Comments to the Editor

Comment on the Article by J. Elgeti, U. B. Kaupp, and G. Gompper: Hydrodynamics of Sperm Cells Near Surfaces

ABSTRACT A recent study by Elgeti et al. used multiparticle collision dynamics to simulate a long-standing problem: the approach of sperm to surfaces, and subsequent accumulation. The authors highlight differences in their predictions with those of the earlier Stokes flow simulations of Smith et al. attributing the differences to methodological flaws in the earlier article. In this Comment, we discuss the criticisms leveled in detail, and review some recently published work that shows how species-specific details of cell morphology provides a more likely explanation for the differing predictions of the two studies. We also highlight experimental work that supports the study of Smith et al.

INTRODUCTION

> "The dominating characteristic of [human] sperm distribution in a tube is their tendency to accumulate near the walls… At the wall the number of motile spermatozoa swimming at $V \geq 30$ μm/s is at least 30% *less than* at 10 μm from the wall…" (Winet et al. (1), *with our italics*).

Sea urchin sperm fertilize in open sea water, whereas mammalian, and more specifically human sperm, are evolved to swim through a liquid film between closely-opposed surfaces. There are therefore strong biological reasons for supposing that their surface-interaction behavior might differ, and hence that model predictions based on marine species do not necessarily translate to mammalian, and vice versa.

A recent article by Elgeti, Kaupp, and Gompper (2) (referred to henceforth as Elgeti et al.) addresses the long-standing problem of sperm accumulation near surfaces, first famously investigated by Lord Rothschild (3) in the early 1960s. Elgeti et al. approach the problem using multiparticle collision dynamics, which simulates a swimming cell as several hundred linked monomer molecules, the surrounding fluid being modeled as a set of discrete fluid particles, interacting in a lattice of "collision cells" through stochastic rotation. Elgeti et al. highlight significant differences between the predictions of their model and the predictions of an earlier Stokes flow simulation study by our group (4) (referred to henceforth as Smith et al.), which they interpret as being due to methodological weaknesses in the latter.

We wish to examine further the criticisms of the methodology of Smith et al., and then to examine some alternative explanations for the differing predictions of the two studies, focusing particularly on the role of species-specific morphological differences. Finally, we review experimental evidence on human sperm, which support the work of Smith et al.

NUMERICAL AND PHYSICAL STABILITY

Smith et al. carried out simulations of human sperm motility near a no-slip plane surface using a combined slender body/boundary integral approach, a key feature being the consideration of the size and shape of the human sperm head. A principal finding was that a sperm initially parallel to, and one body-length away from, the surface would, for certain planar waveforms, perform a pitching behavior that steered it eventually to a trajectory anywhere between ~15% and 60% of the body length away from the surface (Fig. 1, *a* and *b*). In the final stable trajectory, the cell was found to be tilted slightly away from the surface, the component of motility away from the boundary being balanced by a cell- and surface-generated flow field which attracts the sperm back to the boundary. Smith et al. also investigated whether certain observations of Woolley (5) in rodent sperm might apply to human sperm cells.

By contrast, the Elgeti et al. simulations did not predict accumulation at a finite height for initially parallel cells, but rather a stochastic drift toward the boundary, followed by collision. Elgeti et al. interpreted the difference in the predictions as follows: First, that Smith et al. failed to predict that an initially parallel cell would reach the boundary because the numerical simulation study of Smith et al. was "numerically unstable". Second, that Elgeti et al. did not predict the "finite height" accumulation because this state is "Most likely…only marginally stable", and would be obliterated by fluctuations in the simulations of Elgeti et al. To summarize, Elgeti et al. state that:

1. Smith et al. fail to predict the correct state of boundary accumulation due to methodological errors; the correct state is lost due to a numerically unstable algorithm.
2. Smith et al. predict a "marginally stable" and unphysical state instead (which criticisms are considered by us in more detail below).

Submitted Nov 24, 2010, and accepted for publication March 2, 2011.

