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CELL BIOLOGY

Powerful curves

L. Mahadevan and T. J. Mitchison

A cell's contents are organized by a scaffolding of microtubules. These long, thin polymers continuously grow and shrink, and the structures of two forms of the constituent protein provide clues to how this occurs.

Microtubules are long polymers of the protein tubulin that form a network within cells to help arrange the cell components and provide transport tracks for motor proteins. Rather than being static permanent structures, microtubules continuously grow and shrink through the polymerization and depolymerization of tubulin. Such processes are central to the microtubules' spatial organization and their ability to generate the forces necessary to function. In this issue, Wang and Nogales (page 911)[1] report high-resolution structures of two alternative polymeric states of tubulin, which provide insights into the molecular mechanisms that power growth and shrinkage.

Tubulin is a stable dimer of α and β subunits, both of which bind guanine nucleotides. Guanosine triphosphate (GTP) that is bound to β-tubulin is hydrolysed to guanosine diphosphate (GDP) during microtubule assembly, and this nucleotide regulates tubulin conformation and behaviour, with GTP favouring polymerization, and GDP depolymerization. In the presence of tubulin and GTP, individual microtubule ends tend to grow for many micrometres, and then switch to shortening. This transition, called a catastrophe, occurs spontaneously with pure tubulin and constant GTP levels, although in cells it is regulated by other proteins. The resulting 'dynamic instability'[2] allows microtubule ends to efficiently explore their surroundings[3] and to perform mechanical work by pushing and pulling[4]. A central question is how the chemical energy from GTP hydrolysis is harnessed to power both growth and shrinkage of microtubules in dynamic instability.

Initial models emphasized a thermodynamic–kinetic view. GTP-bound tubulin subunits have a high affinity for microtubule ends and dissociate slowly, whereas GDP-bound tubulin subunits have a low affinity and dissociate quickly[2]. A proposed kinetic lag between polymerization and hydrolysis could generate a 'GTP cap' that stabilizes growing ends. Definitive evidence for or against such a cap is still lacking.

More recently, cryo-electron microscopy of growing and shrinking microtubules[5] suggested a complementary structural–mechanical view, based on changes in the arrangement of tubulin subunits in the polymer lattice. Tubulin molecules in microtubules are arranged in 13 lines called protofilaments, which lie parallel to the microtubule axis. When microtubules depolymerize, these protofilaments curve outwards, and in the presence of microtubule-associated proteins or certain divalent cations, they bend back on themselves to form stable rings of GDP-tubulin (Fig. 1a)[6]. GTP hydrolysis was proposed to destabilize microtubules, and drive dynamic instability, by promoting outward curving[5], although the mechanism coupling hydrolysis to curving was unknown.

By comparing the structure of GDP-protofilament rings[1] with that of microtubules[7], Wang and Nogales[1] reveal how GTP hydrolysis promotes protofilament curving and thus destabilizes the microtubule lattice. The GDP-protofilament is bent at both the inter- and intra-dimer interfaces, making it curve outwards from the microtubule. Within the main microtubule, most subunits are bound to GDP, and thus their lowest energy state would be this curved form. However, contact with neighbours in the lattice forces the protofilament to be straight, except at the ends. In this way, the microtubule lattice captures chemical energy from GTP hydrolysis and stores it in the form of mechanical strain energy. Depolymerization releases this strain energy, making the reaction energetically favourable, even in the presence of high concentrations of GTP-tubulin.

Wang and Nogales[1] also solved the structure of tubulin with GMPCPP, an analogue of GTP, bound to β-tubulin. This analogue is not hydrolysed during polymerization, and by mimicking GTP it locks tubulin in the GTP conformation. Simple dynamic instability theory predicts that the preferred conformation of GTP-tubulin should be that of the microtubule lattice; that is, straight protofilaments. But in the GMPCPP structure they in fact curve outwards, albeit to a lesser extent than GDP protofilaments. This structure required cooling, which induces a conformational change in tubulin, so the geometry might differ from anything that occurs normally. With that caveat, the combined data support a two-step model for microtubule growth, with initial polymerization into gently curved sheets, followed by tube closure[1,5]. Exactly when GTP hydrolysis occurs is not clear. GTP analogue protofilaments roll up into microtubules on warming[1], showing that hydrolysis is not necessary for tube closure. The alternative forms of the GTP-tubulin lattice probably have similar energies, and may interconvert at growing ends, while maintaining a GTP cap (Fig. 1a).

