Modeling the Growth of Cancerous Tumors

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Goals:

-Model growth of cancerous tumors through a Gompertz model and pharmacokinetic/pharmacodynamic model

- Pharmacokinetic refers to the movement of drugs within the body

- Pharmacodynamic refers to the effects of drugs and the mechanism of their action

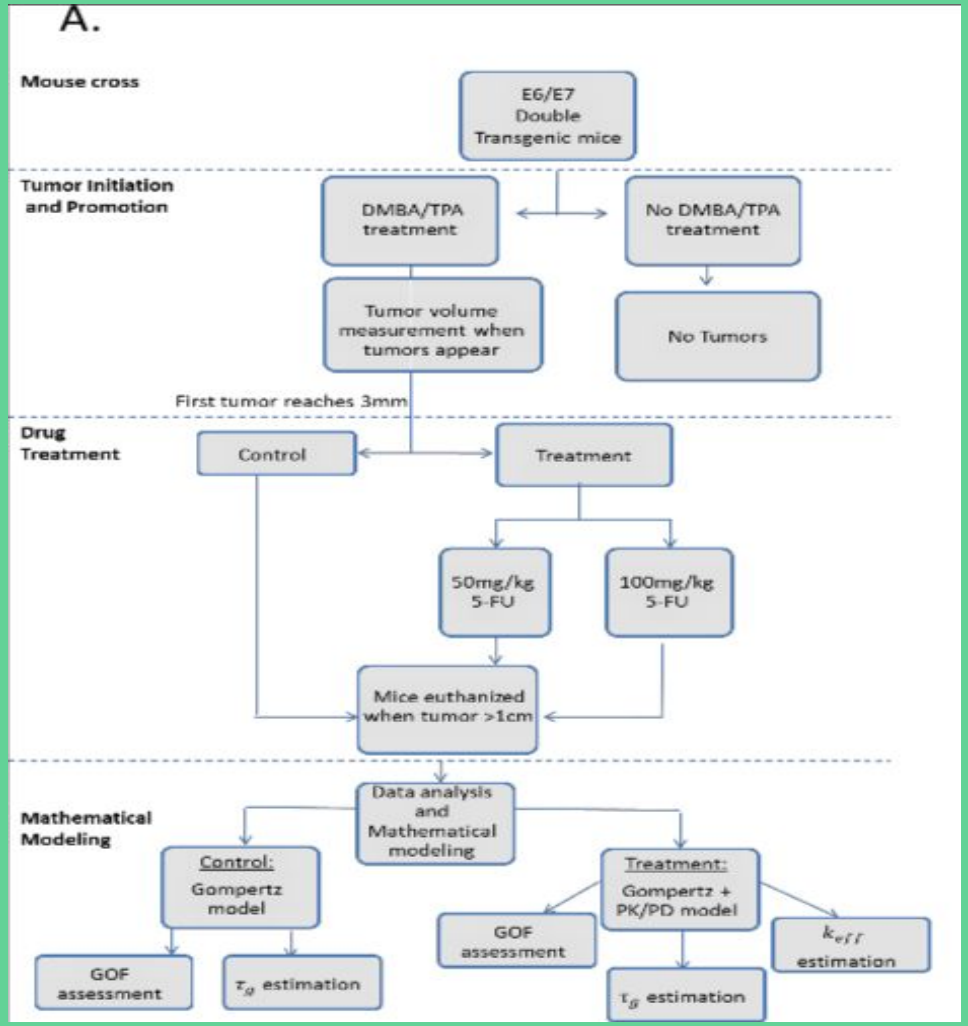
Current Practices and Limitations:

- Tumor growth is complex and has a multitude of parameters that are specific to type, tissue, initial growth, immune system, and more.
- Most studies done on cancer growth using mathematical models have not been validated with clinical or experimental data
- Valid studies have been performed when using experimental data from xenograft mouse models. The downside to this is that mice with xenografts must be immunodeficient meaning they are incapable of initiating an immune response

Solutions from Experiment:

- Mathematical modeling helps determine cancer growth using pre-existing biological knowledge
- This experiment is done on non-xenograft mice
- Used models of *de novo* carcinogenesis that recaptures tumor initiation, progression, and maintenance *in vivo*.
- Fit parameters specific to the initial growth of tumor resulting in more accurate models for each mouse.

