

Presentation outline

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

Outline

Background

Chemotherapy

Model

Metronomic

Optimal control

MDOR

Epidemic

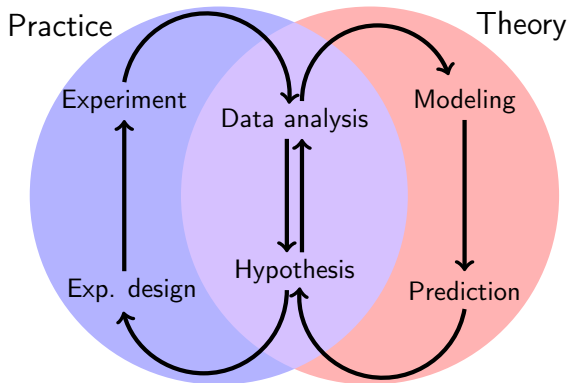
Singel interval SD

Periodic SD

Quasi steady state

Acknowledgment

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 experiments¹ 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.

¹Junjie 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. 4/24

Optimal control techniques for cancer treatment

Early efforts in using optimal control techniques for cancer treatment started in the 1970s for Radiotherapy² and Chemotherapy³ 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.

²K 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.

³Thomas 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.

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

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

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

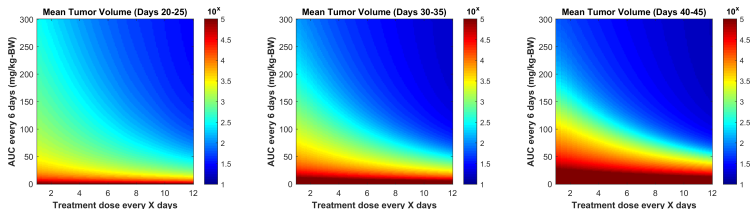
$$\dot{Y}(t) = \frac{I(t)}{k_l + I(t)} - k_m Y(t) C(t), \quad (1d)$$

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

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

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.

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Optimal control problem setup

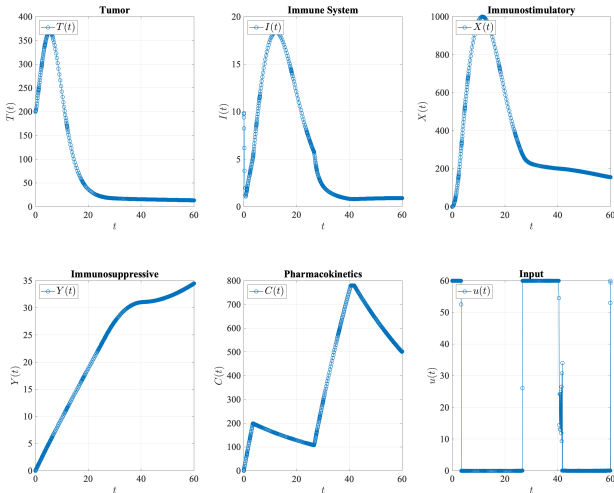
Numerical software GPOPS_II is used to solve the following setup of optimal control problem.

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

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

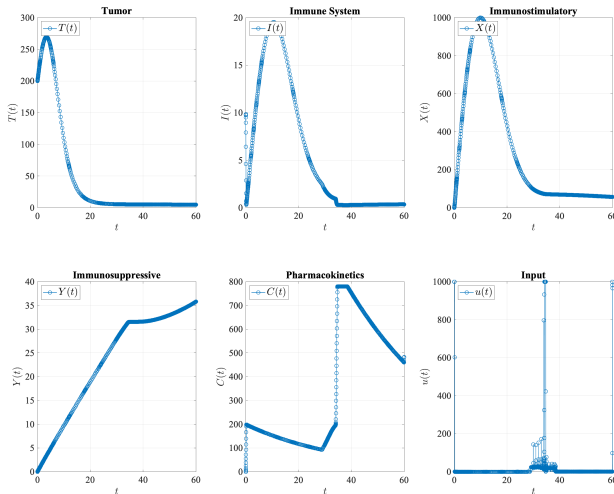
$$\int_0^{t_f} u(t) dt \leq U_m. \quad (2c)$$

Numerical result for a low input upper bound



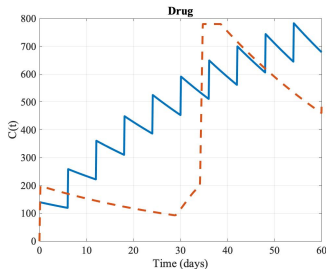
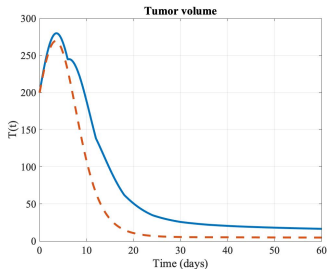
Circles show the final collocation points.

