PNAS Plus Significance Statements

Reconstruction of normal forms by learning informed observation geometries from data

Or Yair, Ronen Talmon, Ronald R. Coifman, and Ioannis G. Kevrekidis

The extraction of models from data (in a sense, the "understanding" of the physical laws giving rise to the data) is a fundamental cognitive as well as scientific challenge. We show a geometric/analytic learning algorithm capable of creating minimal descriptions of parametrically dependent unknown nonlinear dynamical systems. This is accomplished by the data-driven discovery of useful intrinsic-state variables and parameters in terms of which one can empirically model the underlying dynamics. We discuss an *informed* observation geometry that enables us to formulate models without first principles as well as without closed form equations. (See pp. E7865–E7874.)

Effects of thymic selection on T cell recognition of foreign and tumor antigenic peptides

Jason T. George, David A. Kessler, and Herbert Levine

We have developed a model of T cell binding that accurately represents the influence of self-peptides on thymic negative selection. From this, we generated estimates for relevant antigen recognition rates. We found that negative selection only slightly interferes with a T cell's ability to detect antigens that differ from self-peptide by a single amino acid and that these peptides may effectively be regarded as foreign. Moreover, negative selection thresholds chosen to reflect experimentally observed thymic survival rates result in optimal production of T cells that are capable of surviving selection and recognizing foreign antigen. Lastly, our model predicts empirically reasonable donor tissue recognition rates in the context of an HLA-matched transplant. (See pp. E7875–E7881.)

A classical view on nonclassical nucleation

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Nucleation is the process by which constituent building blocks first assemble to form a new substance. In the case of mineral formation from initially free ions in solution, the emergence of intermediary phases often determines the thermodynamics and kinetics of formation for the most stable phase. Our work on $CaCO_3$ mineralization reevaluates a topic of intense discussion: Can nucleation be explained by theories established over a century ago, or should new physical concepts, as recently proposed, be adopted? Our data show that classical theories can indeed be used to describe complex mechanisms of crystallization. In addition, we provide information about the properties of intermediate phases, which will aid in the design of additives to control mineralization. (See pp. E7882–E7890.)

Subnational mobility and consumption-based environmental accounting of US corn in animal protein and ethanol supply chains

Timothy M. Smith, Andrew L. Goodkind, Taegon Kim, Rylie E. O. Pelton, Kyo Suh, and Jennifer Schmitt

Companies and society alike are increasingly concerned with environmental impacts across complex supply chains. Suppliers engaged in upstream intermediate transactions commonly contribute over 75% of the carbon and water impacts of products ultimately consumed by users. These impacts pose risks to downstream customer-facing companies in the form of firm image, supply disruptions, and regulatory action. Policymakers and nonprofit advocacy organizations are increasingly looking to engage actors across supply chains to encourage conservation and environmental impact reduction. Unfortunately, traceability across complex, heterogeneous supply hinders these efforts. We provide a method for estimating mobility of corn from farms through feed and fuel supply chains, making it possible to characterize the variable environmental impacts of US corn inputs into animal protein and ethanol production. (See pp. E7891–E7899.)

Self-report captures 27 distinct categories of emotion bridged by continuous gradients

Alan S. Cowen and Dacher Keltner

Claims about how reported emotional experiences are geometrically organized within a semantic space have shaped the study of emotion. Using statistical methods to analyze reports of emotional states elicited by 2,185 emotionally evocative short videos with richly varying situational content, we uncovered 27 varieties of reported emotional experience. Reported experience is better captured by categories such as "amusement" than by ratings of widely measured affective dimensions such as valence and arousal. Although categories are found to organize dimensional appraisals in a coherent and powerful fashion, many categories are linked by smooth gradients, contrary to discrete theories. Our results comprise

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an approximation of a geometric structure of reported emotional experience. (See pp. E7900–E7909.)

