NETWORK TOPOLOGIES THAT EXHIBIT BIOCHEMICAL ADAPTATION AND INVESTIGATING EFFECT OF MEMBRANES IN ADAPTATION NETWORKS

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1 Introduction

Biological systems present some of the most intricate, extensive and robust networks out there. Systems Biology is about untangling these networks and reducing them to simpler ones or at the very least, classifying these networks on the basis of what they do. Some motifs are common across a lot of different areas while others are associated with very specific systems. The idea is to study large networks in terms of interactions between well-characterised sub-networks.[2] One such network is the adaptation network which has the ability to reset itself after responding to a stimulus.The output of the circuit is very similar to that of an edge-detector, more specifically, a rising edge detector. In their paper on adaptation networks [1],Ma et.al report two important observations:

- At least 3 nodes are needed in a circuit that exhibits adaptation.
- They found only 2 kinds of 3-node adaptation networks - *negative feedback loop with a buffering node*(NFLBB) and *an incoherent feedforward loop with a proportioner node*(IFFLP). These two circuits form the skeletons for all the adaptation circuits founds, additional edges only adding to the robustness or sensitivity or precision of the network.
- Incoherent feedforward loops with proportioner nodes are more robust than Negative feedback loops with buffer nodes.

1.1 Negative Feedback loop with a buffering node [1]

The most elementary three node circuit of this kind is depicted in Figure. The analysis of the circuit is presented through the example given in the figure. In this circuit, **A** merely acts as a relay of the input to the node **C**. Analysis of the constants for which the circuit shows adaptation shows that in such a network, the synthesis and breakdown of **B** must be at saturation. By making appropriate approximations, one finds that the steady state value of **C** is independent of the input value as should be the case for an adaptation circuit. The system still responds to the input change transiently but **C** settles back to the original value. Also, one finds that **B** essentially acts an integral control, commonly used in electronics as a perfect adaptation network.

1.2 Incoherent Feed-Forward loop with proportioner node [1]

The most elementary circuit of this kind is depicted in Figure. The analysis of the circuit is presented through the example given in the figure. In this circuit, the output node **C** is subject to two regulations, both originating from the input but with opposing cumulative signs in the two pathways.The functional architectures all have a proportioner (node **B**) that regulates the output (node **C**) with the opposite sign as the input to **C**.Rather than monitoring the output and feeding back to adjust its level, the feedforward circuit anticipates the output from a direct reading of the input. node **B** monitors the input and exerts an opposing force on node C to cancel the outputs dependence on the input. Mathematical analysis yields that for this topology to exhibit adaptation, the node **B** must act as a proportioner. If the steady state value of **B** is proportional to the steady state value of **A**, then, the steady state value of **C** becomes independent of **A** and hence, the input.

1.3 Role of Membranes

The model suggested by Ma et.al is for well mixed systems but one of the most important features of living cells is the presence of membranes. In the context of the present problem, this allows for

creation of compartments and micro environments within the cell.This allows for more control over reactions. For example, **A** and **B** could react in compartment **X** and the product could then be transported into compartment **Y** for further reactions or, by the mere fact that they limit space that can be occupied, they can dictate extremities for various reactions.

2 Model

For the first part, we try to reproduce the results presented by Ma et.al. We use the same model as presented by them in the paper. A well mixed system is assumed.The network is assumed to have 3 nodes, each of which exist in active and inactive forms such that the total amount of each species is unity. The active form of **A**, for example, is denoted by 'A' and the inactive form is '1-A'. Each node is linked to the others and links can be either positive regulation, negative regulation or no regulation. The external input is provided at node **A** and is positive and the active concentration of **C** is taken as the output. It is assumed that the reactions proceed according to Michaelis- Menten kinetics. To maintain the fixed total amount of each species, an external enzyme of constant concentration acts on each node to keep the concentration in check. For example, say node **B** is positively regulated by node **A**, then a rate term $\frac{k_{AB}A(1-B)}{1-B+K_{AB}}$ is added. if, on the other hand, **B** is negatively regulated by **A**, then the rate term $\frac{k'_{AB}AB}{B+K'_{AB}}$ is subtracted. So, the rate equation will look like:

$\frac{dB}{dt} = \Sigma_i X_i.k_{X_iB}.\frac{1-B}{K_{X_iB}+1-B} - \Sigma_i.Y_i.k'_{Y_iB}.\frac{B}{K'_{Y_iB}+B}$

where X_i's are the positive regulators and Y_i's are the negative regulators.

The rates equations are then solved to obtain A, B and C as functions of time, first for a low input and then for a higher input value. The performance of the circuit is determined by two parameters:

- Sensitivity : The sensitivity is a measure of of how strongly the circuit responds to the change in input.
  $Sensitivity = \frac{|(C_{max}-C_{initial})|/C_{initial}}{|(I_2-I_1)|/I_1}$ where $I_2$and I_1 are the final and initial values of the input and C_{max} is the maximum concentration of C after input is changed.

