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Mathematical and Computational Approach for Study of Tumor Growth

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Abstract: ***This paper discuss about various methods used for study of data related tumor growth using some of mathematical modelling concepts and computational modeling concepts. Model is either continuous or discrete based on the nature and type of variables involved. Depending on the growth of tumor, stage there are different types of mathematical models like Exponential, Gompertz, West law can be applied. Computational Modeling will be applied at different levels like Atomic, Biological. To study biochemical reactions and gene regulation various Markup Languages are available like SMBL, TumorML. Finally it gives a brief exposure of Modelling techniques in biology. This paper focuses on various strategies that are available and useful to study the tumor data to study the prognosis of tumors.***

Keywords: Exponential Growth Model, Gompertz model, West Law, SMBL, CellML, InsilicoML, FieldML, TumorML, Peri Nets, Agent Based Systems

1. Introduction

1.1 About Tumors

The lack of regulation of genes may be cause for tumor formation or growth. The growth or mass of cells is tumor indication. When the tumor remains at fixed position and no spreading then it called Benign. If the tumor spread over an area irrespective of time intervals then it is termed as Malignant. If the cells are identified as cancer cells and if they pass through blood stream which may be cause tumor formation at a different place than it originally positioned, it is Metastasis. A lump, or lumps, is a broad term that refers to anomalies, including discrete masses, several small modules, and more.

A biopsy determines whether a lump is benign or cancerous. A benign tumor is a development that might create bothersome issues but, for the most part, poses no threat to life unless it is present inside the skull, close to a major blood supply or nerve. The cancerous tumor is a malignant one. It grows quickly and abnormally, and it can affect many bodily parts. It has the potential to harm and risk life.

The most popular staging method is based on the three variables MNT where T gives the size of the tumor, the number of lymph nodes involved is given by N, for the existence and location of metastases is M. Stage III cancer is defined as a large tumor (T3) without lymph nodes or distant metastases (N0 or M0), or a somewhat smaller tumor (T2) with lymph nodes involvement (N2) (M0).

1.2 Mathematical Modeling

Use mathematical terms and formulae to represent the nature and behavior of real world problem. Here by using some of the existing mathematical models the data related to tumor is studied. The basic models used are Exponential Growth Model, Gompertz Model and West Law.

1.3 Computational Modeling

The computational models are considered into two categories. The first category consists of Carcinogenesis, cell to cell interactions and genetic instability are considered. Whereas in the second category as tumor tissue and its progression. Collections of these models are considered as hybrid model.

1.4 Markup Languages

There are different approaches to modeling biological systems. The "bottom-up" approach focuses on simulating the system from the point of view of reduction, integrating multiple functional components. The “top down” approach considers the whole subject and develops simulations that are consistent with known observations. For example, in cancer modeling, these two approaches are used to simulate different aspects of cancer, such as cancer progression and tumor growth. Markup Languages helps a lot in this process.

1.5 Modeling Techniques in System Biology

1.5.1 Petri Nets

Petri Nets were developed originally by Carl Adam Petri in 1962. Since then, Petri Nets and their concepts have been extended and developed, and applied in a variety of areas: Office automation, work-flows, flexible manufacturing, programming languages, protocols and networks, hardware structures, real-time systems, performance evaluation, operations research, embedded systems, defence systems, telecommunications, Internet, e-commerce and trading, railway networks, biological systems.

1.5.2 Agent Based Models

In recent years, agent-based applications have been developed inspired by natural systems. The natural systems have a dynamic structure defined by a complex, distributed, open, heterogeneous, and large-scale systems. Therefore, it is too hard to model these systems in the artificial world. Agent-based modeling technique has advantage in explanation of the dynamics of the behavior in the complex systems including biological, physical, and social systems. It is used in the solution or modeling of a problem in the literature seems to be inspired by living systems. Living systems offer an organization and operation at different levels ranging from the genetic to the social experience. The most common applications that can be shown in living systems are biological systems including human physiology which examine major systems such as cardiovascular system, immune system, nervous system, endocrine system, etc., and predator-prey relationship in the ecosystem, birds and fish flocks, organisms that live in colonies such as for aging ants, bees, wasps, and termites.

