

Viscosity-mediated signal amplification enables robust left-right symmetry breaking in the mouse node

Highlights

- Viscous amplification converts weak flow asymmetry into a robust signal
- Secreted macromolecules generate a transient high-viscosity surface layer
- The model unifies mechanosensing and chemosensing in one framework
- A theoretical biophysics model explains robust left-right flow sensing

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In brief

The origin of left-right (LR) asymmetry breaking in the development of vertebrates remains unresolved. Lee and Vermot propose a theoretical biophysics model that reveals how weak flow-generated asymmetries can be amplified into a robust mechanical signal during vertebrate LR symmetry breaking. Secreted macromolecules create a transient viscous layer that enhances the torque on immotile cilia, unifying mechanosensory and chemosensory ideas within a single downstream amplification mechanism.

Article

Viscosity-mediated signal amplification enables robust left-right symmetry breaking in the mouse node

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ACCESSIBLE OVERVIEW Left-right (LR) asymmetry is a defining feature of vertebrate development: although the body appears externally symmetric, many internal organs occupy reproducible LR positions. In mammals, LR symmetry breaking is initiated in a transient embryonic structure called the node, where rotating motile cilia generate a leftward fluid flow. Although this flow is known to be essential, how embryos reliably detect it and convert it into a robust developmental decision has remained unresolved. Two main hypotheses have been proposed. One suggests that immotile cilia directly sense the mechanical forces generated by the flow, whereas the other proposes that the flow transports signaling molecules preferentially to the left side of the node. Although both hypotheses are supported by experimental evidence, each faces important challenges when considered in isolation.

Here, we present a minimal theoretical biophysics model showing how these two perspectives can operate together. We propose that macromolecules secreted by cells within the node locally modify the rheological properties of the near-surface fluid. As these molecules accumulate, they create a transient high-viscosity layer that is entrained by the leftward flow, amplifying the hydrodynamic drag and torque experienced by nearby immotile cilia. Consequently, a weak asymmetry in fluid composition is converted into a much stronger mechanical signal, enabling reliable discrimination between left and right even when the flow itself is nearly symmetric. Assuming an initial leftward flow bias has already been established, our model provides a physically grounded downstream amplification mechanism linking flow-driven transport to mechanical sensing. By integrating concepts from fluid mechanics, rheology, and developmental biology, the theory reconciles several experimental observations and suggests new quantitative tests of how physical processes contribute to vertebrate LR symmetry breaking.

SUMMARY

Left-right (LR) symmetry breaking in vertebrates depends on a directional fluid flow generated in the embryonic LR organizer, yet how this flow is sensed remains unresolved. Mechanosensing and chemosensing models each capture part of the process but face key limitations when considered independently. Here, we introduce a minimal theoretical model of a downstream viscosity-mediated signal amplification mechanism that unifies these perspectives. In this framework, macromolecules secreted by LR organizer cells generate weak spatial variations in the material composition of the near-surface fluid, thereby locally modifying its rheological properties. Once a sufficiently viscous layer develops, it is entrained by the leftward nodal flow and significantly amplifies the drag and torque exerted on immotile perinodal cilia, enabling robust discrimination of flow direction even when flow magnitudes on the left and right are nearly identical. The model naturally incorporates macromolecule secretion, clarifies the complementary roles of motile and immotile cilia, and addresses several major shortcomings of existing mechanosensing and chemosensing proposals. Rather than explaining the origin of LR asymmetry, our theory provides a physically grounded mechanism by which weak flow-generated asymmetries can be mechanically amplified into a robust developmental signal.

INTRODUCTION

Chirality—an asymmetry between an object and its mirror image—has long captivated researchers across physics and biology.^{1,2} In living systems, it emerges at every scale: from chiral cortical flows in single cells³ to tissue-level processes such as left-right (LR) axis determination during embryonic development.^{4–8} Similar principles operate in plants as well, underscoring the ubiquity and biological significance of chirality.⁹

Biological symmetry breaking frequently arises from the intrinsic handedness of molecular motors and cytoskeletal assemblies.^{10–12} Among the most striking examples is LR axis determination in vertebrate embryos, which ensures the asymmetric positioning of internal organs. In these systems, LR specification is initiated by a symmetry-biasing event produced by the chiral beating of motile cilia. These cilia generate a unidirectional fluid flow at the LR organizer (LRO)—the embryonic structure where LR determination takes place.^{13,14} Although the downstream signaling cascade (Nodal-Lefty-Pitx2) is conserved across vertebrates,¹⁵ the upstream mechanism by which the leftward nodal flow is sensed and converted into a robust developmental signal remains incompletely understood.^{10,16–18} Recent reviews have emphasized that both chemosensory and mechanosensory hypotheses possess important experimental support but also unresolved conceptual and experimental challenges and that the question of how weak nodal flow is robustly transduced into LR identity remains open.^{18,19} Here, our objective is not to replace either proposal but to investigate a complementary downstream amplification mechanism that naturally integrates elements of both.

In the mouse, LR symmetry breaking occurs at the node, a transient LRO composed of centrally located pit cells with motile cilia and surrounding crown (perinodal) cells bearing immotile, “sensory” cilia. Tilted, clockwise-rotating motile cilia (~200 nm in diameter and ~4 μm long) generate a robust leftward flow across the node.²⁰ While this flow is known to be essential for LR specification,^{21,22} how it is detected by the perinodal cells remains controversial.

