Control and Decision Making in Systems Biology

Northeastern University

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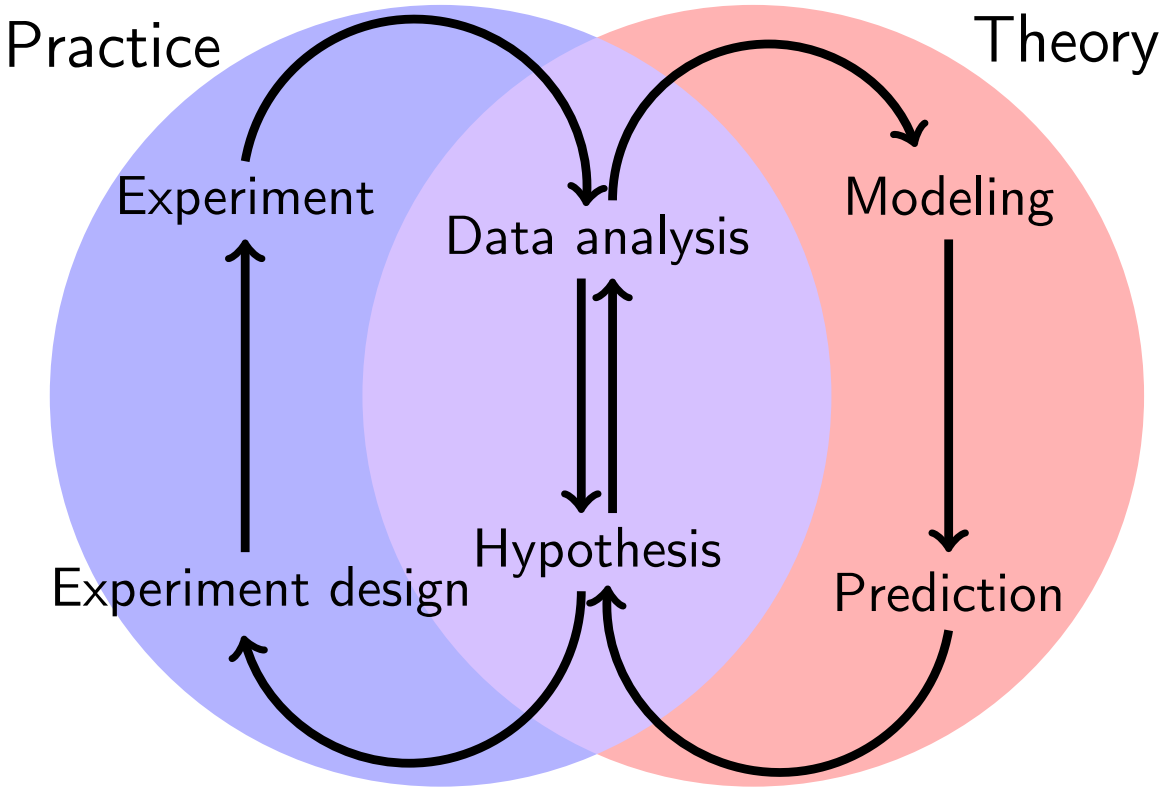
Presentation outline

1. Background
2. Chemotherapy
3. Epidemics
4. Acknowledgement

Practice and theory

Practice and theory in engineering and scientific research. The focus is to use modeling to make predictions outside previous experimental settings to come of with a better control/decision.



Cyclophosphamide: innate immune cell recriutment and tumor regression

The current standard of care limits the regiments used primaritly to daily dose and maximum-tolerated dose (MTD) treatments.

- Motivation: Metronomic/intermittent experiments[1] in mice. A lower dose with a higher frequency than MTD were shown to reqruit immune system and reduce the tumor volume.
- Objective: Use optimal control techniques in order to have a better treatment outcome among all possible dosing strategies.

[1] Junjie Wu and David J Waxman. "Metronomic cyclophosphamide schedule-dependence of innate immune cell recruitment and tumor regression in an implanted glioma model". In: *Cancer letters* 353.2 (2014), pp. 272–280.

Optimal control techniques for cancer treatment

Early efforts in using optimal control techniques for cancer treatment started in the 1970s for Radiotherapy[2] and Chemotherapy[3].

Now, a new generation of quantitative experiments made it possible to have more realistic models of the system.

The goal is to use optimal control techniques to find a mathematically derived optimal regimen (MDOR) to be tested in a similar experimental settings.

[2] K Bahrami and M Kim. "Optimal control of multiplicative control systems arising from cancer therapy". In: *IEEE Transactions on Automatic Control* 20.4 (1975), pp. 537–542.

[3] Thomas L Swan George W Vincent. "Optimal control analysis in the chemotherapy of IgG multiple myeloma". In: *Bulletin of mathematical biology* 39.3 (1977), pp. 317–337.

