Cell Kinetics in Human Acute Lymphoblastic Leukemia: Computer Simulation With Discrete Modeling Techniques

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A model for cell kinetics of human acute lymphoblastic leukemia has been constructed with discrete modeling techniques for computer use with the GPSS/360 computer language. The model has produced results corresponding to observed biological data. It has been possible to explore mechanisms for control of the growth of the leukemic cell population. In addition to the flow of cells from the resting to the proliferative phase, two other important parts of the cell life cycle, cell death and the intracellular events after mitosis, were identified as potentially important regulatory mechanisms. Chemotherapeutic drug effects could be simulated, and in the case of vincristine an unsuspected effect was suggested. This effect of vincristine on transformation of the resting cell to an active proliferative phase has been supported by studies of vincristine effect on blast transformation of phytohemagglutinin-stimulated lymphocytes. A single cell was found to take 3 1/2 yr to grow to a population of $10^{12}$ cells, a clinically recognizable number. Although this observation cannot be confirmed from biological studies, this time has an interesting correspondence to the peak incidence of acute lymphoblastic leukemia in childhood. It indicates that a mutational event in a single cell could account for the leukemic process in childhood acute leukemia.

There has been a considerable growth in our knowledge of the life cycle and proliferative characteristics of the leukemic cell population in human acute leukemia. Sufficient understanding has now been derived from these studies of cell population kinetics to begin design of treatment regimens based on the in vivo effect of chemotherapeutic agents. Further enhancement of our ability to use currently available agents in the most effective manner and to plan for the development of other methods of treatment can be expected as more knowledge of the leukemic cell population and its responses accumulates.

As in other types of investigations, however, more questions as well as some answers have resulted from analysis of the studies to date. It, therefore, became desirable to develop a computer-simulated model of leukemic cell

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kinetics as one method of expanding our understanding of the problems, testing working hypotheses, and assisting in the design of new experiments.

Computer-based models of biological phenomena have served many useful purposes. Perhaps the most important advantage of a model is that it can provide a conceptual framework for seeing interactions and relationships that may be very complex. Often the very act of design with its need to specify the features and relationships to be modeled sharpens the thought processes involved and reveals questions that had not previously been clearly stated.

Once the model is completed and compared for validity with known biological information, it can provide a means for testing various hypotheses in a convenient and safe way. A computer-conducted experiment, for example, may be far less costly in time and materials than the corresponding biological experiment. Several computer based investigations may be done to identify the one significant biological experiment with the best chance for obtaining definitive data. In this manner, unproductive biological experimentation may be avoided. Parenthetically, there should be no need to emphasize the obvious necessity for biological experimentation to provide check points on computer simulation.

Discrete modeling concepts were used in the formulation of the computer simulation model for leukemic cell kinetics. This type of model had the advantage of providing easily recognizable correspondence between the transition of cells from one stage of the mitotic cycle to the next and the components of the computer language on which the simulation was programmed. This approach also allowed for convenient inclusion of statistical descriptions of the time delays experienced by cells during their passage through the mitotic cycle. The cells could also be routed to alternate phases of the cell cycle in a random manner closely corresponding to their actual behavior.

The purpose of this paper will be to describe the background information used in the construction of the model, the development of the model itself, and the results of some explorations of leukemic cell kinetic behavior with the computer simulation process. Some important areas in which further biological information is needed have been identified and these problems for future research will be discussed.

BACKGROUND KINETIC DATA

It was necessary to have information concerning the time requirements for completion of various phases of the mitotic cycle by the leukemic cells in order to construct a discrete form of a computer-simulated model. Also needed was the proportion of cells distributed in these phases. This information was available from several sources and had been obtained primarily by in vivo and in vitro studies with tritiated thymidine.1-4

There is some variability in these reports in the time requirements for mitotic cycle phases. There is even more variability in the proportion of cells distributed in the various phases, not only from patient to patient,
but even in the same patient during different phases of his disease. Therefore, the model was constructed with time and distribution factors characteristic of a representative patient. Alteration to fit any of the described kinetic patterns could be easily accomplished.

