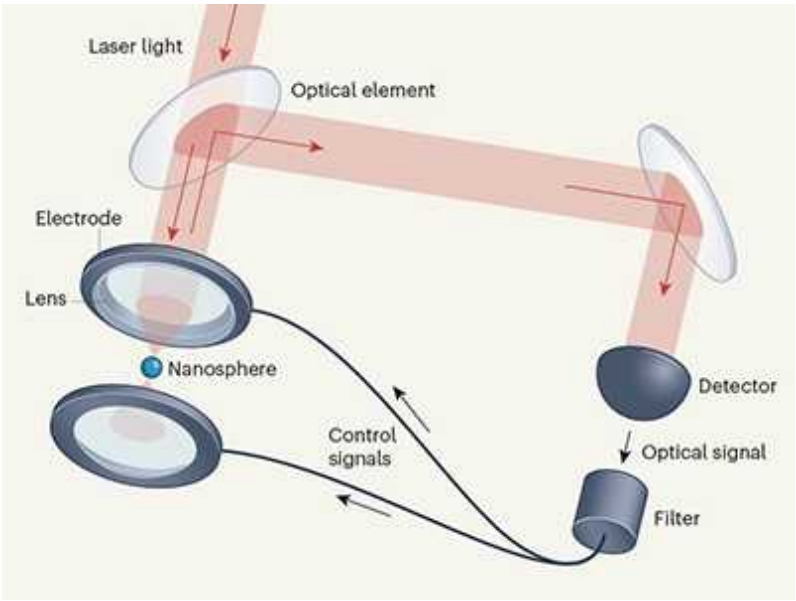


Read the paper: Sympathetic cooling of a trapped proton mediated by an LC circuit

A wealth of knowledge about nature's inner workings comes from studies of fundamental particles, such as electrons and protons. Currently, the most accurate theoretical model of the forces of nature is the standard model of particle physics, which describes how fundamental particles interact with each other and thereby build up the macroscopic world. The standard model has passed many stringent tests using various experimental tools, at particle energies that range from 10^{11} electronvolts in particle accelerators[2] to only about 0.0001 electronvolts in ion traps[3]. However, it is widely accepted that the standard model does not explain some natural phenomena, such as the fact that the Universe is made up of only matter. It also does not account for the existence of dark matter — the invisible and largely unaccounted for mass of the Universe.

High-precision measurements of fundamental particles and their corresponding antiparticles provide opportunities to verify the standard model, and maybe even to find evidence of new physics that goes beyond the currently accepted model[4,5]. Two conditions must be met to perform such measurements: the particles must be spatially confined; and they should be very nearly at rest (that is, the particles must be cooled to almost zero kelvin, to minimize their kinetic energy). The first of these requirements can be solved using a combination of static electric and magnetic fields in a device called a Penning trap.

Laser-cooling methods were first reported[6,7] in 1975, and have since been widely developed to reduce the motion of particles. This approach works well for atoms, but not for particles that do not absorb light, such as protons. Scientists have therefore invented other cooling methods, such as resistive cooling[8] (in which ions dissipate their energy by inducing a current in a cold electric circuit) and synchrotron cooling[9] (in which fast-rotating particles with low mass radiate energy by emitting electromagnetic radiation). However, the lowest particle temperatures achieved using those approaches are roughly 1,000 to one million times higher than those of laser-cooled atoms.



Measurement-based system provides quantum control of nanoparticles

An interesting alternative is to cool a charged particle by bringing it close to another, colder charged particle[10] — an approach commonly known as sympathetic cooling. For example, consider a positively charged atomic ion that is being continuously laser-cooled to one-thousandth of a kelvin, and which is then brought close to a proton that is initially at 4 K in an ion trap. The proton and ion will repel each other within the confinement of the ion trap, effectively transferring kinetic energy from the proton to the ion. Because the ion is constantly being laser-cooled, the repulsive interactions will eventually chill the proton to the same temperature as the ion, even though the proton is not being cooled directly.

Sympathetic cooling works well, but the nearby presence of an ion would be undesirable when making ultraprecise measurements of a proton's properties. Furthermore, the method requires that the particle and the ion have charges of the same polarity, to provide the necessary repulsive interactions. Bohman and colleagues' work provides a potential solution to these issues.

