Control and Decision Making in Systems Biology

A Dissertation Presented

by

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To my father, Dr. Mohammad Sadeghi,
who taught me love, trust, and commitment.

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List of Acronyms

AUC Area Under the Curve. The definite integral of a curve that describes the variation of a drug concentration in blood plasma as a function of time.

FDA Food and Drug Administration. The United States Food and Drug Administration is a federal agency of the Department of Health and Human Services.

MDOR Mathematically Derived Optimal Regimen.

MTD Maximum Tolerated Dose. The maximum tolerated dose is commonly estimated to be the maximum dose that can be administered for the duration of a specific study that will not compromise the survival of the animals by causes other than carcinogenicity.

NPI Nonpharmaceutical Intervention. Actions, apart from getting vaccinated and taking medicine, that people and communities can take to help slow the spread of illnesses like pandemic influenza (flu).

QSS Quasi Steady State. A situation that is changing slowly enough that it can be considered to be constant.

SCID Severe combined immunodeficiencySCID mice have a genetic immune deficiency that affects their B and T cells. Due to the lack of mature B and T lymphocytes, these mouse models are ideal for xenoengraftment of human cells and tissue.

SD Social Distancing. In public health, social distancing, also called physical distancing, is a set of non-pharmaceutical interventions or measures intended to prevent the spread of a contagious disease by maintaining a physical distance between people and reducing the number of times people come into close contact with each other.

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Abstract of the Dissertation

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Theory and practice are the two fundamental tools in engineering and scientific research. With a great increase of quantitative experiments in biological systems over the past decades, mathematical modeling is able to enhance predictions and generate new hypotheses. A "good" model of a system, that is expected to reproduce the experimental observations, is capable of making predictions outside the previous experimental settings. However, the accuracy of predictions based on mathematical models highly depends on the assumptions used to model the system. The objective of this study is to explore possible approaches to deploy such models in order to find new hypotheses to be tested in future experimental settings. From the lens of control and decision-making, a few biological systems relevant to chemotherapy, immunotherapy, and epidemics are considered in this work. Models are analyzed numerically and analytically in order to enhance the outcome of the system with a new control/decision. A new dosing plan for chemotherapy is identified and evaluated via in-silico experiments to optimally reduce the tumor volume at the end of the plan. The new dosing plan consists of two doses starting with a small dose at the beginning of the plan and an increased dose after a few weeks. Unlike traditional chemotherapy plans currently used, the proposed plan is neither a maximum tolerated dose, nor a metronomic/intermittent plan. Moreover, epidemic models under social distancing guidelines are studied. Considering a single interval social distancing based on the start time and the duration of the social distancing shows a linear relationship between optimal timing of the social distancing. Models analyzed in this work are generic and applicable to wide a range of applications.

Chapter 1

Introduction

1.1 Trial and error

Trial and error has been the fundamental method [1]

