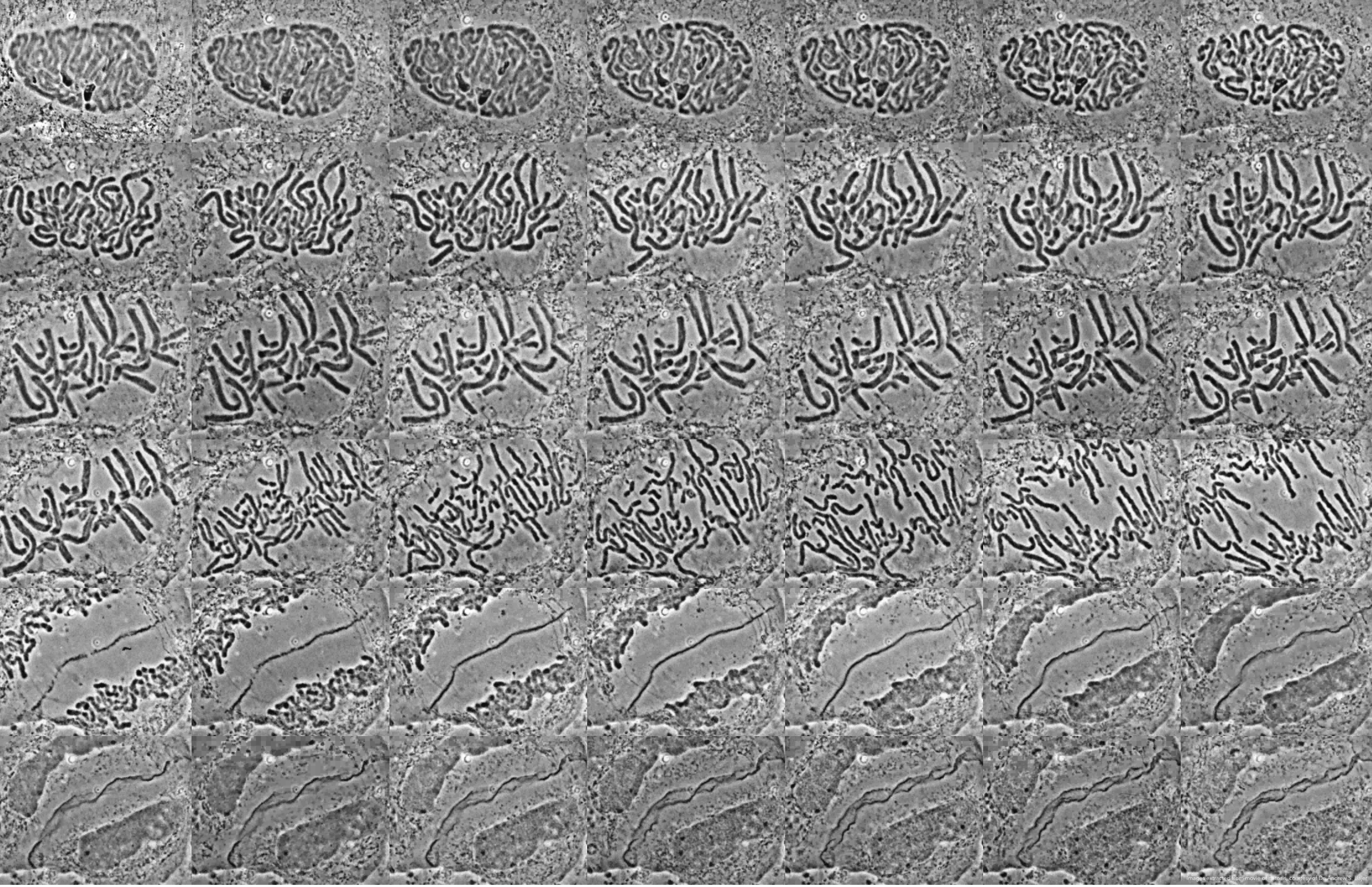


Images extracted from movie of mitosis, courtesy of Dr. Andrew S. Bajer

# MitoSys Systems Biology of Mitosis

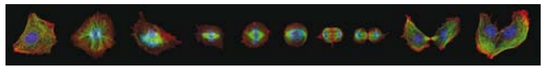
EU 7TH FRAMEWORK PROGRAMME (HEALTH)

Eukaryotic cells pass their genetic information faithfully from one generation to the next through the duplication and segregation of their genomes. This so called 'mitosis' (or 'meiosis' when sperm and egg cells are formed) is one of the fundamental processes of life. Mistakes during mitosis can contribute to cancer whereas those occurring during meiosis are the leading cause of infertility and mental retardation.

Mitosis is an immensely complex process. Although it has been studied intensively for more than a century, our understanding of mitosis at the molecular level is far from being complete. A major advance was recently achieved by the EU-funded project MitoCheck (2004–2009, www.mitocheck.org). Scientists from the MitoCheck consortium systematically inactivated all 22,000 human genes one by one in cultured human cells using RNA interference (RNAi). The cellular phenotypes upon the RNAi treatment were recorded by high-throughput live cell imaging. Automated analyses of the resulting images and movies revealed that some 600 out of the 22,000 human genes play a role in mitosis. For many of these mitotic proteins, their sub-cellular localization at different stages of the cell cycle and their interaction partners have also been identified by MitoCheck.