Based on information derived from studies with tritiated thymidine-labeling in vivo, the following times for the various phases of the cell cycle were assigned; DNA synthesis (S), 20 hr; postsynthesis rest phase (G2), 2 hr; mitosis (M), 2 hr; the interphase between M and S (G1), 35 hr. A proportion of the cells after mitosis return to the cell cycle, and the remainder enter a resting phase (Go). The cells in Go retain their capacity for returning to active cell division after a variable period of time. Other aspects of the leukemic cell life cycle were added as the model developed. For the construction of this model, the cell population was described as that type seen in acute lymphoblastic leukemia in which no maturation or differentiation occurs. The portion of the leukemic cell population that was simulated was that characteristic of the bone marrow at the time of diagnosis or in full relapse.

CONSTRUCTION OF THE MODEL

Previous efforts at modeling the dynamic behavior of cells in the mitotic cycle and the more general problem of cell population dynamics have been through the use of differential equations, because of the prevailing view that all such problems are essentially “rate problems.” If, however, realistic representations of the stochastic nature of the variables are introduced into such models, the resulting equations are either difficult or impossible to solve. With analog computers, answers to some of the more difficult differential equations may be obtained, but even analog computers become awkward to use when time-delayed functions and statistical distributions are required for the description of the model.

To achieve better simulation of leukemic cell kinetics, therefore, a discrete modeling technique was chosen with the use of the computer language GPSS/360. Discrete modeling techniques were developed to simulate systems usually studied under the heading of operations research. Examples of such systems for which this method has been useful are manufacturing processes, aircraft landing systems, data flow in a computer system, and studies of the movement of traffic on highways or shopping in a supermarket. Sophisticated computer languages have been developed to aid in the study of these systems.

Characteristic of each of these systems is the fundamental unit of activity called a ‘transaction.” Transactions may move about in the system under constraints imposed by the system. For example, an automobile may traverse a superhighway system making some random choices of exists, turns or entries into the system but always under the constraints of the speed of adjacent cars, traffic lights, intersections and the general routes available in the highway network.

As our attempts to design a computer-simulated model of leukemic cell
kinetics progressed, it became evident that this discrete modeling system would also be highly appropriate to the biological system as well. There was a close correspondence between cells and transactions—the passage of time and movement in space. The creation of two cells from a single cell in mitosis was analogous to the “splitting” of a transaction in a discrete model, which results in the production of two identical copies. The delay of cells in the various phases of the mitotic cycle corresponded to the delays often required in the discrete models. Furthermore, the computer language provided a means of assigning individual values for the delay from a population of possible values having user-specified distribution functions. In this manner, biological variation could be reproduced. Death of cells could be modeled by removal of transactions from the system at any desired location and at any desired rate by a terminate operation.

A schematic representation of the model is shown in Fig. 1. Each of the phases is designated by a large circle and marked according to the phase represented. The time delays chosen for each phase are shown beside each compartment. Twenty hours was chosen for the S phase delay without any variation considered. Other phases were given the illustrated variation in time delays selected to provide the best fit with available information. For this model, after mitosis 20% of cells reenter the mitotic cycle and 80% move to the Go phase. Each cell entering Go was held there at least 50 hr and then released to the mitotic cycle with delay intervals up to 200 hr. Any cells with a delay after mitosis of less than 50 hr before entering DNA synthesis was considered to be in a prolonged Gi phase.

For the purpose of this model, cell death (designated T for termination) was assigned to occur in the Go phase, according to the information available from studies of animal tumors. Although little is known about this aspect of leukemic cell kinetics in human disease, cell death does occur as a significant factor in determining the rate of solid tumor growth. An opportunity was thus presented to test this possibility in a simulated leukemic cell population.

The small circles designated IC (for initial condition) indicate the me-
Fig. 2. Per cent of labeled leukemic cells in the three compartments of the cell cycle—DNA synthesis (S), mitosis (M), and resting state (G0)—as determined from computer model.

Mechanism by which each compartment of the cell cycle was filled with the proper number of cells at the beginning of the operation of the model. Thereafter, the model ran in a self-maintaining manner.

