Elastohydrodynamic phase-lock in two rotating cilia

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Abstract
Determination of left-right asymmetry of the body plan is achieved in the early embryo. At the 4-6 somite stage, a cavity structure, called a node, is observed in the ventral midline surface, in which hundreds of cilia rotate. Nodal cilia are typically tilted toward the posterior and rotate in the clockwise direction, resulting in the generation of leftward flow in the node. Such leftward flow acts as a trigger of left-specific gene expression, and fluid mechanics plays a role in left-right symmetry breaking. To understand the cilia-driven nodal flow, it is necessary to determine the hydrodynamic interactions among rotating cilia, as ciliary motions interact with each other through fluid motion. In this study, we numerically investigated the elastohydrodynamic synchronization of two rotating cilia, as well as the flow field. The ciliary motion was determined by the balance of cytoskeletal elastic force, motor protein-induced active force, and fluid viscous force. According to the geometric clutch hypothesis, the frequency of rotating cilia is controlled by the bending curvature. Owing to hydrodynamic interactions, bending deformations of two cilia become time-dependent, and the rotation is finally locked in anti-phase regardless of the relative position and initial phase difference. By locking in the reverse phase, the average propulsion flow rate becomes 2-3 times larger than in-phase beating. The results of this study form a basis for understanding cilium-driven nodal flow.

Keywords: Nodal cilia, Left-right asymmetry, Hydrodynamic synchronization, Stokes flow, Computational biomechanics

1. Introduction
Left-right asymmetry of the vertebrate body plan is achieved in the early embryo (Hirokawa et al., 2009; Shinohara et al., 2015). In the mouse embryo, an embryonic cavity structure is found at the ventral midline surface 7-8 days after fertilization (Hirokawa et al., 2009). This cavity, called a node, contains hundreds of monociliated cells. Nodal cilia are posteriorly tilted and rotate in the clockwise direction, forming leftward flow in the node. Such cilia-driven leftward flow acts as the trigger of gene expression for left-right symmetry breaking, such as \textit{Lefty-2} and \textit{Pitx2} (Hirokawa et al., 2009). Nodal flow is then crucial for determination of left and right, and many groups have investigated the node system from the viewpoint of fluid mechanics.

The motion and deformation of nodal cilia are determined by the internal molecular structure. Nodal cilia have nine microtubule doublets and lack the central pairs of microtubules. The 9+0 structure is similar to that of non-motile primary cilia, but nodal cilia can actively rotate using the dynein motor proteins. Dyneins are minus end-directed motors that use conformation-dependent changes associated with adenosine triphosphate (ATP) hydrolysis to attach to and walk along microtubules (Ueno et al., 2012). Each of the nine doublets is also connected by nexin links, and these are considered to be involved in maintaining the axoneme structure.

Several theoretical and computational models have been developed to understand the mechanics of nodal cilia. In an early study, Brokaw (1972) developed a simple cilium model using a generalized resistive force theory. In this model, bending activation was controlled locally by the curvature of the cilium. Hines and Blum (1984) extended the model to three dimensions. A more sophisticated slender body theory was applied for modeling of the cilia (Eloy and Lauga, 2012; Smith et al., 2011). Chen and Zhong (2015) developed a full three-dimensional ciliary axoneme model using a finite
element method. In their model, the distribution of dynein activation was controlled by a time-dependent function, and they concluded that the activation velocity along the microtubules should not be constant for smooth rotation.

Hydrodynamic interactions among cilia have also been investigated analytically and numerically. Takamatsu et al. (2012) investigated the dynamics of two rotating cilia. The cilium was modeled as a rigid rod, and constant torque was applied for rotation. Owing to hydrodynamic interaction, two rotating cilia were weakly synchronized and the phase difference was locked in $\pi/2$. Brumley et al. (2012) developed a simple oscillator model to simulate a collective motion of an array of cilia. The oscillator consisted of an orbital bead with a linear spring. The orbit was then determined by the elasticity of the spring, and showed robust synchronization by introducing elasticity. Although hydrodynamic synchronizations may lead to strong fluid flow (Elgeti and Gompper, 2013), the full mechanics of hydrodynamic interactions has not been clarified because only simple mechanical models of rotating cilia have been developed to date. Greater insight into flow-induced synchronization is required to obtain a better understanding of the nature of nodal cilia.

