Computation of $\mathcal{R}_0$ and Sensitivity for Models of Infectious Disease

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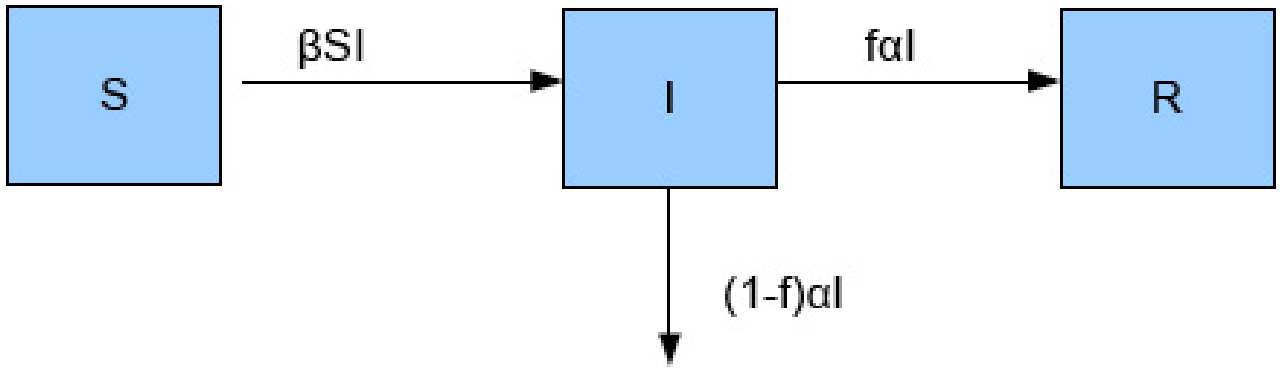
SIR Compartmental Epidemic ODE Model



Simple model for influenza

S, I, R : number susceptible, infectious, recovered at time t

β: transmission coefficient between I and S, mass action βSI

$\frac{1}{\alpha}$: mean infectious time $\quad f$: fraction of I recovering

$$\frac{dI}{dt} = \beta SI - \alpha I$$

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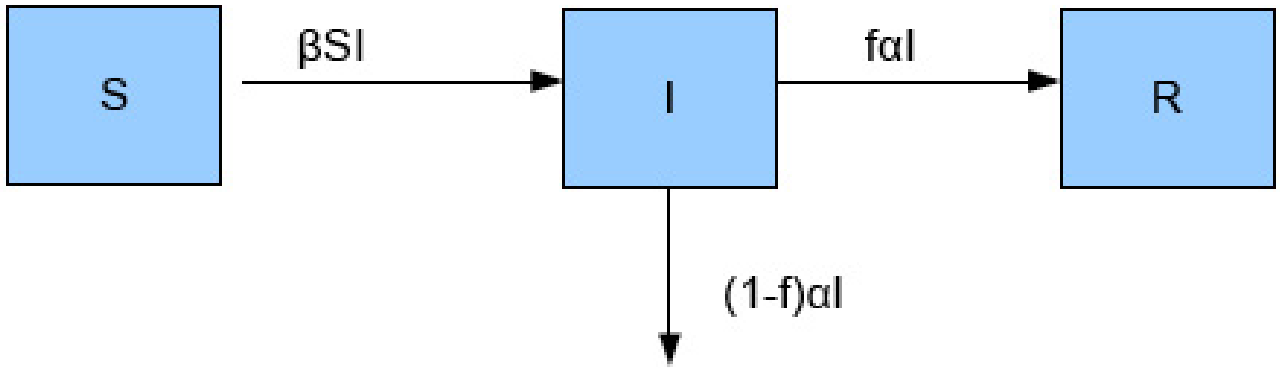

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Disease free equilibrium (DFE): $S = S_0, \quad I = 0, \quad R = 0$

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$$\frac{dI}{dt} = \beta SI - \alpha I$$

DFE is locally asymptotically stable (LAS) if $\mathcal{R}_0 = \dfrac{\beta S_0}{\alpha} < 1$
unstable if $\mathcal{R}_0 > 1$