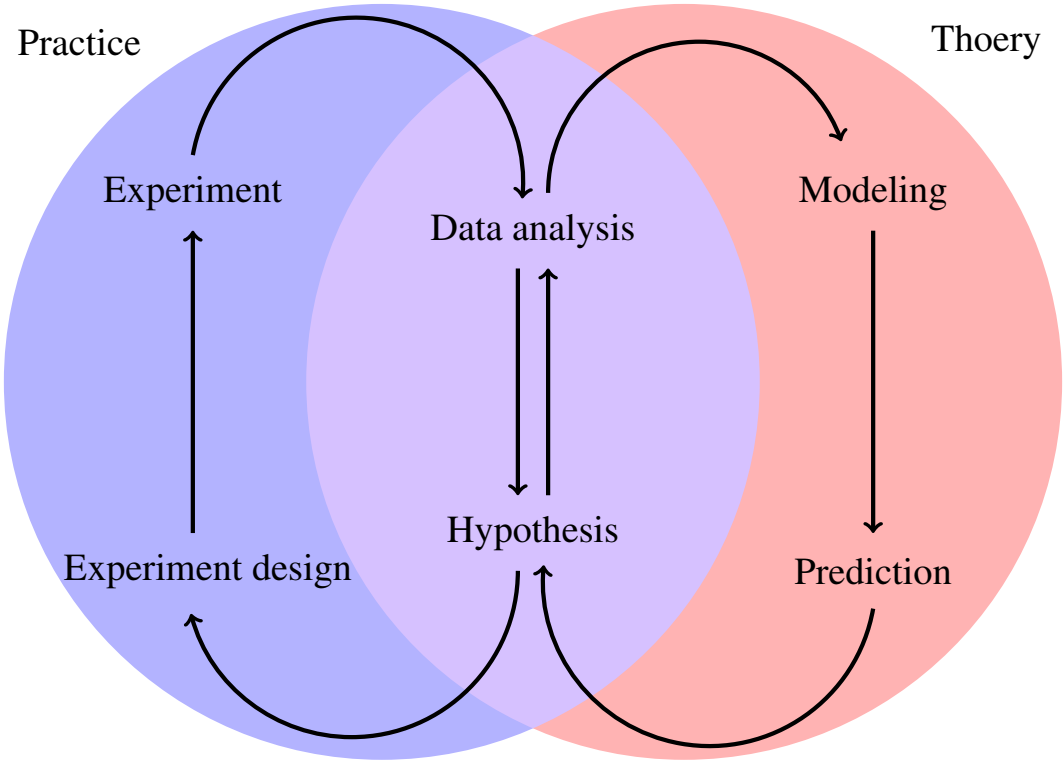

Figure 1.1: Theory and practice in engineering and scientific research.

Chapter 2

Chemotherapy

As the number of cancer treatments increases, together with the dose ranges that will be explored starting earlier in the clinical trial process as encouraged by the Food and Drug Administration (FDA) in Project Optimus, so does the need for more computationally guided approach to dose selection. While it is not experimentally feasible to explore the full spectrum of possible drug doses and regimens, especially if these parameters are allowed to vary from one drug injection to the next, a mathematical framework such as the one presented here can be used to sort through the countless possible combinations. In this work, we build upon a mathematical model that quantitatively captures the complex interactions between tumor, immune system, and a chemotherapy drug. The proposed model is calibrated with experimental data of Severe combined immunodeficiency (SCID) mice implanted with aggressive treatment-resistant glioma tumors and treated with cyclopsphamide under a variety of dosing regimens to capture impact of drug dose and schedule on both the tumor and the immune cells. Next, by applying a numerical implementation of optimal control to this model, we show that the Mathematically Derived Optimal Regimen (MDOR) for this mouse model is neither metronomic nor Maximum Tolerated Dose (MTD) but instead constitutes administering a lower dose in the beginning of treatment, and then a larger dose after 35 days, resulting in maximal tumor control for the first 60 days. The discovered regimen can be interpreted from the lens of ”press-pulse” notion in species extinction theory, when most frequent and expansive mass species extinctions occurred when “press” disturbances on the population (such as climate or sea level change) weakened and destabilized populations over many generations, and were then followed by a “pulse” disturbance that cause extensive mortality. This work highlights the ability of well constructed and validated mathematical models to provide insights into improved dosing and scheduling for long term tumor reduction, which can then be evaluated experimentally. By expanding application of optimal control

to other mouse models and beyond, we can begin to uncover optimal treatment strategies in a quantitatively-guided way.

2.1 Background

Finding the appropriate dosing and scheduling of a chemotherapy drug for a given tumor type is an exceedingly challenging task. The current standard of care limits the regimens used primarily to daily dose and MTD treatments. A MTD regimen attempts to reduce the tumor burden as much as tolerable by the patient with each treatment. In addition to potential severe side effects, the treatment can lose efficacy rapidly and give rise to drug resistance [2–4]. In addition to simply selectively killing non-resistant cells in a "Darwin"-like fashion, high levels of cytotoxicity caused by MTD treatments can greatly weaken the host immune system [3], removing an important line of defense against resistant cells. Metronomic or "intermittent" chemotherapy treatments with lower dose amount and higher frequency than MTD were shown to be able to induce an immune response alongside the cytotoxicity of the drug towards cancerous cells, at least in mouse models, and under specific treatment conditions [5–15]. Furthermore, if the treatments are given too regularly such as seen in the case of daily dose treatments, the elicited immune response can be greatly attenuated [11]. An optimal treatment should ideally strike the right balance of both eliciting a strong immune response and still providing enough cytotoxicity towards cancer cells from the chemotherapy drug [16, 17].

