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Anjishnu Choudhury, Marcel Filoche, Neil Ribe, Nicolas Grenier, Georg F. Dietze

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A. Choudhury[1]†, M. Filoche[2,3], N. M. Ribe[1], N. Grenier[4] and G. F. Dietze[1]

[1]Université Paris-Saclay, CNRS, FAST, 91405, Orsay, France.

[2]Institut Langevin, ESPCI Paris, Université PSL, CNRS, 75005 Paris, France

[3]Institut Mondor de Recherche Biomédicale, INSERM-UPEC, CNRS, 94010 Créteil, France

[4]Université Paris-Saclay, CNRS, LISN, 91405, Orsay, France.

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We present numerical and analytical predictions of mucociliary clearance based on the continuum description of a viscoelastic mucus film, where momentum transfer from the beating cilia is represented via a Navier-slip boundary condition introduced by Bottier et al. (*PLoS Comp. Biol.*, **13**(7), 2017). Mucus viscoelasticity is represented via the Oldroyd-B model, where the relaxation time and the viscosity ratio have been fitted to experimental data for the storage and loss moduli of different types of real mucus, ranging from healthy to diseased conditions. We solve numerically the fully nonlinear governing equations for inertialess flow, and develop analytical solutions via asymptotic expansion in two limits: (i) weak viscoelasticity, i.e. low Deborah number; (ii) low cilia beat amplitude (CBA). All our approaches predict a drop in the mucus flow rate in relation to the Newtonian reference value, as the cilia beat frequency is increased. This relative drop increases with decreasing CBA and slip length. In diseased conditions, e.g. mucus properties characteristic of cystic fibrosis, the drop reaches 30% in the physiological frequency range. In the case of healthy mucus, no significant drop is observed, even at very high frequency. This contrasts with the deterioration of microorganism propulsion predicted by the low-amplitude theory of Lauga (*Phys. Fluids*, **19**(8), 2007), and is due to the larger beat amplitude and slip length associated with mucociliary clearance. In the physiological range of the cilia beat frequency, the low-amplitude prediction is accurate both for healthy and diseased conditions. Finally, we find that shear-thinning, modelled via a multi-mode Giesekus model, does not significantly alter our weakly-viscoelastic and low-amplitude predictions based on the Oldroyd-B model.

Key words:

1. Introduction

Mucociliary clearance (MCC) designates the transport of pulmonary mucus toward the trachea via the coordinated beating of cilia, which cover the epithelium within the first

† Email address for correspondence: anjishnu.choudhury@espci.fr

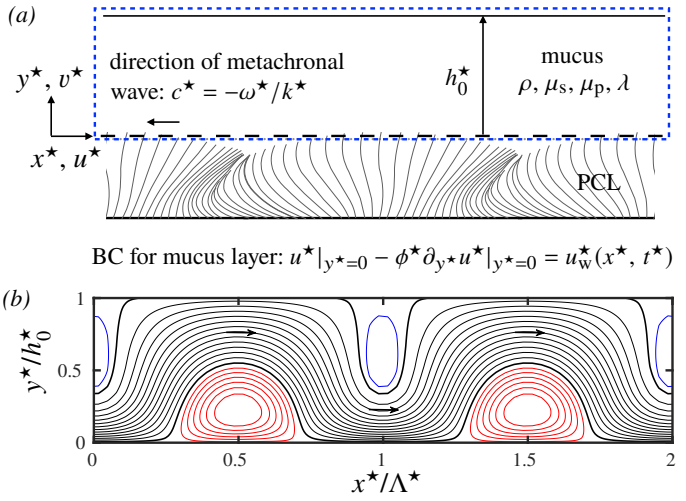

Figure 1: Continuum model of mucociliary clearance. (a) Schematic situating our model of the mucus layer (dashed blue frame) within the mucus/PCL bilayer system. Momentum transfer from the beating cilia is represented via a Navier condition (2.4*b*) applied at $y^\star$=0 (Bottier *et al.* 2017*a*), introducing the wave function: $u_w^\star = a^\star\omega^\star\cos(\theta) + \zeta\frac{1}{2}(a^\star)^2\omega^\star k^\star\,[1-\cos(2\theta)]$, with $k^\star = 2\pi/\Lambda^\star$, $\theta = kx + \omega t$, and $\omega = 2\pi f$; (b) flow structure within the mucus layer for viscoelastic mucus. DNS with the code `Basilisk`, using the Oldroyd-B model (2.2) and periodic boundary conditions: λ=52 ms, β=0.1, $h_0^\star$= 10 µm, $\Lambda^\star$=20 µm, $a^\star$=1.6 µm, $\phi^\star$ = 0, $f^\star$=10 Hz, $t^\star\omega^\star = 9\pi$. Streamlines in the laboratory reference frame.

16 airway generations of the human respiratory network. The cilia are organized in a dense brush-like array (Button *et al.* 2012) and immersed in a layer of low-viscosity Newtonian liquid, called the periciliary liquid (PCL), as shown in figure 1a. On top of the PCL layer lies a layer of viscoelastic mucus, which is responsible for capturing and evacuating alien particles and pathogens (Grotberg 2021). The non-symmetric beat cycle of individual cilia, composed of an active forward and a passive backward stroke, propagates in the form of a so-called antiplectic metachronal wave (Mitran 2007) with frequency $f^\star$, wavelength $\Lambda^\star$, and wave speed $c^\star$ (star superscripts designate dimensional variables throughout), which imparts momentum to the mucus layer and produces a net flow in the opposite direction (Bottier *et al.* 2017*a*). In the present manuscript, we study the effect of viscoelasticity on this net MCC flow, both under healthy conditions and in the case of pulmonary diseases that are known to exacerbate mucus viscoelasticity (Fahy & Dickey 2010), e.g. cystic fibrosis (CF), chronic obstructive pulmonary disorder (COPD), and bronchiectasis. According to Spagnolie (2015), the reason for reduced MCC in such diseases is an open question and there is a need for predictive models that evaluate clearance efficiency versus viscoelastic characterization. Relatively few studies have accounted for the viscoelastic nature of mucus (Vanaki *et al.* 2020; Sedaghat *et al.* 2023), which is imparted by mucins produced by goblet cells situated in the epithelium (Levy *et al.* 2014).

Smith *et al.* (2007) developed a three-layer model, where a thin *traction layer* was introduced between the PCL and mucus to account for the protrusion of cilia tips into the mucus layer (Fulford & Blake 1986). Mucus viscoelasticity was modelled via the linear Maxwell model, introducing the relaxation time λ. The authors reported a significant and non-monotonic variation of the net mucus flow rate with increasing λ. Owing to the use of the linear Maxwell model, the observed viscoelastic effect stems entirely from the traction layer. As we will show, viscoelastic corrections in the force-free mucus layer can enter the

problem only at $O(\mathrm{De}^2)$, where De denotes the Deborah number $\mathrm{De}=\lambda\omega^\star$, based on the angular frequency $\omega^\star=2\pi f^\star$. We go beyond this limitation by accounting for non-linearity in the constitutive model, allowing us to uncover the role of viscoelasticity within the mucus layer itself, where an intricate flow pattern of counter-rotating vortices develops (figure 1b).

Sedaghat *et al.* (2016) used the immersed boundary method (IBM) to simulate arrays of cilia beating within a layer of airway surface liquid (representing mucus and PCL). Viscoelasticity was described with the Oldroyd-B model, introducing the viscosity ratio $\beta=\mu_s/(\mu_s+\mu_p)$, where μ_s and μ_p denote the solvent and polymer viscosities. However, the authors used a cilia density of 0.1 cilia per μm^2 which is significantly lower than typical physiological values, i.e. 5-8 cilia per μm^2 (Bottier *et al.* 2017*a*). It was not clear from this study whether viscoelasticity helps or hinders MCC in real mucus.

In the current study, we analyze MCC via an inertialess continuum hydrodynamic model sketched in figure 1a. We focus only on the mucus layer of height $h_0^\star$, and model momentum transfer from the beating cilia via an experimentally-validated moving-carpet Navier-slip boundary condition (BC) applied at $y=0$ (Bottier *et al.* 2017*a*,*b*). This BC introduces a tangential wall velocity $u_w(x,t)$ that mimicks the metachronal wave. Mucus viscoelasticity is described with the Oldroyd-B model. Following Vasquez *et al.* (2016), we fit the model parameters, λ and β, to experimental mucus data for the storage and loss moduli G' and G'' (Hill *et al.* 2014).

We solve our continuum model via two approaches. Firstly, we perform direct numerical simulations (DNS) based on the full governing equations via the finite-volume solver `Basilisk` (Popinet & collaborators 2013–2020). Secondly, we derive analytical solutions for the stream function within the mucus film, based on asymptotic expansion in two different limits: (1) the weakly-viscoelastic limit ($\mathrm{De}\ll 1$), and (2) the limit of small cilia beat amplitude ($a\ll 1$). The low-amplitude expansion is inspired by Lauga (2007), who used this approach to investigate the effect of mucus viscoelasticity on the propulsion of microorganisms modelled as swimming sheets. As discussed in Lauga (2020), that problem is in some ways equivalent to the mucociliary transport problem considered here. However, there is one important difference. The discrete nature of the cilia, which are packed with some finite density, implies the existence of slip between the mucus and the imaginary envelope of the cilia tips. This effect is accounted for in the moving-carpet Navier BC used in the current manuscript, where we have set the slip length ϕ based on an empirical relation (Bottier *et al.* 2017*b*), linking ϕ to the cilia density. Accounting for slip represents an extension of the low-amplitude analytical solution of Lauga (2007), and we find that this effect is significant in the case of MCC. In contrast to the work of Man & Lauga (2015), who investigated the effect of wall slip on the propulsion of sheet-like microorganisms swimming in a Newtonian fluid, slip affects our problem only in the presence of viscoelasticity. This is because of the stress-free boundary condition imposed at the free surface, which implies zero average shear within the mucus layer in the Newtonian limit.