$\mathcal{R}_0$ is the *basic reproduction number*
= (transmission coefficient)(mean infectious time) S_0

$\mathcal{R}_0$: expected number of secondary infections caused by
a primary case introduced into a susceptible population

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Dynamical behavior:

$\mathcal{R}_0 < 1 \Rightarrow$ number of infectious decreases monotonically to 0

$\mathcal{R}_0 > 1 \Rightarrow$ number first increases (before $\to 0$) : an epidemic
Initial increase $I(t) \approx I(0)\exp[\alpha(\mathcal{R}_0 - 1)t]$

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Estimated Mean Values of $\mathcal{R}_0$ from Data

smallpox Indian subcont. (1968-73)	4.5	[Anderson, May 1991]
poliomyelitis Europe (1955-60)	6	[Anderson, May 1991]
measles Ghana (1960-68)	14.5	[Anderson, May 1991]
SARS epidemic (2002-03)	3.5	[Gumel et *al.* 2004]
1918 Spanish flu in Geneva		
spring wave	1.5	[Chowell et *al.* 2006]
fall wave	3.8	[Chowell et *al.* 2006]
H2N2 flu pandemic US (1957)	1.68	[Longini et *al.* 2004]
H1N1 flu South Africa (2009)	1.33	[White et *al.* 2013]
Ebola Guinea (2014)	1.51	[Althaus 2014]
Omicron S. Korea (Nov-Dec 2021)	1.9	[Kim et *al.* 2021]

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SEIR Compartmental Epidemic Model

In many infectious diseases there is an *exposed period* after the transmission of infection to susceptibles but before infected individuals can transmit infection
If this exposed period is relatively long then an exposed compartment E should be included to give an SEIR model with mean exposed period $\frac{1}{\kappa}$, input A, natural death rate $d > 0$

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$$\frac{dS}{dt} = A - dS - \beta SI \tag{1a}$$
$$\frac{dE}{dt} = \beta SI - (d + \kappa)E \tag{1b}$$
$$\frac{dI}{dt} = \kappa E - (d + \alpha)I \tag{1c}$$
$$\frac{dR}{dt} = \alpha I - dR \tag{1d}$$

with nonnegative initial conditions
DFE $(S_0, E, I, R) = (\frac{A}{d}, 0, 0, 0)$. How to find $\mathcal{R}_0$ for this system?

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Computing $\mathcal{R}_0$ for ODE Compartmental Models

[Diekmann et *al.* 1990; vdD, Watmough 2002; Hastings, vdD, 2016]

$x = (x_1, x_2, \ldots, x_n)^T$ gives number of individuals in each compartment
First $m < n$ compartments contain infected individuals
Assume DFE x_0 exists and is stable in absence of disease
Assume the linearized equations for $x_1, \ldots, x_m$ decouple from the other equations

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Consider $\frac{dx_i}{dt} = \mathcal{F}_i(x) - \mathcal{V}_i(x)$ for $i = 1, 2, \ldots, m$

$\mathcal{F}_i(x)$ is rate of appearance of new infections in compartment i
$\mathcal{V}_i(x)$ is rate of other transitions between compartments
Here $\mathcal{F}_i$ and $\mathcal{V}_i \in \mathcal{C}^2$, $\mathcal{F}_i = 0$ if $i > m \ldots$

Define $F = \left[\frac{\partial \mathcal{F}_i(x_0)}{\partial x_j}\right]$, $V = \left[\frac{\partial \mathcal{V}_i(x_0)}{\partial x_j}\right]$ for $1 \leq i, j \leq m$

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Next Generation Matrix Method

F is entrywise non-negative $(F \geq 0)$

V is a non-singular M-matrix, $V \in \mathcal{M}$ (so $V^{-1} \geq 0$)
Linearizing at the DFE, the Jacobian matrix is $F - V$

Let $\psi(0)$ be the number of initially infected individuals

Then $FV^{-1}\psi(0)$ is expected number of new infections

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$FV^{-1} \geq 0$ and has (i, j) entry equal to the expected number of new infections in compartment i produced by an infected individual introduced in compartment j