Two main classes of hypotheses have been proposed for flow sensing. (I) The mechanosensing model posits that sensory cilia on perinodal cells detect flow-induced mechanical stresses, potentially via mechanosensitive calcium channels such as Pkd2.^{23,24} (II) The chemosensing model suggests that leftward flow transports signaling macromolecules, such as nodal vesicular parcels, preferentially to the left margin, where they are absorbed and initiate downstream signaling.²¹

Both mechanisms have empirical support, yet they are often treated as mutually exclusive. Importantly, our objective is not to explain how the initial LR asymmetry is generated by the nodal flow but rather to investigate how a weak flow-generated asymmetry may be amplified into a robust mechanical signal. Here, we first highlight the key limitations of each model when considered in isolation and then present a minimal biophysical framework that integrates elements of both, demonstrating how their synergy provides a physically plausible downstream amplification mechanism for LR determination in the mouse node.

RESULTS

Limitations of the two existing models

We now highlight the key limitations of each proposal when considered in isolation.

Issues with proposal I (mechanosensing)

- I.1 : Analytical, computational, and experimental studies have shown that fluid-flow magnitudes above immotile cilia are nearly identical on the left and right sides of the node (Figure 1A).^{25–29} Consequently, the mechanical stresses transmitted to immotile cilia on either side should also be comparable, making it unclear how such stresses alone could provide a robust mechanism for LR asymmetry.
- I.2 : Fluid-dynamic analyses indicate that the flow generated by a single rotating cilium decays with the inverse cube of the distance.³⁰ Thus, the flow experienced by any given peripheral crown cell is dominated by contributions from only the nearest rows of motile cilia (Figure 1A). If flow magnitude were the sole relevant factor, it would be puzzling why the mouse node contains a large population of motile cilia concentrated at its center.

Issues with proposal II (chemosensing)

- II.1 : Node cells are known to secrete macromolecules, including polymers and vesicles^{22,31,32}; however, none have been identified as bona fide signaling molecules for LR determination.
- II.2 : This proposal does not assign a role to immotile cilia. Yet experiments show that LR determination can be triggered by mechanically pulling on immotile cilia,^{33,34} strongly suggesting that mechanical stimulation of these cilia is an integral part of the symmetry-breaking mechanism. Although immotile crown cilia are also well known to possess chemosensory capabilities, with their geometry substantially enhancing molecular capture efficiency,³⁵ any successful model should explain the experimentally established mechanosensory role of these cilia. This is precisely the role assigned to them in the mechanism proposed here.

Together, these limitations indicate that neither proposal alone can fully account for LR symmetry breaking. We now show how a reliable LR symmetry-determining mechanism emerges by integrating key elements of both models.

A two-fluid model

The present work focuses on the final stage of LR symmetry breaking: how a weak flow-generated asymmetry is converted into a robust mechanical signal capable of activating the immotile crown cilia. Rather than modeling the biochemical processes that establish this initial asymmetry, we adopt a phenomenological description in which it is represented by a near-surface region with modified rheological properties. Our goal is to determine whether such a rheological asymmetry can robustly amplify the mechanical stimulus experienced by the crown cilia.

Our model is motivated by three well-established experimental observations: (1) nodal cells secrete macromolecules into the fluid environment; (2) an approximately constant leftward

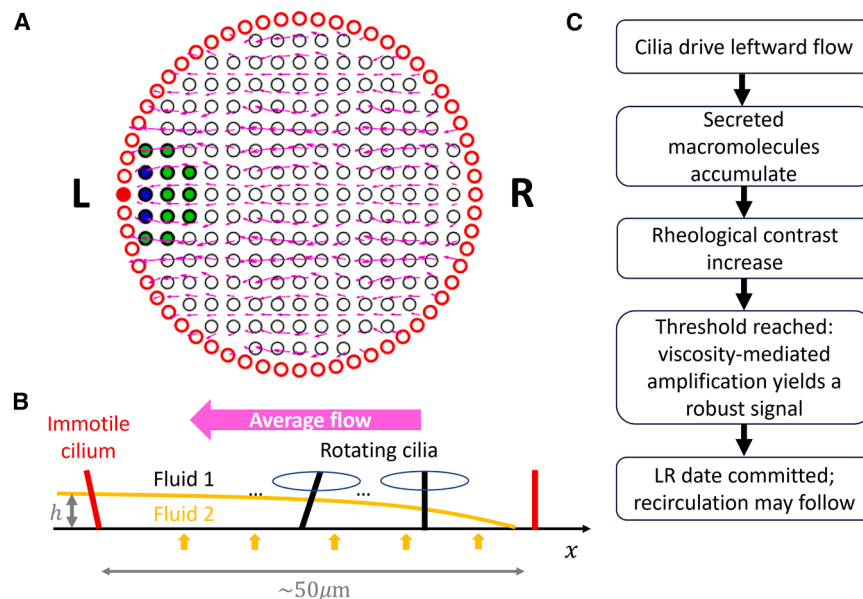


Figure 1. Schematics of the mouse node, the organizer that establishes vertebrate LR asymmetry

(A) Top view. The mouse node ($\sim 50 \mu\text{m}$ in diameter) is represented by 177 cells ($\sim 3 \mu\text{m}$ each, black circles) bearing motile cilia that are posteriorly tilted and rotate clockwise, collectively generating a leftward fluid flow (magenta streamlines). The motile cilia are surrounded by crown cells bearing immotile sensory cilia (red circles), which detect the resulting flow. Because the flow generated by each motile cilium decays rapidly with distance, the local flow experienced by an immotile cilium is dominated by nearby motile cilia. For the highlighted leftmost crown cell, for example, 82% of the flow originates from the three nearest motile cilia (blue), and 98% from the blue and green cilia combined.

