A structural epidemiological model for the optimal allocation of vaccines across countries

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Abstract

Description

Keywords: ...

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1 Introduction

... describe general SIR model, say that for biologists to remark compartmenst are different to biological compartments, thesis serves for both: epidemiologists inetrested in vaccine distribution but also for economcists or social scientists interested in compartment modleing

How it's currently done:

countries can decide to not take vaccine -> would be in our case assignment of zero vaccines

general model description: how do we deal with vaccines (most important), vaccination during infection, no vaccination during infection see here (US Center for Disease Control), no reinfections, no births and other deaths

2 Deterministic Model

We subdivide the classic SIRD compartments, Susceptible (S), Infectious (I), Recovered (R) and Deceased (D), with sub-compartments allowing for heterogeneous areas of residence and vaccination states as well as infections by different virus types. Individuals either live in area A or area B. They are non-vaccinated v_0, vaccinated with vaccine one v_1 or vaccinated with vaccine two v_2. We introduce two virus types. A wild type w that serves as baseline variant and a more infectious mutant m variant. To describe our model we follow the notation in

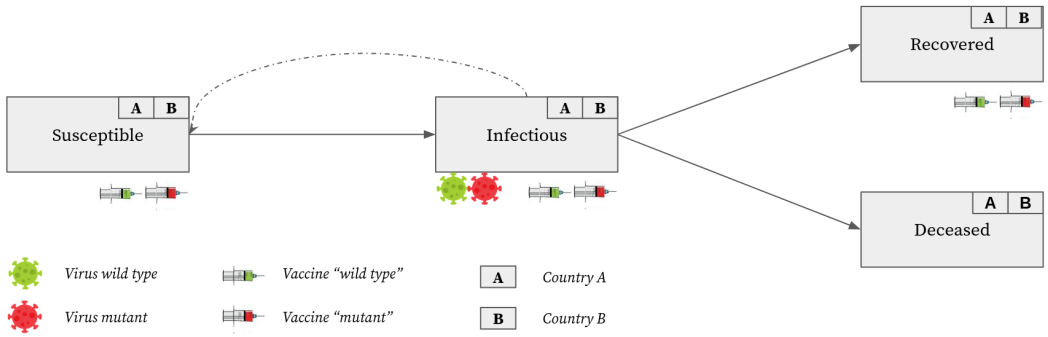

Figure 1: Compartments

Waites et al. (2021) and denote every sub-group of individuals by a set $\mathcal{C}_t(F_n)$, where F_n is a placeholder for features of individuals the set $\mathcal{C}_t$ is representing and t denotes the time at which the set is evaluated. We illustrate this in the following by examples. Let X_i for $i \in \{S, I, R, D\}$ indicate to which general compartment an individual belongs, then, $\mathcal{C}_t(X_S)$ is the set of all susceptible individuals and $\mathcal{C}_t(X_I)$ is the set of all infectious individuals in t. If we want to distinguish not only between general compartments but additionally between countries of residence, we use the feature C_j for $j \in \{A, B\}$ to indicate that the country of residence is j. $\mathcal{C}_t(X_S, C_A)$ is the set of all susceptible individuals of country A and $\mathcal{C}_t(X_S, C_B)$

of country B. Note that the ordinary set operators apply, allowing us to us linkages such as $\mathcal{C}_t(X_S, C_A) \cup \mathcal{C}_t(X_S, C_B) = \mathcal{C}_t(x_S)$ or $\mathcal{C}_t(X_S) \cap \mathcal{C}_t(X_I) = \emptyset$. The negation operator $\neg$ is used to indicate that a certain feature applies for all but the specified compartment, e.g. $\mathcal{C}_t(\neg X_D)$ is the set of all alive individuals. The cardinality $|\cdot|$ represents the respective number of individuals in a set, e.g. $|\mathcal{C}_t(X_S)|$ equals the number of all susceptible individuals. To shorthand notation, we define $y_t(F_n) = |\mathcal{C}_t(F_n)|$ as the number of individuals in the compartment addressed by (F_n).
By definition $\mathcal{C}_t() = \cup_{i\in\{S,I,R,D\}}\mathcal{C}_t(X_i)$ is the set of all individuals. An overview of all features is given in Table 1.

Table 1: Notation

Feature	Code	Indices	Explanaition
General compartment	X_i	$i \in \{S, I, R, D\}$	Individuals can either be Susceptible (S), Infectious (I), Recovered (R) or Deceasesd (D).
Country of residence	C_j	$j \in \{A, B\}$	Individuals can either live in country A or B. We exclude cross-border movements.
Virus Type	V_k	$k \in \{W, M\}$	An infection can either be caused by the wild type (W) or the mutant (M) virus. This feature has to be understood as *is* or *has been* infected with type k.
Vaccine Type	U_l	$l \in \{0, 1, 2\}$	An individual can either be vaccinated with vaccine 1 or 2 or being unvaccinated (0).
Placeholder	F_n	$n \in \mathbb{N}$	A placeholder that is used to address an arbitrary combination of features. $\mathcal{C}_t(F_n)$ should be read as the set of a fixed but arbitrary compartment. If we need to distinguish between two arbitrary compartments, we use F_1 and F_2.

We do not incorporate reinfections. Thus, a susceptible individual cannot be associated with any virus type and therefore $\mathcal{C}_t(X_S, V_k) = \emptyset$ for all $k \in W, M$. Moreover, we impose a set of assumptions to our model.

Assumption 1. *For all $t, r \in \mathbb{R}_+$ and $s \in [-t, \infty)$ let*

$$\mathcal{C}_t(X_I, V_k) \cap \mathcal{C}_{t+r}(X_S) = \emptyset \tag{1.1}$$

$$\mathcal{C}_t(U_1) \cap \mathcal{C}_{t+s}(U_2) = \emptyset \tag{1.2}$$

$$\mathcal{C}_t(C_A) \cap \mathcal{C}_{t+s}(C_B) = \emptyset \tag{1.3}$$

Assumption 1.1 rules out reinfections. An individual that has been infected once cannot become reinfected after it had recovered. According to recent studies **cite paper** this is not true for COVID-19. However, the number of reinfected individuals is negligible and we therefore do not incorporate reinfections to keep our model parsimonious. Assumption 1.2 implies that an individual only receives one type of vaccine. Receiving one vaccination

shot in our model implies that an individual is fully protected according to the vaccine properties making it unrealistic to assign a second shot to this individual. Assumption 1.3 rules out permanent cross-country movements of individuals. According to **cite how many individuals move from one to another country** the number is negligible. We therefore decided to leave out permanent changes of residence. However, we incorporate cross-border infections via meeting rates within the mass actions.

