A NUMERUS WEBKIT™ APPLICATION

# An SIRS Epidemic Modeling Web App

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**Abstract**

This document describes the structure and implementation of the `Numerus SIRS WebKit™ App` for use as an educational "playpen." It is downloadable for free on most web browsers. In its `Run` mode, it can be used to simulate a continuous-time, deterministic, SIRS model for different epidemiological process parameters such as the `effective population size`, the `baseline contact rate`, the `recovery rate`, and the `loss-of-immunity` rate. In its `Sensitivity` mode, it can be used to carry out sensitivity analyses with respect to these parameter values. In its `Fitting` mode, it can be used to fit these parameter values to incidence data using least-squares or maximum-likelihood estimation. In its `Stochastic` mode, it can be used to estimate the probability of an outbreak from a single infected individual for various combinations of parameter values. It its `Intervention` mode, it can be used to explore the impacts of vaccination and treatment rates on the course of an epidemic. The App is intended for use in the classroom to teach students the basics of epidemiological modeling. Through hands-on simulation of epidemic trajectories, the App can be used to teach students various epidemiological concepts including:

1 Disease prevalence curves of unmitigated outbreaks with life-time immunity have a single peak and result in epidemics that 'burn' through the population to become extinguished when the proportion of the susceptible population drops below a critical level.
2 If immunity in recovered individuals wanes sufficiently fast, then the disease may persist indefinitely as an endemic process.
3 The steepness and initial peak of the prevalence curve are influenced by the basic reproductive value $R_0$, which must exceed 1 for an epidemic to occur.
4 The relevance of different epidemiological parameters is best understood in the context of sensitivity analyses.
5 The probability that a single infectious individual in a closed population (i.e., no migration) gives rise to an epidemic requires $R_0 > 1$ and increases with increasing $R_0$.
6 Epidemic outbreaks are stochastic and best understood in the context of the mean and standard deviations of possible epidemic trajectories and outcomes.
7 Behavior that adaptively decreases the contact rate among individuals with increasing prevalence has major effects on the prevalence curve, including dramatically flattening the prevalence curve.
8 The impacts of treatment are complicated to model because they affect multiple processes including transmission, recovery, and mortality.
9 The impacts of vaccination policies constrained by a fixed number of vaccination regimens and by the rate and timing of delivery are crucially important to maximizing the ability of vaccination programs to reduce mortality.

**Keywords:** SIR models; Public health education; Population modeling instruction; Compartmental models; Stochastic simulation; Vaccination and treatment strategies

## Contents

# Context

The material presented here is meant to augment rather than provide an introduction to concepts in epidemiological modeling. This augmentation provides the student with hands-on exposure to simulating basic SIR epidemiology (S = susceptible, I = infected/infectious, R = recovered/removed classes of individuals) and fitting such models to incidence data. Our more advanced simulation mode includes Dead (D class) individuals and provides a platform for the student to explore the effects of vaccination (V class) and treatment (T class) on the course of epidemics. Several excellent texts are available that introduce the student to epidemiological theory and modeling, but experience with hands-on simulation enriches the learning process in ways that take the student beyond the limit of static texts.

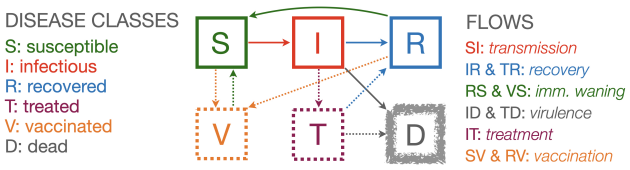



Figure 1: A compartmental flow diagram of an SIRS+DTV epidemic process (disease states/classes S, I and R, the three solid squares) with the addition of deaths (D, fuzzy square) and mitigation classes (V and T, two broken squares). In models presented here, the symbol $\rho_{XY}$ is used to denote the average flow of individuals from compartments X to Y (X, Y = S, I, R, V, T or D). Our `Numerus SIRS WebKit™ App` only includes the top row of states in its `Run`, `Sensitivity`, `Fitting`, and `Stochastic` modes, while the bottom row states are included in its `Intervention` mode.

A comprehensive text that introduces the student to SIR modeling, starting with discrete systems equations and then illustrating their relationship to the more ubiquitous differential equation formulations, followed with more sophisticated models and illustrative examples, is that of Vynnycky and White [1]. A mathematically extensive and rich epidemiological modeling text that starts with the SIR differential equation formulation and then derives its exact discrete time equivalent is that of Keeling and Rohani [2]. Finally, Diekmann and Heesterbeek's more rigorously inclined text [3] provides an elegant introduction to mathematical epidemiology.

Underpinning the simulation of the Numerus SIRS WebKit™ App is a mathematical model, presented in the Technical Material starting in page 27 of this document, that has been coded and configured to run in the User's browser. The App is based on so-called compartment models (Fig 1), where the compartments represent different disease states. In our basic `Run` mode, the course (or trajectories) of S, I, and R over time are computed over a designated time interval $[0, t_{\text{fnl}}]$. Beyond this, the App has `Sensitivity` analysis, model parameter `Fitting`, `Stochastic` simulation, and disease `Intervention` modes (the latter includes dead, vaccinated and treated individuals—see Fig 1) available to the student for deeper exploratory studies of epidemic processes.

All individuals in the population are assumed to be in one of these states and all individuals, apart from their disease state, are assumed to be identical with

respect to the rates at which individuals are transferred from one disease state to the next. The models are dynamic—i.e., driven by a time variable $t$—and track the transfer of individuals from one disease class to the next over time. For reasons of clarity in our Technical Material starting on page 27, we denote the transfer rate of individuals from disease state X→Y by the symbol $\rho_{\mathrm{XY}}$ (X, Y = S, I, R, D, V, or T). Since different texts typically use a text-specific symbol for some of their rates (several texts may use the same symbol), readers are cautioned to ensure that they reconcile their reading of symbols used across various texts to denote the flows from compartments S to I (transmission), I to R (recovery) and R to S (loss-of-immunity or waning immunity) with our presentation here.

# Underlying SIRS Model

Use this link to load the `Numerus SIRS WebKit™ App` in your browser.

## Background

The processes modeled in this App are based on the equations (see the Technical Material starting page 27 for a mathematical formulation of the model)

$$\begin{aligned}
\texttt{Rate-of-change } S(t) &= \texttt{Loss-of-immunity rate} \times R(t) - \texttt{Transmission rate} \times S(t) \\
\texttt{Rate-of-change } I(t) &= \texttt{Transmission rate} \times S(t) - \texttt{Recovery rate} \times I(t) \\
\texttt{Rate-of-change } R(t) &= \texttt{Recovery rate} \times I(t) - \texttt{Loss-of-immunity rate} \times R(t)
\end{aligned}$$

The simulation traces the size of the different disease classes in the population from the start time $t = 0$ to a user selected final time $t_{\mathrm{fnl}}$ and reports their values at each integer point in time: i.e., for $t = 0, 1, \cdots, t_{\mathrm{fnl}}$. The total number of individuals $N(t)$ in the population at time $t$ is given by

$$N(t) = S(t) + I(t) + R(t)$$

We also need to specify and the initial conditions—i.e., the number of individuals at time $t = 0$. At the start of a completely new outbreak of a particular disease—such as COVID-19, we have a single infected individual (so-called patient zero), implying $I(0) = 1$, $S(0) = N(0) - 1$, and $R(0) = 0$. If the epidemic takes-off, then over time the number of individuals in each of these classes changes. In, the model above, however, because each of the total rates `Loss-of-immunity rate` $\times R(t)$, `Transmission rate` $\times S(t)$, and `Recovery rate` $\times I(t)$ appears once as a positive term and once as a negative term in the above three equations, in this model the relationship

$$\texttt{Rate-of-change } N(t) = \texttt{Rate-of-change } (S(t) + I(t) + R(t)) = 0$$

holds, so that $N(t) = N(0) \equiv N_0$ for all $t$. In more complex models where we account for deaths (i.e., in the `Intervention` mode of the App), recruitment (births or sexual maturation of individuals in sexually transmitted diseases), and migration then $N(t)$ is not longer a constant over time.

The transmission rate itself is made up of three components (remember this rate is per capita susceptible individual):

$$\texttt{Transmission rate} = \texttt{(Contact rate)} \times \texttt{(Force-of-transmission per infectious contact)} \times \texttt{Prevalence}$$

Using $\kappa_0$ to denote the contact rate (which is assumed to be a constant indicated by the fact that we subscript it with 0), $\beta$ to denote a "force of transmission" during contact, and the prevalence $I(t)/N(t)$ (which is the proportion of infected individuals in the population at time $t$), then it follows that

$$\texttt{Transmission rate (per susceptible individual)} = \kappa_0 \beta \frac{I(t)}{N(t)}$$

One of the key statistics that is monitored for both endemic (those that have become established and occur continuously all year long into the foreseeable future) and epidemic disease (those the breakout and then disappear or reoccur seasonally) is the incidence rate. This rate is defined as the number of new cases per unit time $t$ and is often normalized per 100,000 individuals. This normalization allows epidemics in different regions to be compared in terms of their relative effects (since, all else equal, larger regions or cities are likely to have more total cases than smaller regions or cities, but not necessarily at a per 100,000 capita rate).

We denote incidence by $\Delta^+ I(t)$ (the $\Delta$ is used to denote change in $I(t)$ and the $+$ superscript that its additions in I due to transmission that are being monitored without including subtractions from I due to recovery) and compute it as follows

$$\underline{\texttt{Incidence (per } 10^5 \texttt{ individuals)}}$$

$$\Delta^+ I(t) = \frac{10^5}{N(t)} \int_t^{t+1} \Big( \texttt{Transmission rate} \times S(\tau) \Big) d\tau$$

For those not comfortable with integral calculus, in differential calculus, using a dummy variable "tau" ($\tau$), this is the same as writing:

$$\begin{aligned} &\text{For } \tau \text{ on the interval } [t-1, t] \\ &\qquad \texttt{Rate-of-change } \Delta^+ I(\tau) \;=\; \texttt{Transmission rate} \times S(\tau) \\ &\Delta^+ I(t-1) = 0 \;\text{ and }\; \Delta^+ I(t) = \texttt{Incidence for time period } t \end{aligned}$$

# Numerus SIRS WebKit™ App Dashboard

The `Numerus SIRS WebKit™` can be accessed in your browser by clicking this link. After loading the dashboard of the App appears in the browser.

The dashboard (see top panel in Fig 2) has six modes (four blue and two green mode select buttons—same color modes share the same presets): `Run`, `Sensitivity`, `Fitting`, `Stochastic`, `Interventions` and `Int. Sensitivity`. The first is for direct simulation of the SIRS model. The second is for multiple runs of the SIRS model, focusing on how solutions are affected by changes in the values of one of four possible user-selected parameters, with the three remaining parameters fixed.


Figure 2: **Numerus SIRS WebKit™ Dashboard.** The Dashboard indicates that the App is in `Run` mode because the mode ribbon just below the title has the `Run` button highlighted (darker shade of gray). Parameter values for the simulation in this mode are indicated in the slider windows (e.g., the `Recovery Rate` has an indicated value of 0.25). Below the slider ribbon is a second ribbon of buttons and windows indicating that this simulation, when initiated after pushing the `Start` button (highlighted with a blue outline) run for $T = 35$ time steps, because the window just to the left of the `Speed` slider initially set at 40 is now 0 after the simulation has ended. The remaining buttons and windows are described in more detail in the text. It is worth noting though that the right-hand-side of this second ribbon indicates that the simulation pictured here used the `Contact Rate: Constant` version of disease transmission. The alternative `Contact Rate: Adaptive` version can be accessed by clicking on the grate on the upper right-side of the dashboard, as depicted in Fig. 3. Note that the `Contact Rate Scaling` and `Switching` parameters do not apply or affect the simulation when the contact rate is constant rather than adaptive. The left hand plots (different scales on left and right side of this plot apply as labeled) depict the proportions of S, I and R individuals in the population, the right hand plots depict `R effective` (denoted mathematically by $R_{\text{eff}}$ and not to be confused with the recovered/immune variable $R(t)$) and the `Incidence rate`. At time $t = 0$ $R_{\text{eff}}$ is the well-known $R_0$ which must exceed 1 for an epidemic to occur. Note, in this case, $R_{\text{eff}}$ dips close to 0 around time $t = 10$, but then recovers to approach 1 as the epidemic enters an endemic state due to waning immunity in the population and continuing reinfection of individuals that have recovered (e.g., as is the case for influenza).