(B) Side view. Motile cilia (black) are located on pit cells in the center of the node, whereas immotile sensory cilia (red) reside on the surrounding crown cells. Recent experiments have shown that nodal cells secrete macromolecules (orange arrows). In our model, these secretions generate a near-surface, high-viscosity layer (fluid 2, thickness h)

adjacent to the tissue on the left side. This viscous layer is entrained by the leftward flow and increases the hydrodynamic drag on left immotile cilia relative to those on the right.

(C) Proposed temporal sequence. Leftward nodal flow first establishes a weak flow-induced asymmetry in the distribution of secreted macromolecules. Continued secretion progressively enhances the local rheological contrast until a threshold is reached, at which point the viscosity-mediated amplification mechanism rapidly converts the weak asymmetry into a robust mechanical signal that specifies LR identity. Any subsequent recirculation or homogenization occurs only after this developmental decision has been made.

flow exists above the cilia; and (3) mechanical pulling of immotile cilia on peripheral crown cells is sufficient to trigger the downstream signaling cascade specifying the “left” direction.

Building on these observations, we introduce two additional assumptions:

Assumption 1: High-viscosity near-surface layer. Secreted macromolecules locally increase the viscosity of the fluid adjacent to the tissue surface. In our minimal model, this region is represented as a high-viscosity fluid layer (fluid 2, Figure 1B) beneath the lower viscosity bulk fluid (fluid 1). For analytical simplicity, we represent this rheological heterogeneity as a distinct layer with a sharp interface. This idealization is not essential to the amplification mechanism. As shown below for a linear viscosity profile, a continuously varying viscosity that decreases linearly from the tissue surface to the bulk fluid also amplifies the torque whenever the near-surface viscosity exceeds the bulk viscosity. The sharp two-layer model should therefore be viewed as a convenient minimal representation of a more general rheological gradient, although the quantitative magnitude of the amplification depends on the detailed viscosity profile.

Assumption 2: Coupled two-phase flow. The high-viscosity layer is entrained leftward by the overlying bulk flow generated by the motile cilia. This model therefore describes a downstream stage of LR determination, after the nodal flow has established a weak spatial asymmetry in the distribution of secreted macromolecules.

The proposed sequence of events is illustrated schematically in Figure 1C. Motile cilia first establish the leftward nodal flow, which progressively generates a weak spatial asymmetry in the material composition of the near-surface fluid through

the continued secretion and transport of macromolecules. These macromolecules are not themselves the developmental signal; rather, they modify the local rheology, producing a viscosity contrast that amplifies the mechanical stimulus acting on the immotile crown cilia. Once this amplification exceeds the threshold required for mechanosensation, LR identity is specified.

A natural question is whether recirculation within the closed nodal cavity would eventually erase this rheological asymmetry. We do not expect the mechanism to require a long-lived steady state. Instead, it relies on a transient window during which rheological contrast develops faster than it is homogenized by mixing. Provided this condition is met, the amplified mechanical signal can specify LR identity before recirculation substantially reduces the contrast. Subsequent homogenization is therefore not expected to affect the developmental decision once it has been made. Importantly, this developmental commitment must precede the earliest detectable asymmetric gene expression, which represents a downstream transcriptional readout of the preceding physical and signaling events.^{4,17}

Together, these ingredients give rise to a simple emergent mechanism: macromolecules secreted by nodal cells locally modify the rheology of the near-surface fluid, enabling leftward flow to generate an amplified mechanical stimulus on immotile cilia. As shown below, this “viscous amplification” mechanism reconciles existing observations and provides a simple, robust explanation for LR symmetry breaking.

Having established the biological and physical setting of the model, we now focus on the fluid dynamics underlying the proposed amplification mechanism. Our aim is to isolate the

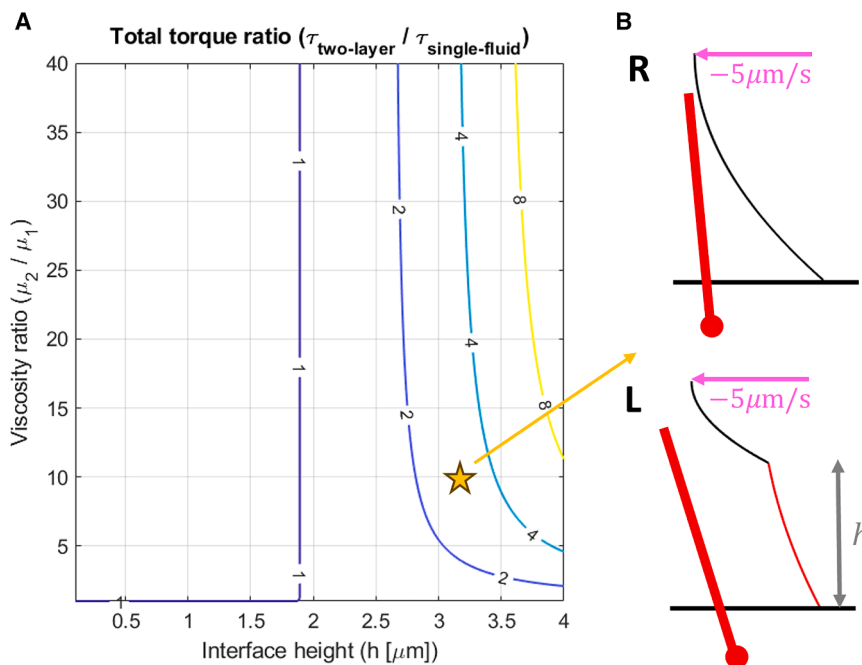


Figure 2. Contour plot of the ratio of total torque experienced by left versus right immotile cilia

