Available online at www.sciencedirect.com

ScienceDirect

IFAC PapersOnline CONFERENCE PAPER ARCHIVE

IFAC PapersOnLine 51-1 (2018) 307–312

A systems-theoretic approach towards designing biological networks for perfect adaptation

Priyan Bhattacharya * **Karthik Raman** **,***,**** **Arun K. Tangirala**† *,***,****

* *Department of Chemical Engineering*
** *Department of Biotechnology, Bhupat and Jyoti Mehta School of Biosciences*
*** *Initiative for Biological Systems Engineering (IBSE)*
**** *Robert Bosch Centre for Data Sciences and Artificial Intelligence (RBC-DSAI)*
Indian Institute of Technology (IIT) Madras, Chennai – 600 036, India

Abstract: Designing biological networks that are capable of achieving specific functionality has been of sustained interest in the field of synthetic biology for nearly a decade. Adaptation is one such important functionality that is observed in bacterial chemotaxis, cell signalling and homoeostasis. It refers to the ability of a cell to cope with environmental perturbations. All of these adaptation networks,involve negative feedback loops or open loop control strategies. A typical enzymatic network is a circuit of enzymes whose connections are characterized by enzymatic reactions that exhibit non-linear dynamics. Previous approaches to design of enzymatic networks capable of perfect adaptation have used brute force searches encompassing the complete set of possibilities to identify suitable circuit designs. In contrast, this work presents a systematic algorithm for circuit design, using a linear systems-theoretic approach. The key idea is to set up a design-oriented problem formulation as against employing a brute force search in the space of possible circuits. To this effect, we first linearize the non-linear dynamical circuit, subsequently, we translate the requirements for adaptation to design specifications for a linear time-invariant system and imposing these design specifications on the linearized system, we obtain the minimal topologies or motifs that can perform perfect adaptation, with an optimal set of rate constants. The optimal set of rate constants is obtained by solving a structure-specific constrained optimisation problem. In effect, we demonstrate that the proposed approach identifies the key motifs of the biological network that were identified by the existing brute force approach, albeit in a systematic manner and with very little computational effort.

Keywords: Adaptation, Control system design, Networks, Network motifs, Robustness, Sensitivity, Systems Biology

1. INTRODUCTION

The field of systems biology adopts a holistic approach towards studying and understanding biological systems. Contrary to reductionist approach, it is based on a ground that a particular biological behaviour is not just a result of a single machinery but a response of a large system of interconnected components. In most of the cases, biological systems are complex, non-linear, multi-scale and assumed to be modular. This assumption of modularity helps in separating a small subsystem from a multi-level, complex biological system.

It is a growing idea which states that design principles for a particular biological function remains nearly the same irrespective of the system (or across the organism space) it is a part of. Current day findings also support this hypothesis (Ma et al., 2009).

According to the very approach of the systems biology and above mentioned hypothesis, it can be concluded that there are a few unified design principles for this biological functionality of adaptation i.e, there are only few topologies or sub-systems which can perform perfect adaptation across the organism space. Now, these design principles in most of the cases constitute the core and governing part of a large network. Therefore, the functionality of the entire system can be well predicted by studying the characteristics of these functional motifs. There are some techniques to identify motifs which involve statistical reasoning (Milo et al., 2002).

Adaptation is the ability for a system to reset itself after sensing an external perturbation.There are two parameters by which the extent of adaptation achieved by a given system can be quantified, namely *Precision* and *Sensitivity*. Mathematically, precision is expressed as

$$P = \frac{O_1}{|O_2 - O_1|} \Big/ \frac{I_1}{|I_2 - I_1|} \tag{1}$$

where, O_2 is the new output steady state level and O_1 is the pre-stimulus output level and I_1 is the initial input where I_2 is the new input.