2.1 System of ordinary differential equations

Since we use a compartment SIRD model based on a system of ordinary differential equations (ODEs) and to make this thesis self-contained, we review how the dynamics of a chemical reaction network are modeled over time. We can limit ourselves to the case of irreversible reactions since recovered and deceased individuals cannot become infectious again and infectious individuals become recovered but not susceptible. Let $\mathcal{C}_t(F_1), \ldots, \mathcal{C}_t(F_n)$ be n disjoint sets. Every irreversible reaction R_j, for $j = 1, \ldots, m$, can be expressed as

$$\nu_{1j} y_t(F_1) + \ldots + \nu_{nj} y_t(F_n) \longrightarrow \mu_{1j} y_t(F_1) + \ldots + \mu_{nj} y_t(F_n), \tag{1}$$

where $\nu_{ij} \in \mathbb{N}_0$ and $\mu_{ij} \in \mathbb{N}_0$ are called stoichiometric coefficients. They describe how much of species $\mathcal{C}_t(F_i)$ is consumed ν_{ij} and produced μ_{ij} within reaction R_j. T difference $\mu_{ij} - \nu_{ij}$ is the total change of $y_t(F_i)$ due to one reaction R_j. In terms of our model we are not only interested in how one reaction (e.g. an infection, a vaccination, etc.) influences the state of the system but rather how often this happens within an interval $[t, t+\tau]$, for $\tau \in \mathbb{R}_+$. For $\tau = 1$ the latter is described according to the law of mass action by

$$v_j = r_j \prod_{i=1}^{n} y_t(F_i)^{\mu_{ij}}, \tag{2}$$

where r_j is a reaction specific constant. The product is the number of combinations to assign individuals from different compartments, that have $\mu_{ij} \neq 0$, together. The change in the magnitude of $y_t(F_i)$, taking into account all m reactions, is given by

$$y_{t+\tau}(F_i) - y_t(F_i) = \sum_{j=1}^{m} (\mu_{ij} - \nu_{ij}) v_j \tau. \tag{3}$$

$(\mu_{ij} - \nu_{ij})$ is, as outlined above, the stoichiometry that specifies how one reaction influences the system, $v_j\tau$ is the number of times reaction R_j happens within the interval $[t, t+\tau]$, and therefore the product is the influence of R_j on $y_t(F_i)$ during this interval. Summed over all reactions yields the change of $y_t(F_i)$ in the system. We divide both sides of (3) by τ, let

$\tau \to 0$ and plug in (2) to obtain the ordinary differential equation (ODE)

$$\dot{y}_t(F_i) = \sum_{j=1}^{m} \left[(\mu_{ij} - \nu_{ij}) r_j \prod_{i=1}^{n} y_t(F_i)^{\mu_{ij}} \right]. \tag{4}$$

We write down the equations for all compartments in matrix form, determining a system of ODEs, which we will use in subsequent chapters.

$$\underbrace{\begin{pmatrix} \dot{y}_t(F_1) \\ \vdots \\ \dot{y}_t(F_n) \end{pmatrix}}_{Y(t)} = \underbrace{\begin{pmatrix} \mu_{11} - \nu_{11} & \dots & \mu_{1m} - \nu_{1m} \\ \vdots & \vdots & \vdots \\ \mu_{n1} - \nu_{n1} & \dots & \mu_{nm} - \nu_{nm} \end{pmatrix}}_{\mathbf{S}} \cdot \underbrace{\begin{pmatrix} v_1 \\ \vdots \\ v_m \end{pmatrix}}_{v} \tag{5}$$

Note that (5) is a linear mapping v for which we can compute the kernel $\mathcal{K} = \{v \in \mathbb{R}^m | \mathbf{S} \cdot v = 0 \in \mathbb{R}^n\}$. Each element of the kernel represents a state where $Y(t) = 0$ and therefore the system is in a steady- state. If the pandemic reaches a state such that $v \in \mathcal{K}$, we would be stuck there. **write how the null space looks like in our model**

Since our model consists of over 100 reactions, we do not write down the ODE system explicitly. However, it can be constructed as stated in this section.

2.2 Reactions

We divide the reactions in three groups: Infections, Recoveries and Deaths, Vaccinations. We group recoveries and deaths together, since they have the same structure. To define a reaction, we must specify the reactants, products, their stoichiometric coefficients and the reaction constants. For each reaction group we first state the general reactions, defining the reactants, products and stoichiometric coefficients, build intuition for it, subsequently specify the reaction constant, and state the reactions explicitly.

2.2.1 Infections

Every infection happens between an infectious individual $i_1 \in \mathcal{C}_t(x_I)$ and a susceptible individual $i_2 \in \mathcal{C}_t(x_S)$ and leads to two infectious individuals. Hence, the general form of the infection reactions is

$$y_t(x_I, F_1) + y_t(x_S, F_2) \longrightarrow y_t(X_I, F_1) + y_t(X_I, F_2), \tag{6}$$

where we use F_1, F_2 to indicate that the reactions differ with respect to not explicitly mentioned features, e.g. vaccinated individuals have a lower risk of becoming infected or trans-

mitting the virus, the mutant virus is more infectious, and cross-border infections are scaled by a factor to make them comparatively rare events. The additional features represented by F_1 and F_2 are incorporated within the reaction constants

$$\text{infection constant} = \text{contacts} \times \text{infectiousness} \times \text{vaccine modifier}$$

In the following we elaborate on how to define each component of the infection constants.

