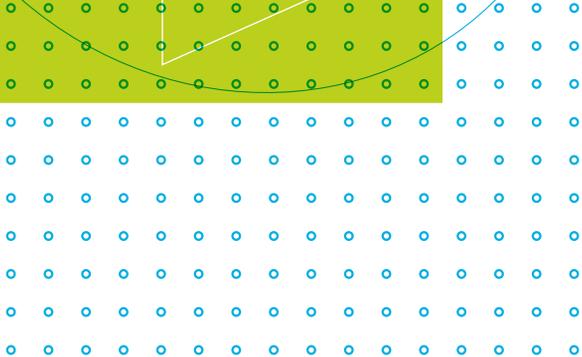


**HIGHLIGHTS**  
**2020** FROM THE YEARBOOK  
OF THE MAX PLANCK SOCIETY





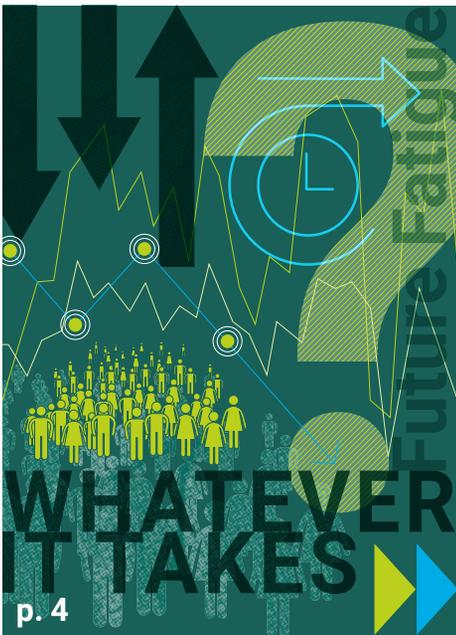
# Editorial

Each year, the Max Planck Society submits a scientific research report in the form of a yearbook to render account of the scientific research performed at its Institutes to the public and its funding providers. The central questions addressed are: where do we stand, and where do we want to go? The Max Planck Institutes are asked to select a work or project from their scientific activities suitable for presentation in the yearbook, as far as these activities have reached a certain degree of completion. All contributions of the Max Planck Institutes are published on our website at [www.mpg.de/jahrbuecher](http://www.mpg.de/jahrbuecher). For this printed collection, 15 articles were selected and edited in a journalistic manner, which seemed particularly suited for publication from a science communication perspective and especially interesting also for non-experts.

Researchers from the Max Planck Institute for the Study of Societies outline why it is important to develop social and economic policy plans for the future in order to overcome the current crisis. Whether politicians can strengthen confidence in the future is also determined by their rhetorical persuasiveness. For example, Mario Draghi's promise of "whatever it takes" during the Euro Crisis in 2012 succeeded in stabilising the situation on the financial markets and saving the Euro for the time being. At the Max Planck Institute for Software Systems, a research group is developing artificial intelligence (AI)-based virtual tutoring systems that help students learn programming in accordance with their individual abilities. This is playing an increasingly important role in STEM education. And at the Max Planck Institute of Molecular Physiology, researchers are putting tumour cells on a radical sugar diet with inhibitors. Because cancer cells are actually addicted to sugar – they need ten times more sugar than normal cells. The substances identified are now being further developed at the Lead Discovery Center to create lead molecules for medicine and, if successful, could one day be used for cancer therapies.

We hope you will enjoy reading our Highlights 2020!

# Content



**1** The future in crisis  
p. 4

**2** Tailor-made catalysts for the green energy industry p. 8

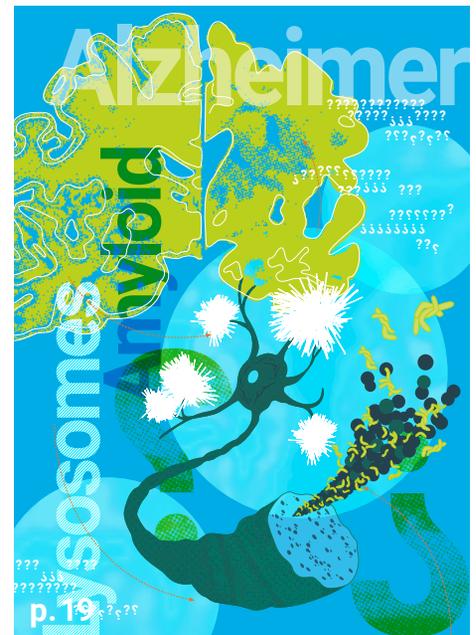
**3** Cancer cells on a diet p. 11



**4** Theory and practice of COVID-19 containment p. 14

**5** Married young – separated by law? p. 17

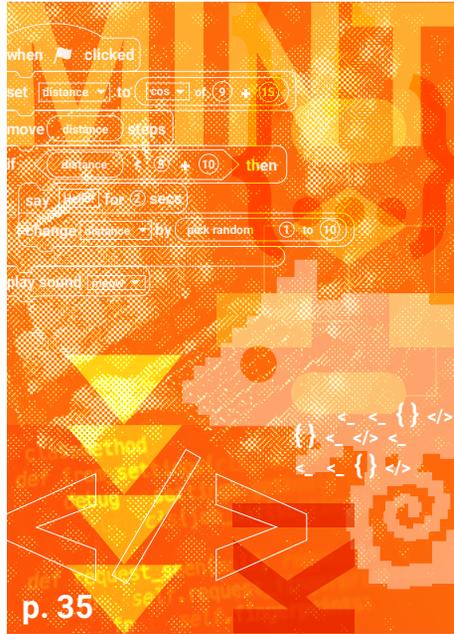
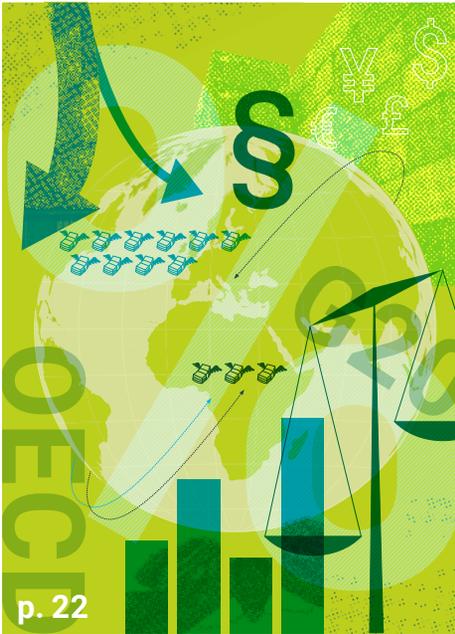
**6** Protein congestion in the brain p. 19



**7** International tax justice p. 22

**8** Better hearing through brain stimulation p. 26

**9** Heavyweight in the heart of a galaxy p. 29



**10** Embryos in deep sleep p.33

**13** The dilemma of triage p.42

**11** Learn to programme with artificial intelligence p.35

**14** A black widow in space p.44

**12** Propagation of hybrid seeds p.39

**15** Artificial genome capable of reproducing itself p.47



Future Education

WHATEVER IT TAKES



# 1 The future in crisis

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In a crisis, the future seems intangible and difficult to grasp. Yet for social science research, perceptions of the future are an important part of understanding crises. As shown by the current coronavirus pandemic – and before that, the 2007 financial crisis or the Brexit vote – to overcome a crisis, socio-political and economic visions for the future are needed just as urgently as vaccines or emergency assistance from the state.

**T**he coronavirus outbreak disrupted routines, hopes, and goals in many areas of life and made them obsolete. We have had to learn to take things one step at a time – and do so indefinitely. Researchers at the Max Planck Institute for the Study of Societies have been working for some time on projects that explore the role of expectations in driving economic and social dynamics. The importance of this approach becomes especially apparent in times of crisis, when images of the future influence very significantly the perception, development, and ways out of crisis.

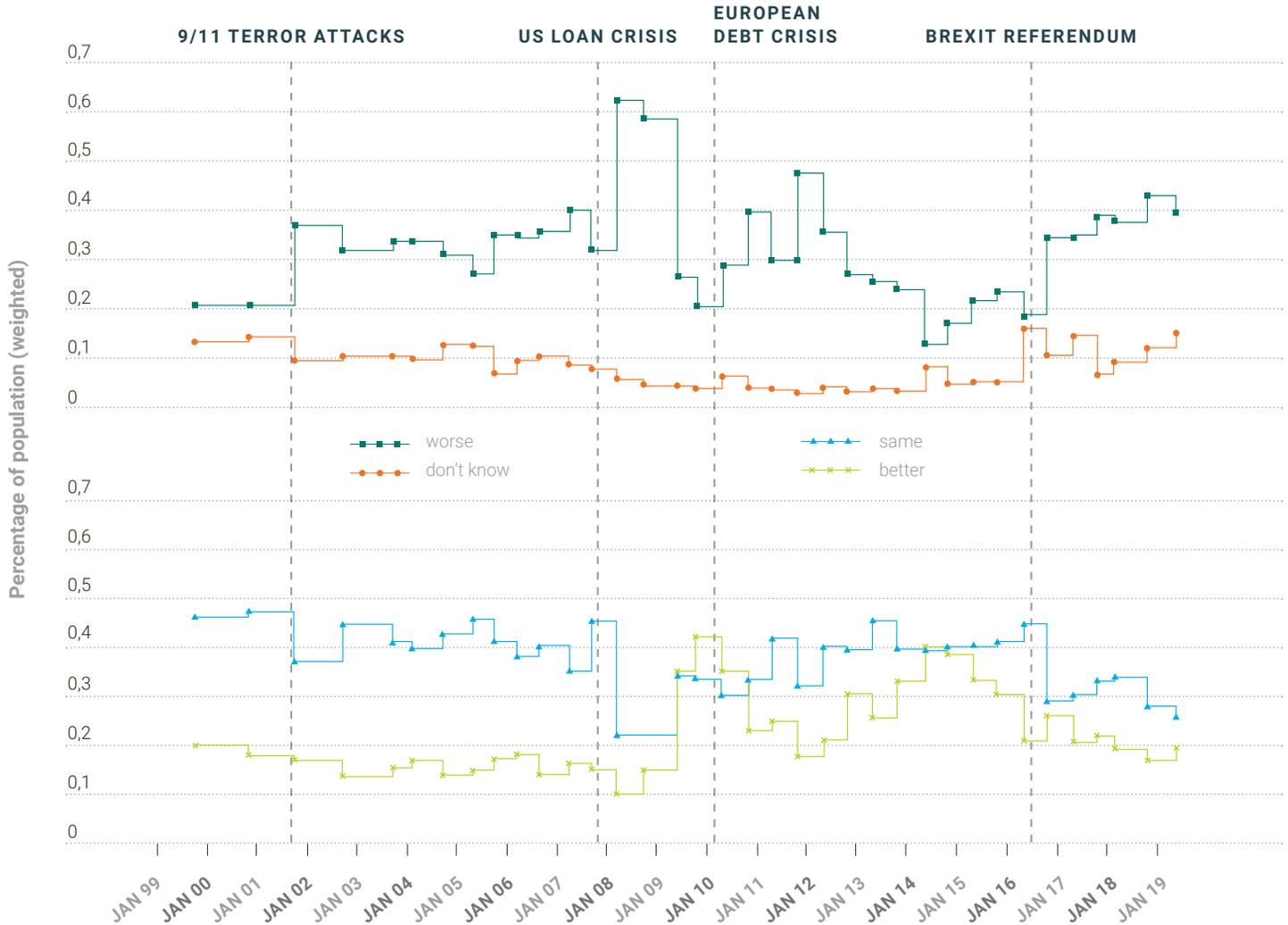
A "crisis" describes a sudden negative turn of events with an uncertain outcome. The financial crash, the Brexit vote, or the coronavirus pandemic are considered crises because they took us by surprise. In a crisis, reality departs from the course it is expected to take. Which is why, paradoxically, our ability to foreknow the future thanks to increasingly accurate forecasts raises the potential for crisis: the more specific our expectations are, the easier it is for them to be disappointed.

Crisis not only disrupts our immediate plans but also challenges some of the fundamental principles underlying how we imagine the future. The impact of the financial crisis made established securitisation

practices suddenly seem questionable, Brexit threatened to undermine the foundations of European integration, and the coronavirus crisis is forcing us to review global mobility. The uncertainty that surrounds a crisis is thus twofold: the immediate turmoil is accompanied by a deeper feeling that the world has stopped making sense. In times of crisis, the experience of the past can no longer serve as a model for the future.

## Real crisis or not such a big deal?

Where long-established standards become obsolete and there are no positive scenarios to look toward, for many people the future seems threatening and unfathomable. In the United Kingdom, the critical events of recent decades have seen this kind of shift in people's perceptions of the future: after the attacks of 9/11, the US subprime mortgage crisis, the European sovereign debt crisis, and the Brexit referendum, there was a decline in the number of British people expecting the economic situation to remain stable or even improve, while the percentage of those who feared it would worsen rose significantly.



Results of Eurobarometer surveys in the United Kingdom: the question was “What are your expectations for the economic situation in the United Kingdom over the next twelve months?”

Whether an unexpected occurrence counts as a turning point or merely as an unfortunate one-off incident is often decided publicly, in heated debate about whether it is a “real” crisis or “not such a big deal.” Was the financial crisis of 2007 a crisis of the global financial system or a case of certain individuals’ misconduct? Would the Brexit vote actually change anything? And is the coronavirus really more dangerous than seasonal flu? Perceptions of the future are important to these debates because they specify negative consequences, paint plausible scenarios, and make the threat of crisis more tangible.

Such discourse is especially significant in an economic crisis because it influences how the crisis develops. Central elements of our economic order, be it wage labor, entrepreneurship, interest rates, or a stable currency, rely on trust in a shapeable future. If expectations are not met and negative scenarios unfold, however, the “engine of capitalism” can start to falter. The resulting vicious circle is very apparent on the financial markets.

In the 2007 housing crisis, negative forecasts undermined trust in the future development. The widespread loss of trust then sparked a crisis that developed first into a global financial and banking crisis and ultimately into a currency and sovereign debt crisis, and brought countries such as Greece to the brink of ruin.

This twofold uncertainty that comes with any crisis has the potential for further economic disruption: uncertain future expectations aggravate economic crises; and crises that are not primarily economic, like the coronavirus pandemic, take on an economic dimension that can be as devastating as the original crisis. Governments are faced with the task of mitigating uncertainties and taking decisive action to create positive expectations. Whether politics is capable of building trust in the future also depends on the persuasive power of rhetoric, however. In the 2012 Eurozone crisis, European Central Bank president Mario Draghi's promise to do "whatever it takes" succeeded in stabilising the situation

on the financial markets and, for the moment, rescuing the Euro.

Although aberrations in the global financial system, political divisions, or a pathogen are hardly likely to be stopped by a show of optimism, intense public debate is the only way to sound out problem-solving scenarios and redefine means and ends. If the future can be seen as open rather than uncertain, and a vision of the future can be established that broad sections of the population share, this can create a climate for recovery. The crisis phase will then give way to a phase of confidence.

