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Effect of bunching of cilia and their interplay on muco-ciliary transport

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ABSTRACT

Cilia are hair-like organelles projecting from a eukaryotic cell, used either for locomotion or as sensors. Cilia commonly occur in patches. To take this into consideration, we represent cilia in multiple patches, instead of the conventional 'dense mat' representation. We focus on the combined action and interplay of these patches. The effects of varying the frequency, spacing and phase lag of the beating of one cilia bunch with respect to the beating of adjacent patches are studied. We model the Airway Surface Liquid (ASL) as a three-layer structure. The possibility of an optimum frequency of beating is noted and the change of mucous flow under different spacing and phase differences are observed.

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1. Introduction

The study of cilia has shown escalating physiological significance in the past decade owing to the discovery of its role in the proper functioning of many mechanisms in the human body and other organisms. In a relatively short period of time, over ten diseases, such as primary ciliary dyskinesia (PCD), hydrocephalus, polycystic liver and kidney disease, some forms of retinal degeneration and Joubert Syndrome, have been linked to the malfunctioning of cilia. They have been classified as 'ciliopathies' (Badano [1]), (Adams et al. [2]). Some of the most vital ciliopathies are caused due to the lack of coordination in ciliary movement in the epithelium. Cilia exhibit a distinctive, complex asymmetric manner of movement. Each beat cycle comprises of an 'effective stroke' and a 'recovery stroke'. In the former, the cilia are relatively straight, and their effect on the fluid is maximized. In the latter, their effect on the surrounding medium is minimized since the cilium has a more curved shape. Any disruption of this characteristic pattern can lead to physiological problems such as when the cilia on the epithelium show hyper/hypo motility or disoriented arrangement and beat direction (Van's Gravesande et al. [3]). The PCD is a classic example of such a condition. It involves the cilia on the respiratory tract and reproductive organs. PCD leads to poor muco-ciliary clearance and hence infection (Rayner et al. [4]), (Bush et al. [5]). This disease manifests itself during

the embryologic phase of development and is a result of inefficient and unsynchronized ciliary movement.

Normally-functioning cilia determine the position of the internal organs during early embryological development. Therefore, individuals with PCD have a 50% chance of developing situs-inversus (El Zein et al. [6]) (major visceral organs are reversed or mirrored from their normal positions), accompanied by progressive sinusitis, and bronchiectasis. A sum total of these effects is called the 'Kartagener Syndrome' (Dhar et al. [7]).

Another severe condition associated with dysfunctional cilia is the Joubert Syndrome (Doherty et al. [8], Brancati et al. [9]) which is a rare genetic disorder that affects the cerebellum. This affects the balancing and coordinating control of the brain on the skeletal muscles. It is caused due to dysfunctional molecular structure of the cilia and adversely affects the numerous critical developmental signaling pathways essential to cellular development.

Also, Usher syndrome (USH), is a heterogeneous disease, which, in rare cases, can be associated with bronchiectasis, chronic sinusitis and reduced nasal mucociliary clearance, which is indicative of ciliary dyskinesia (Bonneau et al. [10]).

The diseases mentioned hitherto are genetically acquired. Several 'acquired diseases' are also consequent upon malfunction of cilia or may have ciliary dysfunction as a symptom. For example, when infected with various common cold viruses, the respiratory epithelium reacts by shedding individual cilia as well as entire ciliated cells (Rautiainen et al. [11]). Cilia may also become withdrawn into the cell body, as is seen in the nasal epithelium during coronavirus infection (Afzelius [12]). A substantial loss of cilia is likely to result in rhinorrhoea (a condition where the nasal cavity

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1 is filled with a significant amount of mucous fluid). A reduction to
2 about half the normal number of ciliated cells has been recorded
3 from the tracheae of hamsters that were deprived of vitamin A
4 since birth (McDowell et al. [13]).

5 The cilia in the ependyma (the thin epithelial membrane lining
6 the ventricular system of the brain and the spinal cord) of the
7 brain, though not exposed to the same harsh environment as the
8 tracheal cilia, can be affected by vitamin A deficiency (McDowell
9 et al. [13]) in the same way as the respiratory cilia. They can also be
10 infected by viruses such as the mumps virus or various types of
11 influenza virus (Johnson [14], Tanaka et al. [15]). The first step of
12 the infection is replication of the virus in close vicinity to the cilia.

13 This leads to a loss of most cilia. As a consequence hereof, there
14 are no cilia to prevent particular matter from settling down on the
15 ependymal surface (Stokroos et al. [16]).

16 Study of the physiology of numerous animals has shown that the
17 synchronization of cilia occurs in patches. Patches are distinct regions
18 of ciliary activity each separated from one-another, and spread over
19 ciliary epithelium lining various organs of the body. These patches of
20 cilia span some few micrometers (Eshel and Priel [17]). It appears
21 that in experimental studies, coordination of cilia has not been seen
22 to exceed distances greater than a few micrometers.

23 In some cases, the patches of cilia are physically separated by
24 clefts or ridges. In Sanderson and Sleight [18], patches of cilia seen
25 on rabbit tracheal epithelium by SEM are separated by such clefts.
26 The patches of ciliated surfaces are pressed together in these cleft
27 regions. It is mentioned that the areas of activity and the direction
28 of metachronic waves traveling across the areas are not randomly
29 changing. Examination of high-speed cine-film showed that the
30 activity on the epithelial surface is comprised of many small
31 patches of regularly beating cilia. The extent of these patches
32 depends on the type of control over ciliary beating. In frog palate,
33 where patches are highly localized, it is under neural control. In
34 rabbit epithelium, where the action of cilia is spontaneous, larger
35 areas can operate in synchronization.