In this study, we numerically investigated the hydrodynamic interactions of two rotating cilia, as well as the flow field. In section 2, we describe the governing equations and numerical method used in this study. Section 3 presents the elastohydrodynamic synchronization of the cilia. We also discuss the cilia-driven flow rate and finally conclude the report in section 4.

2. Governing equations and numerical methods

In this section, we briefly explain the governing equations and our numerical method. We developed a coarse-grained model of nodal ciliary axoneme, and fluid motion was derived using Stokeslets. In the following subsection, we first describe the solid mechanics of the nodal ciliary axoneme ultrastructure.

2.1. Ciliary axoneme model

The nodal ciliary axoneme consists of 9+0 doublets, with each doublet linked to nearby doublets by elastic nexin linkages (Shinohara et al., 2015). The microtubule doublet is composed of a circular A-tubule, which has a complete set of 13 protofilaments, and an adjacent B-tubule (Ueno et al., 2012). We developed a coarse-grained model in which the doublet is discretized by 40 spherical beads, as shown in Figure 1. As the A-tubule diameter is estimated as 20-25 nm (Ueno et al., 2012), the bead diameter $d$ is then equivalent to 40-50 nm. To coincide with the physiological cilium length (3-5 µm, Buceta et al., 2005), the length $L$ has the relationship $L/d = 80$. The microtubule doublet is then arranged in a circle with regular intervals (cf. Figure 1a), and the radius $r_{cilia}$ is set as $r_{cilia} = 4d$.

A conservative elastic force is introduced to tie with two consecutive beads $i$ and $i + 1$ in the microtubule chain:

$$F_{bi} = -F_{bi+1} = K_b(r_i^{bi+1} - r_i^{bi}),$$

(1)
Fig. 2 Dynein force model: (a) due to ATP hydrolysis, dynein heads slide to the minus end of microtubule (MT) and sliding force is generated towards the plus end, indicated as the black arrow in the figure (likewise for the tail). (b) Consider the dynein force acts on the \(i\)-th bead surface and counter force exerted on the \(j\)-th bead. (c) Dynein force is then expressed as the force \(\mathbf{F}_d\) and torque \(\mathbf{T}_d\) acting on the \(i\)-th bead gravity point. (d) Moreover, the torque can be converted to a force pair of \(\mathbf{F}^{+1}\) and \(\mathbf{F}^{-1}\) satisfying with the force free condition.

where \(K_b\) is the elastic constant, and \(r^{i+1} = \|r^{i+1}\|\), \(r^{i+1} = X^{i+1} - X^i\) and \(X^i\) and \(X^{i+1}\) are position vectors of beads \(i\) and \(i + 1\), respectively. \(r^{eq}\) is the equilibrium length of the elastic element, which is set as \(r^{eq} = d\).

Bending elastic energy is also taken into account to control microtubule flexibility. To ensure force-free and torque-free conditions, the bending force acting on the \(i\)-th bead is calculated by the angle formed by nearby beads \(i\), \(i + 1\), and \(i + 2\):

\[
\begin{align*}
F_{a}^{i+1} &= K_a \theta - \theta^{eq} \left( \frac{r^{i+1}}{r^{i+1}} - \cos \theta \frac{r^{i+1}}{r^{i+1}} \right), \\
F_{a}^{i+1} &= K_a \theta - \theta^{eq} \left( \frac{r^{i+1}}{r^{i+1}} - \cos \theta \frac{r^{i+1}}{r^{i+1}} \right), \\
F_{a}^i &= F_{a}^{i+1} - F_{a}^{i+1},
\end{align*}
\]

where \(K_a\) is the angular potential constant, \(\theta\) is the angle made by three beads \(i - 1\), \(i\), and \(i + 1\), and \(\theta^{eq}(=\pi)\) is the equilibrium angle.

The inter-doublet linkage, called a nexin link, is modeled as a linear spring connecting two nearby microtubules. The nexin force is then exerted between the two beads in a cross section perpendicular to the microtubule axis:

\[
F_{n}^i = -F_{d}^j = K_n (r^{ij} - r^{ij}) r^{ij}.
\]

where \(K_n\) is the elastic constant and \(r^{ij}_n = 8\pi d/9\) is the natural length of the nexin link.

