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Inference of Temporally Evolving Network Dynamics with Applications in Biological Systems

Young Hwan Chang and Claire Tomlin

Abstract— **Modeling of biological signal pathways forms the basis of systems biology. Also, the problem of identifying dynamics of biological networks is of critical importance in order to understand biological systems. In this paper, we propose a data-driven inference scheme to identify dynamics with a local point of view, the Jacobian matrix. A graph model is a natural way to represent a biological signal pathway and doesn't require any constraints on dynamics such as mass action kinetics or Hill function representations, used in Ordinary Differential Equation (ODE) models. A graph is a set of vertices which represents state, and a set of edges which depicts the relationship or connection between two or more states. Once a system is abstracted by a graph, in order to identify the activity level of the corresponding interactions based on a given data set, we reformulate the problem as a Linear Quadratic (LQ) Optimal Control problem by transforming the unknown entries of the activity of edges into the control inputs of the LQ setting. In the formulation of the LQ problem, we use an adjacency map as *a priori* information and define a performance index which both drives the connectivity of the graph to match the biological data as well as generates a sparse network. Through simulation studies on simple examples, it is shown that this scheme can help to capture the topological change of a biological signal pathway and show the influence or activity of each edge over time. Also, we sketch briefly the potential application of this approach to correcting the graph model.**

I. Introduction

Systems biology problems focus on modeling or reconstruction of a biological network in which many variables interact with each other over time. Many current data-driven inference algorithms such as Bayesian analysis [1][2][3] are limited in their ability to represent temporally evolving dynamics. Also, many existing modeling methods in systems biology assume a physical model is given, as an ODE model, for example, and try to estimate a large number of parameters, reaction rates for example, based on the given system [4][5][6][7]. But these assumptions about the model structure could be problematic. For example, a key assumption of a mass action kinetics model is that there is large number of molecules which are homogeneously mixed, an assumption which may fail inside a cell because there are only a few molecules governing the reaction. These dynamics might be best modeled using discrete transitions. Therefore, theory-driven modeling such as mass action kinetics requires a good understanding of the dynamics of the signal pathway.

Y.H. Chang is with the Department of Mechanical Engineering, University of California, Berkeley, CA 94720 USA yhchang@berkeley.edu

Prof. Claire Tomlin is with the Department of Electrical Engineering and Computer Sciences, University of California, Berkeley, CA 94720 USA tomlin@eecs.berkeley.edu

Since a graph is a natural way to represent a biological system, if a system can be abstracted into a graph, it might help to understand the underlying dynamics of the system[8]. To address modeling of biological networks without any prejudices of structure, we focus our attention on identifying time varying linear models of sparse biological networks represented as graphs. With this approach in mind, our question becomes how to infer dynamics from a set of data and how to find the most reasonable model among many possible configurations, since our problem formulation has fewer constraints than theory-driven mechanism modeling. In [9], we presented a precursor to this algorithm for discrete time.

In order to find the most biologically reasonable configuration among many representations, we formulate this problem using LQ optimal control with a given graph model. One of the main strengths of our method is the ability to capture key pathways or important influences over time which we use to identify the dynamics. Also, unlike existing ODE-based approaches, we only impose a few constraints such as a graph structure in our model.

The rest of this paper is organized as follows: in Section II and III, we present a problem formulation with a graphical model and reformulate it as an LQ optimal control problem. In Section IV, we apply the proposed algorithm to simple examples through simulation studies. Moreover, we briefly mention a possible application to correction of *a priori* graph structure.

II. Problem Statement

We define a state vector $x(t) = [x_1(t), ..., x_n(t)]^T$, the components of which represent concentrations of proteins or states in a biological network. It is assumed that the state of network evolves over time and this evolution of state $x(t)$ can be usually modeled using an ordinary differential equation (ODE):

$$\dot{x} = f(x, p) \tag{1}$$

where p is a parameter set. Many studies in systems biology impose a structure on $f(\cdot)$, such as mass action kinetics or Hill function dynamics, and identify parameters using least-square criteria. In this paper, however, we are interested in finding the time varying influence map which can be formulated as a time varying linear system. In this, we are motivated by the methodology of [10]. The nonlinear dynamic system (1) can be approximated by a time varying linear system based on forming the Jacobian around steady

states as shown below:

$$\begin{bmatrix} \delta\dot{x}_1(t) \\ \delta\dot{x}_2(t) \\ \cdots \\ \delta\dot{x}_n(t) \end{bmatrix} = \begin{bmatrix} \frac{\partial f_1}{\partial x_1} & \frac{\partial f_1}{\partial x_2} & \cdots & \frac{\partial f_1}{\partial x_n} \\ \cdots & \cdots & \cdots & \cdots \\ \cdots & \cdots & \cdots & \cdots \\ \frac{\partial f_n}{\partial x_1} & \frac{\partial f_n}{\partial x_2} & \cdots & \frac{\partial f_n}{\partial x_n} \end{bmatrix} \begin{bmatrix} \delta x_1 \\ \delta x_2 \\ \cdots \\ \delta x_n \end{bmatrix} = G(t)\delta x(t) \tag{2}$$

where we assume there is no parameter variation ($\delta p = 0$). A system in the form of (2) can be considered as a temporally evolving weighted directed graph. Then, $G(t)$ is a time-varying adjacency matrix, or influence matrix, of dimension $n \times n$ which describes the temporal evolution of the edges with strength change. In general, $G(t)$ is a sparse matrix[11][12][13]:

$$G_{i,j}(t) = \frac{\partial f_i}{\partial x_j} = \begin{cases} \neq 0 & \text{if node } j \text{ can affect node } i \text{ directly} \\ = 0 & \text{otherwise} \end{cases} \tag{3}$$

where $G_{i,j}(t)$ is non-zero if there exists a direct connection between node j (input node) and node i (output node). Otherwise, $G_{i,j}(t)$ is zero.

Definition. Let $G(t)$ be a time-varying adjacency matrix which represents a dynamic graph with n nodes and k edges where k is the number of candidate edges from *a priori* information. The *component* of $G(t)$, denoted $e(t) = comp(G(t))$, is a $k \times 1$ vector whose elements are the nonzero entries of $G(t)$[13].

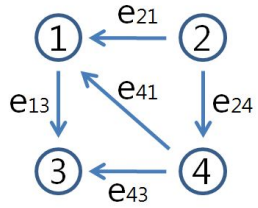


Fig. 1. A simple graph model.

Example 1. Consider the dynamic graph shown in Figure 1. Following the conventions introduced above, the corresponding adjacency matrix $G(t)$ has the form:

$$G(t) = \begin{bmatrix} 0 & e_{21} & 0 & e_{41} \\ 0 & 0 & 0 & 0 \\ e_{13} & 0 & 0 & e_{43} \\ 0 & e_{24} & 0 & 0 \end{bmatrix} \tag{4}$$

Its component $e(t)$ is constructed by extracting the nonzero elements from each column, which produces the vector:

$$e(t) = [e_{13}, e_{21}, e_{24}, e_{41}, e_{43}]^T =: [e_1, e_2, e_3, e_4, e_5]^T \tag{5}$$

Using $e(t)$, we can reformulate system (2) as follows (for Example 1, $n = 4, k = 5$):

$$\begin{aligned} \begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \\ \dot{x}_4 \end{bmatrix}_{n\times 1} &= \begin{bmatrix} 0 & e_{21} & 0 & e_{41} \\ 0 & 0 & 0 & 0 \\ e_{13} & 0 & 0 & e_{43} \\ 0 & e_{24} & 0 & 0 \end{bmatrix}_{n\times n} \begin{bmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{bmatrix}_{n\times 1} \\ &= \begin{bmatrix} 0 & x_2 & 0 & x_4 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ x_1 & 0 & 0 & 0 & x_4 \\ 0 & 0 & x_2 & 0 & 0 \end{bmatrix}_{n\times k} \begin{bmatrix} e_{13}(t) \\ e_{21}(t) \\ e_{24}(t) \\ e_{41}(t) \\ e_{43}(t) \end{bmatrix}_{k\times 1} \\ &= A(x)e(t) \\ &= e_1(t) \begin{bmatrix} 0 \\ 0 \\ x_1 \\ 0 \end{bmatrix} + e_2(t) \begin{bmatrix} x_2 \\ 0 \\ 0 \\ 0 \end{bmatrix} + \\ &\quad e_3(t) \begin{bmatrix} 0 \\ 0 \\ 0 \\ x_2 \end{bmatrix} + e_4(t) \begin{bmatrix} x_4 \\ 0 \\ 0 \\ 0 \end{bmatrix} + e_5(t) \begin{bmatrix} 0 \\ 0 \\ x_4 \\ 0 \end{bmatrix} \end{aligned} \tag{6}$$

where $A(x) \in R^{n\times k}$ is a linear function of x, which can be constructed from *a priori* information, representing possible influence modes of biological networks. For example, the first mode, $[0\ 0\ x_1\ 0]^T$ in equation (6) shows that node 1 activates node 3 (i.e, $x_1 \rightarrow \dot{x}_3 \rightarrow x_3$) in Figure 1. Also, each $e_i(t)$ represents a time varying coefficient or an activity of i-th mode $\in R^{n\times 1}$. Therefore, we can assign the network topology by adding edges, for example, if there are suspicious interactions among nodes.

