SENSAI: R0_README file

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1 How to Define R_0 in SENSAI

SENSAI is capable of automatically defining the basic reproduction ratio, R_0, as defined by the Next Generation method, for appropriate epidemiological models. However, SENSAI is not limited to infection modeling, so specific syntax is required so that SENSAI recognizes if a model is compatible to the definition of R_0. The following guide will instruct the user on how to edit the MuPAD templates so that SENSAI will produce R_0 and its sensitivity analysis.

1. Edit the MuPAD templates to define your model equations. These should be stored as the vector $g[i]$, the right-hand side of the equation for the variable $x[i]$.

2. Define which equations from g define the dynamics of infected classes. Store these indices in the variable $NextGen$. Note that $NextGen$ must be written in *matrix* syntax. Consider the following examples.

   (a) For example, if the model includes three states, S, I, and R, in that order, $NextGen := matrix([2]);$.

   (b) If the model has more than one equation describing an infected class, list them in the order they appear. For example, if the model describes $S_1, I_1, R_1, S_2, I_2, R_2$ in that order, $NextGen := matrix([2, 5]);$.

(c) *If you do not wish to calculate R_0 for the model, define $NextGen = matrix([0])$, or let the first entry of $NextGen$ be 0.*

3. If the model has four or more infected classes, you may want to consider computing R_0 without its sensitivities. R_0 will be a very lengthy expression for such models, and the derivatives will require a lot of time to compute. If this is the case, define "R0_only" to be 1. If you wish to calculate the sensitivities anyway, define "R0_only" = 0.

   (a) While running the SENSAI GUI, you may encounter large delays in "Create MATLAB files using MuPAD" if R0_only = 0. If your patience has run thin, you must terminate the program through the task manager. The emergency stop in MATLAB of CTRL+c in the command window will not work, as the computation of R_0 is done externally in a MuPAD procedure call.

4. If the analytical expression for R_0 is already known, it may be faster (and more accurate if MuPAD can not solve R_0) to use this expression of R_0 for the quantity of interest (*qoi*) instead of re-deriving the expression during the "Create MATLAB files using MuPAD" phase.

1.1 Possible Problems with R_0

There are some examples in which the Next Generation construction of R_0 is not valid, or is not compatible with SENSAI. The following are possible problems the user might encounter when trying to define R_0.

1. **Problems with ODE models.** For R_0 to be valid, the model must satisfy the conditions of Theorem 2 in *Reproduction numbers and subthreshold endemic equilibria for compartmental models of disease transmission*, van den Driessche 2002. Recall for ODEs, the Next Generation definition of $R_0 = \rho(FV^{-1})$ where $F = \dfrac{\partial \mathcal{F}_i}{\partial x_j}(x^\star) \quad 1 \leq i, j \leq m$ describes new infections and $V = \dfrac{\partial \mathcal{V}_i}{\partial x_j}(x^\star) \quad 1 \leq i, j \leq m$ describes transfer of existing infections, $x^\star$ is the disease-free equilibrium, the infected classes are $1, \ldots, m$, and $\rho(\cdot)$ denotes the spectral radius operator.

(a) The fecundity matrix F is not nonnegative. This is part of assumption (A1) of van den Driessche 2002.

(b) The transition matrix V is singular. This can occur if an equation is in the model as a placeholder, but the right-hand side is identically 0. This state must be removed from the system for R_0 to be valid.

(c) The disease-free subspace is not invariant. That is, infection can enter a disease-free population through a nonzero component in a state that is identified as disease-free. This can occur in models with background infection rates, or in models where the infective classes are not identified properly. This is assumption (A4).

(d) The equilibrium is not asymptotically stable in the absence of disease. That is, if $\mathcal{F} = 0$, there is an eigenvalue of the Jacobian of the full system evaluated at $x^\star$ that has a positive real part. This is assumption (A5).

