A mathematical model of pancreatic cancer development and the immune response

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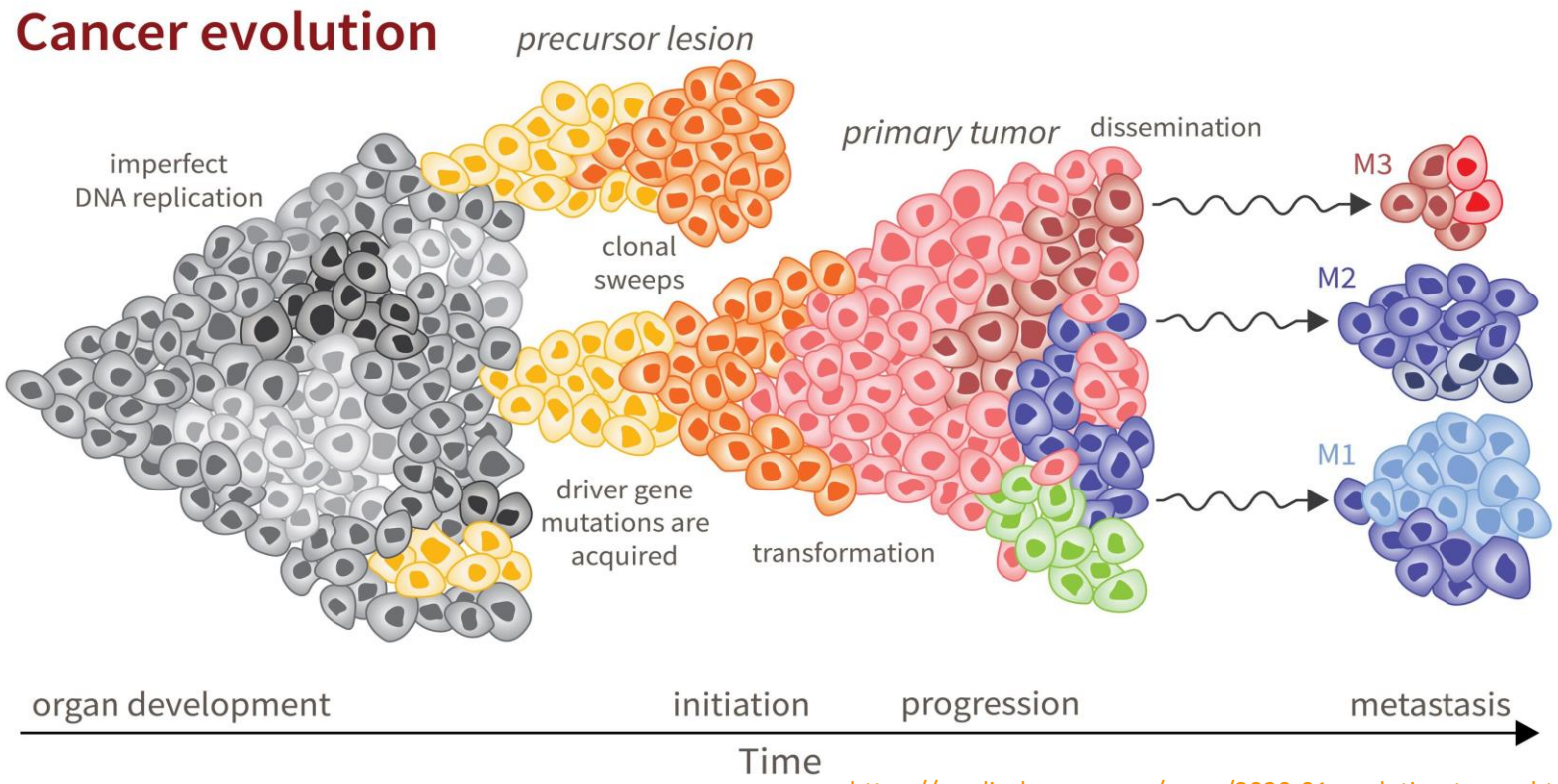
Cancer vs the Immune System

- Cancerous cells contain genetic mutations and possibly epigenetic alterations which allow them a selective advantage
- These mutations also mark the cells as foreign to the body
- The immune system then tries to kill cancer cells

- This creates a battle between the proliferation of the cancer cells and response of the immune system



https://medicalxpress.com/news/2020-01-evolution-tumor.html

The Tumor Microenvironment (TME)

