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Review

Physical constraints for pathogen movement

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ABSTRACT

In this pedagogical review, we discuss the physical constraints that pathogens experience when they move in their host environment. Due to their small size, pathogens are living in a low Reynolds number world dominated by viscosity. For swimming pathogens, the so-called scallop theorem determines which kinds of shape changes can lead to productive motility. For crawling or gliding cells, the main resistance to movement comes from protein friction at the cell–environment interface. Viruses and pathogenic bacteria can also exploit intracellular host processes such as actin polymerization and motor-based transport, if they present the appropriate factors on their surfaces. Similar to cancer cells that also tend to cross various barriers, pathogens often combine several of these strategies in order to increase their motility and therefore their chances to replicate and spread.

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1. Introduction

Some of us enjoy recreational activities that take one into new terrains, like mountain climbing in high altitudes or diving in the sea. In order to survive in these worlds that are commonly not inhabited by humans, one has to learn new skills (e.g. fixing climbing ropes) and develop new technologies (e.g. scuba equipment for diving). It is exactly this kind of challenge that pathogens have solved through evolution when they have successfully adapted to a certain host environment. In this pedagogical review, we will deal with the physical aspects of this challenge, which can be considered either as constraints or as opportunities for pathogens to conquer new worlds.

In their seminal work, Purcell and Berg have pointed out that microorganisms have to move under the very special physical constraints of a low Reynolds number world, for which we humans have to build intuition as we ourselves live in a high Reynolds number world [1–3]. This insight cumulated in the *scallop theorem*, which we will review below and which implies that only certain types of swimmer designs are possible [1,4]. Of course, this insight applies equally well to non-pathogenic cells as it does to bacterial or unicellular eukaryotic pathogens. However, in contrast to many non-pathogenic cell types, pathogenic cells are bound to move from one host environment to the next, because they are constantly under the pressures created by the immune system and

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the potential death of the host. In principle this movement can be passive (e.g. floating in air or being carried with the blood stream), but often the essential steps are active, especially when a barrier has to be crossed between two different environments [5]. Therefore, in contrast to most non-pathogenic model systems studied for cell motility (for example swimming cells like E. coli bacteria or human sperm cells, and crawling cells like Dictyostelium or fibroblasts), pathogens have developed intriguing strategies to move in more than one environment and to actively cross barriers (similar maybe to white blood cells or metastasing cancer cells). Another essential difference to non-pathogenic cells is that some small pathogens (mainly viruses, but also bacteria) have developed means to move by exploiting intracellular host processes, such as motor- or polymerization-based transport. Thus it is not only medically very relevant, but also scientifically highly interesting to study how pathogens have successfully solved the challenge to achieve high levels of variable motility. As it is true for studies of pathogens in general, these studies are not only very instructive regarding pathogen motility, but also regarding host processes.

Here we review some of the physical constraints that shape the solutions pathogens have evolved in order to move in various host environments. We start with a classificiation of the different modes of pathogen movement, which shows the large spectrum of existing phenomena and how they differ in regard to the physical mode of propagation. We then proceed with a short review of the classical work on low Reynolds number physics that strongly determines the way pathogens do move. In particular, we discuss the scallop theorem and its implications for microswimmer design. We then turn to surface-bound motility and discuss crawling and gliding cells. We finally address pathogen movement based on intracellular processes such as recruitment of molecular motors and initiation of actin polymerization.