2. Mathematical Modeling

2.1 Exponential growth model:

Many systems exhibit exponential growth. It is represented mathematically by the equation:

$$y = y_0 e^{kt} \rightarrow \quad (1)$$

Where y_0 the initial state of the system and k is is growth constant which is a positive quantity and t is the time. The rate of growth is represented by a differential equation:

$$\frac{dy}{dx} = k y_0 e^{kt} = ky \rightarrow \quad (2)$$

The key feature of exponential growth is that the rate of growth is proportional to the current function value. This is applied to growth of a bacteria, it is as follows:

Suppose start with initial population size of bacteria is $y_0 = 200 \; and \; growth \; rate \; k = 0.02$ after 2 hours i.e. 120 minutes the population size is ten times the initial size. It is represented in tabular form as:

Table 1: Time Vs Population Size for a selected Bacteria

Time	0	10	20	30	40	50	60	70	80	90	100	110	120
Population size	200	244	298	364	445	543	664	811	990	1209	1477	1805	2204

The corresponding line graph for exponential growth is:

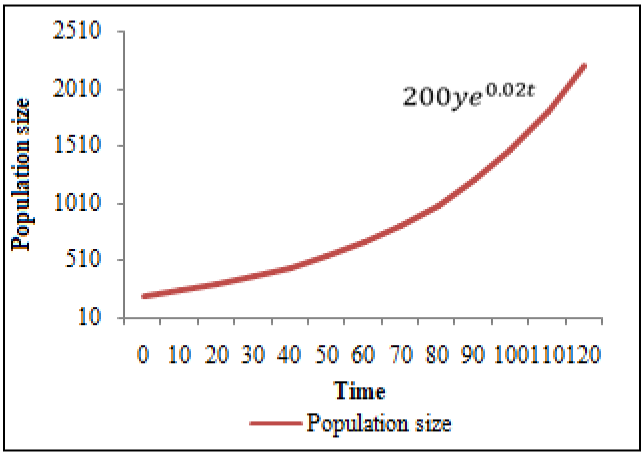

Figure 1: Exponential Growth of Bacteria

The exponential growth model is well suited to calculate tumor size in initial stages and not suitable in long term tumor growth because it may vary indefinitely and does not depend on any constraint.

2.2 Gompertz Model

It is a mathematical model for time series designed by Benjamin Gompertz used to represent the growth is slow in the beginning and end of a given time period. Gompertz curve is used in the Biology where to represent the rapid growth of population size or growth of tumor size when maximum load or population size is able to compute.

The equation is represented as:

$$N(t) = N_0 e^{[\ln(\frac{N_I}{N_0}[1-e^{(bt)}])]} \rightarrow \quad (3)$$

Where N(t) is the Number of cells at time t
N_I is the population number or maximum load
N_0 is the initial number of cells
b is the initial rate of tumor growth

Prof. A.K.Liard successfully represented the growth of tumors using Gompertz curve. The tumor growth depends on the factors like diet, age, ethnicity, metabolism and genetic predispositions, lifestyle etc. In this only a single set of factors or parameters is not sufficient to model the data. Tumor growth depends on patient and their factors and a single patient may also have different growth factors.

2.3 Universal Law (or) West Law:

It describes the growth rates of organisms with the help of energy considerations. West proposed Universal Law. Independent of mass and development time all mammal, birds share a common growth pattern. The same law is used whether tumor growth follows by taking tumor size and growth time. It is taken as ratio given by:

$$r = \left(\frac{m}{M}\right)^{0.25} \rightarrow \quad (4)$$

where m is actual Mass and
M is the asymptotic mass for the taxon
r: is relative proportion of total energy expenditure with respect to time t is given by:

$$t = \frac{1}{4} a M^{-0.25} t - \ln(1 - \left(\frac{m_0}{M}\right)^{0.25}) \rightarrow \quad (5)$$

$$t = \propto r_0 t - \ln(1 - r_0) \quad \rightarrow \quad (6)$$

where $r_0 = \left(\frac{m_0}{M}\right)^{0.25}$ and $\propto = 0.25 a m_0^{-0.25} \rightarrow$ (7)

Here a is a constant proportional to organism’s metabolic rate across taxon. Using the variables t and r, the universal l growth law is as follows:

$$r = 1 - e^{-t} \rightarrow \qquad (8)$$

m_0 and M are the initial and final masses of the tumor and a is a parameter expected to be related to the tumor characteristics.

