Cilia in nature

Nature has devised many different ways of creating fluid flow, most of them for animal propulsion, that is, for flying or swimming. At larger scales, examples are the flapping wings of birds, and the waving tails of fishes. Flapping wings are also found at smaller scales in insects. At really small scales, typically for sub-mm sizes, a fluid manipulation mechanism used by nature is that by *cilia* or *flagella*.

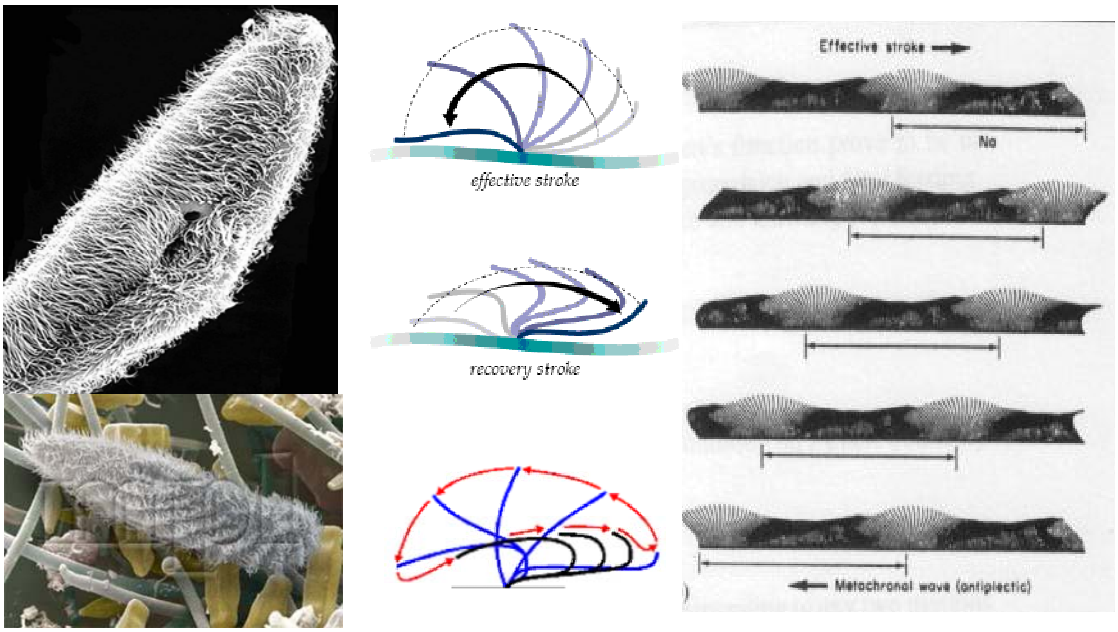

Figure 1: Left: Paramecium, covered with thousands of cilia. The size of the micro-organisms is about 100 μm. Middle: the movement of an individual cilium. The motion is asymmetric: there is an effective stroke and a recovery stroke. Right: the collective wave-like motion of many cilia on a surface. This is called a "metachronic wave". If the wave travels in the direction of the effective stroke, it is called "symplectic", if it travels against it, it is called "antiplectic".[1]

Cilia can be viewed as small hairs or flexible rods, with a typical length between 2 and 15 μm. They cover the outer surface of micro-organisms, such as Paramecium, shown in Figure 1. The length of Paramecium is about 100 μm, and its surface contains some 4000 cilia. These cilia move back and forth in a concerted manner (more about that later), and are very effective in generating flow: the swimming speed of Paramecium, for example, can be approximately 1 mm/s. This means that this micro-organism swims about ten times its own length per second. To get a feeling for this speed: a human Olympic swimming champion swims at a speed of about one times his body length per second.

An individual cilium moves in a particular, asymmetric manner, as illustrated in Figure 1. It has a so-called *effective stroke*, during which the cilium is more or less straight, and its effect on the fluid is maximized. During the so-called *recovery* stroke, its effect on the

[1] Boris Guirao: Propriétés physiques des cellules ciliées, PhD thesis l'Université Pierre et Marie Curie - Paris VI, 2007 ; A. Syred : Protozoa. SEM Image, http ://www.microscopix.co.uk/, 2001.

surrounding fluid is minimized since the cilium has a more curved shape. The micro-organism propulsion is, obviously, in the direction opposite to the effective stroke. The movement of the cilium is always in a plane perpendicular to the surface during the effective stroke. The recovery stroke movement may lie in the same plane, but also in a plane perpendicular to the effective-stroke-plane, so that the movement of a cilium may be truly three-dimensional (the latter is, in fact, the case for Paramecium). The beating frequency of the cilia, typically, is tens of Hz.

