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# Simulated synapses

*Computer scientists from TU Darmstadt are using a trick from astrophysics to predict the rewiring of nerve cells in the brain. The aim of their model is to support neurosurgeons and advance artificial intelligence.*

*By Uta Neubauer*

Gazing into the stars has already helped many people to solve a problem – not just spiritually minded contemporaries but also Professor Felix Wolf and his research associate Sebastian Rinke from the Department of Computer Science at TU Darmstadt. The two researchers aim to calculate the human brain or, to be more precise, the rewiring of its 100 billion nerve cells. No easy task, each nerve cell has a type of cable, called axon, with thousands of terminals. They send out chemical neurotransmitters or emit electric impulses to other neurons, as nerve cells are also termed. For the reception of these signals, each neuron has finely branched antennae that integrate with thousands of terminals from other neurons to form synapses. “Calculating such a network is too much even for a supercomputer”, says Wolf.

> *“We were inspired by this idea of astrophysicists and have built a bridge to the neurosciences”.*

**Astrophysicists face a** similar challenge: our Milky Way has at least 100 billion stars and even more planets. Anyone wanting to calculate the position of a celestial object must account for the gravitational forces exerted by all the others. As this problem cannot be solved by any computer in the world, the astronomers Josh Barnes and Piet Hut developed an approximation method back in the 1980s. It simplifies the calculation by combining the celestial objects to form groups. The interactions are then no longer calculated for pairs, but instead the forces emanating from sufficiently distant objects are grouped. “We were inspired by this idea and have built a bridge to the neurosciences”, says Wolf. Together with Rinke, both still at RWTH Aachen at that time, he started using the Barnes-Hut algorithm to calculate the neural network. According to Wolf, there was a reason why nobody had this idea before: “neuroscientists hardly ever talk to astrophysicists”.

**Wolf, however,** was not only fascinated by astronomy but also by brain research. During his time at RWTH Aachen, where he was a professor from 2009 to 2015, he met the neuroscientist Markus Butz-Ostendorf. A computer model, to a significant extent co-developed by him, simulated the rewiring of neurons and, in doing so, did not restrict itself – as previous models – to the amplification or weakening of existing synapses, but instead created new links. These constantly form in the adult brain.

**The new approach** assumes that neurons strive to achieve a certain level of activity: if they receive too little input, they form more synapses. If they are over-stimulated, they reduce their contacts. Experiments carried out on mice confirm the validity of the model. However, it cannot handle more than 100,000 neurons, equivalent to the brain size of a fruit fly, as the size of the task grows quadratically with the number of nerve cells. That means: doubling the number of nerve cells increases the calculation time by a factor of four. For the almost 100 billion neurons of the human brain, the size of the task becomes overwhelming.

**This is where** the Barnes-Hut algorithm comes into play, however, in a modified form, as Rinke explains: “Unlike astrophysicists, we do not calculate any forces but instead connection probabilities”. The original brain model calculated the probability of synapse formation for all pairs of neurons. The modified model, however, places the nerve cells into groups and calculates the probability of a neuron to connect to such a group. The group is then unfolded, subdivided further and the procedure is repeated. “I perform this until I finally encounter individual neurons again”, explains Rinke. Using this method,

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Dr. Sebastian Rinke (left) and Professor Felix Wolf in the building of the Lichtenberg high-performance computer at TU Darmstadt.


Photo: Katrin Binner

he simulated a network of one billion nerve cells – more than in a rat's brain – as part of his dissertation. "With extrapolations we were able to show that a sufficiently large computer, based on current technology, can even calculate a network comprising 100 billion nerve cells", adds Wolf.

**The simulation of neural networks** is of medical interest as our brain is not at all hardwired: After a stroke, after the amputation of limbs, but also when learning, remembering and for many other processes, new synapses form while defunct ones disappear. If reorganisation could be predicted, doctors could optimize brain surgery and the treatment of neurological disorders. The timing and scope of the treatment of stroke patients, for example, could be planned better if one knew more precisely how and at which speed the brain recovers. Neurosurgeons, in turn, could in particular protect those areas of the brain during surgery that regenerate less well. The clinical application of the model is still a vision, stresses Wolf: "We must first evaluate how our simulations relate to patient data". The computer scientists from Darmstadt are already planning to cooperate with clinical partners to compare their calculations with brain scans of patients before and after surgery.

