Control and Decision Making in Systems Biology

Northeastern University

December 13, 2021

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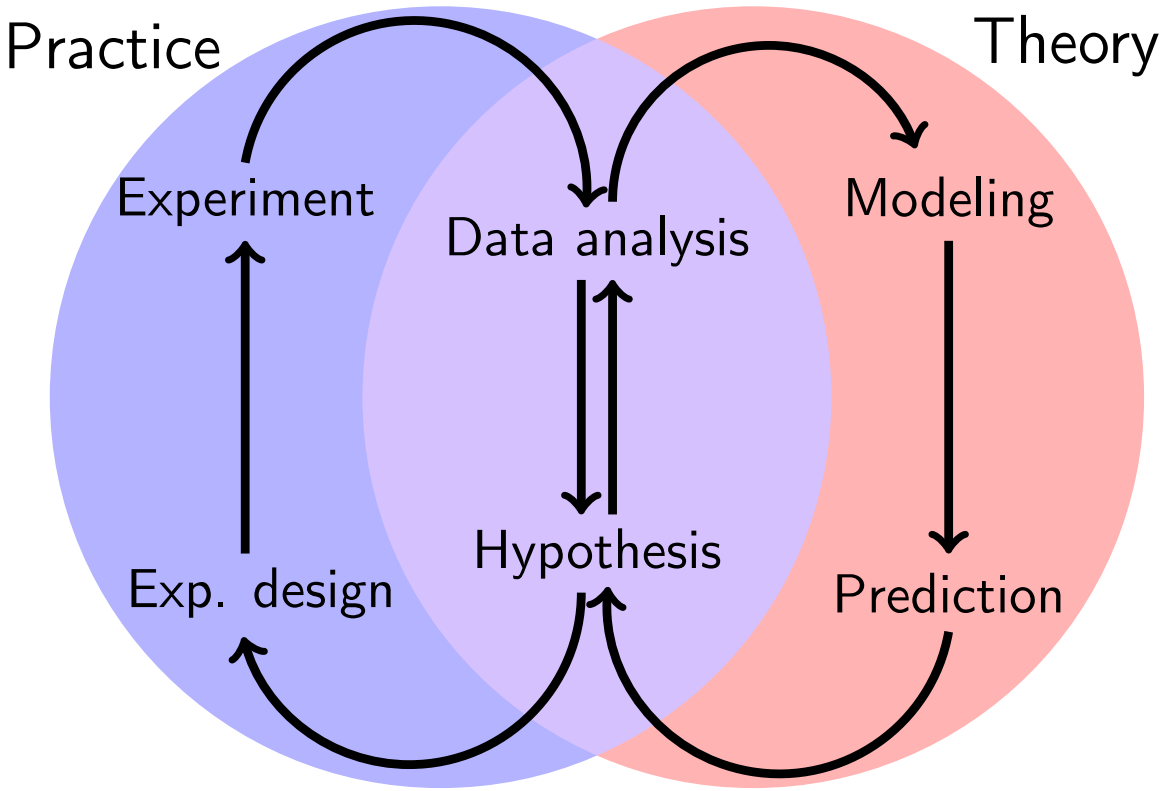
Presentation outline

1. Background
2. Chemotherapy
3. Epidemic
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 recruitment and tumor regression

The current standard of care limits the regimens used primarily 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 was shown to recruit the 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] treatments.

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 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

Model is fitted to the tumor and immune data in mouse experiments.

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

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

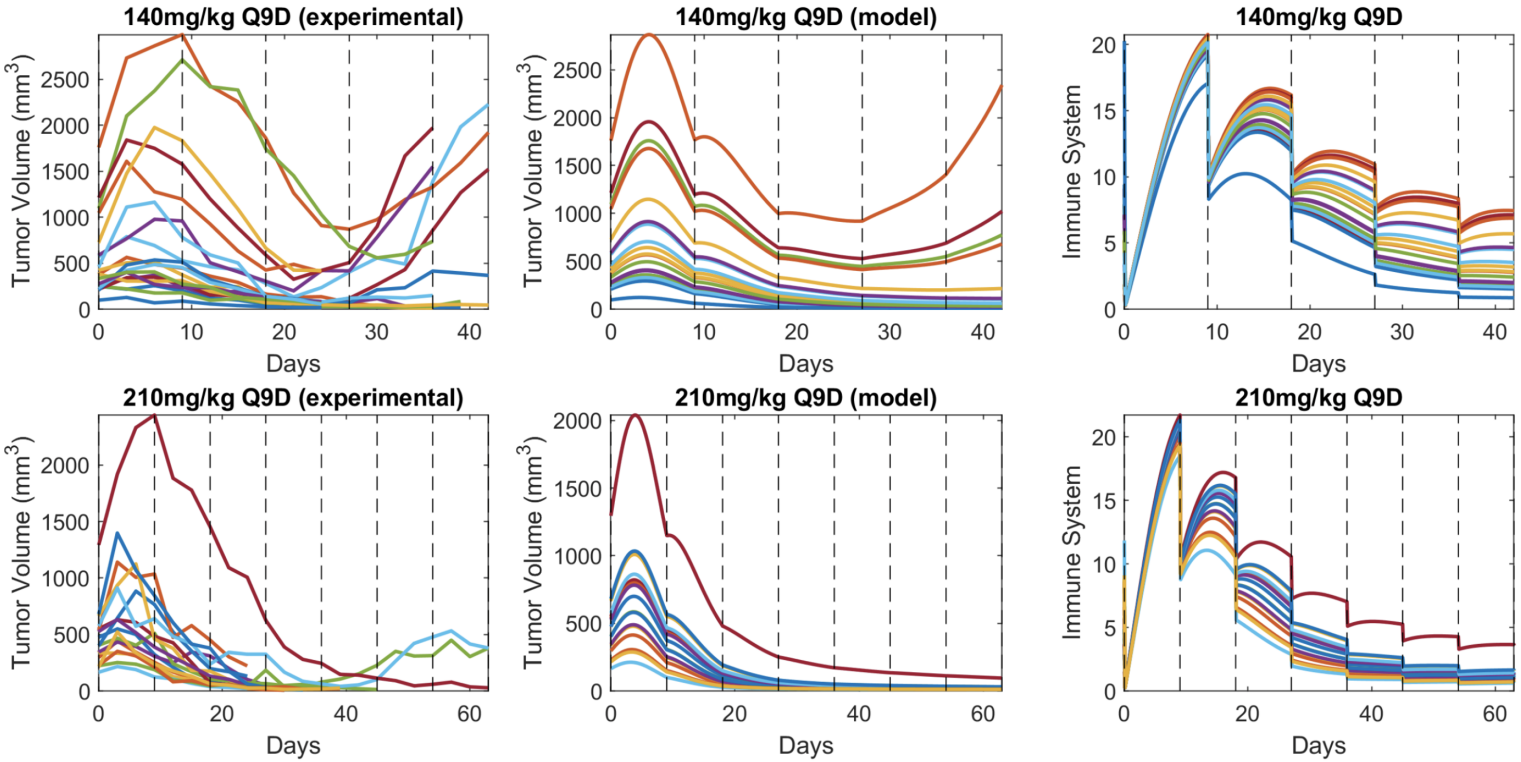
$$\dot{X}(t) = \frac{qC(t) T(t)}{k_i C(t) + T(t)} - k_j X(t) - k_k X(t) Y(t), \tag{1c}$$