The *collective* movement of the cilia seems to happen in a concerted fashion. Neighboring cilia, namely, move somewhat out-of-phase, so that a collective wave-like motion, going over the micro-organism's surface, takes place. It is interesting, that this wave may travel in the same direction as the swimming direction of the micro-organism (but opposite to the effective stroke; this is called an antiplectic metachronic wave, and happens for Paramecium) or in the opposite direction (called symplectic metachronic wave behavior). This is illustrated in Figure 1. The origin, as well as the physiological reason, for this metachronic co-ordination is not completely clear yet.

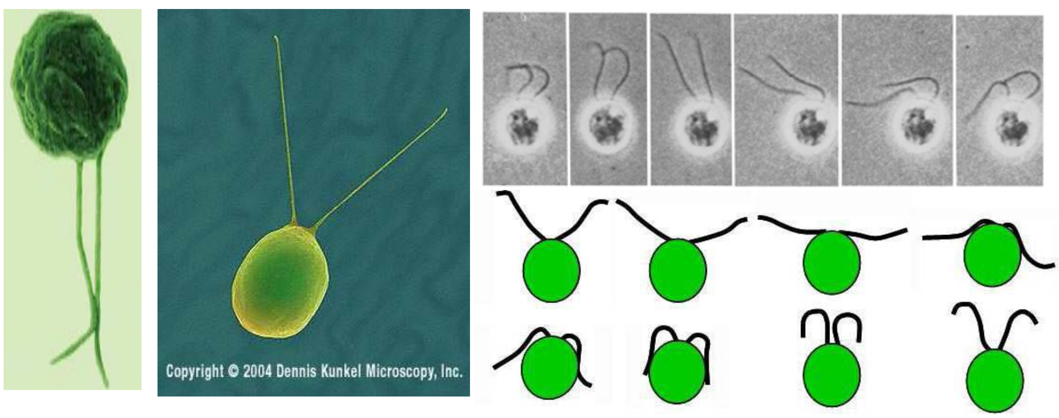

Figure 2: Chlamydomonas (green algae), a micro-organism with two flagella. It swims by an asymmetric beating of the two flagella. The size of the body of Chlamydomonas is about 10 μm, and its flagella are about 12 μm long.[2]

Flagella have the same internal structure as cilia, but they are usually longer, typically between 20 and 100 μm, and they do not cover surfaces in large quantities, such as cilia, but as a single flagellum or with a few. Also, their movement is usually different from those of cilia. Instead of having an effective and a beating stroke, a flagellum mostly makes a helical (cork-skrew) or wave-like motion. The best known example is the flagellum of spermatozoids, see Figure 4 (C). A micro-organism that is classified as a *flagellate* by most, but as a *ciliate* by others, is Chlamydomonas (or green algae), shown in Figure 2. The length of its body is 10 μm, and it has two flagellates with a length of 10-15 μm. The flagella make an effective an a recovery stroke, beating with a frequency

[2] W. Dentler : Sem, University of Kansas, Lawrence, KS; H. Hoops, R. Wright, J. Jarvik and G. Witman : Flagellar waveform and rotational orientation in a Chlamydomonas mutant lackin normal striated fibers. *J. Cell Biol.*, **98**, 818-824, 1984; Boris Guirao: Propriétés physiques des cellules ciliées, PhD thesis l'Université Pierre et Marie Curie - Paris VI, 2007.

of about 50 Hz, giving the organism a swimming speed of 100 μm/s (again, about ten times its main body length).

There are many different micro-organisms that make use of ciliary propulsion or fluid manipulation. Figure 3 depicts some of those that can be found in lakes and rivers. Note the scale bar on the right, representing a length of 1 mm.