(A) The torque ratio is plotted as a function of the viscosity ratio between the two fluid layers (vertical axis) and the thickness h of fluid 2 at the left periphery of the node (horizontal axis; see Figure 1B). In this idealized one-dimensional representation, the flow speed $5\mu\text{m}$ above the tissue surface is fixed at $-5\mu\text{m/s}$ (negative indicates leftward flow), with a no-shear boundary condition.

(B) On the right periphery, the flow reduces to a standard half-Poiseuille profile (top of B). On the left, a two-phase flow forms with viscosities μ_1 (top layer) and μ_2 (bottom layer) (bottom of B). Although the higher viscosity of fluid 2 slows its flow (red profile), drag is proportional to the product of viscosity and velocity, so the net torque on left immotile cilia can exceed that on the right. For instance, when $h = 3.2\mu\text{m}$ and $\mu_2/\mu_1 = 10$ (yellow star), the torque is amplified by around 3-fold due to the additional viscous layer, with the corresponding flow profiles shown in (B).

essential physics of viscosity-mediated amplification, rather than to construct a complete developmental model of the mouse node.

To elucidate the mechanism as transparently as possible, we consider a simplified geometry: (1) we reduce the system to a one-dimensional description along the LR axis, and (2) we quantify the flow-induced drag acting on immotile cilia located on perinodal cells at the left and right boundaries.

For the fluid dynamics, we impose boundary conditions consistent with previous computational and experimental studies: a no-slip condition at the tissue surface and a uniform leftward flow at a short distance above the cilia. The latter is implemented as a no-shear boundary at height $H = 5\mu\text{m}$ above the tissue surface.

The present analysis considers the experimentally established time-averaged leftward nodal flow generated collectively by the rotating motile cilia. Although the flow immediately adjacent to an individual cilium is oscillatory, these high-frequency oscillations average to the persistent leftward transport observed across the node. We therefore model the overlying flow by its mean velocity, which is expected to dominate the net mechanical cue responsible for LR specification.

For a homogeneous single-phase fluid, these boundary conditions yield the standard half-Poiseuille velocity profile below height H (Figure 2B, top),

$$u(z) = \frac{U_{\text{top}}}{H^2} (z^2 - 2Hz), \quad (\text{Equation 1})$$

where U_{top} denotes the flow speed at height H .

When a second fluid layer is present near the tissue surface (fluid 2, viscosity μ_2), it is entrained by the leftward flow of the overlying fluid 1 (viscosity μ_1). Assuming that the fluid-fluid interface remains approximately parallel to the tissue surface, imposing continuity of velocity and shear stress at the interface,

and imposing a no-shear condition at $z = H$, we obtain an analytical expression for the velocity profile experienced by immotile cilia on the left side of the node (Figure 2B, bottom). Although this expression is fully analytical, it is lengthy and not particularly illuminating; we therefore relegate it to the [methods](#).

To quantify the mechanical signal generated by the flow, we use the torque exerted on immotile cilia as a proxy for LR-determining cues. This choice is motivated by experimental evidence that immotile cilia behave as hinged rods anchored approximately $1\mu\text{m}$ beneath the cell surface.³⁶ Although the model is deliberately minimal, we expect the existence of the proposed viscosity-mediated amplification mechanism to be robust to the specific modeling assumptions adopted.

Viscosity-mediated signal amplification

The model predicts a qualitative asymmetry in the mechanical environment experienced by immotile crown cilia. On the right, the cilia are exposed only to the homogeneous Poiseuille flow of fluid 1. On the left, however, they experience a two-layer flow consisting of a slow but more viscous near-surface layer (fluid 2) beneath the faster moving bulk fluid (fluid 1). Although fluid 2 moves more slowly, the hydrodynamic drag depends on both velocity and viscosity. Consequently, the increase in viscosity can more than compensate for the reduction in flow speed, producing a larger drag and torque on left immotile cilia.

Figure 2 quantifies this effect by showing the ratio of the total torque acting on left and right immotile cilia as a function of the viscosity contrast and the thickness of fluid 2 at the left periphery. The analytical solution (Equation 31) shows that once the viscous layer exceeds a critical thickness, increasing either its viscosity or its thickness enhances the left/right torque ratio. Importantly, the amplification factor depends only on the

rheological contrast and the thickness of the near-surface layer and is independent of the absolute flow speed U_{top} . This follows because both the amplified and unamplified torques scale linearly with the imposed flow velocity, so their ratio remains unchanged. The proposed mechanism therefore provides a robust means of converting a weak rheological asymmetry into a strong LR-asymmetric mechanical signal. The existence of this amplification does not depend on the assumed sharp interface between the two fluids. In the [linear viscosity profile](#), we replace the piecewise-constant viscosity by a smooth profile that decreases linearly from η_2 at the tissue surface to η_1 at $z = H$. For the geometric parameters used here, the resulting torque exceeds the homogeneous-fluid value whenever $\eta_2 > \eta_1$ and increases monotonically with η_2/η_1 . Thus, while the detailed amplification factor depends on the spatial viscosity profile, the qualitative mechanism requires only a sufficiently extended region of enhanced near-surface viscosity, rather than a distinct fluid layer or a discontinuous viscosity jump.