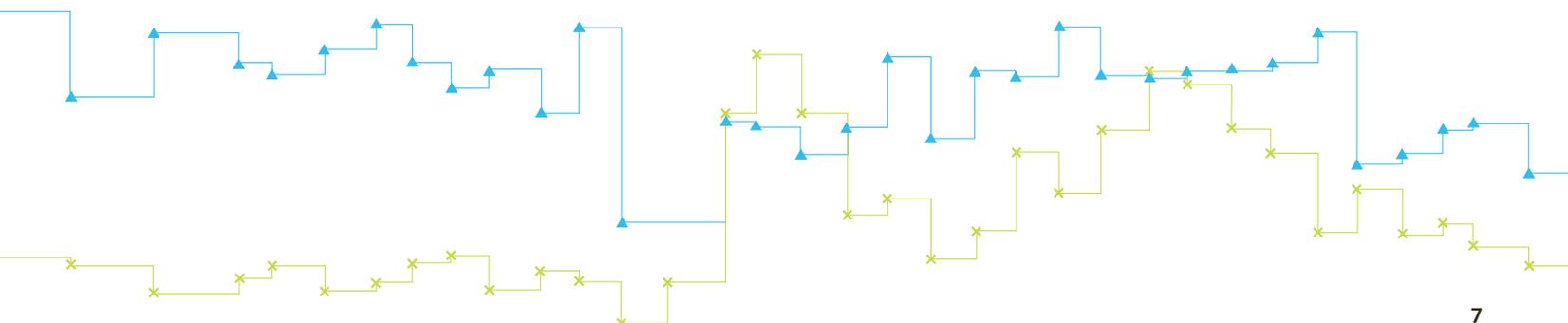
## Few future utopias to hold onto

As Brexit shows, however, this development is not inevitable. The proportion of British people who have a positive outlook on the future was already declining before the referendum. Expectations have continued to decline since, together with a simultaneous rise in the number of people who are too uncertain about the future to give any assessment ("don't know"). The Brexit vote and the controversies that followed were driven not by positive future scenarios but by fears and a nostalgic desire to revive the past.

This kind of "future fatigue" is apparent in many societies at the present time. After a crisis decade in which social divisions have become stronger, it is increasingly difficult even under normal circumstances for fragmented societies to establish a shared vision of what a positive future might look like. The future, it seems, is itself in crisis.

This is an extremely unfortunate position from which to be facing the socio-economic turmoil inflicted by the pandemic. Where progress has already ceased to be a common goal, even in normal times, and there are few future utopias to hold onto, it is all the more difficult in times of crisis to put trust in the future. Overcoming the present crisis therefore requires – at least as urgently as vaccines – socio-political and economic visions for the future that can cut across existing divides and restore lasting confidence. o

## Governments are faced with the task of mitigating uncertainties and creating positive expectations.



# 2 Tailor-made catalysts for the green energy industry

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Producing energy carriers such as hydrogen or hydrocarbons efficiently without emitting carbon dioxide is an essential element of a climate-neutral economy. With the right catalysts, carbon dioxide can be used to produce fuels and even important raw materials for the chemical industry. Our group has successfully observed such a catalyst live in operation, and was able to optimise the production of two economically promising substances from CO<sub>2</sub>.

**T**he transition to green energy is one of the most significant modernisation projects in our society. It will depend on emission-free production of energy carriers such as hydrogen and hydrocarbons.

As an energy carrier, hydrogen has many desirable properties: it is non-toxic, enables energy to be stored and transported, and leaves no pollutants behind when consumed – only water vapour. It can be produced from water by means of electrolysis. If the electricity used stems from renewable energy sources, such as wind power or photovoltaics, no greenhouse gases are emitted.

Recently, researchers have been investigating the possibility of producing other CO<sub>2</sub>-free energy sources. Ethylene, in particular, appears promising. It can be used to generate fuels and, above all, it is an important raw material for the production of chemicals, primarily plastics such as polyethylene. Globally, 158 million tonnes of the gas are produced annually by heating natural gas and the light petroleum naphtha to 850 degrees Celsius.

This high-temperature process is energy inefficient and releases large quantities of CO<sub>2</sub>.

However, ethylene can also be produced directly from CO<sub>2</sub>. Instead of releasing CO<sub>2</sub>, an energy efficient ethylene production would actually remove this greenhouse gas from the atmosphere. However, this is challenging, as CO<sub>2</sub> is extremely stable and inert. Ethylene (C<sub>2</sub>H<sub>4</sub>) production requires the replacement of oxygen atoms (O) in the CO<sub>2</sub> molecule with hydrogen atoms (H). In addition, two carbon atoms (C) need to be bonded, making the reduction process even more complex. This is where electrocatalysts come into play; these bind the desired reaction partners on their surface and drive the chemical reaction directly using electrical power. Such conversion could, in principle, be highly efficient. Our research focuses on identifying the ideal catalysts for this process.

Copper has long been known as an ideal catalyst for ethylene synthesis. In particular, copper-based nanostructures with a specific geometry known as

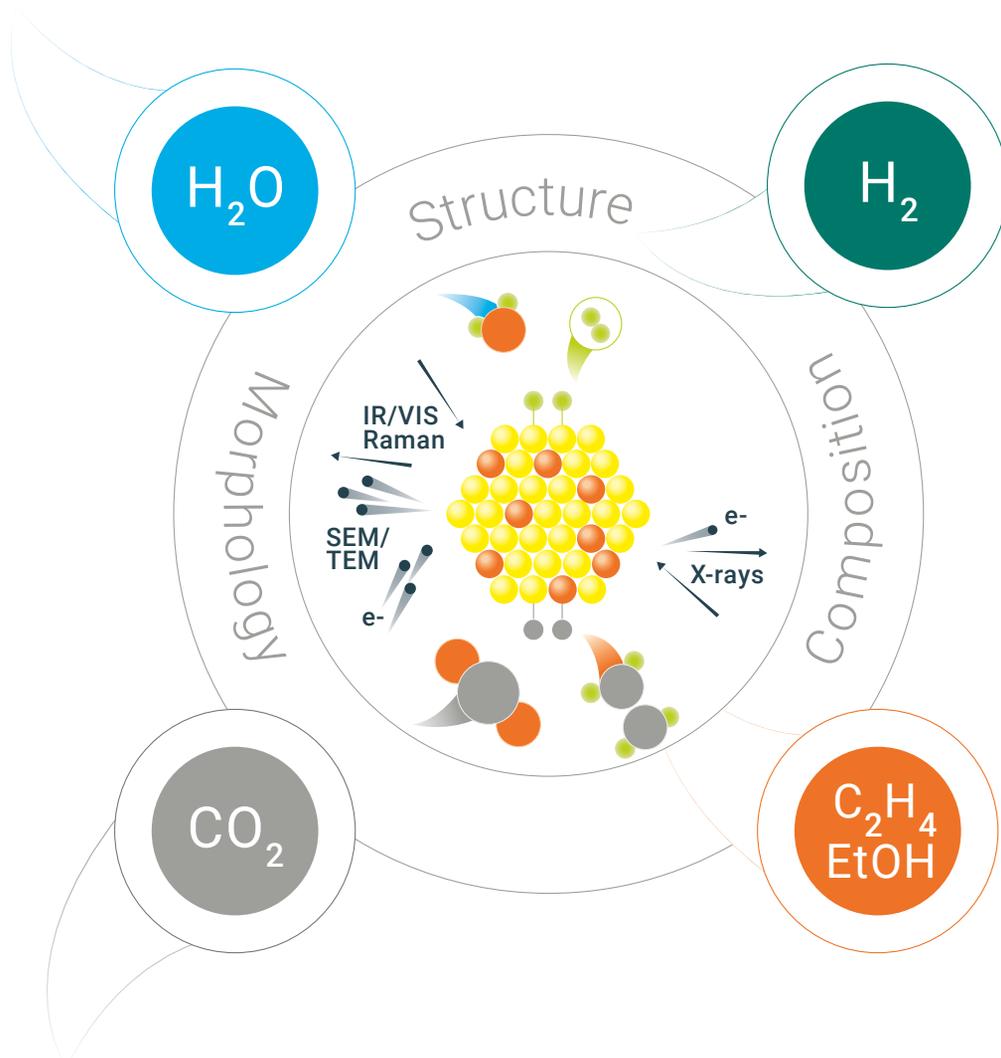
1-0-0 facets are highly selective for forming ethylene. However, the catalyst undergoes continuous changes during the reaction, and its selectivity for ethylene production is therefore not preserved in the long term. To date, this lack of stability and efficiency has rendered such catalysts economically unviable.

### A video of the crime

One key problem has been that the processes underlying the changes to the catalyst surface have never been identified. What is clear is that core properties of catalysts, such as chemical composition and atomic surface structure, change continuously when exposed to reaction conditions in liquids, directly influencing their functional mechanisms. Tracking down how these changes

occur is like detective work: we know the scene before and after the crime, and from there we try and deduce what happened in between. But what would really help us is a video of the crime. We have succeeded in observing the course of such an electrochemical reaction live.

Our success was based on further developing imaging techniques at an atomic and high-temporal resolution allowing them to be employed even in the most unusual conditions, for instance in liquid and during active electrolysis. The tools we chose were electrochemical atomic force microscopy and liquid phase electron microscopy. They allowed us to discover that the catalysis first resulted in the generation of copper nanocubes. However, these then moved on the electrode, and they either shrank and formed small nanoparticles, or tree- or shrub-like structures termed dendrites.



*CO<sub>2</sub> and water (H<sub>2</sub>O) can be electrolysed on a catalyst. In the process, ethylene (C<sub>2</sub>H<sub>4</sub>) or ethanol (EtOH) or hydrogen (H<sub>2</sub>) can be formed. To optimise the process, it was investigated using various methods.*

## Precise control over the ideal morphology can trigger desired electrochemical reactions such as the conversion of CO<sub>2</sub> or hydrogen production.

This dynamic adaptation of the catalyst form due to the reaction conditions illustrates that the function of a catalyst is always linked to its morphology in the active state. In this case, a morphological transformation into small nanoparticles occurred, which is associated with increased production of hydrogen. Conversely, this means that if we can precisely achieve an ideal morphology and preserve it under reaction conditions, we can promote desirable electrochemical reactions such as the conversion of CO<sub>2</sub> to hydrocarbons and fuels (ethylene and ethanol) or the electrochemical production of hydrogen from water.

### An optimised catalyst design

In another experiment, we also demonstrated that the ways in which the electrical voltage is applied to the catalyst likewise influence the chemical reaction. Positive voltage pulses during CO<sub>2</sub> reduction on copper surfaces result in increased production of ethanol compared to other carbon products. Using atomic force microscopy

and X-ray photoelectron spectroscopy, we discovered how the surface changed during this reaction – nanopramids formed and the copper oxidised. As a result, we revealed that the voltage pulses induce morphological changes on the copper surface and create particular oxide structures. Both of these processes influence selective production of ethanol.

The findings might enable us one day to design a catalyst that is optimised specifically either for producing ethylene or other organic substances, such as ethanol, directly from CO<sub>2</sub> at a high efficiency. As we have seen, such electrocatalysts can even be dynamically controlled using targeted voltage pulses under technologically relevant reaction conditions.

However, a number of questions remain unanswered before they can find their way from the laboratory to large-scale applications. Among them are the impact of high electrical current densities or non-pure gaseous feeds on the evolution of the structure and surface composition of the catalyst, and hence its functionality. Our research is aimed at further improving our understanding of these fundamental interactions in the future. o

# 3 Cancer cells on a diet

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HERBERT WALDMANN**  
↳ Max Planck Institute  
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Dortmund

Many of us are all too familiar with a craving for sweet food. Cancer cells are also addicted to sugar – they need ten times more sugar than normal cells. We are exploiting this weakness and use inhibitors to put tumour cells on a strict low-sugar diet. Our substances are now being further developed at the Lead Discovery Center to create “lead molecules” for medicine. If successful, the compounds may one day be used to treat cancer.

**S**ugar in the form of glucose fulfils a variety of functions: it is a readily available source of energy and provides basic building blocks for biomolecules that are required for cell division and growth. Usually, glucose is metabolised highly efficiently in the presence of oxygen to generate the greatest possible quantity of energy.

In 1924, the German biochemist Otto Warburg observed that cancer cells break down glucose in a different way compared to healthy cells. The method they employ to gain energy is faster but more inefficient. Healthy body cells also adopt this metabolic route whenever oxygen is scarce, for example, during high levels of physical activity.

## High sugar demand

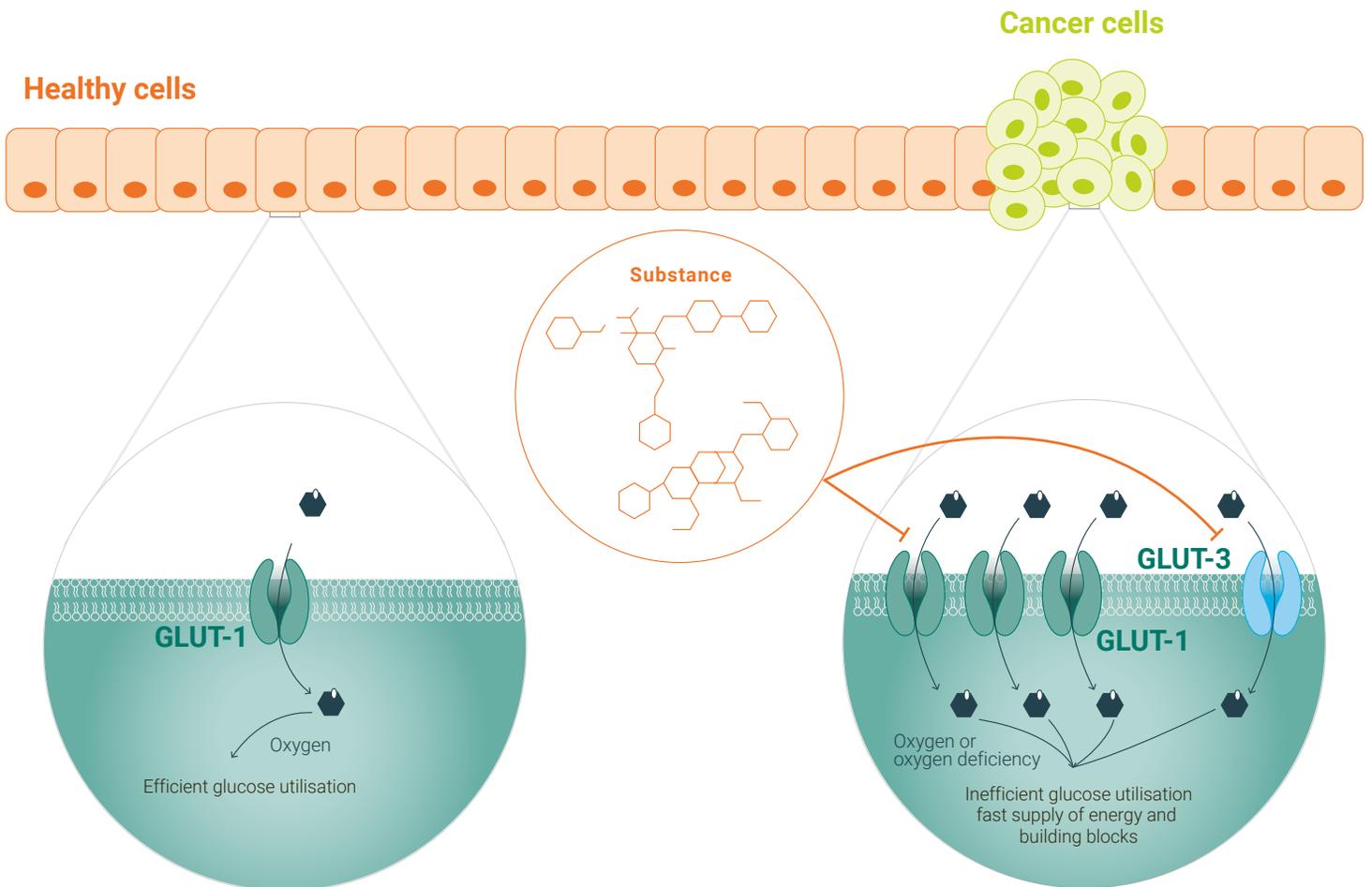
The unusual feature of this “Warburg effect” is that cancer cells prefer to rapidly metabolise sugar even when they have sufficient supply of oxygen. However, as only a fraction of the required energy is provided by this

route, cells compensate the supply shortfall by consuming more than ten times the amount of sugar. Modern methods to diagnose cancer are based on this discovery. Positron emission tomography (PET), for instance, can visualise where in the body more sugar is absorbed and reveal the location and stage of a tumour.