In a similar way, sensitivity is defined as

$$S = \frac{|O_{peak} - O_1|}{O_1} \Big/ \frac{|I_2 - I_1|}{I_1} \tag{2}$$

* Corresponding author, email: arunkt@iitm.ac.in

2405-8963
Peer review under responsibility of International Federation of Automatic Control.
10.1016/j.ifacol.2018.05.033

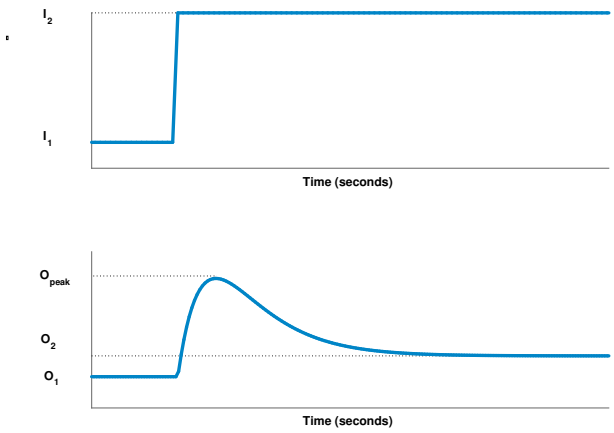


Figure 1. Typical response of adaptation network

where, O_{peak} is the peak value of output, which gives information about how much the system has been able to sense the change in the Input. By definition of perfect adaptation the precision should be as high as possible (ideally infinite) and corresponding sensitivity should be one.

Previously, Ma and co-workers performed an exhaustive search of the entire design space of three-node networks for minimal topologies capable of achieving adaptation. Each combination of the three nodes and edges was tested for thousand different sets of parameters (Ma et al., 2009). The study revealed that there are 395 combinations of the enzymes out of over $\approx 16,000$ possible networks that can perform adaptation with appropriate parameter sets. They observed the presence of any or both of the two main motifs namely Negative Feedback Loop with Buffer node (NFBLB) and Incoherent Feed Forward Loop with Proportioner node (IFFLP) in all 395 combinations from which they concluded that these two motifs are responsible for adaptation. In the present paper, we circumvent the brute force computational efforts of Ma et al. (2009) and propose a generic algorithm that is computationally much less demanding, to determine such minimal motifs for any desired functionality using the fundamentals of linear systems theory.

2. RELEVANT LINEAR SYSTEMS THEORY CONCEPTS

The aim of the paper is to determine the admissible motifs of a three-enzyme network, which are capable of producing a desired output (adaptation) using a systems-theoretic approach. This necessitates a conceptual understanding of LTI systems theory. In this section, we outline relevant concepts from linear systems theory, which are central to understanding our approach.

Linearity is a property of a system which enables the output to change proportionally with the change of the input. Along with scalability a linear system should as well exhibit superposition property (Stefani et al., 2002).

Further, a system is time invariant if the output experiences a δ amount of time delay with the input delayed by the same amount of time.

2.1 State space approach

From the perspective of systems theory, any system of networks can be characterised by the values of its state variables at any given point of time. The generic state space representation for any system can be written as

$$\frac{d\mathbf{x}(t)}{dt} = \mathbf{f}(\mathbf{x}(t),\mathbf{u}(t),\mathbf{r}) \tag{3}$$

$$\mathbf{y}(t) = \mathbf{g}(\mathbf{x}(t),\mathbf{u}(t),\mathbf{r}) \tag{4}$$

where, $\mathbf{x}(t) = [x_1(t)\ x_2(t)\ \cdots\ x_n(t)]^T$ are the states,
$\mathbf{u} = [u_1(t)\ u_2(t)\ \cdots\ u_m(t)]^T$ are the inputs,
$\mathbf{y}=[y_1(t)\ y_2(t)\ \cdots\ y_p(t)]^T$ are the outputs and
$\mathbf{r}=[r_1(t)\ r_2(t)\ \cdots\ r_f(t)]^T$ are the parameters of the system. Now, $\mathbf{f}(\mathbf{x}(t),\mathbf{u}(t),r)$ and $\mathbf{g}(\mathbf{x}(t),\mathbf{u}(t),r)$ can be linearized by evaluating the Jacobian and therefore the above non-linear system(3) can be boiled down to it's linearized form as

$$\frac{d\mathbf{x}}{dt} = \mathbf{A}\mathbf{x}+\mathbf{B}\mathbf{u} \tag{5a}$$

$$\mathbf{y} = \mathbf{C}\mathbf{x}+\mathbf{D}\mathbf{u} \tag{5b}$$

where $\mathbf{A}\in\mathbb{R}^{n\times n}$, $\mathbf{B}\in\mathbb{R}^{n\times m}$, $\mathbf{C}\in\mathbb{R}^{p\times n}$ and $\mathbf{D}\in\mathbb{R}^{p\times m}$ are the state-space matrices for the given system.

