Filament depolymerisation by motor molecules

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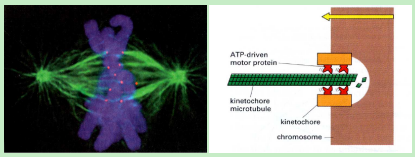
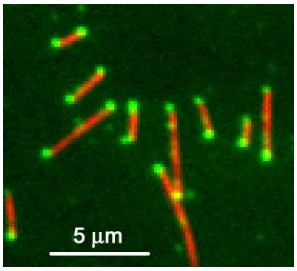
Introduction

We use a one-dimensional describtion to characterise the dynamics of MCAK on microtubules. Because of the depolymerisation activity of the motor the system comprises moving boundaries.
We use Monte Carlo simulations to get numerical results in the microscopic description and a continuum mean-field approach to deal with the problem analytically.

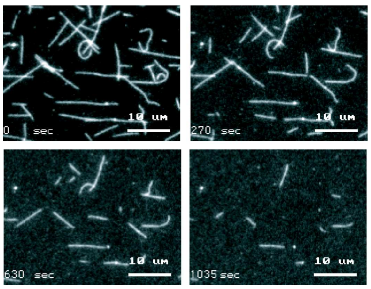
Biological motivation

During cell division Mcak is mainly localised at the kinetochores, which connect the chromosomes to the MT-spindle, and is associated with the shortening of the spindle MTs during mitosis.
MCAK belongs to the unusual Kin I subfamily of kinesin-related proteins [1]. Unlike other motor proteins that move along the surface of microtubules using ATP, these proteins have a high binding affinity to microtubule ends and depolymerise them in the presence of ATP [2].
The rate of tubulin dissociation from microtubule ends, is accelerated approximatly a 100-times through Mcak activity and there is strong evidence that Mcak is working processivly, removing approximatly 20 tubulin dimers before detaching. [3]





Microtubules (red) and accumulation of Mcak molecules (green) at both ends.
Source: Stefan Dietz and Jonathon Howard, MPI-CBG Dresden



Flourescent microtubules are depolimerased by Mcak molecules.
Source: Stefan Dietz and Jonathon Howard, MPI-CBG Dresden

References

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[2] A. Desai, S. Verma, T.J. Mitchison and C.E. Walczak. Cell **96**. 69 (1999).
[3] A.W. Hunter, M. Caplow, D.L. Coy, W.O. Hancock, S. Dietz, L. Wordeman and J. Howard. Mol. Cell **11**, 445 (2003).
[4] A. Parmeggiani, T. Franosch, E. Frey. PRL **90**, 086601-1 (2003).

Macroscopic model

We describe the dynamics of the Mcak molecules by a one-dimensional continuum mean-field theory on a semi-infinite domain. Because of the depolimerisation we have a moving boundary. By transforming into a moving frame, we get fixed boundary conditions, but additional terms in the current of Mcak molecules in the bulk.

Bulk:

$$\partial_t \varrho(x,t) + \partial_x j(x,t) = \omega_a - \omega_a' \varrho(x,t) - \omega_d \varrho(x,t)$$

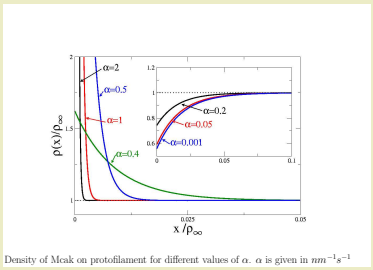
$$j(x,t) = -D\partial_x \varrho(x,t) - v_0 \varrho(x,t) + v_0' \varrho(x,t)^2 - v_B \varrho(x,t)$$

Edge:

$$v_B(t) = \alpha\varrho(0,t) - \beta\varrho(0,t)^2$$

$$j(0,t) = -\Omega_d^{tot}\varrho(0,t) + \Omega_a - \Omega_a'\varrho(0,t)$$

$$\partial_x \varrho(x,t)_{|x\to\infty} = 0$$



Density of Mcak on protofilament for different values of α. α is given in $nm^{-1}s^{-1}$

The steady-state of this system can be solved analytically for $v_0, v_0' = 0$. The solutions are of the form:

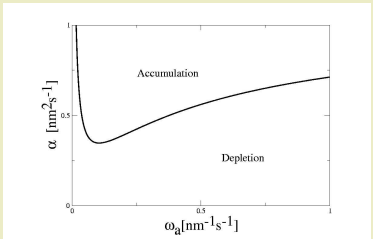
$$\varrho(x) = \varrho_\infty + (\varrho(0) - \varrho_\infty)\, e^{-\lambda_+ x}\,,$$

with

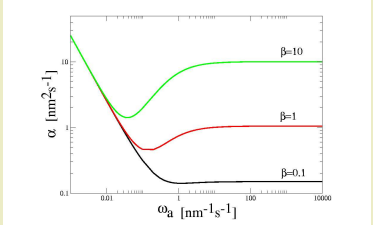
$$\lambda_+ = \frac{(\alpha\varrho(0) - \beta\varrho(0)^2) + \sqrt{(\alpha\varrho(0) - \beta\varrho(0)^2)^2 + 4\,(\omega_a' + \omega_d)\,D}}{2D}\,,$$

$$\varrho_\infty = \frac{\omega_a}{\omega_a' + \omega_d}\,.$$

Determining $\varrho(0)$ self consistently leads to a polynomial of 3rd order in $\varrho(x)$.

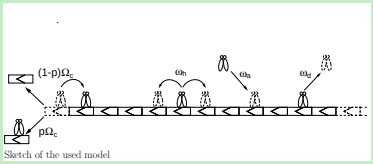


Phase diagram for accumulation and depletion as a function of the attachment rate.



The influence of the parameter β on the phase diagram. β is given in nm^3/s

Microscopic model



Sketch of the used model

In order to describe the time evolution of the particle densities $\langle n_i \rangle$ we look at the currents between one binding site and its neighbouring sites.

Lattice:

$$\begin{aligned} j_i = {} & \bar\omega_h \langle n_i(1-n_{i+1})\rangle - \langle n_{i+1}(1-n_i)\rangle \\ & -\bar\omega_v \langle n_{i+1}(1-n_i)\rangle \\ & -p\,\bar\Omega_c \langle n_1 n_{i+1}\rangle - (1-p)\,\bar\Omega_c \langle n_1(1-n_2)n_{i+1}\rangle \end{aligned}$$

$$\begin{aligned} j_{i-1} = {} & \bar\omega_h \langle n_{i-1}(1-n_i)\rangle - \langle n_i(1-n_{i-1})\rangle \\ & -\bar\omega_v \langle n_i(1-n_{i-1})\rangle \\ & -p\,\bar\Omega_c \langle n_1 n_i\rangle - (1-p)\,\bar\Omega_c \langle n_1(1-n_2)n_i\rangle \end{aligned}$$

$$l_i = \bar\omega_a\langle 1-n_i\rangle - \bar\omega_d\langle n_i\rangle$$

Edge:

$$j_1 = \bar\omega_h\langle n_1 - n_2\rangle - \bar\omega_v\langle n_2(1-n_1)\rangle - p\,\bar\Omega_c\langle n_1 n_2\rangle$$

$$l_i = \bar\Omega_a\langle 1-n_1\rangle - \bar\Omega_d\langle n_i\rangle - p\bar\Omega_c\langle n_1\rangle$$

The time evolution is then given by:

$$\partial_t\langle n_i\rangle = j_{i-1} - j_i + l_i$$

By making a continuum mean-field approximation of the above equations, we recover the equations from the macroscopic description.
For this we let $N \to \infty$, where N is the number of binding sites on the lattice and factorise the two-site correlations,

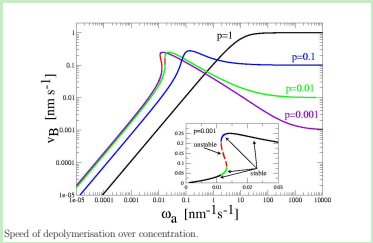
$$\langle n_i n_{i+1}\rangle = \langle n_i\rangle\langle n_{i+1}\rangle$$

and set

$$\langle n_i\rangle \approx \varepsilon\varrho$$

Doing so we get for our parameters $\alpha, \beta, \Omega_d^{tot}$:

$$\begin{aligned} \alpha &= \varepsilon^2\bar\Omega_c \\ \beta &= \varepsilon^3(1-p)\bar\Omega_c \\ \Omega_d^{tot} &= \varepsilon p\bar\Omega_c - \varepsilon\bar\Omega_d \end{aligned}$$



Speed of depolymerisation over concentration.

Outlook

One of the main goals is to make a conction to experiments. Knowing all the reaction rates of MCAK one could use the $v_B - \omega_a$-curve to make predictions about the underlying microscopic processes. Another interesting point would be the examination of the system regarding density phase transitions as reported in [4].

Acknowledgments

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