Breakdown of the Experiment:



Explanation of Experiment:

- Used non-xenograft mice, so the mice have an immune response
- Mice were treated with DMBA/TPA a carcinogenic (dimethylbenzanthracene/12-O-Tetradecanoylphorbol-13-acetate)
- 5-FU (5-Fluorouracil) (50/100 mg/kg) a chemotherapy drug was given weekly after tumors reached a diameter of 3mm
- Recorded data for the treated and untreated mice with a goal of showing that the Gompertz model adequately describes the growth of *in vivo* tumors in mouse models of *de novo* carcinogenesis both with and without treatment

Gompertz Growth Model

The Gompertz model used is an ODE as follows:

$$\frac{dT(t)}{dt} = \frac{1}{\tau_g} ln\left[\frac{ln(\theta_g/T_0)}{ln(\theta_g/2T_0)}\right] T(t) ln\left(\frac{\theta_g}{T(t)}\right) - L(T(t), C_2(t)),$$

With the following parameters: (L describes the decrease in cells due to chemo)

τ_g = Tumor Doubling time (days)

θ_g = Plateau size (mm^3)

T_0 = Initial Tumor size (mm^3)

$T(t)$ = tumor volume (mm^3)

Cell Decrease Term

$$L(T(t), C_2(t)) = k_{eff}(C_2(t) - C_{2,thr})H(C_2(t) - C_{2,thr})T(t),$$

Parameters for Cell Decrease Term:

k_{eff} = Drug Kill rate (mL/(days*ng))

$C_2(t)$ = Drug concentration in tumor site (ng/mL)

$C_{2,th}$ = Therapeutic threshold for drug effect (ng/mL)

$H(x)$ = Heaviside function with output 0 if $x < 0$ and output 1 otherwise

It is important to note that the untreated model has $L \equiv 0$

Pharmacokinetic/Pharmacodynamic Model:

It is assumed that the body is a well-mixed tank so these will also be ODEs.

$$\frac{dC_1(t)}{dt} = k_{21}C_2(t)\frac{V_2}{V_1} - k_{12}C_1(t) - k_{10}C_1(t) + \frac{d(t)}{V_1}$$

$$\frac{dC_2(t)}{dt} = k_{12}C_1(t)\frac{V_1}{V_2} - k_{21}C_2(t)$$

$C_1(t)$ = Drug concentration in plasma (blood) (ng/mL)

$C_2(t)$ = Drug concentration in tumor site (ng/mL)

V_1 = Distributed volume of drug in plasma (blood) (mL)

V_2 = Distributed volume of drug in tumor site (mL)

k_{21} = Rate constant of drug concentration from tumor to plasma (1/day)

k_{12} = Rate constant of drug concentration from plasma to tumor (1/day)

k_{10} = Other elimination processes (1/day)

$d(t)$ = drug dosage (ng/day)

