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DNA MUTATION AND TUMOR FORMATION II: ANALYSIS OF FORMULATED MODEL

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Abstract:

We modeled the mathematical equations describing the formation of tumour due to DNA mutation. In the modeled equations, the effects of environmental factors, DNA replication defect, Viruses and error in DNA repairs were included as the major causes of DNA mutation. These modeled equations were analysed and we saw that once these factors are allowed in our system, the DNA will always be unstable. This means that there are suppressor genes that inactivate the function of the TSG's. Hence, the tumour growth enhancing factors are there in the system and so we cannot rule out the possibility of tumour formation in our body.

Keywords: DNA Mutation, Tumor formation, Equilibrium analysis, Stability.

1. INTRODUCTION

Obviously the gene is the major block that control all happenings in human system. It spearheads growth, differentiation and control/enhancement of diseases growth. The latter is as a result of external influences that change the gene which makes the gene to make wrong interpretations of received signals. As a result, this endangers human system leading to their being susceptible to various degrees of illness; in vivo and in vitro. The gene is contained in an 'X" shaped structure known as the DNA which in turn is embedded in the chromosome.

It has been observed that the number of cells existing in a region in order to maintain equilibrium (proper health) varies at times due to influences that battle with the gene thereby disrupting its normal plan forcing it to misunderstand and misinterpret information to be passed across.

Tumor is one of the diseased conditions that occur as a result of gene over-expression or under-expression. Various kinds of Tumors ranging from; lung, esophageal, tracheal, breast etc has directly or indirectly been associated with gene stretching (over-expression and under-expression).

One of the core causes of gene error is DNA Mutation which in turn leads to spontaneous/ unregulated cell division, chunking out many more cells in the region by doubling, tripling etc of the exact number of cells that should be in the region to maintain balance.

Relatively, this paper is carved out so as to see know and understand the contribution of DNA Mutation in Tumor formation via two major genes; namely; one that stimulates cell division (the proto-oncogene) and the other that stalls/inhibits cell division (Tumor suppressor gene).

CAUSES OF DNA MUTATION

DNA mutation is a change in the base sequence of the DNA. These mutations in DNA sequences generally occur through one or all of these four processes:

- DNA damages from environmental agents such as ionizing radiation, alcohol, smoke and other chemicals. This involves the following:

  Modifying nucleotide bases- Environmental mutagens can damage DNA by altering nucleotide bases so that they look like others. When the DNA strands are separated and copied, the altered base will pair with an incorrect base and cause a mutation.

Breaking the phosphate backbone- They can damage DNA by breaking the bonds between oxygen (o) and phosphate group (p). This creates a mutated form of the gene. Possibly the mutated gene will produce a protein that functions differently. Cells with broken DNA will attempt to fix the broken ends by joining free ends to other pieces of DNA within the cell.

- Mistakes that occur when a cell copies its DNA in preparation for/during cell division (DNA REPLICATION).

  Prior to cell division, each cell must duplicate its entire DNA sequence. This process is called DNA replication. It begins with a protein called DNA helicase which separates the DNA molecule into two strands. Next, a protein called DNA polymerase copies each strand of DNA to create two double-stranded molecule. Any mistake made by the DNA polymerase becomes a mutation.
- Certain viruses.
- Error during DNA repair.

  (http://learn.genetics.utah.edu/archive/sloozeworm/mutationbg.html)

More detailed information the effects of these listed factors can be found [4] and [5]

MODEL EQUATIONS

In our earlier paper, [5], we made the following assumptions in coming out with models given below:

Cells in a region grows/remains as supposed if namely:

The proto-oncogenes are properly functioning (stimulating cell division)
The Anti-oncogenes (Tumor suppressor genes) are also not short-changed in their job (inhibiting cell division)

Using the following factors based on our research/knowledge on how the number of cells in a region increases, we formulate the required models. The factors were:

- ✓ *Influence of environmental agents (ionizing radiation, smoke, Alcohol, Hormone, certain drugs etc.*
- ✓ *Effect of virus (DNA Virus)*
- ✓ *Error during DNA replication without repair (cell copying)*

- ✓ *Error in course of DNA repair (Mismatch repair)*

So let

$T =$ *Number of cells in a region*

$E_T =$ *Effect/influence of environmental agents on cell multiplication.*

$V_T =$ *Effect of DNA virus on cell multiplication.*

$R_T =$ *Effect of error during DNA replication without repair on cell multiplication.*

