A Mathematical Model of Cancer Stem Cell Lineage Population Dynamics with Mutation Accumulation and Telomere Length Hierarchies

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Outline

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   - The Model
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Telomeres and Cell Division

- Definition: repeated sequence of DNA that protects important DNA during the process of cell division.
- Cell Division leads to loss of telomeres.

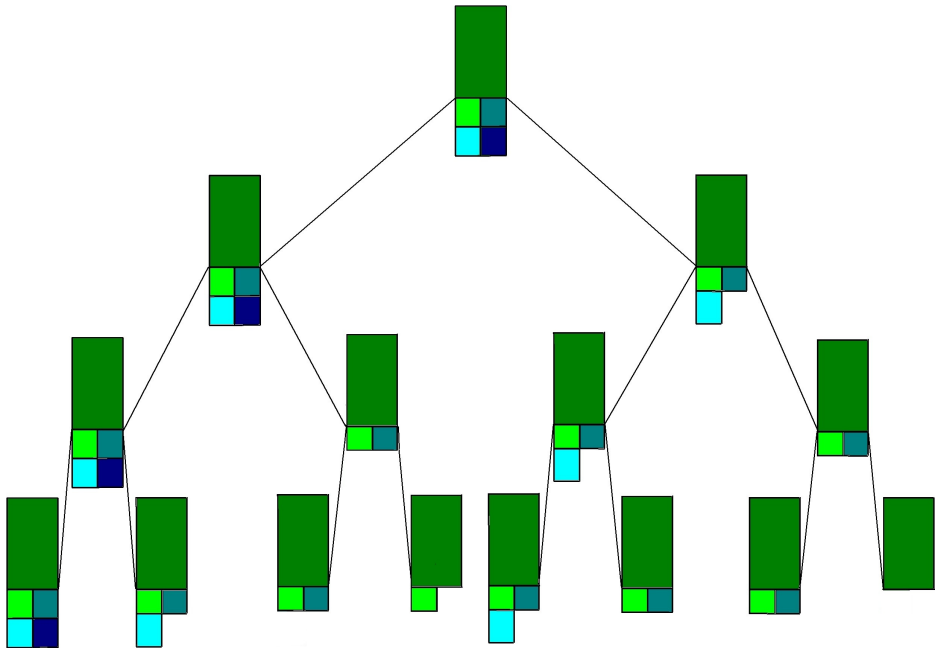

Figure: The process of asymmetrical telomere shortening as a cell divides

Stem Cells

- Properties of stem cell: self-renewal, ability to differentiate.
- Progenitor cells: medium stage of differentiation.
- Mature (differentiated) cells: they have specific functions.

Mutation accumulation

- Vogelgram - represents the sequence of mutations in a cell that eventually leads to a cancerous cell.

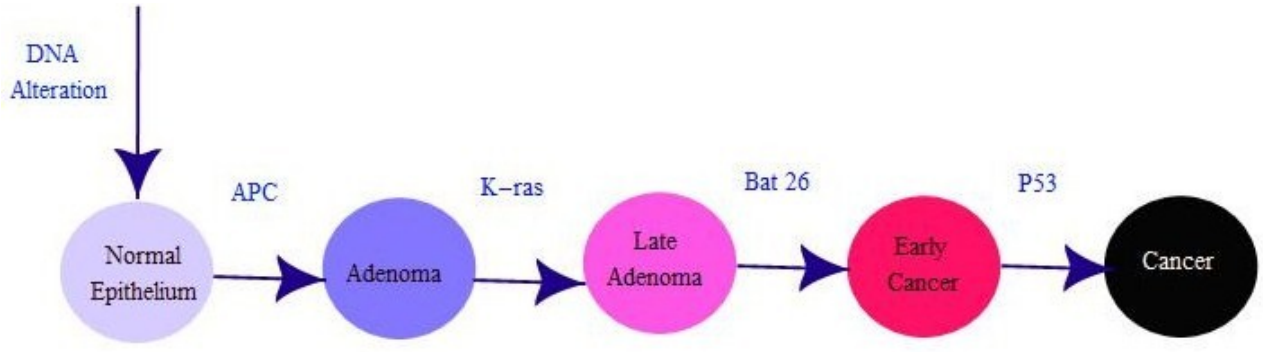

Figure: A Genetic Model for Colorectal Tumorigenesis. This is an example of a Vogelgram - multistep cancer progression model (http://www.hopkinscoloncancercenter.org)

Questions to address

- Considering cell mutation as a dynamic population process, rather than a one-time random event, what can we show about cancer cell population growth in relation to the growth of the populations of non-cancer cells?
- What is the role of stem cells in the cell population dynamics?
- Is the cancer stem cell count as small as scientists have claimed (some results claim that only one in ten thousand cancer cells is a cancer stem cell[32][4])?

