MODELING SPERM: The Finer Points of Fertilization

By Roberta Kwok

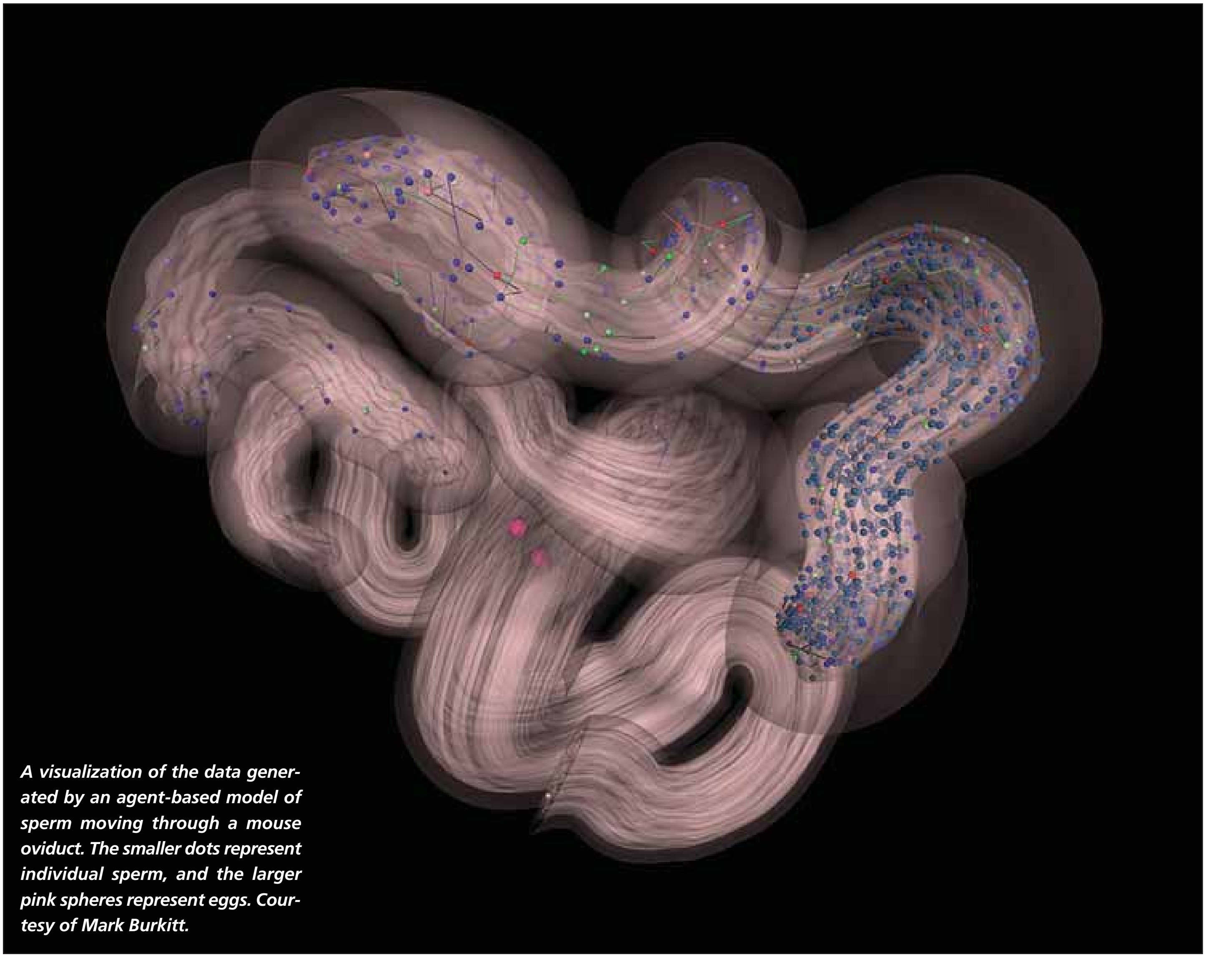
The essential elements of human fertilization are clear: sperm swim through the uterus, travel up the fallopian tube, and fertilize an egg. Not as well understood are the the nitty-gritty details of how sperm navigate the curvaceous fallopian tube, boost their chances of reaching the egg, and pierce the egg's outer layer.

