The Enterprising Life of a Microtubule: "Ups" And "Downs" And Some Peaceful Times

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I constantly toy with the possibility that I am an obsessive germophobe; I wash my hands innumerable times a day, at times causing inconvenience to people around me. Fear of infection is a real concern, and to some extent we all are and should concerned about tiny (micro) organisms that can cause infections. Bacteria, for example, are tiny organisms that can cause a variety of diseases such as cholera, pulmonary tuberculosis, leprosy and many more. Though not all bacteria are bad. Gut bacteria, for example, are good guys who help us digest our food. However, the villainous ones, called pathogenic bacteria, can wreak havoc inside our bodies.

Before we take external medical help, our cells themselves have internal defense mechanism to fight these micro-invaders. Our bodies do this with the help of cells known as phagocytes. Phagocytes engulf the bacterium to form objects called phagosomes. Phagosome, with its captive bacterium, then travels around the cell to find another kind of objects called lysosomes. Lysosomes then join the phagosomes and take it on themselves to destroy the pathogens before they can cause trouble to us. Unless the bacteria itself evolves to avoid destruction (which happens quite frequently), the defense processes happen continuously and efficiently inside our cells. But phagosomes and lysosomes are too small compared to the size of the cell. Then how does a phagosome locate the lysosome to complete the defense action? Turns out there are spatial roads inside cells on which phagosomes are transported by certain protein vehicles, and like in a fantasy movie, these roads and vehicles help the phagosomes to find the lysosomes. But this isn't a fantasy. Biologists have observed the behaviour of these roads

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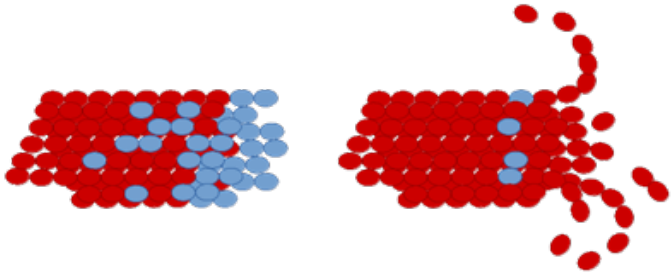
under microscopes; these roads are called "microtubules" and they are no ordinary roads. They have a fascinating life of their own. It is their life that I am trying to understand through my research and it is their story that I am going to share.

Microtubules are shaped like cylinders, and the building blocks which form them are tiny proteins called tubulins, which stack themselves to form these tubes. Microtubules are truly multi-faceted. There are myriads of proteins, carrying various cargo, which walk on microtubules to their own destinations. To enable this transport, microtubules have to remain stable and intact. However, at other times microtubules have to build and collapse their cylindrical structures too rapidly and frequently. This necessity arises before cell division, when the dividing cell has to bequeath its hereditary materials equally to the two daughter cells. They also need to rearrange their structures appropriately to enable the cells to move. Sperms cells, for example, use structures formed from microtubules in order to move inside the female reproductive tract. The research work that I am involved in is an attempt to understand how microtubules, and the tiny tubulins which make them, keep up with this demand to constantly rearrange themselves. More specifically, we try to understand the probable reasons for the sudden collapse of these tubes and the recovery afterwards.

There is more than one way to understand this problem. There is experimental work, which uses actual samples of these proteins and makes measurements from them using suitable techniques. Then there are theoretical techniques, which consider these chemicals as more abstract objects, write equations using them, and then solve them, often with the help of computer simulations. The two approaches can often result in supportive or complementary results, that is good as it provides stronger evidence and improves our understanding of the problem. My work is of the latter kind; we try to understand the behaviour of microtubules by simulating their behaviour using computer programs. In order to do this we simplify the structure of microtubules by assuming a 1-dimensional stack of tubulins in lieu of a 3- dimensional cylinder. This simplification is a reasonable one vis-à-vis the purpose of our study, which will be made clear a little later.

It is known from experiments that tubulin proteins have a dual-face; they can exist in a form attached to a GTP molecule or in an alternate form attached to a GDP molecule. GTP is one of the "energy molecules" of the cell; it can undergo chemical changes to become a GDP molecule while releasing energy as the cell requires. Microtubule cylinders which consist of more number of GTP-attached tubulins (atleast at their ends) are longer and more intact than those with more GDP-attached tubulins. In our simulations, we consider the possibility that this existence of an alter-ego makes a difference in the likeliness of tubulin to attach at the end of a microtubule. We ask the question, what might happen if a free GTP-attached tubulin, that comes near the end of a microtubule, is more likely to join the tube if it sees one of its own kind at the end rather than a GDP-attached tubulin. Our results tell us that the consideration of this individual preference of tubulin is sufficient to capture the incessant collapse-recovery behaviour of microtubules. We can also measure how frequently microtubules shift from the intact form to collapsing form. These results compare well with previous measurements from experiments, so our 3-dimension to 1-dimension simplification has not caused us much trouble so far.



Microtubule cylinders formed by tubulin proteins of GTP-attached form (●) and GDP-attached form (●). The figure on the left shows the cylinder while it is intact and growing and the figure on the right shows the cylinder while it is collapsing.

The formation or collapse of microtubules depends on the amount of GTP-attached tubulin proteins present in the cells. We can denote this quantity by the term "concentration" of free tubulin. If this concentration is very high, proteins readily assemble into long microtubules. If the concentration is too low, tubulins in the microtubule will detach to become free souls before new tubulin have the time to attach. This kind of behaviour of a group of individual objects is aptly named as "collective behaviour". It is not just tiny proteins which exhibit collective behaviour. If you are the sort of person who likes to goggle at the sky during sunset, you would have noticed the orderly patterns formed by flocks of birds flying by. Closer home, you may have noticed the regimented army of ants going about their usual business every day. These are all examples of collective behaviour. It essentially boils down to this: it does not matter what a single individual does at a particular time, but the group of individuals on an average behaves in a certain way depending on a variety of conditions. In the world of tubulin, this behaviour manifests in the form of growing microtubules at high concentrations and collapsing microtubules at low concentrations.

There are many benefits in knowing how rapidly this collective behaviour changes with the amount of tubulin. For example, it tells us what is the amount of tubulin required tosalvagecollapsing microtubules. Results from our simulations tell us that this change of collective growth to collective collapse is extremely rapid, i.e., it takes only a slight change in the amount of tubulin present. We also learn that the individual preference of tubulin that we have earlier talked about is crucial for this rapidity. Between the tubes that grow and the tubes that collapse, there is a small range of tubulin concentration where all hell breaks loose. In this small window of concentration, every individual microtubule can itself constantly rearrange its structure. This knowledge is crucial as this dynamic state of microtubules isessential for cell division. We know that cancer cells undergo unbridled proliferation. This proliferation happens through cell division. Hence, many anti-cancer drugs try to target microtubules in order to suppress cell division. So if we can understand what the conditions conducive to cell division, experiments can be designed to drive microtubules out of those conditions to suppress cell division, and, thereby, act in our favour against diseases like cancer.

There are many ways in which our computational study can be improved by adding additional details about microtubules. The ultimate goal of all research work in this area, including ours, is to understand what factors enable microtubules to perform the myriad duties they occupy themselves with or the ways in which they can be to treat diseases such as cancer.