Case Study – Tumor Immunotherapy Model

SIMIODE EXPO 2021

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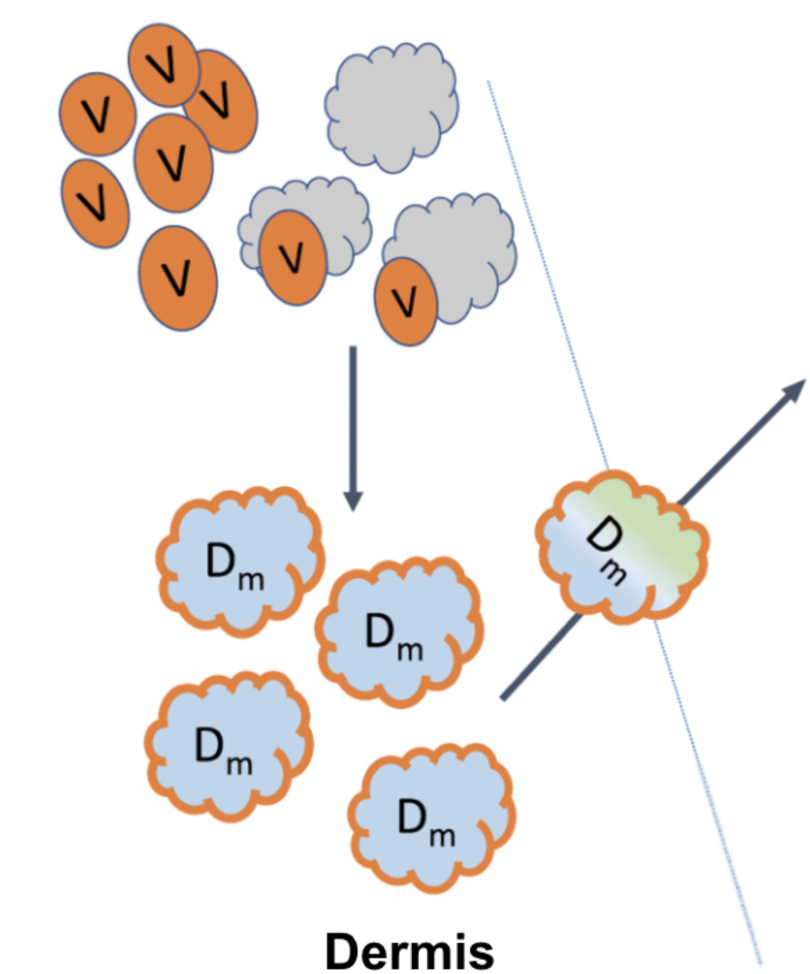
Goals of the Case Study

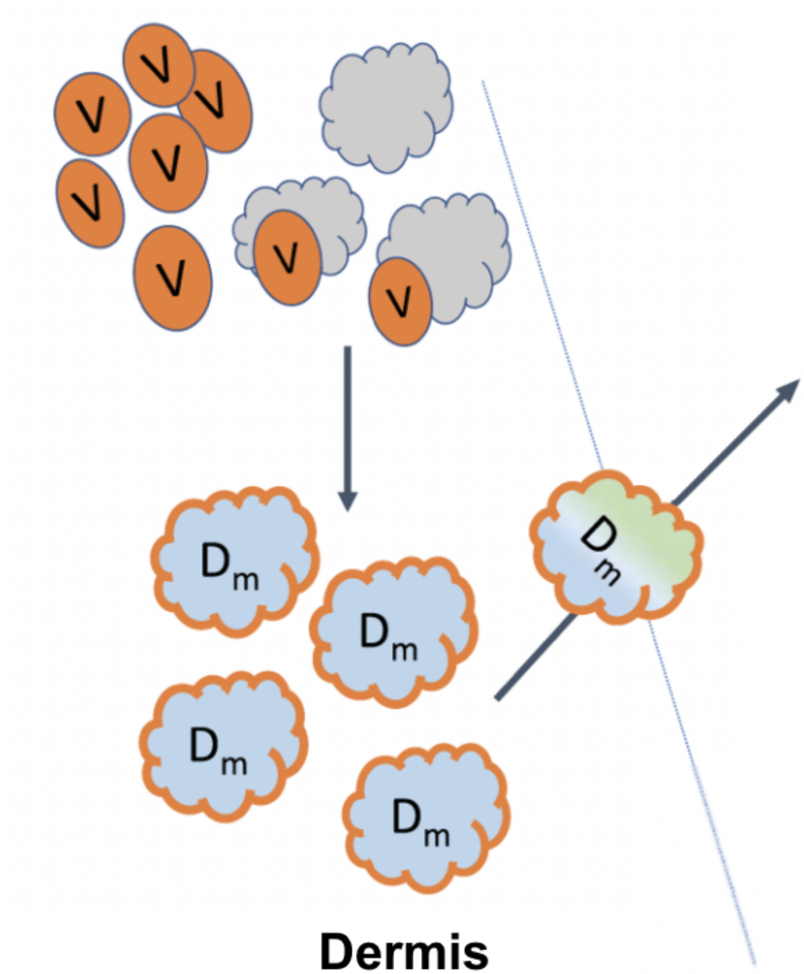
- Understand the importance of modeling in medicine when microenvironments are inaccessible.
- Formulate a system of differential equations that describes the interactions among tumor vaccine cells, immune response, prostate cancer cells.
- Use PSA data to estimate model parameters.
- Use model to test vaccination schedules with the goal of stabilizing the number of tumor cells.
- Perform sensitivity analysis to identify model parameters that, if manipulated, will help stabilize the number of tumor cells.

