Control and Learning in Biological Systems

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.

LIGO Laser Interferometer Gravitational-Wave Observatory. 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).

ODE Ordinary Differential Equations. In mathematics, an ordinary differential equation is a differential equation containing one or more functions of one independent variable and the derivatives of those functions.

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.

Acknowledgments

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Abstract of the Dissertation

Control and Learning in Biological Systems

by

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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

Background

The goal of scientific research is to advance knowledge that does not exist in the literature. Research process starts with a specific question and proposing a hypothesis to answer it. Hypotheses are formed to come up with a solution to an unmet need, or in order to have a better understanding of a phenamena. The next step is testing the proposed hypothesis, which can be done in two ways. Finding an available data set based on previous experiments which can be used to evaluate the newly generated hypothesis, or disigning a new experiment that can generate sufficient data for evaluating the hypothesis.

An in depth understanding of the scientific subject is necessary to come up with a new hypothesis or a new experiment design. Models are usefull in providing a simpler representation of a realworld phenamena, to have a better understanding and easy to test envonriment for creativity. In architecture, models are physical or computational 3D representation of a proposed building design to increase the construction speed and make the planning easier. In computing, emulators are hardware or software models the enable one computer to acts like another system. In biology, animal models are frequently used to create a realistic environment for biological experiments such as, immune cell and tumor, pharmacokinetics of a drug, or disease progression. In dynamic systems, mathematical models can be defined with Ordinary Differential Equations (ODE) to represent a mechanistic representation of the system. Mathematical models can be also defined in numerical formats such as, agent based models, and artificial neural networks. The creation of scientific fields like theoretical biology, math biology, systems biology, computational biology, or systems and computational medicine are all based on using mathematical models in theoretical studies of biological systems. These studeis are interdisciplinary and require collaboration of people with different backgrounds. A simple analogy is that, understanding biology requires chemistry, understanding chemistry requires physics, and

understanding physics requires math.

The objective is to perform numerical and analytical analysis from the control theory perspective. The techniques used in control theory, which deals with the control of dynamical systems in engineered processes and machines, can be applied to mathematical models of biological systems. Medicine can be thought as a control input for a biological system like an animal or a human. Also, considering the spread of an epidemic disease in a society as a biological system, Nonpharmaceutical Intervention (NPI) like social distancing can be thought as a control input. The following section is about the role of mathematical modeling in theory and practice. A couple of well-known examples are discussed to illustrate the importance of modeling in scientific research. The focus and organisation of this study is discussed at the end of this chapter.

1.1 Theory and practice

Theory and practice are the two fundamental tools in scientific research. Classic biology has been thought as a practical science. With a great increase of quantitive experiments in biological systems over the past decates, more theoretical studies are possible in biology.

Figure 1.1 presents a visual representation of the connection between theory and practice. In theory, models that are based on the existing knowledge (data) are being used in order to come up with new hypotheses. Some of the newly generated hypothesis can be tested by using the existing data, which is common in data science. Other hypotheses require a new data set being generated for testing. In practice a hypothesis that is formed based on the existing knowledge, have to be tested with a new experiment design. Two of the most examples in scientific discoveries are stated in the following.

1.1.1 Gravitational waves

Gravity has been the most basic and mysterious force in physics. Understanding gravity is one of the examples that started with theory and mathematical models. Einstein predicted gravitational waves in 1937 [1] based on his theory of relativity. But the universe's gravitational waves have not been detected until 2015, when a large group of researchers used Laser Interferometer Gravitational-Wave Observatory (LIGO), and they recieved the 2017 Nobel prise in physics.

