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COMPUTER MODELS AND AUTOMATA THEORY IN BIOLOGY AND MEDICINE

COMPUTER MODELS OF CARCINOGENESIS AND CANCER CHEMOTHERAPY OPTIMIZATION

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1. INTRODUCTION

The applications of computers to biological and biomedical problem solving goes back to the very beginnings of computer science, automata theory [1], and mathematical biology [2]. With the advent of more versatile and powerful computers, biological and biomedical applications of computers have proliferated so rapidly that it would be virtually impossible to compile a comprehensive review of all developments in this field. Limitations of computer simulations in biology have also come under close scrutiny, and claims have been made that biological systems have limited information processing power [3]. Such general conjectures do not, however, deter biologists and biomedical researchers from developing new computer applications in biology and medicine. Microprocessors are being widely employed in biological laboratories both for automatic data acquisition/processing

and modeling; one particular area, which is of great biomedical interest, involves fast digital image processing and is already established for routine clinical examinations in radiological and nuclear medicine centers, Powerful techniques for biological research are routinely employing dedicated, on-line microprocessors or array processors; among such techniques are: Fourier-transform nuclear magnetic resonance (NMR), NMR imaging (or tomography), x-ray tomography, x-ray diffraction, high performance liquid chromatography, differential scanning calorimetry and mass spectrometry. Networking of laboratory microprocessors linked to a central, large memory computer is the next logical step in laboratory automation. Previously unapproachable problems, such as molecular dynamics of solutions, many-body interaction calculations and statistical mechanics of biological processes are all likely to benefit from the increasing access to the new generation of "supercomputers". In view of the large number, diversity and complexity of computer applications in biology and medicine, we could not review in any degree of detail all computer applications in these fields; instead, we shall be selective and focus our discussion on suggestive computer models of biological systems and those fundamental aspects of computer applications that are likely to continue to make an impact on biological and biomedical research. Thus, we shall consider unifying trends in mathematics, mathematical logics and computer science that are relevant to computer modeling of biological and biomedical systems. The latter are pitched at a more formal, abstract level than the applications and, therefore, encompass a number of concepts drawn from the abstract theory of sets and relations, network theory, automata theory, Boolean and *n*-valued logics, abstract algebra, topology and category theory. The purpose of these theoretical' sections is to provide the ans for approaching a number of basic biological questions:

(1) What are the essential characteristics of a biological organism as opposed to an automaton?

(2) Are biological systems recursively **computable**?

(3) What is the structure of the simplest (primordial) organism?

(4) What are the basic structures of neural and genetic networks?

(5) What are the common properties of classes of biological organisms? (6) Which system representations are adequate for biodynamics?

(7) What is the optimal strategy for modifying an organism through genetic engineering? (8) What is the optimal simulation of a biological system with a digital or analog computer?

(9) What is Life?

The present analysis of relational theories in biology and computer simulation has also inspired a number of new results which are presented here as "Conjectures" since their proofs are too lengthy and too technical to be included in this review. In order to maintain a self-contained presentation-the definitions of the main concepts are given, with the exception of a minimum of simple mathematical concepts.

2. COMPUTER MODELS OF BRANCHING PROCESSES AND TREE-LIKE MORPHOLOGY

One of the simplest but nontrivial applications of computers in biology and medicine has been the generation of "trees" or patterns of branching. Such patterns of branching are common to arteries, bronchi, trees and rivers, and have attracted considerable attention[4-22]. Computer simulation of the geometry of trees, based on branching angles, length ratio of branches and differential rates of growth, has been quite successful introducing models which are closely resembling the morphology of biological systems[7, -19]. In such models of trees, the branching ratio was found to be variable and, therefore, of little descriptive value. A computer program that generates dichotomously various branching trees was recently described[22] and it was employed to investigate if the human bronchial tree could be adequately modelled.

Generation of trees by the computer

According to Horsfield and Thurlbeck[22], each branch is encoded in the computer by providing the three-dimensional (3D) coordinates of the branch ends. Horsfield and Cuming[5] order the branches

by starting at the peripheral ones, which are assigned "order “ and the order is increased by 1 unit at each junction [Fig. l(a)] after Horsfield and lurlbeck[22]). The asymmetry of the branching is represented by an asymmetry parameter (3) which is the difference in order between the two daughter branches. An example asymmetry of branching which was given by Horsfield and Thurlbeck is reproduced Fig. l(b). A stem branch is generated by inputing its coordinates and stating its Horsfield der; the stem bifurcates in the x-y plane, the order of the major daughter branch being le digit less than the parent branch by definition, while the order of the minor branch defined by using a value of 3. By defining the angles of branching and the lengths, the coordinates of the ends of the daughter branches can also be calculated. The daughter branches bifurcate in turn until an order-1 branch is generated recursively, and then bifurcation stops on that selected pathway. The value of 8 for a given bifurcation is determined by a pseudorandom number generated by a digital computer, and takes values between 0 and 9. The probability for a given value of 8 to be realized in a given tree from e pseudorandom string of numbers is defined on input; for example if 8 = 0, the probability is zero.

