Modelling and optimizing testing strategies for epidemic outbreaks

Abstract of Ph.D. Thesis

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Introduction

The aim of the thesis is to develop and analyse dynamical models for the transmission dynamics and propagation of infectious diseases. Our approach can be used to the practical problems of epidemiology, with serious implications to public health policy, prevention, control and mitigation strategies in public health emergencies such as the ongoing pandemic.

Diseases have always been an important part of the life of societies. Since the beginning of written history there have been records of epidemics causing significant burden on human populations, often recurring years or decades later. For example, the Black Death spread from Asia throughout Europe in waves beginning in 1346, and is estimated to have caused the death of more than 30% of the population of Europe between 1346 and 1350. The disease returned regularly in several parts of Europe for centuries, most famously as the Great Plague of London in 1665-1666. After the first World War, the Spanish flu estimated to cause 25 - 50 million deaths worldwide, followed by other severe influenza pandemics in the 50's and 60's. There are still annual influenza epidemics that cause up to 650,000 fatalities worldwide, according to WHO. Recently, we are struggling with the COVID-19 pandemic, with 6,400,000 reported deaths until September 2022, while the true number of deaths may reach 20 millions.

The objective of medical screening and testing is to identify the disease in its still curable phase. This may have been an old challenge in medicine and for a successful testing at least four conditions need to be met: the availability of simple, validated and acceptable forms of tests, the discovery of effective treatments, the establishment of a screening protocol, and the wide access to health care. There are many successes from the history of medical screening: testing for syphilis in the United States army (one of the first applications of group testing), screening for cervical cancer using the Pap test, and screening for breast cancer by mammography. The evaluation of the impact of screening on human health slowly progressed, from obvious changes in the vital statistics to less obvious such as the decline in mortality of cancer of the uterus, to finally more subtle changes, such as the impact of mammography screening on breast cancer mortality.

Screening in non-infectious diseases such as cancer has the main goal of early identification of cases that drastically increases the chance of successful treatment for that individual. The main advantage of testing in combating infectious diseases beyond treating the tested individual is that it enables to recognize asymptomatic infected, who may have a very important role in disease transmission dynamics, thus potentially by breaking chains of infection the testing benefits indirectly all other members of the population. Hence, strategic testing can be used as a mitigation tool of the epidemic on the population level. Testing helps to estimate the proportion of asymptomatic carriers and their role in disease spread. It also helps to find clusters of cases and to have a more precise estimate on transmission rates and death rates. With the application of these results, testing provides a guide to make decisions on social distancing policy and other measures including the allocation of medical resources.

We start with an overview of simple SIS models, then we discuss some of the most important and feasible extensions and generalizations. Then, we introduce a basic mass-testing and isolation intervention and we point out that this modification induces a completely different and richer dynamics.

Then, we investigate the mathematical analysis of a multistage SIS model, where infected hosts progress through different stages of the disease. We calculate the basic reproduction number $\mathcal{R}_0$, and discuss the existence of the endemic equilibrium. Our main result is that the stability of the endemic equilibrium depends strongly on the number of stages: the endemic equilibrium is always stable when $n \leq 3$, while for any $n > 3$ it can be either stable or unstable, depending on the particular choice of the parameters. We generalize previous stability results for $SIRS$ models as well and point out a mistake in the literature for multistage $SEIRS$ models.

Then, we consider an extended $SEIR$-type model for the transmission dynamics of COVID-19. We incorporate symptom-based testing of patients and isolation upon positive result *i.e.* removal from the chain of transmission. The clinical symptoms that trigger the testing of individuals is referred to as *indicator symptoms*. The *force of testing* is defined as the per capita rate at which infected individuals are tested. It is described by a nonlinear function of the state of the epidemic and of all individuals displaying the indicator symptom at a given time, with or without COVID-19 infection, hence, it is considerably different from previous approaches. Our goal is to understand the impact, and especially the limitations of this testing strategy, hence we model neither contact-tracing of patients with positive tests nor the testing of a fraction of non-symptomatic contacts, both of which are common and efficient improvements and result in removal of additional patients from the chain of transmission.

