must self-organize, using some intrinsic, probably physical, property of the axoneme to regulate dynein. Computer simulations showed that regulation of dynein by local curvature of the axoneme, or by modifying the sliding distance between doublets, could both work in principle[7]. Jülicher and colleagues have combined theory and experiment to provide decisive support for the sliding-control model. Their work builds on a simple idea, first proposed by Brokaw[8], for how sliding might regulate motor activity to generate self-organized oscillations, an idea conceptually involving a system of opposed motors and springs (Fig. 2).

Jülicher and colleagues' initial insight[1] was to conceptualize the axoneme as an 'active material', making no assumptions about its microscopic properties. A rod of ordinary material resists a bending force by its stiffness and by frictional resistance to its movement. An axoneme, in contrast, can respond by actively deforming in the direction of the applied force, owing to activation of its internal dyneins by the deformation. This type of response can be quantified using negative values for the stiffness and viscosity parameters. For certain values of these parameters, an instability will propagate down the rod, and it will beat spontaneously[1].

An initial implementation[1] of this concept predicted waveforms that propagated in the wrong direction. This problem was fixed[2] by allowing some relative movement between doublets at the base of the cilium (stiffness of the base enters the mathematics as a boundary condition), leading to the interesting prediction that cells might control beat direction by regulating the stiffness of inter-doublet links at the cilium base. The improved model[2] was compared with experimental data from tethered bull sperm using a 'sperm equation'. This equation predicts sideways oscillations as a function both of distance from the base of the flagellum and of several parameters that describe the physical properties of the axoneme.

Any oscillation can be described as a sum of sinusoidal oscillations of increasing frequency, called Fourier modes; sideways oscillations can be described by the temporal Fourier modes of tangent angles. Power-spectrum analysis showed that experimentally observed oscillations in tangent angles were well approximated using only the first (fundamental) Fourier mode, so the sperm equation could be analytically solved using values of this mode. Tangent angles quantify the curvature of the axoneme at a given position, and the curvature is geometrically related to the sliding distance between doublets at that position. The sperm equation thus relates time-dependent angular movement at each position to the extent and rate of inter-doublet sliding at that position, and to the local forces that either oppose or promote further sliding.

The model contains two adjustable parameters — stiffness and friction of the active material inside the axoneme that deforms and exerts force during bending. It also contains

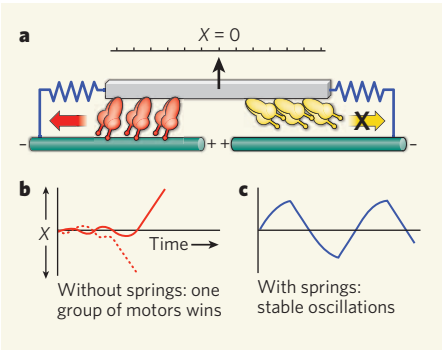

Figure 2 | Self-organized oscillations in a system of opposed motors and springs. a, Thought experiment using an artificial geometry to illustrate how sliding control leads to oscillations, a principle now further refined by Jülicher and colleagues[1–3]. Two groups of dynein motors anchored to a rigid scaffold walk outwards on two static microtubules oriented with their minus ends outwards. The system can omit or include springs (blue zig-zags). **b**, If the springs are absent, the system is unstable and one group of motors wins: the winning motors (solid curve) exert force on the losing motors (dotted curve) in a direction opposite to their walking direction, increasing the likelihood that the losing motors will become detached from the microtubule[8]. **c**, If the springs are present, as in **a**, the system undergoes stable oscillations. Oscillations are self-organized in the sense that no external control of the motors is required. The geometry is more complex in real axonemes, but the same concept applies: dyneins on opposite sides of the axoneme oppose each other, and crosslinking proteins supply the springs. (Redrawn from a presentation by F. Jülicher to illustrate a concept for self-organized oscillations proposed by C. J. Brokaw[8].)

several fixed parameters that Jülicher and colleagues independently measured and fed into the equation. These include the hydrodynamic drag of the moving flagellum and its ordinary stiffness, both of which oppose active deformation, and the beat frequency. The authors obtained an excellent fit to the data, with both internal stiffness and friction taking the negative values expected for an active material. Importantly, a microscopic model of dynein behaviour, incorporating the force-dependent detachment concept illustrated in Figure 2, predicted negative values for stiffness and friction similar to those obtained by fitting the sperm equation.

Jülicher and colleagues first solved the sperm equation analytically using a linear approximation corresponding to small displacements[2], but a full, nonlinear solution was subsequently shown to predict similar waveforms[3]. Overall, the model fits the experimental data well and provides a conceptually satisfying explanation for how cilia and flagella beat that unites Brokaw's mechanistic proposal for controlling sliding[8] with the active-material concept. Predicting beat frequency is a challenging future goal for theorists, but this will probably require a detailed treatment of the microscopic details.

What further experiments are needed to test and refine the model, and what are its biological implications? Single-molecule measurements[9] could test whether experimental force–detachment relationships for axonemal dyneins are within the range required by the theory. Piston-like movement of doublets at the base of cilia, required by the model, has been observed in some systems[10], but needs to be tested more generally. More ambitiously, it might be possible to nano-fabricate simplified model systems, such as those shown in Figure 2, and test their properties.

Further testing will probably require a genetic approach. Here, theory meets medical genetics in a potentially fruitful way. Primary ciliary dyskinesias are inherited diseases characterized by paralysis or defective waveforms in epithelial cilia and sperm flagella due to ultrastructural abnormalities[11]. These are caused most often by mutations in ciliary dyneins, but sometimes in other axonemal proteins[12]. The theory opens up the prospect of formulating causal explanations of the effect of mutations on beat waveform, and the flagellated single-celled organism *Chlamydomonas* provides an ideal model for theory–structure–function studies. Key to this approach will be careful experimental measurement of aberrant waveforms, which the theory can relate to internal molecular behaviour[2].

Could any of this help patients with primary ciliary dyskinesias? In some patients, cilia lacking central pairs still beat, albeit abnormally[12]. Guided by mechanistic understanding of the underlying defect, it might be possible to correct this by using small molecules that weaken or strengthen dynein. ■

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Correction
In the obituary of Vitaly Ginzburg by Malcolm Longair (*Nature* **462,** 996; 2009), editorial intervention introduced the statement that Gorky University was "in what is now Yekaterinburg". That should have read "in what is now Nizhny Novgorod".