At the Max Planck Institute of Molecular Physiology in Dortmund, we are aiming to combat cancer cells by exploiting their sugar addiction. Our strategy is to block the transport of glucose into the cells. But how does sugar enter cells? Glucose is highly soluble in water and can therefore be easily transported to cells via the blood. Various proteins in the glucose transporter (GLUT) family are then responsible for its uptake into cells. In particular, two glucose transporters, GLUT-1 and GLUT-3, are considered to be promising targets.

Nature has given rise to a wide variety of substances that are biologically active; their chemical structure allows them to bind to certain proteins and influence protein activity. Many of these natural products are also active in human cells and serve as inspiration for pharmaceuticals. Well known examples are digitalis

Healthy cells (red) utilise glucose in the presence of oxygen. Fast-growing cancer cells (green) use the sugar without oxygen. This is considerably less efficient, but faster. The cancer cells therefore have to absorb more sugar. To this end, they produce particularly many glucose transporters (GLUTs). Inhibitors block the transport molecules and starve the cancer cells in this way.



(digitalis glycosides) obtained from foxgloves, which has been used as a drug to treat heart disease, and salicylic acid from willows, which is the source of the painkiller aspirin.

## Our inhibitors are currently being developed into “lead structures” – the first step on the way to becoming a drug.

Herbert Waldmann’s research team has developed new substances on the basis of natural products. We break down natural products into their building blocks and combine them in novel ways. This allows us to obtain a large variety of potentially effective substances that do not exist in nature in this form.

Chemical synthetic techniques have expanded the number of potential biologically active substances. We explored a library of more than 150,000 chemical substances that is comparable with the search for “the needle in the haystack”. This led us to three candidates that each block both variants of the sugar transporter. Two of these candidates contain novel combinations of natural building blocks that are not found in nature.

In tumour cell cultures, the resulting pseudo-natural substances showed the desired effect: they slowed down the growth of a number of cancer cell lines until they died. Importantly, healthy cells were not affected.

Unfortunately, tumour cells cannot always be tricked so easily. It is not uncommon for them to develop drug resistance or find another means of escape. If they are short of glucose, cells can also utilise other nutrients, for instance glutamine. To prevent cancer cells – in our experiments a colon cancer cell line – from doing this, we simultaneously exposed them to a GLUT inhibitor and an inhibitor of glutamine metabolism. This combination indeed enhanced the growth-inhibiting effect.

Sugar-starved tumour cells can respond to low glucose levels by producing more glucose transporters, e.g., GLUT-3. Since our GLUT inhibitors block GLUT-1 and GLUT-3, this cancer cell defence mechanism is also bypassed. Hence, these substances may be particularly effective, because they target both, the metabolism and the internal survival mechanisms of cancer cells.

### Effective in the centres of tumours

Tumours, in contrast to flat cell cultures on nutrient plates, are three-dimensional structures. Their outer cells have better access to nutrients than those inside. Are our inhibitors just as effective on such 3D cell formations? To test this in a realistic manner, we investigated the influence of one of the GLUT inhibitors on artificially grown 3D cell structures, known as spheroids. We found that the compound does indeed inhibit the growth of cancer cells in 3D structures. In particular, the cells inside the spheroids died. This observation is consistent with other cancer research findings as cells in the centre of tumours are particularly dependent on metabolising glucose.

Our GLUT inhibitors may represent a promising therapeutic opportunity – not only against cancer, but also for the treatment of other diseases associated with high sugar demand, such as inflammation, specific bacterial and viral infections, and psoriasis. Currently, our GLUT inhibitors are being further developed into “lead structures” at the Lead Discovery Center in Dortmund, founded by the technology transfer organisation Max Planck Innovation – a first step on the way to becoming a drug. ◦

# 4 Theory and practice of COVID-19 containment

**VIOLA  
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MICHAEL WILCZEK**

› *Max Planck Institute  
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In spring 2020, the world was caught off guard by a virus: SARS-CoV-2 has spread rapidly and posed unexpected challenges to each and every individual. Collaborating across departments and research groups at the Max Planck Institute for Dynamics and Self-Organization ever since, we have been providing insights about the spread and containment of COVID-19 and have communicated them to a broad audience.

**A**t first, there were isolated reports of a new respiratory disease in China. At the end of January 2020, Germany declared its first cases. By the end of February 2020, it had become clear that SARS-CoV-2 had arrived in Europe. Immediately after, we designed a model that aimed to extract crucial information from the reported case numbers. It allowed us to estimate the reproduction number  $R$ , i.e. the number of offspring infections an infected individual causes on average, to quantify the effectiveness of mitigation measures (e.g. lockdowns) and make short-term forecasts about the spread. Our work thus allowed critical and urgent assessment of mitigation strategies. This fast and effective work was made possible by a group of interdisciplinary researchers with expertise ranging from medicine to physics at the Göttingen Campus and within the Max Planck Society.

A team around Eberhard Bodenschatz also investigated the physical basis underlying the transmission of the SARS-CoV-2 virus. It is mainly spread via very fine droplets in the air, so-called aerosols. Infected people exhale these every time they breathe – but even more so, for example, when talking or singing. These aerosols then diffuse into the environment. When other people nearby inhale them, they can then contract the virus. At the Max Planck Institute for Dynamics and Self-Organization, we not only performed laboratory measurements on the aerosols themselves with more than 130 test subjects, but also measured how these particles spread and how masks counteract an infection. As a

practical contribution, we also developed an application, which factors in the characteristics of any given room and indicates precisely when it needs ventilation in order to minimise the risk of infection.

Shortly after the pandemic started, we investigated pathways out of it. In the beginning, it was widely discussed whether natural population immunity, that means without vaccination, could be achieved in a controlled manner. Population immunity is reached when a large part of the population has acquired immunity, whether through vaccination or post-infection. The virus can then spread only locally in the population. Using an epidemiological model, a team around Stephan Herminghaus studied whether natural population immunity can be achieved, and if so, under which circumstances. We especially paid close attention to waning immunity. Post-infection immunity slowly fades away, so that a re-infection is possible again after several months or years. We found that this makes vaccination vital for acquiring population immunity against SARS-CoV-2 for the following reason: Because of the capacity limits of intensive care units, the spread of SARS-CoV-2 would have to be stretched over years, so that the first few people could be re-infected before the last ones have acquired immunity.

We demonstrated an alternative containment strategy offering practical advice to control the pandemic: an equilibrium at low case numbers with only moderate contact restrictions. Our calculations show that the infection rates can remain stable around a weekly



incidence of ten or less new infections per 100,000 inhabitants, without requiring very stringent contact reductions. We discovered a novel tipping point, in addition to the well-known one when exceeding an R-value of 1: if incidences grow too fast, the trend tips over to an exponential growth, which is due to the health authorities not being able anymore to efficiently trace and quarantine the contacts of every individual that tested positive. It is thus possible to avoid lockdowns – but only at low case numbers. High infection rates, on the contrary, are highly unstable and repeatedly require strict measures in order not to overwhelm health care systems. Public health, the society and the economy: They all greatly profit from low case numbers. Further facilitation can be expected from vaccination in the midterm.

Restricting mobility mitigates the spread of COVID-19. One particular proposal has been to split regional populations into smaller groups and allow contacts only within these groups. A team around Ramin

growing dark figure at high case numbers. We showed that a large dark figure translates to many infected individuals significantly spreading the virus unknowingly. Undetected, the spread leaps to the elderly. The reported deaths soon rose just as we had predicted. Protecting the elderly, which had been possible at low case numbers, was no longer viable.

Testing, tracing of contacts and isolating infected individuals as well as their contacts (Test–Trace–Isolate – TTI) has contributed greatly to the mitigation of the pandemic. But how effective are these measures in reality? TTI has to face several challenges: it needs to be faster than the virus spreading rate. It also needs to find and reduce pre- and asymptomatic transmissions. It needs to grapple with TTI-avoiders and quarantine orders not being followed impeccably. And once the case numbers grow too large and exceed the TTI capacity, the tipping point we discovered is reached and the spread accelerates rapidly. Case numbers suddenly grow faster than exponentially. We captured all these effects in our model and managed to estimate that TTI still allows us to have almost twice the number of unknown offspring infections than without TTI. Thus, once it breaks down, one has to drastically reduce the number of contacts just to stop the exponential growth. We published these results in mid-September. In fall, we had to watch as exactly this was happening in Germany. District after district reported an increase in case numbers – and as soon as the weekly incidence exceeded roughly 20 new infections per 100,000 inhabitants, the numbers skyrocketed. A few weeks later, restrictions were tightened slightly, but this merely curbed the rise. Only towards the end of December did the more stringent lockdown prescriptions lower the incidence again. This is comparable to a fire: If it has not spread too widely yet (like with a low COVID incidence), it can still be stopped locally with an extinguisher. But let it turn into a blaze, and drastic countermeasures will become necessary.

### Many discussions with politicians

Besides the research, broadly communicating our findings was a key concern for us. Since spring 2020, we have regularly published our results in influential scientific journals. We have also presented them in numerous position papers, newspaper articles, interviews and talk shows, and have frequently talked to politicians. Thereby, the Max Planck Institute for Dynamics and Self-Organization has contributed to explaining and further developing the physics underlying viral spread, exponential growth and the mathematics behind mitigation measures. We very much hope that our fundamental scientific research continues to contribute to the containment of this pandemic in 2021. o

## At incidences below ten per 100,000 inhabitants, local resolute action is especially effective.

Golestanian has shown in a model that random fluctuations can eradicate the virus locally. In the same way, they can reduce the peak height of a whole wave of infections. Similar effects also make regional containment strategies particularly effective at low case numbers. But for this to happen, it is crucial to prevent all trans-regional infection chains. To maximise the impact of these effects, local contact restrictions should be installed already at low incidences of around ten new infections per 100,000 inhabitants in seven days. Yet, this approach would overall require much less contact restrictions than what is necessary under a national lockdown or at higher threshold values.

Our work has always been heavily based on the latest, daily data on the course of the pandemic. Long before the second wave was publicly discussed in Germany, we inferred its early indications from the data. The daily reported case numbers had consistently doubled every two to four weeks, even though at a low level. However, initially only the daily reported deaths remained constant. This apparent discrepancy fueled speculations that merely the number of tests had increased, but not the actual spread. We disproved this hypothesis by breaking down the numbers by age in our calculations. At low incidences, the elderly were well protected. But this proved to be impossible with a

# 5 Married young – separated by law?

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Marriage between minors is prohibited in Germany, primarily to protect girls and young women from the consequences of a premature marriage. However, the scope of the Act to Combat Child Marriage extends beyond Germany and also negates the legitimacy of marriages legally entered under foreign law. Yet it is questionable whether this is compatible with the protection of marriage and the best interests and welfare of the children involved.

**D**uring the influx of refugees into Europe in the autumn of 2015, the fate of a Syrian refugee couple was closely followed by many in the German public. The couple had been separated by the German authorities because the bride had been only 14 years old when they married. The forced separation took place despite the fact that the young woman stated that she wished to remain with her husband, who was eight years older than her. Ought such a marriage be considered legal in Germany?

Not according to the law. In 2017, legislators not only abolished the possibility of marrying under the age of 18 in individual cases (with permission) throughout Germany, but also extended this strict age restriction to marriages entered into abroad: with few exceptions, a marriage must be annulled if at least one of the spouses was between the ages of 16 and 18 at the time of marriage. If either spouse was under the age of 16, the marriage is considered void and is treated as if it were never concluded.

Nowadays, underage marriage is extremely rare in Germany, but the phenomenon has re-entered the country with refugees. The main thrust of the relevant legislation is therefore primarily directed toward marriages entered abroad, all of which are – without exception – not to be recognised if they were concluded when either of the parties was under 18.

The German Federal Court of Justice, which was called upon to decide on the validity of the Syrian couple's marriage at third instance, was sceptical, stating that the German Act to Combat Child Marriage potentially violates the protection of marriage guaranteed under the German Basic Law, and that the underage wife was also entitled to have her status recognised. The German Federal Constitutional Court now has to pronounce the final verdict.

## Variable criteria apply in other countries

In December 2019, the Court sent a request for an expert third-party opinion to the Max Planck Institute for Comparative and International Private Law. Our Institute, however, has no particular expertise in the largely empirical questions posed by the Court relating to the situation of refugees in Germany. What we sought to do, instead, was to provide a position statement based on our core proficiencies, which include comparative private law with a post-colonial focus as well as private international law. We assembled a team of 30 legal scholars to examine the social, legal, and practical

## Particularly the underage wife, who should be protected, is worse off under this German law.

ramifications of child marriage in over 60 jurisdictions, including not only Islamic legal systems and Latin American states, but also European countries (both within and outside the EU) as well as the USA and Japan.

Merely discussing “child marriage” in an undifferentiated manner is problematic, as such marriage also concerns individuals between the ages of 15 and 17, who are generally considered to be adolescents; consequently, we, unlike the legislature, chose to use the term “early marriage” in our position statement so as to encompass all marriages entered into at a young age, with no precise age limit. Indeed, a consideration of different jurisdictions reveals that the age of consent, i.e., the legal assessment of when a person has the necessary physical and mental maturity to foresee the consequences of marriage and to be able to assume them, is only partially linked to fixed age limits. This is determined in many countries on the basis of variable criteria – such as physical or mental maturity or the best interests of the child – which are to be specified by the competent authorities and bodies.

### Marriage as a way out of hardship

Similarly, a focus on the refugee situation narrows the view: even in certain European countries, as well as in the USA and Latin America, people can marry before the age of 18. If, for example, an American woman were to suffer a heart attack during a trip to Germany, her husband would under the new German legislation have no legal right to decide on her treatment if she had

married him while still a minor, since the marriage would not be considered valid in Germany.