A dynamic model for chemotherapy

$$\dot{T}(t) = k_a T(t) - \frac{k_b C(t) T(t)}{k_c C(t) + T(t)} - k_d T(t) I(t), \tag{1a}$$

$$\dot{I}(t) = qX(t) - k_e T(t) I(t) - k_f C(t) I(t) - k_g Y(t) I(t) - k_h I, \tag{1b}$$

$$\dot{X}(t) = \frac{qC(t) T(t)}{k_i C(t) + T(t)} - k_j X(t) - k_k X(t) Y(t), \tag{1c}$$

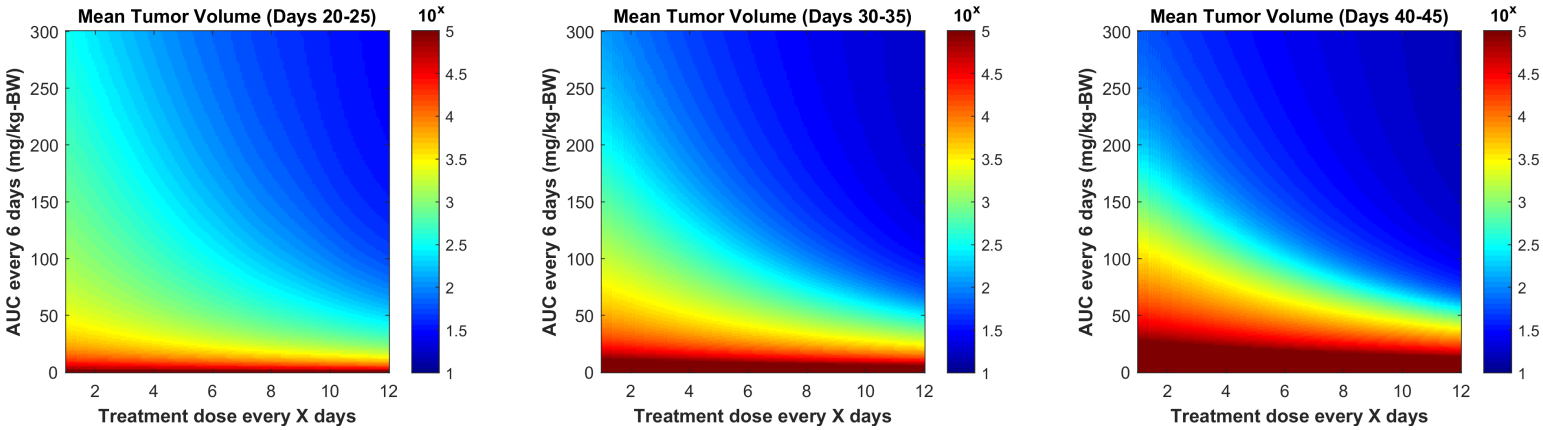
$$\dot{Y}(t) = \frac{I(t)}{k_l + I(t)} - k_m Y(t) C(t), \tag{1d}$$

$$\dot{C}t = u(t) - \frac{k_1 C(t)}{k_2 + C(t)}. \tag{1e}$$

Where Tumor T represents the tumor volume, and the phenamenological variables immune system I, immunostimulatory X, immunossuppressor Y, and drug C represent the dynamics in the tumor microenvinronment.
Model is fitted to the tumor and immune data in mouse experiments.

Efficacy of metronomic regimens

140 mg/kg every 6 days as an optimal metronomic regimen.



The average tumor volume at different time ranges of 20-25 days (left), 30-35 days (middle), and 40-45 days (right) after starting a metronomic regimens. The horizontal axis represent the number of dose between each dose, y axis is the total amount of drug given to the animal every 6 days.

Optimal control problem setup

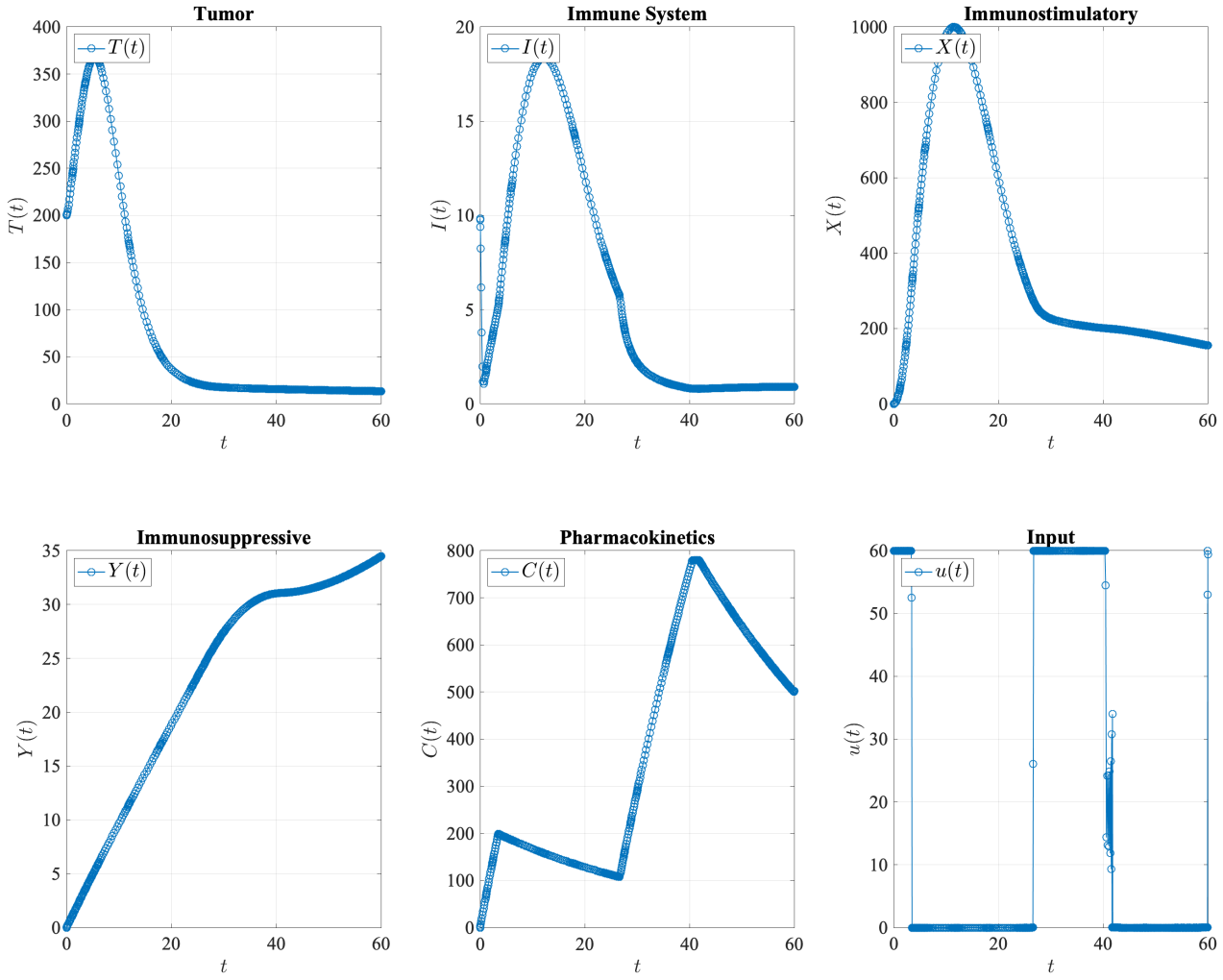
Numerical software GPOPS_II is used to solve the following setup for the optimal control problem.