A greater understanding of how tubulin

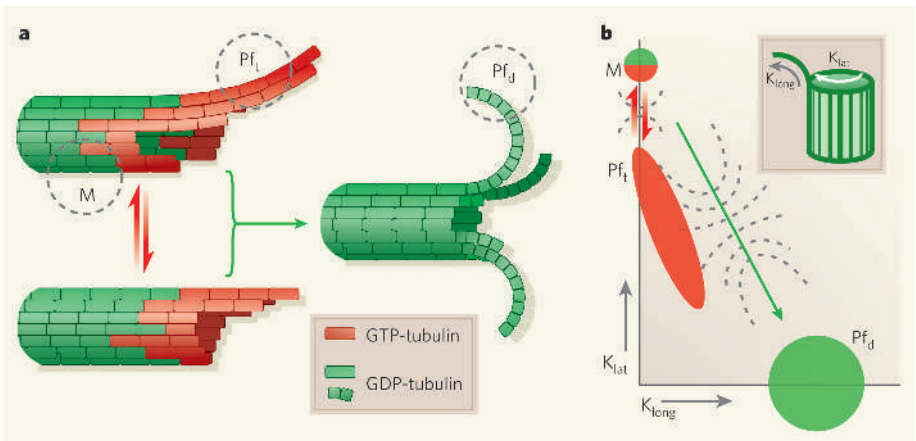

Figure 1 | Dynamic microtubule structure. a, A synthesis of the thermodynamic, kinetic and structural views showing the growing and shrinking microtubule ends. Growing ends (left) fluctuate between gently curved and straight protofilament sheets; shrinking ends (right) are dominated by highly curved, peeling protofilaments. Structures have been solved for three forms of the microtubule lattice: microtubule (M)[7], GTP-protofilament (Pf_t)[1] and GDP-protofilament (Pf_d)[1]. **b,** Our model of a free-energy landscape for the microtubule lattice. Each of the three metastable forms of tubulin polymer can be approximately specified by two curvatures: K_{long} parallel to and K_{lat} perpendicular to the microtubule axis (inset). Coloured shapes represent these forms, corresponding to low-energy wells in the landscape. The larger wells are less geometrically constrained. Dotted lines represent energy barriers. GTP-tubulin (red) interconverts rapidly between M and Pf_t forms across a low barrier. GDP-tubulin (green) crosses the higher barrier between M and Pf_d less frequently, and perhaps irreversibly.

structure and thermodynamics together drive dynamic instability requires modelling. Lattice simulation using molecular dynamics has yielded promising results[8], and the new structures will help to refine such detailed models. A simpler approach that we propose, taking the new findings into account, is to approximate the lattice as an elastic sheet with more than one equilibrium configuration, and with the curvature of the sheet providing a natural description of the geometry (Fig. 1b, inset). Naturally curved elastic sheets can be bistable, interconverting between two forms, where curvature in one direction is partially exchanged for curvature in a perpendicular direction[9]. These forms may have approximately equal free energy, but with a barrier separating them, because interconversion requires local stretching of a small region that must propagate along the sheet.

We have generated a possible energy landscape for GTP-tubulin and GDP-tubulin lattices based on this geometric view (Fig. 1b). For GTP-tubulin, the microtubule (straight) and protofilament (gently curved) forms have similar energies that are separated by a relatively low barrier. They interconvert at the growing microtubule end, crossing the barrier by exchange of curvatures. The energy of the GDP-tubulin protofilament (highly curved) form is lower than that of all other forms. Catastrophes occur when ends occasionally cross the higher barrier separating the straighter microtubule and GTP-protofilament forms from the highly curved GDP-protofilament form. The height of the barrier is determined by the energetic cost of exchanging curvature combined with tearing between protofilaments. Thus, rapid depolymerization is driven by the elastic energy stored in straight GDP-protofilaments as they recover their natural curved shape, after a tear travels down from the free end of the microtubule. In this type of model, the relative stiffness and strength of the intra- and inter-protofilament bonds[10] is crucial in determining the rate of catastrophes.

Our model makes qualitative predictions: microtubules with fewer protofilaments and smaller radii should have higher energies for curvature exchange, and so are likely to grow more slowly and undergo catastrophe less frequently, because both processes require curvature exchange. Once they suffer a catastrophe, however, they should shrink faster, because the density of stored elastic energy is greater. Microtubule radius can vary, which might explain the variation in polymerization dynamics of individual microtubules assembled from pure tubulin[11].