2. **Problems with map models.** For R_0 to be valid, the model must satisfy the conditions of Theorem 2.1 in *The Basic Reproduction Number in Some Discrete-Time Epidemic Models*, Allen 2008. Recall for maps, the Next Generation definition of $R_0 = \rho(F(I - T)^{-1})$, where I is the $m \times m$ identity and F and $-T$ are defined the same as F and V for ODEs, respectively.

   (a) The fecundity matrix F is not nonnegative.

   (b) The transition matrix T is not nonnegative.

   (c) The transition matrix T is singular. This can occur if an equation is in the model as a placeholder, but the right-hand side is identically 0. This state must be removed from the system for R_0 to be valid.

   (d) The transition matrix T is not asymptotically stable. That is, $\rho(T) \geq 1$.

   (e) The equilibrium is not asymptotically stable in the absence of disease. That is, $\rho(C) \geq 1$ where C is the Jacobian of the right-hand side of the noninfectious states.

Notice that assumptions (A2) and (A3) for ODE models are not automatically checked by SENSAI. These assumptions must be verified by the user,

but are usually true. For map models, the assumption of a unique DFE is not checked by SENSAI, nor is the condition that $F+T$ is irreducible. These should also be checked by the user to ensure a valid R_0. It is difficult to check both of these conditions, but again, for most models, $F+T$ is irreducible based on the structure of T having a nonzero main diagonal and a sub-diagonal and the structure of F having a nonzero top row.

There are a number of reasons for any of the problems in lists 1 and 2 to occur. Perhaps the model does not have a valid Next Generation construction of R_0. If this is the case, some alternative means to calculate R_0 should be sought, if desired. Alternatively, SENSAI may not be able to recognize which terms describe new infections and belong in $\mathcal{F}$ and which terms describe transfer of existing infections and belong in $\mathcal{V}$ or $\mathcal{T}$. The following criteria are used by SENSAI to determine the placement of each term. If the terms of the model will not be placed in the biologically correct vectors, SENSAI fails to compute the Next Generation R_0.

1. If the term X in an equation describing an infective class involves a state variable from a noninfectious class, $X \in \mathcal{F}$, unless the occurrence of the noninfectious state variable is part of a sum of all state variables (that is, the term is scaled by the total population).

   Important Note for MuPAD: At this point, MuPAD is not as effective as Maple at analytical computations. There may be examples (like the Hantavirus model) where MuPAD can not account for the scaling by the total population. This problem will hopefully be fixed in a future version of MuPAD and is based on the inefficiency of the `subs()` command.

2. If the term X in an equation describing an infective class does not involve any state variables and is only a parameter, product of parameters, or quotient of parameters, $X \in \mathcal{F}$. If terms like these exist, the disease-free subspace will not be invariant, and the model will not have a valid Next Generation R_0.

3. Every other term X that does not satisfy the above will be placed in $\mathcal{V}$ for ODEs, or $\mathcal{T}$ for maps.

2 Template Examples

2.1 MAP Examples

2.1.1 Caswell 08

This model is from Caswell's *Perturbation analysis of nonlinear matrix population models*, 2008. It involves two stages, juveniles (x_1) and adults (x_2).

$$\mathbf{x}(t+1) = \begin{pmatrix} \sigma_1(1-\gamma) & f \\ \sigma_1\gamma & \sigma_2 \end{pmatrix} \mathbf{x}(t)$$

where the juvenile survival $\sigma_1(\mathbf{x}) = \tilde{\sigma}e^{-\mathbf{e}^{\mathrm{T}}\mathbf{x}}$, where $\mathbf{e}$ is a vector of ones, σ_2 is the adult survival, γ is the maturation probability, and f is the adult fertility. The parameter values given are $(f, \gamma, \tilde{\sigma}, \sigma_2) = (0.25, 1/15, 0.98, 0.95)$.

The main purpose of this model is to verify that SENSAI gives the same equilibrium and sensitivities to those mentioned in the paper. This model also serves as a great template for MAP examples.

