Proceedings of the 28th IEEE
EMBS Annual International Conference
New York City, USA, Aug 30-Sept 3, 2006

A Mathematical Model Relating Chromosome Aberrations to Cancer Progression

Julia DiPierdomenico, Hao Ying, Feng Lin, Henry H.Q. Heng

Abstract— **The main focus of this paper is to mathematically represent the dynamics of cancer evolution by studying patterns of chromosomal aberrations. A mathematical model for the progression and evolution of cancer in cultured fibroblast cells is proposed. Solution of the differential equations was performed for a continuous model by assuming variable genetic aberration pseudo reaction rate constants for each stage of cancer. Calculation of the genetic aberration pseudo reaction rate constants provides useful insight into the evolution of cancer as well as providing a tool which is possibly useful in evaluating the efficacy of various cancer treatment modalities. Lastly, this novel approach to quantifying and predicting the dynamics of cancer in an in vitro model may be extended to other forms of malignancies.**

I. Introduction

ABNORMAL chromosomal cycles forms the basis for many malignant tumors. These anomalies fuel the increase rate of mutational anomalies described as aneuploidy, translocations, recombination, deletions, and amplification of genes involved in cellular proliferation and survival. The orchestration of these events results in the genesis of cancer. In 1997, Mitelman et al found that the total number of chromosomal aberrations is roughly proportional to the risk of metastasis [1].

In order to fully understand the role of chromosome abnormality, more specifically clonal chromosomal aberrations (CCA) and non-clonal chromosomal aberrations (NCCA) [2,3], a kinetic model is required to determine the rate at which NCCAs and CCAs proliferate and their exact role in the genesis of cancer. NCCAs include numerical changes (aneuploidy) and structural aberrations. For the purpose of simplifying data presentation, only the frequencies of translocations were analyzed, and a 20% cut off line was used to distinguish between NCCAs and CCAs for the modeling. If a type of translocation occurred less than 20% then it is considered an NCCA. Furthermore, if the type of translocation occurred more or equal to 20%, then it is classified as a CCA.

The proposal of a mathematical model for the genesis of cancer is greatly dependent on understanding the multiple chromosomal aberrations involved in the development of the malignant process and the progression of the chaotic evolution within the cell populations.

To varying degrees, any mathematical model proposed to describe the evolution of cancer attempts to incorporate at least one or more aspects of cell biology. In 2002, Jain proposed and developed a kinetic model for cancer growth and metastases based on tumor interactions between different compartments of the body. These compartments include an existing tumor mass, plasma, and new tumor mass. This model utilized experimental rate constants to predict tumor growth in different compartments of the body. In essence, the kinetics of the process has been studied rather than the kinetics of a single entity as the cell transforms from a normal cell to a high grade malignancy [4].

In 2000, Patel presented a mathematical model which studied early tumor growth up to and including the early stages of invasion. Using spherical coordinates, differential vector gradients, and diffusion constants, tumor growth was predicted utilizing diffusion gradients for glucose and hydrogen ion concentrations [5]. Their simulations concluded that a small clone of tumor cells will progressively transform and manipulate their local environment to make it hostile for the growth of normal cells and favorable for tumorogenesis. They define the process of acid removal and glucose delivery through an actual vessel network associated with angiogenesis.

A 1996 publication by Gatenby and Gawlinski described a reaction-diffusion model of cancer invasion [6]. They proposed a mechanism for cancer invasion through tumor induced alteration of micro-environmental hydrogen ion concentration.

Further literature reviews identify an additional number of time dependent models that attempt to explain the development and dissemination of cancer. A group of non stochastic models have been developed using systems of partial differential equations. In 1999, Ward and King focused on avascular tumor growth saturation [7]. A model for tumorogenesis was proposed in 1998 by Anderson and Chaplain [8]. In essence all of the aforementioned models study the kinetics of the process rather than the kinetics of a single entity. As such, each of these models share the same weakness which relates to the lack of quantification of mitotic figures, chromosomal aberrations, and other intranuclear developments. Accordingly, an extensive literature review directed at chromosomal aberrations and

Manuscript received April 3, 2006. This research was supported in part by a Wayne State University Research Enhancement Grant and a grant from the Susan G. Komen Breast Foundation.

