PNAS Plus Significance Statements

Lack of group-to-individual generalizability is a threat to human subjects research

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The current study quantified the degree to which group data are able to describe individual participants. We utilized intensive repeated-measures data—data that have been collected many times, across many individuals—to compare the distributions of bivariate correlations calculated within subjects vs. those calculated between subjects. Because the vast majority of social and medical science research aggregates across subjects, we aimed to assess how closely such aggregations reflect their constituent individuals. We provide evidence that conclusions drawn from aggregated data may be worryingly imprecise. Specifically, the variance in individuals is up to four times larger than in groups. These data call for a focus on idiography and open science that may substantially alter best-practice guidelines in the medical and behavioral sciences. (See pp. E6106–E6115.)

Gravity of human impacts mediates coral reef conservation gains

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Marine reserves that prohibit fishing are a critical tool for sustaining coral reef ecosystems, yet it remains unclear how human impacts in surrounding areas affect the capacity of marine reserves to deliver key conservation benefits. Our global study found that only marine reserves in areas of low human impact consistently sustained top predators. Fish biomass inside marine reserves declined along a gradient of human impacts in surrounding areas; however, reserves located where human impacts are moderate had the greatest difference in fish biomass compared with openly fished areas. Reserves in low human-impact areas are required for sustaining ecological functions like high-order predation, but reserves in high-impact areas can provide substantial conservation gains in fish biomass. (See pp. E6116–E6125.)

Reproduction in the Baka pygmies and drop in their fertility with the arrival of alcohol

Fernando V. Ramirez Rozzi

Humans are a polymorphic species with a broad geographical distribution. Diversity in growth and development plays an important role in biological adaptation and can be addressed through studies of life-history variation across different populations, particularly in hunter-gatherer societies. This paper reports the results from our study on fertility and mortality in the Baka pygmies based on individuals of known age. The Baka are characterized by low infant and juvenile mortalities, slow growth, and high fertility at an early age. However, the arrival of cheap alcohol has drastically reduced fertility early in life, which seriously compromises this population's survival. We provide empirical evidence of the effects of alcohol consumption on the fertility rate of a hunter-gatherer society. (See pp. E6126–E6134.)

Hyperstimulation of CaSR in human MSCs by biomimetic apatite inhibits endochondral ossification via temporal down-regulation of PTH1R

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Bone formation occurs through two distinct pathways, namely, endochondral ossification (EO) and intramembranous ossification (IMO). While significant effort has gone into understanding the role of various soluble signals in EO and IMO, the impact of the bone inorganic interface in triggering these ossification pathways has remained unexplored. Herein, we report the discovery that the bone-like mineral phase promotes formation of bone by mesenchymal stem/stromal cells (MSCs) exclusively via IMO even in the presence of soluble signals that promote the EO paradigm. Furthermore, we provide mechanistic insights into our observations and illustrate a previously unidentified role for extracellular calcium-sensing receptor (CaSR) in dictating the choice of ossification pathway in MSCs. These findings have significant implications for developing new strategies for bone repair and understanding bone homeostasis. (See pp. E6135–E6144.)

Antibody selection using clonal cocultivation of *Escherichia coli* and eukaryotic cells in miniecosystems

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We constructed a library of miniecosystems that can translate the information from antibody phage display directly into signals of biological function, thereby allowing for rapid selection of antibodies with the function of interest. Compared with the conventional phage display platform that can only isolate antibodies based on their binding affinity toward antigens, our new method bypasses the step of affinity-based selection, and the selection is based purely on the activity of antibodies in a biological system without concern for their relative affinity for antigens. This new method bridges the gap, which has existed for almost three decades, between affinity- and activity-based antibody selection for phage display of combinatorial antibody libraries, thus advancing antibody drug discovery. (See pp. E6145–E6151.)