- Precision: It is a measure of how close the circuit subjected to the change in input is to the initial system after it comes to equilibrium.
  $Precision = \frac{|I_2-I_1|/I_1}{|C_{final}-C_{initial}|/C_{initial}}$

Circuits with sensitivity greater than 1 and precision greater than 10 are accepted as adaptation circuits.

3 Methods

3.1 Sampling

All possible 3 node topologies are investigated. For each topology, 1000 parameter sets are scanned. These parameters are the rate constants in the rate equations, i.e, the *k's* and the *K's*. The *k's* are taken from a log-uniform distribution ranging from 0.1 to 10 and *K's*, from a log-uniform distribution ranging from 0.001 to 100. All the parameters are independent and are generated using the *rand* function in **C** as the generating function.

3.2 Equation solving

3.2.1 Forward Euler Method

Euler's method uses the first order Taylor approximation to solve an ordinary differential equation numerically. Let the differential equation be:

$$d\mathbf{y}/dt = \mathbf{f}(\mathbf{y}, t), \text{ where } \mathbf{y} \text{ and } \mathbf{f} \text{ are vectors.}$$

Let t_k , $\mathbf{y}_k$ and h_k denote respectively the time, the value and the step size after the $\mathbf{k}^{th}$ step . Then, the numerical solution to the ODE is given by:

$$\mathbf{y}_{k+1} = \mathbf{y}_k + h_k \times \mathbf{f}(\mathbf{y}_k, t_k)$$

i.e, the solution is obtained by extrapolating along a straight line whose slope is $\mathbf{f}(\mathbf{y}_k, t_k)$. The method has obvious benefits of very low computational complexity and the error is $\mathrm{O}\ (\mathrm{h}^2)$, i.e, Euler's Method is first order accurate.
However, major drawbacks of the method are that if the family of general solutions diverge, then, so does the error. Consider for example, the solutions of the equation
$dy/dt = y$

The method was used only for a preliminary survey and was quickly abandoned in favour of Fourth Order Runge-Kutta Method.

3.2.2 Fourth Order Runge-Kutta with Adaptive Step Size

For solving ODE's Runge Kutta methods have been very popular. The method is similar to to the forward Euler method, but instead of using only the first term of the taylor expansion, we use k terms. We also compute k steps of the from the origin to take the next step. This way, we can eliminate the first k^{th} order terms of the Taylor expansion and thus the error term is of $k + 1^{th}$.

The 4th order method is described below.

3.2.3 4th Order Runge Kutta

Suppose we want the numerical solution of the ODE

$$\dot{y} = f(t, y) \text{ and } y(t_0) = y_0$$

Suppose we know then n^{th} step for which we have

$$y = y_n \text{ and } t = t_n$$

Then the next step is computed as

$$y_{n+1} = y_n + h \times (k_1 + 2k_2 + 2k_3 + k_4) \text{ and } t_{n+1} = t_n + h$$

Where

$$\begin{aligned} k_1 &= f(t_n, y_n) \\ k_2 &= f(t_n + \frac{h}{2}, y_n + \frac{h}{2}k_1) \\ k_3 &= f(t_n + \frac{h}{2}, y_n + \frac{h}{2}k_2) \\ k_4 &= f(t_n + h, y_n + hk_3) \end{aligned}$$

The order of this error is $\mathcal{O}(h^5)$

3.2.4 Adaptive step size RK (Cash-Karp method)

This is similar to RK45 above but has adaptive step size, i.e. we change the step size whenever the error is too large and make it larger when we can afford to as too much precision is not required.

In this, instead of the four function evaluations above, we use six function evaluations. Using these six, we calculate the value of the function using 4th order and 5th order. Then we use the difference between these two as an estimate of error of the solution. Then using this estimate, we calculate the estimated step size that will give us the required error bounds. Then we repeat the procedure, until the error estimate is less than the upper error threshold. Then the step is taken. If the error estimate is much smaller than the lower error threshold, then we increase the step size by an appropriate amount. Thus, every step is roughly taken is roughly optimal. Thus in this method we don't have an absolute control over step size, the error in the solution is very well controlled.

This method takes smaller steps when the higher order terms are more significant and long steps when they are not. Thus it optimizes the computation time.

4 Results

The simulations could not be completed due to very long computation time and no results of note could be obtained. We were unable to investigate effect of presence of membranes.

5 Suggestions for improvement

- Optimization of codes.
- Shift to parallel processing.
- Since for the initial input, only the equilibrium value is required, one could reduce the differential equations to algebraic equations for this input and solve those instead.
- Since it is know that atleast 3 nodes are needed in the network, all other networks can be eliminated, thus saving on unnecessary computation time.

References

[1] Wenzhe Ma, Ala Trusina, Hana El-Samad, Wendell A Lim, and Chao Tang. Defining network topologies that can achieve biochemical adaptation. *Cell*, 138(4):760–773, 2009.

[2] Kim Sneppen, Sandeep Krishna, and Szabolcs Semsey. Simplified models of biological networks. *Annual review of biophysics*, 39:43–59, 2010.