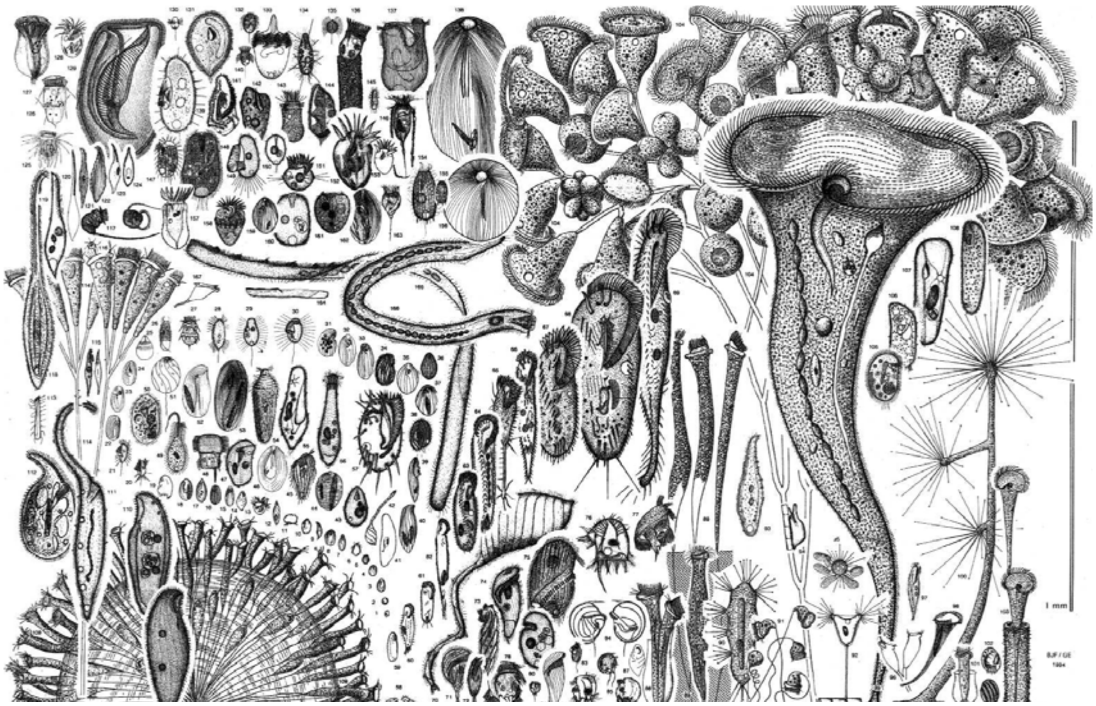

Figure 3: Ciliated micro-organisms, living in lakes and rivers. The bar on the right indicates the scale (1 mm).[3]

Next to active cilia, that are used to induce movement, cilia are also used for sensing, for example of fluid flow, but also for detecting other physical and chemical signals. Both motile and non-motile cilia and flagella are present in the human body, at various locations and with various functions, as shown in Figure 4. For example, there are cilia in the cochlear, the inner ear, that contribute in detection of vibration caused by sound. As already mentioned, spermatozoids swim by beating a flagellum. Also, the Fallopian tube of females is covered with cilia that move the fertilized ovum from the ovary to the uterus, where the ovum attaches itself. Motile cilia are also present in the lining of human lungs and the windpipe (trachea), to sweep mucus and dirt out of the airways in order to avoid infections. More examples of cilia within the human body can be found in [I. Ibanez-Tallon, N. Heintz et H. Omran : To beat or not to beat: roles of cilia in development and disease. *Hum Mol Genet*, 12 Spec No 1: R27-35, 2003].

[3] B.J Finlay et G.F. Esteban : The Ciliate Diversity Chart. Drawing, Institute of Freshwater Ecology, Windermere Laboratory, UK.