2. Classification of pathogen movement

In general, motility of pathogenic cells can be classified along the same lines as cell motility in general [6,7]. Table 1 presents such a classification with representative examples for pathogens. We first distinguish between swimming cells and cells moving on surfaces. Swimming cells either use appendages like cilia or flagella or whole body shape changes to move. For pathogenic bacteria like enterohemorrhagic E. coli (EHEC), *Salomella* or *Vibrio cholerae* (the causative agent of cholera), the main organelle is the bacterial flagellum whose rotation is driven by ion gradients [8] (see also review by Chaban, Hughes and Beeby in this issue). Interestingly, bacterial *spirochetes* (which among other illnesses cause syphilis or Lyme disease) also swim using a flagellum, but in contrast to most other bacteria, flagella in spirochetes are localized within the bacterium and do not protrude from the surface (see review by Wolgemuth in this issue). Therefore they swim effectively by the resulting changes in cell shape. Pathogenic unicellular eukaryotes like *leishmania* (the causative agents of the disease leishmaniasis) or *trypanosomes* (the causative agents of sleeping sickness) use the eukaryotic flagellum, whose beating is caused by molecular motors [9] (see also review by Krüger and Engstler in this issue). Similar to the spirochete case and in contrast to most of their non-pathogenic counterparts (e.g. human sperm cells), the trypanosomes have their flagellum attached to the cell body, leading to swimming through global changes in cell shape [10].

Table 1
Classification of pathogen motility.

Movement	Mechanism	Examples
Swimming	Bacterial (rotating) flagellum	EHEC, Salmonella, Vibrio cholera
	Eukaryotic (beating) flagellum	Leishmania (in the gut of sandflies), Plasmodium (as gametes)
	Cell shape changes through flagellum attached to cell body	Spirochetes, Trypanosomes
Crawling	Actin polymerization	Acanthamoeba
Gliding	Conveyer belt (motor-based)	Plasmodium (as sporozoites)
	Pilli (twitching motility)	Neisseria
Host transport	Motor-based transport	Adeno virus, Herpes simplex virus, Influenza virus, Human immunodeficiency virus (HIV)
	Actin polymerization	Poxviruses, Listeria, Shigella

Surface-bound motility can be further classified into crawling and gliding. Crawling is achieved by pushing out the cell front by polymerization of an actin-based lamellipodium, a process which for several model cell types has been quantitatively investigated in large detail [11]. Typical cases are pathogenic amoebae like the *Acanthamoeba* (which can cause encephalitis and keratitis) [12] (see also review by Dufour, Olivo-Marin and Guillen in this issue). Gliding can be achieved by several means, including motor-based conveyer belt systems (like for *Plasmodium*, the causative agent of malaria, in the skin phase, see also the review by Heintzelman in this issue) [5,13] or twitching motility that is based on pili retraction (e.g. of *Neisseria gonorrhoeae*, the causative agent of gonorrhea) [14,15]. A well-studied model system for gliding motility is the social bacterium *Myxococcus xanthus* (see also review by Islam and Mignot in this issue).

In contrast to bacterial or unicellular eukaryotic pathogens, viral pathogens cannot use shape changes or appendages such as flagella to move. Therefore they are more dependent on exploiting movement-generating processes in their host cells, such as transport based on molecular motors (e.g. adenovirus exploiting endosomal pathways) [16] or polymerization of cytoskeletal filaments (e.g. actin polymerization by poxviruses) [17]. Interestingly, the same processes are also exploited by some pathogenic bacteria (e.g. *Listeria* and *Shigella*) [18], which like viruses are relatively stiff objects that can control host processes by placing appropriate factors on their surfaces (see also review by Newsome and Marzook in this issue).

3. Low Reynolds number world

We first discuss the universal physical constraints that shape the life of microorganisms. We start with life inside a cell and observe that the typical size of a biomolecule is $R = 1$ nm (e.g. the radius of a small globular protein of mass 30 kDa). This immediately gives us an estimate for its typical diffusion constant D according to the Stokes-Einstein relation

$$D = \frac{k_B T}{6\pi\eta R} \approx \frac{(10\,\mu\mathrm{m})^2}{\mathrm{s}} \approx \frac{(10\,\mathrm{nm})^2}{\mu\mathrm{s}}$$

Here k_B is the Boltzmann constant, $T \approx 300$ K the ambient temperature and $\eta \approx 10^{-3}$ Pa s the viscosity of the aqueous medium. Because the three physical variables R, T and η used for this estimate have values that are roughly universal for biological systems, this estimate is very general for a small biomolecule in solution (the passive diffusion constant could be diminished by transient binding processes or obstacles, but it cannot be higher). The time to