



# Mechanisms and functions of multiciliary coordination

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## Abstract

Ciliated organisms are present in virtually every branch of the eukaryotic tree of life. In diverse systems, cilia operate in a coordinated manner to drive fluid flows, or even propel entire organisms. How do groups of motile cilia coordinate their activity within a cell or across a tissue to fulfil essential functions of life? In this review, we highlight the latest developments in our understanding of the mechanisms and functions of multiciliary coordination in diverse systems. We explore new and emerging trends in bioimaging, analytical, and computational methods, which together with their application in new model systems, have conspired to deliver important insights into one of the most fundamental questions in cellular dynamics.

## Addresses

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## Introduction

The Last Eukaryotic Common Ancestor (LECA) was likely ciliated and motile. In fact, it is hypothesised to have possessed two cilia with morphological traits resembling modern-day excavate flagellates [1]. In most extant flagellates, cilia on the same cell have unequal lengths and distinct beat patterns and can be coordinated dynamically to fulfil distinct roles such as for feeding, surface attachment, and swimming. For over one billion years, cilia and ciliated organisms have diversified significantly to occupy many phyla across the tree of eukaryotes [2].

While some solitary cells such as choanoflagellates and diverse sperm cells actuate just a single cilium (or flagellum), most ciliated systems possess between two and up to hundreds of thousands of cilia that are organised in

patches, arrays and circular bands. Wherever multiple cilia occur, they invariably exhibit some form of coordination that may be essential for maintaining normal function in locomotion or transport [3,4]. This includes propelling mucociliary flows across ciliated epithelia in vertebrates, or enabling microorganisms and small plankton to swim and navigate through aquatic habitats [5,6]. Despite a long and rich history of investigation into the phenomenology of ciliary coordination [7,8], we still have only a limited understanding of the key mechanisms and biophysical rules that underlie coordination, except in a few isolated systems.

In this topical review, we identify and dissect the main ciliary coordination states that have been encountered in different organisms, and discuss the key strategies involved in each case. We consider how conserved patterns can emerge at different spatial scales, and conversely how distinct mechanisms may operate simultaneously in the same organism. Finally, we highlight the importance of accessing new biological models, experimental platforms, and emerging quantitative tools for understanding and exploring the functional and evolutionary benefits resulting from different ciliary coordination phenomena.

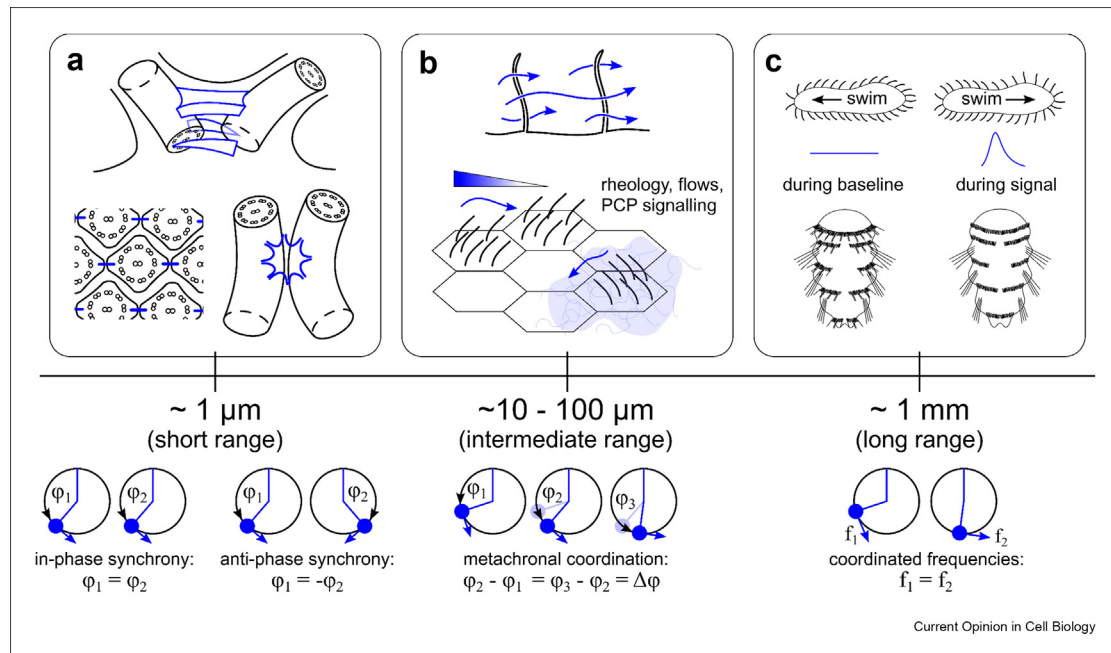
## Hallmarks of ciliary coordination across scales

