PNAS Plus Significance Statements

Beyond the classical thermodynamic contributions to hydrogen atom abstraction reactivity

Daniel Bím, Mauricio Maldonado-Domínguez, Lubomír Rulíšek, and Martin Srnec

Hydrogen atom abstraction reactivity is a key property of many important biological and synthetic compounds that depends on their proton-coupled reduction potentials. These potentials quantify the ability of species to acquire an electron and proton pair. Intuitively, a species with a higher proton-coupled reduction potential abstracts hydrogen atoms more easily, which translates into a lower reaction barrier. Beyond this classical thermodynamic effect on reactivity, we discovered a significant contribution arising from a factor reflecting propensity for (a)synchronicity in concerted H^+/e^- transfers, which stems directly from the reduction potentials and acidity constants of reactants and products. We show that the most synchronous hydrogen atom abstractions tend to pass over the highest barriers, as exemplified by computations on $Fe^{IV}O$ oxidants. (See pp. E10287–E10294.)

Faraday cage screening reveals intrinsic aspects of the van der Waals attraction

Musen Li (李木森), Jeffrey R. Reimers, John F. Dobson, and Tim Gould

How the van der Waals dispersion interaction relates to chemical electron-correlation effects presents a critical challenge to density functional theory development. Here, recently observed screening of the dispersion force between two insulating objects caused by the insertion of an intermediary graphene layer is explained in terms of Dobson's general description of dispersion. This then provides a much-needed handle concerning how density functional approaches relate such long-range dispersion interactions to the subtleties of covalent bonding. Screening at intermediate distances appears to change the London expression from r^{-6} to r^{-7}, an effect that becomes antiscreening (dispersion enhancement) at distances shorter than van der Waals contact. This provides basic insight into modern revelations that dispersion forces can outcompete covalent forces to control chemical structure. (See pp. E10295–E10302.)

Nematic twist–bend phase in an external field

Grzegorz Pająk, Lech Longa, and Agnieszka Chrzanowska

The twist–bend nematic liquid crystalline phase is the fifth nematic structure recognized in nature [Chen D, et al. (2013) *Proc Natl Acad Sci USA* 110:15931–15936], and its stabilization is explained by assuming a coupling between polar and nematic orderings. It exhibits macroscopically chiral heliconical orientational order on the 10-nm scale and represents a unique example of spontaneous chiral symmetry breaking for a system of achiral molecules. Understanding how an external field affects the stability of this phase can shed further light on the origin of this induced twist and is of relevance to potential applications. Within the Landau–de Gennes theory we find that for compounds with positive anisotropy the helix unwinds to a polar nematic, however negative material anisotropy gives rise to a rich sequence of new nematic phases obtained via a mechanism of flattening the conical spiral. (See pp. E10303–E10312.)

Comparing continual task learning in minds and machines

Timo Flesch, Jan Balaguer, Ronald Dekker, Hamed Nili, and Christopher Summerfield

Humans learn to perform many different tasks over the lifespan, such as speaking both French and Spanish. The brain has to represent task information without mutual interference. In machine learning, this "continual learning" is a major unsolved challenge. Here, we studied the patterns of errors made by humans and state-of-the-art neural networks while they learned new tasks from scratch and without instruction. Humans, but not machines, seem to benefit from training regimes that blocked one task at a time, especially when they had a prior bias to represent stimuli in a way that encouraged task separation. Machines trained to exhibit the same prior bias suffered less interference between tasks, suggesting new avenues for solving continual learning in artificial systems. (See pp. E10313–E10322.)

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Transcription initiation defines kinetoplast RNA boundaries

François M. Sement, Takuma Suematsu, Liye Zhang, Tian Yu, Lan Huang, Inna Aphasizheva, and Ruslan Aphasizhev

It is held that in trypanosomes both mitochondrial DNA strands are transcribed into polycistronic precursors. An unknown endonuclease presumably cleaves primary transcripts to liberate monocistronic mRNAs. However, this model is incongruent with an established event of mRNA processing by 3′–5′ exonucleolytic degradation. Our work suggests that each gene is transcribed individually and the pre-mRNA undergoes 5′-end modification and controlled 3′-end trimming. We identified the pyrophosphohydrolase protein complex as responsible for pyrophosphate removal from the 5′ nucleoside and mRNA stabilization. We characterized antisense noncoding RNAs originating near mRNA 3′ termini and investigated their potential role in 3′-end demarcation. It is conceivable that transcription, in addition to mRNA editing and decay, plays a significant role in regulation of mitochondrial gene expression. (See pp. E10323–E10332.)