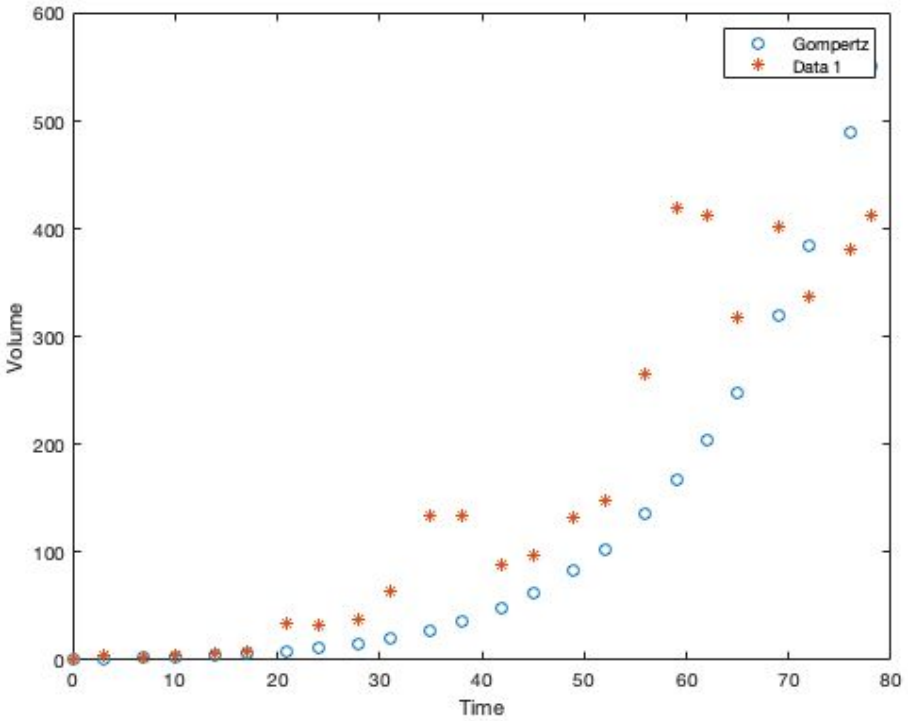
Examples of the Untreated Model

Parameters for CM37 Tumor 1:

$\boldsymbol{\tau}_{g,1}$ = 6.650 (days)

θ_g = 10^6 (mm^3)

$\boldsymbol{T}_0$ = 1.057345 (mm^3)



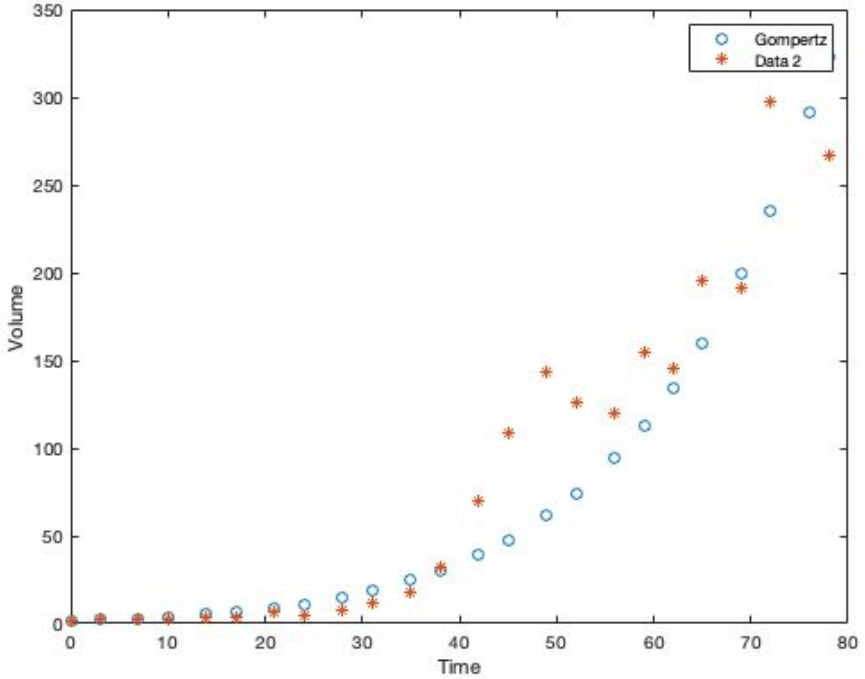
Examples of the Untreated Model

Parameters for CM37 Tumor 2:

$\boldsymbol{\tau}_{g,2}$ = 8.256 (days)

θ_g = 10^6 (mm^3)

$\boldsymbol{T}_0$ = 1.648452 (mm^3)