Equations

- $\frac{\partial u_{j,i}(a,t)}{\partial t} + \frac{\partial u_{j,i}(a,t)}{\partial a} = -(\mu_{j,i}(a) + \beta_{j,i}(a))u_{j,i}(a,t)$
- $u_{j,i}(0,t) = 2\sum_{k=j}^{n}(p_{j,k,i}\int_0^\infty \beta_{k,i}(a)u_{k,i}(a,t)da +$
  $q_{j,k,i-1}\int_0^\infty \beta_{k,i-1}(a)u_{k,i-1}(a,t)da)$
- $u_{j,i}(a,0) = \phi_{j,i}(a)$

Explanation of the Terms

- $j = 1, ..., n$ represents the number of telomeres of a cell.
- $i = 0, ..., m - 1$ is the number of mutations a cell has accumulated.
- For $t \geq 0$, $u_{j,i}(a, t) \in L_1([0, \infty))$, represents the density of cells with age a at time t, in the j^{th} telomere class, with i mutations.
- $\mu_{j,i}(a) \geq 0$, is the age-specific mortality rate of cells in the j^{th} telomere, i^{th} mutation class.
- $\beta_{j,i}(a) > 0$, is the age-specific proliferation rate of cells in the j^{th} telomere, i^{th} mutation class.
- $p_{j,k,i} > 0$, is the probability that one of the daughters of a cell in the k^{th} telomere, i^{th} mutation class will be a cell in the j^{th} telomere, i^{th} mutation class.
- $q_{j,k,i-1} > 0$, is the probability that a cell in the k^{th} telomere, $(i-1)^{th}$ mutation class will produce, by acquiring a mutation during division, a cell in the j^{th} telomere, i^{th} mutation class.

Hypotheses

- $p_{j,j,i} = \frac{1}{2}, \forall 1 \leq j \leq n, 0 \leq i \leq m-1.$
- $p_{j,k,i} = 0$ for $j > k, \forall 2 \leq j \leq n, 0 \leq i \leq m-1.$
- $q_{j,k,i} = 0$ for $j > k, \forall 2 \leq j \leq n, 0 \leq i \leq m-1.$
- $\sum_{k=j+1}^{n} p_{j,k,i} + \sum_{k=j}^{n} q_{j,k,i} = \frac{1}{2}, \forall 1 \leq j \leq n; 0 \leq i \leq m-2.$
- $\mu_{j,i}(a) = \mu_{j,i} \geq 0, \forall 1 \leq j \leq n; 0 \leq i \leq m-1$
- $\beta_{j,i}(a) = \beta_{j,i} > 0, \forall 1 \leq j \leq n; 0 \leq i \leq m-1$

Recasting the problem

- New system of equations: $\vec{U}'(t) = A\vec{U}(t)$
- Initial conditions: $\vec{U}(0) = \vec{\Phi}$
- Solution: $\vec{U}(t) = e^{tA}\vec{\Phi}$
-
$$\begin{bmatrix} P_0 & 0 & 0 \\ Q_1 & P_1 & 0 \\ 0 & Q_2 & P_2 \end{bmatrix}$$
-
$$\begin{bmatrix} -\mu_{1,0} & 2p_{1,2,0}\beta_{2,0} & 0 & 0 & 0 & 0 \\ 0 & -\mu_{2,0} & 0 & 0 & 0 & \\ 2q_{1,1,0}\beta_{1,0} & 2q_{1,2,0}\beta_{2,0} & -\mu_{1,1} & 2p_{1,2,1}\beta_{2,1} & 0 & 0 \\ 0 & 2q_{2,2,0}\beta_{2,0} & 0 & -\mu_{2,1} & 0 & 0 \\ 0 & 0 & 2q_{1,1,1}\beta_{1,1} & 2q_{1,2,1}\beta_{2,1} & -\mu_{1,2} & 2p_{1,2,2}\beta_{2,2} \\ 0 & 0 & 0 & 2q_{2,2,1}\beta_{2,1} & 0 & -\mu_{2,2} \end{bmatrix}$$