Then, we develop a compartmental model to study the applicability of group testing and compare different pooling strategies: regular and Dorfman pooling. The model includes isolated compartments as well, from where individuals rejoin the active population after some time delay. We develop a method to optimize Dorfman pooling depending on disease prevalence and establish an adaptive strategy to select variable pool sizes during the course of the epidemic. It is shown that optimizing the pool size can avert a significant number of infections. The adaptive strategy is even more efficient, and may prevent an epidemic outbreak in situations when a fixed pool size strategy can not. The dissertation is based on three articles of the author. These publications are the following:

[1] G. Röst, T. Tekeli, Stability and oscillations of multistage SIS models depend on the number of stages, *App. Math. and Comp.*, (380), **2020**, 125259, 0096-3003, `https://doi.org/10.1016/j.amc.2020.125259`.

[2] F. Bartha, J. Karsai, T. Tekeli, G. Röst, Symptom-based testing in a compartmental model of COVID-19, in: P. Agarwal, J. J. Nieto, M. Ruzhansky, D. F. M. Torres (Eds.), Analysis of infectious disease problems (Covid-19) and their global impact, Springer, Singapore, **2021**, pp. 357–376. `https://doi.org/10.1007/978-981-16-2450-6_16`

[3] T. Tekeli, A. Dénes, G. Röst, Adaptive group testing in a compartmental model of COVID-19. *Math. Biosci. and Eng.*, **2022**, 19(11): 11018-11033, `https://doi.org/10.3934/mbe.2022513`

SIS epidemic models

The simplest SIS model is

$$S'(t) = -\beta S(t)I(t) + \gamma I(t), \tag{1}$$
$$I'(t) = \beta S(t)I(t) - \gamma I(t), \tag{2}$$

where β is the transmission rate and γ is the recovery rate.

The dynamics of the infected population is equivalent to the dynamics of the logistic equation, so that for all $I(0) \geq 0$ it holds that

$$\text{if } \frac{\beta}{\gamma} < 1, \text{ then } \lim_{t\to\infty} I(t) = 0;$$
$$\text{if } \frac{\beta}{\gamma} \geq 1, \text{ then } \lim_{t\to\infty} I(t) = 1 - \frac{\gamma}{\beta} = 1 - \frac{1}{\mathcal{R}_0},$$

where the basic reproduction number $\mathcal{R}_0 = \dfrac{\beta}{\gamma}$ shows the expected number of new infections directly generated by one infectious person in a completely susceptible population. A reasonable extension to make the simple SIS model more realistic is to divide the infectious period into stages $I_1, I_2, \ldots, I_n$, following the progression of the disease within the host, given that the infectiousness of an individual may change during the course of infection. The so-called *linear chain trick* consists in replacing a single infectious stage with n exponentially distributed sub-stages as substage I_i having its own mean period γ_i^{-1}. We can consider such cases with the help of a probability density function. Let's denote the density of a cohort whose infection age is v at time moment t by $g(t, v)$. Then

$$g(t, v) = \beta \left(1 - I(t - v)\right) I(t - v)\mathcal{F}(v), \tag{3}$$

where we denote by $\mathcal{F}(a)$ the probability of an individual being infected after time a since infection. Here $\mathcal{F}$ is non-increasing with

$$\mathcal{F} : [0, \infty] \to [0, 1],$$
$$\mathcal{F}(0) = 1 \text{ and } \lim_{t\to\infty} \mathcal{F}(t) = 0.$$

Integration of (3) yields

$$I(t) = \beta \int_0^\infty \left(1 - I(t - v)\right) I(t - v)\mathcal{F}(v)dv. \tag{4}$$

Hethcote and van den Driessche made the conjecture that the endemic equilibrium, whenever it exists, is globally asymptomatically stable, regardless of the particular form of $\mathcal{F}$. Röst and Nakata proved in [4] that this conjecture holds, if the support of $\mathcal{F}$ is compact. This model assumes constant β infectivity, regardless of infection age. We generalize this by varying (4) to

$$I(t) = \int_0^\infty \beta(v) I(t - v) \left(1 - I(t - v)\right) \mathcal{F}(v)dv, \tag{5}$$

and show that varying infectivity can cause richer, oscillatory dynamics. We prove this for a discretized version of (5) with multiple stages. Moreover, extending (1) with introducing a simple testing and isolating method can also change its dynamics.

The following simple delay differential equation model can be derived from the basic SIS-setup by adding testing and a quarantined compartment with fixed length of isolation:

$$\begin{aligned} S'(t) &= -\beta \cdot S(t) \cdot I(t) + \gamma \cdot I(t) + \sigma \cdot I(t-\tau) \\ I'(t) &= \beta \cdot S(t) \cdot I(t) - \gamma \cdot I(t) - \sigma \cdot I(t) \\ Q'(t) &= \sigma \cdot I(t) - \sigma \cdot I(t-\tau). \end{aligned} \tag{6}$$

Theorem 1. *The endemic equilibrium of system* (6) *can be stable or unstable, depending on parameters* β, γ, σ *and* τ.