FV^{-1} is the *next generation matrix*

$$\mathcal{R}_0 = \rho(FV^{-1})$$

where ρ denotes the spectral radius

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Linear stability of DFE determined by $s(F-V)$
where s is the maximum real part of the eigenvalues

Theorem

If x_0 is a DFE, then x_0 is locally asymptotically stable (LAS) if $\mathcal{R}_0 = \rho(FV^{-1}) < 1$, but unstable if $\mathcal{R}_0 > 1$, i.e. sign $s(F-V) =$ sign $(\mathcal{R}_0 - 1)$

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Proof: Matrix $V - F$ has Z sign-pattern (off-diagonals - or 0)

$$\begin{aligned} s(F-V) < 0 &\Leftrightarrow V - F \in \mathcal{M} \\ &\Leftrightarrow I - FV^{-1} \in \mathcal{M} \\ &\Leftrightarrow \rho(FV^{-1}) < 1 \\ \text{Also } s(F-V) = 0 &\Leftrightarrow \rho(FV^{-1}) = 1 \\ \text{Thus } s(F-V) > 0 &\Leftrightarrow \rho(FV^{-1}) > 1 \end{aligned}$$

Therefore x_0 is LAS if $s(F-V) < 0$, equivalently $\mathcal{R}_0 < 1$, and x_0 is unstable if $s(F-V) > 0$, equivalently $\mathcal{R}_0 > 1$. ■

Computation of $\mathcal{R}_0$ for SEIR Model

The infected compartments are E and I
At DFE matrices F and V are

$$F = \begin{bmatrix} 0 & \beta S_0 \\ 0 & 0 \end{bmatrix}, \quad V = \begin{bmatrix} d+\kappa & 0 \\ -\kappa & d+\alpha \end{bmatrix}, \quad FV^{-1} = \begin{bmatrix} \frac{\kappa\beta S_0}{(d+\kappa)(d+\alpha)} & \frac{\beta S_0}{d+\alpha} \\ 0 & 0 \end{bmatrix}$$

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So FV^{-1} has eigenvalues 0 and $\mathcal{R}_0$ where

$$\mathcal{R}_0 = \frac{\kappa\beta S_0}{(d+\kappa)(d+\alpha)}$$

βS_0 is infection rate of 1 person in a population of S_0 susceptibles
$\kappa/(d+\kappa)$ is the fraction progressing from E to I
$1/(d+\alpha)$ is the mean time in I
The (1,1) entry of FV^{-1} is the expected number of secondary infections produced in compartment E by an infected person originally in E

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Extension of the SEIR Model

Suppose that individuals in E are mildly infectious at a reduced rate $\epsilon\beta SE$ with $0 < \epsilon < 1$

Show that

$$\mathcal{R}_0 = \frac{\kappa\beta S_0}{(d+\kappa)(d+\alpha)} + \frac{\epsilon\beta S_0}{(d+\kappa)}$$

and interpret the result

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SIS with heterosexual transmission

At the DFE the Jacobian matrix is:

$$J = \begin{bmatrix} -(d+\gamma_F) & \lambda_{MF} \\ \lambda_{FM} & -(d+\gamma_M) \end{bmatrix}$$

Eigenvalues of J are given by the roots of the characteristic equation

$$z^2 + z(2d + \gamma_F + \gamma_M) + (d+\gamma_F)(d+\gamma_M) - \lambda_{MF}\lambda_{FM} = 0$$

DFE is linearly stable iff constant term is positive

$$F = \begin{bmatrix} 0 & \lambda_{MF} \\ \lambda_{FM} & 0 \end{bmatrix} \quad V = \begin{bmatrix} d+\gamma_F & 0 \\ 0 & d+\gamma_M \end{bmatrix}$$

So $\mathcal{R}_0 = \rho(FV^{-1}) = \sqrt{\frac{\lambda_{MF}\lambda_{FM}}{(d+\gamma_M)(d+\gamma_F)}}$