3. Computer Models of Neural Networks.

An extensive review of neural networks with approximately 100 references up to 1986 is presented summarizing the results reported to be relevant to basic brain control functions. Alternate approaches based on an enzymatic network in single functional neurons by M. Conrad were also reviewed in detail, and were later considered by other authors to lead to tthe possibility of quantum processing and the emergence of consciousness.

4. COMPUTER MODELS OF CARCINOGENESIS AND CANCER CHEMOTHERAPY

Computer simulation studies of carcinogenesis are closely related to theoretical studies of the cell cycle, the control of cell division and the growth of cell populations [43-52].In a

computer model of erythroleukemia, Düchting[51] considered a control process (cell proliferation of the form shown in Fig. 8 (also see Fig. 9). The simulation of this process was performed on an AEG- Telefunken TR440 digital computer using an ASIM computer program. This program is written in the block-oriented language for Analogous SIMulation. The digital logic device in this model ascertains and registers the presence of each cell in a specific compartment; the analog transfer elements were integrators and switching components. The model is therefore a combination of analog and digital devices, and the simulation process is in this case more complex than in the more popular, digital-only models. This model mimicked malignancy through an uncontrollable increase in compartment population, but as many other computer models of carcinogenesis, is limited by the lack of a detailed, experimental analysis of the parameters controlling carcinogenesis. An attempt to introduce such parameters into a model of malignant "stem" cell growth was recently made by Rittgen [53]. Rittgen's basic model is sketched in Fig. 10, where G1, S, G2, *M, Q1* and *Q2* are cell cycle phases; Q1 and Q2 are the resting phases, while S is the synthesis phase. Mitosis starts either after G2 or after *Q2,* and the daughter cells begin in the resting phase *Q*1. The simulation was executed with a special stochastic system [54]. With this model, it was possible to calculate the number of malignant proliferating, maturing and mature cells, as a function of time. The simulated malignant cell population growth was exponential, with growth velocities depending on the cell cycle parameters.

Computer Models and Cancer Chemotherapy.

A model conceptually similar to the Rittgen simulation, but simpler, was applied to the analysis of cancer chemotherapy by Chuang and Soong [55]). A FORTRAN IV program was developed for a PDP 15!76 computer which was employed for simulations of scheduled chemical treatments with cell-cycle specific, phase specific and cycle non- specific drugs. It also allowed for Gompertzian tumor growth and variation of kinetic parameters in relation to tumor size. Typical simulated curves of synchronization and thymidine blocking effects in cancer chemotherapy are discussed in Ref. [55]. Complications, not considered in this model, can arise in cancer chemotherapy due to the fact that tumor cells can begin to divide parasynchronously following interruption of the treatment. The agreement between this model and the two experimental animal tumor systems, L1210 leukemia and Lewis lung carcinoma, cannot yet be considered as conclusive because of the paucity of experimental data available. In an interesting report by Swan and Vincent[56], the problem of minimizing the total amount of cycle nonspecific cytotoxic drug in the body of the patient was investigated. Their solution was in terms of optimal control theory and their theoretical results were compared with clinical data stored in a computer at the Arizona Medical Center. For patients suffering from bone cancer known as multiple myeloma, a treatment with melphalan, combined with intravenously administered cyclophosphamide, and an oral, fiXed dosage of prednisone was pursued; then the optimal control data was compared with the clinical data. The optimal treatment suggested by the Swan and Vincent model [56] is a relatively small dose at the beginning, followed by a gradually increasing dose as the cancer cells decrease in number. The total amount of drug accumulated with such a treatment appears to be a minimum but the authors warn that their model assumes that the drug effectiveness parameter does not change significantly due to a change in the

drug "program" ; they also suggest that clinical tests should be run to determine the nature and extent of variation of the drug effectiveness parameter. As in the model of Chuang and Soong[55], tumor growth was assumed to be Gompertzian, similarly to the earlier studies of Laird[57] and also as in the clinical applications of the Gompertz model by Sullivan and Salmon[58] to tumor growth and regression in IgG multiple myeloma in human subjects. In a subtle development of the optimal control approach to cancer chemotherapy, Zietz and Nicolini [59] proposed that the optimum treatment should keep the tumor size low and the normal population high, for as long as possible, during the treatment, while achieving tumor cell kill. There mathematical model is also based upon the Gompertzian growth and the earlier studies of Nicolini and Kendal [60] and Nicolini et al. [61]; the model leads to an expresssion of switching times for drug administration, and rest, which could. Computer models and automata theory in biology and medicine (152) could not be explicitly evaluated. Therefore, it was suggested that computer analysis will be needed to determine the optimum treatment strategy (optimal trajectory), and the numerical values of the switching function. An algorithm was then developed to uniquely define the switching function. This algorithm, when applied to two cell populations for a treatment period of 21 units, and a weighting of 4: 1 normal-to-tumor cell division rate predicted that the optimum treatment would be dose administration for the first 8 time units, followed by a rest for the next 13 time units. It was pointed out, however, that additional computations will be needed to improve this algorithm. The model was claimed to be also suitable, with some modifications, for the optimization of chemotherapy with cycle-specific drugs.