$$\min_{u(t)} \quad T(t_f), \tag{2a}$$

$$s.t. \quad \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \leq \begin{bmatrix} C(t) \\ T(t) \\ I(t) \\ X(t) \\ Y(t) \\ u(t) \end{bmatrix} \leq \begin{bmatrix} C_m \\ T_m \\ I_m \\ X_m \\ Y_m \\ u_m \end{bmatrix}, \tag{2b}$$

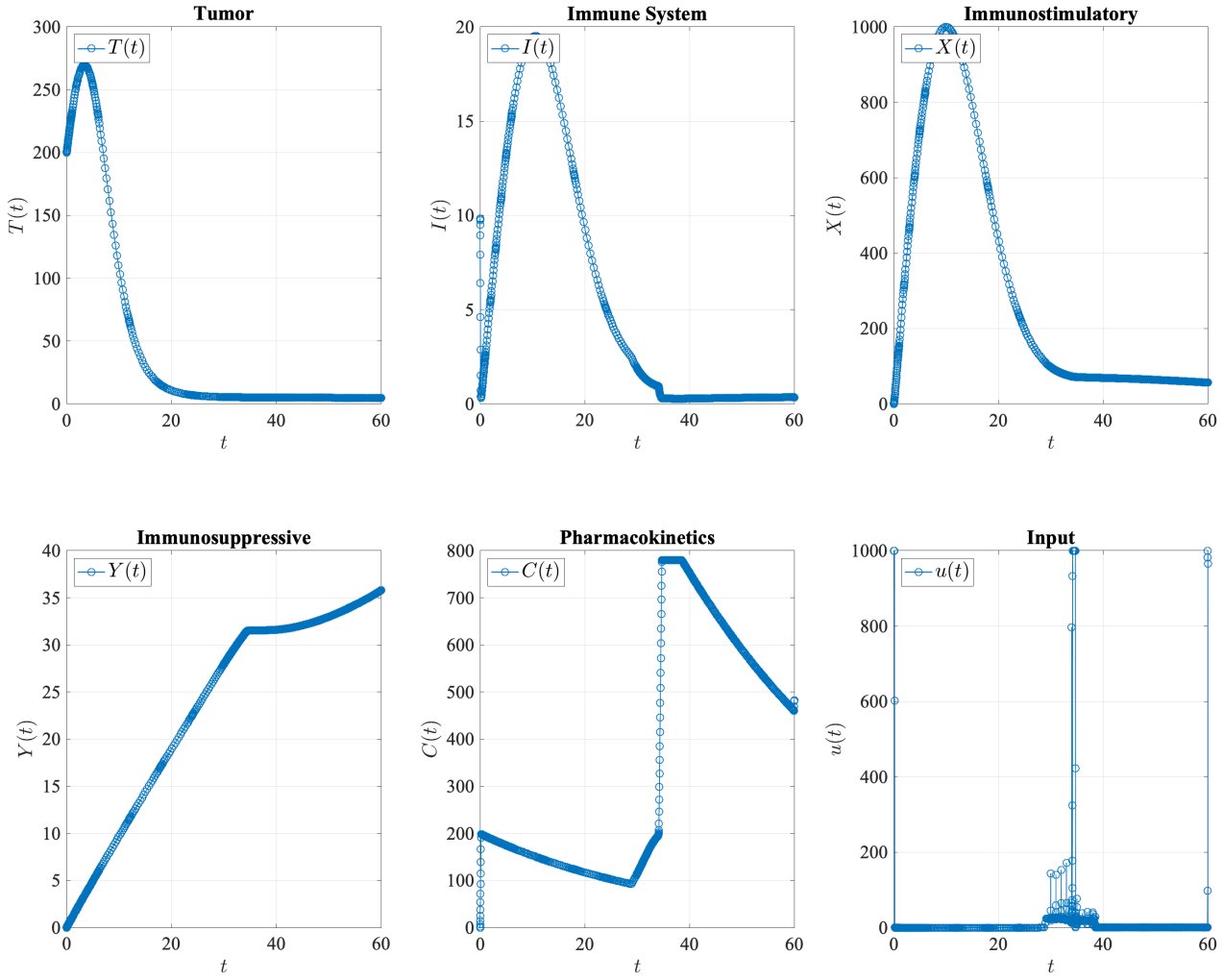
$$\int_0^{t_f} u(t)dt \leq U_m. \tag{2c}$$