The structural complexity of growing microtubule ends may have important consequences in cells. Tip-tracking proteins associate with growing plus-ends, where they regulate polymerization dynamics by unknown mechanisms[12]. Perhaps such proteins target growing ends by binding to protofilament sheets, and regulate dynamics by influencing tube closure. Investigating how tubulin lattice conformation influences tip-tracking proteins, and vice versa, will probably reveal some interesting biology. ■

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NUCLEAR PHYSICS

Elusive magic numbers

Robert V. F. Janssens

Gaps in nuclear levels, which cause nuclei with 'magic' numbers of protons or neutrons to be especially stable, seem to be different for nuclei with an excess of neutrons. But are all magic numbers aberrant in exotic species?

The idea of a shell structure is often cited by physicists as an essential aid to understanding the atomic nucleus. But the exact number of protons or neutrons required to fill a particular nuclear shell has not yet been conclusively settled. In a study of the neutron-rich silicon nucleus ^{42}Si, Fridmann and colleagues[1] (page 922 of this issue) provide an important contribution to the discussion.

The concept of shell structure is familiar from atomic theory: the energy needed to remove the last electron from an atom varies with atomic number. Certain elements — those with a full outer shell of electrons — are more tightly bound than others, and are thus particularly stable chemically, not readily bonding or forming molecules with other atoms. These are the noble gases: helium, neon, argon, krypton, xenon and radon, with a total of 2, 10, 18, 36, 54 and 86 electrons, respectively.

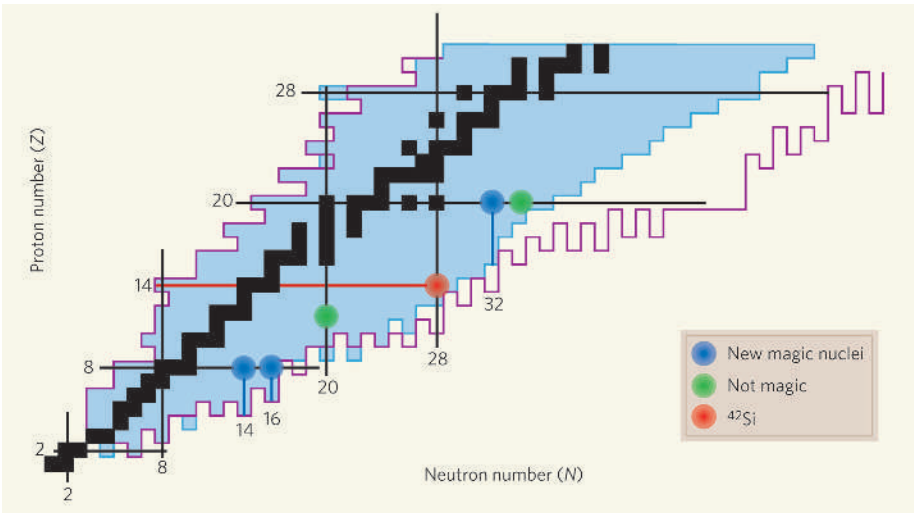

Figure 1 | Nuclear landscape. The stable elements from hydrogen (proton number $Z = 1$) to zinc ($Z = 30$) are represented by black squares; all other known bound nuclei are contained in the light blue area. At the 'drip lines' (violet lines), the forces between neutrons and protons are no longer sufficiently strong to hold nuclei together. The vertical and horizontal black lines indicate the magic numbers 2, 8, 20 and 28 that apply to stable nuclei. Some anticipated 'magic' nuclei are, in fact, not magic (green dots): the beryllium isotope ^{12}Be ($Z = 4$, neutron number $N = 8$) and the exotic magnesium nucleus ^{32}Mg ($Z = 12$, $N = 20$) are examples. Besides the doubly magic standard oxygen isotope, ^{16}O ($Z = N = 8$), the oxygen isotope with 20 neutrons, ^{28}O, should be particularly stable — but experiments show that it is not even bound. Conversely, there are strong indications of new magic numbers at $N = 14$, 16 and 32 in neutron-rich nuclei (dark blue dots). The silicon isotope ^{42}Si, the main subject of the work of Fridmann and colleagues[1], is marked by a red dot.