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## Mucus and ciliated cells of human lung : Splitting strategies for particle methods and 3D stokes flows

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### Abstract

This proceeding is introducing a fractional step algorithm for diffusion-transport allowing computation of flows with sharp variations of viscosity. This splitting also allows to perform transport with Lagrangian methods and diffusion with Eulerian methods, using hybrid grid-particle formulation. This splitting algorithm is globally second order. It is applied to computation of mucus mobility in human lungs, where epithelium ciliated cells are beating. A sufficient mobility is required to have healthy configurations. Our goal is to study the dependency of mucus mobility with respect to its viscosity in order to investigate mechanisms involved in pathologies such as cystic fibrosis.

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**Keywords:** Particle methods, Transport, 3D Stokes flows, Non-homogen flows, Complex geometries, Biological flows, Mucus flows.

### 1. Context and motivation

Scientific computing involving phenomena where transport effects are dominant, is still a challenge for realistic modeling of complex flows. Among the most famous problems, one can find Euler and Navier-Stokes equations, in velocity-pressure or velocity-vorticity formulations, with various boundary conditions. Particle and vortex methods are a well-known and efficient tool for this kind of problem.

In the present paper we describe some aspects on how to use particle methods in the context of highly viscous flows. The application investigated is the propulsion of pulmonary mucus in human lungs. A meaningful model is 3D Stokes flows with a variable viscosity, depending on concentration of proteins (mucins), itself following a diffusion-transport equation. In additions to this coupling, the mucus film covering lung walls is interacting with epithelium ciliated cells, vibrating in the range of 4 to 20 Hz, as shown on figure 1. In the present study we neglect interactions between mucus and air (proven to be a non-dominant interaction), and visco-elastic effects. The aspect we aim at developing in this article is how to split diffusion and transport in this context.

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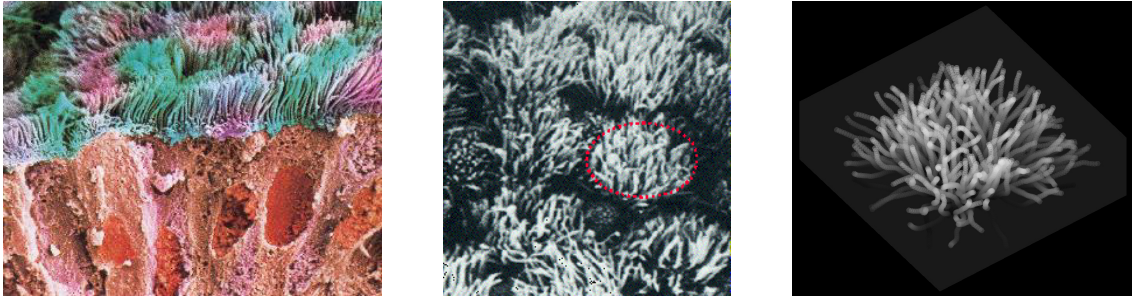


Fig. 1. Views of respiratory epithelial cells (to the left and to the middle, red dots show a cell delimitation) and ciliated cells used in numerical simulation (to the right).

Below we describe briefly, on the one hand, how are usually introduced particle formulations for the Navier–Stokes equations, and on the other hand, how they are introduced here for Stokes equations when coupled with transport. Section 3 introduces the splitting algorithm with demonstration of global second order accuracy. Section 4 is presenting how 3D Stokes equation are solved in complex and mobile geometry, by means of a combination of fast solvers. Section 5 finally uses this method for computation of mucus dynamics, and shows a parametric study with respect to mucus viscosity.

## 2. Transport and splitting strategy for regularization

### 2.1. A dynamical system for Lagrangian formulation of the Navier–Stokes equations

In the context of the Navier–Stokes equations, for an incompressible fluid in a domain  $\Omega$ , of constant density  $\rho$  and constant dynamics viscosity  $\mu$ :

$$\rho \frac{\partial \mathbf{u}}{\partial t} + \rho \mathbf{u} \cdot \nabla \mathbf{u} - \mu \Delta \mathbf{u} = \mathbf{f} - \nabla p, \quad (1)$$