*Correspondence: d.j.smith.2@bham.ac.uk

0006-3495/11/05/2318/3 $2.00

doi: 10.1016/j.bpj.2011.03.014

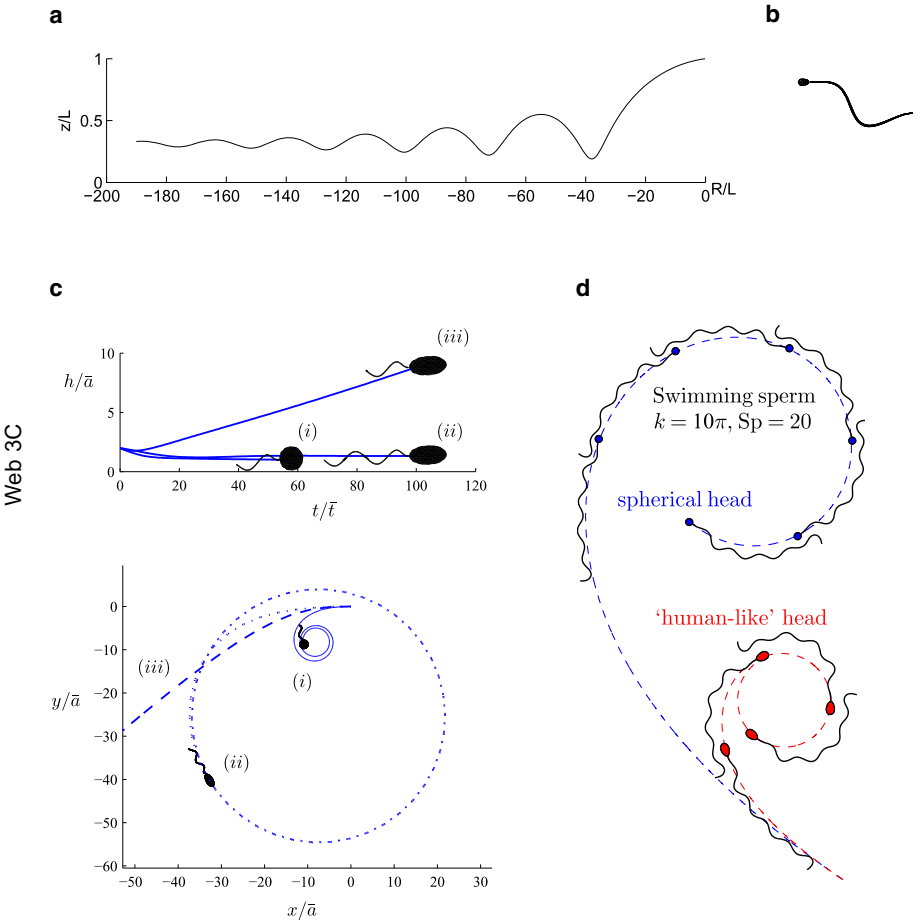

FIGURE 1 (*a* and *b*) Predicted trajectory of a cell initially parallel to, and one body length away from, a no-slip plane surface showing eventual convergence to a finite accumulation height, which depends on wavenumber and head size being in the range 8.5–22 μm for human sperm. The interaction of the cell with the surrounding fluid and surface was simulated using a combined boundary element-slender body model. (Figure copyright Cambridge University Press 2009, reprinted with permission from Smith et al. (4).) (*c*) Bacterial cell simulation results using the boundary element method establish that head geometry has significant effects on whether cells accumulated, and their eventual accumulation height. For helically propelled cells, this in turn significantly affects circling behavior. (Reprinted from Shum et al. (7).) (*d*) Geometrically nonlinear elastodynamic simulation establishes that asymmetric beating can occur in a symmetrically actuated cell through a buckling instability, which in turn causes circling swimming. A crucial determinant is the force-velocity relation for the head, determined by its geometry. A spherical head model gives very different results from a physiological head model, in this case modeled on human sperm. The parameter *Sp* is the sperm-compliance parameter quantifying the relative importance of viscosity and elasticity; the parameter k is the wavenumber of the actuation. (Reprinted from Gadêlha et al. (10).)