Numerical result for a low input upper bound



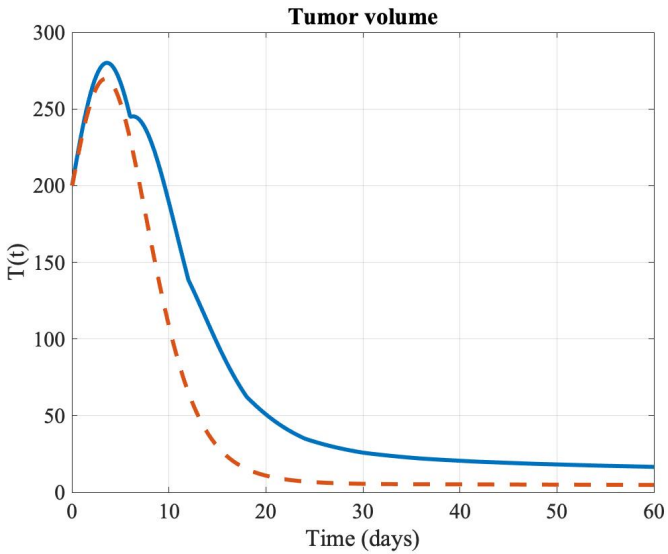
Circles show the final collocation points.

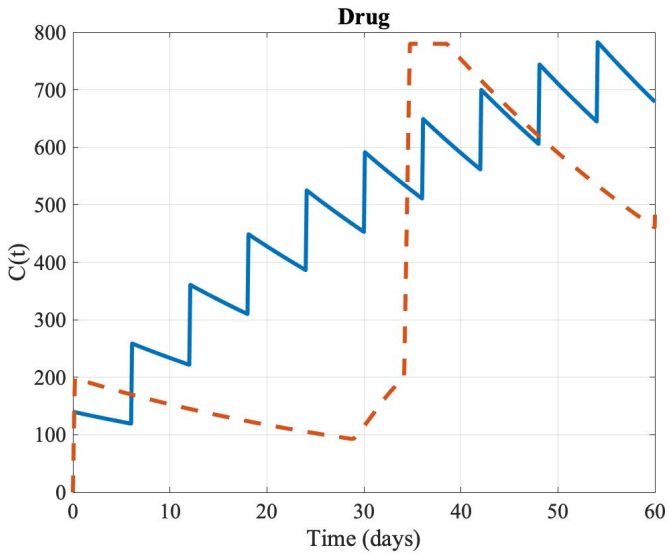
Numerical result for a high input upper bound



Circles show the final collocation points.

Optimal control vs. metronomic regimen

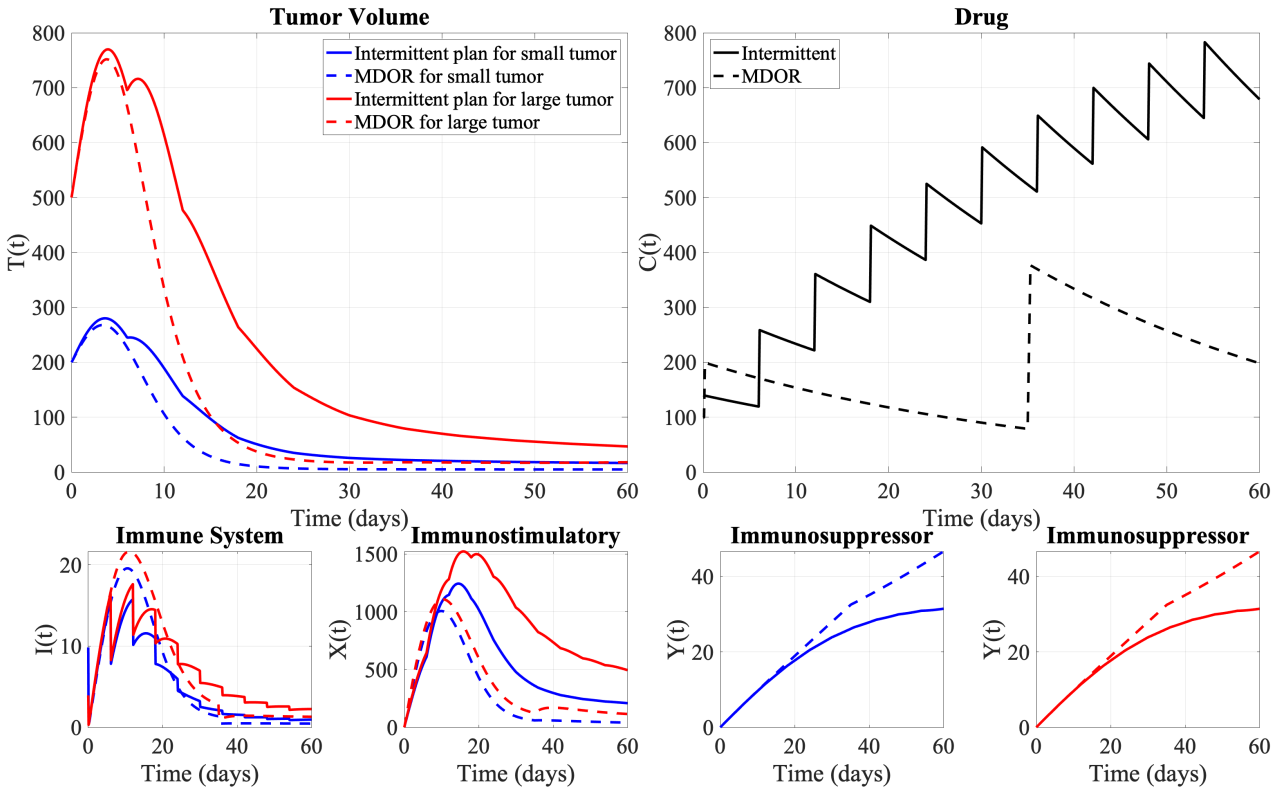




Comparing a standard 140 mg/kg Q6D metronomic chemotherapy plan (solid lines) with the obtained optimal control (dashed lines).