Linear Case Results

- If, for every $1 \leq j \leq n$ and for every $0 \leq i \leq m-1$, $\mu_{j,i} > 0$, then $\lim_{t\to\infty} U_{j,i}(t) = 0$.
- If, for every $1 \leq j \leq n$ and for every $0 \leq i \leq m-1$, $\mu_{j,i} = 0$, then $U_{j,i}(t)$ is a polynomial in t of degree $n-j+i$. Furthermore, the coefficient of t^{n-j+i} of this polynomial is a multiple of $\Phi_{n,0}$.

Numerical Results for Linear Model - Figure 1

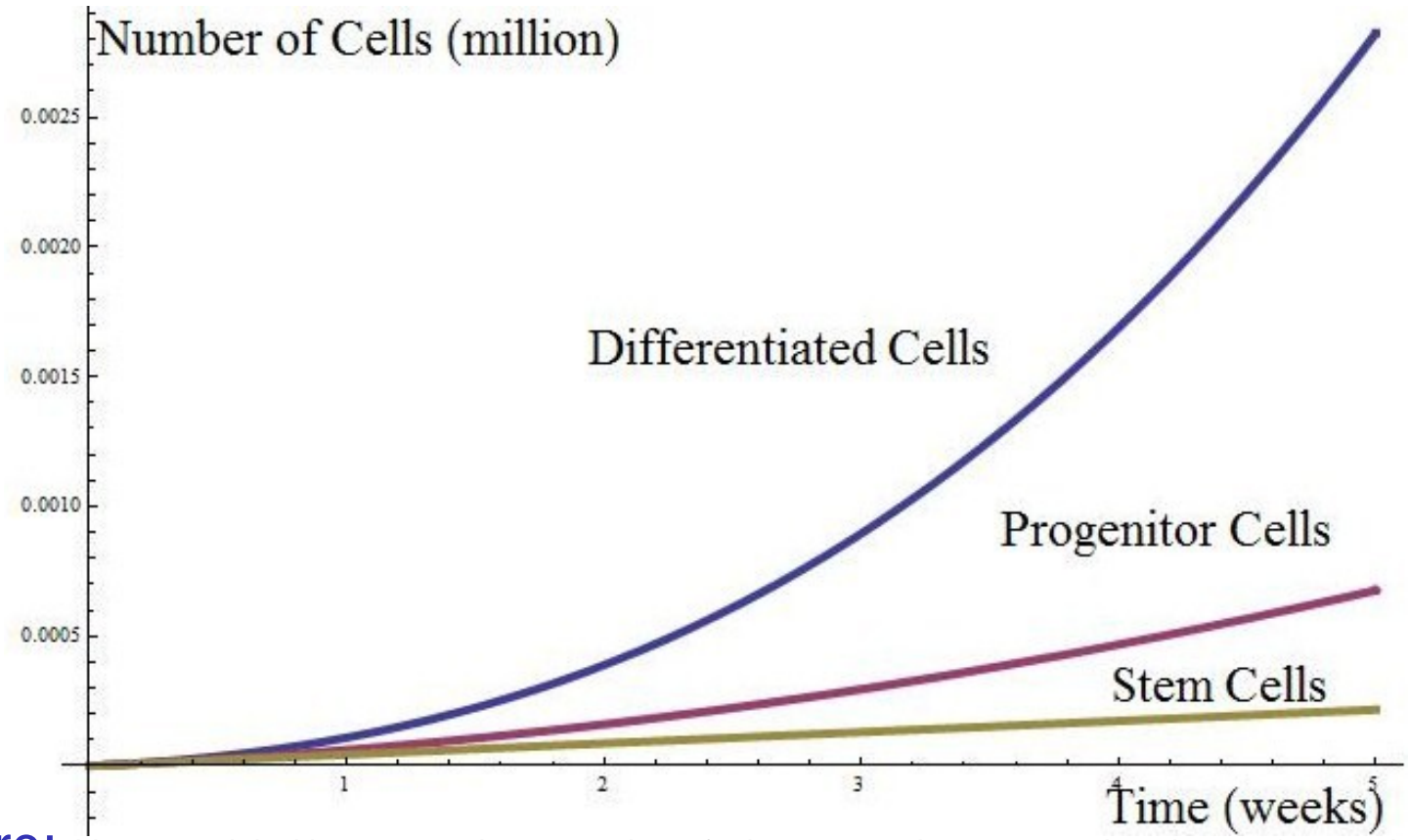

Figure: Linear model with n = 3 maximum number of telomeres and m = 3 mutation classes (2 mutations necessary to reach malignancy). Polynomial growth of cells with one mutation ($i = 1$ mutation). Stem cells ($j = 3$ telomeres) grow linearly, progenitor cells ($j = 2$ telomeres) in t^2, and differentiated cells ($j = 1$ telomere) in t^3.