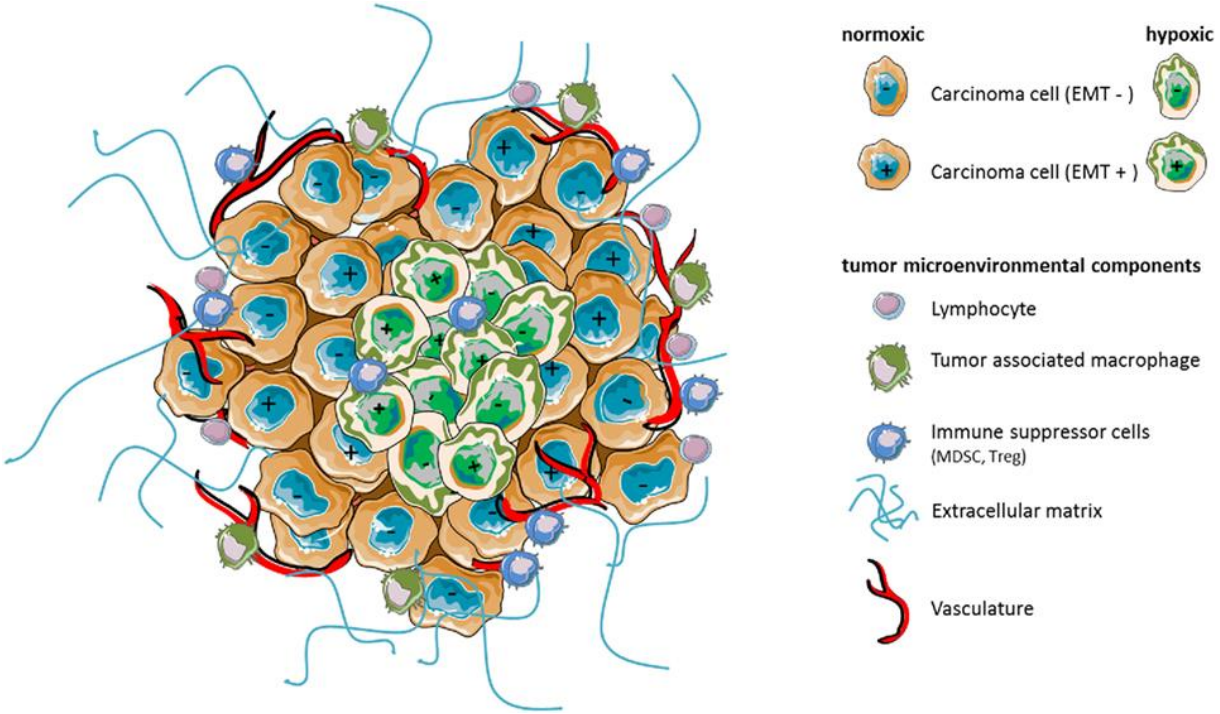
Contains cancer cells as well as normal and immune cells, we consider:

Cancerous tumor cells: rapidly proliferate, recruit the following:

- T-cells: recognize foreign antigens, force apoptosis
- Tumor-Associated Macrophages (TAMs): macrophages polarize in the tumor to promote cancer cell proliferation
  - Secrete growth factor
  - Suppress T-cell function

Hypoxic environment

- Tumor cells are largely unaffected
  - anaerobic glycolysis (Warburg effect)
- Macrophages are activated
- T-cells die, can't make it into tumor core



Terry, StePhane, Buart, StePhanie, & Chouaib, Salem. (2017). Hypoxic Stress-Induced Tumor and Immune Plasticity, Suppression, and Impact on Tumor Heterogeneity. *Frontiers in Immunology, 8*, 1625.

How can we model these interactions over time and throughout the course of various therapies to determine the optimal treatment strategy for pancreatic cancer?

Model Equations

effective populations of

Cancer cells

$$\frac{dC}{dt} = \mathrm{C}(a + eM)\left(1 - \frac{C+T+M}{K}\right) - bCT$$

growth rate; macrophages secrete growth factor; size constraint; T-cells kill cancer cells

T-cells

$$\frac{dT}{dt} = \mathrm{st} + \mathrm{h}T\,\frac{C}{ft+C}\left(1 - \frac{C+T+M}{K}\right) - gT - sTM$$

Constant circulation; Recruitment saturation; hypoxia constraint; death/ migration; macrophages suppress T-cell function

