bundles undergo deformations highly similar to a twisted rod under compression. Our data suggests that tau-like proteins minimize microtubule lattice interactions and the prevent torque generation that leads to extreme neuron deformations. These experimental results, together with mechanical modeling of the neuron, suggest that spectrin tension and microtubule bundle mechanics are crucial for stabilizing chiral cytoskeletal networks and produce a specialized cell shape that we propose is critical for neuronal function.

152-Plat
Torque Generation in the Bacterial Flagellar Motor
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The bacterial flagellar motor (BFM) drives swimming in a wide variety of bacterial species. Its fundamental role in a variety of biological processes, including chemotaxis and biofilm formation, has made understanding its dynamics an important question in biophysics. We put forward a mechanically-specific model for motor rotation, pinpointing critical residues and structures for motor function. We implicate a steric interaction between the rotor and the torque-generating complexes (stators). Two surprising predictions of our model are: (1) the duty ratio of the motor is not close to unity as previously believed; and (2) motor rotation is loosely coupled to ion flux. We show that these predictions, while contrary to previous reports, are consistent with current experimental evidence. We also put forward several further experiments and measurements designed to directly test the validity of this model and its implications.

153-Plat
Fission Yeast Contractile Ring Tension Increases ~2-Fold Throughout Constriction and Regulates Septum Closure but does not Set the Constriction Rate
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What is the role of the cytokinetic contractile ring? The tensile actomyosin ring is central to cytokinesis, and widely thought to drive cell cleavage as it constricts. Here we directly addressed this question by measurements of cytokinetic ring tension and mathematical modeling. In the model organism fission yeast, as in other fungi, ring constriction is accompanied by septation, the inward growth of cell wall in the wake of the constricting ring that seals daughter cells in new cell wall.
We measured ring tensions in live fission yeast protoplasts using a novel method based on measuring membrane tension and the furrow geometry. As constricted progressed, ring tension increased from ~ 400 pN to ~ 800 pN. To our knowledge these are the first measurements of the evolving ring tension throughout constriction.
We used these tension values in a mathematical model of septum growth, mediated by beta-glucan synthases (Bgs) at the septum edge, hypothesized mechanosensitive (Thiyagarajan et al., 2015). The stochastic septum growth produced faceting, defects and edge roughness. In simulations, ring tension modulated Bgs growth rates in a curvature-dependent fashion, suppressing defects and roughness so septum edges were nearly circular. Simulated edges had low roughnesses (~5%) and a roughness exponent ~0.5, consistent with septum edges we measured in live cells. Our model revealed a mechanosensitivity ~15% per pN per Bgs complex.
Thus, ring tension regulates septum growth to ensure the septum closes as a shrinking circle (not a slit) and daughter cells are properly sealed by new cell wall. However, the model showed constriction rates are set by the septum growth machinery, while ring tension had little effect on the mean rate, explaining why experimentally the rate is constant in time.

Platform: Protein Structure and Conformation I

154-Plat
The HIV-1 Pre-Integration Complexes: Structures, Functions and Dynamics
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After retroviral infection of a target cell, during the early phase of replication, the HIV-1 genomic viral RNA is reverse transcribed by the viral reverse transcriptase to generate the double-stranded viral DNA that interact with viral and cellular proteins to form the pre-integration complex (PIC). Viral integrase (IN) is a key component of the PIC and is involved in several steps of replication notably in reverse transcription, nuclear import, chromatin targeting and integration. Viral components such as IN cannot perform these functions on their own and need to recruit host cell proteins to efficiently carry out the different processes. IN is a flexible protein, property allowing its interaction with multiple partners and enabling its multiple functions in viral replication. The molecular mechanisms and dynamics of these processes remain largely unknown. Purification of proteins that participate in these large transient complexes is impeded by low amounts, heterogeneity, instability and poor solubility. To circumvent these difficulties we develop methodologies that enable the production of stable complexes for structural and functional studies [1] as well as system for the production of multi-protein complexes from mammalian cells enabling assembly of entire complexes within cells. Using these strategies we reconstruct in vitro stable and soluble complexes around IN. We use cryo-EM combined with X-ray crystallography to solve structures of the IN/LEDGF/DNA [2] and IN/LEDGF/INI1/DNA [3] complexes. Other IN complexes involved in the PIC nuclear translocation and integration as well as IN post-translational modifications (phosphorylation and acetylation) have been characterized and are under study.
[1] Levy et al. (2016) Nature comm. 7: 10932
[2] Michel et al. (2009) EMBO J., 28, 980-991
[3] Maillot et al. (2013) PLoS ONE 8(4): e60734

155-Plat
Mechanisms of Sequence Dependent Translational Stalling
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Ribosomal stalling during protein synthesis in bacteria occurs in different ways and under different conditions. Stalling of specific peptide sequences can be a pre-programmed means of detecting the presence of potentially lethal antibiotics and constitute the initial step of a complex resistance pathway. An example of this is the stalling of ErmBL peptide synthesis in the presence of the antibiotic erythromycin. In other cases, stalling seems to be an effect of unusually slow, sequence dependent, rates of amino acid incorporation. This is the case for translation of proteins containing poly-proline stretches. Poly-proline sequences are known to stall ribosomes, normal translation rates are achieved only by recruiting a special elongation factor (EF-P in bacteria). Here, we investigate the stalling mechanisms in the two scenarios described above by explicit-solvent, all-atom molecular dynamics simulations of the ribosome. The simulations are started from high-resolution cryo-EM structures and performed under stalling and non-stalling conditions. We find networks of allosteric interactions between the nascent peptide chain and the ribosome that differently affect the positioning and the dynamics of the peptidyl tRNA relative to the A-site tRNA in such a way as to hinder peptide bond formation depending on the presence of the antibiotic (in the first scenario) or the absence of the elongation factor (second scenario). The simulation results not only explain the stalling mechanism, but can also predict the effect of mutations on stalling. In the case of erythromycin induced stalling, these predictions have been experimentally confirmed by a toe-printing assay. Our results illustrate the fine details of how the efficiency of peptide bond formation can be modulated by external factors in a way that depends on the specific sequence being translated.

156-Plat
Quantitative Analysis and Modeling of Translation using Ribosome Profiling Data: How Biophysical Properties of the Ribosome Exit Tunnel and the Nascent Polypeptide Modulate the Elongation Rate
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Ribosome profiling provides a detailed view into the complex dynamics of translation. Although the precise relation between the observed ribosome footprint densities and the actual translation elongation rates remains elusive, the data clearly suggest that elongation speed is quite heterogeneous along the transcript. Previous studies have shown that elongation is locally regulated by multiple factors, but the observed heterogeneity remains only partially explained. To dissect quantitatively the different determinants of translation speed, we here use a probabilistic model of the translation dynamics to estimate transcript-specific initiation and local elongation rates from ribosome profiling data. Using this model-based approach, we infer the extent of interference between ribosomes on the same transcript (which cannot be observed directly