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

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

T:tumor volume. Variables I:immune system, X:immunostimulatory, Y:immunossuppressor, and C:drug are phenomenological.

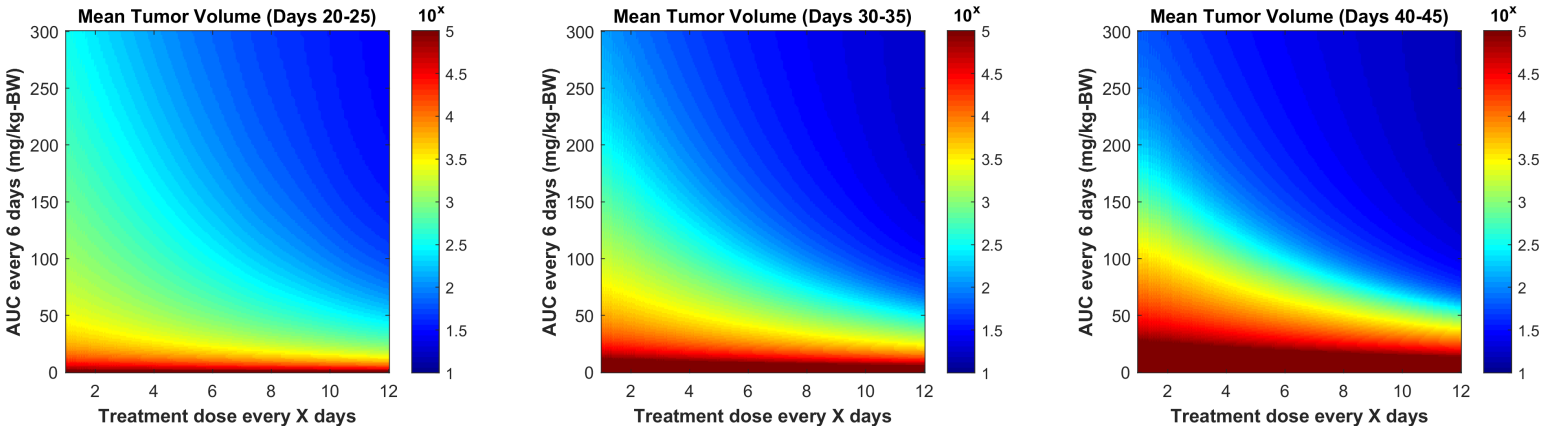
Fit to the experimental data



The measured tumor volume (left), modelled tumor volume (middle), and modelled immune system (right) for two metronomic regimens.

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 metronomic regimens. The horizontal axis represents the number of days between each dose, y-axis is the total amount of drug given to the animal every 6 days.

Optimal control problem setup

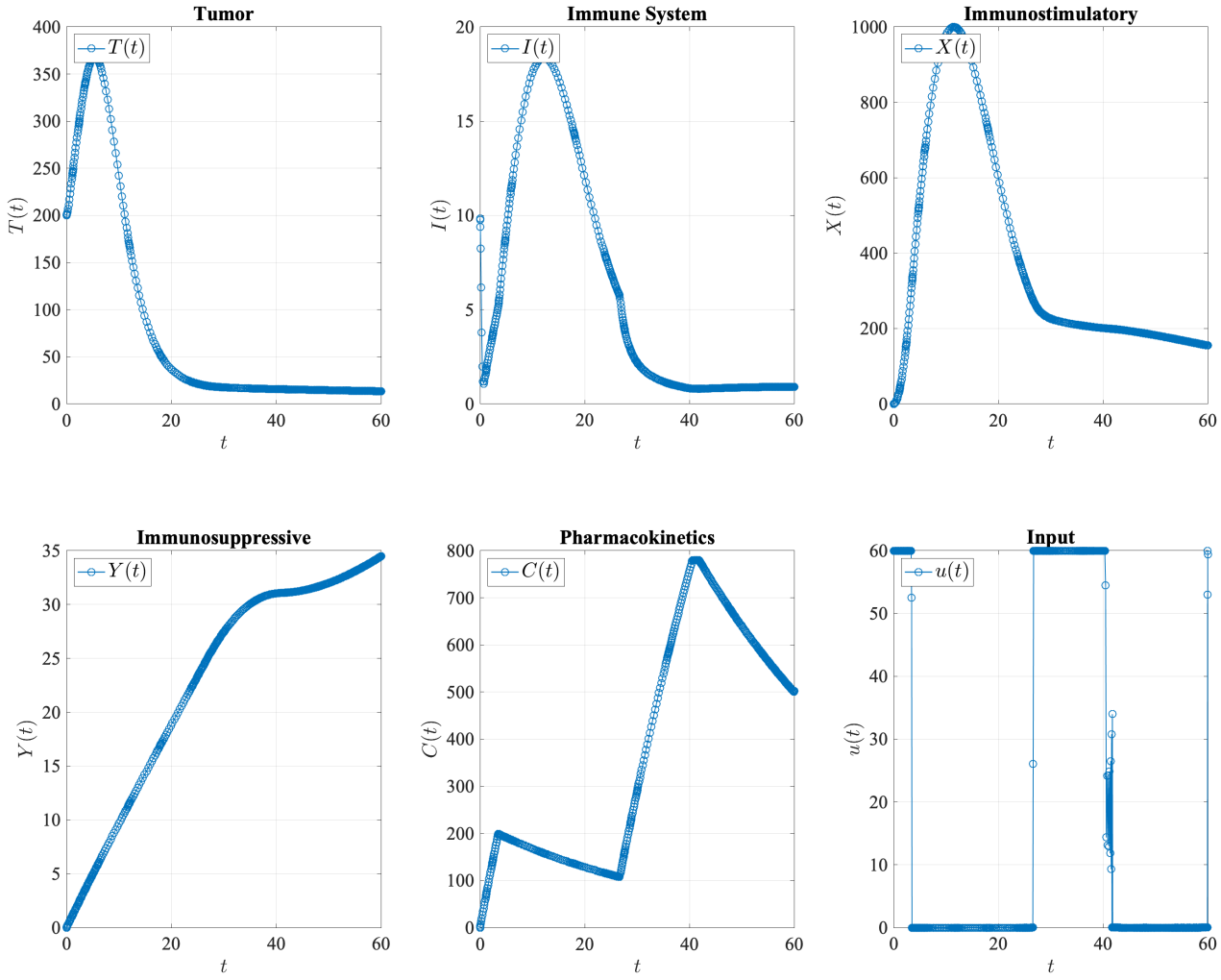
Numerical software GPOPS_II is used to solve the following setup of optimal control problem.