36 In other cases the patches of cilia are separated by groups of
37 other cell types. In a publication by Blake [19] which describes
38 various mechanisms of mucus clearance in the mammalian lung, it
39 is stated that cilia certainly do not occur in a dense mat form as
40 was previously thought and while ciliated cells cover approxi-
41 mately 30–60% of the epithelium, goblet cells occupy approxi-
42 mately 20–40% of the epithelium.

43 Also in a study by Antunes et al. [20] using 'Scanning Electron
44 Microscopy (SEM)', the degree of ciliation of the murine respira-
45 tory system was observed. It was found that the ciliated cells occur
46 only in scattered patches. However, the degree of ciliation varied
47 from area to area; for example, while the mouse tracheal epithe-
48 lium had 30–35% of the surface covered in ciliated epithelium,
49 the mouse nasal septum had approximately 90% of the epithelial
50 surface covered with cilia.

51 Thus, whether groups of ciliated cells are separated by clefts or
52 simply by other cell types, the overall ciliary function is in patches.

53 Studies which assume the cilia to exist in a dense mat form
54 are mostly mathematical. In such sources, attention is paid to the
55 beating characteristics and function of individual cilia. In order to
56 extend the effect of individual cilia over some area, the treatment
57 of individual cilia is simply extended over some space. Indeed
58 cilia are represented either as slender bodies or with a spatially
59 continuous force distribution (Phenomenological modeling) (Smith
60 et al. [21]). While the discrete cilia method is more mathematically
61 precise, volume force models are generally used to include physical
62 effects that are difficult to take into account in a more precise
63 mathematical model even though such models require a number of
64 simplifying approximations in their formulation.

55 In neither of the above approaches does one appreciate the
66 reality of the situation i.e. that cilia in fact occur in patches.

Therefore, we realize the need for one more factor to be analyzed,
i.e. how the cilia, in different locations of the epithelium assist
each-other in muco-ciliary clearance.

In an analytical work by Blake [19], cilia are considered to exist
in an infinite array. The mucous flow rate is evaluated as a function
of ciliary beat frequency (CBF), cilium length and cilia concentra-
tion. Though this provides a comprehensive study of how mucous
flow is affected by important parameters of ciliary action, it does
not fully capture the reality of cilia, i.e. that cilia are unevenly
distributed over the epithelium and hence another parameter to
be studied is how these tufts of cilia interact and cooperate with
each-other. Similar models have been considered by Smith et al.
[21] and Keller [22].

In this study, we try to understand this hitherto ignored aspect
of ciliary action i.e. the collective behavior of the cilia patches. We
do so by investigating the effects of varying the frequency, spacing
and phase lag of the beating of one cilia bunch with respect to the
beating of adjacent patches. Such an integrated study of all these
factors is previously unseen.

Before proceeding with the analysis of our results, it is
important to realize the implications of our studies. As mentioned
earlier, an understanding of the biological mechanisms underlying
ciliary motion plays a vital role in diagnosis and treatment of many
fatal diseases. Extending the scope further, we find that the study
of the synchronized movement of cilia has inspired to mimic
them and develop 'artificial cilia'. These artificial cilia, apart from
application in MEMS and micro-robotics, have been used on lab-
on-a-chip devices for varied applications including microfluidic
pumps, acoustic detection, and heat transfer (Khaderi [23], Brei-
denich [24]).

Further, 'grafting' of ciliary epithelium has been shown to be
possible. 'Grafting' of cilia into organ systems of those with vast
areas of impaired ciliary function could be life-saving. In a study by
Bootz, and Reuter [25], the aim was to establish whether it was
possible to carry out such grafting in an animal model. They used
purebred strains of Lewis blood group rats to avoid host-versus-
graft rejections of mucous membrane transferred from a donor to
a recipient animal. Their findings showed that respiratory epithelia
heal when grafted onto a recipient site which has an adequate
blood supply but do not lose their initial differentiation or
functions. Such results are important clinically for reconstruction
of the respiratory tracts.

Also, in experimental studies it has been shown that the
frequency of ciliary beating plays a key role in altering the rate
of transport of the fluid medium. Alteration of levels of ATP and
ACH (acetylcholine) in the physiological environment has shown
to drastically enhance ciliary beating, leading to an almost linear
increase in ciliary tip forces (Zvi Teff [26]). In regard to inter-ciliary
spacing, it has been studied by Grönbaum [27] in a computational
hydrodynamic model of the ciliated tentacle arrays (using *M.edulis*
as a case study), that spacing between cilia can alter the efficiency
of clearance of the fluid medium in which cilia occur. Therefore
a good understanding of the parameters looked at in our study
can gain us valuable insight about the efficiency of muco-ciliary
clearance.

Our approach is computational and uses a hydrodynamic
model that calculates mucus flow rates induced by ciliary move-
ment. We model a generic ciliary epithelium and this model
could be used to represent ciliated epithelia in various organs
and species.

At the beginning, we validate our computational model using
published experimental and analytical studies. Our model of the
ciliary epithelium is based on the three layered model of the ASL.
Having proved that our model corresponds to reality, we then
extend our model to incorporate the ciliary patches, since in real
life cilia do not occur as a dense mat, but rather in patches. Finally,

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