Initial events following vaccination



$$V(t) = \text{amount of vaccine}$$
$$D_m(t) = \text{antigen-presenting dermal dendritic cells}$$

Initial events following vaccination



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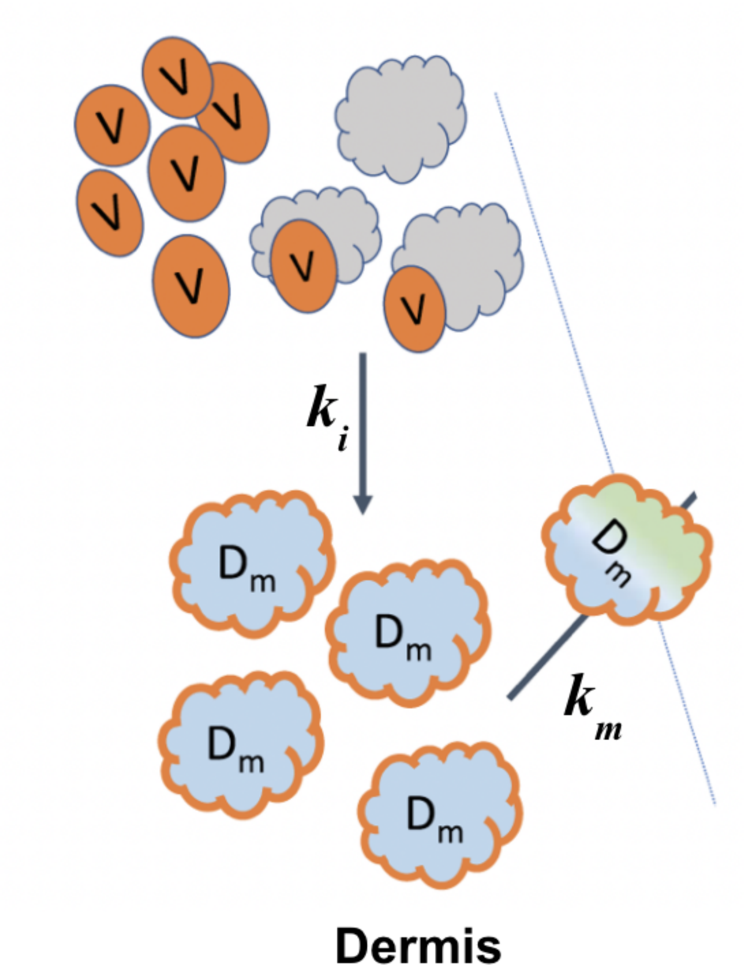
$$D_m(t) = \text{antigen-presenting dermal dendritic cells}$$

Exercise:
(https://jamboard.google.com/d/1rYxy3EaTAlfFk
usp=sharing)
Given an injection of vaccine cells at time zero, how would you expect the amounts of $V(t)$ and $D_m(t)$ to change over time? On the same plot, sketch V versus t and D_m versus t.

Initial events following vaccination



$$\frac{dV}{dt} = -k_i n_v V$$

$$\frac{dD_m}{dt} = k_i V - k_m D_m$$

Dynamics of $V(t)$ and $D_M(t)$

Vd:

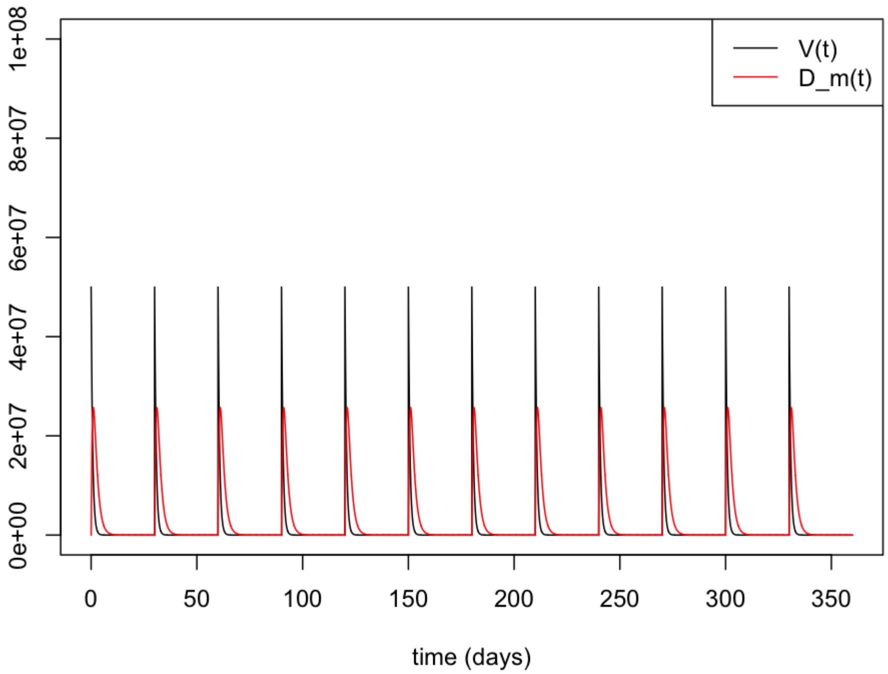
10,000,000 50,000,000 100,000,000

10,000,000 28,000,000 46,000,000 64,000,000 82,000,000 100,000,000

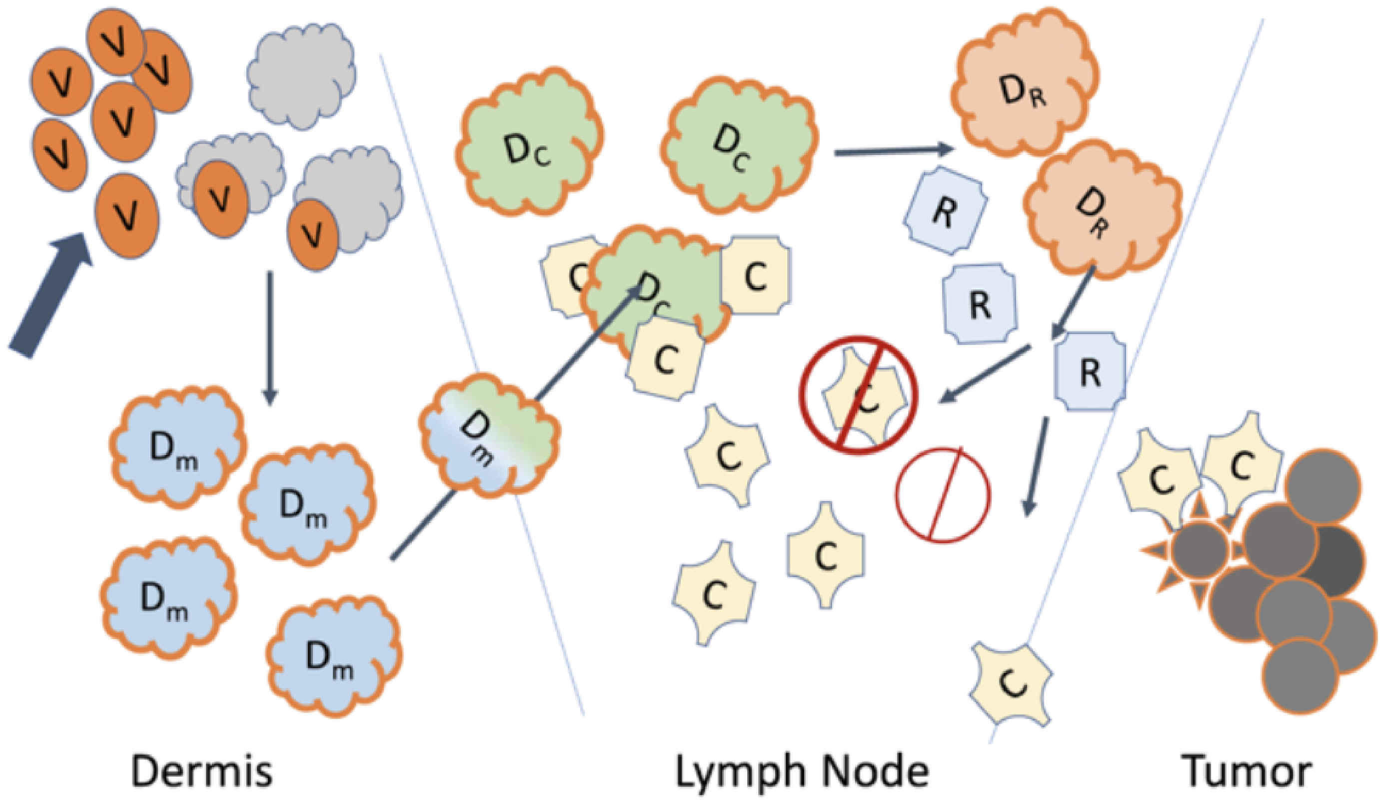
Injection Intervals:

15 30 45

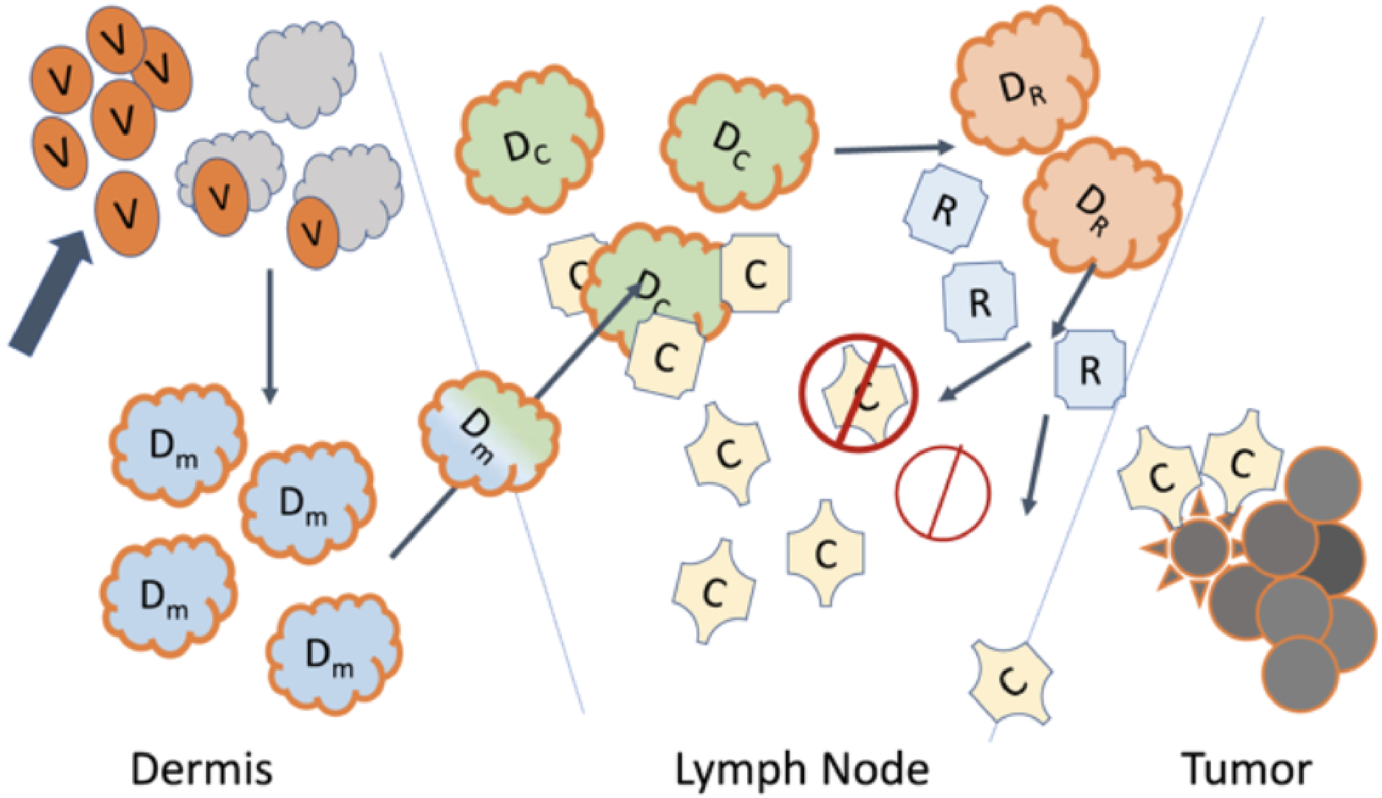
15 18 21 24 27 30 33 36 39 42 45



Tumor Cells


V
V
V
V
V
V
V
V
D_m
D_m
D_m
D_m
D_m
D_C
D_C
D_C
C
C
C
C
C
C
C
C
C
D_R
D_R
R
R
R
C
C
Dermis
Lymph Node
Tumor

Tumor Cells



Exercise: (https://jamboard.google.com/d/1rYxy3EaTAlfFKYvbTQFHPTDHkTrXJ1k7o26xBidj6Ic/edit?usp=sharing)

Assuming no vaccine is injected, how do you expect the number of tumor cells ($P(t)$) to change over time? Sketch P versus t.

How do you expect this curve to differ if vaccine is injected once a month? Sketch P versus t for this scenario.

Tumor Cells

$$\frac{dP}{dt} = rP - a_P C P \frac{h_P}{h_P + P}$$

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r: proliferation rate of tumor

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Tumor Cells

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r: proliferation rate of tumor
a_P: maximal tumor killing efficacy by CTLs
h_P: effector cell efficacy damping coefficient

Tumor Cells

Vd:

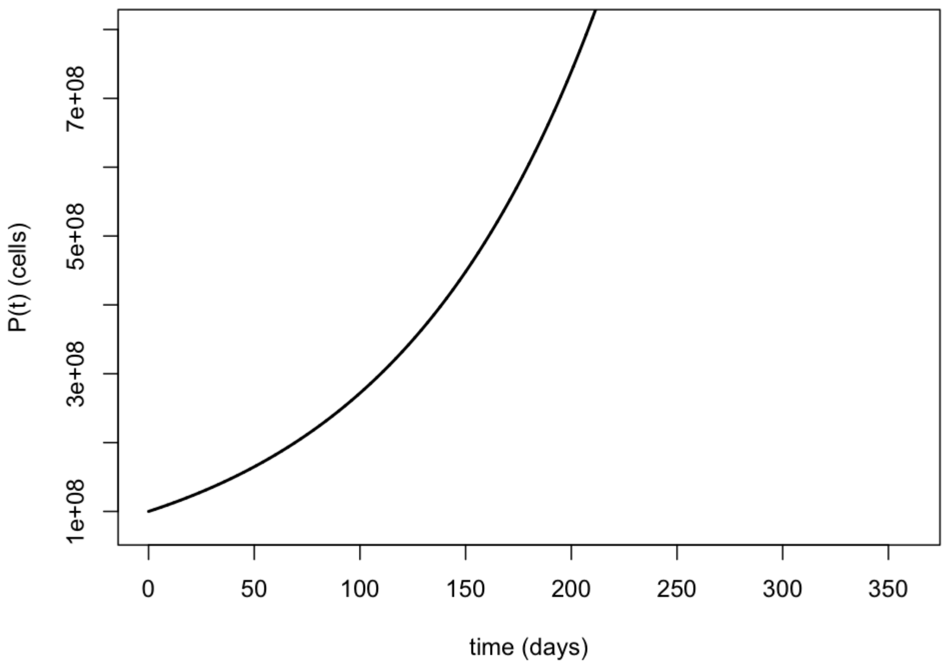
0 60,000,000

0 6,000,000 12,000,000 24,000,000 36,000,000 48,000,000 60,000,000

Injection Intervals:

15 30 45

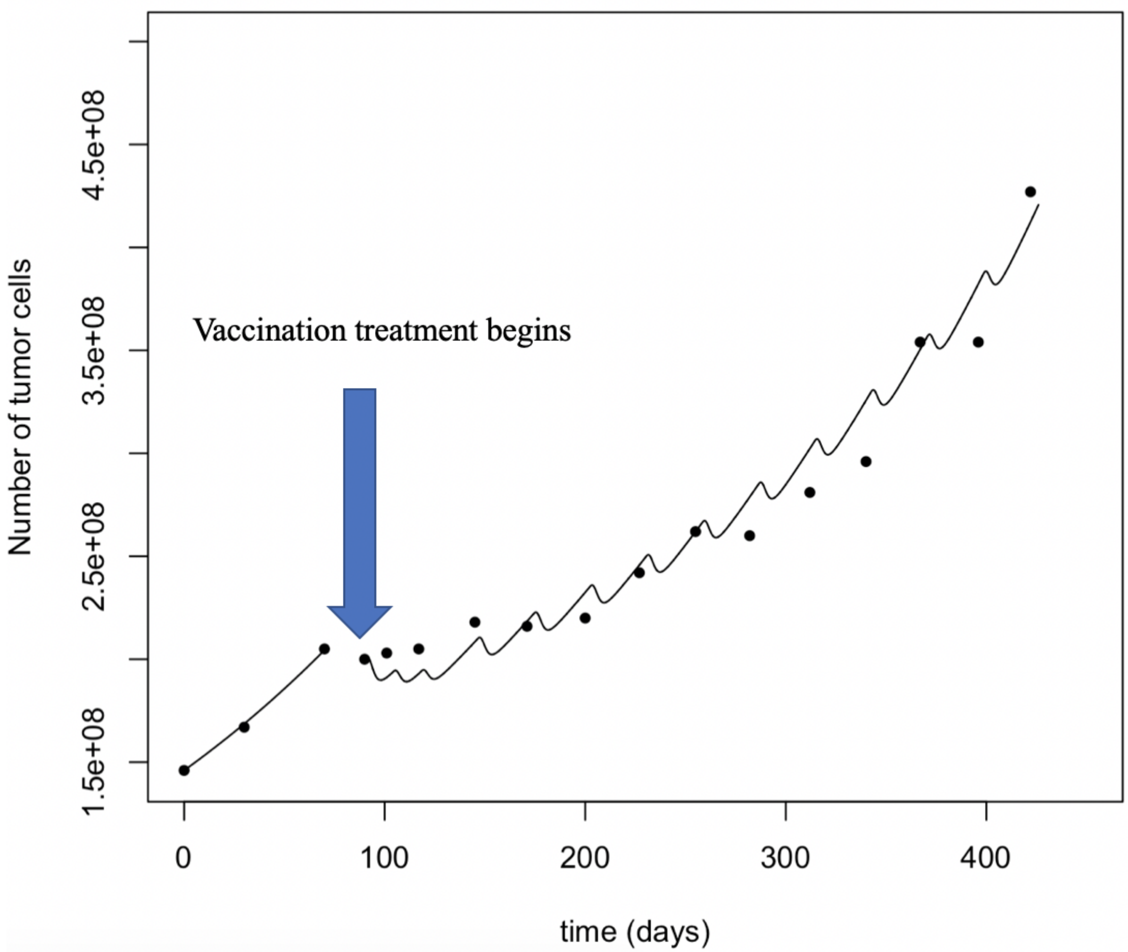
15 18 21 24 27 30 33 36 39 42 45



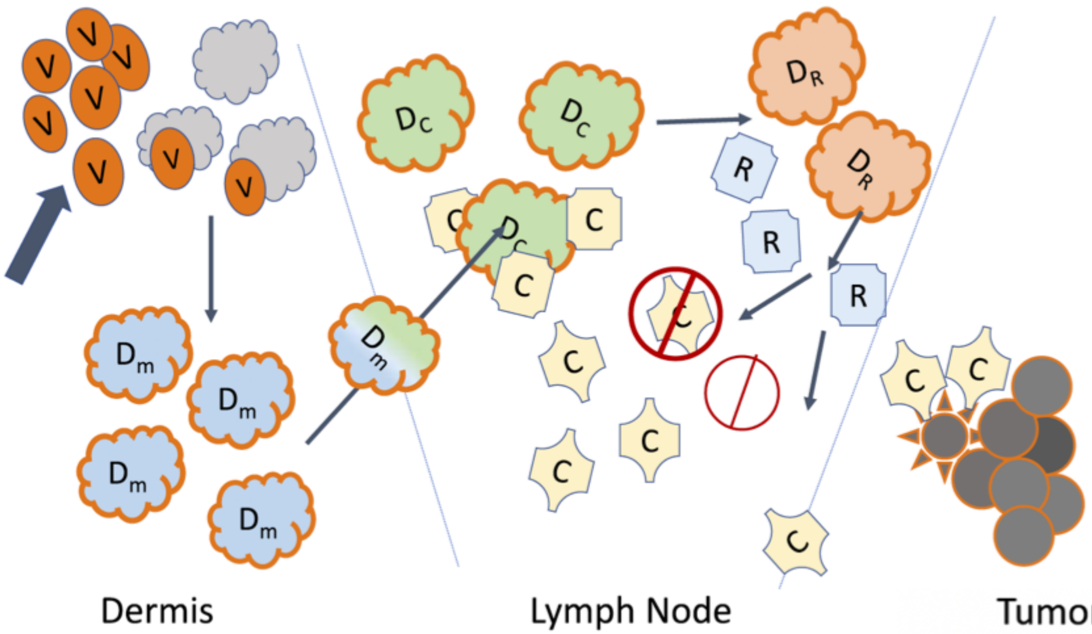
Parameter Estimation

Estimate patient-specific parameters, r and a_P:

$$\frac{dP}{dt} = rP - a_P C P \frac{h_P}{h_P + P}$$



How can we reduce the number of tumor cells?