Ultrafast epithelial contractions provide insights into contraction speed limits and tissue integrity

Shahaf Armon, Matthew Storm Bull, Andres Aranda-Diaz, and Manu Prakash

We report the fastest epithelial contractility observed to date in the primitive invertebrate *Trichoplax adhaerens*: Single-cell contraction events reduce cells' apical area by 50% in one second, at least an order of magnitude faster than other examples. Typically, epithelial contractions enable embryonic systems to change shape during development. Their contractility machinery (actomyosin) is working against high load to achieve dramatic tissue deformation. Here we show that the same machinery can achieve the fast contraction we observe in *T. adhaerens*, in the lack of load. We also show that unique cell and tissue architecture indeed minimizes the load on a contracting cell. Finally, we suggest a physiological role for these contractions: maintaining the integrity of such a minimalistic tissue. (See pp. E10333–E10341.)

Peptide design by optimization on a data-parameterized protein interaction landscape

Justin M. Jenson, Vincent Xue, Lindsey Stretz, Tirtha Mandal, Lothar "Luther" Reich, and Amy E. Keating

Medicine, agriculture, and the biofuel industry use engineered proteins to perform functions such as binding, catalysis, and signaling. Designing useful proteins faces the "needle in a haystack" problem posed by the astronomical number of possible sequences. Proteins of utility can be found by experimentally screening 10^2–10^9 molecules for properties of interest. We posit that such screens can serve as the beginning of a powerful computationally aided design process. Data collected in high-throughput experiments can be used to learn aspects of the relationship between protein sequence and function. We show how models trained on data can guide computational exploration of huge sequence spaces. This can enable rational design of molecules with custom properties that would be difficult to discover using other techniques. (See pp. E10342–E10351.)

RPA1 binding to NRF2 switches ARE-dependent transcriptional activation to ARE-NRE–dependent repression

Pengfei Liu, Montserrat Rojo de la Vega, Saad Sammani, Joseph B. Mascarenhas, Michael Kerins, Matthew Dodson, Xiaoguang Sun, Ting Wang, Aikseng Ooi, Joe G. N. Garcia, and Donna D. Zhang

Our findings shift the paradigm of NRF2 as a transcriptional activator to one in which NRF2 can also act as a transcriptional repressor, which we believe will stimulate new research areas and interests among scientists from other fields. While the majority of the data provided in this paper center on suppression of *MYLK* expression and the resulting pathological significance, the more far-reaching findings are the in silico and RNA-seq datasets indicating that the NRF2-replication protein A1 (RPA1)-ARE-NRE complex transcriptionally represses other genes as well, again highlighting the broad scope and significance of NRF2 repression of target genes. (See pp. E10352–E10361.)

mTORC1 signaling suppresses Wnt/β-catenin signaling through DVL-dependent regulation of Wnt receptor FZD level

Hao Zeng, Bo Lu, Raffaella Zamponi, Zinger Yang, Kristie Wetzel, Joseph Loureiro, Sina Mohammadi, Martin Beibel, Sebastian Bergling, John Reece-Hoyes, Carsten Russ, Guglielmo Roma, Jan S. Tchorz, Paola Capodieci, and Feng Cong

The Wnt/β-catenin signaling pathway plays prominent roles during embryonic development and adult tissue homeostasis by maintaining somatic stem cell functions. The mammalian target of rapamycin complex 1 (mTORC1) signaling pathway has also been implicated in regulating stem cell functions in multiple tissue types. However, the crosstalk between these two pathways remains largely unclear. Herein, using in vitro cell lines, ex vivo organoids, and an in vivo mouse model, we made striking findings in support of a paradigm that mTORC1 signaling cell autonomously suppresses Wnt/β-catenin signaling through down-regulating the Wnt receptor FZD level to influence stem cell functions, with implications in the aging process. (See pp. E10362–E10369.)

TRPM7 and $Ca_V3.2$ channels mediate Ca^{2+} influx required for egg activation at fertilization

Miranda L. Bernhardt, Paula Stein, Ingrid Carvacho, Christopher Krapp, Goli Ardestani, Aujan Mehregan, David M. Umbach, Marisa S. Bartolomei, Rafael A. Fissore, and Carmen J. Williams

At fertilization, repetitive calcium signals are induced in mammalian eggs that are essential for activating embryo development. These signals are supported by calcium influx from the surrounding medium. Two ion channels supporting calcium influx into eggs, $Ca_V3.2$ and TRPV3, were identified previously. Here we find that a third channel, TRPM7, is essential for this function. In the absence of both TRPM7 and $Ca_V3.2$, the calcium signals induced by the fertilizing sperm stop prematurely. Female mice carrying eggs lacking TRPM7 and $Ca_V3.2$ are subfertile. Because TRPM7 channel function is modulated by ions in culture medium, these findings highlight the importance of exact culture medium composition used during laboratory procedures for human assisted reproduction therapies. (See pp. E10370–E10378.)