Here, we are using a similar notion to modal analysis in mechanical vibration systems but the main difference is that our mode is constructed by a graph model. For example, each $e_i(t)$ is similar to a generalized coordinate in modal analysis and each column vector (influence mode) represents the eigenvector in modal analysis. In order to find all $e_i(t)$ which drive our system dynamics with influence modes, we formulate a Linear Quadratic (LQ) optimal control problem, as a regulation problem ($x(t) \rightarrow x_d(t)$) with control inputs both $e(t)$ and $\dot{e}(t)$. Once we solve the LQ problem, $e_i(t)^*$ shows the optimal activity or sequence of each mode over time which drives our dynamic system to match biological data.

III. Time Varying Linear System

In order to formulate the LQ optimal control problem, we define the controlled system as follows:

$$\frac{dx(t)}{dt} = A(x)e(t) \tag{7}$$

and the optimal control is sought to minimize the quadratic performance index as follows:

$$\begin{aligned} J &= \frac{1}{2}(x(t_f) - x_d(t_f))^T S_1(x(t_f) - x_d(t_f)) \\ &\quad + \frac{1}{2}\int_0^{t_f} \{[x(t) - x_d(t)]^T Q_1 [x(t) - x_d(t)] \\ &\quad + \dot{e}(t)^T R\dot{e}(t) + e(t)^T Q_2 e(t)\} dt \end{aligned} \tag{8}$$

where S_1, Q_1 and Q_2 are positive semidefinite matrices and R is a positive definite matrix. The LQ problem as formulated above is concerned with tracking of the desired trajectory ($x_d(t)$, biological data). In the performance index J, the first term penalizes the deviation of $x(t_f)$ from the desired trajectory at the final time. Inside the integral, the first term penalizes the transient deviation of $x(t)$ from the desired trajectory $x_d(t)$ which represents the error dynamics. The second penalizes the change of activity of edges (dynamic graph) which attempts to minimize the variation of activity of edges over time (smoothly evolving). Also, the third term penalizes the activities of edges. Therefore, the second and third term attempt to achieve a sparse and smoothly evolving biological network. In order to use a general LQ framework, first, we define $\dot{e}(t) = v(t)$ and $\bar{x}(t) = x(t) - x_d(t)$. Here, we assume that we know $x_d(t)$ and $\dot{x}_d(t)$ for $0 \leq t \leq t_f$ because once we have $x_d(t)$ then we can get $\dot{x}_d(t)$ by using the derivative of a polynomial fitting. We define an $(n+k) \times 1$-dimensional state $X(t) = [\bar{x}(t)^T, e(t)^T]^T$. Then, the state equation for the enlarged state vector can be formulated as follows:

$$\begin{aligned}\frac{d}{dt}\begin{bmatrix}\bar{x}(t)\\ e(t)\end{bmatrix} &= \begin{bmatrix}0_{n\times n} & A(x)_{n\times k}\\ 0_{k\times n} & 0_{k\times k}\end{bmatrix}\begin{bmatrix}\bar{x}(t)\\ e(t)\end{bmatrix} + \begin{bmatrix}-\dot{x}_d(t)\\ v(t)\end{bmatrix}\\ &= \mathcal{A}(x)X(t) + \begin{bmatrix}-\dot{x}_d(t)\\ 0_{k\times 1}\end{bmatrix} + \begin{bmatrix}0_{n\times 1}\\ v(t)\end{bmatrix}\\ &= \mathcal{A}(x)X(t) + W(t) + V(t) \qquad (9)\end{aligned}$$

where $\mathcal{A}(x)$ is also a linear function of x. Note that the augmented system is still a linear system because there is no multiplication between $A(x)$ and $\bar{x}(t)$. Also, the performance index (8) can be written as follows:

$$\begin{aligned}J &= \frac{1}{2}X(t_f)^T\begin{bmatrix}S_1 & 0\\ 0 & 0\end{bmatrix}X(t_f) +\\ &\quad \frac{1}{2}\int_0^{t_f}\{X(t)^T\begin{bmatrix}Q_1 & 0\\ 0 & Q_2\end{bmatrix}X(t)\\ &\quad +V(t)^T\begin{bmatrix}0 & 0\\ 0 & R\end{bmatrix}V(t)\}dt\\ &= \frac{1}{2}X(t_f)^T\mathcal{S}X(t_f) + \frac{1}{2}\int_0^{t_f}\{X(t)^T\mathcal{Q}X(t) +\\ &\quad V(t)^T\mathcal{R}V(t)\}dt \qquad (10)\end{aligned}$$

The problem is now reformulated as a standard LQ problem with the exception of $\mathcal{R}$ which is a singular matrix. However, we are interested in $v(t)$ so the solution of the continuous time LQ problem is given by the state feedback control law as shown below:

$$\begin{aligned}V(t) &= -\mathcal{R}^+P(t)X(t) = -\begin{bmatrix}0 & 0\\ 0 & R^{-1}\end{bmatrix}P(t)X(t)\\ &= \begin{bmatrix}0\\ v^*_{opt}(t)\end{bmatrix} \qquad (11)\\ -\frac{dP(t)}{dt} &= \mathcal{A}(x)^TP(t) + P(t)\mathcal{A}(x) - P(t)^T\mathcal{R}^+P(t)\\ &\quad +\mathcal{Q} \qquad (12)\end{aligned}$$

where $P(t_f) = \mathcal{S}$ and (12) is a Riccati equation.

Proof:

(for convenience, we will use abbreviated notations without $(x), (t)$)

$$\begin{aligned}&\int_0^{t_f}\frac{d}{dt}\{X^TPX\}dt\\ &= X(t_f)^TP(t_f)X(t_f) - X(0)^TP(0)X(0)\\ &= \int_0^{t_f}\{\dot{X}^TPX + X^T\dot{P}X + X^TP\dot{X}\}dt\\ &= \int_0^{t_f}\{(\mathcal{A}X + W + V)^TPX + X^T\dot{P}X\\ &\quad +X^TP(\mathcal{A}X + W + V)\}dt \qquad (13)\end{aligned}$$

Select P which satisfies following equation:

$$\mathcal{A}^TP + \frac{dP}{dt} + P\mathcal{A} = -\mathcal{Q} + P^T\mathcal{R}^+P, P(t_f) = \mathcal{S} \qquad (14)$$

Using P, we can reformulate (13) as follows:

$$\begin{aligned}0 &= -\frac{1}{2}X(t_f)^T\mathcal{S}X(t_f) + \frac{1}{2}X(0)^TP(0)X(0)\\ &\quad +\frac{1}{2}\int_0^{t_f}\{X^T(-\mathcal{Q} + P^T\mathcal{R}^+P)X\\ &\quad +(W+V)^TPX + X^TP(W+V)\}dt \qquad (15)\end{aligned}$$

Then, we can combine the cost function (8) and above equation as follows:

$$\begin{aligned}J &= \frac{1}{2}X(0)^TP(0)X(0) + \int_0^{t_f}\{X^TP^T\mathcal{R}^+PX\\ &\quad +(W+V)^TPX + X^TP(W+V) + V^T\mathcal{R}V\}dt \qquad (16)\end{aligned}$$

We have the following relation because of the specific structure of $\mathcal{R}, V$ and W as follows:

$$\begin{aligned}V^T\mathcal{R}V &= \begin{bmatrix}0_{1\times n} & v(t)^T\end{bmatrix}\begin{bmatrix}0_{n\times n} & 0_{n\times k}\\ 0_{k\times n} & R_{k\times k}\end{bmatrix}\begin{bmatrix}0_{n\times 1}\\ v(t)\end{bmatrix}\\ &= \begin{bmatrix}-\dot{x}_d(t)^T & v(t)^T\end{bmatrix}\begin{bmatrix}0_{n\times n} & 0_{n\times k}\\ 0_{k\times n} & R_{k\times k}\end{bmatrix}\begin{bmatrix}-\dot{x}_d(t)\\ v(t)\end{bmatrix}\\ &= (W+V)^T\mathcal{R}(W+V) \qquad (17)\end{aligned}$$