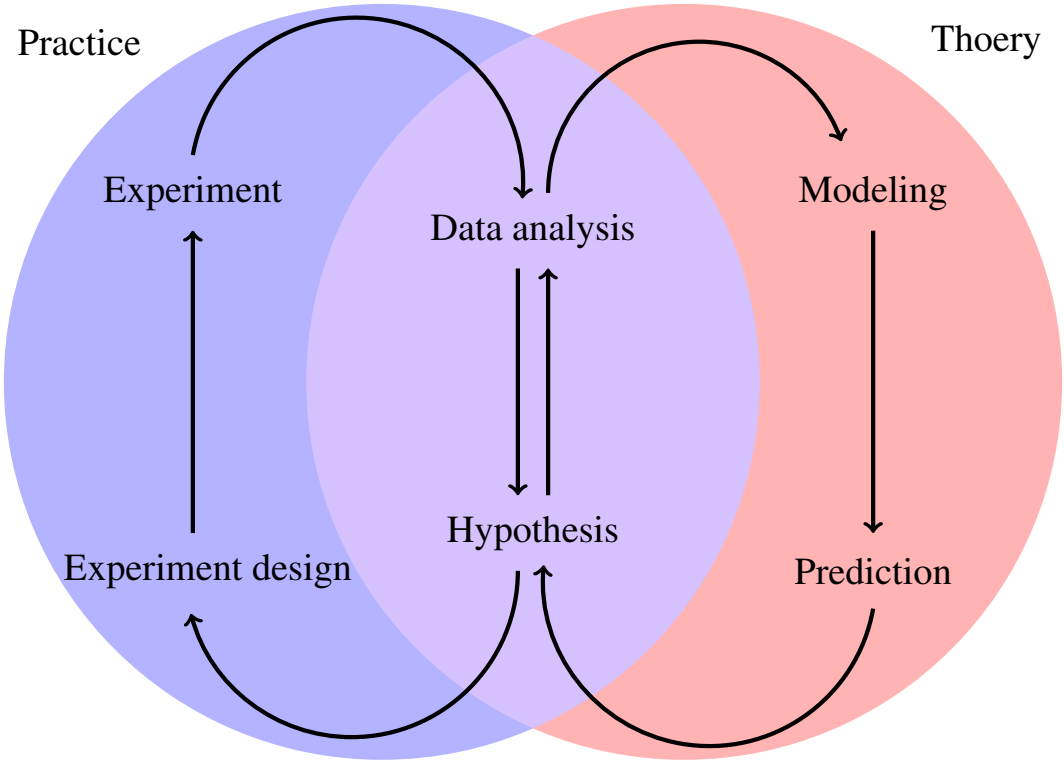


Figure 1.1: Theory and practice in research: In practice, the left circle, the objective is to come up with a new experiment design that can produce a data set for answering a scientific hypothesis. In theory, the right circle, the objective is to use a model that *reasonably* represents the existing data to come up with new predictions and hypotheses. In data science, the objective is to come up with new hypotheses that can be answered with the existing data sets, which is becoming more popular.

1.1.2 Genetic heredity

Mendel used pea plants for cross-breeding experiments to discover the fundamental laws of genetic inheritance [2]. The discovery of the law of segregation, the law of indepdents assortment, and the law of dominance took him eight years, when he grew over 10,000 pea plants to track their genetic heredity. Mendel's dicovery was not widely accepted in scientific communities until Fisher pushlished a statistical analysis of Mendel's data [3].

1.2 Focus

Trial and error has been the fundamental method in practice. Trial comes from the Anglo-French trier meaning "to try", and error means "a mistake". The procedue of trial and error strats by testing a hypothesis that might pass or fail, and iterating over modified versions of the starting hypothesis until it gets to a desired solution. The focus of this work is to utalize mathematical models in order to speed up the trail and error process. The number of possible experiment designs are not limited and mathematical models are capable to bring more insight into the problem to optimize the number of tries.

1.3 Organization

Each of the following chapter in this work constits of using mathematical models for control of a biological systems. Chapter 2 is based on *in-vivo* experiments of a chemotherapy drug. Chapter 3 is dedicated to bispecific T-cell engagers. Chapter 4 discusses social distancing in compartmental epidemic models.

Chapter 2

Chemotherapy

This chapter proposes a computationally guided approach to dose selection in cancer treatments. As it is not experimentally feasible to explore the full spectrum of possible drug doses and regimens, a mathematical framework is used to sort through the countless possible combinations. Our approach is based upon a mathematical model that quantitatively captures the complex interactions between a tumor, the host immune system, and a chemotherapy drug. The proposed model is calibrated with experimental data collected from Severe combined immunodeficiency (SCID) mice implanted with aggressive treatment-resistant glioma tumors. A variety of cyclopsphamide doses and schedules are considered, and data is collected on both tumor volume and immune cell markers. After calibration, a Mathematically Derived Optimal Regimen (MDOR) is computed using optimal control techniques. For this mouse model, we find that the MDOR that minimizes tumor size after 60 days is neither a classical metronomic schedule nor a Maximum Tolerated Dose (MTD) schedule. Instead, our MDOR consists of administering a lower dose at the beginning of treatment, followed by a larger dose after 35 days. The discovered regimen is analogous to the "press-pulse" theory in ecology. In that theory, frequent and expansive mass species extinctions occur after "press" disturbances (such as climate or sea level change) weaken and destabilize populations over many generations, and are then followed by a "pulse" disturbance that causes extensive mortality. This work highlights the ability of mathematical models derived from experimental data to provide insights into improved dosing and scheduling for long-term tumor reduction, to be subsequently experimentally evaluated.

2.1 Introduction

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 [4–6]. 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 [5], 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 [7–17]. On the other hand, 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 [13]. An optimal treatment should ideally strike the right balance: eliciting a strong immune response yet still providing enough cytotoxicity towards cancer cells from the chemotherapy drug [18, 19].

Approaches like what is presented in this chapter, expanded to other mouse models and beyond, can begin to uncover optimal treatment strategies in a quantitatively-guided way, thus addressing the stated need to explore dosing ranges earlier in the clinical trial process, as encouraged by the Food and Drug Administration (FDA) in Project Optimus.

2.1.1 Chemotherapy drugs with immunogenic response

Only a subset of chemotherapy drugs are known to induce an immunogenic cancer cell death pathway that produces a strong anti-cancer immune response. This effect is dependent on various factors, including the tumor type or subtype, the regimen that is being applied, and the class of chemotherapy drug. Drugs that are able to induce this type of immunostimulatory effect include cyclophopshamide, anthracyclines, 5-fluorouracil, mitoxantrone, idarubicin, and doxorubicin [11, 12, 20–22]. In addition to using an appropriate drug, eliciting an anti-tumor immune response requires an appropriate balance of drug dosing and scheduling [18, 19, 23]. Much remains to be understood about the complex dynamics involved in this trade-off, as examplified by 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 [9, 13, 14].

