



# The dynamics of sperm detachment from epithelium in a coupled fluid-biochemical model of hyperactivated motility



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## HIGHLIGHTS

- We examine the role that bonds and surfaces make in epithelial detachment of spermatozoa in the oviduct.
- We propose two models for bond behavior at the epithelial surface and demonstrate the differences in detachment events.
- Considering forces alone is not sufficient to understand detachment and surface interactions.
- Both asymmetry and high amplitudes of the flagellar wave form are necessary for sperm to effectively break free of a surface.

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## ABSTRACT

Hyperactivation in mammalian sperm is characterized by a high-amplitude, asymmetric flagellar waveform. A mechanical advantage of this hyperactivated waveform has been hypothesized to be the promotion of flagellar detachment from oviductal epithelium. In order to investigate the dynamics of a free-swimming sperm's binding and escaping from a surface, we present an integrative model that couples flagellar force generation and a viscous, incompressible fluid. The elastic flagellum is actuated by a preferred curvature model that depends upon an evolving calcium profile along its length. In addition, forces that arise due to elastic bonds that form and break between the flagellar head and the surface are accounted for. As in recent laboratory experiments, we find that a hyperactive waveform does result in frequent detaching and binding dynamics that is not observed for symmetric flagellar beats. Moreover, we demonstrate that flagellar behavior depends strongly on the assumptions of the bond model, suggesting the need for more experimental investigation of the biochemistry of epithelial bonding and the shedding of binding proteins on the sperm head.

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## 1. Introduction

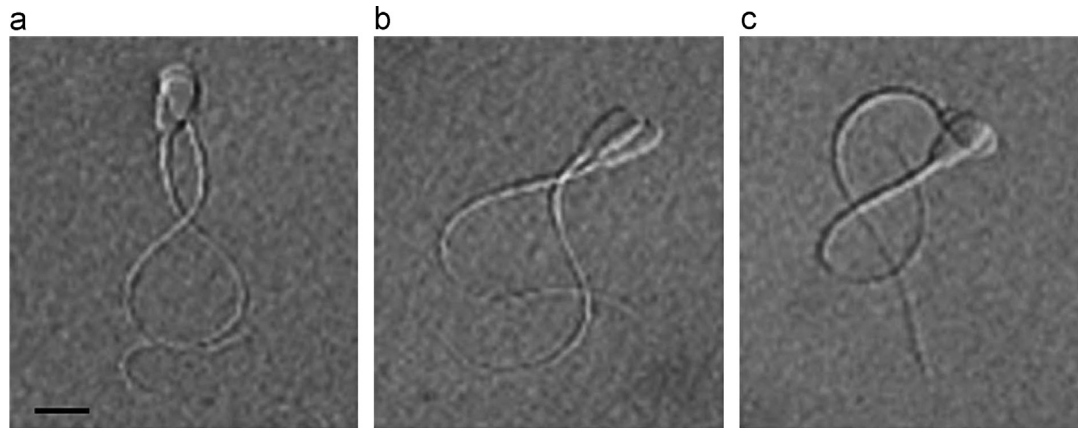
Successful fertilization in mammalian species requires sperm flagellar waveforms to change dramatically as the sperm travels through the female reproductive tract. One change that must occur is the transition from a symmetric, sinusoidal flagellar beatform to an asymmetric beatform with larger bending amplitudes along the flagellum, first observed in Yanagimachi (1970). Fig. 1 shows a series of micrographs of a bull sperm during active motility, transitional motility, and hyperactive motility (Marquez and Suarez, 2004). This intriguing motility change naturally raises the questions: What are the biochemical signaling pathways that initiate and maintain hyperactivation? Given these pathways, how

is the internal dynein–microtubule force generation system of the flagellar axoneme altered to achieve this hyperactivated waveform? Moreover, what is the mechanical function of this hyperactivated waveform? As our focus is on the last question, we will consider the coupled system of a motile flagellum and a viscous, incompressible fluid.

Although there are still many open questions surrounding the details of the biochemistry of hyperactivation, it has been established that hyperactivation is mediated by calcium signaling pathways (Carlson et al., 2005; Ho et al., 2002; Suarez et al., 1993), and that mice whose sperm lack necessary membrane calcium (CatSper) channels do not exhibit hyperactivated motility and are infertile (Qi et al., 2007; Quill et al., 2003). Exactly how changes in calcium levels act to produce different bend patterns expressed by the axoneme is not known. It has been hypothesized that the asymmetric bending may be due to calcium binding directly to a subset of dynein arms (Lindemann and Kanous, 1995) or due to calcium binding to calmodulin receptors (Suarez, 2008).

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**Fig. 1.** Bull sperm exhibiting (a) activated motility, (b) hyperactivated motility, and (c) maximally hyperactivated motility. Reproduced with permission from Marquez and Suarez (2004).