A microprocessor model of perturbed cell renewal

Duchting[62] re-approached the problem of computer simulation of carcinogenesis a the more basic level of perturbed cell renewal by considering the interactions between adjacent cells on a two-dimensional grid. Such questions were also considered previously by Gardner[63], Lindenmayer[64], Reshodko and Bures[65], Ransom[66] and Arbib[67] The approach is close to what Arbib describes as a "tessellation" model, and

involve~ basic concepts from automata theory (see also Sec. 10). Duchting's simulation of disturbed cell renewal [62] was carried out by means of an Intel 8080 microprocessor and we expect that his model could also be programmed on the now popular IBM PC/ ATT microprocessors. The organization of the programs run by the Intel 8080 for this simulation is reproduce< in Fig. 13 from Duchting[62]. This simulation yielded some interesting results, such a' the onset of metastasis after "surgery" even if only one "malignant" cell is left amongst the "normal" cells of the grid (Fig. 6 in Ref. [62]); in the case of no surgery , the mode predicts that normal cells would eliminate the few malignant cells present. Related to this tessellation approach to population growth, Lieberman considered in an earlier report [68] a stochastic model in which the population distribution is confined within a limited space. The simulation was carried out with an IBM Model 360 and showed that the size and abundance of organisms are linked by a logarithmic relationship if the organisms are limited by a single resource. It would be interesting to adapt this model to the study of tumor growth, under conditions of limited nutrient supply since the tumor cell proliferation is strictly dependent upon the local availability of nutrients supplied by tumor vessels[69]. The tumor vascularization itself is, however, induced by the elaboration of a tumor antigenic factor (T AV by the tumor cells[70]. In a detailed model of tumor growth, Liotta *et al.[71]* considered both vascularization and necrosis of tumors by taking into account both diffusion an(proliferation of tumor cells. Coupled diffusion equations with a nonlinear source and sine terms described the proliferation, migration and necrosis of tumor cells. According to Liotta *et al.[71],* their diffusion model is superior to lumped parameter models of tumor growth such as that .of Saidel *et al.[72]* because "the lumped-parameter simulation doe: not yield any information about the spatial distribution of the tumor cells and vessels in the tumor. The results of the diffusion model are qualitatively similar to those determined by the experiment (Figs. I and 3, respectively, in Ref. [71]). One major limitation of this diffusion model of tumor growth is that the tumor was assumed to be spherically sym metric. Other limitations of the model are discussed in Ref. [71].