Infectiousness. Let $c \in R_+$ be the average number of contacts per individual and day and $\alpha \in [0, 1]$ be the proportion of susceptible individuals that become infected if they meet a wild type infected individual without any vaccination of both individuals. Let $\eta \in (1, 1/\alpha]$ be the factor with which the mutant is more infectious than the wild type. Then $\beta = \alpha c$ is the average number of individuals infected per day by i_1 if $i_1 \in \mathcal{C}_t(X_I, V_w, U_0)$. If $i_1 \in \mathcal{C}_t(X_I, V_M, U_0)$ the average infected number increases to $\eta\beta$.

Vaccine modifier. To account for the influence of vaccines on vaccinated susceptible individuals, we introduce the parameters $\delta_{k,l} \in [0, 1]$, where $k \in \{W, M\}$ indicates the virus type and $l \in \{1, 2\}$ the vaccine type. If $i_2 \in \mathcal{C}_t(X_S, U_l)$ for all individuals that $i_1 \in \mathcal{C}_t(X_I, V_k)$ meets, the infection rate is multiplied by $1 - \delta_{k,l}$, and thus the reaction constant in the respective reaction. Hence, $\delta_{k,l}$ is interpreted as reduce in the probability of becoming infected while meeting an infectious individual.

Moreover, vaccinated individuals have a lower probability of transmitting the virus (**Quelle**). We account for this by introducing the parameter $\gamma \in [0, 1]$ and multiplying the average number of infected individuals by $(1 - \gamma)$ if $i_1 \in \mathcal{C}_t(X_I, U_1) \cup \mathcal{C}_t(X_I, U_2)$. γ is the reduction in the probability of not transmitting the virus after being vaccinated. We assume that γ is constant over time and across vaccines (**Quelle**).

Contacts. We want to distinguish between how many of the average contacts per day c are within individuals from the same country and how many are within individuals from another country. We do so by defining probabilities that given a meeting occurs, it is with an individual from another country and multiply c with the respective probability to obtain the average number individuals infected by one individual in a certain country. We use the relative population number of a country as baseline probability and add a penalty term for cross-border meetings.

In the following we establish how we specify all probabilities. We first define the (time dependent) probability that a randomly drawn living individual i_2 lives in country B

$$\mathbb{P}_t\left(i_2 \in \mathcal{C}_t(\neg X_D, C_B)\right) = y_t(\neg X_D, C_B)/y_t(\neg x_D). \tag{7}$$

The probability depends on the state of the whole system $Y(t)$. To increase readability we omit conditioning on $Y(t)$ and directly define $\mathbb{P}_t$ to be conditioned on the state of the system $Y(t)$. Second, we define the conditional probability that given i_1 is from country A, i_2 is from country B by adding a multiplicative penalty term $b(\cdot)$ reducing the probability of meeting individuals from other countries

$$\mathbb{P}_t(i_2 \in \mathcal{C}_t(\neg X_D, C_B) | i_1 \in \mathcal{C}_t(\neg X_D, C_A)) = \mathbb{P}_t\left(i_2 \in \mathcal{C}_t(\neg X_D, C_B)\right) \cdot b(d(A,B)),$$

where $d(A,B)$ is a distance between country A and country B and $b : \mathbb{R}_+ \to [0,1]$ is a function that maps the distance to the penalty value. By mapping the distance into the unit interval, we allow the probability of a cross-border meeting to be maximally as high as the relative population size. The distance can be interpreted as geographical distance. However, it could also serve to incorporate other factors, like favored holiday destinations, that encourage or discourage cross-border meetings. We impose three conditions on the function b

$$\lim_{b \to \infty} = 0 \tag{B.1}$$

$$b(0) = 1 \tag{B.2}$$

$$b(d_1) < b(d_2) \quad \text{if } d_1 > d_2. \tag{B.3}$$

Condition $(B.1)$ ensures that countries that a very large distance only have small influences onto each other, $(B.2)$ defines a rather theoretical case where cross-border meetings are as likely as within-country meetings, and $(B.3)$ ensures that countries that have a greater distance have a smaller influence on each other. We define all possible conditional meeting probabilities depending on the countries of residence analogously. To increase readability when we define the reaction rates explicitly below, we collect them in a matrix $\mathbf{M} \in \mathbb{R}^{2\times 2}$, such that we can address them via m_{j_1,j_2} for $j_1, j_2 \in \{A, B\}$

$$\begin{aligned}
\mathbf{M} &= \begin{pmatrix} m_{A,A} & m_{A,B} \\ m_{B,A} & m_{B,B} \end{pmatrix} \\
&= \begin{pmatrix} \mathbb{P}(i_1 \in \mathcal{C}_t(\neg X_D, C_A) | i_1 \in \mathcal{C}_t(\neg X_D, C_A)) & \mathbb{P}(i_1 \in \mathcal{C}_t(\neg X_D, C_A) | i_2 \in \mathcal{C}_t(\neg X_D, C_B)) \\ \mathbb{P}(i_2 \in \mathcal{C}_t(\neg X_D, C_B) | i_1 \in \mathcal{C}_t(\neg X_D, C_A)) & \mathbb{P}(i_2 \in \mathcal{C}_t(\neg X_D, C_B) | i_2 \in \mathcal{C}_t(\neg X_D, C_B)) \end{pmatrix} \\
&= \begin{pmatrix} 1 - y_t(\neg X_D, C_B)/y_t(\neg X_D) & y_t(\neg X_D, C_A)/y_t(\neg X_D) \\ y_t(\neg X_D, C_B)/y_t(\neg X_D) & 1 - y_t(\neg X_D, c_A)/y_t(\neg X_D) \end{pmatrix} \cdot b\left(\mathrm{d}(a_1, a_2)\right).
\end{aligned} \tag{8}$$

Since we are interested in specifying an infection reaction for each compartment, we show subsequent how we define the average numebr of contacts for concrete F_1 and F_2 from (6). We set $i_2 \in \mathcal{C}_t(X_S, C_B, U_0)$ and $i_1 \in \mathcal{C}_t(X_I, V_W, C_A, U_0)$. We need conditional probability $\mathbb{P}_t(i_2 \in \mathcal{C}_t(X_S, X_B, U_0) | i_1 \in \mathcal{C}_t(X_I, V_W, C_A, u_0))$. This to say, the probability that

the individual that can be infected (i_2) is susceptible, unvaccinated and from area two given that individual i_1 is infected with the wild type, unvaccinated and from area one. We facilitate our model and assume that the vaccination status as well as the type of virus infection of individual i_1 are independent of the features of i_2. Assuming independence of the vaccination status implies that an unvaccinated individual i_1 does not change her contact habits, given a certain number of meetings, compared to her counterfactual vaccinated self. Note that this does not mean that we assume that vaccinated and unvaccinated individuals have the same average number of contacts since the probabilities are defined on *conditioned a meeting occurs*. Differences in the average number of contacts between vaccinated and unvaccinated individuals can be incorporated implicitly via the vaccination parameter $\delta_{k,l}$.

