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**The NetBuilder' project: development of a tool for constructing, simulating, evolving, and analysing complex regulatory networks** Katja Wegner\*, Johannes Knabe, Mark Robinson, Attila Egri-Nagy and Maria Schilstra

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#### **Regulatory networks**

Regulatory networks specify how processes such as gene expression or cell-cell signalling are controlled by regulators. Such regulatory networks may contain feedback loops, non-linear interactions and processes working on varying timescales, and can be very complex. Moreover, regulators often act in concert. Particularly in genetic regulatory networks, regulatory agents such as transcription factors may take part in various combinations, each of which may have a specific effect, and may be present at specific developmental stages in specific cells or tissues. To handle this complexity and to understand different relationships in the network, modelling and simulation techniques are used. "In silico" techniques enable researchers to study networks in a very flexible, cheap and fast way compared to "in vitro" and "in vivo" experiments. Therefore, we are developing NetBuilder' http:// strc.herts.ac.uk/bio/maria/Apostrophe, a tool for integrating the construction, simulation, evolution, and analysis of complex regulatory networks. NetBuilder' uses the Petri Net formalism to aid the modelling and analysis processes, and to support understanding of the network structure and the role of the various elements.

#### **NetBuilder'**

NetBuilder' consists of a model designer and a simulation engine, and modules for visualisation and analysis of the

network structure and simulation results are under development.

1. *Network construction*: the creation of Petri Net network representations is facilitated by a graphical model designer, but can also be done relatively easily (and in principle in a more flexible way) by programming the appropriate commands in a Python driver module.

2. *Simulation:* NetBuilder' automatically converts the Petri Net model into the set of vectors required to perform the simulation of its dynamics (a state vector, a stoichiometric matrix, and a vector containing information about the regulatory interactions). This mathematical model can then be simulated by using either stochastic (Gillespie algorithm) or deterministic (standard numerical ODE integration) methods. Techniques for carrying out hybrid stochastic-deterministic simulations are being developed and implemented.

3. *Evolution:* we have developed a (genetic) algorithm to evolve genetic regulatory networks that show a specified output behaviour on the basis of a given input function. We are currently attempting to generalise the procedures somewhat, and make them suitable for integration into NetBuilder'.

4. *Analysis*: methods for reducing the complexity of networks, for finding network motifs, and for comparing dynamic behaviour are being developed, implemented, and integrated.

5. *Interoperability:* NetBuilder' supports SBML. Connection to Systems Biology Workbench (offering further simulation and analysis tools) is planned.

#### Emphasis on regulatory interactions

The model designer and simulation engine can be used to create and simulate the dynamics of a wide range of biological reaction networks. Although its graphical user interface does not allow definition of arbitrary rate equations (a large number of existing modelling and simulation tools can be used to do this), NetBuilder is intended to support the specification of complex combinatorial regulatory interactions on the basis of a limited set of relatively simple primitives (to describe the interaction) and operators (to describe their combination).

#### Conclusion

NetBuilder' aims to offer a range of methods and tools that are useful for modelling, simulating, evolving, and analysing complex regulatory networks, and it is hoped that it will thereby assist in the understanding of the structure and dynamics of these networks.