A non-linear system can be linearized with respect to an equilibrium point, by evaluating the Jacobian of the system. Jacobian is a popular operator in vector calculus which computes the first order partial differentiation of a vector valued function with respect to a vector valued variables. So, for a vector valued function ζ the jacobian of ζ with respect to a vector ε is defined as

$$\mathbf{J}_{ij} = \frac{\partial \zeta_i}{\partial \varepsilon_j} \tag{6}$$

In this case the associated $\mathbf{A}$ and $\mathbf{B}$ matrices are the jacobian of $\mathbf{f}$ with respect to the states $\mathbf{x}$ and control inputs $\mathbf{u}$ respectively evaluated at initial conditions. Similarly, the corresponding $\mathbf{C}$ and $\mathbf{D}$ matrices for the linearized system are the jacobian of $\mathbf{g}$ with respect to $\mathbf{x}$ and $\mathbf{u}$ respectively evaluated at initial conditions.

2.2 Conversion from state space to transfer function

The system represented in the state space form (5), can also be expressed in it's equivalent transfer function form as

$$\mathbf{Y}(s) = \mathbf{G}\mathbf{U}(s) \tag{7a}$$

$$\mathbf{G}(s) = (\mathbf{C}(s\mathbf{I}-\mathbf{A})^{-1}\mathbf{B}+\mathbf{D}) \tag{7b}$$

where, $\mathbf{G}\in\mathbb{R}^{p\times m}$ and s is the Laplace variable For a single input single output(SISO), the transfer function matrix boils down to a scalar function of the Laplace variable s.

2.3 Effect of poles and zeros

A linear time invariant system can be characterized by some of it's parameters which are poles, zeros e.t.c.. Typically, poles are associated with the stability of the system. If the system poles are situated in the left half of the s-plane then the system is said to be stable. Depending on the values of pole (real or imaginary) the system shows different transient characteristics.
Zero mainly determines the direction of output response a zero on the right half s plane results in inverse response of the system output. Adding a zero to the system can result into high

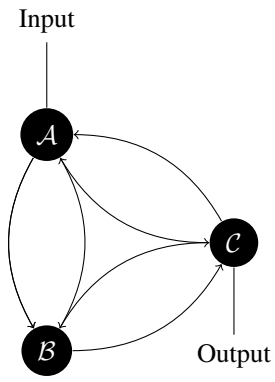


Figure 2. A generic 3-node network

overshoot, lower settling and peak time. For a fixed set of poles, the value of the peak time and rise time are minimum if the system consists of a zero at the origin.

2.4 Relative stability

In linear systems theory, relative stability is defined as the distance of the poles of left-half s plane from the origin. For a system specified by equations (3) & (4) the eigenvalues of the **A** are the poles of the system. For a linearized system, **A** is only a function of the parameters. Therefore, to tune a system for maximising the relative stability, it is a common idea to maximise the absolute values of the poles:

$$O = \max(\arg(\Pi_{i=1(i)n}\lambda_i)) \tag{8}$$

Where, λs are the eigenvalues of **A** and also the poles of the system. Now, for a system with zero situated near origin, maximisation of the above optimisation problem will be equivalent to the minimisation of gain, which can enable the system to achieve its initial value asymptotically.

3. PROBLEM STATEMENT

3.1 System Description and Kinetics

The network, as illustrated in Fig. 3.1 contains three enzymes which catalyses the activation or repression of other enzymes. Enzyme (A) is the input node and the output of the system is the concentration profile of (C).