2.1.2 Hantavirus

This model is from Allen and van den Driessche, *The Basic Reproduction Number in Some Discrete-Time Epidemic Models*, 2008. It involves susceptible and infected male and female rodents.

$$\left.\begin{aligned} S_m(t+1) &= \left[\frac{B}{2} + e^{-\beta_m I_m(t) - \beta_f I_f(t)} S_m(t)\right] D(N) \\ I_m(t+1) &= \left[(1 - e^{-\beta_m I_m(t) - \beta_f I_f(t)}) S_m(t) + I_m(t)\right] D(N) \\ S_f(t+1) &= \left[\frac{B}{2} + e^{-\beta_f I_m(t) - \beta_f I_f(t)} S_f(t)\right] D(N) \\ I_f(t+1) &= \left[(1 - e^{-\beta_f I_m(t) - \beta_f I_f(t)}) S_f(t) + I_f(t)\right] D(N) \end{aligned}\right\}$$

where the logistic growth is scaled by

$$D(N) = \frac{K}{K + (b/2)N}.$$

where K is the carrying capacity and N is the total population; the harmonic mean birth function is

$$B(N_m, N_f) = \frac{2bN_mN_f}{N}$$

where $N_m = S_m + I_m$ is the total number of males, $N_f = S_f + I_f$ is the total number of females, and $b > 0$ is the average litter size, k is the number of contacts that result in an infection, and β_m and β_f are the infection rate constants of males and females, respectively. Parameter values are not provided in the paper, but some reasonable values are $K = 1000$, $\beta_f = 0.09$, $\beta_m = 0.9$, and $b = 6$.

The main purpose of this model is to verify that SENSAI gives the same value of R_0 as the paper. This example exhibits two common practices in model formulation which SENSAI performs extremely well *in the Maple version*. First, every term is scaled by the total population N. Second, the infection rate is given by a probability of a non-infection not occurring. Unfortunately, while SENSAI handles the second issue, it is not able to handle the first. This is due to MuPAD's ineffective `subs()` command.

As an illustration, consider the following term. Suppose there are two states x_1 and x_2 and the term in consideration is $p_1 x_2/(p_1 + x_1 + x_2)$. If x_2 is the infectious state, then this term belongs in $\mathcal{V}$, since the only appearance of a non-infective state is in the denominator, which is just a scaling by the total population. This illustrates what occurs for the Hantavirus model with the scaling $D(N)$, with p_1 acting as K. While the Maple command `subs(term,` $x_1 + x_2 = N$`)` converts this term to $p_1 x_2/(p_1 + N)$, the identical MuPAD command does not. If p_1 were not in the denominator, the MuPAD command would work as desired. Unfortunately, the computation of R_0 for models with the scaling of the total population is not available in the MuPAD version of SENSAI, although it is available for the Maple version.

2.1.3 Six Stage Genetics

This model is based on Caswell08, adding partially dominant selection based on viability and two alleles.

2.2 ODE Examples

2.2.1 SIR

This model is a typical SIR model with logistic growth.

$$\left.\begin{aligned} \frac{dS}{dt} &= rN\left(1-\frac{N}{K}\right) - \beta SI - \delta S, \\ \frac{dI}{dt} &= \beta SI - \gamma I - \mu I - \delta I, \\ \frac{dR}{dt} &= \gamma I - \delta R, \end{aligned}\right\}$$

where $N = S + I + R$ is the total population at any time t, r is the per capita growth rate, K is the carrying capacity, β is the infection rate, δ is the natural death rate of the species, γ is the recovery rate, and μ is the disease specific death rate. Some reasonable parameter values are $r = 0.5$, $K = 1000$, $\beta = 0.1$, $\delta = 0.2$, $\gamma = 0.02$, and $\mu = 0.1$.

The main purpose of this model is that it is a standard ODE infection model with a simple R_0 that can be easily verified by hand. This model also serves as a great template for ODE examples.

2.2.2 SI (Indirect Transmission)

This model is an SI model that involves indirect transmission of the infection.

$$\left.\begin{aligned} \frac{dS}{dt} &= rN\left(1-\frac{N}{K}\right) \\ \frac{dI}{dt} &= \beta - \gamma I \end{aligned}\right\}$$

where $N(t) = S(t) + I(t)$ is the total population, r is the per capita growth rate, K is the carrying capacity, β is the background transmission probability, and γ is the recovery rate.