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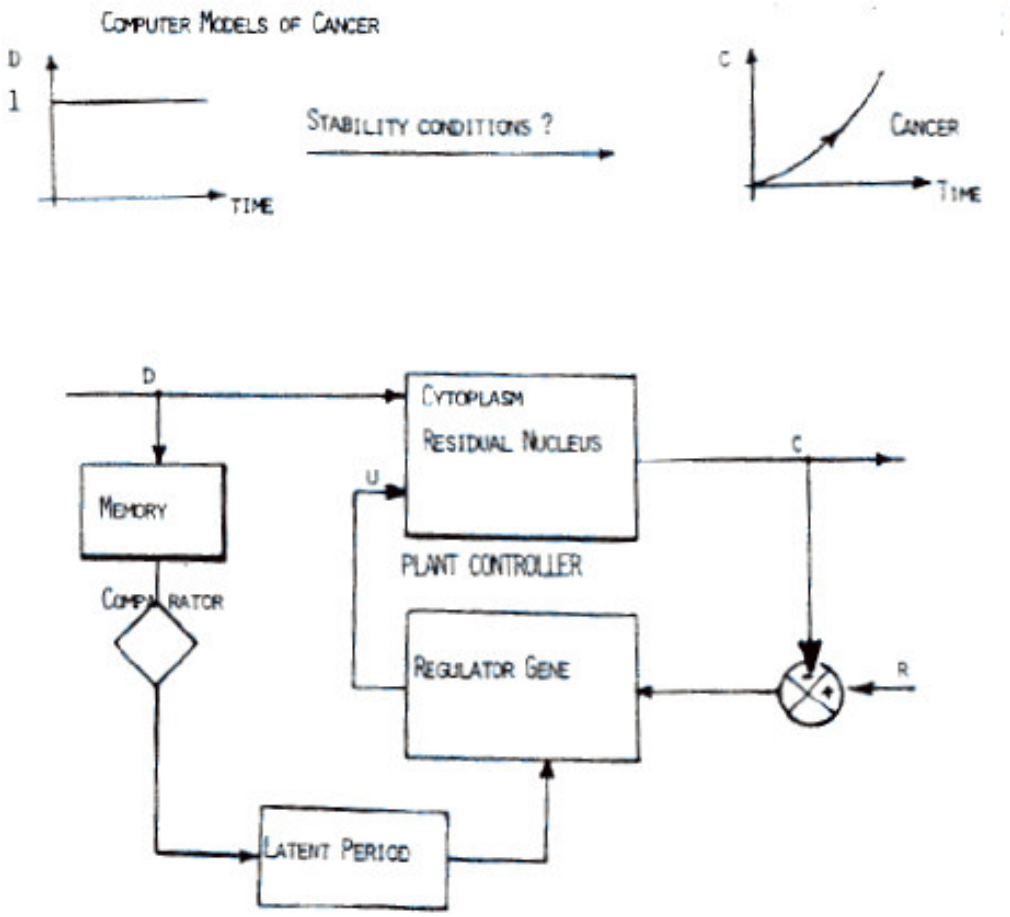
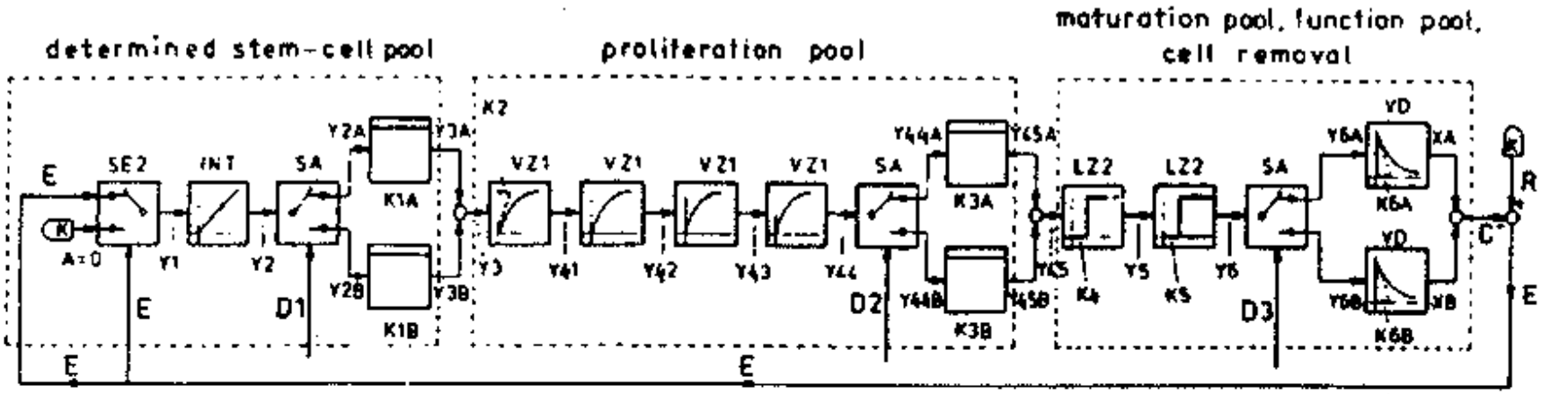


ASIM computer program listed in Table 2. This program is written in the block-oriented language for Analogous SIMulation.

Figure 8. Block diagram of a control model of cell proliferation (from Ref. [51]). **r** is the reference input, for examples, hormones; c is the controlled variable, such as the deviation of the number of cells from the steady –state value; d represents disturbances such as carcinogens: (u) represents the control signal, for example, enzymes with specific regulatory roles.



A6: leading to the respective disturbances D

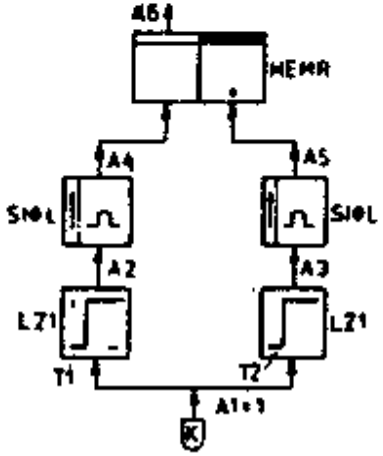


Figure 9. A model of the erythropoiesis control system (from Ref. [51]). Y1= determined stem cells; Y3= committed stem cells; Y41 = proerythroblasts; Y42 = macroblasts; Y44 = polychromatic erythroblasts; Y45 = orthochromatic erythroblasts; Y5 = orthochromatic erythroblasts; Y6= erythrocytes/reticulocytes; C= controlled variables = red blood cells: R= reference input = desired number of erythrocytes (related to the required tissue oxygen); E= error or deviation = quantity of erythropoeitin : D = disturbance(s) such as viruses, x-rays UV, vitamin or iron deficiency, bleeding, sudden hypoxia.