The authors used separate Penning traps to confine a cloud of beryllium ions and a proton in an ultrahigh vacuum, and continuously laser-cooled the ions (Fig. 1). The proton and the ions were then set up to 'talk' to an electrical resonator circuit, which enables the two trapped-particle systems to interact

only when the natural oscillation frequencies (the resonance frequencies) of the two systems match exactly. Bohman *et al.* demonstrated the influence of the ions on the proton using an established technique, in which electrical 'noise' in the resonator circuit is analysed to directly determine the temperatures of the two systems.

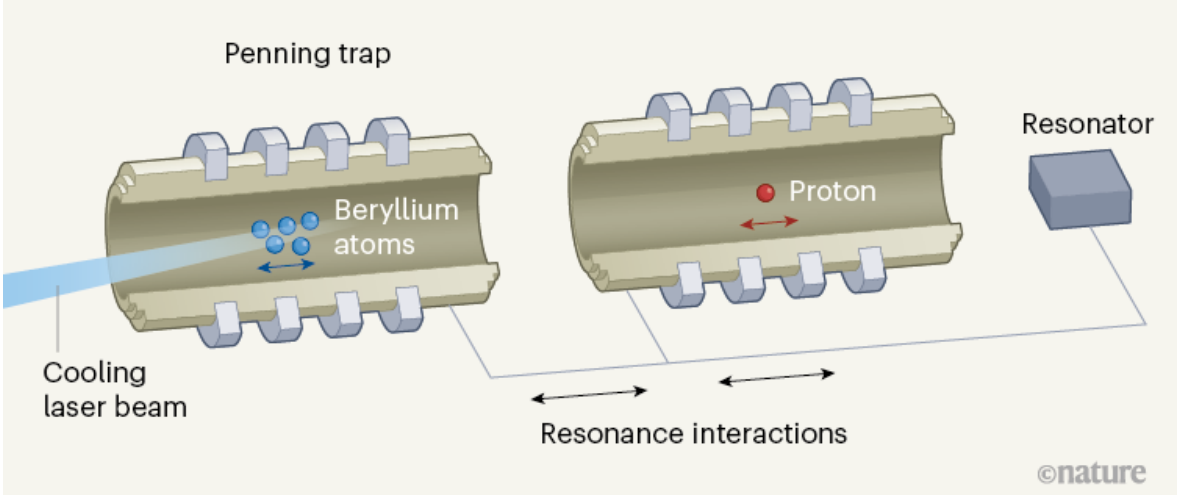


Figure 1 | Sympathetic cooling at a distance. Bohman *et al.*[1] used devices called Penning traps to capture a proton at 17 kelvin and a cloud of beryllium ions, which was continuously cooled by a laser to a much lower temperature. The traps were connected by a wire to a circuit known as a resonator. Oscillations (coloured arrows) of the proton and of the ions generate electrical currents (not shown) in the electrodes of their respective traps; these currents oscillate at the same frequency as the particles that generate them. If the natural oscillation frequency of the proton is the same as that of the ions and of the electrical current in the resonator circuit, a phenomenon called resonance allows the currents in the system to interact. The ions therefore cool the resonator, which, in turn, cools the proton. Such indirect cooling of the proton by the ions is called sympathetic cooling through the resonator.

To further ensure that the proton cooling is indeed caused by the ions, the authors fixed the oscillation frequency of the proton, and then varied the oscillation frequency of the ions. They observed that cooling interactions occurred only when the ions' natural oscillation frequency matched that of both the proton and the resonator circuit, as expected. Furthermore, the researchers found that numerical simulations of the cooling set-up matched

the observed experimental result, confirming the ions' proton-cooling influence.

Impressively, Bohman *et al*. show that the proton temperature can be reduced by 85%, which would be a substantial amount in an ultraprecise measurement of a fundamental particle. The authors' technique opens up the possibility of being able to cool any charged particle by 'wiring it up' to laser-cooled ions, with any distance between the particle and the ions.

The results also have implications for research in quantum information. A goal for this field is to exchange single bits of quantum information between spatially separated quantum systems. However, it is challenging to do this using a conducting wire. Bohman and colleagues' findings suggest a possible solution to this problem, but it will first be necessary to broaden our understanding of how single quanta of energy are exchanged over large distances, and to greatly improve the rate of energy exchange between the separated systems.

Nature **596**, 490-491 (2021)

doi: https://doi.org/10.1038/d41586-021-02267-2

References

1. 1.

   Bohman, M. *et al. Nature* **596**, 514–518 (2021).

2. 2.

   CMS Collaboration. *Phys. Lett. B* **716**, 30–61 (2012).