The explaination of this model in detail can be found in *Sensitivity Analysis of the Basic Reproduction Number and other Quantities for Infectious Disease Models*, Masters Thesis by Mikucki, 2012. Parameter values may be chosen as $r = 0.5$, $\beta = 0.8$, $\gamma = 0.02$, and $K = 1000$.

The main purpose of this model is to show that models with a background (indirect) transmission of the disease through the environment or some alternative source do not have a valid R_0.

2.2.3 Plague

This model is given by Buzby et. al. in *Analysis of the sensitivity properties of a model of vector-borne bubonic plague*, 2008. The first three classes are the SIR classes of rats, N is the average number of fleas living on a rat, and F is the number of free infectious fleas that are searching for a new host.

$$\left.\begin{aligned}
\dot{S}_R &= r_R S_R\left(1-\frac{T_R}{K_R}\right) + r_R R_R(1-p) - d_R S_R - \beta_R \frac{S_R}{T_R} F(1-e^{-aT_R}) \\
\dot{I}_R &= \beta_R \frac{S_R}{T_R} F(1-e^{-aT_R}) - (d_R + m_R) I_R \\
\dot{R}_R &= r_R R_R\left(p-\frac{T_R}{K_R}\right) + m_R g_R I_R - d_R R_R \\
\dot{N} &= r_F N\left(1-\frac{N}{K_F}\right) + \frac{d_F}{T_R} F(1-e^{-aT_R}) \\
\dot{F} &= (d_R + m_R(1-g_R)) I_R N - d_F F
\end{aligned}\right\}$$

where $T_R = S_R + I_R + R_R$ is the total size of the rat population, r_R is the net rat reproduction rate, K_R is the rat carrying capacity, p is the proportion of offspring that inherity the disease, d_R is the natural rat death rate, β_R is the transmission rate from rats to fleas, m_R is the rate that rats leave the infected class, g_R is the fraction of rates that become resistant, a is the searching efficiency of the fleas, r_F is the net flea reproductive rate, d_F is the natural flea death rate, and K_F is the flea carrying capacity.

2.2.4 Dengue

This model is given by Garba in *Backward bifurcations in dengue transmission dynamics*, 2008. It is an SEIR model that descirbes the dynamics of dengue fever, an infection carried by a vector, mosquiteos. The equations

are

$$\left.\begin{aligned}
\frac{dS_H}{dt} &= \Pi_H - \lambda_H S_H - \mu_H S_H \\
\frac{dE_H}{dt} &= \lambda_H S_H - (\sigma_H + \mu_H) E_H \\
\frac{dI_H}{dt} &= \sigma_H E_H - (\tau_H + \mu_H + \delta_H) I_H \\
\frac{dR_H}{dt} &= \tau_H I_H - \mu_H R_H \\
\frac{dS_V}{dt} &= \Pi_V - \lambda_V S_V - \mu_V S_V \\
\frac{dE_V}{dt} &= \lambda_V S_V - (\sigma_V + \mu_V) E_V \\
\frac{dI_V}{dt} &= \sigma_V E_V - (\mu_V + \delta_V) I_V
\end{aligned}\right\}$$

where $\lambda_H = \frac{C_{HV}}{N_H}(\eta_V E_V + I_V)$ is the human infection rate, $\lambda_V = \frac{C_{HV}}{N_H}(\eta_H E_H + I_H)$ is the vector infection rate, and $N_H = S_H + E_H + I_H + R_H$ is the total human population. The parameter values provided are $\mu_H = 0.0195$, $\sigma_H = 0.5300$, $\Pi_H = 10$, $\delta_H = 0.9900$, $\eta_H = 0.9900$, $\tau_H = 0.2000$, $\mu_V = 0.0140$, $\sigma_V = 0.2000$, $\Pi_V = 30$, $\delta_V = 0.0057$, $\eta_V = 0.9800$, and $C_{HV} = 0.038$.