Specifically, our position statement was guided by the question of just when it is that foreign marriages not meeting the requirements of German law are nevertheless deserving of protection. Marital traditions are shaped in particular by values relating to marriage itself and towards family, as well as by the position of minors and gender roles: in some places, sexual relations are permissible solely between spouses, and in others, only marriage ensures a recognised social position. It appears that, in certain situations, early marriage offers a way out of economic hardship or provides an escape from a violent family. As such, there are many reasons for entering into an early marriage.

### Those affected forfeit claims

Where any such marriage is denied legal validity in an undifferentiated manner upon arrival in Germany, the social and legal status of the couple concerned is violated, with the outcome that they will forfeit certain property rights, such as the right to marital maintenance or, in the event of death, the spousal right of inheritance. As a result, it is in particular the underage wife – exactly the individual who is purportedly to be protected – who often ends up worse off.

What the global comparison shows is that by abolishing any consideration of the individual case and by equating domestic and foreign marriages, the Act to Combat Child Marriage risks creating unusual hardship. It allows no leeway for the assessment of individual concerns or the specific life circumstances of the persons involved, nor does it allow these individuals to assert their own position within the framework of a legal procedure. They no longer have a voice.

One of the challenges of living in a globalised world is dealing with different legal cultures. If marriages that are entered under foreign law and conducted and pursued in good faith are declared invalid with no examination of the individual case, the status guaranteed by another legal system is entirely withheld, a pronouncement which is not the job of the law. o

# 6 Protein congestion in the brain

**IRINA DUDANOVA**  
↳ Max Planck Institute  
of Neurobiology,  
Martinsried

Neurodegenerative diseases such as Alzheimer's, Parkinson's, and Huntington's disease are incurable brain disorders. A common feature of these diseases is accumulation of protein deposits in the brain. Together with my team, I am investigating how these deposits affect the survival and function of nerve cells.

**H**ealthy cells are masters of protein folding. In order for proteins to carry out their respective tasks, they must assemble into a complex three-dimensional structure. Every cell has strict quality control mechanisms in place to ensure that proteins fold correctly. Special folding helper molecules recognise and repair damaged proteins or promote their degradation, thus maintaining proteostasis – the balance of protein functions in the cell.

This balance is particularly important in nerve cells. Because they are long-lived and do not divide, nerve cells are particularly susceptible to ageing. In the case of neurodegenerative diseases, misfolded proteins accumulate and form deposits in nerve cells instead of being degraded. Depending on the disease, this can affect memory, muscle control, and/or elementary bodily functions. But what is the link between protein misfolding and disease symptoms? My team at the Max Planck Institute of Neurobiology is investigating this in cultured cells and in living mice, which serve as models of human diseases.

In neurodegenerative diseases, the protein quality control system is overloaded by the accumulation of damaged proteins, and proteostasis gets out of balance. In order to study this disturbance of proteostasis in the

mouse brain, we are using a fluorescent sensor molecule that allows us to visualise the state of proteostasis under a microscope. To make sure that the sensor protein itself does not interfere with cellular processes, we are using firefly luciferase, the protein that makes fireflies glow. This protein is normally not found in mice. Importantly, this protein is optimised for the insect's lower body temperature. In the warmer mammalian cells, it constantly requires assistance of the folding helpers to stay in shape. The sensor fluorescence therefore shows how well the folding helpers are working.

## Sensor for protein folding

Healthy nerve cells have sufficient folding capacity to keep the small amounts of the sensor protein correctly folded. Under these conditions, the sensor is evenly distributed in the cell. However, if the protein quality control systems is overwhelmed, the sensor protein can no longer maintain its correct shape. Then it starts forming small clusters inside the cells; these appear as green fluorescent dots under the microscope. Using this method, proteostasis disturbances associated with various diseases can be detected and studied in detail.

# Alzheimer



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In the future, the sensor can also be used to assess the efficacy of potential therapies.

What else happens in the cell when proteins misfold? To answer this question, we studied artificial aggregating proteins together with colleagues from the Max Planck Institute of Biochemistry. These proteins mimic the typical misfolded structure of the proteins involved in neurodegenerative diseases, and form deposits in the cells. However, these proteins are not directly related to any disease-relevant protein, and therefore can be used to investigate the basic mechanisms these diseases have in common.

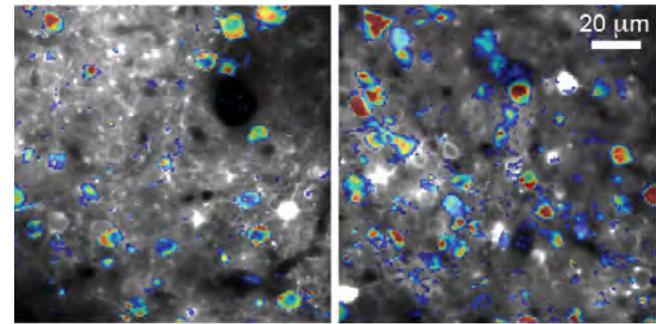
## Problems with the waste disposal

Studies with the electron microscope show that cells with artificially generated protein deposits have impaired lysosomes, vesicle-like organelles responsible for waste disposal. These organelles normally take up misfolded proteins and other cellular waste and digest them. However, in this case, the lysosomes are swollen and obviously contain undigested material.

We know from biochemical analyses that protein deposits are sticky and tend to trap functional proteins in the cell. We investigated the proteins that stick to the deposits, and found a protein involved in the transport of lysosome building blocks. Defects of lysosomes cause a congestion of the cellular disposal system. This in turn impairs the survival of nerve cells. In our joint study, we demonstrated a new link between the protein deposits, the impairment of degradation in nerve cells, and ultimately cell death.

Not only do protein deposits damage nerve cells, they also disrupt cell-to-cell communication. Using a special microscopy technique, we are investigating these changes in mice with Huntington's disease. Patients suffering from this disease develop involuntary muscle twitches, among other symptoms. With our method, we can measure the activity of nerve cells in the living animal and follow the course of its changes over several weeks. Our results show that the nerve cells in the part of the cerebral

*Microscope images of nerve cells in the cerebral cortex of a healthy mouse (left) and a mouse with a Huntington's-like disease (right). Cells with strong activity are red, weakly active cells are shown in blue. The stronger activity in the brain of the sick animal could be due to damage to inhibitory nerve cells.*



cortex responsible for muscle control become more active before the behavioural changes occur. Histological studies on tissue samples from mice and humans with Huntington's disease, combined with biochemical analyses, indicate that this hyperactivity may be related to reduced inhibition in the nerve cell junctions (synapses).

## Plans for the future

Each neurodegenerative disease manifests differently. This is because certain nerve cell types are affected particularly early and severely, while others are spared. Why this happens is still unclear. In future studies, we would like to investigate the characteristics of the differently affected cell types in more detail. This will help us understand which processes play a role in triggering the disease. ◦

# 7 International tax justice

**JOHANNA STARK**

Max Planck Institute  
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Munich

The international tax system is facing fundamental reforms. Recent times have seen growing calls for considerations of justice to be given a greater role in the international distribution of taxing rights. Agreement is still missing, however, as to what justice means in this context. A look at various philosophical theories of justice does not provide a consistent picture when it comes to allocating taxing rights between states.

**A**pple designs a new iPhone in California, has it assembled in China, then sells it to German customers and, via intra-group agreements, attributes the final profits to a subsidiary based in Ireland – which state may tax the final profits and to what extent? For answers to these questions we must look to International Tax Law, a regulatory body of international agreements whose main elements date back about one hundred years, and which determine the allocation of taxing rights with respect to profits generated from cross-border business activities.

## Adapting the entire regulatory structure

This regulatory system is now facing fundamental reforms. There is agreement that the international tax system needs more than piecemeal adjustment: instead, the entire regulatory structure must be adapted to the growing integration of the world economy, the increased mobility of taxpayers and capital, and to primarily digital business models.

Less agreement has been found on the structural and guiding principles that such a realignment of the international tax system should follow. There are increasing calls for the international community to focus on how a new international tax system can be designed to be not only efficient and enforceable, but also meet requirements of justice. The demand for international tax justice comes not least from developing and emerging countries, which want to see their contribution to the overall value generated by multinational enterprises translated into a larger piece of the 'tax cake' coming from these activities than is the case under the current rules.

Inasmuch as this is a matter of re-weighting of contributions to value creation, what we are essentially talking about here is a plausible understanding of the concept of value creation itself. The goal of distributing taxing rights according to where value is created makes sense at first glance; on closer inspection, however, it turns out that the concept of value creation does not help when it comes to determining how much value is created where. Beyond excluding the attribution of value to tax havens in which multinational enterprises tend to enjoy a mere paper presence based on 'letterbox compa-



*Slums in Dhaka,  
the capital of Bangladesh.  
People living in slums  
could probably benefit  
from changes in the  
international tax code.*

nies', the concept of value creation hardly provides guidance on how to distribute taxing rights among all those states that claim a territorial nexus to factors such as development, production, marketing, and sales.

There is, however, another dimension to the discussion on increasing justice in international taxation. Here, it is the drastically unequal distribution of resources and life opportunities across the globe that calls for legal and political reform, including international taxation. This argument takes the needs and (human) rights of individuals as its starting point. Satisfying these needs and protecting basic rights, such as the right to education, requires resources.

## Redistribution across borders?

It would be possible, in principle, to use international taxation as an instrument for redistributing financial resources, particularly to the benefit of developing countries. In the national context, the tax system is seen as one of the primary political instruments for resource redistribution, even if design and scope of such schemes are a regular subject of political dispute. Dealing with global poverty and inequality, however, has rarely played a role in this context.

**The realisation of basic rights,  
such as the right to education,  
requires resources.**

## An increase in taxing rights for a state is not necessarily accompanied by an improvement in the living conditions of its inhabitants.

This discrepancy between national and international perspectives on the moral imperative of redistribution can be explained in terms of social psychology. The stronger the social, political and economic relationships are among people, the more likely they are to see redistribution as a duty of justice. But what about the normative force of this claim? In other words: are there stronger reasons of justice for supporting fellow human beings in Germany with tax-financed social benefits than for helping starving children in Bangladesh? If so, what is the justification for this distinction? Different theories of justice vary in their answers to these questions. While the 'global justice debate' has primarily engaged political philosophers and theorists, it has implications for the emerging international tax justice debate as well.

### Combat profit shifting

Beyond the territorial scope of justice obligations, one should ask: is international tax law the right instrument for redistribution across national borders? It is important to distinguish between the reasons for or against international redistribution of resources in general and the advantages and disadvantages of different ways of achieving such redistribution, and thus ultimately improving the living conditions and opportunities of people, especially in developing countries. The full picture must include a comparison with other instrumental options, such as humanitarian aid and develop-

ment aid, but also a strengthening of human rights protections in the early stages of international supply chains. While acknowledging the need for political action with regard to the situation of people in many less affluent parts of the world, it is important to realise that an increase in taxing rights for a particular state is not necessarily accompanied by an improvement in the living conditions of its inhabitants. If the basic needs, rights, and life chances of individuals and the glaring inequality between people are what constitutes the justice problem, a redistribution of taxing rights between states, thus on a necessarily collective level, is no guarantee for success.

Even if there is no ideal solution for a fair design of this multi-layered distributional scenario, the debate about it has at least led to political momentum and collective willingness to act on a related problem: taxing rights are worth little if there is hardly any profit to be taxed at all. As a consequence, political agreement must be found that ends Apple & Co's ability to legally shift profits around the globe until they disappear into a tax-free nirvana. With a coordinated package of various measures, the OECD and the G20, the group of the twenty most important industrialised and emerging countries, are currently trying to combat such profit shifting by multinational enterprises, especially in the digital sector. While the extent to which this initiative will achieve its aims remains to be seen, the promise that some of its parts hold in terms of increasing justice, for example by ensuring a global minimum taxation of certain profits, should not be underestimated. o



## 8

# Better hearing through brain stimulation

**MOLLY J HENRY,  
YURANNY  
CABRAL-CALDERIN**

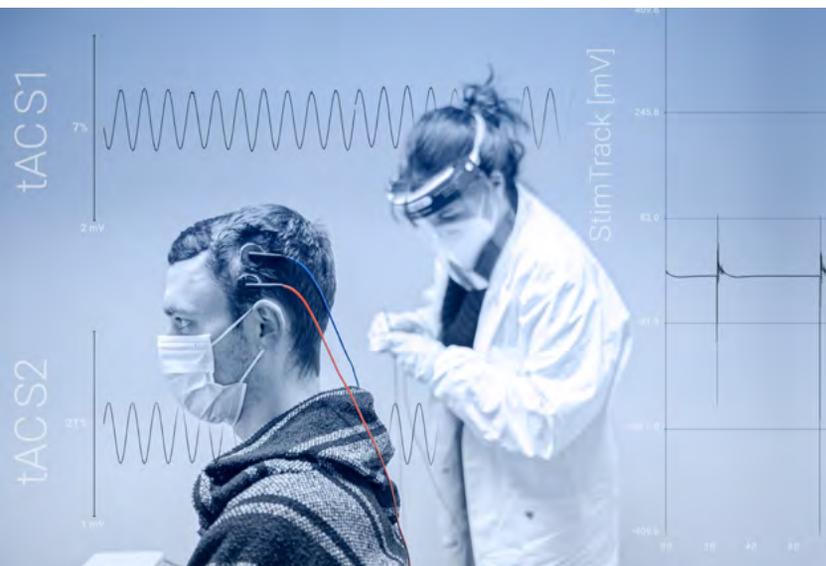
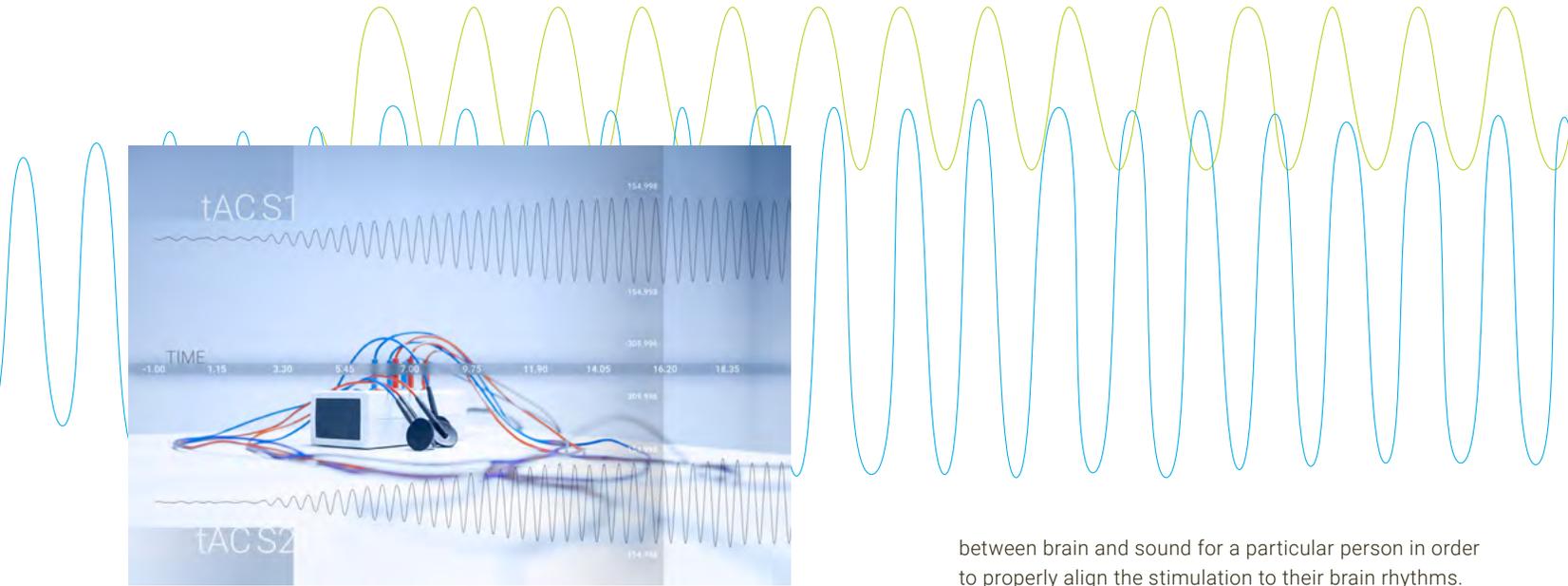
↳ *Max Planck Institute  
for Empirical Aesthetics,  
Frankfurt am Main*

The activities of human brain cells have certain rhythms. These brain rhythms synchronise with the rhythms of sounds we hear, including spoken language. The more successfully our brain and our surroundings are synchronised, the better we understand what we hear. New brain stimulation techniques have the potential to increase synchrony and thus hearing if the stimulation can be precisely targeted to the brain. We looked at whether such an alignment is possible in terms of stability of brain rhythms from day to day.