The concept of coordination is remarkably broad. Coordination describes the ability of multiple agents to work together effectively and robustly towards a common purpose, often displaying some form of temporal correlation or patterning. In the case of oscillators, the existence of coordination also gives rise to their possible entrainment and control by external influences.

The coordinated activity of motile cilia is manifest in a number of different ways and often in a species or context dependent manner, extending beyond the basic realisation of perfectly synchronously beating cilia [9]. The primary purpose of natural ciliated surfaces is to create fluid flows for motility, feeding or transport. Unsurprisingly, the mechanism of interaction between cilia depends strongly on the lengthscale over which these cilia operate (Figure 1).

At the cellular or even sub-cellular scale, multiple cilia can bundle together to beat similarly to the other cilia

Figure 1



**Mechanisms of ciliary coordination across scales.** (a) At the cellular or subcellular scale: physical coupling of cilia basal bodies (as in *Chlamydomonas*), physical linkages along the length of the cilia (as in ctenophore comb plates), and steric interactions, generally lead to synchronised (or anti-synchronised) ciliary beating. (b) At intermediate scales: hydrodynamic interactions between neighbouring cilia give rise to synchrony and metachrony, while rheological properties of the bulk fluid, flows, and planar cell polarity signalling pathways result in alignment of the ciliary beat direction. (c) At the whole-body or tissue scale: intracellular signalling through membrane potential or second messengers can rapidly change the frequency and direction of multiple cilia (here shown in the unicellular *Paramecium* and multicellular *Platyneis* larvae). Small circles show representative phase relationships between the neighbouring cilia.

within the group (Figure 1a). Notable examples include the complex ciliary organelles of ciliated protists, the cirri – specialised walking appendages of spirotrich ciliates comprising ~50 individual cilia bundled together [10], and the oral (or buccal) membranelles – two of three rows of densely-packed compound cilia used for ‘wafting the food down the gullet’ of such cells [11]. These specialised cilia remain structurally united or in very close association throughout development and often beat as a single entity. In some cases, individual basal bodies of the compound ciliary structures may be connected physically by accessory fibres. In the ctenophore *Bolinopsis*, among the largest organisms that use cilia for self-propulsion, a specialised protein (CTENO64) localised to structures connecting the adjacent cilia in a comb plate was shown to be indispensable for coordinated ciliary beating and effective paddling of the large comb plates [12,13].

Many auxiliary cytoskeletal structures are associated with cilia and basal bodies, forming orderly patterns or lattices which provide further mechanical coupling and stability (Figure 1a). Fibrous interconnections between cilia, sometimes extending beyond the ciliary field, may be both active or passive, and can be stimulated

mechanically or biochemically. This type of basal coupling has been demonstrated in small algae and ciliates including *Chlamydomonas* [14] and *Tetrahymena* [15]. The putative role of these filaments in functionally coupling nearby cilia has been explored in recent theoretical studies [16–18].

In this regime, nearby cilia experience local repulsion due to their inability to occupy the same space, leading to physical contact and steric interactions (Figure 1a). As a possible mechanism of cilia coordination, this type of interaction has received little attention until recently [19,20], but may be important in establishing the coordination state of ciliary arrays in the limit of very high cilia density. In collectives of undulatory robotic filaments (comprising rigid rods and servo motors), gait synchronisation can indeed result from purely contact-induced interactions/collisions [21].