Frequent monoallelic or skewed expression for developmental genes in CNS-derived cells and evidence for balancing selection

Sergio Branciamore, Zuzana Valo, Min Li, Jinhui Wang, Arthur D. Riggs, and Judith Singer-Sam

While most mammalian genes are expressed from both chromosomal copies, many autosomal genes randomly express only one allele in a given cell, resulting in somatic cellular mosaicism. To better understand the mechanisms, developmental aspects, and evolution of autosomal monoallelic expression (MAE), we used nucleotide polymorphism differences between hybrid mice to analyze MAE of clonal neural stem cell lines as they differentiated to astrocytes. We found that genes showing MAE are highly enriched among developmental stage-specific genes. Genes showing strong skewed expression are similarly enriched. We also found evidence suggestive of balancing selection not just for genes with MAE but also, for developmental stage-specific genes. (See pp. E10379–E10386.)

Collective decision making by rational individuals

Richard P. Mann

Humans and animals use the decisions they observe others making as valuable information about the quality of potential choices. We anticipate that behavioral rules that better approximate the decisions of a rational, expected fitness-maximizing agent will be favored by natural selection. In this paper I show that many aspects of collective decision making can be predicted through considering what a rational agent would do. I also show that a theory of strictly rational agents explains much of the variability between and within species and makes sometimes counterintuitive predictions that can be experimentally tested. Most importantly, my model shows that how collective decision making is observed and measured is critically important in interpreting and understanding behavior. (See pp. E10387–E10396.)

Climate-driven declines in arthropod abundance restructure a rainforest food web

Bradford C. Lister and Andres Garcia

Arthropods, invertebrates including insects that have external skeletons, are declining at an alarming rate. While the tropics harbor the majority of arthropod species, little is known about trends in their abundance. We compared arthropod biomass in Puerto Rico's Luquillo rainforest with data taken during the 1970s and found that biomass had fallen 10 to 60 times. Our analyses revealed synchronous declines in the lizards, frogs, and birds that eat arthropods. Over the past 30 years, forest temperatures have risen 2.0 °C, and our study indicates that climate warming is the driving force behind the collapse of the forest's food web. If supported by further research, the impact of climate change on tropical ecosystems may be much greater than currently anticipated. (See pp. E10397–E10406.)

Adaptation limits ecological diversification and promotes ecological tinkering during the competition for substitutable resources

Benjamin H. Good, Stephen Martis, and Oskar Hallatschek

Most mutations are subject to competitive exclusion: Their descendants will either take over the population or go extinct. In special cases, a mutant may evade competitive exclusion by exploiting a different ecological niche. Both types of mutations can be found in large microbial populations, yet little is known about how they interact. By generalizing consumer-resource theory to include heritable beneficial mutations, we show that interactions between diversification and competitive exclusion can produce dramatic departures from existing models of evolution or ecology alone. These results suggest that short-term evolutionary processes could play an important role in shaping the structure of microbial communities. (See pp. E10407–E10416.)

Molecular profiling of nonalcoholic fatty liver disease-associated hepatocellular carcinoma using SB transposon mutagenesis

Takahiro Kodama, Jing Yi, Justin Y. Newberg, Jean C. Tien, Hao Wu, Milton J. Finegold, Michiko Kodama, Zhubo Wei, Takeshi Tamura, Tetsuo Takehara, Randy L. Johnson, Nancy A. Jenkins, and Neal G. Copeland

Nonalcoholic fatty liver disease (NAFLD) is the fastest rising cause of hepatocellular carcinoma (HCC) in Western countries; however, the molecular mechanisms driving NAFLD-HCC remain elusive. Using Sleeping Beauty transposon mutagenesis in two mouse models of NAFLD-HCC, we identified hundreds of NAFLD-HCC candidate cancer genes that were enriched in pathways often associated with NAFLD and HCC. We also showed that Sav1, which functions in the Hippo signaling pathway and was the most frequently mutated gene identified by SB in both screens, prevents progression of steatohepatitis and subsequent HCC development in coordination with PI3K signaling via suppression of Yap, a downstream effector of the Hippo pathway. Our forward genetic screens have thus identified pathways and genes driving the development of NAFLD-HCC. (See pp. E10417–E10426.)