Web 3C

It is correct to state that the Stokes flow model requires increasingly fine spatial and temporal discretization as the cell and surface approach, and for this reason, Smith et al. chose to terminate simulations of cells initially angled toward a surface. Any accurate simulation of the very close interaction of a solid body with a surface in Stokes flow is likely to be very expensive, both for continuum dynamics models and for molecular simulation techniques (see, for example, the recent high-precision simulation study of Padding and Briels (6)).

This is not, however, the same thing as numerical instability. There were also no numerical accuracy issues in simulations of initially parallel-swimming cells, so numerical error does not explain why Smith et al. did not obtain the same results for initially parallel-swimming cells. Shum et al. (7) achieved numerically accurate simulation of bacterial cells swimming very close to surfaces (Fig. 1 *c*) due to a combination of refined numerics, and reduced the yawing of bacteria relative to sperm. However, to preserve the correct physics, simulations were terminated at the approximate distance at which electrostatic interactions would likely occur—35 nm—based on experimental observations (8).

The physical state predicted by Smith et al. was described by Elgeti et al. as "likely only marginally stable". However, the state arises as a basin in the dynamics, and as such is de facto stable. It is also unlikely that this state would be obliterated by thermal fluctuations: we do not observe a 50-μm sperm being subject to Brownian motion in the manner of submicron beads. We argue that careful specification of the relative importance of Brownian motion is necessary before dismissing the predictions of the Stokes flow model in this way. We now explore some alternative explanations for these discrepancies, based around the effects of cell morphology.

CELL MORPHOLOGY, SPECIES DIFFERENCES, AND ASYMMETRIC WAVEFORMS

Sperm biology presents an array of species-specific morphology, including spade-shaped, wedge-shaped, hook-shaped, and twist-drill spermatozoa. The bacteria model of Shum et al. (7) suggests that the use of different-sized and -shaped heads can lead to very different accumulation behavior (Fig. 1 *c*), in particular that spherical-headed cells will approach to within molecular distances of the wall, whereupon surface interactions can potentially allow swimming with very close head-surface proximity. Hence morphological differences may be the reason that Elgeti et al. did not replicate our findings or (as discussed below)

experimental observations. We do not argue that the findings of the bacterial model—which differs also in beat pattern—are definitive for sperm in this respect; however, they do illustrate the need to take into account morphology as a potential source of discrepancy.

Another important issue considered by Elgeti et al. is the role of circling motility. Although sea urchin sperm characteristically travel on "drifting circles" near surfaces, with this being part of the behavioral mechanism underlying chemotaxis, this behavior is much less evident in mammalian sperm. Circling motility in the Elgeti et al. study is a consequence of an imposed flagellar asymmetry, and indeed flagellar asymmetry is known in mammalian sperm to have a role in the induction of nonprogressive motility in hyperactivated cells (9). Another recent study by our group (10) has recently shown how asymmetric flagellar beating can occur within symmetrically actuated cells over certain physiologically realistic parameter ranges. This behavior is a result of the buckling instability predicted by geometrically nonlinear elasticity theory coupled to a surrounding viscous fluid. This model predicted that changes to the head morphology will result in very significant changes to the flagellar wave and hence the resultant trajectory, as shown in Fig. 1 *d*.

These findings emphasize that predictions obtained with a spherical head do not necessarily faithfully reflect behavior with mammalian head morphology. Furthermore, morphology has long been known to have significant effects on sperm penetration and migration in mammalian fertilization (11), evidencing the need for this to be taken into account in motility simulation.

EXPERIMENTAL EVIDENCE

The quotation at the beginning of this Comment provides ample evidence that the predictions of Smith et al. are consistent with physical reality: human sperm swim "near" surfaces somewhat more frequently than they swim "at" surfaces. Why did Elgeti et al. (2) not predict this dominant mode of near-surface swimming? We suggest one possible explanation may lie in species-specific differences: Elgeti et al. did not explicitly consider human or mammalian sperm morphology, but rather a cell somewhat closer in morphology to sea urchin, with very different hydrodynamic behavior.

