BIOMEDICAL MODELLING and simulation
J. Eisenfeld and D.S. Levine (editors)
J.C. Baltzer AG, Scientific Publishing Co. © IMACS, 1989
pp. 65-67

MICROCOMPUTER MODELING OF SELF-ORGANIZATION IN BIOLOGICAL SYSTEMS

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Abstract

A new class of models, called Movable Finite Automata (MFA) models, for simulation of self-organization of biological systems on microcomputers is described. Their use in simulating the interaction of protein molecules in the self-assembly and operation of the T4 bacteriophage is described.

Introduction

Living systems are quite complex; understanding them requires experimental investigations which yield concrete results about specific cases and modeling to generalize these results.

Computer simulation models involve the creation of an artificial system on a computer which displays a behavior close to that of the real system. They are simply a convenient way of expressing general principles in a fashion which is (1) precise, since the symbols in the computer language have precise defined meanings, and (2) complete, since if essential steps or features are omitted from a computer model, it won t work. They require a scientist to think and communicate as clearly as possible. Computer models allow easy, rapid, inexpensive, and controlled experimentation in order to infer properties of the real system. They enable one to design alternate systems capable of performing better or different functions. In some cases, computer models also serve as theories in biology and in others they are the only means of thoroughly testing and examining a large and intricate theory.

Biological systems have a great richness of behavior, which needs to be modeled and understood. However, there is one aspect, the phenomenon of self-organization which is more amenable than others to successful computer modeling. This paper is devoted to the computer models of self-organization. We will summarize a new class of models, the Movable Finite Automata (MFA) models, for studying self-organization and discuss a specific model for T4 bacteriophage assembly and operation; the details can be found elsewhere [1-2]

T4 Bacteriophage Assembly and Operation- Biophysical Background

Bacteriophages (or simply phages) are viruses which infect bacterial cells, take over their replicating mechanisms, and use them to generate more viruses [3]. T4 bacteriophage infects the bacterium *E-Coli* strain B. It consists of an elongated icosahedral head, formed out of protein, and filled with DNA (Fig. 1). It is attached by a neck to a tail consisting of a hollow core surrounded by a contractile sheath and based on a spiked end plate to which six fibers are attached. The spikes and fibers affix the virus to a bacterial cell wall. The sheath contracts, driving the core through the wall, and viral DNA enters the cell.

Extensive investigations into the phage assembly process have led to the pathway as shown in Fig. 2. These investigation suggest that the following principles are involved in the assembly: (1) *Subassembly*- assembly of subunits in stages as in an automobile assembly; (2) *Minimization of Thermodynamic Free Energy*; and (3) *Sequential Assembly*-in a specific temporal order or pathway (e.g., the sheath subunits must not associate with one other until the tube-baseplate is assembled and is ready to receive them; likewise, the head-tail connector must not attach to the tail until the sheath is assembled around the tube). The controls required for specific assembly appear to be built into the structural proteins themselves, and seem to be achieved through *conformational switching*. (According to this idea, proteins C and B may not bond together until B has combined with another protein A. This is achieved by a conformational change in B which occurs when it combines with A, and which makes it able to combine with C. This will lead to a sequence ABC of formation and not any other sequence.)

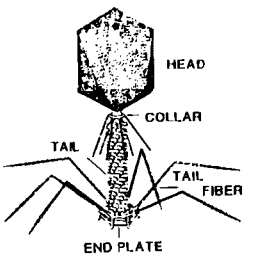

Fig. 1. A Diagram of the Structure of a T4 Bacteriophage.

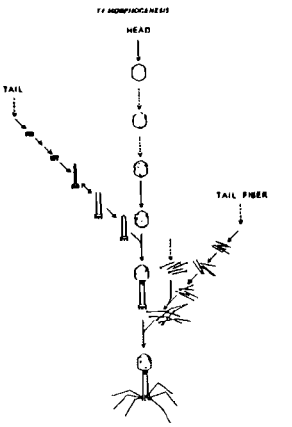

Fig. 2. The Pathways of T4 Bacteriophage Assembly.

MFA Model for T4 Phage

The Movable Finite Automata (MFA) models are based on the Cellular Automaton Models [4]. In general, such a model consists of an array of simple automata situated at the sites in a one, two, or three-dimensional lattice of integers. The automata all obey the same rules, each one can be in one of a finite number of different states, and each one changes its state in accordance with information obtained from the automata which are its immediate neighbors in the lattice.