North–south polarization of European electricity consumption under future warming

Leonie Wenz, Anders Levermann, and Maximilian Auffhammer

We statistically analyze 2006–2012 high-frequency temperature and electricity load data from 35 European countries to compute climate change impacts on electricity demand until 2100. Extrapolating countries' load responses to temperature beyond currently experienced climate, we find a future polarization of both peak load and electricity consumption in Europe. Specifically, while total European consumption remains constant under future warming, we project significant increases in the south, decreases in the north, and a shift of seasonal peak load from winter to summer for 19 countries. This changing spatial and temporal pattern of consumption and peak load has important implications for the build-out of transmission infrastructure, the construction of peak-generating capacity, and the design of energy-efficiency policy and storage capacity. (See pp. E7910–E7918.)

Injectable biomimetic liquid crystalline scaffolds enhance muscle stem cell transplantation

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Most research aiming to achieve muscle regeneration focuses on the biology of "muscle stem cells," but delivery methods that enhance transplantation efficiency of these cells are at early stages. We report on a liquid crystalline scaffold that encapsulates the cells and gels upon injection in vivo without requiring an external stimulus. As a unique structural feature, the scaffold contains nanofibers that align preferentially with surrounding natural muscle fibers. The biomimetic scaffold can have a stiffness that matches that of muscle, has great ability to retain growth factors, and has a biodegradation rate that is compatible with regeneration time scales. Most importantly, the scaffold enhances engraftment efficiency of the cells in injured muscle, and without injury when combined with growth factors. (See pp. E7919–E7928.)

Differential diagnosis of Alzheimer's disease using spectrochemical analysis of blood

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Vibrational spectroscopy is an ideal technique for analysis of biofluids, as it provides a "spectral fingerprint" of all of the molecules present within a biological sample, thus generating a holistic picture of the sample's status. Neurodegenerative diseases lack early and accurate diagnosis, and tests currently used for their detection are either invasive or expensive and time-consuming. This study used blood plasma to diagnose and differentiate various neurodegenerative diseases; the achieved sensitivities and specificities are equal to, or even higher than, the ones obtained by clinical/molecular methods. Herein, we show that spectroscopy could provide a simple and robust diagnostic test. Additional work should include asymptomatic individuals for an early screening test and exploration of neurodegenerative diseases at all stages of severity. (See pp. E7929–E7938.)

Loquacious-PD facilitates *Drosophila* Dicer-2 cleavage through interactions with the helicase domain and dsRNA

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Drosophila melanogaster use RNA interference to respond to a viral infection. Dicer-2 cleaves viral double-stranded RNA (dsRNA), producing siRNAs that silence viral gene expression. Dicer-2 recognizes the ends of dsRNA, and this property likely evolved to distinguish between viral and cellular dsRNA. Loquacious-PD (Loqs-PD), a dsRNA binding protein, is not required for Dicer-2's antiviral activity. However, by allowing Dicer-2 to cleave in a termini-independent manner, Loqs-PD facilitates cleavage of endogenous substrates with more complex termini. Our studies are significant because they provide a mechanistic basis for how Loqs-PD modulates Dicer-2 activity. For example, they reveal a previously unrecognized protein–protein interaction interface on the helicase domain of Dicer-2. (See pp. E7939–E7948.)

Role of remodeling and spacing factor 1 in histone H2A ubiquitination-mediated gene silencing

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Histone H2AK119 ubiquitination (H2Aub), as mediated by Polycomb repressive complex 1 (PRC1), is a prevalent modification which has been linked to gene silencing. We report that remodeling and spacing factor 1 (RSF1), a subunit of the RSF complex, is a H2Aub-binding protein. It reads H2Aub through a previously uncharacterized ubiquitinated H2A binding (UAB) domain. We show that RSF1 is required both for H2Aub-target gene silencing and for maintaining stable nucleosome patterns at promoter regions. The role of RSF1 in H2Aub function is further supported by the observation that RSF1 and Ring1, a *Xenopus* PRC1 subunit mediating H2Aub, regulate in concert mesodermal cell specification and gastrulation during *Xenopus* embryogenesis. This study reveals that RSF1 mediates the gene-silencing function of H2Aub. (See pp. E7949–E7958.)