Understanding how treatment strategies affect the dynamics and interactions between the drug, the immune system, and the tumor holds a key to developing more effective treatment strategies.

2.1.2 Mathematical modeling of chemotherapy

Developing realistic mathematical models of these biological interactions is a challenging task, since a large number of phenomena need to be considered. A detailed model of the immune system alone needs consideration of different immune cell types and chemicals (cytokines and chemokines). Even for a given cell type, the same cell may play very different roles (e.g., T-cells can be cytotoxic 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 in therapy, such as individual variability between patients, tumor heterogeneity, the particular drug used for treatment, and how the chosen drug is administered. The fact that a cytotoxic 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. Although there is a rich literature on mathematical models that attempt to capture the mechanisms behind cancer chemotherapy and how it affects the immune system [18, 24–26], as well as many attempts at modeling drug resistance (see e.g. [27] and references there), the particular question that we address has been less well studied.

2.1.3 Mathematically derived optimal regimen

In this work, a computationally guided approach to dose optimization for cancer treatments is proposed that takes account of some of the introduced myriad factors. The central idea is to formulate a realistic yet simplified and phenomenological representation of the phenomena that arise during 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 experimental dataset of tumor trajectories collected from SCID mice implanted with aggressive treatment-resistant glioma tumors. A variety of cyclopsphamide doses and schedules are included in this dataset, on both tumor and immune cell markers, and treatment conditions were varied in various ranges [13]. After calibration of model parameters, we use optimal control techniques in order to compute what we

call a Mathematically Derived Optimal Regimen (MDOR), derived as the strategy that minimizes tumor size at 60 days from the start of treatment. In contrast to a classical metronomic schedule or a Maximum Tolerated Dose (MTD) schedule, our derived MDOR consists of administering a lower dose at the beginning of treatment, followed by a larger dose around half-way through the 60 days.

2.1.4 Press-pulse theory

An analogy can be drawn between the proposed MDOR and the "press-pulse" theory in ecology, in which frequent and expansive mass species extinctions occur after "press" disturbances (climate or sea level change, for example) create stress so that a subsequent "pulse" disturbance causes extensive mortality. Interestingly, a press-pulse therapeutic strategy for cancer management was also proposed in the very different context, that of calorie restricted ketogenic diets [28], where such diets are proposed as a way to stress tumor cell energy metabolism.

2.1.5 Organization of this chapter

The rest of this paper is organized in three sections. Section 2.2 includes the descriptions of the mathematical model, parameter fitting, and optimal control problem setup that is used obtain the MDOR. The mathematical model presented in this work is a modified version of the model presented in [19], and, most importantly, expands the parameter fitting process to incorporate immune system data in addition to tumor volume data. The numerical optimal control results are used in the Results Section to derive a clinically feasible optimal regimen (MDOR) and we analyze its sensitivity to dose values. The last section discusses the key findings of this paper.

2.2 Methods

Here a mathematical model based on the previous modeling effort [19] for the data set [13] is introduced. The model is fitted to tumor and immune data with aa customized cost function, and used to apply optimal control techniques to find potential dosing and scheduling regimes that might be superior to the ones that were tested before.

2.2.1 Mathematical model

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 [19], 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 [19]. 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:

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

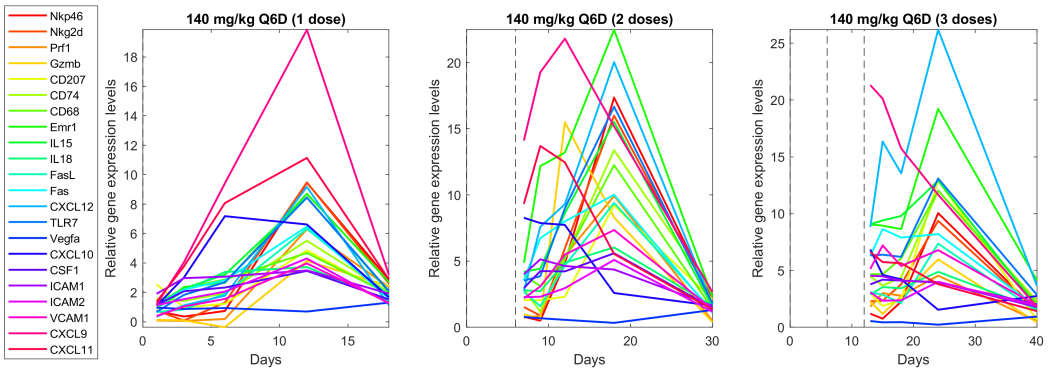
with ϵ representing a small deviation. Where $I_{simulated}$ is the immune system level $[I(t_1), I(t_2), \ldots, I(t_n)]$ at the same time points that $I_{measured}$ the immune system markers were measured $t_1, t_2, \ldots, t_n$, and $f_2(x)$ is the sum of the errors for all of the experimental immune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