Each enzyme can have three types of effects either on itself or on the other two enzymes: it can activate (itself or other), repress (itself or other) or have no effect. Thus, for a three-enzyme network, the possible combinations of enzyme interactions (or topologies) is 3^{n^2} where, n is the number of interacting enzymes. For this three node network, $n = 3$, the number of possible combinations is $3^9 = 19,683$.
For the fully connected network of fig 3.1 the rate equations can be written as follows

$$\frac{d\mathcal{A}}{dt} = k_{\mathcal{IA}}\mathcal{I}\frac{1-\mathcal{A}}{1-\mathcal{A}+K_{\mathcal{IA}}} + k_{\mathcal{BA}}\mathcal{B}\frac{1-\mathcal{A}}{1-\mathcal{A}+K_{\mathcal{BA}}} + k_{\mathcal{CA}}\mathcal{C}\frac{1-\mathcal{A}}{1-\mathcal{A}+K_{\mathcal{CA}}} \tag{9a}$$

$$\frac{d\mathcal{B}}{dt} = k_{\mathcal{AB}}\mathcal{A}\frac{1-\mathcal{B}}{1-\mathcal{B}+K_{\mathcal{AB}}} + k_{\mathcal{CB}}\mathcal{C}\frac{1-\mathcal{B}}{1-\mathcal{B}+K_{\mathcal{CB}}} - k_{\mathcal{FB}}F_{\mathcal{B}}\frac{B}{K_{\mathcal{FB}_0}-\mathcal{B}} \tag{9b}$$

$$\frac{d\mathcal{C}}{dt} = k_{\mathcal{AC}}\mathcal{A}\frac{1-\mathcal{C}}{1-\mathcal{C}+K_{\mathcal{AC}}} + k_{\mathcal{BC}}\mathcal{B}\frac{1-\mathcal{C}}{1-\mathcal{C}+K_{\mathcal{BC}}} \tag{9c}$$

where $F_{\mathcal{B}}$, is the basal enzyme acting on $\mathcal{A}$ and $\mathcal{B}$ it is repressing the concentration of $\mathcal{A}$ and $\mathcal{B}$.

3.2 Objectives

The objectives of this paper are

(1) To design minimal motifs (containing not more than three edges) capable of performing adaptation.
(2) To obtain the optimal values of the parameters, i.e. the rate constants for the motifs so identified.

4. METHODOLOGY

This section addresses the problem of determining suitable structures for adaptation along with the search for optimal parameters. As it can be seen from the equations (9), the system follows non-linear dynamics. There may be a number of ways of achieving perfect adaptation in a non-linear system that can be found after a careful and systematic investigation. This paper addresses this reality and works with the linearised version of the system for better clarity to start with. The paper aims for outlining a generic computation friendly strategy to obtain the design principles for any biological functionality followed by a clever search in the parameter space. In order to resolve the structure, the system of rate equations are linearized and it is reduced to a *single zero three poles* system. From this, the admissible pole zero location for adaptation can be mapped on the linearized system as a condition for adaptation. With these, the possible structures are determined. Then to search for appropriate rate constants the optimization problem mentioned above (expression 8) is formulated along with the structure specific constraints.

4.1 Linearization

The fact that the desired response of the adaptation network can be achieved by standard linear time invariant systems of specific pole zero combinations and along with that, it is possible to map the characteristics (*sensitivity and precision*) to *gain and peak value* of the equivalent LTI system justifies the analysis of the non-linear system of M-M equation in its linearized domain.
It is found that the enzymatic network following Michaelis–Menten kinetics equation (9) has a single stable steady state.

As the non-linear system is linearized with respect to a stable equilibrium point it is evident that the eigenvalues of the corresponding **A** matrix or the system poles are situated in negative s plane.

4.2 Conditions on the linearized system for adaptation

The main task after linearizing the non-linear system is to map the precision and the sensitivity of the non-linear system to some of the characteristics of linearized system.

(1) The system should be stable, i.e. all the eigenvalues of **A** matrix should be negative.
(2) The steady state value of the non-linear system should be the same as the initial output level. That means the final value of the linearized system should be zero ideally, if the linear system was relaxed before. This in turn leads to the condition of zero gain system.