Numerical Results for Linear Model - Figure 2

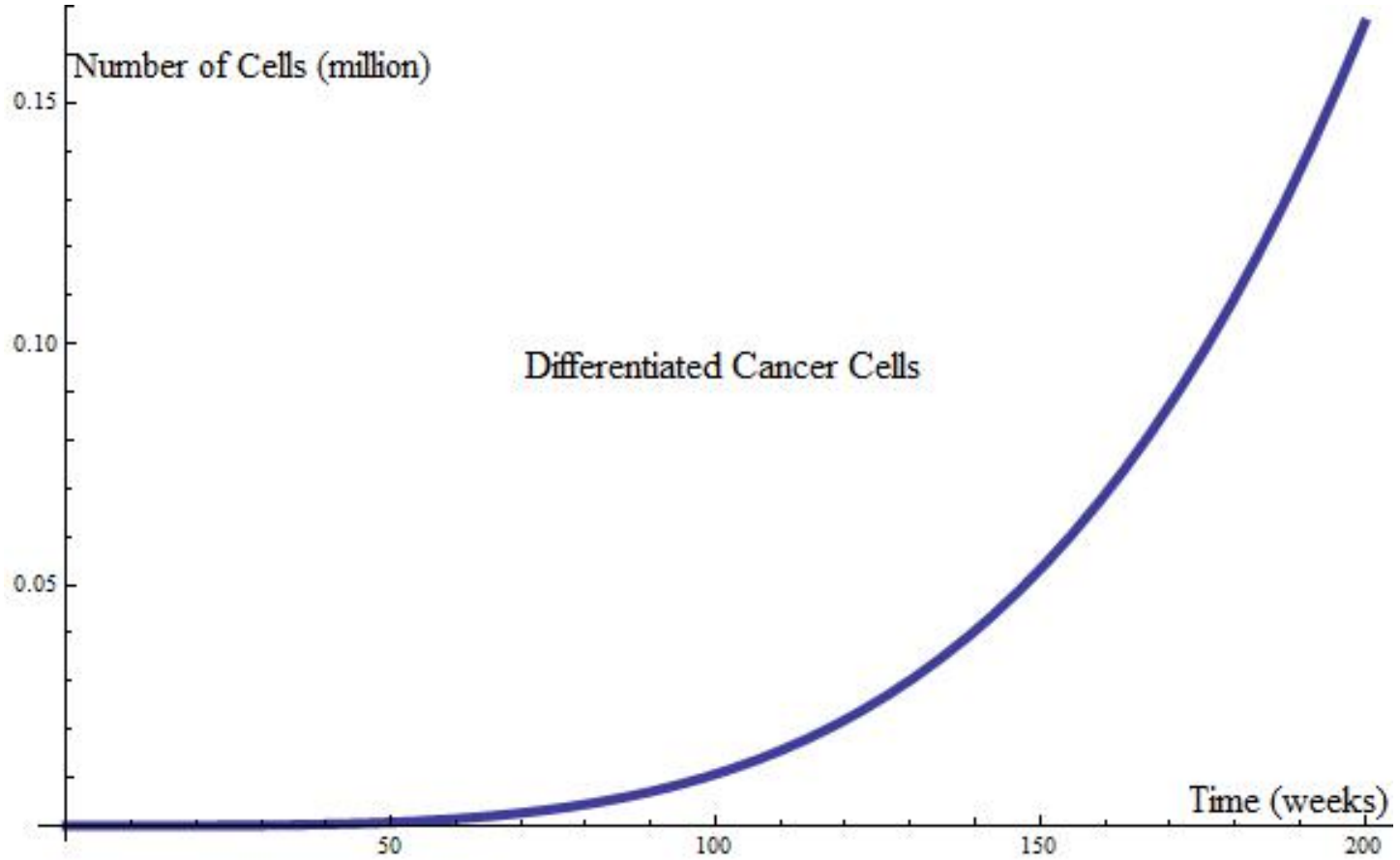

Figure: Linear model with n = 3 maximum number of telomeres and m = 3 mutation classes (2 mutations necessary to reach malignancy). Polynomial growth (t^4) of differentiated cancer cells($j = 1$ telomere, $i = 2$ mutations).