The model also resolves several limitations of existing proposals. First, it is fully consistent with analytical, computational, and experimental evidence showing that the flow magnitude above immotile cilia is nearly identical on the left and right, thereby resolving issue I.1. Second, it explains why the large population of centrally located motile cilia is beneficial: collectively, they generate the leftward flow, while nodal cells provide the macromolecular secretion required to establish the rheological contrast, resolving issue I.2. At the same time, because the amplification factor is independent of the absolute flow speed, reducing the number of motile cilia lowers the baseline mechanical stimulus without reducing the degree of hydrodynamic amplification. The observation that as few as two motile cilia can establish LR asymmetry is therefore fully compatible with, and may even strengthen the case for, a downstream amplification mechanism. Third, the model removes the need for secreted macromolecules to function as signaling molecules; their role is simply to modify the local rheology, making their molecular identity irrelevant for LR determination, thereby resolving issue II.1. Finally, it identifies the immotile crown cilia as mechanosensors that detect the amplified torque generated by the viscous layer, resolving issue II.2.

DISCUSSION

The present work proposes a phenomenological amplification mechanism operating downstream of the well-established leftward nodal flow. Rather than addressing how the initial LR asymmetry is established, we investigate how a weak flow-generated asymmetry in the composition of the near-surface fluid can be converted into a robust mechanical cue. In this picture, chemosensing and mechanosensing are not competing hypotheses but complementary stages of a single transduction process.

Our two-fluid model provides a minimal physical framework for LR determination in the mouse node. Secreted macromolecules do not act as developmental signaling ligands; instead, they locally modify the rheology of the near-surface fluid, thereby amplifying the torque exerted by the leftward flow on immotile crown cilia. This viscous amplification enables reliable discrimination between left and right even when the flow magnitude above the cilia is nearly symmetric.

The model also clarifies the role of the centrally located motile cilia. Collectively, they generate the leftward flow, while nodal cells provide the macromolecular secretion required to establish the rheological contrast. Moreover, because the amplification factor depends on the rheological contrast rather than the absolute flow speed, reducing the number of motile cilia decreases the baseline mechanical stimulus without reducing the amplification itself. The observation that as few as two motile cilia are sufficient to establish LR asymmetry is therefore fully compatible with, and may even strengthen the motivation for, a downstream amplification mechanism capable of boosting weak mechanical signals.^{37,38} More generally, we expect the proposed mechanism to be robust to variations in flow strength, cilia geometry, the molecular identity of the secreted macromolecules, and the detailed form of the rheological profile, because the minimal model captures the essential physical ingredients underlying the amplification process. In particular, [linear viscosity profile](#) shows that replacing the sharp two-fluid interface by a smooth linear viscosity gradient preserves the amplification. The precise torque ratio is profile dependent, but the mechanism itself requires only that the near-surface fluid be sufficiently more viscous than the bulk over an appreciable fraction of the cilium length.

Finally, the present work proposes a physically grounded, testable hypothesis for a downstream amplification mechanism and should be viewed as a proof of principle rather than a complete developmental model. The proposed mechanism requires only a transient rheological asymmetry during the developmental window in which LR identity is specified, after which subsequent recirculation is not expected to alter the developmental outcome.

The persistence of this transient rheological asymmetry will depend on the transport properties of the secreted macromolecules, including their Péclet number, adsorption kinetics, and interactions with the tissue surface. Depending on the values of these parameters, homogenization by recirculation may be substantially delayed, thereby extending the temporal window over which viscosity-mediated amplification can operate.

A quantitative assessment will require a coupled transport-rheology model incorporating secretion, transport, adsorption, recirculation, and the evolution of local rheological properties. Extending the analysis to realistic three-dimensional node geometries and incorporating the oscillatory flow generated by rotating cilia will likewise be important for establishing the quantitative robustness of the mechanism. Experimentally, direct measurements of the composition, spatial distribution, and rheology of the near-surface fluid would provide particularly valuable tests of the proposed viscous-amplification mechanism.

METHODS

The analytical methods and hydrodynamic derivations used in this study are provided in this section.

Physical setup

We consider steady, planar, laminar flow in a fluid with two regions of different effective viscosities separated by an idealized sharp interface located at $z = h$ ($0 < h < H$). The lower region occupies $0 \leq z \leq h$ and has viscosity μ_2 , while the upper region occupies $h \leq z \leq H$ and has viscosity μ_1 . We

nondimensionalize by the bulk viscosity, setting $\mu_1 \equiv 1$ and defining the viscosity ratio $\mu = \mu_2/\mu_1$.

The tissue surface at $z = 0$ satisfies the no-slip condition. At the upper boundary $z = H$, corresponding to the experimentally measured mean flow above the cilia, we prescribe the mean leftward flow speed and impose vanishing shear,

$$u(H) = U, \quad u'(H) = 0, \quad (\text{Equation 2})$$

where $U = -U_{\text{top}} < 0$ denotes the signed velocity of the mean leftward flow.

