Learning Model Parameter Dynamics in a Combination Therapy for Bladder Cancer from Sparse Biological Data

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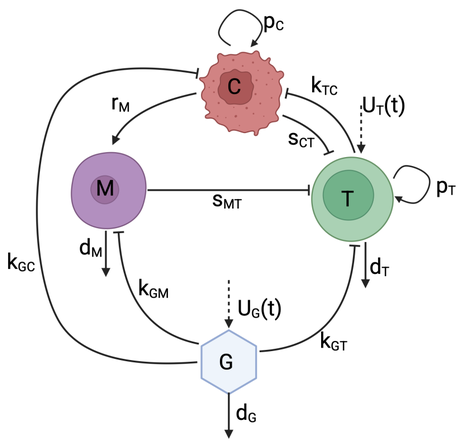
Background

- Bladder cancer is a major cause of cancer mortality worldwide.
- ODE models capture interactions among cells in the bladder tumor microenvironment.
- External interventions such as chemotherapy and immunotherapy can make model parameters time-varying.
- Sparse experimental data in oncology makes it challenging to train data-driven differential equations model.

GEM+OT-1 ODE Model



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Objectives

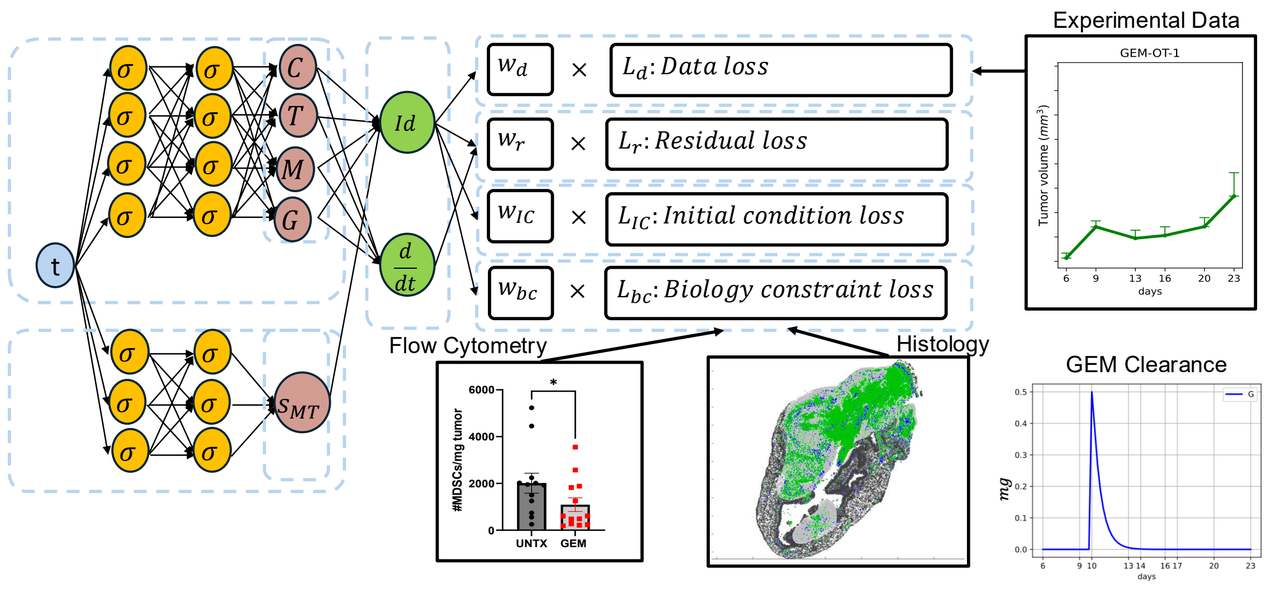
- To develop a method that uses sparse tumor-volume data from a preclinical murine model to predict unobserved trajectories for tumor cells (C), OT-1 T cells (T), and myeloid-derived suppressor cells (M).
- To demonstrate that these trajectories match known biology.
- To model tumor growth under combined gemcitabine (GEM) chemotherapy and T-cell immunotherapy.
- To evaluate treatment effects on interaction dynamics, focusing on the time-varying MDSC suppression of T cells s_{MT}.