Stability and instability in multistage SIS models

We investigate the stage progression SIS model

$$\begin{aligned} S'(t) &= b(N(t)) + p_n I_n(t) - \sum_{k=1}^{n} \beta_k I_k(t) S(t) - \mu S(t), \\ I_1'(t) &= \sum_{k=1}^{n} \beta_k I_k(t) S(t) - p_1 I_1(t) - \mu I_1(t), \\ I_2'(t) &= p_1 I_1(t) - p_2 I_2(t) - \mu I_2(t), \\ &\vdots \\ I_n'(t) &= p_{n-1} I_{n-1}(t) - p_n I_n(t) - \mu I_n(t), \end{aligned} \tag{7}$$

which describes the spread of a non-fatal infectious disease in a population with recruitment rate $b(N)$ and natural death rate μ. For simplicity, we will assume $b(N) = \mu N$, hence the total population $N(t) = S(t) + \sum_{j=1}^{n} I_j(t)$ will remain constant. Here, $S = S(t)$ represents the susceptible compartment, $I_1 = I_1(t), I_2 = I_2(t), \ldots, I_n = I_n(t)$ represent the infected compartments corresponding to stages $1, 2, \ldots, n$. We denote by β_i $(i = 1, 2, \ldots, n)$ the disease transmission rates in compartment I_i, and by p_i $(i = 1, 2, \ldots, n)$ the progression rates from disease stage i to $i+1$, i.e. from compartment I_i to I_{i+1}. Normalizing the constant population to unity yields $S = 1 - \sum_{k=1}^{n} I_k$, therefore we can decouple the S-equation from (7) to

$$\begin{aligned} I_1' &= \sum_{k=1}^{n} \beta_k I_k \left(1 - \sum_{k=1}^{n} I_k\right) - p_1 I_1 - \mu I_1, \\ I_2' &= p_1 I_1 - p_2 I_2 - \mu I_2, \\ &\vdots \\ I_n' &= p_{n-1} I_{n-1} - p_n I_n - \mu I_n. \end{aligned} \tag{8}$$

Proposition 1. *The basic reproduction number of system* (8) *is*

$$\mathcal{R}_0 = \sum_{k=1}^{n} \frac{\beta_k}{p_k + \mu} \left(\prod_{j=1}^{k-1} \frac{p_j}{p_j + \mu} \right). \tag{9}$$

Proposition 2. *For system* (8)*, a unique endemic equilibrium* $(I_1^*, I_2^*, \dots I_n^*)$ *(with* $I_k^* > 0$ *for all* $1 \le k \le n$*) exists if and only if* $\mathcal{R}_0 > 1$*. It is given by*

$$I_k^* = \frac{p_{k+1} + \mu}{p_k} \dots \frac{p_n + \mu}{p_{n-1}} \cdot \frac{1 - \frac{1}{\mathcal{R}_0}}{Q}, \text{ where } Q = 1 + \frac{p_n + \mu}{p_{n-1}} + \dots + \prod_{i=1}^{n-1} \frac{p_{i+1} + \mu}{p_i}. \tag{10}$$

We introduce the notation $D = \{\boldsymbol{I} \in \mathbb{R}_+^n | \sum_{j=1}^n I_j \le 1\}$ for the feasible phase space of model (8).

Theorem 2. *If* $\mathcal{R}_0 \le 1$ *then the disease free equilibrium is globally asymptotically stable in the domain* D*, that is, the disease will be eradicated. If* $\mathcal{R}_0 > 1$ *then the disease persists uniformly in the population.*

Theorem 3. *In* (8)*, if* $\mathcal{R}_0 > 1$ *and* $n = 1, 2, 3$*, then, the endemic equilibrium is locally asymptotically stable.*

Stable cases in higher dimensions

Let us set in (8) $\beta := \beta_1 = \beta_2 = \dots = \beta_n$, and $p := p_1 = \dots p_n$, and $\mu = 0$. Then we have

$$\begin{aligned} I_1' &= \beta \sum_{k=1}^{n} I_k \left(1 - \sum_{k=1}^{n} I_k \right) - pI_1, \\ I_2' &= pI_1 - pI_2, \\ &\vdots \\ I_n' &= pI_{n-1} - pI_n. \end{aligned} \tag{11}$$