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

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

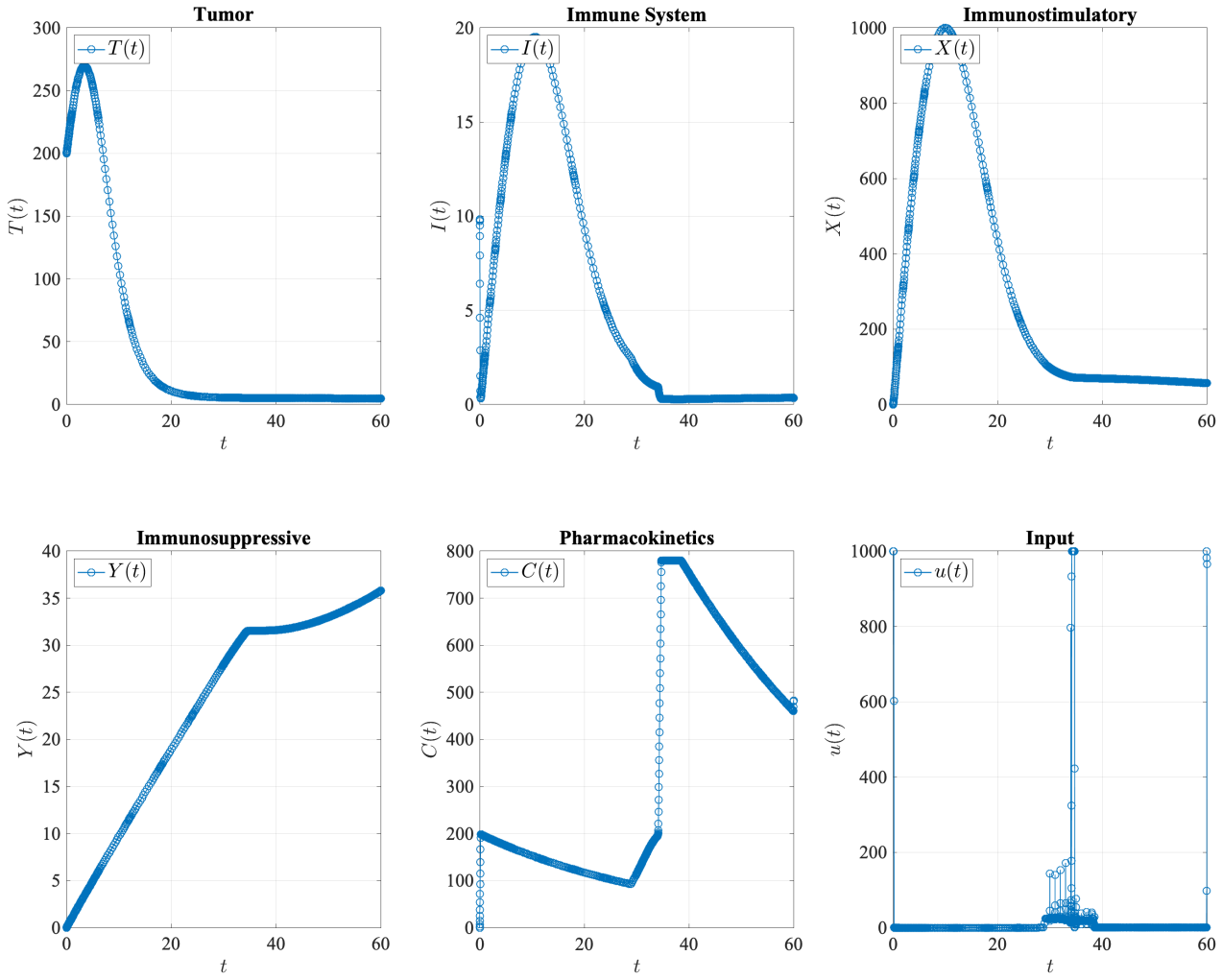
$$\int_0^{t_f} u(t)dt \leq U_m. \tag{2c}$$

Numerical result for a low input upper bound



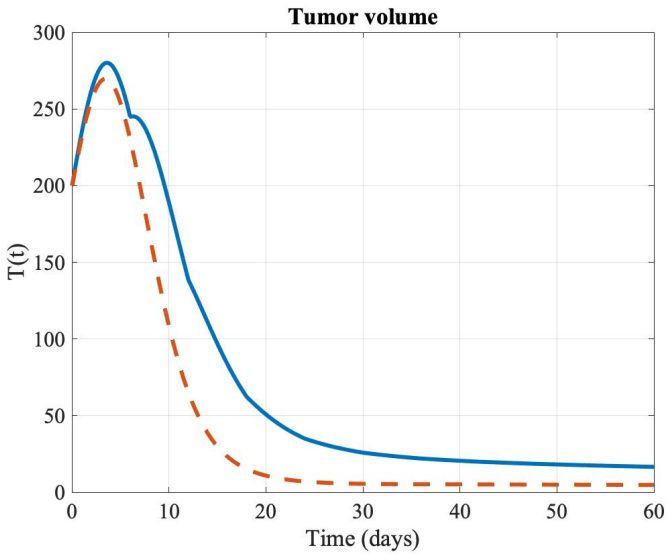
Circles show the final collocation points.