Numerical Results for Linear Model - Figure 3

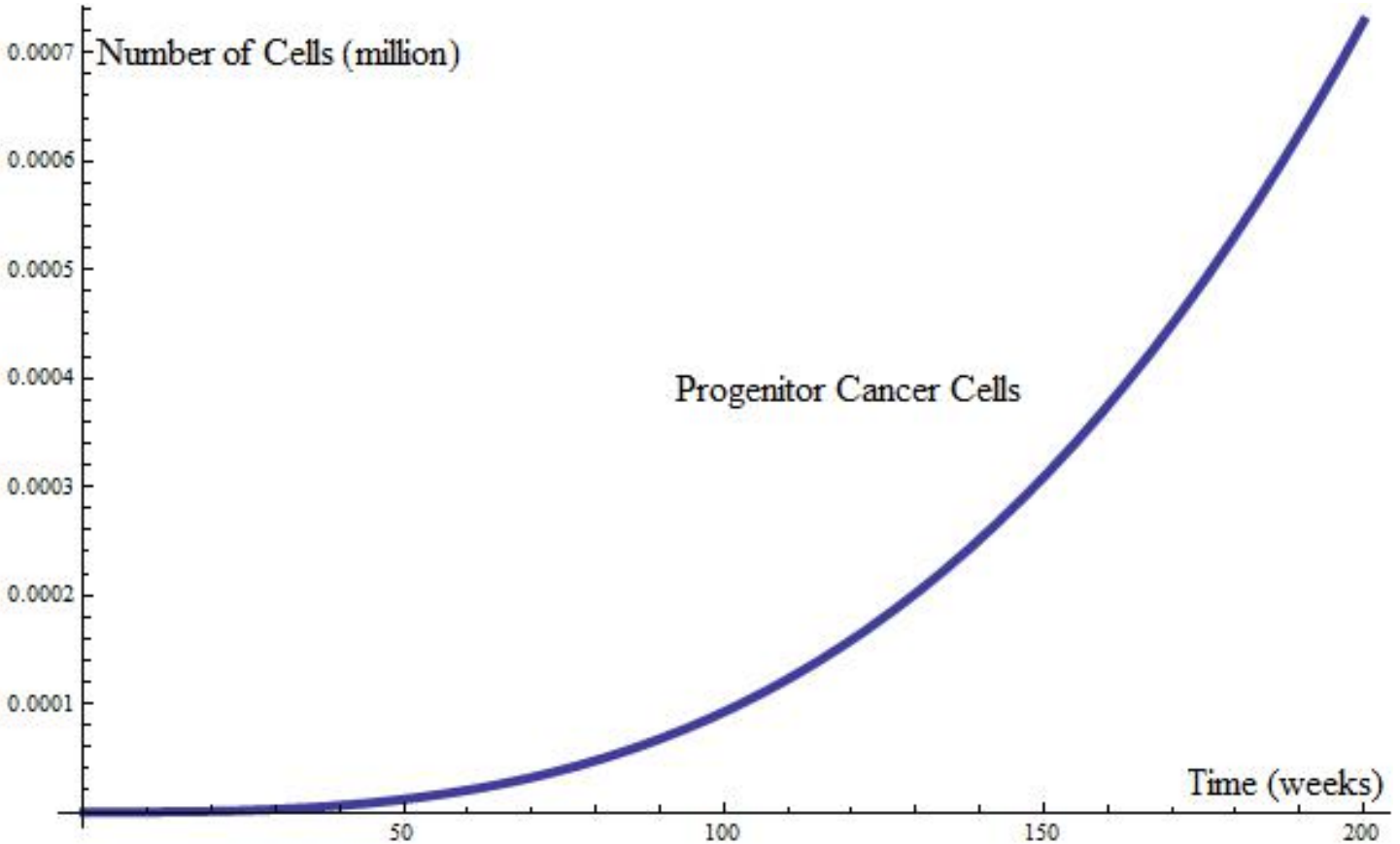

Figure: Linear model with n = 3 maximum number of telomeres and m = 3 mutation classes (2 mutations necessary to reach malignancy). Polynomial growth (t^3) of progenitor cancer cells ($j = 2$ telomeres, $i = 2$ mutations).

