PNAS Plus Significance Statements

Bistable emergence of oscillations in growing *Bacillus subtilis* biofilms

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Cell communities can become resilient to stress by undergoing collective growth oscillations, which provide periodic stress relief and are collective in the sense that they arise only for large enough numbers of cells. Collective oscillatory phenomena usually emerge continuously as the system size increases, with oscillations starting with small amplitude and slowly growing as the cells proliferate. This behavior, however, is not appropriate in situations in which the population needs to implement a full-sized response quickly. Our combined theoretical and experimental study shows that collective oscillations in bacterial biofilm communities emerge via a discontinuous transition as their size increases. This behavior may provide an evolutionary advantage to cell communities, by allowing them to quickly alter qualitatively their dynamics in response to variations in external conditions such as stress. (See pp. E8333–E8340.)

Closely packed, low reorganization energy π-extended postfullerene acceptors for efficient polymer solar cells

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For producing electricity, polymer solar cells (PSCs) offer properties tunability, light weight, scalability, and earth-abundant materials. PSC active layers typically consist of donor polymer and fullerene acceptor blends having discrete conduits for photogenerated hole and electron conduction. The spherical fullerene shape, which enables close packing, orbital degeneracies, and low charge-transfer reorganization energies, is thought to be essential for efficient photocurrent generation and high power conversion efficiencies (PCEs). However, the recent advent of irregularly shaped indacenodithienothiophene (IDTT) acceptors yielding higher PCEs challenges the fullerene paradigm. In a combined experimental and theoretical study with two new isomeric IDTT derivatives, we shed light on the basis of this performance in terms of surprisingly close molecular packing, strong electronic coupling, and low reorganization energies. (See pp. E8341–E8348.)

Decreasing fire season precipitation increased recent western US forest wildfire activity

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Wildfires have profound impacts on forested ecosystems and rural communities. Increases in area burned by wildfires in the western United States have been widely attributed to reduced winter snowpack or increased summer temperatures. Trends in precipitation have previously been dismissed as has their feedback to regional temperature trends. We show that declines in summer precipitation and wetting rain days have likely been a primary driver of increases in wildfire area burned. Understanding the climatic drivers of fire activity is important for informing forest management. Our findings are consistent with future climate projections, which predict further decreases in summer precipitation and longer dry periods between rain events across much of the West. (See pp. E8349–E8357.)

Morphological intelligence counters foot slipping in the desert locust and dynamic robots

Matthew A. Woodward and Metin Sitti

Animals in natural environments necessarily come into contact with surfaces having differing orientations and materials. However, not much is known about how their feet contribute to friction, particularly in the case of dual-attachment mechanisms and passive mechanics (morphological intelligence). We study the desert locust's (*Schistocerca gregaria*) morphology, spines and adhesive pads, and jumping behavior to extract traits that contribute to enhancing friction. Our results demonstrate the potential contribution of morphological intelligence to solving complex dynamic locomotion problems. We anticipate that this study will inspire further research of the strategies used by animals to interact dynamically with diverse surfaces. Furthermore, the concepts presented can be easily adapted to, for the enhancement of, existing simple miniature and state-of-the-art large-legged terrestrial robots. (See pp. E8358–E8367.)

Material microenvironmental properties couple to induce distinct transcriptional programs in mammalian stem cells

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Cells have been shown to respond to a host of physical properties of the environments that surround

them. However, given that these properties vary considerably across tissues, how these individual properties interact to form unique regulatory environments for cells is largely unknown. This work analyzes the transcriptional responses of cells to unique combinations of microenvironmental material properties to gain broad insights into the coupling among different properties, the magnitude of the transcriptional effects, and the role of cell type. We find significant coupling among these properties, large variation in the magnitude of the transcriptional changes, and qualitative differences in the responses based on cell type, demonstrating the significant context dependence of microenvironmental material sensing. (See pp. E8368–E8377.)