3. 3.

   Neuhauser, W., Hohenstatt, M., Toschek P. E. & Dehmelt, H. *Phys. Rev. A* **22**, 1137–1140 (1980).

4. 4.

Ulmer, S. *et al. Nature* **524**, 196–199 (2015).

5. 5.

Schneider, G. *et al. Science* **358**, 1081–1084 (2017).

6. 6.

Hänsch, T. W. & Schawlow, A. L. *Opt. Commun.* **13**, 68–69 (1975).

7. 7.

Wineland, D. J. & Dehmelt, H. *Bull. Am. Phys. Soc.* **20**, 637 (1975).

8. 8.

Cornell, E. A. *et al. Phys. Rev. Lett.* **63**, 1674 (1989).

9. 9.

Wineland, D. J. & Dehmelt, H. G. *J. Appl. Phys.* **46**, 919 (1975).

10. 10.

Drullinger, R. E., Wineland, D. J. & Bergquist, J. C. *Appl. Phys.* **22**, 365–368 (1980).

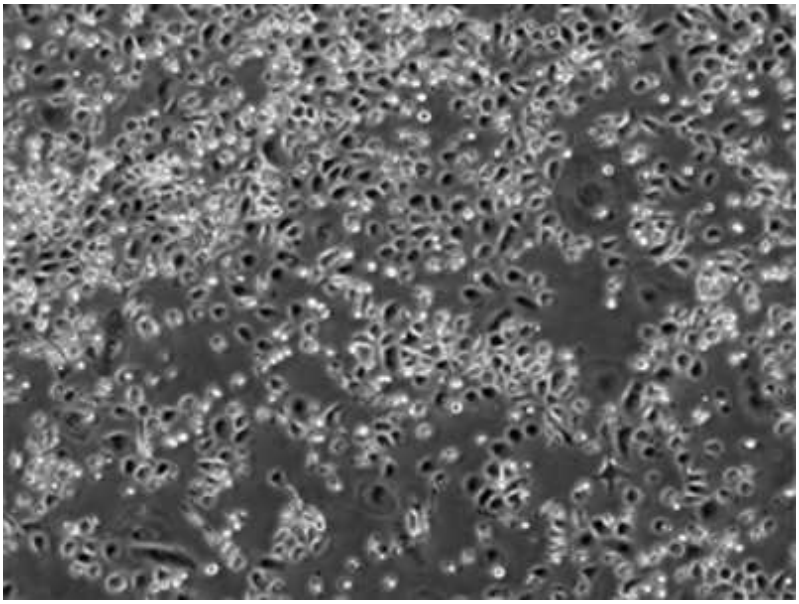
- NEWS AND VIEWS
- 11 August 2021

A persistent look at how tumours evade therapy

Understanding how resistance to chemotherapy occurs could lead to better anticancer treatments. Persister cells in tumours can contribute to this resistance. A method to characterize these cells in detail sheds light on their origins.

- Karen Gomez [0] &
- Raul Rabadan [1]

Cancer can recur when a subset of tumour cells, called persister cells, survive chemotherapy. Most of these persisters are non-dividing (quiescent) in the presence of the therapeutic drug, but a rare subpopulation can re-enter the cell cycle during treatment, which enables them to proliferate. Much research has focused on the genetic mechanisms underlying such resistance to treatment. However, emerging data suggest that non-genetic mechanisms (such as changes to the complex of DNA and protein called chromatin) might also have a role in the development of a persistent state. Writing in *Nature*, Oren *et al.*[1] examine the cellular lineages and gene-expression profiles of persister cells by using a method called DNA barcoding to trace tumour cells and their descendants. Their findings illuminate the role of non-genetic, reversible mechanisms in resistance to chemotherapy for a range of tumours from different tissues.



[Read the paper: Cycling cancer persister cells arise from lineages with distinct programs]

The authors analysed cell divisions in human lung cancer cells grown *in vitro* that have a mutation in the gene encoding the epidermal growth factor receptor (EGFR). The cells were treated with osimertinib, an inhibitor of this receptor. Oren and colleagues tracked the outcomes for cellular lineages of the tumour cell line and found that 8% of the lineages gave rise to persister cells after 14 days, and 13% of the persisters resumed the cell cycle and proliferated to form cell colonies. These results show that these cycling and non-cycling persisters arise early during the course of treatment, and that they evolve from separate cell lineages.