Macrophages

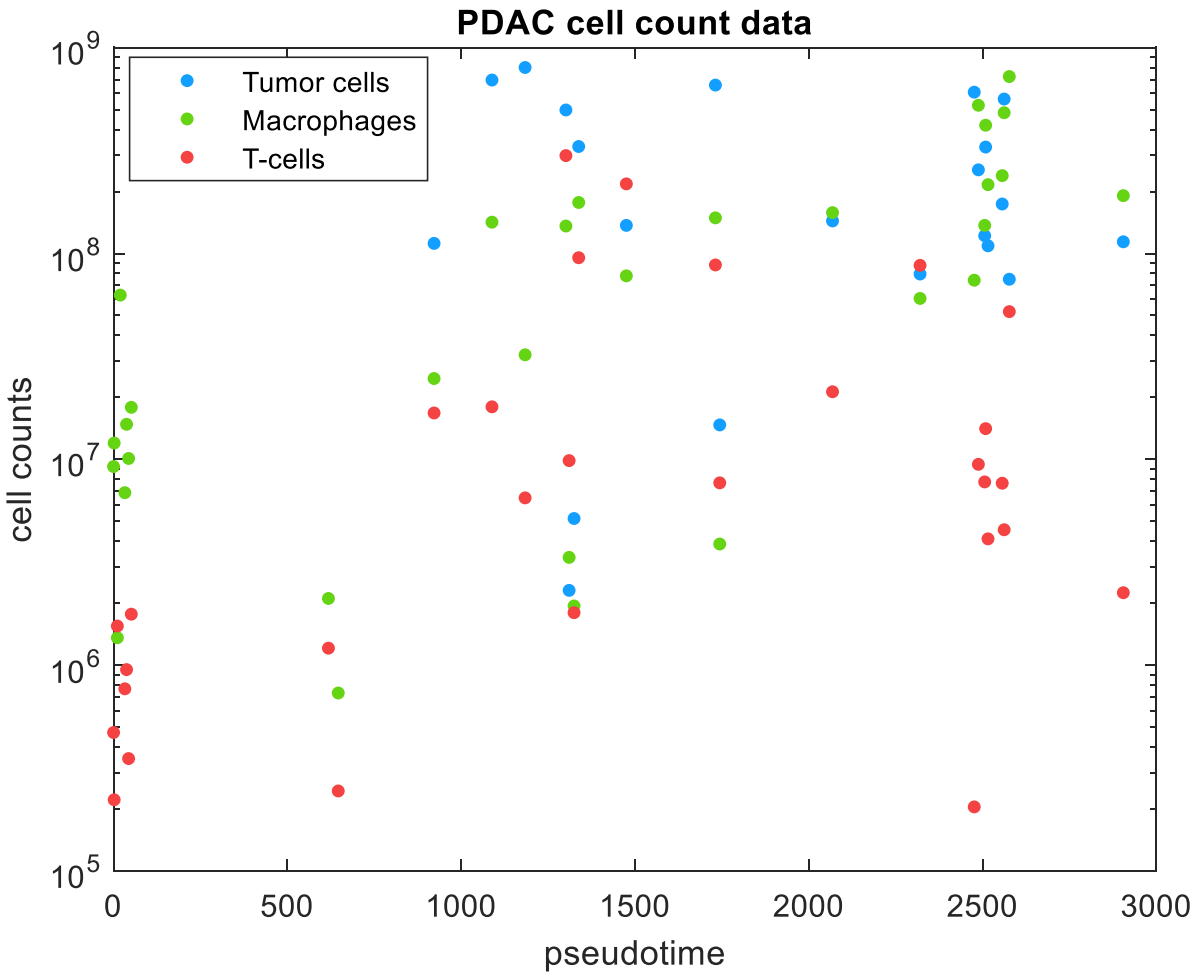
$$\frac{dM}{dt} = \mathrm{sm} + \mathrm{r}M\,\frac{C}{fm+C}\,\frac{C+T+M}{K} - uM$$