**A**s soon as any sound – a voice or a song, for example – hits our ear, the sound wave is converted into an electrical signal and sent to the brain. In the brain, certain nerve cells are synchronised to the electrical signal coming from the ears, and so switch on or off in time with the rhythm of the sound. This brain-environment synchronisation is important for our ability to make sense of the sounds in the world. For example, the more successfully our brain rhythms synchronise with the rhythms in speech, the better we understand the person who is speaking, the better we later remember what they said, and the better we are at picking out that speaker's voice from background noise. This last point is very important, because listening to someone speak in a noisy situation is one of the things we start to struggle with most as we grow older. This had led scientists to the idea that if we can find a way to improve brain-environment synchrony, we might be able to alleviate some of the problems that older people have with listening in noisy situations.

One technique that has shown promise for its potential to improve synchrony between brain rhythms and sound rhythms is called transcranial alternating current stimulation. The stimulation works by applying a weak electrical current to the outside of a person's head by placing electrodes on their scalp. This technique is perfectly safe, and the person being stimulated usually cannot feel the stimulation at all. The electrical current has been shown to link up with electrical brain rhythms, and so is a tool that we can use to alter brain rhythms' natural timing and shape. In the context of listening, the idea is that if we could line up the electrical current with a person's brain rhythms, we could help them get in sync better with the rhythms of sounds. In fact, there are already a number of studies attempting to test this idea (all conducted on young, normal-hearing adults), but the results have been inconsistent.

Each person's brain rhythms lag behind rhythms in the world with a time lag that is specific to that individual person. Therefore, we have to first know the time lag



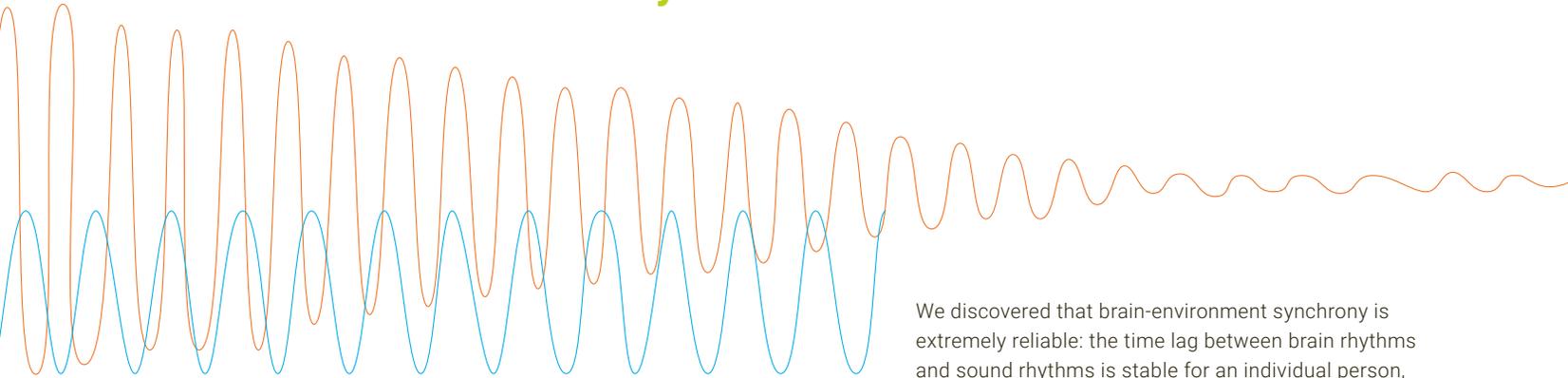
*In transcranial alternating current stimulation, two electrodes on each side of a person's head control the auditory system. The waves show the weak electric current applied to the two electrodes. The person stimulated cannot feel the stimulation at all.*

between brain and sound for a particular person in order to properly align the stimulation to their brain rhythms. However, one problem is that the prospect of improving brain-environment synchrony depends on an assumption that has never been tested before: is brain-environment synchrony the same from one day to the next? We might measure a person's brain rhythms one day, and then have them come back for the stimulation treatment on another day after we've had a chance to analyse their data. Or, we might measure a person's brain rhythms in the morning, and apply the technique later in the afternoon. However, no one has ever tested whether brain rhythms synchronise with sound rhythms in the exact same way from one day to the next. This is surprising, since it is one of the most important prerequisites to being able to use electrical stimulation to improve brain-environment synchrony.

## A promising result

In our experiment, we asked listeners to come for two separate sessions, and we measured their brain-environment synchrony both times using a technique called electroencephalography (EEG), which measures electrical brain activity. The time between sessions varied between 2 and 42 days. We measured brain activity while the participants listened to sound rhythms, and we kept their attention by asking them to listen for difficult-to-detect silences in the sounds they heard. In addition to quantifying brain-environment synchrony, we tested which brain states were associated with good performance on the silence-detection task: that is, which brain rhythms were associated with successfully detecting the silences, and which brain rhythms were associated with failing to hear them. Here, we use the detection of short silences as a target task because this is exactly what we are doing when we successfully tell the difference between a "b" and a "p", for example.

## Two different brain rhythms interact to determine how successfully we hear.



We discovered that brain-environment synchrony is extremely reliable: the time lag between brain rhythms and sound rhythms is stable for an individual person, even after one month. This is promising news for the prospect of using transcranial alternating current stimulation in a targeted way to improve brain-environment synchrony.

We also discovered that the brain states that lead to successful detection of the short silences are composed of two different types of brain rhythms. First, successful perception depends on the brain rhythms that are actually synchronised to the sound rhythms (here, at a rate of two cycles per second, or 120 beats per minute in musical terms); this confirms what we have observed in previous experiments. Second, successful perception also depends on a brain rhythm that is not synchronised to sounds – the so-called alpha rhythm, which is understood to be related to attention. These different brain rhythms work together in tandem to determine how successfully we hear. This observation is an important breakthrough, because it indicates that improving brain-environment synchrony using the stimulation technique might not be enough to improve hearing in noise, but we should also consider how to simultaneously target synchronised brain rhythms as well as the alpha rhythm.

### Increasing the efficacy of the approach

This project is ongoing. We are currently using a brain imaging technique known as functional magnetic resonance imaging (fMRI) to gather information about an individual's brain anatomy. With the help of this knowledge, we want to determine more precisely where to place the stimulation electrodes on a person's scalp to make sure the electrical current reaches its neural target. We believe that by taking an individualised approach, we will be able to increase the efficacy of transcranial alternating current stimulation for improving hearing by influencing the brain's response to sounds, in particular in older age. o

# 9 Heavyweight in the heart of a galaxy

**KIANUSCH  
MEHRGAN,  
JENS THOMAS**

↳ Max Planck Institute  
for Extraterrestrial Physics,  
Garching

At the centre of the galaxy cluster Abell 85 resides a gigantic galaxy. This giant galaxy, called Holm 15A, literally has it all: at its centre lurks the largest black hole yet observed, weighing in at 40 billion solar masses. The central region of Holm 15A contains a particularly meagre number of stars. The discovery that, of all places, this region is home to an exceptionally large gravitational trap provides astronomers with the chance to estimate the mass of black holes even in galaxies that are too far away to determine their mass directly.

**T**he galaxy Holm 15A at the centre of the galaxy cluster Abell 85 is enormous. Its stars alone add up to a mass equivalent to that of more than two trillion suns. Nevertheless, the centre of this gigantic galaxy, some 700 million light years from Earth, is rather diffuse and faint viewed through telescopes. In smaller galaxies with smaller black holes, in contrast, the density of stars progressively increases towards the centre, as is the case in our Milky Way. This means that smaller black holes are surrounded by bright galactic nuclei.

But for the very largest galaxies, like Holm 15A, things are quite different: they are still most luminous at their centres, but there is a small inner region, characteristic of giant galaxies, which is much fainter than might be expected from the distribution of light in the rest of the galaxy. In the central regions of these galaxies, light appears to be “missing” – sometimes as much as would be emitted by billions of suns. Evidently, the centres of the most massive galaxies suffer from a stellar deficit.

This difference in the structure of the galaxies can be explained by different stages of evolution. The current theoretical model predicts that galaxies grow as a result of collisions and mergers with smaller galactic systems. At each of these cosmic accidents, the black holes of the two galaxies sink into the centre of the newly forming system, where they initially form a rotating pair. Before these dark gravitational traps can merge into a new, more massive black hole, they first have to lose their excess angular momentum. Without a surrounding medium to absorb the angular momentum, they would continue to orbit around each other as a pair for an extremely long time.

However, if the merging galaxies have reached the end of their evolutionary history, they will have exhausted the supply of freely available gas. Hence, there is no longer any surrounding medium to absorb their angular momentum. Instead, this is transferred to the surrounding stars. In the process, stars with orbits too close to the rotating pair end up in more energetic orbits, eject-



*Galaxy in focus: the cluster Abell 85, imaged at the Wendelstein Observatory of the Ludwig Maximilian University of Munich. The bright galaxy in the centre of the image, named Holm 15A, has an extended, diffuse core. From new data, astronomers have directly determined the black hole mass of this Milky Way system.*

ing them from the galactic centre. This process works in a similar manner to the (albeit much gentler) sling-shot manoeuvres exploited by space probes to gain energy during close fly-bys of planets.

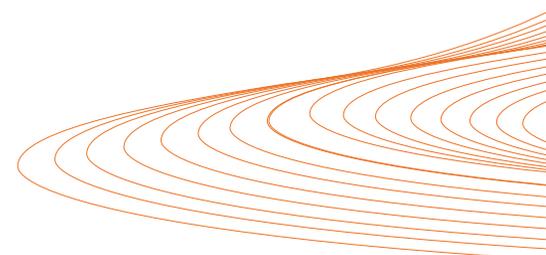
### New stars make up for the deficit

It results in billions of stars being catapulted out of the heart of the emerging galaxy. In smaller galaxies, in which not all the gas has been exhausted, a temporary stellar deficit can be compensated over time by the birth of new, young stars. In older giant galaxies, this is not possible; their gas supply is for the most part depleted. Once these systems have lost the stars in their central regions, no new ones can arise.

Our research in recent years has shown that the distinct, diffuse inner regions of giant galaxies are a direct reflection of the black hole's sphere of influence. Such regions therefore mark precisely that galactic region in which gravity is dominated first by the rotating pair and then subsequently by the merged black hole. Because massive black holes release much more

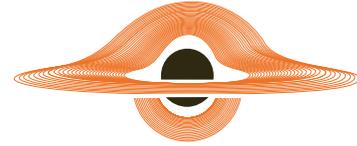
gravitational energy before they merge than low-mass ones, and because the black holes in large galaxies are particularly massive, the cores of the largest galaxies appear particularly faint and extended.

A preliminary photometric analysis of Holm 15A had already shown that the black hole ought to have a sphere of influence with a diameter corresponding roughly to the distance of the Sun from the centre of our Milky Way – some 26,000 light years. Using the Multi Unit Spectroscopic Explorer (MUSE) at the European Southern Observatory's Very Large Telescope and the Wide-Field Imager at the Wendelstein Observatory of the Ludwig Maximilian University of Munich, we were then able to obtain a very high resolution image of Holm 15A.