Governing equations and general solution

In each layer, the steady Stokes equation reduces to

$$\mu(z) \frac{d^2 u}{dz^2} = \frac{\partial p}{\partial x} \equiv G, \quad (\text{Equation 3})$$

where $\mu(z) = \mu$ for $0 \leq z \leq h$ and $\mu(z) = 1$ for $h \leq z \leq H$, and G is constant (uniform pressure gradient). Therefore the velocity profiles are quadratic in z :

$$u_1(z) = a z^2 + b z + c, \quad h \leq z \leq H, \quad (\text{Equation 4})$$

$$u_2(z) = d z^2 + e z, \quad 0 \leq z \leq h, \quad (\text{Equation 5})$$

where the no-slip boundary condition at $z = 0$ has been imposed. Further, the second derivatives are

$$u_1''(z) = 2a, \quad u_2''(z) = 2d. \quad (\text{Equation 6})$$

From $\mu u_2'' = u_1'' = G$, it follows that

$$a = \mu d. \quad (\text{Equation 7})$$

Boundary and interface conditions

We impose the following boundary and interface conditions:

$$\text{No slip at } z = 0: u_2(0) = 0, \quad (\text{Equation 8})$$

$$\text{Velocity at } z = H: u_1(H) = U, \quad (\text{Equation 9})$$

$$\text{Zero shear at } z = H: u_1'(H) = 0, \quad (\text{Equation 10})$$

$$\text{Velocity continuity at } z = h: u_1(h) = u_2(h), \quad (\text{Equation 11})$$

$$\text{Shear - stress continuity at } z = h: \mu u_2'(h) = u_1'(h). \quad (\text{Equation 12})$$

Since

$$u_1'(z) = 2az + b, \quad u_2'(z) = 2dz + e, \quad (\text{Equation 13})$$

shear-stress continuity with $a = \mu d$ implies

$$b = \mu e. \quad (\text{Equation 14})$$

Velocity continuity determines c as

$$\begin{aligned} c &= u_2(h) - a h^2 - b h = d h^2 + e h - \mu d h^2 - \mu e h \\ &= (1 - \mu) (d h^2 + e h). \end{aligned} \quad (\text{Equation 15})$$

Enforcing $u_1(H) = U$ then yields a linear equation for d and e :

$$\mu d H^2 + \mu e H + c = U \quad (\text{Equation 16})$$

$$\Rightarrow \mu d H^2 + \mu e H + (1 - \mu) (d h^2 + e h) = U. \quad (\text{Equation 17})$$

The zero-shear condition at the upper boundary gives

$$2aH + b = 0. \quad (\text{Equation 18})$$

Using $a = \mu d$ and $b = \mu e$ therefore yields

$$e = -2Hd. \quad (\text{Equation 19})$$

Substituting this relation into Equation 17 gives

$$d = -\frac{U}{D}, \quad e = \frac{2UH}{D}, \quad (\text{Equation 20})$$

where

$$D = H^2 + (\mu - 1)(H - h)^2. \quad (\text{Equation 21})$$

Further,

$$a = \mu d = -\frac{\mu U}{D}, \quad b = \mu e = \frac{2\mu UH}{D}, \quad (\text{Equation 22})$$

$$c = \frac{(\mu - 1) U h (h - 2H)}{D}. \quad (\text{Equation 23})$$

Two-phase velocity profiles

The distinct two-layer velocity profiles are thus

$$\begin{aligned} u_1(z) &= \left(-\frac{\mu U}{D}\right) z^2 + \left(\frac{2\mu UH}{D}\right) z + \frac{(\mu - 1) U h (h - 2H)}{D}, \\ &h \leq z \leq H, \end{aligned} \quad (\text{Equation 24})$$

$$u_2(z) = \left(-\frac{U}{D}\right) z^2 + \left(\frac{2UH}{D}\right) z, \quad 0 \leq z \leq h. \quad (\text{Equation 25})$$

Total torque exerted on an immotile slender rod

We assume that the immotile cilium is approximately perpendicular to the flow direction. The local hydrodynamic drag per unit length is therefore dominated by transverse drag:

$$f_x(z) \approx \xi u(z), \quad (\text{Equation 26})$$

where ξ is the transverse drag coefficient per unit length.

For a slender rod of length L and radius r_c , the transverse drag coefficient per unit length is proportional to the local fluid viscosity. Within a local resistive-force approximation, we neglect variations in the geometric drag factor along the cilium and write

$$\xi_i \simeq C_{\perp} \mu_i \quad (\text{Equation 27})$$

where $C_{\perp}$ is a dimensionless geometric factor that depends weakly on the cilium aspect ratio and hydrodynamic boundary conditions. Since the same cilium spans both fluid layers, we take $C_{\perp}$ to be the same in the two regions. Consequently,