activation by hypoxia

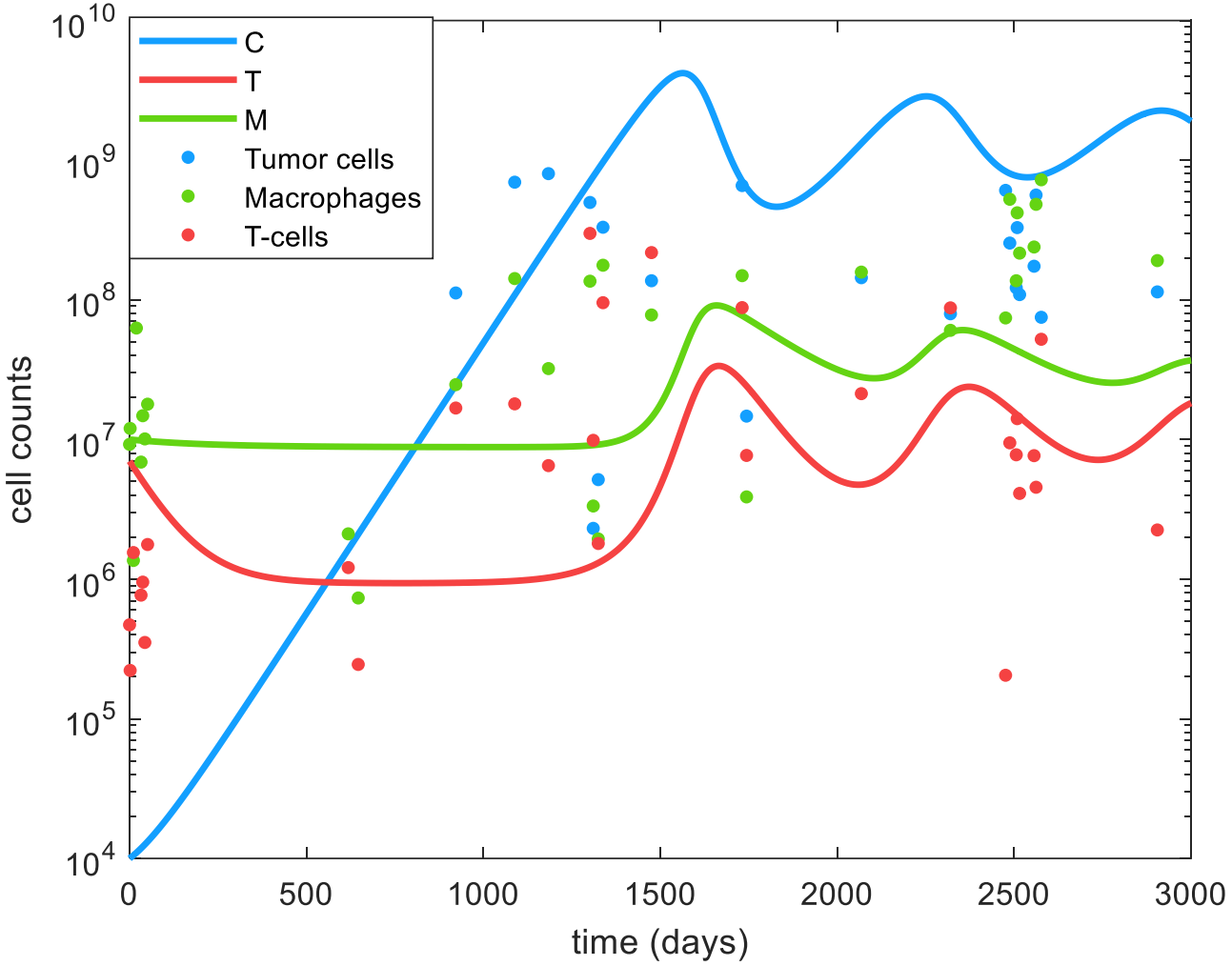
a	Cancer cell growth rate
e	Growth rate of cancer cells due to macrophages
b	Death rate of cancer cells due to T-cells
h	Maximum Growth rate of T-cells
g	Death/migration rate of T-cells
s	Inactivation rate of T-cells due to macrophages
r	Maximum Growth rate of macrophages
u	Death/migration rate of macrophages
ft	Steepness coefficient of T-cell production
fm	Steepness coefficient of macrophage production
st	Rate of T-cell influx
sm	Rate of macrophage influx
K	Carrying capacity

PDAC cell count data- cell counts from samples from pancreatic adenocarcinoma tumors