where  $\mathbf{u}$  is the divergence-free velocity field satisfying the no-slip condition  $\mathbf{u} = 0$  on  $\Gamma = \partial\Omega$ ,  $p$  the pressure, and  $\mathbf{f}$  the external force, assumed to derive from a potential (that is to say, the gradient of a scalar function). Taking the curl of (1) and introducing the vorticity as  $\omega = \text{curl } \mathbf{u}$ , one gets Navier–Stokes equation in vorticity formulation:

$$\frac{\partial \omega}{\partial t} + \mathbf{u} \cdot \nabla \omega - \omega \cdot \nabla \mathbf{u} - \nu \Delta \omega = 0 \quad (2)$$

with boundary conditions  $\mathbf{u} = 0$ , where  $\nu = \mu/\rho$  is the kinematic viscosity. As  $\mathbf{u}$  and  $\omega$  are linked by means of the partial differential equation on stream  $-\Delta \psi = \omega$  (with adequate boundary conditions [5]) followed by the derivation  $\mathbf{u} = \text{curl } \psi$ , one can assume that the velocity is a function of vorticity  $\mathbf{u} = F(\omega)$ . Using the notation of convective derivation

$$\frac{D\omega}{Dt} = \frac{\partial \omega}{\partial t} + \mathbf{u} \cdot \nabla \omega \quad (3)$$

one gets equation (2) reading :

$$\frac{D\omega}{Dt} = \omega \cdot \nabla F(\omega) + \nu \Delta \omega \quad (4)$$

In practice, using particle methods, this last equation is usually split into two steps over a time-step : firstly a convection sub-step  $D\omega/Dt = \omega \cdot \nabla F(\omega)$  and secondly a diffusion sub-step  $\partial_t \omega - \nu \Delta \omega = 0$ . This allows the use of Lagrangian methods on the convection part and Eulerian methods on the diffusion part. Both formulations can be estimated by the other, by means of high order interpolations (such as convolution with  $M'_4$  [7] or  $M'_6$  [2] compact supported kernels).

Such a splitting is first order in time, but can be extended to second order by using Strang formulæ, or to any order by using Trotter permutation formulæ.

## 2.2. Lagrangian formulation of Stokes equations coupled with diffusion-transport

When considering highly viscous biological flows, such as pulmonary mucus, the meaningful model is the Stokes equations with variable dynamics viscosity  $\mu$  :

$$-\operatorname{div}(2\mu\mathbf{D}(\mathbf{u})) = \mathbf{f} - \nabla p \quad \text{and} \quad \operatorname{div}\mathbf{u} = 0 \quad (5)$$

everywhere on fluid domain  $\Omega \subset \mathbb{R}^3$ , with periodic, or homogeneous Dirichlet or Neumann boundary conditions on the computational box. Moreover, the strain tensor  $\mathbf{D}(\mathbf{u})$  is the symmetric part of velocity gradient  $\mathbf{D}(\mathbf{u}) = (\nabla\mathbf{u} + \nabla\mathbf{u}^T)/2$ . This equation can also be written

$$-\mu\Delta\mathbf{u} = \mathbf{D}(\mathbf{u})\nabla\mu + \mathbf{f} - \nabla p \quad \text{and} \quad \operatorname{div}\mathbf{u} = 0 \quad (6)$$

Moreover, this fluid is also in adherence with the ciliated cells, a complex ciliary geometry moving at a prescribed velocity  $\bar{\mathbf{u}}(x,t)$ . The domain delimited by cilia is denoted  $\mathcal{B}(t)$ , where condition  $\mathbf{u} = \bar{\mathbf{u}}$  has to be satisfied. Consequently, given the complexity of the shape of epithelial ciliated cells, it turns out that the penalization method fits very well [8]. If we denote  $\Omega$  the computational box, penalized formulation of equation (6) reads:

$$-\mu\Delta\mathbf{u} + \frac{\chi_{\mathcal{B}(t)}}{\varepsilon}(\mathbf{u} - \bar{\mathbf{u}}) = \mathbf{D}(\mathbf{u})\nabla\mu + \mathbf{f} - \nabla p \quad \text{and} \quad \operatorname{div}\mathbf{u} = 0 \quad (7)$$

and  $\mathbf{u}$  periodic or  $\mathbf{u} = \mathbf{g}(t)$  on boundaries ( $\mathbf{g}(t)$  given), where  $\chi_{\mathcal{B}(t)}$  is the characteristic function of cell domain  $\mathcal{B}(t)$  (1 inside  $\mathcal{B}(t)$  and 0 otherwise), and  $\bar{\mathbf{u}}$  is cell velocity, following a damped wave equation on each cilia, as described in [3, 4].