Now, the condition for a system to have a precision of infinity (i.e. the system returns to its initial value at large times) turns out to be a linearized system having a gain of zero. The corresponding sensitivity of the system can be mapped with the peak value of the linearized system. The zero position for the linearized three pole one zero system is at

$$z = \frac{df_{\mathcal{A}}}{d\mathcal{I}} \frac{\frac{df_{\mathcal{B}}}{d\mathcal{A}}\frac{df_{\mathcal{C}}}{d\mathcal{B}} - \frac{df_{\mathcal{C}}}{d\mathcal{A}}\frac{df_{\mathcal{B}}}{d\mathcal{B}}}{\frac{df_{\mathcal{C}}}{d\mathcal{A}}} \tag{10}$$

Now the transfer function in pole-zero format, using (7a) is

$$G = \frac{s - \frac{b_1(a_{21}a_{32} - a_{31}a_{22})}{a_{31}}}{\Pi_i(s - eig_i(\mathbf{A}))}, \tag{11}$$

where a_{ij} is the (i,j)th element of $\mathbf{A}$ and b_i is the ith element of $\mathbf{B}$.

4.3 Determining potential structures of the three enzyme circuit

After obtaining the conditions of adaptation for the linearized system i.e, zero gain and high peak value we translate these conditions as some constraints on pole zero position. Using these constraints along with the requirement of minimum no. of edges it is possible to determine the possible circuit structures capable of performing adaptation.

The gain for the linearized system is obtained as

$$K = \alpha \frac{Z}{\prod_{i=1}^{3} P_i} \tag{12}$$

where, Z is the only zero, α is a constant and P_i's are the three poles of the linearized system. Hence, to have a gain nearly zero, the zero position should be less than the pole position and ideally, the zero should be placed at the origin of the s-plane. As a_{31} cannot be zero to have a finite zero the numerator in equation 10 should be zero. This in turn can be achieved in two ways:

(1) Both terms of the numerator are zero individually.
(2) Both terms of the numerator are non-zero and equal.

Therefore, where both the terms are zero individually, there can be three scenarios:

(1) $a_{22} = 0, a_{32} = 0, a_{21} = 0$
(2) $a_{22} = 0, a_{21} = 0$
(3) $a_{22} = 0, a_{32} = 0$

Scenario 1 Now, we know a_{31} cannot be zero-valued to have a zero positioned at a finite distance from the origin. Implying the condition $|\mathbf{A}| < 0$, and restricting number of connections to three we get $a_{12}a_{23} < 0$

So, a_{12} and a_{23} has to be of opposite sign because $\mathcal{A}$ has to activate $\mathcal{C}$ that means a_{31} has to be positive. So it yields a set of structures where $\mathcal{A}$ *activates* $\mathcal{C}$, $\mathcal{C}$ *activates/represses* $\mathcal{B}$ *and* $\mathcal{B}$ *represses/activates* $\mathcal{A}$(Figure 3(a)).

Scenario 2 $a_{22} = 0$ and $a_{21} = 0$

Now, imposing $|\mathbf{A}| < 0$ and minimal number of edges (i.e. 3),

$$a_{11}(-a_{32}a_{23}) < 0$$

Now, for the stability condition the matrix $\mathbf{A}$ should be negative definite, i.e.

$$a_{11} < 0$$
$$a_{32}a_{23} < 0$$

So, a_{32} and a_{23} will be of the opposite sign; the corresponding structure, therefore, is: $\mathcal{A}$ *activates* $\mathcal{C}$, $\mathcal{C}$ *activates/represses* $\mathcal{B}$, $\mathcal{B}$ *represses/activates* $\mathcal{C}$ (see Figure 3(b)).

Scenario 3 Now, for the third case
$a_{22} = 0, a_{32} = 0$
$-a_{12}a_{21}a_{33} + a_{12}a_{31}a_{23} < 0$

Now imposing the same conditions as above $a_{12}a_{21} < 0$

$\mathcal{A}$ *activates* $\mathcal{C}$, $\mathcal{B}$ *activates/represses* $\mathcal{A}$, $\mathcal{A}$ *represses/activates* $\mathcal{B}$ (Figure 3(c)).
In all of the above three scenarios there is one thing common in the minimal structures of the network which is a presence of a net negative feedback involving the node $\mathcal{B}$.This kind of minimal network is called *Negative Feedback Loop with Buffer Node (NFBLB)*.
Now, for the second type problem

where,
$a_{21}a_{32} = a_{22}a_{31}$ and none of the elements are zero
So imposing the condition of $|\mathbf{A}| < 0$ and minimal edges(3 edges)

