Treatment Outcome Prediction for Cancer Patients

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Dynamics and Data Assimilation, Physiology and Bioinformatics: Mathematics at the Interface of Theory and Clinical Application

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Outline

Approaches for Prediction

- Physiology-Based Mechanistic Modeling
- Machine Learning Modeling

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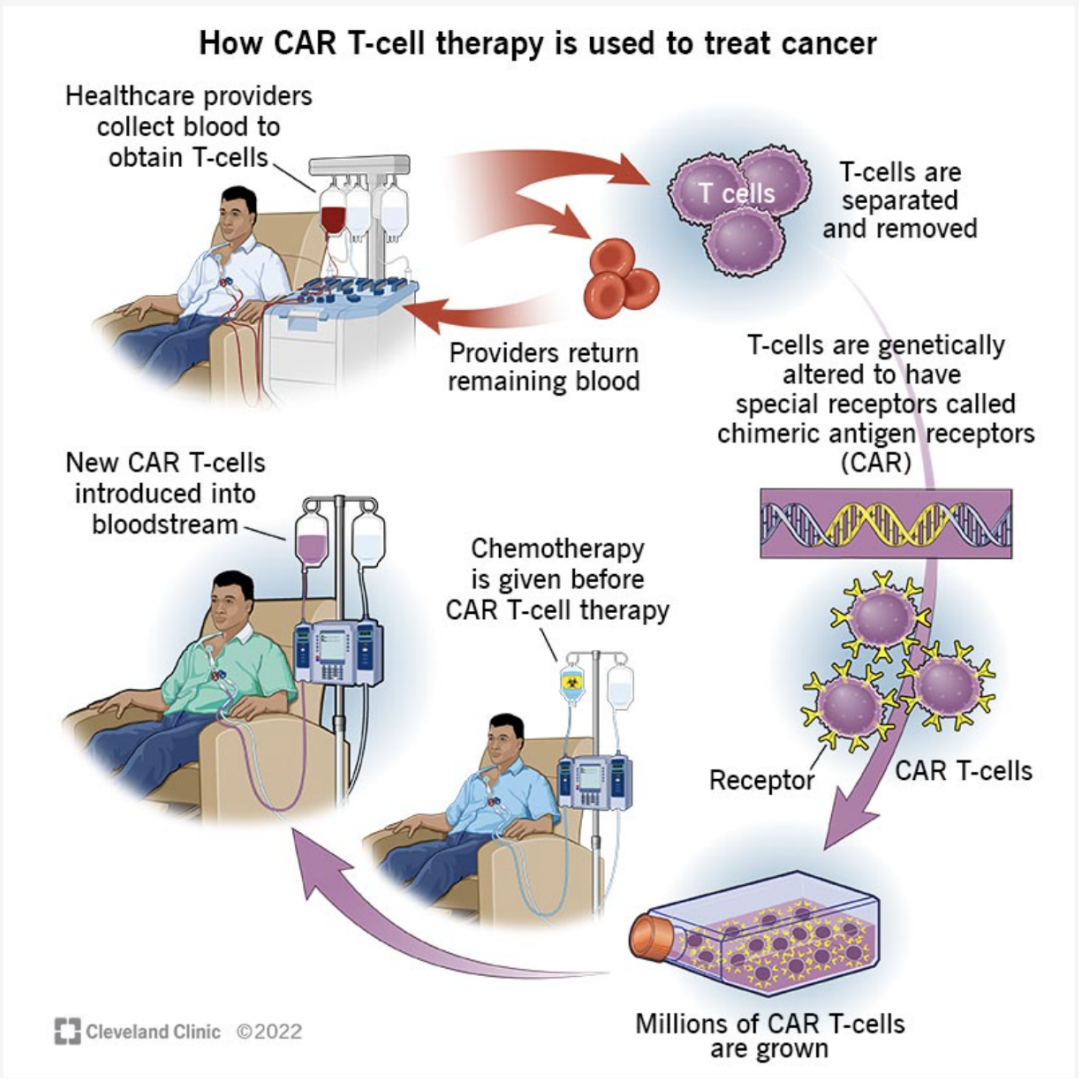
This is very extensive field. We will focus on

- one treatment $\rightarrow$ chimeric antigen receptor (CAR) T-cell therapy
- one disease $\rightarrow$ diffuse large B-cell lymphoma (DLBCL)
- one modeling approach $\rightarrow$ mechanistic modeling

CAR T-cell Therapy[1]



[1] URL: https://my.clevelandclinic.org/health/treatments/17726-car-t-cell-therapy.