In terms of physical insights, we find that mucus elasticity significantly reduces MCC relative to the Newtonian limit, causing a drop in mucus flow rate that increases with increasing De, decreasing a, and decreasing slip-length ϕ. In the case of diseased mucus (characteristic of cystic fibrosis), we find a 30% reduction of MCC in the physiological frequency range, $f^\star\sim 10$ Hz. By contrast, Vasquez *et al.* (2016), who also applied a continuum approach but assumed a spatially-invariant (temporally-asymmetric) wall velocity $u_w(t)$, concluded that the mucus flow rate is insensitive to mucus rheology. It turns out that our account of the metachronal cilia wave via $u_w(x,t)$ is necessary for capturing the effect of viscoelasticity on MCC. Interestingly, a flow rate reduction also occurs in the limit of a zero-mean wall velocity $\bar{u}_w=\int_0^\Lambda u_w dx=\int_0^{1/f} u_w dt=0$. In that case, viscoelasticity produces a net

negative flow rate, i.e. in the direction of the metachronal wave, as a result of memory effects. This result contrasts with Stokes' second problem for viscoelastic liquids (Mitran *et al.* 2008; Ortín 2020), where $u_w = u_w(t)$ is spatially invariant and the net flow rate is zero, and it further underlines the importance of the metachronal wave in MCC. Past studies have shown that a change in the waveform underlying the swimming motion of sheet-like microorganisms (Riley & Lauga 2015) or the geometry of the swimmer itself (Angeles *et al.* 2021) can switch the effect of viscoelasticity from hindering to enhancing propulsion.

Although we mainly focus on the role of viscoelasticity by using the Oldroyd-B model, we have also checked the additional effect of shear-thinning, another known non-Newtonian property of mucus (Jory *et al.* 2022). For this, we have employed the Giesekus model, which accurately accounts for both viscoelasticity and shear-thinning properties of mucus (Vasquez *et al.* 2016; Sedaghat *et al.* 2022). We find that neither our low-amplitude nor our weakly-viscoelastic predictions are significantly affected by shear-thinning. This is due to the nature of the associated nonlinear terms in the Giesekus model, which are quadratic in the stresses and scaled by the Deborah number. As a result, shear-thinning is weak at small amplitudes and subordinate to viscoelasticity. We find that this leads to a qualitatively different MCC response versus a generalized Newtonian description of mucus via the Carreau model (Chatelin *et al.* 2017).

Our manuscript is structured as follows. In section 2, we introduce the governing equations constituting our mathematical model of MCC. Next, in section 3, we quantify the viscoelastic properties of the different types of mucus considered in our computations, as well as relevant kinematic parameters linked to MCC. Section 4 details the methods employed. In subsection 4.1, we derive analytical solutions for the mucus flow rate based on asymptotic expansion in different limits. In subsection 4.2, we describe the solver employed for our DNS. Results are presented in section 5, where we first focus on characterizing the effect of viscoelasticity on the mucus flow rate (subsection 5.1) by comparing with the Newtonian limit. Then, in subsection 5.2, we discuss the additional effect of shear-thinning via calculations based on the (multi-mode) Giesekus model. Conclusions are drawn in section 6, and the manuscript is completed by appendices A and B, where we have written out several expressions intervening in the analytical solutions derived in subsection 4.1.

2. Mathematical description

We consider a viscoelastic mucus layer of constant height $h_0^\star$ on the interval $y^\star{=}0$ to $y^\star{=}h_0^\star$, as sketched in Figure 1a. The mucus rheology is represented via the Oldroyd-B model, with solvent and polymeric viscosities μ_s and μ_p, and relaxation time λ. Both the Reynolds number $Re{=}\rho\, h_0^{\star 2}\omega^\star/\mu_s{\sim}10^{-3}$ and the capillary number $\mathrm{Ca}{=}\mu_s h_0^\star\omega^\star/\sigma{\sim}10^{-3}$, where ρ and σ denote the liquid mass density and surface tension, are small and thus we assume inertialess flow and a flat surface of the mucus layer (Smith *et al.* 2007). In this limit, the flow is governed by the (dimensionless) continuity and Stokes equations with additional polymeric viscous stresses τ_{ij}:

$$\partial_x u + \partial_y v = 0, \tag{2.1a}$$

$$0 = -\partial_x p + \left(\partial_{xx}u + \partial_{yy}u\right) + \partial_x \tau_{xx} + \partial_y \tau_{xy}, \tag{2.1b}$$

$$0 = -\partial_y p + \left(\partial_{xx}v + \partial_{yy}v\right) + \partial_x \tau_{xy} + \partial_y \tau_{yy}, \tag{2.1c}$$

where we have scaled lengths with $\mathcal{L}{=}h_0^\star$, velocities with $\mathcal{U}{=}h_0^\star\,\omega^\star$, and τ_{ij} as well as pressure p with $\mathcal{P}{=}\mu_s\mathcal{U}/\mathcal{L}$, using the angular frequency of the cilia beat cycle $\omega^\star$. The components of the polymeric stress tensor τ_{ij} are governed by the upper-convected Maxwell

(UCM) model:

$$\tau_{xx} + \mathrm{De}\left[\partial_t \tau_{xx} + u\partial_x \tau_{xx} + v\partial_y \tau_{xx} - 2\tau_{xx}\partial_x u - 2\tau_{xy}\partial_y u\right] = 2\frac{1-\beta}{\beta}\partial_x u, \tag{2.2a}$$

$$\tau_{xy} + \mathrm{De}\left[\partial_t \tau_{xy} + u\partial_x \tau_{xy} + v\partial_y \tau_{xy} - \tau_{xx}\partial_x v - \tau_{yy}\partial_y u\right] = \frac{1-\beta}{\beta}\left(\partial_y u + \partial_x v\right), \tag{2.2b}$$

$$\tau_{yy} + \mathrm{De}\left[\partial_t \tau_{yy} + u\partial_x \tau_{yy} + v\partial_y \tau_{yy} - 2\tau_{xy}\partial_x v - 2\tau_{yy}\partial_y v\right] = 2\frac{1-\beta}{\beta}\partial_y v, \tag{2.2c}$$

where we have scaled time with $\mathcal{T}=1/\omega^\star$, yielding the Deborah number $\mathrm{De} = \lambda\omega^\star$, and the viscosity ratio $\beta=\mu_s/(\mu_s+\mu_p)$. The system is closed with the following boundary conditions. At the film surface, $y=1$, we impose:

$$\partial_y u + \tau_{xy} = 0, \tag{2.3a}$$

$$v = 0, \tag{2.3b}$$

where we have assumed impermeability and neglected viscous stresses in the gas above the mucus layer. At the bottom boundary, $y=0$, we impose the Navier-slip boundary condition introduced by Bottier *et al.* (2017*b*) for modelling momentum transfer from the beating cilia:

$$u - \phi\partial_y u = u_w(x,t), \quad v = 0, \tag{2.4a}$$

where ϕ denotes the (dimensionless) slip length. Here, the cilia kinematics is represented via the wave function $u_w(x,t)$:

$$u_w(x,t) = a\cos(kx+t) + \zeta\frac{1}{2}a^2 k\left[1-\cos\{2(kx+t)\}\right], \tag{2.4b}$$

introducing the cilia beat amplitude a, and the metachronal wave number $k=2\pi/\Lambda$, where the dimensionless wavelength $\Lambda=\Lambda^\star/h_0^\star$, due to the scaling chosen, sets the aspect ratio of our geometry. Without loss of generality, we have phase shifted $u_w(x,t)$ by $\pi/2$ w.r.t. the classical formulation of Bottier *et al.* (2017*b*). The parameter ζ is a binary parameter that takes values $\zeta=0$ and $\zeta=1$, and can be used to deactivate the second and third RHS terms in (2.4*b*). In that limit, i.e. $\zeta=0$, the phase average $\bar{u}_w$ is zero, which, in the case of a Newtonian fluid, leads to a symmetrical cellular flow pattern (e.g. figure 2a). This reference case is convenient for illustrating the signature of viscoelasticity, which tends to break the symmetry of the flow field (e.g. figure 6e). The *moving carpet* boundary condition written in (2.4) has been validated versus particle image velocimetry (PIV) measurements in the vicinity of live beating cilia (Bottier *et al.* 2017*a*).

As a key observable in our study, we evaluate the net mucus flow rate q:

$$q = \int_0^1 u\,dy, \tag{2.5}$$

which is spatially invariant due to continuity and the flat-surface assumption, i.e. $\partial_x q = -\partial_t h = 0$, and time invariant due to the wave-nature of u_w (2.4*b*). In the Newtonian limit (subscript N), the governing equations become linear, and, thus, the flow field is a simple superposition of the solutions associated with the three terms in the wave function (2.4*b*). Because the phase-average of the two harmonic terms is zero, only the constant term contributes to the net flow, yielding:

$$q_N = \zeta q_{ref}, \quad \text{with} \quad q_{ref} \equiv \frac{1}{2}a^2 k, \tag{2.6}$$

Mucus type	G' (Pa)	G'' (Pa)	λ (ms)	β	$a^\star$ (µm)
HBE-2 *wt*%	0.02	0.179	3	0.4	5
HBE-3 *wt*%	0.12	0.3	10	0.19	4
HBE-4 *wt*%	0.3	0.5	16	0.13	3
HBE-5 *wt*%	9.09	2.98	52	0.002	1.6

Table 1: Human bronchial epithelium (HBE) mucus types and cilia beat amplitude $a^\star$ used in our simulations. Measurement data for G' and G'', ranging from healthy to diseased mucus, are taken at $f^\star \sim 10$ Hz from Hill *et al.* (2014). Oldroyd-B model parameters λ and β were fitted via (3.1), assuming $\mu_s = 1$ mPa·s.

which corresponds to a plug flow with wall velocity $u_w = \zeta a^2 k/2$. Throughout the paper, we will use q_N (and q_{ref}) as a reference value to quantify the effect of viscoelasticity.