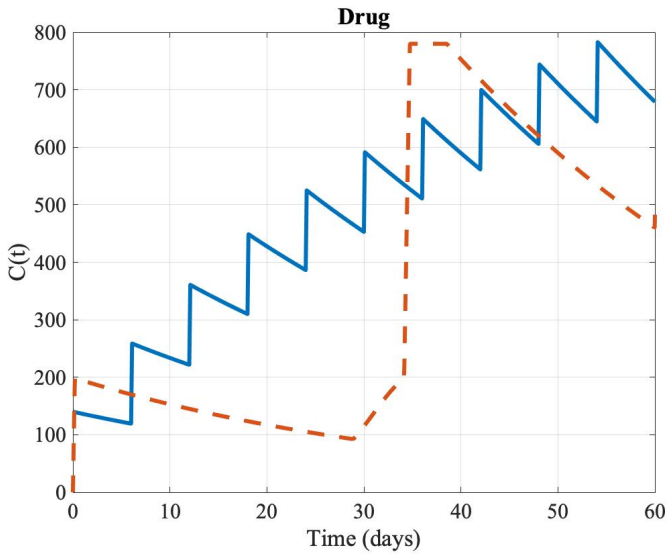
Numerical result for a high input upper bound



Circles show the final collocation points.

Optimal control vs. metronomic regimen

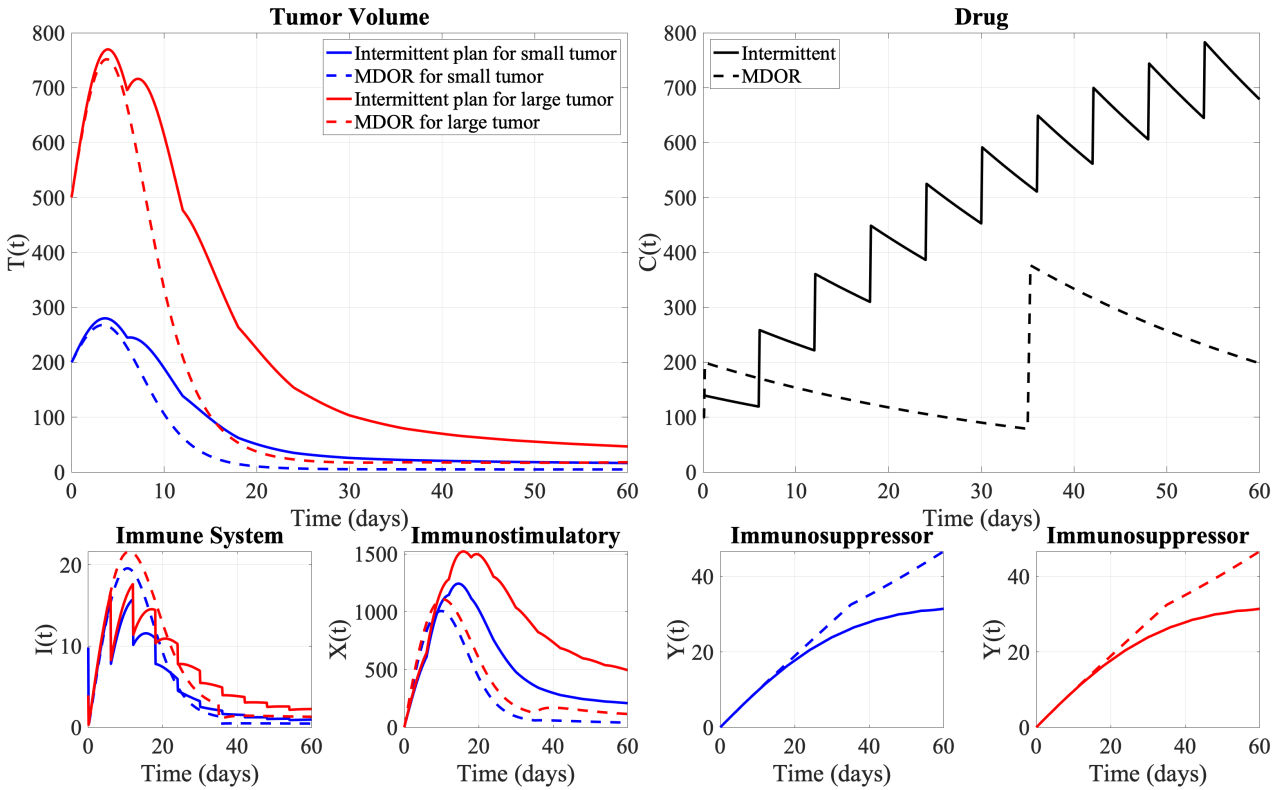




Comparing a standard 140 mg/kg Q6D metronomic chemotherapy plan (solid lines) with the obtained optimal control (dashed lines).

