

# Conformation-driven computing: simulating the context-conformation-action loop

Klaus-Peter Zauner and Michael Conrad\*

Wayne State University, Department of Computer Science, Detroit, MI 48202, USA

Function follows conformation in biological macromolecules. In general there are a number of possible conformational states. Which state is favored is determined by physicochemical context. The fusion of the features that comprise this context to form a particular conformational state is at the core of cellular control and biological information processing. We have developed a simulation system to investigate the information processing capabilities of networks of context-sensing macromolecules (to be illustrated by a simple example). © 1998 Elsevier Science Limited. All rights reserved

(Keywords: molecular computing; biochemical simulation; control; adaption)

## CONFORMATIONAL FUSION OF CONTEXT INFORMATION

Macromolecular conformation depends on the cumulative effect of numerous interactions that are individually weak relative to thermal energy. Atoms belonging to the covalently bonded structure interact with each other and also with atoms that constitute the environment. Usually, the folding process leads to a well defined conformation in a given environment. But this process does not simply terminate at an arbitrary point in time, independent of changes in the environment. The conformation remains sensitive to its surroundings. The functional activity inherent in the conformation must be sensitive as well. Furthermore the surround itself is affected by this activity (*Figure 1*)<sup>1–4</sup>. Natural biochemical systems can accordingly be viewed as complex interaction networks in which macromolecules play the role of signal integrating nodes. It should be possible to design artificial systems that exploit the same organizational principle<sup>5, 6</sup>.

To investigate such complex networks we have developed a software tool, the CKSD simulator<sup>7</sup>. The CKSD system is designed to address issues connected with the interplay of conformation, kinetics, structure and dynamics (hence the acronym). Our purpose in this paper is to indicate how the system represents these features and then to illustrate its operation with a simple example involving conformational, kinetic, and spatial factors.

## THE CKSD SIMULATOR

The CKSD simulator models biochemical networks in 3D space. The key is a highly abstracted macromolecule

representation that compromises molecular level dynamics with potentially high network complexity. Each macromolecule is represented as a dodecahedron, each of whose twelve faces is a finite automaton. The conformational states of the macromolecule correspond to the states of these automata. Dodecahedra corresponding to all the macromolecules in a network are placed in a mixture of signaling molecules (referred to as microcomponents) which diffuse throughout the simulation space. Changes in the local milieu of signaling molecules trigger state transitions of the finite automata. Shape properties and catalytic functions inherent in the conformational states of the macromolecule are associated with the states of the corresponding dodecahedron. The shape properties may lead to self-assembly of the dodecahedra into higher order 3D structures (*Figure 2*), or to their disassembly. The catalytic properties cause alterations of the milieu.

## SIGNAL PROCESSING IN AN ASYMMETRIC STRUCTURE

We are currently employing the CKSD simulator to investigate small networks with up to 25 macromolecules as transformers for signal patterns. The milieu is a superposition of concentration gradients of molecules, each of which serves as a signal to at least one type of macromolecule (by influencing its conformation). Each macromolecule responds, in accordance with its predefined selectivity, to features of this complex environment. The response is either activation or deactivation of its catalytic activity. While active, a macromolecule can transform milieu components in its immediate neighborhood into other milieu components. Diffusion communicates this action on the milieu to other macromolecules in the simulation space. These may respond with a

