

Reliable Computation by Circuits of Unreliable Biochemical Gates

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ABSTRACT

Biochemical circuits are responsible for information processing and algorithmic control tasks within the cell, such as regulation of gene expression, phosphorylation and dephosphorylation of enzymes, and self-assembly [2]. Networks of interacting kinase enzymes, as in signal transduction cascades, are among the simplest and fastest of these mechanisms. These biochemical circuits are composed of a set of enzymes whose conversion between activated and inactivated state is regulated by other enzymes in the circuit; this binary state suggests a natural connection to digital logic in computer science.

Previous studies of logical computation by biochemical reactions have shown that, in principle, arbitrary logical circuits can be constructed from biochemical gates [6, 5]. These studies represented biochemical reactions using deterministic chemical kinetics for the concentrations of enzymes, an approximation only valid in the limit of a large number of molecules. However, for cell-scale systems, where a single copy of certain molecules may have a significant effect, stochastic analysis is necessary: the presence of reverse reactions and the unpredictable timing of reaction events makes biochemical circuits inherently unreliable [1]. Therefore, questions arise concerning whether large, reliable circuits can be constructed using biochemistry, and if so, whether sophisticated error correction techniques are necessary.

In this work, we consider error analysis of biochemical circuits with one or few copies of each enzyme, by adopting a stochastic model of evaluation [4]. This approach uncovers an interesting connection to the study of unreliable logical computation, where a number of theorems on error analysis of parallel computation in faulty logical circuits have been proved [8, 7, 3]. Our goal is to devise a formalism allowing us to translate the theorems on logical circuits to biochemical circuits, mapping each enzyme onto a logical gate. A challenge to making this interpretation precise is that a sequential model of evaluation has traditionally been adopted for faulty logical circuits. However, to extend the analysis to biochemical circuits, it is more appropriate to use an asynchronous model of evaluation, wherein each gate has an equal probability of being evaluated at any given step.

Our approach, therefore, is:

1. to define a class of biochemical reactions based on kinase cascades, and to express the stochastic kinetics

- as a continuous Markov process,
2. to define a class of asynchronous logical circuits, and to derive an exact correspondence to the biochemical systems,
3. to demonstrate that for circuits that are formulas, output error rates are identical to traditional faulty circuits, but that general feedforward circuits may have different output error probabilities,
4. to show that von Neumann's multiplexing technique for traditional faulty circuits corresponds to increasing the number of copies of molecules in biochemical circuits.

We have not yet been able to establish general bounds relating error probabilities in the traditional sequential model and the new asynchronous model; this will be necessary in order to rigorously apply the results of classical studies to biochemical circuits. Nonetheless, we hope that our approach will provide a useful framework for studying the fundamental limits to biochemical computation, scaling laws relating performance and energy use, and the optimal design of cell-scale biochemical circuits.

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