Numerical result for a high input upper bound



Circles show the final collocation points.

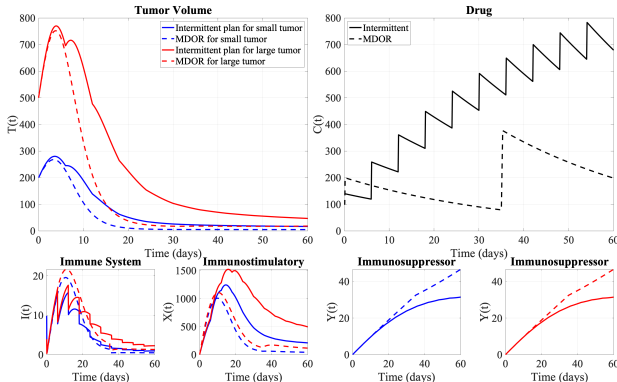
Optimal control vs. metronomic regimen



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

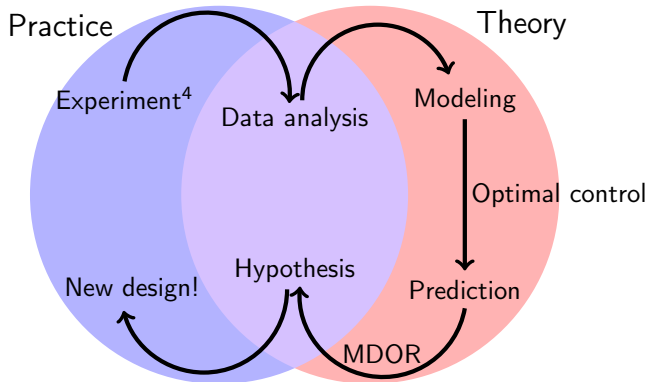
However, The maximum tolerated dose is 300 mg/kg/day for CPA.

Mathematically derived optimal 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



⁴Junjie 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._{13/24}

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Singel interval SD

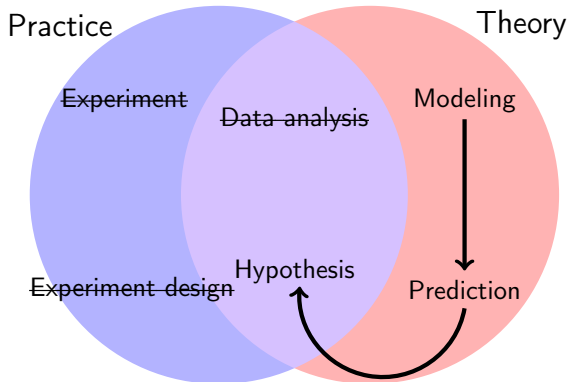
Periodic SD

Quasi steady state

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- ▶ 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!

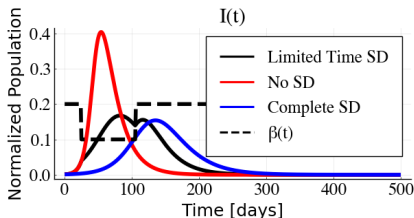


Mathematical model for a single interval SD

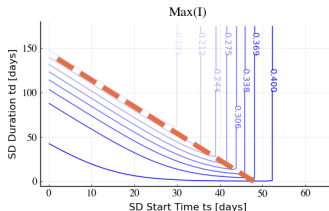
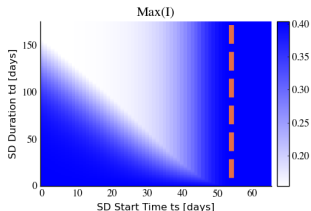
Assuming that β , the disease transmission rate, can be effectively reduced from β_n (contact rate during normal time for non-distanced population) to β_d (contact rate during social distancing) during distancing.