Diffuse Large B-cell Lymphoma

- An aggressive and the most common type of Non-Hodgkin lymphoma (NHL)
- 81,560 estimated new cases and 20,270 deaths in 2021 due to NHL
- DLBLC accounts for 30-35% of the newly diagnosed cases
- The number of new cases is projected to increase in the next 5 years
- CAR T-cell therapy is FDA-approved as the third-line of treatment option (for leukemia, lymphoma, myeloma)

Why do we want to predict the therapy outcome?

- Even though it has shown improvement, CAR T-cell therapy does not work for everyone
- It may cause severe adverse events: toxicity
- It is a costly treatment

When can we predict?

Modeling CAR T-cell in Glioma Setting[2]

$$\underbrace{\frac{dX}{dt}}_{\substack{\text{cancer cell}\\ \text{rate of change}}} = \overbrace{\rho X\left(1-\frac{X}{K}\right)}^{\substack{\text{logistic growth}\\ \text{of cancer cells}}} - \overbrace{\kappa_1 XY}^{\substack{\text{CAR T-cell}\\ \text{induced cancer cell death}}}$$

$$\underbrace{\frac{dY}{dt}}_{\substack{\text{CAR T-cell}\\ \text{rate of change}}} = \underbrace{\kappa_2 XY}_{\substack{\text{cancer cell stimulated proliferation}\\ \text{or exhaustion of CAR T-cells}}} - \underbrace{\theta Y}_{\text{CAR T-cell death}}$$

States:

X: cancer cell count

Y: CAR T-cell count

Model Parameters:

ρ: Cancer cell net growth rate (day^{-1})

K: carrying capacity (cell)

κ_1: CAR T-cell killing rate (day^{-1} cell^{-1})

κ_2: Net rate of proliferation and exhaustion of T-cells when stimulated by cancer cells (day^{-1} cell^{-1})

θ: CAR T-cell net death rate (persistence) (day^{-1})

[2] Prativa Sahoo et al. "Mathematical deconvolution of CAR T-cell proliferation and exhaustion from real-time killing assay data". In: *Journal of the Royal Society Interface* 17.162 (2020), p. 20190734.

Modeling CAR T-cell in Glioma Setting

By re-scaling time and state variables,

$$\tau = t\rho, \quad y = \frac{\kappa_1}{\rho} Y, \quad x = \frac{1}{K} X,$$

we obtain an equivalent dimensionless system

$$\frac{dx}{d\tau} = x(1-x) - xy$$
$$\frac{dy}{d\tau} = Bxy - Ay$$

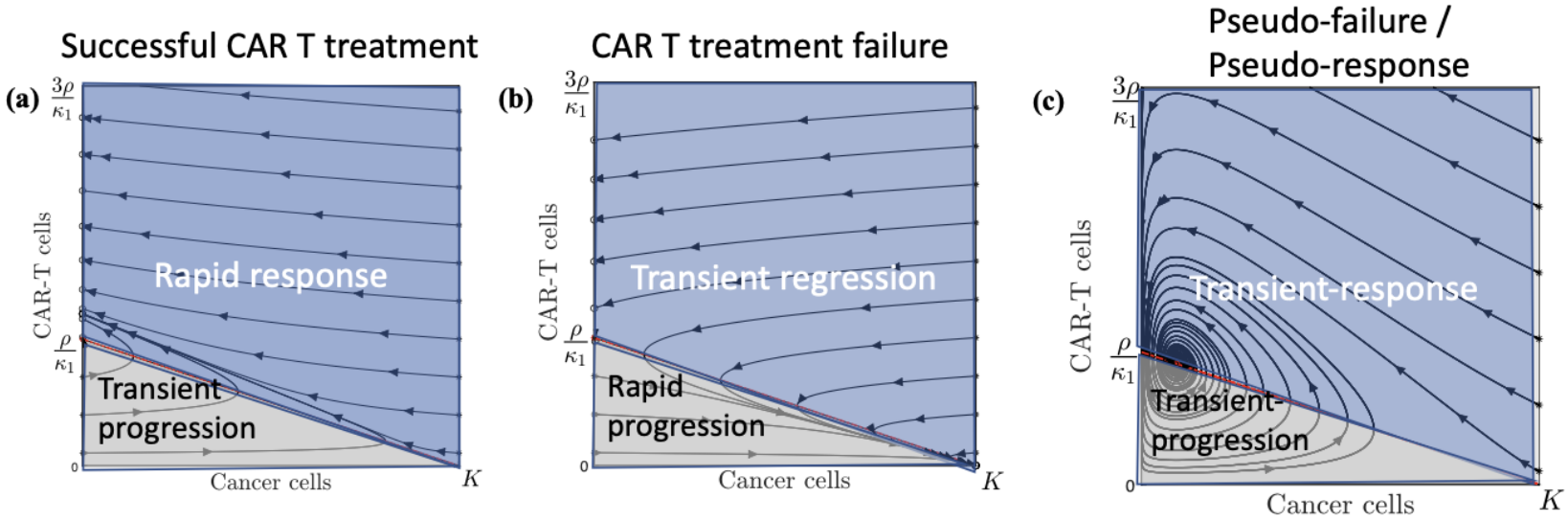
with the following dimensionless parameters