Only a subset of chemotherapy drug are known to induce this immunogenic cancer cell death pathway that produces a strong anti-cancer immune response. This effect is dependent on various factors that include the tumor type or subtype, the regimen that is being applied, as well as the class of chemotherapy drug. Drugs that are able to induce this immunostimulatory effect include cyclophopshamide, anthracyclines, 5-fluorouracil, mitoxantrone, idarubicin, and doxorubicin [9, 10, 18–20]. In addition to using the appropriate drug, eliciting an anti-tumor immune response requires an appropriate balance of drug dosing and scheduling [16, 17, 21]. There remains much to be understood about the complex dynamics that leads to the observation of a strong immune recruitment in a 6-day repeating schedule (Q6D) at 140 mg/kg per dose of cyclophosphamide administered to treat GL261 glioma and 9L gliosarcoma tumors, a response that a daily dose or maximum tolerated treatment dose does not elicit to a noticeable extent [7, 11, 12]. Understanding how treatment strategies affect the dynamics and interactions between the drug, the immune system, and the tumor holds the key to developing more effective treatment strategies.

Developing realistic mathematical models of these biological interactions is a challenging task due to the number of phenomena that need to be considered. The immune system alone needs various considerations for immune cell types, chemicals (cytokines and chemokines), and various roles that these immune cells can play (e.g. T-cells can be cytoxotic or memory). Each of these immune components has distinct dynamics that makes it difficult to predict the aggregate behavior of the biological system as a whole from its various components. There are additional factors to consider such as individual variability between patients, variability in the tumor, the drug used for treatment, and how the chosen drug is administered. The fact that a cytototoxic drug like cyclophosphamide can be both immunostimulatory and immunosuppressive in a metronomic treatment makes designing accurate mathematical representations of the interactions at play particularly difficult. There is a rich literature on mathematical models that attempt to capture the mechanisms behind cancer chemotherapy and how it affects the immune system [16, 22–24]. There are also considerations that have been made to model drug resistance [25].

A central idea that guided this chapter was coming up with a realistic representation of the phenomena that arise during a metronomic chemotherapy: drug-mediated suppression of the immune system, recruitment of immunostimulatory factors by the immunogenic cancer cell death pathway, drug resistance that arises during treatment, tumor-immune interactions, tumor growth, and drug pharmacokinetics. The parameters of the developed mathematical model are fitted to a large dataset of tumor trajectories for which the treatment conditions were varied [11]. Using this mathematical representation of the drug-immune-tumor interactions, a numerical optimal control scheme was used to find a potentially better treatment schedule for the analyzed data. The results illustrate the potential of model-guided chemotherapy treatments can potentially be one day used in the clinic.

2.2 Modeling

A major challenge of modeling the immune system resides in the complex interactions between its components. Even using the SCID mouse model as was used in [11], which eliminates the impact of B and T cells, maintains the impact of innate immune cells, such as NK cells, macrophages, dendritic cells, and neutrophils. An attempt to model each of these immune components individually greatly increases model complexity and the number of parameters to be fitted, and may come even at a detriment to the model's ultimate utility. Instead, experimentally observed immune data from [11] can be clustered into the following three categories by response type :

- an early response from immunostimulatory chemokines (e.g. CXCL9, CXCL10, CXCL11)
- a correlated response from immune cell markers shortly after the release of immunostimulatory chemokines
- the response of vascular endothelial growth factor A (VEGF-A), which is inversely correlated with the other measured immune cell markers

To build upon the previous modeling effort for this data set [17], and use it to apply optimal control techniques to find potential dosing and scheduling regimes that might be superior to the ones that were tested in the following section. The model takes into account the effects of immune recruitment, drug resistance, and the complex interactions between the drug, the tumor, and the immune system. Compared to the model introduced in [17], here it has been modified to become more generalizable; specific modifications and the corresponding rationale are given below.

$$\dot{T}(t) = k_a T(t) - \frac{k_b C(t) T(t)}{k_c C(t) + T(t)} - k_d T(t) I(t), \tag{2.1a}$$

$$\dot{I}(t) = qX(t) - k_e T(t) I(t) - k_f C(t) I(t) - k_g Y(t) I(t) - k_h I, \tag{2.1b}$$

$$\dot{X}(t) = \frac{qC(t)T(t)}{k_i C(t) + T(t)} - k_j X(t) - k_k X(t) Y(t), \tag{2.1c}$$

$$\dot{Y}(t) = \frac{I(t)}{k_l + I(t)} - k_m Y(t) C(t), \tag{2.1d}$$

$$\dot{C}t = u(t) - \frac{k_1 C(t)}{k_2 + C(t)}. \tag{2.1e}$$

subjected to the following initial conditions $[T, I, X, Y, C](0) = [T_0, \frac{k_n}{k_o + T_0}, 0, 0, 0]$. The unit of phenomenological variables C, I, X, and Y is 1, and the unit of variable T, tumor volume, is mm^3. A detailed description for each parameter and variable used in this model is presented in Table 2.1.