Furthermore, we assume that the probability is dependend on whether an individual is alive but not on the exact general compartment S, I or R. Making use these assumptions, we can omit conditioning on V_w and U_0 and change X_I to $\neg X_D$ such that the exercise facilitates to defining $\mathbb{P}_t(i_2 \in \mathcal{C}_t(X_S, C_B, U_0) | i_1 \in \mathcal{C}_t(\neg X_D, C_A))$. Using Bayes' formula we can rewrite this as

$$\begin{aligned}
\mathbb{P}_t(i_2 \in \mathcal{C}_t(X_S, C_B, U_0) | i_1 \in \mathcal{C}_t(\neg X_D, C_A)) &= \mathbb{P}_t(i_2 \in \mathcal{C}_t(\neg X_D, C_B) | i_1 \in \mathcal{C}_t(\neg X_D, C_A)) \\
&\quad \cdot \mathbb{P}_t(i_2 \in \mathcal{C}_t(X_S, U_0) | i_1 \in \mathcal{C}_t(\neg X_D, C_A), i_2 \in \mathcal{C}_t(\neg X_D, C_B)) \\
&= \mathbb{P}_t(i_2 \in \mathcal{C}_t(\neg X_D, C_B) | i_1 \in \mathcal{C}_t(\neg X_D, C_A)) \\
&\quad \cdot \mathbb{P}_t(i_2 \in \mathcal{C}_t(X_S, V_0) | i_2 \in \mathcal{C}_t(\neg X_D, C_B)) \\
&= \mathbb{P}_t(i_2 \in \mathcal{C}_t(\neg X_D, C_B) | i_1 \in \mathcal{C}_t(\neg X_D, C_A)) \\
&\quad \cdot \mathbb{P}_t(i_2 \in \mathcal{C}_t(X_S, C_B, V_0)) \qquad (9)
\end{aligned}$$

The conditional probability is therefore the product of the probability that i_2 is from country B given that i_1 is from country A and the probability that i_2 is a susceptible, unvaccinated individual from country B. Using equations (8) and (9) we obtain

$$\mathbb{P}_t(i_2 \in \mathcal{C}_t(X_S, C_B, U_0) | i_1 \in \mathcal{C}_t(X_I, V_W, C_A, U_0)) = m_{B,A} \cdot y_t(X_S, C_B, U_0) / y_t(\neg X_D, C_B). \quad (10)$$

Explicit reactions. With the derived probabilities we are able to specify the compartment specific infection constants. We illustrate this by two examples.

The first example deals with the compartments $\mathcal{C}_t(X_I, C_A, V_W, U_0)$ and $\mathcal{C}_t(X_S, C_B, U_0)$. The corresponding reaction is

$$y_t(X_I, C_A, V_W, U_0) + y_t(X_S, C_B, U_0) \xrightarrow{r_{j_1}} y_t(X_I, C_A, V_W, U_0) + y_t(X_I, C_B, V_W, U_0), \qquad (11)$$

where r_j denotes the reaction rate. By assumption, every individual $i_1 \in \mathcal{C}_t(X_I, C_A, V_W, U_0)$ has on average c contacts per day. Equation (10) defines the fraction of contacts which are

between the two compartments of interest. Since both compartments are non-vaccinated compartments and $i_1 \in \mathcal{C}_t(V_W)$ the fraction of infectious contacts is α. Thus, i_1 infects on average $\beta m_{B,A} \cdot y_t(X_S, C_B, V_0)/y_t(\neg X_D, C_B)$ susceptible, unvaccinated individuals from country B. Both individuals are non-vaccinated and therefore the vaccine modifier is simply one. The respective infection constant is given by

$$r_{j_1} = \frac{\beta \cdot m_{B,A}}{y_t(\neg X_D, C_B)} \tag{12}$$

For the second example, we consider vaccinated and mutant infected compartments $\mathcal{C}_t(X_I, C_A, V_M, U_1)$ and $\mathcal{C}_t(X_S, C_B, U_2)$ to showcase the influence of the vaccine and the mutant modifier.

$$y_t(X_I, C_A, V_M, U_1) + y_t(X_S, C_B, U_2) \xrightarrow{r_{j_2}} y_t(X_I, C_A, V_M, U_1) + y_t(X_I, C_B, V_M, U_2). \tag{13}$$

We derive the infection constant analogously to the previous example. Using the vaccine modifiers γ, $\delta_{M,2}$ and the increase in infectiousness of the mutant η

$$r_{j_2} = \frac{(1-\delta_{M,2})(1-\gamma)\eta\beta \cdot m_{B,A}}{y_t(\neg x_D, c_B)}. \tag{14}$$

Technically we multiply α by $(1-\delta_{M,2})(1-\gamma)$ to reduce the degree of infectiousness accounting for vaccinations and increase it by multiplying it by η, to account for the more infectious mutant. To ensure readability we refrain from writing down all exact infection rules. They are defined for all possible combinations of features F_1 and F_2. Their infection constants can be derived analogously to what we have showcased.

2.2.2 Infectious to Recovered/Deceased

The transition from the infectious state to the recovered or deceased state is independent of any other compartments. The general reactions are

$$\begin{aligned} \mathcal{C}_t(X_I, F_1) &\longrightarrow \mathcal{C}_t(X_D, F_1) \\ \mathcal{C}_t(X_I, F_2) &\longrightarrow \mathcal{C}_t(X_R, F_2). \end{aligned} \tag{15}$$

Defining the reaction constants, depends on the state of the product, deceased or recovered and on the vaccination status, since vaccinated individuals have a much lower probability of having severe course of disease **Quelle**.

