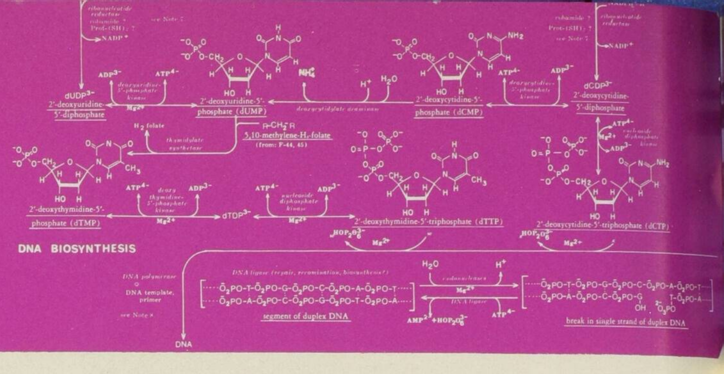
# Computer model of the cell— A program for life




How could a computer be programmed to act like a living cell? How could a mass of electrical circuitry, transistors, metal and glass simulate the myriad of interlocking chemical reactions that characterize the protoplasm, the inner fluids and structures of the cell? Not only are there many hundreds of chemical processes taking place continuously, but they all intermesh to maintain the cell in a state of dynamic equilibrium, a condition of balance determined by sophisticated feedback mechanisms governing the levels of the various chemicals. Who would presume then that mere machinery could simulate this incredibly complex substance, this manifestation of the vital phenomenon in nature?

Well, an engineering professor at the University of Toronto, for one.

Professor E.J. Davison of the Electrical Engineering Department has worked out a computer program that simulates the steady state behavior of a cell as it grows and divides through normal stages from one generation to another. Though in itself this is a feat worthy of note in the control systems field, it is superseded in importance by the second stage of his work. By tinkering with the internal dynamics of the computer model of the cell, Dr. Davison caused it to change (or mutate) into a larger, faster growing system that appears to mimic cancerous growth. Further, his model is sufficiently exact that he can look into the maze of interlocking molecular machinery and pinpoint the precise chemical change responsible for the conversion to the malignant state.

Dr. Davison is the 1974 recipient of the E.W.R. Steacie Memorial Fellowship, awarded each year by the National Research Council of Canada to a young scientist who has distinguished himself in a particular field of research. Dr. Steacie was President of NRC from 1952 until his death in 1962. At present Dr. Davison is a leading authority in linear control theory, a field that translates at the practical level into mathematical models that describe the behavior of such physical systems as rockets, aircraft, nuclear reactors, and the various production systems of industry.

Mathematical modeling has been in use for years in the engineering sciences, but it has never been applied to a problem as complex as that posed by the chemistry of life. Linear control theory tends to be an abstract field, far removed from the down to earth, practical research of cell biology, but Dr. Davison has been able to bridge the gap between these two diverse disciplines.

"The motivation for the study," says Dr. Davison, "lay in the fact that these mathematical models have been shown to work beautifully in their simulation of the real world. Take the flight of the Mariner spacecraft to Mars as an example. The mathematics predicted the precise path the probe would take as it flew by the planet, and sure enough, observations demonstrated that the actual trajectory correlated well with the computer model."

Though mathematical modeling may sound like an esoteric subject that lies beyond the reach of the average man, the principles involved are actually quite straightforward. The structure of the mathematics is simply arranged to correspond with the physics of the system being considered. In describing a rocket and the nature of its flight, for instance, the observer has a great deal of information at his disposal. There are characteristics such as the rocket mass, the thrust generated by fuel, the gravitational force of the Earth, the angle of flight and so on. There are also the experimental laws of physics such as the conservation of mass, energy, and momentum, and Newton's laws of motion.

"One simply applies these laws to obtain a mathematical model of the rocket", says Dr. Davison. "A series of ordinary differential equations are set up, one for each of the characteristics listed, and fed into a computer for solution. The resultant model is then compared with the real physical system to see how well its predictions correlate with the rocket's behavior. Usually you start with a relatively simple model which does not correlate well, and increase its complexity (by taking more characteristics into account) until the input-output data agrees with the experimental set-up. For example, an additional characteristic that could be included in this model to increase its precision is the moon's gravity; though not a force that would significantly alter atmospheric or earth orbital flights, nonetheless it has some small effect on the real system."

Attempting to describe the workings of a cell in the same manner is much more difficult because of the far greater complexity of the system. Since Dr. Davison was interested in simulating a cell actively growing and dividing, he confined his description to the chemistry of the nucleus, the site of the reproductive events in cell division. As a cell matures from the daughter stage — the beginning of its creative life — the levels of the various constituent chemicals, both in the nucleus and the surrounding cytoplasm, increase until growth stops and division occurs. The process then recurs in the new generation and so on.

"The criterion we imposed on the model system was as follows," says Dr. Davison. "From the daughter stage to the mature parent cell about to divide, our hypothesis was that all chemical constituents of the nucleus, such as proteins, nucleic acids, lipids and sugars, double their mass. That way the contents of the next daughter generation will be exactly the same as the original (one parent gives *two* daughter cells) and a steady state system will be maintained. After preliminary tests, it was decided that, in order to achieve a model that satisfactorily simulated a living system, at least 19 chemical levels, or characteristics, would have to be described by the mathematics. Comparing this number to the seven or eight characteristics used to describe a rocket system gives some idea of the complexity involved in cellular chemistry. Now, the problem we faced was that these levels are maintained by over 100 known chemical reactions in the nucleus, and few if any of the quantitative factors (rate constants) that determine how fast these chemical reactions occur are known with any accuracy. Though much is known of the cell nucleus in a qualitative sense, very little is known of the quantitative relationships between these cell constituents."

The general form of the mathematical model constructed by Dr. Davison was a set of differential equations embodying the 100 unknown rate constants and describing the changes in the various chemical levels with respect to time. The computer was instructed to arbitrarily assign values to the rate constants and to begin solving the equation, observing all the time intervals from the beginning to see if there was a point when all 19 levels were double their original or daughter stage values. When the