The identification of most, if not all, mitotic proteins provided the puzzle pieces for a complete picture of mitosis. The next obvious challenge is to assemble all the pieces together, or in molecular terms, to figure out how mitotic proteins function and interact with each other in a mitotic cell to generate a system that drives chromosome segregation and subsequent cell division. The MitoSys (systems biology of mitosis) project (2010-2015) will take on this challenge to tackle mitosis from a systems biology perspective. Internationally leading biologists, mathematicians, biochemists/ biophysicists working at thirteen research institutes, universities, international organizations and companies in eight different European countries will collaborate on this project to reveal how genes and proteins orchestrate mitosis in human cells. MitoSys will receive ten million Euro from the European Union under its seventh framework programme (FP7).





Normal rat kidney cells in different stages of cell division stained for chromosomes (blue), microtubules (green) and actin (red).

## MAIN PROJECT GOALS

- to develop quantitative assays for the behavior of mitotic proteins
- to use these assays to generate data that can be used for building mathematical models for key aspects of mitosis in human cells
- to experimentally test predictions of these models
- to merge the individual models of mitotic processes into a first comprehensive model of mitotic division in human cells
- to disseminate the knowledge about mitosis and systems biology to the scientific community and the general public

## SPECIFIC OBJECTIVES

- to obtain a systems level understanding of the assembly and organization of a functional mitotic spindle and its interaction with the cell cortex in human cells
- to obtain a systems level understanding of the spindle assembly checkpoint (SAC) and kinetochore function in human cells
- to obtain a systems level understanding of chromosome segregation in human cells
- to obtain a systems level understanding of mitotic exit regulation in human cells
- to develop technologies which will enable the generation of quantitative data on human proteins, in particular data concerning their abundance and functional dynamics with high spatial and temporal resolution, and the stoichiometry of their subunits in protein complexes
- to develop a comprehensive and quantitative model for mitotic progression
- to generate a bioinformatics resource for systems biology of human mitosis



- to organize a training course on mathematical modelling for scientists within and outside the consortium
- to create a public exhibition about cell division, its relevance to human health and beyond by combining science with contemporary art

## THE MITOSYS CONSORTIUM

**Jan-Michael Peters** (Research Institute of Molecular Pathology (IMP), Vienna/ Austria, *www.imp.ac.at*)
*Main research interests:* to understand the regulation of mitosis at the molecular level in vertebrate cells, in particular, how sister chromatid cohesion is regulated.
*Tasks in MitoSys*: Besides coordinating the MitoSys project, Jan and his colleagues at the IMP will isolate and functionally characterize a set of proteins involved in regulating various mitotic events. The purified proteins will be used in relevant biochemical and biophysical assays.

**Jan Ellenberg** (European Molecular Biology Laboratory (EMBL), Heidelberg/Germany, *www.embl.de*)
*Main research interests:* to elucidate the mechanisms underlying mitotic nuclear remodeling in intact cells. Jan has also been pioneering in developing quantitative confocal microscopy technology that enables direct observation of proteins in real time in live cells.
*Tasks in MitoSys*: Together with the MitoSys industrial partner Carl Zeiss Jena, Jan's team at the EMBL will develop a quantitative imaging platform that allows the acquisition of quantitative data in high throughput suitable for systems biology. Meanwhile, the EMBL team will establish a bioinformatics platform to integrate the data and their exchange among the consortium members as well as their dissemination to the public.

**François Nédélec** (European Molecular Biology Laboratory (EMBL), Heidelberg/ Germany, *www.embl.de*)
*Main research interests:* to understand microtubule organization in living cells, in particular, the behavior and function of spindle fibers during cell division.



*Tasks in MitoSys*: to integrate biochemical data on microtubules and *in vivo* data on protein kinetics during mitosis as well as computer simulation approaches in order to establish models for the mitotic spindle.

**Béla Novák** (Department of Biochemistry, University of Oxford, UK, *www.bioch.ox.ac.uk*)
*Main research interests:* Originally trained as a bioengineer, Béla has always been fascinated by living cells as a dynamic system of molecular interactions. He has been successfully using mathematical modelling to address biological problems.
*Tasks in MitoSys*: to develop mathematical models for key mitotic events such as spindle assembly checkpoint control, chromosome segregation and mitotic exit.

**Kim Nasmyth** (Department of Biochemistry, University of Oxford, UK, *www.bioch.ox.ac.uk*)
*Main research interests:* chromosome biology, in particular, how cohesin activities regulate chromosome behavior during cell cycle.
*Tasks in MitoSys*: to study sister-chromatid segregation and its control by the spindle assembly checkpoint during cell division.

**Jean-François Joanny** (Physical Chemistry Unit, Institut Curie, Paris/France, *www.curie.fr*)
*Main research interests:* to combine physical, chemical and biological approaches to understand physical features of cell morphology and dynamics.
*Tasks in MitoSys*: to study the roles of cytoskeleton at various stages of cell division.