Data from Bassel Ghaddar



Cell counts over time in fitted model



Immunotherapy

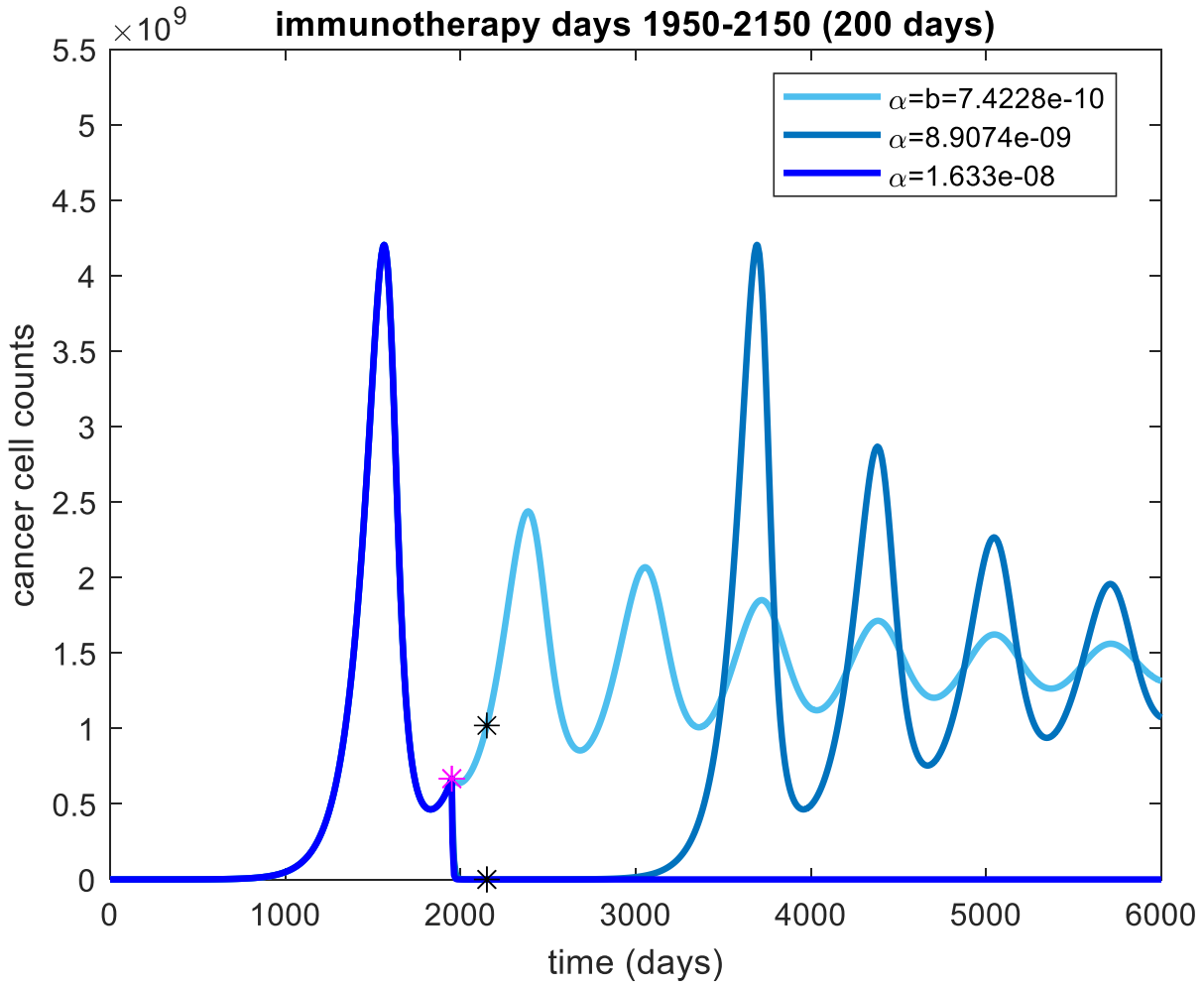
- Here we consider CAR (chimeric antigen receptor) T-Cell therapy
  - T-cells are removed from the patient's body, genetically engineered to be more effective at killing cancer cells, multiplied, and returned

$$\frac{dC}{dt} = \mathrm{C}(a + eM)\left(1 - \frac{C+T+M}{K}\right) - \alpha CT,$$

