Mathematical models of tumor growth and radiation response

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Learning objectives

1. To learn the mathematical models of tumor growth and its response to radiation.
2. To get insight on the applicability of simple models to clinical cases.
3. To brainstorm for future research by asking questions about simple biological models.
What is the goal of the study?

Metastatic brain tumor

Gamma Knife SRS
Aim

➢ To find *simple* but fundamental equations, which can reproduce and predict the change of tumor volume before and after single fraction of high dose radiotherapy.
Biological model

1. Tumor volume increases with a growth rate.
2. The growth rate is proportional to the ratio of the vasculature and tumor volume.
3. Single fraction irradiation with a short pulse, or the duration much shorter than 1 day.
4. After irradiation, cells inside the tumor volume are composed of two components.
5. The two components are
   1) Dividing cells (may eventually stop dividing.)
   2) Non-dividing cells
5. Only dead cells are removed from the tumor with a constant clearance rate.
6. The visible tumor volume (by eyes or contrast-enhanced MRI) is made of two components.
How does the volume of tumor change in time?

- Tumor grows exponentially up to 1 cm$^3$.
- Volume doubling time is about 4 days.
- The growth rate slows down when the volume > 1 cm$^3$.

**Tumor growth is not exponential.**

A model of tumor growth

- Tumor cells divide in a doubling time $T_d$.
- All cancer cells have the same volume (about $10^{-9} \text{ cm}^3$). $\Rightarrow$ The tumor volume is proportional to the number of cells.

✓ To proliferate/or divide, cells need energy and material. $\Rightarrow$ Blood carries these.

**Hypothesis I:** The volume of blood in a tumor increases slower than the tumor.
The growth formula

- The growth rate, \( \lambda(t) \), is proportional to the ratio of the blood (or vascular) volume \( V_v \) and tumor volume \( V_T \).

\[
\frac{d\lambda}{dt} = \left( \frac{1}{V_v} \frac{dV_v}{dt} - \frac{1}{V_T} \frac{dV_T}{dt} \right) \lambda \approx (\lambda_v - \lambda_T)\lambda = (\theta - 1)\lambda_0 \lambda \quad (1)
\]

\[
\frac{dV_T}{dt} = \lambda(t)V_T \quad (2)
\]

\[\theta = \frac{\lambda_v}{\lambda_T} < 1 \quad : \text{Tumor growth retardation factor}\]

A solution of (1) and (2) is a classic Gompertzian growth:

\[
V_T(t) = V_T(0) exp \left\{ -\frac{\lambda_0}{1 - \theta} \left( e^{- (1 - \theta)t} - 1 \right) \right\}
\]
Cell population model:
Two populations (could be more than 2)

One time of Dose, $D$

How do cells die?

- **Lysis** (Programmed cell death)
  - Necrosis (secondary necrosis)
- **Apoptosis**
  - Senescence (Permanent cell cycle arrest)
    - Mitotic catastrophe
  - Radiation damage
    - p53 impaired
- **Necrosis**
  - pyknosis/karyopyknosis
  - cell shrinkage
  - internucleosomal breakage of chromatin
  - enlarged/flattened
  - metabolically active
  - delayed apoptosis

Lethally damaged cells divide!
Monte Carlo simulation of cell proliferation after irradiation.

- The number of cells, \( N \), keeps increasing without irradiation.
- For 10 Gy, one cell becomes up to 48 cells before they die. \( \rightarrow 6 \) divisions.
- For 20 Gy, one cell becomes up to 18. \( \rightarrow 4 \) divisions.

\[ 6 \text{ cycles} \rightarrow 2^6 = 64 \]

Modelling radiation effects

- Single dosage of radiation, $D$, gives permanent damage to a fraction of cancer cells. Those “doomed” cells divide a few more times before the death for a time period $\tau_{\text{rad}}$
- Radiation induced death term is $-gV_T$

The death rate $g$ is proportional to $\chi(D) = \alpha \left( D + \frac{D^2}{\alpha/\beta} \right)$

$g = \frac{\chi(D)}{3T_m}$
Traditional radiation effect model  
(Model A)

• The cancer cells are instantly killed at the time of irradiation.
• The fraction of the cell death is
  \[ K = 1 - \exp(-\chi(D)) \]
• After irradiation at time \( t \), the tumor volume decreases and the dead cells increases suddenly.
  \[
  V_T(t_+) = (1 - K) \cdot V_T(t_-) \\
  V_{ND}(t_+) = K \cdot V_T(t_-)
  \]
Clearance of dead cells

- Assume the dead cells are cleared from the original site with a mean clearance time $T_C$.
- Cells dying due to mitotic catastrophe and apoptosis disintegrate and are swept away.
- Cells which died by the necrosis and senescence are trapped and might stay at the original location.
The tumor volume observed on the image is $V_T + V_{ND}$.