As  $\mu$  and  $\chi_{\mathcal{B}(t)}$  are exhibiting sharp variations, the use of velocity-vorticity formulation of Stokes problem is not relevant. Indeed taking the curl of equation (7) would be showing singular terms very hard to handle numerically.

Furthermore, viscosity is directly driven by concentration of mucins, a set of proteins moving through the mucus. One can introduce the mass fraction of mucins  $\alpha$ , which follows a diffusion transport equation

$$\frac{\partial\alpha}{\partial t} + \mathbf{u} \cdot \nabla\alpha - \eta\Delta\alpha = 0 \quad (8)$$

where  $\eta > 0$  is the mucin diffusion coefficient. Mucus viscosity  $\mu$  is a function of mucin mass fraction  $\mu = \phi(\alpha)$ , which gives a diffusion-transport equation on viscosity reading:

$$\frac{\partial\mu}{\partial t} + \mathbf{u} \cdot \nabla\mu - \eta\Delta\mu = -\eta\phi''(\alpha)\|\nabla\alpha\|_2^2 \quad (9)$$

As the linear model for  $\phi$  is physically meaningful, one gets a standard diffusion-transport equation on viscosity. Through penalised Stokes equation (7), velocity  $\mathbf{u} : \Omega \subset \mathbb{R}^3 \rightarrow \mathbb{R}^3$  can be considered as a function of viscosity  $\mu : \Omega \rightarrow \mathbb{R}^+$ , and can be denoted  $\mathbf{u} = F(\mu)$ , in a similar way as Navier–Stokes equation in the previous section.

Equation (9) can finally be written autonomously as :

$$\frac{\partial\mu}{\partial t} + F(\mu) \cdot \nabla\mu - \eta\Delta\mu = 0 \quad (10)$$

where  $F$  is in practice a call to the Stokes solver, or equivalently

$$\frac{D\mu}{Dt} = \eta\Delta\mu \quad (11)$$

in the same spirit as equation (4) for the Navier–Stokes equations.

It follows that the particle methods used for Navier–Stokes equations can be used straightforward for the transport of mucins, since equations (4) and (11) are of the same kind.

### 2.3. ODE resulting from particle formulation and admissibility of numerical solutions

A usual particle formulation of these equations consists in introducing a measure quadrature of its solution : with Particle-in-cell methods unknowns are discretized in the domain  $\Omega$  on a set of  $N$  particles (or cells) of volume  $v_p$ , position  $\xi_p$ , and viscosity  $\mu_p$ ,  $p$  indexing particles from 1 to  $N$ . One gets then the quadrature

$$\mu = \sum_{p=1}^N \mu_p \delta_{\xi_p} v_p, \quad (12)$$

where  $\delta_{\xi_p}(\zeta) = \zeta(\xi_p)$ , for any test function  $\zeta$ , is the Dirac function in  $\xi_p$ . Without time-splitting considerations, these quantities, featuring particles, are following a set of ordinary differential equations :

$$\frac{d\mu_p}{dt} = \eta \Delta \mu(\xi_p), \quad \frac{d\xi_p}{dt} = \mathbf{u}(\xi_p), \quad \frac{dv_p}{dt} = 0 \quad (13)$$

for  $p = 1, \dots, N$ , with conservation of volumes  $v_p$  due to divergence free velocity field.

Despite the same nature of equations (4) and (11), there are some major differences in the admissibility of solutions. Indeed, for Navier–Stokes equations, the vorticity can be interpolated using a high order kernel leading potentially to negative weights in interpolation : second (or higher) order kernel requires a zero second moment and thus negative domain in kernel definition. This is not admissible for viscosity fields which has to keep strictly positive.