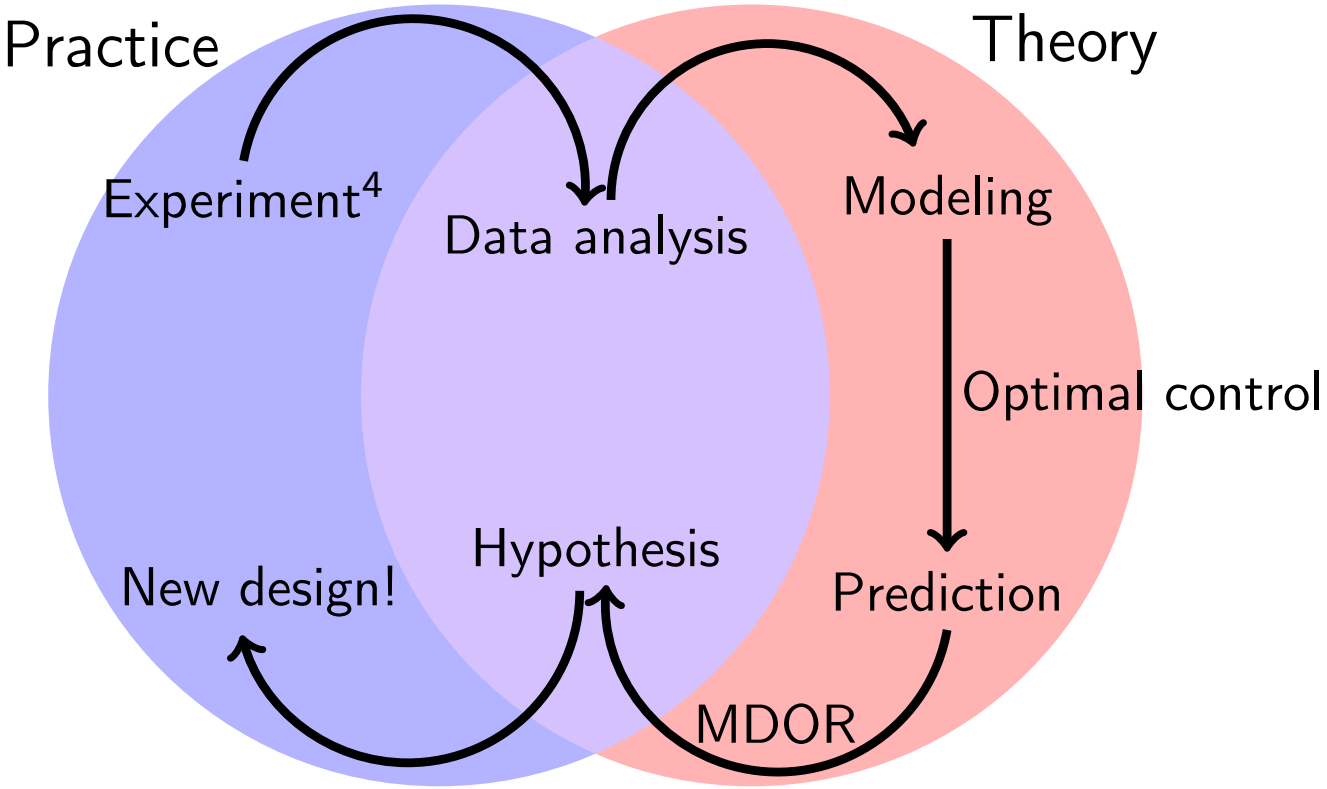
However, The maximum tolerated dose is 300 mg/kg/day for CPA.

Mathematically derived optimal regiment



Comparing a standard 140 mg/kg Q6D metronomic/intermittent plan (solid lines) and the mathematically derived optimal regimen (dashed lines).