Viral genetic diversity and protective efficacy of a tetravalent dengue vaccine in two phase 3 trials

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Dengue virus (DENV) vaccine development is complicated by the existence of four genetically diverse DENV serotypes. A high degree of antigenic match between vaccine strains and circulating DENVs may be important to achieve high vaccine efficacy (VE). Using data from two phase 3 trials of the CYD-TDV vaccine, we assessed whether and how VE against virologically confirmed dengue varied with amino acid sequence characteristics and genotypes of the disease-causing DENVs. VE decreased with the degree of amino acid dissimilarity between the vaccine insert and disease-causing DENVs. After accounting for differential VE by serotype, this effect seemed to occur only for younger children, who also had lower baseline seropositivity and potentially a less broadly protective immune response. (See pp. E8378–E8387.)

Genotype-targeted local therapy of glioma

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Lower-grade gliomas are often characterized by mutations in metabolism-related genes isocitrate dehydrogenase 1 (*IDH1*) and *IDH2*. Resection of these tumors is constrained by adjacent eloquent cortex, resulting in local failures. Studies showed that IDH mutant cells are sensitive to metabolic therapeutics, but these drugs are limited by systemic toxicities. We hypothesized that application of metabolism-altering therapeutics at the surgical margin would improve tumor control and minimize toxicity. We developed an intraoperative diagnostic assay to identify IDH mutations. We show that intratumoral administration of sustained release formulations of metabolism-altering compound prolongs survival in a mouse model of IDH mutant glioma. This genotype-based paradigm introduces a workflow in surgical oncology that can be extended to other tumors characterized by targetable molecular alterations. (See pp. E8388–E8394.)

Two novel protein *O*-glucosyltransferases that modify sites distinct from POGLUT1 and affect Notch trafficking and signaling

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The Notch-signaling pathway is normally activated by receptor–ligand interactions. Extracellular domains (ECDs) of Notch receptors are heavily modified with *O*-linked glycans, such as *O*-glucose (*O*-Glc), *O*-fucose (*O*-Fuc), and *O*-GlcNAc. The significance of multiple types of *O*-glycans on Notch is not understood. NOTCH1 ECD interacts with ligands at multiple points, including an *O*-Glc monosaccharide on the 11th Epidermal Growth Factor (EGF) repeat (EGF11). Here, we identify two novel protein *O*-glucosyltransferases that modify NOTCH1 EGF11 with *O*-Glc. Combined deletion of the *O*-Glc site on EGF11 with *O*-Fuc modification sites on EGF8 or EGF12 markedly reduced NOTCH1 cell-surface expression or activation of NOTCH1 by Delta-like ligand 1, respectively. This study identifies a cooperative mechanism for fine-tuning the Notch-signaling pathway by different types of *O*-glycans. (See pp. E8395–E8402.)

Auto-fatty acylation of transcription factor RFX3 regulates ciliogenesis

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Regulatory Factor X 3 (RFX3) is one of the key transcription factors involved in cilia formation and functions. Our study reveals that auto-fatty acylation is a critical regulatory mechanism for RFX3 transcriptional activities. Fatty acylation of RFX3 is required for its dimerization, leading to transcription of cilia-associated genes. More importantly, fatty acylation of RFX3 regulates ciliogenesis and Hedgehog signaling pathways, which are associated with developmental and degenerative disorders known as ciliopathies. Our results indicate a major role of auto-fatty acylation in the regulation of RFX3 function and ciliogenesis, providing a potential link between deregulation of fatty acid metabolism to ciliopathies and diabetes. (See pp. E8403–E8412.)

Redox-coupled quinone dynamics in the respiratory complex I

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Complex I is the primary energy-converting enzyme of aerobic respiratory chains. By reducing quinone to quinol, this gigantic enzyme pumps protons across its membrane domain, which in turn powers ATP synthesis and active transport. Despite the recently resolved molecular structures of complex I, the quinone dynamics and its coupling to the pumping function remains unclear. Here we show by large-scale molecular simulations that the quinone reduction leads to ejection of the quinol molecule from the active site into a second binding site near the proton-pumping membrane domain of complex I. The identified region has been linked with human mitochondrial disorders. Our work suggests that the quinone dynamics provides a key coupling element in complex I. (See pp. E8413–E8420.)

