PNAS Plus Significance Statements

Phase transitions in semidefinite relaxations

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Modern data analysis requires solving hard optimization problems with a large number of parameters and a large number of constraints. A successful approach is to replace these hard problems by surrogate problems that are convex and hence tractable. Semidefinite programming relaxations offer a powerful method to construct such relaxations. In many instances it was observed that a semidefinite relaxation becomes very accurate when the noise level in the data decreases below a certain threshold. We develop a new method to compute these noise thresholds (or phase transitions) using ideas from statistical physics. (See pp. E2218–E2223.)

Necessity of capillary modes in a minimal model of nanoscale hydrophobic solvation

Suriyanarayanan Vaikuntanathan, Grant Rotskoff, Alexander Hudson, and Phillip L. Geissler

Hydrophobic effects, which play a crucial role in many chemical and biological processes, originate in the statistics of microscopic density fluctuations in liquid water. Chandler has established the foundation for a simple and unified understanding of these effects, by identifying essential aspects of water's intermolecular structure while accounting for its proximity to phase coexistence. Here, we show that coarse-grained models based on this perspective, when constructed to include the statistics of capillary waves at interfaces, can achieve remarkable agreement with results of atomistically detailed simulations. Highly efficient and lacking adjustable parameters, such models hold promise as powerful tools for studying multiscale problems in hydrophobic solvation. (See pp. E2224–E2230.)

Real-time monitoring of metabolic function in liver-on-chip microdevices tracks the dynamics of mitochondrial dysfunction

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Microfluidic organ-on-a-chip technology is poised to replace animal toxicity testing, but thus far has demonstrated few advantages over traditional methods. Here we demonstrate a sensor-integrated platform permitting real-time tracking of the dynamics of metabolic adaptation to mitochondrial dysfunction. Our approach permits detection of chemical toxicity before any effects on cell or tissue viability can be observed. (See pp. E2231–E2240.)

Population size does not explain past changes in cultural complexity

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Archaeologists have long tried to understand why cultural complexity often changed in prehistory. Recently, a series of highly influential formal models have suggested that demography is the key factor. According to these models, the size of a population determines its ability to invent and maintain cultural traits. In this paper, we demonstrate that the models in question are flawed in two important respects: They use questionable assumptions, and their predictions are not supported by the available archaeological and ethnographic evidence. As a consequence, little confidence can be invested in the idea that demography explains the changes in cultural complexity that have been identified by archaeologists. An alternative explanation is required. (See pp. E2241–E2247.)

A neural link between affective understanding and interpersonal attraction

Silke Anders, Roos de Jong, Christian Beck, John-Dylan Haynes, and Thomas Ethofer

Humans interacting with other humans must be able to understand their interaction partner's affect and motivations, often without words. We examined whether people are attracted to others whose affective behavior they can easily understand. For this, we asked participants to watch different persons experiencing different emotions. We found the better a participant thought they could understand another person's emotion the more they felt attracted toward that person. Importantly, these individual changes in interpersonal attraction were predicted by activity in the participant's reward circuit, which in turn signaled how well the participant's "neural vocabulary" was suited to decode the other's behavior. This research elucidates neurobiological processes that might play an important role in the formation and success of human social relations. (See pp. E2248–E2257.)

Cellular uptake and anticancer activity of carboxylated gallium corroles

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Corroles are macrocyclic molecules related to porphyrins that exhibit intense light absorptions in the visible region. They also are very bright emitters, with luminescence quantum yields over 50% in some cases. Importantly, we have discovered that two corroles

functionalized with carboxylate groups at different ring locations exhibit anticancer activity superior to cisplatin. Although the synthetic route to direct carboxylation of the tetrapyrrolic framework requires the use of phosgene, installing aminocaproate on the fluorophenyl ring by nucleophilic aromatic substitution uses mild conditions with biocompatible reagents, requiring only simple purification and providing ready access to structurally complex corroles. Carboxylated corroles are very rapidly taken up by cells, with an order of magnitude gain in dark cytotoxicity likely owing to greater cell permeability. (See pp. E2258–E2266.)

Functional architecture of the Reb1-Ter complex of *Schizosaccharomyces pombe*

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Transcription termination of rRNA genes by RNA polymerase I (pol I) in fission yeast requires the binding of the Reb1 protein to a terminator site (Ter). Termination is physiologically necessary because its elimination can cause replication–transcription collision and induction of genome instability. Furthermore, without termination, pol I can become unproductively sequestered on the DNA templates. We have determined the crystal structure of fission yeast terminator protein Reb1-Ter complex revealing its functional architecture. Structure-guided functional analysis revealed that it is not just tight binding of the protein to Ter but protein–protein interactions with the Rpa12 subunit of RNA polymerase I that causes transcriptional arrest. (See pp. E2267–E2276.)

Kinetic selection vs. free energy of DNA base pairing in control of polymerase fidelity

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We address a fundamental biological issue: the source of free energy enabling high-fidelity DNA replication. DNA polymerase errors occur at about 1 per 1,000–10,000 bp, indicating "right" vs. "wrong" free energy differences $\Delta\Delta G_{inc}$ = 3–5 kcal/mol. A recent paper using high inorganic pyrophosphate concentrations to "equilibrate" right and wrong forward and reverse incorporation reactions concluded that base pairing in DNA alone is sufficient to account for polymerase fidelity. By performing an explicit analysis of forward and reverse reactions, we show that steady-state pol incorporation levels are far from equilibrium for wrong incorporations, so that polymerase fidelity cannot depend solely on intrinsic DNA properties. DNA polymerases must operate under kinetic control to achieve high fidelity. (See pp. E2277–E2285.)