$$+1x10^{7}\ \mathrm{T} - \mathrm{Cells\ on\ day\ 1\ of\ treatment}$$

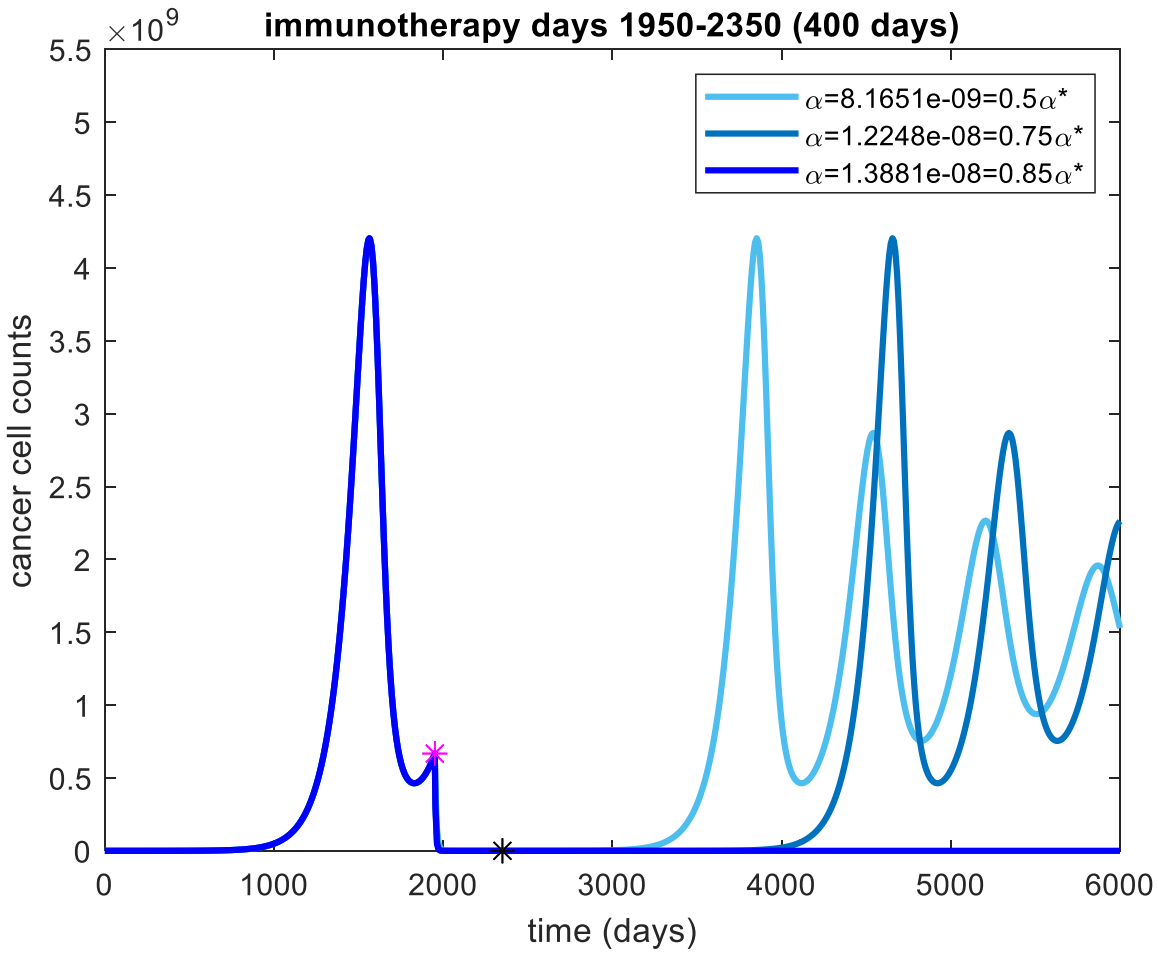
  - New parameter α represents new average effectiveness of T-cells after transfusion
  - Consider CAR T-cells persist for about 6 months in the body

Varying strength of CAR T-cells (vary α)



At α*=1.6x10^{-8} , T-cells are strong enough to fully eliminate tumor

Twice the persistence in the body can only make up for a 15% decrease in efficacy



