Demonstrating a complete clinical to genomics through systems biology workflow with the BioBridge portal

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Abstract

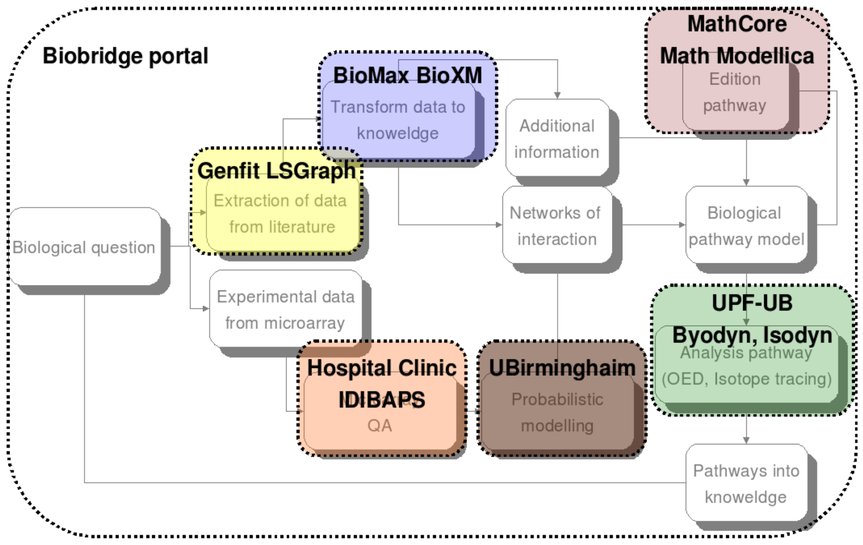
Information coming from omics disciplines is currently fragmented, and frequently the lack of appropriate tools for their integration into global models severely limits progress in the understanding of the underlying mechanisms of complex chronic disorders. EC-funded BioBridge project (FP6-2005-LIFESCIHEALTH-7 037909, http://www.biobridge.eu) focusses on the creation of systemic dynamical models to link molecular mechanisms to complex diseases. Thus, the BioBridge portal integrates:

- structured databases (including metabolic pathways affected by complex disorders);
- tools for the integration of this data into mathematical models;
- analysis of multilevel data through simulation to improve previous knowledge;
- interface for the management of computing resources.

Here we present the integration of chronic obstructive pulmonary disease (COPD) transcriptomics data (specifically oligonucleotide microarrays from local or public data) into the simulation of a previously reported model for central metabolism. First, fold change (FC) values of contrasts of interest on these datasets were incorporated into the BioXM-based BioBridge database. Quantitative integration of the FC and correlation values is being considered for the modulation and refinement of the set of parameters used in the differential equations of the model.

BioBridge web portal

The Biobridge portal is a common point of access, share and process of information between different users as clinicians, omics, modellers, academics and teachers. In order to create a biological question, and to propose a model which can explain it, the following road map shows a flow and the components involved in the project.



Components

• **MathModelica**: an easy-to-use modelling and simulation environment for the Modelica language with SBML i/o capabilities.

• **Byodyn**: designed to provide an easily extendible computational framework to estimate and analyze parameters in highly uncharacterized models. Offers parameter estimation, and optimal experimental design on several computational frameworks.

• **Isodyn**: metabolomics tool for isotope tracing modelling

• **BioXM:** a fully customizable knowledge management (KM) solution for better integrated and knowledge-based drug discovery and development, although it can be used for any biological purpose.

• **Rrep**: Bioconductor and other related libraries can be directly imported into the BioXM KM to manage/analyze data from within the portal.

• **Other tools for probabilistic models:** mutual inference and Bayesian networks analysis tools (ARACNE and BANJO) can be easily accessed from the portal.