A new viable regimen to be tested experimentally



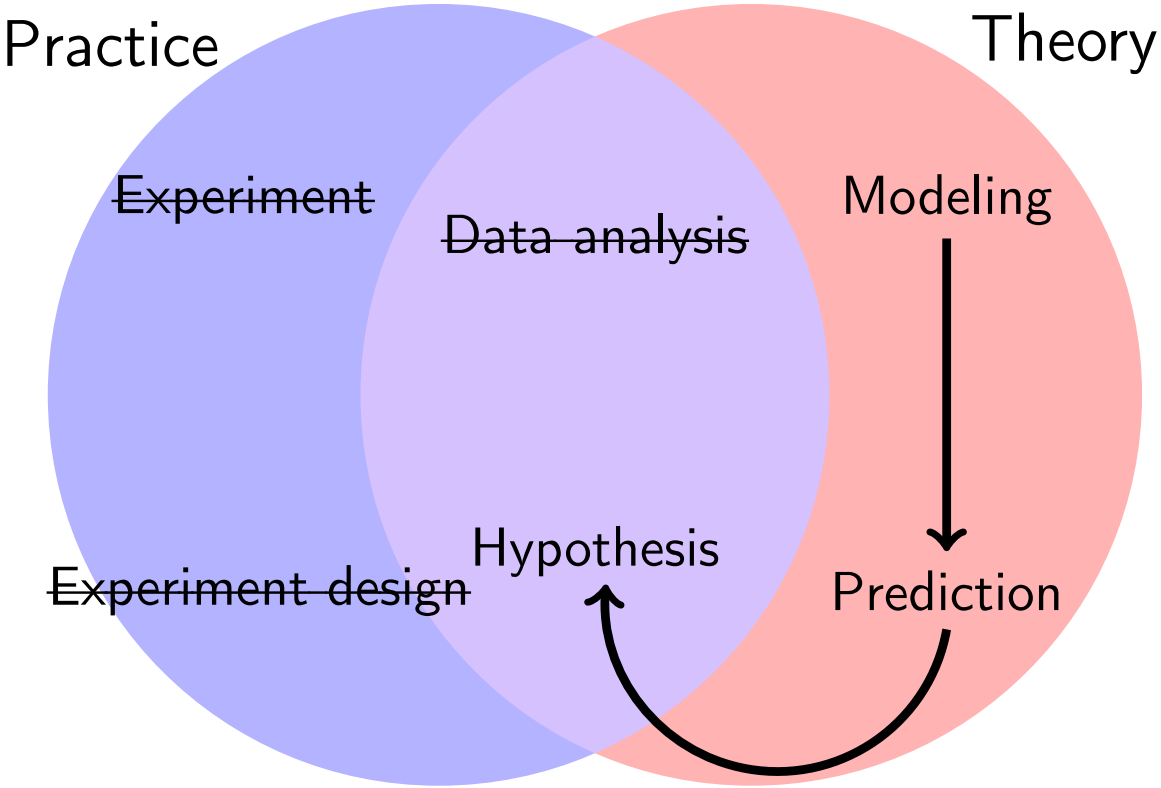
[4] Junjie Wu and David J Waxman. "Metronomic cyclophosphamide schedule-dependence of innate immune cell recruitment and tumor regression in an implanted glioma model". In: *Cancer letters* 353.2 (2014), pp. 272–280.

Social distancing (SD) in epidemics

During the COVID-19 epidemic, social distancing as a form of non-pharmaceutical intervention has been enacted in the US and other countries.

- Motivation: Shortening the period of time that populations are socially distanced is economically advantageous.
- Objective: To reduce the disease burden (here measured as the peak of the infected population) while simultaneously minimizing the length of time that the population is socially distanced.

Early days and limited data!

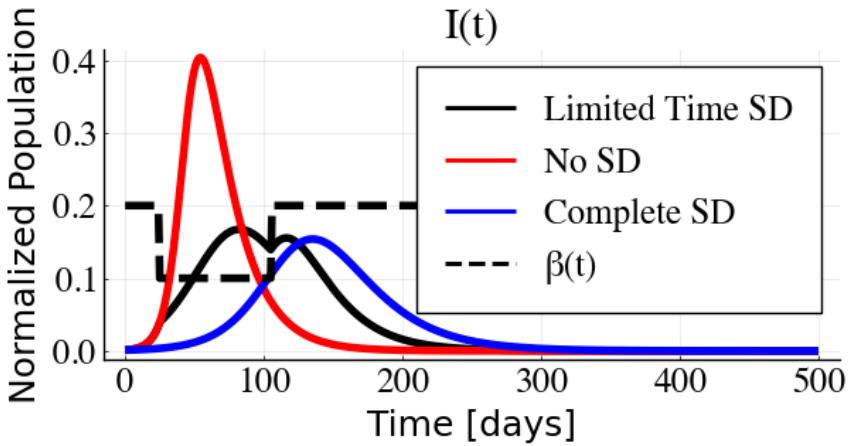


Mathematical model for a single interval SD

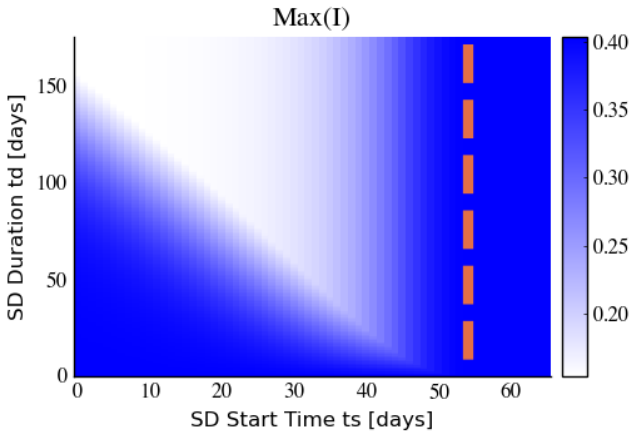
Assuming that β, the disease transmission rate, can be effectively reduced from β_n (contact rate during normal time for non-distanced population) to β_d (contact rate during social distancing) during distancing.

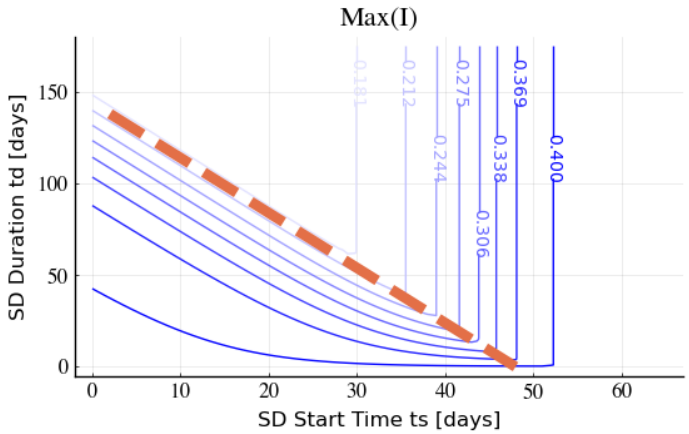
$$\beta(t) = \begin{cases} \beta_n & 0 \leq t_s \\ \beta_d & t_s \leq t < t_s + t_d \\ \beta_n & t_s + t_d \leq t \end{cases} . \tag{3}$$

Normalized infected population in *SIR* model, with no re-infection.