The third is used to fit the parameters in the model to incidence data. The fourth is to run a discrete-time stochastic version of the continuous-time, deterministic SIRS model simulated in `Run` mode. The fifth is an extension of this continuous-time, deterministic SIRS model to include deaths (D), treated (T) and vaccinated (V) individuals (i.e., the SIRS+DTV presented in [4]). The sixth is for multiple runs of the SIRS+DTV model, focusing on how solutions are affected by changes in the values of one of 12 possible user-selected parameter, with the remaining 11 parameters fixed.

When the dashboard is loaded the App is in its `Run` mode. In this mode, the dashboard consists of a row of six sliders on the top left hand side allowing one to set the `Initial Pop Size` $N_0$, `Baseline Contact Rate` $\kappa_0$, `Recovery`

`Rate`, and `Loss-of-Immunity Rate`, as well as the `Contact Rate Scaling` $P_\kappa$ and `Switching Parameter` $\sigma_\kappa$ that are only needed for the adaptive contact case. Below this are a set of five control buttons (`Restart, Reset, Step, Start`) a `Speed` slider two windows (the left most keeps track of time, the right most allows one to set the time). a `Preset` selector dial (activated once the `Restart` button has been selected), two windows indicating the `method` and simulation iteration step-size `dt` that have been selected, as we all as text indicating whether the contact process is `Constant` or `Adaptive`.

The bottom left of the dashboard has two graphs: the one on the left graphs the proportion of susceptible (S), infectious (I), and immune (R) individuals in the population as the simulation proceeds, the one on the right.

We note that if the default initial value $N_0 = 10^5$ in our `Numerus SIRS WebKit`™ `App` is not overridden by the user at the start of a simulation, then the associated initial conditions of $I(0) = 1$, $S(0) = N(0) - 1$, and $R(0) = 0$ implies that at start of an epidemic the prevalence is 0.00001 and the proportion of susceptibles is 0.99999. As explained, in the Technical Material starting on page 27, the deterministic version of the model behaves in the same way with respect to prevalence and proportions of susceptible and immune individuals irrespective of the nominal size given to the population being modeled.

# Run Mode

## Run Mode Dashboard

The various, slider, button, graph features, window and option selection features available in `Run` mode (See highlighted `Run` mode button in Fig 2) are listed below starting with the upper left features of the left hand window of the dashboard (Fig 2), and finishing with the lowest features in the lower right hand window of the dashboard.

**Slider ribbon**


**Slider values and ranges**

**Initial Pop Size** $N_0$**:** $[0, 10^7]$ in steps of $10^3$
**Baseline Contact Rate** $\kappa_0$**:** $[0, 10]$ in steps of $10^{-3}$
**Recovery Rate:** $[0, 1]$ in steps of $10^{-3}$
**Loss-of-Immunity Rate:** $[0, 0.1]$ in steps of $10^{-3}$
**Contact Rate Scaling** $P_\kappa$**:** $[0.001, 0.1]$ in steps of $10^{-3}$
**Switching Parameter** $\sigma_\kappa$**:** $[1, 20]$ in steps of 1.0

**Button ribbon**


**Live simulation time window** This keeps track of the simulation's progress.

**Restart button.** Use this button to redo the simulation with the current parameters. Use the web browsers reload button ↻ to get back to the factory settings.

**Reset button.** Use this button to clear the dashboard for the next simulation.

**Step button.** This manually progresses the simulation through one time step.

**Start button.** Used to start a simulation.

**Set simulation length window.** This is to see the value $t_{\text{fnl}}$ for simulation over the time period $[0, t_{\text{fnl}}]$

**Speed slider.** Used to slow down the simulation to observe graphs being generated (e.g., for purposes of creating videos).

**Presets rotor.** Used to select a desired `Preset` (see discussion in section on Presets)

**Methods.** Two methods can be chosen: `Euler` or `RK4` (Runge-Kutta 4). Choose the latter for solving differential equations and the former with $dt = 1$ for stepping through the equations discretely.

**dt.** Choose 1/2 or 1/4 for rapid simulations unless more numerical accuracy is needed in which case 0.01 or even 0.0001 can be selected (e.g., when incidence values change rapidly so the the incidence peak is spiked rather than rounded). The time to complete the simulation scales with the reduction in the size of dt.

**Contact Rate.** This indicates whether the `Constant` or `Adaptive` contact rate has been selected (Fig 3)

**Download CSV.** At the end of each run, the User can use this button to download a CSV file containing all the results of the run. This file has a machine generated name that is both unique (date and time stamp) and informative (includes all parameter values and run settings) to run that was just made.

**Graph options ribbon** 

From left to right this are: "download plot as a png," "zoom," "pan," "zoom in," "zoom out," "auto scale," "reset axes," and "link to the plotly website,"

**Proportions graph.** The left-hand graph of the User Interface in `Run` mode (Fig 2 is used to plot the proportions of susceptible, infectious (i.e., prevalence) and immune individuals in the population. Each one of this graphs may be displayed or not displayed by clicking on the text in the legend on the upper right of this graph. A graph ribbon accessible by passing a mouse just above the left side of the graph can be used to reset axes, zoom in our out, or download the graph as a `png` image.

**Values graph.** The right-hand graph of the User Interface in `Run` mode (Fig 2 is used to plot the Values of R-effective (scale on right-side vertical axis) and Incidence (scale on left-side vertical axis). Each one of this graphs may be displayed or not displayed by clicking on the text in the legend on the upper right of this graph. A graph ribbon accessible by passing a mouse just above the left side of the graph can be used to reset axes, zoom in our out, or download the graph as a `png` image.

## RAM Selections and Modifications Windows in Run Mode

The grate icon at the upper left corner of the App Dashboard can clicked open to obtain the windows depicted in Fig 3.

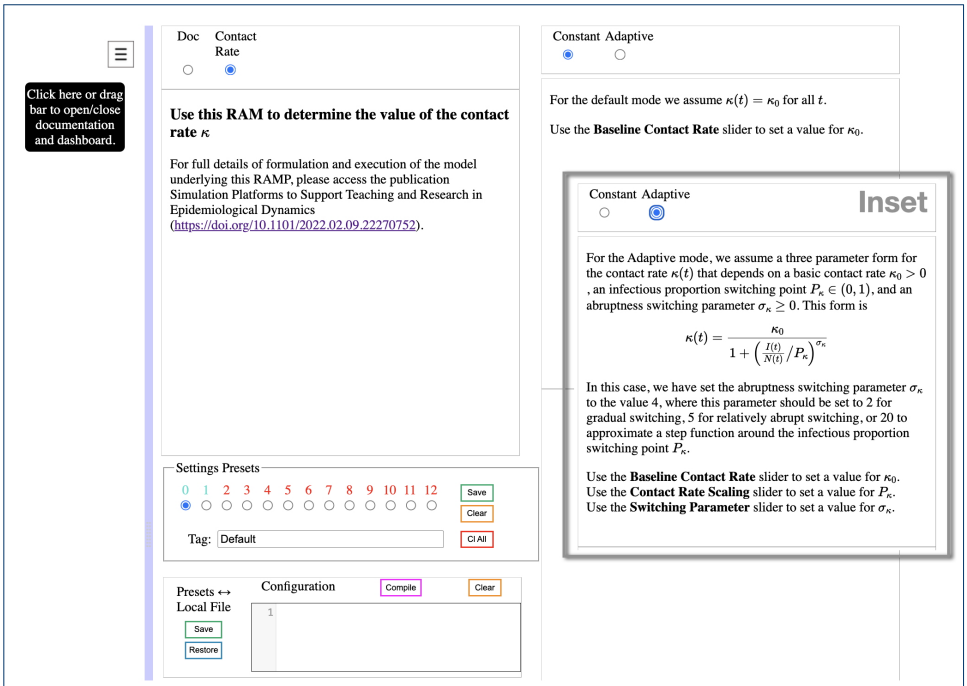



Figure 3: **Selecting the form of the contact rate function.** Once the windows to the right of the dashboard are opened, as mentioned in Fig. 2 (upper right-hand grate icon), the User has the option of selecting either the `Constant` or (pasted here as in **Inset**) the `Adaptive` forms of the `Contact Rate`.

## Things to explore using the RUN Mode

1 Epidemics with lifelong immunity. Suppose the loss of immunity rate for a particular disease is zero, as is the case is for disease where life-long immunity typically occurs (e.g., measles, mumps and rubella, which is why the MMR vaccine administered to young protects individuals for the rest of their lives.) Describe the shape of the epidemic curve if this disease is introduced into a large population that has never experienced this disease before. E.g. You can use the factory settings of the `Numerus Deterministic SIRS WebKit`™ `App`, which are a `Baseline Contact Rate` $\kappa_0 = 1$, a `Recovery Rate` $= 0.5$, and a `Constant Contact` process. Hence the value of the `Contact Scale parameter`, $P_\kappa$, and `Switching parameter`, $\sigma_\kappa$, do not apply.

2 The reproductive number R-zero. A key concept in epidemiology is a quantity called $R_0$ (i.e., R-zero; not to be confused with the quantity $R(0)$, which is the number of immune individuals in the population at time $t = 0$—unfortunately this confusing use of standard symbols is baked into epidemiological theory). This quantity, known as the basic reproduction number of an infection (sometimes called the basic reproduction ratio or basic reproductive rate), is the

expected number of cases that will be generated at the start of an epidemic by patient zero (i.e., the initial infected individual). Over time as more individuals become infected and acquire immunity the expected number of cases that each subsequent infectious individual will generate will change so that $R_0$ is reduced to a quantity R-effective that will vary with time (and by denoted by $R_{\text{eff}}(t)$). By selecting different values for `Basic Contact Rate` $\kappa_0$ (while leaving the `Recovery Rate` at 0.5 and the `loss-of-immunity rate` at 0, the default values of the App) show that an epidemic will only occur if $\kappa_0$/(recovery rate) $> 1$. What happens if $\kappa_0$/(recovery rate) $< 1$. By varying both $\kappa_0$ and the `Recovery Rate` demonstrate that R-zero ($R_0$) is equivalent to the ratio `Basic Contact Rate`/`Recovery Rate` (i.e., in our mathematical notation in the Technical Material section $R_0 = \kappa_0/\rho_{\text{IR}}$—see Eq 8).

3 Epidemic Peak, Duration and Final. For the case where the `Loss-of-immunity Rate` is zero, discuss how the epidemic peak and duration (time from the start of the epidemic until the prevalence drops below 0.00001, which implies fewer than one infected individuals in a population of a hundred thousand) are influenced by the values of the values of the `Basic Contact Rate` and, `Recovery Rate`. Relate your findings to the epidemiological concepts of *Herd Immunity* and the final size of the susceptible population (sometimes referred to as $S_\infty$).

4 Endemicity. Assume that the `Loss-of-immunity Rate` is no longer zero, as in measles, mumps or rubella, but that immunity wanes over time, as is the case for many respiratory viruses, such the influenza or corona viruses. In the context of the default case `Baseline Contact Rate` $\kappa_0 = 1$, a `Recovery Rate` $= 0.5$, and a `Constant Contact` process, explore what happens the `Loss-of-Immunity Rate` is increased from 0 to 0.1 in steps of 0.01. Describe what you see? Note this study is most easily undertaken in the `Sensitivity` mode; and, to see the full effect of these runs, select $t_{\text{fnl}} = 300$, as illustrated on page 26.

