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Equations of Inter-Doublet Separation Explain Wave Propagation and Oscillations in Flagella
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Introduction: The mechanism of dynein coordination in cilia and flagella remains incompletely understood. In one hypothesis, the ''geometric clutch'' (GC) model (Lindemann, J theor Biol,1994), dynein is regulated by inter-doublet separation. A continuum mechanical model and associated partial differential equations (PDEs) of the GC model have remained lacking. Such PDEs would provide insight into the biophysics, enable mathematical analysis of the behavior, and facilitate rigorous comparison to other models. In this study equations of motion for the flagellum and its doublets are derived and analyzed to reveal mechanisms of wave propagation and instability in the GC model.
Methods: A simplified mechanical model of the flagellum is considered, consisting of two pairs of doublets (Lindemann, 1994). Each doublet pair experiences external viscous forces and inter-doublet forces parallel and perpendicular to its long axis (Hines and Blum, Biophys J,1978). The equations of force and moment balance are used to derive PDEs for the shape of the flagellum and the separation between doublets. The equations of inter-doublet separation reduce to an excitable system in the form of the Extended Fisher-Kolmorogov (EFK) equation (van den Berg et al., SIAM J, 2001), which exhibits propagating solutions similar to those of reaction-diffusion equations. These equations are then coupled to the global equations of flagella motion and solved numerically.
Results: The model exhibits propagation of disturbances of inter-doublet separation and dynein activity. Autonomous propulsive oscillations are seen at typical parameter values (L=12 μm; EI=500 pN/μm2; diameter a=200 nm).Transition from large-amplitude asymmetric waveforms (forward swimming) to small-amplitude symmetric waveforms (backward swimming) is achieved by varying baseline dynein activity. These results support the ability of the GC hypothesis to explain dynein coordination in flagella and provide a mathematical foundation for comparison to other models.
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How Cilia or Eukaryotic Flagella Beat
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Cilia or eukaryotic flagella are slender minute organelles responsible for moving the immersing fluid relative to a cell and sensing the environment. When motile these 200-nm-diameter ''hairs'' are driven by thousands of tiny motors along their length to facilitate traveling waves of bending. These motors overcome the energy dissipation of moving the surrounding fluid. Their core structure is nine doublet microtubules arranged around a central-pair. In planar beating, motors walk toward where the cilium is attached to the cell body. In so doing, they bend the elastic cilium; then motors on the other side bend it in the opposite direction. Existing models lack consistency with the data; hence there is no consensus on how cilia beat. However, this self-organized mechanical oscillator can be explained by the collective properties of the ATP-fed motors and the compliant viscoelastic elements of the longitudinal and bending springs of the longitudinally differentiated cilium in interaction with the dissipative environment. For the uniform diameter *Ciona* sperm cilium whatever the [ATP] or external viscosity each wave formed and propagated has close to the same energy. The motors switch side dominance at zero ciliary curvature when the bend reaches maximum mechanical potential energy and bend instability. The flexure rigidity and spring constants have been determined along the length. Ciliary beating frequency, wavelength, amplitude and wave energy are explained. Our model fits the data well. It will be interesting to see what modifications cilia with different beat patterns and tapering have made in terms of mechanism. Also interesting will be how temporal control of the described physical and chemical parameters of beating enables their diverse behavior as in phototaxis, chemotaxis and avoidance of obstacles.