An interesting initial condition for the model is $\mathbf{x_0} = (\frac{\Pi_H}{\mu_H}, 0, 0, 0, \frac{\Pi_V}{\mu_V}, 0, 200)$, which will show that even thought $R_0 < 1$, infection may still persist in the population.

2.2.5 Typhoid

This model is given by Bailey and Duppenthaler in *Sensitivity Analysis in the Modelling of Infectious Disease Dynamics*, 1980. It is a 9-stage SIR type model where x_1 = susceptibles, x_2 = incubating noninfectious, x_3 = incubating infectious, x_4 = sick infectious, x_5= sick noninfectious, x_6 = temporary carrier, x_7 = permanent carrier, x_8 = short resistance, and x_9 = long resis-

tance.

$$\left.\begin{aligned}
\dot{x_1} &= -(\rho_{12}+\rho_{13})x_1 y + \rho_{41}x_4 + \rho_{51}x_5 + \rho_{61}x_6 + \rho_{81}x_8 + \rho_{91}x_9 - \mu x_1 + \mu \\
\dot{x_2} &= \rho_{12}x_1 y - (\rho_{23}+\rho_{24}+\rho_{25}+\mu)x_2 + \rho_{32}x_3 \\
\dot{x_3} &= \rho_{13}x_1 y - (\rho_{32}+\rho_{34}+\rho_{35}+\mu)x_3 + \rho_{23}x_2 \\
\dot{x_4} &= \rho_{24}x_2 + \rho_{34}x_3 + \rho_{54}x_5 - (\rho_{41}+\rho_{45}+\rho_{46}+\rho_{48}+\mu)x_4 \\
\dot{x_5} &= \rho_{25}x_2 + \rho_{35}x_3 + \rho_{45}x_4 - (\rho_{51}+\rho_{54}+\rho_{58}+\mu)x_5 \\
\dot{x_6} &= \rho_{46}x_4 - (\rho_{61}+\rho_{67}+\rho_{68}+\mu)x_6 \\
\dot{x_7} &= \rho_{67}x_6 - \mu x_7 \\
\dot{x_8} &= \rho_{48}x_4 + \rho_{58}x_5 + \rho_{68}x_6 - (\rho_{81}+\rho_{89}+\mu)x_8 \\
\dot{x_9} &= \rho_{89}x_8 - (\rho_{91}+\mu)x_9
\end{aligned}\right\}$$

Parameter values are provided by Bailey are as follows: $\rho_{12} = 8.43381 \times 10^{-3}$, $\rho_{13} = 8.51900 \times 10^{-5}$, $\rho_{23} = 2.85720 \times 10^{-3}$, $\rho_{24} = 6.78585 \times 10^{-2}$, $\rho_{25} = 7.14300 \times 10^{-4}$, $\rho_{32} = 7.14300 \times 10^{-4}$, $\rho_{34} = 6.42870 \times 10^{-2}$, $\rho_{35} = 6.42870 \times 10^{-3}$, $\rho_{41} = 3.46000 \times 10^{-3}$, $\rho_{45} = 3.46000 \times 10^{-3}$, $\rho_{46} = 3.46000 \times 10^{-3}$, $\rho_{48} = 2.40124 \times 10^{-2}$, $\rho_{51} = 3.46000 \times 10^{-3}$, $\rho_{54} = 6.92000 \times 10^{-3}$, $\rho_{58} = 2.40124 \times 10^{-2}$, $\rho_{61} = 1.11100 \times 10^{-3}$, $\rho_{67} = 3.33300 \times 10^{-3}$, $\rho_{68} = 6.66600 \times 10^{-3}$, $\rho_{81} = 2.74000 \times 10^{-4}$, $\rho_{89} = 2.46600 \times 10^{-3}$, $\rho_{91} = 2.74000 \times 10^{-4}$, and $\mu = 5.48000 \times 10^{-5}$.

This example demonstates SENSAI's ability to implement a large system and compute R_0 effectively. In this model, equations 2-7 are considered infective, so the next generation matrix is a 6×6 matrix with analytical (not numerical) components.