For $\lambda \in \mathbb{R}_+$ we assume that on average an individual stays $1/\lambda$ days in the infectious state before it transmits either to the recovered or the deceased state. Thus, on average λ individuals transmit out of each infectious compartment every day. We assume that a fraction

$p \in [0,1]$ of unvaccinated individuals transmits to the deceased state and $(1-p)$ to the recovered state. Note that the assumption that deceasing and recovering individuals might not hold in reality, since recovering individuals might not be infectious as long as deceasing individuals. However, incorporating this would raise the need for more compartments. Since we allow for vaccination of recovered and infectious individuals, this should not influence the vaccinationr ate anyways. We therefore we assume that the influence on our model results are negligible.

p can be interpreted as the probability of dying after becoming infected. Note that p does not depend on the virus type. The virus type therefore only influences the number of infections but not the probability of dying for infected individuals. **realistisch? Quelle** The explicit reactions for unvaccinated individuals are for $i \in \{A,B\}$ and $k \in \{W,M\}$

$$\begin{aligned} \mathcal{C}_t(X_I, C_j, V_W, U_0) &\xrightarrow{p\lambda} \mathcal{C}_t(X_D, C_j, V_w, U_0) \\ \mathcal{C}_t(X_I, C_j, V_w, U_0) &\xrightarrow{(1-p)\lambda} \mathcal{C}_t(X_R, C_j, V_w, U_0) \end{aligned} \tag{16}$$

We introduce the parameters $\omega_{k,l} \in [0,1]$, for $k \in \{W,M\}$ and $l \in \{1,2\}$, to account for the reduce in the probability of dying after being vaccinated. We use $p\omega_{k,l}$ as new probability of dying due to being infected with virus k after being vaccinated with vaccine l.$\omega_{k,l}$ is thus the reduction in the probability of dying. The corresponding reactions for vaccinated individuals are for $i \in \{A,B\}, k \in \{W,M\}$ and $l \in \{1,2\}$

$$\begin{aligned} \mathcal{C}_t(X_I, C_j, V_k, U_l) &\xrightarrow{p\omega_{k,l}\lambda} \mathcal{C}_t(X_D, C_j, V_k, U_l) \\ \mathcal{C}_t(X_I, C_j, V_k, U_l) &\xrightarrow{(1-p\omega_{k,l})\lambda} \mathcal{C}_t(X_R, C_j, V_k, U_l) \end{aligned} \tag{17}$$

2.2.3 Vaccination

The general setting of vaccination reactions is the same as for recoveries and deaths in (15). Besides susceptible individuals, we allow for vaccinations of infectious and recovered individuals as well. We do the former to account for vaccinations of asymptomatic individuals (**cite 30%**) and the latter to account for vaccination shots that are assigned to recovered individuals. **cite why recovered are vaccinated**. Let $\phi_{t,l,j} \in \mathbb{R}_+$ be the vaccination constant of vaccine l in country j at time t. The vaccination constant of one vaccine is assumed to be equal for all vaccination subcompartments of S, I, R within one country, which is to say, that the decision of vaccinating an individual is independent whether it is susceptible, infectious or recovered. The corresponding reactions are $j \in \{A,B\}$, $k \in \{W,M\}$

and $l \in \{1, 2\}$

$$\begin{aligned} \mathcal{C}_t(X_S, C_j, U_0) &\xrightarrow{\phi_{t,l,j}} \mathcal{C}_t(X_S, C_j, U_l) \\ \mathcal{C}_t(X_I, C_j, V_k, U_0) &\xrightarrow{\phi_{t,l,j}} \mathcal{C}_t(X_I, C_j, V_k, U_l) \\ \mathcal{C}_t(X_R, C_j, V_k, U_0) &\xrightarrow{\phi_{t,l,j}} \mathcal{C}_t(X_R, C_j, V_k, U_l). \end{aligned} \tag{18}$$

We explain in greater detail how the vaccination constant is derived in Chapter 3.

3 Optimal vaccine allocation

We denote the number of vaccination shots of type U_l available at time t in country j by $W_{l,j}(t)$ and the total number number of vaccine l by $W_l(t) = W_{l,A}(t) + W_{l,B}(t)$. $W_{l,j}(t)$ is fully exogenous in our model and based on the true number of COVID-19 vaccine doses allocated to Germany. **In contrast to other models this is exogenous** We assume that all doses of vaccines are immediately vaccinated. Thus, it must hold that

$$W_{l,j}(t) = \phi_{t,l,j} \cdot y_t(\neg X_D, C_j, U_0). \tag{19}$$

Which is to say that the total number of vaccine l at t must equal the number of individuals vaccinated with l at t. As opposed to other models (**cite**), we do not directly optimize the vaccination rates but rather the fraction of vaccines that are allocated to a certain country. Let $f_l(\theta_l; t)$, with $f_l : \mathbb{R}^z \times [0, \tau] \to [0, 1]$, be the function that defines the fraction of vaccine l allocated to country A. The fraction depends on the time t and a parameter vector $\theta_l \in \mathbb{R}^z$ that defines the form of $f_l(\theta_l; t)$. The fractions enter the model through the vaccination rates. The total number of doses of vaccine l assigned to country j equals the total number of doses times the fraction of vaccine l allocated to country j $W_{l,A}(t) = f_l(\theta_l; t) W_l(t)$ and $W_{l,B}(t) = [1 - f_l(\theta_l; t)] W_l(t)$. Combining this with Equation (19) yields for the vaccination rates

$$\begin{aligned} \phi_{l,A} &= \frac{f_l(\theta_l; t) W_l(t)}{y_t(\neg X_D, C_A, U_0)} \\ \phi_{l,B} &= \frac{[1 - f_l(\theta_l; t)] W_l(t)}{y_t(\neg X_D, C_B, U_0)}. \end{aligned}$$

Given a specific functional form of f_l, choosing a specific $\bar{\theta}_l \in \mathbb{R}^z$ is called a *strategy* for vaccine l. A *vaccination strategy* $\bar{\Theta} = \begin{pmatrix} \bar{\theta}_1 \\ \bar{\theta}_2 \end{pmatrix}$ is a collection of strategies defined for both vaccines l.