Aldehydes are the predominant forces inducing DNA damage and inhibiting DNA repair in tobacco smoke carcinogenesis

Mao-wen Weng, Hyun-Wook Lee, Sung-Hyun Park, Yu Hu, Hsing-Tsui Wang, Lung-Chi Chen, William N. Rom, William C. Huang, Herbert Lepor, Xue-Ru Wu, Chung S. Yang, and Moon-shong Tang

Tobacco smoke (TS) contains numerous carcinogens. Intriguingly, while TS itself is a weak carcinogen in animal models, many of the TS components, such as 4-(methylnitrosamine)-1-(3-pyridyl)-1-butanone (NNK) and polycyclic aromatic hydrocarbons (PAHs), are strong carcinogens. We found that TS induces mainly aldehyde-DNA adducts in mice and humans. TS reduces DNA repair activity and repair proteins in mouse lung. All of these TS-induced effects can be reduced by diet polyphenols. Aldehydes prevent PAHs and NNK from inducing DNA damage in human cells. We propose that, because they act to damage DNA, reduce DNA repair activity, and inhibit NNK and PAHs from becoming DNA-damaging agents, aldehydes are the major TS carcinogens. These insights allow for better TS cancer risk assessment and the design of effective preventive measures. (See pp. E6152–E6161.)

Asf1a resolves bivalent chromatin domains for the induction of lineage-specific genes during mouse embryonic stem cell differentiation

Yuan Gao, Haiyun Gan, Zhenkun Lou, and Zhiguo Zhang

ES cells possess the unique capacity to self-renew as well as differentiate into specialized cell types. It is known that transcription factors and chromatin regulators regulate the cell-fate choices during differentiation. We report unexpectedly that Asf1a, a histone chaperone involved in nucleosome assembly, regulates mouse ES cell differentiation. Mechanistically, we show that Asf1a functions in nucleosome disassembly to resolve the bivalent chromatin domains at lineage-specific genes for gene activation during differentiation. These insights will likely be applicable for understanding human ES cell differentiation and regenerative medicine. (See pp. E6162–E6171.)

Broadly conserved Na^+-binding site in the N-lobe of prokaryotic multidrug MATE transporters

Emel Ficici, Wenchang Zhou, Steven Castellano, and José D. Faraldo-Gómez

MATE transporters deplete the bacterial cytosol of natural and human-made antibiotics and contribute to confer multidrug resistance to a wide range of human pathogens. Despite being a compelling pharmacological target, little is known about their molecular mechanism. Based upon crystallographic and computational data, we gain insights into the mechanism by which drug efflux is energized by transmembrane electrochemical gradients of ions by identifying a Na^+-binding site in the N-terminal domain of the transporter. This site can be clearly discerned in two different high-resolution structures and is broadly conserved within the MATE superfamily. Our structural analysis also provides a plausible rationale for the observation of H^+-coupled drug transport and other pH-dependent effects. (See pp. E6172–E6181.)

Sodium and proton coupling in the conformational cycle of a MATE antiporter from *Vibrio cholerae*

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Transporters from the multidrug and toxic compound extrusion (MATE) superfamily protect the cell from cytotoxic molecules through an efflux mechanism that is dependent on ion electrochemical gradients. This study examined the role of specific residues in supporting conformational changes associated with ion and drug binding in NorM, an archetype of MATE transporters. The results show that a network of conserved residues in the N-terminal domain is critical for Na^+- and H^+-driven conformational changes, whereas residues in the C-terminal domain mediate drug binding. Informed by a correlation of conformational dynamics with transport activity, we propose a model that describes how conserved residues mediate ion-coupled structural changes underlying drug efflux. (See pp. E6182–E6190.)

Separating the effects of nucleotide and EB binding on microtubule structure

Rui Zhang, Benjamin LaFrance, and Eva Nogales

We report three high-resolution structures of microtubules in different nucleotide states—GMPCPP, GDP, and GTPγS—in the absence of any binding proteins, allowing us to separate the effects of nucleotide- and microtubule (MT)-associated protein (MAPs) binding on MT structure. End-binding (EB) proteins can bind and induce partial lattice compaction of a preformed GMPCPP-bound MT, a lattice type that is far from EBs' ideal binding platform. We propose a model in which the MT lattice serves as a platform that integrates internal tubulin signals, such as nucleotide state, with outside signals, such as binding of MAPs. These global lattice rearrangements in turn affect the affinity of other MT partners and result in the exquisite regulation of the MT dynamics. (See pp. E6191–E6200.)