Binding mechanism and dynamic conformational change of C subunit of PKA with different pathways

Wen-Ting Chu, Xiakun Chu, and Jin Wang

PKA is one of the largest kinase families in eukaryotes. The conformational change of catalytic subunit of PKA (PKAc) is linked to the substrate recognition and catalytic activity. We quantified the free energy landscapes of PKAc dynamics and uncovered the binding mechanism of two different ligands, ATP and PKI to PKAc, by using the weighted coarse-grained model and molecular dynamics simulations. Our results suggest mixed binding mechanism of induced fit and conformational selection and favor the pathway with PKAc-ATP as an intermediate (ATP binding first). Also, our studies indicate the critical residues at different stages of binding during the conformational change process from open to closed states. (See pp. E7959–E7968.)

Osmotaxis in *Escherichia coli* through changes in motor speed

Jerko Rosko, Vincent A. Martinez, Wilson C. K. Poon, and Teuta Pilizota

Bacterial taxis has been a subject of active investigation for over 100 years, serving as a model of both biological sensory transduction and self-propulsion. Consequently, chemotaxis of *Escherichia coli* is one of the best-understood biological networks. Nevertheless, the exact roles of taxis and motility in *E. coli's* life cycle, particularly in host invasion, remain unknown, partly because of the complexity of its natural habitat. By looking at the response of both individual bacterial motors and a swimming population, we investigate *E. coli's* response to changes in external osmolalities similar to those found in the human gastrointestinal tract. We find that, unlike chemotaxis, osmotic response changes the motor speed and discuss how the observation can lead to previously observed osmotaxis. (See pp. E7969–E7976.)

Multiple proteolytic events in caspase-6 self-activation impact conformations of discrete structural regions

Kevin B. Dagbay and Jeanne A. Hardy

Caspases are central players in programmed cell death. Among caspases, caspase-6 is unique for its association with neurological disorders, including Alzheimer's, Huntington's, and Parkinson's diseases. The structural details underlying caspase-6 activation are still limited but are requisites in understanding caspase-6 function. The prodomain and linker play essential roles in caspase function and regulation; however, while the long prodomains in initiator caspases are known, the structures of the short prodomains in executioner caspases remain elusive, despite efforts using crystallography and NMR. Here, we used hydrogen/deuterium exchange MS and revealed two important findings: the prodomain and intersubunit linker are intrinsically disordered, and the presence or absence of these regions results in distinct structural dynamics as procaspase-6 progresses through its proteolytic activation. (See pp. E7977–E7986.)

Structure of the Ebola virus envelope protein MPER/TM domain and its interaction with the fusion loop explains their fusion activity

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Current models of virus entry by type 1 viral envelope glycoprotein-mediated membrane fusion place the fusion domains (fusion peptides or fusion loops) and transmembrane (TM) domains of these proteins in close proximity, but a direct molecular interaction and functional cooperation of these domains have not been previously demonstrated for any viral envelope glycoprotein. In the present work, we determined the structure of the only missing pieces of the Ebolavirus glycoprotein 2 [namely, its membrane proximal external region (MPER) and TM domains], demonstrate MPER's direct molecular interaction with the fusion loop of the same protein, and provide evidence for the functional significance of this interaction. (See pp. E7987–E7996.)

Dual role of mitochondria in producing melatonin and driving GPCR signaling to block cytochrome c release

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This paper describes the finding that mitochondria synthesize and release melatonin and have their selective G protein-coupled receptor (GPCR) in the outer membrane. We further demonstrate that mitochondrial melatonin type 1 receptors respond to melatonin by activating heterotrimeric G proteins located in the intermembrane space and inhibit stress-mediated cytochrome c release. This remarkable insight changes our classical understanding of biological GPCR function by showing that a cellular organelle both synthesizes and has a signaling receptor for a specific ligand. Implicit with our original work is the existence of an automitocrine signaling pathway by which melatonin prevents neurodegeneration associated with mitochondrial cytochrome *c* release and downstream caspase activation. (See pp. E7997–E8006.)