If $\bar{\Theta}$ is the solution to the minimization problem

$$
\begin{aligned}
&\underset{\Theta \in \mathbb{R}^{2z}}{\arg\min} && y_t(X_D) \\
&\text{subject to} && \nu_{l,A} = \frac{f_l(\theta_l;t)W_l(t)}{y_t(\neg X_D, C_A, U_0)} && \text{for } l \in \{1,2\}, && \text{(C.1)} \\
& && \nu_{l,B} = \frac{[1-f_l(\theta_l;t)]\,W_l(t)}{y_t(\neg X_D, C_B, U_0)} && \text{for } l \in \{1,2\}, && \text{(C.2)} \\
& && W_l(t) = w_l(t) && \text{for } l \in \{1,2\}, && \text{(C.3)} \\
& && Y(0) = Y_0, && && \text{(C.4)} \\
& && \Theta = \begin{pmatrix} \theta_1 \\ \theta_2 \end{pmatrix}, && && \text{(C.5)} \\
& && \beta, \eta, \gamma, \delta_{k,l}, \omega_{k,l}, \mathbf{M} && && \text{(C.6)}
\end{aligned}
$$

we call it *optimal vaccination strategy* with respect to the given minimization problem. The given problem is specified through the vaccination rates $(C.1)/(C.2)$, the exogenous inflow of vaccines $(C.3)$, the initial conditions of the ODE system $(C.4)$, and the fixed parameters introduced in Chapter 2 $(C.6)$. Note that our objective is the total number of deceased individuals. Other objectives, like the total number of infectious individuals or some combination of both, could be considered as well. We decided to choose the total number of deaths such that the death protection parameters $\omega_{k,l}$ influence the solution. **Quelle vaccine gegen schwere erkrankungen**. However, we include sensitivity checks using the total number of infectious individuals as objective function.

In this paper we examine three different functional forms of f_l. Each form is parameterized via θ_l. 1) f_l is a stepwise function, 2) f_l is a logistically transformed third order spline function, and 3) f_l is a neural network. To define the functional forms, we subdivide the interval $[0, \tau]$ into a partition $0 = t_0 < t_1 < \cdots < t_z = \tau$. Let $T_i = [t_{i-1}, t_i)$, for $i = 1, \ldots, z$, be the corresponding intervals of the tagged partition. We label T_i as the i-th decision period.

Stepwise. The functional form of f_l is a stepwise function. In this world, policy makers determine a fraction that is allocated to country A for a fixed decision period T_i, evaluate, and then adjust before the next decision period T_{i+1} begins. We subdivide $\theta_l = \begin{pmatrix} \theta_{l,1} & \theta_{l,2} & \ldots & \theta_{l,z} \end{pmatrix}'$ such that $\theta_{l,i} \in [0,1]$ is the fraction of vaccine l that is assigned to country A if $t \in T_i$. The resulting stepwise functions are determined by

$$f_l(t) = \theta_{l,i} \quad \forall t \in T_i$$

In 2 we show an exemplary vaccination strategy for vaccine l. Note that the COVID-19

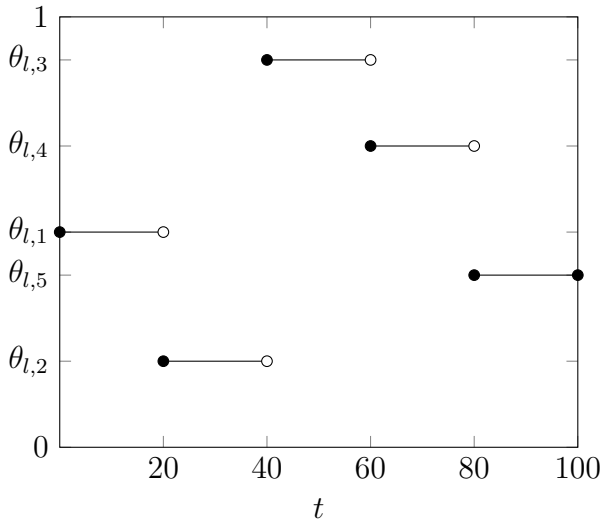

Figure 2: Example for a stepwise vaccination strategy of vaccine l

vaccine allocation is a special case of a step function, where $\theta_{l;1} = \theta_{l,2} = \ldots = \theta_{l,z} = y_0(\neg X_D, C_l)/y_0(\neg X_D)$, assuming that the allocations are not adjusted for small changes in the population sizes over the course of the pandemic.

Splines. Policy makers decide on a flexible fraction, which is depending on t, assigned to each country. By using polynomials, rather than constant functions in the stepwise approach, we allow for more complex policy decisions within one decision period T_i. However, one should note that this exercise is rather theoretical and aims to show what strategies could be achieved theoretically. Figure **??** shows an exemplary spline and how it is shrinked into the unit interval via the logistic function.

f_l follows a spline $S(t)$ of order three that is transformed via the logistic function $\sigma(x)$ to obtain values between zero and one.

$$f_l(\theta; t) = \frac{1}{1 + \exp\left(-P_{l,i}(t)\right)} \quad \forall t \in T_i. \tag{21}$$

$P_{l,i}(t) \in \mathbb{R}_3(t)$ is a polynomial from the third order polynomial ring over the real numbers. We chose $P_{l,i}(t)$ to be in cubic hermite form, such that we can parameterize it by specifying the polynomial values at the boundaries

$$\begin{aligned} P_{l,i}(t_{i-1}) =& \theta_{l,i-1} \\ P_{l,i}(t_i) =& \theta_{l,i} \end{aligned} \tag{22}$$

and using finite differences as approximations of the derivatives $P'_{l,i}(t)$. To compute the