Numerical Results for Linear Model - Figure 4

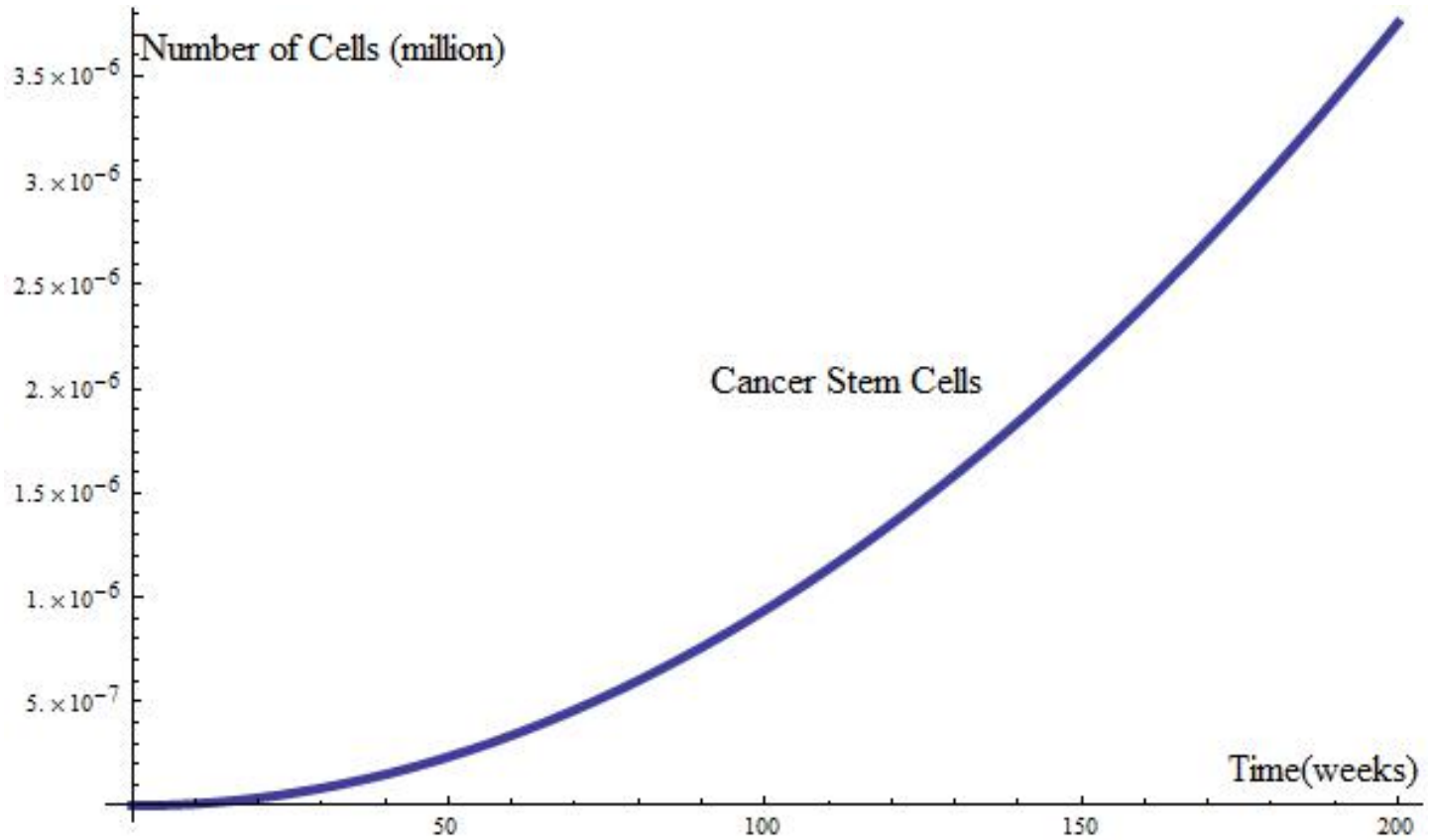

Figure: Linear model with n = 3 maximum number of telomeres and m = 3 mutation classes (2 mutations necessary to reach malignancy). Polynomial growth (t^2) of cancer stem cells ($j = 3$ telomeres, $i = 2$ mutations).