The digital logic device in this model ascertains and registers the presence of each cell in a specific compartment; the analog transfer elements were integrators and switching components. The model is therefore a combination of analog and digital devices, and the simulation process is in this case more complex than in the more popular, digital-only models. This model mimicked malignancy through an uncontrollable increase in compartment population, but as many other computer models of carcinogenesis, is limited by the lack of a detailed, experimental analysis of the parameters controlling carcinogenesis. An attempt to introduce such parameters into a model of malignant "stem" cell growth was recently made by Rittgen [53]. Rittgen's basic model is sketched in Fig. 10, where G_1, S, G_2, M, Q_1 and Q_2 are cell cycle phases; Q_1 and Q_2 are the resting phases, while S is the synthesis phase. Mitosis starts either after G_2 or after Q_2 and the daughter cells begin in the resting phase Q_1. The simulation was executed with a special stochastic system [54].

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Computer and cancer chemotherapy.

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developed for a PDP 15/76 computer which was employed for simulations of scheduled chemical treatments with cell-cycle specific, phase specific and cycle non- specific drugs. It also

allowed for Gompertzian tumor growth and variation of kinetic parameters in relation to tumor size. Typical simulated curves of synchronization and thymidine blocking effects in cancer chemotherapy are reproduced in Fig. 12 from Ref. [55].

Table 2: Computer program ASIM (from Ref. [51])

```
*----REGELKREIS MIT TOTZEIT UND NICHTSTETIGEM ELEMENT STRUKTUR
Y1 = SE2(XD,A,XD)
Y2 = INT(0,Y1)
Y2A,Y2B = SA(Z1,Y2)
Y3A = K1A * Y2A
Y3B = K1B * Y2B
Y3  = Y3A + Y3B
Y41 = VZ1(0,K2,Y31)
Y31 = Y3
Y62 = KB*Y61
Y61 = VZ1(0,K7,Y45)
Y42 = VZ1(0,K2,Y41)
Y43 = VZ1(0,K2,Y42)
Y44 = VZ1(0,K2,Y43)
Y44A,Y44B= SA(Z2,Y44)
Y45A = K3A * Y44A
Y45B = K3B * Y44B
Y45  = Y45A + Y45B
Y5   = LZ2(K4,Y45)
Y6   = LZ2(K5,Y5)
Y6A,Y6B = SA(Z3,Y6)
XA   = VD(0,K6A,Y6A)
XB   = VD(0,K6B,Y6B)
X    = XA + XB
XD   = W - X
A1   = 1
A2   = LZ1(TZ1,A1)
A3   = LZ1(TZ2,A1)
A4   = SIML(0,A2)
A5   = SIML(0,A3)
A6   = MEMR (0,A4,A5)
```

```
*----------PARAMETER
A = 0
W = 100
H1 = ABS(XD) - 1.E.10
K1A = 0.02
K1B = 0.025
K2  = 0.25
K3A = 12
K4  =1
K5  =2
K6A =30
K6B =10
K7  = 0.1
K8  = 0.2
Z1  = 0
Z2  = A6
Z3  = 0
TZ1 =50
TZ2 = 0
K3B =10
```

```
*--------BEARBEITUNG
SKIP H1
RZEIT (0.,0,1,160.)
PLOTTER (A4Q,T/D,15,X/ERYS,7)0.,160.,T,*
        *200.,200.,X
END
```

Complications, not considered in this model, can arise in cancer chemotherapy due to the fact that tumor cells can begin to divide parasynchronously following interruption of the treatment. The agreement between this model and the two experimental animal tumor systems, L1210 leukemia and Lewis lung carcinoma, cannot yet be considered as conclusive because of the paucity of experimental data available.

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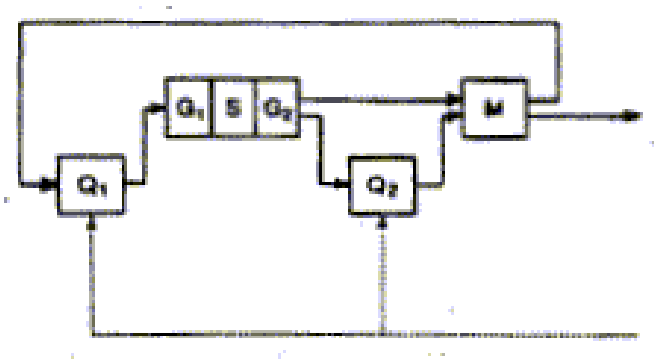

Fig 10. Cell cycle scheme for a stem cell (according to Rittgen [53]). G_1, S, G_2, and M are known steps of the cell cycle, with G_1 and G_2 representing the "gap" intervals, S representing the synthesis step, and M representing the mitosis. Q_1 and Q_2 are resting phases.