Furthermore, and this aspect is crucial, time splitting algorithm used for Navier-Stokes equation splits apart transport and diffusion. It means that pure convection part  $D\omega/Dt = \omega \cdot \nabla \mathbf{u}$  has no regularization, and sharp interface of vorticity can appear, which are smoothed afterward in both diffusion substep and velocity reconstruction through the Poisson equation. This is not a problem due to the nature of vorticity, but too much sharpness cannot be handled for viscosity fields, otherwise one may encounter all the numerical issues arising in stability of multiphase flows.

Consequently, an algorithm smoothing numerical solutions after any sub-step of transport is required. Such an algorithm is described thereafter.

One other advantage of particle methods for transport is the absence of CFL condition which are arising in standard straightforward discretization. This comes from the reduction of a PDE to a set of ODE. Moreover no distinction have to be made on the nature of velocity field for discretisation which has traditionally to be made upwind in all directions to avoid numerical instabilities.

### 3. Linear consistency of a Runge-Kutta inspired scheme

A critical analysis of different splitting strategies can be done. Indeed, one can consider several algorithms for Lagrangian methods and diffusion-transport equations, used in the literature:

1. A full time-step splitting: A transport step is followed by a diffusion step whose initial condition is the final value of the transport step. The final solution is smooth but the algorithm is first order.
2. A full Runge-Kutta scheme without time splitting: this requires to compute diffusion and transport together, which does not fit Lagrangian methods, except if using Particle-Strength-Exchange methods, which has a high computational cost if used at full second order.
3. A time splitting using Strang (or Trotter) formula and Runge-Kutta method for transport: this is probably the most efficient way to split apart diffusion and transport for high order Lagrangian methods. Nevertheless, this implies that there is no diffusion in the Runge-Kutta sub-steps. This is usually not restrictive, especially for Navier-Stokes equation, but this is not satisfactory for viscosity convection-diffusion in biological flows with large viscosity variations.

Moreover, we will below introduce an algorithm that is smoothing the solution at every sub-step and is more accurate than first order splitting.

For transport, an algorithm based on the second order mid-point Runge-Kutta method is built. For a dynamical system  $y' = f(y)$ , the solution is approximated by a sequence  $y_n$  close to the exact solution  $y(t_n)$  at time  $t_n = n\delta t$ , and the sequence is defined recursively by

$$y_{n+1} = y_n + \delta t f(y_{n+1/2}) \quad \text{where} \quad y_{n+1/2} = y_n + \frac{\delta t}{2} f(y_n) \tag{14}$$

Now we want to integrate equation (11), whose shape is  $y' = f(y)$ , by a scheme similar to mid-point rule to reach a global second order with smooth function at each sub-step.

Indeed, this equation can be written  $y' = (\mathcal{D} + \mathcal{T})y$  where  $\mathcal{D}$  is an approximation of diffusion operator  $\eta\Delta$  and  $\mathcal{T}$  is an approximation of transport operator  $-\mathbf{v} \cdot \nabla$  along field  $\mathbf{v}$ . Any numerical scheme for such an ordinary differential equation is second order if and only if it satisfies

$$y_{n+1} = \left[ 1 + \delta t (\mathcal{D} + \mathcal{T}) + \frac{\delta t^2}{2} (\mathcal{D} + \mathcal{T})^2 + \mathcal{O}(\delta t^3) \right] y_n \tag{15}$$

so it matches the expansion of  $e^{(\mathcal{D}+\mathcal{T})\delta t}y_n$ . A particular attention has to be given to the quadratic term of this expansion.

We introduce then the following algorithm, over a time step  $[t_n, t_{n+1}]$ :

1. Solution at the beginning of time step  $t_n$  is denoted  $y_n$ ,
2. Half a step of transport is performed :

$$\tilde{y}_{n+1/2} = y_n + \frac{\delta t}{2} \mathcal{T} y_n \tag{16}$$

3. Half a step of diffusion is performed using the final value of transport as initial condition :

$$y_{n+1/2} = \tilde{y}_{n+1/2} + \frac{\delta t}{2} \mathcal{D} \tilde{y}_{n+1/2} \tag{17}$$

4. A full step of transport is performed using the initial position at the beginning of the time step and the velocity obtained at step 3 (standard mid-point itegration) :

$$\tilde{y}_{n+1} = y_n + \delta t \mathcal{T} y_{n+1/2} \tag{18}$$

5. A full step of diffusion is performed using the result of step 4 as initial condition, but diffusing the field obtained at step 3 again :

$$y_{n+1} = \tilde{y}_{n+1} + \delta t \mathcal{D} y_{n+1/2} \tag{19}$$

That way, any transport sub-step is made in the Lagrangian way, then interpolated on grid and followed by diffusion sub-step made by Eulerian method. Interpolations between particles and grids are performed using  $M'_4$ , which is a bit less efficient and accurate than tensorialized  $M'_6$ , but sufficiently accurate and computationally neglectful toward velocity computation.