A key concept became evident in the course of producing the model. Cells traverse the mitotic cycle independently; therefore, separate models could be used to represent a population of cells that were radioactively labeled (as if flash labeled in S by tritiated thymidine) and a population of unlabeled cells. This separation of models also allowed each model to have many more transactions. Thus, better statistical properties were possible than if labeled and unlabeled cells were required to exist simultaneously in a single model where the size would be ultimately limited by the computing facilities available. When the results of the two models were superimposed at corresponding points in time, they could be portrayed as the per cent of labeled cells present in each phase of the mitotic cycle that allowed for the direct comparison with the data from in vivo tritiated thymidine studies.

The model could be simply altered in an attempt to reproduce the effects of drugs such as vincristine, cytosine arabinoside, and methotrexate, because these effects may be described in terms of additional delays, changes in death rates, or specific blocks in cell cycle movement. The changes in the number of cells in each compartment could be followed, as well as the effect on the total number of cells in the population.

Growth rates could also be studied. As an example, in one model, the development of a single cell to a projected population of $10^{12}$ cells was followed. An application of the GPSS "user's chains" was developed for this model to provide a self-scaling system, as the total population exceeded the computer capacity.

Further details of the techniques involved in construction of this discrete model with the GPSS/360 computer language are given in the appendix.

RESULTS

In Fig. 2 are shown the results of the simulation of flash labeling in vivo of cells in the S phase by tritiated thymidine. The time and distribution
Factors were set to resemble a typical patient's observed kinetic pattern. An indication of the closeness with which the computer model has simulated the appearance of labeled cells in the mitotic phase is shown in Fig. 3. Data points for labeled mitotic figures are shown in conjunction with the computer-derived curve. The number of data points that can be obtained from the patient study is necessarily limited. The comparison indicated that the model constructed for the computer did adequately reproduce the experimental data. The flow of cells into the resting G₀ compartment with subsequent equilibration between resting and proliferating cells was likewise adequately reproduced.⁵,⁶

Critical points in this model for control of population growth rates were evaluated. An obvious point for control was the modification of the flow of cells from G₀ back to the proliferative cycle. Another point was the cell death factor. The influence of elimination of cell death on population growth rates is shown in Fig. 4. With the model as shown in Fig. 1, the population of cells grew with a doubling time of 18 days, which is consistent with clinical observations. If the removal of cells was stopped, as shown in Fig. 4 at 100 hr, then the doubling time was reduced to 5 days, which is a rate too rapid to be consistent with most cases of acute lymphoblastic leukemia at the time of diagnosis. At a death rate of 62.5% of cells entering G₀, growth stopped.
Fig. 5. Influence of events occurring after mitosis and determining cell entry into Go or G1 on growth rates for leukemic cell population.

The effect of events occurring immediately after mitotic division on cell population growth rates was studied, and the results are shown in Fig. 5. For these studies, cell death was held constant at 50% of cells entering Go. The distribution of cells entering G1 and Go after mitosis was then varied from 20:80%, 50:50%; and 80:20%. The resulting doubling times were 18, 7, and 4 days, respectively.

With the model as shown in Fig. 1, a single cell was entered and allowed to grow until a population mass of $10^{12}$ cells was reached. This growth required a calculated 3½ yr to accomplish.

Models were also designed to simulate drug effects. An example for

Fig. 6. Model for representation of vincristine effect on leukemic cell population. With this model simulation of the observed events, as shown in Fig. 7, could not be simulated until an additional block in flow of cells from G0 into G1 was introduced.
vincristine is shown in Fig. 6. After a period of model equilibration, the group of cells in S were tagged to denote the effect of vincristine administration. As these cells entered mitosis, they were subjected to a 24 hr delay to simulate trapping of the vincristine-treated cells in metaphase. Seventy-five per cent of these cells were terminated or killed in metaphase.

To our surprise, however, the model failed to reproduce completely the observed effect of vincristine in the patient, an example of which is shown in Fig. 7. All aspects of the results were similar, except for the marked decrease in the number of cells in the S phase found 48 hr after injection. In this model, most of the cells in S come from cells emerging from Go, and, therefore, only minimal effect from trapping of cells in M would be expected at this time. Thus, to simulate the biological data, an additional block from vincristine effect had to be imposed on the flow of cells from Go into G1 at the time of injection. In this manner complete agreement of model simulation and biological information was achieved.