2.2.2 Immune cell markers

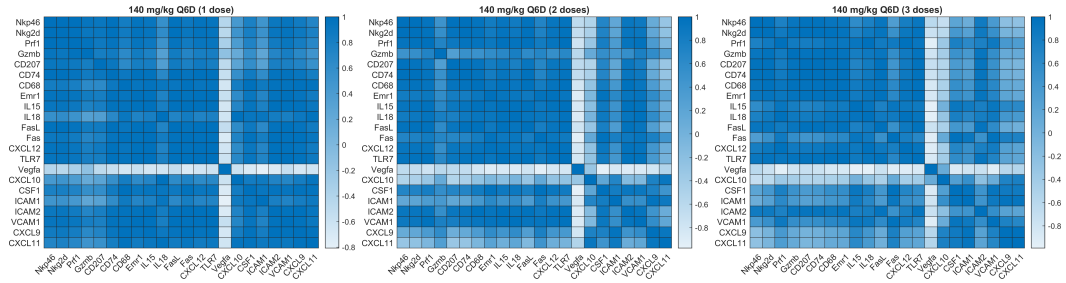
A major challenge of modeling the immune system resides in the complex interactions between its components. Even using the SCID mouse model as was used in [13], which eliminates the impact of B and T cells, maintains the impact of innate immune cells, such as NK cells, macrophages, dendritic cells, and 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 [13] can be clustered into the following three categories by response type:

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

In Fig. 2.1(a), we depict trends in the measured gene expression data of immune cells subject to different treatment regimens, as reported in [13]. As one can see in Fig. 2.1(b), there exists a positive correlation between most immune markers with the exception CXCL9, CXCL10, CXCL11, and VEGF-A. For instance, unlike the other immune cell markers, VEGF-A (Fig. 2.1(a)) initially decreases before increasing again, which results in negative correlation of VEGF-A and other immune cell markers. Finally, the immunostimulatory chemokines CXCL9, CXCL10 and CXCL11 are highlighted in Fig. 2.1(c) showing how increase in their relative gene expression precedes that of immune cell markers. Using this information, we concluded that averaging the time-series data from the correlated immune markers should provide a realistic proxy for the drug-induced immune response, allowing us to proceed with a mathematical model of smaller dimensionality while preserving the key relationships observed in experimental data.



(a)



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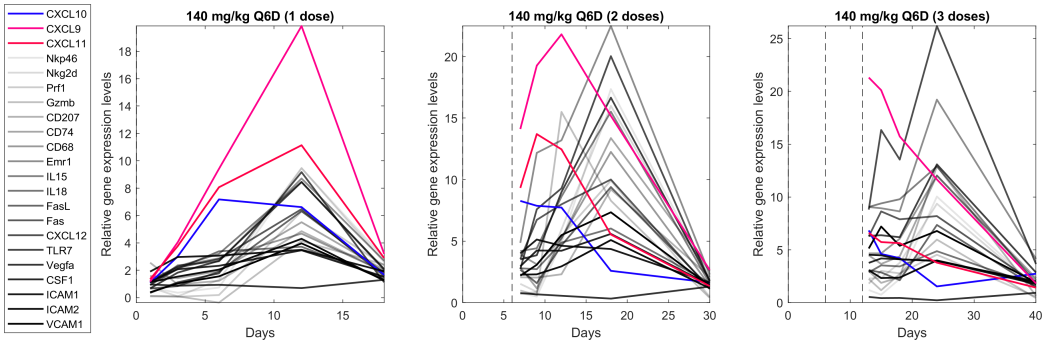

(c)

Figure 2.1: Correlations and trends in the experimentally measured gene expression data of immune cells [13]. In (a), the time-series experimental data on the immune markers are shown for the 3 measured experimental conditions for which they were measured. In (b), the correlation analysis of the data in (a) is shown for the case of 1 dose and 3 doses of cyclophoshamide with a dose of 140 mg/kg and 6 days apart. In (c), the hypothesized immunostimulatory factors CXCL9, CXCL10, and CXCL11 are highlighted.

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 [29], and has resulted in a worldwide economic downturn [30]. 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 [31–39].

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 [40–45], including studies of (integral) input to state stability [46], network stability of epidemic spread [47, 48], and optimal control strategies for meta-population models [49]. 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 [50]. Most models are variations on the classical *SIR* model [51–53] 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 [54–59], as it is currently thought that COVID-19 is significantly spread through *asymptomatic* individuals [60–62].

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 [63, 64]. The latter technique has recently been applied to COVID-19 [65, 66].

3. Sub-dividing populations into regions, each described by *local* parameters. Such regions may be cities, neighborhoods, or communities [67]. This framework allows modelers to capture the virus spread and population mobility geographically [68–71]. These models have been recently used to understand the spread of COVID-19 in China [72], Italy [73], Netherlands and Belgium [74], and India [75, 76].

