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Molecules and computation

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Computing with molucles

Devices that convert information from one form into another according to a definite procedure are known as automata. One such hypothetical device is the universal Turing machine, which stimulated work leading to the development of modern computers. The Turing machine and its special cases, including finite automata, operate by scanning a data tape, whose striking analogy to information-encoding biopolymers inspired several designs for molecular DNA computers. Laboratory-scale computing using DNA and human-assisted protocols has been demonstrated, but the attempts to realize computing devices operating autonomously on the molecular scale remain rare.

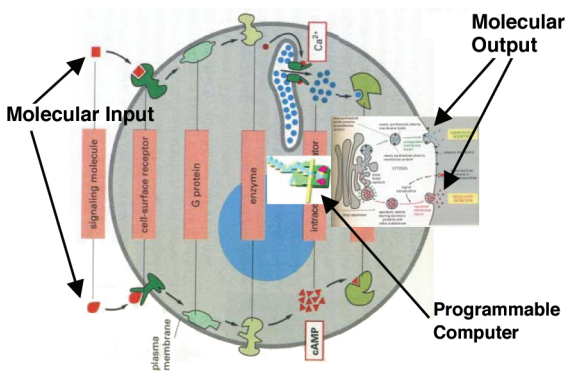

Fig. 1 *Medicine in 2050: "Doctor in a Cell"*

Autonomous biomolecular computers would in principle be able to operate *in vivo*, communicating with their biochemical environment via molecular input and output (Fig. 1). This ability might result in numerous biomedical application. Our research group aims to develop prototypes for such computers. We are currently developing *in vitro* systems with less-than-universal computation capability.

One such system that has already been successfully tested is a programmable finite automaton comprising DNA and DNA-manipulating enzymes (Fig. 2). A finite automaton is a notional computing machine that operates on finite sequences of symbols. The machine can be in one of a finite number of internal states, of which one is designated an initial state and some are designated accepting states. Its software consists of transition rules, each specifying a next state based on the current state and the current symbol. It is initially positioned on the leftmost input symbol in the initial state. In each transition the machine moves one symbol to the right, changing its internal state according to one of the applicable transition rules. Alternatively, it may suspend without completing the computation if no transition rule applies. A computation terminates upon processing the last input symbol. An automaton is said to accept an input if a computation on this input terminates in an accepting final state.

Our molecular finite automaton has two states and it operates on binary strings of symbols. It solves computational problems autonomously. The automaton's hardware consists of a restriction nuclease and ligase, the software and input are encoded by double-stranded DNA, and programming amounts to choosing appropriate software molecules. Upon mixing solutions containing these components, the automaton processes the input molecule via a cascade of restriction, hybridization and ligation cycles, producing a detectable output molecule that encodes the automaton's final state, and thus the computational result. In our implementation 10^{12} automata sharing the same software run independently and in parallel on inputs (which could in principle be distinct) in 120 μL solution at room temperature at a combined rate of 10^9 transitions per second with transition fidelity greater than 99.8%, consuming less than 10^{-10} Watt. Additional *in vitro* systems are currently under construction in our laboratory and are on various stages of testing.

Computing what molecules do

The BioSPI project is concerned with developing predictive models for molecular and biochemical processes. Such processes, carried out by networks of proteins, mediate the interaction of cells with their environment and are responsible for most of the information processing inside cells. Recently, much interest has been focused on system level studies of such networks, and several approaches have been proposed for their representation and analysis. However, none of the existing approaches fully integrates dynamics, molecular, and biochemical detail.