$$A = \frac{\theta}{\rho}, \quad B = \frac{\kappa_2 K}{\rho}.$$

Modeling CAR T-cell in Glioma Setting

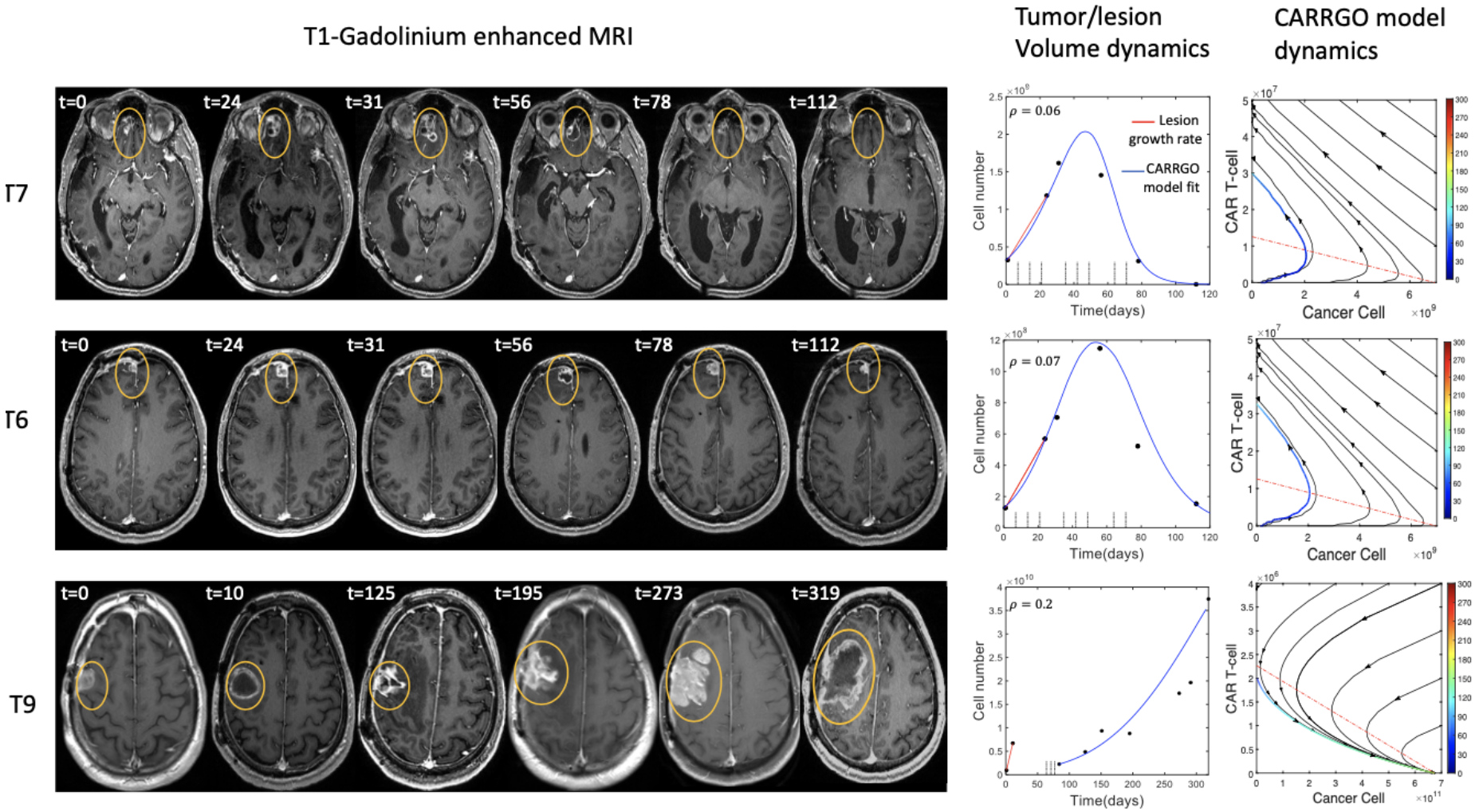
Possible Dynamics of the CARRGO Model:

$$A = \frac{\theta}{\rho} \quad \text{and} \quad B = \frac{\kappa_2 K}{\rho}$$



1. Successful CAR T-cell treatment: $A = 0, B > 0$
2. CAR T-cell treatment failure: $A = 0, B < 0$
3. Pseudo-failure or pseudo-response: $A > 0, B > 0$