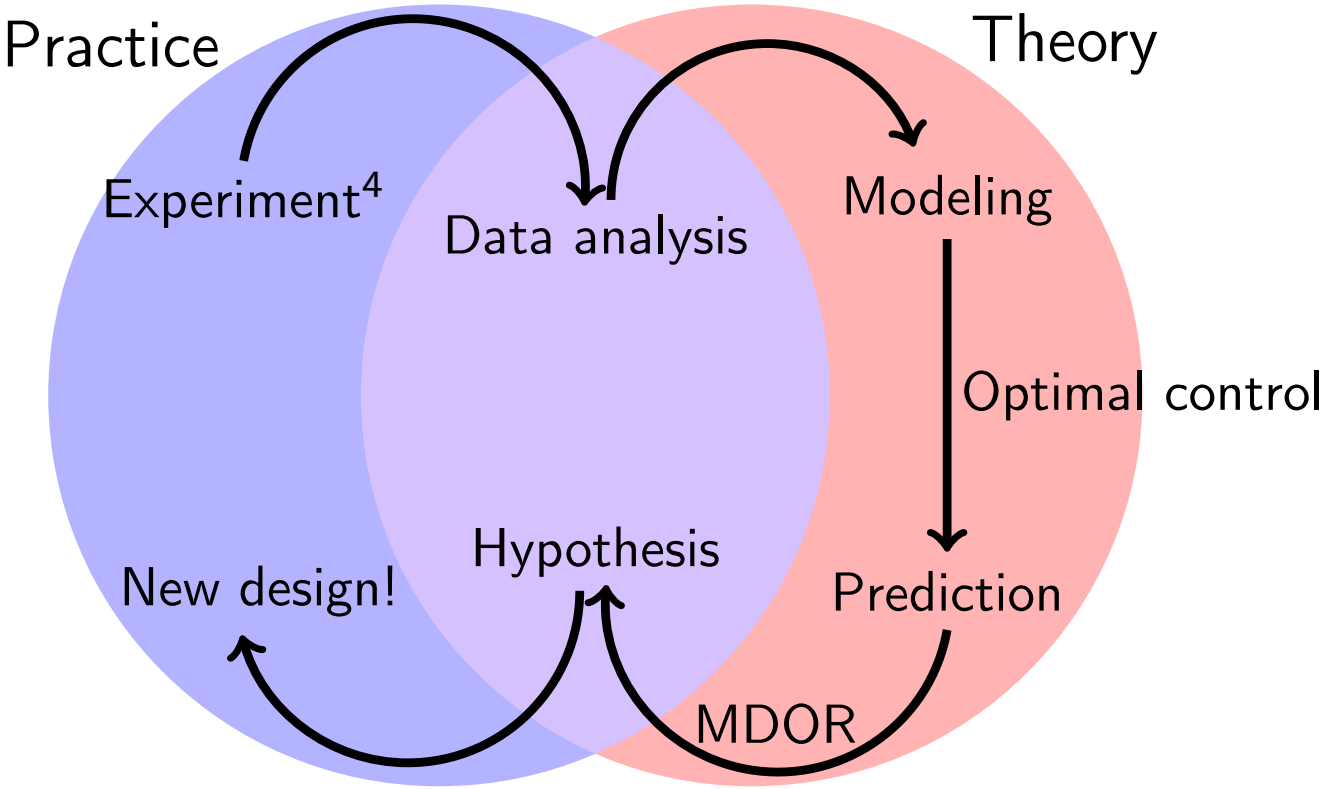
The numerical results can be interpreted as two-dose of 200mg/kg and 600mg/kg regimen. However, the maximum tolerated dose is 300mg/kg/day for the chemotherapy drug.

Mathematically derived optimal regimen



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



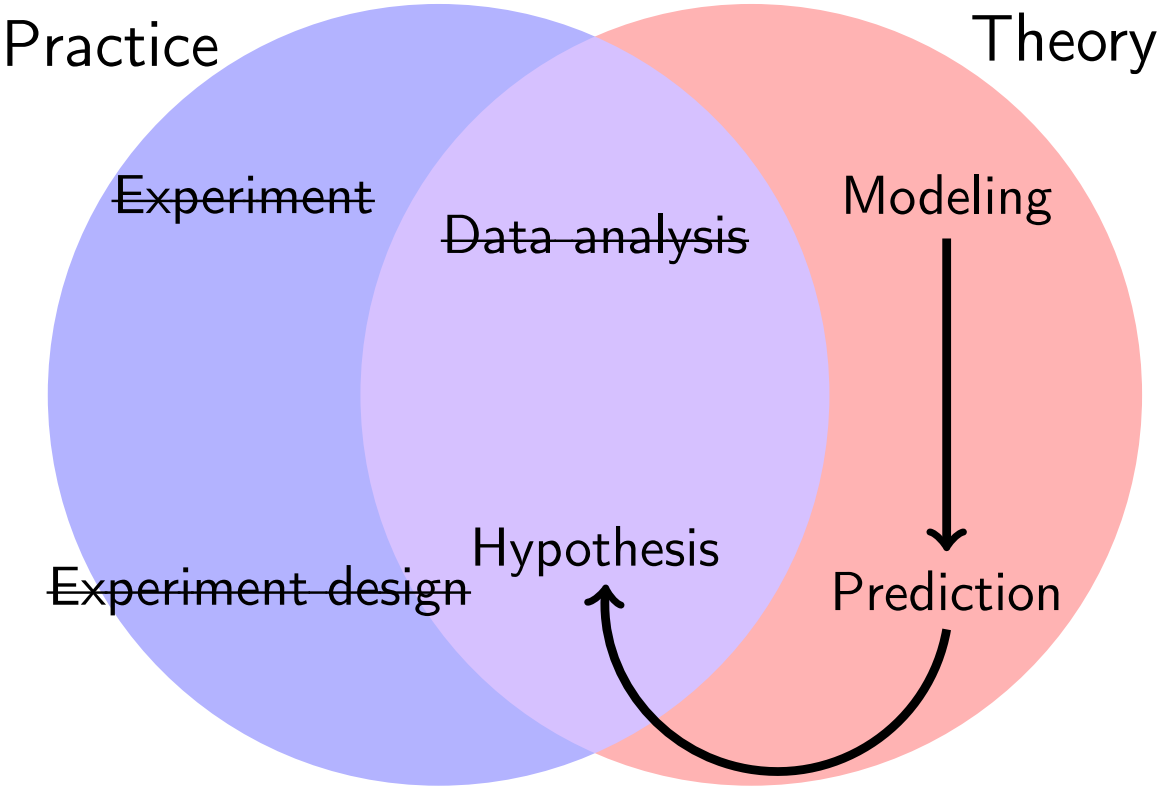
[4] Junjie Wu and David J Waxman. "Metronomic cyclophosphamide schedule-dependence of innate immune cell recruitment and tumor regression in an implanted glioma model". In: *Cancer letters* 353.2 (2014), pp. 272–280.