Nonlinear Case

- $\vec{U}'(t) = A\vec{U}(t) - F(\vec{U}(t))\vec{U}(t)$
- F is a positive linear functional from $L_1(\mathbb{R}_+^N)$ to $\mathbb{R}_+$

Assumptions for the Nonlinear Case

- $\mu_{j,i}(a) = \mu_{j,i} > 0, \forall 1 \leq j \leq n; 0 \leq i \leq m-1.$
- $\beta_{j,i}(a) = \beta_{j,i} > 0, \forall 1 \leq j \leq n; 0 \leq i \leq m-1.$
- $p_{j,k,i} = 0$ for $j > k, \forall 1 \leq j \leq n; 0 \leq i \leq m-1.$
- Note: $p_{j,j,i}$ need not equal $\frac{1}{2}, \forall 1 \leq j \leq n, 0 \leq i \leq m-1.$
- $\lambda_0 = -\mu_{n,m-1} - \beta_{n,m-1} + 2p_{n,n,m-1}\beta_{n,m-1}.$

Result for Nonlinear Case

- There is a unique solution to the equation above and the eigenspace of the dominant eigenvalue λ_0 of A is one dimensional. Further, the first $n(m-1)$ entries of $\vec{\Psi}$ are 0, the last n are non-zero, and $\lim_{t\to\infty} \vec{U}(t) = \frac{\lambda_0 \Pi_0 \vec{\Phi}}{F(\Pi_0 \vec{\Phi})} = \frac{\lambda_0 \vec{\Psi}}{F(\vec{\Psi})}$, where Π_0 is the eigenprojection associated with λ_0, $\vec{U}(t)$ is the unique solution to the equation, and $\vec{\Psi}$ is an eigenvector of λ_0.

