Brunel University London | Institute of Environment, Health and Societies

Network-based Computational Design of Bacterial Genome Scale Metabolic Systems

David Gilbert, Monika Heiner, Yasoda Jayaweera, Bello Suleiman, Alessandro Pandini, Arshad Khan, Nigel J Saunders

Network-based design

The Synthetic Biology Computational Design Group focuses on the development and application of methodologies for the design of novel microbacterial strains, in collaboration with the Microbial BioEngineering Group. This research involves the use of biochemical pathway models as design 'templates' which can act as guidelines for bioengineering implementation.

The design models describe the biochemical reactions of bacterial strains as systems of continuous or stochastic equations, resulting in an overall bipartite graph structure which can be represented as a Petri net. Our work involves model construction, analysis and modification. The models can be analysed for both their static and dynamic properties in order to confirm that they are sound and consistent, and checked against observations of the bacteria that they describe.

The Challenges

Currently models of biochemical networks which can be simulated dynamically are quite limited in size mainly due to issues of **model stiffness**. This causes a bottleneck to the development of methods for computational analysis of genome scale models, inhibiting progress in whole-system based design.

Even when these models can be simulated to generate dynamic behaviour, there is a further challenge to analyse the **large amount of data produced**. Bacterial whole genome metabolic models (GEMs) can comprise about 5000 reactions and metabolites, and encode a huge variety of growth conditions.

Our approach

We have developed a methodology and related workflow comprising methods and associated software tools to explore the dynamic behaviour of genome scale metabolic models, and providing a guidance framework for modellers and designers of synthetic bacterial systems.

We use delta-leaping, an efficient approximative stochastic simulation algorithm, coupled with model checking over time series (metabolite concentration &reaction activity), as well as advanced data analytics methods.
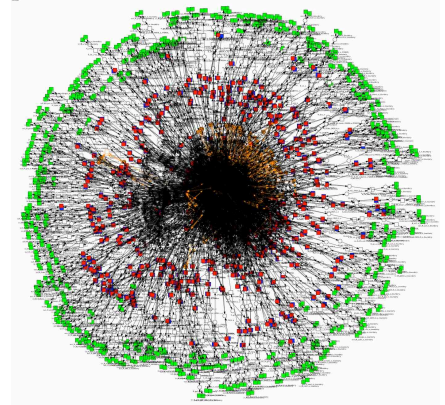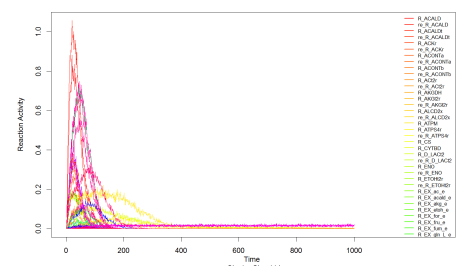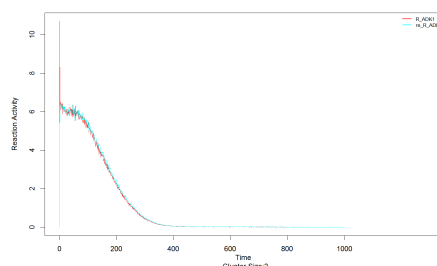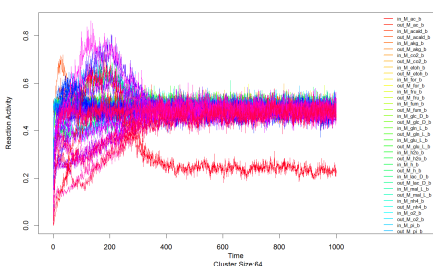
Application scenarios

We apply our techniques to explore model behaviours under different growth conditions, with a focus on the reaction perspective related to functionally meaningful subsystems (pathways).

Other application scenarios include the comparison of model versions arrived at by model development, manual curation, variant exploration (knock out, etc), production target based optimisation (e.g. within the framework of synthetic biology or metabolic engineering) across populations and over generations for evolutionary approaches.

The intention is that our techniques will aid the exploration and understanding of large models, and comparison between model versions and configurations. These methods will also support the modification of such models as part of the design process in synthetic biology.

Workflow

Model preparation for dynamic simulation

Rectifying typos;
Converting SBML into internal format;
Identifying main connected subgraph and deleting all others;
Rectifying source and sink places;
Initialising metabolite concentrations;
Adding kinetic rates following the mass action law.

↓ Models

Model simulation (trace generation)

Model selection (strains, versions or variants);
Model configuration (selecting growth conditions);
Simulator configuration (selecting solver, number of runs, simulation time and observation steps, observed variables), and execution.

↓ Traces

Trace analysis

Over reactions, metabolites and subsystems for one or more models
(strains, versions, variants, growth conditions)

| Model checking | Whole systems data analytics | Subsystems data analytics. |

Hierarchical clustering using Euclidean distance as dissimilarity measure of a minimum growth model based on reaction activity traces; the dendrogram shows three distinctive clusters of behaviour.

Contact details: {david.gilbert,monika.heiner}@brunel.ac.uk