5 Adaptive Contact. An adaptive contact rate assumes that individuals reduce the rate the `Basic Contact Rate` with other individuals as the

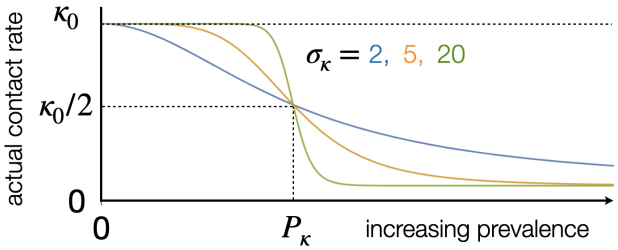
$$\texttt{Prevalence}(t) = I(t)/N(t)$$

of infectious individuals increases over time $t$ and vice-versa as the prevalence decreases later on in the epidemic. This is the situation we saw with COVID-19 as individuals were either mandated or voluntarily adjusted their contact rate with others over time (waring masks had the effect of reducing the rate of effective contacts if not actual contacts). Specifically, in the `Numerus Deterministic SIRS WebKit`™ `App` the following equation is used

$$\texttt{Contact Rate}(t) = \kappa_0 \frac{1}{1 + \left(\frac{\texttt{Prevalence}(t)}{P_\kappa}\right)^{\sigma_\kappa}}$$

The `Contact Rate Scaling` parameter $P_\kappa$ is the level of `Prevalence` at which the `Contact Rate`(t) is reduced by half to $\kappa_0/2$. The effect of the `Switching Parameter` $\sigma_\kappa$ is how rapidly the contact rate is reduced at as

the prevalence `Prevalence`$(t)$ passes through the value $P_\kappa$, as illustrated in the figure below.




For a switching parameter value $\sigma_\kappa = 4$, explore how the value of the `Contact Rate Scaling` parameter $P_\kappa$ over the range $[0, 0.1]$ affects the simulation results explored in suggested activities 3 and 4 above.

6 Effect of adaptive scaling: By varying the value of the contact rate scaling parameter $\kappa_0$ between 0.5 and 5 in steps of 0.5, with other parameter values fixed at `Recovery Rate` $= 0.25$, `Loss-of-Immunity Rate` $= 0.1$, `Contact Rate Scaling` $= 0.1$, and `Switching Parameter` $= 4$, use the App in the `Adaptive Contact` mode to:

- **a.** explore the relationship between the time $t^*$ and THE value $I(t^*)/N(t^*)$ of maximum prevalence
- **b.** explore the relationship between the time $t^*$ of maximum prevalence and the time $t_1$ when prevalence first rises above 0.1%
- **c.** explore the relationship between the time $t^*$ of maximum prevalence and the time $t_2 - t_1$ it takes for prevalence to drop below 0.1% at time $t_2$, and note the value of $R_{\text{eff}}(t_2)$ in each case
- **d.** plot the proportion of individuals that escape infection in each case as a function of your computed value for $R_0$ as a function of the selected value for $\kappa$.

Note this study is most easily undertaken in the `Sensitivity` mode, but in this case do each run for each value of $\kappa_0$ individually and then download the CSV file at the end of each run and use the data in these files to answer questions a.-d. above.

7 Exercise from Reference [4]: Plot (either as a series of 1-D curves or a 2-D surface) the relationship between the ratio of peak to endemic prevalence as a function of $R_0$ (through manipulation of the value $\kappa_0$) and the mean residence time in the disease class R, which is given by the reciprocal of the flow rate from disease class R to S—that is

$$\text{Mean residence time in class R} = \frac{1}{\texttt{Loss-of-Immunity Rate}}$$

8 Exercise from Reference [4]: By varying the strength of adaptive behavior through changes in the prevalence values of the behavioral switch parameter $P_\kappa$ estimate the period of endemic oscillations that dampen over a 60 time period simulation interval as a function of the values of $P_\kappa$ and the mean residence time in the disease class R for combinations of these parameters where dampened oscillatory behavior is evident.

# Presets

The preset facility of the `Numerus SIRS WebKit`™ `App` allows the user to save a whole bank of settings for later use and to help keep a record of various run settings. See the caption to Fig 4 for some details on how do to this.

All blue modes (`Run`, `Sensitivity`, `Fitting`, and `Stochastic`) share the same set of presets, so the User might want to indicate on the tags in which mode the preset was setup. Similarly the green modes (`Interventions` and `Int Sensitivity`) share the same presets, but these are a different set from the blue mode presets.


Figure 4: **A.** Selection of the `Default` Preset, which cannot be changed and can always be re-implemented by closing and then reopening, or simply reloading, the `Numerus SIRS WebKit`™ `App` in the User's browser. The row of buttons labeled 1-12 in red provide and opportunity for the User to save 12 sets of runtime settings that differ from the `Default` (see panel **B**). The slider and runtime ribbons below indicate the values of the "factory default" settings. **B.** On changing the `Default` settings to `Loss-of-Immunity`=0.03, replacing the 50 in the run length window with 20.0000, and pressing `Save` in the green-outlined button, preset 1 turns from red to green and is preserved for future use, provided the orange-outlined `Clear` button or the red-outline `Cl All` (clear all) button is not pressed, where the latter clears all previously defined presets, apart from 0 (the `Default`). C. This window provides the User with the ability to Save and Reload a whole bank of up to 12 previously defined presets.

# Sensitivity Mode

Sensitivity analyses are used to compare simulation results when one or more of the model parameters are perturbed from a set of values that we refer to as the baseline values. The sensitivity of the simulation trajectory can be assessed to perturbations in the value of the various epidemiological parameters (`Baseline Contact Rate`, `Recovery Rate`, `Loss-of-Immunity Rate`, or in the case of adaptive contact ,the `Contact Rate Scaling`) in terms of key epidemic features such as: i) time to and ii) size of peak incidence, iii) proportion of individuals still susceptible at the end of the epidemic in case the epidemic peters out, or iv) the endemic level of prevalence in case the epidemic continues to be fueled indefinitely by previously immune individuals becoming infectious once more.

An example of a sensitivity run is provided in Fig 5 where 11 different prevalence trajectories (left graphics panel) and their mean and one standard devation on either side of the mean (right graphics panel) are depicted for the `Loss-of-Immunity Rate` parameter ranging from 0 to 0.1 in steps of 0.01. Notice the final prevalence is 0 when the `Loss-of-Immunity Rate` is 0, but seems to plateau out at increasingly high values as the `Loss-of-Immunity Rate` increases keeps an increasingly high flow of previously immune individuals becoming susceptible once more as their immunity wanes (much as we have with influenza and covid but not measles or, in the past, small pox for which vaccinations typically confer life long immunity).

## *Sensitivity Mode Dashboard*

In `Sensitivity` mode the `Numerus SIRS WebKit`™ `App` dashboard has the following ribbon of simulation control windows immediately above the its graphics panels.

**Sensitivity analysis options**

Parameter: Baseline Contact Rate Runs: 11 From: 0.5 To: 1.5 Increment: 0.1

**Parameters.** This window can be used to select the single a parameter—`Baseline contact rate` $\kappa_0$, `Recovery Rate`, or `Loss-of-Immunity Rate`, with additional parameters included for Interventions—that will vary during the sensitivity runs with the other values as indicated in the windows of the slider ribbon.

**Runs.** This is the total number of runs to be executed during the sensitivity simulation.

**Range.** (From, TO). The sensitivity runs will begin with the selected parameter have the `From` starting value and end with the `To` ending value in increments of size $(\texttt{To} - \texttt{From})/(\texttt{No. of Runs} - 1)$.

**Increment.** Once the values for `Runs`, and `Range` have been entered, the `Increment` window will show the computed increment. Alternatively, a value can be entered into the `Increment` window once the range has been established, following which the number of required runs is computed and entered in the `Runs` window.

Note that distinct values are maintained by these fields for each of the available parameters. These values will be part of a preset when saved on the Sensitivity Mode page, and can be restored by selecting the preset on the same page.


Figure 5: **Sensitivity Mode.** The `Sensitivity` mode button is highlighted for a sensitivity analysis with `Preset Default` settings as indicated in the ribbon immediately above the graphs: i.e., on the `Baseline Contact Rate` parameter, ranging in value from 0.5 to 1.5. Since 11 runs were selected (11 was entered in the `Runs:` window, which now reads 0, since it counts down as the runs proceed, the increments from 0.5 to 1.5 are 11 steps (including the endpoints) with an increment of 0.1. The remaining parameter values are listed in the slider windows. The results of all 11 runs and their means and $\pm$ their standard deviations are depicted in the left- and right-hand graphs respectively. The plots show that we have selected to graph `Prevalence`, but other variables could be selected using the buttons below the left-hand graph.

## Things to explore using the Sensitivity Mode

Exercise 1: Endemicity. Assume that the `Loss-of-immunity Rate` wanes over time, as is the case for many respiratory viruses, such the influenza or corona viruses. In the context of the default case `Baseline Contact Rate` $\kappa_0 = 1$, a `Recovery Rate` $= 0.5$, and a `Constant Contact` process, explore what happens the `Loss-of-Immunity Rate` is increased from 0 to 0.1 in steps of 0.01. Describe what you see (hint: select $t_{\text{fnl}} = 300$, as illustrated on page 26).

Exercise 2: Adaptive Contact. Assume that the `Loss-of-immunity Rate` wanes over time, as is the case for many respiratory viruses, such the influenza or corona viruses. In the context of the default case `Baseline Contact Rate` $\kappa_0 = 1$, a `Recovery Rate` $= 0.5$, `Loss-of-immunity Rate` $= 0$, and the `Switching Parameter` $\sigma_k appa = 4$, explore the effects of an `Adaptive Contact` process when the `Contact Rate Scaling` parameter $P_\kappa$ is increased from 0.01 (strongest effect) to 0.1 (weakest effect) in steps of 0.01. Describe what you see (hint: select $t_{\text{fnl}} = 200$, as illustrated on page 26).

Exercise 3. By selecting 100 perturbations at random in the baseline parameters listed in Exercise 1 above, in the range of [-5%,5%] on either side of each parameter value, carry out a statistically based sensitivity analysis along the lines of [5].

## Fitting Mode

In fitting epidemic models to empirical data, one needs to use data that are in line with the output of our simulated model. In our SIRS simulations, simulated data include time lines for the number of susceptible ($S(t)$), infected ($I(t)$), and recovered ($R(t)$) individuals at each point $t$ in time, as well as the incidence rate $\Delta^+ I(t)$ at each point in time. The latter data begins with $\Delta^+ I(0) = 1$ at the start of an epidemic and ends with $\Delta^+ I(t) =$, some time later which we treat as the end of the epidemic if $\Delta^+ I(t_{\text{fnl}}) = 0$ and no more infected individuals are observed in the population for a period beyond this point. Thus, once we have a complete set of empirical data that starts with 1 or more infected individuals cases reported in the first time period (initially, an epidemic might be detected because several infectious individuals are observed in the first time period—e.g., day or week, depending on the frequency at which the data are reported) and ended at a time we designate as $t_{\text{fnl}}$ because there are 0 cases at this time and no more cases are detected beyond this point.

The best data to fit the model to are the incidence data $\Delta^+ I(t)$, $t = 0, 1, \cdots, t_{\text{fnl}}$. The model can also be fit to prevalence data, but this is not as good as incidence data, since we do not usually know quite how long individuals remain infectious once they are showing symptoms and so prevalence data are not quite as reliable as incidence data. Also since incidence occurs at a point in time, while prevalence occurs over a period of time, incidence data are less smooth and hence the model fit is more sensitive (read sharper) when incidence rather then prevalence data are used.