CONCLUSIONS

In summary, the discrepancies between the recent study of Elgeti et al. and Smith et al. may be due to species-specific differences in morphology and flagellar waveform; the predicted finite-distance accumulation of Smith et al. is supported by experimental evidence in human and mammalian cells, and reflects a stable basin of the dynamics.

A diversity of approaches in unraveling the complexities of sperm motility and other biophysical systems is important; there are myriad potential sources of discrepancy between different modeling approaches which may not be immediately clear to nonspecialists. We suggest that all potential sources of discrepancy between different models should be examined and taken into consideration, particularly when readers may infer that the discrepancy arises from a methodological flaw.

D.J.S. and J.C.K.-B. acknowledge current funding from Birmingham Science City and the Medical Research Council UK for funding research reviewed in this article during the period 2006–2009 (Special Training Fellowship G0600178). H.G. acknowledges the CAPES Foundation, Brazil, for sponsorship under contract grant BEX-4676/06-8. H.S. acknowledges St. Catherine's College, Oxford, UK, for an Alan Tayler Scholarship.

D. J. Smith,[†§**] E. A. Gaffney,[§¶] H. Shum,[§¶] H. Gadêlha,[§¶‖] and J. Kirkman-Brown[‡§]
[†]*School of Mathematics, University of Birmingham, Birmingham, United Kingdom;*
[‡]*Clinical and Experimental Medicine, University of Birmingham, Birmingham, United Kingdom;*
[§]*Centre for Human Reproductive Science, Birmingham Women's National Health Service Foundation Trust, Birmingham, United Kingdom;*
[¶]*Centre for Mathematical Biology, Mathematical Institute, University of Oxford, Oxford, United Kingdom;*
[‖]*The CAPES Foundation, Ministry of Education of Brazil, Brasilia, Brazil;*
[**]*School of Engineering and Center for Scientific Computing, University of Warwick, Coventry, United Kingdom*

REFERENCES

1. Winet, H., G. S. Bernstein, and J. Head. 1984. Observations on the response of human spermatozoa to gravity, boundaries and fluid shear. *J. Reprod. Fertil.* 70:511–523.
2. Elgeti, J., U. B. Kaupp, and G. Gompper. 2010. Hydrodynamics of sperm cells near surfaces. *Biophys. J.* 99:1018–1026.
3. Rothschild, L. 1963. Non-random distribution of bull spermatozoa in a drop of sperm suspension. *Nature.* 198:1221–1222.
4. Smith, D. J., E. A. Gaffney, J. R. Blake, and J. C. Kirkman-Brown. 2009. Human sperm accumulation near surfaces: a simulation study. *J. Fluid Mech.* 621:289–320.
5. Woolley, D. M. 2003. Motility of spermatozoa at surfaces. *Reproduction.* 126:259–270.
6. Padding, J. T., and W. J. Briels. 2010. Translational and rotational friction on a colloidal rod near a wall. *J. Chem. Phys.* 132:054511.
7. Shum, H., E. A. Gaffney, and D. J. Smith. 2010. Modeling bacterial behavior close to a no-slip plane boundary: the influence of bacterial geometry. *Proc. R. Soc. Lond. A.* 466:1725–1748.
8. Klein, J. D., A. R. Clapp, and R. B. Dickinson. 2003. Direct measurement of interaction forces between a single bacterium and a flat plate. *J. Colloid Interface Sci.* 261:379–385.
9. Suarez, S. S. 1988. Hamster sperm motility transformation during development of hyperactivation in vitro and epididymal maturation. *Gamete Res.* 19:51–65.
10. Gadêlha, H., E. A. Gaffney, …, J. C. Kirkman-Brown. 2010. Nonlinear instability in flagellar dynamics: a novel modulation mechanism in sperm migration? *J. R. Soc. Interface.* 7:1689–1697.
11. Jeulin, C., A. Soumah, and P. Jouannet. 1985. Morphological factors influencing the penetration of human sperm into cervical mucus in vitro. *Int. J. Androl.* 8:215–223.