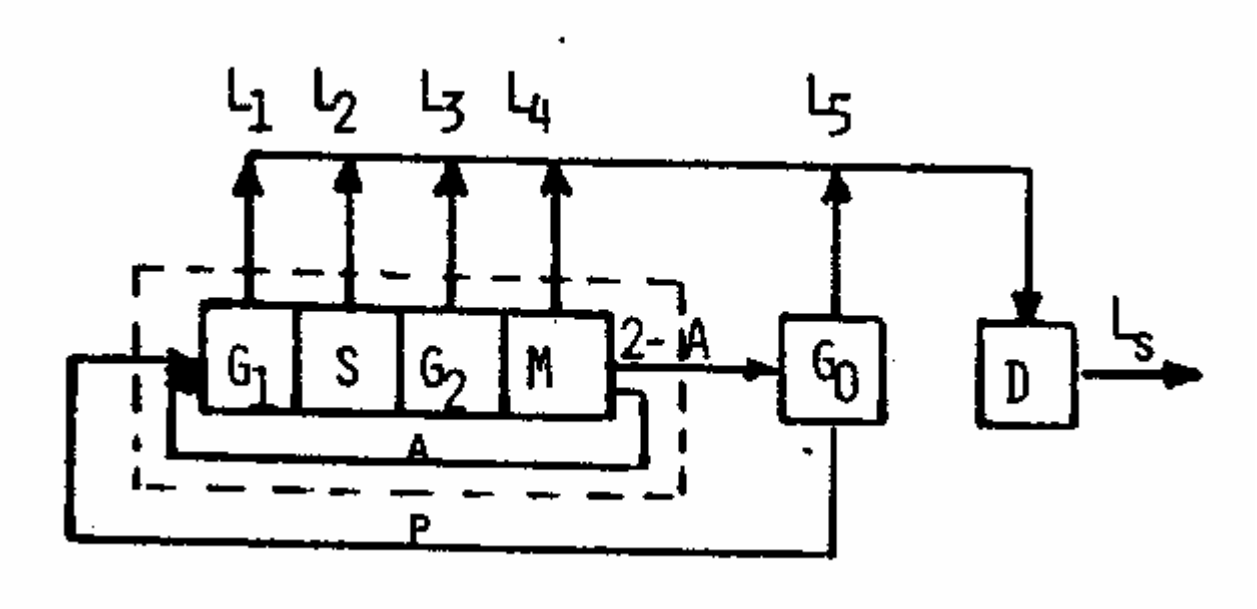

Figure 11. A model of tumor growth and of the drug treatment effects (according to Ref [55]). The proliferative compartment has the four phases G_1, S, G_2, and M. Cell may die either naturally or because of the drug treatment, as determined by the functions Li(t), i=1,..., 5. When leaving G_1, S, G_2, M or G_0 such cell enter the dead cell compartment D. After each binary fission, (2 – A) cell enter the nonpoliferative compartment G_0, which A cells ($1 \leq A \leq 2$) continue their proliferation cycle. Loss from the tumor site is determined by I_h. A proportion p of G_0-cells may re-enter the proliferation cycle at G_1.

