

**Master International Centre for Fundamental Physics ICFP**  
**PHYSICS FOR BIOLOGY**

**Examination (3 hours), December 2015**

Based on the article : How molecular motors shape the flagellar beat  
H. Riedel-Kruse *et al.* *HFSP Journal* . **1**, 192-208. (2007)

### 1. Experimental section

**1.1** Describe the system studied in this article. Why is this interesting from a biological viewpoint. From a physical viewpoint. What are the main experimental findings reported in this work. What does the comparison between experiments and theory teaches us. You can be brief and give bullet-point answers.

**1.2** It is said that for a collection of molecular motors, the real and imaginary part of the response function  $\chi(\omega)$  can become negative (just after Eq.5 in the paper). Are we in this situation in the experimental system studied in this paper ?

**1.3** Is the result presented in Fig.3C.concerning the zeroth mode  $\tilde{\psi}^{(0)}(s)$  in agreement with the “sperm equation” (Eq. 6 of the paper). What could explain the shape of Fig.3C. Can you explain the sentence (in the caption of Fig.3) : “ Note that variations of  $\tilde{\psi}^{(0)}(s)$  as a function of  $s$  lead to curved trajectories of freely swimming sperm cells.”

**1.4** Explain why the amplitude of the first mode  $|\tilde{\psi}(s)|$  increases with  $s$  in Fig.3D. What is the meaning of the phase of the first mode for  $s = 0$  in Fig.3E. What does the almost linear dependency of the phase with the arclength  $s$  corresponds to (in Fig.3E). Is this significant for the function of the flagellum ? If released from the clamp, would such flagellum move ? If yes in which direction ?

### 2. Theoretical section

We are going to derive the “sperm equation” from the energy functional

$$G = \int_0^L ds \left( \frac{\kappa}{2} C(s)^2 + f(s)\Delta(s) + \text{constraints} \right) \quad (1)$$

where  $C(s)$  is the local curvature of the flagellum, and where other terms have the same meaning as in the paper. We will not have to worry about additional “constraints” here.

**2.1** Explain the physical meaning of the two terms in the integral.

**2.2** In the limit of small deformations  $\psi(s) \ll 1$ , use the Monge representation and express the energy as a function of the local position of the flagellum ( $h(s)$ ) with respect to a fixed axis of reference (such as the dashed line in the Fig.1 of the paper). This requires Eq.2 of the paper. Why can  $s$  be identified with the coordinate  $x$  along the fixed axis in this regime ?

**2.3** Show that the “sperm equation” (Eq.6 of the paper) can be obtained as a spatial derivative of the force balance equation

$$\xi_{\perp} \frac{\partial h}{\partial t} = - \frac{\delta G}{\delta h} \quad (2)$$

where the RHS of Eq.(2) is the functional derivative of the energy  $G$  with respect of the (normal) displacement  $h(s)$ . Explain why Eq.(2) is a force balance equation.

**2.4** The functional derivative of the energy  $G$  (Eq.(1)) performed in the previous question also gives the boundary forces and torques from the boundary conditions following the integration by part. Use these relations to explain the boundary condition at the flagellum free end ( $\bar{s} \equiv s/L = 1$ ) given in Table 1 of the paper.

### 3. Extension 1 - Synchronisation of an array of cilia

We are going to see in which conditions the array of cilia beating at the surface of many eukaryotic cells such as *paramecium* may coordinate, thanks to hydrodynamics interactions, so as to beat all in the same direction and to create a net flow of fluid over the cell, possibly leading to cell swimming. We consider that each individual cilium beats in a non-symmetric fashion (Fig.1a), with an effective stroke that propels fluid (towards the right in Fig.1a) and a recovery stroke where the cilium is quite bent and experiences lesser viscous resistance from the fluid. The beating is essentially planar, and we want to understand how the beating planes of different cilia can coordinate. To do this, we will model the force exerted by the cilium on the fluid (averaged over a beating period) by a point force  $f$  applied a distance  $h$  from the wall and in the direction of the effective stroke (Fig.1b). Fig.1c shows a hexagonal array of cilia with a lattice size  $d$ , where cilium  $j$  exerts a force at an angle  $\phi_j$  from the reference x-axis. In the following, we will assume (without loss of generality) that the cilia coordination leads to a net flow  $\vec{U} = U\vec{e}_x$ . We also assume that the plane of beating of each cilium is free to rotate.

