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BIOPHYSICS

Helpful disorder in the lungs

Microscopic motile cilia, beating in synchrony across large scales, move the liquid lining of our lungs, protecting from infection and dirt. Surprisingly, a disordered arrangement of cilia, as observed in nature, is shown to be optimal for airway clearance.

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A number of living organisms have evolved cell surfaces covered in microscopic actively beating filaments, called motile cilia. These ciliated epithelia play an essential role in mammals, for example by moving fluid within the brain ventricles and in the lungs and airways. The displacement of fluids in the airways is essential to keeping the lungs free of infection and particulate matter, and is known as mucociliary clearance. One might imagine that defects in the ciliary order would be disadvantageous to the clearance process. Now, writing in *Nature Physics*, Guillermina Ramirez-San Juan and colleagues[1] have shown by computer simulation that a degree of disorder in the tissue, as seen in organisms, can in fact promote clearance.

In order to push fluid efficiently along a tissue surface, millions of cilia need to synchronise their periodic beating, across large distances of many cell diameters. This is a formidable achievement, in the context both of variability across cells, and of external perturbations. In the case of the airways, this ciliary beating takes place through a viscoelastic fluid — mucus — of quite complex rheology and spatial structure[2]. Ramirez-San Juan and colleagues considered airway tissues of a range of organisms, characterized the degree of ciliary ordering and investigated the impact of disorder on clearance in computer simulations. The advantage of disorder for particle clearing can perhaps be understood through an analogy to a network of roads with different speed limits, which enables a higher overall vehicle throughput; the ciliary disorder seems to lead to the emergence of similar fast velocity lanes. Examples of helpful disorder are often counterintuitive and in this case a better understanding of airway physiology could lead to improved therapies for many diseases.

This work by Ramirez-San Juan and colleagues is an example of a new wave of biological physics. Frameworks have emerged to describe certain biological processes quantitatively, often by combining soft matter physics with elements of fluid dynamics, statistical physics and dynamical systems. The strength of these contributions lies in the physical grounding of the mechanistic descriptions, which allows us to connect these modules together, across scales, and to trust them beyond the specific conditions in which they were validated[3]. This remarkable build-up of quantitative approaches is of particular value today, because of the amount of high-resolution biological data available. Hence, it might be tempting to think that we have all the facts to develop physical theories with predictive power for investigating how a living organism works.

However, various physical phenomena, from superconductivity to turbulence, caution us against assuming that we can always draw the links effectively across scales, even when the basics are known and the data is solid. Still, there are collaborative projects aiming, for example, at understanding the brain, cancer, infections, ecological communities or how an embryo