3. MCC scenarios: mucus types and cilia parameters

Experimentally, the mechanical response of viscoelastic mucus is quantified via the complex modulus $G = G' + iG''$, containing the storage and loss moduli G' and G'', which are related to the parameters of the Oldroyd-B model according to Siginer (2014):

$$\frac{G'}{\mu_s \omega^\star} = \frac{(1-\beta)}{\beta} \frac{\lambda\omega^\star}{1+(\lambda\omega^\star)^2}, \quad \frac{G''}{\mu_s \omega^\star} = 1 + \frac{(1-\beta)}{\beta[1+(\lambda\omega^\star)^2]}. \tag{3.1}$$

We focus on four types of mucus corresponding to Human Bronchial Epithelial (HBE) cultures with varying mucin concentration (Hill *et al.* 2014), ranging from healthy patients (2 *wt*%) to patients diagnosed with CF or COPD (5 *wt*%). The properties of these mucus types are provided in table 1. We have assumed water as the solvent phase, i.e. $\mu_s = 1$ mPa·s, and fitted β and λ to experimental values of G' and G'' (Hill *et al.* 2014) at a representative cilia beat frequency $f^\star \sim 10$ Hz. Accounting for the frequency dependence of β and λ does not change our results significantly (as will be shown in figure 3a).

In the case of CF, the PCL layer is depleted in favor of the mucus layer, which can considerably reduce the mucus velocity imparted by the cilia (Guo & Kanso 2017). We account for this by adjusting the beat amplitude a in terms of the mucin concentration (see table 1), by interpolating between experiments for healthy mucus (Bottier *et al.* 2017*a*), $a^\star = 5$ µm, and diseased mucus (Bottier *et al.* 2022), $a^\star = 1.6$ µm.

Bottier *et al.* (2017*a*) established experimentally a relation between the cilia density and the slip length $\phi^\star$. We use a cilia density of 86% in our simulations, which is representative of the patient data reported in that reference, yielding a slip length of $\phi^\star = 10$ µm.

4. Methods

4.1. *Analytical solutions via asymptotic expansion*

We obtain analytical solutions for our boundary value problem (2.1)-(2.4) in two different limits: (i) small Deborah number (De$\ll$1), and (ii) small cilia beat amplitude ($a \ll 1$). For this, we introduce the stream function Ψ:

$$\partial_y \Psi = u, \quad -\partial_x \Psi = v, \tag{4.1}$$

to which we apply a regular perturbation expansion:

$$\Psi(x,y,t) = \Psi_0(x,y,t) + \epsilon\Psi_1(x,y,t) + \epsilon^2\Psi_2(x,y,t), \tag{4.2}$$

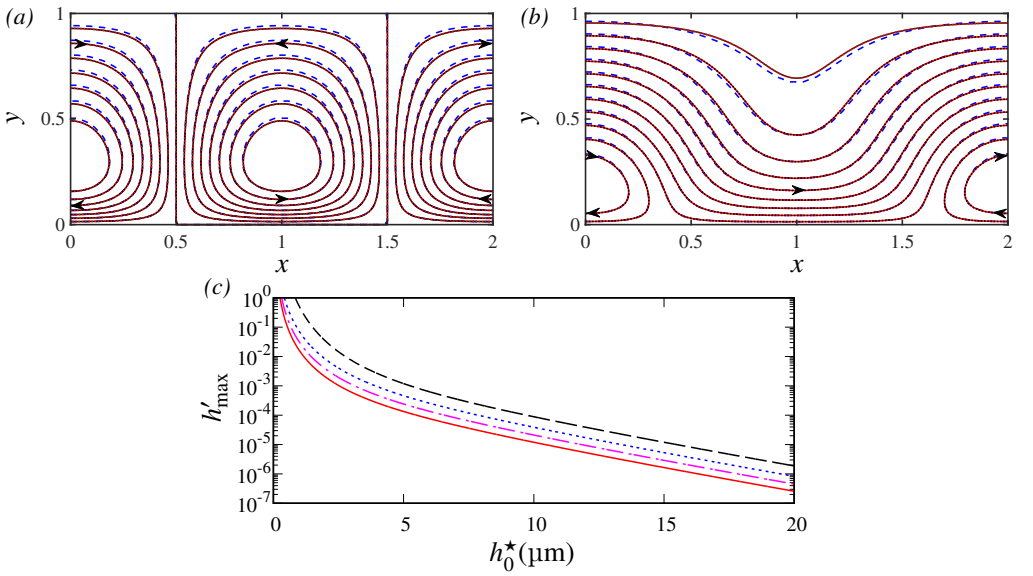

Figure 2: Flow structure within the mucus film. Newtonian limit: De=0, $\Lambda^\star$=20 μm. *(a,b)* Streamlines for two forms of the wave function (2.4*b*): $a^\star$=1.6 μm, $\phi^\star$=0, t=π. Solid red: analytical solution (4.3*a*), dashed blue: DNS using Δx=1/64, dotted black (almost perfectly overlapping solid red): DNS using Δx=1/128. *(a)* ζ=0: cellular flow pattern; *(b)* ζ=1: meandering flow; *(c)* estimation of maximum film surface deflection according to (4.5) for different values of the slip length $\phi^\star$: $a^\star$=5 μm, Ca=1×10^{-3}. Dashed: $\phi^\star$=0, dotted: $\phi^\star$=2 μm, dot-dashed: $\phi^\star$=5 μm, solid: $\phi^\star$=10 μm.

where the small parameter ϵ is either De or a, depending on the expansion considered. Then, introducing (4.2) into (2.1)-(2.4) and truncating appropriately, we may obtain Ψ_i order by order. We point out that Ψ_0 is the solution of the biharmonic equation, obtained by eliminating pressure from the truncated forms of (2.1*b*) and (2.1*c*) via cross differentiation.

In the weakly-viscoelastic limit, we expand in terms of ϵ=De and obtain at $O(\mathrm{De}^2)$:

$$\Psi_0(x,y,t) = \left[(A_1+B_1ky)e^{ky}+(C_1+D_1ky)e^{-ky}\right]\cos(kx+t)+\zeta A_2 y$$
$$+\zeta\left[(A_3+2B_3ky)e^{2ky}+(C_3+2D_3ky)e^{-2ky}\right]\cos\{2(kx+t)\}, \tag{4.3a}$$

$$\Psi_1(x,y,t) = 0, \tag{4.3b}$$

$$\Psi_2(x,y,t) = \Psi_H(x,y,t)+\Psi_P(x,y,t), \tag{4.3c}$$

where A_i, B_i, C_i, and D_i are integration constants, and $\Psi_H(x,y,t)$ and $\Psi_P(x,y,t)$ denote homogenous and particular solutions, which are all written out in appendix A, and in a supplementary Mathematica notebook. A simple relation for the flow rate q=$\Psi|_{y=1}$-$\Psi|_{y=0}$ can be obtained by considering (4.3) in the limit ζ=0:

$$\left.\frac{q}{q_{\mathrm{ref}}}\right|_{\zeta=0} = -(1-\beta)\mathrm{De}^2\frac{(S^2+6k\phi SC)}{(S+2k\phi C)^2}+O(\mathrm{De}^3), \tag{4.4}$$

where S=sinh(2k)-2k and C=cosh(2k)-1. We see that viscoelasticity enters at $O(\mathrm{De}^2)$, and constitutes a negative flow rate contribution. The full form of q/q_{ref} for ζ=1 is too long to be written here. Instead, we provide it in the supplementary Mathematica notebook. In the Newtonian limit (De=0), (4.2) reduces to Ψ_0, which we have plotted in figures 2a and 2b for

the reduced (ζ=0) and full (ζ=1) form of (2.4*b*), respectively. In the former case, the flow pattern is cellular (figure 2a), and, in the latter, it is meandering (figure 2b).

The leading-order solution Ψ_0 can also be used to estimate the deflection of the liquid-gas interface h':

$$h' = \mathrm{Ca}\left\{\frac{4a\cosh(k)}{S+2k\phi C} - \frac{4a^2k\zeta\cosh(2k)\cos(kx+t)}{S'+2k'\phi C'}\right\}\sin(kx+t), \tag{4.5}$$

where S'=sinh$(2k')-2k'$ and C'=cosh$(2k')-1$, introducing k'=$2k$. This relation is obtained by balancing the normal stress acting at our flat liquid-gas interface, y=1, with the capillary pressure jump of a deformable film surface, h=1+h':

$$p - 2\partial_y v - \tau_{yy} = -\mathrm{Ca}^{-1}\partial_{xx}h, \tag{4.6}$$

where we have neglected the gas stresses, then truncating at $O(\mathrm{De}^0)$, and substituting the leading-order solutions for Ψ (4.3*a*) and for p (4.7) into (4.6). The leading-order pressure, p_0, is obtained by integrating (2.1*c*) in y-direction and (2.1*b*) in x-direction, after having applied (4.2), truncated, and substituted (4.3*a*):

$$p_0 = 2e^{-2ky}k^2\sin(kx+t)\{e^{ky}(D_1+B_1e^{2ky}) + 8\zeta\cos(kx+t)(D_3+B_3e^{4ky}))\}, \tag{4.7}$$

where, without loss of generality, we have assumed $p_0(x{=}0, y{=}0, t){=}0$.