J. DiPierdomenico, was with the College of Electrical and Computer Engineering at Wayne State University, Detroit Michigan 48202 (julesdp11@yahoo.ca).

H. Ying, is with Wayne State University, Department of Electrical and Computer Engineering, Detroit Michigan 48202 USA (phone: 313-577-3738; fax: 313-578-5833; e-mail: hao.ying@wayne.edu).

H. H. Heng, is with Wayne State University School of Medicine, Center for Molecular Medicine and Genetics, Detroit Michigan 48202 USA (hheng@genetics.wayne.edu).

F. Lin, is with the Electrical and Computer Engineering Department, Wayne State University, Detroit Michigan 48202 (flin@ece.wayne.edu).

reaction rate kinetics was performed and found to be unproductive.

Cancer research to date reveals a relative lack of shared clonal chromosomal aberrations during the early stages of cancer development. Because of this, Heng et al have focused on the increasing rates of non-clonal chromosomal aberrations as the key predictor of genomic instability even though NCCAs have received inadequate attention in the field of clinical cancer [2-3]. Heng proposes that "NCCAs are the key elements initiating the formation of CCAs and that NCCAs provide the basis for various populations of CCAs that causes the formation of karyotypical heterogeneity in cancer" [9].

The purpose of this research is to mathematically represent the dynamics of cancer using a cellular immortalization process as a model. In turn this will provide insight into cancer initiation and progression and guide further experimentation and development of new therapies.

II. Proposed Model

A. Kinetic Model

The proposed model focuses on stage specific constants describing the actual chaotic process occurring within the cell populations. During the process of cancer development there is a chaotic process occurring within the cell populations. This chaotic process can be describes as the formation of NCCAs and CCAs and the dynamic relative relationship between the two. This model attempts to trace this chaotic process mathematically. Furthermore, the proposed model utilizes dynamic genetic aberration pseudo reaction rate constants and describes the role of CCA and NCCA in the evolution of cancer on a population basis. The advantages of proposing the present model is that there is no requirement to assume parameter values or derive reaction rate constants from additional laboratory experimentation as with the past models. The model presented here does not assume rate constants but rather derives the constants directly from the defining differential equations and the experimental data.

Figure 1 describes an intranuclear biological process where a normal cell containing normal chromosomes is approaching chromosome aberrations. As these normal cells are eliminated, the ones that survive contribute to aberrational defects described as NCCA and CCA. Furthermore, there is a relationship between NCCA and CCA as described in Figure 1. Lastly, some NCCA and CCA will be eliminated through cell death.

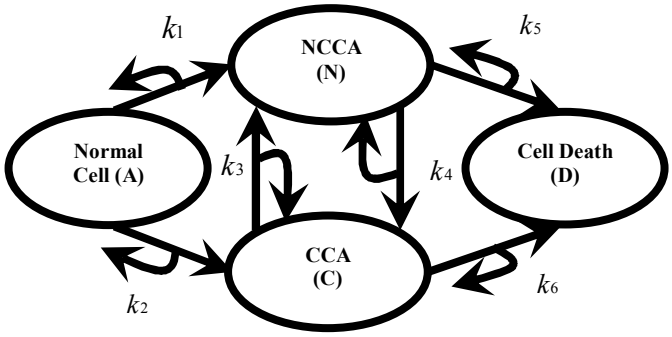

Fig. 1. Proposed Pathway for Cancer Evolution and Progression when k_n is equal to the pseudo reaction rate constant.

