Computational Systems Biology Group

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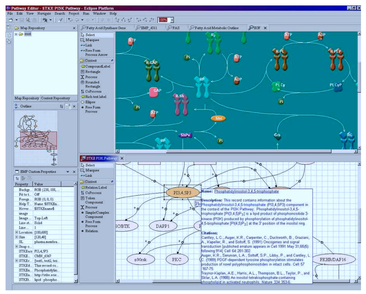
Computational Systems Biology Group

The research in the group of Computational Systems Biology is focused on kinetic and static modeling of biological processes by linking diverse data and modesl through multiple iterations, ranging from static *ab initio* models to highly constrained kinetic models that cross multiple scales. This continuum of modeling approaches reflects the realistic evolution of a systems level approach, which has proven to be successful in other disciplines and now is tailored to biological systems. Our models of cellular networks underlying complex diseases and of microbial pathways models are particularly applicable for industry. Modelling will be supported by the Systems Biology Software Infrastructure, , a new integrated platform, facilitating the modelling process from databases to knowledge discovery, which is currently under development in our group.

Edinburgh Pathway Editor

EPE is a visual editor designed for annotation, visualization and presentation of wide variety of biological networks, including metabolic, genetic and signal transduction pathways. It based on a metadata driven architecture, which makes it very flexible in drawing, storing, presenting and exporting information related to the network of interest.

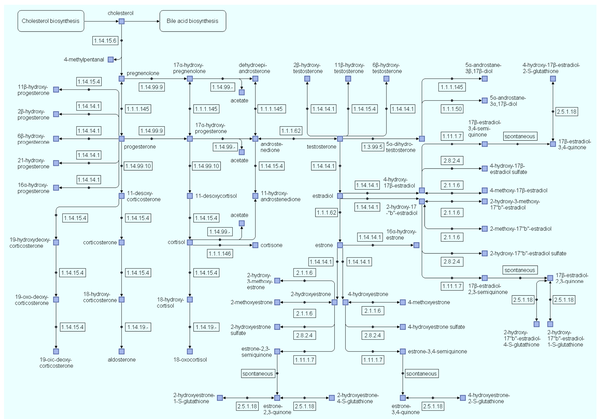


EPE was created as an Eclipse stand-alone application, with Eclipse open framework architecture. This enables the development of extensions to enhance the existing capabilities. Specific plug-ins, to perform scientific computing and other tasks can be easily incorporated.

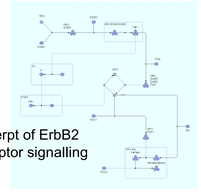
- **Implemented Notations**
- EMP/WIT metabolic pathway
- KEGG-like metabolic pathway description
- Edinburgh process notation
- STKE
- Kitano process notation
- Kitano state notation
- Biocarta-like artistic notation

Human Networks Reconstruction

A high quality human metabolic network was reconstructed by combining genome annotation information and information from literature. The nearly 3000 metabolic reactions in the network were reorganized into about 50 human specific pathways with low overlap (as an example a pathway is shown below).



Modeling Breast Cancer Pathways

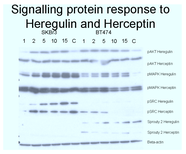


Excerpt of ErbB2 receptor signalling

We are developing a computational model to model the effect of Herceptin on the ErbB receptor system. Although a significant advance in cancer therapy Herceptin's exact mechanism of action is still a matter for debate. We hope our model will shed some light on this.

Developing signalling model for ErbB2 from experimental data

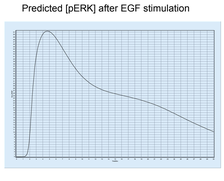
The project is a collaboration between the CSB and the Edinburgh University Cancer Research Centre. They obtain quantitative proteomics data for two cell lines (see Western Blot left) that are used to validate the computational model. We are developing a computational model for multiple cell lines.



Predicting Cell Fate

ErbB receptor signalling has a profound affect on gene expression which in turn affects cell fate decisions, e.g. apoptosis or proliferation. Understanding these decisions is critical to understanding cancer processes.

We are developing a computational model to predict gene expression profiles from the output of our computational model of ErbB receptor signalling.



"Personalised" Diagnostic Computational Models

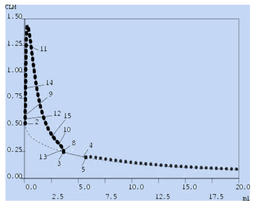
Our ultimate goal is to integrate our models with clinical data from breast cancer patients. Thus for each patient we will be able to develop a "personalised" computational model could assisting clinicians in selecting appropriate anti-breast cancer therapies or provide a better understanding of patient prognosis.

Mathematical modelling and large-scale computational simulation of complex biological systems

The purpose of this project to develop modular open source software to assist researchers in the building and modelling of circuits. Dynamical system theory including bifurcation analysis and global optimisation is employed to model the evolution of extremely complex biochemical pathways of living organisms, using high performance large-scale parallel computational techniques with aids of supercomputers. This accounts may include, but not limited to, circadian rhythms, living cells, disease treatment, and drug discovery.

Bifurcation Analysis

Dynamical systems are widely used to describe complex biological phenomena. Bifurcation analysis is the way to describe how topological features (such as the number of stationary points and periodic orbits) change as one or more parameters of the system are varied, and the behaviour of the whole system under changes as the parameters vary. However, there is no general way to investigate a system as a function of all its parameters. Common practise is to fix some parameters, thus reducing the number of free parameters to a manageable number. Regions of interest in parameter space usually involve those with steady state and oscillatory periodic behaviour. Therefore, using bifurcation analysis to search for bifurcation points which may give the signature of the existence of such interesting dynamics in differential-equation-based models is very important in complex biological systems. Numerical computations are usually used for simulations and bifurcation analysis of high dimensional dynamical systems. As complex biological systems are often high dimensional dynamical systems, supercomputers (such as IBM BlueGene) are used in order to handle the numerical computation of the analysis which is otherwise impossible to do.



Bifurcation diagram for LHY mRNA as a function of maximum rate of LHY mRNA degradation under constant light. Points 2, 3, and 5 are Hopf bifurcation points.
Fully dark circles show the maximum values of the stable periodic solutions, and full lines show the stable steady state solutions; dashed lines represent the unstable steady state solutions.