Using this relation, we can reformulate J as follows:

$$\begin{aligned}J &= \frac{1}{2}X(0)^TP(0)X(0) + \int_0^{t_f}\{X^TP^T\mathcal{R}^+PX\\ &\quad +(W+V)^TPX + X^TP(W+V)\\ &\quad +(W+V)^T\mathcal{R}(W+V)\}dt\\ &= \frac{1}{2}X(0)^TP(0)X(0) +\\ &\quad \int_0^{t_f}\{(\mathcal{R}^+PX + W + V)^T\mathcal{R}(\mathcal{R}^+PX + W + V)\}dt \qquad (18)\end{aligned}$$

To minimize J, $V_{opt} = -\mathcal{R}^+PX - W$ but as we defined the structure of V and W in equation (9), V only satisfies the following condition: $V^* = -\mathcal{R}^+PX$. However, when

we plug in V^*, the optimal cost is $J^* = \frac{1}{2}X(0)^T P(0)X(0)$ which is the same as using V_{opt} since $W^T \mathcal{R} W = 0$. ■

Note that the Riccati equation (14) includes $A(x)$ term in $\mathcal{A}$, yet we can handle this easily by replacing x by x_d: this trick is reasonable because our optimal control input, $v^*_{opt}(t)$, drives $x(t)$ to $x_d(t)$ by choosing proper Q_1, Q_2 and R. Otherwise, we would have to solve a Two Point Boundary Value Problem (TPBVP) by numerical iteration.

Proposition. The Ricaati equation (14) can be solved by replacing x by x_d, using $\mathcal{Q}, \mathcal{R}$ which drive x to x_d.

Proof: Consider $\mathcal{L} = X^T P_2 X$ as a Lyapunov function, then we can differentiate a Lyapunov function as follows:

$$\begin{aligned}\dot{\mathcal{L}} &= X^T\{\mathcal{A}(x)^T P_2 + \dot{P}_2 + P_2\mathcal{A}(x)\}X \\ &\quad +(W+V)^T P_2 X + X^T P_2 (W+V) \end{aligned} \tag{19}$$

Select a Riccati equation which satisfies $\mathcal{A}(x_d)^T P_2 + \dot{P}_2 + P_2\mathcal{A}(x_d) = -\mathcal{Q} + P_2^T \mathcal{R}^+ P_2$ and consider $\Delta\mathcal{A}$ satisfying $\mathcal{A}(x_d) = \mathcal{A}(x) + \Delta A$, then we can reformulate the Riccati equation as follows:

$$\begin{aligned}&\mathcal{A}(x)^T P_2 + \dot{P}_2 + P_2\mathcal{A}(x) \\ &= -\mathcal{Q} + P_2^T \mathcal{R}^+ P_2 - (\Delta\mathcal{A}^T P_2 + P_2 \Delta\mathcal{A}) \end{aligned} \tag{20}$$

where intuitively, if $x \to x_d$, $\Delta\mathcal{A}$ becomes zero matrix.

Also, we can reformulate $\dot{\mathcal{L}}$ as follows:

$$\begin{aligned}\dot{\mathcal{L}} &= X^T\{-\mathcal{Q} + P_2^T\mathcal{R}^+P_2 - (\Delta\mathcal{A}^T P_2 + P_2\Delta\mathcal{A})\}X \\ &\quad +(W+V)^T P_2 X + X^T P_2 (W+V) \end{aligned} \tag{21}$$

$$\begin{aligned}&= -X^T\mathcal{Q}X + \\ &\quad (\mathcal{R}^+P_2^T X + (W+V))^T \mathcal{R}(\mathcal{R}^+P_2^T X + (W+V)) \\ &\quad -(W+V)^T\mathcal{R}(W+V) - X^T(\Delta\mathcal{A}^T P_2 + P_2\Delta\mathcal{A})X \end{aligned} \tag{22}$$

We pick the optimal input $V = -\mathcal{R}^+ P_2^T X$ and we can use the relations $(W+V)^T\mathcal{R}(W+V) = V^T\mathcal{R}V = X^T P_2^T \mathcal{R}^+ P_2 X$ and $W^T\mathcal{R}W = 0$:

$$\begin{aligned}\dot{\mathcal{L}} &= -X^T\mathcal{Q}X + W^T\mathcal{R}W - (W+V)^T\mathcal{R}(W+V) \\ &\quad -X^T(\Delta\mathcal{A}^T P_2 + P_2\Delta\mathcal{A})X \end{aligned} \tag{23}$$

$$= -X^T(\mathcal{Q} + P_2^T\mathcal{R}^+P_2 + \Delta\mathcal{A}^T P_2 + P_2\Delta\mathcal{A})X \tag{24}$$

