

**Microtubules are composed** of many individual tubulin subunits. The subunits form a tube of 13 parallel and slightly staggered columns (protofilaments).



**When the microtubule** breaks down, columns splay apart and peel backwards. The peels then snap off from the disassembling microtubule, break down into smaller pieces, and eventually into individual subunits.

## Molecules in Motion Animation shows the complex lyricism of chromosome movement in a dividing cell.

LIKE THE STRANGE, DREAMLIKE UNDERWATER WORLD of Jacques Cousteau, particles flow freely, but with purpose, through a liquid atmosphere. Tranquil music further sets the marine-like scene. Eva Nogales’s movie uses captivating animation and real molecular structures to offer an eye-opening view of how microtubules—the long protein polymers that help cells divide their genetic material—assemble and disassemble.

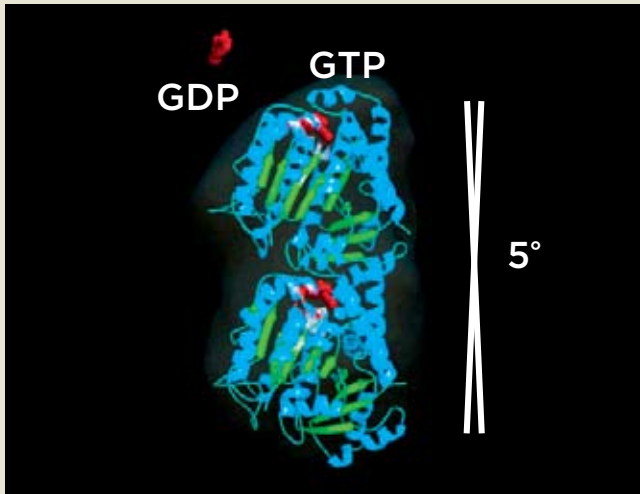
Although most biologists are familiar with microtubules, Nogales, an HHMI investigator at the University of California, Berkeley, found that when she described her work to colleagues they had a hard time *seeing* what she was talking about. Especially when she described how individual protein subunits, called tubulin, add onto a growing microtubule filament or fall away from it.

Then Nogales attended a lecture by one of her Berkeley colleagues in which he played a video of a parasite’s life cycle. The movie allowed the audience to observe, and then understand, what her colleague had discovered. She decided to make a movie of her own to convey some of the details that she and her team had discovered through their use of electron microscopy.

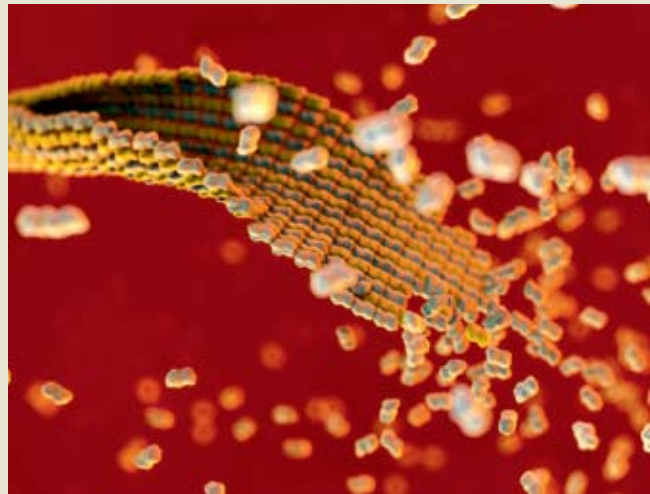
In the animation, the Zen-like music underlies Nogales’s guiding narration. The viewer is transported along the three-

dimensional microtubule polymer, swooping in for close-up views of the building-block tubulin subunits, then panning wide to watch them join the growing end of the microtubule. Three subunits add on to the microtubule, like individual railroad cars joining a waiting train, and the video settles on the mature polymer—a tube of 13 full-length columns.

The researchers believe a tubulin subunit must undergo a subtle change in shape before it can join in the process. They propose that in solution tubulin can have at least two shapes: curved with a kink at the midpoint or straighter. To show how this might work, the filmmakers overlay a colorful crystal structure of the protein backbone on the animated image of a tubulin subunit. As a small nucleotide with two phosphates (guanosine diphosphate, or GDP) drifts off the subunit and one with three phosphates (guanosine triphosphate, or GTP) slides in to replace it, the subunit straightens. Only when it takes on the straighter conformation can it add onto a growing polymer. Once the sheet reaches a critical length, the edges seal together like a zipper closing up a jacket, resulting in a long, tube-shaped microtubule polymer. [Here’s where the moving pictures come in handy. See link at end.]



**Individual subunits can** then recycle by becoming straighter following the exchange of GDP for GTP.



**The newly activated** subunits form a sheet that will soon zip up to form the tubular polymer.

Nogales's insight into microtubule *disassembly*, also called depolymerization, has shed new light on a long-standing puzzle in cell biology: How do microtubules manage to pull chromosomes to the poles in a dividing cell, even though the chromosomes attach to the end of the microtubule that is falling apart? As Nogales puts it, "the kinetochore [a large complex of proteins that acts like a dock for the chromosome to connect with the microtubule] is grabbing onto the microtubule, but the microtubule starts breaking down. So it's like grabbing onto a rope that is burning. Yet somehow the chromosomes are being pulled instead of falling off."

Her revelation came from two key pieces of data. First, her group characterized how the microtubules break down, defining how the columns of the polymer peel back, a bit like the peels of a banana. Second, by studying a key kinetochore complex in budding yeast, they observed that about 16 copies of the complex snap into a ring *around* the microtubule. When microtubules start fraying apart, with their ends curling backward, the fraying action pushes the ring, which then slides along the intact portion of the microtubule, toward the edge of the cell, taking the chromosome with it.

Nogales made her film before she and her collaborators discovered the kinetochore ring. Even so, she says, having the movie makes it easier for people to understand how the system might work. "When you see something moving, you get a feeling of motion in your brain that you don't get from seeing a picture," she says. "Now the only thing we have to do is tell them to imagine a ring around the microtubules, and they see what will happen."

With audiences following her work more completely, Nogales says the value of the movie far exceeds what she paid for it. The company that made it was still testing its product, and so charged her only \$5,000. The real cost for the time-intensive project (it took about 2 months of twice-weekly meetings with the filmmakers) would have been \$50,000. At that rate the company couldn't find any takers and closed its doors. Although she's not sure if NIH or HHMI would agree, Nogales says even that fee might not be too much. She expects her movie to be useful for several years to come, adding, "It was the best \$5,000 I've ever spent." ■ – RABIYA S. TUMA

FOR MORE INFORMATION: See Eva Nogales's video at [www.hhmi.org/bulletin/may2007](http://www.hhmi.org/bulletin/may2007).