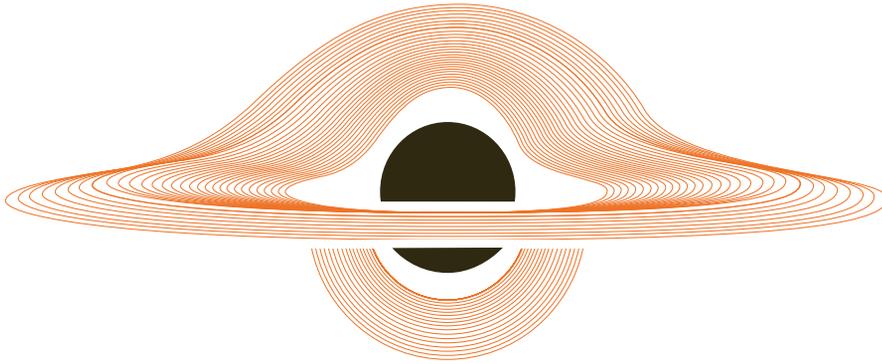


## BLACK HOLES

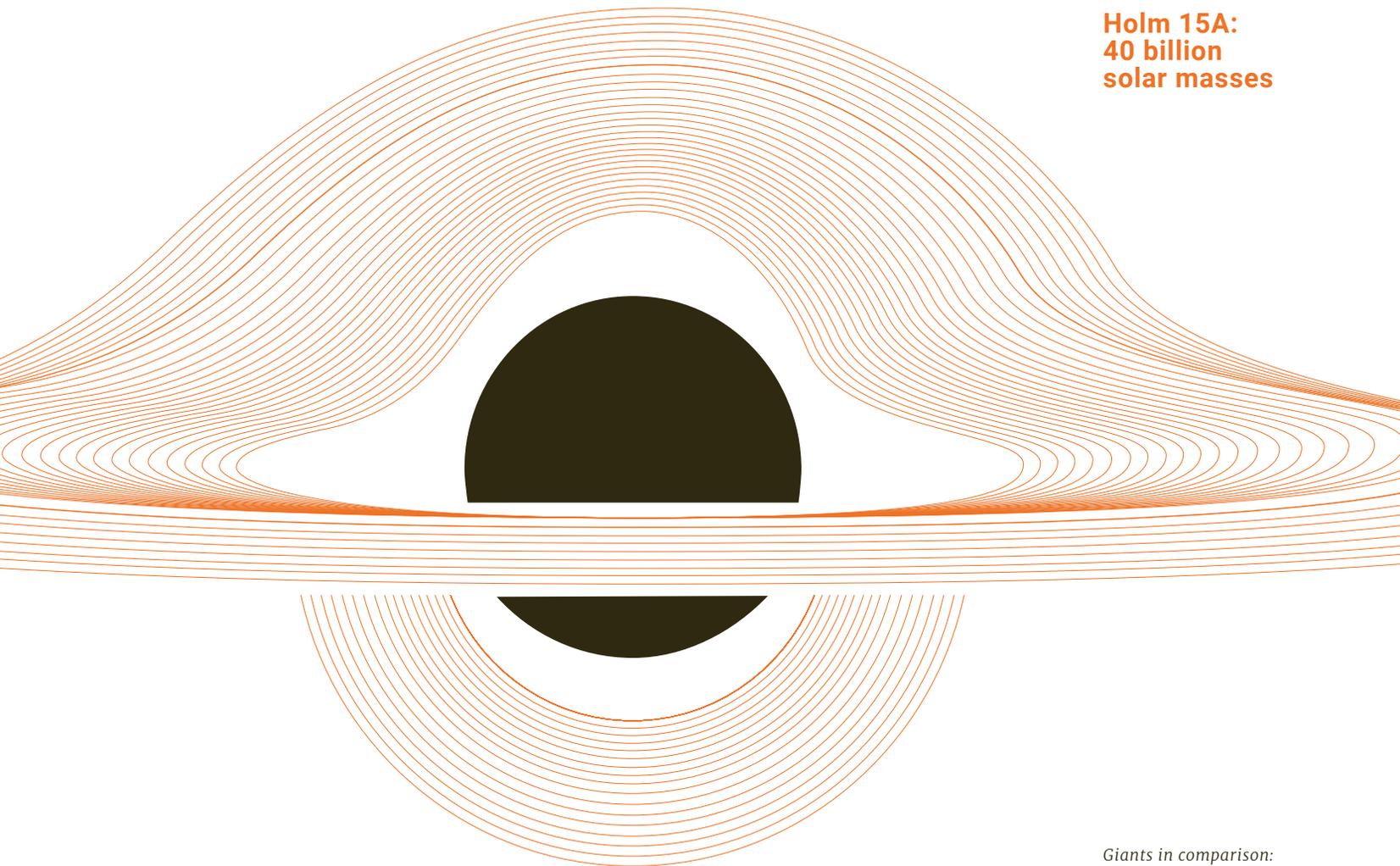
NGC 4472:  
2.5 billion  
solar masses



NGC 1600:  
17 billion  
solar masses



Holm 15A:  
40 billion  
solar masses



*Giants in comparison:  
most galaxies contain  
heavyweight black holes.  
The record of 40 billion  
solar masses is held by the  
gravity trap in Holm 15A.*

## The mass monster is comparatively small, but still about five times the size of the orbit of the dwarf planet Pluto around our Sun.

This allowed us to effectively zero in on the black hole at the heart of Holm 15A and determine its mass to be equivalent to 40 billion suns – a record! The black hole at the heart of our Milky Way, for example, is only a ten thousandth of this mass. In doing so, we also confirmed the size of the black hole's sphere of influence from the photometric analysis mentioned above. Compared to the mass monster itself, this is comparatively small, but still approximately five times the size of the orbit of the dwarf planet Pluto around our sun – a diameter of approximately 30 billion kilometres.

### A look into the distant past

To determine the mass of the black hole, we studied the motions of the stars in the centre of Holm 15A and analysed them using an elaborate numerical model. This technique is based on "phase space models" of the galaxy. It is obtained on the basis of many thousands of stellar orbits simulated on the latest high-performance computers. Using these stellar orbits, the inner structure of a galaxy and its mass distribution can be derived particularly precisely from observations. The Max Planck Institute for Extraterrestrial Physics is playing a leading role worldwide in the development and application of this technique.

To explain the growth of black holes and their interaction with the evolution of galaxies, we have to look far back into the past. We can do this in astronomy by looking at very distant objects whose light was emitted many billions of years ago. However, the spectroscopic signals needed to measure the movement of the stars become progressively weaker with distance. The observation of Holm 15A has now confirmed that the existence of very massive black holes in large galaxies can be inferred by precise photometric analysis of the distribution of their stars. With a degree of uncertainty, this can even be used to determine their mass. Such photometric methods can analyse objects at a great distance. They can, therefore, open up new observational approaches to studying the evolution of black holes in the early Universe. o

# 10 Embryos in deep sleep

**IVAN BEDZHOV**  
Max Planck Institute  
for Molecular Biomedicine,  
Muenster

In science fiction novels, astronauts spend long interstellar journeys in so-called stasis capsules, in which all their bodily functions have been extremely slowed down. By doing so, they can survive even journeys of thousands of years – at least that’s the theory. In fact, many animal species do indeed enter a state of “suspended animation” at the beginning of their development. Together with my colleagues, we study dormant mammalian embryos using the mouse as a model system.

**H**ormonal changes can cause the physiological functions of insects to slow down into a state known as diapause. It is their way of adapting to seasonal fluctuations in the environment. Diapause, for instance, can be triggered in silk moth eggs due to changes in temperature and light conditions. Diapause can also occur in mammals. Roe deer, for instance, mate during the summer, but the pregnancy does not advance for several months. The embryos pause their development at a very early stage just before implantation in the uterus. This delay means that the fawns are not born until spring, when their chances of survival are better.

Embryonic diapause has now been established in more than 130 species of mammals, including the house mouse, which is the preferred model organism for biomedical research. Just how diapause is regulated in mice is still largely a mystery.

At the Max Planck Institute for Molecular Biomedicine, we are investigating how the position and the communication between cells determine embryonic development. We are particularly interested in finding out whether specific signalling molecules are activated in the dormant state to preserve the developmental potential of the embryo.

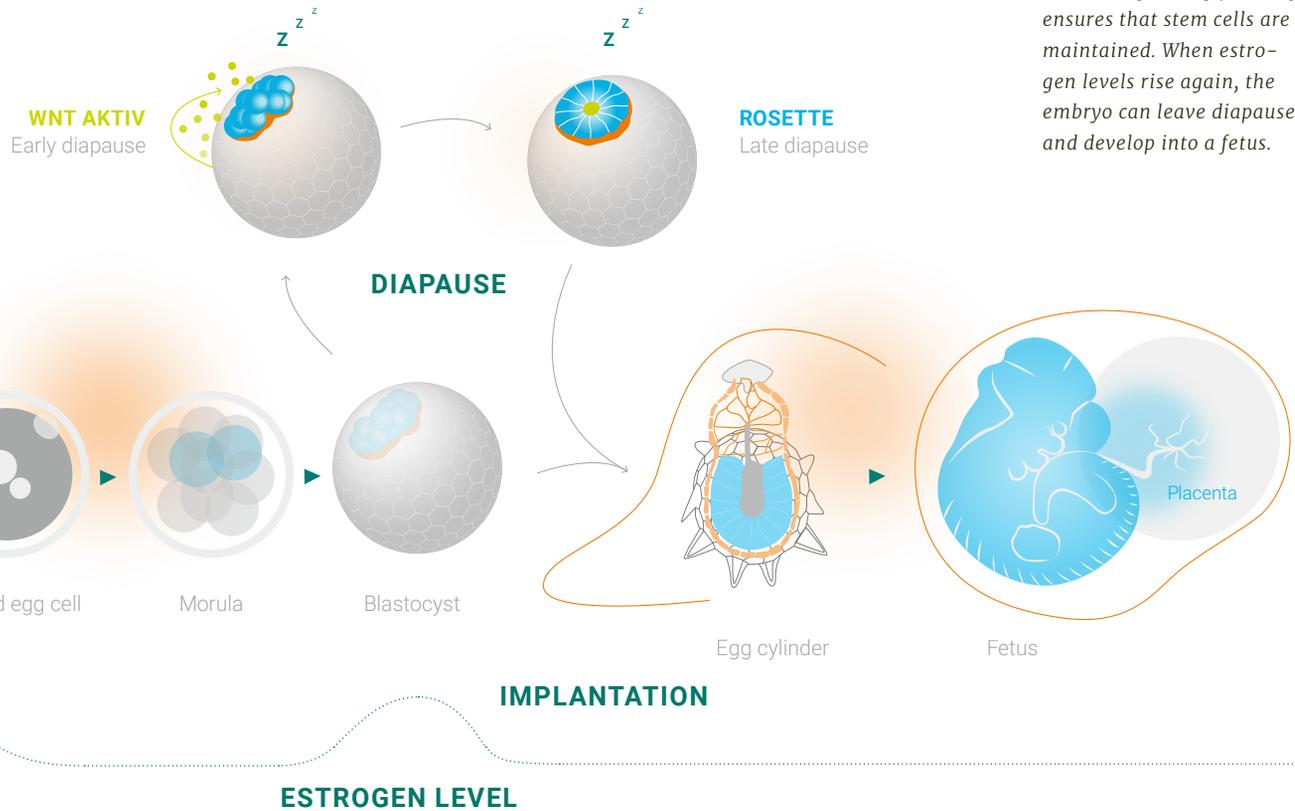
In mice, it takes about four and a half days for the embryo to develop from the fertilised egg into a blas-

tocyst, a spherical structure consisting of about one hundred cells. The blastocyst is comprised of stem cells, which can develop into any type of cell in the body, along with two other supporting cell lineages that will form the placenta and the yolk sac.

## A pause caused by low hormones

At this stage, if estrogen levels rise, the blastocyst will implant in the uterus and the embryo will continue to develop further. It is this rise that we exploit in our experiments: by artificially lowering maternal estrogen activity, we can prevent implantation and thus trigger diapause. By analysing the activity of genes during the diapause of mouse embryos, we have discovered a signalling pathway known as Wnt, which is activated exclusively within this period of time. This pathway is one of the oldest evolutionarily signalling pathways in embryogenesis, which controls cell growth and differentiation.

During normal embryonic development, however, the Wnt signalling pathway is dispensable; it is only required later at gastrulation. So what role does the Wnt pathway play in the dormant blastocyst? We found that it controls the transformation of the stem cells from a simple ball of cells into a rosette-like structure. In



After fertilisation, the early embryo undergoes several divisions until it becomes a blastocyst. When estrogen levels are low, it enters diapause. During diapause, the Wnt signalling pathway ensures that stem cells are maintained. When estrogen levels rise again, the embryo can leave diapause and develop into a fetus.

experiments in which we inactivated the Wnt signalling pathway during diapause, the stem cells quickly disintegrated.

### Signalling substances of the embryo

We also discovered that not the mother, but the embryo itself produces the signalling molecules that activate the Wnt pathway. This pathway ensures that the stem cells are preserved during diapause, while the dormant embryo is gradually reshaped in the process.

Why the stem cells self-organise into a rosette is still a mystery. We found a small hollow in the middle of the rosette in which the cells may be able to exchange

messenger molecules. Thus, in addition to the Wnt proteins, other still unknown signalling factors could play an active role during diapause.

The embryo dormancy is a truly fascinating phenomenon. It remains to be seen, however, whether the Wnt signalling pathway is also employed during diapause in other mammalian species – and, similarly, whether human embryos can also enter a state of suspended animation. o

# 11 Learn to programme with artificial intelligence

## SINGLA ADISH

↳ *Research Group  
Machine Teaching,  
Max Planck Institute  
for Software Systems  
(Saarbruecken site)*

Teaching programming skills is playing an increasingly important role in modern STEM education. At the Max Planck Institute for Software Systems (Saarbruecken site), we develop artificial intelligence (AI)-based virtual tutoring systems that support students according to their needs and abilities.

**P**roviding cost-effective and inclusive education that promotes the computer-based thinking and problem-solving skills of students can be a social challenge. The current curriculum up to the general qualification for university entrance is placing an increasing emphasis on solving open-ended tasks – a fundamental skill for success in subjects such as science, technology, engineering, and mathematics (STEM).

Programming in particular can teach important basics. Students often require individual support, but there are often not enough teachers or tutors available. Tutorial systems supported by artificial intelligence offer a promising alternative and complement teaching in STEM subjects. However, the techniques currently available for online teaching are limited. Although they were developed with the aim of offering courses on a large scale, they were not designed to develop the problem-solving skills of students.

In recent years, we have developed next-generation techniques for STEM teaching in our Machine Teaching research group at the Max Planck Institute for Software Systems. The focus is on question-based problem solving, which can be used for programming, proving mathematical theorems, or solving difficult puzzles. In order to efficiently support students in these areas, we are developing novel, computer-based learning models and techniques for machine-based instruction.

To do this, we first design calculation models that can be used to individually assess the learning process of the students. We are also developing decision theory models that can be used to quantify what kind of support students can best benefit from. Based on these results, we use AI to create personalised curricula that take into account the individual learning processes of the students. These programs can assign students additional tasks based on the ones they have already

when  clicked

set  to  of  +

move  steps

if  <  +  then

say Hello! for  secs

change  by   to

play sound

```
class Method
def from_set
  @bug
end

def request_send
  self.request_send
end
```

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{ } <_ </> <_
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```



## We have developed a novel algorithm for task synthesis. It combines techniques from software testing and machine learning.

solved or even compile new tasks individually. Our AI programmes are also able to give the students hints if they get stuck when solving a particular task.

### Block-based programming

In our work, we specifically rely on “block-based visual programming environments”. In this programming technique, students use predefined image elements corresponding to certain higher-level programming commands. They can thus learn the logic of programming without having to master a programming language or write code. Such visual programming environments are increasingly being used to introduce computer science concepts to novice programmers. Led by the success of projects such as Scratch, initiatives such as the Hour of Code (HOC) of Code.org, and online platforms such as CodeHS.com, block-based programming has become an integral part of introductory computer science education. Thanks to the HOC initiative alone, over 50 million

students worldwide have completed over one billion hours of block-based programming activities.

One of the main pedagogical challenges is designing new exercises that correspond to a desired level of difficulty and train specific programming concepts. Because the programming tasks are usually edited by the teachers themselves, the range of tasks available is limited. For example, Classic Maze of the HOC initiative provides for a sequence of 20 tasks. Millions of students have tried their hand at these tasks. However, if they do not succeed in a particular task, they cannot practise similar ones. If they do not receive support, they cannot develop their skills further.

### Publicly accessible online application

At the Max Planck Institute for Software Systems, we have responded to this pedagogical challenge by developing a methodology to generate new exercises for students that correspond to a desired level of difficulty



*Visually presented and predefined image elements, which are assigned to certain programming commands, help children understand the logic of programming without having to learn a programming language.*

and train specific programming concepts. Among other things, we also vary the visual appeal of tasks with similar concepts in order to keep the students engaged. Putting together these new programming tasks is by no means trivial. Although an unlimited number of tasks can be designed automatically, only some of them have meaningful solutions. In order to solve these problems, we have developed a novel algorithm for task synthesis by combining techniques from software testing, formal methods, and reinforcement learning to perform mutation and symbolic execution efficiently. The task synthesis algorithm can generate 1,000 new similar tasks to those taken from the Hour of Code: Classic Maze challenge of Code.org and the Intro to Programming with Karel course from CodeHS.com. Through an extensive empirical evaluation and user study, we evaluated the efficiency of the synthesis algorithm. We are currently developing an online application specifically for this purpose. This will soon be made publicly accessible. o

# 12 Propagation of hybrid seeds

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Due to their high yields, farmers and many vegetable gardeners prefer to employ hybrid seeds. Such seeds, including those with high economic yields, are extremely difficult to produce; they need to be created anew each time by cross-hybridisation of pure-bred parental lines. Our research is focused on producing seeds that naturally maintain their hybrid state, enabling simple and rapid propagation of such high quality seeds.