Thus, by choosing $\mathcal{Q}, \mathcal{R}$ large enough to guarantee $\dot{\mathcal{L}} < 0$, we can drive $x \to x_d$ (i.e., $\Delta\mathcal{A}$ becomes zero matrix). ■

Also, we can evaluate the dynamic graph $e(t)$ by integration:

$$e^*(t) = \int_0^t v^*_{opt}(\tau)d\tau \tag{25}$$

Therefore, this proposed LQ optimal control framework allows us to capture pivotal development events and dynamics of the temporally evolving system.

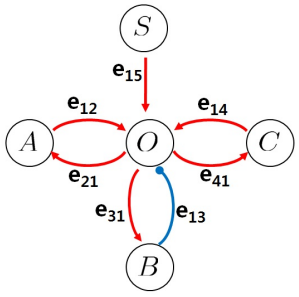
IV. Numerical Example

In this section, we consider numerical examples to illustrate the proposed scheme. In order to understand the method, we present the procedure step by step with a biological system.

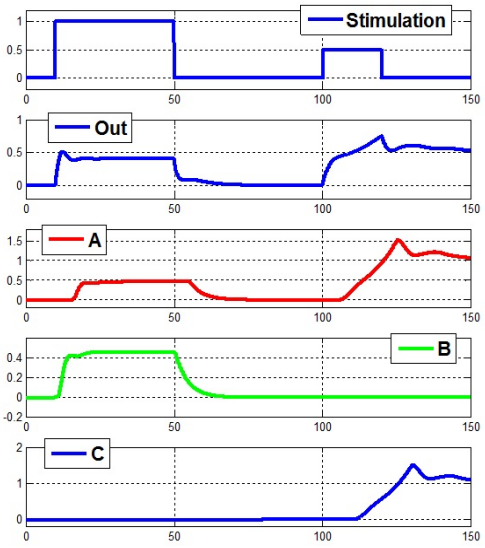
Example 2. [Biological Signaling Pathways] Consider the system of coupled positive and negative feedback networks as follows [14]:

$$\begin{aligned}\frac{dA}{dt} &= k_1 h(out, \tau_A)(10 - A) - k_2 A \\ \frac{dB}{dt} &= k_1 h(out, \tau_B)(10 - A) - k_2 B \ \text{(short term)} \\ \frac{dC}{dt} &= k_1 h(out, \tau_C)(10 - C) - k_2 C \ \text{(long term)} \\ \frac{dO}{dt} &= (k_{sti} S + f_A A + f_C C)(10 - O) - (f_B B + k_{min})O \end{aligned} \tag{26}$$

where $k_{sti} = 0.04$, $k_{min} = 0.4$, $f_A = 0.012$, $f_B = 1.5$, $f_C = 0.008$, $k_1 = 0.2$, $k_2 = 0.25$, $\tau_A = 5$, $\tau_B = 0$, $\tau_C = 10$ and $h(out, \tau) = \dfrac{out(t-\tau)^3}{out(t-\tau)^3 + 1^3}$. Here, we consider the