Modeling CAR T-cell in Glioma Setting

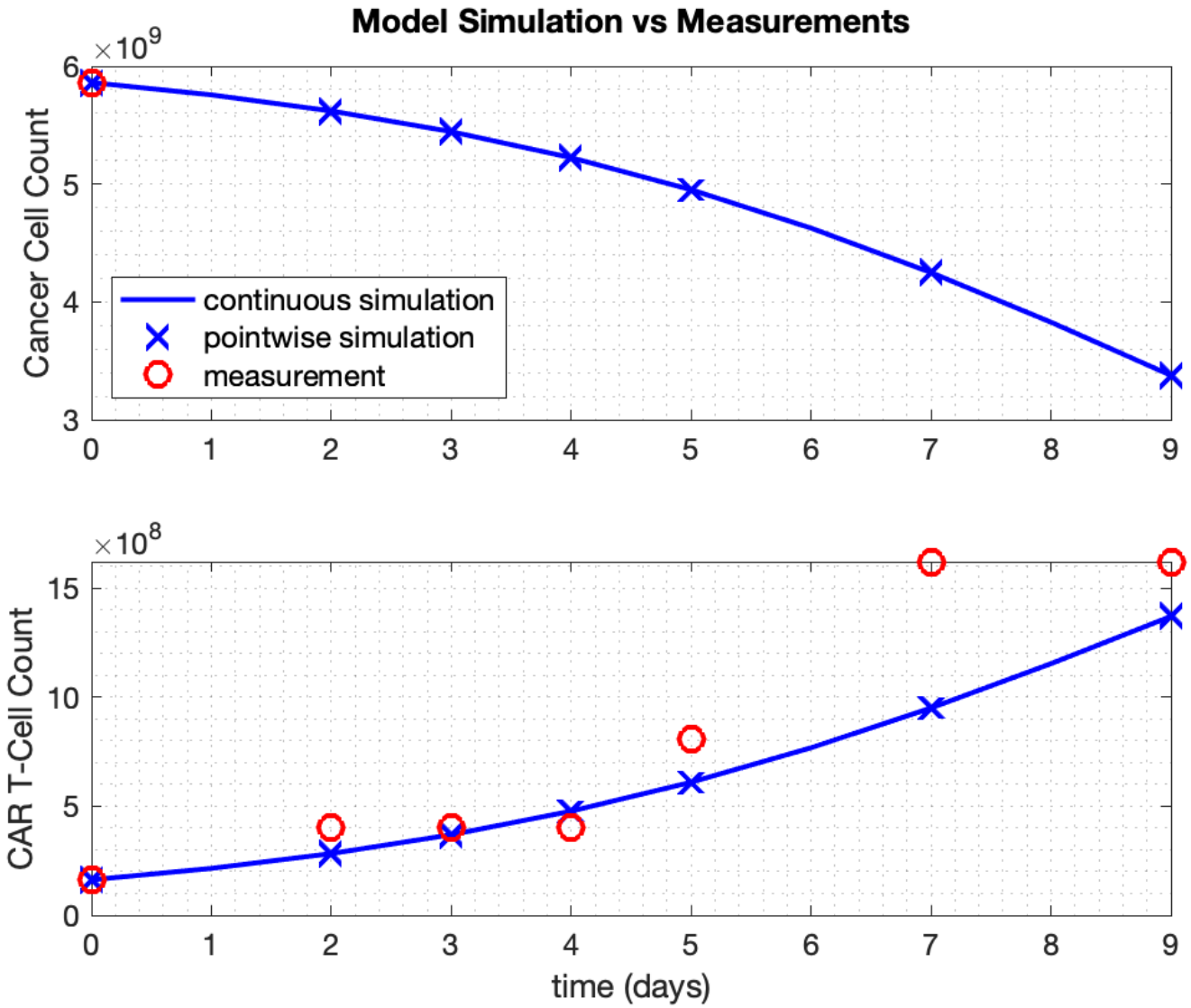


Pilot Study

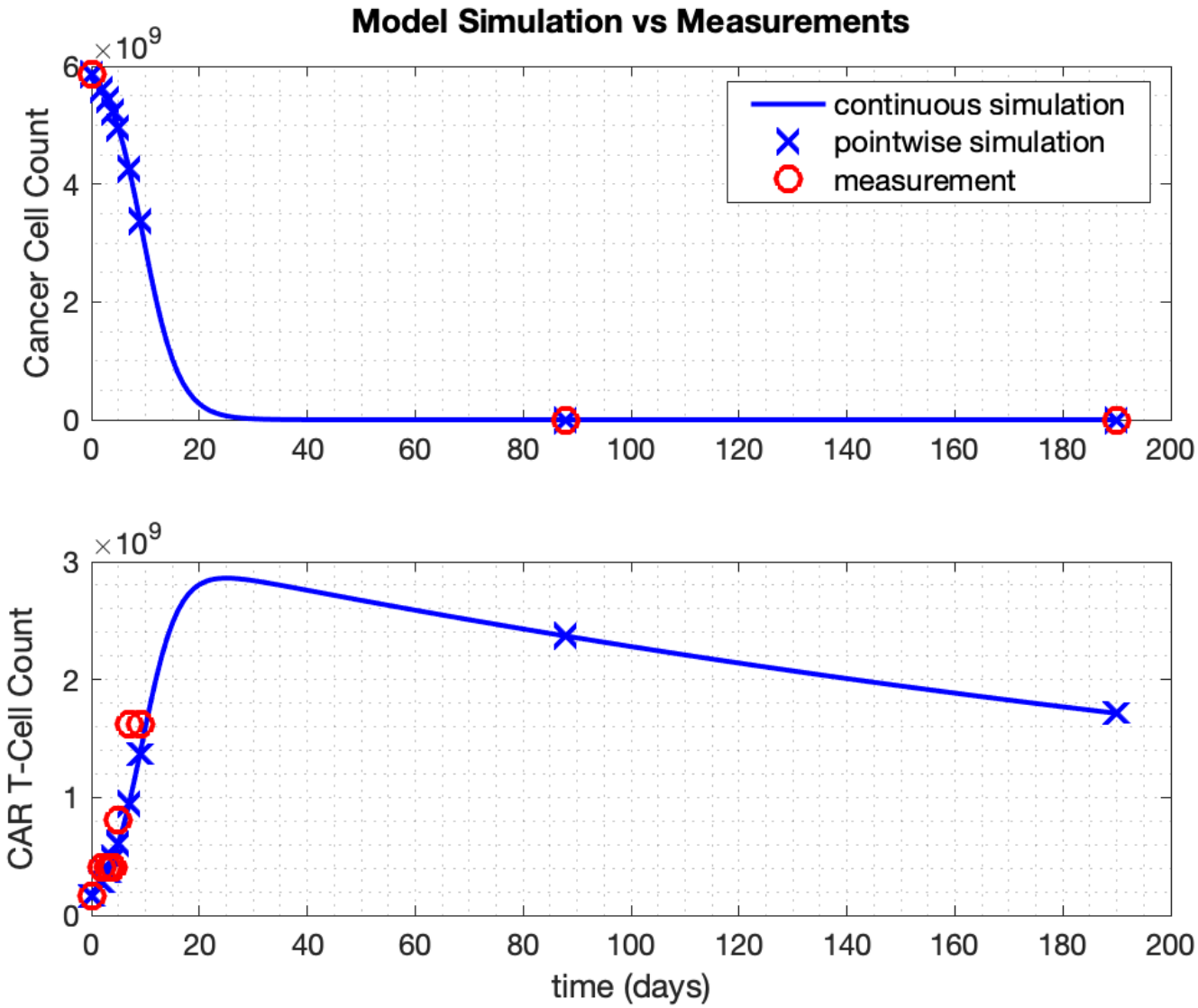
Dataset:

- TMTV measurements $\rightarrow$ cancer cell count
  1 measurement used as the initial condition
- ALC measurements $\rightarrow$ CAR T-cell count
  at most 10 measurements collected until after 15 days of CAR T-cell infusion

Model Estimation



Prediction


Model Simulation vs Measurements
×10^9
Cancer Cell Count
continuous simulation
pointwise simulation
measurement
×10^9
CAR T-Cell Count
time (days)

Conclusion

Mechanistic modeling could

- provide insight into cancer cell-CAR T-cell dynamics
- handle the data sparsity limitations
- provide more information than binary outcome prediction, e.g., timing of relapse

Future Directions

- More accurate estimation of the TMTV (cancer cell count) at the time of infusion
- Investigating use of other biomarkers for more accurate and direct estimation of cancer and CAR T-cell counts
- Identifying CAR T-cell proliferation and exhaustion time windows accurately
- Investigating optimal dosing strategies to enhance the treatment outcome

Thank you!

Questions?