To characterize the molecular mechanisms associated with cycling and non-cycling persister cells, the authors developed a system that they call Watermelon, to simultaneously trace each cell's lineage, proliferation status and transcriptional state (Fig. 1). To determine whether the persister state was due to a genetic, irreversible property of the persister cells, the authors re-exposed the persister cell population to osimertinib after a pause in treatment. They found that cells from both cycling and non-cycling populations reacquired drug sensitivity, suggesting that a non-genetic, reversible mechanism underlies persistence.

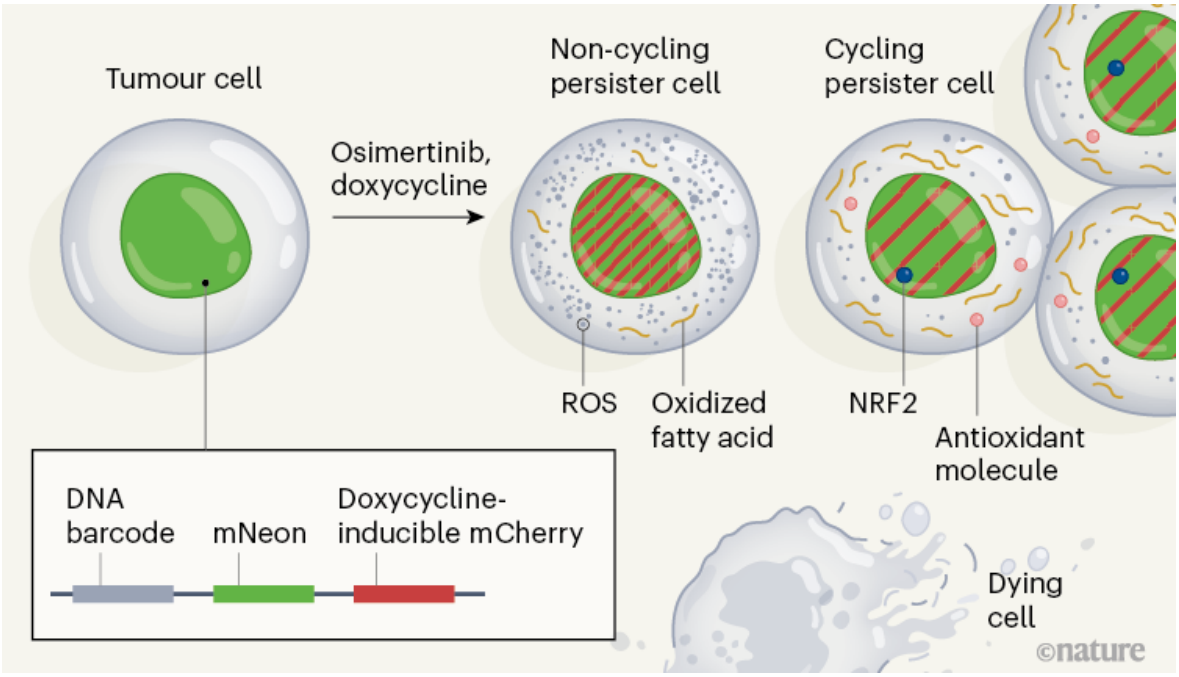
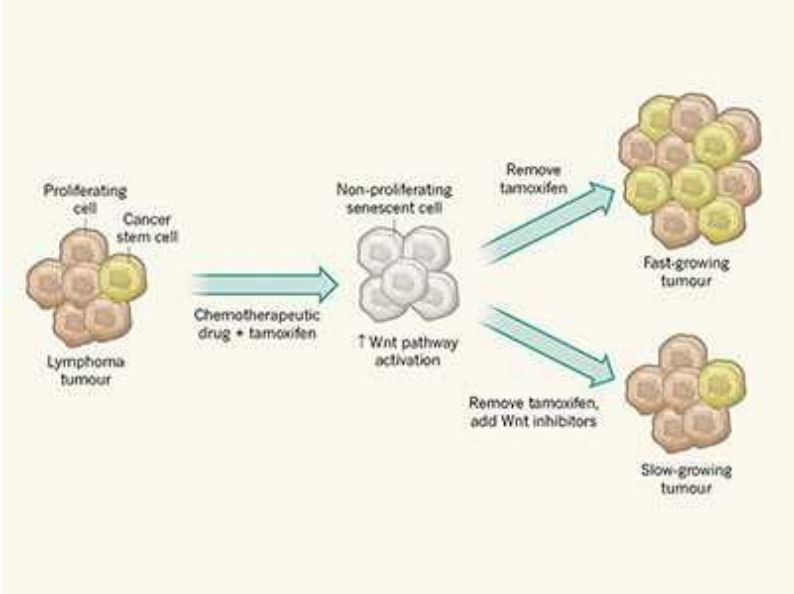