At intermediate scales, signatures of coordinated activity in ciliary arrays include metachronal waves, where cilia in successive rows display a constant phase offset from the neighbouring row (see next section). Various scenarios have been proposed to explain the emergence of ciliary metachronism. The earliest of these suggest

that cilia interact hydrodynamically (through the fluid) (Figure 1b), leading to the synchronous swimming of nearby sperm [22] and coordinated group dynamics [23,24]. This mechanism of *hydrodynamic synchronisation* has also been studied extensively through computational modelling [25–28]. Direct proof of this phenomenon was provided using pairs of *Volvox* cilia, that were isolated from colonies, and held on separate micropipettes at varying distances [29]. At these scales, mechanical or basal coupling may resist hydrodynamic interactions to establish the requisite coordination state for a given organism [14,15].

Even when the cilia are patchy or otherwise distributed heterogeneously, ciliary beating can still be entrained by fluid flows [30], for example in the ciliated epithelium of *Xenopus* [31], and in cultured mouse ependymal cilia [32]. In these cases there may not be global synchrony or phase waves, but instead coordination may only result in entrainment of beat frequency and/or beat direction. The latter constitutes a weaker form of coordination (Figure 1b). In vertebrates, placement and orientation of cilia are important co-determinants of tissue-scale alignment and coordination, involving a feedback between planar cell polarity signalling and external flows [33,34], though the molecular mechanism is not universally clear.

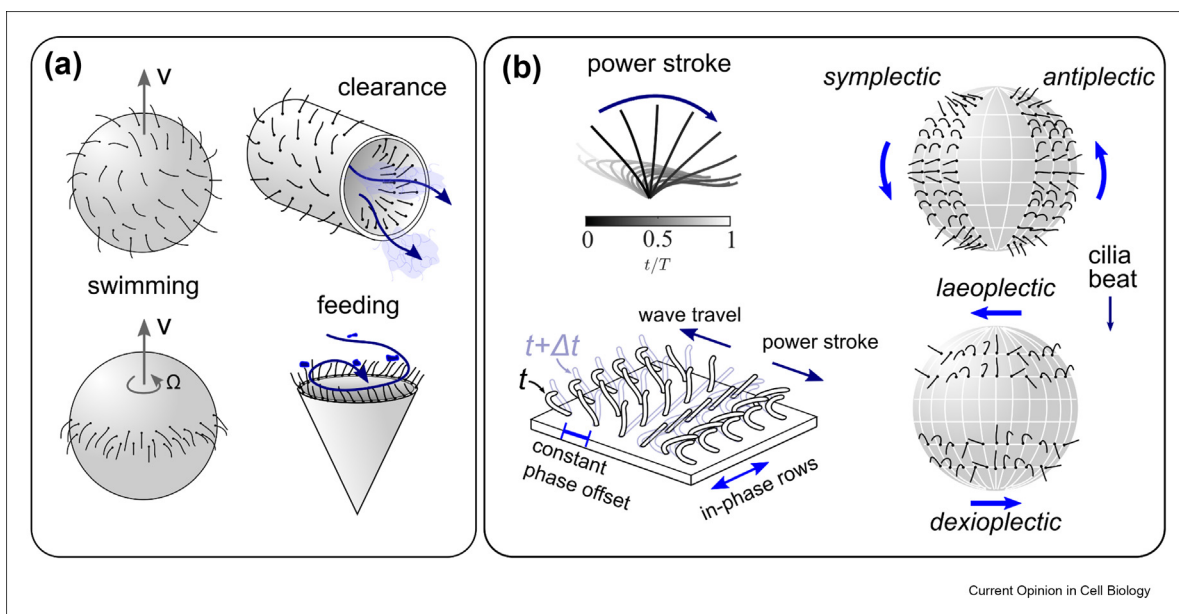
Sometimes, mucus – which has non-trivial rheological properties – is indispensable for proper ciliary function [35,36]. Mucus, when deposited above cultured lung epithelial cells, can alter the upper boundary condition of the ciliated surface, and thus the propagation direction of ciliary metachronal waves [37]; steric effects may also be present. In *Paramecium*, the ciliary wave direction can vary with viscosity [38], though this response is not necessarily physiological.

Finally, cilia can also be coordinated over the whole-body or tissue scale (Figure 1c). In some ciliates, rapid whole-body changes in ciliary beat frequency and orientation can be triggered by membrane electrical depolarisations [39]. This is the mechanism of fast-reversals in the *Paramecium* escape reaction. In planktonic larvae, neuronal circuits coordinate whole-body ciliary arrests, where all the cilia simultaneously stop beating in response to calcium elevation [5,40].

