CELL KINETICS AND CELLISM

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In the field of cell cycle kinetics there have been a number of computer simulation models that have been developed and reported in the literature (1), (2), (3). However, this valuable tool is often not applied in this area because of two basic problems:

(1) The cell biologists who are engaged in cell kinetics research usually do not have the computer background required to develop these programs. Thus, in most cases, if they desire to use computer simulation they must communicate their models to a computer programmer, who usually does not have a biological background.

(2) Because most cell models assume rapid cell proliferation, a large amount of computer memory is required to store the information on the ever-increasing number of cells in the models. The alternative is to only simulate a short time frame and this reduces the usefulness of the model.

CELLSIM is a cell kinetics simulation system which is intended to solve these problems. The user interfaces to the system through a simple problem-oriented language which uses the conventions and the vocabulary common to the cell biologist. Therefore, a cell biologist should be able to develop his own computer simulation models after very little instruction. An added dividend to the use of this language is that the assumptions and the logic of the model are apparent to other researchers who examine the program. This is not true of the simulation models that have been developed to date using a variety of computer languages. This simulation system uses a number of built-in collection algorithms that automatically re-group and re-assign cells when the cell population approaches the memory limit of the computer system on which it is being run. These algorithms have been designed so that they have a minimum of disturbance on the models being simulated. Thus a researcher can simulate a cell model for any length of simulated time without concern for exceeding memory limits.

A sample program written in CELLSIM is shown below:

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CELL TYPES HELA;
STATES(1) G1,S,G2,M;
FLOW(1) G1-S(ALL),
        S-G2(ALL),
        G2-M(ALL),
        M-G1(ALL);
TIME IN STATES(1)
        S:NORMAL(10,2),
        G2:NORMAL(3,.6),
        G1:NORMAL(5,1),
        M:NORMAL(2,.4);
PROLIFERATION(1) M:2;
INOCULUM(1) 1000;
REPORTS 1 HOURS;
GRAPH TOTAL,
      M(1)/TOTAL;
SIMULATE 60 HOURS;
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In this program the user is simulating a cell population that he names HELA. He identifies the states in his model G1, S, G2, M. He then describes the flow in his model. All cells that leave state G1 go to S, all cells that exit S go to G2, etc. He describes how long the cells are to spend in the various states. In S, for example, the time is to be a random variable from a normal distribution with expected value 10 hours, and standard deviation 2 hours. The proliferating state in the model is M, and the proliferation rate is 2.0. The initial inoculum in the cycle is 1000 cells. The system is to report on the status of the model at every hour of simulated time. There are to be two graphs produced, the first a graph of the total number of cells in the model, and the second a graph of the proportion of the cells in the M state. The simulation is to run for 60.0 hours.

The user has other commands available which are able to simulate the effect of drug or radiation treatment on a cell population. These commands kill cells, block their movement through the cycle, or transfer them to some other population. The user can also alter the initial parameters in his model at any later point. The language has been used on a wide variety of cell kinetics experiments (4). It is an easy to learn language, and cell kinetics researchers with no previous computer background have been able to write their own programs after two hours of instruction.

The CELLSIM interpreter has been entirely written in FORTRAN IV so that it may be implemented on most computer systems. A user's manual has been prepared to assist in learning the language (5).

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