**In the future,** the model could also boost the further development of artificial intelligence. "The network in our brain is key to our learning ability", says Wolf, "and if the rewiring is understood better, biologically inspired learning processes and artificial neural networks could be optimised". Likewise, this is only a rough concept. Anyway, apart from the potential applications, this research is primarily about one thing: a deeper understanding of the processes in our most important organ.

*The author is a science journalist and holds a doctorate in chemistry.*

## Parallel programming

Professor Felix Wolf is head of the parallel programming research group in the Department of Computer Science at TU Darmstadt. His team's remit includes the development of programs for complex computational tasks that require the power of more than one processor. For the simulation of the network comprising one billion neurons, Sebastian Rinke used 250,000 processors on a supercomputer at Forschungszentrum Jülich. Moreover, he carried out calculations on the Lichtenberg high-performance computer at TU Darmstadt. So-called grid computing, however, where distributed individual processors are linked to form a virtual supercomputer, is not suitable in this case. Because, for the simulation of the neural network, all nerve cells have to be observed simultaneously, the calculation cannot be distributed to different workstations. A supercomputer, in which individual processors are closely connected, is the only option. The neuroscientific work of the computer scientists from Darmstadt is supported through the EU's Human Brain Project.

## Publications

S. Rinke *et al.,* A scalable algorithm for simulating the structural plasticity of the brain, Journal of Parallel and Distributed Computing, 120, 251-266 (2018)

S. Rinke *et al.,* Critical periods emerge from homeostatic structural plasticity in a full-scale model of the developing cortical column, 178-200, in: The Rewiring Brain, Arjen van Ooyen und Markus Butz-Ostendorf, Academic Press, 2017

# More power for the green transformation

*International treaties set the framework but the future of our planet is decided largely in the nation states. Political scientists at TU Darmstadt analyse climate protection policy in the global South.*

Photo: Katrin Binner

Professor Markus Lederer from the Institute of Political Science researches climate policy in the global South.

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*By Jutta Witte*

Climate change, the extinction of species and the risk to the world's seas: the consequences of worldwide environmental destruction impact particularly on the people of the global South. But they also number among the key players deciding jointly on the success or failure of worldwide climate protection endeavours. Professor Markus Lederer, head of the international relations research group at TU Darmstadt, sees developing and emerging countries as more than just victims. For, a growing middle and upper class increasingly embedded in global consumption patterns, industrial expansion and extensive land exploitation makes them on the one hand co-responsible for the imminent ecological collapse. On the other hand, multiple official initiatives intended to push ahead with a sustainable change in environmental policy are currently being launched in these nations.

**"Without these countries,** we will not get climate problems under control", Lederer stressed. Since the Paris Treaty of 2015 at the latest, they are also obliged under international law to formulate objectives for sustainable climate protection policies and monitor the attainment of these objectives on an ongoing basis. "This can however only initiate change and it would be naive to believe that a climate treaty automatically leads to better policies", the expert warned. Even Germany will be unable to meet the climate protection objectives it set itself for 2020. “And the countries of the global South find themselves in a far more complex situation than us.” How can global climate protection policies that bring all players together succeed? Lederer and his research team are convinced: what is needed is a fundamental green transformation encompassing ecology, the economy and social welfare that works towards far-reaching changes in all sectors from energy supply via agriculture through to mobility – a radical change scientists compare to the industrial revolution.

**Together with their** Potsdam research partner, they have scrutinised the framework conditions and implementation strategies for such a transformation in Indonesia, India, South Africa and Brazil, whereby their aim was primarily to find out how the agreements negotiated and initiatives launched for climate protection on an international level impact on the nations and their administrations and on the interaction of different political levels. Moreover, they examined the centrally controlled climate and environmental protection policies in Vietnam and Costa Rica.

> *“Without the emerging and developing countries, we will not get climate problems under control”.*

**As such, two initiatives** with different implementation strategies were the focus of the research of the DFG project “Global Climate Protection initiatives and the Nation State”. On the one hand, they examine the meanwhile largely established concept REDD+ (Reducing Emissions from Deforestation and Forest Degradation). It adopts a “top down” approach as its regulation mechanism is intended to give incentives via financial compensation measures to protect the remaining tropical forest areas. On the other hand, the international network C 40 (Cities Climate Leadership Group), an alliance of more than 80 major cities worldwide, supports climate protection rather of a “bottom up” nature as the cities can potentially influence the policies of the central state too with their projects.