The square root (geometric mean) indicates that it takes two "generations" for infected M to produce another infected M

Note: $R_0 < (>)1$ exactly when the constant term is positive (negative)

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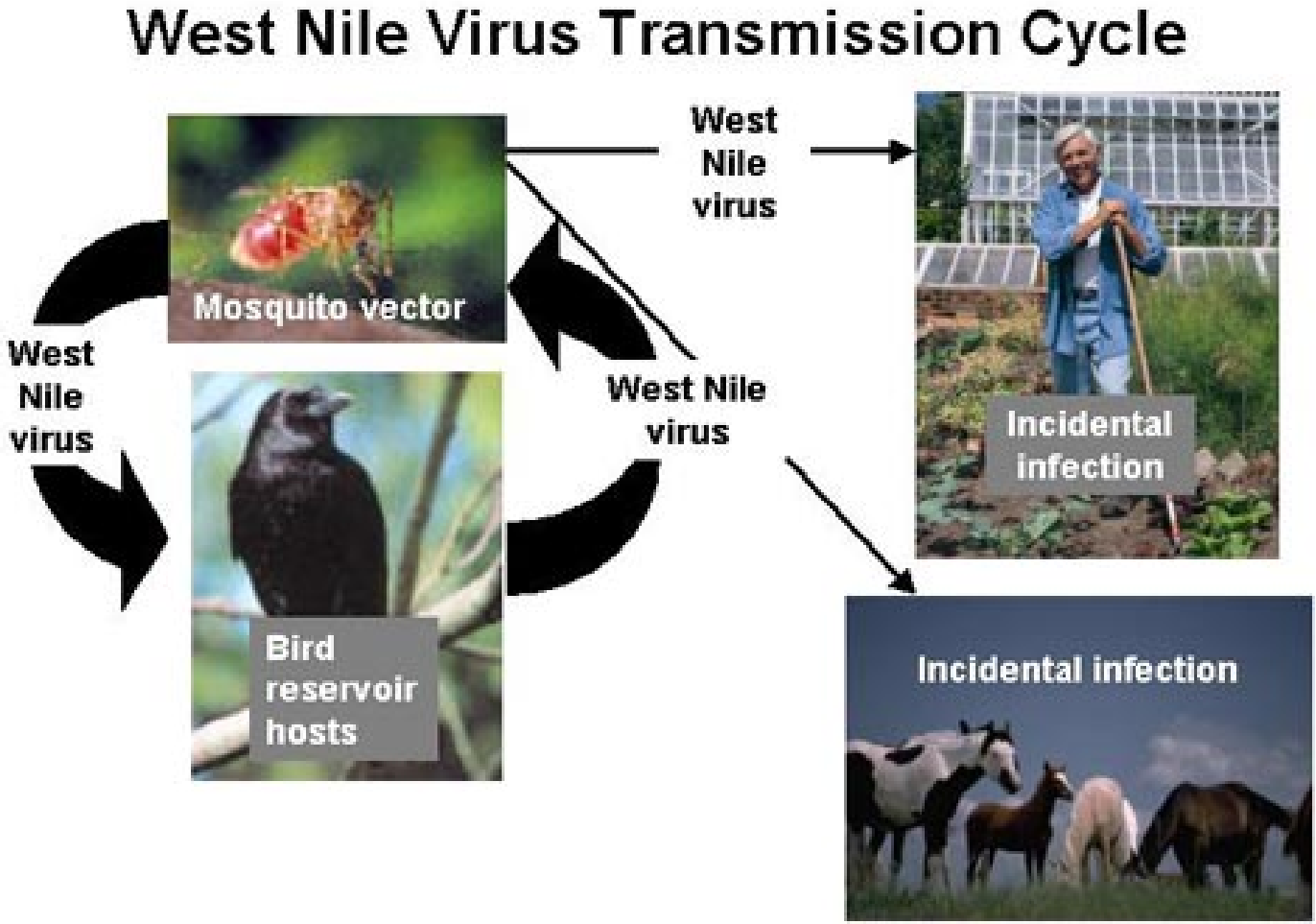
A Vector-Host Model