This algorithm leads to

$$y_{n+1/2} = \tilde{y}_n + \frac{\delta t}{2} (\mathcal{D} + \mathcal{T}) \tilde{y}_n + \frac{\delta t^2}{2} \mathcal{D} \mathcal{T} \tilde{y}_n \tag{20}$$

and consequently to

$$y_{n+1} = \left[ 1 + \delta t (\mathcal{D} + \mathcal{T}) + \frac{\delta t^2}{2} (\mathcal{D} + \mathcal{T})^2 + \frac{\delta t^3}{4} (\mathcal{D} + \mathcal{T}) \mathcal{D} \mathcal{T} \right] y_n \tag{21}$$

which is proving that the scheme is globally second order.

One can notice that if step 5 of the algorithm diffuses  $\tilde{y}_{n+1}$  instead of  $y_{n+1/2}$ , as in most fractional step methods, then quadratic term of the expansion is  $\mathcal{T}^2 + \mathcal{T} \mathcal{D} + 2 \mathcal{D} \mathcal{T} \neq (\mathcal{D} + \mathcal{T})^2$  and the scheme would fall back to first order.

Eventually, this second order numerical method is used to solve diffusion transport equation (10), and can manage sharp variations in viscosity due to the diffusion sub-step performed every time before transport and thus velocity computation. Now we will give how to compute velocity from viscosity, that is to say we will define function  $F$  of equation (10).

#### 4. A velocity-pressure splitting for 3D Stokes equations

In this section, the function computing velocity  $\mathbf{u}$  from viscosity  $\mu$  is defined by means of the penalized 3D Stokes equation (7) :

$$-\mu\Delta\mathbf{u} + \frac{\chi_{\mathcal{B}(t)}}{\varepsilon}(\mathbf{u} - \bar{\mathbf{u}}) = \mathbf{D}(\mathbf{u})\nabla\mu + \mathbf{f} - \nabla p \quad \text{and} \quad \text{div}\mathbf{u} = 0 \quad (22)$$

with periodic or prescribed boundary conditions  $\mathbf{u} = \mathbf{g}$ .

In the spirit of hybrid grid-particle methods, matrix assembly is avoided. This assembly comes from discretization of this equation with finite difference–element–volume methods. Instead, it is split into Poisson and Helmholtz problems, for which fast solvers are available.

As described in [3], pressure is split apart by using a projection on divergence free fields. Given a field  $\mathbf{v}$ , one considers the solution (unique up to a constant as pressure field) of following equation :

$$\begin{cases} -\Delta\zeta = -\text{div}\mathbf{v} \\ \frac{\partial\zeta}{\partial\mathbf{n}} = \mathbf{v} \cdot \mathbf{n} \quad \text{on boundary} \end{cases} \quad (23)$$

Let  $\Pi$  be the function of  $\mathbf{v}$  giving  $\Pi(\mathbf{v}) = \mathbf{v} - \nabla\zeta$ . It satisfies the projection definition  $\Pi^2 = \Pi$ , and is also giving divergence free field as  $\text{div}\Pi(\mathbf{v}) \equiv 0$ . Such a projection can be computed by means of the fast solver FISHPACK using FFT and Chebychev methods [9].