### Patterns of multiciliary structure and coordination

Cilia are often found in multiciliated arrays, in a variety of geometries (Figure 2a). Cilia in such arrays normally do not beat either randomly or synchronously but coordinate into a metachronal wave (Figure 2b). This pattern comprises rows of synchronously beating cilia,

Figure 2



**Natural configurations of ciliary arrays and their metachronal coordination.** (a) Ciliary arrays occur in many geometries and topologies, including: uniformly distributed over a convex body; on the outer or inner surface of a tube; localised into rings or bands on a larger swimmer; running along an edge of a conical body. These arrays perform various functions including: linear ( $v$ ) and rotational ( $\Omega$ ) swimming; clearance of unwanted fluids; and generating feeding flows. (b) a representative ciliary waveform; (antipleptic) ciliary metachrony with rows of synchronously beating cilia with a constant phase offset between each row. At a time  $\Delta t$  after the initial snapshot, the wave pattern has moved along in the opposite direction to the power stroke; snapshots of cilia performing the four basic wave directions.

with a constant offset between the beat phase of each successive row. Wave ‘crests’ (a row of cilia in the middle of the power stroke) propagate as the cilia beat. Ciliary metachronism is a robust condition in many ciliates [41,42] and marine larvae [40,43].

The wave can travel in different directions with respect to the ciliary power stroke direction, which is generally fixed. The four principal wave directions are symplectic, antiplectic, laeoplectic and dexioplectic (Figure 2b), and intermediate wave directions are also observed. Phylogenetically related organisms tend to exhibit metachronal waves of the same type, but this has not been analysed systematically.

How waves emerge is still subject to debate. In this intermediate regime, multiple physical mechanisms dictate the final coordination state. In addition to hydrodynamic and basal coupling, steric effects likely promote synchronisation in the beat-direction [43–45]. Geometrical and topological constraints, boundary conditions, and whether cilia emanate from the interior or exterior of a closed surface, also contribute (Figure 2a). Experiments in *Paramecium* show that a wave continues to propagate between two halves of a cell that are hydrodynamically isolated from each other by a physical boundary, implicating elastic compliance of the cell membrane as another mechanism of wave transmission [41]. Meanwhile metachronal solutions can still arise in some parameter regimes in simulations of linear chains or arrays of cilia that interact only hydrodynamically, [26,28,46,47]. Regarding wave directionality, a recent theoretical/computational study found that the wave propagation direction varies when the ciliary beat plane is tilted from the vertical [48], indicating that interspecies variation in beat patterns - and particularly the 3D nature of many ciliary beats - may contribute to the variety in observed wave directions. Experimental characterisation of beat chirality has been achieved for *Paramecium* and *Chlamydomonas*, but is generally challenging [49,50].

### Robustness and heterogeneity

Since form is coupled to function, and function to survival, the global patterning of cilia comes under strict developmental control in many species. In the ciliate *Stentor*, regeneration and remodelling of the oral membranellar band cilia after loss or injury follows a stereotyped sequence, leading to a diaplectic metachronal wave [42,51]. The infraciliature of *Tetrahymena* is also robustly reproduced at each round of cell division, but exhibits plasticity during environmental dispersal [52], where to achieve faster swimming cells become shorter so that the density of basal bodies (and cilia) increases, while conserving the overall basal body number [53]. In vertebrates, while PCP proteins bias the basic structural alignment of the basal bodies, cilia

respond to fluid flows which further refine the beat direction [34].

However, a degree of disorder can sometimes be advantageous. Most vertebrate ciliated tissues do not present uniformly with cilia, but instead with multiciliated cells (with ~100 cilia each) assuming a heterogeneous, sometimes patchy distribution. Ciliated cells in the mouse trachea are only well-aligned locally, and this stochasticity is conjectured to enhance the global clearance rate [30]. Similarly, cilia in the zebrafish nose are synchronised only locally, with heterogeneous beat frequencies, yet exhibit stable tissue-scale metachrony [45]. The somatic cilia of *Volvox*, a colonial alga, exhibits symplectic metachronal waves [47,54], which may rely on an intrinsic anterior-posterior gradient in ciliary beat frequencies [55].