In the proposed model, k_n represents the neoplastic aberration pseudo reaction rate constant, n represents 1-6, A equals the concentration ratio of normal chromosomes, N equals the concentration ratio of NCCA, C equals the concentration ratio of CCA, D equals the concentration of non-functional chromosomes, and τ is equal to the cancer stage. The basic assumptions that were used when developing the kinetic model are: k_n is a function of extrinsic and intrinsic genetic, epigenetic and environmental factors including genomic internal and induced genomic instability. k_1 and k_2 represent the balance between depletion of A, if positive, and the repair and replication of A if negative. k_3 and k_4 represent the balance between the depletion of CCA and NCCA respectively if positive and the repair and replication of CCA and NCCA if negative. k_5 and k_6 represent the balance between the demise of NCCA and CCA respectively if positive and the repair and replication of NCCA and CCA if negative. Each chromosome is in equilibrium between development of mutation and repair of mutations and eventually the mutation process is greater than the repair process and leads to structural changes. Lastly, at some point in time when chromosomal damage is excessive, the repair genes become totally ineffective and the chromosomal structure severely deteriorates thereby resulting in the demise of the cell.

B. Normalized Data

The data for this paper was generated by the laboratory of Dr. Heng and represents stage visual snapshots of the biological process for a specific cancer stage. The experiments involved a skin specimen harvested from a patient with p 53 mutation was placed inside a petri dish and cultured for various generations. The mitotic figures of the last generation were then randomly analyzed with the FISH and SKY methods and the chromosome number and translocations were determined and further classified as NCCA or CCA.

Normalized data represents the data expressed as a fraction, ratio, or pseudo concentration. The following equations were used to normalize the data from the experimental results:

$$A(\tau) = \frac{\sum A(\tau)}{\sum A(\tau) + \sum CCA(\tau) + \sum NCCA(\tau)} \quad (1)$$

$$CCA(\tau) = \frac{\sum CCA(\tau)}{\sum A(\tau) + \sum CCA(\tau) + \sum NCCA(\tau)} \quad (2)$$

$$NCCA(\tau)=\frac{\sum NCCA(\tau)}{\sum A(\tau)+\sum CCA(\tau)+\sum NCCA(\tau)} \quad (3)$$

where: $$A(\tau)+N(\tau)+C(\tau)=1 \quad (4)$$

Because the above process is thought to be defined by the laws of nature, and giving proper consideration to the shape of the curves represented by the experimental data, it is assumed that:

$$A(\tau)=\alpha_1 e^{f_1(\tau)} \quad (5)$$

$$N(\tau)=\alpha_2 e^{f_2(\tau)} \quad (6)$$

$$C(\tau)=\alpha_3 \ln\left(e^{f_3(\tau)}\right)=\alpha_3 f_3(\tau) \quad (7)$$

Least-squares curve fitting reveals that $\alpha_1=0.990$, $\alpha_2=1.000$ and $\alpha_3=1.000$. Substitution of these values into equations (5), (6) and (7) gives the following equations:

$$f_1(\tau)=-1.0986\tau^2 \quad (8)$$

$$f_2(\tau)=\frac{-2.1533+1.2083\tau-0.1702\tau^2}{1+0.6286\tau-0.3574\tau^2+0.0402\tau^3} \quad (9)$$

$$f_3(\tau)=\frac{7.6289(10)^{-5}+1.7209\tau-0.9534\tau^2-0.1312\tau^3}{1+3.5118\tau^2-1.8469\tau^2+0.2310\tau^3} \quad (10)$$

Equations (8), (9) and (10) are graphically represented with the experimental data:

a)

b)

c)