Axonemal dyneins are minus end-directed motors associated with ATP hydrolysis, arranged in a repeating pattern along the microtubule. Dyneins are organized in two rows, the outer and inner dynein arms, which generate the force bending the doublet microtubules. The dynein tail is anchored to the doublet A-tubule and the head is attached to the neighboring B-tubule and walks to the proximal side. Then, dyneins generate a shearing force between the doublets (Figure 2a). In this study, the dynein force is modeled as follows. Consider the dynein force acting on the \(i\)-th bead surface and counter force is exerted on the \(j\)-th bead (Figure 2b). The dynein force can then be described by force \(\mathbf{F}_d\)
and torque $\mathbf{T}_d'$ (likewise $\mathbf{F}_d'$ and $\mathbf{T}_d'$). The torque can be rewritten as a force pair of $\mathbf{F}_d'^{+1}$ and $\mathbf{F}_d'^{-1}$ satisfying the force-free condition (Figure 2d). Accordingly, the dynein force is given by:

$$
\mathbf{F}_d^i = -\mathbf{F}_d'^i = f_d s^i, \\
\mathbf{F}_d'^{-1} = \mathbf{F}_d'^{+1} = -\mathbf{F}_d^i = \frac{1}{4} f_d n^i,
$$

where $f_d$ is the dynein force magnitude, and $s^i$ and $n^i$ are unit tangential and normal vectors of bead $i$, respectively.

### 2.2. Fluid motion

We next present the numerical method for fluid motion. Nodal cilia are assumed to be immersed in an incompressible Newtonian fluid with viscosity $\mu$. Owing to the small size of the cilia, the Reynolds number around the cilium becomes much smaller than unity ($\text{Re} \approx 10^{-5}$). Then, we assume that fluid flow is governed by the Stokes equation, and the velocity of bead $i$ is approximated by simulation of far-field Stokeslets:

$$
\mathbf{v}'(X^i) = \frac{1}{3\pi \eta \mu d} \left( \frac{9}{16 h' \pi} + \frac{1}{16 h' \pi} \right) \mathbf{F}_d'^{\parallel} + \frac{1}{3\pi \eta \mu d} \left( \frac{9}{32 h^2} + \frac{1}{64 h' \pi} \right) \mathbf{F}_d'^{\perp} + \frac{1}{8\pi \mu d} \sum_{j \neq i} J(X^i, X^j) \cdot \mathbf{F}'(X^j). 
$$

(5)

The first and second terms on the right-hand side express the modified Stokes law of bead $i$ (Kim and Karrila, 2005), and the third term expresses the flow generated by bead $j$. $\mathbf{F}'$ is the total force acting on the bead $i$, which balances the summation of elastic, nexin, and dynein forces; $\mathbf{F}' = \Sigma \mathbf{F}_{b}' + \Sigma \mathbf{F}_{n}' + \Sigma \mathbf{F}_{d}'$. $\mathbf{F}_d'^{\parallel}$ and $\mathbf{F}_d'^{\perp}$ are the total force parallel and normal to the wall, and $h'(=h/d)$ is the normalized height of the bead $i$. $\mathbf{J}$ is the Stokeslet of the Green’s function, which can express an infinite plane wall at $x_3 = 0$ by using the Blakelet (Blake, 1971):

$$
\mathbf{J} = \mathbf{G}(X^i, X^j) + \mathbf{W}(X^i, X^j),
$$

(6)

where $X^j$ is the mirror image of $X^i$, $\mathbf{G}$ is the Stokeslet of infinite fluid domain

$$
\mathbf{G}_{ao}(X^i, X^j) = \frac{\delta_{ao}}{r^{ij}} + \frac{r^j_ao}{r^{ij} r^{aj}}
$$

(7)

$\mathbf{W}$ is the image system Stokeslet

$$
\mathbf{W}(X^i, X^j) = -\mathbf{G}(X^i, X^j) + 2h^2 \mathbf{W}^{D}(X^i, X^j) - 2h \mathbf{W}^{SD}(X^i, X^j),
$$

(8)