Figure 1 | A method to analyse persister cells in tumours. Oren *et al*.[1] present the Watermelon technique for analysing persisters — tumour cells that evade destruction by chemotherapeutic drugs such as osimertinib. The authors introduced an engineered DNA sequence into human tumour cells grown *in vitro*. The sequence contains a unique DNA 'barcode', which identifies the cells in that lineage. Also included are genes encoding a green fluorescent protein (mNeon), and a red fluorescent protein, mCherry, that requires the molecule doxycycline for its expression. The authors treated the cells with osimertinib and doxycycline, and analysed the surviving persister cells using single-cell analysis. The non-cycling (non-dividing) persister cells had a higher level of mCherry compared with the cycling (dividing) persisters. The persister cells contain reactive oxygen species (ROS), which cause oxidative damage. Cycling persister cells had lower levels of ROS and higher levels of oxidized fatty acids compared with the non-cycling persister cells. Cycling persister cells display hallmarks of antioxidant defences, including the expression of antioxidant molecules and the transcription factor NRF2.

The authors assessed gene expression using the method of single-cell RNA sequencing at different time points during a two-week treatment, and compared these signatures in cycling and non-cycling persisters. The cycling persistent state was uniquely characterized by the upregulation of defence

programs that produce antioxidant molecules — including expression signatures characteristic of the metabolism of the antioxidant glutathione, as well as production of the protein NRF2, which is a transcription factor induced in response to oxidative stress. Moreover, the expression of several genes that are NRF2 targets correlated with lineages that had a large number of descendant persister cells, and the genetic engineering of cells to deplete a negative regulator of NRF2 resulted in an increase in the fraction of persisters that were cycling.

Osimertinib treatment induced the formation of reactive oxygen species (ROS), which can cause oxidative stress. At the end of treatment, cycling persisters had significantly lower levels of ROS compared with the non-cycling persisters. When the authors decreased ROS levels in cells through the addition of ROS scavenger molecules, the fraction of persister cells that were cycling increased. These analyses therefore suggest that the redox state of cells has a role in the regulation of cycling persisters.



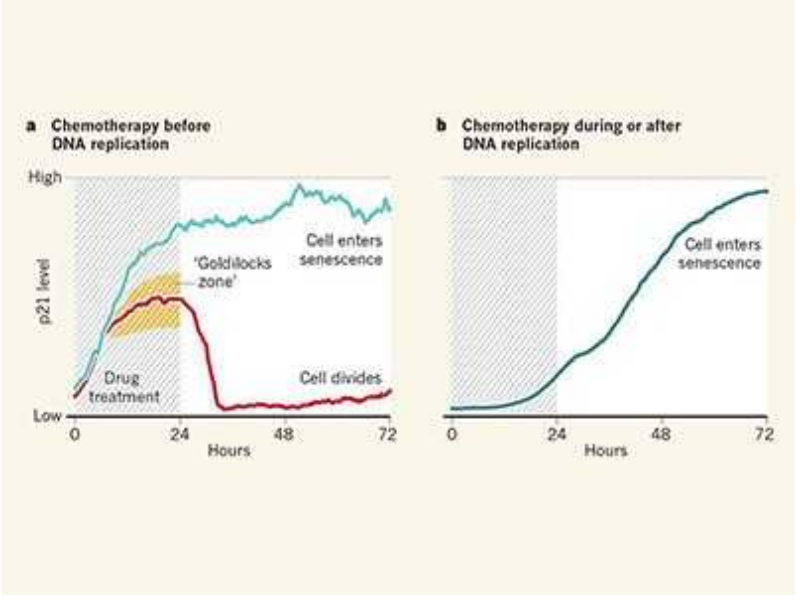
[Escape from senescence boosts tumour growth]

Recognizing that redox balance is linked to metabolism, the authors profiled the products of metabolism in the cycling and non-cycling persisters, and identified 56 products that differed in their abundance between these two cell populations. The authors found a greater abundance of fatty acids linked to the molecule carnitine (a result of a preliminary step in the oxidation of

fatty acids) in cycling states than in non-cycling states. The authors also noted an increase in the oxidation of fatty acids as a consequence of osimertinib treatment. Modulation of the pathway affecting fatty-acid oxidation revealed that increasing or decreasing fatty-acid oxidation leads to an increase or decrease in the fraction of cycling persisters, respectively. These results support the idea that a metabolic shift in fatty-acid oxidation affects the proliferative capacity of persisters.