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Some disease, e.g., West Nile Virus, Dengue fever, malaria, Zika virus are transmitted through a vector
Simple vector-host model is SIS for the hosts and SI for the vector

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Susceptible hosts S_h become infectious hosts I_h at rate $\beta_{vh} S_h I_v$
by bites from infectious vectors I_v

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Let A_h, A_v be recruitment rates, d_h, d_v be removal rates
γ be recovery rate of I_h where I_v are assumed to be infectious for life

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$$\frac{dS_h}{dt} = A_h - d_h S_h - \beta_{vh} S_h I_v + \gamma I_h \tag{2a}$$

$$\frac{dI_h}{dt} = \beta_{vh} S_h I_v - (d_h + \gamma) I_h \tag{2b}$$

$$\frac{dS_v}{dt} = A_v - d_v S_v - \beta_{hv} S_v I_h \tag{2c}$$

$$\frac{dI_v}{dt} = \beta_{hv} S_v I_h - d_v I_v \tag{2d}$$

Infected compartments are I_h , I_v
DFE is $S_{h0} = A_h/d_h, S_{v0} = A_v/d_v, I_h = I_v = 0$

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$$F = \begin{bmatrix} 0 & \beta_{vh} S_{h0} \\ \beta_{hv} S_{v0} & 0 \end{bmatrix}, \; V = \begin{bmatrix} d_h + \gamma & 0 \\ 0 & d_v \end{bmatrix}$$

$$FV^{-1} = \begin{bmatrix} 0 & \frac{\beta_{vh} S_{h0}}{d_v} \\ \frac{\beta_{hv} S_{v0}}{d_h + \gamma} & 0 \end{bmatrix}$$

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The entries of FV^{-1} are interpreted as the number of secondary infections produced by infected vectors and hosts during the course of their infections
Note the cross infection between vectors and hosts

$$\mathcal{R}_0 = \sqrt{\frac{\beta_{vh}\beta_{hv}S_{h0}S_{v0}}{d_v(d_h+\gamma)}}$$

This is a geometric mean
The square root indicates that it takes two generations for infected hosts to produce new infected hosts

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In practise the square root is often omitted
giving the same threshold at 1

Control measures: reduce S_{v0} by spraying, reduce β_{vh} by bed nets.....

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Sensitivity and Elasticity

To determine best control measures, the relative importance of the different factors responsible for transmission is needed
Initially disease transmission is related to $\mathcal{R}_0$ and sensitivity predicts which parameters have a high impact on $\mathcal{R}_0$

The *sensitivity index* of $\mathcal{R}_0$ with respect to a parameter ω is $\frac{\partial \mathcal{R}_0}{\partial \omega}$

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Another measure is the *elasticity index* (*normalized sensitivity index*) that measures the relative change of $\mathcal{R}_0$ with respect to ω

$$\Upsilon_{\omega}^{\mathcal{R}_0} = \frac{\partial \mathcal{R}_0}{\partial \omega} \times \frac{\omega}{\mathcal{R}_0}$$

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For the simple SIR model with $\mathcal{R}_0 = \frac{\beta S_0}{\alpha}$:

$$\Upsilon_{\beta}^{\mathcal{R}_0} = 1, \quad \Upsilon_{\alpha}^{\mathcal{R}_0} = -1$$

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Model of Bovine Babesiosis (BB)

Bovine Babesiosis is a disease of cattle (bovine) that is endemic in many regions including Africa
Transmitted by ticks, which can also transmit the pathogen vertically
Juvenile cattle have an innate resistance to BB, once infected they rarely show clinical symptoms, and once recovered they acquire natural immunity

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ODE Model of BB [Saad-Roy, Shuai, vdD, 2015]
related to the PDE model [Friedman, Yakubu, 2014]

S_{BJ}, S_{BA} denote the susceptible junior, adult bovine population
A_{BJ} denotes the asymptomatic infectious juvenile bovine population
I_{BA}, R_{BA} denote the infectious, recovered adult bovine population
S_T, I_T denote the susceptible, infectious tick population