Table 2.1: Definition of the variables and parameters used in the model (2.1).

Parameter/Variable	Unit	Value	Definition
$T(t)$	mm^3	$T(0) = T_0$	Tumor volume
$I(t)$	1	$I(0) = \frac{k_n}{k_o+T_0}$	Immune system
$X(t)$	1	$X(0) = 0$	Immunostimulatory intermediate
$Y(t)$	1	$Y(0) = 0$	Immunosuppressor intermediate
$C(t)$	1	$C(0) = 0$	Drug (input)
k_a	1/day	1.555×10^{-1}	Tumor growth rate
k_b	mm^3/day	1.334×10^{-1}	Cytotoxic effect rate of the drug on the tumor
k_c	mm^3	5.195×10^{-1}	Saturation term of drug and tumor interaction
k_d	1/day	1.992×10^{-2}	Cytotoxic effect of the immune system on the tumor
k_e	1/day/mm^3	3.463×10^{-5}	Negative effect of the tumor on the immune system
k_f	1/day	2.940×10^{-1}	Cytotoxic effect of the drug on the immune system
k_g	1/day	6.497×10^{-1}	The immunosuppressor effect on the immune system
k_h	1/day	1.369×10^{-1}	The immune system natural decay rate
k_i	mm^3	1.837×10^{-1}	Saturation term of the immunostimulatory recriutment term caused by the tumor debris
k_j	1/day	5.987×10^{-4}	The immunostimulatory natural decay rate
k_k	1/day	1.249×10^{-1}	The immunosuppression effect rate
k_l	1	1.435×10^{-3}	Saturation term of immunosuppressor increase in response to the immune system
k_m	1/day	3.997×10^{-5}	Cytotoxic effect of the drug on the immunosuppressor intermediate
k_n	mm^3	$1.966 \times 10^{+3}$	Initial immune system parameter
k_o	mm^3	2.040×10^{-4}	Initial immune system parameter
k_1	1/day	$1.525 \times 10^{+2}$	Mechaelis-Menton elimination term parameter
k_2	1	$5.594 \times 10^{+3}$	Mechaelis-Menton elimination term parameter
q	1 /day	1	Makes the phenamenological variables unitless.

Tumor growth inhibition data has been previously used to identify the parameters in our previous work [17]. Here, the objective function is defined to compare the tumor and immune data for fitting the parameters in model (2.1). It is made up of two components: $f_1(x)$ the error with respect to the tumor data and $f_2(x)$ the error with respect to the immune data. Where x is a vector of fitting parameters represented in the model and introduced in table 2.1, and X is the physically meaningful parameters space search defined by upper bound and lower bound of each parameter. This is to incorporate both the experimentally measured tumor growth inhibition and immune markers into the model.

$$\min_{x \in X} \quad w_1 \times \underbrace{f_1(x)}_{\text{based on the measured tumor volume}} + w_2 \times \underbrace{f_2(x)}_{\text{based on the average of measured immune system markers}} . \tag{2.2}$$

A best set of parameters represented in table 2.1 are identified to result in minimum value of the objective function. To remove bias of the fitted parameters to immune or tumor data, the weights w_1 and w_2 are selected such that both error terms of similar magnitude. In this work, the values for w_1 and w_2 were picked to be 1 and 18, respectively.

For calculating the objective function the simulated tumor data and immune data are needed to be compared with the experimentally measured data. Comparing the experimental tumor data to its corresponding simulated data is obvious because they constitute similar measurements. In the case of the immune data, there are 18 measured correlated immune markers excluding the immunostimulatory chemokines and VEGF-A. Since there is only one variable *I* accounting for the drug-induced immune response, these relative gene expression values were averaged.

Another challenge for calculating the mean immune data in the objective function is that the experimental data was normalized as a ratio of the measured gene expression in the untreated case at a specific day. Thus, before the values are to be compared, the values of I from the simulated model needs to be averaged between the different starting volumes, then normalized with respect to the simulated untreated case.

The error function used for the immune system is given by:

$$f_2(x) = \frac{|I_{simulated} - I_{measured}|}{I_{measured} + \epsilon} \tag{2.3}$$

with ϵ representing a small deviation. Where $I_{simulated}$ is the immune system level $[I(t_1), I(t_2), \ldots, I(t_n)]$ at the same time points that $I_{measured}$ the immune system markers were measured $t_1, t_2, \ldots, t_n$, and $f_2(x)$ is the sum of the errors for all of the experimental immune data points.