Optimize start time t_s and duration t_d of SD.



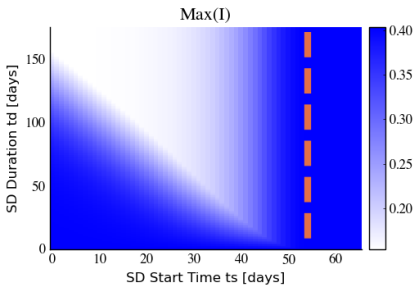


Infected peak, Max(I), in *SIR* model under single interval SD policy. The vertical dashed line represents the time of infected peak for a normal population with no distancing. The diagonal dashed line represents an analytically derived slope approximation.

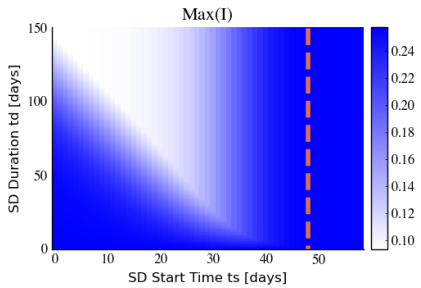
A common "V" shape pattern.

Each model is simulated with parameters in the respective papers and thought to be appropriate, based on data available at the time, for the COVID-19 pandemic.

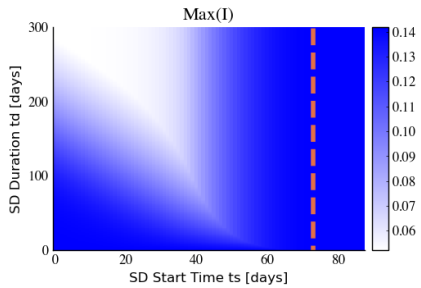
SIR



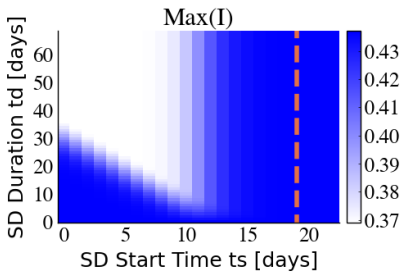
SAIR



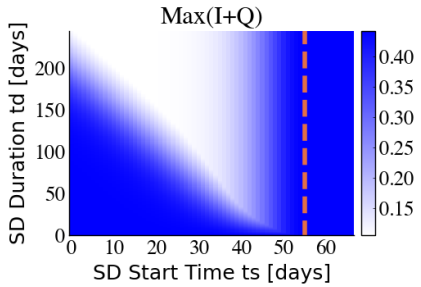
f-SIR



6-SIR



SIQR



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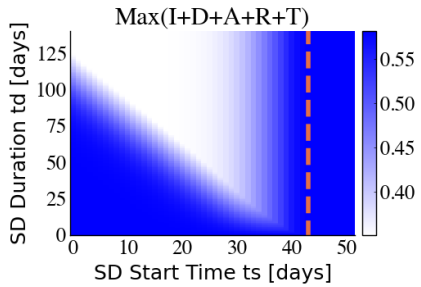
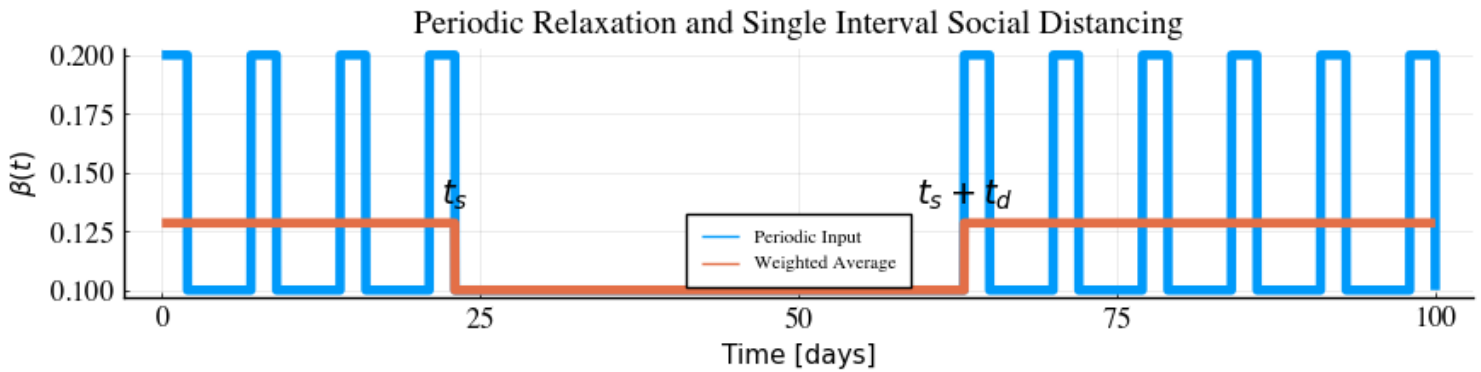


Periodic relaxation is economically favorable.