From (9) and (10), we obtain the basic reproduction number and the endemic equilibrium as

$$\mathcal{R}_0 = \frac{\beta \cdot n}{p}, \quad I_1^* = I_2^* = \dots = I_n^* = \frac{1 - \frac{p}{\beta n}}{n}. \tag{12}$$

Proposition 3. *The characteristic polynomial of (11) at the endemic equilibrium is*

$$\chi_n(\lambda) = (-1)^n \left((p + \lambda)^n + \left(\beta - \frac{2p}{n} \right) \cdot \sum_{i=0}^{n-1} (p + \lambda)^i \cdot p^{n-1-i} \right). \tag{13}$$

Theorem 4. *The endemic equilibrium of (11) is stable.*

Unstable cases in higher dimensions

If we set in (8) $\beta_1 = \beta > 0$, $\beta_2 = \beta_3 = \cdots = \beta_n = 0$, $p_1 = p > 0$, $p_2 = p_3 = \cdots = p_n = q > 0$ and $\mu = 0$, then (8) is reduced to

$$\begin{aligned} I_1' &= \beta I_1 \left(1 - \sum_{k=1}^{n} I_k\right) - pI_1, \\ I_2' &= pI_1 - qI_2, \\ I_3' &= qI_2 - qI_3, \\ &\vdots \\ I_n' &= qI_{n-1} - qI_n. \end{aligned} \tag{14}$$

It is easy to calculate the basic reproduction number as $\mathcal{R}_0 = \dfrac{\beta}{p}$. The endemic equilibrium satisfies $I_2^* = \cdots = I_n^* = \frac{p}{q} I_1^*$, and substituting to the first equation yields

$$I_1^* = \frac{1 - \frac{p}{\beta}}{(n-1)\frac{p}{q} + 1}, \quad I_2^* = \cdots = I_n^* = \frac{p}{q} \frac{1 - \frac{p}{\beta}}{(n-1)\frac{p}{q} + 1}. \tag{15}$$

Proposition 4. *The characteristic polynomial of (14) is*

$$\chi_n(\lambda) = (-1)^n \left((q+\lambda)^{n-1}(\beta \cdot I_1^* + \lambda) + \frac{p \cdot \beta \cdot I_1^*}{\lambda} \Big((q+\lambda)^{n-1} - q^{n-1} \Big) \right). \tag{16}$$

Theorem 5. *For every $n \geq 4$ there is a suitable parameter set $p, q, \omega > 0$ that the characteristic polynomial $\chi_n(\lambda)$ has pure imaginary roots $\lambda = i\omega$ and the appropriate transversality condition is satisfied.*

Instability in an SEIRS model

In [5], the transmission dynamics of an $SEIRS$ model was investigated for an infectious disease with n infectious stages, given by the system

$$\begin{aligned} S' &= \pi + \theta R - \sum_{k=1}^{n} \frac{\beta_k I_k}{N} S - \mu_S S, \\ E' &= \sum_{k=1}^{n} \frac{\beta_k I_k}{N} S - \sigma_E E - \mu_E E, \\ I_1' &= \sigma_E E - \sigma_1 I_1 - \mu_1 I_1 - \delta_1 I_1, \\ I_j' &= \sigma_{j-1} I_{j-1} - \sigma_j I_j - \mu_j I_j - \delta_j I_j, \quad j = 2, 3, \ldots, n \\ R' &= \sigma_n I_n - \theta R - \mu_R R, \end{aligned} \tag{17}$$

where π is the recruitment rate of susceptible individuals into the population, θ is the rate of the loss of immunity among recovered individuals, β_k are the effective contact rates and

$\sigma_E, \sigma_{I_k},\ \mu_S, \mu_E, \mu_{I_k}, \mu_R, \delta_k$ $(k = 1, 2, \ldots, n)$ describe per capita rates of disease progression, natural death and disease-induced death, respectively. We assume that all these parameters are nonnegative. We denote by N the total population ($N = S+E+\sum_{k=1}^{n} I_k+R$), by E the compartment of exposed individuals, by I_j the compartment of infected individuals in disease stage j, and by R the compartment of recovered and immune individuals. By applying a similar method as in Theorem 5, we can show that the endemic equilibrium can be unstable. In [5], the authors claimed that the endemic equilibrium is always stable whenever exists, which we disprove.

