**EMBL Group Leader Lecture**
**17:00-17:30, Tuesday 8th September 2015**
**The AIAS Auditorium, Aarhus University**

## Systems biology of human cell division using light microscopy

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Human cells contain over 20 000 different genes and essential functions of life, such as cell division, require several hundreds of these to be expressed. Using systematic gene silencing by RNA interference and subsequent phenotyping by high throughput microscopy we have defined close to 600 proteins that are needed for a human cell to divide normally. These proteins have to be precisely orchestrated in space and time to drive the faithful segregation of the genome and the cleavage of one cell into two. Understanding how this dynamic network of mitotic proteins drives one of the most dramatic morphological and functional changes cells can undergo, will require to map their interactions in space and time. To address this challenge, we have established an integrated systems biology workflow, consisting of genome editing, imaging and computational modeling to map the mitotic network in live dividing human cells. After homozygous genome editing to tag all endogenous copies of a given mitotic protein fluorescently, we image its absolute abundance and subcellular distribution by calibrated 4D imaging relative to spatio-termporal landmarks of cell division. Computational image analysis and modeling then allows us to align the dynamic cell morphology in space and time to obtain a standard mitotic cell into which we can integrate the data of all proteins imaged. Using image parameterization and machine learning, we can measure the dynamic subcellular localization of mitotic proteins as well as fluxes between subcellular compartments and structures. This allows us to predict protein clusters, the chronological order of their formation and disassembly and the abundance of their subunits. To validate the predicted network behavior, we then perform high-throughput fluorescence cross correlation spectroscopy (HT-FCCS) of fluorescently tagged pairs of binding partners during division. Our integrated computational and experimental method is generic and makes many dynamic cellular processes amenable to dynamic protein network analysis.