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

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



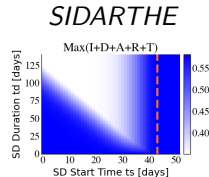
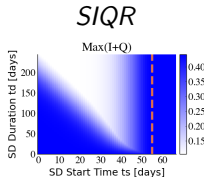
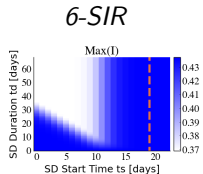
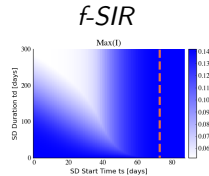
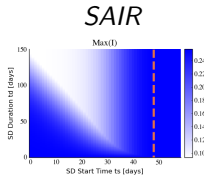
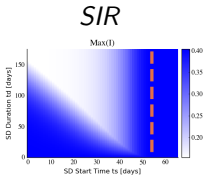
Optimize start time t_s and duration t_d of SD.



Infected peak, $\text{Max}(I)$, 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.



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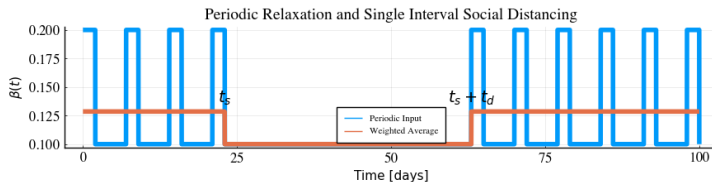
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Periodic relaxation is economically favorable.

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.

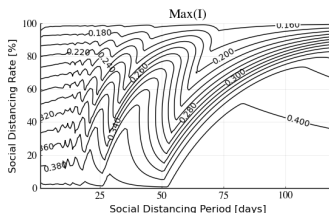
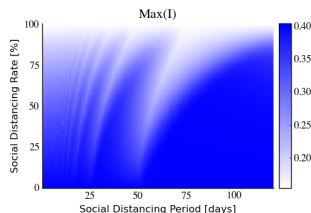


Periodic relaxation and non-monotonicity

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.



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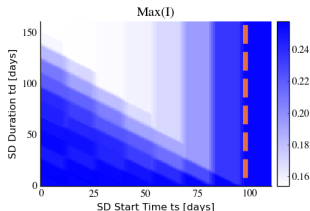
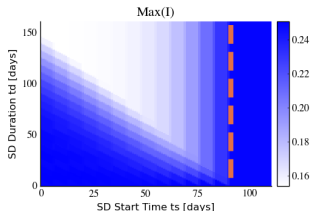
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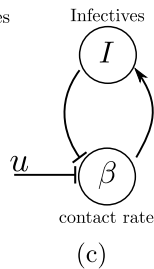
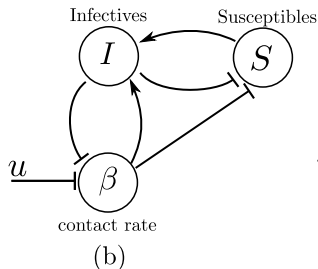
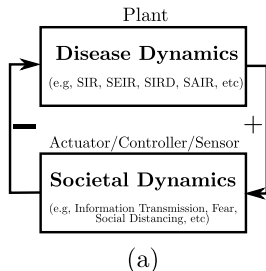
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A similar pattern for a combination of a single interval SD and a periodic relaxation policy

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



Modeling a prolonged outbreak

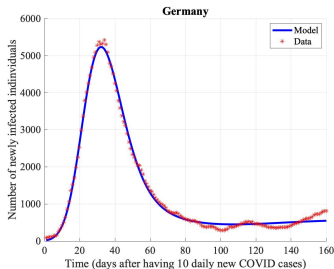
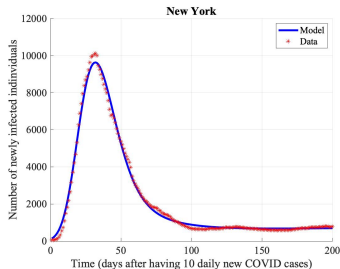


(a) Standard control theoretic framework for an epidemic model. (b) A minimal regulated SIR model, and (c) the reduced regulated SIR model in the case of a large population over short time periods (e.g., less than a year).

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.



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Bioconductor project.

Acknowledgment