3. Computational Modeling

3.1 Atomic Level
3.2 Molecular Level
3.3 Microscopic Level
3.4 Macroscopic Level
3.5 Biological Level

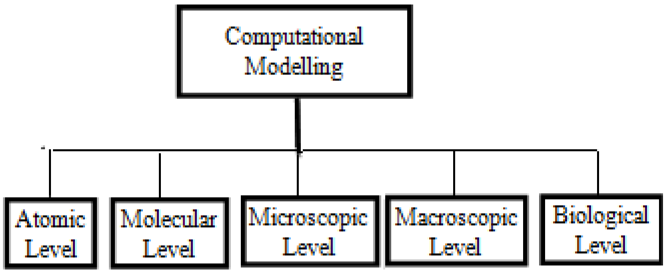

Figure 2: Different Levels of abstraction in Computational Modeling

Atomic Level considers the function, structure and properties of proteins, peptides and lipids.
Molecular Level considers cell signaling processes.
Microscopic Level considers cell progression.
Macroscopic Level considers tissue progression.
Biological Level considers computational tumor models.

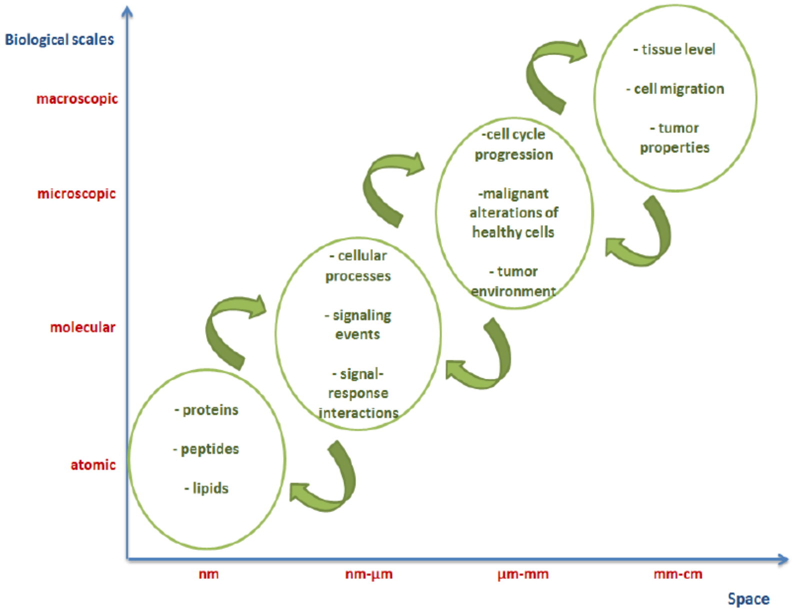

Figure 3: Computational Models for Tumor Study

4. Markup Languages

The most commonly used markup languages are as follows:
a) SMBL
b) CellML
c) FieldML
d) TumorML

a) **SMBL:**
Systems Biology Markup Language (SBML) is a xml (eXtensible Markup Language) based language. It is a description language for simulations in systems biology. SBML is suitable for representing biochemical networks, which includes cell signaling pathways, metabolic pathways, biochemical reactions, gene regulation, and many others. It is a represented format of computational models. Modeling process involves the following steps. SBML allows models of uniformed complexity to be represented. Each type of model is described using a specific type of data structure which organizes the relevant information. The data structures conclude how the resulting model is encoded in XML.

b) Cell ML:
The CellML language is an open standard based on the XML markup language. CellML is developed by the Auckland Bioengineering Institute at The University of Auckland and affiliated research groups. Just as HTML is

the common language for encoding the words on your web browser, CellML is the XML language and software toolkit used to script, store and exchange computer models of biological systems. CellML makes it easy for people to share models, even if they are using different model-building software, and it can easily fit in with models at the tissue and molecular levels. It also lets people build new models and test their models' reliability against other models using CellML validation tools.

c) Field ML:

A Field descriptive language in XML format termed FML (Field Markup Language) as a possible language for the currently undefined FieldML. FML would contain field information with the ability to incorporate CellML models to create tissue-scale representations. A field is defined as a physical property that varies over space and possibly time. It is usually described in terms of tensor, vector or scalar quantities, and can range from global model geometry information through to spatially-varying tissue properties such as cellular parameters.

d) Tumor ML:

Tumor ML, to describe computational cancer models within TUMOR. The motivation for such a markup language is two-fold: To describe the implementation of these cancer models in an abstract manner that is not tied to any particular programming notation. The challenges posed in developing TumorML include formalizing cancer terminology, linking biological entities with computational and mathematical elements of models, and incorporating features to allow for curating models in online repositories. Conceptually, the design of TumorML will take a similar approach to that of CellML in how models are structured to allow modularization and connectivity between components. TumorML, to three key functions: curating cancer models, computationally interfacing with cancer models, and connecting cancer models together.