SNARE zippering requires activation by SNARE-like peptides in Sec1/Munc18 proteins

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Soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor(SNARE) proteins drive membrane fusion by zippering into coiled-coil bundles between membrane bilayers. In this work, we showed that certain layers in the SNARE bundle are dispensable for SNARE-mediated membrane fusion. However, these layers are required for fusion reactions activated by the cognate Sec1/Munc18 (SM) protein or a synthetic Vc peptide derived from the vesicular SNARE. Strikingly, we identified a conserved SNARE-like peptide (SLP) in SM proteins that structurally and functionally resembles Vc peptide. Like Vc peptide, SLP binds and activates target SNAREs, stimulating the fusion reaction. These data suggest that the SM protein uses its SNARE-like sequence to promote the SNARE zippering pathway, ensuring the efficiency of vesicle fusion. (See pp. E8421–E8429.)

Identification of a multipotent Twist2-expressing cell population in the adult heart

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Adult mammalian hearts have limited self-renewal capacity. Although mounting evidence indicates that new cardiomyocytes are derived from dedifferentiation and proliferation of existing cardiomyocytes, the contribution of adult cardiac progenitors to cardiomyocyte renewal during homeostasis and upon injury remains under debate. The basic helix–loop–helix transcription factor Twist2 is expressed in interstitial cells in the adult myocardium. Using genetic lineage tracing, we identified a Twist2-expressing cell population that gives rise to a small number of adult cardiomyocytes in vivo. These Twist2-expressing cells can differentiate into cardiomyocytes, endothelial cells, and fibroblasts in culture and contribute to cardiac renewal through cell fusion and de novo differentiation. Our findings add Twist2-expressing cells to the cellular constituents involved in adult cardiac maintenance and remodeling. (See pp. E8430–E8439.)

Rapid diffusion-state switching underlies stable cytoplasmic gradients in the *Caenorhabditis elegans* zygote

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Intracellular concentration gradients regulate essential processes including the organization of the mitotic spindle, cytokinesis, and cell polarity. Unlike tissue-scale gradients, little is known about how intracellular gradients form. We used single-particle tracking to characterize the behaviors of individual molecules that sculpt gradients in the cytoplasm of the *Caenorhabditis elegans* zygote. Our findings suggest that MEX-5 and PIE-1 rapidly switch between fast- and slow-diffusing states with kinetics that vary along the axis of the cell. As a consequence, slow-diffusing MEX-5 and PIE-1 particles are highly polarized, giving rise to their respective gradients. Using mathematical modeling, we show that rapid diffusion-state switching can quickly pattern gradients across a range of temporal and spatial scales. (See pp. E8440–E8449.)

Evolutionary history of human *Plasmodium vivax* revealed by genome-wide analyses of related ape parasites

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Chimpanzees, bonobos, and gorillas harbor close relatives of human *Plasmodium vivax*, but current knowledge of these parasites is limited to a small number of gene fragments derived almost exclusively from mitochondrial DNA. We compared nearly full-length genomes of ape parasites with a global sample of human *P. vivax* and tested the function of human and ape *P. vivax* proteins believed to be important for erythrocyte binding. The results showed that ape parasites are 10-fold more diverse than human *P. vivax* and exhibit no evidence of species specificity, whereas human *P. vivax* represents a bottlenecked lineage that emerged from within this parasite group. Thus, African apes represent a large *P. vivax* reservoir whose impact on human malaria eradication requires careful monitoring. (See pp. E8450–E8459.)

Circadian clock protein BMAL1 regulates IL-1β in macrophages via NRF2

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The molecular clock provides an anticipatory mechanism, allowing organisms to prepare and respond to daily changes in the external environment. The response of the innate immune system to pathogenic threats is dependent on time of day; however, the molecular mechanisms underlying this have yet to be fully uncovered. We observe that the core molecular clock component, BMAL1, is crucial in promoting an antioxidant response in myeloid cells. Deletion of *Bmal1* in macrophages disrupts NRF2 activity, facilitating accumulation of reactive oxygen species and the proinflammatory cytokine, IL-1β. Thus the molecular clock directly controls NRF2 transcriptional activity and antioxidant capacity to regulate IL-1β in myeloid cells. (See pp. E8460–E8468.)