Shortening the period of time that populations are socially distanced is economically advantageous [30, 77, 78]. 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 [51, 79] 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 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 [80], social distancing as a form of NPI has been enacted in the United States [81], and other countries [82, 83] for reducing the spread of the virus, as neither herd immunity nor a viable vaccine yet existed [84]. Many countries have implemented strict quarantine, isolation, or social distancing policies early in the epidemic [82], while countries such as Belarus [85] and Sweden [86, 87] 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 [88–90]. 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.

Bibliography

[1] Albert Einstein and Nathan Rosen. “On gravitational waves”. In: *Journal of the Franklin Institute* 223.1 (1937), pp. 43–54.

[2] Gregor Mendel. “Experiments in plant hybridization (1865)”. In: *Verhandlungen des naturforschenden Vereins Brünn.) Available online: www. mendelweb. org/Mendel. html (accessed on 1 January 2013)* (1996).

[3] Ronald A Fisher. “XV.—The correlation between relatives on the supposition of Mendelian inheritance.” In: *Earth and Environmental Science Transactions of the Royal Society of Edinburgh* 52.2 (1919), pp. 399–433.

[4] Hiba Zahreddine and Katherine Borden. “Mechanisms and insights into drug resistance in cancer”. In: *Frontiers in pharmacology* 4 (2013), p. 28.

[5] Irina Kareva, David J Waxman, and Giannoula Lakka Klement. “Metronomic chemotherapy: an attractive alternative to maximum tolerated dose therapy that can activate anti-tumor immunity and minimize therapeutic resistance”. In: *Cancer Letters* 358.2 (2015), pp. 100–106.

[6] Ami B Shah, Katarzyna A Rejniak, and Jana L Gevertz. “Limiting the development of anti-cancer drug resistance in a spatial model of micrometastases”. In: *Mathematical biosciences and engineering: MBE* 13.6 (2016), p. 1185.

[7] Oliver Kepp et al. “Immunogenic cell death modalities and their impact on cancer treatment”. In: *Apoptosis* 14.4 (2009), pp. 364–375.

[8] Oliver Kepp et al. “Molecular determinants of immunogenic cell death elicited by anticancer chemotherapy”. In: *Cancer and Metastasis Reviews* 30.1 (2011), pp. 61–69.

[9] Joshua C Doloff and David J Waxman. “VEGF receptor inhibitors block the ability of metronomically dosed cyclophosphamide to activate innate immunity–induced tumor regression”. In: *Cancer research* 72.5 (2012), pp. 1103–1115.

[10] Guido Kroemer et al. “Immunogenic cell death in cancer therapy”. In: *Annual review of immunology* 31 (2013), pp. 51–72.

[11] Erika Vacchelli et al. “Trial Watch: Chemotherapy with immunogenic cell death inducers”. In: *Oncoimmunology* 3.3 (2014), e27878.

[12] L Bracci et al. “Immune-based mechanisms of cytotoxic chemotherapy: implications for the design of novel and rationale-based combined treatments against cancer”. In: *Cell Death and Differentiation* 21.1 (2014), p. 15.

[13] 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.

[14] Chong-Sheng Chen, Joshua C Doloff, and David J Waxman. “Intermittent metronomic drug schedule is essential for activating antitumor innate immunity and tumor xenograft regression”. In: *Neoplasia* 16.1 (2014), p. 84.

[15] Lucillia Bezu et al. “Combinatorial strategies for the induction of immunogenic cell death”. In: *Frontiers in immunology* 6 (2015), p. 187.

[16] Junjie Wu and David J Waxman. “Metronomic cyclophosphamide eradicates large implanted GL261 gliomas by activating antitumor Cd8+ T-cell responses and immune memory”. In: *Oncoimmunology* 4.4 (2015), e1005521.

[17] Junjie Wu, Marie Jordan, and David J Waxman. “Metronomic cyclophosphamide activation of anti-tumor immunity: tumor model, mouse host, and drug schedule dependence of gene responses and their upstream regulators”. In: *BMC Cancer* 16.1 (2016), p. 623.

[18] Derek S Park et al. “The Goldilocks Window of Personalized Chemotherapy: Getting the Immune Response Just Right”. In: *Cancer Research* 79.20 (2019), pp. 5302–5315.

[19] Anh Phong Tran et al. “Delicate balances in cancer chemotherapy: modeling immune recruitment and emergence of systemic drug resistance”. In: *Frontiers in Immunology* 11 (2020), p. 1376.

[20] L. Zitvogel et al. “Immunological Aspects of Cancer Chemotherapy”. In: *Nature Reviews Immunology* 8.1 (Jan. 2008), pp. 59–73.

[21] Gang Chen and Leisha A Emens. “Chemoimmunotherapy: reengineering tumor immunity”. In: *Cancer Immunology, Immunotherapy* 62.2 (2013), pp. 203–216.

[22] Jonathan Pol et al. “Trial Watch: Immunogenic cell death inducers for anticancer chemotherapy”. In: *Oncoimmunology* 4.4 (2015), e1008866.

[23] Junjie Wu and David J Waxman. “Immunogenic chemotherapy: dose and schedule dependence and combination with immunotherapy”. In: *Cancer Letters* 419 (2018), pp. 210–221.