New computational models are helping researchers hone in on answers to these questions using such tools as agent-based simulations and classic mechanical engineering principles.

The studies could eventually improve diagnosis and treatment of infertility, a problem that's gaining more attention as couples increasingly wait until they're older to conceive. Clinics currently test basic properties such as the number and movement of sperm, but knowing which other characteristics are important for fertilization could help doctors pinpoint the problem, calculate a couple's chances of successful conception, and filter sperm for the best candidates. Scientists also could use this knowledge to design new male birth control treatments—for example, by knocking out functions essential for sperm motility. And sperm might even inspire better "micro-swimming" devices that deliver drugs in the bloodstream.

Navigating the Oviduct

A team at the University of Sheffield has focused on interactions between sperm and the female oviduct, a tube connected to the uterus where fertilization occurs (known as the fallopian tube in humans). In the past, researchers had modeled individual sperm moving in a fluid. But little had been done to account for the shape of the oviduct which, contrary to popular belief, is not simply a cylinder but includes



A visualization of the data generated by an agent-based model of sperm moving through a mouse oviduct. The smaller dots represent individual sperm, and the larger pink spheres represent eggs. Courtesy of Mark Burkitt.

complicated bends and internal folds. "It's the first time that anyone's looked at how the sperm move about, using a conceptual model, within a representation of the oviduct environment," says **Mark Burkitt, PhD**, who reported the results in his 2011 doctoral thesis and is now director of the consulting and software development company Scientific Online Systems Ltd.

Burkitt's team chose to employ agent-based modeling, with each sperm represented as an individual entity. The sperm followed a specific set of rules—for example, they stuck to the oviduct wall and switched to a more mature, "capacitated" state with a certain probability; and died shortly after becoming capacitated. The researchers also analyzed histology images of mouse oviducts and developed algorithms to recreate the oviduct's 3-D structure.

When Burkitt's team removed bends and folds from the oviduct model, "we ended up with massive amounts of polyspermy," he says. Polyspermy occurs when more than one sperm fertilizes the egg, resulting in a non-viable embryo. The results suggest that the oviduct's complicated geometry prevents too many sperm from reaching the egg at once. "The purpose of the complexity of the internal system is to allow a slow progression of these sperm," Burkitt says.

Asymmetrical Motion

To reach the egg, sperm have to swim in specific patterns. Each sperm's tail, called a flagellum, beats in a sine-wavelike motion to propel the cell in a straight line. But the sperm also must enter a state called hyperactivation, in which the tail bends more in one direction than another and makes the sperm swim in circles. Hyperactivation might help the sperm free itself after getting stuck to the oviduct wall, and switching between linear and circular paths could improve its chances of finding the egg. "If you're just going straight, you could potentially swim right by it," says **Sarah Olson, PhD**, assistant professor of mathematical sciences at Worcester Polytechnic Institute.

In a study published in the *Journal of Theoretical Biology* in 2011, Olson's team investigated how sperm switch to hyperactivated movement. Scientists know that calcium signals play an important role: To become hyperactivated, sperm need channels in the cell membrane that let calcium in. Olson and her colleagues hypothesized that the calcium influx makes motor proteins called dyneins on one side of the flagellum generate more force than normal, causing the tail to beat asymmetrically.

To test this idea, Olson's team modeled a simplified sperm moving through fluid and linked calcium levels in the tail to forces driving its movement. The team accounted for calcium flowing into the flagellum from its environment and calcium released from an internal store in the sperm's "neck." The model generated tail waveforms characteristic of hyperactivation, matching the patterns seen in mouse and bull sperm. And the virtual sperm swam in circles as expected.