Figure 2c represents the maximum displacement $h'_{\max}$ obtained from (4.5) versus the dimensional film height $h_0^\star$, demonstrating that our flat-surface assumption ($\partial_x h{=}\partial_{xx}h{=}0$) is valid within the physiological film thickness range $h_0^\star$=5-20 µm, for the largest cilia beat amplitude considered, i.e. $a^\star$=5 µm.

In the low-amplitude limit, we expand (4.2) in terms of ϵ=a and seek a solution for the time-averaged stream function $\overline{\Psi}(y)$. For ζ=1, we obtain:

$$\overline{\Psi}(y) = a^2\overline{\Psi}_2(y) + O(a^3), \tag{4.8}$$

$$\overline{\Psi}_2(y) = \left(I_0 + I_1y + I_2y^2\right)e^{2ky} + \left(J_0 + J_1y + J_2y^2\right)e^{-2ky} + K_1y + K_2y^2,$$

where the constants I_i, J_i, and K_i are given in appendix B. Based on (4.8), we obtain the normalized flow rate:

$$\frac{q}{q_{\mathrm{N}}} = 1 - \frac{(1-\beta)\mathrm{De}^2(S^2+6\phi kSC)}{(1+\mathrm{De}^2)(S+2\phi kC)^2} + O(a^3). \tag{4.9}$$

In the no-slip limit ϕ=0, (4.9) collapses with equation (26) in Lauga (2007), which predicts the normalized swimming speed U/U_N of microorganisms represented as Taylor swimming sheets. In figure 3a, we have plotted the average mucus velocity $\bar{u}^\star$=$q^\star/h_0^\star$ based on (4.9) versus the cilia beat frequency $f^\star$. The dot-dashed and dashed red curves correspond to viscoelastic mucus, assuming constant (dot-dashed) or frequency-dependent (dashed) values of G' and G'', based on experimental data of Hill *et al.* (2014). Comparing these curves, we may conclude that our approximation to neglect the frequency-dependence of G' and G'' is reasonable in the considered frequency range. The solid black curve in figure 3a corresponds to the Newtonian limit (De=0), where $q^\star$ increases linearly with $f^\star$ (Blake 1973; Sedaghat *et al.* 2016). The exact relation underlying this curve is $q^\star$=$q_{\mathrm{N}}^\star$=$\pi a^{\star 2}kf^\star$, which follows from (2.6) upon re-dimensionalizing with the scale $\mathcal{UL}$=$h_0^{\star 2}\omega^\star$.

4.2. *Direct numerical simulation*

We solve numerically the fully nonlinear governing equations (2.1)-(2.4) on a periodic domain using the academic code `Basilisk`, which employs the log-conform approach

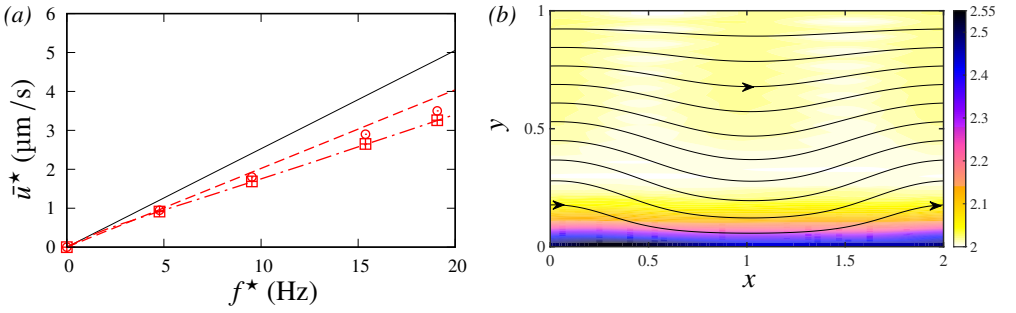

Figure 3: Features of the flow within a viscoelastic mucus layer: HBE-5wt% mucus, $h_0^\star$=10 µm, $\Lambda^\star$=20 µm, $a^\star$=1.6 µm, $\phi^\star$=10 µm. *(a)* Average mucus velocity $\bar{u}^\star=q^\star/h_0^\star$. Solid: Newtonian limit, dot-dashed: based on (4.9) with λ=52 ms, β=0.1, dashed: based on (4.9) with frequency dependent λ and β according to G' and G'' data in Hill *et al.* (2014), symbols: our DNS. Circles: Δx=1/32, squares: Δx=1/64, plus signs: Δx=1/128; *(b)* streamlines and contours of the trace tr($\mathbf{C}$) of the conformation tensor $\mathbf{C}$=De τ_{ij}+$\mathbf{I}$ based on the Oldroyd-B model: λ=52 ms, β=0.1, $f^\star$=19 Hz, t=9π.

(López-Herrera *et al.* 2019) for resolving the constitutive relations (2.2). It is a pressure-based solver, and thus the Poisson equation for the pressure is solved instead of (2.1a) to enforce continuity (Popinet 2015), using the boundary conditions $\partial_y p = 0$ at $y = 0$ and (4.6) at y=h, in the limit h=1. The same code was recently used by Romano *et al.* (2021) to investigate the effect of viscoelasticity on airway occlusion, and validated versus several relevant benchmarks. The code relies on a finite-volume spatial discretization, using the second-order upwind Bell–Collela–Glaz advection scheme (Bell *et al.* 1989). Time discretization is implicit for diffusion and explicit for advection terms, and the time step is adapted according to a CFL criterion. Our DNS were typically performed on a uniform quadtree grid, with grid size Δx=2^{-6}=1/64, and the time step was limited by a lower bound Δt=10^{-7}. A typical DNS run took 5-18 hours on 8 CPUs to reach a fully developed state (after 3-10 periods).

In figures 2a and 2b, we have included grid convergence results obtained with our DNS for the Newtonian reference case. Dashed blue curves correspond to a grid size of Δx=1/64, and dotted black curves to Δx=1/128. Agreement with our analytical predictions (solid red curves) according to (4.3a) is visually perfect for the fine grid and remains excellent for the reference grid. The same conclusion can be drawn from figure 3a, which confronts DNS using three different grids (symbols) with our low-amplitude asymptotic solution (dot-dashed curve) according to (4.9), for a viscoelastic mucus film.

Figure 3b represents streamlines for one of our DNS from figure 3a. In the same plot, we have represented contours of the trace tr($\mathbf{C}$) of the conformation tensor $\mathbf{C}$=Deτ_{ij}+$\mathbf{I}$ based on the Oldroyd-B model, where $\mathbf{I}$ is the identity matrix. The quantity tr($\mathbf{C}$) allows to gauge the polymer extension associated with our flow field. We find that the maximum value, observed near the cilia-mucus interface, is tr($\mathbf{C}$)$\sim$2.5, which implies a moderate fluid element extension relative to the Newtonian limit tr($\mathbf{C}$)=2. Thus, the Oldroyd-B model employed here is expected to behave well for our flow.

In our problem, the mucus viscosities μ_s and μ_p intervene only via β. Thus, the total viscosity μ=μ_s+μ_p can be chosen freely. For numerical convenience, we choose a low value μ=1 mPa·s, allowing us to limit the viscous-diffusion time scale. The log-conform approach is an effective remedy against numerical instabilities associated with large values of De (Fattal & Kupferman 2005), and we have encountered no such instabilities in our DNS. However, in our simulations of HBE-5wt% mucus, we needed to increase β from its target value β=0.002 to β=0.1, because of the degeneracy of the constitutive relations (2.2) in the

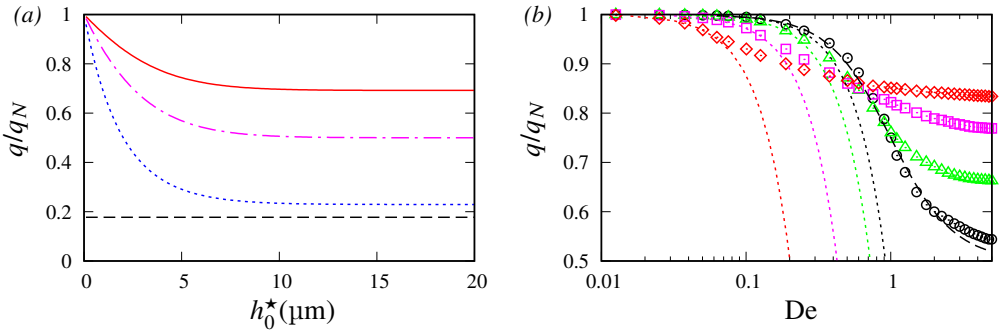

Figure 4: Effect of slip length ϕ and CBA a on the MCC flow rate of viscoelastic mucus: $\Lambda^\star$=20 μm. (a) Effect of slip-length: De=3, β=0.1. Low-amplitude prediction (4.9). Dashed: $\phi^\star$=0, dotted: $\phi^\star$=2 μm, dot-dashed: $\phi^\star$=5 μm, solid: $\phi^\star$=10 μm. (b) Effect of CBA: ϕ=0, β=0.5, $h_0^\star$=10 μm. Dotted: based on low-De prediction (4.3), dashed line: (4.9), symbols: DNS. Circles: $a^\star$=1.6 μm, triangles: $a^\star$=3 μm, squares: $a^\star$=5 μm, diamonds: $a^\star$=8 μm.

limit $\beta \to 0$. We have checked via (4.9) that this change in β has no appreciable effect on the MCC flow rate.

5. Results and discussion

Our main results are presented in subsection 5.1, where we focus solely on the effect of viscoelasticity. In subsection 5.2, we will discuss the additional implications of shear-thinning, which is another non-Newtonian property of mucus.