Intestinal host defense outcome is dictated by PGE_2 production during efferocytosis of infected cells

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Citrobacter rodentium infection, a murine colitis model to study human intestinal diseases, causes exacerbated apoptosis of intestinal epithelial cells and triggers Th17 immune responses. Here, we identified a heretofore unknown role for the bioactive lipid mediator prostaglandin E_2 (PGE_2) in the inhibition of Th17 cell differentiation during intestinal *C. rodentium* infection. When the PGE_2 receptor EP4 was antagonized, we detected enhanced colonic Th17 cells, increased expression of antimicrobial peptides, and decreased bacterial numbers in the colon. These results suggest that pharmacological intervention of the PGE_2 signaling may be an important target to enhance Th17 actions and improve intestinal host defense. (See pp. E8469–E8478.)

Metastatic cells are preferentially vulnerable to lysosomal inhibition

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We show that there is a functional reciprocal relationship between lysosome activity and metastasis that allows chloroquine (CQ) and other inhibitors of lysosome function, such as bafilomycin A_1, to preferentially kill human metastatic bladder cancer cells by targeting autophagy-independent lysosome functions. In addition, CQ treatment of bladder cancer cells and subsequent acquisition of resistance to this therapy lead to altered gene expression programs that drive a less aggressive and metastatic phenotype via upregulation of ID4 (inhibitor of DNA binding 4). Clinically, this work provides a conceptual foundation for using ID4 expression as a predictive and prognostic biomarker of CQ sensitivity and metastasis in patients with bladder cancer. (See pp. E8479–E8488.)

Stunted childhood growth is associated with decompartmentalization of the gastrointestinal tract and overgrowth of oropharyngeal taxa

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Stunting globally affects an estimated 155 million children under 5 years of age, representing about 25% of children worldwide. Due to poor understanding of the underlying pathophysiology, therapeutic interventions to efficiently correct for linear growth delay or associated pathophysiological disturbances are still lacking. Here, we describe the microbial composition of duodenal fluids from stunted children. We show that these children are affected by small intestinal bacterial overgrowth and harbor a characteristic microbial community composed mainly of oropharyngeal bacteria. This microbial signature is also reflected in their feces and conserved between countries. Stunting is traditionally considered to arise from recurrent enteric infections. This study shows that oropharyngeal taxa are associated with stunting, suggesting that alternative pathophysiological mechanisms are involved. (See pp. E8489–E8498.)

Macrophages release plasma membrane-derived particles rich in accessible cholesterol

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Earlier studies suggested that particles are released from the macrophage plasma membrane, but the mechanism has been unclear. We found that filopodia of macrophages release large numbers of vesicular particles. Nanoscale secondary ion mass spectrometry revealed that these particles are enriched in cholesterol, including the "accessible" pool of cholesterol detectable by the cholesterol-binding protein. The cholesterol content of macrophage particles increased when the cells were loaded with cholesterol and could be depleted by incubating the cells with high-density lipoproteins. Our studies suggest that the release of particles by macrophages could be one mechanism for cholesterol efflux and that particles could be an intermediate in the movement of cholesterol to high-density lipoproteins. (See pp. E8499–E8508.)

Polyprotein strategy for stoichiometric assembly of nitrogen fixation components for synthetic biology

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The requirement of maintaining balanced expression of a large number of gene products represents a major challenge to the engineering of nitrogen fixation in cereal crops, necessitating reiterative combinatorial assembly cycles to optimize monocistronic gene expression. In this study, we have explored a "fuse-and-cleave" virus-derived polyprotein strategy to reduce gene numbers and achieve balanced expression of protein components required for nitrogenase biosynthesis and activity. After testing and regrouping assemblies on the basis of expression profiles, cleavage patterns, and activity, 14 essential genes were selectively assembled into 5 giant genes that enable growth on dinitrogen. This strategy has potential advantages, not only for transferring nitrogen fixation to plants, but also for the engineering of other complex systems of profound agronomic and ecological importance. (See pp. E8509–E8517.)

