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Art advancing science at the nanoscale

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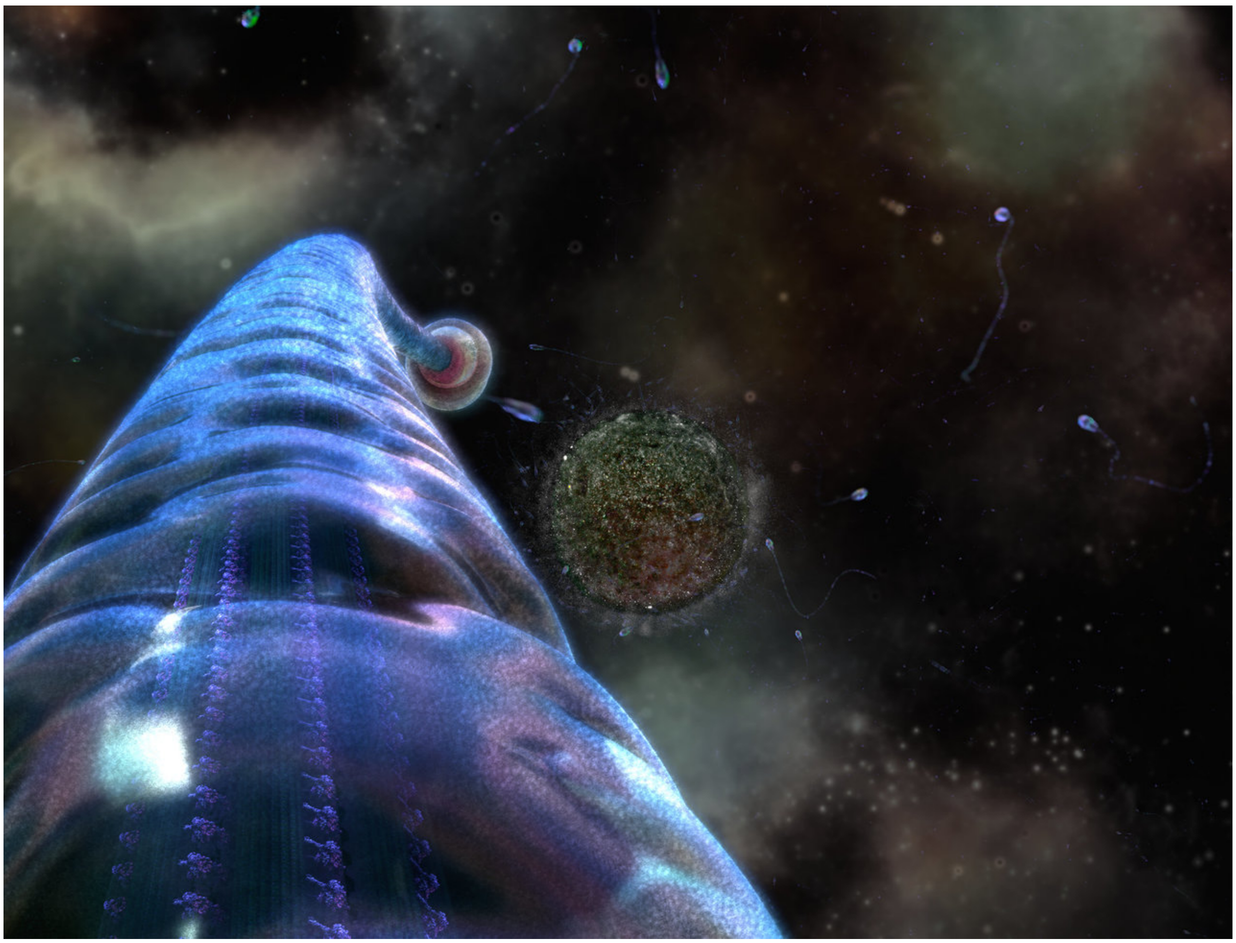
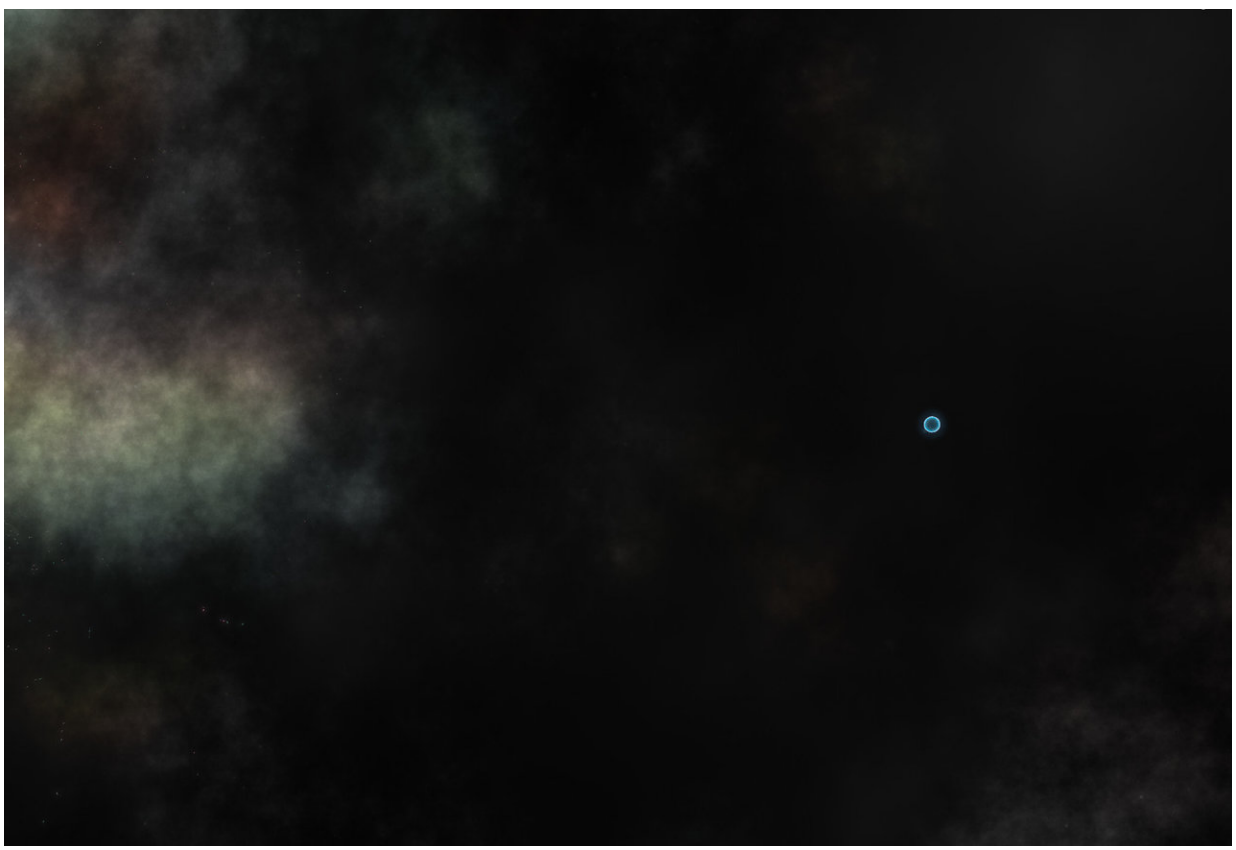