Using this, the solution of (7) or (22) can be computed as the projection  $\mathbf{u} = \Pi(\mathbf{u}^*)$  where  $\mathbf{u}^*$  is the limit of the following fixed point algorithm, with boundary relaxation :

$$\begin{cases} -\mu\Delta\mathbf{u}_{k+1}^* - 2\mathbf{D}(\mathbf{u}_k)\nabla\mu + \frac{\chi}{\varepsilon}(\mathbf{u}_{k+1}^* - \mathbf{u}_k^* + \Pi\mathbf{u}_k^* - \bar{\mathbf{u}}) = \mathbf{f} \quad \text{in computational box} \\ \mathbf{u}_{k+1}^* = \mathbf{g} + (1 - \theta)(\Pi\mathbf{u}_k^* - \mathbf{u}_k^*) + \theta(\Pi\mathbf{u}_{k-1}^* - \mathbf{u}_{k-1}^*) \quad \text{on boundary} \end{cases} \quad (24)$$

where  $\theta = -1$  is the Richardson extrapolation formula (see [3] for more details). This loop is made necessary because the projection is not preserving both boundary conditions and condition  $\mathbf{u} = \bar{\mathbf{u}}$  in solid domain.

This equation reads  $-\mu\Delta\mathbf{u}_{k+1}^* + \chi_{\mathcal{B}(t)}\varepsilon^{-1}\mathbf{u}_{k+1}^* = RHS_k$ , which is a Helmholtz equation with large jumps (from 0 to  $1/\varepsilon$ ) in coefficient. For such a kind of partial differential equations, we use the multi-grid fast solver MUDPACK [1].

#### 5. Application to mucus dynamics

The algorithms described in previous sections are coupled together. It gives a robust tool to compute dynamics of highly viscous flows with large variations of viscosity, as displayed on figure 2, showing the snapshot of a sphere rotating in a variable viscosity 3D Stokes flow.

In this section simulations of a mucus film flow around a ciliated epithelium cell are presented. In the human lung mucus plays a barrier role which protects bronchial walls from inhaled dust and pathogen agents. It is a highly viscous gel essentially composed of polymers and proteins.

Among these proteins, mucins play an important role: they are hydrophilic proteins released by goblet cells situated on bronchial walls so the film is hydrated at bottom whereas lung air flow is dehydrating the top of the film so it is much less viscous at the bottom (where viscosity is very close to water's) than at the top (where it can be 10 to 10000 times more viscous with pathologies such as cystic fibrosis [6]).

In fact two fluid layers are constituting the film: close to bronchial wall this low viscous fluid is called periciliary fluid and mucus gel is above. Nevertheless both fluids are miscible (essentially composed of water as human body) and interface is not identifiable. Mucins are moving from periciliary fluid to mucus and a linearly variable viscosity with potentially large gradients is relevant to model the initial condition of this fluid. One gets a function of  $z$ , the distance from lung wall, depending on the mucus height  $L$ . For example a linear profile:

$$\mu(z, t = 0) = \mu_{water}(1 + \beta z/L) \quad (25)$$

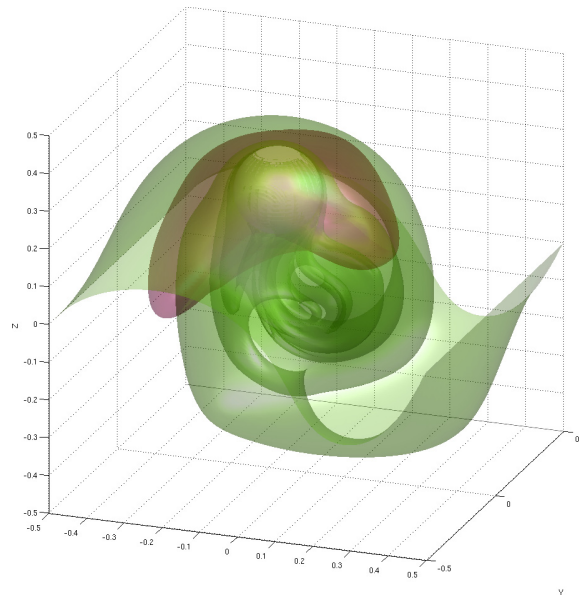


Fig. 2. Sphere moving in a variable viscosity Stokes flow. Coupling between Stokes and transport equation generates strong non-linear effects. The picture shows isosurfaces of viscosity (in green) and velocity norm (in red) for a  $256^3$  simulation.