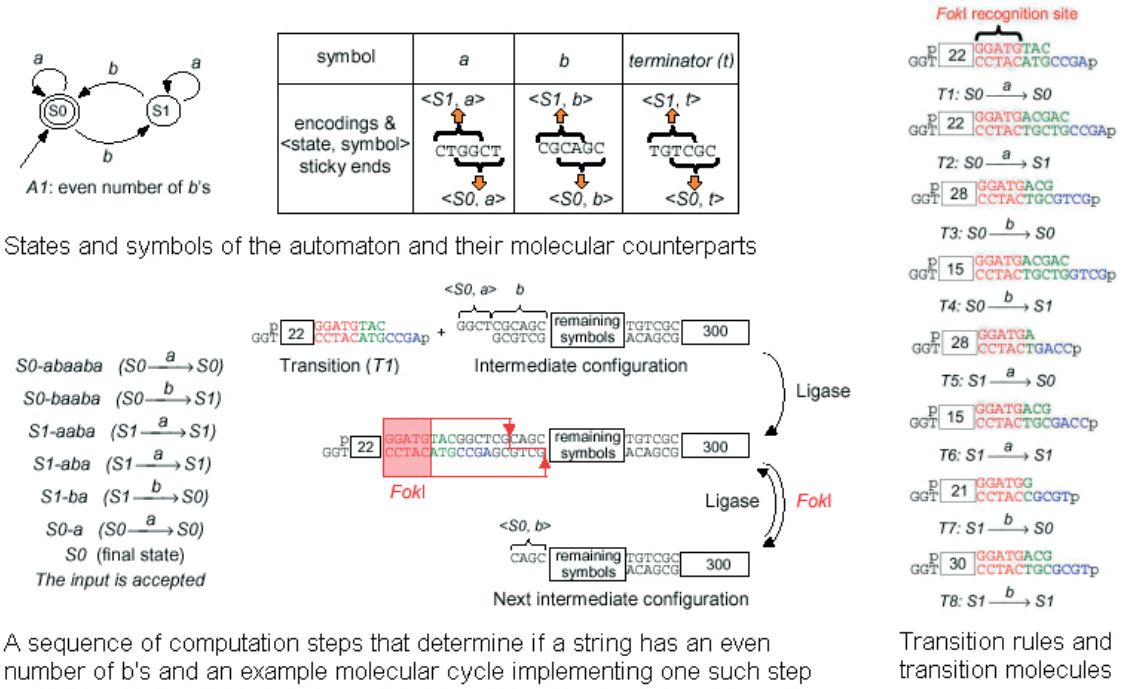

fig.2 *Design details and mechanism of operation of the molecular finite automaton*

We develop predictive models for biochemical processes using the pi-calculus, a process algebra originally developed for describing distributed computer processes. In our model, biochemical processes are mathematically well defined, while remaining biologically faithful and transparent. To allow accurate quantitative modeling of biochemical networks, we employ a stochastic variant, the spi-calculus, where actions are assigned rates according to the rates of the corresponding biochemical reactions. Based on this model, we developed a new computer system, called BioSPI, for representation and simulation of biochemical networks.

The modular nature of the calculus allows incremental modeling of complex networks and alternation between different levels of complexity. This is instrumental for studying the modular design of biological systems. We have used the BioSPI system to study a recently proposed model of the circadian clock. Using the ability of the calculus to capture modular structures, we investigated the circadian machinery at two levels of abstraction. First, we modeled the molecular interactions explicitly. Second, we identified a functional module in the system - a hysteresis module - and described the system using this functional module. By using two BioSPI programs, we show that both levels of description are equally good at capturing the behavior of the system, and establish the function of the hysteresis module within the clock and in a wider cellular context.

We are currently extending our modular framework to represent various aspects of molecular localization and compartmentalization, including the movement of molecules between compartments and dynamic rearrangement of cellular compartments. We intend to incorporate the adapted calculus as part of the BioSPI system, to provide a fuller modular framework for molecular interaction, localization and compartmentalization.

Selected Publications

Benenson, Y., Paz-Elizur, T., Adar, R., Keinan, E., Livneh, Z. Shapiro, E. (2001) Programmable and autonomous computing machine made of biomolecules. Nature, 414, 430-434.

Acknowledgements

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