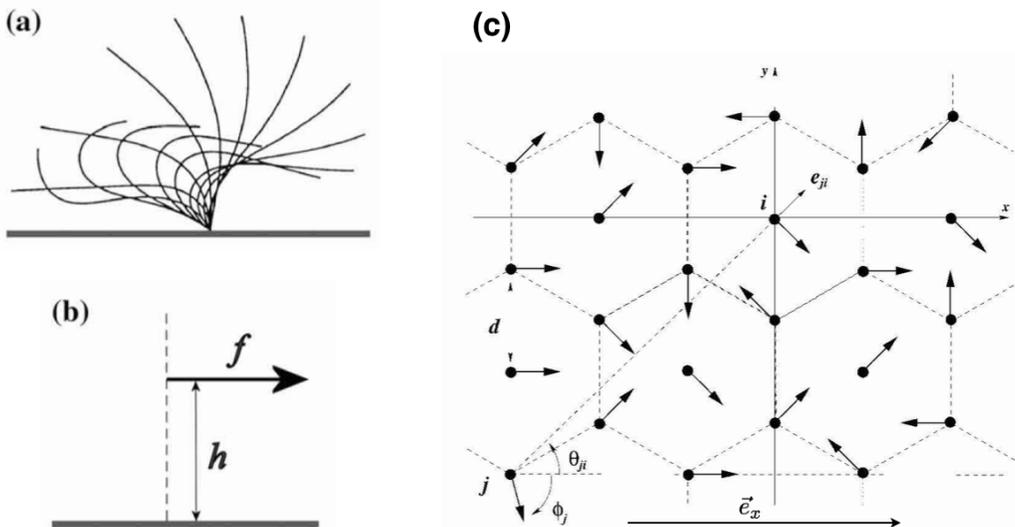


FIGURE 1 – (a) Sketch of the asymmetric beating pattern of a cilium attached to a wall. (b) Effective cilium force (averaged over a beating period) on the fluid  $\vec{f}$  applied at a height  $h$  above the cell membrane. (c) Hexagonal lattice of cilia with a distance  $d$  between neighbours. With respect to the reference axis (unit vector  $\vec{e}_x$ ), cilium  $j$  exerts a force  $f$  in the direction  $\phi_j$  and  $\theta_{ji}$  is the angle of the unit vector  $\vec{e}_{ji}$  from cilium  $j$  to cilium  $i$ .

**3.1** Probability distribution of cilia orientation. Let's call  $P(\phi)$  the probability that a cilium makes an angle  $\phi$  with the x-axis, under conditions where there is a net fluid flow  $U\vec{e}_x$  (with  $\int_{-\pi}^{\pi} d\phi P(\phi) = 1$ ). The stationary distribution is solution of the stationary Fokker-Planck equation

$$\partial_{\phi} J_{\phi} = 0 \quad \text{with} \quad J_{\phi} = -D_r \partial_{\phi} P(\phi) + P(\phi) \dot{\phi} \quad (3)$$

where  $J_{\phi}$  is the probability current,  $D_r$  is a rotational diffusion coefficient associated to the rotation of the beating plane and  $\dot{\phi}$  is the mean of the time derivative of the filament angle at  $\phi$ .

