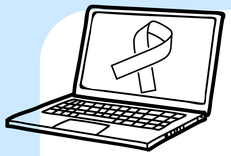
COMPARATIVE ANALYSIS OF ORDINARY DIFFERENTIAL EQUATION MODELS FOR CANCER GROWTH

Julia, Christos, Vera, Jessica, Rose



THE PROJECT

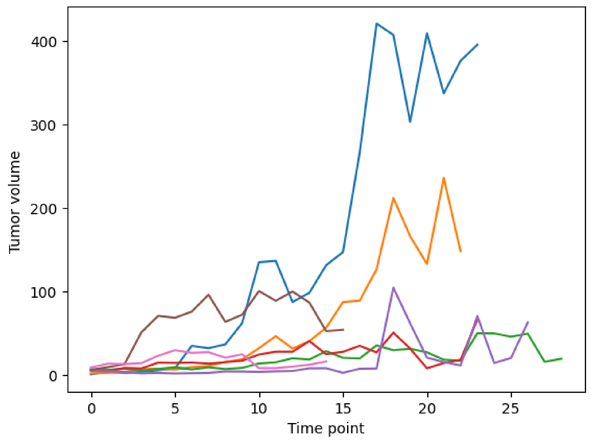
Cancer is a complex and diverse group of genetic diseases. There are many challenges in developing effective diagnostics and treatments since we don't fully understand how cancer works or know how to properly model its activity. One important aspect of modeling cancer activity is tracking the rate of tumor growth. We hope to explore cancer growth by using various ordinary differential equation models.

INTRODUCTION

- Tumor growth depends on many factors, and it has been shown that tumor growth dynamics are both tumor and organism specific [1].
- Many ODE models have been proposed to model tumor growth [2].
- We compare three different ODE models combining three different iterators we learned from class, fitting their parameters and then assessing their fits for the data.

METHODS

Tumor Growth Data: (Untreated Mice, Skin Cancer)
Tumor length, tumor width ⟶ tumor volume



ODE Iterators:

Forward Euler (FE): $V_{n+1} = V_n + V_n' \cdot \Delta t$

Backward Euler (BE): $V_{n+1} = V_n + V_{n+1}' \cdot \Delta t$

Leapfrog (LF): $V_{n+1} = V_{n-1} + 2 \cdot V_n' \cdot \Delta t$

★ NOTE: time was discretized and dt = 1

Pipeline:

1. Formulas: $V = \frac{\pi}{6} \cdot L \cdot W \cdot \frac{L+W}{2}$

   $NMSE = \frac{\Sigma_i (y_i - \hat{y}_i)^2}{\Sigma_i y_i^2}$

2. Extract tumor growth data from xl file
   - partition mice based on treatment
   - calculate tumor volumes
3. Per mouse:
   1. Fit three different ODE models
      a. for each model, use three different iterators
      b. nine sets of parameters in total
   2. Asses fit of models based on normalized mean square error (NMSE)
      a. determine best iterator for each model
      b. determine best model
   3. Plot curves

Parameter Fitting:

- (a, b) in the ODE models
- iterator solution curve vs. data
- Python scipy.optimize ⟶ curve_fit

DISCUSSION

- One big limitation is that the tumor volume data may be noisy, so a fitted smooth curve will never have zero error.
- The volume formula assumes a certain shape of the tumor, but this may not be the case.
- There is a lot of intra-mouse variability, with some mice having slow growing tumors and others fast growing tumors.
- The results show that there is great variability of cancer progression, emphasizing the importance of pursuing subject and/or tumor-specific modeling approaches in order to quantify tumor growth dynamics.

NEXT STEPS

(With the same dataset)

- Take into account time intervals between measurements.
- Try adding drug treatment condition.
- Compare growth of different tumors within the same mouse.
- Asses intra- and inter-mouse variability of tumor growth given different drug conditions.
- Assess drug efficiencies.