5.1. *Role of viscoelasticity*

We seek to quantify the effect of mucus viscoelasticity on MCC by comparing the actual flow rate q (2.5) to its Newtonian limit q_N. For this, we characterize the ratio q/q_N versus three control parameters of our problem, i.e. De, ϕ, and a. We start with figure 4 by establishing the effect of the slip length ϕ and beat amplitude a, in order to assess to what extent the no-slip low-amplitude theory of Lauga (2007) is applicable to the MCC problem studied here. Figure 4a shows predictions of q/q_N based on our low-amplitude solution (4.9) for different slip lengths ϕ and representative values of De and β. Firstly, we see that viscoelasticity can greatly reduce the MCC flow rate (q/q_N<1). Secondly, this effect is much larger in the no-slip limit (long dashes) than for realistic values of ϕ (solid curve). Thirdly, the no-slip limit cannot represent the q/q_N variation in terms of the film height $h_0^\star$.

Figure 4b represents the effect of the CBA a in the no-slip limit ϕ=0 via DNS data (symbols). We see that q/q_N becomes very small at the lowest CBA (circles, $a^\star$=1.6 μm), which corresponds to CF conditions. The low-amplitude analytical prediction (4.9) (black dashed curve) is able to accurately capture this scenario versus the DNS (open circles). By contrast, a significant discrepancy is observed for the CBA corresponding to healthy conditions (diamonds, $a^\star$=8 μm). Thus, the low-amplitude asymptotic expansion is not applicable in the entire physiological range of MCC, owing to potentially large values of CBA. The dotted curves in figure 4b represent our low-De solution (4.3). These show good agreement with the DNS for low values of De, but cannot predict the levelling off of q/q_N with increasing De. The deviation from the DNS data sets in at lower values of De the larger a becomes.

We now turn to the MCC scenarios characterized in table 1. If not otherwise mentioned, we use $h_0^\star$=10 μm, $\phi^\star$=10 μm, and $\Lambda^\star$=20 μm. Figures 5a and 5b represent DNS and analytical

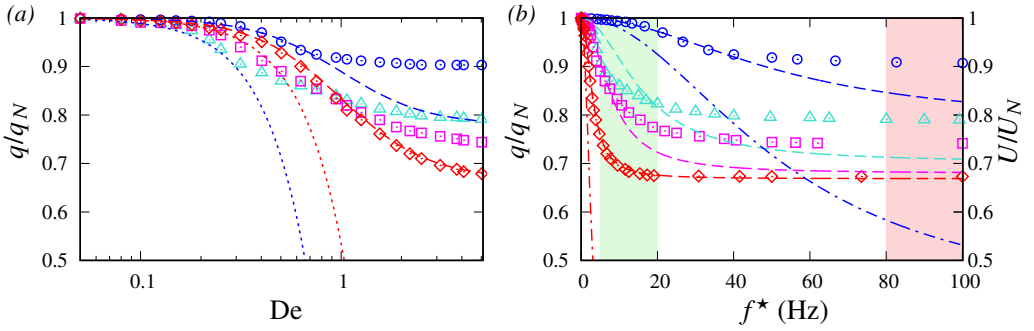

Figure 5: Viscoelasticity-induced flow rate reduction for mucus types from table 1: $\phi^\star$=10 µm, $h_0^\star$=10 µm, $\Lambda^\star$=20 µm. Symbols: DNS. Blue circles: HBE-2wt%, cyan triangles: HBE-3wt%, magenta squares: HBE-4wt%, red diamonds: HBE-5wt%, dotted lines: (4.3), dashed lines: (4.9). (a) Versus Deborah number De=$\lambda\omega^\star$; (b) versus cilia beat frequency $f^\star$. Dot-dashed lines (right ordinate): normalized swimming speed U/U_N of microorganisms according to Lauga (2007). Green/pink shaded regions mark frequency range for MCC and microorganism propulsion, respectively.

predictions of q/q_N for the four considered mucus types versus the Deborah number De and versus the cilia beat frequency $f^\star$, respectively. In the case of healthy mucus (HBE-2 wt%, blue circles), which is characterized by a rather small relaxation time λ, viscoelasticity reduces MCC only slightly ($q/q_N \sim 0.995 - 0.98$) within the physiological frequency range $f^\star$=5-20 Hz (green shaded region in figure 5b). This contrasts with the very significant reduction in the swimming speed U of non-ciliated microorganisms (dot-dashed blue curve), which operate at much greater frequencies ($f^\star > 80$ Hz, pink shaded region) and do not experience slip, as predicted by the theory of Lauga (2007). We point out however that particular types of swimming motions and swimmer geometries can lead to a viscoelasticity-induced increase of the swimming speed (Riley & Lauga 2015; Angeles *et al.* 2021).

In the case of mucus corresponding to CF conditions (HBE-5wt%, red diamonds in figure 5), which displays a much greater relaxation time λ, the MCC flow rate drops by as much as 30% versus the Newtonian limit. This is mainly due to the reduced CBA associated with CF conditions. Dashed curves in figure 5b represent our low-amplitude analytical prediction (4.9). Upon comparing these with our DNS data (symbols), we may conclude that the analytical prediction accurately captures q/q_N in the MCC frequency range for the healthy mucus (circles) and for the most unhealthy mucus (diamonds). However, significant deviations are observed for the intermediate mucus types (triangles and squares).

Next, we turn to the mechanism underlying the viscoelasticity-induced flow rate drop observed in figure 5. To this end, it is useful to reduce the problem to a simpler version by setting ϕ=0 and ζ=0 in (2.4b), which leads to $\bar{u}_w$=0. We have shown in figure 2a that the corresponding flow pattern in the Newtonian limit is cellular and symmetrical, and, consequently, q=q_N=0. Adding viscoelasticity, which we now know to affect the flow rate q, will thus cause a topological change in the flow field.

Figure 6a demonstrates via DNS data (symbols) that a similar flow rate reduction is observed for the reduced form of the wave function (2.4b), i.e. ζ=0 (squares), as compared to the full form, i.e. ζ=1 (circles). Further, the mucus flow rate q becomes negative for ζ=0, and this effect holds at arbitrarily low De. The effect is captured by our low-De solution (4.4), which is represented via a dotted blue curve in figure 6a. Figure 6b shows how viscoelasticity modifies the flow field in this limit, by plotting Ψ_0 and Ψ_2 according to (4.3). We see that the $O(\mathrm{De}^2)$ correction (dashed lines) causes a net flow to the left, which distorts the $O(\mathrm{De}^0)$ cellular flow pattern (solid lines) when superimposed on the latter. Figures 6c-6f display the

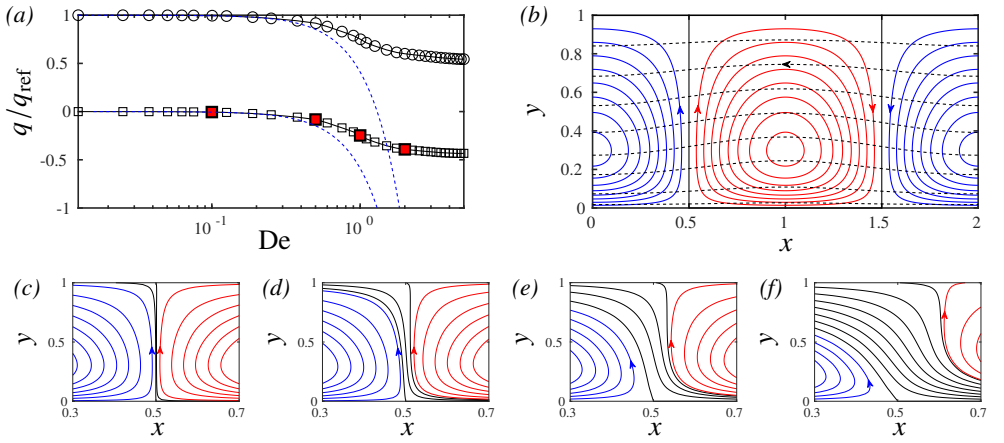

Figure 6: Change in flow topology within a viscoelastic mucus film under an increase of the cilia beat frequency: HBE-5 $wt\%$ (see table 1), ϕ=0, $a^\star$=1.6 µm, $\Lambda^\star$=20 µm, $h_0^\star$=10 µm. *(a)* Normalized flow rate for two forms of (2.4*b*). Circles: DNS for ζ=1, squares: DNS for ζ=0, dotted blue curves: low-De solutions based on (4.3); *(b)* Ψ_0 (solid) and Ψ_2 (dashed) according to (4.3): De=0.1; *(c-f)* streamlines from DNS corresponding to filled squares in panel *a*, showing the emergence of a negative meander (black lines) sandwiched between clockwise (red lines) and anti-clockwise (blue lines) vortices, as De is increased. *(c)* De=0.1; *(d)* De=0.5; *(e)* De=1; *(f)* De=2.