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Inhibition of Ca^{2+} Transport Triggers Changes in Ciliary Intraflagellar Transport Rate and Particle Composition
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The primary cilium is a specialized microtubule-based organelle that extends from the apical surface of many cell types. It has been found to play important roles in chemo- and mechano-sensation acting as a signal transducer of extracellular stimuli into intracellular signaling. The cilium is assembled and maintained by the transport of biomolecules in and out of this cellular compartment. Defects in the proteins that make cilia, such as those mutations found in so-called human ciliopathy genes can cause defects in cellular signaling that result in severe phenotypes including retinal degeneration, kidney cysts, and tissue homeostasis disruption. Primary cilia were found to be unique calcium compartments regulated by the polycystin (PKD) family of transient receptor potential channels (PKD2, PKD2L1) in mice and humans. The effect of ciliary Ca^{2+} regulation on intraflagellar transport (IFT), bidirectional transport system required for establishing, maintaining and disassembling of cilia, and the relation of these to developmental patterning and renal disease, is currently under study. Gadolinium known to be a powerful inhibitor of the Ca^{2+} transport was utilized to perturb the ciliary calcium balance. A genetically encoded calcium sensor GCaMP3 targeted to the primary cilium was used to monitor the level of the ciliary calcium. Changes in IFT motility in the primary cilia of mammalian kidney epithelial cells were measured via live cell TIRF microscopy. Fluorescence image moment analysis together with dSTORM super-resolution techniques were hired to investigate the stoichiometry of IFT particles. The biophysical measurements performed in the current study helped to understand the connection between ciliary Ca^{2+} balance and IFT transport in mammalian primary cilia.

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Using in vivo Optical Sectioning to Investigate Mechanical Aspects of Volvox Development
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Volvox is a genus of swimming algae consisting of a spherical single sheet of cells. At the end of cell division, embryos form a sphere with their flagella pointing the wrong way (to the inside) and must complete their development by turning themselves inside out. Although this phenomenon was observed hundreds of years ago and has been the subject of extensive study, no quantification of the mechanics has been performed. The simple geometry and connectivity of the cells makes these organisms a tractable example for studying morphogenic processes, while their development still shares features with more complicated mechanisms of gastrulation in animals. Previous study of embryo shapes during inversion required chemical fixation, so that individuals could not be followed through all stages and dynamics were lost. An open-source selective plane illumination microscope (SPIM) [1], has enabled accurate recording of the shapes of embryos as they progress through their inversion process. Unprecedented views of the progress of cell division and the growth of mature spheroids are also within reach. With this dynamic, three-dimensional data, new analysis of embryo and tissue mechanics become possible.
[1] Pitrone P. G., Schindelin J., Stuyvenberg L., Preibisch S., Weber M.; Eliceiri K. W., Huisken J., Tomancak P. OpenSPIM: an open access light sheet microscopy platform Nature Methods 10, 598-599 (2013).

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Self-Healing Biomaterials: Entangled DNA Networks
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The material that the cell uses to store genetic information actually becomes self-healing material when it must be segregated, transported across the length of the cell even in the face of its entanglements with itself, or condensed to prepare for this large scale transport. This is a naturally-occuring soft material that is capable of self-repair. Moreover, there is evidence that the material first senses the possibility of a stress-inducing, potentially fatal (to genome stability) topological entanglement, and quickly fortifies itself to limit or prevent the damage. The issue of how topology is conserved (controlled) by this type of biomaterial is itself an interesting mystery. I will present our experimental results using a bottom-up design approach, borrowing the naturally-occurring materials from the cell to study the design principles of this behavior. We incorporated micron-sized particles in lambda-DNA entangled networks in the presence of the topoisomerase II motor that performs the strand passage, at controllable ratio of enzyme units per average DNA entanglement and ATP concentration. We used bright-field microscopy to directly track the movement of the particles, which couple to the DNA fluctuating movement. Our observed scaling behavior suggests entangled dynamics in the bare DNA system, and nonentangled Rouse dynamics, with enzyme performing topological constraint relaxation, in the DNA+topo II + ATP system. These very time-dependent scaling behaviors are all predicted theoretically for entangled polymers with inclusion of a constrained release process in the case of presence of active topo II. The material self-heals to such a degree that, at saturating topoisomerase II motor and ATP concentrations, the long DNA polymer molecules do not even ''feel'' one another despite being entangled. We compare our experimental results to predictions of the constraint release model, measuring the ''healing rate'' at different dynamical length scales.