These models have the advantage that they can be readily analyzed and simulated on microcomputers [5], but have the disadvantage that they lack any physical realism. MFA models are similar to cellular automata models but are endowed with rules of operation that mimic as closely as possible some of the key biophysical principles governing the interaction of biological macro-molecules, cells, and other natural subunits. The key feature allowing for greater biophysical realism in MFA models is that the automata are allowed to move about and interact with one another.

Any of the movable automata can have a number of bond sites x on its perimeter. All parameters in the model are integers, including the position coordinates of bond sites and the size of the

automata. Each bond site x is associated with a bond site number b(x), which defines how that site will interact with sites on other automata.

In one specific form, b(x) consists of three parts: b(x) = L:VV:II. Here L denotes the bond length which is allowed to take on two values, 0 and 1, to simulate the stretching and compression of a bond between two molecules. VV denotes an arbitrary scale of "strength" for the site. A high value of VV for a site indicates that a bond formed at such a site will be strong. II provides a label for the configuration of the site and is used to determine whether or not two sites have "complementary" configurations, thus allowing them to form a bond. This label for a bond site may change due to changes in the configuration of other sites on the molecule (caused by the formation or dissolution of bonds). This change in label is introduced to emulate the conformational changes occurring in one part of the subunit as a result of changes made in another part (conformational switching).

The following assumptions are made about the interactions between two automata: (1) Two automata cannot overlap one another, and they generally repel each other in proportion to the area of direct contact. (2) Two bond sites on different automata can form a bond only when the two sites are directly opposite one another on facing surfaces. For two sites x and y, if b(x) = b(y), a strong bond of strength 4VV will be formed. A bond can also be formed if b(x) and b(y) differ by 1 but it will be a weaker bond, of strength 2VV. On the other hand, if they differ by 2 or more, no bond will be formed.

With these rules two sites can bond only if their bond lengths (L) and site strengths (VV) are identical, and their configuration labels (II) do not differ by more than 1. The key justification for this assumption is that the affinity for bond formation between two subunits depends on how well their shapes match (the lock-and-key concept).

Figure 3 illustrates the operation of these rules. There, four subunits are represented by two-dimensional boxes, and bond sites are indicated by

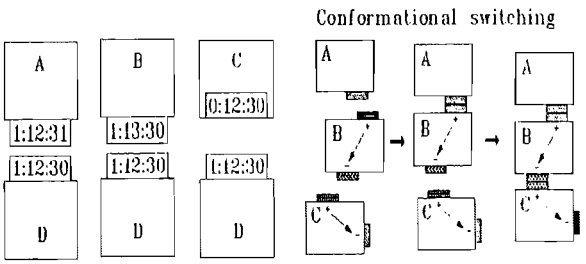

Fig. 3. Illustration of Subunit Bonding Rules. See text.

Fig. 4. Illustration of Conformational Change Rules. See text.

rectangles containing values of L:VV:II. These rectangles lie outside of the subunits in the case of bonds of length 1 (L=1), and they lie inside in the case of bonds of length 0 (L=0). According to the rules, A and D can form a bond of strength 24, whereas neither B and D nor C and D can form bonds.

Figure 4 illustrates the rules for conformational change. Here the bond site numbers b(x) are represented by different hatching patterns. Initially A and B are able to form a half strength bond, but B and C have no affinity for one another. Once the bond between A and B has formed, the upper bond site on B undergoes the change b(x)-->b(x)+1, bringing the A-B bond to full strength. This change in the upper bond site causes the lower bond site to make a corresponding change of the form b(y)-->b(y)-1. As a result, B and C are able to form a half strength bond, and similar conformational changes occur in the bond sites of C.

A total configurational energy U is defined for the complex of all subunits. This consists of the sum of all repulsions minus the sum of the strengths of all bonds which have formed in accordance with the bonding rules. Subunits are allowed to move and interact with other subunits. However, changes in the total complex of subunits are allowed only if they do not result in an increase of U (free energy minimization). This fully defines the dynamics of the model.

The MFA models can be used to simulate on a microcomputer and display in color the self-assembly of a phage-like entity from its components. A few steps in the self-assembly of an artificial "phage" are shown in Fig. 5. Here, for simplicity, we have made the following assumptions.

(1) All subunits are boxes with rectangular sides and fixed shapes. Also, the simulated bacterial cell wall, is an array of rectangular boxes that tend to stick together to form a flexible sheet.