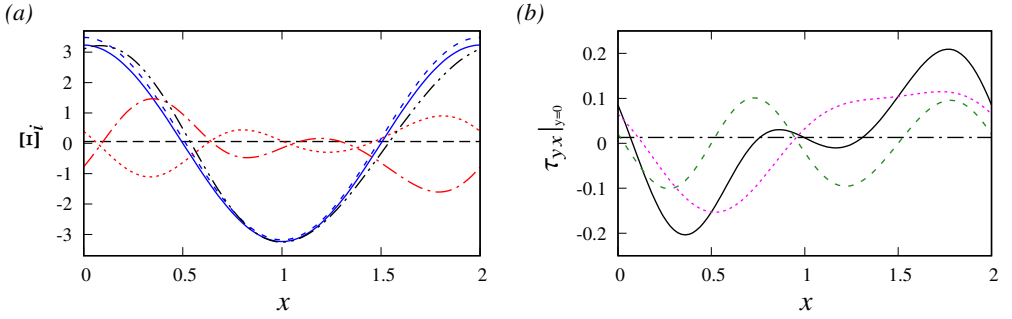

Figure 7: Mechanism underlying the negative meander in figure 6: ϕ=0, ζ=0, $h_0^\star$=10 µm, $\Lambda^\star$=20 µm, De=0.1. *(*a*)* Profiles of terms Ξ_i in the x-momentum equation (2.1*b*) evaluated at y=0, based on our low-De solution (4.3), and their phase averages $\overline{\Xi}_i$. Dashed: $\Xi_1=\partial_{xx}u+\partial_{yy}u$, $\overline{\Xi}_1$=0.18, solid: $\Xi_0=\Xi_1|_{\mathrm{De}=0}=\partial_{xx}u^{(0)}+\partial_{yy}u^{(0)}$, $\overline{\Xi}_0$=0, dotted: $\Xi_2=\partial_x\tau_{xx}$, $\overline{\Xi}_2$=0.004, dot-dashed: $\Xi_3=\partial_y\tau_{yx}$, $\overline{\Xi}_3$=-0.16, dot-dot-dashed: $\Xi_4=\partial_x p$, $\overline{\Xi}_4$=0.024 (long dashes); *(*b*)* polymeric wall shear stress τ_{xy}^{VE} according to (5.1). Solid: τ_{yx}^{VE}, $\overline{\tau}_{yx}^{\mathrm{VE}}$=0.013 (dot-dashed), dashed: τ_{yx}^{res}, $\overline{\tau}_{yx}^{\mathrm{res}}$=0.0003, dotted: τ_{yx}^{mem}, $\overline{\tau}_{yx}^{\mathrm{mem}}$=0.0127.

total flow field obtained from DNS for the points marked by filled symbols in figure 6a. We see that viscoelasticity causes a negative meander (as opposed to the positive meander observed in figures 1b and 2b), which winds between the counter-rotating vortices and increases in thickness as De is increased (from panels 6c to 6f). This negative meander transports mucus in the direction of the metachronal wave, i.e. in the negative x-direction, and, thus, the wrong direction from the point of view of MCC. It is associated with the $\cos(kx+t)$ term in the wall velocity u_{w} (2.4*b*), and, in the full MCC problem (ζ=1), it opposes the positive flow induced by the term with the form $a^2k/2$.

To unravel what causes the negative meander observed in figure 6, we analyze the different terms in the x-momentum equation (2.1*b*) evaluated at y=0, based on our low-De solution

(4.3) in the limit ζ=ϕ=0. Profiles of these terms, which we denote Ξ_i, are plotted in figure 7a, and their phase averages $\overline{\Xi}_i$ are given in the caption. The dashed blue curve represents the contribution of the solvent stresses Ξ_1=$\partial_{xx}u$+$\partial_{yy}u$, which allows to gauge the degree of symmetry of the flow field. This curve is shifted toward positive values compared to the Newtonian limit Ξ_0=$\Xi_1|_{\mathrm{De}=0}$=$\partial_{xx}u^{(0)}$+$\partial_{yy}u^{(0)}$ (solid blue curve, $\overline{\Xi}_0$=0), i.e. its phase average is non-zero ($\overline{\Xi}_1$=0.18), indicating a viscoelasticity-induced loss of symmetry. This is mainly caused by the contribution of the tangential polymeric stress Ξ_3=$\partial_y\tau_{yx}$ (dot-dashed red curve, $\overline{\Xi}_3$=-0.16), the contributions of the normal stress Ξ_2=$\partial_y\tau_{yx}$ (dotted red curve, $\overline{\Xi}_3$=0.004) and the pressure Ξ_2=$\partial_x p$ (dot-dot-dashed black curve, $\overline{\Xi}_2$=0.024) being weaker.

We focus next on the tangential polymeric stress at y=0:

$$\tau_{yx}\big|_{y=0} = \frac{1-\beta}{\beta}\,\partial_y u^{(0)}\Big|_{y=0} + \underbrace{\mathrm{De}\;\tau_{yx}^{(1)}\Big|_{y=0} + \mathrm{De}^2\;\tau_{yx}^{(2)}\Big|_{y=0}}_{\tau_{yx}^{\mathrm{VE}}} + O(\mathrm{De}^3), \tag{5.1a}$$

where τ_{yx}^{VE} is the viscoelastic contribution, which we decompose formally into a memory term τ_{yx}^{mem}, containing all time derivatives intervening through (2.2), and a residual term τ_{yx}^{res}, containing all other contributions:

$$\tau_{yx}^{\mathrm{VE}} \equiv \tau_{yx}^{\mathrm{mem}} + \tau_{yx}^{\mathrm{res}}. \tag{5.1b}$$

Figure 7b represents profiles of τ_{yx}^{VE} (solid black), τ_{yx}^{mem} (dotted magenta), and τ_{yx}^{res} (dashed green), and the corresponding phase averages are given in the caption. We see that $\overline{\tau}_{yx}^{\mathrm{VE}}$ is positive (dot-dashed black line, $\overline{\tau}_{yx}^{\mathrm{VE}}$=0.013), which corresponds to a negative tangential stress acting on the mucus, and that this non-zero phase average is mainly due to the memory term ($\overline{\tau}_{yx}^{\mathrm{mem}}$=0.0127). Thus, it is the memory terms in the viscoelastic constitutive relations (2.2) that causes a non-symmetrical stress distribution, breaking the symmetry of the cellular flow pattern observed in the Newtonian limit. We point out that τ_{xy}^{mem} contains time derivatives stemming from (2.2*a*) and (2.2*c*), due to the nonlinear terms in the upper-convected derivative.

5.2. *Additional role of shear-thinning*

It has been demonstrated by Jory *et al.* (2022) that mucus also exhibits a shear-thinning behavior over a considerable range of strain rate $\dot{\gamma}$, which we quantify via the second principal invariant of the deformation tensor $\mathbf{D}$:

$$\dot{\gamma} = D_{xx}D_{yy} - D_{xy}D_{yx}, \quad \mathbf{D} = D_{ij} = \frac{1}{2}\left\{\partial_{x_i}u_j + \partial_{x_j}u_i\right\}, \tag{5.2}$$

$$x_i = [x, y]^T, \quad u_i = [u, v]^T, \tag{5.3}$$

where we have used Einstein notation. In figure 8a, we have reproduced the steady-state rheometry data (open circles) measured by Jory *et al.* (2022) via a viscosity μ versus $\dot{\gamma}$ plot. The green shaded region marks the range of $\dot{\gamma}$ observed in one of our MCC computations from section 5.1, for which figure 8b represents streamlines and $\dot{\gamma}$ contours. Based on these data alone, one would expect the shear-thinning nature of mucus to greatly affect MCC in our configuration. However, the extent of this effect depends on how shear-thinning enters the constitutive relations for the viscous stresses.

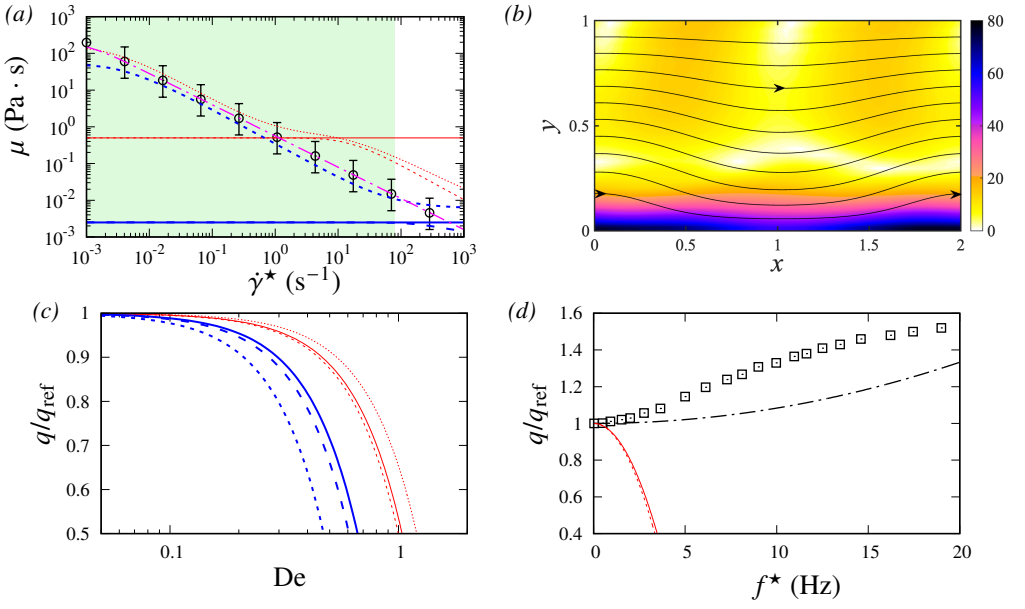

Figure 8: Additional effect of shear-thinning on MCC. *(a)* Steady-state stress-strain responses for constitutive models according to table 2. Total mucus viscosity μ versus strain rate $\dot{\gamma}^\star$ (5.2). Thin red curves: HBE-5$wt\%$, thick blue curves: HBE-2$wt\%$. Circles: experimental data of Jory *et al.* (2022), dot-dashed: Carreau-Yasuda model (5.6) with λ=1 × 10^3 s, μ_0=200 Pa · s, μ_∞=0, m=2, n=0.15, solid: Oldroyd-B, dashed: single-mode Giesekus, dotted: 5-mode Giesekus; *(b)* streamlines and contours of $\dot{\gamma}^\star$ for parameters according to figure 3b; *(c)* corresponding low-De predictions of MCC flow rate for the three viscoelastic models from panel *(a)*; *(d)* corresponding MCC flow rate for Carreau-Yasuda model (5.6) from panel *a*. Squares: DNS, dot-dashed: low-λ asymptotic solution, dashed/solid: Giesekus/Oldroyd-B predictions from panel *(c)*.