Dermis

$$\frac{dV}{dt} = -k_i n_v V$$

$$\frac{dD_m}{dt} = k_i V - k_m D_m$$

Lymph Node

$$\frac{dD_C}{dt} = \alpha_l k_m D_m - k_{CR} D_C$$

$$\frac{dD_R}{dt} = k_{CR} D_C - \mu_D D_R$$

$$\frac{dC}{dt} = a_C D_C - \mu_C C - k_R C R$$

$$\frac{dR}{dt} = a_R D_R - \mu_R R$$

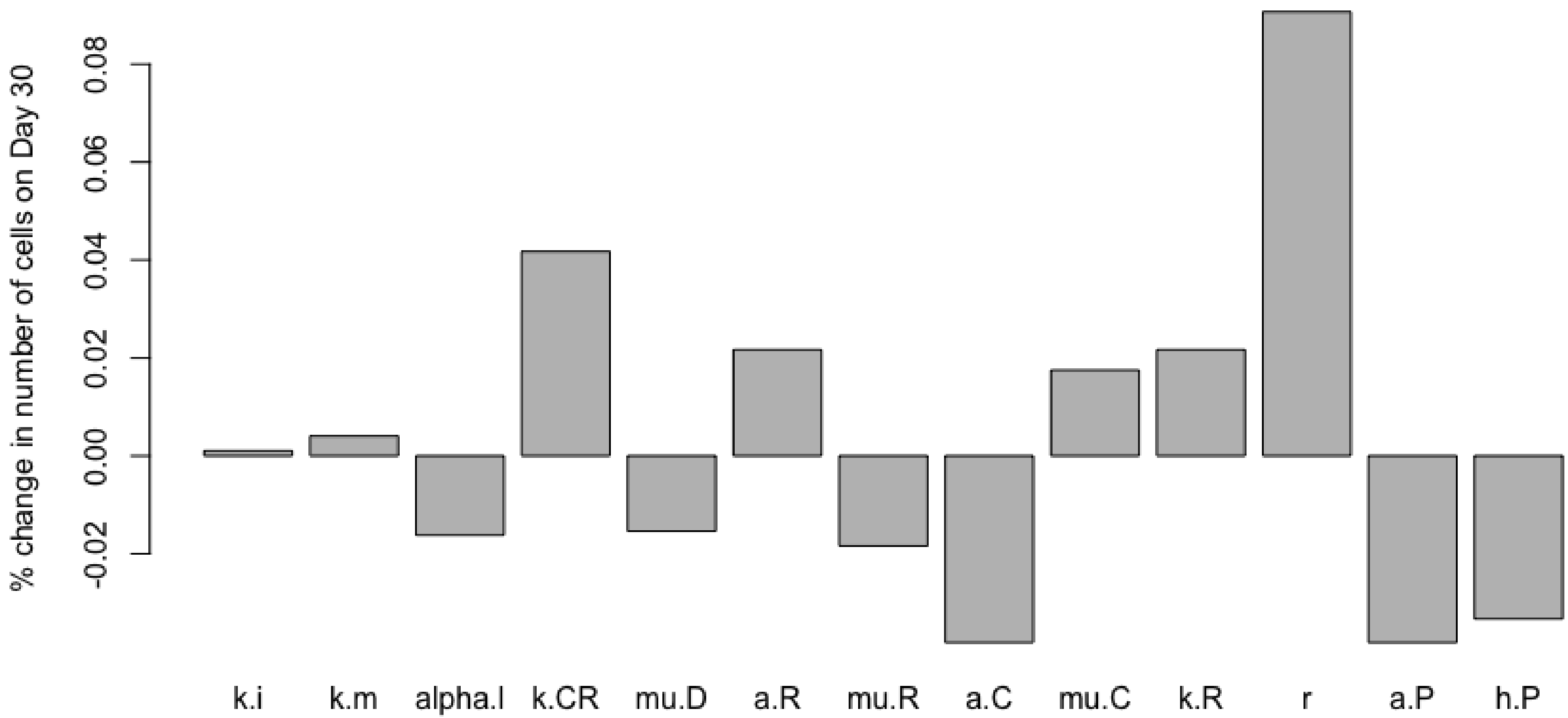
Tumor

$$\frac{dP}{dt} = rP - a_P C P \frac{h_P}{h_P + P}$$

Sensitivity Analysis

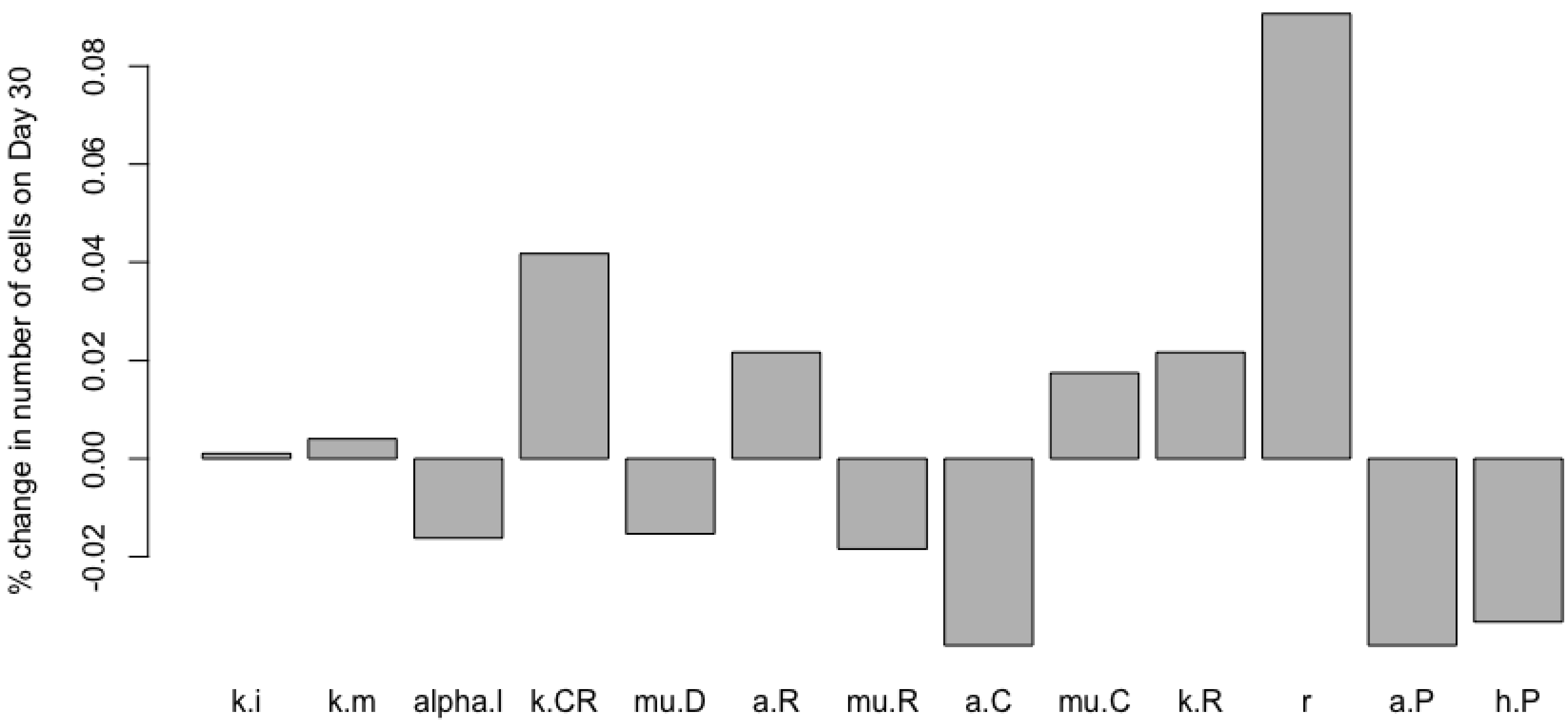
Increase each parameter by 1%

Exercise: What parameters have the greatest effect on the size of the tumor?