Fitting models to data is a rather daunting challenge for the many reasons including the following

1. Real epidemics are much more complicated processes than are described by any model, but in particular by SIRS models that make many simplifying assumptions (some of which are discussed in the Technical Material starting on page 27).
2. The model being fit has been normalized to predict data per 100,000 individuals. In practice the data are coming from a population whose size is either unknown or, because of heterogeneity in the population from which the data are coming (some individuals leave in high density inner city areas and travel on buses and trains, while others live in low density suburban and peri-urban areas and travel in cars or avoid large crowds). In this case, it may be best to regard the "effective population size" as a parameter $N_0$ that should also be fitted along with the contact rate $\kappa_0$ and the recovery rate, so that the predicated incidence rate should then be multiplied by a factor $\frac{10^5}{N_0}$ if the data to which the model is fitted are "raw" incidence numbers (as discussed in [6])
3. We can ignore the waning parameter if the rate of waning of immunity is well beyond the length of the epidemic (e.g., a seasonal epidemic may last several months will immunity to the disease in question may last a few years or more), otherwise it should be estimate along with the contact and recover rate parameters
4. If disease-induced mortality rates are high, then these rates can be estimated from a mortality data time series of the number of individuals dying in each time period. In this case, however, the `Numerus Deterministic`

`SIRS WebKit™ App` is too limited and the `Numerus Deterministic SIR+DTV WebKit™ App` used with vaccination and treatment rates either set to 0 (as would be the case when fitting a model to the early stages of an epidemic outbreak) or include actual treatment and vaccination rates in the model, as applied during the course of the epidemic from which the data have been obtained.

5 Data are often noisy and unreliable. For example, during the Covid-19 pandemic rates mortality rates in many countries were reported on a daily basis, but the rates on weekends were generally lower, with noticeably higher rates on Mondays or Tuesday, because of delay in reporting weekend deaths.

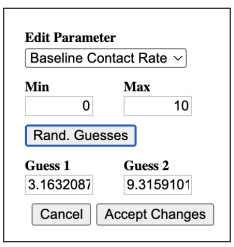
6 A number of computationally intensive, statistically well-founded or rigorous methods can be used to fit models to data—viz., namely maximum-likelihood and Bayesian Markov Chain Monte Carlo (MCMC) methods are the most commonly employed. Here, for didactic reasons, we will focus on the much simpler, though less statistically justifiable, Residual-Sum-of-Squares (RSS) minimization methods (these work well if the noise in the data are Gaussian and the models themselves do not have strong biases). This measure sums up the square of the difference between predicted and observed values ("the residuals") each time period and finds model parameter values using some optimization procedure, that minimize this RSS. The `Numerus Deterministic SIR+DTV WebKit™ App` uses the Nelder-Mead optimization method to identify the parameters in the model that best predict the course of the incidence data. We will also allow the user to select a maximum likelihood optimization, using the approach presented in the Technical Material starting on page 31.

In Fig 6, we see the results of using the `Numerus SIRS WebKit™ App` to fit a set of weekly incidence data associated with and Ebola epidemic that swept through Sierra Leone in 2014 [7, 8, 9]. We note that when fitting such data the appropriate initial conditions are generally uncertain because detection of the putative index case does not generally pin down the start of the epidemic. Thus, as part of the fitting procedure, we may allow the initial population size $N_0$ to be fitted to the data and compare fits in which we treat the first observed case as the first week of the epidemic, or we can posit an early start to the epidemic and fill in a set of weeks prior to the first observed case with 0 observed cases, assuming that these had gone undiagnosed or unreported (Fig 6 Inset).

## *Fitting Mode Dashboard*

In `Fitting` mode the `Numerus SIRS WebKit™ App` dashboard has the following windows. buttons and sliders between the simulation control ribbon and a single graphics panel at its bottom right-hand corner.

**Parameter set up window**



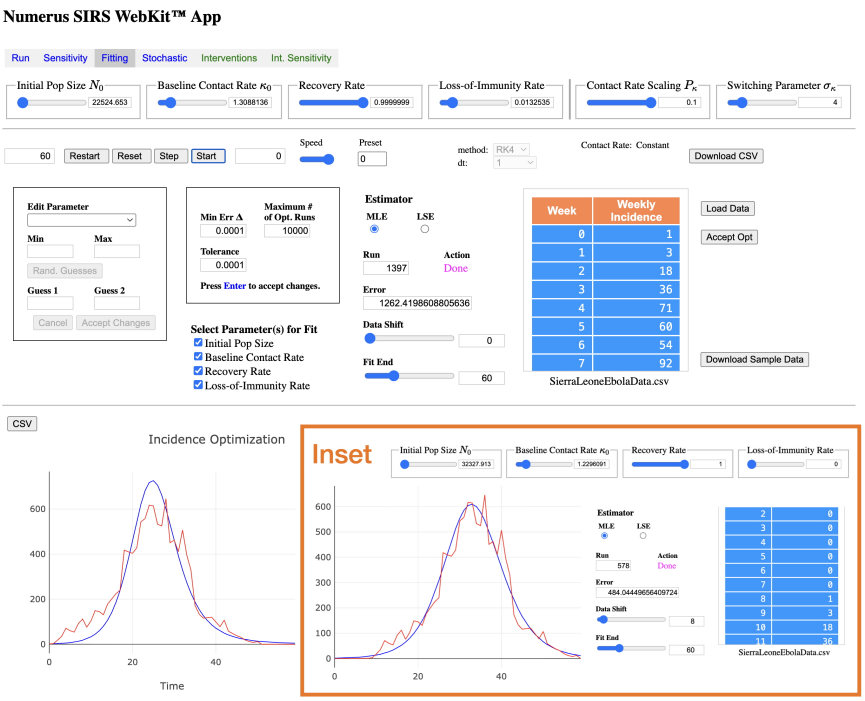



Figure 6: Fit of an Ebola data set[6] using Least-Squares Estimation. The dashboard shows that this fit was terminated (`Action = Done`) after 743 runs. The final fitted parameter values are indicated within the slider windows ($P_\kappa$ and $\sigma_\kappa$ do not apply when `Contact Rate = Constant`). The **Inset** shows that a much better fit (MLE = 516.8 versus 1277.7) is obtained when the supposed start data is shifted back 8 weeks and it is assumed that 0 cases were observed in the first 0-7 weeks rather the fit obtained assuming the start of the epidemic began with the first observed case (i.e., so-called patient zero). Notes: 1). The headings "Week" and "Weekly Incidence" in the data window are copied from the data file. In faster spreading disease than Ebola, such as Covid-19 or influenza, daily incidence data may be available, so that each time step in the simulation is a day rather than a week. 2). `method = RK4` because a differential equation model is being simulated, but the numerical iteration step size is `dt = 1`, because the simulation and empirical data values line up by integral time step.)

***Edit Parameter*:** This window is used to select each of the following four parameters, one-by-one—`Initial Pop Size`, `Baseline Contact Rate`, `Recovery Rate`, and `Loss-of-Immunity Rate`—to enter values, as specified next.

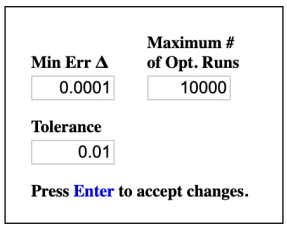
***Min/Max*:** The optimization will take place for the selected parameter above on the constrained interval `Min` $\leqslant$ `Opt value` $\leqslant$ `Max`. If the optimal parameter value is equal to its `Min` value, then it can either be accepted (e.g., if it is 0 and negative values are not permitted) or the `Min` value can be lowered and the optimization rerun. Similarly for `Max` and then raising this `Max` value.

***Random Guesses*—*Guess 1/Guess 2*:** If this is selected then random "starting" guesses (between `Min` and `Max`) at possible optimal values can be implemented or, if not selected, then these must be intered by hand in `Guess 1` and `Guess 2`.

***Cancel*:** Use this to clear and reinter the information in this box.

***Accept Changes*:** Once all windows have been filled in this box, press to accept as values to be used in the optimization.

**Optimization control window**



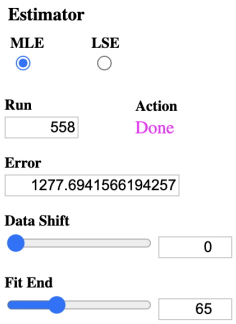

***Min Err* Δ:** Stopping criterion: minimum change in MLE/LSE measure required for algorithm to continue.

***Maximum # of Opt. Runs*:** Stopping criterion: maximum number of runs allowed.

***Tolerance*:** Stopping criterion: minimum change in estimated best parameter values tolerated for algorithm to continue.

***Accept Changes*:** Once algorithm has stopped automatically due to one of the above three criteria or manually by pressing the `Stop` button, by pressing this button the final values indicated in the ribbon of parameter sliders will be saved for use in the Apps other modes.

**Optimization output window**



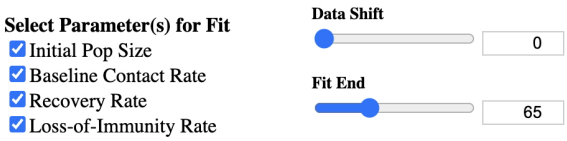

***Estimator*:** Select either to perform and Maximum-Likelihood or Least-Squares Estimation procedure

***Run*:** This window keeps tracks of the number of runs performed by the algorithm as it proceeds to completion

***Action*:** This is used to inform the user of the procedure of the next type of step used by the Nelder-Mead optimization procedure to obtain an updated guess (reflected, contracted, expanded, or done) as it approaches the optimal values for each of the parameters being optimized.

***Error.*** This is the current value of the MLE or LSE performance functions as the optimization procedure proceeds to completion.

**Optimization Parameters**



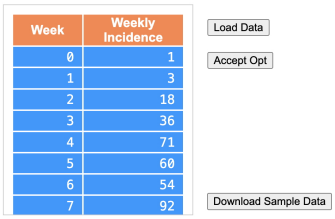

***Select Parameters for Fit*:** The User can select from any one to four of the `Initial Pop Size`, `Baseline Contact Rate`, `Recovery Rate`, and

`Loss-of-Immunity Rate` parameters to be optimized with respect to the fitting procedures with the non-selected parameters having fixed values set using their corresponding sliders.

***Fit End*:** This is the length ($t_{\text{fnl}}$) of the time interval over which the fit will take place, starting time period 0 of the data set

***Data Shift*:** If the User wants the data to be shifted so that the first non-zero entry of their data set does not correspond to time period 0, but rather $t_{\text{delay}}$ time periods early, then zeros will be filled in for time periods $t = 0, \cdots, t_{\text{delay}}$ but the fit will still be until $t_{\text{fnl}}$, even if there are non-zero entries now beyond $t_{\text{fnl}}$. Thus the user should set $t_{\text{fnl}}$ to be sufficiently large to include all the incidence data as the User selects different values for $t_{\text{delay}}$ (i.e. the User should make sure that $t_{\text{fnl}}$ is larger than the time of last non-zero value in their incidence data increased by the maximum of all intended $t_{\text{delta}}$'s time units to be tested).

**Data Loading and Accepting Result**




***Viewing panel*:** The loaded data can be viewed here and scrolled up or down as desired (the name at the bottom of this panel is the file used in the optimization depicted in Fig 6).

***Load Data*:** The User clicks this button to navigate to the folder where a csv file of the incidence data to be fitted is stored.

***Accept Opt*:** Once the optimization is completed, when this button is clicked the results are recorded for use if the User then selects the `Run`, `Sensitivity`, or `Intervention` modes for further analysis.

***Download Sample Data*:** This button can be used to download the depicted data set `SierraLeoneEbolaData.csv`.

## Things to explore using the Fitting Mode

For the set of exercises, use the provided data set `SierraLeonaEbolaData.csv`

Exercise 1: Compare 5 MLE fits (parameter and error values) of the `SierraLeonaEbola.csv` data with the `Data Shift` $= 8$ using different `Random Guesses` starting conditions.