Effect of cell cycle arrest on intermediate metabolism in the marine diatom *Phaeodactylum tricornutum*

Joomi Kim, Christopher M. Brown, Min Kyung Kim, Elizabeth H. Burrows, Stéphane Bach, Desmond S. Lun, and Paul G. Falkowski

We examined the effect of cell cycle arrest in the diatom *Phaeodactylum tricornutum*. When the cycle is disrupted in G1 phase, it leads to unbalanced growth and the accumulation of storage products, especially lipids. In contrast to nitrogen-stressed cells, however, cells arrested in G1 do not cannibalize photosynthetic proteins and show little change in photosynthetic energy conversion efficiency. This study provides insight into how intermediate metabolism is scheduled with respect to the cell cycle in a marine diatom. (See pp. E8007–E8016.)

MicroRNA-277 targets *insulin-like peptides 7* and *8* to control lipid metabolism and reproduction in *Aedes aegypti* mosquitoes

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Hematophagous female mosquitoes transmit devastating human diseases. Owing to their obligatory blood feeding, they require an extremely high level of lipid metabolism for reproduction. We found that microRNA-277 (miR-277) plays a critical role in lipid metabolism of *Aedes aegypti* mosquitoes. The genetic disruption of miR-277 using the CRISPR-Cas9 system showed impairment of both lipid storage and ovarian development. Insulin/FOXO signaling was up-regulated after miR-277 depletion. Comprehensive screening and functional identification revealed that insulin-like peptides *ilp7* and *ilp8* are direct targets of miR-277. CRISPR-Cas9 depletions identified differential actions of these ILPs in lipid

accumulation and utilization. Thus, miR-277 serves as a monitor that controls ILP7 and ILP8 mRNA levels to maintain the lipid homeostasis required for reproduction. (See pp. E8017–E8024.)

Escherichia coli responds to environmental changes using enolasic degradosomes and stabilized DicF sRNA to alter cellular morphology

Oleg N. Murashko and Sue Lin-Chao

The prevalent habitat of *Escherichia coli* is the predominantly anaerobic environment of the gastrointestinal tract of humans and other warm-blooded organisms. We found that, under anaerobic conditions, the presence of enolase in the RNA degradation machinery regulates cell morphology and induces *E. coli* filamentation by stabilizing a small RNA, DicF, that inhibits the cell division gene *ftsZ*. Cell filamentation has previously been linked to bacterial pathogenesis. In contrast to *E. coli* nonpathogenic strains, pathogenic *E. coli* strains possess multiple copies of sRNA DicF in their genomes. Our data provide a mechanism by which bacterial cells can adopt a filamentous form during infection under anaerobic conditions. (See pp. E8025–E8034.)

CK1α ablation in keratinocytes induces p53-dependent, sunburn-protective skin hyperpigmentation

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UV tanning is a common social behavior, which increases melanin production and pigmentation of the skin. UV irradiation is a standard treatment of depigmenting diseases such as vitiligo. However, recurrent UV irradiation is genotoxic and facilitates skin aging and cancer. Here, we identified a method of inducing hyperpigmentation by inhibition of casein kinase 1α (CK1α). UV tanning is induced through activation of p53, via the Pomc/α-MSH/Mc1r/Mitf pathway, but both *Pomc* and *Mc1r* function can be compromised by aging or allelic polymorphism. In contrast, inhibition of CK1α activates a different pathway, p53/KitL/Kit, and raises protective eumelanin without the procarcinogenic pheomelanin. Inhibition of CK1α is therefore expected to be an effective strategy for skin protection from sunlight and for treating depigmenting diseases. (See pp. E8035–E8044.)