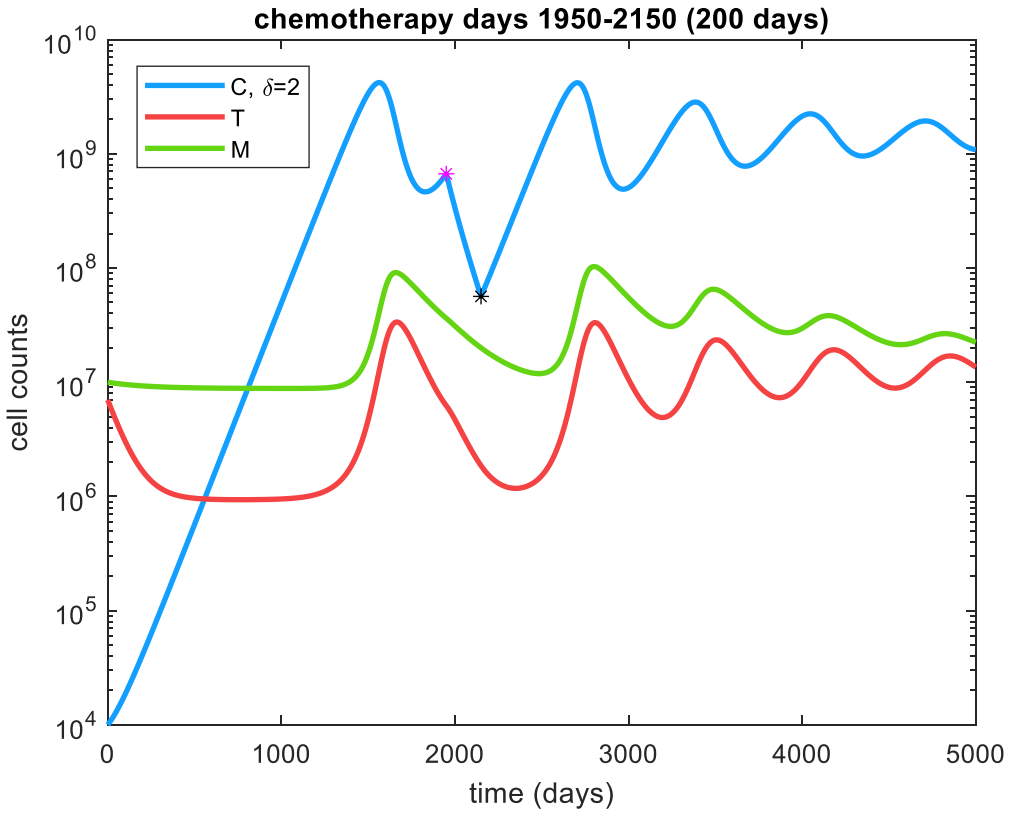
Chemotherapy

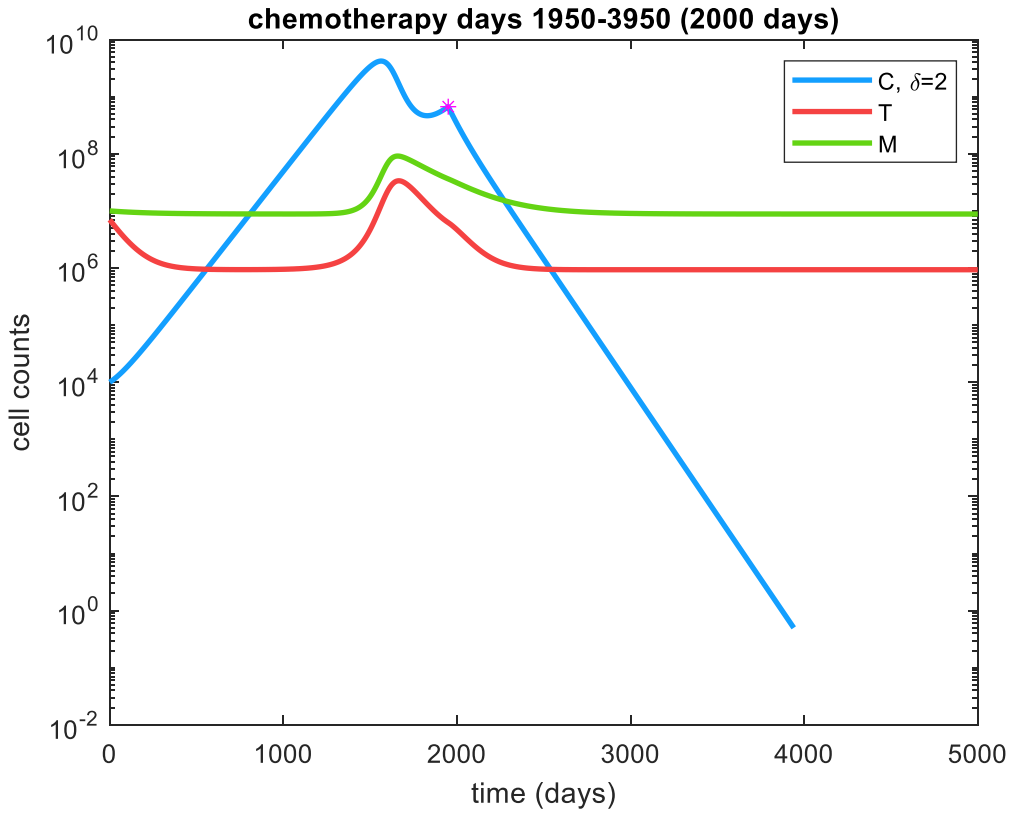
- Chemo drugs target cells while dividing and stop division and/or kill dividing cells

$$\frac{dC}{dt}=\mathrm{C}(a+eM)\left(1-\frac{C+T+M}{K}\right)(1-\delta)-bCT$$

- New factor (1- δ), where 0< δ≤2,
  - δ=0 is normal
  - δ=2 is every dividing cell killed