(2) The phage neither possesses the head capsule nor the neck, which is needed to attach the head to the tail. The main function of the head is to store the DNA molecule, and to channel it into the tail tube after the tube has penetrated the bacterial cell wall. To simulate this function, a standardized test molecule is introduced, which will be injected through the cell wall. (The self organization of the head is not well understood, and seems to be much more complex than that of the tail that we are considering.)

(3) The phage does not possess flexible tail fibers. Thus, the initial attachment of the fibers to the cell wall and their bending to allow base plate attachment to the cell wall are not simulated. Instead, the base plate is allowed to make direct

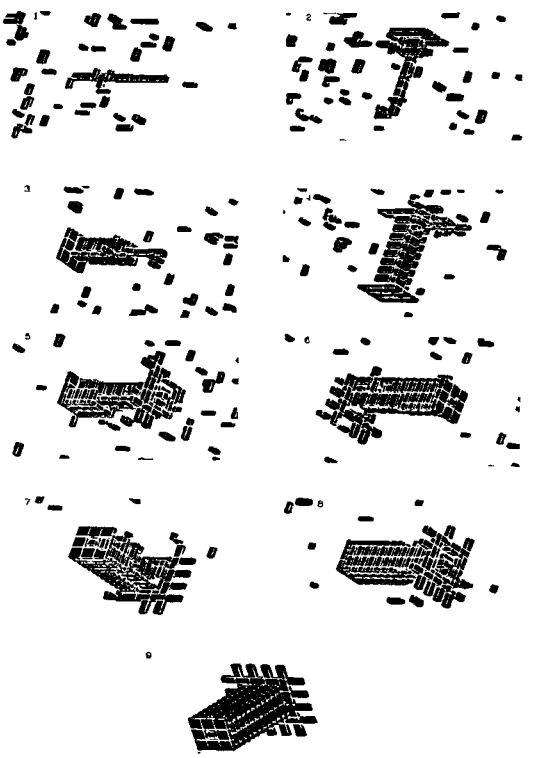

Fig. 5. Computer Generated Graphics Representing few Successive Stages in the Self-assembly of Phage.

contact with the wall.

As indicated in Fig. 5, it is possible to characterize the bonding sites on each of the subunits so that the phage will self-assemble. In addition, the attachment of this phage to the cell wall triggers conformational changes which propagate through the body of the phage, forcing the central tube to penetrate the cell wall and release the "DNA" test molecule on the other side of the wall. A few stages in the penetration process are shown in Fig. 6. Thus the basic rules used to specify self-assembly can also ensure that the assembled phage will carry out the operation it is supposed to perform.

Concluding Remarks

In this paper we have presented the Movable Finite Automata (MFA) models for simulating living systems on a microcomputer. We used these models to simulate bacteriophage assembly and operation. Elsewhere [1] we have used these models to simulate the elongation cycle in the protein biosynthesis. Although models of this kind cannot represent molecular interactions on a detailed biophysical level, they can faithfully represent the logical steps in the conformational that governs the behavior of macromolecular complexes in biological systems.

The model for phage by no means represent the biological systems as realistically as one would like. With sufficiently realistic computer models, one can study the effects of design changes either by (1) simply running the model's program for different designs, or (2) by performing a general mathematical analysis of the model. Such investigations can be useful in studying the origin and evolution of biological systems, since this is a field where general theoretical principles play an essential role. The question: can we devise computer models which are sufficiently realistic to be applicable to such general studies? To answer this, it is necessary to pursue both model building and experimental research in parallel. We are optimistic that the answer will be in the affirmative.

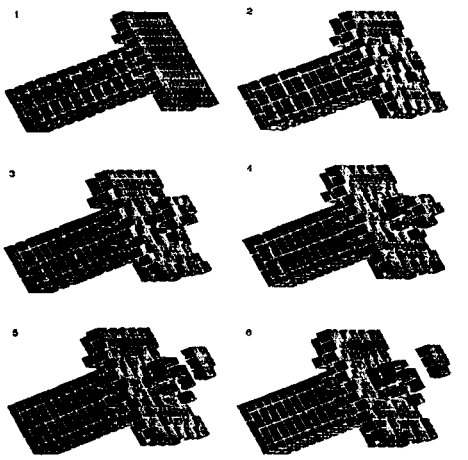

Fig. 6. A Few Stages in the Penetration of the Simulated Cell Wall by the Phage of Fig. 5. A Section of Cell Wall is Represented by the Grid of Boxes.

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