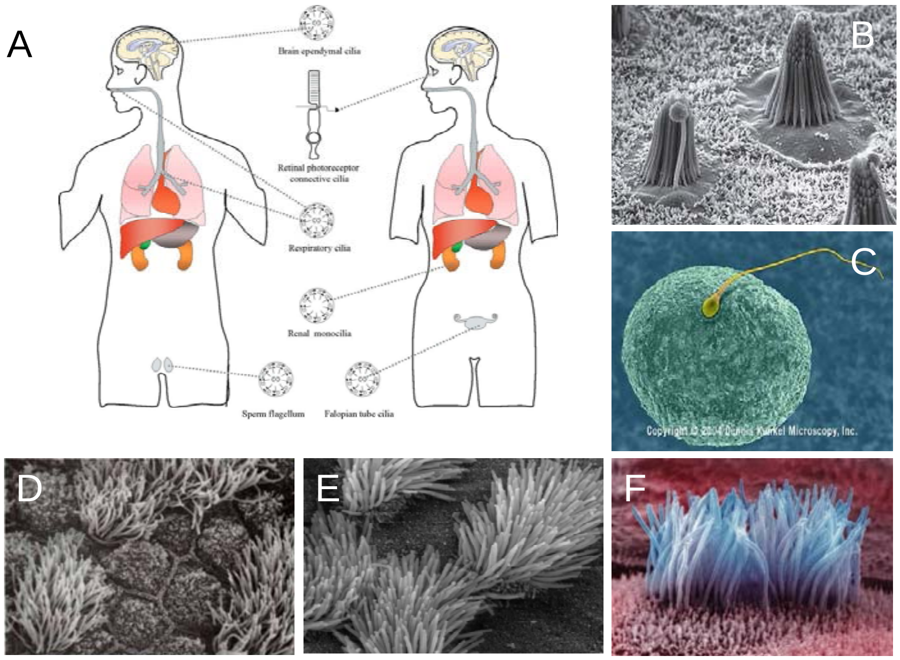

Figure 4: Cilia and flagella in the human body. (A) Several locations at which cilia can be found.[9] (B) Sensing cilia in the cochlear.[4] (C) Spermatozoid and ovum. (D) Cilia in the Fallopian tube.[5] (E) Cilia in the trachea (windpipe), and (F) in the lungs. [6]

Motile cilia and flagella both have the same characteristic **internal structure**. The “skeleton” of a cilium (or flagella) is made up by a flexible cylindrical structure that is called “axoneme”. Figure 5 (A) schematically depicts the constituents of the axoneme, showing the structure that is so characteristic for all motile cilia and flagella. An electron micrograph of the cross section of a cilium can be seen in Figure 5 (B). Nine pairs of microtubules are arranged along the periphery, and one pair of microtubules is situated at the center. Microtubules are biopolymer filaments, which, for example, can also be found in the cytoskeleton (the internal skeleton of cells). They are hollow rods approximately 25 nm in outer diameter and 14 nm inner diameter. The tubular structure is made up of two polypeptides, alpha-tubulin and beta-tubulin, see Figure 5 (C).[7] For obvious reasons, the axoneme structure shown is known as the 9+2 axoneme.

The nine outer pairs of microtubules are connected by nexin links. Also, each of the outer pairs is linked to the central pair by a radial spoke. And, a closer inspection of the outer microtubules shows that they have side arms of proteins, called dyneins. These proteins are actually mechanical motors, and they are instrumental in the movement of the cilia.[8]

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[4] D. Corey : SEM Image, http ://focus.hms.harvard.edu/2002/March222002/research briefs.html.
[5] D.E. Kelly, R.L. Wood et A.C. Enders : Bailey's textbook of microscopic anatomy. Williams & Wilkins, Baltimore, 18th edition, 1983.
http ://www.cgu.edu.tw/Anatomy/His-picture-female1.htm.
[6] C. Daghlian : SEM Image, http ://remf.dartmouth.edu/imagesindex.html, DATABASE : Powered by Cilia. Science, 313(5789):895e-, 2006.
[7] S. Suresh: *Biomechanics and biophysiscs of cancer cells*. Acta Biomaterialia **3**, 413-438 (2007).
[8] There are three large families of molecular motors: kinesines, myosines, and dyneins.

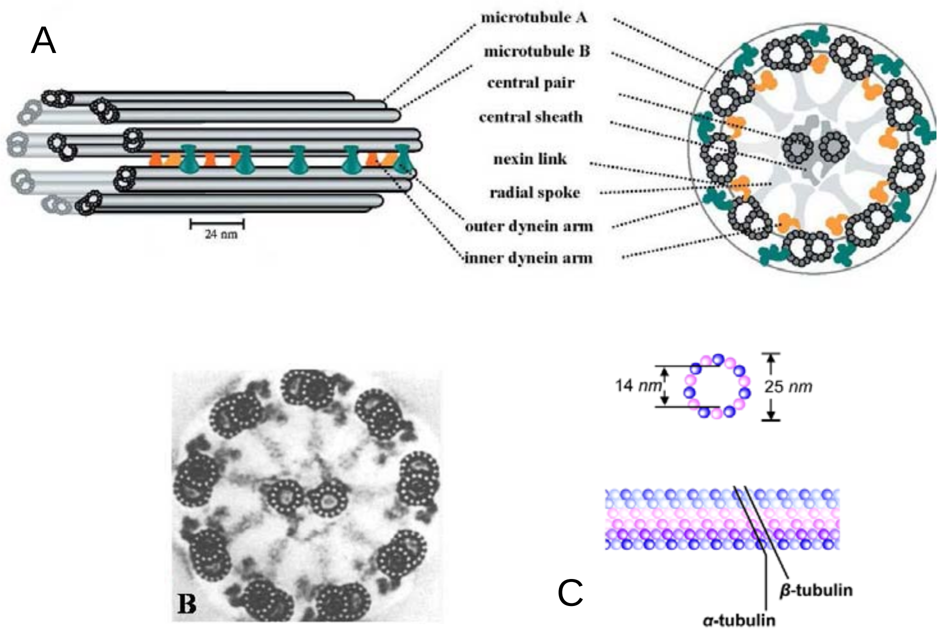

Figure 5: The internal structure of motile cilia or flagella: the "axoneme". (A) A schematic, showing the 9+2 arrangement of microtubules, and the various other constituents: nexin links between the outer microtubules, radial spokes connecting the inner and outer tubules, and the dynein arms attached to the outer microtubules.[9] (B) Electron micrograph of a cross section through a cilium.[10] (C) Structure of a microtubule.[7]

