Turing Patterns in Prokaryotic and Eukaryotic Cell Division.

Axel Hunding, Dep. of Chemistry, Univ. of Copenhagen
axhun@osc.kiku.dk
Author arrives late Friday

Overview

The cell division plane in prokaryotes is defined by

recurrent protein waves
based on destabilization of Turing structures.

The proteins bind cooperatively to a quasistationary matrix (like the cell membrane or DNA). Rather than waves, stationary bipolar pattern formation may arise as well. In eukaryotic cells, tubulin polymerizes to microtubules in the spindle. Mitotic microtubules are in a highly dynamical state, frequently undergoing rapid shortening (catastrophe), and fragments formed from the microtubule ends are inferred to enhance the destabilization. Here we show that cooperative binding of such fragments to microtubules may set up a similar pattern forming mechanism as seen in prokaryotes. The result is a

well controllable,
bipolar state of microtubule dynamics

in the cell, which may contribute to defining the bipolar spindle.

1 The bipolarity problem

The spontaneous organization of microtubules into a bipolar spatial structure and the role of the spindle to determine the division plane of the cell is still a much studied, somewhat enigmatic subject. Experiments with laser destruction of one or both centrosomes resulted in reformed bipolar spindles devoid of centrosomes. However, anaphase and cytokinesis appeared normal (Khodjakov *et al.* (2000)). Other experiments with *Drosophila* male meiosis without chromosomes also resulted in spindle assembly and cytokinesis (Bucciarelli *et al.* (2003)). The possibility exists that the ability to form a bipolar spindle without centrosomes is present throughout eukaryotes (Hyman (2000)).

2 Turing based protein waves determine cleavage plane in prokaryotes

Bacterial cells were for a long time considered to have a very crude mechanism for genome separation, but the actual mechanism seems to be highly dynamic. Recurrent waves of MinD,E proteins run back and forth (so-called pole-to-pole oscillations) in the rod-shaped cells. The mean concentration is lowest in the middle of the cell, thus allowing the tubulin-like GTPase FtsZ to assemble a ring of polymer underneath the membrane at midcell as a prelude to cell division (Raskin and de Boer (1999)).

3 Prokaryotes: Turing pattern from cooperative protein binding to membrane
Eukaryotes: cooperative protein binding to unfolding microtubules

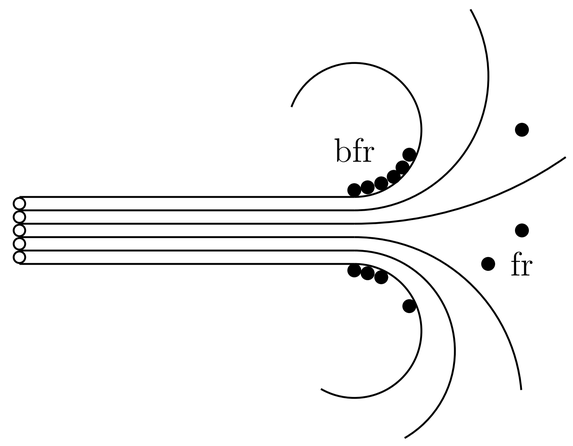

Figure 1: Microtubule during catastrophe. The plus end shows protofilaments curling outwards. If destabilizing proteins (solid circles) bind cooperatively (bfr) to the unfolding protofilaments and the free destabilizing proteins (fr) diffuse much faster than the bound form, this may create a so-called activator-depletor reaction-diffusion system, known to form spatial patterns. This may induce a stable, dynamic spatial pattern in the cell. If parameters are right, a bipolar pattern as in Fig. 3 may form spontaneously.

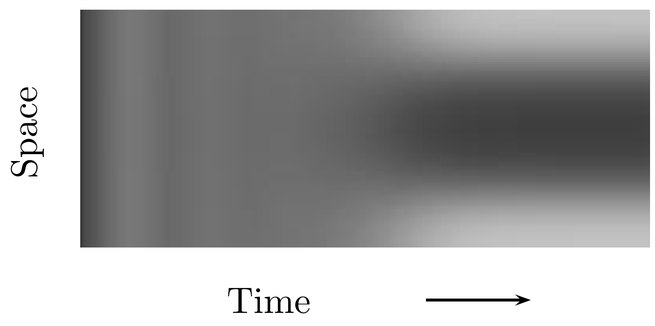

Figure 2: Bipolar pattern formation in microtubule dynamics. The concentration C_m of total tubulin assembled in microtubules is displayed with gray scale over a cell length (vertical coordinate) $L = 50\mu\mathrm{m}$. At first, a homogeneous (grey) distribution of microtubules is recorded (left part of frame), but in due time, the small random perturbations present spontaneously generate an inhomogeneous bipolar concentration pattern (right part of frame) with high concentration at the bottom and top, low in the middle of the cell.