$h$ is the height of $X^j$ from the wall, $\mathbf{W}^{D}$ is the source doublet

$$
\mathbf{W}_{ao}^{D}(X^i, X^j) = (1 - 2\delta_{o} - \delta_{ao} \frac{r^j_{ao} r^j_{ao} r^{aj}_{ao}}{(r^{ij})^3} - 3 \frac{r^j_{ao} r^j_{ao} r^j_{ao}}{(r^{ij})^3} - 3 \frac{r^j_{ao} r^j_{ao} r^{aj}_{ao}}{(r^{ij})^3})
$$

(9)

$\mathbf{W}^{SD}$ is the Stokes doublet

$$
\mathbf{W}_{ao}^{SD}(X^i, X^j) = (1 - 2\delta_{o} - \delta_{ao} \frac{r^j_{ao} r^j_{ao} r^{aj}_{ao}}{(r^{ij})^3} - 3 \frac{r^j_{ao} r^j_{ao} r^j_{ao}}{(r^{ij})^3} - 3 \frac{r^j_{ao} r^j_{ao} r^{aj}_{ao}}{(r^{ij})^3})
$$

(10)

and Greek subscripts represent the index of the Cartesian component. Once the velocity $\mathbf{v}'$ is given, the material point $X^j$ is updated by the explicit Euler method.

In this study, the force was normalized by the viscous force $\mu U$, where $U$ is the characteristic velocity. The potential constants can also be normalized and given as $K_a/\mu U = 100$, $K_n/\mu Ud^2 = 50$, and $K_d/\mu U = 0.5$. Elasticity of nexin links was measured experimentally in a previous study, and the value was estimated as $K_a = 2.0 \times 10^{-3}$ N/m (Minoura et al., 1999). If we assume the fluid viscosity $\mu = 10^{-3}$ Pa.s, the characteristic velocity of the simulation is given by $U = 4.0$ m/s. Accordingly, the elastic constant of microtubules used in this study is equivalent to $K_a = 0.4$ N/m, which is 100 times smaller than the experimental estimation (Gittes et al., 1993). If we use a large value of $K_a$, the time step $\delta t$ must be sufficiently small to guarantee that the simulation is stable. Although the value is smaller than the experimental estimation, it would be high enough to express the rigidity of the microtubules because the elastic resistance is 100 times greater than the viscous force density $\mu U$. Howard (2001) reported a load force generated by dynein of 7 pN. Axonemal dyneins are organized in two rows, the outer and inner dynein arms, and normalized dynein force magnitude was set as $f_d/\mu U = 10^{-3}$ pN/m, which is 10 times smaller than the experimental force density $\mu U = 6.2 \times 10^{-3}$ pN/m. Therefore, $f_d/\mu U = 0.08$ throughout this study.
3. Results and discussion

3.1. Rotation of cilium model

We first investigated the single cilium dynamics. Although several groups have investigated dynein regulatory mechanisms, the precise nature of the temporal and spatial control mechanisms is unknown. We developed two dynein regulatory models: (i) commonly used time control model and (ii) geometric clutch model.

3.1.1. Time control model

In previous computational studies (Chen and Zhong, 2015; Omori et al., 2017), simple time-controlled activation propagating models were commonly used. In the time-controlled model, dynein activation propagates in the circumferential direction. Dynein activation moves sequentially from microtubule to neighboring microtubule in the clockwise direction with an interval of $T_0/9$, where $T_0$ is the period. Chen and Zhong (2015) investigated the effects of dynein activation patterns on ciliary motion by varying the dynein activation time. They showed the smoothest rotation when 3.5 microtubules were activated at a time. In accordance with Chen and Zhong (2015), three microtubules were activated at a time in this study. The time sequence of ciliary rotation during one period is shown in Figure 3. Dynein activation, shown in red in the figure, propagates in the clockwise direction. As the time period $T_0$ is large enough, the bending deformation reaches a steady state within this interval. The resulting open angle of the ciliary deformation (cf. $\psi$ in Figure 5) becomes about $\pi/6$, which corresponds to previous experimental observations (Hirokawa et al., 2009).

