Building the components for a biomolecular computer

Clint Morgan[1] Darko Stefanovic[1] Cristopher Moore[1] Milan N. Stojanovic[2]
[1]Department of Computer Science, University of New Mexico
[2]Department of Medicine, Columbia University

Abstract

We propose a new technology for amorphous bio-compatible computing, using deoxyribozyme-based logic gates, and derive specific designs for a biomolecular realization of elementary components for a digital computer, including bistable memory elements (flip-flops) and oscillators. An eventual goal of this technology is the development of *in-vivo* computational devices. Thus, our system for chemical computation offers functionality similar to conventional electronic circuits with the potential for deployment inside of living cells.

Oligonucleotides can act as enzymes, or *ribozymes*, on other oligonucleotides, yielding oligonucleotide products. Moreover, these reactions can be controlled by inputs which are also oligonucleotides [1]. We interpret these reactions as logic gates, and the concentrations of chemical species as signals. Since these reactions are *homogeneous*, i.e., they use oligonucleotides for both their inputs and their outputs, we can compose them to construct complex logic circuits.

Previously, this technology was demonstrated in closed-system batch reactions, which limited its computational ability to simple feed-forward circuits. In this work, we go beyond closed systems, and show how to use thermodynamically open reactors to build biomolecular circuits with feedback, including basic building blocks of recurrent digital circuits such as flip-flops and oscillators.

The behavior of an open chemical system is determined both by its chemical reaction network and by the influx and efflux of chemical species. This makes the design process very different from that for batch reactions in a closed system. Rather than focusing solely on the stoichiometry of the chemical reactions, we must carefully examine the kinetics of these reactions. Systems of differential equations and the theory of dynamical systems become the appropriate tools for designing and analyzing such *in vitro* systems.

Using these tools, we first present two *inverters* with contrasting static and dynamic properties. These properties offer tradeoffs that can be exploited in the design of larger circuits.

Next, by introducing feedback into the reaction network, we construct devices with a sense of state—a flip-flop and an oscillator. The feedback terms introduce an additional level of complexity to the chemical kinetics, and we analyze them using techniques from nonlinear dynamics. We show how a combination of analytical approximation techniques and numerical methods allows us to tune the dynamics of these systems, and analyze the *bifurcations* in parameter space where bistability and oscillations first appear.

In particular, we demonstrate a flip-flop which exhibits behavior similar to the RS flip-flop of electronic computation. It has two states, in which the concentration of one oligonucleotide is high and the other is low or vice versa. As long as we maintain a certain influx of the substrates, both of these states are stable, allowing us to store a bit of information. We can "write" to this bit, i.e., set or reset the flip-flop, by changing the influx of the substrates. Moreover, there are large regions of parameter space in which this behavior is robust, and we show how to tune the influx rates as a function of the chemical reaction rates in a way that ensures bistability.

Another basic building block of computation is an oscillator. We show that by coupling three inverters together in a cycle, we can create robust oscillations in the concentrations of three oligonucleotides. We analyze the appearance of these oscillations in terms of a *Hopf bifurcation*, and show how to tune the influx rates to obtain a range of frequencies. This oscillator could be used to produce a clock signal for future implementations of biomolecular computation.

References

[1] Milan N. Stojanovic, Tiffany Elizabeth Mitchell, and Darko Stefanovic. Deoxyribozyme-based logic gates. *Journal of the American Chemical Society*, 124(14):3555–3561, April 2002.