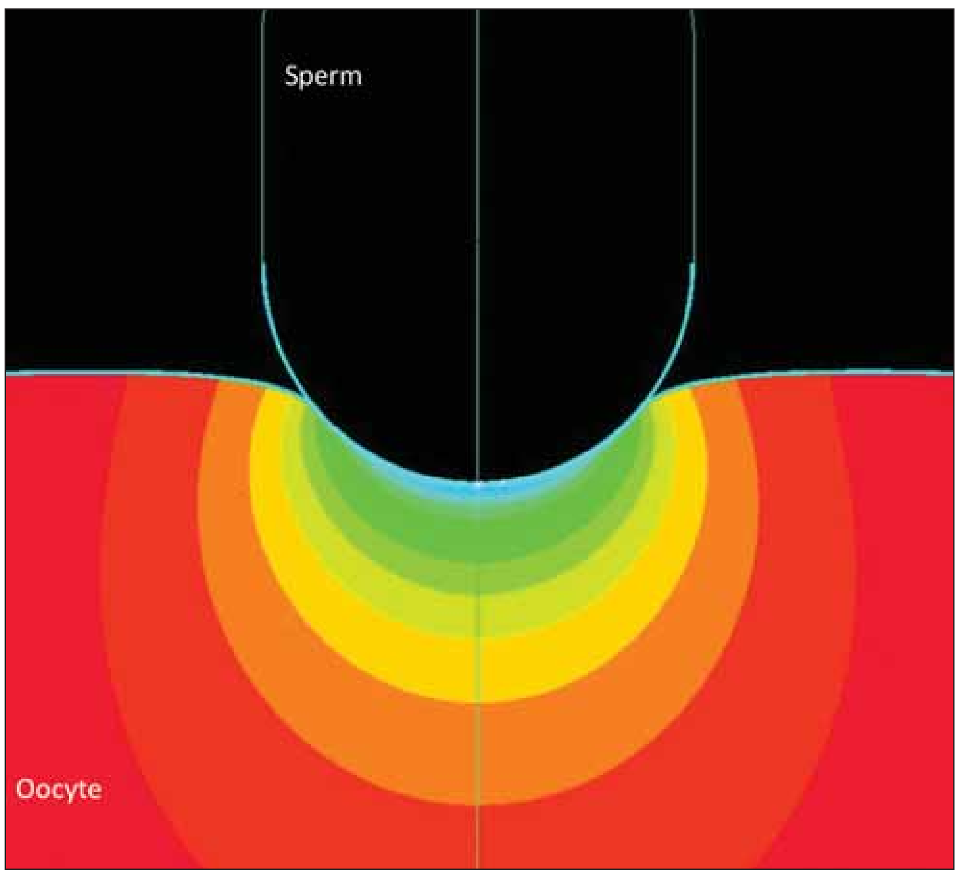
Final Steps in Fertilization

One of the last steps is penetrating the egg, which requires breaching an outer layer called the zona pellucida. Receptors on the sperm bind the egg's surface, and the sperm releases enzymes to soften the barrier. Defective binding between sperm and the zona pellucida is a major cause of failure to fertilize an egg *in vitro*.

In a study published in the *Journal of Theoretical Biology* in 2012, **Amit Gefen, PhD**, associate professor of biomedical engineering at Tel Aviv University, and a colleague modeled this process using mechanical engineering principles: They compared the mechanical forces generated by the sperm propelling itself forward to the chemical binding forces generated by receptors locking in place. In simulations of normal sperm, the chemical forces were 4 to 17 times lower than the mechanical forces. But in a simulated sperm with an unusually sparse population of receptors (one-sixth that of the normal sperm), they were 63 times lower. With insufficient locking, Gefen speculates, a sperm's powerful forward motion might make it slide across the egg's surface instead of staying put.

This year, Gefen's team published a study with a slightly different approach in *Computer Methods in Biomechanics and Biomedical Engineering*. The team used finite element modeling to represent the geometry of the sperm and egg wall more precisely. The researchers tested three shapes of sperm heads, ranging from sharp to blunt, and simulated softening of the egg wall. Not surprisingly, they found that sperm with sharper heads pierced farther into the egg. The model also suggested that the zona pellucida must soften to 10 percent of its original stiffness to allow penetration.

Gefen envisions that fertility clinics could one day test sperm's ability to soften an artificial, egg-mimicking material in the lab. But practical applications aside, he is fascinated by the science of how fertilization—the beginning of life—happens. "This is why we're all here," he says. □



A simulation of the deformations generated when a sperm head pushes on the surface of an egg. Courtesy of Amit Gefen, Department of Biomedical Engineering, Tel Aviv University.