Proposition 5. *There exist a parameter set for (17) such that the endemic equilibrium exists and it is unstable.*

Dynamics of a COVID-type model with symptom-based testing

To assess the effectiveness of indicator symptom based testing in controlling the spread of COVID-19, we developed a compartmental population model based on the general $SEIR$ formulation without vital dynamics. The equations read as

$$\begin{aligned}
S'(t) &= -\beta \frac{S(t)}{N(t)} \left(P(t) + I(t)\right), \\
L'(t) &= \beta \frac{S(t)}{N(t)} \left(P(t) + I(t)\right) - \alpha L(t), \\
P'(t) &= \alpha L(t) - \rho P(t), \\
I'(t) &= \rho P(t) - \gamma I(t) - k \frac{pI(t)}{pI(t) + \sigma}, \\
R'(t) &= \gamma I(t) + k \frac{pI(t)}{pI(t) + \sigma}.
\end{aligned} \tag{18}$$

The *force of infection* is the rate associated with the outward flow from S to L, namely,

$$\lambda = \beta \frac{1}{N}(P + I).$$

The indicator symptom-based testing is represented by the term

$$k \frac{pI}{pI + \sigma},$$

where k gives the number of tests done per unit time also referred to as the *testing rate*, the probability p describes how likely is that a member of compartment I displays the chosen indicator symptom. Note that this probability removes the need for an asymptomatic/mild compartment as it is straightforward to adjust p to account for all COVID-19 patients. The final term σ (possibly time-dependent) represents those individuals who are not infected

by COVID-19, yet they show the very same symptom we base our testing upon. In this chapter, we refer to σ as the *secondary symptom pool*, whereas, the *primary symptom pool* Σ is composed of all members (with or without COVID-19 infection) of the population displaying the indicator symptom at a given time, that is

$$\Sigma = pI + \sigma.$$

The testing rate k has a natural upper bound, namely,

$$k \leq \Sigma$$

as we solely test patients displaying the indicator symptom. By reformulating the testing term as

$$k\frac{pI}{pI+\sigma} = \frac{k}{\Sigma} \cdot p \cdot I,$$

it is interpreted as the removal of the $\frac{k}{\Sigma}$ fraction of COVID-19 patients displaying the indicator symptom.

The rate of the testing-induced outward flow from I to R is referred to as the *force of testing* given by

$$\tau_{k,p,\sigma} = k\frac{p}{pI+\sigma}. \tag{19}$$

Finally, we introduce the *positivity rate* of testing as

$$\theta = \frac{pI}{pI+\sigma}, \tag{20}$$

that may serve as a real-time indicator of the severity of an ongoing epidemic, and the adequateness of the testing rate. The basic reproduction number $\mathcal{R}_0 = \beta\left(\frac{1}{\rho}+\frac{1}{\gamma}\right)$ is obtained by the next generation matrix method. Similar key characteristics are the *control reproduction number* $\mathcal{R}_c$ and the *effective reproduction number* $\mathcal{R}_t$. The former describes the epidemic incorporating the effect of interventions, in our case indicator symptom-based testing, but still at the beginning of the outbreak. In contrast, the latter is suitable to measure the spread of the disease as the epidemic is progressing. The corresponding formulae may be obtained via analogous computations to those above as

$$\mathcal{R}_c = \beta\left(\frac{1}{\rho} + \frac{\sigma}{\sigma\gamma + kp}\right) \tag{21}$$

and

$$\mathcal{R}_t = \beta\,\frac{S(t)}{N}\left(\frac{1}{\rho} + \frac{1}{\gamma+\tau_{k,p,\sigma}}\right).$$

We analyzed the symptom-based testing strategy with emphasis on how the force of testing and the effective reproduction number are affected by the particular choice of strategy.

Proposition 6. *Given a fixed state of* (18)*, the force of testing* $\tau_{k,p,\sigma}$ *is*

a) monotonically increasing in k*,*

b) monotonically increasing in $\frac{k}{\Sigma}$.

Proposition 7. *The force of testing* $\tau_{k,p,\sigma}$ *is monotonically decreasing in* $\frac{\sigma}{p}$.