Kinetic analysis of the multistep aggregation pathway of human transthyretin

Xun Sun, H. Jane Dyson, and Peter E. Wright

Aggregation of amyloidogenic proteins is implicated in a number of debilitating human diseases. A mechanistic understanding of their aggregation behavior requires a quantitative description of the multistep equilibria involved in the self-assembly processes. Here we report the application of an integrative aggregation assay combining ^{19}F-NMR and turbidity measurements to reveal the kinetics and energetics of the human transthyretin aggregation pathway. A highly sensitive trifluoroacetyl probe enables direct observation and quantification of a weakly populated aggregation intermediate and reveals the importance of hydrophobic interactions for self-association. Extension of these studies to common pathogenic variants that are associated with early onset familial disease provides insights into the effect of the mutations on the kinetics and energetics of transthyretin aggregation. (See pp. E6201–E6208.)

Inverse enzyme isotope effects in human purine nucleoside phosphorylase with heavy asparagine labels

Rajesh K. Harijan, Ioanna Zoi, Dimitri Antoniou, Steven D. Schwartz, and Vern L. Schramm

Enzymes achieve catalytic efficiency by optimizing contacts between reactants and catalytic site amino acids. The transition state forms rarely, with a lifetime of a few femtoseconds. Femtosecond motions required for transition state formation are investigated with heavy enzymes containing ^{2}H, ^{13}C, and ^{15}N amino acids to alter bond vibrational modes. Asparagine is a critical amino acid at the catalytic site of human purine nucleoside phosphorylase (PNP). PNP with heavy asparagine, or with all heavy amino acids except asparagine, yields PNPs more efficient at forming the transition state. Computational chemistry reveals that essential catalytic site contacts become more frequently optimized in the labeled enzymes than in the normal enzyme. Heavy enzymes provide unprecedented detail for understanding enzymatic catalysis. (See pp. E6209–E6216.)

Indel-correcting DNA barcodes for high-throughput sequencing

John A. Hawkins, Stephen K. Jones Jr., Ilya J. Finkelstein, and William H. Press

Modern high-throughput biological assays study pooled populations of individual members by labeling each member with a unique DNA sequence called a "barcode." DNA barcodes are frequently corrupted by DNA synthesis and sequencing errors, leading to significant data loss and incorrect data interpretation. Here, we describe an error correction strategy to improve the efficiency and statistical power of DNA barcodes. Our strategy accurately handles insertions and deletions (indels) in DNA barcodes, the most common type of error encountered during DNA synthesis and sequencing, resulting in order-of-magnitude increases in accuracy, efficiency, and signal-to-noise ratio. The accompanying software package makes deployment of these barcodes straightforward for the broader experimental scientist community. (See pp. E6217–E6226.)

A versatile nanobody-based toolkit to analyze retrograde transport from the cell surface

Dominik P. Buser, Kai D. Schleicher, Cristina Prescianotto-Baschong, and Martin Spiess

Retrograde transport from the cell surface to intracellular compartments is essential for homeostasis and cell physiology. We developed derivatized nanobodies to follow proteins from the cell surface to endosomes and the *trans*-Golgi network. Nanobodies are an emerging class of protein binders with many advantages over conventional antibodies: they are small and noncross-linking, and can be produced in bacteria. Using a nanobody against GFP, our tool is widely applicable to any GFP-tagged protein of interest. It allows the quantitative analysis of endocytic and retrograde transport biochemically, by fixed- and live-cell imaging and by electron microscopy. As proof-of-principle, we applied them to determine the contribution of adaptor protein-1/clathrin in retrograde transport of the mannose-6-phosphate receptors to the *trans*-Golgi. (See pp. E6227–E6236.)