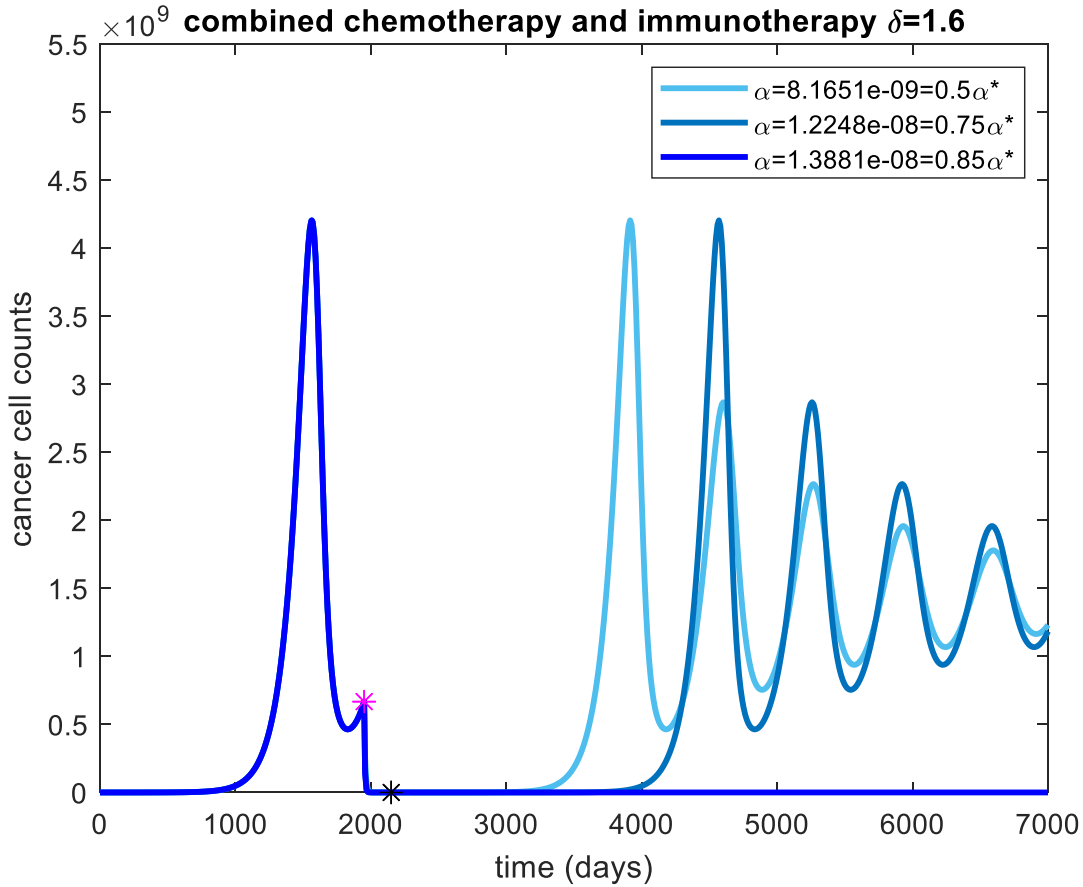
Even with a “perfect” chemo drug (every dividing cell killed, i.e. δ=2), it takes nearly 5.5 years (1990 days) to fully kill tumor





Note: This is just behavior of the model and is not realistic, as chemotherapy has been useful in the past for pancreatic cancer treatment- the model should be refined in the future to reflect known responses

Combination: Immunotherapy and Chemotherapy at the same time Allows for complete tumor reduction with less effective T-cells



Even with 15% less effective T-Cells compared to those needed for immunotherapy alone cancer can still be completely reduced

Conclusions

- Immunotherapy can be effective in eliminating tumor with a high degree of CAR T-cell efficacy, or at least reducing tumor for some time
- CAR T-cell efficacy matters more than persistence
- With a combination of chemotherapy and immunotherapy, the tumor can be eliminated even with lower precision T-cells
  - A combination of chemotherapy drugs with immunotherapy drugs has been proven to be more effective than cytotoxic chemotherapy drugs alone in melanoma, lung carcinoma, and colon cancer according to Bailly et al., *NAR Cancer* 2020

Future Directions and Practical Applications

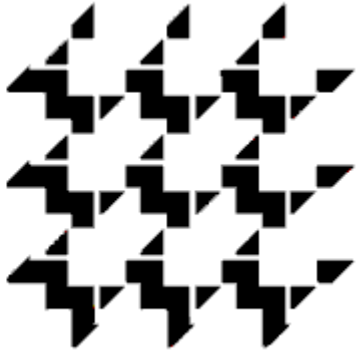
- How can combination therapy use be optimized: timing and strength?
- Future research should:
  - Adapt model to include side effects
  - ➢Optimize use of treatments to reduce side effects while eliminating tumor
- Can this be applied practically?
  - Is it safe to use chemotherapy and immunotherapy at the same time?
  - How effective can we make CAR T-cells at killing cancer cells?

Acknowledgments

- DIMACS REU program
- NSF grant CCF-1852215
- Bassel Ghaddar for cell count data
- Mentor: Dr. Subhajyoti De

DIMACS

Center for Discrete Mathematics & Theoretical Computer Science
Founded as a National Science Foundation Science and Technology Center



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