Web Application

The portal is built following an OO framework in PHP 5.0, supporting a range of Web 2.0 technologies. It has a support of SOAP webservices. Through AJAX, it also offers the interactivity of executing the program as if it was executed from terminal, due to synchronizing ability. The portal itself is divided into four layers. For the presentation layer (the part visible to the user), it uses SVG for graphics as graphs or microarray data representation; and the Extensible Hyper Text Markup language (XHTML) for common components (tables filled up with data coming from Data Bases). This XML (XHTML + SVG) is formed from PHP objects of the BioBridge infrastructure.

A set of GUIs have been built allowing the user to create graphical representations of models, microarray data and information from literature. The data model for the application uses a UNIX like set of permissions to operate on the information and to create individual workspaces.

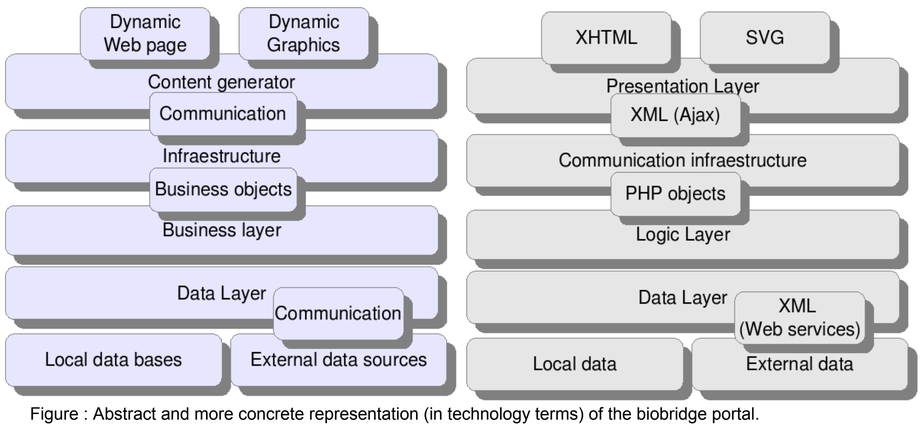
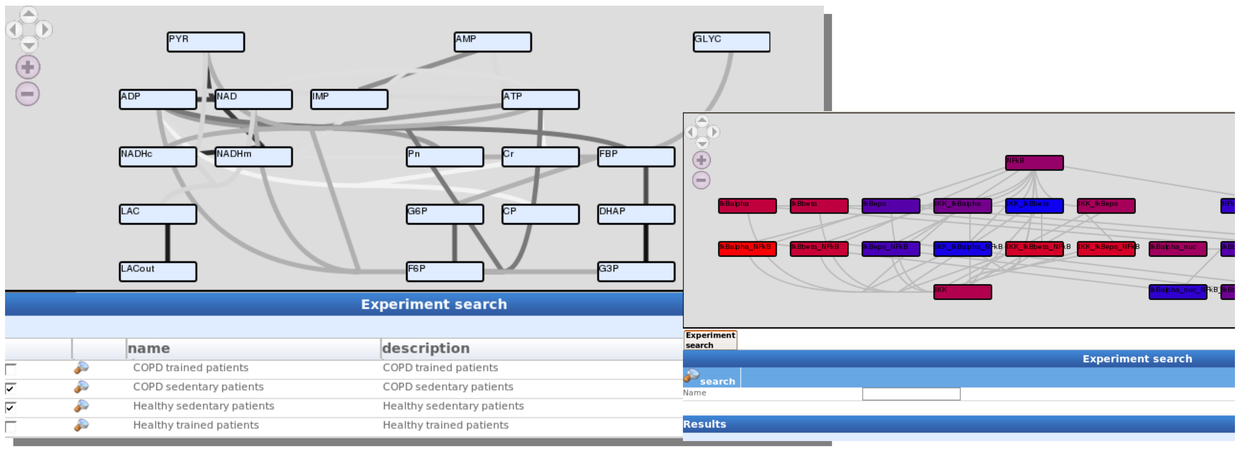


Figure : Abstract and more concrete representation (in technology terms) of the biobridge portal.