Numerical Result for Nonlinear Model

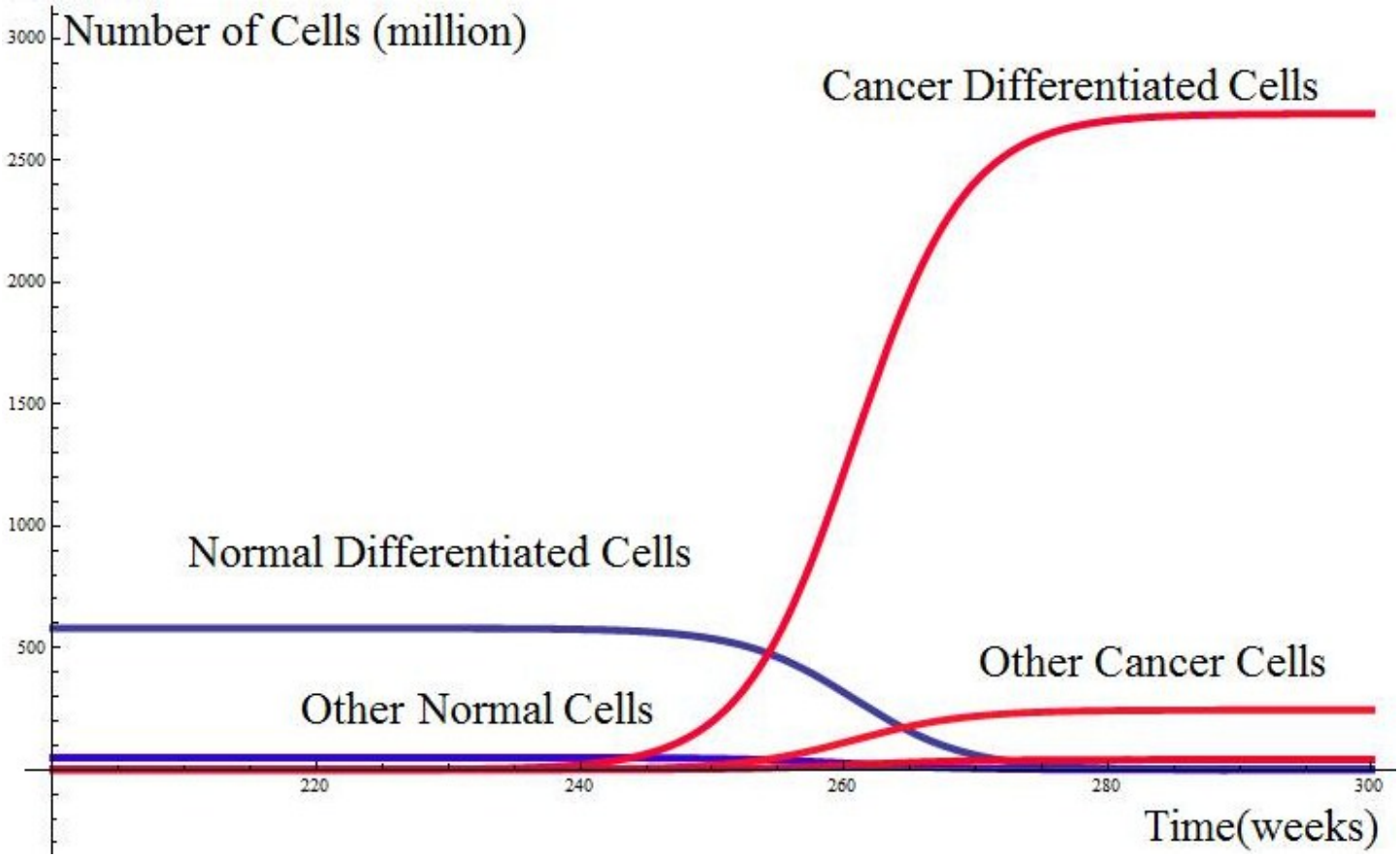

Figure: Nonlinear model with $n = 8$ maximum number of telomeres and $m = 6$ mutation classes (5 mutations necessary to reach malignancy). Cancer cells ($i = 5$ mutations) taking over the tissue environment according to the asymptotic steady state result.

Summary and Discussion

- Question 1: Considering cell mutation as a dynamic population process, rather than a one-time random event, what can we show about cancer cell population growth in relation to the growth of the populations of non-cancer cells?
  - Answer: The theorem for the linear model proves that the number of cancer cells grows faster polynomially than any other type of cell and it is the nature of mutation acquisition that explains the higher population growth of cancer cells.
  - However, cancer cells do need to exhibit high proliferation rate in order for their population to grow to levels dangerous for the organism in a realistic time frame.

- Question 2: What is the role of stem cells in the cell population dynamics?
  - Answer: Stem cells are crucial for the development of all other cell classes and are also important for the rate at which those different cell populations grow.

- Question 3: Is the cancer stem cell count as small as scientists have claimed?
  - Answer: A relatively small subpopulation of cancer stem cells can generate the total population of cancer cells.

References


O. Arino, M. Kimmel, and G.F. Webb, *Mathematical modeling of the loss of telomere sequences*, J. theor. Biol. **177** (1995), 45–57.


O. Arino, E. Sánchez, and G.F. Webb, *Polynomial growth dynamics of telomere loss in a heterogeneous cell population*, Dynamic Control Discrete Impulsive System **3** (1997), 263–282.


Dennis S. Bernstein, *Matrix mathematics, second edition*, Princeton University Press, 2009.


Dominique Bonnet and John E. Dick, *Human acute myeloid leukemia is organized as a hierarchy that originates from a primitive hematopoetic cell*, Nature Medicine **3** (1997), 730–737.


Peter M. Lansdorp Janis L. Abkowitz Bryan E. Shepherd, Peter Guttorp, *Estimating human hematopoietic stem cell kinetics using granulocyte telomere lengths*, Experimental hematology **32** (2004), 1040–1050.


Ahmed et. al., *Telomerase does not counteract telomere shortening but protects mitochondrial function under oxidative stress*, Journal of Cell Science **121** (2008), 1046–1053.


Deasy et. al, *Modeling stem cell population growth: Incorporating terms for proliferative heterogeneity*, Stem Cells **21** (2003), 536 – 545.


Dyson et. al., *Asymptotic behaviour of solutions to abstract logistic equations*, Mathematical Biosciences **206** (2007), 216–232.


Enderling et. al., *The importance of spatial distribution of stemness and proliferation state in determining tumor radioresponse*, Math. Model. Nat. Phenom. **4** (2009), 117–133.


Hyde et. al., *Prospective identification of tumorigenic prostate cancer stem cells*, Cancer Res **65** (2005), 10946–10951.