Excercise 2: Compare MLE and LSE fits to the `SierraLeonaEbola.csv` data using the same starting conditions for both.

Excercise 3: Compare the MLE fits (parameter and error values) obtained to the `SierraLeonaEbolaData.csv` for the cases `Data Shift` $= 0, \cdots, 10$. (Hint: it may be useful to plot the error value versus the shift/delay value).

# Stochastic Mode

## Underlying model

The basic discrete dynamic model is based on the simple fact that for each variable the following equation applies:

$$\text{Value}(t+1) = \text{Value}(t) + \Big(\text{Change in value}\Big)|$$

This change could, of course, be positive or negative. In our case the change occurs in terms of the proportion (denoted by "`Prop.`" of individuals entering and exiting each of the disease classes as the make the transition (denoted by "→") from one disease class the next. Thus our model is:

$$\begin{aligned} S(t+1) &= S(t) + \Big(\texttt{(Prop.R→S)} \times R(t) - \texttt{(Prop.S→I)} \times S(t)\Big) \\ I(t+1) &= I(t) + \Big(\texttt{(Prop.S→I)} \times S(t) - \texttt{(Prop.I→R)} \times I(t)\Big) \\ R(t+1) &= R(t) + \Big(\texttt{(Prop.I→R)} \times I(t) - \texttt{(Prop.R→S)} \times R(t)\Big) \end{aligned}$$

If the population is large, then we treat proportions as deterministic quantities that are related to rates at which individuals leave one disease class to go to another, as described in the SIRS modeling section § below. If populations are small, then the proportions at each time transition will vary stochastically, according to random sampling theory. We will use the notation

$$\text{Number-Leaving} \sim \texttt{Binomial}\,[\text{Number-in-State}, \text{Designated-Probability}]$$

to mean that the number of individuals leaving a particular disease state is given by a binomial drawing of individuals from the compartment in question where each individual will leave with the designated probability. Thus, if the underlying probability for each individual to move out of disease state X, denoted by `(Prob.X→)` then the actual randomly drawn number that move is given by:

$$\text{Number leaving X} \sim \texttt{BINOMIAL}\,[X(t), \texttt{Prob.X→}]$$

In our SIRS models, all individuals moving out of one disease class all go the same succeeding disease class in the sequence `S→I→R→S`. If a disease-induced death rate occurs, and all individuals leaving `I` do not go to `R`, but some die and go to `D` then we have to replace a `BINOMIAL` drawing with a `MULTINOMIAL` drawing as discussed in § below. However, since this is not the case for our SIRS model, the stochastic version of discrete time model is

$$\begin{aligned} S(t+1) &= S(t) + \text{Number leaving } \texttt{R} - \text{Number leaving } \texttt{S} \\ I(t+1) &= I(t) + \text{Number leaving } \texttt{S} - \text{Number leaving } \texttt{I} \\ R(t+1) &= R(t) + \text{Number leaving } \texttt{I} - \text{Number leaving } \texttt{R} \end{aligned}$$

where we use the binomial drawing process above to compute the number leaving each disease class using `Prob.R→` = `(Prop.R→S)`, `Prob.S→` = `(Prop.S→I)`, `Prob.I→` = `(Prop.I→R)` as our probabilities.

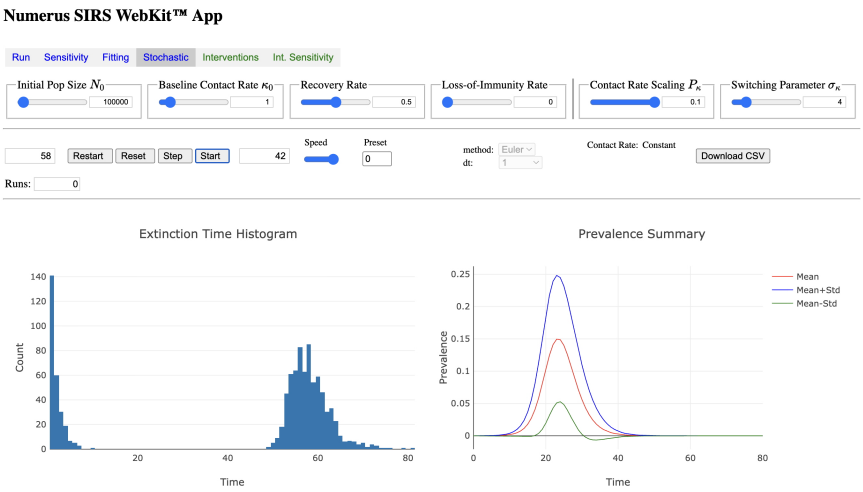



Figure 7: The `Stochastic` mode button is highlighted for a set of 1000 stochastic simulations. The number of simulations was entered into the window labeled `Runs:` on the extreme left-hand side immediately above the two graphs. This window now reads 0 since it counts down the runs as the simulation proceeds until no runs are left. The ribbons above it are as explained in the `Run` and `Sensitivity` modes. In this case A histogram of the times the prevalence first reaches 0 in all 1000 runs and the means and $\pm$ the standard deviations of prevalence over time for these 1000 runs are depicted in the left- and right-hand graphs respectively. The reproductive number,R-zero, which in the case of an SIRS model (recalling that $\beta = 1$ in the `Numerus SIRS WebKit`$^{\texttt{TM}}$ `APP`) is $R_0 = \frac{\beta\kappa_0}{\texttt{Recovery rate}}$ ($= 0.8/0.5 = 1/6$ in this depicted case). We note, here that provided $R_0 > 1$ the extinction time histogram will have two components, a probability mass just beyond the origin, representing epidemic failure in which pathogen transmission "quickly burns out" before an epidemic can get underway, and a probability mass that occurs after an epidemic has "burnt through" the population and eventually burns out for lack of enough susceptible individuals to keep the epidemic "burning." The proportion of simulations for which the epidemic failure component of histogram just beyond the origin represents a declining proportion of runs as the value of $R_0$ increases. Note: `method = Euler` and `dt = 1` because the simulation is discrete time (See Technical Material sections for details).

## *Stochastic Mode Dashboard*

The `Stochastic` mode dashboard (Fig 2) has the same parameter ribbon and run control ribbons as the `Run mode` dashboard (Fig 7), except for an additional number of `Runs:` window on the left-hand side immediately above the graph panels. The graphs below this are an histogram of extinction times (i.e., that time $t$ that $I(t) = 0$ first occurs after the start of the epidemic simulation) and a statistical summary (mean and standard deviation on either side of the mean) of the all prevalence ($I(t)$) trajectories including their 0 values beyond each their individuals extinction times, for each of the individual runs made. In the depicted graphs, the number of runs was 1000 and the 0 in the `Run` window indicates that no runs are left to be made (i.e., the simulation terminated aftr 1000 runs were completed). We stress in this mode that the integration step `dt` must be left at its default value of 1 (the stochastic model is discrete time, as formulated in the Technical Material starting on page 32).

### Things to explore

1 By varying the value of $\kappa_0$ between 0.5 and 5 in the `Constant Contact Rate` case, with other parameter values fixed at `Recovery Rate`=0.25 and `Loss-of-Immunity Rate`=0.0, construct a histogram of times at which the prevalence $I(t)$ becomes 0, as shown in Fig. 7. Note for each value $\kappa_0$ at least 500 runs should be made and use the data that in the downloadable CSV file available after each run to evaluate the outbreak probability for the set of model parameters used in the simulations. In addition, evaluate the proportion of simulations which resulted in a major outbreak, as an estimation of the outbreak probability. Plot the two results as function of $\kappa_0$.

2 In the `Constant Contact Rate` case, discuss the impact of changing both $\kappa_0$ and `Recovery Rate` on the probability of an outbreak while keeping fixed the ratio of their values at $\kappa_0$/`Recovery Rate` = 2.

3 In the `Constant Contact Rate` case, discuss the impact of changing the `Loss-of-Immunity Rate` on the probability of an outbreak for varying combinations of values for $\kappa_0$ and `Recovery Rate`.

4 What is the affect of an `Adaptive Contact Rate` on the probability of an outbreak? Support your answer with selected comparisons of simulations under different parameter conditions.

# Intervention Mode

### Underlying model

Before you use this App, you should have some experience using the `Numerus Deterministic SIRS WebKit`™ `App` discussed above. The `Numerus Deterministic SIRS WebKit`™ `App with Interventions App` adds three disease classes to the basic SIR model: dead (`D`), treated (`T`) and vaccinated (`V`) individuals. The SIRS model of the `Numerus Deterministic SIRS WebKit`™ `App with Interventions` is augmented as follows:

1 Individuals in the susceptible `S` and recovered class `R` exit to the vaccinated (Vac for short) class `V` at a rate given by

$$\texttt{Actual Vac Rate} = \begin{cases} \texttt{Vac Rate} & \text{for } t \geqslant \texttt{Vac Onset Time} \text{ and number vaccinated} \leqslant \texttt{Vac Max} \\ 0 & \text{otherwise} \end{cases}$$

The fact that the vaccination rate only apply to classes `S` and `R` is equivalent to assuming that no cognizance is taken of whether or not the individual was previously infected or was vaccinated sufficiently long ago to have had the vaccination effects wane to the point where the previously vaccinated individual had reentered the susceptible class. If the waning rate for vaccinated individuals is sufficiently small, however, then vaccinated individuals are highly unlikely to be re-vaccinated. Additional, the assumption is that individuals while under treatment are not vaccinated. Of course, the validity of these assumptions are disease specific and can be changed as needed by suitably modifying the default version of the `Numerus Deterministic SIRS+DTV WebKit`™ `App`.

2 Individuals in the infectious class `I` experience a disease-induced mortality rate. This `Disease Death Rate` parameter has a default value of 0.01 and ranges over [0,0.1] in steps of 0.001. As with incidence, mortality rates are compute and presented in graphs normalized to a rate per $10^5$ individuals.

3 Individuals in the infectious class `I` (whose number is $I(t)$ at time $t$( exit to the treatment class `T` (where the number under treatment at time $t$ is $T(t)$) at a rate given by

$$\text{Actual treatment rate} = \begin{cases} \texttt{Treat Rate} & \text{when } T(t) \leqslant \texttt{Treat Capacity} \\ 0 & \text{otherwise} \end{cases}$$

This implies an upper-bound to the number of individuals that can be undergoing treatment at anyone time so that the model can be used to determine if extra treatment capacity is needed to come online, as happen during during the recent COVID-19 pandemic.

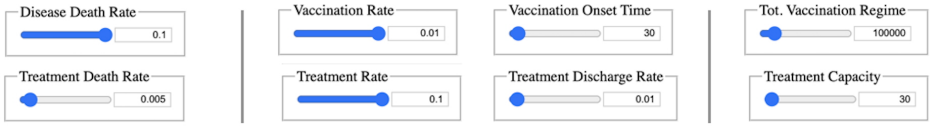
4 Individuals in the treatment class `T` are released from treatment to enter the recovered class `R` at a rate given by the `Treat Discharge Rate` parameter, which has a default value of 0.1 and a range of [0,0.5] in steps of 0.01.

5 Individuals in the treatment class `T` die at a rate that one expects to be less than the `Disease Death Rate` so the user can also set value for a `Treat Death Rate` The default value for the `Treat Death Rate` 0 and ranges from [0,0.1] in steps of 0.001.

## *Interventions Mode Dashboard*

In addition to the top ribbon of parameters in `Interventions` mode that are the same as in `Run` mode (See highlighted `Interventions` mode button in Fig 8) are listed below, as illustrated.