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

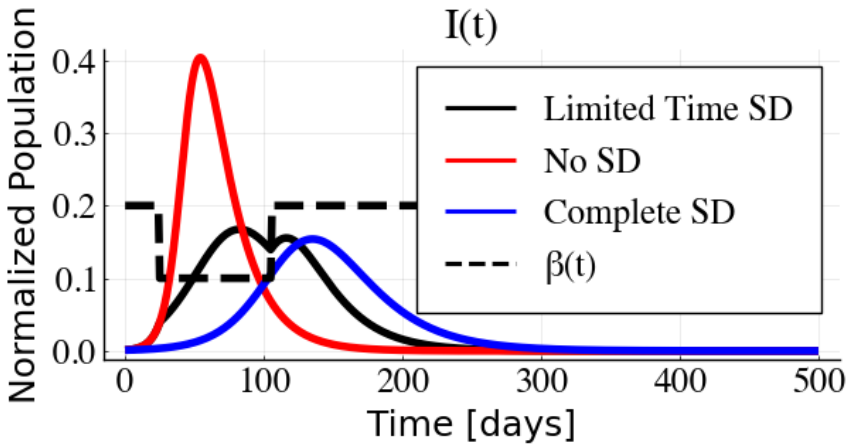


Mathematical model for a single interval SD

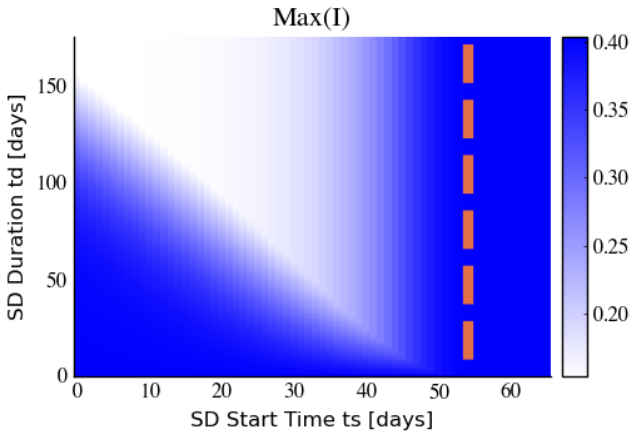
Assuming that β, the disease transmission rate, can be effectively reduced from β_n (contact rate during normal time for non-distanced population) to β_d (contact rate during social distancing) during distancing.

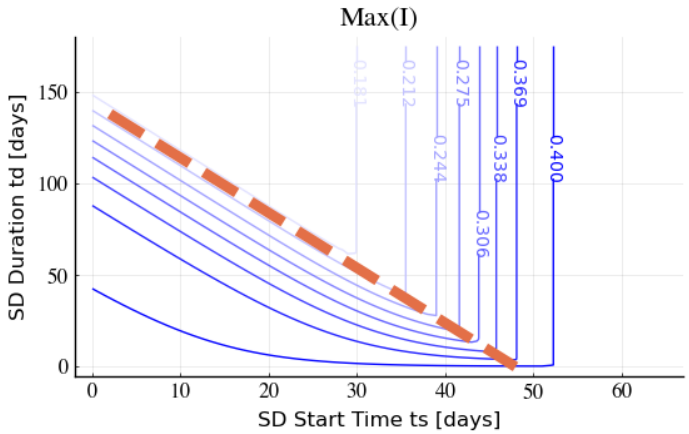
$$\beta(t) = \begin{cases} \beta_n & 0 \leq t_s \\ \beta_d & t_s \leq t < t_s + t_d \\ \beta_n & t_s + t_d \leq t \end{cases} . \tag{3}$$

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



Optimize start time t_s and duration t_d of SD



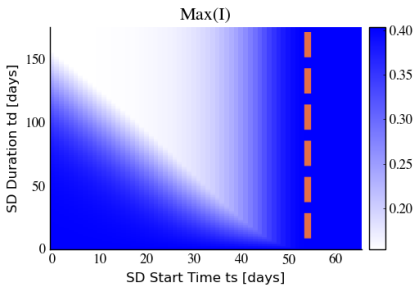


Infected peak, Max(I), in *SIR* model under single interval SD policy. The vertical dashed line represents the time of infected peak for a normal population with no distancing. The diagonal dashed line represents an analytically derived slope approximation.

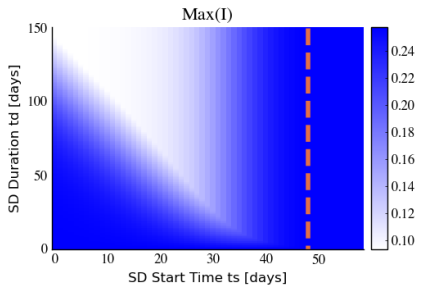
A common "V" shape pattern

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

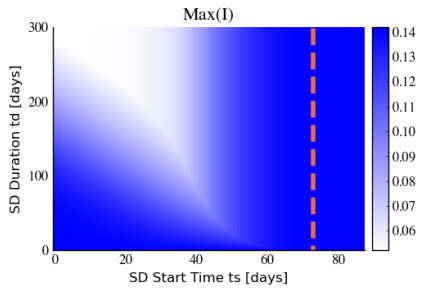
SIR



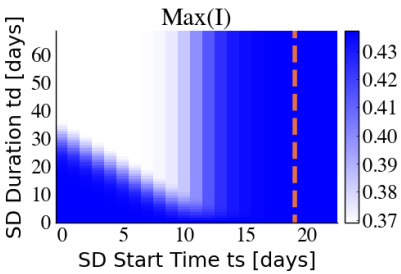
SAIR



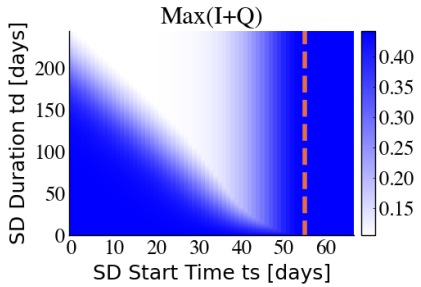
f-SIR



6-SIR



SIQR



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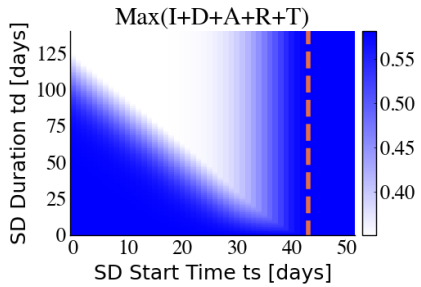


Single interval social distancing

The V-shape pattern is robust for various epidemic models with no reinfection assumption.