**3.1.1** Explain Eq.(3)

**3.1.2** The mean angular velocity  $\dot{\phi}(\phi)$  is obtained from a balance between the torque exerted by the flow (of velocity  $\vec{U}$ ) of norm :  $|M_{\text{flow}}| = \alpha U \sin \phi$  that drive alignment with the flow, and the viscous torque, of norm  $|M_{\text{visc}}| = \zeta \dot{\phi}$  that opposes rotation, where  $\alpha$  and  $\zeta$  are coefficients. Write the torque balance equation and use

it with Eq.(3) to obtain an equation for  $P(\phi)$  involving  $\phi$  and  $u$  (defined Eq.(4)). Show that the solution of this equation is

$$P(\phi) = \frac{e^{u \cos \phi}}{2\pi I_0(u)} \quad \text{with} \quad u \equiv \frac{\alpha U}{\zeta D_r} \quad (4)$$

Here and below, you will need to use the following properties of the Bessel functions  $I_0(u)$  and  $I_1(u)$  :

$$I_0(u) = \frac{1}{2\pi} \int_{-\pi}^{\pi} d\phi e^{u \cos \phi} \quad \text{and} \quad I_1(u) = \frac{dI_0(u)}{du} = \frac{1}{2\pi} \int_{-\pi}^{\pi} d\phi \cos(\phi) e^{u \cos \phi} \quad (5)$$

**3.2 Velocity created by an array of cilia.** We are going to calculate the velocity self-consistently by writing the velocity at a given cilium  $i$  as the sum of the average contribution of all other cilia :

$$\vec{U} = \sum_{j \neq i} \langle u_j(\vec{r}_i) \rangle = \sum_{j \neq i} \int_0^{2\pi} d\phi P(\phi) \vec{u}_j(\vec{r}_i) \quad (6)$$

where  $u_j(\vec{r}_i)$  is the velocity created by cilium  $j$  at the location of cilium  $i$ .

**3.2.1** The approximate expression for the velocity of a flow created by a point force at  $h$ , averaged over the length  $L$  of the cilium, is (in the limit  $d \gg L, h$ ) :

$$\vec{u}_j(\vec{r}_i) = \frac{3fhL}{2\pi\eta|\vec{r}_i - \vec{r}_j|^3} \cos(\theta_{ji} - \phi_j) \vec{e}_{ji} \quad (7)$$

where  $\eta$  is the fluid viscosity,  $\vec{r}_i$  and  $\vec{r}_j$  are the location of cilia  $i$  and  $j$ , and the angles are defined Fig.1c. Show that combining Eq.(6) and Eq.(7) gives a self-consistent expression for the velocity :

$$U = \mathcal{K} \frac{fhL}{\eta d^3} \frac{I_1(u)}{I_0(u)} \quad (8)$$

where  $I_0$  and  $I_1$  are defined Eq.(5),  $d$  is the distance between cilia (Fig.1c) and  $\mathcal{K}$  is a numerical prefactor that depends only on the geometry of the cilia array. Give the expression for  $\mathcal{K}$  as sum over all cilia.

**3.2.2** The function  $I_1(u)/I_0(u)$  is linear for small  $u$  and saturates to unity for large  $u$ . Using the expansion

$$I_0(u) \xrightarrow{u \rightarrow 0} 1 + \frac{u^2}{4} + \frac{u^4}{64} \quad I_1(u) \xrightarrow{u \rightarrow 0} \frac{u}{2} + \frac{u^3}{16}, \quad (9)$$

show that there may be spontaneous symmetry breaking and a global synchronisation between cilia, equivalent to saying that Eq.(8) has a non-vanishing solution, only if a particular combination of the physical parameters of the problem, to be determined, is larger than a given value.

**3.2.3** Discuss the condition obtained in **3.2.2** as a function of the physical parameters involved. Assuming that the cilia's radius is much smaller than their length, can you guess how the effective force  $f$  depends on the tangential and normal friction coefficients per unit length of an infinite rod,  $\zeta_{\parallel}$  and  $\zeta_{\perp}$ , discussed in class.

**3.2.4** Justify that the above analysis relies on a mean-field hypothesis. Do you think it is exact here? You can use an analogy with a classical problem of statistical mechanics. Even if the system is out of equilibrium (justify), argue that it can be mapped to an equilibrium problem by defining an effective pairwise interaction energy between cilia.