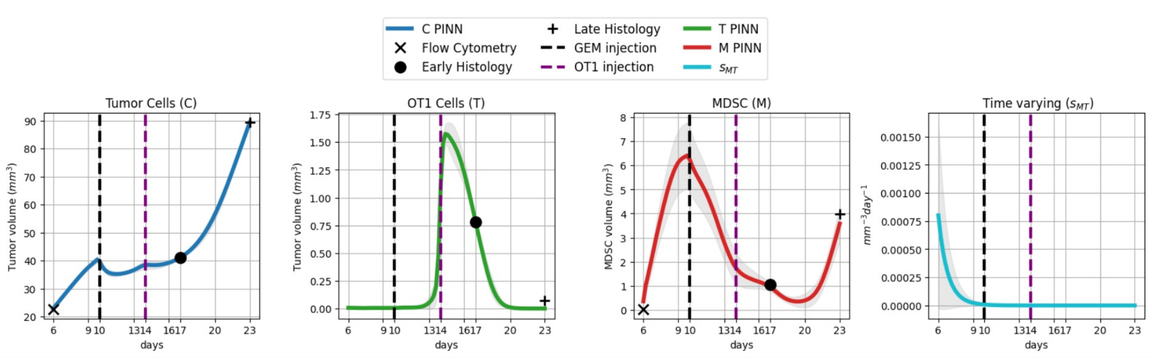
Preclinical Murine Model

- ✓ **Day 0**: 1×10^5 MB49-OVA bladder cancer cells instilled orthotopically.
- ✓ **Day 6**: proportions of tumor cells (C) and MDSCs (M) measured by flow cytometry.
- ✓ **Day 10**: $500\mu g$ GEM delivered intravesically to deplete immunosuppressive MDSCs.
- ✓ **Day 14**: 5×10^6 OT-1 T cells administered intravesically.
- ✓ **Days 17 & 23**: early and late histology collected from GEM+OT-1–treated mice.
- ✓ **Days 6, 9, 13, 16, 20, & 23**: overall tumor volume recorded.

Methods and Results

- A physics-informed neural network (PINN) with a feedforward architecture was used to model C, T, M, G, and the time-varying parameter s_{MT}.
- Experimental data were augmented using spline interpolation.
- The total loss, $L_{total} = w_r L_r + w_d L_d + w_{IC} L_{IC} + w_{bc} L_{bc}$, combines ODE residual L_r, data loss L_d, initial condition loss L_{IC}, and biological constraint loss L_{bc}.
- The weights w_r, w_d, w_{IC}, w_{bc} were adaptively adjusted using a multi-task learning of the total loss function.
- Data loss assumes $u_{GEM-OT1}$ = C + T + M, while L_{IC} enforces initial C, T, M proportions from flow cytometry ($t_0 = 6$). Biology constraint loss L_{bc} uses histology data at days 17 and 23 to match subpopulation proportions.

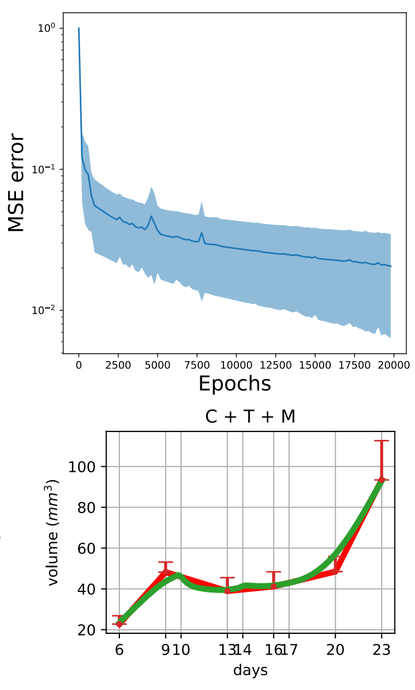




- PINN learns possible dynamics for the subpopulations C, T, and M, aligning with biological constraints at the flow cytometry point (black cross) and histology time points (black circle dot and plus).
- At the GEM injection (black vertical dash line), we see the effect of local depletion of the MDSCs and some killing of the tumor cells.
- The OT-1 injection (purple vertical dash line) indicate some killing of the tumor cells.
- PINN learns possible interaction dynamics for the model parameter s_{MT} in an unsupervised way.

Conclusions

- This work captures the dynamics of three interacting cell types and drug Gemcitabine in a limited-data setting.
- The time-varying parameter s_{MT} reveals how the two anticancer treatment may impact the suppression of T cells by MDSCs. This is a hypothesis that can be validated through a biological experiment.
- The learned dynamics of the time-varying s_{MT} showed a rapid decay to 0. It also revealed that the instillation of Gemcitabine (day 10) and the OT-1 T cells (day 14) ensured that T cell suppression by MDSCs is significantly reduced post-treatment.
- The MSE error of the PINN loss converges after 20,000 epochs (top figure).
- We demonstrated that the learned PINN solution C+T+M (green curve in the right figure below) matched the experimental overall tumor volume data at points where data were collected (red curve in the bottom figure).
- Using PINNs, we incorporated biological data as regularization to constrain solutions, an approach applicable to other differential equation models of interacting biological systems.



Acknowledgement

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