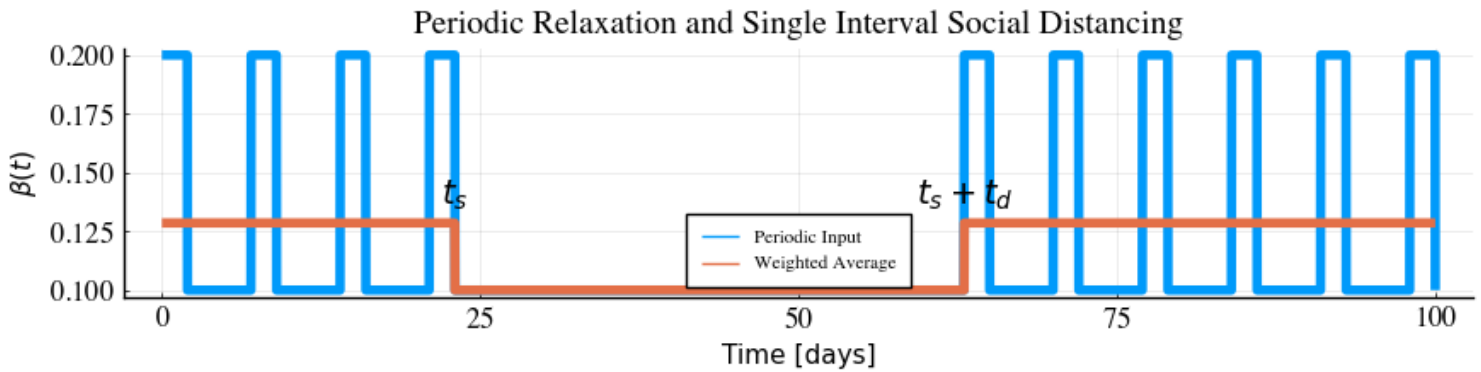
A too late social distancing mandate is not effective in reducing the infected peak.

An early social distancing mandate is effective to delay the infected peak, but not effective in reducing the infected peak (e.g. India).

Populations should not practice social distancing synchronously.

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.

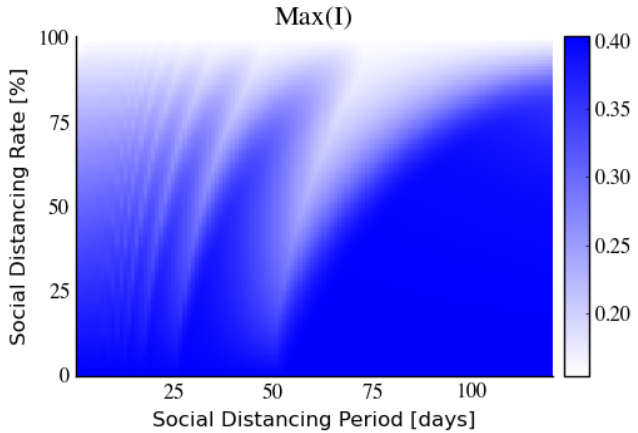


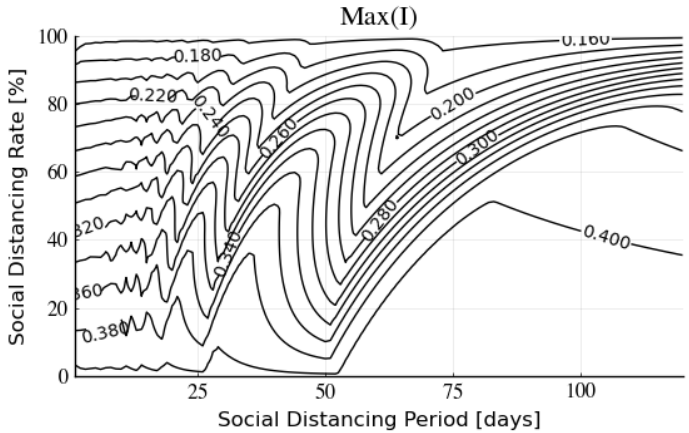
Periodic relaxation and non-monotonicity

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).

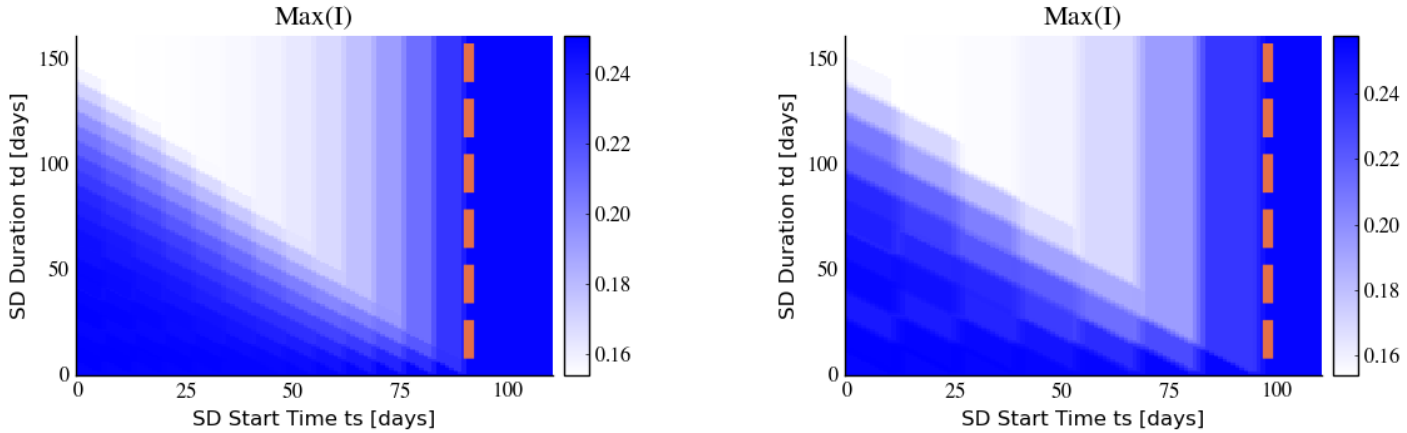
Or it may lead to a well-timed strategy and hence significantly reduce the infected peak.