$\overline{R}_T =$ *Effect of error during DNA repair on cell multiplication.*

Combining the factors, hence a model equation describing change in number of cells in a region with respect to Proto-oncogene mutation (OM) and Anti-oncogenic (Tumor suppressor gene) mutation (AOM) respectively, with time are given as:

$$\frac{dT}{dt}\Big|_{OM} = a_0T + a_1E_T + a_2V_T + a_3R_T + a_4\overline{R}_T \text{ ----------(1)}$$

$$\frac{dT}{dt}\Big|_{AOM} = b_0T - b_1E_T - b_2V_T - b_3R_T - b_4\overline{R}_T \text{ ----------(2)}$$

$$\frac{dT}{dt} = \text{equation}(1) + \text{equation}(2) \text{ ----------(3)}$$

where a_0 *is a model parameter that estimates the exact number of cells that maintain balance in a region through* OM, a_1 *measures the increase in the number of cells produced due to the effect of environmental agents on the cells in a region,* a_2 *measures the increase in the number of cells due to interception by a DNA Virus,* a_3 *measures additional increase in the number of cells due to cell copying error,* a_4 *estimate additional increase in the number of cells due to mismatch repair error.*

b_0, b_1, b_2, b_3 *and* b_4 *are same as above but with respect to* AOM.

$$\frac{dT}{dt} = a_0T + a_1E_T + a_2V_T + a_3R_T + a_4\overline{R}_T + b_0T - b_1E_T - b_2V_T - b_3R_T - b_4\overline{R}_T$$

and $a_0 + b_0 = z_0$ (since we are working on same region)

where E_T, V_T, R_T are given as

$$\left.\begin{aligned}
(i)\quad & \frac{dE_T}{dt} = c_0E_T + c_1E_T + c_2E_T + c_3E_T \\
(ii)\quad & \frac{dV_T}{dt} = d_0V_T + d_1V_T + d_2V_T \\
(iii)\quad & \frac{dR_T}{dt} = e_0R_T + e_1R_T + e_2R_T \\
(iv)\quad & \frac{d\overline{R}_T}{dt} = f_0\overline{R}_T + f_1\overline{R}_T + f_2\overline{R}_T + f_3\overline{R}_T
\end{aligned}\right\} OM$$

And

$$\left.\begin{aligned}
&(v)\quad \frac{dE_T}{dt} = k_0E_T - k_1E_T - k_2E_T - k_3E_T \\
&(vi)\quad \frac{dV_T}{dt} = m_0V_T - m_1V_T \\
&(vii)\quad \frac{dR_T}{dt} = n_0R_T - n_1R_T - n_2R_T - n_3R_T \\
&(viii)\quad \frac{d\overline{R}_T}{dt} = p_0\overline{R}_T - p_1\overline{R}_T - p_2\overline{R}_T
\end{aligned}\right\} AOM$$

ANALYSIS

EQUILIBRIUM ANALYSIS

In this section, we discuss the condition for equilibrium of the various states. In other words, presenting the conditions for which there are no variations in the states.

PROTO-ONCOGENE CASE

Here we present the equations which are the models for the state variable under study. They are thus listed below

$$\frac{dT}{dt} = a_0T + a_1E_T + a_2V_T + a_3R_T + a_4\overline{R}_T \text{ ----------} (1.1)$$

$$\frac{dE_T}{dt} = c_0E_T + c_1E_T + c_2E_T + c_3E_T \text{ ----------} (1.2)$$

$$\frac{dV_T}{dt} = d_0V_T + d_1V_T + d_2V_T \text{ ----------} (1.3)$$

$$\frac{dR_T}{dt} = e_0R_T + e_1R_T + e_2R_T \text{ ----------} (1.4)$$

$$\frac{d\overline{R}_T}{dt} = f_0\overline{R}_T + f_1\overline{R}_T + f_2\overline{R}_T + f_3\overline{R}_T \text{ ----------} (1.5)$$