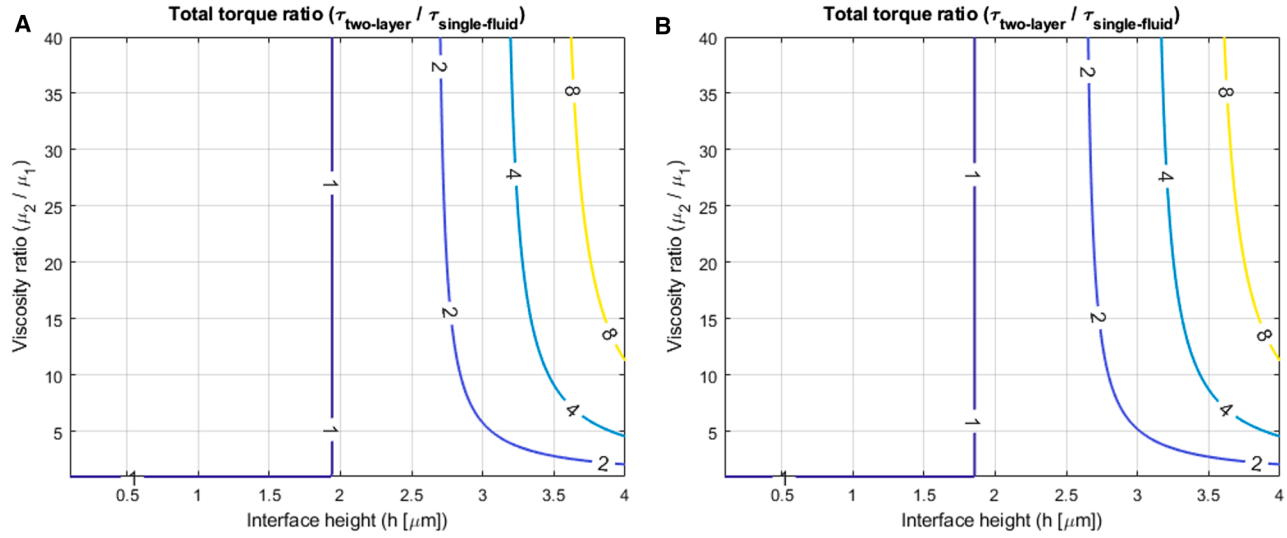


Figure 3. Torque amplification is robust to variations in cilium hinge depth

Contour plot of the ratio of total torque experienced by left versus right immotile cilia as in Figure 2A, but for different values of ℓ —the distance of the cilium hinge from the cell surface. (A) $\ell = 0.5 \mu\text{m}$, (B) $\ell = 1.5 \mu\text{m}$.

$$\frac{\xi_2}{\xi_1} = \frac{\mu_2}{\mu_1} = \mu. \quad (\text{Equation 28})$$

In what follows, we consider the experimentally relevant regime

$$0 < h \leq L, \quad (\text{Equation 29})$$

for which the interface intersects the immotile cilium. The contour plots in Figure 2 are computed entirely within this range.

In a two-layer flow, the total torque about the hinge point (at a distance ℓ below the cell surface about the y axis) due to the distributed force is

$$\tau_{\text{two-layer}} = \xi_2 \int_0^h (z + \ell) u_2(z) dz + \xi_1 \int_h^L (z + \ell) u_1(z) dz. \quad (\text{Equation 30})$$

Since we are interested in the amplification effect of a two-layer flow, we will consider the ratio of the total torque in the two-layer flow to that in the homogeneous single-fluid flow. Using our expression for flow profiles, the ratio $\tau_{\text{two-layer}}/\tau_{\text{single-fluid}}$ is

$$\frac{\tau_{\text{two-layer}}}{\tau_{\text{single-fluid}}} = \frac{H^2 [B + (\mu - 1)Q]}{DB}, \quad (\text{Equation 31})$$

where

$$B = L^2(12H\ell + 8HL - 4\ell L - 3L^2), \quad (\text{Equation 32})$$

and

$$Q = 8HL^3 + 12HL^2\ell - 12HL^2h - 24HL\ell h + 24H\ell h^2 + 12Hh^3 - 3L^4 - 4L^3\ell + 6L^2h^2 + 12L\ell h^2 - 12\ell h^3 - 6h^4. \quad (\text{Equation 33})$$

The aforementioned expression is used to compute the contour plot in Figure 2A, with the following parameters: $H =$

$5 \mu\text{m}$, $L = 4 \mu\text{m}$, and $\ell = 1 \mu\text{m}$. The values for H and L are well documented from existing experiments. The value for ℓ (the distance between the hinge of the cilium and the cell surface) is an estimate. Since the hinge is likely located between the basal body and the nuclear membrane, we take ℓ to be $1 \mu\text{m}$.³⁶ However, the quantification shown in Figure 2A is relatively insensitive to what the actual value is, as shown in Figure 3.

Linear viscosity profile

To distinguish the continuously varying viscosity field considered here from the piecewise-constant viscosities μ_1 and μ_2 used above, we denote the viscosity in this section by $\eta(z)$. As an alternative to the sharp two-layer model, we consider a continuously varying viscosity that decreases linearly from the tissue surface to the bulk fluid,

$$\eta(0) = \eta_2, \quad \eta(H) = \eta_1, \quad (\text{Equation 34})$$

so that

$$\eta(z) = \eta_2 - \frac{\eta_2 - \eta_1}{H}z. \quad (\text{Equation 35})$$

The steady Stokes equation is

$$\frac{d}{dz} \left(\eta(z) \frac{du}{dz} \right) = G, \quad (\text{Equation 36})$$

where $G = \partial_x p$ is the constant pressure gradient.