ER-phagy requires Lnp1, a protein that stabilizes rearrangements of the ER network

Shuliang Chen, Yixian Cui, Smriti Parashar, Peter J. Novick, and Susan Ferro-Novick

The endoplasmic reticulum (ER) undergoes autophagy in response to starvation in a process utilizing Atg40, a cortical ER receptor that serves to recruit the machinery needed to assemble an autophagosome. Little is known about the components that work in conjunction with ER cargo receptors. Here we show that autophagy of the ER requires Lnp1, a protein that helps to maintain the structure of the ER by stabilizing rearrangements of the ER network. In the absence of Lnp1 or upon depolymerization of actin, Atg40 puncta fail to distribute to the cell interior, where the autophagy machinery resides, thus blocking incorporation of ER into autophagosomes. These studies show that the localization of Atg40 is critical for its function as a cargo receptor. (See pp. E6237–E6244.)

Error-prone protein synthesis in parasites with the smallest eukaryotic genome

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Microsporidia are poorly treatable eukaryotic pathogens that threaten human health and industrially valuable insects and fish, yet we are only beginning to understand the complex biology of these emerging pathogens. Here we combine bioinformatics, biochemistry, and mass spectrometry analyses to show that Microsporidia carry an error-prone machinery of protein synthesis, and that their protein synthesis is accompanied by a remarkable number of translation errors. This finding reveals a previously unknown aspect of protein synthesis in these emerging parasites and creates a potential opportunity to use the defective protein synthesis machinery as a therapeutic target to treat microsporidia infections. (See pp. E6245–E6253.)

Macrophage phenotype and bioenergetics are controlled by oxidized phospholipids identified in lean and obese adipose tissue

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Adipose tissue macrophages (ATMs) maintain adipose tissue homeostasis. However, during obesity ATMs become inflammatory, resulting in impaired adipose tissue function. Oxidative stress increases during obesity, which is thought to contribute to adipose tissue inflammation. To date, the connection between oxidative stress and adipose tissue inflammation remain unclear. In this study, we identify two classes of phospholipid oxidation products in lean and obese adipose tissue, which polarize macrophages to an antioxidant or proinflammatory state, respectively. Furthermore, we show that these phospholipids differently affect macrophage cellular metabolism, reflecting the metabolisms of ATMs found in lean and obese adipose tissue. Identification of pathways controlling ATM metabolism will lead to novel therapies for insulin resistance. (See pp. E6254–E6263.)

Microglia inhibit photoreceptor cell death and regulate immune cell infiltration in response to retinal detachment

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Photoreceptor cell death resulting from retinal detachment (RD) causes significant visual loss. While the immune system is activated during RD, its role is still unclear. Microglia are resident immune cells in the retina and are thought to be either protective or deleterious in response to neuronal injury, suggesting context-dependent effects. Here, we demonstrate that microglia limit retinal damage during acute injury, since microglial ablation led to increased photoreceptor death. Microglial morphological–activation changes triggered their migration into injured tissue where they formed intimate connections with infiltrating immune cells and phagocytized injured photoreceptors. These findings provide insight into the microglial response and function during RD, indicating microglia promote photoreceptor survival during acute phase injury by removing potentially damaging cell debris. (See pp. E6264–E6273.)

Impairment of gamma-glutamyl transferase 1 activity in the metabolic pathogenesis of chromophobe renal cell carcinoma

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The mechanisms of chromophobe renal cell carcinoma (ChRCC) pathogenesis remain a key knowledge gap. Through metabolomics, this study uncovered a fundamental metabolic mechanism underlying the pathogenesis of ChRCC, with key therapeutic implications for this rare tumor type, for which there are currently no specific targeted therapies. Further understanding of the impact of glutathione salvage pathway on mitochondrial function, tumor progression, and targeted therapy can provide insight into other cancers characterized by aberrant glutathione salvage pathway. (See pp. E6274–E6282.)

Early loss of mitochondrial complex I and rewiring of glutathione metabolism in renal oncocytoma

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Renal oncocytomas are benign kidney tumors with numerous mitochondria. Here, we analyze the mitochondrial (mtDNA) and nuclear genomes of these tumors. Our analysis finds mtDNA mutations in complex I (the first step in mitochondrial respiration) to be early genetic events that likely contribute to tumor formation. Since mtDNA mutations can lead to severe degenerative disorders, the cellular responses allowing renal oncocytoma cells to grow are important to consider. To properly understand authentic gene expression changes in tumors, we found it important to consider the gene expression pattern of the tumor's cell of origin, the distal nephron. By doing so, we uncover alterations in glutathione synthesis and turnover that likely represent an adaptive metabolic response in renal oncocytoma. (See pp. E6283–E6290.)