A policy with regular periods of distancing and relaxation can significantly delay the time of the peak of the epidemic, while still allowing limited economic activity.

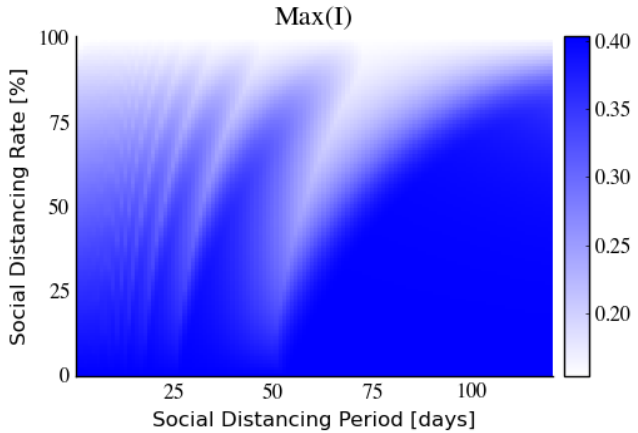


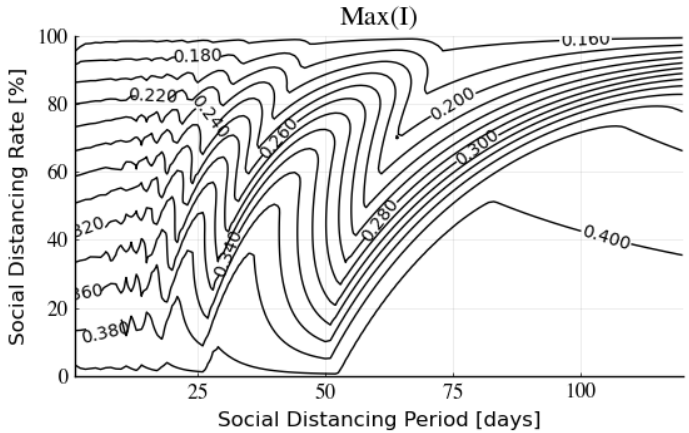
Periodic relaxation and non-monotonicity

The peak of infected population depends non-monotonically on both the period T and ratio r of periodic policies.

A periodic social distancing relaxation policy with a large period time T may lead to high transmission rates at the critical time of an epidemic (e.g. at the potential peak of the infected population).

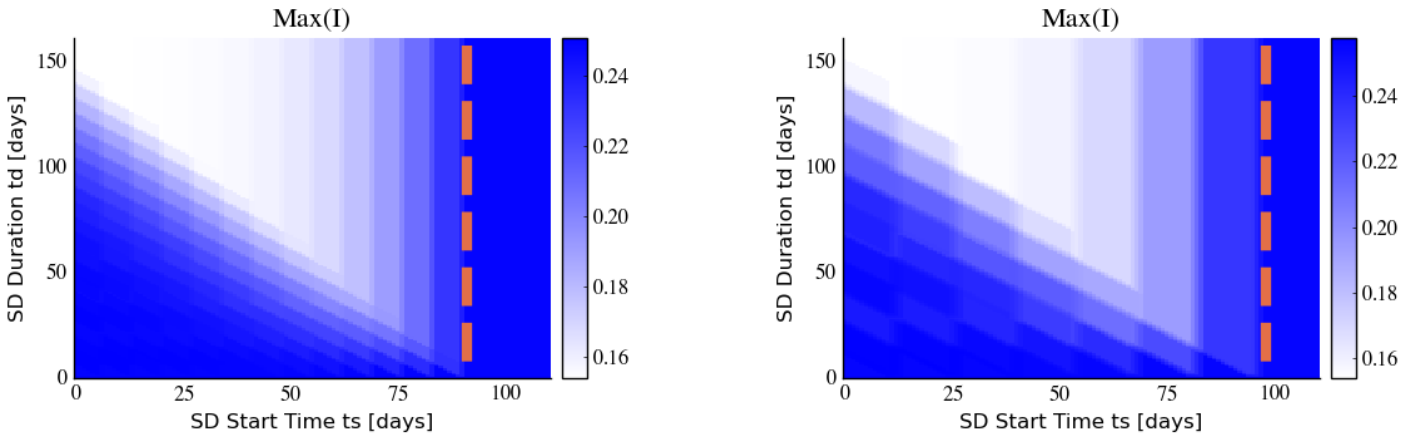
Or it may lead to a well-timed strategy and hence significantly reduce the infected peak.





Periodic relaxation is economically favorable.

Effect of periodic relaxation policy in combination with a single interval social distancing for *SIR* model with. The dashed orange lines represent the infected compartment peak time without single interval social distancing policy.



Optimize start time t_s and duration t_d.

This work is a result of teamwork

Advisor: Eduardo Sontag

Lab members: M. Ali Alradhawi, Anh Phong Tran, Zheming An, William Cho, Shu Wang, Tianchi Chen.

Presented projects

Chemotherapy: Anh Phong Tran, Irina Kareva, M. Ali Alradhawi, and Waxman Lab.

Epidemics: James Greene, M. Ali Alradhawi.

Other projects

Immunotherapy: Irina Kareva, Kumpal Madrasi, Abed Alnaif, Anup Zutshi, and EMD Serono Inc team.

Parkinson's Disease: AMP-PD research community, and Sanofi team.

Ribosome: M. Ali Alradhawi, Michael Margaliot, Nikolai Slavov, Edward Emmott.

Open-source community: Julia team, Gleb Pogudin, Esteban Vargas. Bioconductor project.