DISCUSSION

The purposes for constructing this computer-based model for simulation of leukemic cell kinetics have been fulfilled. In the design of the model, discrete modeling concepts were used that allowed better simulation of the actual biological events and a much greater latitude in modifying the model to explore various aspects of the leukemic cell life cycle. Some factors were chosen based on the best available information but can easily be altered as newer knowledge becomes available. A comparison of the results obtained with the model and actual biological data supported the validity of the model design. One such comparison was the ability to simulate the flash labeling in vivo of a population of leukemic cells in DNA synthesis by tritiated thymidine. By running two models, an "unlabeled" and "labeled" model, and then superimposing them at similar time periods, the per cent of the labeled cells in the various compartments of the cell cycle closely simulated actual results from studies of patients.
It is becoming increasingly important to know more concerning the mechanisms by which the growth rate of the leukemic cell population is controlled. Some biological information is already available indicating that the growth rate is primarily determined by the proportion of cells in the resting state. The best hypothesis at present is that an increasing number of cells enter the resting phase with increasing duration of the growth phase of the population. In this way it seems similar to cells in tissue culture or bacteria in a broth suspension. The mechanisms by which this transition takes place or the factors determining the shift are unknown.

One important area for control of this shift, the flow of cells from Go into the active proliferative cycle, has already been studied in response to drug therapy. There is indication that recruitment of resting cells can be induced. This recruitment is of importance therapeutically because most agents in current use are maximally effective during some stage of the mitotic cycle, that is having cycle-dependent activity.

Two other important areas for control of leukemic cell population growth were indicated from the results of studies with the computer model. The role of cell death in determining rates of solid tumor growth are well appreciated. No similar biological information is available concerning the regulatory role of cell death in the growth of leukemic cell populations. Yet the results of computer studies indicate that unrealistically rapid growth rates take place unless a significant amount of cell death occurs. It would be important to have confirming biological information and then, if significant cell death occurs, to determine the mechanisms by which it takes place. An appreciation of these mechanisms may provide new methods for inducing complete elimination of the leukemic cell population.

The other important area for control of growth rates is the time period after mitosis when the events within the cell determine the progression into a resting phases or back into the proliferative cycle. Very little is known about these important events. If, however, the processes allowing for entry into the resting phase could be blocked, then the cells could be kept within the drug sensitive proliferative cycle. On the other hand, if entry into the proliferative cycle could be blocked, then the resulting static leukemic cell population might be reasonably well tolerated. In these two areas, cell death and postmitotic events, the studies with the computer model have highlighted the opportunities for future research.

One particularly attractive aspect of the model has been the ability to simulate drug effects on the leukemic cell population. Of interest were the results of attempted simulation of vincristine effects. It was found that an additional, unsuspected drug effect had to be applied to the model to simulate completely the observed biological effects. This block to the flow of cells from Go into active proliferation was then studied in an in vitro model for conversion of resting cells to a proliferative phase. Indeed, vincristine could be demonstrated to block the blast transformation of lymphocytes exposed to phytohemagglutinin. This effect was associated with early inhibition of RNA synthesis. In this manner, the studies with the computer model
provided insights into drug action that could be checked by design of new experiments.

Some studies were possible that cannot be duplicated in the patient. It was of interest to see the time it took for a single cell to grow to a population size commensurate with the clinical diagnosis in the patient. The time of 3½ yr with a model, using the distribution of cells usually seen at the time of diagnosis, corresponds well to the peak incidence of acute lymphoblastic leukemia in childhood. Therefore, a single mutational event involving a single cell some time around birth could account for the evolution of the leukemic process. Faster and slower growth rates could also occur, of course, by modification of the model.

In summary, a useful model for leukemic cell kinetics has been constructed with discrete modeling techniques for computer use. The model has provided interesting insights into the leukemic cell population, most of which are capable of evaluation by biological investigation. Further studies, such as an investigation of parameter sensitivity, are in progress. In such studies, values for time and cell distribution factors can be altered to fit other reported kinetic data to determine the effects of these alterations on growth characteristics. Further studies of simulation of drug effects are likewise in progress.