**Intervention Slider ribbons**




**Slider values and ranges**

**Disease Death Rate:** $[0, 0.1]$ in steps of 0.001. This is the disease-induced mortality rate that comes in addition to other mortalities (senescence, accidents, predation) that are not included in the model.

**Treat Death Rate:** $[0, 0.1]$ in steps of 0.001. One assumes under treatment the the disease-induced mortality rate is reduced, although this may not necessarily be the case (as might be the situation if we modeled pandemics in medieval times when blood letting was rife).

**Vac Rate:** $[0, 0.1]$ in steps of 0.001.

**Vac Onset Time:** $[0, 100]$ in steps of 1. The vaccination rates are only applied once the simulation time $t$ has reached the value of this parameter.

**Tot Vac Regimen:** $[0, 10^6]$ in steps of 1. This is the total amount of vaccines that will be available during the course of the epidemic (assumed to apply from the start of the vaccination program).

**Treat Rate:** $[0, 1]$ in steps of 0.01. This is the rate at which individuals in that are infected are moved into treatment (i.e., transfer from I to T, and it implicitly incorporates a rate for detecting sick individuals or diagnosing their disease).

**Treat Discharge Rate:** $[0, 1]$ in steps of 0.01. This is the rate at which treated individuals (class T) are released from treatment, and assumes these individuals immediately transfer to the recovered (R) class of individuals.

**Treat Capacity:** $[1, 10^4]$ in steps of 1.0. We note that $T(t)/N$ is the total proportion of individuals under treatment in the population so that this parameter

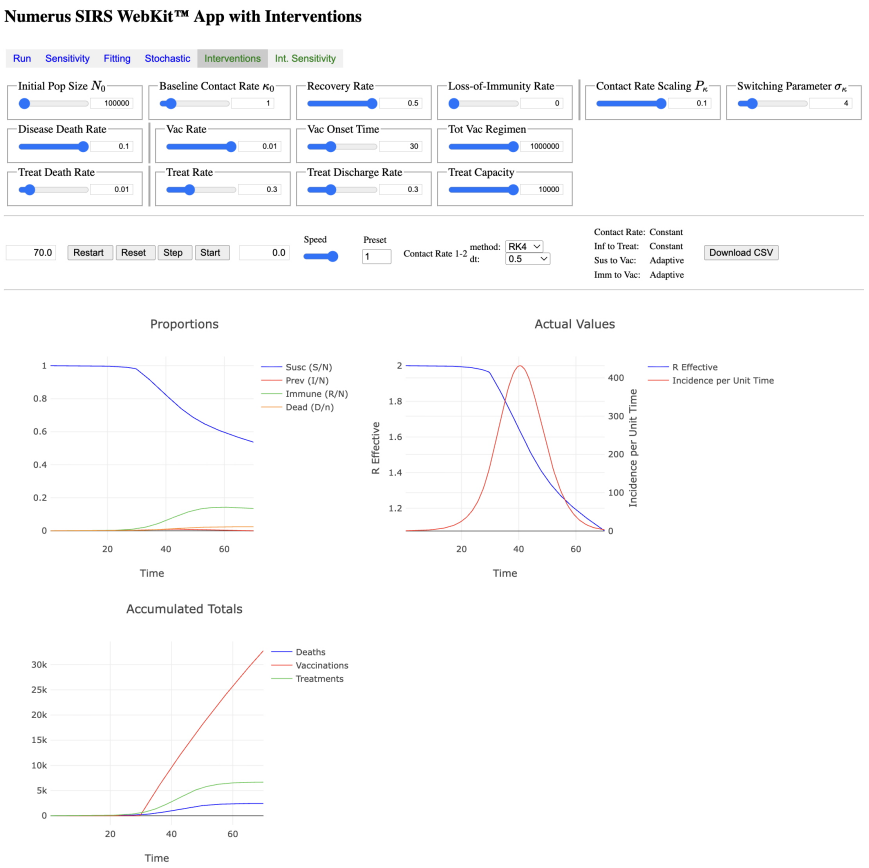



Figure 8: The `Intervention` mode button is highlighted for a run in the Intervention mode. The top ribbon of parameter sliders is the same as in `Run` mode, as as the top left and right graphs. The second and third ribbons of parameters allow for setting death rate and intervention rate parameters as described in the text. The bottom left-hand graphics panel depicts accumulated totals for the number of deaths, vaccinated and treated individuals. This particular mode includes 4 RAMS (see text for more details) that can be used to switch between constant and adaptive contact formulations (top of list on right-hand side just above the graphs), as well as allows the user to modify the flow rates of infecteds (I) to treated (T) (second from the top of the list), susceptibles (S) to vaccinated (V) (third from the top of the list) and immune (R) to vaccinated (bottom of the list). The results are for the parameter and RAM selections, as indicated.

divided by $N$ represents the proportion of individuals that can be under treatment (i.e., reflecting the capacity of the healthcare infrastructure) at any one time.

# Interventions Sensitivity Mode

As with the `Sensitivity` mode in the context of the SIRS model, the `Int. Sensitivity` mode is used to compare simulation results when one or more of the model parameters in the SIRS+DTV model are perturbed from a set of values that we refer to as the baseline values. In this extended mode, the sensitivity of the simulation trajectory can be assessed to perturbations in the value of the (`Baseline Contact Rate`, `Recovery Rate`, `Loss-of-Immunity Rate`, `Contact`

Rate Scaling (Adaptive contact option), Disease Death Rate, Vac Rate, Vac Onset Time, Tot Vac Regimen, Treat Death Rate, Treat Discharge Rate, and Treat Capacity.

An example of a sensitivity run is provided in Fig 5 here 11 different prevalence trajectories (left graphics panel) and their mean and one standard deviation on either side of the mean (right graphics panel) are depicted for the Baseline Contact Rate parameter ranging from 0.5 to 1.5 in steps of 0.1. Notice the peak prevalence moves to the left and increases as the contact rate increases from 0.5 to 1.5.

### *Int. Sensitivity Mode Dashboard*

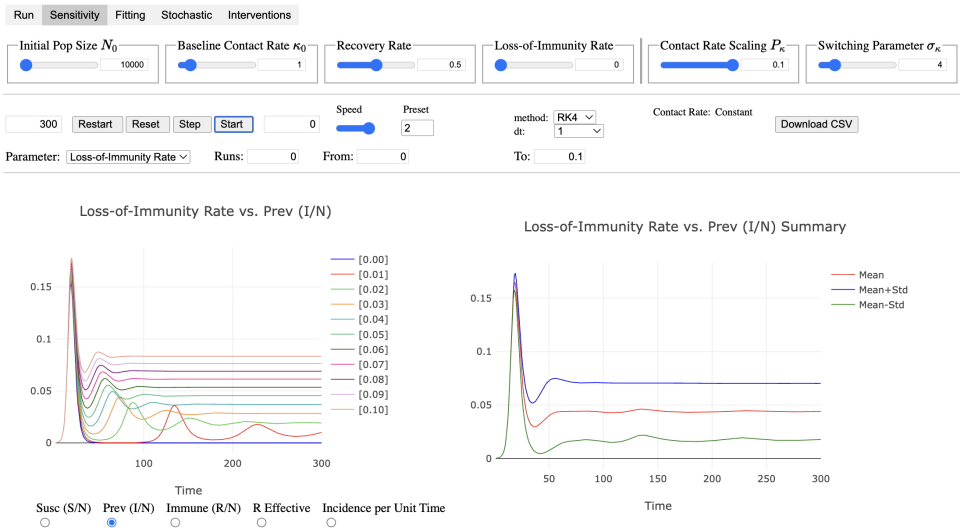
The Int. Sensitivity mode has the same dashboard as the Numerus SIRS WebKit™ App with Interventions dashboard with the addition of the same simulation control windows as the Sensitivity mode dashboard. Thus Users should familiarize themselves with both the Numerus SIRS WebKit™ App Sensitivity mode (blue button) and the Numerus SIRS WebKit™ App with Interventions regular Interventions (green button) mode before using the Numerus SIRS WebKit™ App with Interventions Int. Sensitivity mode.

## Things to explore

1. For the Interventions mode default parameter set Baseline Contact Rate $\kappa_0 = 1$, Recovery Rate $= 0.5$, and a Constant Contact process (Contact Scale parameter, $P_\kappa$, and Switching parameter, $\sigma_\kappa$ values are irrelevant), with all the intervention parameters set to 0, explore the effects of varying the Treat Rate parameter from 0 to 0.3 in steps of 0.05 on the timing and size of the peak incidence rate of the epidemic.
2. For the Interventions mode default parameter set Baseline Contact Rate $\kappa_0 = 1$, Recovery Rate $= 0.5$, and a Constant Contact process (Contact Scale parameter, $P_\kappa$, and Switching parameter, $\sigma_\kappa$ values are irrelevant), with all the intervention parameters set to 0, explore the effects of varying the Vac Rate parameter from 0 to 0.05 in steps of 0.01 on the timing and size of the peak incidence rate of the epidemic.
3. For the Interventions mode default parameter set Baseline Contact Rate $\kappa_0 = 1$, Recovery Rate $= 0.5$, and a Constant Contact process (Contact Scale parameter, $P_\kappa$, and Switching parameter, $\sigma_\kappa$ values are irrelevant), with all the intervention parameters set to 0, except for the Vac Rate=0.05, explore the effect of the value of the Vac Onset parameter value over the range of 5 to 15 days in steps of 1 day on the timing and size of the peak incidence rate of the epidemic, as well as the total number of vaccinations. Note: for this study both the Sus to Vac and Imm to Vac should be set to the Adaptive RAM option and the Tot Vac Regimen parameter must be large enough so that the User does not run out of vaccines.

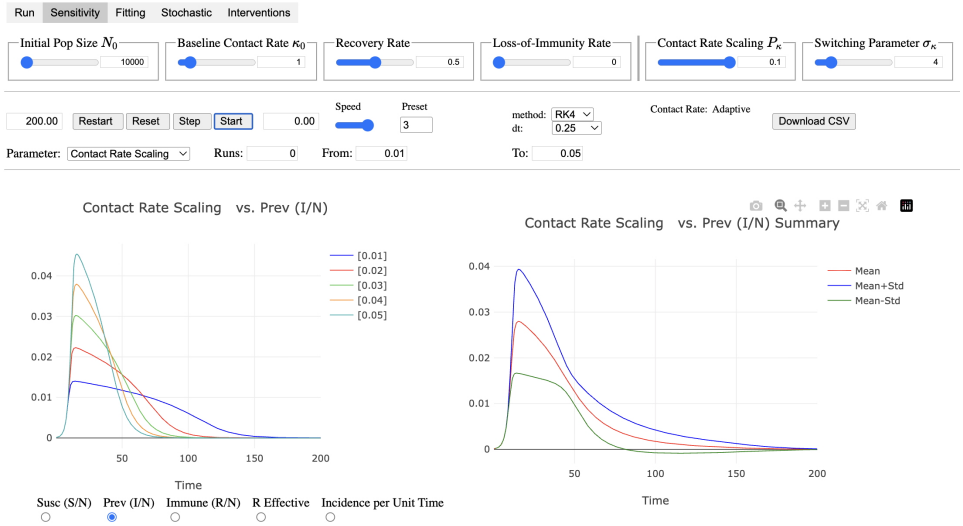
# Selected Answers

Endemicity (Q4 in `Run` mode).




Note that dampened oscillations are induced by the fact that it takes som time for the susceptible population to be restored and become reinfected with the effect most noticeable at the smallest `Loss-of-Immunity Rate` values.

Sensitivity to Adaptive Scaling (Q4 in `Run` mode).




Note how the curve is flattened as the effect of prevalence kicks in with decreaseing values of the `Prevalence Scaling` parameter (smaller values mean the contact rates are reduced at lower prevalence levels).