Phospholipid retention in the absence of asymmetry strengthens the outer membrane permeability barrier to last-resort antibiotics

Matthew J. Powers and M. Stephen Trent

The outer membrane of Gram-negative bacteria prevents the entry of many antibiotics and limits treatment options for Gram-negative infections. This unique membrane is effective due to its asymmetric lipid composition, with the glycolipid lipid A [LPS or lipooligosaccharide (LOS)] in the outer leaflet at the cell surface and glycerophospholipids in the inner leaflet. Furthering our understanding of how outer membrane asymmetry is maintained is critical for the development of novel therapeutics to target multidrug-resistant bacteria. Here, we used a Gram-negative bacterium without LOS to probe for factors that impact cell-envelope maintenance in the absence of LOS. Our approach enabled us to explore fundamental mechanisms of cell-envelope biology and expand our holistic view of the asymmetrical, Gram-negative outer membrane. (See pp. E8518–E8527.)

Bacterial symbionts use a type VI secretion system to eliminate competitors in their natural host

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Competition among cooccurring bacteria can change the structure and function of a microbial community. However, little is known about the molecular mechanisms that impact such interactions in vivo. We used the association between bioluminescent bacteria and their squid host to study how environmentally transmitted bacteria compete for a limited number of host colonization sites. Our work suggests that *Vibrio fischeri* use a type VI secretion system, acting as a contact-dependent interbacterial "weapon," to eliminate competing strains from cooccupying sites in the host. This work illuminates a mechanism by which strain-specific differences drive closely related bacteria to engage in lethal battles as they establish a beneficial symbiosis, revealing how genetic variation among potential colonizers directly impacts

the spatial structure of the host-associated population. (See pp. E8528–E8537.)

Chance, long tails, and inference in a non-Gaussian, Bayesian theory of vocal learning in songbirds

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Skilled behaviors are learned through a series of trial and error. The ubiquity of such processes notwithstanding, current theories of learning fail to explain how the speed and the magnitude of learning depend on the pattern of experienced sensory errors. Here, we introduce a theory, formulated and tested in the context of a specific behavior—vocal learning in songbirds. The theory explains the observed dependence of learning on the dynamics of sensory errors. Furthermore, it makes additional strong predictions about the dynamics of learning that we verify experimentally. (See pp. E8538–E8546.)

Mutation-independent rhodopsin gene therapy by knockdown and replacement with a single AAV vector

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A number of gene-augmentation strategies are entering clinical trials for the treatment of inherited retinal blindness. Gene therapy for autosomal dominant diseases faces significant obstacles that include allelic heterogeneity and the potential need to silence the mutated gene. Here we show that a single-gene therapy vector that combines knockdown of the causative gene with its replacement by a resistant wild-type copy can prevent photoreceptor cell death and vision loss in a canine model of autosomal dominant retinitis pigmentosa. (See pp. E8547–E8556.)

Involvement of advillin in somatosensory neuron subtype-specific axon regeneration and neuropathic pain

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An estimated 20 million people in the United States have chronic neuropathic pain, but current analgesics are nonspecific or insufficiently effective. Here we show that advillin, a sensory neuron-specific protein, modulates axonal regeneration of a specific subset of pain-sensing afferent neurons (nociceptors) that binds with isolectin B4 and neuropathic pain. In addition, we identify the cell behavior of advillin shed-off from the growth cone in the context of axonal regeneration and thus detected advillin protein in the cerebrospinal fluid in mice with painful peripheral neuropathy. Advillin is a potential biosignature to diagnose the lesion cause of neuropathic pain associated with isolectin $B4^+$ nociceptors. (See pp. E8557–E8566.)

Local field potentials of subthalamic nucleus contain electrophysiological footprints of motor subtypes of Parkinson's disease

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Despite the fact that deep-brain stimulation (DBS) of the subthalamic nucleus (STN) has emerged as an effective surgical treatment for Parkinson's disease (PD), there is no available neurobiomarker providing information about the symptoms of PD subtypes in STN. In this paper, we report the finding of neural correlates of two motor phenotypes of PD in the territories of STN. Despite advances in imaging, microelectrode recording continues to be best practice and the dominant method for STN localization during DBS surgery [Abosch A, et al. (2013) *Stereotact Funct Neurosurg* 91:1–11]. Hence, we anticipate our findings will provide possibilities for the intraoperative interpretation of oscillatory dynamics of STN and that these well-localized patterns can be used as objective tools for future neuromodulation technologies. (See pp. E8567–E8576.)