To test whether their observations extended beyond the model system of lung cancer, Oren *et al.* generated Watermelon models of further types of human cancer, using melanoma, lung, breast and colorectal tumours. They treated the cells with suitable inhibitors, characteristic of chemotherapies, depending on the genetics underlying the particular cancer. In most of these models, the cycling persisters showed elevated fatty-acid metabolism, antioxidant responses and NRF2 signatures compared with the non-cycling persisters, showing that the authors' findings extend to cancer types other than lung cancer.

These *in vitro* findings were validated using an engineered mouse model in which the animals had an inducible version of a mutant EGFR in lung tumours. After osimertinib treatment, the persister cells had a higher level of ROS and gene-expression signatures characteristic of fatty-acid metabolism compared with the cells in mice that had not received treatment. The authors also assessed gene-expression changes before and after chemotherapy in samples of cells from people with EGFR-driven lung adenocarcinoma, with melanoma driven by a mutant version of the enzyme BRAF (treated with inhibitors of BRAF and the enzyme MEK), and with breast cancer driven by a mutant version of the HER2 protein (treated with lapatinib). In all these scenarios, signatures of ROS production and fatty-acid metabolism were increased in the persister cells after treatment compared with samples of untreated tumour cells, and were higher in cycling than in non-cycling persisters.



A dynamic view of chemotherapy effectiveness

Oren and colleagues' study fits into the wider context of current work highlighting the importance of non-genetic mechanisms in persister-cell survival and proliferation[2–4]. One major problem when studying persisters is that they are a small fraction of the initial population of tumour cells, making it difficult to characterize them by sequencing cells in bulk. The value of the authors' Watermelon method is that it enables the detailed characterization of persisters at the resolution of single cells. One future direction might be to apply similar single-cell approaches to study non-genetic mechanisms of resistance in other types of cancer, such as pancreatic[5] or prostate[6] tumours, which are fields where such research is emerging.

Understanding the dynamics of persister cells is crucial to the development of more-effective chemotherapies for cancer treatment. Previous studies found that the response pathway to the hormone oestrogen[7], which has a role in breast cancer, and the pathway related to the cell-death process termed ferroptosis[8,9] are associated with the persister state. Oren *et al*. found that, although inhibiting these pathways did decrease the amount of persister cells, there was an increase in the fraction of persisters that were cycling, suggesting that these would not be optimal chemotherapy targets.

By contrast, the authors report that inhibiting the pathway for fatty-acid oxidation using the inhibitor drug etomoxir resulted in a decrease in both the fraction of cells that were persisters and the fraction of the persisters that were cycling. This promising result indicates that modulation of this pathway, and genes that have functions related to this pathway, might be worth considering in the development of new treatment strategies.

Nature **596**, 491-493 (2021)

doi: https://doi.org/10.1038/d41586-021-02117-1

References

1. 1.

   Oren, Y. *et al. Nature* http://doi.org/10.1038/s41586-021-03796-6 (2021).

2. 2.

   Salgia, R. & Kulkarni, P. *Trends Cancer* **4**, 110–118 (2018).

3. 3.

   Sharma, S. V. *et al. Cell* **141**, 69–80 (2010).

4. 4.

   Hata, A. N. *et al. Nature Med.* **22**, 262–269 (2016).

5. 5.

   Chen, P.-Y. *et al. Cancer Res.* **78**, 985–1002 (2018).

6. 6.

   Jolly, M. K., Kulkarni, P., Weninger, K., Orban, J. & Levine, H. *Front. Oncol.* **8**, 50 (2018).

7. 7.

Garon, E. B. *et al. J. Thorac. Oncol.* **8**, 270–278 (2013).

8. 8.

Angeli, J. P. F., Shah, R., Pratt, D. A. & Conrad, M. *Trends Pharmacol. Sci.* **38**, 489–498 (2017).

9. 9.

Hangauer, M. J. *et al. Nature* **551**, 247–250 (2017).

- NEWS AND VIEWS
- 04 August 2021

A bridge across the democracy–expertise divide

An innovative algorithm provides a way of fairly selecting representative individuals for citizens' assemblies to learn about and deliberate on certain topics. Such groups hold promise for closing the gap between democracy and expertise.