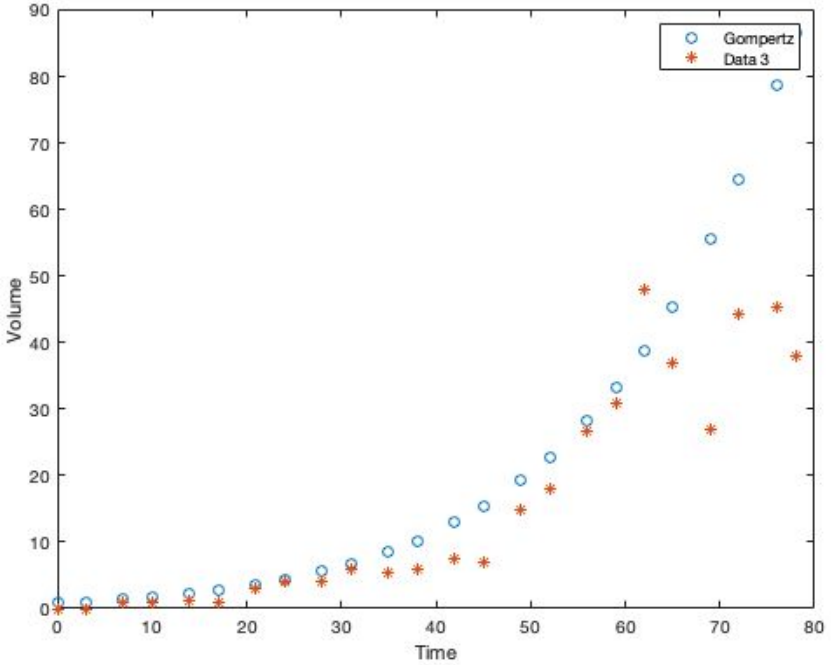
Examples of the Untreated Model

Parameters for CM37 Tumor 3:

$\boldsymbol{\tau}_{g,3}$ = 9.868 (days)

θ_g = 10^6 (mm^3)

$\boldsymbol{T}_0$ = 0.848010 (mm^3)



Examples of the Treated Model

Parameters for CM41 Tumor 1:

τ_g = 7.373 (days)

θ_g = 10^6 (mm^3)

T_0 = 0.878996 (mm^3)

k_{eff} = 5.02 * 10^{-5} (mL/(days*ng))

$C_{2,th}$ = 10 * 10^3 (ng/mL)

V_1 = 0.71 * 10^3 (mL)

V_2 = 0.1 * 10^3 (mL)

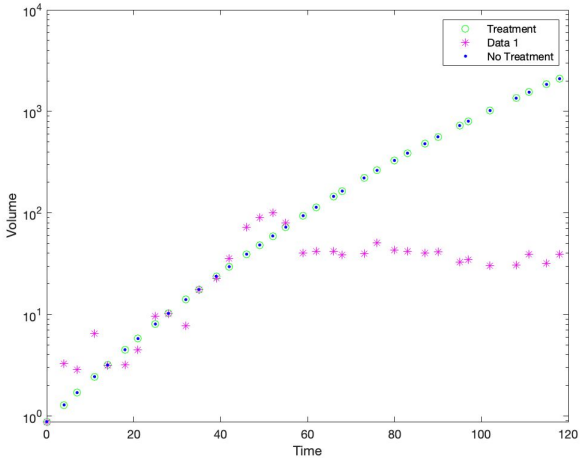
k_{21} = 2.31 (1/day)

k_{12} = 5.62 (1/day)

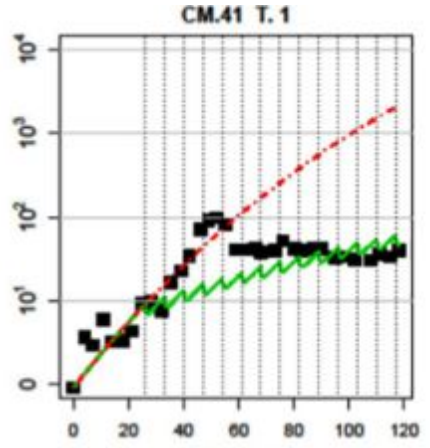
k_{10} = 151.2 (1/day)

$d(t)$ = Characteristic function on the set of injection days (ng/day)

Mine:



Experiment:



Future Goals

- Perfect the portion of the ODEs pertaining to $C_1(t)$ and $C_2(t)$
- Analyze more of the mice data
- Try to construct another system of ODEs that is based off of fibroblast cell growth activation

Thank you!

Bibliography:

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