For equilibrium we must have

$$\frac{dT}{dt} = 0$$

i.e

$$a_0T + a_1E_T + a_2V_T + a_3R_T + a_4\overline{R}_T = 0 \text{ ---------- } (1.6)$$

$$c_0E_T + c_1E_T + c_2E_T + c_3E_T = 0 \text{ ---------- } (1.7)$$

$$d_0V_T + d_1V_T + d_2V_T = 0 \text{ ---------- } (1.8)$$

$$e_0R_T + e_1R_T + e_2R_T = 0 \text{ ---------- } (1.9)$$

$$f_0\overline{R}_T + f_1\overline{R}_T + f_2\overline{R}_T + f_3\overline{R}_T = 0 \text{ ---------- } (1.10)$$

From equation (1.7)

$$E_T(c_0 + c_1 + c_2 + c_3) = 0$$

$$\Rightarrow E_T \neq 0 \quad \text{and} \quad c_0 + c_1 + c_2 + c_3 = 0$$

$$\Rightarrow c_3 = -(c_0 + c_1 + c_2)$$

This implies that the rate at which the selective effect of oncogenic mistake due to long lasting alteration of adaptive pathway influences the effect of environmental agents is greater than the rate at which other factors (over expression, inhibiting guanine etc), affects the system at equilibrium

From equation (1.8)

$$d_0V_T + d_1V_T + d_2V_T = 0$$

$$\Rightarrow V_T(d_0 + d_1 + d_2) = 0$$

$$\Rightarrow V_T \neq 0 \quad \text{and} \quad d_0 + d_1 + d_2 = 0$$

$$\Rightarrow d_0 = -(d_1 + d_2)$$

We can see that at equilibrium the rate at which virus affects the number of cells in a region is greater than the sum of the rates at which it increases the cell growth 'an' oncogene binding and cellular proto-oncogene activation.

From (1.9)

$$e_0R_T + e_1R_T + e_2R_T = 0$$

$$\Rightarrow R_T(e_0 + e_1 + e_2) = 0$$

$$\Rightarrow R_T \neq 0 \quad \text{and} \quad e_0 + e_1 + e_2 = 0$$

$$\Rightarrow e_1 = -(e_0 + e_2)$$

It is observed that at equilibrium the increased rate of mitosis contribute higher in the number of cells than the sum of the rate of increase in number of cells rising from gene over expression and that which ensures balance in DNA replication error without repair.

From (1.10)

$$f_0\overline{R}_T + f_1\overline{R}_T + f_2\overline{R}_T + f_3\overline{R}_T = 0$$
$$\Rightarrow \overline{R}_T\left(f_0 + f_1 + f_2 + f_3\right) = 0$$
$$\Rightarrow \overline{R}_T \neq 0 \text{ and } f_0 + f_1 + f_2 + f_3 = 0$$
$$\Rightarrow f_3 = -\left(f_0 + f_1 + f_2\right)$$

It can be deduced that the rate at which cell number increases at equilibrium due to loss of binding and failure to turn on some protein is less than the contribution from gene amplification.

From equation (1.6)

$$\frac{dT}{dt} = a_0T + a_1E_T + a_2V_T + a_3R_T + a_4\overline{R}_T = 0$$
$$\Rightarrow a_0T = -\left(a_1E_T + a_2V_T + a_3R_T + a_4\overline{R}_T\right)$$
$$\Rightarrow T = \frac{-1}{a_0}\left(a_1E_T + a_2V_T + a_3R_T + a_4\overline{R}_T\right)$$

At equilibrium state

$E_T = V_T = R_T = \overline{R}_T = 0$

$\Rightarrow T = 0$ and thus $\frac{dT}{dt} = 0$

ANTI-ONCOGENIC (TSG) CASE

$$b_0T - b_1E_T - b_2V_T - b_3R_T - b_4\overline{R}_T = 0 \text{----------}(1.11)$$
$$k_0E_T - k_1E_T - k_2E_T - k_3E_T = 0 \text{----------}(1.12)$$
$$m_0V_T - m_1V_T = 0 \text{----------}(1.13)$$
$$n_0R_T - n_1R_T - n_2R_T - n_3R_T = 0 \text{----------}(1.14)$$
$$p_0\overline{R}_T - p_1\overline{R}_T - p_2\overline{R}_T = 0 \text{----------}(1.15)$$

From equation (1.12)

$$k_0E_T - k_1E_T - k_2E_T - k_3E_T = 0$$
$$\Rightarrow E_T\left(k_0 - k_1 - k_2 - k_3\right) = 0$$
$$\Rightarrow E_T \neq 0 \text{ and } k_0 - k_1 - k_2 - k_3 = 0$$
$$\Rightarrow k_3 = k_0 - k_1 - k_2$$

At equilibrium, the rate at which some tumor suppressor gene are down regulated equals the difference between the parameter that measures balance due to environmental agents and sum of

the rate of influence by loss/inactivation of some tumor suppressor genes and loss of heterozygosity.