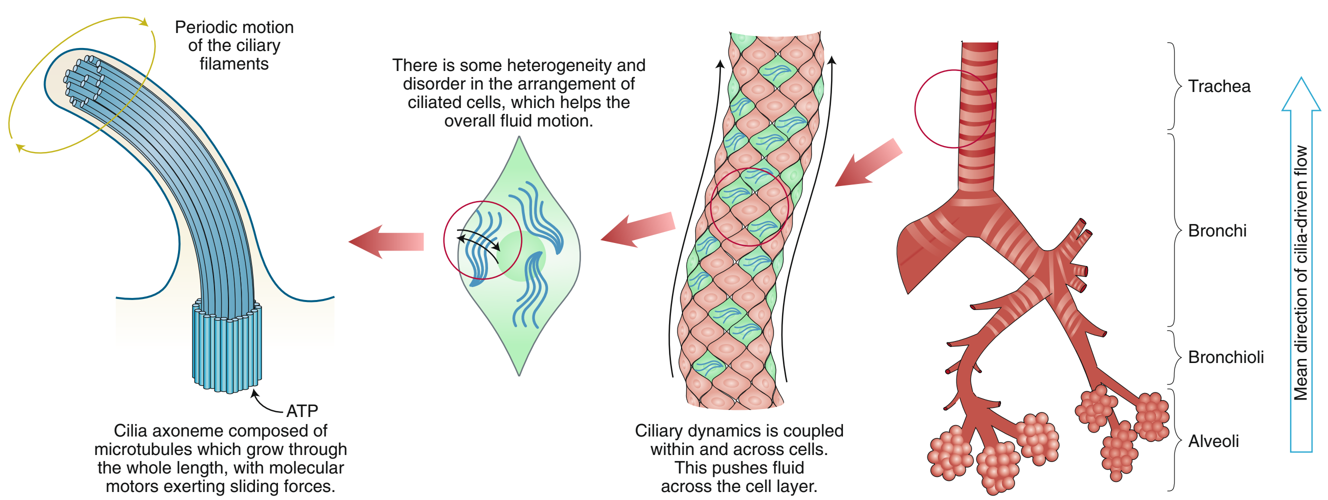

Fig. 1 | Multiple scales of the lung clearance mechanism. Mucociliary clearance in mammalian airways results in a macroscopic manifestation of a series of emergent behaviours across several scales. The microscopic agent is a beating cilium, maintained in active periodic motion. These interact strongly with other cilia in the same cell, and adjacent cells, leading to directed propulsion of fluid. The ciliated cells are arranged with some disorder, which Ramirez-San Juan and colleagues have shown to be an optimal arrangement for overall fluid flow.

develops from a single cell to an organism. These broad challenges require bringing together mechanisms from the appropriate scales and linking across those scales to explain emergent properties, a process that is rich in interesting physics.

The question of how the lung tissue works is very much in this new bold spirit. There is a developmental biology angle: how this tissue, with three or four important cell types, comes to be, and then remains in a stable state over the course of adult life. There are all kinds of connections to diseases and immune responses, since the vast surface of the lung is the first interface of our bodies to any airborne microbes and particulate matter. There is a physical sciences angle, which is itself highly complex and multi-scale (Fig. 1). A full picture would have tremendous implications in healthcare: for example, in genetic diseases such as cystic fibrosis and infectious conditions such as influenza, the mucus rheology is affected and cilia are unable to maintain clearance[4,5]. These are still scenarios for future work.

Even if we narrow the challenge down to understanding clearance of healthy lungs we still have a wealth of fascinating science. The paper by Ramirez-San Juan and colleagues took the fluid propulsion by cilia as a given and explored the importance of the position and alignment of ciliated cells at the macroscopic scale. Underlying this is the coordinated beating of cilia which provides surface propulsion — a multiscale problem with rich physics still to be investigated. Coordination emerges from the non-linear coupling of these cilia, which can be seen as active oscillators. Each cilium itself is a complex system of hundreds of molecular motors, and effective models can be made to explain the periodic waveforms of cilium bending[6]. At the molecular scale, there is the traditional biophysics universe of how the molecular motors convert chemical energy to mechanical force, and how diffusion and active transport regulate the fluxes and the transport of all the required species[7]. On the sides are other (difficult) questions such as the role played by the complex fluid known as mucus, with a highly non-linear flow behaviour and spatially stratified properties, and how the cilia and ciliated tissue are maintained at a steady state.

Some of these mucociliary clearance questions, relevant to human health, can be addressed on simpler organisms, which are easier to study in the lab. This is because essentially the same motile cilia as in mammals are present in other eukaryotic cells and organisms, such as sperm cells and motile algae. A comparison across species, where different geometrical and beating properties have evolved to fulfil slightly different purposes, shows fascinating non-linear dynamics at play. It is becoming clear that the nature of the phase-locked state is set by the details of how individual cilia bend and impart force on the surrounding fluid over their periodic motion[8], and that this is optimized differently in organisms that aim to transfer momentum to the fluid (direct propulsion) as opposed to creating collective beating states (surface propulsion)[9].

There are still a lot of critical experiments to be done in this area. It is not clear if all the important physical aspects have been considered in addressing synchronisation of cilia: it could be that the rheology of the fluids, or the very close range of cilia in some tissues, needs to be looked at more carefully. In terms of lung physics, the most exciting experiments will come with new perturbations, to address stability[10] and the ability to renew and maintain the optimal tissue configuration. This will require connecting the cilia level to the macroscopic clearance level, building on the work of Ramirez-San Juan and colleagues. A major goal would be to one day regenerate parts of airways for transplants with the correct physiological properties. ❐

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