**The comparison between** Indonesia, South Africa, Brazil and India shows that mechanisms such as REDD+ can further reinforce the influence of central governments such as those of Brazil and Indonesia while the C40 network is a “catalyst” for just a few climate protection initiatives notably in the major cities but is overall no “game changer” in terms of the decentralisation or even the further development of climate policies. It is however apparent above all that neither of the two strategies is superior to the other one. “Their impact depends on national, regional and local framework conditions and, in so doing, to a large extent on the persons actively involved, their political possibilities, their normative concepts and respective self-interests”, emphasised Chris Höhne, researcher at the Institute of Political Science at TU Darmstadt.

**Thus, for example,** the measures for the enhanced protection of forests and peat moors via REDD+ in the Indonesian province Central Kalimantan came to an abrupt end when a new governor came into office whose family invested heavily in the cultivation of palm oil plantations. In contrast, a far-sighted governor in East Kalimantan committed to a strong increase in forest protection as a contribution to the ecological reorientation of the province at a time when Indonesia’s national government was in the process of cutting back its forest protection efforts.

**How, however, do countries** choosing the “top down” path implement green transformation? This issue numbers among those addressed by the research project “GreeTS”. Thus, the socialist single-party state Vietnam, which is faced with increasing environmental and climate problems as a result of enormous economic and population growth, is pushing ahead with change in the energy sector and is attempting to link this with the objectives of green growth and generally more sustainable development. “A holistic strategy has been missing so far”, observed Höhne’s research colleague Linda Wallbott. Costa Rica too, the democratic role model in Central America, has committed to climate, environmental and forest protection. Despite initial successes with its energy policies and political leadership that rigorously supports the green agenda incorporating the economy and civil society, a “look behind the scenes” offers a more varied picture. Thus, for example, the deforestation of large areas of forest for reservoir projects was enforced against the will of the indigenous population.

**Both projects show,** therefore, not only the complex and heterogeneous starting position, from which the countries of the global South have to combat climate change. They also demonstrate that there is no single globally valid patent recipe for climate protection policy. “Change is possible. But its course is incremental and slow and it relies on strong player constellations”, Lederer explained. Whether it succeeds, stands and falls, the three specialists are convinced, with the political economy, an administrative structure functioning well across all levels, clear economic benefits for the countries involved and “normative change in peoples’ minds”. On a microlevel, they see many successful initiatives and purposeful partnerships between donor and recipient countries. On a macrolevel, however, the decisive drive for a truly transformative change was still missing.

*The author is a science journalist and holds a doctorate in history.*

**Cooperation networks**

The project “Carbon Governance Arrangements and the Nation State: The Reconfiguration of Public Authority in Developing Countries” was supported by the German Research Foundation from 2015 to the end of March 2019. TU Darmstadt’s cooperation partner is the Chair for International Politics at Potsdam University.

The project Europe and Green Transformation in the global South (GreeTS) is being funded by Volkswagenstiftung, Riksbanken’s Jubiläumsfonds and the Wellcome Trust until the end of June 2019. Under the leadership of TU Darmstadt, the Tropical Agricultural Research & Higher Education Center (CATIE) in Costa Rica, the School of Oriental and African Studies (SOAS) at the University of London and the Vietnamese Academy of Social Sciences (VASS) in Hanoi are participating in the project.

**Further information:**

https://bit.ly/31ti2jl
https://bit.ly/2IAd3o7

**Current publications:**

Hickmann, Thomas, Harald Fuhr, Chris Höhne, Markus Lederer, Fee Stehle (2017): “Carbon Governance Arrangements and the Nation-State: The Reconfiguration of Public Authority in Developing Countries”, in: Public Administration and Development 37 (5), S. 331–343.

Lederer, Markus, Linda Wallbott and Frauke Urban (2019 in print): Green Transformations and State Bureaucracy, in Fouquet, Roger (ed.): Handbook on Green Growth, Cheltenham, Edward Elgar.

# Cool technology

Photo: Katrin Binner

In the laboratories of the Integrated Micro-Nano Systems group, Professor Thomas Burg and his team combine methods from microsystems technology, biology and chemistry.