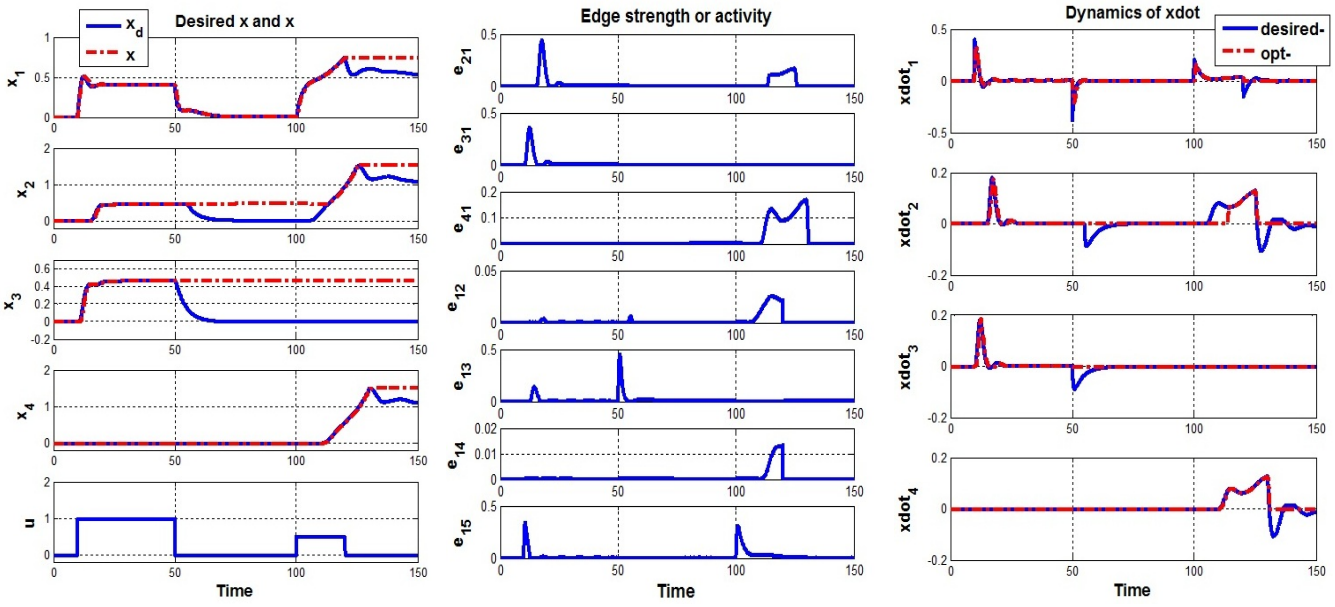


(a)



(b)

Fig. 2. (a) A graph model of simple biological network (b) simulation result (PN feedback (for short-term) and PP feedback (for long-term behavior)).



(a) (b) (c)

Fig. 3. (a) x and x_d (b) the activity of edges (c) $\dot{x}$ and $\dot{x}_d$

change of topology of the network (for the short term, Positive Negative (PN) feedback (A, B only) and for the long term, Positive Positive (PP) feedback (A, C only))[14]. In Figure 2, we can see that output signal (O) goes to zero once the stimulation (S) or input signal goes to zero for short term behavior because of PN feedback. However, for the long term, even a small pulse input can make the output signal stay with high amplitude because of PP feedback. Define $x_d(t) = [x_1, x_2, x_3, x_4, u] = [O, A, B, C, S]$, $e(t) = [e_{21}, e_{31}, e_{41}, e_{12}, e_{13}, e_{14}, e_{15}]$ and the *a priori* map as shown in Figure 2 (a). Then, a time varying linear system can be formulated as follows:

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \\ \dot{x}_4 \end{bmatrix} = \begin{bmatrix} 0 & 0 & 0 & x_2 & x_3 & x_4 & u \\ x_1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & x_1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & x_1 & 0 & 0 & 0 & 0 \end{bmatrix} \begin{bmatrix} e_{21} \\ e_{31} \\ e_{41} \\ e_{12} \\ e_{13} \\ e_{14} \\ e_{15} \end{bmatrix} \tag{27}$$

Here, we introduce constraints that all edges $e_{ij}(t)$ are positive, representing activation edges. Therefore, for inhibition edges such as $e_{13}(t)$, we replace x_3 by $-x_3$ in order to satisfy our constraints. Also, we use a gradient projection method for constrained optimization which makes our feasible solution satisfy these constraints.

Figure 3 shows that the optimal activities of all edges $(e(t))$ cannot drive our system to be consistent with desired output (biological data) at some points. This result is expected because our simulation data are generated by equation (26) which includes self-degradation terms such as $-k_2A, -k_2B, -k_2C$. However, in our graphical representation in Figure 2 (a), there are no self-degradation edges so there is no way to decrease the concentration of states themselves. Therefore, if our graphical model cannot represent the experimental data, we should suspect our graphical model and update or modify by adding new edges, which are self-degradation edges (e_{11}, e_{22}, e_{33}, and e_{44}) as shown in Figure 4.