Inhibition of translation initiation complex formation by GE81112 unravels a 16S rRNA structural switch involved in P-site decoding

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Eubacterial protein synthesis entails formation of an unlocked preinitiation complex consisting of the 30S ribosomal subunit, initiation factors, mRNA, and initiator tRNA. A conformational change in the subunit accompanies mRNA–tRNA codon–anticodon base-pairing generating a locked 30S complex. If correctly formed, this complex associates with the 50S ribosomal subunit forming a 70S complex, and the initiation factors are ejected. We show that the translational inhibitor GE81112 targets this essential step, hampering formation of a canonical codon–anticodon interaction and stalling the 30S in an unlocked state. Moreover, in the presence of GE81112 three rRNA helices, h44/h45/h24a, are stabilized in a disengaged conformation, suggesting that their conformation is associated with tRNA/mRNA decoding and transition of the 30S from unlocked to locked state. (See pp. E2286–E2295.)

Twist-open mechanism of DNA damage recognition by the Rad4/XPC nucleotide excision repair complex

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Impairment of global genome nucleotide excision repair (NER) leads to extreme sun sensitivity and predisposition to cancers. The xeroderma pigmentosum C (XPC) complex senses diverse environmentally induced DNA lesions from predominantly normal DNA, and initiates NER by recruiting downstream factors. Using unique fluorescent approaches, this study unveils previously unresolved DNA dynamics during lesion recognition by radiation-sensitive 4 (Rad4; yeast XPC ortholog) and demonstrates that Rad4 nonspecifically deforms ("twists") the DNA before specifically recognizing ("opening") target lesions. These results mark the first observation, to our knowledge, of DNA distortional dynamics that reflect a nonspecific search/interrogation process by a DNA repair protein that relies entirely on DNA deformability to recognize its lesions, and provides keys to understanding the protein's ability to search rapidly and yet also reliably recognize diverse lesions. (See pp. E2296–E2305.)

PDGF-AB and 5-Azacytidine induce conversion of somatic cells into tissue-regenerative multipotent stem cells

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In this report we describe the generation of tissue-regenerative multipotent stem cells (iMS cells) by treating mature bone and fat cells transiently with a growth factor [platelet-derived growth factor–AB (PDGF-AB)] and 5-Azacytidine, a demethylating compound that is widely used in clinical practice. Unlike primary mesenchymal stem cells, which are used with little objective evidence in clinical practice to promote tissue repair, iMS cells contribute directly to in vivo tissue regeneration in a context-dependent manner without forming tumors. This method can be applied to both mouse and human somatic cells to generate multipotent stem cells and has the potential to transform current approaches in regenerative medicine. (See pp. E2306–E2315.)

Nuclear transfer nTreg model reveals fate-determining TCR-β and novel peripheral nTreg precursors

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T cells generate their T-cell receptors (TCR) through somatic rearrangement of their underlying genomic V(D)J regions. Contrary to previous transgenic TCR models, our TCR models generated through somatic cell nuclear transfer are precise copies of the original T cell. Here, we developed a novel somatic cell nuclear transfer model of natural arising regulatory T (nTreg) cells. In our monoclonal model, we found a well-defined nTreg population

in the thymus, contradicting previous reports that intraclonal competition and thymic niche are limiting factors in nTreg development. Moreover, we found a novel fate-determining role for the TCR β-chain in nTreg cells. Interestingly, we also discovered a novel T-cell subset that functions as peripheral precursor of nTreg cells. (See pp. E2316–E2325.)

Discovery of unfixed endogenous retrovirus insertions in diverse human populations

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The human endogenous retrovirus (HERV) group HERV-K contains nearly intact and insertionally polymorphic integrations among humans, many of which code for viral proteins. Expression of such HERV-K proviruses occurs in tissues associated with cancers and autoimmune diseases, and in HIV-infected individuals, suggesting possible pathogenic effects. Proper characterization of these elements necessitates the discrimination of individual HERV-K loci; such studies are hampered by our incomplete catalog of HERV-K insertions, motivating the identification of additional HERV-K copies in humans. By examining >2,500 sequenced genomes, we have discovered 19 previously unidentified HERV-K insertions, including an intact provirus without apparent substitutions that would alter viral function, only the second such provirus described. Our results provide a basis for future studies of HERV evolution and implication for disease. (See pp. E2326–E2334.)

BK_{Ca} channel regulates calcium oscillations induced by alpha-2-macroglobulin in human myometrial smooth muscle cells

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The large-conductance, voltage-gated, calcium (Ca^{2+})-activated potassium channel (BK_{Ca}) plays an important role in regulating the membrane potential of uterine muscle cells. We demonstrate that BK_{Ca} interacts with the immunomodulator α-2-macroglobulin (α_2M) and its receptor low-density lipoprotein receptor-related protein 1 in human uterine muscle cells isolated from pregnant women. Furthermore, we report that activated α_2M regulates BK_{Ca} activity and that activated α_2M and BK_{Ca} together control Ca^{2+} oscillations in the cells, a process dependent on store-operated Ca^{2+} entry. This study reveals a previously unidentified modulator of the BK_{Ca} channel and may imply a link between inflammatory processes and excitation changes in the uterine muscle during pregnancy. (See pp. E2335–E2344.)