APPENDIX

The basic element in a discrete model is a transaction. The transaction represents some identifiable component in a system, and it is the transaction that is generally considered to move through the system. Examples of such basic components are customers moving through a supermarket, aircraft moving through the airport traffic pattern, parts moving through a factory and being assembled into some product, and packets of information being processed by a computer. In each case, the transaction must be identified by some attributes. For example, the supermarket customers will be women, men, and children who will have the additional attributes of age, product preferences, etc. Messages in a data processing computer will be identified by type, length of service required, and perhaps by their priority rating. Each of these transactions is acted on by the system in which it is embedded. Aircraft may experience delays in getting landing clearance, customers may experience delays at the checkout counter, or messages may be held in a queue because the central processor is busy with another task. The delays may have a statistical distribution that needs to be represented in the model. Systems amenable to discrete modeling often exhibit a random behavior in the individual transactions. The general behavior of the population of customers is the basic interest, but impulse buying is known to influence the movements of individual customers in the store. The general distributions of message lengths of transactions in a computer may be known, but the length of an individual message is probably a random variable. Other analogies may be made. Another aspect of the randomness characterizing such systems is in the decision-making process. For example, cars at an intersection may make right and left turns in a random fashion with some
known probability describing the behavior of a population of cars, but the direction of turning of any car is a random variable. Some means of keeping track of the system timing is required.

The necessary computer programs needed to model such systems, as mentioned above, have been developed to meet the requirements of engineers and operation research analysts who seek to understand existing systems or to design better systems. GPSS/360 (General Purpose Simulation System) is one such computer program that requires a minimum of special training and no programming knowledge of the machine on which it is executed. The user has only to prepare the input to the program, which then conveys to the computer the basic relationships of the system under study. Some version of GPSS is available in many computing centers. Such discrete modeling languages were developed to collect statistics on the behavior of the system under study, and these results were usually reported after the termination of the run. The output can be in the form of histograms or tables.

In the leukemia model that has been described in this paper, certain features in GPSS were found to be of particular value. The SNAPSHOT feature allows one to report out data, such as the number of transactions at a certain point in the system, at some particular point in time. Repeated use of SNAPSHOT will give a dynamic picture of the condition of the system as a function of time, which is just what is wanted in a dynamic study. The HELP block allows the transfer of information to a FORTRAN program that in turn can control a plotter, thereby producing the output in the form of easily understood curves that have time as the independent variable. The normal histogram output feature provides a means of verifying the accuracy of the delay distributions that were incorporated in the model. Of special value is the feature of a USER CHAIN whereby transactions are placed in ordered lists that can be manipulated by the programmer. This capability provided a means of producing a self-scaling model for the investigation of the growth of a single cell to a population size that can be clinically detected.

The above description may seem a far cry from the requirement of a growing population of leukemia cells, but in fact there is a close correspondence. A transaction represents a single cell or a specified number of identical cells. The phases of mitosis are modeled by the contents of the GPSS blocks called STOREs. The program keeps track of the number of transactions in each of the stores (compartment or phases), and individual transactions (cells) reside in the stores for amounts of time that are assigned in a random fashion from a specified distribution that matches the best clinical estimates. When the residence time of a cell has been completed, the program moves that cell to the next phase of the mitotic cycle. In case there is a choice of the next destination, a random number generator with a specified probability assigned to each of the alternative paths determines the actual path that the cell takes. A SPLIT block in GPSS makes a copy of the information associated with a particular transaction and thereby creates two transactions from one, a neat analogy to mitosis. TERMINATE blocks in GPSS remove
transactions from the system and thereby give us a means of introducing the death of cells into the model. The capability of GPSS to utilize FUNCTIONs provides the mechanism for the introduction of the best estimates of the statistical distributions of the time delays associated with each phase of the mitotic cycle, and in the case where only crude estimates are known at the outset, one can modify the functions and observe the performance of the system and thereby establish a better estimate of the distribution. A GENERATE block creates transactions at a specified time and rate and is useful in the process of initialization.

Thus, it can be seen that GPSS provides the subcomponents that have a strong correspondence with the basic elements needed to describe the kinetic behavior of a population of cells. It is this identification of the parts and the total performance of the parts in concert that matches the biological check points, thereby giving an intuitively satisfying model of the process. The question of uniqueness of the model may be raised at this point. To be sure, the models developed to describe complex systems are seldom unique, but the clear identity and performance of the subcomponents coupled with the total system behavior suggest that this model has the essential characteristics with fewer approximations than have been found necessary in previous continuous system approaches.

