Computational Systems Biology of Cell Signalling

COSBICS

Objective

Cell signalling investigates the transmission of information from receptors to gene activation by means of biochemical reaction pathways. COSBICS has established and applied a novel computational framework in which to investigate cellular signalling. Instead of simply mapping proteins in a pathway, COSBICS is concerned with "dynamic pathway modelling". Dynamic pathway modelling establishes mathematical models to quantitatively predict the spatial-temporal response of signalling pathways.

Aims

- Predictive dynamic models of the JAK2-STAT5, the Ras/Raf1/MKE/ERK and the NFkB pathway, three signalling pathways commonly subverted in cancer
- Implementation of methodologies to support design of experiments
- Investigation of cross-talk and its coordination via mathematical modelling
- Investigation of the effects of space and time in the dynamics of signalling pathways
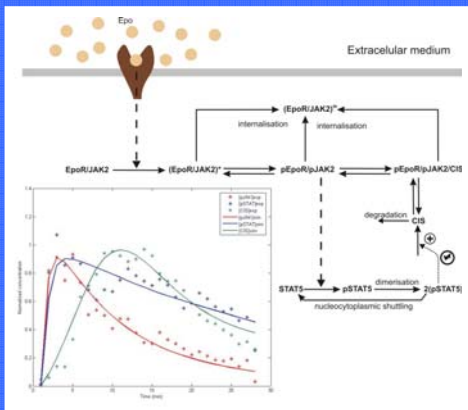
The systems biology approach

- Set up of mathematical models using modeller-experimentalist interaction
- Model calibration using quantitative experimental data
- Model assessment and model refinement
- Model validation through experiments
- Model based predictions on the basic features of the system
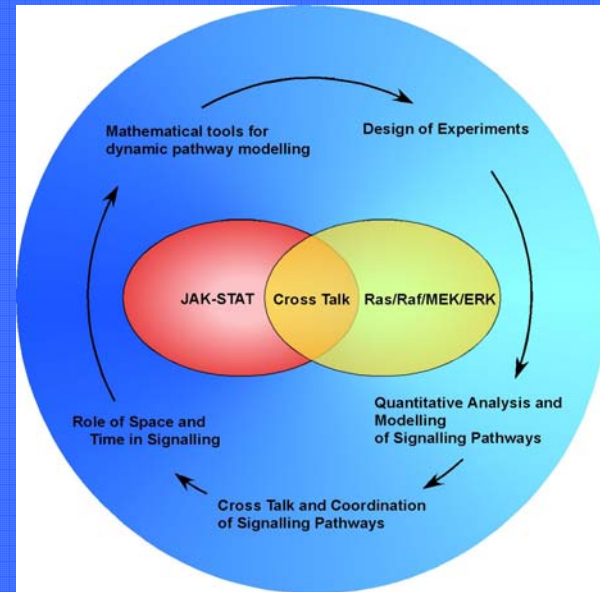
Methodologies for data-driven modelling

- New parameter estimation techniques for nonlinear systems
- New algorithms for optimal designs of experiments
- Theoretical studies of cross-talk, model reduction and delays

Experimental techniques

- Advanced quantitative time course data generation
- Live cell imaging as a basis for dynamical modelling

The diagram to the left shows one of several hypothesised model structures for the JAK2-STAT5-pathway. Given a set of preliminary experimental data, genetic algorithms were employed to estimate the parameter values for a model. The solid lines show the simulation results. The mismatch between data and simulations is used to hypothesize further modifications to the model structure and help design new experiments.

Western Blot of siRNA transfection in HEK293 cells. HEK 293 cells were transiently transfected with different siRNAs against human RKIP using Amaxa Nucleofector.
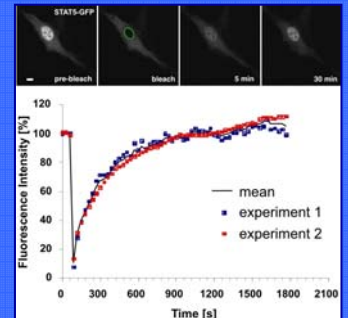
FRAP analysis of STAT5 nucleo-cytoplasmic cycling. NIH3T3-EpoR cells transduced with pMX-STAT5A-GFP. After Epo addition, the nuclear pool of STAT5-GFP was photobleached with high laser intensity and recovery of fluorescence into the nucleus was followed for 30 minutes.

Results

- Set up of kinetic models to describe the JAK2-STAT5, RAS/RAF1/MEK/ERK and NFkB pathway under the biological conditions investigated in the project
- Demonstration of the functioning of JAK2-STAT5 pathway as a robust amplifier
- Demonstration of the role of RKIP modulating oscillations in the NFkB pathway
- Adaptation of a plethora of quantitative experimental techniques for the modelling these pathways (quantitative western blots, life cell imaging, ELISA kits...)
- Design, implementation and test of theoretical and experimental techniques to investigate protein gradients and diffusion effects in the JAK2/STAT5 pathway
- Design and application of a strategy for the reduction of dimensionality in non-linear kinetic models of cellular signalling
- Implementation and application of a strategy to use kinetic models based on power-law terms in cell signalling modelling
- Development and implementation of a MATLAB toolbox for parameter estimation and optimal design of experiments

Key publications

- **A systems biology approach to analyse amplification in the JAK2-STAT5 signalling pathway.** Vera *et al. BMC Systems Biology* 2:38, 2008
- **An error model for protein quantification.** Kreutz *et al. Bioinformatics*, 23 (20), 2007
- **Dynamic pathway modeling - Feasibility analysis and optimal experimental design.** Maiwald *et al. Annals New York Acad Sci* 1115, 2007
- **Power-Law Models of Signal Transduction Pathways.** Vera, J. *et al. Cellular Signalling*, 19, 2007
- **The role of inhibitory proteins as modulators of oscillations in NFkB signalling.** Nikolov *et al. IET Systems Biology (in press)*

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