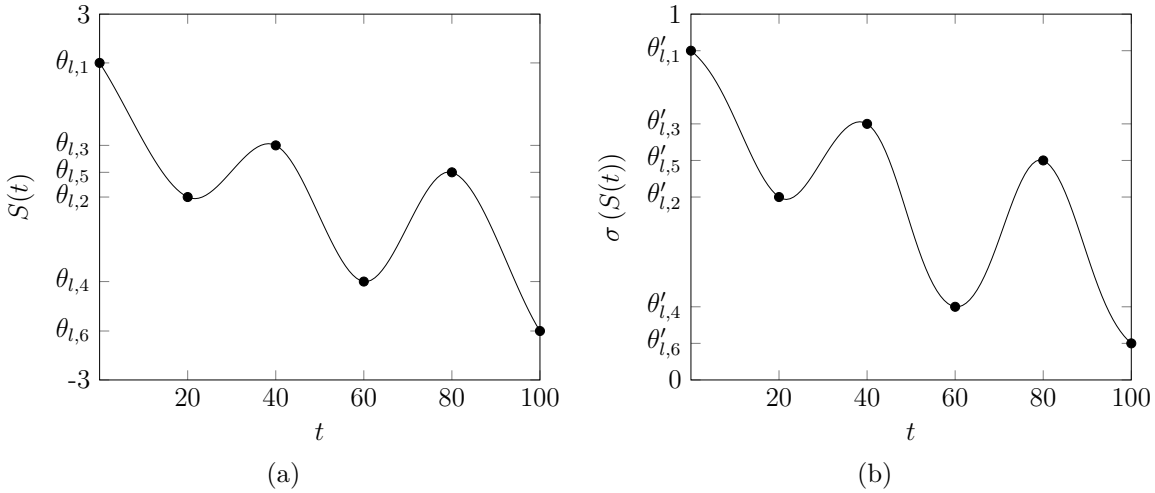

Figure 3: Exemplary spline (a) and the logistically transformed spline (b)

approximations, we use central finite differences and forward as well as backward finite differences at the respective boundaries t_0 and t_z

$$\begin{aligned} P'_{l,1}(t_0) &\approx \frac{P_{l,1}(t_1) - P_{l,1}(t_0)}{t_1 - t_0} \\ P'_{l,i}(t_{i-1}) &\approx \frac{1}{2}\left[\frac{P_{l,i}(t_i) - P_{l,i}(t_{i-1})}{t_i - t_{i-1}} + \frac{P_{l,i-1}(t_{i-1}) - P_{l,i-1}(t_{i-2})}{t_{i-1} - t_{i-2}}\right] \\ P'_{l,z}(t_z) &\approx \frac{P_{l,z}(t_z) - P_{l,z}(t_{z-1})}{t_z - t_{z-1}} \end{aligned} \tag{23}$$

Let $t' = (t - t_{i-1})/(t_i - t_{i-1})$. The polynomial $P_{l,i}(t)$ is given as a linear combination of four basis polynomials $B_1(t), B_2(t), B_3(t), B_4(t) \in \mathbb{R}_3(t)$ with the boundary values of the polynomial and its derivative

$$\begin{aligned} P_{l,i}(t) = B_1(t') \overbrace{P_{l,i}(t_{i-1})}^{\theta_{l,i-1}} &+ B_2(t')(t_i - t_{i-1})P'_{l,i}(t_{i-1}) \\ + B_3(t') \underbrace{P_{l,i}(t_i)}_{\theta_{l,i}} &+ B_4(t')(t_i - t_{i-1})P'_{l,i}(t_i) \quad \forall t \in T_i. \end{aligned} \tag{24}$$

The scalars are dependent on the parameter vector θ_l through (22) and (23). The basis polynomials are defined by$B_1(t) = 2t^3 - 3t^2 + 1, B_2(t) = t^3 - 2t^2 + t, B_3(t) = -2t^3 + 3t^2$ and $B_4(t) = t^3 - t^2$. We show subsequently that they indeed form a basis of $\mathbb{R}_3(t)$. Showing the basis property aims to proof that the four polynomials span $\mathbb{R}_3(t)$ and we therefore do not exclude any polynomials from the space of policies that could be implemented.

Theorem 1. *$B_1(t), B_2(t), B_3(t), B_4(t) \in \mathbb{R}_3(t)$ form a polynomial basis of $\mathbb{R}_3(t)$.*

Proof. We need to show that the four polynomials are linearly independent. We do so by

writing the polynomials in vector form, collect them in a matrix and show that this matrix has full rank.

$$\begin{pmatrix} 2 & 1 & -2 & 1 \\ -3 & -2 & 3 & -1 \\ 0 & 1 & 0 & 0 \\ 1 & 0 & 0 & 0 \end{pmatrix} \Leftrightarrow \begin{pmatrix} 0 & 0 & -2 & 1 \\ 0 & 0 & 1 & -1 \\ 0 & 1 & 0 & 0 \\ 1 & 0 & 0 & 0 \end{pmatrix} \Leftrightarrow \begin{pmatrix} 0 & 0 & 0 & -1 \\ 0 & 0 & 1 & -1 \\ 0 & 1 & 0 & 0 \\ 1 & 0 & 0 & 0 \end{pmatrix} \Leftrightarrow \begin{pmatrix} 0 & 0 & 0 & 1 \\ 0 & 0 & 1 & 0 \\ 0 & 1 & 0 & 0 \\ 1 & 0 & 0 & 0 \end{pmatrix}$$

Since $B_1(t), B_2(t), B_3(t), B_4(t)$ are four linearly independent polynomials of degree 3, they form a basis of $\mathbb{R}_3(t)$. □

Neural network.