[24] Milly E De Jonge et al. “Clinical pharmacokinetics of cyclophosphamide”. In: *Clinical Pharmacokinetics* 44.11 (2005), pp. 1135–1164.

[25] Lisette G de Pillis, Weiqing Gu, and Ami E Radunskaya. “Mixed immunotherapy and chemotherapy of tumors: modeling, applications and biological interpretations”. In: *Journal of Theoretical Biology* 238.4 (2006), pp. 841–862.

[26] Joseph Ciccolini et al. “Pharmacokinetics and pharmacodynamics-based mathematical modeling identifies an optimal protocol for metronomic chemotherapy”. In: *Cancer Research* 77.17 (2017), pp. 4723–4733.

[27] James M Greene, Jana L Gevertz, and Eduardo D Sontag. “Mathematical Approach to Differentiate Spontaneous and Induced Evolution to Drug Resistance During Cancer Treatment”. In: *JCO Clinical Cancer Informatics* 3 (2019), pp. 1–20.

[28] T. N. Seyfried et al. “Press-pulse: a novel therapeutic strategy for the metabolic management of cancer”. In: *Nutr Metab (Lond)* 14 (2017), p. 19.

[29] World Health Organization et al. *WHO Coronavirus Disease (COVID-19) Dashboard. Geneva: World Health Organization; 2020*.

[30] Olivier Coibion, Yuriy Gorodnichenko, and Michael Weber. *The Cost of the COVID-19 Crisis: Lockdowns, Macroeconomic Expectations, and Consumer Spending*. Tech. rep. National Bureau of Economic Research, 2020.

[31] Joshua S Weitz et al. “Awareness-driven behavior changes can shift the shape of epidemics away from peaks and toward plateaus, shoulders, and oscillations”. In: *Proc. Natl. Acad. Sci. U. S. A.* 117.51 (2020), pp. 32764–32771.

[32] Michelangelo Bin et al. “On fast multi-shot epidemic interventions for post lock-down mitigation: Implications for simple COVID-19 models”. In: *arXiv preprint arXiv:2003.09930* (2020).

[33] Elisa Franco. “A feedback SIR (fSIR) model highlights advantages and limitations of infection-based social distancing”. In: *arXiv preprint arXiv:2004.13216* (2020).

[34] Dylan H Morris et al. “Optimal, near-optimal, and robust epidemic control”. In: *arXiv preprint arXiv:2004.02209* (2020).

[35] Giulia Giordano et al. “Modelling the COVID-19 epidemic and implementation of population-wide interventions in Italy”. In: *Nature Medicine* (2020), pp. 1–6.

[36] Yunxiu Zhou, Simon A Levin, and Naomi Ehrich Leonard. “Active Control and Sustained Oscillations in actSIS Epidemic Dynamics”. In: *3rd IFAC Workshop on Cyber-Physical & Human Systems*. 2020.

[37] Matthew D Johnston and Bruce Pell. “A dynamical framework for modeling fear of infection and frustration with social distancing in COVID-19 spread”. In: *arXiv preprint arXiv:2008.06023* (2020).

[38] Jana L Gevertz et al. “A novel COVID-19 epidemiological model with explicit susceptible and asymptomatic isolation compartments reveals unexpected consequences of timing social distancing”. In: *J. Theor. Biol.* 510 (2021), p. 110539.

[39] Mahdiar Sadeghi, James Greene, and Eduardo Sontag. “Universal features of epidemic models under social distancing guidelines”. In: *bioRxiv* (2020).

[40] Esteban A. Hernandez-Vargas and Jorge X. Velasco-Hernandez. “In-host Mathematical Modelling of COVID-19 in Humans”. In: *Annual Reviews in Control* 50 (2020), pp. 448–456. ISSN: 1367-5788. DOI: https://doi.org/10.1016/j.arcontrol.2020.09.006. URL: http://www.sciencedirect.com/science/article/pii/S1367578820300638.

[41] Philip E. Paré, Carolyn L. Beck, and Tamer Başar. “Modeling, estimation, and analysis of epidemics over networks: An overview”. In: *Annual Reviews in Control* 50 (2020), pp. 345–360. ISSN: 1367-5788. DOI: https://doi.org/10.1016/j.arcontrol.2020.09.003. URL: http://www.sciencedirect.com/science/article/pii/S1367578820300614.

[42] Emeric Scharbarg et al. “From the hospital scale to nationwide: observability and identification of models for the COVID-19 epidemic waves”. In: *Annual Reviews in Control* 50 (2020), pp. 409–416. ISSN: 1367-5788. DOI: https://doi.org/10.1016/j.arcontrol.2020.09.007. URL: http://www.sciencedirect.com/science/article/pii/S136757882030064X.

[43] Santosh Ansumali et al. “Modelling a pandemic with asymptomatic patients, impact of lockdown and herd immunity, with applications to SARS-CoV-2”. In: *Annual Reviews in Control* 50 (2020), pp. 432–447. ISSN: 1367-5788. DOI: https://doi.org/10.1016/j.arcontrol.2020.10.003. URL: http://www.sciencedirect.com/science/article/pii/S1367578820300699.