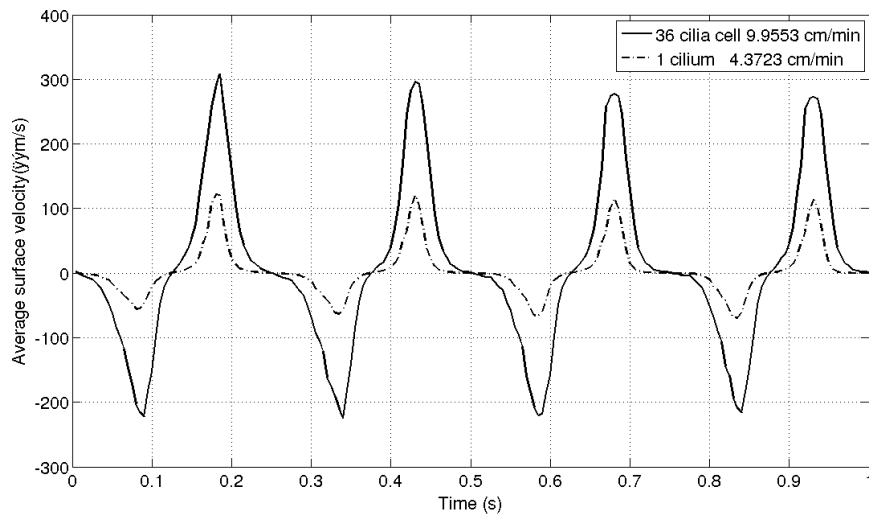


Fig. 3. Mucus surface average velocity with respect to time over 4 beating periods, with 36 cilia.



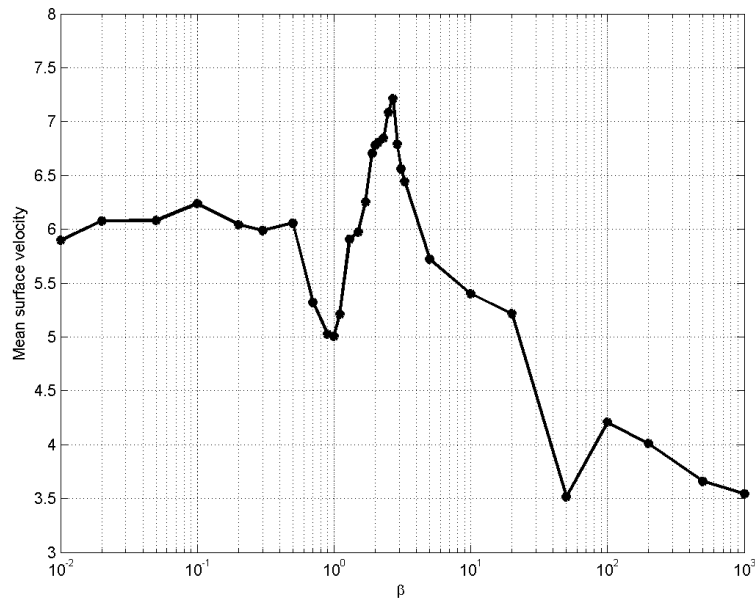


Fig. 4. Mucus surface average velocity in  $cm/min$ , averaged in time over 4 beating periods, with 19 cilia beating, with respect to parameter  $\beta$  (see equation 25).

Ciliated epithelium cells are located on the bronchial wall. Their cilia are immersed in mucus and beating at frequencies from 4 to 20Hz. One cilium is 7 to 10 micrometers long with a radius of 100 to 500 nanometers. A global displacement of a few centimeters per minute of mucus film has been observed [10]. So the characteristic Reynolds number of this flow is about  $10^{-4}$  close to the wall and it is decreasing as viscosity is increasing (in pathologic situations).

Cilia motion described in [4] is defining penalized domain  $\mathcal{B}(t)$  and its velocity  $\bar{\mathbf{u}}$ . With 36 cilia beating at 4Hz (snapshot on figure 5), one gets a surface mean velocity close to  $10cm/min$ , as displayed on figure 3 for four beating cycles. When pathologies such as cystic fibrosis mucus layer becomes more and more viscous, with means a coefficient  $\beta$  larger and larger. Figure 4 shows the mean velocity obtained with various values of  $\beta$ , for a 19 staggered cilia beating. This exhibits a lack of mucus mobility as mucus layer becomes more viscous.