# Technical Material

## SIRS Deterministic Continuous Time Formulation

### The underlying deterministic mathematical model

The first of the Numerus WebKit™ Apps is the **Deterministic SIRS**. This App implements simulations of the following differential equation model with $\rho_{\rm ID} = 0$ (i.e., it assumes no disease-induced mortality, which means that $D(t) = 0$ and the fourth equation does not apply). We include deaths here to provide a more general approach that is needed later, once we consider the effects of vaccination and treatment on the severity of the mortality experienced in some epidemics (below $N(0) = N_0 = 100,000$ so that all numbers are normalized to values per one-hundred-thousand individuals):

$$\begin{aligned}
\frac{dS}{dt} &= \rho_{\rm RS}R - \rho_{\rm SI}S, \quad S(0) = N_0 - 1 (= 99,999) \\
\frac{dI}{dt} &= \rho_{\rm SI}S - \rho_{\rm IR}I - \rho_{\rm ID}I, \quad I(0) = 1 \\
\frac{dR}{dt} &= \rho_{\rm IR}I - \rho_{\rm RS}R, \quad R(0) = 0 \\
\frac{dD}{dt} &= \rho_{\rm ID}I, \quad D(0) = 0
\end{aligned} \tag{1}$$

where $S(t)$, $I(t)$, $R(t)$, and $D(t)$ are the number of individuals in disease compartments S, I, R, and D at time $t$, and the total number of individuals in the population at time $t$ is

$$N(t) = S(t) + I(t) + R(t) = N_0 - D(t) \tag{2}$$

Notes.

1 Large population size assumption. Equation 1 only holds when stochastic effects associated with small populations sizes can be ignored and averages are all that are needed to reliably predict the dynamics of the system. This is never true at the start of an epidemic when the number of infectious individuals is 1, so the model presented above must be replaced by a stochastic model (i.e., our Numerus WebKit™ App **Stochastic SIRS**) must be used to determine the dynamics of an epidemic at its start. However, once an epidemic has started and each of the compartments contains at least some hundreds of individuals, then the behavior of that epidemic, as predicated by Eq 1, becomes more reliable.

2 Initial conditions and proportions. Some nominal size $N_0$ is needed to set the initial conditions. Specifically, if we think of the variables $S(t)$, $I((t)$, and $R(t)$ in terms of numbers, and we use $I(0) = 1$ (see Eq 1) to represent the start of the epidemic, then the initial prevalence of the disease is $I(0)/N_0$. In our Deterministic SIRS WebKit™ App, we have set $N_0 = 100,000$, so that at the start of the epidemic the prevalence is $1/100,000 = 0.00001$. Thus selection of $N_0$ effects the starting prevalence in the population, the dynamical properties of an epidemic as described by Eq 1 applies to modeling proportions, and

hence prevalence, (just rescale all the variables in Eq 1 by N to see the same equations still apply), but otherwise does not affect other predictions such as what the peak prevalence will be or the shape of the prevalence curve beyond whatever starting prevalence is used.

3 Dead compartment. The dynamics of the system are really three rather than four dimensional because the last equation can be replaced by

$$D(t) = \int_0^t \rho_{\rm ID} I(t) dt, \quad D(0) = 0$$

4 No demography. When epidemics are rapid we use Eq 2 to determine the number of individuals in the population at time $t$. This ignores the fact that $N(t)$ is driven by births and non-disease induced deaths, not to mention immigration and emigration. These process come into play in modeling slowly progressing epidemics such as TB or HIV-AIDs, but can be ignored in rapidly progressing epidemics such as measles or influenza. We have also ignored age and sex structure, which becomes important with transmission and disease-induced death rates are age or sex dependent.

5 Disease transmission. The disease transmission rate $\rho_{\rm SI}$ can be broken down into the concatenated processes of a rate $\kappa(t)$ at which individuals at time $t$ make contact other individuals (i.e., each individual on average contacts $\kappa(t)$ other individuals at time $t$) and the proportion of those contacts that lead to disease transmission when a susceptible individual makes contact with an infectious individual. In the continuous time setting, this proportion is influenced by a "force of transmission" parameter $\beta$ such that the actual transmission rate—i.e., when a susceptible individual contacts another individual of which a proportion $I(t)/N(t)$ are infections—is

$$\rho_{\rm SI} = \beta \kappa(t) I(t)/N(t) \tag{3}$$

6 Incidence. The incidence rate, or the rate at which individuals transfer from disease class `S` to disease class `I` is given by

$$\rho_{\rm SI} S(t) = \beta \kappa(t) \frac{S(t) I(t)}{N(t)} \tag{4}$$

Therefore, the incidence over the interval $[t, t+1]$, which we denote by $\Delta^+ I(t)$ ($\Delta^+$, is used to denote change due to new additions to I, before accounting for the individuals that leave I), is given by

$$\text{Incidence per unit time:} \qquad \Delta^+ I(t) = \int_t^{t+1} \beta \kappa(t) \frac{I(t) S(t)}{N(t)} dt$$

7 Constant and seasonal transmission Most SIR models implicitly assume a constant or ***baseline contact rate*** $\kappa_0$

$$\text{Constant contact:} \qquad \kappa(t) = \kappa_0 \tag{5}$$

For many diseases, however, transmission varies with the season. In such cases, if $t$ is measure in days, then an easy way to introduce seasonality is to assume that $\kappa(t)$ is periodic with period 365 days. For example, the function

$$\underline{\text{Seaonal variation:}} \qquad \kappa(t) = \left(\frac{\kappa^{\max} - \kappa^{\min}}{2}\right)\left(1 + \sin\left(\frac{2\pi(t-\theta)}{365}\right)\right) + \kappa^{\min} \tag{6}$$

will fluctuate sinusoidally between $\kappa^{\max}$ and $\kappa^{\min}$, and $\theta$ is a parameter used to translate the points where the maximum and minimum contact rates occur during the course of each year.

8 Adaptive contact rate. Arguably, one of the most important modifications to the contact rate is to account for changes in once a pandemic has started. One way to deal with this is to assume the contact rate adapts, by decreasing either as a function of the proportion of individuals that are infectious (i.e., $I(t)/N(t)$). If we assume the latter, then a three parameter form for the contact rate $\kappa(t)$, that depends on a basic contact rate $\kappa_0 > 0$, an infectious proportion switching point or ***contact rate scaling*** factor $P_\kappa \in (0, 1)$, and an abruptness ***switching parameter*** $\sigma_\kappa \geqslant 0$ is given by the function [10]:

$$\underline{\text{Adaptive contact:}} \qquad \kappa(t) = \frac{\kappa_0}{1 + \left(\frac{I(t)}{N(t)} \Big/ P_\kappa\right)^{\sigma_\kappa}} \tag{7}$$

The switching point parameter $\sigma_\kappa$ may be set to 2 for gradual switching, 5 for relatively abrupt switching, or 20 to approximate a step function around the infectious proportion switching point $P_\kappa$.

9 Why we can set $\beta = 1$. If we look at Eqs 3-7, we see that the parameters $\beta$ and $\kappa_0$ are always paired multiplicatively so they act as a single quantity $\beta\kappa_0$. Thus, without loss of generality, we can set $\beta = 1$ if we think of the contact parameter $\kappa_0$ as an "effective contact rate" since the concept of a "contact event" in epidemiology is extremely inexact and influenced by how close individuals get one another and how long they spend together. Thus, in practice, the value $\beta\kappa_0$ must be estimated from data rather than computed from mechanistic principles.

10 Other rates are constant. For simplicity, most epidemic models assume the all the remaining rates in Eq 1 are constant. These are

(a) ***Recovery rate***, $\rho_{\text{IR}}$. The rate at which individuals transition from disease state I to R.

(b) ***Loss of immunity rate***, $\rho_{\text{RS}}$. The rate at which immunity wanes—i.e., that individuals transition from disease state R back to S.

(c) ***Disease-induced mortality rate***, $\rho_{\text{ID}}$. The rate at which individuals transition from disease state I to D—i.e. direct cause of death is disease (this may be hard to pull apart in practice in elderly individuals subject to morbidity factors prior to getting the modeled disease).

11 Ignored disease states. Several other disease can be added to the basic SIR epidemic process and are usually disease specific. They may play a secondary role

in terms of their overall influence on the epidemic, although the asymptomatic infectious states associated with COVID 19 made it harder than otherwise to control the spread its etiologically corona virus. In some disease models a latent disease state is included in which it is assumed that an individual has been exposed to a pathogen and enters a class denoted by E = exposed before entering the infectious class I once the latent period is over. Such extended models are often referred to as SEIR models. Since the addition of a latent period does not influence the probability of epidemic spill if no deaths occur while individuals are in class E[11] we have not included it in our model. The main effect of this state is to introduce a small time-delay in the rate at which an epidemic breaks out when spill overs occurs and play a minor role in slowing down the rate of disease spread in epidemics.

## The basic reproductive rate R-zero and probability of infection

The basic reproductive rate, $R_0$, of a disease at the start of an epidemic in a population that has never been exposed to the pathogen causing the outbreak represents the number of expected new cases that the index case (aka patient zero) will cause. This number is represented by

$$\begin{aligned} R_0 &= \text{contact rate} \times \text{force of transmission per contact} \times \text{infectious period} \\ &= \kappa \times \beta \times \frac{1}{\rho_{\text{IR}}} = \frac{\kappa\beta}{\rho_{\text{IR}}} \end{aligned} \tag{8}$$

The product $\kappa\beta$ can be used to obtain the incidence per susceptible over a short time interval $\Delta t$ at the start of the epidemic (also interpreted as the probability of a susceptible becoming infected over $[0, 1]$) by solving for the incidence over the period $t \in [0, \Delta t]$, assuming $I_0 = 1$. This number can be obtained by first solving the differential equation

$$\frac{dS}{dt} = -\kappa\beta I_0 S, \qquad \text{i.e., } I(t) = I_0 \text{ treated as constant for } t \in [0, \Delta t]$$

Integrating the above equation for the condition $I_0 = 1$ (to see how many susceptibles are infected by a single inectious individual; and assuming both $\kappa$ and $\beta$ constant over this interval) implies that $S(\Delta t) = e^{-\kappa\beta\Delta t} S_0$. Since the expected proportion of susceptibles that will become infected over $[0, \Delta t]$ (i.e., those that leave class S for class I) is given by $p_{\text{inf}} = \frac{S(0)-S(\Delta t)}{S(0)}$ (also interpreted as the initial probability of infection), we obtain the expression for the probability $p_{\text{infect}}(0, \Delta t)$ of infection per contact on $[0, \Delta t]$ for small $\Delta t$:

$$p_{\text{infect}}(0, \Delta t) = \left(1 - e^{-\kappa\beta\Delta t}\right) \tag{9}$$

Finally, we reiterate that most SIRS formulations do not explicitly identify a contact rate $\kappa$ so that this parameter does not appear at all in these formulations and also that $\gamma$ is used instead of $\rho_{\text{IR}}$ ($\gamma \equiv \rho_{\text{IR}}$). In such cases, $R_0 = \beta/\gamma$ and $p_{\text{infect}}(0, \Delta t) = \left(1 - e^{-\beta\Delta t}\right)$. But, as previously mentioned, it is useful to explicitly include $\kappa$ because it is needed to discuss adaptive contact and provide the structure needed to introduce quarantine rates in a sensible way.

## Fitting Models to Data

Methods for fitting epidemiological and other types of dynamical systems models to data is a vast area of research in its own right. Here we only touch the surface of the topic and discuss how the `Numerus Deterministics SIRS WebKit™ App` can be used to address the issue under relatively straightforward and manageable situations (i.e., not too many equations and with a few parameters at most free to vary during the fitting procedure). A gentle introduction to the field of fitting population models to data is provided by Hilborn and Mangel [12]. The issue of model selection itself [13, 14]—i.e., fitting models with different numbers of parameters to data based on information theoretic concepts—is beyond the scope of our presentation.