\*To whom correspondence should be addressed

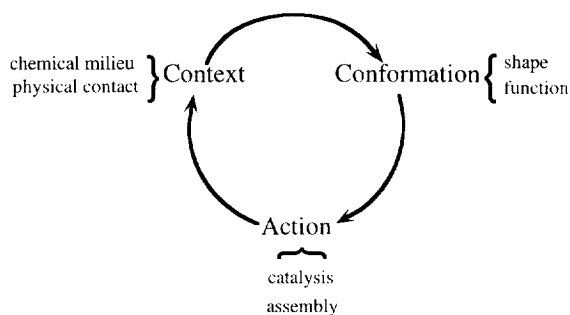


Figure 1 Context-conformation-action loop

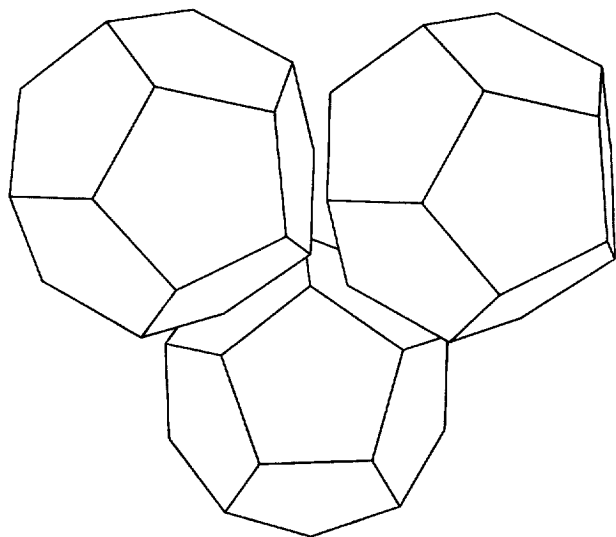


Figure 2 Representation of macromolecular structure formation in the CKSD simulation system

corresponding change in their activity. The collective action of the macromolecules alters the signal composition of the milieu.

To illustrate the operations of the simulator consider the relatively simple cyclic competitive reaction depicted in Figure 3. The cycle is driven by free energy decrease at each step, for example by coupling to ATP reactions (which, however, are not considered here). Furthermore, we assume that the free energy decreases are large enough for the reverse reactions to be negligible. Substrate (C) is converted either to product A (by enzyme  $E_1$ ) or to product B (by enzyme  $E_2$ ). The rate of these conversions depends on regulators  $R_1$  and  $R_2$ , which are injected from the outside and serve as input signal molecules. A and B, in turn, are converted to D by enzymes  $E_3$  and  $E_4$ . This decay is cross-activated, with B enhancing the decay of A (by activating  $E_3$ ) and A enhancing the decay of B (by activating  $E_4$ ). Additionally, C has inhibitory effects on  $E_3$  and  $E_4$ . D is finally converted back to C by  $E_5$ . The input signals are provided by regulators  $R_1$  and  $R_2$ , including their locations relative to the locations of the enzymes (which for the present run were fixed).

As illustrated in Figure 4, 12 macromolecules were distributed in a cubic simulation space consisting of  $30 \times 30 \times 30$  elementary cells. Enzymes  $E_1$  to  $E_4$  were present in equal numbers (2 of each) and each were

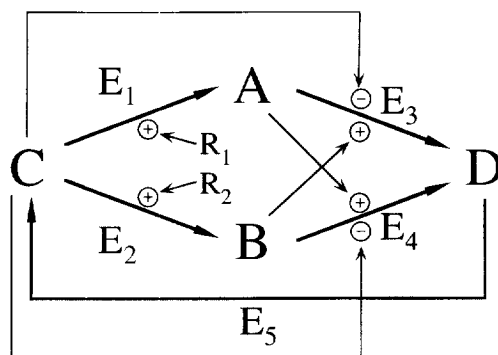


Figure 3 Cyclic competitive reaction scheme. The scheme is used to illustrate the operation of the CKSD simulator. Enzymes  $E_1$  to  $E_5$  are distributed asymmetrically in the simulation space (see Figure 4)