Vasquez *et al.* (2016) have shown that a five-mode Giesekus model is required to capture quantitatively both the viscoelastic and shear-thinning behavior of mucus:

$$\boldsymbol{\tau} = \sum_{m=1}^{N} \boldsymbol{\tau}_m, \quad \boldsymbol{\tau}_m + \mathrm{De}_m \left[\overset{\nabla}{\boldsymbol{\tau}}_m + \alpha_m \frac{1-\beta_m}{\beta_m} \boldsymbol{\tau}_m \cdot \boldsymbol{\tau}_m \right] = \frac{1-\beta_m}{\beta_m} \mathbf{D}, \tag{5.4a}$$

$$\overset{\nabla}{\boldsymbol{\tau}}_m = \partial_t \boldsymbol{\tau}_m + \boldsymbol{u} \cdot \nabla \boldsymbol{\tau}_m - (\nabla \boldsymbol{u})^T \cdot \boldsymbol{\tau}_m - \boldsymbol{\tau}_m \cdot \nabla \boldsymbol{u}, \tag{5.4b}$$

where N is the number of modes (N=5 for the 5-mode model), m is the mode index, De_m=$\lambda_m \omega^\star$, β_m=$\mu_s/(\mu_s + \mu_p^{(m)})$, and $\alpha_m \leqslant 0.5$ denotes the so-called mobility parameter. Here, we have used Gibbs notation for brevity, and the decoration ∇ denotes the upper-convected derivative. For N=1 and α=0, (5.4) reduces to the (single-mode) Oldroyd-B model (2.2), which is devoid of shear-thinning.

The shear-thinning property of mucus is imparted by the α_m term in (5.4). From the quadratic nature of this term, it is straightforward to show that it intervenes only at $O(a^4)$ in a low-amplitude expansion of the governing equations. Thus, our result in (4.9) remains unaltered when using a (single-mode) Giesekus constitutive model (5.4). The equivalence of the Oldroyd-B and Giesekus models in the low-a limit has been demonstrated by Lauga (2007), and we have confirmed it for our current configuration. As our low-amplitude predictions based on (4.9) in figure 5 (dashed curves there) agree very well with our DNS (symbols in figure 5) for the HBE-2 $wt\%$ (circles) and HBE-5 $wt\%$ (diamonds) mucus in the MCC frequency range, we may conclude that these results are unaffected by shear-thinning.

HBE	N	$[\beta'_1,\ldots,\beta'_N]$	$[\lambda_1,\ldots,\lambda_N]$ (s)	$[\alpha_1,\ldots,\alpha_N]$
5wt%	5	[64,32,3.2,0.3,0.03]$\times 10^{-2}$	[521,201,51,0.06,0.03]	[0.5,0.5,0.5,0.3,0.2]
2wt%	5	[9994,2,2,0.2,0.2]$\times 10^{-4}$	[1453,1.85,1.2,0.91,10^{-5}]	[0.01,0.1,0.1,0.5,0.5]
5wt%	1	[0.998]	[0.052]	[0.5]
2wt%	1	[0.6]	[0.003]	[0.5]
5wt%	1	[0.998]	[0.052]	[0]
2wt%	1	[0.6]	[0.003]	[0]

Table 2: Parameters according to (5.4) for the constitutive models underlying curves in figure 8c, i.e. 5-mode Giesekus, single-mode Giesekus, and Oldroyd-B models. The solvent viscosity is μ_s=1 $\times$ 10^{-3} Pa $\cdot$ s. All other parameters have been fitted to the complex modulus data of Hill *et al.* (2014), listed in table 1, and the shear-thinning rheology measured by Jory *et al.* (2022). The steady-state stress-strain responses of the three models are plotted in figure 8a.

We now consider the low-De limit. For this, we assume $\lambda_1 \geqslant \lambda_m$ in (5.4), and define $\mathrm{De}_m=\Pi_m \mathrm{De}$, where $\mathrm{De}=\lambda_1\omega^\star$ and $\Pi_m=\lambda_m/\lambda_1$. This allows us to apply the regular perturbation expansion (4.2) using $\epsilon=\mathrm{De}$. In the limit ζ=0, we obtain:

$$\left.\frac{q}{q_{\mathrm{ref}}}\right|_{\zeta=0} = -\mathrm{De}^2 \sum_{m=1}^{N} \beta'_m \Pi_m^2 \frac{(S^2+6k\phi SC)}{(S+2k\phi C)^2} + O(\mathrm{De}^3), \tag{5.5}$$

where $\beta'_m=\mu_{\mathrm{p}}^{(m)}/\left(\mu_{\mathrm{s}}+\sum_{m=1}^{N}\mu_{\mathrm{p}}^{(m)}\right)$. In the limit N=1, we obtain $\beta'_1=1-\beta_1$, and (5.5) reduces to our solution (4.4) obtained from the Oldroyd-B model (2.2). This is because the mobility parameters α_m do not enter (5.5), and, thus, shear-thinning plays no role, at least in the ζ=0 limit, which was considered in figures 6 and 7. The α_m do appear in the full analytical solution (ζ=1), which is too long to reproduce here. Instead, we plot this solution in figure 8c for parameters corresponding to HBE-2 wt% (thin blue curves) and HBE-5 wt% (thick red curves) mucus.

All curves in figure 8c represent low-De predictions of q/q_{N} for ζ=1. Dotted and dashed curves correspond to the Giesekus model (5.4) with N=5 and N=1, respectively, and solid curves to the Oldroyd-B model (2.2). The associated rheological parameters, β'_m, λ_m, and α_m, are given in table 2. These were fitted to recover the complex moduli G' and G'' in table 1 based on (3.1), and, in the case of the Giesekus model, additionally to recover the shear-thinning rheology measured by Jory *et al.* (2022), based on the *material functions* given in Bird *et al.* (1987). The steady-state μ versus $\dot{\gamma}$ relationships underlying the different curves in figure 8c are plotted in figure 8a using the same line styles. Whereas the total viscosity μ is constant for the Oldroyd-B model (solid curves in figure 8a), the 5-mode Giesekus model (dotted curves in figure 8a) reproduces the shear-thinning behavior displayed by the experimental data (open circles).

Comparing the dashed and solid curves in figure 8c, we may conclude that the shear-thinning nature of mucus does not significantly affect the MCC flow rate in the low-De limit. Thus, all our conclusions based on (4.3) in section (5.1) remain valid. This is due to the way in which shear-thinning enters the problem via (5.4), i.e. the α_m term there is multiplied by De_m. As a result, the shear-thinning property of mucus is enslaved to its viscoelastic nature. In that sense, the former effect is subordinate to the latter. In other words, shear-thinning only enters our MCC problem via viscoelasticity-induced perturbations of the flow field.

Of course, a final account of the role of shear-thinning requires full DNS based on the Giesekus model (5.4). In particular, this concerns the intermediate mucus types in figure 5, where neither the low-a nor the low-De predictions accurately follow the DNS within the MCC frequency range. Such new DNS are outside the scope of our manuscript, as they would require substantially modifying the `Basilisk` solver to implement the Giesekus model (5.4).

To emphasize the particular way in which shear-thinning enters the Giesekus model, we compare our results with predictions based on a generalized Newtonian description for a shear-thinning fluid. In this case, the mucus is purely viscous, and we choose the Carreau-Yasuda model (Carreau *et al.* 1979) to describe its viscosity:

$$\mu(\dot\gamma) = \mu_\infty + (\mu_0 - \mu_\infty)\left[1 + (\lambda\dot\gamma)^l\right]^{\frac{n-1}{l}}, \tag{5.6}$$

where the relaxation time λ is not to be confused with an elastic relaxation time, μ_0 and μ_∞ are the low- and infinite-strain-rate limits, and $l>0$ and $n<1$ are adjustable parameters. We set $\mu_\infty=0$ and $l=2$, and we fit λ, μ_0, and n to the experiments of Jory *et al.* (2022), which yields the dot-dashed magenta curve in figure 8a.

Figure 8d compares predictions of the MCC flow rate q based on (5.6), as obtained from our own DNS (open squares) and a low-λ asymptotic solution (dot-dot-dashed black curve), with our low-De predictions based on the 5-mode Giesekus (dot-dashed red curve) and Oldroyd-B (solid red curve) models. In the case of the Giesekus model, shear-thinning amplifies (very slightly) the flow rate reduction caused by viscoelasticity. By contrast, an increase in flow rate is observed in the case of the Carreau-Yasuda model ($q/q_{\mathrm{ref}}>1$). At first sight, the latter observation seems to contradict the conclusions of Chatelin *et al.* (2017), who reported conditions where the MCC velocity is reduced due to shear-thinning. However, these authors also found that the shear-thinning effect is highly non-monotonic, and their figure 3 exhibits regions of parameter space where the MCC velocity is increased.

6. Conclusion

We have studied analytically and numerically the effect of viscoelasticity on MCC in a continuous force-free mucus layer, where momentum transfer from the beating cilia is modelled via the experimentally-validated Navier-slip moving-carpet boundary condition of Bottier *et al.* (2017*a*). In our continuum model, we have represented physiologically realistic conditions by appropriately choosing the mucus rheology (healthy and diseased conditions), cilia kinematics, and cilia density (which controls the slip length), based on literature data. We find that viscoelasticity can reduce the MCC flow rate by as much as 30% versus the Newtonian limit, under conditions representative of cystic fibrosis (CF), whereas no significant reduction is observed under healthy conditions. Moreover, the observed flow rate reduction is highly sensitive to the slip length and the cilia beat amplitude (CBA).