4 Stochastic model

move this part (partly) to introduction The aim of a Stochastic Simulation algorithm (SSA) is to provide a computational model that allows for stochastic reactions. They can be classified as exact and approximate SSAs. Exact algorithms, like the Gillespie-Algorithm (Gillespie, 1977), do not group reactions together but model them one after another. Approximate algorithms, like $\tau - leaping$ (Gillespie, 2001), group reactions together and update the propensities within a larger interval τ. Thus, approximate algorithms might have an advantage when it comes to speed. However, by updating the propensities less often, we lose some accuracy. For speed purposes, we decided to implement the τ-leaping algorithm with efficient step size selection as in Cao et al. (2006). **or stochastic Euler**

τ-leaping. In this section we impose an arbitrary order to all subcompartments. We do so by using n features $F_1, \dots F_n$, such that $\cup_{i=1}^{n} \mathcal{C}_t(F_i) = \mathcal{C}_t()$ and $\mathcal{C}_t(F_1), \dots, \mathcal{C}_t(F_n)$ are mutually disjoint. We specify the state of the system in terms of the subcompartments $Y(t) = \begin{pmatrix} y_t(F_1) & y_t(F_2) & \dots & y_t(F_n) \end{pmatrix}'$. Let $\mathbf{S} \in \mathbb{R}^{n \times m}$ be the stoichiometric matrix, as defined in (5), with coefficients s_{ij} and columns $s_{\cdot j}$. Let R_j, for $j = 1, \dots, m$, be the j-th reaction and $V_{t,j}$ the random variable counting the number of times R_j will fire within the interval $[t, \tau)$, for $\tau \in \mathbb{R}_+$. We denote by V_j the random vector collecting the random variables. Dividing the whole period of interest $[0, T]$ in intervals of length τ, the leaping is an iterative update of the discretizised system's state.

$$Y(t + \tau) = Y(t) + \mathbf{S}V_t. \tag{25}$$

This equation is similar to equation (3). Only the number of reactions within a given interval is in (25) random. Let us examine the latter in more detail. The change in the system's state

$\Delta Y(t) = Y(t+\tau) - Y(t) =$ can be written in terms of a linear combination of the columns of $\mathbf{S}$ with random scalars $K_{t,j}$

$$\Delta Y(t) = \sum_{j=1}^{m} K_{t,j} \cdot s_{\cdot j}. \tag{26}$$

$s_{\cdot j}$ consists of the magnitudes of the mass actions for each compartment i according to reaction R_j and therefore indicates how the state of the system changes if reaction R_j happens. $K_{t,j}$ is the number of occurences of reaction R_j. Thus, the product is the system's change due to R_j. Aggregating over all reactions yields the total change of the system R_j, similar to the deterministic equation (3).

So far we have not specified the distribution of K_t. We are interested in the conditional joint probability distribution $\mathbb{P}_t(K_{t,1} = k_{t,1}, \ldots, K_{t,m} = k_{t,m}|\tau)$ of the random vector $K_t = \Big(K_{t,1}, \ldots, K_{t,m}\Big)'$ conditioned on the state of the system and a fixed interval size. Recall that we have defined $\mathbb{P}_t$ to be the conditional distribution with respect to the state of the system and we therefore omit to write it explicitly in the condition statement. Assuming independence, we bring the problem down to specifying the margins. Let $a_j(y)$ be the propensity function $\mathbb{P}_t(K_{t,j} = 1|\tau = 1)$ of the j-th reaction with respect to the state of the system $Y(t) = y$. We assume that for infinitesimal small dt

$$\mathbb{P}_t(K_{t,j} = 1|\tau = dt) = a_j(y) \cdot dt, \tag{27}$$

is the probability that R_j fires once within the interval $[t, t+dt)$ and $(K_{t,j}|Y(t), \tau = dt)$ is Bernoulli $\text{Ber}(a_j(y) \cdot dt)$ distributed. The Bernoulli assumption is justified by choosing dt infinitesimal small, such that R_j fires at most once almost surely.

If we assume that $a_j(y)$ is constant within $[t, t+\tau)$, we can partition the interval in $\frac{\tau}{dt}$ subintervals with length dt. Note that for simplicitly we assume that $\frac{\tau}{dt}$ is an integer. In each of these subintervals $(K_{t+s\cdot dt,j}|Y(t), \tau = dt)$, for $s = 0, 1, \ldots, \frac{\tau}{dt} - 1$, is Bernoulli $\text{Ber}(a_j(y) \cdot dt)$ distributed and thus the sum

$$\sum_{s=0}^{\frac{\tau}{dt}-1} (K_{t+s\cdot dt,j}|Y(t), \tau = dt) \sim \text{B}\left(\frac{\tau}{dt}, a_j(y) \cdot dt\right)$$

follows a binomial distribution. The practical problem of this Binomial distribution is that sampling from it requires to define a value for dt. By definition dt is infinitesimal small, such that we actually aim for $dt \to 0$. The literature has found a solution to circumvent by breaking the problem down to draw from a Poisson random variable that can be specified by τ and $a_j(y)$.

Theorem 2. $B\left(\frac{\tau}{dt}, a_j(y) \cdot dt\right) \xrightarrow{d} Po(a_j(y) \cdot \tau)$ *if* $dt \to 0$.

Proof. A general Binomial random variable $\mathrm{B}(n', p')$ converges in distribution to a Poisson random variable $\mathrm{Po}(n' \cdot p')$ if $n' \cdot p'$ is constant, $n' \to \infty$ and $p' \to 0$. Note that by definition τ is fixed and by assumption $a_i(y)$ is constant within $[t, t+\tau)$. Thus, $\lim_{dt \to 0} \frac{\tau}{dt} = \infty$, $\lim_{dt \to 0} a_i(y) \cdot dt = 0$ and $\frac{\tau}{dt} \cdot a_i(y) \cdot dt = \tau \cdot a_i(y)$. Using the convergence property mentioned above yields the result. □

The τ- leaping algorithm we use is the stochastic Euler algorithm

Initialize $Y(0) = Y_0$ and set fixed $\tau, \mathbf{S}$
Initialize $a_i = a_j(Y(0))$ for all $j = 1, \ldots, m$ and $t = 0$
for _ = 1 to $\frac{maxPeriod}{\tau}$ **do**
    Set y = Y(t)
    Draw $K_{t,j} \sim \mathrm{Po}(a_j(y)\tau)$ for all $j = 1, \ldots, m$
    Compute $Y(t+\tau) = Y(t) + \mathbf{S}K_t$
    Store $Y(t+\tau)$
    Update $a_j = a_j(Y(t+\tau))$ for all $j = 1, \ldots, m$
    Update $t = t + \tau$
end for

5 Results

write about implementation

6 Sensitivity analysis

References

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