Mutation in human *CLPX* elevates levels of δ-aminolevulinate synthase and protoporphyrin IX to promote erythropoietic protoporphyria

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Although heme synthesis is ubiquitous, specific regulatory mechanisms couple heme production to cellular demand and environmental conditions. The importance of these regulatory mechanisms is highlighted by clinical variability in porphyrias caused by loss-of-function mutations in heme synthesis enzymes. Heme synthesis is also controlled by the mitochondrial AAA+ unfoldase ClpX, which participates in both heme-dependent degradation of δ-aminolevulinate synthase (ALAS) and ALAS activation. This study reports a human familial mutation in *CLPX* that contributes to erythropoietic protoporphyria (EPP) by partially inactivating CLPX. Reduced CLPX activity increases ALAS post-translational stability, causing pathological accumulation of protoporphyrin IX (PPIX) in human patients. Our results thus identify an additional gene that promotes PPIX overproduction and EPP and highlight the complex gene network contributing to disorders of heme metabolism. (See pp. E8045–E8052.)

Methylation-dependent DNA discrimination in natural transformation of *Campylobacter jejuni*

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Campylobacter jejuni is naturally transformable but is selective in the DNA used in transformation. Natural transformation allows for rapid adaptation and provides a means for DNA repair, both of which enhance bacterial fitness. Our work demonstrates that the methylation status of *C. jejuni* DNA is critical for transformation; methylation of a single 6-bp sequence in proximity to the transforming DNA is sufficient to allow non-transforming DNA to transform *C. jejuni*. Our data argue against previously described means for DNA discrimination; specifically, there is no evidence that a restriction enzyme recognizes the unmodified 6-bp sequence, and no evidence of a typical DNA uptake sequence. Therefore, we have identified a distinct DNA discrimination mechanism in *Campylobacter*. (See pp. E8053–E8061.)

Dendritic space-filling requires a neuronal type-specific extracellular permissive signal in *Drosophila*

Amy R. Poe, Lingfeng Tang, Bei Wang, Yun Li, Maria L. Sapar, and Chun Han

Neurons develop diverse dendrite morphologies to achieve specialized functions. Certain neurons completely fill their receptive fields with evenly spaced dendrites, while others only partially occupy available space with sparse dendrites. How a similar extracellular environment regulates dendrite patterning of different neurons has been elusive. Here we show that *Drosophila* space-filling neurons require epidermis-derived heparan sulfate proteoglycans (HSPGs) to cover the body wall, while other sensory neurons sharing the same receptive fields are insensitive to extracellular HSPGs. HSPGs promote dendritic growth and maintenance of space-filling neurons by stabilizing microtubules in dynamic high-order branches. HSPGs do not function through the only known HSPG receptor leukocyte antigen-related (Lar) nor by transporting extracellular diffusible ligands. Our results reveal important mechanisms by which HSPGs regulate neuronal morphogenesis. (See pp. E8062–E8071.)

Schwann cells use TAM receptor-mediated phagocytosis in addition to autophagy to clear myelin in a mouse model of nerve injury

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Myelin is a potent inhibitor of axon regeneration. In the central nervous system, failure to clear myelin debris after injury presents a major roadblock to recovery. In contrast, rapid myelin clearance in the peripheral nervous system (PNS) contributes to this system's remarkable regenerative capacity, but the mechanisms involved have remained incompletely understood. In this work, we set out to identify novel mechanisms of PNS myelin clearance to generate new ideas about activating myelin clearance in the injured CNS. We provide evidence that Schwann cells, myelinating glia of the PNS, engulf myelin debris using two receptors, Axl and Mertk. We hypothesize that astrocytes have the potential to use this same

mechanism to engulf myelin debris after CNS injury. (See pp. E8072–E8080.)