**Information**

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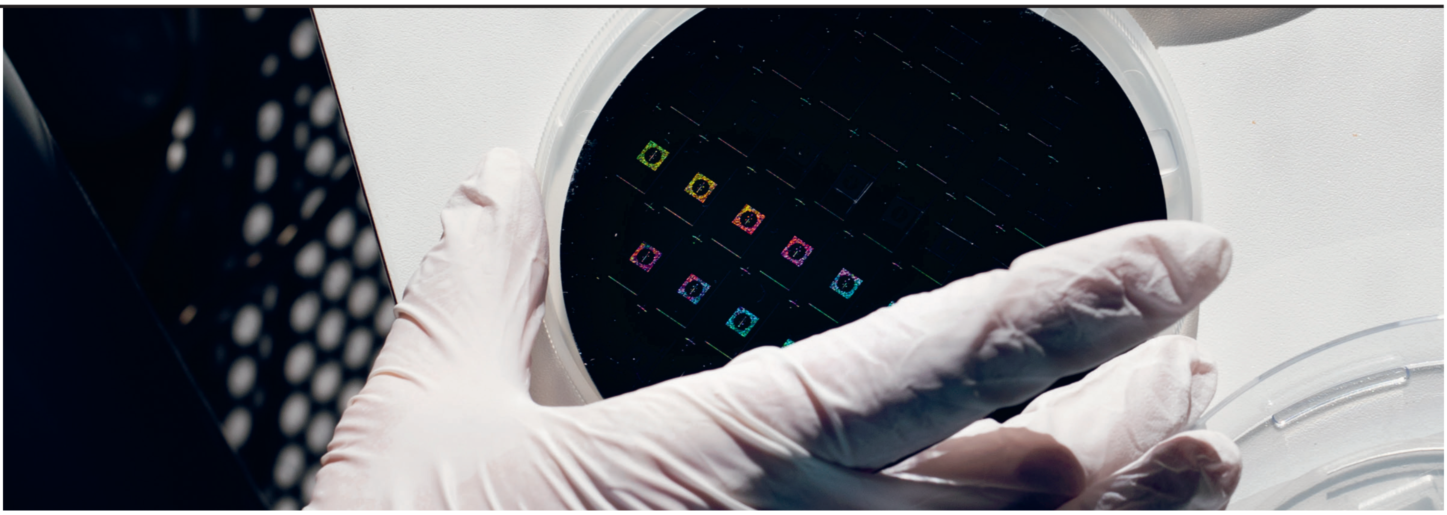
*Professor Thomas Burg freezes living cells and organisms under the light microscope without a time delay. His aim: a better link between light and electron microscopy.*

*By Hildegard Kaulen*

The physicist Thomas Burg loves extremes. The objects he studies are extremely small, extremely cold and extremely difficult to resolve. Burg has been a professor at TU Darmstadt since September 2018 and heads the “Integrated Micro-Nano Systems“ research group. His aim is to investigate new technologies for studying cellular processes with high resolution in space and time, as life is not static, but dynamic. To this end, however, light and electron microscopy must be integrated better than they are today. Burg’s research is worth around two million euros to the European Research Council (ERC) over the coming five years.

**Light microscopy** can reveal the dynamics of living cells and organisms, and it allows specific molecules to be marked and highlighted with fluorescent dyes. However, the resolution of standard fluorescent light microscopy is limited to some 200 nanometres due to the wave characteristics of light. Although a trick has recently been invented to overcome this limitation, detailed structural analysis in the range 0.1 to 10 nanometres is still only possible with electron microscopy. Cells and organisms have to be fixed in place to this end. This can only be done without damage using cryofixation. Using this method, samples are cooled down rapidly to temperatures below -135° Celsius. This is the only way water can retain its glassy, disordered structure. In this way, cellular structures remain largely unchanged due to the lack of ice formation.

**“But to observe dynamic processes** remains a challenge”, says Burg, who led a research group at the Max Planck Institute for Biophysical Chemistry in Göttingen for ten years prior to his move to TU Darmstadt. “The samples observed in the light microscope have to be moved to a different instrument for cryofixation. There is therefore a transfer step. The manual transfer sometimes takes minutes, depending on the operator. Automatic transfer takes one to five seconds. There always remains therefore a gap between the last observation of the dynamic process in the living object under the light microscope and the flash-frozen state in the cryofixed object. Part of the chain of events is therefore always missing“.