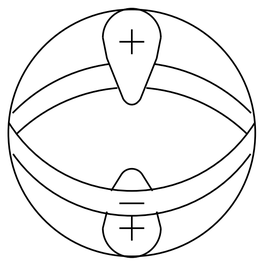

Figure 3: Bipolar pattern in 3D spherical cell. If parameters in the model favors the bipolar one dimensional pattern in Fig. 2 in a cell of length $L = 50\mu\mathrm{m}$, a spherical cell with about a 6% larger diameter ($2R \simeq 1.06 \times 50\mu\mathrm{m}$) is predicted to form the 3D pattern shown here in a corresponding simulation in 3D. This pattern has two poles with high concentration and a low concentration region in an equatorial band close to the cell surface. The recent proposal that the division plane is determined by a local minimum of microtubule density (Dechant and Glotzer (2003)), (or maximal rate of depolymerizing microtubules), is imminently compatible with the above structure, which directly yields such a density minimum (or maximal depolymerizing rate) close to the cell surface in the equatorial plane.

The first proposed model for prokaryotic protein waves (Meinhardt and de Boer (2001)) assumes that the MinD and MinE proteins diffuse in the cytoplasm, but under appropriate conditions, they may associate cooperatively with the membrane of the cell. This introduces an autocatalytic step in the formation of the bound state of the protein, a prerequisite for Turing pattern formation. Another crucial feature is the large spread in effective diffusion rates of the two forms of the proteins, the free and the bound form.

The prokaryotic waves come about by the formation of a Turing-structure with high concentration in one end of the cell, low at the other. This structure is destabilized by an antagonist, only to reform at the other end of the cell, etc., and recurrent waves are thus produced. A modification to the M-deB mechanism was formulated, where the antagonist was non-moving. However, its effect is to convert the bound protein into an alternative form (say, ParA-ATP and ParA-ADP), which may act as a seed to destabilize the Turing-pattern (Hunding *et al.* (2003)).

The above schemes may be particular examples of a general class of pattern forming mechanisms, based on protein oligomerization upon a template (membranes, DNA, etc, see below) with resulting enhanced ATPase (or NTPase) function in the oligomer state, which may bring the oligomer into an unstable internal state. An effector may then destabilize the oligomer and in the process produce seeds, which may spread an act as further destabilization agents. Thus NTPases may be an ancient class of proteins capable of setting up spontaneous spatial patterns by mechanisms related to the M-deB model. The actual protein used may thus have varied, and many particular pattern forming systems may be possible, which may contribute to the emerging picture that homologous proteins in prokaryotes and eukaryotes seem to have interchanged function. F. ex. FtsZ forms the ring at the divison site in prokaryotes whereas this role is assigned to actin in eukaryotes. Weak homologs of actin, being involved in cytoskeletal morphogenesis, have been found in bacteria (Mreb,Mbl) (van den Ent *et al.* (2001)).

The eukaryotic homolog of FtsZ is tubulin, which however forms microtubules. The polymerization process of tubulin involves GTPase activity as well, and the microtubule is in a metastable state, stabilized by a cap at the plus end. Catastrophe exposes the plus end and the internal unstable protofilaments curl out in bulls-horn like structures. Products formed during depolymerization may act as seeds for further destabilization, much as described above.

Under the assumption that prokaryotic and eukaryotic cell divison mechanisms may have common roots, the spatial pattern forming capabilities of such a seed mechanism has been explored recently (Hunding, in press). The main idea is that fragments from the depolymerization process may interact cooperatively with microtubule ends during catastrophe, much like the above described proteins in prokaryotes. The quasistationary matrix to which binding occurs is now not the cell membrane or DNA, but the unfolding microtubules, see Fig. 1. The model for microtubule dynamics was a modification of the scheme in (Bolterauer *et al.* (1999)), which accounts for oscillations recorded experimentally for microtubule assembly.

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