5. Modeling techniques in Systems Biology

The commonly used Modeling techniques in systems Biology are:

1) Peri Nets
2) Agent Based Models

5.1 Peri Nets

A Petri Net is a collection of directed arcs connecting places and transitions. Places may hold tokens. The state or marking of a net is its assignment of tokens to places. Here is a simple net containing all components of a Petri Net:

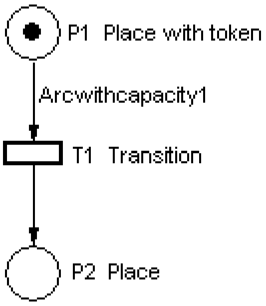

Figure 4: Peri Net model

Notations:

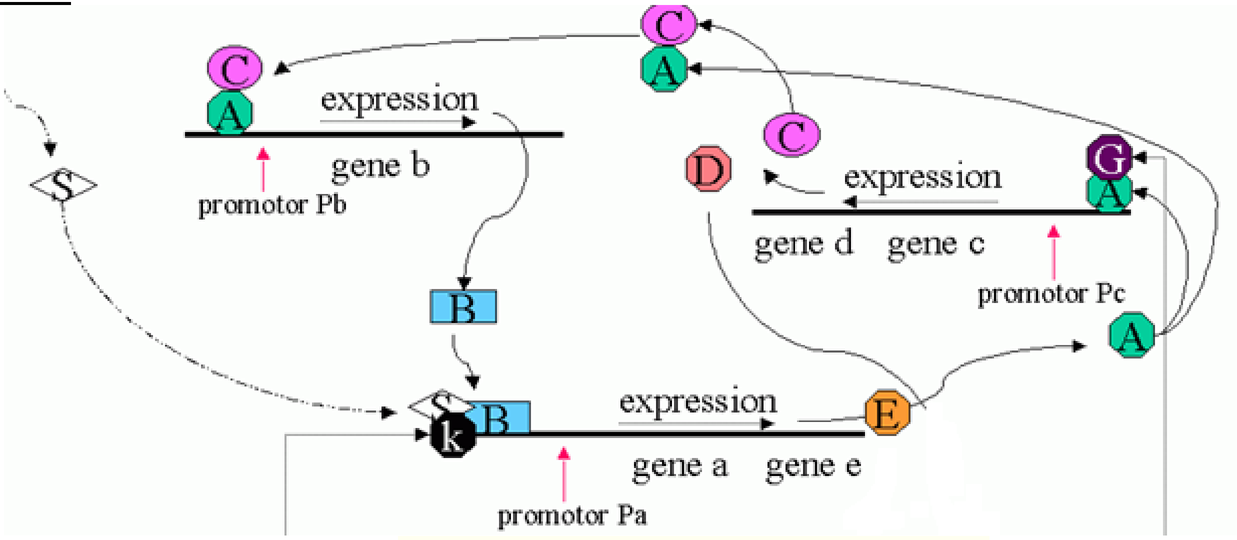

Figure 5: A Petri Net model for the control of a metabolic pathway

1. Dashed Arrows → the direction of transcription of genes
2. The Curved Arrows ↗ denote the transportation of a gene encoded Protein
3. The Straight arrows → denote biochemical reaction
4. The elbow arrows ↱ denote the feedback
5. The double dashed arrows ⇢ denote the signal transduction.

5.2 Agent Based Models

The characteristics of agent-based models important to biological studies include:

1) Modular structure: The behavior of an agent-based model is defined by the rules of its agents. Existing agent rules can be modified or new agents can be added without having to modify the entire model.
2) Emergent properties: Through the use of the individual agents that interact locally with rules of behavior, agent-based models result in a synergy that leads to a higher level whole with much more intricate behavior than those of each individual agent.
3) Abstraction: Either by excluding non-essential details or when details are not available, agent-based models can be constructed in the absence of complete knowledge of the system under study. This allows the model to be as simple and verifiable as possible.
4) Stochasticity: Biological systems exhibit behavior that appears to be random. The probability of a particular behavior can be determined for a system as a whole and then be translated into rules for the individual agents.

6. Conclusion

In this paper we discussed about different mathematical modeling approaches and various Computational Modeling Methods and some of Markup Languages followed by techniques used for Analysis of cancer data especially Tumor related data. This paper gives an introductory review about the approaches to use and apply for data analysis. The proposed extension of this paper is applicability by taking a case based study.

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