2.3 Optimization

In the previous section we used the model to evaluate the relationship between drug exposure and mean tumor volume. The model revealed that more frequent dosing would counter-intuitively require higher drug exposure to achieve lower final tumor volume, while less frequent drug administration may achieve good tumor reduction with lower Area Under the Curve (AUC), unlike is expected from MTD protocol. In this section we apply optimal control to further explore additional drug administration strategies, which may go beyond administering a fixed dose at fixed time intervals.

The optimal drug dosing strategy based on the mathematical model and fitted parameters defined in the previous section is implemented using a numerical optimal control software GPOPS-II [26]. The output is shown in Fig. **??**. To set up the optimal control problem, the following objective function and boundary conditions are used:

$$\begin{aligned} &\min_{u(t)} \quad T(t_f), \\ &s.t. \quad \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \leq \begin{bmatrix} C(t) \\ T(t) \\ I(t) \\ X(t) \\ Y(t) \\ u(t) \end{bmatrix} \leq \begin{bmatrix} C_m \\ T_m \\ I_m \\ X_m \\ Y_m \\ u_m \end{bmatrix}, \\ &\int_0^{t_f} u(t)dt \leq U_m. \end{aligned} \tag{2.4}$$

where $C_m = 780$ mg/kg, $T_m = 4000$ mm^3, $I_m = 100$, $X_m = 1000$, and $Y_m = 1000$ are the maximum acceptable values for the state variables. Input upper bound u_m is set to 1000 1/day (SI Figs.**??** and **??**) and 60 1/day (SI Figs. **??** and **??**) to setup two different optimal control problems for the numerical solver. Different input bounds are helpful to understand how instant large dose of drug is making different in the optimal control results. Boundary conditions for the state variables were identified through metronomic treatment simulations based on treatment constraints that were deemed reasonable. U_m is the maximum possible total amount of drug used in aggregate. Other constraints were placed, such as C_m to limit the maximum value of the phenomenological drug variable. The objective function $T(t_f)$ minimizes the tumor volume at the final time $t_f = 60$ of the treatment. The boundary conditions $C_m = 780$, and $U_m = 1400$ are based on the standard 140

mg/kg Q6D treatment. Fig. **??**(a) compares the treatment outcome and administered drug dose of metronomic treatment with the optimal control problem with input bound of $u_m = 60$.

Chapter 3

Immunotherapy

Chapter 4

Epidemics

COVID-19, a highly contagious disease, has been spreading between continents and has already claimed more than 2.5 million lives globally during its first year [27], and has resulted in a worldwide economic downturn [28]. Unsurprisingly, this has sparked a renewed interest in the dynamical modeling and analysis of infectious diseases, particularly in the control theory and dynamical systems communities [29–37].

There has been much recent theoretical work revisiting, expanding, and studying dynamical and control properties of classical epidemic models so as to understand the spread of COVID-19 during quarantine and social distancing [38–43], including studies of (integral) input to state stability [44], network stability of epidemic spread [45, 46], and optimal control strategies for meta-population models [47]. These models have been used to predict the potential number of infected individuals and virus-related deaths, as well as to aid government agencies in decision making [48]. Most models are variations on the classical *SIR* model [49–51] which have been modified to more closely predict the spread of COVID-19. Some such extensions are listed below:

1. Expanding the *SIR* model to include additional population compartments. Such compartments may describe individuals that are placed under quarantine and/or in social isolation. Other models explicitly subdivide populations into both symptomatic and asymptomatic infected individuals [52–57], as it is currently thought that COVID-19 is significantly spread through *asymptomatic* individuals [58–60].

2. Modeling the effects of social distancing for an infection aware population. This can be done by changing the contact rates between the compartments, or by modeling the behavior of a

population that alters its social interactions because of observed infections or deaths [61, 62]. The latter technique has recently been applied to COVID-19 [63, 64].

3. Sub-dividing populations into regions, each described by *local* parameters. Such regions may be cities, neighborhoods, or communities [65]. This framework allows modelers to capture the virus spread and population mobility geographically [66–69]. These models have been recently used to understand the spread of COVID-19 in China [70], Italy [71], Netherlands and Belgium [72], and India [73, 74].

Shortening the period of time that populations are socially distanced is economically advantageous [28, 75, 76]. The main objective of this study is 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.