## 6. Conclusion

A particle method for diffusion-transport of viscosity was built, coupled with 3D penalized Stokes equation in complex and mobile geometry. With a special splitting between diffusion and transport, we are able to smooth viscosity before computing velocity. It allows to consider flows with sharp variations of viscosity using large time steps.

This numerical method is applied to mucus mobility in human lungs, in order to investigate mechanisms involved in cystic fibrosis. It was shown that with a prescribed beating motion of cilia, mucus motion is decreasing dramatically (by half) as mucus viscosity increases. This is qualitatively what was expected by medical observation of pathologies as cystic fibrosis and this first parametric analysis will be the base of future work on the study of different mechanisms.

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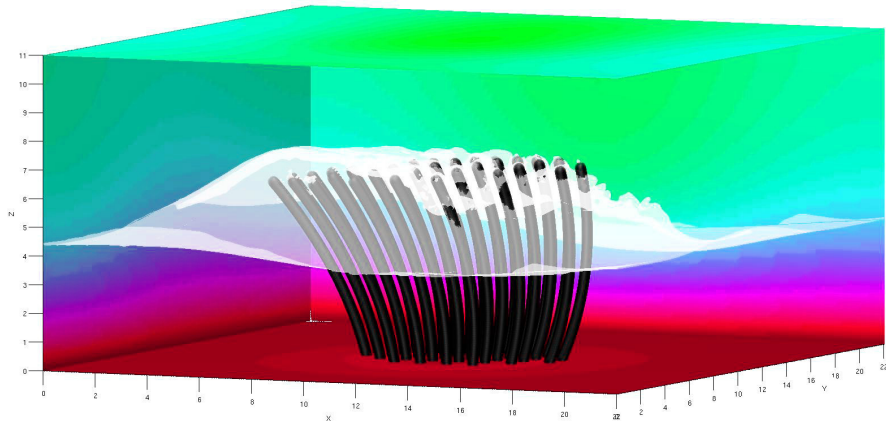


Fig. 5. Snapshot of 36 cells beating. White surface is an isosurface of viscosity, color at boundary is velocity (increasing from red to green).

## References

- [1] Adams J., MUDPACK: Multigrid Fortran Software for the Efficient Solution of Linear Elliptic Partial Differential Equations, *Appl. Math. Comp.* 1989; **34**: 113–146.
- [2] Bergdorf M., Koumoutsakos P. A lagrangian particle-wavelet method. *Multiscale Modeling and Simulation: A SIAM Interdisciplinary Journal* 2006; **5**: 980–995.
- [3] Chatelin R., Poncet P. A hybrid grid-particle method for moving bodies in a 3D Stokes flow with variable viscosity *SIAM J. Sci. Comp.* 2013; **35**(4): B925–B949.
- [4] Chatelin R., Poncet P. Particle methods for 3D biological flows with variable density and viscosity. *6th ECCOMAS Conference, Vienna, Austria*; 2012.
- [5] Cottet G.-H., Poncet P. Advances in direct numerical simulations of three-dimensional wall-bounded flows by Particle in Cell methods. *J. Comp. Phys.* 2003; **193**: 136–158
- [6] Damy T., Burgel P.-R., Pepin J.-L., Boelle P.-Y., Cracowski C., Murriss-Espin M., et al. Pulmonary acceleration time to optimize the timing of lung transplant in cystic fibrosis. *Pulmonary Circulation* 2012; **2**(1): 75–83.
- [7] Monaghan J. J. Extrapolating B-Splines for interpolation. *J. Comp. Phys.* 1985 **60**(2): 253–262.
- [8] El Ossmani M., Poncet P. Efficiency of multi-scale hybrid grid-particle vortex methods. *SIAM MMS* 2010; **8**(5): 1671–1690.
- [9] Sweet R. A Parallel and Vector Variant of the Cyclic Reduction Algorithm. *SIAM J. Sci. and Stat. Comp.* 1988; **9**: 761–766
- [10] Thiriet M. *Tissue Functioning and Remodeling in the Circulatory and Ventilatory Systems (Vol. 5)*. Series Biomathematical and Biomechanical Modeling of the Circulatory and Ventilatory Systems, Springer, New York; 2012.