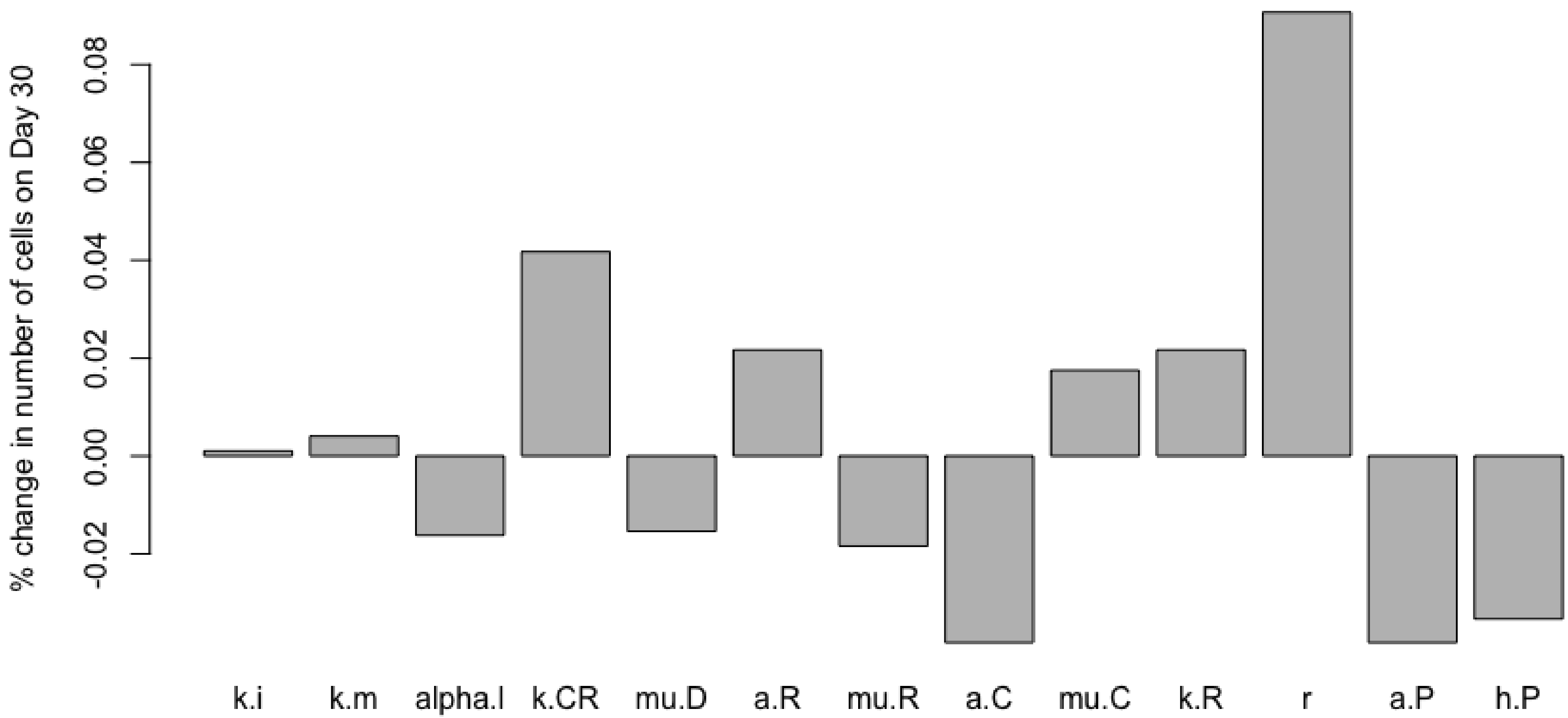
Sensitivity Analysis

Exercise: A large range of values for the tumor growth rate r and cell killing efficacy a_P have been found among patients. Knowing this and given the results below, discuss why we might use caution in using this particular model as a tool to implement a vaccination regime for some general population of patients.



Sensitivity Analysis

Exercise: Choose one strategy to test with our model by adjusting the value of the parameter affected by your treatment option. Prepare a short report on the potential to stabilize or decrease the cancer assocated with manipulating your parameter.



Resources

Textbook:

Sanft, Rebecca, and Anne Walter. “Experimenting with Mathematical Biology.” PRIMUS 26.1 (2016): 83-103. (https://www.tandfonline.com/doi/abs/10.1080/10511970.2015.1064050)

Model and data:

Kronik, Natalie, et al. “Predicting outcomes of prostate cancer immunotherapy by personalized mathematical models.” PloS one 5.12 (2010): e15482. (https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0015482)

Overview of St. Olaf College class:

Sanft, Rebecca, and Anne Walter. Exploring Mathematical Modeling in Biology Through Case Studies and Experimental Activities. Academic Press, 2020. (https://www.elsevier.com/books/exploring-mathematical-modeling-in-biology-through-case-studies-and-experimental-activities/sanft/978-0-12-819595-6)

MathBio Concentration at St. Olaf College:

https://wp.stolaf.edu/mathbio/ (https://wp.stolaf.edu/mathbio/)

THANK YOU!