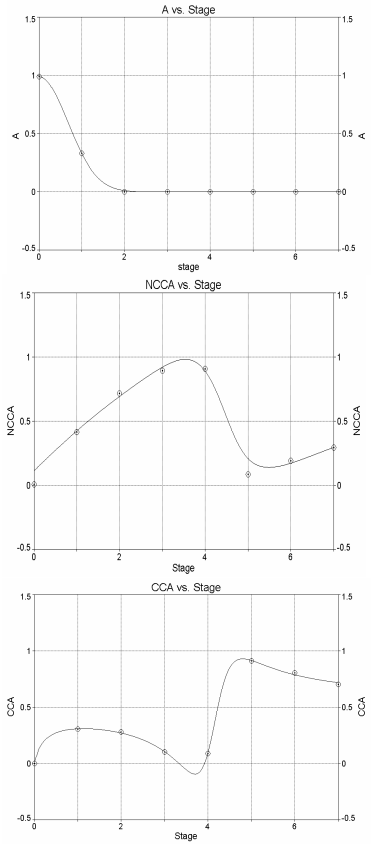

Fig. 2. Curve fitting for a) A as a function of stage, b) NCCA as a function of stage and c) CCA as a function of stage.

C. Theoretical Consideration

The following equations were developed by balancing the entrance and exit normalized ratios of A, CCA and NCCA using the kinetic model in Figure 1. Considering stage τ, to be continuous, a balance was determined such that:

$$\frac{dA(\tau)}{d\tau}=-k_{12}A \quad (11)$$

$$\frac{dC(\tau)}{d\tau}=k_2A(\tau)+k_4N(\tau)-k_{36}C(\tau) \quad (12)$$

$$\frac{dN(\tau)}{d\tau}=k_1A(\tau)+k_3C(\tau)-k_{45}N(\tau) \quad (13)$$

Where $k_{12}=k_1+k_2$, $k_{36}=k_3+k_6$ and $k_{45}=k_4+k_5$.

From the above relationships, stage specific pseudo reaction rate constants are calculated and illustrated below.

TABLE I
STAGE SPECIFIC MUTATION PSEUDO REACTION RATE CONSTANTS

Stage	k1	k2	k3	k4	k5	k6
0.5	0.3570	1.7184	0.5829	2.0579	-2.1074	3.6334
1.5	0.2329	0.4361	0.6583	-0.0043	-0.0733	-0.3289
2.5	-2.2540	0.0311	0.5793	-0.3865	0.2343	-1.2784
3.5	undefined	undefined	2.5799	-0.2894	0.3028	-2.4589
4.5	undefined	undefined	-1.4807	1.4906	-1.1675	0.9254
5.5	undefined	undefined	-0.4786	0.4282	-3.1675	0.7142
6.5	undefined	undefined	0.0809	0.4338	-0.6497	0.1562

D. Solution of the differential equations with boundary conditions

It is known that when $\tau=0$, $C(\tau)=0$, $N(\tau)=0.01$ and $A_0=0.99$, the following equations are obtained:

$$A(\tau)=A_0e^{-k_{12}\tau} \quad (14)$$

$$C(\tau)=A_0\left(\frac{k_2-k_4}{k_{346}-k_{12}}\right)e^{-k_{12}\tau}-\left[A_0\left(\frac{k_2-k_4}{k_{346}-k_{12}}\right)+\frac{k_4}{k_{346}}\right]e^{-k_{346}\tau}+\frac{k_4}{k_{346}} \quad (15)$$

$$N(\tau)=A_0\left(\frac{k_1-k_3}{k_{345}-k_{12}}\right)e^{-k_{12}\tau}-\left[\left(A_0\left(\frac{k_1-k_3}{k_{345}-k_{12}}\right)+\frac{k_3}{k_{345}}\right)-0.01\right]e^{-k_{345}\tau}+\frac{k_3}{k_{345}} \quad (16)$$

where $k_{346}=k_3+k_4+k_6$ and $k_{345}=k_3+k_4+k_5$. When $A_0=0$, the above equations reduce to:

$$C(\tau)=\frac{k_4}{k_{346}}\left(1-e^{-k_{346}\tau}\right) \quad (17)$$

$$N(\tau) = \frac{k_3}{k_{345}}\left(1 - e^{-k_{345}\tau}\right) + 0.01e^{-k_{345}\tau} \quad (18)$$

Now, substitution of stage pseudo rate constants in the theoretically derived functions of $C(\tau)$ and $N(\tau)$ allows comparison of the interpolated observational data verses theoretical data illustrated in Table 2.

