Understanding the dynamics of a complex biological network without parameter information: Case study on the cell-cycle network of fission-yeast (*S.pombe*)

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Introduction: Understanding and predicting the dynamics of complex biochemical networks is one of the fundamental goal of Systems Biology. Although, even a single cell is way too complex in nature for us to model all its biochemical behaviours using our current understanding and compute capacity, scientists have been successful in modelling some of the biochemical pathways essentials in every living organism. One of the computationally feasible ways to predict the dynamical behaviours of these networks is to numerically solve a bunch of coupled Ordinary Differential Equations (ODEs) with appropriate kinetic parameters that can be experimentally measured. But that process requires extensive wet-lab experiments to find out the vast array of biochemical parameters necessary to model even modests of the biological pathways, which slows down the process of building the models. This has motivated scientists to come up with innovative ideas to be able to gain insight into a biochemical pathway without extensive knowledge of the parameters involved in it. In this article I am going to discuss two such ways of modelling a network and show how they can be useful by applying them in the cell-cycle pathway of fission-yeast (*S.pombe*).

Discrete Method: One of the most simple yet elegant way to model the essentials of a network is to model it as a graph model with each protein / regulator can be assumed as a node and the interaction between those regulators as the edges of the graph. The edges will only represent the the sign of the relation between those two nodes. What I mean, is that the node will only take into account of the fact that the interaction is activating (+1) or inhibiting (-1). After that, in each discrete ieration the state of the the daughter nodes of the initialized nodes (can be themselves as well if self-activation or self-inhibition is present) will be updated as per the update rule mentioned below.

$$S_i(t+1) = \begin{cases} 0, & \text{if } \sum_j a_{ij} S_j(t) < \theta_i \\ 1, & \text{if } \sum_j a_{ij} S_j(t) > \theta_i \\ S_i(t), & \text{if } \sum_j a_{ij} S_j(t) = \theta_i \end{cases}$$

Here, $S_j(t) \in \{0,1\}$ in the binary value assigned to node j at iteration t, which discretely denotes if the protein is present in the system at that iteration or not. $a_{ij} = 1$ denotes an activating interaction from node j to node i, and similarly a_{ij} denotes an inhibiting edge and $a_{ij} = 0$ denotes no interaction (no edge between those two nodes). θ_{ij} is a threshold of activation of node i which is generally 0, unless otherwise mentioned [1].

One interesting aspect of this Boolean modelling is that, we can actually start the model iteration using all the possible initial conditions and that will be in most cases very much computationally feasible. For example, if our network of interest has 7 nodes, then there will be in total $2^7 = 128$, which means we can effectively sample the total solution space of the network which is absolutely not possible in a continuous scenario.

So, in this manner, without any knowledge of the kinetic parameters in the model or ever solving any ODE at all, we can gain insight into the dynamics of the model as I shall discuss using a case study in the later half of the report.

Continuous Method: Although the discrete method in theory can provide us a lot of information regarding the network of interest, the harsh reality is that no biological system is actually discrete and introducing even moderate amount of realism requires us to write the ODE of the reaction kinetics and solve them numerically to observe the dynamics of the network. But that requires access to the set of kinetic parameters that we are trying to avoid in our modelling paradigm.

So, to tackle that exact challenge Huang et al. 2018 [2] published an article on a software that they named “RACIPE: Random Circuit Perturbation”. It takes, just like the Boolean method, only the topology of the core regulatory circuit and unbiasly generates an ensemble of mathematical models, each of which is characterized by a unique set of kinetic parameters From the ensemble of models, we can analyze the robust dynamical properteis of the core circuit via downstream statistical analysis. In RACIPE, the effects of the ”peripheral factors” are modeled as random perturbations to the kinetic parameters. RACIPE samples its parameters across a wide range (via some random distribution) keeping the half functional rule (which states that each regulatory link has about 50% chance to be activated) valid. The RACIPE generated gene-expression data can later be analyzed using differnt statistical tools (primarily Hierarchical clustering analysis (HCA), and Principal Component Analysis (PCA)) to get a holistic view of the dynamical feature of the network. All these are based of the previous studies that says that robust features in any gene regulatory network remains conserved against large parameter purturbations due to the the restraints from the circuit topology itself.

