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Sampling Criteria that Preserve Monotone Regulation in Gene Regulatory Networks

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I. INTRODUCTION

A mathematical model for the dynamics of gene expression in a genetic regulatory network with N genes can be written as:

$$\frac{dx_i}{dt} = f_i(x_1, \cdots, x_N),\ i \in \{1, \cdots, N\}, \qquad (1)$$

where $x_i(t)$ is the time-dependent expression activity of Gene i. Following standard models of gene regulation (see e.g. [1]), we can assume that the regulation function f_i is continuous and monotonic. That is, $\frac{\partial f_i}{\partial x_j}(\mathbf{x})$ does not change sign for any $\mathbf{x} \in \mathbb{R}^n$. Note that the topology of the regulatory network is encoded in the regulatory functions $f_1, \cdots, f_N$.

$$\text{Gene } j \text{ is } \begin{bmatrix} \text{an activator} \\ \text{a repressor} \\ \text{not a regulator} \end{bmatrix} \text{ of Gene } i \text{ if } \begin{bmatrix} \frac{\partial f_i}{\partial x_j} > 0 \\ \frac{\partial f_i}{\partial x_j} < 0 \\ \frac{\partial f_i}{\partial x_j} = 0 \end{bmatrix} \qquad (2)$$

One of the canonical problems in systems biology is to determine the topology of the network, given gene expression data. The data are naturally discrete, e.g. they can be obtained from sampling the signal $\mathbf{x}(t)$. One way to deal with discrete data is to approximate the model in (1) with a discrete-time model:

$$\frac{x_i(k\Delta + \Delta) - x_i(k\Delta)}{\Delta} = F_i(x_1(k\Delta), \cdots, x_N(k\Delta)), \qquad (3)$$

for $i \in \{1, \cdots, N\}$, where $x_i(k\Delta)$ is the expression activity of Gene i at the k^{th} sampling time. Note that here we assume that the sampling is periodic with sampling period Δ. The continuous time regulation function f_i is replaced by its discrete time counterpart, F_i, which is assumed to be continuous and similarly monotonic. In [2], [3], we derive necessary and sufficient conditions for the existence of continuous and monotonic regulatory functions that interpolate the given gene expression time-series. These conditions can be formulated as an Linear Programming (LP) feasibility test, making them computationally easy to check.

The investigation of monotonicity and gene network identification has also been performed by others in the community. For example, the work by Porreca *et al* [4] proposed a two-staged process in identifying a continuous-time differential equation model for GRNs. In the first stage, network topologies that are inconsistent with the data are rejected. This first stage is also based on monotonicity argument. In a more recent work, Angeli and Sontag [5] exploit the monotonicity argument to reject regulation hypothesis based on the sign pattern of the expression data's temporal gradient.

In the current work, we aim to establish a theoretical foundation for the discrete-time approximation that is discussed in the previous paragraph. Specifically, we want to find conditions on Δ such that the monotonicity of the continuous-time model $f \triangleq (f_1, \cdots, f_N)^T$, which is derived from first principle, is preserved by the discrete-time model $F \triangleq (F_1, \cdots, F_N)^T$. Since validation of the discrete-time model using experimental data has been fully characterized in [2], [3], results from this paper can be used to inform the experimentalists about suitable sampling frequency for the purpose of network identification.

II. RESULTS

Before we proceed with discussing the results, let us state a few assumptions that will be used throughout the paper.

Assumption. We assume that the functions $(f_1, \cdots, f_N)$ are continuously differentiable, and that for any $i, j \in \{1, \cdots, N\}$ the following bounds exist

$$L \leq \left| \frac{\partial f_i}{\partial x_j} \right| \leq M, \qquad (4)$$

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for some $0 \leq L \leq M$, if Gene j is a regulator of Gene i. Note that this implies that $(f_1, \cdots, f_N)$ are Lipschitz.

Let us define the function $\xi : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R}^n$ such that $\xi(\mathbf{x}_0, \Delta)$ is the vector of gene expressions at time $t = \Delta$, given the dynamics in (1) and the initial condition

$$\mathbf{x}(0) = \mathbf{x}_0 = (x_{1,0}, \cdots, x_{N,0})^T.$$

The discrete-time system F as described in (3) can then be written as

$$F(\mathbf{x}_0; \Delta) \triangleq \frac{\xi(\mathbf{x}_0, \Delta) - \mathbf{x}_0}{\Delta} = \frac{1}{\Delta} \int_0^\Delta f(\xi(\mathbf{x}_0, \tau))\ d\tau. \tag{5}$$

Because f is continuously differentiable, so is F with respect to $\mathbf{x}_0$. We are interested in finding conditions for Δ such that F inherits the monotonicity structure of f. We are now ready to state our main result.

Theorem 1: The monotonicity of the continuous-time model $f \triangleq (f_1, \cdots, f_N)^T$ is preserved by the discrete-time model $F \triangleq (F_1, \cdots, F_N)^T$ if the sampling period Δ satisfies

$$\Delta \leq \frac{\ln 2}{NM}, \tag{6}$$

$$\frac{e^{NM\Delta} - 1}{NM\Delta} \leq \left(1 + \frac{L}{L + (N-1)\,M}\right). \tag{7}$$

Remark 2: A sufficient condition for the monotonicity structure to be preserved under sampling is given by both (6) and (7). However, a simple numerical calculation reveals that for practically large enough network $(N \geq 3)$, (6) is implied by (7).

III. DISCUSSION

A natural question that arises is why we need a sampling theorem as shown in the previous section, instead of the more general one such as the well known Nyquist Theorem. The answer is, because Nyquist Theorem is concerned with perfect reconstruction of the sampled signal, while we are only interested in maintaining the monotonic structure of the regulatory functions. In a sense, the Nyquist Theorem is too restrictive for this purpose. To illustrate this point, let us consider the simple special case of $N = 1$. In this case, both f and F are scalar valued functions. We can compute

$$\frac{\partial F}{\partial \mathbf{x}_0} = \frac{1}{\Delta} \int_0^\Delta \left.\frac{df}{dx}\right|_{x=\xi(\mathbf{x}_0,\tau)} \cdot \frac{\partial \xi(\mathbf{x}_0, \tau)}{\partial \mathbf{x}_0}\ d\tau. \tag{8}$$

Given that f is monotonic, we know that $\frac{df}{dx}$ is sign definite. Observe that the sensitivity function

$$s(\tau) \triangleq \frac{\partial \xi(\mathbf{x}_0, \tau)}{\partial \mathbf{x}_0}, \tag{9}$$

satisfies the following ODE and boundary condition [6]:

$$\frac{ds}{d\tau} = \left.\frac{df}{dx}\right|_{x=\xi(\mathbf{x}_0,\tau)} s(\tau),\ s(0) = 1. \tag{10}$$

We can easily prove that $s(t) \geq 0,\ \forall t \geq 0$. Hence, $\frac{\partial F}{\partial \mathbf{x}_0}$ inherits the sign of $\frac{df}{dx}$, regardless of Δ!

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