Still shot from the short film "The Beginning" by the Wyss Institute. Credit: Wyss Institute at Harvard University

Like many other scientists, Don Ingber, M.D., Ph.D., the Founding Director of the Wyss Institute, is concerned that non-scientists have become skeptical and even fearful of his field at a time when technology can offer solutions to many of the world's greatest problems. "I feel that there's a huge disconnect between science and the public because it's depicted as rote memorization in schools, when by definition, if you can memorize it, it's not science," says Ingber, who is also the Judah Folkman Professor of Vascular Biology at Harvard Medical School and the Vascular Biology Program at Boston Children's Hospital, and Professor of Bioengineering at the Harvard Paulson School of Engineering and Applied Sciences (SEAS). "Science is the pursuit of the unknown. We have a responsibility to reach out to the public and convey that excitement of exploration and discovery, and fortunately, the film industry is already great at doing that."

To see if entertainment could offer a solution to this challenge, Ingber teamed up with Charles Reilly, Ph.D., a molecular biophysicist, professional animator, and Staff Scientist at the Wyss Institute who previously worked at movie director Peter Jackson's Park Road Post film studio, to create a film that would capture viewers' imaginations by telling the story of a biological process that was accurate down to the atomic level. "Don and I quickly found that we have a lot of things in common, especially that we're both systems thinkers," says Reilly. "Applying an artistic process to science frees you from the typically reductionist approach of analyzing one particular hypothesis and teaches you a different way of observing things. As a result, we not only created an entertaining tool for public outreach, we conducted robust theoretical biology research that led to new scientific insight into molecular-scale processes." The research is now published in *ACS Nano*.

Any good movie needs characters and drama, and a "hook" to get the audience invested in watching. The scientists decided to make a parody of a trailer for a Star Wars movie, but instead of showing starship cruisers hurtling through space towards the Death Star, they chose a biological process with its own built-in narrative: the fertilization of an egg by a sperm, in which millions of sperm race to be the one that succeeds and creates the next generation of life. The patterns and mechanics of sperm swimming have been studied and described in scientific literature, but visually showing the accurate movement of a sperm tail required tackling one of the toughest challenges facing science today: how to create a multi-scale biological model that maintains accuracy at different sizes, from cells all the way down to atoms. That would be like starting with the Empire State Building and then zooming in close enough to see every individual screw, nut and bolt that holds it together, as well as how individual water molecules flow inside its pipes, while maintaining crystal-clear resolution - not an easy task.