From equation (1.13)

$$m_0 V_T - m_1 V_T = 0$$
$$\Rightarrow \mathrm{V_T}\left(m_0 - m_1\right) = 0$$
$$\Rightarrow V_T \neq 0 \text{ and } m_0 - m_1 = 0$$
$$\Rightarrow m_0 = m_1$$

It is observed that at the intrusion of DNA viruses in the tumor suppressor genes, parameter that estimates balance in the cell population equals the factor that measures the rate at which the loss of function of some protein affects the cell growth at equilibrium

From (1.14)

$$n_0 R_T - n_1 R_T - n_2 R_T - n_3 R_T = 0$$
$$\Rightarrow R_T\left(n_0 - n_1 - n_2 - n_3\right) = 0$$
$$\Rightarrow R_T \neq 0 \text{ and } n_0 - n_1 - n_2 - n_3 = 0$$
$$\Rightarrow n_3 = n_0 - n_1 - n_2$$

This means that at equilibrium the measure of rate at which some TSGS fails to function equals the difference between the measure of rate that maintains balance during cell copying error without repair and the sum of the rates from homozygous deletion and triggering of apoptosis.

From (1.15)

$$p_0 \overline{R}_T - p_1 \overline{R}_T - p_2 \overline{R}_T = 0$$
$$\Rightarrow \overline{R}_T\left(p_0 - p_1 - p_2\right) = 0$$
$$\Rightarrow \overline{R}_T \neq 0 \text{ and } p_0 - p_1 - p_2 = 0$$
$$\Rightarrow p_0 = p_1 + p_2$$

It follows that the measure that estimate balance in the number of cells in a region equals the sum of the measure of change due to loss of mismatch and reduction homozygosity in the course of error during repair at equilibrium.

From (1.11)

$$b_0 T - b_1 E_T - b_2 V_T - b_3 R_T - b_4 \overline{R}_T = 0$$
$$\Rightarrow b_0 T = +\left(b_1 E_T + b_2 V_T + b_3 R_T + b_4 \overline{R}_T\right) = 0$$
$$\Rightarrow T = \frac{1}{b_0}\left(b_1 E_T + b_2 V_T + b_3 R_T + b_4 \overline{R}_T\right)$$

At eqilibruim state, we expect

$$E_T = 0 = V_T = R_T = \overline{R}_T.$$
$$\Rightarrow T = 0$$

thus $\frac{dT}{dt} = 0$

STABILITY ANALYSIS

STABILITY FOR A SYSTEM OF LINEAR EQUATION.

For system of equation in E_T , V_T, R_T and $\overline{R}_T$ which can be represented in vector form U we define

$$\frac{dU}{dt} = f(\tau, U) \text{----------} (2.1)$$

$$f_i(\tau, V) = A_{ij}(\tau)u_j + B_{ijk}(\tau)u_j u_k + C_{ijk}(\tau)u_j u_k u_l + 0(\|u\|)' \text{----------} (2.2)$$

and u_j can be E_T, V_T, R_T or $\overline{R}_T$. We try to establish the condition for the stability of the system.

The same equation (2.1) and (2.2) hold in R^n .

In general, the subscripts range over (1, 2, ---n) in R^n

To test the stability of the steady solution $u(\tau)$

Corresponding to the zero solution $U = 0$ of (2.1), we examine the evolution of a disturbance δ of $U = 0$, which in the linearised approximation satisfies

$$\frac{d\delta}{dt} = f_u(\tau, 0/\delta) = A(\tau)\cdot\delta \text{---------} (2.3)$$

Or in index notation

$$\frac{d\delta_i}{dt} = A_{ij}(\tau)\delta_j \text{----------} (2.4)$$

The stability for small disturbance of the solution $U = 0$ is controlled by the eigenvalues of $A(\tau)$ (2.3)

Using the concept of the spectral problem and stability of the solution $U = 0$

in R^n for such problem. We get $\delta = e^{\alpha t}X$ in (2.3)

$$(A(\tau))X = \alpha X \text{----------} (2.5)$$

Where $\alpha(\tau) = \xi(\tau) + i\eta(\tau) \text{----------} (2.6)$

is an eigenvalue of $A(\tau)$ if $X \neq 0$, we say that $U = 0$ is stable by the criterion of the spectral problem if $\xi(\tau) < 0$ for all eigenvalues $\alpha(\tau)$ and is unstable if there is a value α solving (2.5) with $A \neq 0$ for which $\xi(\tau) > 0$, [2].