Shift from androgen to estrogen action causes abdominal muscle fibrosis, atrophy, and inguinal hernia in a transgenic male mouse model

Hong Zhao, Ling Zhou, Lin Li, John Coon V, Robert T. Chatterton, David C. Brooks, Enze Jiang, Li Liu, Xia Xu, Zhiyong Dong, Francesco J. DeMayo, Jonah J. Stulberg, Warren G. Tourtellotte, and Serdar E. Bulun

Inguinal hernia is one of the most common disorders that affect elderly men. A major pathology underlying inguinal hernia is the fibrosis and other degenerative changes that affect the lower abdominal muscle strength adjacent to the inguinal canal. Here we describe a critical role of estrogen and its nuclear receptor that enhance fibroblast proliferation and muscle atrophy, leading to inguinal hernia. Further research may reveal a potential role of estrogen ablation to prevent muscle fibrosis or hernia in a subset of elderly men. (See pp. E10427–E10436.)

Impaired hematopoiesis and leukemia development in mice with a conditional knock-in allele of a mutant splicing factor gene *U2af1*

Dennis Liang Fei, Tao Zhen, Benjamin Durham, John Ferrarone, Tuo Zhang, Lisa Garrett, Akihide Yoshimi, Omar Abdel-Wahab, Robert K. Bradley, Paul Liu, and Harold Varmus

Somatic mutations in some splicing factor genes are frequently found in myelodysplastic syndromes (MDS) and MDS-related acute myeloid leukemia (AML), blood cancers with few effective treatment options. However, the pathophysiological effects of these mutations remain poorly characterized. Here,

we report the establishment of mouse models to study a common splicing factor mutation, *U2AF1*(S34F). Production of the mutant protein in the murine hematopoietic compartment disrupts hematopoiesis in ways resembling human MDS. We further identified deletion of the *Runx1* gene and other known oncogenic mutations as changes that might collaborate with *U2af1*(S34F) to give rise to frank AML in mice. However, the *U2af1*(S34F) mutation was absent in two of the three AML cases, raising the possibility that this mutant protein plays a dispensable role in tumor maintenance. (See pp. E10437–E10446.)

Prevalent reliance of bacterioplankton on exogenous vitamin B1 and precursor availability

Ryan W. Paerl, John Sundh, Demeng Tan, Sine L. Svenningsen, Samuel Hylander, Jarone Pinhassi, Anders F. Andersson, and Lasse Riemann

Virtually all organisms require vitamin B1, including bacterioplankton that impact nutrient cycling and productivity in aquatic systems and Earth's climate. Here, we show that B1 auxotrophy, the need for exogenous B1 or precursors for survival, is widespread among wild bacterioplankton. Genetic analyses of wild bacterioplankton revealed that most are B1 auxotrophs and the abundance of several B1-related genotypes changes temporally at an estuarine monitoring station, suggesting that B1/precursor availability influences bacterioplankton succession. Complementarily, in-field nutrient-amendment experiments and bioassays indicate that B1/precursor bioavailability periodically limits bulk growth of bacterioplankton. Together the presented data highlight the prevalent reliance of bacterioplankton upon exogenous B1/precursors and suggest a hitherto overlooked influence of B1/precursor availability on aquatic biochemical cycling. (See pp. E10447–E10456.)

ADP-ribosyl–binding and hydrolase activities of the alphavirus nsP3 macrodomain are critical for initiation of virus replication

Rachy Abraham, Debra Hauer, Robert Lyle McPherson, Age Utt, Ilsa T. Kirby, Michael S. Cohen, Andres Merits, Anthony K. L. Leung, and Diane E. Griffin

Alphaviruses are mosquito-borne RNA viruses that cause encephalitis, rash, and arthritis. Alphavirus nonstructural protein 3 (nsP3) has a highly conserved macrodomain that can bind and remove ADP-ribose (ADPr) residues from ADP-ribosylated proteins, but its role in virus replication was not known. We show that alphavirus replication in neural cells depends on protein ADP ribosylation and that nsP3s with mutations that eliminate ADPr binding cannot form a functional replicase. Mutations that decrease ADPr binding result in fewer infected cells, while mutations that increase binding but decrease hydrolase activity infect cells normally but amplify replication complexes less well. Therefore, alphavirus replication requires nsP3 macrodomain interaction with one or more ADP-ribosylated proteins, as is consistent with the observed high conservation of this region. (See pp. E10457–E10466.)