Microchannels produced in the clean room for the rapid freezing of cells in the light microscope – here during an intermediate stage of fabrication.

Photo: Katrin Binner

**Burg's aim is** thus to flash-freeze cells and organisms directly under the light microscope so that they can then be examined in the frozen state using light and electron microscopy. To this end, the heat has to be removed rapidly and the sample cooled down and kept at below -135º Celsius continuously to ensure that the water molecules do not slowly rearrange into ice crystals, destroying the delicate structure.

**Burg has crossed** an important hurdle on this path. For freezing the objects under the light microscope, he uses components from microsystems technology. These include an electrically heated microchannel, in which the cells or organisms can initially be observed at physiological temperatures. A heating element located under the microchannel has contact to a silicon chip that is cooled with liquid nitrogen. When the heating element is switched off, the stored heat dissipates rapidly via this silicon chip. At the same time, the sample freezes rapidly. This method gives the observer the opportunity of studying the cellular processes up to the point at which the heating element is switched off, causing the temperature difference between the object under examination and the liquid nitrogen bath to collapse and the sample to freeze within milliseconds. The frozen object can then be examined under the electron microscope too following appropriate preparation.

> *“We also want to look at the cryofixed samples directly using light microscopy. But cryo-light microscopy is still at the beginning“.*

**“By eliminating the** transfer step, we improve the link between light and electron microscopy“, Burg says. “But we want more. We also want to examine the cryofixed samples directly using light microscopy“. However, this so-called cryo-light microscopy is still in its infancy. One challenge is the inevitable temperature difference between the microscope at room temperature and the sample cooled down to -140º Celsius. For the best-possible resolution, the air gap between the objective lens of the microscope and the sample has to be filled with an immersion liquid. This must be done without damaging the delicate lenses by the low temperature and without transferring too much heat to the frozen sample via the objective. Moreover, Burg and his colleagues need an immersion liquid with the same refractive index at this low temperature as water at room temperature.

**The physicist and his colleagues** have solved the first problem by cooling the very small front lens of a high-quality immersion objective and shielding it from the microscope via a carefully heated ceramic mount. In this way, the cold front lens and the sample are thermally camouflaged to not affect the larger and more delicate lenses of the microscope. Burg and his team have also discovered a suitable immersion liquid. It is called ethoxynonafluorbutane. “It wasn't easy to find something suitable“, Burg says. “There is very little data on the refractive index of liquids at these low temperatures. There is some data for temperatures down to -80º Celsius, but not lower. We had to try a lot of things“. Burg currently achieves a resolution of 350 nanometres with his cryo-light microscopy set-up. As their next aim, he and his team want to improve the method further, make it suitable for routine application and use it in conjunction with so-called super-resolution methods that make a 10-fold higher resolution possible with the same lens.

**Burg wants to use** the financial support of the European Research Council to also test whether the rapidly frozen cells can be thawed again without damage. “It would be ideal if the cells had no recollection of the freezing after they're thawed, so that they resume their activity at the point at which they were stopped by the freezing“. Burg knows that this is a long way off but he is aware of the problems needing to be solved. Extremely high cooling rates are required, for example and the cells and organisms must be frozen with very little cryoprotectants or none at all. But improved cryoprotectants would be desirable too. Perhaps Burg may ultimately succeed in freezing cells under the microscope and thawing them without any damage at all. Dynamic processes could then be observed, stopped and restarted on demand. There is still a long way to go however till that point is reached.

*The author is a science journalist and holds a doctorate in biology.*

# Longstanding puzzle about beta decay solved

*An international collaboration including contributions from TU Darmstadt solved a 50-year-old puzzle that explains why beta decays of atomic nuclei are slower than what is expected based on the beta decay of free neutrons.*

The findings, published in the scientific journal Nature Physics, fill a long-standing gap in our understanding of beta decay, an important process in nuclear physics applications and in the synthesis of heavy elements in stars.

**Beta decay** is the main decay channel of atomic nuclei: a conversion of a neutron inside the nucleus into a proton (or vice-versa), which produces a different element with proton number plus (or minus) one. In this way beta decay plays a central role in the synthesis of new elements in our universe. As an interplay of the strong force that binds neutrons and protons inside the nucleus and the weak interaction, beta decay also holds important clues for physics beyond the Standard Model and has been the focus of concentrated efforts in physics since the early 1900s.