- Mark E. Warren [0]

There is a growing gulf between experts and citizens. Distrust in science is on the increase, as are conspiracy theories that challenge evidence-based decision-making. Populist attacks on institutions that provide expertise for democratic societies and processes — administrative agencies, universities and research organizations — are on the increase, facilitated by social media. Can we strengthen democracy while also ensuring that governance benefits from expertise? Writing in *Nature*, Flanigan *et al.*[1] present a way of fairly and democratically selecting representative groups of citizens tasked with advising on issues that often combine politics and expertise. As supplements to the conventional institutions of electoral democracy, these bodies show promise as a means of bridging the democracy–expertise gulf.

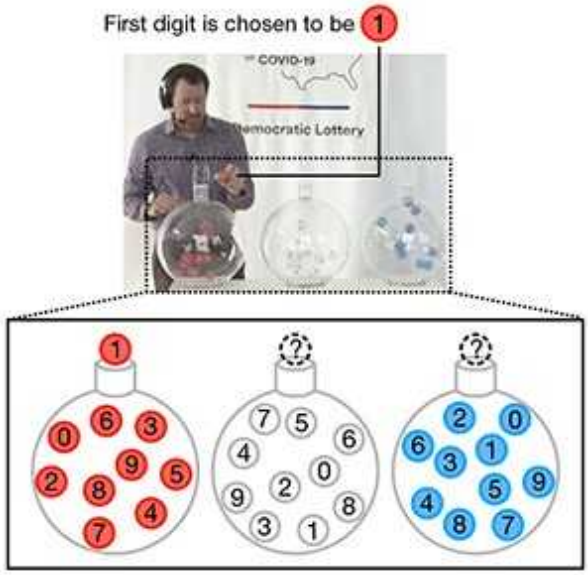
Citizens' assemblies, the term used by Flanigan and co-authors, are a form of deliberative minipublic, the term I use here: bodies of 20–500 ordinary citizens selected near-randomly, through a process often known as sortition, and convened to learn, deliberate and make recommendations to decision makers and sometimes to the broader public (Fig. 1). They achieve three things that more-familiar institutions of democratic government do not[2].

Figure 1 | Members of Climate Assembly UK, a citizens' assembly on climate change. Citizens' assemblies are a form of deliberative minipublic, in which 20–500 individuals who are representative of the demographics of a broader public are near-randomly selected to learn about, deliberate on and make recommendations on certain topics. Flanigan *et al.*[1] devised an algorithm to select individuals for citizens' assemblies fairly and in a way that ensures assemblies are demographically representative.Credit: Fabio De Paola/Alamy

First, because members of deliberative minipublics are selected to mirror a relevant public (they are descriptively representative of the public), they do a better job of representing groups that tend to be under-represented in elected bodies (such as legislatures), or in processes for which participants self-select (such as public hearings, petitioning and lobbying). Second, because a few ordinary citizens are acting as representatives of other citizens, the public tends to like and trust these bodies, probably because they are non-elitist, and not invested in professional politics. Third, deliberative

minipublics integrate expertise, because members are tasked with learning about an issue, hearing from experts and advocates, and then deliberating over recommendations.

There is abundant evidence[3,4] that, when supported in well-designed processes, ordinary citizens can integrate expertise with moral, value-based and political considerations. On ‘hot’ issues (such as abortion, climate change and Brexit), deliberative minipublics’ demographically representative samples of citizens tend to be less polarized than are advocates and elected representatives. This is in part because the selection process does not over-represent what are known as motivated reasoners — people who select information to support a pre-conceived position.



Read the paper: Fair algorithms for selecting citizens’ assemblies

Flanigan and colleagues focus on the composition of deliberative minipublics. They propose and test an algorithm that maximizes fairness in selecting members by equalizing the probability of selection. Why is this important? As political entities, deliberative minipublics must be viewed as legitimate representative bodies by the broader public, if they are to bridge the democracy–expertise divide. Although research remains patchy, evidence[5] suggests that their legitimacy, as perceived by the broader public, is driven by their being representative of people who are ‘like us’ — underscoring the political value of such descriptive representation.

Our current understanding is that people like deliberative minipublics in part because they represent ordinary citizens, and not elites with political agendas. As such, people are more likely to trust the results obtained[5]. Furthermore, recommendations delivered by these citizens' assemblies often have greater impact on the public than does the same information delivered by experts[4]. To achieve this kind of legitimacy, those who organize deliberative minipublics must ensure the credibility of the selection processes.