The cell proliferation rate $\lambda$ is modified by the dose and the tumor and vascular volumes.
Solution methods:
Parameter optimization

1. Forward method: solve the ODEs for given model parameters.

2. Inverse solution (i.e., the least square fitting) to obtain the best fit between the model and the data by simulated annealing.

\[
F = \min \left\{ \sum_{n=1}^{N} (y_n - f_n(\hat{\rho}))^2 \right\}
\]

\(\hat{\rho} = \) a vector containing the model parameters: \(\{\alpha, \theta, T_d(0), T_c\}\)
Rat Rabdomyosarcoma

Model parameters used for rat experiments

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Control</th>
<th>1000</th>
<th>2000</th>
<th>3000</th>
<th>4000</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha$</td>
<td>Gy$^{-1}$</td>
<td>0.30</td>
<td>0.20</td>
<td>0.16</td>
<td>0.145</td>
<td></td>
</tr>
<tr>
<td>Dose</td>
<td>Gy</td>
<td>10</td>
<td>20</td>
<td>30</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>$T_{d(0)}$</td>
<td>days</td>
<td>1.35</td>
<td>1.35</td>
<td>1.35</td>
<td>1.35</td>
<td></td>
</tr>
<tr>
<td>$\theta$</td>
<td></td>
<td>0.72</td>
<td>0.72</td>
<td>0.74</td>
<td>0.795</td>
<td>0.838</td>
</tr>
<tr>
<td>$T_{cl}$</td>
<td>days</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>$S^{(++)}$</td>
<td></td>
<td>1.00E+00</td>
<td>9.83E-01</td>
<td>2.84E-01</td>
<td>5.38E-02</td>
<td>4.51E-03</td>
</tr>
</tbody>
</table>

Initial volume = 0.0157cm$^3$, $\alpha/\beta$=10 Gy, active radiation-effect time $\tau_{rad} = 8$ days, cell cycle time $T_{cc} = 1$ day, colony counting time $T_m = 10$ days.

$S^{(++)}$ is the fraction of surviving cells after irradiation. It shows the degree of cell kill by radiation.
Gamma Knife: metastatic cancers

A. Cells die instantly by radiation.
B. Delayed death

Radiation response types
CR: complete response
PR: partial response
SD: stable disease
PD: progressive disease
Gamma Knife: metastatic cancers
Gamma Knife: metastatic cancers

- Two graphs showing tumor volume over time for metastatic cancers.
  - Right graph: Tumor Volume [cm³] vs. Time [Days] comparing Clinical data with Model A and Model B.
## Model parameters used for Gamma Knife

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Unit</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha$</td>
<td>1/Gy</td>
<td>0.09</td>
<td>0.19</td>
<td>0.19</td>
<td>0.1</td>
<td>0.05</td>
</tr>
<tr>
<td>Tumor doubling time $T_d(0)$</td>
<td>days</td>
<td>29.0</td>
<td>6.0</td>
<td>9.0</td>
<td>6.6</td>
<td>7.8</td>
</tr>
<tr>
<td>Cell clearance time $T_{cl}$</td>
<td>days</td>
<td>13.0</td>
<td>38.0</td>
<td>40.0</td>
<td>10.0</td>
<td>20.0</td>
</tr>
<tr>
<td>Retardation factor $\theta$</td>
<td>No dim.</td>
<td>0.62</td>
<td>0.77</td>
<td>0.53</td>
<td>0.78</td>
<td>0.99</td>
</tr>
<tr>
<td>Mean dose</td>
<td>Gy</td>
<td>38.3</td>
<td>21.2</td>
<td>26.0</td>
<td>22.0</td>
<td>24.3</td>
</tr>
<tr>
<td>Initial volume</td>
<td>cm$^3$</td>
<td>0.126</td>
<td>0.0065</td>
<td>0.271</td>
<td>0.031</td>
<td>0.101</td>
</tr>
<tr>
<td>Irradiation day for GKSRS</td>
<td>day</td>
<td>34</td>
<td>117</td>
<td>22</td>
<td>78</td>
<td>29</td>
</tr>
<tr>
<td>Tumor volume at GKSRS</td>
<td>cm$^3$</td>
<td>0.268</td>
<td>0.392</td>
<td>0.662</td>
<td>6.933</td>
<td>1.314</td>
</tr>
<tr>
<td>Tumor doubling time at GKSRS</td>
<td>days</td>
<td>32.6</td>
<td>28.0</td>
<td>11.2</td>
<td>16.1</td>
<td>7.9</td>
</tr>
<tr>
<td>Volume ratio, $R_{40}$ (**)*</td>
<td></td>
<td>0.16</td>
<td>0.57</td>
<td>0.58</td>
<td>0.69</td>
<td>10.0</td>
</tr>
<tr>
<td>% Cell survival fraction</td>
<td></td>
<td>2.24</td>
<td>6.03</td>
<td>1.99</td>
<td>25.4</td>
<td>70.0</td>
</tr>
</tbody>
</table>