[44] Esteban A. Hernandez-Vargas et al. “First special section on systems and control research efforts against COVID-19 and future pandemics”. In: *Annual Reviews in Control* 50 (2020), pp. 343–344. ISSN: 1367-5788. DOI: https://doi.org/10.1016/j.arcontrol.2020.10.007. URL: http://www.sciencedirect.com/science/article/pii/S1367578820300730.

[45] Pablo Abuin et al. “Characterization of SARS-CoV-2 dynamics in the host”. In: *Annual Reviews in Control* 50 (2020), pp. 457–468. ISSN: 1367-5788. DOI: https://doi.org/10.1016/j.arcontrol.2020.09.008. URL: http://www.sciencedirect.com/science/article/pii/S1367578820300651.

[46] Hiroshi Ito. “Feedback control on immigration to reduce spread of infectious diseases with an ISS guarantee”. In: *2020 59th Annual Conference of the Society of Instrument and Control Engineers of Japan (SICE)*. IEEE. 2020, pp. 736–741.

[47] Canrong Tian, Qunying Zhang, and Lai Zhang. “Global stability in a networked SIR epidemic model”. In: *Applied Mathematics Letters* (2020), p. 106444.

[48] Fangzhou Liu et al. “On the Stability of the Endemic Equilibrium of A Discrete-Time Networked Epidemic Model”. In: *arXiv preprint arXiv:2001.07451* (2020).

[49] Yujing Liu et al. “Epidemic spreading on midscopic multi-layer network with optimal control mechanism”. In: *Physica A: Statistical Mechanics and its Applications* 537 (2020), p. 122775.

[50] Greg Stewart, Klaskevan Heusden, and Guy A Dumont. “How control theory can help us control COVID-19”. In: *IEEE Spectrum* 57.6 (2020), pp. 22–29.

[51] William Ogilvy Kermack and Anderson G McKendrick. “A contribution to the mathematical theory of epidemics”. In: *Proceedings of the royal society of london. Series A, Containing papers of a mathematical and physical character* 115.772 (1927), pp. 700–721.

[52] Fred Brauer, Carlos Castillo-Chavez, and Zhilan Feng. *Mathematical Models in Epidemiology*. Springer, 2019.

[53] Giacomo Albi, Lorenzo Pareschi, and Mattia Zanella. "Control with uncertain data of socially structured compartmental epidemic models". In: *arXiv preprint arXiv:2004.13067* (2020).

[54] Jana L Gevertz et al. "A novel COVID-19 epidemiological model with explicit susceptible and asymptomatic isolation compartments reveals unexpected consequences of timing social distancing". In: *Journal of Theoretical Biology* 510 (2020), p. 110539.

[55] Weijie Pang. "Public health policy: COVID-19 epidemic and SEIR model with asymptomatic viral carriers". In: *arXiv preprint arXiv:2004.06311* (2020).

[56] Aritz Etxeberria-Iriondo, Manuel De la Sen, and Santiago Alonso-Quesada. "A New Epidemic Model Under Vaccination". In: *2019 14th IEEE Conference on Industrial Electronics and Applications (ICIEA)*. IEEE. 2019, pp. 2388–2392.

[57] Tingzhe Sun and Dan Weng. "Estimating the Effects of Asymptomatic and Imported Patients on COVID-19 Epidemic Using Mathematical Modeling". In: *Journal of Medical Virology* (2020).

[58] Giuseppe Gaeta. "Asymptomatic infectives and R_0 for COVID". In: *arXiv preprint arXiv:2003.14098* (2020).

[59] Amirarsalan Rajabi et al. "Investigating dynamics of COVID-19 spread and containment with agent-based modeling". In: *medRxiv* (2020).

[60] Yan Bai et al. "Presumed asymptomatic carrier transmission of COVID-19". In: *Jama* 323.14 (2020), pp. 1406–1407.

[61] Xingxia Yu and Rongrong Yang. "COVID-19 transmission through asymptomatic carriers is a challenge to containment". In: *Influenza and Other Respiratory Viruses* (2020).

[62] Zhiliang Hu et al. "Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China". In: *Science China Life Sciences* (2020), pp. 1–6.

[63] KM Ariful Kabir, Kazuki Kuga, and Jun Tanimoto. "Analysis of SIR epidemic model with information spreading of awareness". In: *Chaos, Solitons & Fractals* 119 (2019), pp. 118–125.

[64] Timothy C Reluga. "Game theory of social distancing in response to an epidemic". In: *PLoS computational biology* 6.5 (2010).

[65] Elisa Franco. "A feedback SIR (fSIR) model highlights advantages and limitations of infection-based social distancing". In: *arXiv preprint arXiv:2004.13216* (2020).

[66] Navid Ghaffarzadegan and Hazhir Rahmandad. “Simulation-based Estimation of the Spread of COVID-19 in Iran”. In: *medRxiv* (2020).

[67] Bing Wang et al. “Network structure-based interventions on spatial spread of epidemics in metapopulation networks”. In: *Physical Review E* 102.6 (2020), p. 062306.