A use case: Biochemical model for COPD

Some prevalent chronic diseases, such as chronic obstructive pulmonary disease (COPD) are associated with significant systemic alterations. The mechanisms underlying such effects are not completely understood but disruption of the physiologic signalling equilibrium between nitric oxide (NO) and reactive oxygen species (ROS) production is thought to play a central role. This situation of nitroso-redox imbalance is clearly linked to mitochondrial dysfunction characterised by a decreased mitochondrial capacity to oxidative phosphorylation and/or distortion of oxygen transport into the cells, leading to an increase in ROS production.
The model shows the mathematical description of the mitochondrial respiratory chain and the reactive oxygen species (ROS) generation as a side product of respiratory electron transport.
Since respiration and ROS production are linked with the state of central metabolism, such module needs to be incorporated into the model. The model of ATP consumption by myofibrils, which takes into account the spatial structure of the cell and diffusion barriers for ATP energy delivery, provides a link between the main muscle cell function and the regulation of muscle cell energy metabolism. To provide the interface between the model and clinical data the module of oxygen and lactate diffusion between intracellular volume and blood is linked to the other parts of the integrated model. Integration of these modules provides a tool for understanding the biochemical basis of the considered diseases.

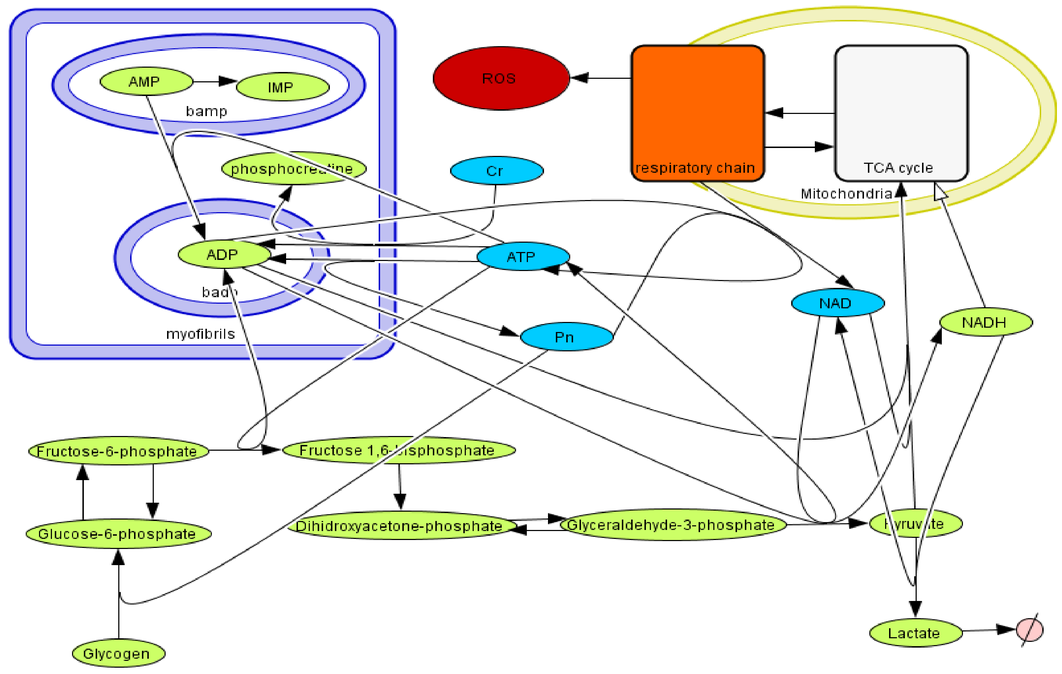
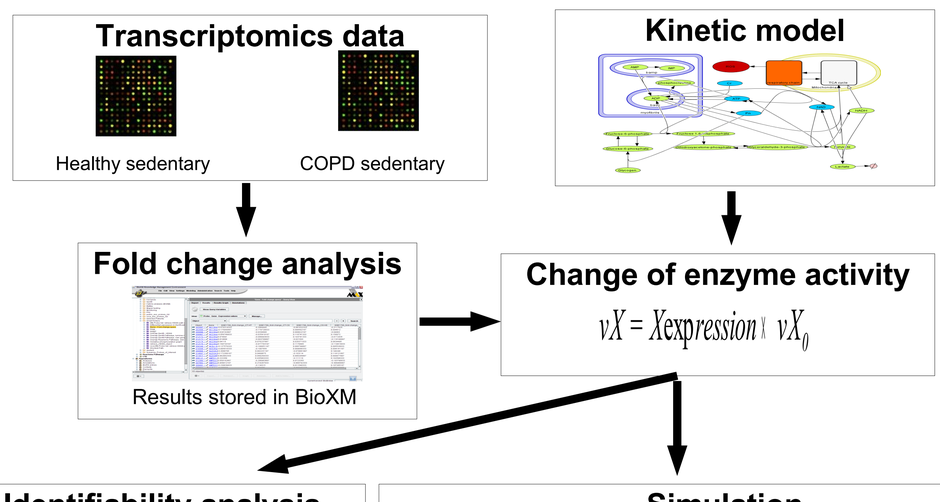