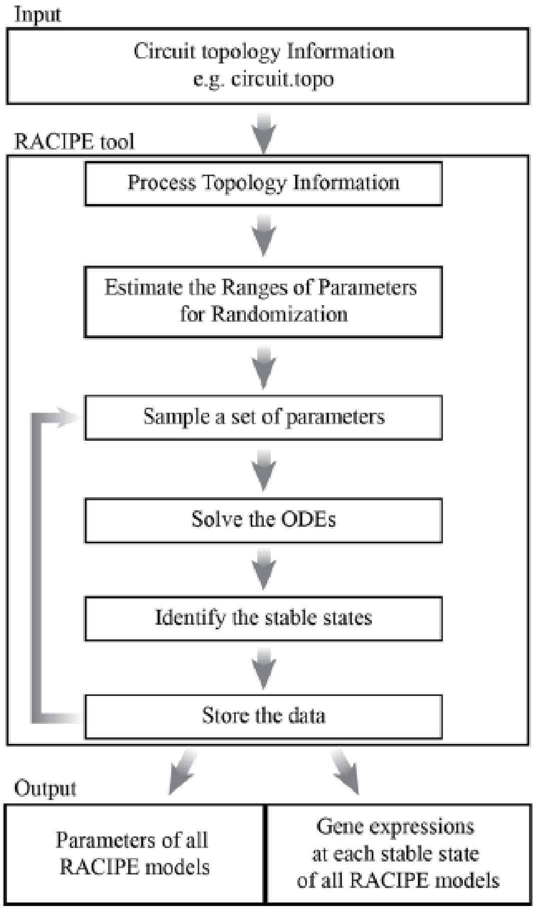
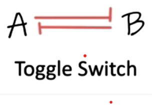

Input
Circuit topology Information
e.g. circuit.topo
RACIPE tool
Process Topology Information
Estimate the Ranges of Parameters for Randomization
Sample a set of parameters
Solve the ODEs
Identify the stable states
Store the data
Output
Parameters of all RACIPE models
Gene expressions at each stable state of all RACIPE models

Figure 1: Workflow of RACIPE [2]

Input: The primary input of this toolbox is the circuit topology that is written in a '.topo' file (e.g. "circuit.topo"). Each line of this file specifies a regulatory link, which contains the source node, target node and mode of interaction (1 for activation, 2 for inhibition). Example of a .topo file is shown below.

```
Source      Target      Type
  A           B           2
  B           A           2
```

The above .topo file represents a 'Toggle Switch' network which is essentially two master regulators mutually inhibiting each other.



Process Topology Information: This process builds the ODEs based on the circuit topology (input). As an example the above circuit will be represented as

$$\frac{dA}{dt} = G_A H^S(B, B_A^0, n_{BA}, \lambda_{BA}^-) - k_A A$$
$$\frac{dB}{dt} = G_B H^S(A, A_B^0, n_{AB}, \lambda_{AB}^-) - k_B B$$

Where, A and B represents the concentration of the protein A and B as a function of time, G_A and G_B are the maximum production rate of A and B. k_A and k_B are the innate degradatino rates of the the corresponding proteins, and H^S is non-linear shifted Hill function defined as

$$H^S(B, B_A^0, n_{BA}, \lambda_{BA}^-) := \lambda_{BA}^- + \frac{1 - \lambda_{BA}^-}{1 + \left(\frac{B}{B_A^0}\right)^{n_{BA}}}$$

λ_{BA}^- is the maximum fold change of A caused by inhibitor B.

When multiple regulators target a gene, the function form of the rate equations assumes that these regulators are independent and hence, the overall production rate becomes the product of the innate production rate of the target genes and the shifted Hill functions for all the regulatory links.

Estimatation of parameters: Ranges of the threshold values in the shifted Hill functions are estimated numerically to satisfy the “half-functoinal” rule. Most of the other parametes are preset and sampled via a random distribution (which is ‘uniform distribution’ by default). All these parameters are stored in a ‘.prs’ (parameter) file (e.g. “circuit.prs”).

Solve the ODE, Identify the stable steady states: RACIPE repeats the simulates teh coupled ODEs numerically for each sampled parameter set for a large number of random initial conditions (optional input to RACIPE) and the steady state solutions for eac parameter set are stored in the output solution files.

References

[1] M. I. Davidich and S. Bornholdt. Boolean network model predicts cell cycle sequence of fission yeast. *PLOS ONE*, 3(2):1–8, 02 2008.

[2] B. Huang, M. Lu, D. Jia, E. Ben-Jacob, H. Levine, and J. N. Onuchic. Interrogating the topological robustness of gene regulatory circuits by randomization. *PLOS Computational Biology*, 13(3):1–21, 03 2017.