mRNA-binding protein tristetraprolin is essential for cardiac response to iron deficiency by regulating mitochondrial function

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Iron deficiency is the most common nutrient deficiency, yet cardiomyopathy rarely develops in these patients. We solved this paradox and identified a protective mechanism involving the mRNA-binding protein tristetraprolin (TTP), which adjusts mitochondrial function in response to iron deficiency. Mice lacking TTP in their hearts were phenotypically normal at baseline but developed spontaneous cardiomyopathy under iron deficiency and exhibited increased reactive oxygen species (ROS)-mediated damage in their hearts. We further demonstrate that down-regulation of specific iron-containing mitochondrial complexes by TTP is the mechanism preventing the formation of dysfunctional mitochondria, subsequent ROS production, and cellular damage. In summary, we show that activation of TTP is part of a required pathway protecting critical organ function when iron becomes scarce. (See pp. E6291–E6300.)

Timing of DNA damage responses impacts persistence to fluoroquinolones

Wendy W. K. Mok and Mark P. Brynildsen

Bacterial persisters are able to survive high concentrations of antibiotics that kill their genetically identical kin. Their tolerances are thought to arise from decreased activity of cellular processes, which limits damage from antibiotics. However, persistence to fluoroquinolones in growth-inhibited populations is not as cut-and-dried, with survivors of treatment exhibiting similar DNA damage as cells that die. In this article, we use a model system of persistence to reveal that the timing of events, such as DNA repair, following fluoroquinolone treatment is critical to survival and show that the same is true for WT populations. These data highlight the importance of processes following antibiotic treatments to persister phenotypes and establish that timing matters for genetically susceptible bacteria struggling to survive fluoroquinolone treatments. (See pp. E6301–E6309.)

Species-specific disruption of STING-dependent antiviral cellular defenses by the Zika virus NS2B3 protease

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To shed light on the host range of Zika virus (ZIKV), we surveyed the virus' ability to infect cells of evolutionarily diverse species. ZIKV replicates efficiently in human, great ape, Old and New World monkey, but not rodent cells. These observations correlated with ZIKV's ability to blunt the cGAS/STING signaling pathway in all primate cells tested but not in mice. We demonstrate that an enzyme shared by many flaviviruses (NS2B3) is responsible for functionally inactivating this antiviral defense. Our results highlight the importance of the cGAS/STING pathway in shaping the host range of ZIKV, which in turn may guide the development of murine models with inheritable susceptibility to ZIKV and other flaviviruses. (See pp. E6310–E6318.)

A second RNA-binding protein is essential for ethanol tolerance provided by the bacterial OLE ribonucleoprotein complex

Kimberly A. Harris, Zhiyuan Zhou, Michelle L. Peters, Sarah G. Wilkins, and Ronald R. Breaker

Although large bacterial noncoding RNAs (ncRNAs) are rare, those whose functions have been experimentally established perform fundamental roles in genetic information transfer, RNA processing, and protein production and localization. OLE (ornate, large, extremophilic) RNAs represent one of the most widespread and well-conserved classes of bacterial ncRNAs whose activities remain unknown. We have identified mutations in an OLE-associated protein (OapA), an essential partner for OLE RNA, which cause more severe inhibition of host bacterial growth under cold or ethanol stress conditions compared with knockout strains lacking OLE or OapA. A genetic screen using a bacterial strain carrying the mutant OapA protein revealed another protein partner that also forms a complex with OLE RNA, and is essential for the biological function of this mysterious bacterial ncRNA. (See pp. E6319–E6328.)

Sparse bursts optimize information transmission in a multiplexed neural code

Richard Naud and Henning Sprekeler

Understanding the neural code is to attribute proper meaning to temporal sequences of action potentials. We report a simple neural code based on distinguishing single spikes from spikes in close succession, commonly called "bursts." By separating these two types of responses, we show that ensembles of neurons can communicate rapidly changing and graded information from two sources simultaneously and with minimal cross-talk. Second, we show that this multiplexing can optimize the information transferred per action potential when bursts are relatively rare. Finally, we show that neurons can demultiplex these two streams of information. We propose that this multiplexing may be particularly important in hierarchical communication where bottom–up and top–down information must be distinguished. (See pp. E6329–E6338.)