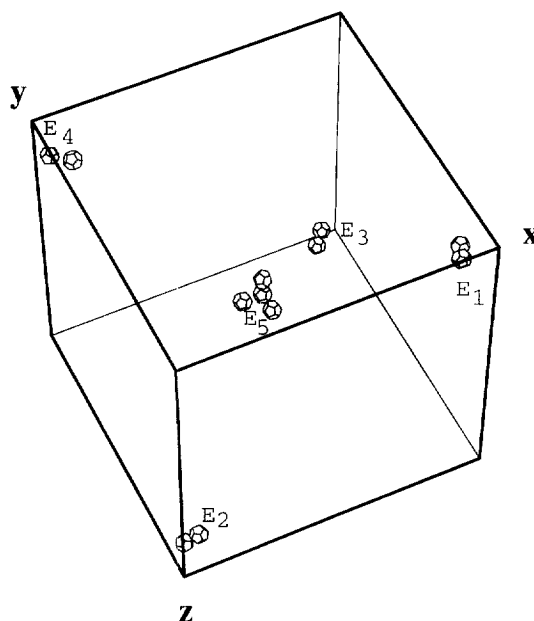
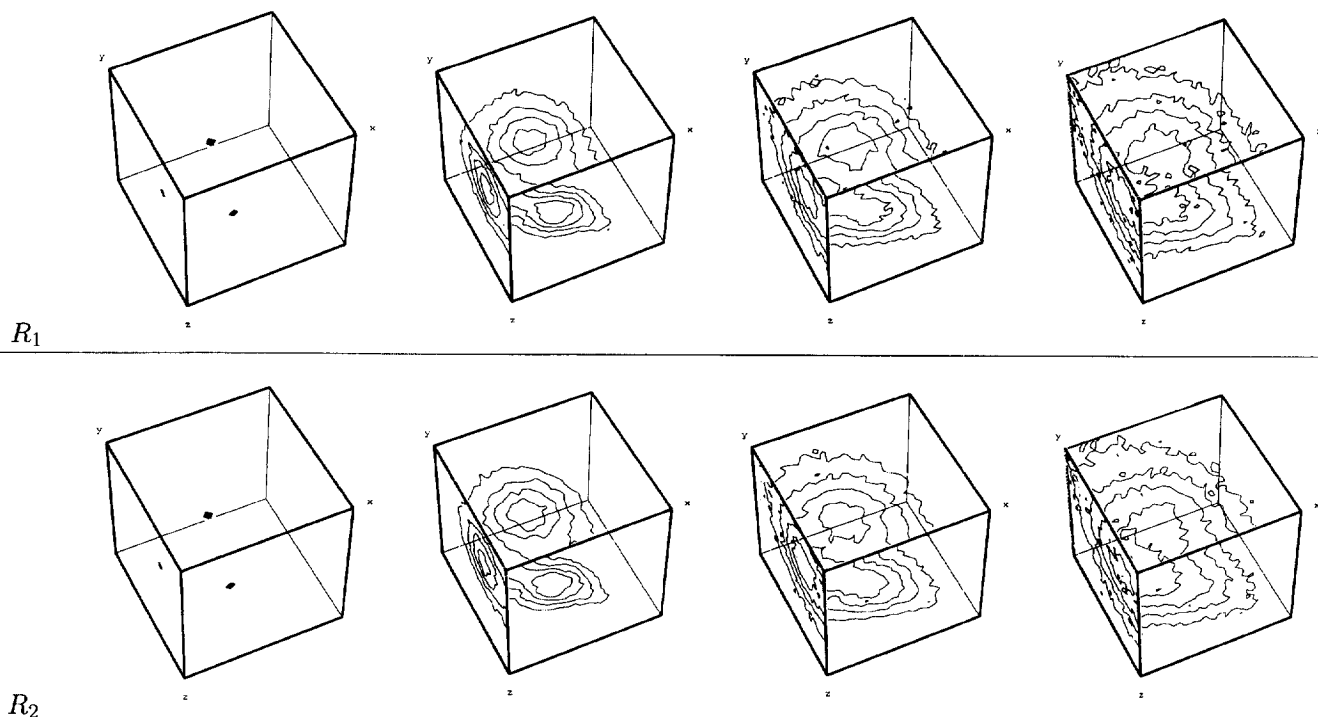


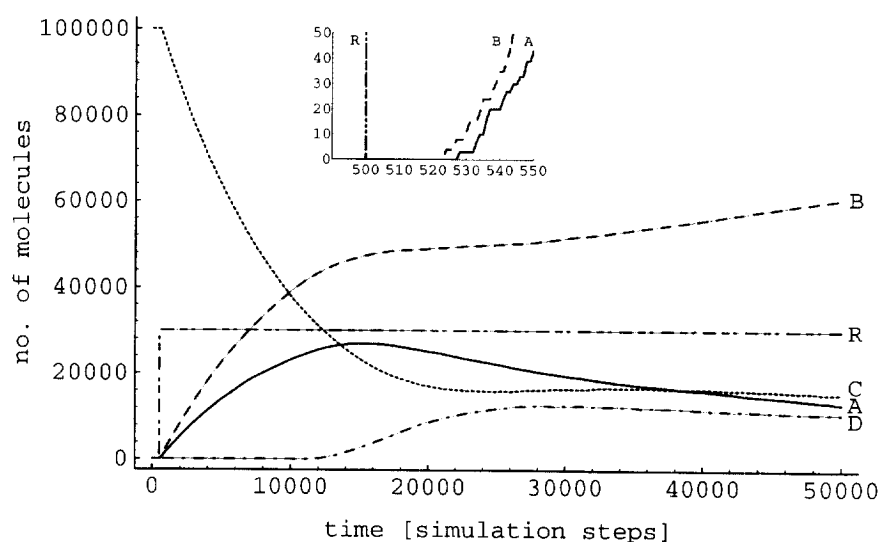
Figure 4 Asymmetric immobilization of enzymes assumed in the simulation of the reaction scheme illustrated in Figure 3

