A Biomathematical Approach for Investigating the Evolution of Tumors During a Course of Chemotherapy

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Outline

- General evolution of a tumor
- Structure of a Tumor
- Two Compartment Model of tumor behavior
- Combine these two models in a growth phase
- Tumor behavior during the course of chemotherapy
- Models in the presence of anti-cancer drug
- Results and discussions.
Gompertzian Model

- Charts Tumor growth as a function of time, $N(t)$.

$$N(t) = N_0 \exp \left[ \left( \frac{k_+}{k_-} \right) \left( 1 - \exp \left( -k_- t \right) \right) \right]$$

- $N_0$ = Initial cellularity.
- $k_+$ = Growth constant.
- $k_-$ = Retardation of growth constant.
- After the tumor’s initial rapid growth, the rate begins to decrease.
- At this point, the tumor has reached its carrying capacity.

For the graph above:
- $N_0 = 1$
- $k_+ = 2.76$
- $k_- = 0.134$

Structure of Tumor

- A Tumor is comprised of two types of cells:
  - proliferating cells: P
  - quiescent cells: Q

Proliferating Subpopulation (P)
Two Compartment Model

Mathematically, this diagram can be explained as follows:

\[ N = P + Q \]

\[ \frac{dQ}{dt} = r_0(N)P - [r_i(N) + \mu_q]Q \]

\[ \frac{dP}{dt} = [\beta - \mu_P - r_0(N)]P + r_i(N)Q \]

P: proliferating cells
Q: quiescent cells
\( \beta \): proliferating rate
\( \mu_q \): Q cell death rate
\( \mu_p \): P cell death rate
\( r_i(N) \): transition rate of Q to P
\( r_o(N) \): transition rate of P to Q

Combining Models

\[ P(t) = \frac{\mu_q + k e^{(-k_\ast t)}}{\beta - \mu_p + \mu_q} N(t) \]

Combining Models of Tumor Growth

- Combining the two models allows us to express tumor growth in terms of the proliferating subpopulation.
- Mathematically, combining the two models gives this equation:

\[ P = \frac{\mu_q + k_+ e^{-k_t}}{\beta - \mu_p + \mu_q} N = P_0 \frac{\mu_q + k_+ e^{-k_t}}{k_+ + \mu_q} N \]

\( \mu_q \) : remaining parameter  \( k_- \) and \( k_+ \) : Find from Curve Fitting

Simulation

\[ N(t) = N_0 \exp\left(\frac{k_-}{k_+} (1 - \exp(-k_- t))\right) \]
\[ P = P_0 \frac{\mu_q + k_+ e^{-k_- t}}{k_+ + \mu_q} N \]

\( k_+ = 2.76 \)
\( k_- = 0.134 \)

\( k_+ = 6.47 \)
\( k_- = 0.314 \)
Behavior of a Tumor During the Course of Chemotherapy

Chemotherapeutic affect on Gompertzian Growth:
- Decrease the total number of tumor cells (shrinkage behavior)

Different factors are involved in this Behavior:
- The starting time
- The aggressiveness
- Tumor cell resistance

Shrinkage During Chemotherapy

To determine $k_+$ and $k_-$, curve fitting for growth and decay data of total cell population is used.

Two Compartment Model:

\[ f(t) = \begin{cases} 
  c, & \text{during the course of therapy} \\
  0, & \text{otherwise.} 
\end{cases} \]

\( f(t) \) is an external additional death rate and does not diffuse by time.

Evolution of Total Number of Tumor Cells in Phases of Growth and Shrinkage

\[ N_I(t) = N_{0I} \exp \left[ \frac{k_{+I}}{k_{\rightarrow I}} \left( 1 - \exp(-k_{\rightarrow I}t) \right) \right], \]

\[ N_{II}(t) = N_{0II} \exp \left[ \frac{k_{+II}}{k_{\rightarrow II}} \left( 1 - \exp(-k_{\rightarrow II}t) \right) \right]. \]
Evolution of P Cells in Phases of Growth and Shrinkage

The decay is more rapid with a larger retardation factor. The function will decrease until reaching a minimum, then will increase.

Behavior of proliferation subpopulation during the course of therapy when $\mu_q = 0.2$ for two different values of $k_{-II}$. 

\[ P(t) = \frac{P_0(t_0)(\mu_q - k_{-II} \exp^{-(\mu_q + k_{II})(t-t_0)})}{(\mu_q - k_{-II} \exp^{-(\mu_q + k_{II})(t-t_0)})} \exp \left[ \frac{k_{-II}}{k_{II}} (1 - \exp(+(k_{II}t'))) \right] \]
Future Work

- Analyze chemotherapeutic drugs as a function of time with a decaying behavior rather than an on-off term
- Improve the function that illustrates tumor evolution during therapy based on medical data
- Improve anti-cancer tumor drugs