$$a_{11}a_{22}a_{33} < 0$$

$$a_{22} < 0$$

So, $a_{21}\frac{a_{32}}{a_{31}} < 0$

Now a_{31} is always positive so, a_{21} and a_{32} has to be of the opposite sign always so, it is
$\mathcal{A}$ *activates* $\mathcal{C}$, $\mathcal{B}$ *activates/represses* $\mathcal{C}$, $\mathcal{A}$ *represses/activates* $\mathcal{B}$ (Figure 3(d)).
In the second case it can be inferred from the structure of these motifs that there are two paths between node $\mathcal{A}$ to node $\mathcal{C}$. As it can be seen in the both the cases the net signs of the path from $\mathcal{A}$ to $\mathcal{C}$ are opposite, which leads to a special class of motifs named Incoherent Feed Forward Loop with Proportioner node (IFFLP).

4.4 Search for Optimal Parameters

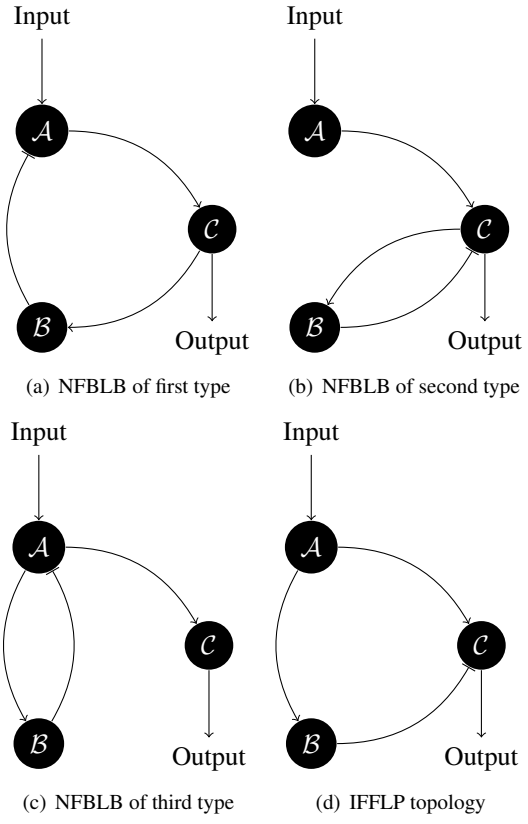
From different case studies executed in the previous section for resolving the uncertainties it can be inferred that fixing the topology only is not enough to guarantee adaptation because the conditions for the adaptation cannot be fulfilled completely by ensuring suitable structures. For NFBLB to ensure adaptation a_{22}, which is a function of the parameters has to be zero and for IFFLP to do the same $a_{22}a_{31} - a_{21}a_{32}$ should be equal to zero. The optimal values of the parameter can be resolved by maximising the relative stability (Chen et al., 2005) of the system. Now, for the *NFBLB* class motif, the optimisation problem can be posed as:

$$\min(\prod_{i=1}^{3} eig(\mathbf{A})_i) \quad s.t.\ a_{22} = 0 \tag{13}$$

For the *IFFLP* class motif, the problem can be formulated, using the knowledge of the model, as:

$$\min(\prod_{i=1}^{3} eig(\mathbf{A})_i) \quad s.t.\ a_{22}a_{31} - a_{21}a_{32} = 0 \tag{14}$$

It can be seen from the optimization function, the minimization of the objective function takes care of the stability of the system because it in turn increases the distance between the poles and the origin in the direction of the left half s-plane.



(a) NFBLB of first type (b) NFBLB of second type

(c) NFBLB of third type (d) IFFLP topology

Figure 3. Different combinations of admissible topologies

Algorithm 1 Generic algorithm for obtaining design principles

1: Linearize the non-linear system based on suitable equilibrium point.
2: Identify the admissible transfer functions which can achieve the desired functionality.
3: Map the necessary conditions on the non-linear systems on the linearized version of it.
4: Impose these conditions on the parameters of the transfer function of the linearized system(e.g. poles, zeros, gain) to resolve the structural uncertainty.
5: Use equation (8) along with some structure specific constrains to maximise the relative stability and hence obtain optimal parameters.