Translating the data reported in this study into dimensional terms, our calculations predict a 90% reduction of the MCC flow rate under CF conditions versus a healthy configuration, i.e. the average mucus velocity drops from 24-61 µm /s for healthy mucus ($a^\star$=5-8 µm, HBE-2wt%) to 1.7 µm /s for CF mucus ($a^\star$=1.6 µm, HBE-5wt%). This is a result of two effects associated with respiratory illnesses: reduced CBA and increased viscoelasticity. The role of CBA is both direct (via the imparted mucus velocity) and indirect (via viscoelasticity).

Thus, accurately predicting the effect of diseased conditions on CBA is an important modelling task. For example, in the case of CF, the PCL layer is depleted and so the cilia beat far into the viscoelastic mucus, reducing the CBA. Predicting this requires modelling the retro-action of mucus rheology on cilia kinematics. Very few studies have accounted

for such a retro-action. A promising route is the traction-layer model of Smith *et al.* (2007), which could be extended to account for a nonlinear viscoelastic rheology in the mucus layer.

Our analytical solution in the low-amplitude limit, which extends the theory of Lauga (2007) by accounting for wall slip, accurately predicts MCC flow rates versus our DNS for healthy and unhealthy conditions. Such low-cost predictions could be highly useful in large-scale models of the pulmonary network (Filoche *et al.* 2015). On the other hand, our low-De asymptotic solution has allowed us to elucidate the mechanism of viscoelasticity-induced MCC flow rate reduction. We find that memory effects associated with the metachronal wave are responsible for this, explaining why earlier studies that did not account for metachronicity (Vasquez *et al.* 2016; Ortín 2020) did not observe any effect of rheology on the net mucus flow rate. In the case of microorganisms swimming in an unbounded fluid domain and modelled via Taylor's swimming sheet approach, Riley & Lauga (2015) have shown that a waveform consisting of two superimposed counter-travelling waves can lead to a viscoelasticity-induced increase in the swimming speed. However, such a waveform has not been reported in the context of MCC. Our analytical asymptotic solutions in the low-amplitude and low-De limits are not significantly affected by the shear-thinning nature of mucus, which we have represented via a multi-mode Giesekus model following Vasquez *et al.* (2016); Sedaghat *et al.* (2022). This is because shear-thinning enters this model via a quadratic stress term that is enslaved to viscoelasticity. As a result, all our conclusions based on the Oldroyd-B model remain valid when the additional effect of shear-thinning is accounted for.

Our continuum model can be extended in several ways. Firstly, the effect of an adjacent gas flow can be incorporated, in order to study the role of viscoelasticity in cough-induced clearance (Modaresi & Shirani 2022). Secondly, our model can be adapted to account for altered metachronicity, either due to gaps in the cilia carpet (Loiseau *et al.* 2020; Choudhury *et al.* 2021) or due to ciliary dyskinesia. Thirdly, the model can be modified to account for mucus secretion and occlusion in axisymmetric configurations (Halpern *et al.* 2010; Romano *et al.* 2021). Finally, DNS based on the multi-mode Giesekus model would allow us to elucidate the role of shear-thinning for arbitrary CBA and De. For this, the `Basilisk` solver needs to be significantly modified.

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Author ORCIDs. A. Choudhury, https://orcid.org/0000-0001-9814-5483; M. Filoche, https://orcid.org/0000-0001-8637-3016; N.M. Ribe, https://orcid.org/0000-0003-0584-888X; N. Grenier, https://orcid.org/0000-0001-5436-7041; G.F. Dietze, https://orcid.org/0000-0003-1495-5505

Appendix A. Expressions intervening in the low-De solution (4.3)

The coefficients A_i, B_i, C_i, and D_i appearing in (4.3*a*) are given by:

$$A_1 = -\frac{a}{S + 2k\phi C}, \quad B_1 = \frac{ae^{-k}\sinh(k)}{k(S + 2k\phi C)}, \quad C_1 = -A_1, \quad D_1 = B_1 e^{2k}, \tag{A 1}$$

$$A_2 = \frac{1}{2}a^2 k, \tag{A 2}$$

$$A_3 = \frac{a^2 k'}{4(S' + 2k'\phi C')}, \quad B_3 = -\frac{a^2(1 - e^{-2k'})}{8(S' + 2k'\phi C')}, \quad C_3 = -A_3, \quad D_3 = B_3 e^{2k'}, \tag{A 3}$$

where we have introduced S=sinh(2k) − 2k, C=cosh(2k) − 1, S'=sinh(2k') − 2k', and C'=cosh(2k') − 1, with k'=2k. The homogenous and particular solutions $\Psi_H(x,y,t)$ and $\Psi_P(x,y,t)$ in (4.3c) are:

$$\begin{aligned}\Psi_H(x,y,t) =& A_{10}y + B_{10}y^2 \\ &+ \sum_{n=1}^{6}\left\{\cos(n\theta)\left(e^{nky}(A_{1n}+B_{1n}ky)+e^{-nky}(C_{1n}+D_{1n}ky)\right)\right\}, \qquad \text{(A 4)}\\ \Psi_P(x,y,t) =& \sum_{n=1,2}\sum_{p=0}^{3}\left(e^{2nky}I_{pn}y^p + e^{-2nky}J_{pn}y^p\right) \\ &+ \sum_{n=1,2}\sum_{p=2}^{5}\left\{\cos(n\theta)\left(e^{nky}Y_{pn}y^p + e^{-nky}Z_{pn}y^p\right)\right\} \\ &+ \cos(\theta)\sum_{n=1,2}\sum_{p=0}^{3}\left(e^{(2n+1)ky}Q_{pn}y^p + e^{-(2n+1)ky}R_{pn}y^p\right) \\ &+ \cos(2\theta)\sum_{n=0,2,3}\sum_{p=0}^{3}\left(e^{2nky}K_{pn}y^p + e^{-2nky}L_{pn}y^p\right) \\ &+ \cos(3\theta)\sum_{n=0,2}\sum_{p=0}^{3}\left(e^{(2n+1)ky}E_{pn}y^p + e^{-(2n+1)ky}F_{pn}y^p\right) \\ &+ \cos(4\theta)\sum_{p=0}^{3}\left(e^{2ky}M_p y^p + e^{-2ky}N_p y^p + X_p y^p)\right) \\ &+ \cos(5\theta)\sum_{n=0,1}\sum_{p=0}^{3}\left(e^{(2n+1)ky}G_{pn}y^p + e^{-(2n+1)ky}H_{pn}y^p\right) \\ &+ \cos(6\theta)\sum_{p=0}^{3}\left(e^{2ky}O_p y^p + e^{-2ky}P_p y^p\right), \qquad \text{(A 5)}\end{aligned}$$

where θ=$kx+t$ and $L_{p0}=0$. The constants A_{ij}, B_{ij}, C_{ij}, . . ., and M_i, N_i, O_i, P_i, and X_i can be obtained in a straightforward manner via the method of undetermined coefficients. The fully substituted forms of Ψ_H and Ψ_P are given in the supplementary Mathematica notebook.

Appendix B. Coefficients intervening in the low-amplitude solution (4.8)

The coefficients contained in (4.8) are given by:

$$\begin{aligned} I_0 &= \frac{(1-\beta)\mathrm{De}^2 k\left(2k+e^{-2k}-1\right)}{4\left(1+\mathrm{De}^2\right)(S+2k\phi C)^2}, \quad I_1 = -\frac{(1-\beta)\mathrm{De}^2\left(e^{2k}-1\right)k\left(e^{-2k}(4k-1)+e^{-4k}\right)}{8\left(1+\mathrm{De}^2\right)(S+2k\phi C)^2}, \\ I_2 &= \frac{(1-\beta)\mathrm{De}^2 e^{-4k}\left(e^{2k}-1\right)^2 k^2}{8\left(1+\mathrm{De}^2\right)(S+2k\phi C)^2}, \quad J_0 = -\frac{(1-\beta)\mathrm{De}^2 k\left(2k-e^{2k}+1\right)}{4\left(1+\mathrm{De}^2\right)(S+2k\phi C)^2} \\ J_1 &= -\frac{(1-\beta)\mathrm{De}^2\left(e^{2k}-1\right)k\left(4k-e^{2k}+1\right)}{8\left(1+\mathrm{De}^2\right)(S+2k\phi C)^2}, \quad J_2 = -\frac{(1-\beta)\mathrm{De}^2\left(e^{2k}-1\right)^2 k^2}{8\left(1+\mathrm{De}^2\right)(S+2k\phi C)^2}, \qquad \text{(B 1)}\end{aligned}$$

$$K_1 = \frac{1}{2}e^{-2k}\Big[-8k\phi(J_0k + J_1(k-1)) - 4J_2(2(k-2)k+1)\phi + e^{2k}\Big(4J_0k(2k\phi+1) - 2J_1(4k\phi+1) + 4J_2\phi + I_0k(8k\phi-4) + 8I_1k\phi + k + 4I_2\phi - 2I_1\Big) - 4e^{4k}\Big(2k(I_0k + I_1(k+1)) + I_2(2k(k+2)+1)\Big)\phi\Big],$$

$$K_2 = e^{-2k}\Big[2k\left(-(J_0+J_1+J_2)\,k + J_1 + 2J_2\right) - J_2 - e^{4k}\Big(2k\left(I_0k + I_1(k+1)\right) + I_2(2k(k+2)+1)\Big)\Big], \tag{B 2}$$

where we have once again used S=sinh$(2k) - 2k$ and C=cosh$(2k) - 1$.

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