Figure 1: Schema of the biochemical model t, we can see as the different parts are linked. The image have been created using CellDesigner.

Integrating genomic information to kinetic model



Identifiability analysis

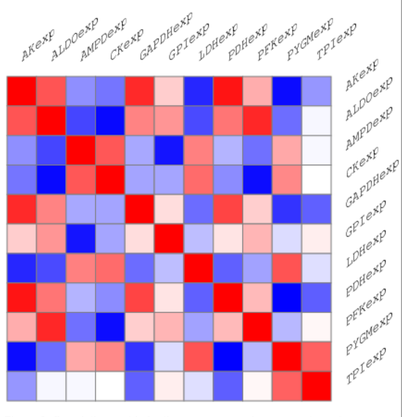
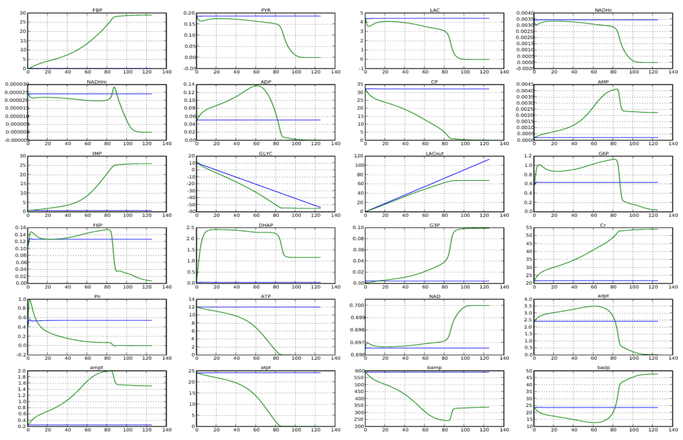


Figure 3: Correlation matrix for the gene expression parameters of each enzyme in the system.

Correlation analysis of the model parameters.

Simulation



Fiigure 2: Simulation using the differential gene expression profile between CS and HS. The trajectories for a specific metabolite are represented in each sub-plot. The initial HS simulations is the blue line and the green line is the simulation obtained modifying the model according the FC value of the comparison CS vs HS. The vertical axis in each sub-plot is the concentration and the horizontal axis is the time.

Modifications of the dynamical behaviour of the biochemical model in different conditions characterized by differential gene expression levels

Conclusions

•The Biobridge portal provides a tool for easy integration of clinical and “omics” data, and the ability to query about the effect of the observed data into the dynamics of the underlying biochemical models

•We have demonstrated the use of the portal in a particular case of clinical and biological interest, relating inflamatory diseases to a biochemical model

References

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