Dyneins convert energy, that is released in the body by hydrolysis of ATP (adenosinetriphosphate), into mechanical work by changing their molecular conformation. These successive conformation changes allow the molecule to take "steps" along the micro-tubules in a certain direction (one step per hydrolyzed ATP molecule). The outer dyein arms attached to the microtubule pairs are different in molecular structure than the inner dynein arms. The molecular structures are shown in Figure 6.

[9] I. Ibanez-Tallon, N. Heintz and H. Omran : To beat or not to beat : roles of cilia in development and disease. *Hum Mol Genet*, 12 Spec No 1: R27-35, 2003.

[10] B. Alberts, D. Bray, J. Lewis, M. Raff, K. Roberts et J.D. Watson : *Molecular Biology of the Cell.* Garland, New York, 4th edition, 1994.

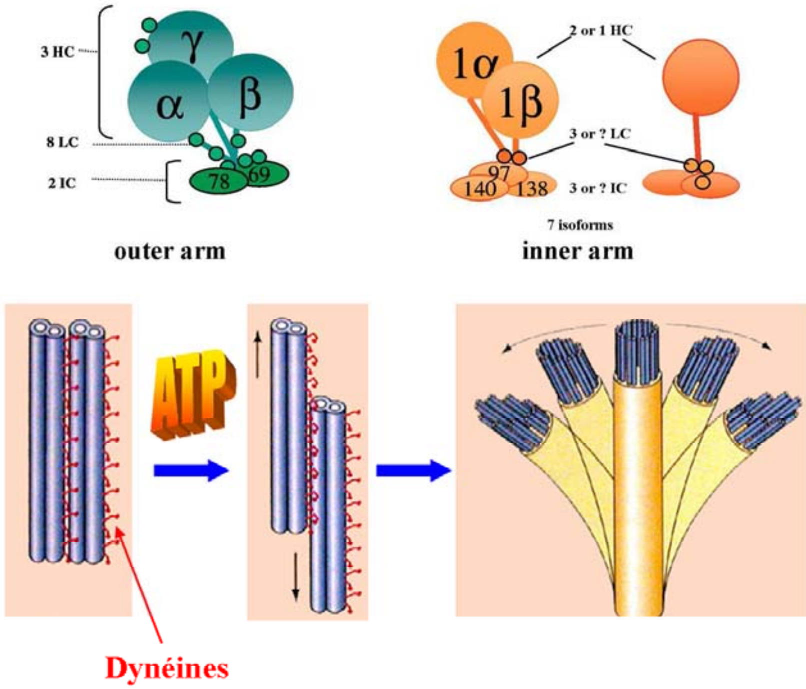

Figure 6: The mechanism of cilia movement. The microtubules have side arms consisting of dyneins. The molecular structure of the dyeins is different for the inner and the outer arms; both are shown here[9] (see also Figure 5). The dyneins change molecular conformation by converting energy released by hydrolysis of ATP. The change in conformation leads to a relative change in position of the pairs of microtubule, resulting in a bending motion of the axoneme.[11]

Now, in the absence of ATP, the dyneins fixed to each peripheral microtubule pair are also attached to the adjacent microtubule pair. The presence and hydrolysis of ATP provokes the detachment, movement, and re-attachment of the dyneins in such a way that the pairs of neighboring microtubule pairs slide along one another, see Figure 6 (the dyneins indeed take steps along the microtubules). Since the microtubules are connected, through the nexin connections, trough the central microtubule pair, and through the anchorage in the cell wall, this gliding motion results in an overall bending of the cilium.

The details of the **control** of the beating of cilia is still not completely understood, and this is a topic of ongoing research. It is the combination of the properties of the molecular motors, their interaction with the elastic properties of the axoneme, as well as the hydrodynamic coupling, through the fluid, that determines the cilia movement: their asymmetry in motion, their frequency, the direction of beating, and the metachronic characteristics.

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[11] Boris Guirao: Propriétés physiques des cellules ciliées, PhD thesis l'Université Pierre et Marie Curie - Paris VI, 2007.