*With the notations above, for 2-dimensional interacting spin systems at equilibrium with pairwise interaction  $\epsilon_{ij} \propto \cos(\phi_i - \phi_j)/|\vec{r}_i - \vec{r}_j|^\alpha$ , it can be shown that for  $\alpha < 4$  there is a transition to long range order at finite temperature.*

## 4. Extension 2 - Fluctuation dynamics of a dead cilium

We consider a free cilium at equilibrium in a fluid at temperature  $T$ . Here dead means that there is no energy supply (ATP) and therefore no motor activity. In the Monge representation, we assume that the dynamics of  $h(x, t)$  is still given by equation Eq. (2), to which a random force  $\zeta(x, t)$  is added. We assume  $\langle \zeta(x, t) \rangle = 0$  and  $\langle \zeta(x, t) \zeta(x', t') \rangle = \Gamma \delta(t - t') \delta(x - x')$ , and consider that the cilium is long enough to neglect boundary effects; it can be assumed infinitely long in practice.

**4.1** For this system at equilibrium, what are the constraints on the real and imaginary parts of the function  $\chi$  defined in the paper? We will assume below that  $\text{Im}(\chi) = 0$  and  $\text{Re}(\chi) \equiv \chi_0$  is independent of  $\omega$ . Write down finally the Langevin equation for  $h(x, t)$  and justify that it describes the dynamics of a polymer. What is the meaning of  $\chi_0$  in this context?

**4.2** In this question we analyze the contribution of noise only and set formally  $G \equiv 0$ . Compute  $\langle h(x, t)h(x', t) \rangle$ . For a fixed  $x$ , what is the stochastic process  $h(x, t)$  in that case? Justify that  $\Gamma \propto k_B T$ .

**4.3** Compare the relative magnitude of the 2 terms in  $-\frac{\delta G}{\delta h}$  and show that this defines a typical length  $l_c$ .

**4.4** We consider length scales much smaller than  $l_c$ . Show that the term in  $-\frac{\delta G}{\delta h}$  coming from the contribution of  $f(s)\Delta(s)$  in  $G$  can be neglected. Compute the Fourier transform (with respect to  $x$ )  $\tilde{h}(k, t)$  explicitly as an integral involving  $\tilde{\zeta}(k, t)$ . It can be assumed for simplicity that  $h(x, t = 0) = 0$  for all  $s$ . Deduce an integral expression of  $h(s = 0, t)$ . Show finally that  $\langle h^2 \rangle \propto t^\alpha$ , where  $\alpha$  is to be determined.

**4.5** Reproduce quickly the argument in the opposite regime  $l_c \rightarrow 0$  and compute the exponent  $\alpha$  in this case. Deduce that in the general case the time dependence of  $\langle h^2 \rangle$  displays 2 regimes. Comment on the effects of the 2 terms in  $G$  on the diffusion of an element of the cilium.

## 5. Extension 3 - Instabilities and waves in the cilium

We consider the sperm equation (6) of the paper in the case of an infinitely long cilium. As discussed above in the Monge representation the curvilinear coordinate  $s$  is identified to the cartesian coordinate  $x$ . We assume as in the paper that  $\chi = K + i\omega\lambda$ .

**5.1** Look for wave solutions of the form  $\Psi(x, t) \propto e^{i\omega t - ikx}$  and find the dispersion relation. Show that for  $K < 0$  or  $\lambda < 0$  the solution  $\Psi = 0$  is unstable. Conclude that  $\Omega$  introduced in equation B10 is a control parameter. Can the threshold  $\Omega_c$  be deduced from the analysis of the infinite system?

**5.2** What is the condition for a plane wave  $\Psi(x, t) \propto e^{i\omega t - ikx}$  (with  $\omega, k \in \mathbb{R}$ ) to propagate? Is it relevant to the beating cilium? What determines the beating frequency and wave length in the real system? Is the “wave vector”  $k$  real in the observed beating patterns?