**Tony Hyman** (Max Planck Institute of Molecular Cell Biology and Genetics, Dresden/ Germany, *www.mpi-cbg.de*)
*Main research interests:* spatial control of the microtubule cytoskeleton and how this applies to various cellular events such as mitosis. Tony has pioneered in functional genomics screening using RNA interference to look for genes required for various aspects of cell division.



*Tasks in MitoSys*: to generate human cell lines that stably express tagged genes and their mutant forms relevant for spindle structure and assemble; to purify some of these proteins for further biophysical and biochemical analyses.

**Joe Howard** (Max Planck Institute of Molecular Cell Biology and Genetics, Dresden/ Germany, *www.mpi-cbg.de*)
*Main research interests:* to explore the biochemical and biophysical basis of cell shape and motion using a wide range of modern techniques.
*Tasks in MitoSys*: to produce spindle assembly factors and assess the effects of these proteins on spindle dynamics during mitosis.

**Frank Jülicher** (Max Planck Institute of for the Physics of Complex Systems, Dresden/Germany, *www.mpipks-dresden.mpg.de*)
*Main research interests:* to develop concepts or models to improve our understanding of the principles that govern a variety of cellular processes such as cell division.
*Tasks in MitoSys*: to develop theoretical approaches and models to describe the assembly and dynamics of the mitotic spindle and the biophysics of cytokinesis.

**Andrea Musacchio** (European Institute of Oncology, Milan/Italy, *www.ifom-ieo-campus.it*)
*Main research interests:* to understand the inner workings of the spindle assembly checkpoint and its interaction with kinetochores using combined biochemistry, cell biology and structure biology approaches.
*Tasks in MitoSys*: to produce recombinant proteins of the spindle checkpoint and of the kinetochore and subject them for a variety of *in vitro* assays.



**Daniel Gerlich** (Eidgenössische Technische Hochschule Zürich, Switzerland, *www.ethz.ch*)
*Main research interests:* to study how different cytoskeletal and membrane structures coordinately accomplish faithful cell division, using various light- and electron microscopy techniques and computational image analysis.
*Tasks in MitoSys*: to integrate technological resources and experimental data from a number of MitoSys labs into a common model for mitotic exit regulation.

**Marie-France Carlier** (Centre national de la recherche scientifique (CNRS), Paris/ France, *www.lebs.cnrs-gif.fr*)
*Main research interests:* to study the molecular and physical mechanisms of how actin filaments and microtubules are assembled and their dynamic changes in response to cell signaling, using physical-chemical bulk solution measurements, single polymer dynamics and reconstitution approaches.
*Tasks in MitoSys*: to analyze the functional relationship between actin filaments and microtubules during mitosis and cytokinesis.

**Marcos Malumbres** (Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid/Spain, *www.cnio.es*)
*Main research interests:* to establish mouse models to assess *in vivo* function of genes such as cell cycle regulators during normal development as well as in diseases.
*Tasks in MitoSys*: to generate and analyze mouse models and/or primary cultured cells of additional mitotic regulators; to test predictions derived from the mathematical models of various mitotic events in relevant mouse models.



**Nynke Dekker** (Delft University of Technology, Delft/The Netherlands, *www.tnw.tudelft.nl*)
*Main research interests:* single-molecule techniques to study the dynamics of DNA and RNA as well as their interaction with proteins.
*Tasks in MitoSys*: using single-molecule techniques to analyze the properties of cohesins, kinetochore proteins and other proteins involved in chromosome replication and separation.

**Melina Schuh** (MRC Laboratory of Molecular Biology, Cambridge/UK, *www2.mrc-lmb.cam.ac.uk*)
*Main research interests:* to understand how mammalian oocytes mature into eggs.
*Tasks in MitoSys*: to develop quantitative live cell imaging assays for early mouse embryos that will allow us to validate predictions of the model for the mitotic spindle *in vivo*.

MitoSys Consortium, 2010.



**Carl Zeiss MicroImaging GmbH** (Jena/Germany, *www.zeiss.de*)
Carl Zeiss MicroImaging GmbH is one of the global market leaders in providing the state-of-the-art microscopy solutions and systems for life science research and beyond.
*Tasks in MitoSys*: Carl Zeiss MicroImaging will team up with Jan Ellenberg's group at the EMBL to develop an automated quantitative microscopy system with high throughput suitable for systems biology studies.

**Marina Wallace** (Central Saint Martins College of Art & Design, University of the Arts London, UK, *www.csm.arts.ac.uk*)
*Main research interests:* As an art historian, writer, lecturer, and artist, Marina has a unique grasp of the relationship between science and art. She has curated several internationally acclaimed exhibitions, among them 'Gregor Mendel: the Genius of Genetics' in Mendel's Abbey in Brno.
*Tasks in MitoSys*: Marina will head a team of artists and the scientists from the MitoSys project to create a public exhibition on mitosis, its relevance to human health and beyond. The exhibition will be displayed in at least three European cities during the final two years of MitoSys.

## CONTACT

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