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Table: Parameter values from Aranda et al. [2012], time unit = 1 day

Parameter	Value	Definition
b_B	0.0002999	Bovine birth rate
d_B	0.0002999	Bovine death rate
b_T	0.001609	Tick birth rate
d_T	0.001609	Tick death rate
τ_B	0.000265	Bovine natural recovery rate
α_B	0.00100	Bovine loss of immunity rate
β_{BT}	0.000610	Infectivity rate, tick to bovine
β_{TB}	0.000480	Infectivity rate, adult bovine to tick
p	0.1	Probability of no vertical transmission in ticks
m_{BJ}	0.003703	Maturation rate of juvenile cattle
$\epsilon\beta_{TB}$	$\epsilon = 0.5$	Infectivity rate, juvenile bovine to tick

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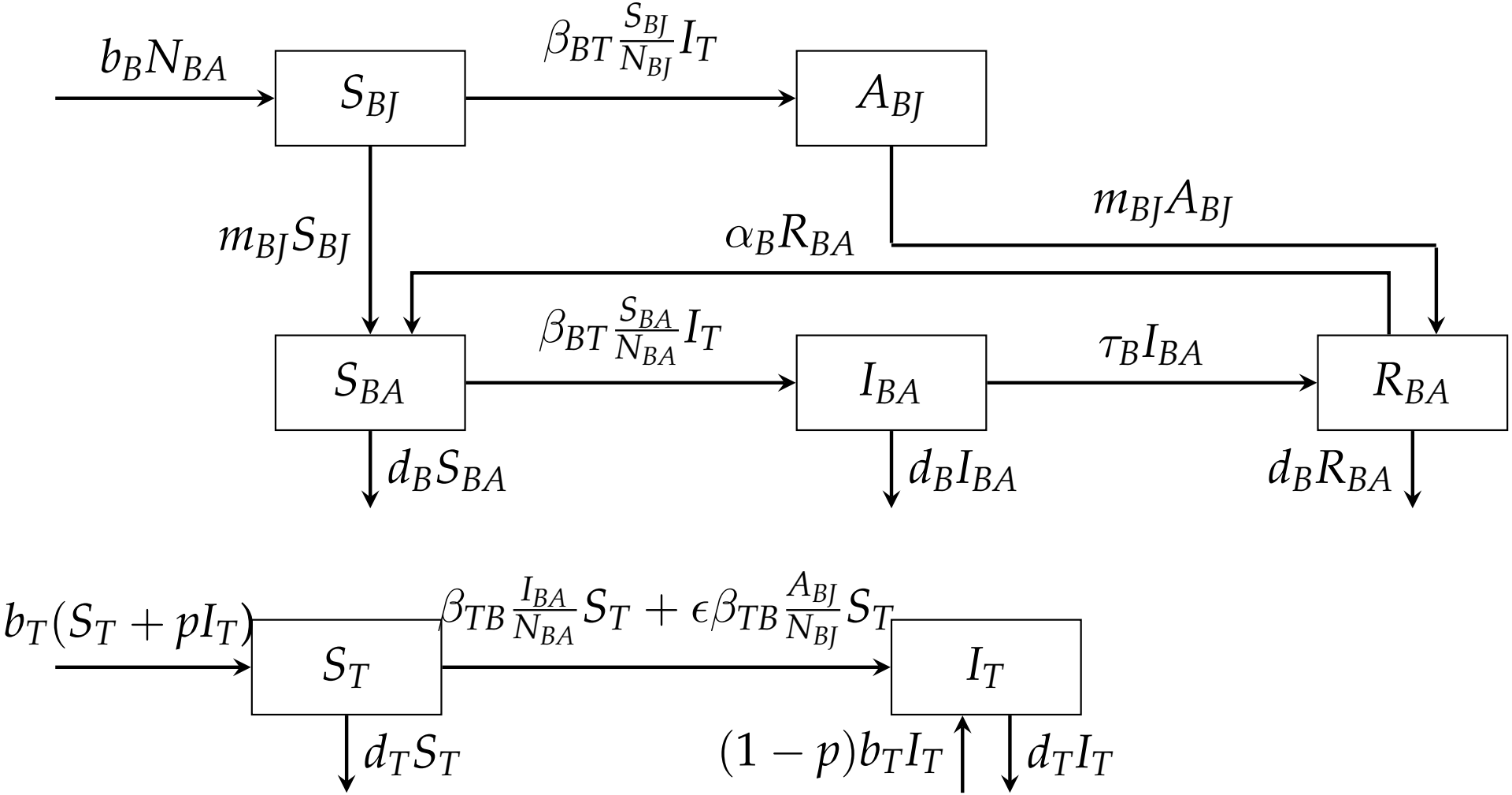

