Dr Edward Davison examines readout material associated with his computer-simulation of the living cell. • Le Dr Edward Davison examine des résultats de la simulation de la cellule vivante à l'aide d'un ordinateur.

computer recognized that the cell was not doubling up, that it was not in fact behaving like a cell, it then rejected these rate constant values and chose another set. The problem with this trial and error approach however was in the astronomical number of possible sets involved. It would have taken the world's largest computer literally thousands of years to complete the job.

"Instead of leaving the search purely to chance then," says Dr. Davison, "a sophisticated search technique (appropriately called the Monte Carlo procedure) was employed to narrow the field of possibilities. The procedure, which amounts to imposing restraints on the problem while at the same time allowing the computer to do the search as automatically as possible, took over two years of computation and interpretation on an IBM 370, one of the largest computers in Canada. In the 100 or so hours of machine time used, the computer examined millions of rate constant sets before finding the one that fulfilled the requirements of the doubling-up criterion.

The successful model arrived at by the computer contained a set of chemical rate constants that resulted in all 19 characteristics doubling their mass at the same time after initiation of the cell's 'life'. The chemistry of the living, growing nucleus had thus been emulated, at least insofar as it satisfied the basic hypothesis. (Although there is no direct experimental justification for this doubling-up criterion, it is a simple and reasonable assumption in cell division, an area of biology that is not well understood). The acid test for the cell model, as for the rocket, was in how well its performance agreed with the living system.

Though most of the published data in this area is qualitative (there are few quantities available) Dr. Davison's search of the literature showed that the experimental output of the biologist correlated well with the mathematical output of the cell model.

"If living cells in a culture medium absorb too much iron for example," says Dr. Davison, "experiment shows that they will die. Similarly, if the computer model is 'fed' too much iron the steady state is disrupted very quickly and it dies too."

Satisfied that the computer cell was a good simulation of the real thing, Dr. Davison then began introducing disturbance into the model to see how it would react. By varying the rate constants or the chemical levels of the normal system, (that is, by disturbing it) he hoped to learn something of its flexibility and perhaps the answers to some basic biological questions.

What alterations would lead to cellular death? What, if any, were the changes that would result in mutation?

"It turned out that almost every disturbance of the model resulted in death," Dr. Davison says. "Of the multitude of alterations imposed on the cell over an entire year there were only four cases in which death did not occur, and it turned out that these four alterations were simply different ways of effecting the same specific change in the nuclear chemistry."

Instead of dying, the cell swept through a transitional stage and emerged in a new steady state that was two to ten times larger and grew at a rate that was about five times faster than the 'nominal' or normal cell. The energy requirement of this new 'fast' cell was considerably larger than the nominal and it was extremely robust in the sense that most disturbances would not kill it. Further, the opposite disturbance to the one that initiated the change had no effect on the mutant. Large, robust, and distinguished by rapid growth — it had all the earmarks of a cancer cell.

"In each of the four cases, the change that caused the 'malignancy' was in the rate constant of a chemical reaction contributing to the synthesis of messenger-RNA." says Dr. Davison. "This substance acts as a template or pattern for the synthesis of protein, a vital building material in cell growth. The shift itself was not very large, but as the cell continued to divide the effect accumulated until the originally small error had become very significant by the fourth or fifth generation. When the transition was over and the 'fast' cell steady state was attained, a return to the normal rate constant did not lead to a reversion to the nominal state.

"What was really surprising was that there were not other chemical changes that would cause the transition. It appeared that this disturbance of messenger-RNA synthesis was the only alteration that would effect the transformation to malignancy."

This work has generated such interest that university groups from Cambridge in Britain and Princeton and Berkeley in the United States intend to test predictions of the model in the laboratory, hopefully in a quantitative manner. A basic problem in comparing the living system with the computer model of the cell is in the correlation of real external effects such as cosmic radiation or toxic agents with the variation of the parameters in the model. The precise effects of these outside stimuli on the inner cell are simply not well known. How, for example, does a blast of radiation affect the internal chemistry? What is the mechanism whereby a cell's neighbors shut down its reproductive machinery? A knowledge of these effects would make the computer model a very powerful tool in biological research, allowing experimenters to do work in seconds on the machine model that would take months in the laboratory.

One of the reasons that cures for the various types of cancer have been so long in coming is a lack of knowledge concerning both the causes of the disease and the preliminary steps that lead to the condition. Science must have a handle, a grasp of the disease's cause and mechanism, before effective cures can be considered. Dr. Davison's model may not only help to elucidate the primary chemical steps involved, but give some idea of what cancer actually is as well.

"The structure of the model is that of a cell without contact with the outside," says Dr. Davison. "The description is of the nuclear chemistry alone, and none of the interactions between the nucleus and the cytoplasm or between neighboring cells are considered in the model. The model's behavior therefore suggests that cancer is a very basic property of the cell, that it moves into the malignancy mode in a spontaneous manner when exposed to certain types of disturbance." □

Wayne Campbell