3.1.2. Geometry control model

Although the time control model showed agreement with previous experiments, the rotational frequency was fixed and the motion became time-invariant. To discuss time-dependent hydrodynamic...
interactions between two rotating cilia, we also developed another mechanical model of nodal cilia. Lindemann (2002) proposed a dynein regulatory mechanism, which is called the geometric clutch hypothesis. This theory is based on the premise of transverse forces (t-forces) acting on the outer doublets. The t-force results from tension and compression on the doublets when a bend is present on the cilium. A ciliary beat is then a transition from effective stroke to recovery stroke by the geometry, namely, bending curvature of the cilium. Taking the geometric clutch hypothesis into account, we developed a geometry control model of nodal cilia. In this model, the propagation speed is controlled by the bending curvature. For the criterion of propagation, we used an open angle \( \psi_c \), which is defined as the angle between the rotational axis and ciliary tip (cf. Figure 5). When the open angle \( \psi_c \) becomes larger than the threshold value \( \psi_{c,\text{th}} \), dynein activation moves to the neighboring microtubule. The number of activated microtubule is fixed to 3, and the dynein activation is propagated in clockwise direction one by one. For simplicity of the discussion, the propagation occurs during one time step \( \Delta t \) without time delay. Such modeling may produce discontinuous rotations, but cilia-driven flow does not change so much even if we set smooth activation propagating model, which was confirmed in the previous study (Omori et al., 2017).

\[ T / T_0 = \frac{1}{2 \pi} \left( \frac{\psi_c}{\psi_{c,\text{th}}} \right) \]

The rotational period with various \( \psi_c \) is shown in Figure 4(b). When \( \psi_c \) is sufficiently small, the propagation frequency becomes too high and the cilium shows only small bending deformation (Figure 4a, \( \psi_c / \pi = 0.01 \)). The period \( T \) increases with \( \psi_c \) and rapidly becomes larger when \( \psi_c / \pi \geq 0.1 \). As the open angle in the steady deformation converges to about \( \pi/6 \), the period goes to infinity when we set \( \psi_c > \pi/6 \). In the next section, we use \( \psi_c / \pi = 0.14 \) to discuss hydrodynamic interactions between two cilia.

### 3.2. Two rotating cilia

We next investigated the hydrodynamic interactions between two rotating cilia. Nodal cilia are posteriorly tilted and rotate in the clockwise direction in the node (Hirokawa et al., 2009). The tilt angle was estimated as \( 2\pi/9 \) in a previous experimental study (Okada et al., 2005). By tilting toward the posterior, cilia can induce leftward flow even...
Fig. 6 Elastohydrodynamic phase-lock in two rotating cilia (a-d) Two rotating cilia are finally converged to anti-phase. $\theta_i$ indicates the rotational phase of cilium1. (e) Time change of phase difference between two cilia.

Fig. 7 Effect of relative ciliary positions on the final phase difference

with symmetric rotation. To reproduce the experimental conditions, nodal cilia are tilted toward the -$x_2$-direction with tilt angle $\eta = 2\pi/9$, as shown in Figure 5. The plus $x_1$-direction then corresponds to the left of the embryo, whereas the minus $x_1$-direction indicates the right. To represent the relative positions between two cilia, we introduce the polar coordinate $(R, \phi)$, where $R$ is the distance between two cilia, and $\phi$ is the angle made by the $x_1$-axis and the line segment of cilium1 and cilium2. The origin is set to the base of cilium1.  

3.2.1. Elastohydrodynamic phase-lock Figure 6 shows the dynamics of two rotating cilia. The ciliary position of cilium2 in the polar coordinate is set to $(R, \phi) = (L, 0)$. Cilium1 is located on the upstream side of cilium2. The initial phase difference is set to 0. Initially, the two cilia rotate in-phase, but due to fluid-structure interactions, the rotation becomes time-dependent. After a certain duration (about six to seven rotations), the two cilia stably rotate in anti-phase. For more quantitative discussion, we define the phase difference: $\theta_2 - \theta_1$, where $\theta_i$ is the phase of cilium $i$. The time change of the phase difference is shown in Figure 6(e). It can be seen that $\theta_2 - \theta_1$ increases with time and converges about $\pi$. The sign of the phase difference is positive, suggesting that downstream cilium2 always takes the lead over upstream cilium1. This type of phase propagation (downstream to upstream) is similar to an antiplectic metachronal wave, which is widely observed in nature (Kiyota et al., 2014; Sleigh, 1962).