Proposition 8. *Given a fixed state of* (18)*, consider two secondary symptom pools,* $0 \leq \sigma_1 \leq \sigma_2$ *for the same indicator symptom that appears amongst members of the compartment* I *with probability* p*. Let* k_1 *and* k_2 *be two testing rates corresponding to the testing strategies for* σ_1 *and* σ_2*, respectively. Then,*

$$\frac{k_2}{k_1} = \frac{\sigma_2}{\sigma_1}$$

implies

$$\tau_{k_1,p,\sigma_1} \leq \tau_{k_2,p,\sigma_2}.$$

Proposition 9. *Let* $0 \leq k_1 \leq k_2$ *be two testing rates. Consider an epidemic described by* (18) *with daily testing rate* k*, and the associated effective reproduction number* $\mathcal{R}_t(k)$ *as a function of* k*. Then, the following inequality holds:*

$$\max\left\{\frac{k_1}{k_2}, \frac{\gamma}{\rho+\gamma}\right\} \leq \frac{\mathcal{R}_t(k_2)}{\mathcal{R}_t(k_1)} \leq 1.$$

The implications of Prop. 9 on goals for the testing strategy are rather important as they point out some hard limitations. For COVID-19 parameters, $0.43 \sim \frac{\gamma}{\rho+\gamma}$. As an example, if our current estimates for $\mathcal{R}_t$ are above 2.4, then we cannot expect the pure indicator symptom-based testing strategy (without contact-tracing) to be able to suppress the epidemic, no matter our testing capacity or indicator symptom, since $2.4 \cdot 0.43 > 1$. We have discussed from various aspects that increasing the testing rate k decreases the effective reproduction number $\mathcal{R}_t$, mitigating the severity of the epidemic. Nevertheless, this positive effect is gradually decreasing as described by the following Proposition.

Proposition 10. *The logarithmic derivative of* $\mathcal{R}_t$ *w.r.t. the testing rate* k*,*

$$\mathcal{R}_t^* = \frac{\partial}{\partial k}\log(\mathcal{R}_t),$$

is negative and monotonically increasing in k*.*

This relationship between θ and $I(t)$ carries a certain benefit for the authorities as the increase of the positivity rate precedes that of the epidemic curve, hence, it may serve as a primary indicator for the progress of an epidemic.

Adaptive group testing in a compartmental model of COVID-19

In this section, we develop a compartmental model to describe mass testing along with the application of various pooling methods and confinement of those tested positively. In the case of regular pooling, we select k individuals and perform a single RT-PCR test on their combined (pooled) samples. Even if the test comes back as positive, no additional tests are

performed to identify the infected individuals, instead of that, everybody in the pool will be confined. The delay differential equation system describing the dynamics (we start to test individuals at $t = 0$) can be written as

$$\begin{aligned}
S'(t) = & -\beta\frac{S(t)}{N(t)}\left(I(t)+P(t)\right)-\sigma\cdot\frac{S(t)}{N(t)}\cdot U(t)\\
& +\sigma\cdot\frac{S(t-\tau)}{N(t-\tau)}\cdot U(t-\tau)\cdot H(t-\tau),\\
L'(t) = & \beta\frac{S(t)}{N(t)}\left(I(t)+P(t)\right)-\alpha_{_L}L(t)-p\sigma\frac{L(t)}{N(t)},\\
P'(t) = & \alpha_{_L}L(t)-\alpha_{_P}P(t)-p\sigma\frac{P(t)}{N(t)},\\
I'(t) = & \alpha_{_P}P(t)-\gamma I(t)-p\sigma\frac{I(t)}{N(t)},\\
R'(t) = & \gamma I(t)-U(t)\sigma\frac{R(t)}{N(t)}\\
& +H(t-\tau)p\sigma\frac{L(t-\tau)+P(t-\tau)+I(t-\tau)}{N(t-\tau)}\\
& +H(t-\tau)\cdot U(t-\tau)\sigma\frac{R(t-\tau)}{N(t-\tau)},
\end{aligned}\tag{22}$$

where

$$H(t-\tau)=\begin{cases}0, & t<\tau,\\ 1, & t\geq\tau\end{cases}$$

is the Heaviside step function and

$$\begin{aligned}
U(t) &= \left[1-\left(\tfrac{S(t)+R(t)}{N(t)}\right)^{k-1}\right]\cdot p+\left(\tfrac{S(t)+R(t)}{N(t)}\right)^{k-1}\cdot\rho\\
&= \left[1-(1-\pi(t))^{k-1}\right]\cdot p+(1-\pi(t))^{k-1}\cdot\rho
\end{aligned}$$

is the expected number of individuals being isolated from the S or R compartment, where $\pi(t)=\frac{L(t)+P(t)+I(t)}{N(t)}$ stands for the disease prevalence. The parameter β is used for disease transmission rate, $\alpha_{_L}^{-1}$ denotes the average length of the latent period, $\alpha_{_P}^{-1}$ stands for the average time from becoming infectious until symptoms onset, while γ denotes recovery rate.