[68] Matteo Chinazzi et al. “The effect of travel restrictions on the spread of the 2019 novel coronavirus (COVID-19) outbreak”. In: *Science* 368.6489 (2020), pp. 395–400.

[69] Seth Flaxman et al. “Estimating the effects of non-pharmaceutical interventions on COVID-19 in Europe”. In: *Nature* (2020), pp. 1–8.

[70] Xue-Feng San, Zhi-Cheng Wang, and Zhaosheng Feng. “Spreading speed and traveling waves for an epidemic model in a periodic patchy environment”. In: *Communications in Nonlinear Science and Numerical Simulation* (2020), p. 105387.

[71] Atefe Darabi and Milad Siami. “Centrality in Epidemic Networks with Time-Delay: A Decision-Support Framework for Epidemic Containment”. In: *arXiv preprint arXiv:2010.00398* (2020).

[72] Moritz UG Kraemer et al. “The effect of human mobility and control measures on the COVID-19 epidemic in China”. In: *Science* 368.6490 (2020), pp. 493–497.

[73] Marino Gatto et al. “Spread and dynamics of the COVID-19 epidemic in Italy: Effects of emergency containment measures”. In: *Proceedings of the National Academy of Sciences* 117.19 (2020), pp. 10484–10491.

[74] Eline van den Broek-Altenburg and Adam Atherly. “Adherence to COVID-19 Policy Measures: Behavioral Insights from the Netherlands and Belgium”. In: *Available at SSRN 3692644* (2020).

[75] Bhalchandra S Pujari and Snehal M Shekatkar. “Multi-city modeling of epidemics using spatial networks: Application to 2019-nCov (COVID-19) coronavirus in India”. In: *medRxiv* (2020).

[76] Buddhananda Banerjee, Pradumn Kumar Pandey, and Bibhas Adhikari. “A model for the spread of an epidemic from local to global: A case study of COVID-19 in India”. In: *arXiv preprint arXiv:2006.06404* (2020).

[77] Cristina Arellano, Yan Bai, and Gabriel P Mihalache. *Deadly Debt Crises: COVID-19 in Emerging Markets*. Working Paper 27275. National Bureau of Economic Research, May 2020. DOI: 10.3386/w27275. URL: http://www.nber.org/papers/w27275.

[78] Tommy Andersson et al. "Optimal Trade-Off Between Economic Activity and Health During an Epidemic". In: *arXiv preprint arXiv:2005.07590* (2020).

[79] Herbert W Hethcote. "The mathematics of infectious diseases". In: *SIAM Review* 42.4 (2000), pp. 599–653.

[80] Austin L Wright et al. "Poverty and economic dislocation reduce compliance with COVID-19 shelter-in-place protocols". In: *University of Chicago, Becker Friedman Institute for Economics Working Paper* 2020-40 (2020).

[81] Michael S Wolf et al. "Awareness, attitudes, and actions related to COVID-19 among adults with chronic conditions at the onset of the US outbreak: a cross-sectional survey". In: *Annals of Internal Medicine* (2020).

[82] Tran Phuoc Bao Thu, Pham Nguyen Hong Ngoc, Nguyen Minh Hai, et al. "Effect of the social distancing measures on the spread of COVID-19 in 10 highly infected countries". In: *Science of the Total Environment* 742 (2020), p. 140430.

[83] Anil Sarin and Akhil Sarin. "Coronavirus Disease (COVID-19): Spread, Awareness and Strategic Containment". In: *Journal of Communicable Diseases (E-ISSN: 2581-351X & P-ISSN: 0019-5138)* 52.1 (2020), pp. 22–31.

[84] Anthony McDonnell et al. *COVID-19 Vaccine Predictions: Using Mathematical Modelling and Expert Opinions to Estimate Timelines and Probabilities of Success of COVID-19 Vaccines*. 2020.

[85] Valentina Gritsenko et al. "COVID 19 Fear, Stress, Anxiety, and Substance Use Among Russian and Belarusian University Students". In: *International Journal of Mental Health and Addiction* (2020), p. 1.

[86] Matz Dahlberg et al. "Effects of the COVID-19 pandemic on population mobility under mild policies: Causal evidence from Sweden". In: *arXiv preprint arXiv:2004.09087* (2020).

[87] Sang-Wook Cho. "Quantifying the impact of nonpharmaceutical interventions during the COVID-19 outbreak: The case of Sweden". In: *The Econometrics Journal* 23.3 (2020), pp. 323–344.

[88] Yonatan Berman. “The Distributional Short-Term Impact of the COVID-19 Crisis on Wages in the United States”. In: *arXiv preprint arXiv:2005.08763* (2020).

[89] Charles Courtemanche et al. “Strong Social Distancing Measures In The United States Reduced The COVID-19 Growth Rate: Study evaluates the impact of social distancing measures on the growth rate of confirmed COVID-19 cases across the United States.” In: *Health Affairs* (2020), pp. 10–1377.

[90] William F Maloney and Temel Taskin. “Determinants of social distancing and economic activity during COVID-19: A global view”. In: *World Bank Policy Research Working Paper* 9242 (2020).

Appendix A

First Appendix Headline

Appendix B

Second Appendix Headline