**T**he use of hybrid seeds has risen sharply in recent decades, as they have a particularly high yield and their performance is highly predictable. In 1995, for instance, more than 80 percent of broccoli, tomato and Brussels sprout varieties were hybrids. This tendency is ongoing, and many cultivated plant varieties are hybrids, including in maize, rice and rapeseed.

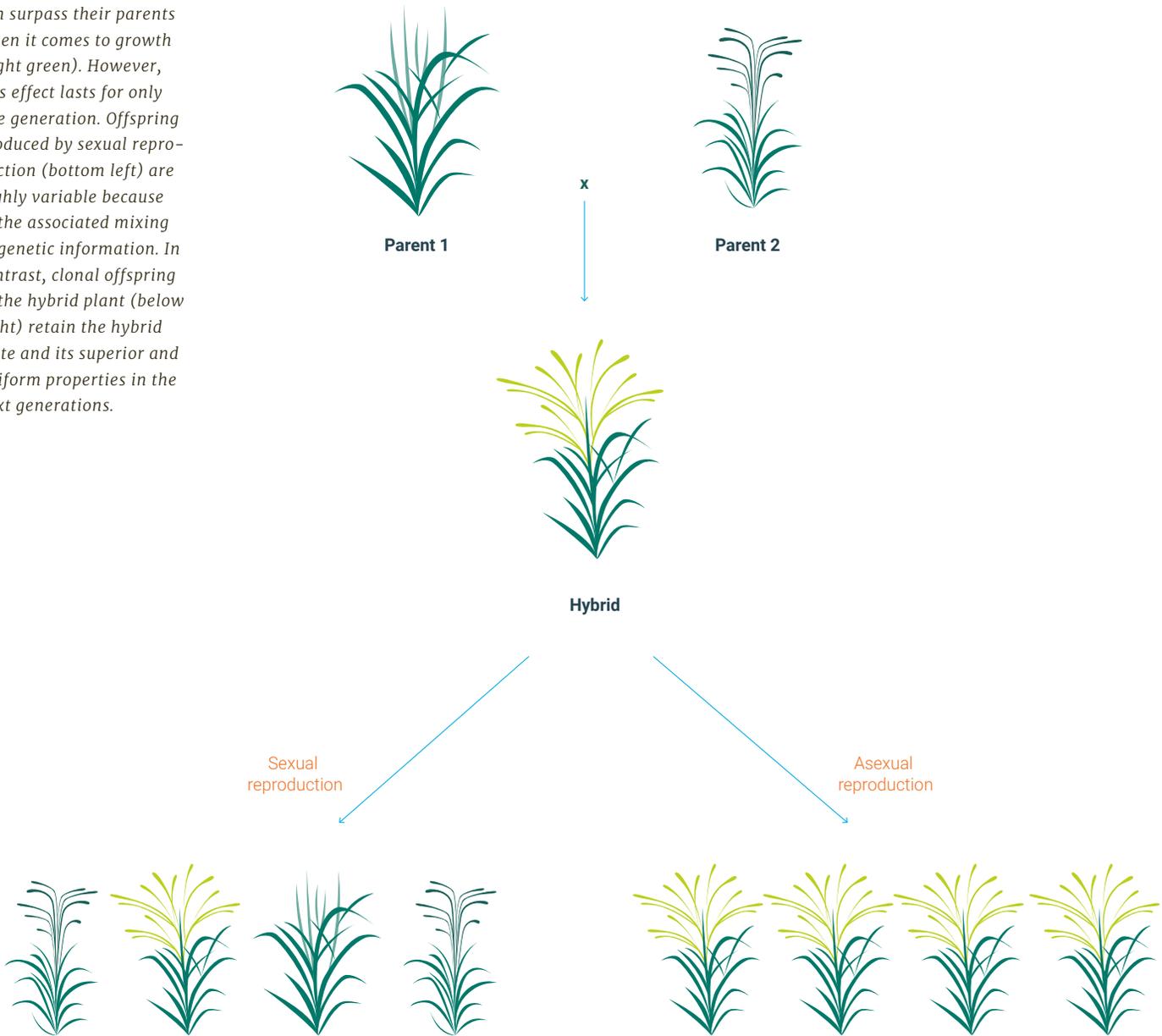
Seeds produced from crossing two different pure-bred parent plants can thrive particularly well, a phenomenon known as the "heterosis effect". The German botanist Joseph Gottlieb Kölreuter observed the effect as early as the 18th century – the hybrid progeny of two homozygous tobacco lines grew stronger than their parental plants. Kölreuter suspected that the strength of this effect was dependent on the diversity of the parents. Gregor Mendel also observed the effect in his famous pea hybridisation experiments, from which he established the fundamental rules of inheritance. It is these rules of inheritance that we observe, and try to

break, in our research group, as breaking them could contribute to more sustainable agricultural practices.

Specifically, while hybrid plants (from F1 hybrid seeds) grow strongly and are uniform, the plants of the next generation (F2) – those that grow from the seeds of the F1 plants – are the exact opposite: they are extremely variable, and some thrive excellently, while others remain small. Some are seriously affected by pests, others only slightly. One plant has many flowers, while its neighbour has only a few and, hence, produces barely any fruit. Consequently, seed cultivation from hybrid plants is considerably less successful.

This is due to the sexual reproduction of the F1 hybrids. The egg cells and pollen required for sexual reproduction are the result of a specialised type of cell division called meiosis. This involves the separation of the chromosomes, and halving the chromosome number in the gametes. However, during meiosis, chromosomes can generate new genetic combinations in a

Hybrid crops result from crossing two pure lines (Parent 1 and Parent 2). The hybrid offspring inherit half of their chromosomes from the mother and the other half from the father. Hybrids can surpass their parents when it comes to growth (light green). However, this effect lasts for only one generation. Offspring produced by sexual reproduction (bottom left) are highly variable because of the associated mixing of genetic information. In contrast, clonal offspring of the hybrid plant (below right) retain the hybrid state and its superior and uniform properties in the next generations.



process termed recombination, making each cell unique. If an egg cell is then fertilised by a pollen sperm cell, an embryo develops, which, although possessing the correct number of chromosomes, is nevertheless genetically unique.

### Asexual reproduction for uniform seed propagation

Sexual reproduction thus increases genetic diversity – which is presumably why it evolved in the first place. However, when it comes to cultivating high-yielding crops that are as uniform as possible, sexual reproduction is a disadvantage. Asexual, clonal reproduction would be more advantageous. This would require that neither meiosis nor fertilisation take place during seed formation. Our aim is to preserve the entire maternal genetic material in the egg and trigger embryo development without the involvement of a male parent. Our experiments have demonstrated that we can modify meiosis to prevent both the halving of chromosome numbers and recombination. Rather than meiosis, only “simple” cell divisions take place, as occur in all of the other cells of a plant. All these cells possess the same genetic material.

This approach, known as “mitosis instead of meiosis” (MiMe), depends on mutating three genes that are essential for each of the three principal differences between meiosis and mitosis. A few years ago, we developed MiMe initially in the model plant *Arabidopsis thaliana* and later in rice. The result is a genetically unreduced and non-recombinant egg cell that retains the

(hybrid) state of the mother plant. However, this is still not sufficient for clonal reproduction, since fertilisation must take place before the egg cell divides.

### Embryos from unfertilised egg cells

This breakthrough was achieved in rice by activating the “BBM1” gene in unfertilised eggs to form an embryo. In conventional rice plants, BBM1 is only active in the pollen and triggers embryonic development when the pollen sperm cell has fused with the egg cell. However, an active BBM1 gene in the egg cell can kick off the formation of the embryo directly, without fertilisation by the pollen.

Hence, the combination of an egg cell containing all the maternal genetic information and embryonic development without fertilisation gives rise to offspring that are genetically identical to their parents. They are clones. The process yields new, uniform and high-yielding hybrid seeds directly from the hybrids, and these seeds only need to be produced at the beginning of cultivation via cross-breeding. This process has not yet been optimised and the next step is to increase the current rate of clonal seed formation from 35 to 100 percent. To achieve this, however, we need to better understand how embryonic development is genetically controlled.

This development is a huge step towards using clonal seed production to grow crops. It will enable direct transmission of the hybrid state from one generation to the next. The result will be a reduction in the cost of hybrid seed production, easier cultivation of hybrids overall and a significant increase in the vigour of crops that are not currently grown as hybrids, such as barley and wheat. This may help guarantee yields for the growing global population and promote more sustainable agriculture. ◦

**When an egg cell develops without fertilisation, genetically identical offspring are produced. In this way, we can produce uniform seeds from hybrids.**

# 13 The dilemma of triage

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The COVID-19 pandemic has at times made it impossible to treat every patient with a life-threatening illness. There are no laws on triage. Which selection criteria – such as age or the likelihood of successful treatment – are appropriate and permissible, and who gets to determine them, is a highly controversial issue. What are the regulations in German constitutional and criminal law? Is ex-post triage a criminal offence? We have reviewed such ethical and legal questions with experts from several disciplines.

**T**he events in Bergamo, Italy, in March 2020 are scorched into the memories of many. Thousands of people died there from COVID-19 at the beginning of the pandemic. Hospitals were so overloaded that only patients with a good chance of survival were admitted into intensive care. Such scenarios may arise again in the future. If infectious diseases spread at great speed, a shortage of life-saving resources (especially trained personnel, but also drugs and equipment such as ventilators) can again be expected. Difficult medical ethics issues and legal questions arise then. What criteria should be applied when choosing among patients who have the same need for intensive care? Which regulations have been developed from ethical principles in medicine, and which ones from the German constitution? Who should determine the selection criteria – doctors on-site, medical associations, or the legislator? Is there the threat of criminal charges for manslaughter if a controversial selection criterion is applied and the person has been denied intensive care dies as a consequence?

When comparing expert opinions, it is evident how varied opinions are on questions like these. The clinical-ethical recommendations of German medical associations from 17 April 2020 attach primary importance to the prospects of treatment success, and they assume that the use of limited resources must be re-evaluated at regular intervals and adjusted where necessary. The last part means that discontinuing treatment in favour of newly admitted patients (so-called ex-post triage) may be permissible. The Ad-hoc recommendations of the German Ethics Council of 27 March 2020, however, set a different tone: they conclude that ex-post triage is unlawful.

In a research project of the Departments of Criminal Law and Public Law, we have worked together with experts from the fields of constitutional law, medical law, criminal law, philosophy of law, and practical ethics, to analyse this heterogeneous field of opinion. Our aim is to better structure legal-political discussion through the systematic pooling of questions, opinions, and arguments.



*COVID-19 ward at Leipzig University Hospital, Saxony. Due to the high number of cases in the state, hospitals in Saxony were almost faced with the situation of having to apply triage in December 2020.*

There are no legal regulations on triage. During the coronavirus crisis, there were calls for a triage law to be passed because, under German constitutional law, the parliament is required to decide on important matters. The counter-argument, held by Steffen Augsberg in our project, emphasises that the state should not lay down criteria that place a value on human life.

### Estimate chances or decide by lot?

It is strongly contested, both from an ethical and legal point of view, whether the likelihood of treatment success – which from a medical point of view must be taken into account by all means – is an acceptable selection criterion. Prioritising patients with a greater chance of recovery from acute illness discriminates the frail and those with pre-existing conditions, argues a constitutional complaint filed in 2020. The petitioners demand that in case of distribution conflict, the

decision should be made by lot. A second position, in contrast, supports the clinical-ethical recommendations of medical associations, which put the likelihood of success criterion in the foreground. This argument is supported by the fact that doctors, who are exposed to particularly high personal risks and burdens in a pandemic, cannot be expected to ignore whether their efforts are likely to be successful or not.

Another issue, not covered by the clinical-ethical recommendations, asks what should be the deciding factor if the chances of successfully treating competing patients are similar. Do other selection criteria such as age then become permissible? Elisa Hoven argues (contrary to mainstream legal opinion) in favour of allowing age as a selection criterion. This is based on a population survey conducted for our project, which shows that 77 percent of all respondents would give a ventilator to a child rather than an 80-year-old with the same odds, and that only a small minority favours selection by lot.

### Fulfillment of duty or criminal act?

My own paper focuses on how the criminal law evaluates terminating one treatment in favour of new patients who are more likely to survive if they receive the scarce resource. This 'ex-post triage' is regarded as a criminal offence (manslaughter) by many legal academics. I argue that a conviction for intentional killing would be inappropriate. Doctors face a collision of duties (they have to treat more than one patient with a life-threatening condition). This collision of duties is a defence under criminal law, which is also relevant when doctors re-evaluate the prospects of success and reallocate resources accordingly.

The survey of the general public mentioned above shows more heterogeneous moral intuitions on this issue than in this case when using age as a selection criterion: 41 percent were in favour of ex-post triage if patients with a better chance of success were given ventilators. However, 32 percent would leave it with the patient who was treated with it first, and 27 percent were in favour of lots. But the question of which selection criterion is the fairest is not the same as the question of whether those who apply ex-post triage should face a prison sentence in criminal court. Great restraint in the application of criminal law is called for as it is too sharp an instrument to enforce distributive justice in existential emergencies. o

# 14 A black widow in space

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The mystery of a gamma-ray source known for two decades has finally been solved. The radiation comes from an extremely fast rotating neutron star – a pulsar that belongs to a binary star system. To make this discovery, the Einstein@Home volunteer computing project searched through data collected by the Fermi Gamma-ray Space Telescope over 10 years. The intensive study of this pulsar and its companion revealed a stellar system of extremes.

**W**hen a massive star runs out of fuel at the end of its life, it explodes as a supernova. As it hurls its outer layers into space, its inside collapses under its own gravity. If the original star is not too heavy, the core is transformed into a neutron star. Such an object consists of extremely dense and partly exotic matter, has a diameter of around 20 km, and has more mass than our Sun – and thus an unimaginably high density: a single teaspoon of a neutron star would weigh billions of tonnes on Earth.

Of the neutron stars known so far, more than 2800 were revealed to be pulsars. This is because rotating neutron stars emit focused radiation from their magnetic poles over large parts of the electromagnetic spectrum. If such a beam of light happens to cross the Earth, the star flashes in the earthly sky like a cosmic lighthouse. Most known pulsars have been detected in the radio range. But 250 pulsars have also been detected based on their high-energy gamma radiation.

Such gamma-ray pulsars are observed by the telescope on board NASA's Fermi satellite. With a relatively small collection area of one square metre, it receives a photon from typical gamma-ray pulsars only once a day. If it is not known in advance from radio observations how fast the pulsar is rotating, the flashing in the gamma-ray range is difficult to find. This is because typical

pulsars rotate millions of times around their own axis in the time between the measurements of two gamma-ray photons.

