François Nédélec

PhD 1998, Université Paris 11, France.
At EMBL since 1998.
Team Leader since 2002.
Group Leader since 2005.

Group Members 2005

Group Leader
François Nédélec

Postdoctoral Fellows
Thomas Clausen
Maria Jesus Mora-Corral

PhD Students
Dietrich Foethke
Cleopatra Kozlowski

Technician
Petra Samenfeld*

Diploma Students
Martin Loose*

Trainees
Elizabeth Loughlin*
Christine Plet*

**indicates part of the year only*

Cellular architecture

The post-genome era has seen rejuvenated the question of how the cellular components interact collectively in order to produce biological functions (systems biology). This corresponds in effect also to a renewed interest in the cellular level of biological organisation: instead of focusing on the strict molecular aspects, we want to understand how proteins work together to "make" a cell. This superior level of organisation is very difficult to address, because the number of ways in which proteins can be networked is enormous, and because proteins are little machines rather than passive blocks: they often interact in an active (energy-dissipating) and therefore complicated manner. Consequently, even simple networks exhibit non-intuitive behaviour which we may not understand intuitively. The current challenge is to create accurate models of key cellular process, to show that we can quantitatively understand them! Developing such an accurate model requires a constant interplay between theory and experiments. Besides its expected predictive power, quantitative modelling should also be seen as an essential step to synthesise and curate the experimentally collected information.

Our laboratory focuses on mitosis and interphase organisation, which are important processes sustained by the microtubule cytoskeleton. However, we approach these problems in several different eukaryotes, to experience the combinatorial power present at the cellular level, i.e. to study how similar cytoskeletal elements may lead to different functional organisations when they are networked appropriately. Looking for a mechanistic understanding of each process, we seek to deduce the collective behaviour from the properties of the individual components. To achieve this, our laboratory pursues two lines of research:

1) We develop *cytosim* (http://www.cytosim.org), a physically realistic computer simulation which solves the equations of motion for fibres and associated proteins, and in particular the mechanical aspects associated with fibres.

2) We develop assays to better characterise microtubule structures experimentally, using live digital light microscopy and image analysis. The two approaches are complementary: simulations are based on well-defined "virtual molecules" while experiments are based on imperfectly characterised but real ones.

2005 has been a busy and successful year, and we made important progress in all projects led in the laboratory.

- Dietrich Foethke has developed in *cytosim* a model of interphase microtubule organisation in the fission yeast *S. pombe*. He can combine the models of nucleus positioning by Tran et al., with the observation relating to polarity establishment by Brunner et al.
- Rose Loughlin has joined the laboratory as an exchange student. Combining the actions of molecular motors and microtubule nucleators, she built a model of bundle formation in *S. pombe*.
- Cleopatra Kozlowski studied asymmetric spindle positioning in the first division of the nematode *C. elegans*. She has developed a model in which the positioning is due to pulling by cortical motors, and does not involve any pushing forces from the cortex. This was confirmed by laser-induced severing of the centrosome.
- Maria Mora developed a novel assay to control the geometry of chromatin. Using *Xenopus* laevis egg extract, she will now study how chromatin mass and geometry determine the mitotic spindle that form around it.
- Thomas Clausen has studied the formation of Ran-induced microtubule asters in *Xenopus laevis* egg extracts. Based on the idea that nucleation of microtubules occurs preferentially on existing microtubules (as in *S. pombe*), his model fits the initial exponential increase of aster size.
- Christine Plet has joined the laboratory for a summer training of two months. She has developed a new *in vitro* gliding assay by combining a minus-end directed motors: dynein with a plus-end directed motor, kinesin. This is predicted to lead to interesting microtubule patterns if the motors are disposed appropriately. The project will be continued in Dresden by Stefan Diez.

- Martin Loose has joined the laboratory for his *diplomarbeit*. He has managed to cover the top PDMS pillars with a layer of gold, in order to attach thiol-DNA specifically on the top of pillars.

In a collaborative work, we used computer simulations to study how kinetochores are mechanically attached to the centrosomes in mitotic spindles of drosphila culture cells. The connection is not due to microtubules that would be continuous from the centrosome to the kinetochore. Instead, two classes of fibres interact: dynamic microtubules growing from the centrosome, and microtubule bundles (kinetochore-fibres) associated with the chromosomes at their plus-ends. Microtubules and kinetochore-fibres are interconnected by specific proteins and together form a strong mechanical link, which is essential to segregate the chromosomes. RNAi have identified Dynein and Ncd has having a major role in this interactions. We have reconstituted in simulations the synergetic contribution of Dynein and Ncd, showing that the system can organise independently of its initial configuration. It was shown in particular that a key element of the system is that Ncd is carried at the plus-end of growing microtubules by Eb1, a microtubule end-tracking protein. Ncd can connect the plus ends of centrosomal-microtubules to kinetochore-fibres, and focus them to the pole. This study is a step towards reconstituting a complete mitotic figure, with two asters and numerous chromosomes.

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Publications during 2005

Goshima, G., Nédélec, F. & Vale, R.D. (2005). Mechanisms for focusing mitotic spindle poles by minus end-directed motor proteins. J. Cell Biol., 171, 229-240

Other references

Nédélec, F., Surrey, T. & Karsenti, E. (2003). Self-organisation and forces in the microtubule cytoskeleton. Curr. Opin. Cell Biol., 15, 118-124

Nédélec, F. (2002). Computer simulations reveal motor properties generating stable anti-parallel microtubule interactions. Journal of Cell Biology, 6, 1005-1015