THE ODE MODELS

Logistic

Growth function: a = growth rate, a/b = carrying capacity

$$\frac{dV}{dt} = aV\left(1 - \frac{V}{K}\right) \Rightarrow V' = aV - bV^2$$

Analytic Solution:

$$V(t) = \frac{V_0 \left(\frac{a}{b}\right) e^{at}}{\frac{a}{b} - V_0 + V_0 e^{at}}$$

von Bertalanffy

Growth function:

$$\frac{dV}{dt} = V' = aV^{\frac{2}{3}} - bV$$

Analytic Solution:

$$V(t) = \left[\frac{a}{b} + \left(V_0^{\frac{1}{3}} - \frac{a}{b}\right) e^{-\frac{bt}{3}}\right]^3$$

Gompertrz

Growth function:

$$\frac{dV}{dt} = V' = (a - b \ln V)V = aV - bV \ln V$$

derivation

$$\frac{dV}{dt} = r(t)V(t), \quad \frac{dr}{dt} = -br(t)$$

$$\Rightarrow \frac{d}{dt} \ln V = \frac{1}{V}\frac{dV}{dt} = r(t) = -\frac{1}{b}\frac{dr}{dt}$$

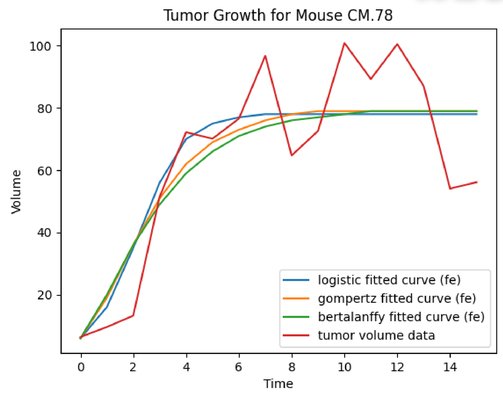
$$\Leftrightarrow \ln V = \left(-\frac{1}{b}\right)(r(t) - a)$$

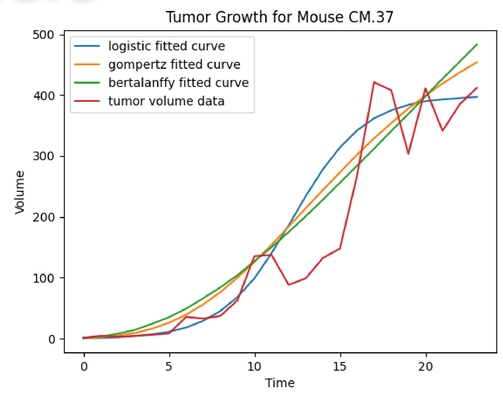
$$\Rightarrow r(t) = a - b \ln V$$

Analytic Solution:

$$V(t) = e^{\left(\ln V_0 - \frac{a}{b}\right)e^{-b(t-t_0)} + \frac{a}{b}}$$

RESULTS





Optimal Fitted Models:

- Forward Euler iterator performed the best for all mice and all models.
- Backward Euler iterator outputted unstable solutions for some tumors.
- Fitted parameters varied greatly for different tumors, even if their growth followed the same model.

Mouse id	*Model*	*Iterator*	*Parameters (a, b)*	*NMSE*
CM.37	Gompertz	FE	(0.903, 0.142)	0.069
CM.38	Logistic	FE	(0.307, 0.001)	0.089
CM.53	Logistic	FE	(0.122, 0.003)	0.135
CM.76	Gompertz	FE	(0.516, 0.144)	0.169
CM.77	Gompertz	FE	(0.088, 0.000)	0.473
CM.78	Logistic	FE	(1.158 0.015)	0.045
CM.79	Bertalanffy	FE	(4.867, 1.834)	0.130

REFERENCES

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[2] Koziol JA, Falls TJ, Schnitzer JE. Different ODE models of tumor growth can deliver similar results. BMC Cancer. 2020 Mar 17;20(1):226. doi: 10.1186/s12885-020-6703-0. PMID: 32183732; PMCID: PMC7076937.

[3] Rodallec A, Vaghi C, Ciccolini J, Fanciullino R, Benzekry S (2022) Tumor growth monitoring in breast cancer xenografts: A good technique for a strong ethic. PLOS ONE 17(9): e0274886.

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