5. RESULTS AND DISCUSSION

Two different cases are considered for simulation. In all the cases an input of twenty percent step change is applied at node $\mathcal{A}$. The corresponding output is measured as the concentration of $\mathcal{C}$. IFFLP is clearly a better choice than NFLB for simulation studies because it can be seen that the system matrix for a IFFLP class motif turns out to be diagonal which is not the case for NFBLB. So, the objective function formulation ((8)) becomes easier for IFFLP than NFBLB. Further it is possible to club the parameters of the objective function in the case of IFFLP which betters the rate of convergence.

5.1 Case 1: IFFLP with an arbitrary set of parameters

In this case, IFFLP is chosen for illustration (Figure 3(d)) For simulation of the considered motif, an arbitrary but biologically feasible set of parameters are chosen (Figures 5.2, The system poles are situated at $s = -0.2268, -0.0815, -0.0992$ and the only zero was situated at $s = -0.407$. Clearly, due to inappropriate choice of the parameters the system fails to attain perfect adaptation but as the zero is located before the poles the system attains a non-zero finite value of sensitivity and precision.

5.2 Case 2: IFFLP with optimized set of parameters

The parameters are obtained by solving the motif specific optimization problem discussed in the above section equation (14). As it seems from the figures(Figures 6 and 5.2) the systems senses the change in the input, rises accordingly and at large times almost settles to the previous steady state value. The linearized system (Figure 5.2) has poles at $s = -3.0864, -0.0352 and -1.5277$ and the only zero of the system is situated at $s = 0.00034$.

5.3 General inferences

The peak value of the linearized system depends on the initial rate of change of concentration of $\mathcal{B}$. If $\frac{d\mathcal{C}}{dt}|_{t=0} > \frac{d\mathcal{B}}{dt}|_{t=0}$ then it is possible to have a high sensitivity and to have a certain amount of precision $(1-\mathcal{B}) >> \mathcal{K}_{\mathcal{AB}}$ and $\mathcal{B} << \mathcal{K}_{\mathcal{FB}}$ subject to satisfy the condition of proportionality.

For NFFBLB to achieve adaptation of infinite precision a_{22} has to be zero, which essentially turns out to be a condition on the rate equation for $\mathcal{B}$ to be independent of $\mathcal{B}$.

$$\frac{\partial \frac{d\mathcal{B}}{dt}}{\partial \mathcal{B}} = a_{22} = 0 \tag{15}$$

This happens only for a few restricted sets of parameters where $\mathcal{B}$ works as an non-linear integral controller node which integrates the difference between the steady state and the concentration of $\mathcal{C}$ at any instant generates the controller input. At the

Table 1. Parameters obtained and arbitrary parameters

Parameters	Arbitrary	Optimal
$k_{\mathcal{IA}}$	2	10
$K_{\mathcal{IA}}$	5	0.5
$k_{\mathcal{AB}}$	0.665	0.5001
$K_{\mathcal{AB}}$	0.758	0.0011
$k_{\mathcal{BC}}$	6.433	14
$K_{\mathcal{BC}}$	37.82	25
$k_{\mathcal{AC}}$	2.801	10
$K_{\mathcal{AC}}$	4.551	0.551
$k_{\mathcal{FA}}$	0	7.8539
$K_{\mathcal{FA}}$	0	100.3914
$K_{\mathcal{FB}}$	0	10
$K_{\mathcal{FB}}$	0	100.012
Sensitivity	0.35	0.8
Precision	3.4	12

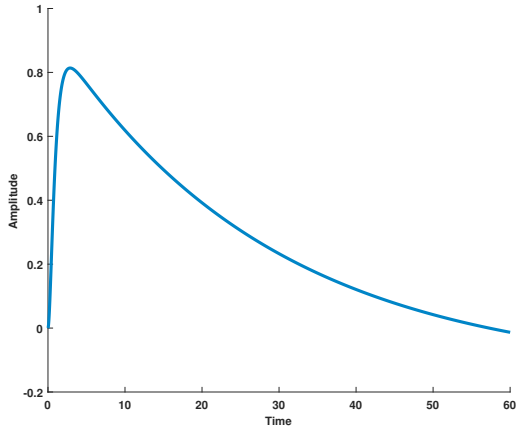


Figure 4: Optimally parametrized linear system (response)