The starting point in modern epidemiological modeling is the Kermack-McKendrick model [49, 77] which is known as the Susceptible-Infectious-Removed (SIR) model. It assumes a well-mixed homogeneous population, and it can be written as the three-compartment model:

$$\begin{aligned} \dot{S}(t) &= -c\beta S(t)I(t), \\ \dot{I}(t) &= \quad c\beta S(t)I(t) - \gamma I(t), \\ \dot{R}(t) &= \qquad\qquad\quad \gamma I(t), \end{aligned} \tag{4.1}$$

where $S(t), I(t), R(t)$ refer to the susceptible, infective, and removed individuals at time t. The product $b = c\beta$ and the parameter γ are called the *infection rate* and the *removal rate*, respectively. We factored the infection rate as $b = c\beta$, where we call c and β the *intrinsic infection rate* and the *contact rate* respectively, to emphasize that b depends on both *biological* and *societal* conditions.

4.1 Optimal timing

Social Distancing (SD) as a form of Nonpharmaceutical Intervention (NPI) has been enacted in many countries as a form of mitigating the spread of COVID-19. There has been a large interest in mathematical modeling to aid in the prediction of both the total infected population and virus-related deaths, as well as to aid government agencies in decision making. As the virus continues to spread, there are both economic and sociological incentives to minimize time spent with strict distancing mandates enforced, and/or to adopt periodically relaxed distancing protocols, which

allow for scheduled economic activity. The main objective of this section is to reduce the disease burden in a population, here measured as the peak of the infected population, while simultaneously minimizing the length of time the population is socially distanced, utilizing both a single period of social distancing as well as periodic relaxation. A linear relationship is derived among the optimal start time and duration of a single interval of social distancing from an approximation of the classic epidemic *SIR* model. Furthermore, there is a sharp phase transition region in start times for a single pulse of distancing, where the peak of the infected population changes rapidly; notably, this transition occurs well *before* one would intuitively expect. By numerical investigation of more sophisticated epidemiological models designed specifically to describe the COVID-19 pandemic, we see that all share remarkably similar dynamic characteristics when contact rates are subject to periodic or one-shot changes, and hence lead us to conclude that these features are *universal* in epidemic models. On the other hand, the nonlinearity of epidemic models leads to non-monotone behavior of the peak of infected population under periodic relaxation of social distancing policies. This observation led to hypothesize that an additional single interval social distancing at a *proper time* can significantly decrease the infected peak of periodic policies, and verified numerically. While synchronous quarantine and social distancing mandates across populations effectively minimize the spread of an epidemic over the world, relaxation decisions should not be enacted at the same time for different populations.

After the shelter-in-place ordinances [78], social distancing as a form of NPI has been enacted in the United States [79], and other countries [80, 81] for reducing the spread of the virus, as neither herd immunity nor a viable vaccine yet existed [82]. Many countries have implemented strict quarantine, isolation, or social distancing policies early in the epidemic [80], while countries such as Belarus [83] and Sweden [84, 85] have taken more lenient approaches at the onset of the outbreak. Understanding optimal strategies for social distancing will both “flatten the curve” and hopefully ease the economic burden experienced due to prolonged economic stagnation [86–88]. The goal of this section is thus to investigate the response of the disease to different time-varying social distancing strategies.

4.2 Singular purterbation approach

In order to control highly-contagious and prolonged outbreaks, public health authorities intervene to institute social distancing, lock-down policies, and other NPIs. Given the high social, educational, psychological, and economic costs of NPIs, authorities tune them, alternatively

tightening up or relaxing rules, with the result that, in effect, a relatively flat infection rate results. For example, during the summer in parts of the United States, daily COVID-19 infection numbers dropped to a plateau. This paper approaches NPI tuning as a control-theoretic problem, starting from a simple dynamic model for social distancing based on the classical SIR epidemics model. Using a singular-perturbation approach, the plateau becomes a Quasi Steady State (QSS) of a reduced two-dimensional SIR model regulated by adaptive dynamic feedback. It is shown that the QSS can be assigned and it is globally asymptotically stable. Interestingly, the dynamic model for social distancing can be interpreted as a nonlinear integral controller. Problems of data fitting and parameter identifiability are also studied for this model. The paper also discusses how this simple model allows for a meaningful study of the effect of population size, vaccinations, and the emergence of second waves.

Chapter 5

Conclusion

Writing a long manuscript is easy ... only if one starts early enough.

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Appendix A

First Appendix Headline

Appendix B

Second Appendix Headline