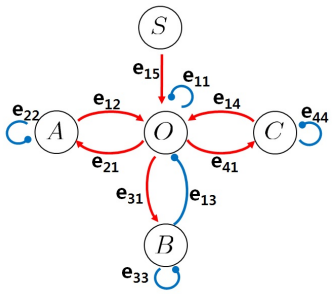
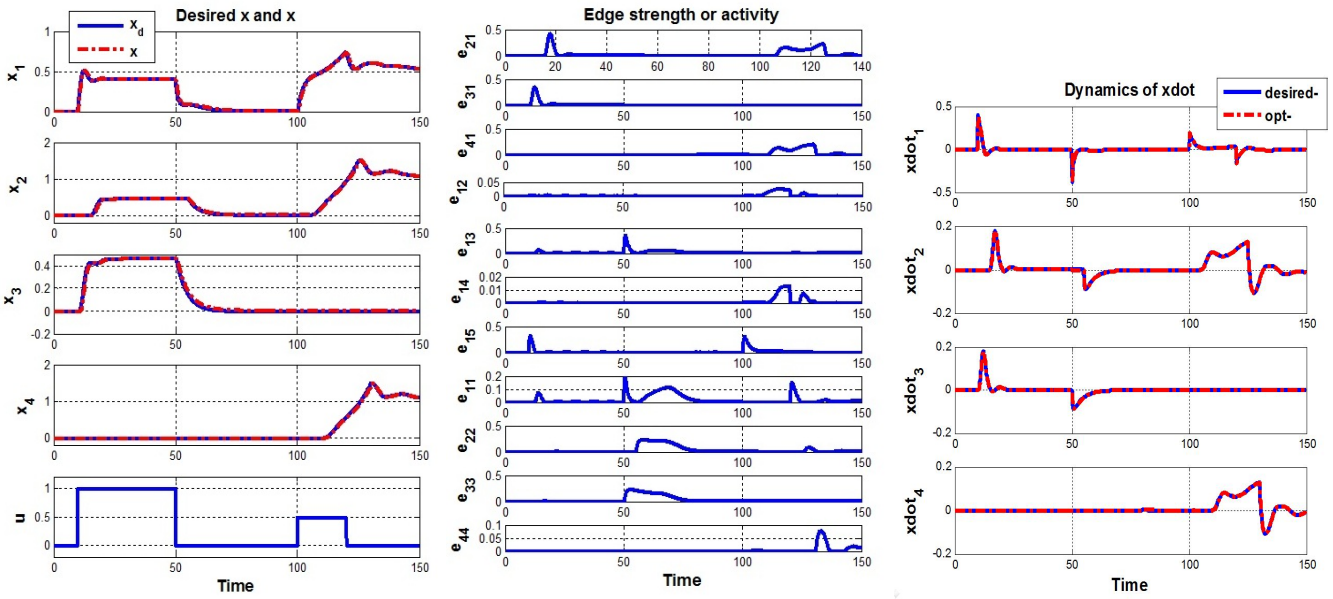


Fig. 4. A modified graphical model of the simple biological network of Figure 2 (a).

Figure 5 shows that the optimal control input can drive our system to be consistent with desired output quite well. Here we have included degradation edges ($e_{11}, e_{22}, e_{33}, e_{44}$) so it can reflect the underlying dynamics (26). Also, we can understand the behavior with a systematic point of view. For example, we can see that for the short term, the edges (e_{21}, e_{31}, e_{13}) related to [A] and [B] are activated, meaning PN feedback. For long term, the edges related to [A] and [C] are activated, showing PP feedback ($e_{21}, e_{12}, e_{41}, e_{14}$). Also, for example, $e_{21}(t)$ shows a step input at the point at which [A] start to increase. We can interpret this pulse as a



(a) (b) (c)

Fig. 5. (a) x and x_d (b) the activity of edges (c) $\dot{x}$ and $\dot{x}_d$.

trigger which activates the relation between x_1 and x_2. Once, $e_{21}(t)$ shows zero value meaning that the edge is deactivated (switched off). Therefore, by using a continuous model, we can capture the underlying dynamics or key signal pathways over time. Also, this method can be useful to build time series models with fine sampled data set such as neural activities and identify general systems with graphical representation.

V. Conclusions

In this paper, we proposed a data-driven inference method in order to understand and identify underlying dynamics for temporally evolving biological networks with a local point of view. The identification problem has led to an LQ control problem with two main penalty functions by which we can match the experimental data with a sparse representation using *a priori* information of structure. We show that the proposed schemes can be useful to capture the dynamic evolution of the network and understand the biological system with a systems point of view through examples. A logical next step would be to develop a theory-driven mechanism model such as an ODE by understanding the actual dynamics. Also, we presented the possible application of correcting graph model.

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