**However, a puzzle** has withstood a first-principle understanding: the beta decay of neutrons bound within nuclei are significantly slower than what would be expected on the basis of decay times of free neutrons. In the past, this systematic discrepancy was taken care of by implementing a constant called ‘quenching’.

**This workaround** was able to reconcile observed beta-decay rates of neutrons inside and outside the nucleus and realigned theoretical models with experimental measurements.

**“For a long time,** we have lacked a fundamental understanding of nuclear beta decay”, said Professor Achim Schwenk from TU Darmstadt, who is part of the collaboration. “In complex microscopic computations we now demonstrated for the first time that strong correlations in the nucleus as well as the strong interaction with another neutron or proton slow down beta decay inside the nucleus. Such interaction effects are predicted in effective field theories of the strong and weak interactions”.

**To demonstrate this,** the theoretical physicists systematically calculated beta decays for a variety of light and medium-mass nuclei, starting from a nucleus with only three nucleons up to tin-100 with 50 protons and 50 neutrons. The beta decay of tin-100 was first observed at GSI Helmholtzzentrum für Schwerionenforschung in the year 2012. The results of the collaboration were in very good agreement with experimental data and demonstrate that the quenching factor is not needed when both the strong and weak interaction effects are considered consistently.

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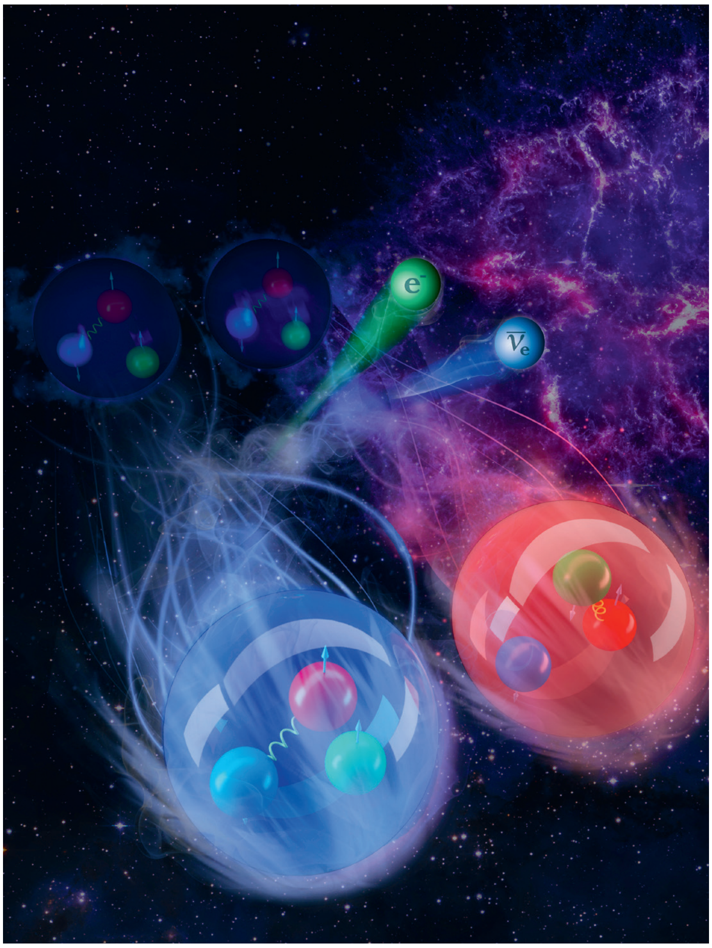
**The advances** in taking the weak interaction with single neutrons and protons to large atomic nuclei have been made possible by theoretical developments of effective field theory, as well as by great progress in many-body theory and powerful supercomputing capabilities.

**In addition to a better** understanding of beta decays for the synthesis of heavy elements in supernovae and neutron star mergers, the researchers also hope to gain new insights into double-beta decays, in particular neutrino-less double-beta decay, where an analogous quenching puzzle exists.



Picture: Andy Sproles, Oak Ridge National Laboratory, U.S. Department of Energy

Graphical representation of the beta decay of a neutron (red) into a proton (blue), which can interact with another proton (blue next to it) in the nucleus. These two-particle effects as well as strong correlations in the atomic nucleus lead to slower beta decays than would be expected from the decay of a single (free) neutron.

**Publication:** https://www.nature.com/articles/s41567-019-0450-7