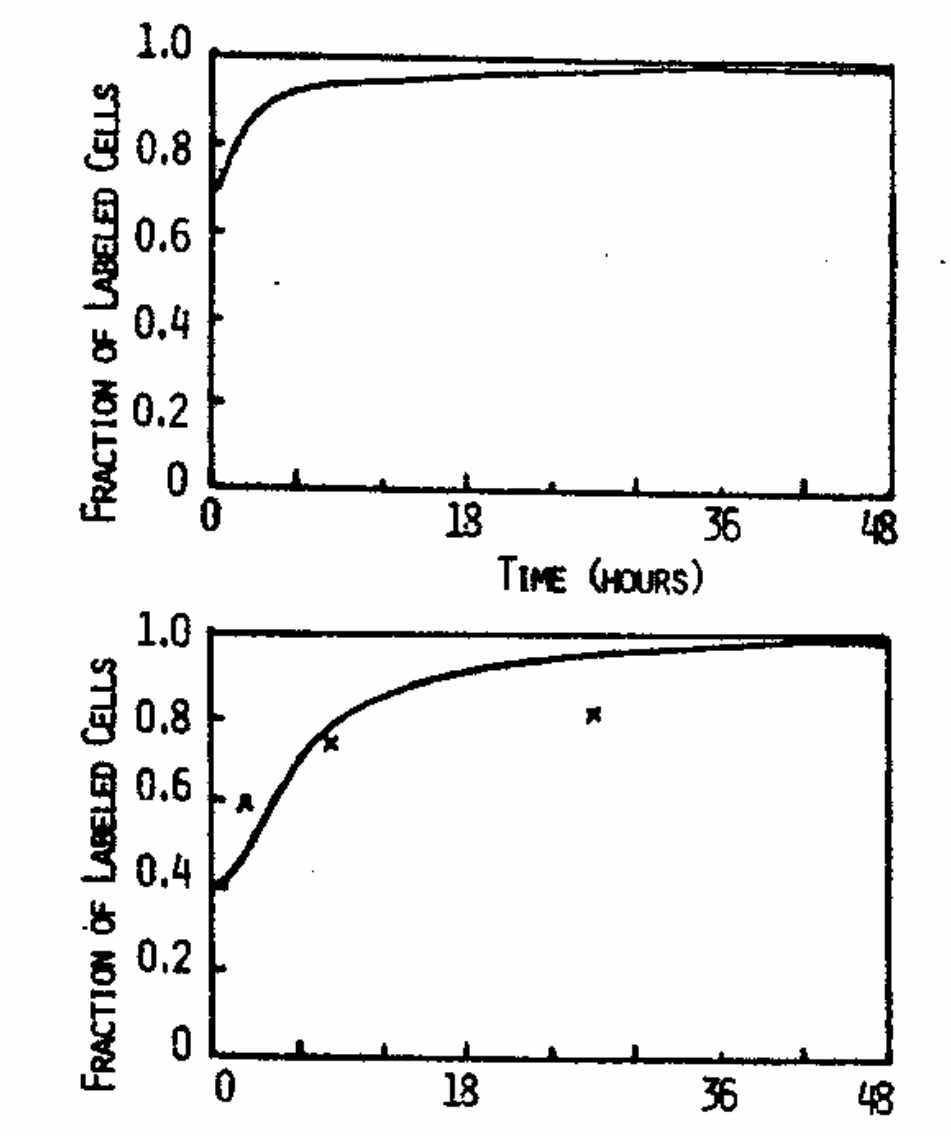

Figure 12. Simulated CL curves of synchhronization and thymidine blocking effects in cancer chemotherapy are shown together with observed values (from Ref [55]).

A microprocessor model of perturbed cell renewal

Düchting [62] re-approached the problem of computer simulation of carcinogenesis at the more basic level of perturbed cell renewal by considering the interactions between adjacent cells on a two-dimensional grid. Such questions were also considered previously by Gardner [63], Lindenmayer

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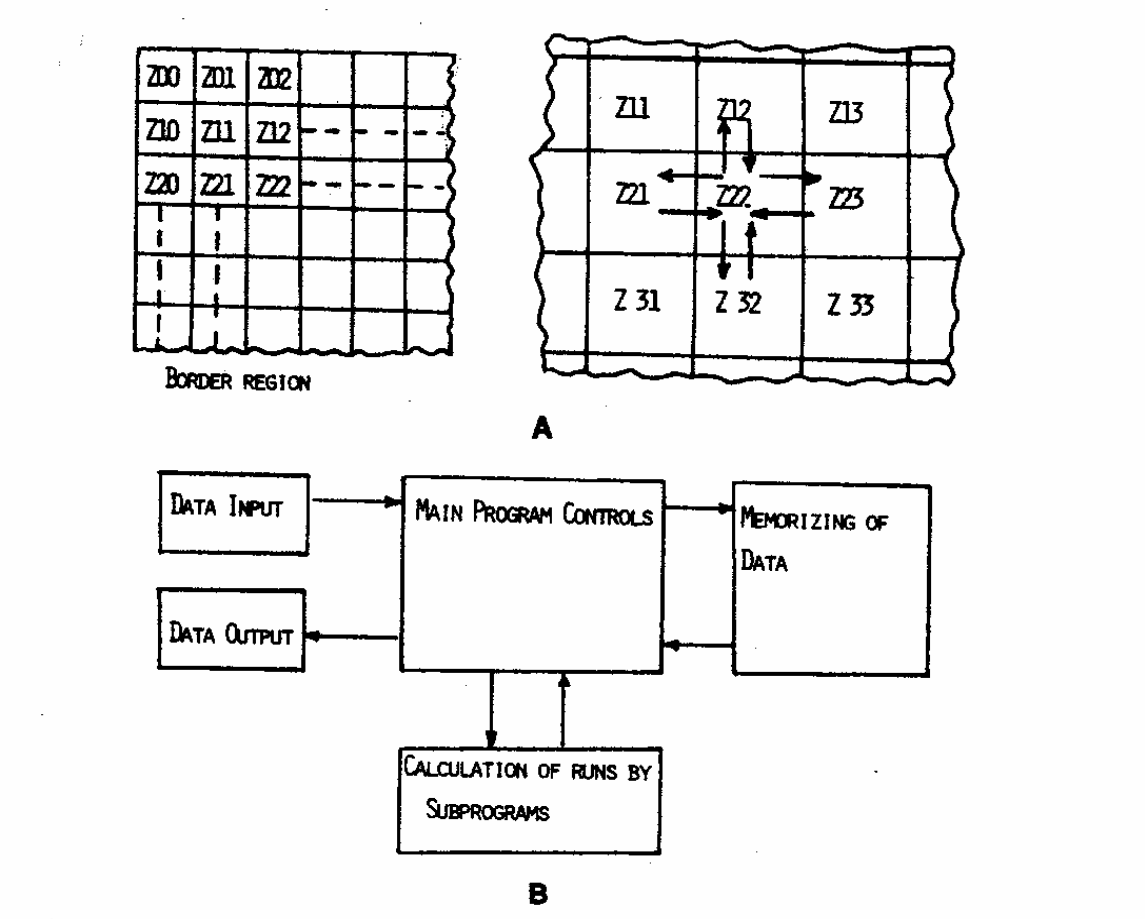