### Impact on physiological function

The patterning and coordination modes of cilia are strongly linked to function. Disruption of this can be detrimental, for example in human ciliopathies including primary ciliary dyskinesia [56]. For single cells with few cilia, such as flagellate algae or zoospores, coordination ensures an effective swimming gait and fast dispersal [57–59]. In aquatic organisms with simple or even no nervous systems, such as the sponge, ciliated choanocytes lining the canal system of the adult animal pump large volumes of fluid for filter feeding [60].

The ability for multiciliary arrays to perform various functions including propulsion and fluid transport has been evaluated in depth by several biophysical studies. In water, fully multiciliated swimmers were maximally efficient (i.e. obtaining a maximum velocity for a given rate of energy dissipation) when their cilia performed antiplectic waves, compared to symplectic or synchronous beating [61,62]. For ciliary sheets resembling ciliated tissues or epithelia, all types of metachronal waves improve fluid transport efficiency compared to synchronous beating [26]. In artificial ciliary arrays, the antiplectic wave can be optimal for fluid transport, but other wave directions produce higher fluid mixing [63]. In simulations of two-phase flows (mucus on water), antiplectic waves were maximally efficient for both transport and mixing [64], although experiments have suggested that a diaplectic wave, which minimises power dissipation by the cilia, appears when the mucus dries and becomes ‘stuck’ [37].

Thus, antiplectic waves are widely considered optimal. However, this is not the preferred state in many biological systems, which instead display diaplectic waves [43]. It is possible that different ciliary waveforms are optimal for different functions, e.g. pumping versus swimming, so efficiency may also depend on the waveform [65]. Furthermore, the limit of very dense ciliary

arrays found in many organisms remains challenging to reproduce even for current simulation methods [44]. Optimisation for physiological functions is therefore non-trivial, but some form of metachrony or coordination is always better than none.

### Outlook: Emerging models and approaches

In recent years, the study of multiciliary coordination has entered a new interdisciplinary era. Here, we have highlighted universal mechanisms that exist across scales to couple and coordinate ciliary activity, and across a variety of organisms. It is clear that while we owe much of our understanding of cilia biology and the biophysics of the coordination dynamics to such model species such as *Chlamydomonas* and *Xenopus* [34,66], important insights can be gained from studying diverse and emerging non-model systems, and even non-animal models. Embracing and appreciating this diversity of form and function across the entire eukaryotic tree could help us establish a more comprehensive picture of all possible natural functions of motile cilia assemblages. Indeed, several other specialised functions of cilia remain largely unexplored, for example, their collective role in driving Planarian gliding motility [67], or in the selective filter-feeding habits of various ciliates and marine organisms [60], or the metachronal coordination of compound cilia for inertial swimming in ctenophores [68]. All of these examples rely on dynamic integration of local activity, self-organisation, and global, systems-level control.

Our review has emphasised the value of integrating multiple approaches. Now more than ever, it is possible to establish the precise, nearly *in situ* patterns of 3D multiciliary organisation across an entire tissue or organism using electron-microscopy, and as well to observe and quantify the dynamic activity of cilia with advanced live-imaging, optical, and analytical methods [44,69]. In parallel, next-generation modelling and computational methods [19,70] enable *in silico* experiments and hypothesis-testing, particularly with respect to patterns or behaviours of cilia that are not readily accessible or measurable in living organisms. There has also been increasing interest in harnessing the capabilities of natural cilia using synthetic mimics, such as magnetically actuated ciliary arrays [71,72]. Even if these latter approaches might not always help explain the *emergence* of various coordination strategies nor how organisms implement these in real-time, they can provide useful quantitative insights into downstream function. These advances, both tangible and conceptual, are central to shaping our understanding of how this remarkably conserved structure, the cilium, came to acquire such diversity and sophistication of function.

### Author contributions

KYW drafted the article with help from RNP. RNP prepared the figures.

### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### Data availability

No data was used for the research described in the article.

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  - \*\* of outstanding interest
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This study is an example of the latest developments in miniaturising artificial ciliary arrays (combines simulations and experiments)