immobilized at different corners of the space. Four molecules of  $E_5$  were present and immobilized in the center. The distribution of macro-molecules in the space is thus inherently asymmetric. Of the substrate molecules initially only C was present (at the level of  $10^5$  molecules). The first 500 time steps of the simulation allowed C to diffuse uniformly throughout the space. The input signal molecules  $R_1$  and  $R_2$  were then introduced, in each case at the level of  $3 \times 10^4$  molecules. As shown in Figure 5 they were introduced at loci nearer to  $E_2$  than to  $E_1$ . Thus the context of  $E_2$  changed earlier than that of  $E_1$ . The time development of the spatial distribution of the regulators is also presented in Figure 5.

Figure 6 illustrates the global time development of all microcomponents. The input signal molecules  $R_1$  and  $R_2$  are the only milieu molecules in the present scheme whose concentrations are not controlled by the action of enzymes. The important feature to note is that the initial spatial asymmetry in the locations of  $R_1$  and  $R_2$  relative



**Figure 5** Time development of input signal concentration gradients. The input signals ( $R_1$  and  $R_2$ ) are injected at time step 500. Each cube represents 4D information about the distribution of one component of the milieu at a given point in time. The sequence of cubes in a row represents the time development of that component. Each cube face is a contour map of the concentration of either  $R_1$  or  $R_2$  projected onto this face. The projections are made by summing all the concentrations along lines perpendicular to the face. The contours connect points of equal value



**Figure 6** Time course of the total number of microcomponents of each type in the simulation space. The sampling rate is every ten time steps. The insert shows the time lag (due to diffusion) between the injection of the signal molecules and the appearance of  $A$  and  $B$ .  $R$  represents both  $R_1$  and  $R_2$  (since these are present in equal numbers)

to the enzymes, though rapidly eliminated by diffusion, leaves a trace by being converted to an asymmetry in the global concentrations of  $A$  and  $B$ . In effect, an initial short lived spatial asymmetry leading to a small time difference in activating  $E_1$  and  $E_2$  is amplified to a global macroscopic effect.

Let us now look at these runs from the point of view of the cyclic interactions among context, conformation, and catalytic action. The context of an enzyme comprises all

the influences that the enzyme fuses to yield its conformation and consequent function. The context of enzyme  $E_1$ , for example, consists of  $C$  and  $R_1$  molecules in its local environment. The number of  $R_1$  molecules is globally constant subsequent to being introduced into the simulation space, but the number in the immediate neighborhood of  $E_1$  changes as a result of diffusion and, after equilibration, as a result of fluctuation. The same is true for the context of  $E_2$ . The asymmetry observed in

Figure 6 between *A* and *B* is due to the fact that the context requisite for the catalytic action of  $E_2$  developed slightly faster than that for  $E_1$ .

#### TOWARDS ADAPTIVE INFORMATION PROCESSING

The example reaction scheme considered is extremely simple relative to nature and actually also simple relative to what the CKSD simulator can handle. The extent of context sensitivity did not exceed three influences on any given enzyme and structure formation through self-assembly did not play a role. The simulator is capable of handling cases that are much more complicated in these respects. The example presented, however, serves to show that even very simple biochemical reaction schemes can be viewed in terms of a cyclic interaction between context and enzyme action. The action of the enzyme and the context that results from and controls this action forms a self-consistent field. The input signals  $R_1$  and  $R_2$  are processed by this self-consistent field dynamics. Suppose we add an external feedback loop that provides an error signal based on an external evaluation of the network's response to these signals and that this error signal acts on the structure formation characteristics of the network (e.g., modifies the immobilization asymmetry). The self-

consistent field dynamics will then change. Our working hypothesis is that this should provide the basis for an adaptive response<sup>8</sup>.

#### ACKNOWLEDGEMENTS

This research was supported by NSF Grant No. ECS-9704190.

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