We next investigated the effects of relative positions (Figure 7) and initial phase differences (data not shown). The phase lag always locks in $\pi$, regardless of $R$, $\phi$, and initial conditions. In the 2-body system, the distance $R$ just controls the time taking to the synchronization, and the final phase difference is independent of $R$. These results suggest the
robust and strong coupling of two cilia. We note that the relative positions of cilium1 and cilium2 are reversed in the special case of $\phi = \pm \pi/2$, and the phase difference converges to $-\pi$ when $\phi = \pi/2$ (Figure 7b). Takamatsu et al. (2013) analytically investigated hydrodynamic interactions of two rotating cilia. The cilium was modeled as a rigid rod, and constant rotational torque was applied for rotation. The phase difference was weakly locked in $\pi/2$, but the range of phase locking was narrow and the rotation was rarely locked when two cilia were identical size. Although rigid body rotations showed weak synchronization, the deformability may produce strong synchronization. Brumley et al. (2012) investigated the effects of elasticity on an oscillator model. In their paper, the oscillator model was simply sustained by a linear elastic spring, and each oscillator was coupled by fluid motion. They concluded that orbit compliance, namely, elasticity of the spring, can produce fast and robust synchronization. Our numerical model, where the elasticity was taken into account, also showed robust synchronization, similar to the model of Brumley et al. (2012). Such elastohydrodynamic self-synchronization likely contributes to the emergence of a metachronal wave even without chemical signaling.

### 3.2.2 Cilia-induced flow rate

We next investigated the propulsive flow rate in the node system. In the node, nodal cilia rotate clockwise and produce leftward flow. As the $x_1$-direction indicates the left in this simulation, here we discuss the $x_1$-component of the flow rate. To calculate the cilium-driven flow rate, we first calculate the flow velocity $v_1$ using Stokeslets, where $v_1$ is the $x_1$-component of the velocity vector. The temporal velocity $v_1$ in the $(x_2, x_3)$-plane at $x_1 = 2L$ is shown in Figure 8(a). It can be seen that larger $v_1$ appears near the tip of cilia. We then calculate the flow rate at $x_1 = 2L$ using the following infinite boundary integral equation:

$$Q_1(t, x_1) = \int_0^\infty \int_{-\infty}^{\infty} v_1(t, x) dx_2 dx_3.$$  \hspace{1cm} (11)

By introducing the truncation distance $r_c$ in the $(x_2, x_3)$-plane, the above integration can be divided into near-field and far-field effects:

$$Q_1 = Q_{near} + Q_{far}. \hspace{1cm} (12)$$

As the flow magnitude is proportional to $r^{-3}$ (Omori et al., 2017), the far-field flow rate $Q_{far}$ can be analytically calculated by assuming that $v_1$ decreases with $r^{-3}$, while $Q_{near}$ is computed from a numerical Gaussian integration scheme. As in a previous study (Omori et al., 2017), the truncation $r_c$ is set to $r_c = 8L$, which is sufficiently large to estimate $Q_{far}$.

The time-average flow rate as a function of relative position $\phi$ is shown in Figure 8(b). It can be seen that, by locking anti-phase rotation, the net flow becomes about 2-3 times greater than the in-phase beating. When the two cilia rotated in-phase, a relatively large time variance was observed and temporally strong minus flow was generated. In the anti-phase, relatively steady flow was generated by consecutive rotations of two cilia. Leftward flow in vertebrate embryos causes left-right asymmetry, and strong flow with elastohydrodynamic synchronization may be helpful for left-right determination. There are now few experimental studies about hydrodynamic synchronization of two rotating cilia, we expect our numerical results will stimulate further experiments of rotating cilia in the near future.
4. Conclusion

In this study, we numerically investigated elastohydrodynamic interactions between two rotating cilia. To describe time-dependent ciliary rotations, we developed a geometry control ciliary model. Elasticity of the model cilia could produce strong synchronization and the final phase difference was locked in $\pi$. By locking in anti-phase, the flow rate became 2-3 times greater than in-phase beating. As leftward flow in vertebrate embryos is important for left-right determination, elastohydrodynamic self-synchronization is useful for inducing asymmetry. These results may be helpful to obtain a better understanding of the nature of the embryonic node system.

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