The above mentioned compartment $Q(t)$ is aggregated as

$$\begin{aligned}
Q'(t) = U(t)\cdot\sigma\frac{S(t)+R(t)}{N(t)} & -H(t-\tau)U(t-\tau)\sigma\frac{S(t-\tau)+R(t-\tau)}{N(t-\tau)}\\
& +p\sigma\frac{L(t)+P(t)+I(t)}{N(t)}-H(t-\tau)p\sigma\frac{L(t-\tau)+P(t-\tau)+I(t-\tau)}{N(t-\tau)}.
\end{aligned}$$

In the case of Dorfman pooling, we select k individuals and perform a single *RT-PCR* test on their combined (pooled) samples. If the pooled test yields a positive result, then

each sample is retested separately and we only remove those individuals who were retested as positive; otherwise, everyone is declared negative. The system describing the dynamics can be written as

$$\begin{aligned}
S'(t) =& -\beta\frac{S(t)}{N(t)}\left(I(t)+P(t)\right) - U(t)\cdot\sigma\frac{S(t)}{N(t)} + H(t-\tau)U(t-\tau)\sigma\frac{S(t-\tau)}{N(t-\tau)},\\
L'(t) =& \beta\frac{S(t)}{N(t)}\left(I(t)+P(t)\right) - \alpha_{_L}L(t) - p^2\sigma\frac{L(t)}{N(t)},\\
P'(t) =& \alpha_{_L}L(t) - \alpha_{_P}P(t) - p^2\sigma\frac{P(t)}{N(t)},\\
I'(t) =& \alpha_{_P}P(t) - \gamma I(t) - p^2\sigma\frac{I(t)}{N(t)},\\
R'(t) =& \gamma I(t) - U(t)\sigma\frac{R(t)}{N(t)} + H(t-\tau)p^2\sigma\frac{L(t-\tau)+P(t-\tau)+I(t-\tau)}{N(t-\tau)}\\
&+ H(t-\tau)\cdot U(t-\tau)\sigma\frac{R(t-\tau)}{N(t-\tau)},
\end{aligned} \tag{23}$$

where

$$U(t) = \left(\left[1-\left(\tfrac{S(t)+R(t)}{N(t)}\right)^{k-1}\right]\cdot p\cdot\rho + \left(\tfrac{S(t)+R(t)}{N(t)}\right)^{k-1}\cdot\rho^2\right).$$

The equation for the quarantine compartment $Q(t)$ is obtained as

$$\begin{aligned}
Q'(t) =& U(t)\cdot\sigma\frac{S(t)+R(t)}{N(t)} - H(t-\tau)U(t-\tau)\sigma\frac{S(t-\tau)+R(t-\tau)}{N(t-\tau)}\\
&+ p^2\sigma\frac{L(t)+P(t)+I(t)}{N(t)} - H(t-\tau)p^2\sigma\frac{L(t-\tau)+P(t-\tau)+I(t-\tau)}{N(t-\tau)}.
\end{aligned}$$

Theorem 6. *The following relation holds:*

$$\sigma = \frac{\mathcal{T}}{\frac{1}{k} + P\left(a\ pool\ is\ positive\right)} = \frac{\mathcal{T}}{\frac{1}{k} + \left(1-\left(1-\pi\right)^k\right)\cdot p + \left(1-\pi\right)^k\cdot\rho}. \tag{24}$$

To determine the optimal pool size k in order to maximize the denominator in (24), we differentiate $\frac{1}{k} + \left(1-\left(1-\pi\right)^k\right)\cdot p + \left(1-\pi\right)^k\cdot\rho$ w.r.t. k to obtain the extreme value rounded up to the nearest integer, depending on π, see Figure 1.

First we consider different pool size values k which we apply in (23) regardless of the prevalence, and a corresponding optimized σ according to (24). In the example, the daily testing capacity $\mathcal{T}$ is fixed to $100,000$ which is 1% of the total population. Figure 1 shows a comparison for these scenarios for different k values. We can see that choosing pool size $k=4$ is the best strategy, and considering $\Pi = 10,000,000$, 2% of the total population can avoid the infection simply by choosing another, more appropriate pool size.

