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BIOLOGICAL SIGNALING CHAINS: MODELING AND CONTROL

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Abstract: A mathematical model of biological signaling chains is presented. It is proposed as a basis for the design of controllers that correct defects in biological signaling chains.

Introduction: A biological signaling chain is an orderly sequence of biochemical events, proceeding in discrete well defined steps. Signaling chains drive many biological actions, including muscle activation, vision, smell, wound healing, and cell growth and division. Malfunctions in biological signaling chains cause debilitative geriatric processes, pre-cancerous or cancerous transformations, and other harm.

An example of a signaling chain: A signaling molecule attaches to a receptor protein and activates it; the activated receptor activates G protein molecules; each activated G protein molecule releases a sub-unit activating an adenylyl cyclase enzyme molecule; an activated adenylyl cyclase molecule catalyses the generation of cAMP molecules; each cAMP molecule activates an A-kinase enzyme molecule; the activated A-kinase enzyme catalyzes the activation of another enzyme; each molecule of the enzyme catalyzes the creation of final product molecules (e.g., [1]).

Modeling: Due to their sequential nature, signaling chains can be modeled by sequential machines (see also [1], [2], [3]). Let Z be the set of integers, and consider a signaling chain Σ that operates in a medium. Let $\sigma^1, ..., \sigma^m$ be the relevant species of molecules in the medium. Let $\pi_k^i \in Z$ represent the molecular population of species σ^i at step k, and define the vector $\pi_k = (\pi_k^1, \pi_k^2, ..., \pi_k^m) \in Z^m$.

The operation of Σ may also be affected by other quantities, such as the temperature or the irradiation intensity. Let $\tau_k^1, ..., \tau_k^d$ be integers that represent discretized measures (at the step k) of these quantities. Create an integer *state vector* s_k that describes the state of the system at the step k:

$$s_k := (\pi_k^1, \pi_k^2, ..., \pi_k^m, \tau_k^1, ..., \tau_k^d) \in Z^n, \; n = m+d.$$

The operational conditions within the signaling chain can be altered by injecting more molecules, changing temperature, or changing other conditions. These changes can be represented by an additive input vector $u_k \in Z^n$, so that, immediately preceding step k+1, the state of the signaling chain is given by $(s_k + u_k)$. This state determines the outcome of the reaction step, and the next state is given by

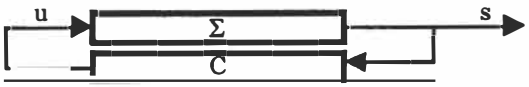
$$(1) \quad s_{k+1} = f(s_k+u_k), \; k = 0, 1, 2, ...,$$

where the function f, called the *recursion function*, describes the outcome of each reaction step; it is determined from empirical data. In this way, biological signaling chains can be represented as sequential machines over the integers.

Substantial uncertainties are involved in the modeling of biological systems due to many factors, including the lack of complete understanding of some biological mechanisms, natural differences among multiple occurrences of the same process, the probabilistic nature of biochemical reactions, or inaccuracies in experimental data. To account for these uncertainties, we represent a signaling chain by a family $M = \{\Sigma_1, ..., \Sigma_q\}$ of *potential models*, where each member Σ_i is a discrete system of the form (1). The actual model of the system, called the *active model*, is a member M.

Control: Assume that from empirical data, a family $M = \{\Sigma_1, ..., \Sigma_q\}$ of potential models has been derived for a malfunctioning signaling chain Σ. Then, M can be used as a basis for the development of a biochemical control device that counteracts and corrects the malfunction. This device serves as the controller C in the following diagram.

(2)



Here, C generates the input u of Σ so as to make the closed loop system (denoted Σ_c) function correctly. The simplest controllers are *static controllers*, given by

$$u_k = h_c(s_k), \; k = 0, 1, 2, ..., \; h_c : Z^n \to Z^n;$$

here h_c is the *controller function*. Static controllers are combinatorial logic circuits; they can be implemented by mimicking the mechanism of gene promoters.

Model Matching: Assume that when Σ_i is the active model of Σ, the correct function is given by the model Δ_i. It is then necessary to find a controller C such that

$$(3) \quad \Sigma_{ic} = \Delta_i, \; i = 1, ..., q,$$

i.e., a controller that corrects the operation of each potential model of Σ. Let f_i be the recursion function of Σ_i, and let g_i be the recursion function of Δ_i. Build the two vector functions (see [4] for more details)

$$f := \begin{pmatrix} f_1 \\ ... \\ f_q \end{pmatrix}, \; g := \begin{pmatrix} g_1 \\ ... \\ g_q \end{pmatrix}.$$

THEOREM. The following are equivalent:
(i) There is a static controller C that transform Σ_i into Δ_i for all $i = 1, ..., q$.
(ii) $\text{Im } g \subset \text{Im } f$.

When a controller C exists, it can be implemented by a genetically engineered system. Efforts are currently being made in this direction.

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