Several models were developed in this investigation. Since radioactive identification of the cells is basic to leukemia research, it was initially thought necessary to have the model contain cells that were labeled and other cells that were unlabeled. This process could have been accomplished by the identification of PARAMETERs associated with each transaction. However, on further reflection it became apparent that the mitotic activity of the labeled cells is independent of the mitotic activity of the unlabeled cells. Therefore, it is possible to model the two activities separately and then to combine the observed results at the same points in system time to yield the desired composite result. Curves can then be plotted in terms of percentage of labeled cells in each compartment at each point in time. Thus it becomes possible to use greater numbers of transactions in each of the separate models and thereby obtain closer approximations to the desired statistical distributions. It must be noted that there is a finite number of transactions that can be handled by any GPSS program and that longer program execution times are associated with larger numbers of transactions in the system. Because of the above reasons, we utilized two models—one referred to as the unlabeled model and the other as the labeled model. However, both incorporate the same statistical delay functions and the same system structure in the model. The only difference in the two models is that in the unlabeled model all compartments had to be initialized with cells and the desired proportions of the total population of cells and the desired rate of flow of cells from one compartment to another had to be established. In the labeled model, cells were initialized in only the S compartment to correspond to the uptake of a radioactive tracer by the cells in synthesis.

The preliminary development of the model led to the specification of death rates that were higher than previously suspected. The unlabeled model was
used to investigate the effect of drugs that alter the mitotic cycle. For example, vincristine has the effect of inhibiting the cell division and of altering the death rate. These effects were modeled by introducing a PARAMETER value to the cells in synthesis at the system time corresponding to the injection of the drug. Additional GPSS blocks then routed the cells so identified to additional delays and to TRANSFER blocks that removed a different proportion of these cells from the system, corresponding to the altered death rate. An interesting consequence of the model was that the results of the model did not correspond adequately to the clinical expectations until an additional delay was added to the system between Gs and Gi. This effect of vincristine had been suspected from other experimental work, but the model made this requirement even more apparent. Similar techniques were employed to study the effect of cytosine arabinoside, and the results of combinations of drug therapy can be investigated.

Another interesting use of the model was in the study of the growth of a single cell to a population of cells that is clinically detectable. The present estimate of the detectable population size is approximately $10^{12}$ cells, so it is clearly impossible to model the system in terms of actual cell count. However, a program was devised that placed the transactions on USER CHAINS, and each transaction was given a scheduled time of departure from the chain. This more complex representation of the usual delay block allowed alternate cells to be purged from the CHAINs at any time the total system population had grown to a point where overflow of the computer memory was imminent. Thus, a single cell was introduced into the system and allowed to divide and redivide. Periodically then half of the cells were removed, which then left the remaining cells counting for two in the previous population. When this process was repeated and the results plotted, it was found that the system was growing exponentially with a doubling time of 675 hr.

The use of the GPSS system for further investigation should not be considered an obstacle to the uninitiated. The manual is reasonably lucid, the concepts are not abstract, and the actual format of card preparation is straightforward. Some of the techniques found useful in our experience have been mentioned. The initialization procedure requires that one establish within the GPSS program a transaction count for each STORE block that represents a compartment of the mitotic cycle. This was accomplished by using GENERATE blocks to produce the transactions for each STORE and by ASSIGNing a PARAMETER to the transactions before they pass into the ENTER block associated with the STORE. A TRANSFER block directs these identified transactions to a TERMINATE block without passing through the usual LEAVE block. Thus, the STORE count is incremented but not decremented, and an initial compartment cell count is established. Thereafter, other GENERATE blocks injected transactions into the STOREs at a rate dictated by the clinical requirements, so as to establish the desired flow rates. The system is allowed to operate for a period of time until steady state is achieved, and then the effects of specified drug are introduced into the GPSS model.
The more advanced user will find the features of the HELP block most useful in allowing the transfer of dynamic data from the various compartments of the model to auxiliary FORTRAN programs that can later control a digital plotter to produce plots of the output data. The value of the USER CHAIN has been discussed in connection with the self-scaling model.

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