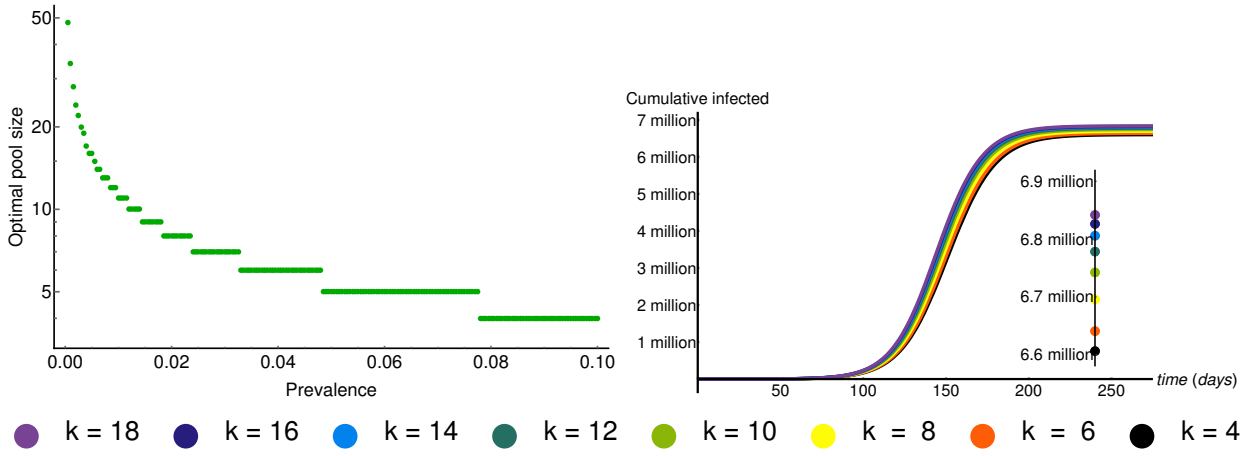

Figure 1: Optimal pool size as a function of disease prevalence (left) and epidemic curves of the cumulative infected with a fixed pool size during the course of the epidemic (right).

Finally, we consider a changing pool size $k(\pi(t))$ dependent on the disease prevalence. We state that choosing a large pool size and a corresponding σ at the early phase of the epidemic allows a widespread testing opportunity in the population. Sometimes this intervention is enough to prevent an outbreak. In the case of a higher reproduction rate, it becomes necessary to reduce the pool size when prevalence increases, but even in this case the adaptive strategy is capable to shift the peak and flatten the curve for a foreseeable time period.

Összefoglaló

A disszertáció célja, hogy fertőző betegségek terjedésének dinamikáját leíró matematikai modelleket állítson fel, valamint e modellek matematikai analízisét végezze el. Először az SIS járványterjedési modelleket tekintjük át, a legegyszerűbbtől kezdve az általánosított és továbbfejlesztett konstrukciókig.

Majd, egy több fertőző szakaszból álló $SI_1I_2 \dots I_nS$ modellt vizsgálunk. Fő eredményünk, hogy ha a fertőző I osztályt $n = 1, 2$ vagy 3 szakaszra osztjuk, a paraméterek választásától függetlenül az endemikus egyensúly mindig stabil, amikor létezik. Viszont, $n \geq 4$ fertőző szakasz esetén minden n-re választhatók a paraméterek úgy, hogy az endemikus egyensúly stabil legyen, de ugyanolyan n-re létezik olyan paraméterválasztás is, hogy az endemikus egyensúly instabil legyen.

Ezután a COVID-19 indikátortünet-alapú tesztelésének hatásait vizsgáljuk. A k tesztelési ráta növelésének előnyeit mutatjuk be. Az indikátortünet megfelelő megválasztása is nagy jelentőséggel bír, megmutatjuk, hogy ehhez nem csak a p prevalenciát kell figyelembe venni, hanem az ún. *másodlagos tünetesek* csoportjának méretét és szezonalitását. Szimulációink megmutatják, hogy az indikátortünet-alapú tesztelés önmagában nem alkalmas egy járványkitörés megelőzésére, pusztán a járvány csúcsának mérsékelt késleltetésére és a terjedés csillapítására.

Végül, tömeges tesztelési eljárások modellezését mutatjuk be. Kétféle ún. *pooling* tesztelés-sel is foglalkozunk, bemutatjuk e tesztelés reguláris, illetve Dorfman-féle variációját. Megmutatjuk, hogy Dorfman-féle tesztelésnél, optimalizált csoportméretet választva, jelentős számú megbetegedést és elhalálozást akadályozhatunk meg. Továbbá rámutatunk, hogy adaptív módszerrel, a prevalenciától függő, optimalizált csoportméretet használva a járvány terjedése még jobban csillapítható.

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