TABLE 2
OBSERVATIONAL AND THEORETICAL DATA

τ	$N(\tau)_{obs}$	$N(\tau)_{theor.}$	$C(\tau)_{obs}$	$C(\tau)_{theor.}$
0.5	0.2741	0.2038	0.2749	0.2901
1.5	0.5667	0.4156	0.3039	0.3081
2.5	0.8159	0.8934	0.2129	0.3324
3.5	0.9816	0.9947	-0.0532	-1.3798
4.5	0.5343	-230.9005	0.8489	1.5700
5.5	0.1503	-6734661.9870	0.8477	0.6283
6.5	0.2403	0.8659	0.7479	0.6383

It can be seen that experimental static stage sampling through microscopy reveals the earliest demise or discontinuation of CCA in stage 2. The model however predicts the demise of normalized CCA in stage 0-1 followed by repair and replication of CCA from stages 2-4 even though the normalized values of CCA falls. At the same time, the normalized values of NCCA are increasing. Beyond stage interval 0-1, all other stage intervals reveal reciprocal changes between normalized NCCA and CCA.

A broad overview of k_n trends reveals a repetitive synchrony within stage interval 0-1 and 4 to 7. That is a positive k_4 is in synchrony with a positive k_6 and the two positives are always associated with a negative k_5. In addition in stage interval 2-3 and 3-4 a positive k_5 is in synchrony with a positive k_3 and the two positives are always associated with a negative k_6. Furthermore there is no period or interval in which the relative demise of normalized CCA and NCCA exits simultaneously. This pattern of alternating change is very well supported by the microscopic observations that as previous members of one species are eliminated and become discontinuous the second species begins domination to produce a more complex form of the first species. This type of reciprocal enhancement guarantees a cyclical process of chaos which breeds more specialized and resistant form of chaos in perpetuity. The stage interval mutation pseudo rate constants allow a quantitative assessment of species vulnerability and may be useful for intervention with either pharmacologic or radiation therapy.

Stage interval 4-5 deserves special attention in recognition of the explosive changes that are occurring. In this stage interval, even though there is a significant demise of normalized CCA species, this loss is small compared to the repair and replication of CCA and significant contribution from NCCA. Even though NCCA species is falling, there is no relative demise of NCCA but rather significant repair and replication. These factors are confirmed microscopically and truly represent the traditional hallmark of cancer. Again these observations and mathematical predictions may translate into pharmacotherapeutic value in cancer treatment.

Lastly, as stage interval progresses from stage 4 through 7, the mathematical model predicts moderate cell demise through species CCA although the values of k_6 become progressively smaller indicating progressive specialization of cells to evade cell death. Both normalized NCCA and CCA approach the same value without major pattern reversals. This trend supports the formation of highly specialized cell lines which have increased their homogeneity and capacity to reproduce indefinitely.

A comparison of observational and theoretical values of $N(\tau)$ and $C(\tau)$ reveals a breakdown in model validation corresponding to values of τ when k_{345} and k_{346} approach zero.

IV. Conclusion

Examination of the results obtained by curvilinear analysis of normalized data reveals theoretical values which are most consistent with experimental data. This model represents a dynamic tool to describe the evolution of cancer. In summary, a continuous curvilinear mathematical model for the development and evolution of cancer in an *in vitro* model was developed. Genetic aberration pseudo reaction rate constants were calculated by using first order differential equations. Clinical application for this research as a tool for evaluating the efficacy of cancer treatment modalities is a real possibility. This novel analytical technique can be used to identify early clonal patterns of change thought to be shared by the same types of tumors and thus identifying a common pathway for the development of cancer.

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