Alleviating catastrophic forgetting using context-dependent gating and synaptic stabilization

Nicolas Y. Masse, Gregory D. Grant, and David J. Freedman

Artificial neural networks can suffer from catastrophic forgetting, in which learning a new task causes the network to forget how to perform previous tasks. While previous studies have proposed various methods that can alleviate forgetting over small numbers ($\leq$10) of tasks, it is uncertain whether they can prevent forgetting across larger numbers of tasks. In this study, we propose a neuroscience-inspired scheme, called "context-dependent gating," in which mostly nonoverlapping sets of units are active for any one task. Importantly, context-dependent gating has a straightforward implementation, requires little extra computational overhead, and when combined with previous methods to stabilize connection weights, can allow networks to maintain high performance across large numbers of sequentially presented tasks. (See pp. E10467–E10475.)

Control of movement vigor and decision making during foraging

Tehrim Yoon, Robert B. Geary, Alaa A. Ahmed, and Reza Shadmehr

How long should one stay and accumulate reward, and then, how fast should one travel to the next reward site? Marginal value theorem describes the decision-making process: the brain compares the immediate rate of harvest with its global history of capture, deciding to leave when the immediate rate falls below the average. Here, we extended the theory, showing that the same principle can be used to control speed of movements: the brain should compare the immediate rate of energy expenditure during movement with the global capture rate, planning to arrive at the destination when the two become equal. Experimental results confirmed many of the predictions, suggesting that a shared principle may underlie decision making and control of movement vigor. (See pp. E10476–E10485.)

Lawful tracking of visual motion in humans, macaques, and marmosets in a naturalistic, continuous, and untrained behavioral context

Jonas Knöll, Jonathan W. Pillow, and Alexander C. Huk

We characterize spatiotemporal integration of naturalistic, continuous visual motion of three primate species (humans, macaques, and marmosets). All three species volitionally, but naturally, track the center of expansion of a dynamic optic flow field. Detailed analysis of this flow-tracking behavior reveals lawful and repeatable dependencies of the behavior on nuances in the stimulus, revealing that even unconstrained and continuous behavior can exhibit the sort of precise dependencies typically studied only in artificial and constrained tasks. (See pp. E10486–E10494.)

Mutant UBQLN2 promotes toxicity by modulating intrinsic self-assembly

Lisa M. Sharkey, Nathaniel Safren, Amit S. Pithadia, Julia E. Gerson, Mark Dulchavsky, Svetlana Fischer, Ronak Patel, Gabrielle Lantis, Naila Ashraf, John H. Kim, Alia Meliki, Eiko N. Minakawa, Sami J. Barmada, Magdalena I. Ivanova, and Henry L. Paulson

UBQLN2, a ubiquitin-linked quality-control protein, accumulates in common neurodegenerative diseases and, when mutated, directly causes neurodegeneration. Employing a range of model systems, we show that UBQLN2 is intrinsically prone to self-assemble, leading to the formation of liquid-like droplets and amyloid aggregates. A disease-causing mutation in UBQLN2 impairs droplet dynamics and favors amyloid-like aggregation associated with neurotoxicity. Self-assembly is regulated by ubiquitin-linked domains in UBQLN2, implying a functional relationship between oligomerization and ubiquitin-dependent protein quality control. Our results emphasize a critical link between UBQLN2's role in ubiquitin-dependent pathways and its propensity to self-assemble and aggregate in neurodegenerative diseases. (See pp. E10495–E10504.)

Discovery of a small-molecule inhibitor of specific serine residue BAD phosphorylation

Vijay Pandey, Baocheng Wang, Chakrabhavi Dhananjaya Mohan, Ainiah Rushdiana Raquib, Shobith Rangappa, Venkatachalaiah Srinivasa, Julian E. Fuchs, Kesturu S. Girish, Tao Zhu, Andreas Bender, Lan Ma, Zhinan Yin, Basappa, Kanchugarakoppal S. Rangappa, and Peter E. Lobie

Despite the initial success of therapeutic agents targeting the *RAS/MAP* kinase and PI3K/AKT/mTOR signalling networks in oncology, development of acquired resistance to such therapeutics represents a significant challenge in successful disease management. BCL-2–associated death promoter (BAD) is a common and core downstream molecule for both the *RAS/MAP* kinase and PI3K/AKT/mTOR pathways and regulates cancer cell survival. In its unphosphorylated state, BAD sequesters BCL-2, which results in BAK/BAX activation and apoptosis. Herein, we identified and characterized a small molecule which specifically inhibits BAD phosphorylation on Ser99. This molecule may be therapeutically useful, either alone or in combination, to delay or obviate the development of resistance to other therapeutic agents. (See pp. E10505–E10514.)