Based on this, we consider the set of equation for PROTO-ONCOGENE MUTATION AND TSG MUTATION to determine whether they are stable or unstable at the equilibrium point.

THE STABILITY FOR PROTO-ONCOGENE MUTATION MODEL

$$\frac{dT}{dt} = a_0 T + a_1 E_T + a_2 V_T + a_3 R_T + a_4 \overline{R}_T$$

$$\frac{dV_T}{dt} = d_0 V_T + d_1 V_T + d_2 V_T = V_T (d_0 + d_1 + d_2)$$

$$\frac{dR_T}{dt} = e_0 V_T + e_1 R_T + e_2 R_T = R_T (e_0 + e_1 + e_2)$$

$$\frac{d\overline{R}_T}{dt} = f_0 \overline{R}_T + f_1 \overline{R}_T + f_2 \overline{R}_T + f_3 \overline{R}_T = \overline{R_T} (f_0 + f_1 + f_2 + f_3)$$

In Matrix form this becomes

$$\begin{pmatrix} \dot{T} \\ \dot{E} \\ \dot{V}_T \\ \dot{R}_T \\ \dot{\overline{R}}_T \end{pmatrix} = \begin{pmatrix} a_0 & a_1 & a_2 & a_3 & a_4 \\ 0 & (c_0 + c_1 + c_2 + c_3) & 0 & 0 & 0 \\ 0 & 0 & (d_0 + d_1 + d_2) & 0 & 0 \\ 0 & 0 & 0 & (e_0 + e_1 + e_3) & 0 \\ 0 & 0 & 0 & 0 & (f_0 + f_1 + f_2 + f_3) \end{pmatrix} \begin{pmatrix} T \\ V_T \\ R_T \\ \overline{R}_T \end{pmatrix}$$

The eigenvalues of the Matrix are given by

$$\left|\begin{pmatrix} a_0 & a_1 & a_2 & a_3 & a_4 \\ 0 & (c_0+c_1+c_2+c_3) & 0 & 0 & 0 \\ 0 & 0 & (d_0+d_1+d_2) & 0 & 0 \\ 0 & 0 & 0 & (e_0+e_1+e_3) & 0 \\ 0 & 0 & 0 & 0 & (f_0+f_1+f_2+f_3) \end{pmatrix} - \gamma \begin{pmatrix} 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}\right| = 0$$

$$\Rightarrow \left|\begin{pmatrix} a_0-\gamma & a_1 & a_2 & a_3 & a_4 \\ 0 & (c_0+c_1+c_2+c_3)-\gamma & 0 & 0 & 0 \\ 0 & 0 & (d_0+d_1+d_2)-\gamma & 0 & 0 \\ 0 & 0 & 0 & (e_0+e_1+e_3)-\gamma & 0 \\ 0 & 0 & 0 & 0 & (f_0+f_1+f_2+f_3)-\gamma \end{pmatrix}\right| = 0$$

$$\Rightarrow (a_0-\gamma)(c_0+c_1+c_2+c_3-\gamma)(d_0+d_1+d_2-\gamma)(e_0+e_1+e_2+-\gamma)(f_0+f_1+f_2+f_3-\gamma)=0$$

$$\Rightarrow \gamma_1 = a_0; \quad \gamma_2 = c_0+c_1+c_2+c_3; \quad \gamma_3 = d_0+d_1+d_2$$

$$\gamma_4 = e_0+e_1+e_2; \quad \gamma_5 = f_0+f_1+f_2+f_3$$

Thus all the eigen- values are

$$a_0 > 0; c_0+c_1+c_2+c_3 > 0; \ d_0+d_1+d_2 > 0, e_0+e_1+e_2 > 0, \ f_0+f_1+f_2+f_3 > 0. \square$$

Hence by definition it implies that the origin is unstable. By the origin being unstable, it means that at all times, there is always changes in the cell population due to daily encoding of proto-oncogene activities. In otherwords, cell mutation will always occur in an individual as far as there is proto-oncogene activities taking place in that individual. It equally means that we cannot profer a solution to stop proto-oncogene activities as these are usually triggered on naturally. However, we can only influence the rate at which this is going on by controlling our daily activities such as smoking, exposure to dangerous rays, alcohol intake, boosting the immunity through what we eat, etc.