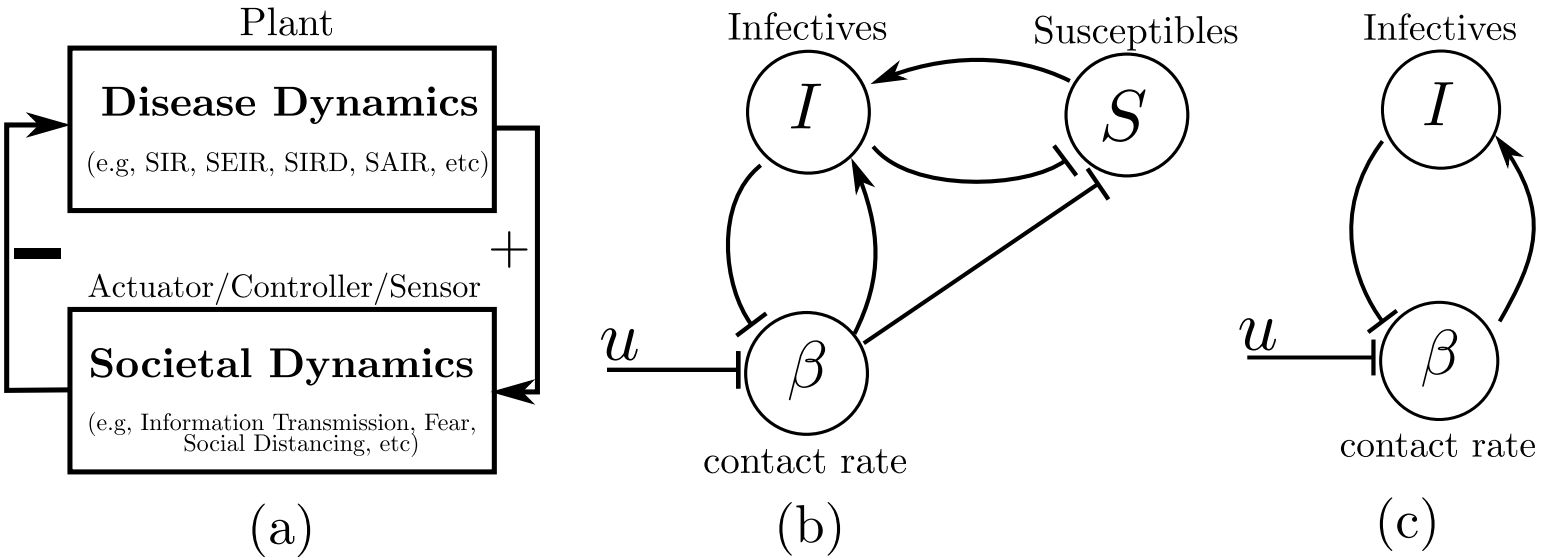


A similar pattern for a combination of a single interval SD and a periodic relaxation policy

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



Modeling a prolonged outbreak

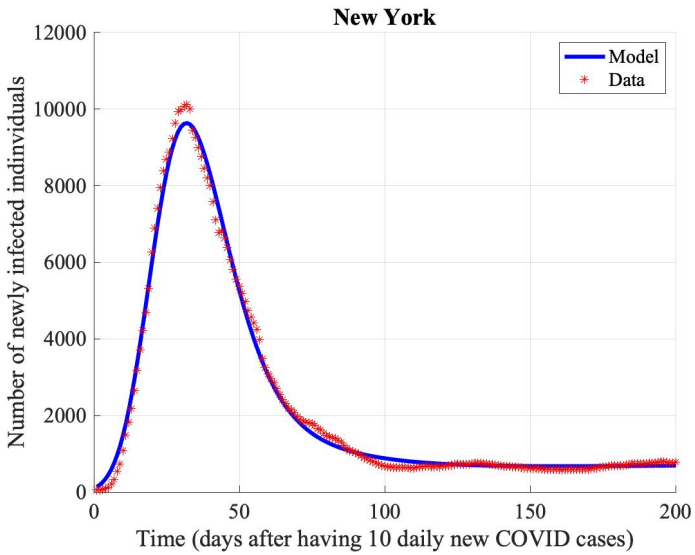


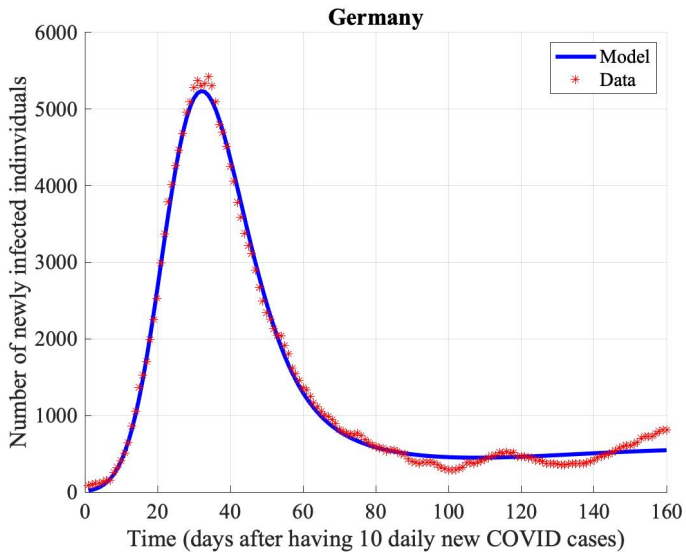
(a) Standard control theoretic framework for an epidemic model. (b) A minimal regulated SIR model, and (b) the reduced regulated SIR model in the case of a large population over short time periods (e.g., less than a year).

Fitting to published data

An initial surge followed by a plateau during the summer 2020.

This can be interpreted as a QSS in the proposed model.





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.