Still shot from the short film "The Beginning" by the Wyss Institute. Credit: Wyss Institute at Harvard University

"It turns out that creating an accurate biological model and creating a believable computer-generated depiction of life in film are very similar, in that you're constantly troubleshooting and modifying your virtual object until it fits the way things actually look and move," says Reilly. "However, for biology, the simulations also have to align with recorded scientific data and theoretical models that have previously been experimentally validated." The scientists created a design-based animation pipeline that integrates physics-based film animation software with molecular dynamics simulation software to create a model of how a sperm tail moves based on scientific data, with the criterion that the model had to work across all size scales. "This is really a design thinking approach, where you have to be willing to throw out your model if it doesn't work correctly when you integrate it with data from another scale," Reilly says. "A lot of scientific investigations use a reductionist approach, focusing on one molecule or one biological system with higher and higher resolution without placing it in context, which makes it difficult to converge on a picture of the larger whole."

The core of a sperm's whip-like tail is the axoneme, a long tube consisting of nine pairs of microtubules arranged in a column around a central pair, all of which extend the entire length of the tail. The axoneme's rhythmic bending and stretching is the source of the tail's movement, and the scientists knew they needed to realistically depict that process in order to show the film's viewers how a sperm moves. Rather than construct a model in a linear fashion by "zooming in" or "zooming out" to add more information to a single starting structure, they built the model at different scales simultaneously, repeatedly checking it against scientific data to ensure it was accurate and modifying it until the pieces fit together.

The axoneme's movement is accomplished via rows of motor proteins called dyneins that are attached along the microtubules and exert force on them so the microtubules "slide" past each other, which then causes the entire axoneme and sperm tail to bend and move. The dynein protein has a long "arm" portion that grabs onto the neighboring microtubule and, when the protein changes from one shape to another, pulls the microtubule along with it. Dynein switches between these different conformations as a result of the conversion of a molecule of ATP to ADP at a specific binding site on the protein, which releases energy as a chemical bond is broken. To model this molecular motor, the scientists created a molecular dynamics simulation of a dynein protein and applied energy at the ATP binding site to approximate the transfer of energy from ATP. They found that this caused atoms in the entire protein to move in random directions when they performed their simulation of dynein floating in solution, as most conventional scientific simulations do. However, when they then "fixed" a specific hinge region of the dynein molecule that is known to connect dynein to its microtubule, they discovered that the dynein to spontaneously moved in its characteristic direction when force was applied at the ATP binding site, matching the way it moves in nature.

"Not only is our physics-based simulation and animation system as good as other data-based modeling systems, it led to the new scientific insight that the limited motion of the dynein hinge focuses the energy released by ATP hydrolysis, which causes dynein's shape change and drives microtubule sliding and axoneme motion," says Ingber. "Additionally, while previous studies of dynein have revealed the molecule's two different static conformations, our animation visually depicts one plausible way that the protein can transition between those shapes at atomic resolution, which is something that other simulations can't do. The animation approach also allows us to visualize how rows of dyneins work in unison, like rowers pulling together in a boat, which is difficult using conventional scientific simulation approaches."

Using this biologically accurate model of how dynein moves the microtubules within the axoneme, Ingber and Reilly created a short film called "The Beginning," which draws parallels between sperm swimming toward an egg and spaceships flying toward a planet in space, giving an artistic bent to a scientific topic. The film depicts several sperm attempting to fertilize the egg, "zooms in" on one sperm's tail to show how the dynein proteins move in sync to cause the tail to bend and flex, and ends with the sperm's successful journey into the egg and the initiation of cell division that will ultimately create a new organism. The scientists submitted the film along with the paper to several academic journals, and it took a long time before they found an open-minded editor who recognized that the paper and film together were a powerful demonstration of how starting with an artistic goal can end up generating new scientific discoveries along with a tool for public outreach.

"Both science and art are about observation, interpretation, and communication. Our goal is that presenting science to the public in an entertaining, system-based way, rather than bogging them down with a series of scattered facts, it will help more people understand it and feel that they can contribute to the scientific conversation. The more people engage with science, the more likely humanity is to solve the world's big problems," says Reilly. "I also hope that this paper and video encourage more scientists to take an artistic approach when they start a new project, not necessarily to create a narrative-based story, but to explore their idea the way an artist explores a canvas, because that makes the mind open to a different form of serendipity that can lead to unexpected results."

"The Wyss Institute is driven by biological design. In this project, we used design tools and approaches borrowed from the art world to solve problems related to motion, form, and complexity to create something entertaining, which ultimately led to new scientific insights and, hopefully, new ways to excite the public about science," says Ingber.

"We've demonstrated that art and science can benefit each other in a truly reciprocal way, and we hope that this project spurs future collaborations with the entertainment industry so that both art and science can get even closer to depicting reality in ways that anyone can appreciate and enjoy."

More information: Art Advancing Science: Filmmaking Leads to Molecular Insights at the Nanoscale *ACS Nano*, Article ASAP, DOI: 10.1021/acsnano.7b05266 , pubs.acs.org/doi/10.1021/acsnano.7b05266

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