STABILITY ANALYSIS FOR THE TSG MODEL

$$\frac{dT}{dt} = b_0T - b_1E_T - b_2V_T - b_3R_T - b_4\bar{R}_T$$
$$\frac{dE_T}{dt} = k_0E_T - k_1E_T - k_2E_T - k_3E_T$$
$$\frac{dV_T}{dt} = m_0V_T - m_1V_T$$
$$\frac{dR_T}{dt} = n_0R_T - n_1R_T - n_2R_T - n_3R_T$$
$$\frac{d\bar{R}_T}{dt} = p_0\bar{R}_T - p_1\bar{R}_T - p_2\bar{P}_T$$

$$\begin{pmatrix} \dot{T} \\ \dot{E}_T \\ R_T \\ \dot{\bar{R}}_T \end{pmatrix} = \begin{pmatrix} b_0 & -b_1 & -b_2 & -b_3 & -b_4 \\ 0 & (k_0 - k_1 - k_2 - k_3) & 0 & 0 & 0 \\ 0 & 0 & (m_0 - m_1) & 0 & 0 \\ 0 & 0 & 0 & (n_0 - n_1 - n_3) & 0 \\ 0 & 0 & 0 & 0 & (p_0 - p_1 - p_2) \end{pmatrix} \begin{pmatrix} T \\ E_T \\ V_T \\ R_T \\ \bar{R}_T \end{pmatrix}$$

The eigenvalues γ of the matrix are given by

$$\left| \begin{pmatrix} b_0 & -b_1 & -b_2 & -b_3 & -b_4 \\ 0 & (k_0 - k_1 - k_2 - k_3) & 0 & 0 & 0 \\ 0 & 0 & (m_0 - m_1) & 0 & 0 \\ 0 & 0 & 0 & (n_0 - n_1 - n_3) & 0 \\ 0 & 0 & 0 & 0 & (p_0 - p_1 - p_2) \end{pmatrix} - \gamma \begin{pmatrix} 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix} \right| = 0$$

$\Rightarrow$

$$\left| \begin{pmatrix} b_0 - \gamma & -b_1 & -b_2 & -b_3 & -b_4 \\ 0 & (k_0 - k_1 - k_2 - k_3) - \gamma & 0 & 0 & 0 \\ 0 & 0 & (m_0 - m_1) - \lambda & 0 & 0 \\ 0 & 0 & 0 & (n_0 - n_1 - n_2) - \gamma & 0 \\ 0 & 0 & 0 & 0 & (p_0 - p_1 - p_2) - \gamma \end{pmatrix} \right| = 0$$

$$\Rightarrow (b_0 - \gamma)(k_0 - k_1 - k_2 - k_3 - \gamma)(m_0 - m_1 - \gamma)(n_0 - n_1 - n_2 - n_3 - \gamma)(p_0 - p_1 - p_2 - \gamma) = 0$$

$$\Rightarrow \gamma_1 = b_0,\ \gamma_2 = k_0 - k_1 - k_2 - k_3,\ \gamma_3 = n_0 - n_1 - n_2 - n_3,\ \gamma_4 = m_0 - m_1,\ \gamma_5 = p_0 - p_1 - p_2.$$

Thus all the eigenvalues are

$$b_0 > 0,\ k_0 - k_1 - k_2 - k_3 > 0,\ \ m_0 - m_1 > 0,\ n_0 - n_1 - n_2 - n_3 > 0,\ p_0 - p_1 - p_2 > 0.$$

Hence by definition, it implies that the origin is unstable. By this analysis, we can see that at all times, there are suppressor genes that inactivate the function of TSG'S. It might be

environmental or not but the fact remains that, we have this tumor growth enhancing factors in our system at all times although many of these can be controlled. Hence, we may advice that one can reduce the level of development of tumor but do not have the power to stop its development. It is only the immune system as well as the genetic composition of an individual that has the final say on the rate at which tumor may develop in an individual.

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