Fig. 13 A. Organization of the Intel 8080 program for modeling cell renewal (according to Düchting [62]). B Grid configuration of cells, or tessellation model of cell renewal (after Düchting[62]).

It would be interesting to adapt this model to the study of tumor growth, under conditions of limited nutrient supply since the tumor cell proliferation is strictly dependent upon the local availability of nutrients supplied by tumor vessels[69]. The tumor vascularization itself is, however, induced by the elaboration of a tumor antigenic factor TAV by the tumor cells[70]. In a detailed model of tumor growth, Liotta *et al.[71]* considered both vascularization and necrosis of tumors by taking into account both diffusion an(proliferation of tumor cells. Coupled diffusion equations with a nonlinear source and source terms described the proliferation, migration and necrosis of tumor cells. According to Liotta *et al.[71],* their diffusion model is superior to lumped parameter models of

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5. AUTOMATA THEORY AND COMPUTABLE MODELS OF BIOLOGICAL SYSTEMS

The formal theory of automata or sequential machines is considered in the context of network models of biological systems.
The collection of discrete automata semigroups is organized as an abstract category whose algebraic, universal properties have been determined and that presents realizability problems ressembling those of the simplest biomathematical network models

6. GENERAL COMPUTABILITY QUESTION FOR BIODYNAMICS, NEUROSCIENCES AND COGNITIVE-RELATED FIELDS

Conjecture:

Generalized, algebraic-symbolic computations of biodynamics may become possible with a topological semigroup machine (Baianu, 1971a, b) such as a quantum computer. On the other hand, existing digital computers are known to be limited in their ability to compute complex biodynamics such as the cell network dynamics.

7. Łukasiewicz Algebraic Logic Networks of Genomes

A detailed review of both Boolean and Łukasiewicz logic networks of the genome, or genetic network models are presented with a view to future applications such as the dynamic applications to the human genome analysis. Related spin offs may occur in n-state models of non-random, nonlinear neural networks by modeling cognitive systems with categories of Łukasiewicz Logic Algebras.

8. (M,R)-Systems Models and the simplest Metabolic-Repair-Replication Models

Generalizations of Robert Rosen's (M,R)-system models are discussed in terms of general categories whose objects are not restricted to sets, by endowing such objects with algebraic and topological structures as in the theory of organismic supercategories (Baianu, 1970; 1971; 1973, 1974; 1980; 1983; 1985). Further extensions of (M,R)-systems to self-replication and reverse-transcription are also constructed and their categorical-algebraic properties are derived.

CONCLUSIONS

Several answers provided to the questions posed in the introduction are summarized and conclusions are drawn concerning the future directions of computer modeling and automata theory in biology and medicine, such as the nature of the diagnostic, cognitive processes currently employed in medicine that could benefit from the Luksiewicz Logic Algebraic models developed in the context of non-random, nonlinear Genetic Networks. The computability Conjecture for Biodynamic Models and networks is again stated in the broader cognitive context of the medical sciences that will increasingly depend on automatic processes and computations for data analysis and diagnostics.

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Applications of the Theory of Categories, Functors and Natural Transformations, N-categories, (Abelian or otherwise) to:

Cognitive Systems Automata Theory/ Sequential Machines, Bioinformatics, Complex Biological Systems /Complex Systems Biology, Computer Simulations and Modeling, Dynamical Systems , Quantum Dynamics, Quantum Field Theory, Quantum Groups,Topological Quantum Field Theory (TQFT), Quantum Automata, Graph Transformations, Logic, Mathematical Modeling, etc.

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