Briefly, fitting dynamic models to a set of observed incidence rates $\mathbf{\Delta^+ I} = \{\Delta^+ I_1, ..., \Delta^+ I_n\}$, where the index $i$ in $\Delta^+ I_i$ refers to time $t = i$, $i = 1, .., n$, typically involves generating a set of comparable values $\mathbf{\Delta^+ I}(\hat{\boldsymbol{\theta}}) = \{\Delta^+ I(1; \hat{\boldsymbol{\theta}}), ..., \Delta^+ I(n, \hat{\boldsymbol{\theta}})\}$ from a model that has a set of $m$ parameters $\boldsymbol{\theta} = \{\theta_1, ..., \theta_m\}$, where $\Delta^+ I(i; \hat{\boldsymbol{\theta}})$ is the incidence value in the model at time $t = i$ when the parameter values are $\boldsymbol{\theta} = \hat{\boldsymbol{\theta}}$.

The two dominant approaches to fitting models to data are least-squares estimation (LSE), which is equivalent to maximum likelihood estimation (MLE) [15] when errors are normal or asymptotically approaches MLE when sample sizes are very large. The latter is typically embedded in a Markov Chain Monte Carlo (MCMC) algorithm that constructs a probability distribution for $\boldsymbol{\theta}$ using Bayes theorem [16, 17, 18, 19]. MCMC requires the likelihood function to be known. This can be obviated, though, by assuming the distribution of model outcomes to be Poisson (as we do below), using likelihood-function-free methods [20], or using approximate Bayesian approaches [21].

The LSE method, used in the `Numerus Deterministics SIRS WebKit™ App` minimizes the sum-of-squares residuals (or error) measure over all admissible choices of parameters $\boldsymbol{\theta}$ where

$$\mathcal{R}_{\mathrm{SS}}(\boldsymbol{\theta}) = \sum_{i=1}^{m} \left(\Delta^+ I(i, \boldsymbol{\theta}) - \Delta^+ I_i\right)^2 \tag{10}$$

where we remind the reader that $\Delta^+ I_i$ are the data and $\Delta^+ I(i, \boldsymbol{\theta})$ are the simulated values obtained using the parameter values $\boldsymbol{\theta}$ in the simulation.

On the other hand, MLE methods that assume model outcomes are Poisson, but with a different simulated Poisson mean $\Delta^+ I(i, \boldsymbol{\theta})$ for each data point $\Delta^+ I_i$, $i = 1, ..., t$, in $\mathbf{\Delta^+ I}$ involves maximizing the log-likelihood function

$$\ln \mathcal{L}(\mathbf{\Delta^+ I}|\boldsymbol{\theta}) = \sum_{i=1}^{t} \ln \left( \frac{\Delta^+ I(i, \hat{\boldsymbol{\theta}})^{\Delta^+ I_i} e^{-\Delta^+ I(i, \boldsymbol{\theta})}}{\Delta^+ I_i!} \right)$$

## SIRS Discrete and Stochastic Formulations

The discretized version of the SIRS model when disease-induced deaths are not considered is given by the following set of $t = 0, 1, ..., t_{\text{fnl}}$ when simulated over the interval $[0, t_{\text{fnl}}]$

SIRS discrete-time model

$$\begin{aligned} S(t+1) &= (1-p_{\text{SI}})\,S(t) + p_{\text{RS}}R(t), \quad S(0) = N_0 - 1 \\ I(t+1) &= (1-p_{\text{IR}})\,I(t) + p_{\text{SI}}S(t), \quad I(0) = 1 \\ R(t+1) &= (1-p_{\text{RS}})\,R(t) + p_{\text{IR}}I(t), \quad R(0) = 0 \end{aligned} \tag{11}$$

where the proportions $p_{XY}$ are related to the rates $\rho_{XY}$ by the equation (see Box 1 and cf. Eq. 9)

$$p_{\text{XY}} = 1 - e^{-\rho_{\text{XY}}}, \quad \text{X}\neq\text{Y, and X, Y} = \text{S, I, and R} \tag{12}$$

Thus, as required, $p_{\text{XY}} = 0$ when $\rho_{\text{XY}} = 0$ and $p_{\text{XY}} \to 1$ as $\rho_{\text{XY}} \to \infty$.

A discrete-time stochastic version of this model is obtained from Eq. 11 by assuming that the quantities $p_{\text{SI}}$ represent probabilities proportions. (Note: Continuous-time stochastic models require a level of mathematical treatment beyond the scope of this presentation; e.g, see [22]). In this case, the simulation takes the form of a discrete-time Monte Carlo process in which drawings from a binomial distribution are considered rather than computations of proportional change. Specifically, simulation involves the following drawings, using the following notation to denote such drawings (aka samplings):

$$\hat{X}_p \sim \texttt{BINOMIAL}[X, p] \quad \text{with expected value } pX \text{ and variance } p(1-p)X$$

We note that $\hat{X}_p$ is the actual number of actual objects drawn or sampled from a total of $X$ objects, where each object has the probability $p$ of being selected (and hence $1-p$ of not being selected).

Formally, our stochastic model is the following Monte Carlo simulation that begins with specified values for $S(0)$, $I(0)$, $R(0)$ and $D(0)$ and continues with successive samplings for $t = 1, 2, ..., t_{\text{fnl}}$ :

SIRS stochastic model

$$\begin{aligned} \hat{S}_{\text{I}}(t) &\sim \texttt{BINOMIAL}[S(t), p_{\text{SI}}] \\ \hat{I}_{\text{R}}(t) &\sim \texttt{BINOMIAL}[I(t), p_{\text{IR}}] \\ \hat{R}_{\text{S}}(t) &\sim \texttt{BINOMIAL}[R(t), p_{\text{RS}}] \\ S(t+1) &= S(t) - \hat{S}_{\text{I}}(t) + \hat{R}_{\text{S}}(t), \quad S(0) = N_0 - 1 \\ I(t+1) &= I(t) - \hat{I}_{\text{R}}(t) + \hat{S}_{\text{I}}(t), \quad I(0) = 1 \\ R(t+1) &= R(t) - \hat{R}_{\text{S}}(t) + \hat{I}_{\text{R}}(t), \quad R(0) = 0 \end{aligned} \tag{13}$$

## Treatment and Vaccination in the Continuous Time SIRS Model

We now add treatment (T), and vaccination (V) classes to our SIRS+D model and define

$$N(t) = S(t) + I(t) + R(t) + T(t) + V(t) \quad N(0) = N_0 (= 100,000) \tag{14}$$

For simplicity, we assume that individuals under treatment are no longer able to transmit pathogens to the population at large—i.e., they are essentially completely quarantined. In reality, however, the situation is much more complicated than this: the ability of individuals under treatment to transmit pathogens depends on how strict the quarantine procedures are. In addition, if we structure the population to include healthcare workers or members of the infected individuals household, then clearly these healthcare workers and household members are likely to be at some particular risk of infection from individuals under treatment. Thus, moving beyond our simplifying assumption of individuals under treatment being effectively completely quarantined requires additional model structure and transmission parameters, which is not included in the model formulated here.

*Deterministic Formulation*

The dynamic equations consist of the following system of 5 differential equations, augmented by the three integrations that allow us to keep track of the accumulating deaths ($D(t)$), cases that are treated ($T^{\text{total}}(t)$), and individuals that are fully vaccinated ($V^{\text{total}}(t)$)

SIRS+DTV deterministic cont.-time model

$$\begin{aligned}
\frac{dS}{dt} &= \rho_{\text{RS}} R + \rho_{\text{VS}} V - (\rho_{\text{SI}} + \rho_{\text{SV}}) S, \quad S(0) = S_0 \\
\frac{dI}{dt} &= \rho_{\text{SI}} S - (\rho_{\text{IR}} + \rho_{\text{IT}} + \rho_{\text{ID}}) I, \quad I(0) = I_0 \\
\frac{dR}{dt} &= \rho_{\text{IR}} I + \rho_{\text{TR}} T - (\rho_{\text{RS}} + \rho_{\text{RV}}) R, \quad R(0) = R_0 \\
\frac{dT}{dt} &= \rho_{\text{IT}} I - (\rho_{\text{TR}} + \rho_{\text{TD}}) T, \quad T(0) = T_0 \\
\frac{dV}{dt} &= \rho_{\text{SV}} S + \rho_{\text{RV}} R - \rho_{\text{VS}} V, \quad V(0) = V_0 \\
D(t) &= \int_0^t \big(\rho_{\text{ID}} I(t) + \rho_{\text{TD}} T(t)\big) dt \\
T^{\text{total}}(t) &= \int_0^t \rho_{\text{IT}} I(t) dt \\
V^{\text{total}}(t) &= \int_0^t \big(\rho_{\text{SV}} S(t) + \rho_{\text{RV}} R(t)\big) dt
\end{aligned} \tag{15}$$

For simplicity, we will initially assume a constant treatment rate $\rho_{\text{IT}} = \rho_{\text{treat}}$ that is implemented from the onset of the epidemic being modeled. However, we will place a maximum $T^{\max}$ on the number of individuals that can be in treatment at anyone time, due to a limited capacity of the healthcare system to take care of sick

individuals. Thus, we have

$$\underline{\text{Treatment intervention}} \qquad \rho_{\mathrm{IT}}(t) = \begin{cases} \rho_{\mathrm{treat}} & \text{when } T(t) \leqslant T^{\max} \\ 0 & \text{otherwise} \end{cases} \tag{16}$$

This intervention, however, will be available to the user to elaborate through a RAM (runtime alternative module) that is the hallmark of our RAMP (runtime alterable model platform) technology. Eq. 16 will be the `Default` formulation while alternative 1 will be constant application of $\rho_{\mathrm{IT}}$ with not upper limit.

For the sake of completeness, we note that since the outflow from I now includes both flows to R, T, and D the expression for $R_0$ in Eq. 8, while individuals in T and D are assumed not to transmit pathogen (note for disease, such as Ebola, pathogen is transmitted from individuals in D preparation of the corpses for burial; [23]) now becomes, for the case that includes quarantined treatment and disease-induce death

$$\underline{\text{Reproductive value}} \text{ (with treatment \& virulence)} \qquad R_0 = \frac{\kappa\beta}{\rho_{\mathrm{IR}} + \rho_{\mathrm{IT}} + \rho_{\mathrm{ID}}} \tag{17}$$

For simplicity, we will initially assume a constant vaccination rate $v$ that is implemented from time $t_{\mathrm{V_{on}}}$ onwards. As with treatment, we will place an upper bound on the number of vaccination regimens that can be administered, where a vaccination regimen is defined to be a complete course that consists of one or more shots over a specified interval of time. Note, for simplicity, we assume that the full effect of the vaccination starts at the time of administering the first shot in the prescribed regimen (at which time the individual is transferred to V from S, C, L, R, or Q, as the case may be). An individual that later transfers from R back to S may then receive a second regime in an ongoing vaccination rollout program. The vaccination rate $v$ itself will be available to the user to elaborate through our `Vacc` RAM (runtime alternative module). Thus our default ***vaccination rollout program*** is defined by

$$\underline{\text{Vaccination}} \qquad \rho_{\mathrm{XV}}(t) = \begin{cases} v & \text{for } t \geqslant t_{\mathrm{V_{on}}} \text{ and } V^{\mathrm{total}} \leqslant V^{\max}, \text{ X = S and R} \\ 0 & \text{otherwise} \end{cases} \tag{18}$$

Note, that in our default settings, this vaccination rate applies equally well to both susceptible and recovered/immune individuals. In the `Numerus SIRS WebKit™ with Interventions App`, this rate is set up as a RAM for both $\rho_{\mathrm{SV}}(t)$ and $\rho_{\mathrm{RV}}(t)$ formulations to allow the user to explore more sophisticated vaccination regimens where, say, vaccinations are only give the susceptible, but not individuals that are in the recovered class, and so on.

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