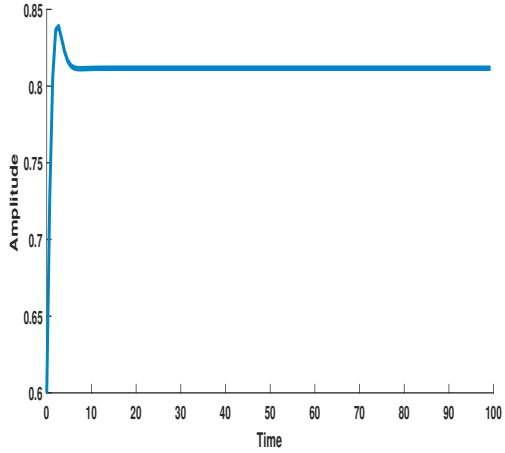


Figure 5: An ill-parametrized non linear system (response)

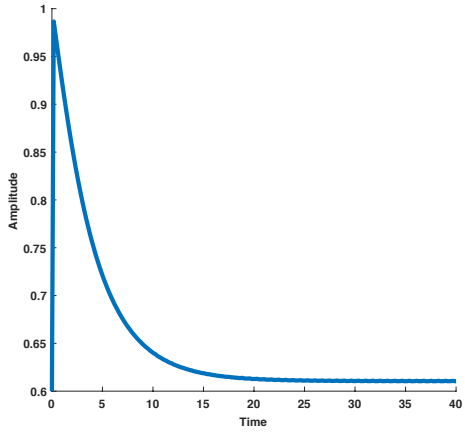


Figure 6. Optimally parametrized non linear system (response)

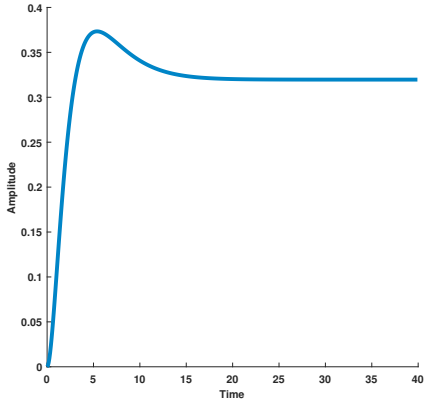


Figure 7. An ill-parametrized linear system (response)

steady state the concentration of $\mathcal{C}$ remains independent of $\mathcal{A}$ and $\mathcal{B}$. In order to improve the robustness, an NFBLB with a self-loop is considered, which upon subsequent analysis is found to have better robustness over the pure NFBLB class.

6. CONCLUSIONS

Biological networks are complex in nature. It is the inherent non-linear, retroactive and multi-scale nature of the biological system that makes it very challenging to analyse, model or predict their responses. The proposed methodology is systematic as against the exploratory and computationally loaded brute-force method. It has been shown to successfully identify the same motifs as the brute-force method was reported to, namely the NFBLB and IFFLP motifs. Furthermore, a method to determine the optimal set of parameters (for one of the motifs) that impart the desired precision and sensitivity. Thereby, it is demonstrated that that the extent of adaptation, i.e., the quantitative metrics of adaptation, can be bettered by tuning the parameters of the underlying motif. The principles and ideas of the present work are also generic in the sense that they can, with minor modifications, be applied to the design of biological circuits for achieving other biological functionalities. Future work involves several exciting possibilities, among which generalization to other functionalities, determining whether linearization results in false positives / negatives motifs (with respect to the true non-linear process), and extensions to non-linear systems attract attention.

REFERENCES

Chen, B.S., Wang, Y.C., Wu, W.S., and Li, W.H. (2005). A new measure of the robustness of biochemical networks. *Bioinformatics*, 21(11), 2698–2705.

Ma, W., Trusina, A., El-Samad, H., Lim, W.A., and Tang, C. (2009). Defining network topologies that can achieve biochemical adaptation. *Cell*, 138(4), 760–773.

Milo, R., Shen-Orr, S., Itzkovitz, S., Kashtan, N., Chklovskii, D., and Alon, U. (2002). Network motifs: simple building blocks of complex networks. *Science*, 298(5594), 824–827.

Stefani, R.T., Shahian, B., Clement, J., and Savant, J. (2002). *Design of feedback control systems*. Oxford University Press, Inc.