Changes in white matter in mice resulting from low-frequency brain stimulation

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Meditation has been shown to modify brain connections. However, the cellular mechanisms by which this occurs are not known. We hypothesized that changes in white matter found following meditation may be due to increased rhythmicity observed in frontal areas in the cortex. The current study in mice tested this directly by rhythmically stimulating cells in the frontal midline. We found that such stimulation caused an increase in connectivity due to changes in the axons in the corpus callosum, which transmit impulses to and from the frontal midline. This work provides a plausible but not proven mechanism through which a mental activity such as meditation can improve brain connectivity. (See pp. E6339–E6346.)

Altering gain of the infralimbic-to-accumbens shell circuit alters economically dissociable decision-making algorithms

Brian M. Sweis, Erin B. Larson, A. David Redish, and Mark J. Thomas

Synaptic remodeling in the infralimbic-to-accumbens shell (IL–NAcSh) circuit is linked to addiction relapse susceptibility; however, how these changes interact with decision-making computations remains unclear. We develop a neurophysiological assay to measure the strength of a specific circuit at the ensemble level. We then use that assay in combination with a neuroeconomic task to provide causal evidence that synaptic strength of the IL–NAcSh mediates distinct aspects of decision-making information processing. We find that individual differences in IL–NAcSh strength mediate reevaluations behaviorally resolvable from parallel, co-occurring deliberative valuations. An important implication of our work is that acutely delivered circuit-specific plasticity manipulations can produce long-lasting computation-specific effects on certain kinds of choices and can potentially serve as a therapeutic neuromodulation intervention. (See pp. E6347–E6355.)

The impact of traditional neuroimaging methods on the spatial localization of cortical areas

Timothy S. Coalson, David C. Van Essen, and Matthew F. Glasser

Most human brain-imaging studies have traditionally used low-resolution images, inaccurate methods of cross-subject alignment, and extensive blurring. Recently, a high-resolution approach with more accurate alignment and minimized blurring was used by the Human Connectome Project to generate a multimodal map of human cortical areas in hundreds of individuals. Starting from these data, we systematically compared these two approaches, showing that the traditional approach is nearly three times worse than the Human Connectome Project's improved approach in two objective measures of spatial localization of cortical areas. Furthermore, we demonstrate considerable challenges in comparing data across the two approaches and, as a result, argue that there is an urgent need for the field to adopt more accurate methods of data acquisition and analysis. (See pp. E6356–E6365.)

Cellulose synthase complexes display distinct dynamic behaviors during xylem transdifferentiation

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Cellulose, the most abundant biopolymer on earth, is the major constituent of plant cell walls and is ubiquitously used by industry. This biopolymer is made by plasma membrane-localized CELLULOSE SYNTHASE (CESA) enzymes. To transit from deposition of a growing primary cell wall to a strong secondary cell wall, xylem cells must remodel the CESA machinery to express a new set of CESA isoforms specific to secondary cell wall synthesis. We outline a detailed framework for how this change in cellulose synthesis occurs. Our work provides the principles for how plants change their capacity to produce cellulose and therefore plant biomass. (See pp. E6366–E6374.)

Predicting perturbation patterns from the topology of biological networks

Marc Santolini and Albert-László Barabási

The development of high-throughput technologies has allowed mapping a significant proportion of interactions between biochemical entities in the cell. However, it is unclear how much information is lost given the lack of measurements on the kinetic parameters governing the dynamics of these interactions. Using biochemical networks with experimentally measured kinetic parameters, we show that a knowledge of the network topology offers 65–80% accuracy in predicting the impact of perturbation patterns. In other words, we can use the increasingly accurate topological models to approximate perturbation patterns, bypassing expensive kinetic constant measurement. These results could open new avenues in modeling drug action and in identifying drug targets relying on the human interactome only. (See pp. E6375–E6383.)