Integrating once and imposing the no-shear condition

$$\left. \frac{du}{dz} \right|_{z=H} = 0, \quad (\text{Equation 37})$$

gives

$$\eta(z) \frac{du}{dz} = G(z - H), \quad (\text{Equation 38})$$

or

$$\frac{du}{dz} = G \frac{z - H}{\eta(z)}. \quad (\text{Equation 39})$$

Introducing

$$A(z) = \int_0^z \frac{s - H}{\eta(s)} ds, \quad (\text{Equation 40})$$

the velocity satisfying $u(0) = 0$ is

$$u(z) = GA(z). \quad (\text{Equation 41})$$

For the linear profile in Equation 35, the integral can be evaluated analytically. Defining

$$r = \frac{\eta_2}{\eta_1}, \quad \delta = r - 1, \quad x = \frac{z}{H}, \quad (\text{Equation 42})$$

one obtains

$$A(z) = -\frac{H^2}{\eta_1} \frac{\delta x - \ln\left(\frac{r}{r - \delta x}\right)}{\delta^2}, \quad (\text{Equation 43})$$

and therefore

$$A(H) = -\frac{H^2}{\eta_1} \frac{\delta - \ln r}{\delta^2}. \quad (\text{Equation 44})$$

Imposing the upper boundary condition

$$u(H) = U, \quad (\text{Equation 45})$$

where $U < 0$ is the signed mean leftward velocity, determines

$$G = \frac{U}{A(H)}, \quad (\text{Equation 46})$$

so that

$$u(z) = U \frac{A(z)}{A(H)}. \quad (\text{Equation 47})$$

Within the same local resistive-force approximation used above, the drag per unit length on the cilium is

$$f(z) = \xi(z)u(z), \quad (\text{Equation 48})$$

with

$$\xi(z) \simeq C_{\perp} \eta(z), \quad (\text{Equation 49})$$

where $C_{\perp}$ is the same geometry-dependent factor introduced above. The total torque about the hinge is therefore

$$\tau = C_{\perp} \int_0^L (z + \ell) \eta(z) u(z) dz. \quad (\text{Equation 50})$$

Introducing the dimensionless variables

$$\lambda = \frac{L}{H}, \quad \varepsilon = \frac{\ell}{H}, \quad (\text{Equation 51})$$

the torque relative to that in a homogeneous fluid of viscosity η_1 becomes

$$\frac{\tau}{\tau_0} = \frac{\int_0^{\lambda} (x + \varepsilon) [r - \delta x] \left[\delta x - \ln\left(\frac{r}{r - \delta x}\right) \right] dx}{(\delta - \ln r) \left[\frac{2\lambda^3}{3} + \varepsilon\lambda^2 - \frac{\lambda^4}{4} - \frac{\varepsilon\lambda^3}{3} \right]}. \quad (\text{Equation 52})$$

The remaining integral also admits an exact closed-form expression. Defining

$$y = r - \delta\lambda, \quad k = r + \delta\varepsilon, \quad (\text{Equation 53})$$

and

$$\Phi(t) = \frac{krt^2}{2} - \frac{(k+r)t^3}{3} + \frac{t^4}{4} - k \left[\frac{t^2}{2} \ln\left(\frac{r}{t}\right) + \frac{t^2}{4} \right] + \left[\frac{t^3}{3} \ln\left(\frac{r}{t}\right) + \frac{t^3}{9} \right], \quad (\text{Equation 54})$$

the amplification factor is

$$\frac{\tau}{\tau_0} = \frac{\Phi(r) - \Phi(y)}{(r - 1)^2(r - 1 - \ln r) \left[\frac{2\lambda^3}{3} + \varepsilon\lambda^2 - \frac{\lambda^4}{4} - \frac{\varepsilon\lambda^3}{3} \right]}. \quad (\text{Equation 55})$$

In the limit $r \rightarrow 1$, the apparent singularity is removable and

$$\lim_{r \rightarrow 1} \frac{\tau}{\tau_0} = 1, \quad (\text{Equation 56})$$

recovering the homogeneous-fluid result exactly.

For the parameters used throughout this work,

$$H = 5 \mu\text{m}, \quad L = 4 \mu\text{m}, \quad \ell = 1 \mu\text{m}, \quad (\text{Equation 57})$$

the corresponding dimensionless parameters are

$$\lambda = \frac{L}{H} = 0.8, \quad \varepsilon = \frac{\ell}{H} = 0.2. \quad (\text{Equation 58})$$

Evaluating Equation 56 for these parameter values yields

η_2/η_1	1	2	5	10	20
τ/τ_0	1	1.34	2.31	3.88	6.95

The continuous-viscosity model therefore predicts substantial hydrodynamic amplification even in the absence of a sharp interface. For a viscosity that decreases linearly from η_2 at the tissue surface to η_1 at $z = H$, the total torque acting on an immotile cilium exceeds that in a homogeneous fluid whenever $\eta_2 > \eta_1$. The amplification increases monotonically with the viscosity ratio, demonstrating that the proposed mechanism does not depend on either a discontinuous viscosity jump or a constant-viscosity near-surface layer but instead reflects the more general effect of a rheological gradient within the fluid.

RESOURCE AVAILABILITY

Lead contact

Requests for further information and resources should be directed to the lead contact, Chiu Fan Lee (c.lee@imperial.ac.uk).

Materials availability

This study did not generate new materials.

Data and code availability

All analytical results supporting this study are included in the article. No original code or datasets were generated.

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AUTHOR CONTRIBUTIONS

Conceptualization, C.F.L. and J.V.; methodology, C.F.L.; formal analysis, C.F.L.; writing – original draft, C.F.L. and J.V.; writing – review and editing, C.F.L. and J.V.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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