In any case, the underlying biochemistry significantly alters the internal force generation to produce the observed hyperactive waveform. A mechanical advantage of this type of waveform has been hypothesized to be the generation of greater propulsive forces for the sperm to pass through the outer layers of the oocyte–cumulus complex (Alasmari et al., 2013; Quill et al., 2003; Stauss et al., 1995; Suarez and Dai, 1992; Suarez et al., 1991; Suarez, 2008). In addition to promoting penetration of the complex, viscoelastic matrix surrounding the oocyte, hyperactivated flagellar beating is hypothesized to enhance the sperm's ability to break free of the oviductal epithelium (DeMott and Suarez, 1992; Katz et al., 1989; Smith and Yanagimachi, 1991). Attachment occurs along cilia lining the epithelium and some candidates for binding receptors have been proposed (Baillie et al., 1997; Ignatz et al., 2007). Recently, it was confirmed that this motility pattern does accompany frequent attachment to and detachment from the oviductal epithelium in vivo (Chang and Suarez, 2012). This binding behavior is attributed to the forces generated by hyperactivation as well as the shedding of binding proteins on the head of the sperm, but the interplay between motility and protein shedding is unclear (Hung and Suarez, 2012; Pacey et al., 1995; Suarez et al., 2008; Suarez and Pacey, 2006). Sperm that do not undergo hyperactivation are unable to move through the oviduct (Ho et al., 2009).

While an asymmetric waveform of a free-swimming hyperactivated sperm results in a circular or curved trajectory (Yanagimachi, 1970), it may also generate both thrusting and tugging forces on a tethered sperm that could enable it to detach from a surface. To begin to address this question, a recent study (Curtis et al., 2012) considered a simple fluid dynamic model that calculated the total force generated by a filament with specified kinematics, clamped or freely hinged at the head. For a specified symmetric waveform with biologically realistic parameters, the total force at every phase of the wave was always a thrusting force, opposite the direction of the propagated wave. However, it was found that a specified asymmetric waveform could achieve total force both opposite the wave direction (thrust) and in the wave direction (tugging), depending upon the phase of the wave.

Motivated by the work in Curtis et al. (2012), here we present a model of the fully coupled system of an actuated, elastic filament in a three-dimensional Stokes fluid bounded by a planar wall. We use the preferred curvature model presented in Olson et al. (2011) that incorporates calcium dynamics to determine flagellar bending forces. We develop a model of sperm attachment to an epithelium layer by allowing elastic linkages between the planar boundary and the flagellum 'head' to form when the free-swimming flagellum comes within a threshold distance of the wall. In addition, detachment of

the bound sperm can occur when the elastic linkage is stretched by the fluid beyond a given threshold. As in the recent experiments of Chang and Suarez (2012), we find that flagella with symmetric beat patterns (non-hyperactivated) tend to stay attached to the wall, and that hyperactivated flagella do dynamically attach and detach from the wall, and their resulting swimming trajectory may, indeed, allow them to swim away from the wall. While examining the resultant force for a given kinematic wave does give some insight about possible detachment, we see that other features, such as rotational motion of the flagellum induced by the wall and the nature of the elastic bonds, are essential mechanical elements contributing to the dynamics of flagellar detachment.

In the following sections, we will briefly describe the three-dimensional method of regularized Stokeslets (Ainley et al., 2008; Cortez et al., 2005) that allows us to couple the forces of the elastic flagellum with a Stokesian fluid in the presence of a planar wall. We will also briefly describe the coupled calcium, preferred curvature model of hyperactivation presented in Olson et al. (2011). We will present in detail the model of flagellar attachment and detachment to epithelia. We will show simulation results that examine the dynamics of a free-swimmer interacting with a planar surface, and discuss the differences observed for small amplitude, symmetric swimmers; large amplitude, symmetric swimmers; and hyperactivated swimmers whose waveform emerges from their internal calcium dynamics.

## 2. Stokes flow bounded by a plane wall

The velocity and length scales of sperm motility are small enough that inertial effects are negligible, with resulting Reynolds number on the order of  $10^{-4}$ – $10^{-2}$ . The governing fluid equations in this low Reynolds number regime are the incompressible Stokes equations:

$$\begin{aligned} \mu \Delta \mathbf{u} &= \nabla p - \mathbf{F}(\mathbf{x}) \\ \nabla \cdot \mathbf{u} &= 0 \end{aligned} \quad (1)$$

with fluid velocity  $\mathbf{u}$ , dynamic viscosity  $\mu$ , pressure  $p$ , and external force density (force per unit volume)  $\mathbf{F}$ . This force  $\mathbf{F}$  represents the force that the sperm flagellum is exerting on the fluid. For simplicity, we will ignore the effects of the shape of the sperm head, which can vary widely in mammalian species. A slender filament such as a sperm flagellum can be approximated as a curve immersed in a fluid, exerting forces along its length. This system will be non-dimensionalized using characteristic scales listed in Table 1, which allow us to scale out the factor of  $\mu$  in the equations.

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