The distance between the Earth and the pulsar also varies because of the orbital motion of our planet around the Sun. These distance fluctuations as well as the finite speed of light change the time between two incoming pulses. If the pulsar also has a companion star, the resulting proper motion of the pulsar further complicates the search.

## Companion star evaporates

In order to detect such a gamma-ray pulsar with a companion, we need to determine the properties that describe the neutron star and the binary star system. For this purpose, we have developed new methods with which we can test these parameters in a systematic way and as efficiently as possible. If we can observe the companion star in visible light, the search ranges for some parameters can be narrowed in advance.

In close binary star systems, the pulsars heat up some companion stars on the side facing them to a considerable extent through their high-energy radiation. This leads to the evaporation of material from the surface of

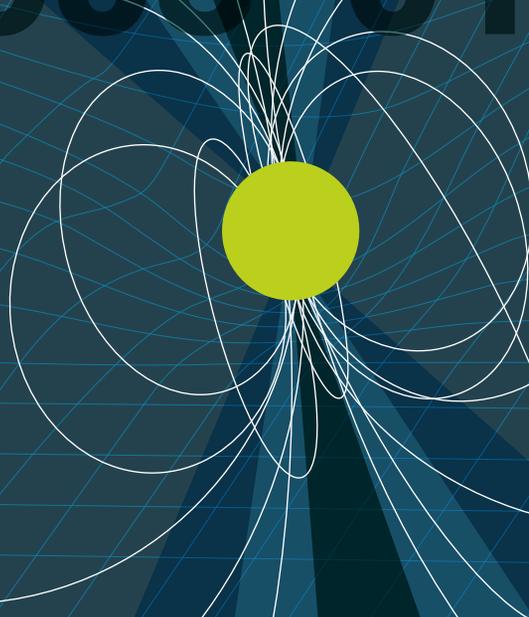
# Einstein @Home

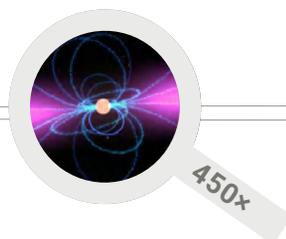


PSR

J1653-0158

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111010





*Unequal pair: pulsar J1653-0158 with its slowly evaporating companion star (bottom) compared to the Earth-Moon system (top). Except for the pulsar shown magnified 450 times, all objects and orbits are shown to scale. The tremendous tidal forces of the pulsar deform the partner star into an egg-like shape.*

the partner, which can be completely disintegrated over time. This is where the nickname black-widow pulsars came from. After mating, the larger female black-widow spider kills and eats the male. The fact that the pulsar companion is hotter on one side can be observed with telescopes in visible light and used to measure certain properties of the star – such as its orbital period around the common centre of gravity of the system.

### Discovery tour with the computer

A gamma-ray source in the constellation of the Ophiuchus known for 20 years has long been of particular interest. Some astronomers have suspected that this is a system of a pulsar and a normal star as described above. A number of optical telescope observations have therefore helped us narrow our search of the Fermi data to specific areas. Nevertheless, we still had to try  $10^{17}$  (i.e. one hundred million billion) different parameter combinations in order to detect possible pulsations.

Even in the best case scenario, such a search would still take more than half a century on a normal computer. We therefore took advantage of the immense computing power of Einstein@Home. This project was launched in 2005 and is based on the participation of volunteers who donate idle computing time on their computers, tablets, and smart phones. Highly elaborate scientific analyses are thus made possible. Within the framework of this citizen science, each and everyone can make astronomical discoveries.

For this purpose, the data is divided into smaller packages, which are then combed using around 35,000 computers by around 22,000 volunteers. Together, they achieve an estimated computing power equivalent to that of one of the 25 fastest supercomputers in the world. In fact, Einstein@Home completed our search within just under two weeks and found the black-widow pulsar PSR J1653-0158. Both the pulsar itself and the binary star system in which it is located are special in many ways.

From the observations of the companion star in visible light and the pulsar in gamma light, we were able

to determine many properties. The pulsar rotates around its own axis more than 500 times per second and has a mass twice that of our Sun. The slowly evaporating companion has only about one percent of the Sun's mass but is six times denser than lead. This unequal pair orbits each other in just 75 minutes – faster than any comparable system. From the long-term observations, we were able to deduce that the pulsar's magnetic field is many times stronger than any magnetic field artificially produced on Earth. However, it appears to be exceptionally weak for a neutron star.

Once we had accurately characterised the gamma-ray pulsar in this way, we conducted a thorough search for radio emission. Although we used some of the world's largest and most sensitive telescopes to do this, we were still unable to detect any radio waves. The most likely reason for this is that the material that evaporated from the companion star completely absorbs this long-wave radiation. However, this is no obstacle for the high-energy gamma light.

PSR J1653-0158 is only the second rapidly rotating pulsar that cannot be observed in the radio range. Its discovery suggests that there are other exciting pulsars like this in our galaxy. These can be exposed only by their gamma rays. We are therefore optimistic that we will be able to use our methods to find more previously undetected pulsars in binary star systems. And we believe that the valuable services of Einstein@Home will help us to achieve this. ◦

# 15 Artificial genome capable of reproducing itself

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RENATE  
HORNBERGER,  
MICHAEL HEYMANN,  
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Martinsried*

From cell division of a microbe to the birth of a higher organism, reproduction is a defining feature of what we know as “life”. Before cells can divide and multiply, they first need to duplicate their genetic material. We are working on developing a system in the test tube that can independently synthesise a portion of its own DNA and protein building blocks. It is an important step towards creating an artificial cell.

**W**hat is life? The answer to that question can differ greatly depending on your point of view. Scientists have attempted to define life in a number of ways, most focusing on self-maintenance, reproduction and adaptability of chemical systems. To better grasp the principles behind these properties, synthetic biologists follow the maxim of the Nobel Prize winning physicist Richard Feynman: “What I cannot create, I do not understand.” By this he meant that he could not understand something until he could recreate it himself. And that’s why synthetic biologists are pursuing the goal of recreating processes occurring in cells and combining individual modules into functional units.

Our research focuses on the “bottom-up” approach of synthetic biology. Our aim, in other words, is to develop life-like systems from inanimate molecular building blocks. Our team focuses on mimicking the replication of DNA molecules and the production of proteins; as mentioned, a fundamental property of all life forms is their ability to maintain themselves as distinct entities, including the ability to reproduce and, thus, duplicate genetic material.

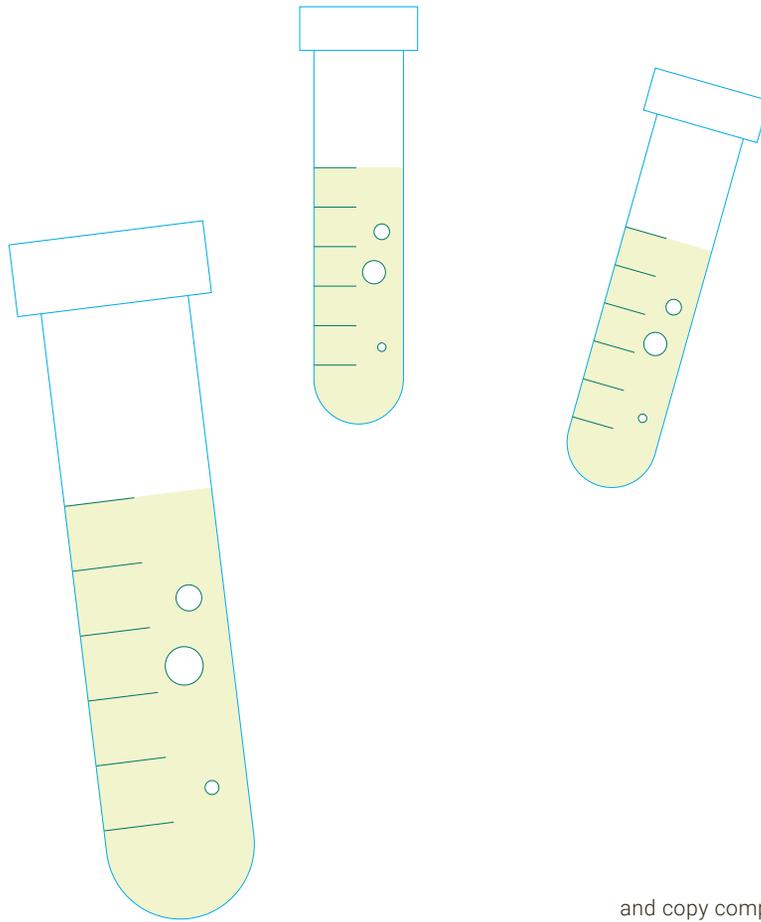
In order to replicate genetic material and produce proteins in a test tube, we needed a blueprint for molecular machines and nutrients. DNA that has stored the

information for building proteins serves as just such a blueprint. Proteins are molecular machines for biosynthesising substances thanks to their ability to accelerate specific biochemical reactions. In turn, translating the genetic code into chains of amino acids to synthesise proteins from the DNA blueprint requires specific proteins and RNA molecules.

## 150 genes for DNA reproduction

Building a minimal self-regenerating system, capable of growth, requires a great number of components to support the individual sub-reactions. Overall, we estimate that a self-replicating genome needs to encode around 150 essential genes. Interestingly, over 95 percent of these genes are required solely for translating genetic information into proteins.

Our artificial system can now duplicate its own DNA blueprint and, in parallel, independently produce the necessary proteins for this in the test tube. “DNA polymerases” can copy DNA molecules – including those that are blueprints for assembling themselves. In other words, the system itself generates a significant proportion of its own molecular components. It can also read



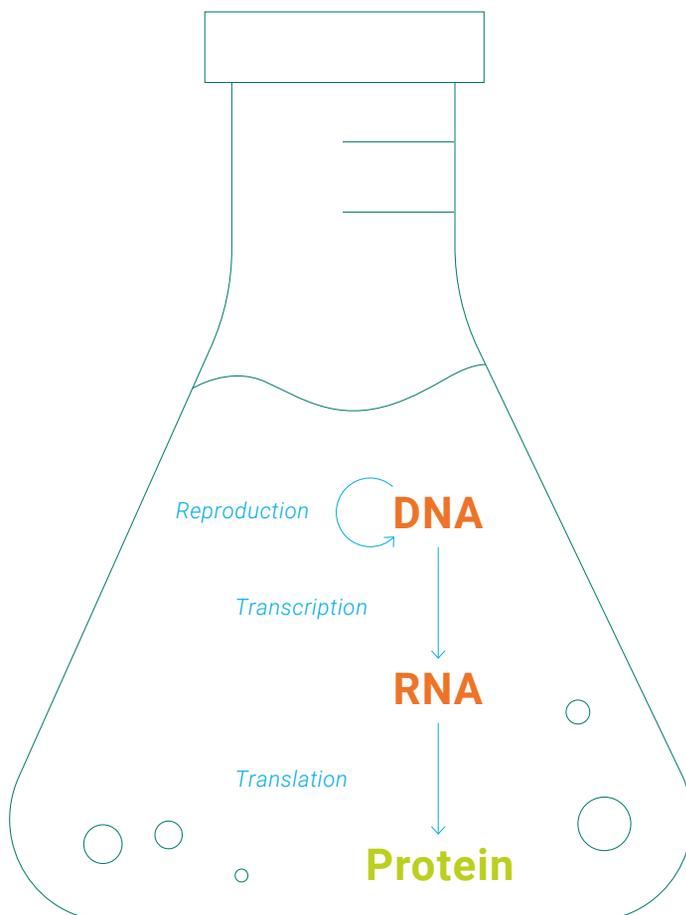
**An artificial cell could be used as a production site for drugs and vaccines or for energy production.**

and copy comparatively long DNA chains. To achieve this, we assembled our artificial genomes from up to eleven ring-shaped DNA fragments. This modular structure allows us to insert certain DNA segments into the blueprint or remove them again if they turn out not to be useful for our system. Our largest replicated genome consists of more than 116,000 base pairs, a length already similar to that of very simple cells in nature.

### **Molecules for the translation of DNA**

In addition to polymerases, required for DNA replication, our artificial genome encodes other proteins, for example 30 different translation factors derived from the bacterium *Escherichia coli*. Translation factors are vital for translating DNA instructions into proteins and are therefore essential for self-replicating systems that take existing biological systems as their model. To show that our test tube system can not only replicate DNA but also produce its own translation factors, we determined the amount of proteins that it produces. Surprisingly, it turned out that some translation factors were even present in larger amounts after the reaction than before they were introduced. This is a significant step closer to a continuously self-replicating system that mimics biological processes.

*A self-replicating genome in the test tube. From the DNA, RNA molecules are read from the DNA for the formation of proteins. For this seemingly simple process, many components are necessary. A self-replicating genome must therefore consist of at least 150 genes.*



## Protocell with its own metabolism

In the future, we intend to expand our artificial genome to include additional DNA segments and, in collaboration with colleagues, to fashion an enveloped system that is capable of remaining active over a longer period of time through the addition of nutrients and the simultaneous disposal of waste products. Such an artificial cell would have very limited capabilities, but would already possess its own simple metabolism. It could be used in biotechnology as a machine for producing substances of all kinds, including novel pharmaceuticals, vaccines or food additives. Such a minimal cell could also be employed to conserve natural resources or reduce the burden on the environment by creating alternatives to fossil fuel energy production, for instance via artificial photosynthesis.

Even after the development of artificial self-regeneration and a metabolism, we cannot answer the question of what cellular life fundamentally needs for its existence until it is able to sustain its independent division and reproduction. At present, however, we are a long way from achieving that goal. ◦

# The Max Planck Society

The Max Planck Society ([www.mpg.de/en](http://www.mpg.de/en)) is one of the world's leading research institutions with a workforce of around 24,000 professionals. In 86 Max Planck institutions, more than 6,900 scientists and 6,100 early career researchers as well as visiting scientists conduct basic research in the natural sciences, life sciences, and the humanities.

**M**ax Planck Institutes work in research areas which are particularly innovative and require a special commitment in terms of funding or time. Their research spectrum is constantly growing. New Institutes or departments are being set up and existing ones rededicated in order to find answers to seminal scientific questions. This process of constant renewal preserves the Max Planck Society's leeway to pick up quickly on new scientific developments. It was founded in 1948 as the successor organisation to the Kaiser

Wilhelm Society, which had been in existence since 1911. Since then, 20 Nobel Prize winners have emerged from its ranks. In addition to five Institutes abroad, the Max Planck Society runs a further 21 Max Planck Centers with research facilities such as Princeton and Harvard University in the USA, Science Po in France, University College London/UK or the University of Tokyo in Japan. Funded in equal measure by the Federal and State Governments, the Max Planck Society enjoys a total annual budget of 1.92 billion euros.



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### Embryos in deep sleep

p. 34: illustration: mattweis, based on an illustration  
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### Learn to programme with artificial intelligence

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### Propagation of hybrid seeds

p. 40: illustration: mattweis, based on an illustration  
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### The dilemma of triage

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### A black widow in space

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