But this is easier said than done. Deliberative minipublics are often constituted in a two-step process: invitations are sent to a certain number of people — usually more or less randomly selected from, say, voter lists. As Flanigan and colleagues note, those who respond positively, however, are not representative of the broader population: they are usually older, more educated, more likely speak the dominant language or belong to a dominant ethnicity, and more likely to have stable residence. A random selection from this group would thus not produce a descriptively representative body.

Because of this, organizers typically impose demographic quotas for certain categories when they select a minipublic from a pool of volunteers, so that they can produce a body that looks like the broader public. This is where the algorithm designed by Flanigan and colleagues does its work: using ideas from the field of 'fair division', an aspect of game theory, the algorithm equalizes the chances that someone will be selected to serve, even given the quota constraints necessary to correct for bias in the volunteer pool. Doing this maximizes the chances that the body will look like the broader public, without unfairness in the selection process.

Encounters with inequality lead to demands for taxes on the rich

Challenges remain. Broader publics, especially those with a high proportion of distrustful citizens, still need to be persuaded that the selection processes used are fair, and few are likely to understand the selection algorithm itself. Therefore, much depends on the credibility of the organizers, and on their ability to translate the selection algorithm into a visible, transparent process that intuitively makes sense — showing, for example, that the algorithm performs like a lottery. Organizers must avoid perceptions that quotas to remove bias 'rig' the process. And it is not only citizens who must have confidence in deliberative minipublics, but also political elites, whose views of citizens' capacity to understand a topic might be affected by the successes of populist politicians who mobilize ignorance.

Despite these challenges, deliberative minipublics are one of the most promising ways of reducing the widening gulf between democracy and expertise. And they are gaining in use and effectiveness[6]. Although there is no authoritative census of such initiatives, a search on the crowdsourcing website *Participedia.net* (https://participedia.net) combining the search terms "random sampling" or "stratified random sampling" with a method involving a "deliberative and dialogic process" returns more than 520 events from around the world in which randomly selected groups learn and deliberate. A report[6] published last year from the Organisation for Economic Co-operation and Development (OECD) lists 290 "representative

deliberative" processes in OECD countries, including some that started back in the 1990s, although most were organized within the past decade.

As deliberative minipublics become more widely used, it is crucial that citizens and political elites view them as credible and legitimate. Flanigan and colleagues' selection algorithm is a key step forwards, and is likely to provide a global benchmark for boosting this promising democratic innovation.

Nature **596**, 493-494 (2021)

doi: https://doi.org/10.1038/d41586-021-02006-7

References

1. 1.

   Flanigan, B., Gölz, P., Gupta, A., Hennig, B. & Procaccia, A. D. *Nature* https://doi.org/10.1038/s41586-021-03788-6 (2021).

2. 2.

   Setälä, M. & Smith, G. in *The Oxford Handbook of Deliberative Democracy* (eds Bächtiger, A., Dryzek, J. S., Mansbridge, J. & Warren, M. E.) 300–314 (Oxford Univ. Press, 2018).

3. 3.

   Fishkin, J. S. *Democracy When the People are Thinking: Revitalizing Our Politics Through Public Deliberation* (Oxford Univ. Press, 2018) .

4. 4.

   Gastil, J. & Knobloch, K. *Hope for Democracy: How Citizens Can Bring Reason Back into Politics* (Oxford Univ. Press, 2020).

5. 5.

Warren, M. E., & Gastil, J. *J. Polit.* **77**, 562–574 (2015).

6. 6.

OECD. *Innovative Citizen Participation and New Democratic Institutions: Catching the Deliberative Wave* (OECD, 2020).

Amendments & Corrections

- **Author Correction: Molecular logic of cellular diversification in the mouse cerebral cortex** [02 August 2021]
  Author Correction •
- **Author Correction: Quantum-enhanced nonlinear microscopy** [02 August 2021]
  Author Correction •
- **Author Correction: DHODH-mediated ferroptosis defence is a targetable vulnerability in cancer** [02 August 2021]
  Author Correction •
- **Publisher Correction: Observation of first and second sound in a BKT superfluid** [02 August 2021]
  Publisher Correction •
- **Publisher Correction: A highly magnetized and rapidly rotating white dwarf as small as the Moon** [02 August 2021]
  Publisher Correction •

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