(*) In all cases, $\alpha/\beta = 10$, $\tau_{rad} = 8$ days, $T_{CC} = 1$ day, and $T_m = 10$ days.

(**) $R_{40}$ = the ratio of the volume on the 40$^{th}$ day after GKSRS and the volume at GKSRS.
Can the model parameters predict the outcome?

Correlation of model parameters and $R_{40}$

<table>
<thead>
<tr>
<th>Predictor</th>
<th>$T_d$(GKSRS)</th>
<th>$\alpha$</th>
<th>$\theta$</th>
<th>$V_T$(GKSRS)</th>
<th>$D_{\text{mean}}$ (*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-value:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>linear</td>
<td>0.269</td>
<td>0.246</td>
<td>0.0950</td>
<td>0.652</td>
<td>0.720</td>
</tr>
<tr>
<td>P-value:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd order</td>
<td>0.302</td>
<td>0.0264</td>
<td>0.0073</td>
<td>0.324</td>
<td>0.817</td>
</tr>
</tbody>
</table>

(*) $D_{\text{mean}}$ is the mean dose delivered to the tumor for GKSRS.
Questions

1) Why is the tumor volume growth rate not constant?
2) How is the tumor volume related to the number of cancer cells?
3) How many times does the damaged cell divide after irradiation?
4) What cells are in the T1w Contrast enhance MRI image?
5) What is the effect of other treatment?
6) What is the mechanism for clearance of dead cells?
7) Do the non-damaged cells grow at the same rate under the effect of irradiation?
8) What fraction of tumor cells must die to observe clinically the “local control” of the tumor?
Extension to multi-dimensions

\[
\begin{aligned}
\frac{\partial \rho_T}{\partial t} &= \nabla \cdot (D_T \nabla \rho_T) + \lambda \rho_T - g(D) \rho_T \\
\frac{\partial \rho_{ND}}{\partial t} &= \nabla \cdot (D_{ND} \nabla \rho_{Nd}) + g(D) \rho_T - \mu_c \rho_{ND}
\end{aligned}
\]

\[
\begin{aligned}
\rho_T(\vec{r}, 0) &= f(\vec{r}) & \rho_T(\infty, t) &= 0 \\
\rho_{ND}(\vec{r}, 0) &= 0 & \rho_{ND}(\infty, t) &= 0 \\
\rho_{min} &\leq \rho_T(\vec{r}, t) \leq 1.0
\end{aligned}
\]

Growth rate of tumor volume \( \propto v_T^3 t^2 \)

Here, the constant expansion speed \( v_T = \sqrt{2 \lambda D_T} \)

\( \Rightarrow \) The volume increases as a function of \( t^2 \) (not exponential!)
3D model results:
Spherical mouse tumor

- 10 Gy
- 20 Gy
- 30 Gy
- 40 Gy
R = the tumor volume decreases with a half life of $T_{1/2}$

$S = \text{intact cells after treatment with the doubling time } T_d$

after the onset time $T_k$. 

\[
\begin{align*}
\frac{dR(t)}{dt} &= -\frac{\ln 2}{T_{1/2}} [R(t) - S(t)], \\
\frac{dS(t)}{dt} &= S(t) \left[ -(1 - S_2) + \frac{\ln 2}{T_d} \right].
\end{align*}
\]
3D model of brain tumor response to standard fractionated RT


✓ One population
✓ Instant cell death
✓ Fractionated RT

Cell proliferation rate prior to RT predicts $\alpha$. 
Conclusions

✓ Mathematical modelling requires deeper understanding of biological processes.

✓ Model parameters can be used as therapy response predictors.
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Bibliography