Efficient stimulus-secretion coupling at ribbon synapses requires RIM-binding protein tethering of L-type Ca^{2+} channels

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This paper investigates the organization of the active zone at ribbon synapses in the retina, using deletions of the active zone protein RIM-binding protein (RBP) as a tool. The results demonstrate that, at these synapses, which, different from other synapses, use presynaptic L-type calcium channels for triggering vesicle exocytosis, RBPs mediate the recruitment of L-type calcium channels adjacent to release sites, thereby allowing efficient stimulus-secretion coupling. Thus, this paper presents a demonstration of how calcium channels are organized at the presynaptic active zone of ribbon synapses. (See pp. E8081–E8090.)

Dissection of the *Drosophila* neuropeptide F circuit using a high-throughput two-choice assay

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The perception and processing of rewarding events are essential for organismal survival. In *Drosophila*, several groups of neurons have been shown to mediate reward perception or processing. However, a complete description of the reward circuit is missing. Here, we describe a simple two-choice, high-throughput assay suitable for performing large neuronal activation screens for neural circuits involved in reward perception/processing. We characterized this assay using activation of neuropeptide F (NPF) neurons, a known rewarding experience for flies. Furthermore, using genetic intersectional strategies, we subdivided the NPF neurons into different classes and showed that the activation of a subset of small NPF neurons located in the dorsomedial brain is sufficient to trigger preference. (See pp. E8091–E8099.)

Discovery of peptide ligands through docking and virtual screening at nicotinic acetylcholine receptor homology models

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Predicting how conotoxins bind to nicotinic acetylcholine receptors (nAChRs) is hard. Not only are these venom-derived peptides large, but the structures of many nAChRs are unknown. In response, we developed an ensemble-docking algorithm named ToxDock. We used ToxDock to reliably dock the conotoxin α-GID to a homology model of the α4β2 nAChR, a main nAChR in the brain and target for nicotine addiction therapeutics. A virtual screen with ToxDock identified four α-GID analogs and, based on experimental evidence, correctly predicted their activity at the α4β2 nAChR in all cases. More screening showed that two of these analogs have substantially reduced antagonism at the human α7 nAChR, a key step in optimizing α-GID into a tool for studying brain nAChRs. (See pp. E8100–E8109.)

A chloroplast thylakoid lumen protein is required for proper photosynthetic acclimation of plants under fluctuating light environments

Jun Liu and Robert L. Last

Photosynthesis harnesses sunlight to assimilate carbon dioxide and produce biomass essential for life on earth. Photosystem integrity and activity are negatively impacted by fluctuations in incident light from the sun. How plants regulate photosynthetic dynamics under natural fluctuating growth light is relatively poorly understood. Loss of the *Arabidopsis thaliana* chloroplast lumenal protein MPH2 causes photosystem II (PSII) repair deficiency under changing light. PSII repair mutants are impaired in growth under greenhouse fluctuating light environments, while photoprotection mutants grow normally. These findings inform strategies for engineering plant photosynthetic performance under field conditions, to sustainably address increasing needs for food, fiber, and fuel at a time of changing climate and rapid population growth. (See pp. E8110–E8117.)

Receptor-mediated chitin perception in legume roots is functionally separable from Nod factor perception

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Like 80–90% of land plants, legumes form endosymbioses with arbuscular mycorrhizal fungi, host endophytes, support a rhizosphere community, and are attacked by pathogens. The ability of root cells to distinguish between these soil microbes and the mixture of chitinaceous compounds they display as signal molecules is important for an appropriate plant response. We show that legumes possess very similar receptors enabling root cells to separate perception of chitin, which triggers responses to pathogens, from perception of lipochitin oligosaccharides (Nod factors), which trigger endosymbiosis with rhizobial bacteria. The chitin receptors bind chitin in biochemical assays, and inactivation of the corresponding genes impairs defense responses toward pathogens. Together this establishes a long-sought foundation for dissecting plants' response mechanisms toward different soil microbes. (See pp. E8118–E8127.)