Figure: Bovine and Tick Populations Flowchart

Calculation of $\mathcal{R}_0$ and Elasticity Indices

If vertical transmission in ticks is taken as a transfer (i.e., in V matrix)

$$\mathcal{R}_0 = \sqrt{\frac{\beta_{BT}\beta_{TB}N_T}{pb_T N_{BA}}\left(\frac{\epsilon}{b_B} + \frac{1}{\tau_B + b_B}\right)}$$

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Elasticity indices:

$$\Upsilon^{\mathcal{R}_0}_{\beta_{BT}} = \Upsilon^{\mathcal{R}_0}_{\beta_{TB}} = 0.5, \qquad \Upsilon^{\mathcal{R}_0}_{p} = \Upsilon^{\mathcal{R}_0}_{b_T} = -0.5$$

$$\Upsilon^{\mathcal{R}_0}_{\epsilon} = \frac{\epsilon(\tau_B + b_B)}{2[\epsilon(\tau_B + b_B) + b_B]}, \qquad \Upsilon^{\mathcal{R}_0}_{\tau_B} = -\frac{b_B}{2[\epsilon(\tau_B + b_B) + b_B]}\frac{\tau_B}{\tau_B + b_B}$$

$$\Upsilon^{\mathcal{R}_0}_{b_B} = -\frac{(\tau_B + b_B)b_B}{2[\epsilon(\tau_B + b_B) + b_B]}\left(\frac{\epsilon}{b_B} + \frac{b_B}{(\tau_B + b_B)^2}\right)$$

Note that all indices are sign determined

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Table: Elasticity Indices

Parameter	Value of Parameter	Index of $\mathcal{R}_0$
β_{BT}	0.0006100	0.5
β_{TB}	0.0004800	0.5
b_T	0.0016090	-0.5
p	0.1	-0.5
b_B	0.0002999	-0.3792
ϵ	0.5	0.2425
τ_B	0.0002650	-0.1208

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For control, infectivity rates need to be reduced, or vertical transmission reduced (p increased)

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For control, infectivity rates need to be reduced, or vertical transmission reduced (p increased)

Further sensitivity analysis indicates that for this model, targeting only one parameter may not be a feasible method of eliminating BB

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Calculation of $\mathcal{R}_0$ for a Discrete-Time Model

[Cushing, Zhou, 1994; Li, Schneider, 2002; Allen, vdD, 2008]

$$\begin{aligned} x(t+1) &= \mathcal{F}(x(t), y(t)) + \mathcal{T}(x(t), y(t)) \\ y(t+1) &= \mathcal{G}(x(t), y(t)) \end{aligned}$$

$x(t), y(t)$ represent the population sizes in the disease and non-disease compartments at time t

$\mathcal{F}_i$ represents the density of new infections that appear in i

$\mathcal{T}_i$ represents the population size of individuals that transition between compartment i and other compartments

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$\mathcal{T}_i$ represents the population size of individuals that transition between compartment i and other compartments

Assume disease-free system has unique LAS equilibrium $y(t) = y_\infty$

Define

$$F = \left[\frac{\partial \mathcal{F}_i(0, y_\infty)}{\partial x_j}\right] \text{ and } T = \left[\frac{\partial \mathcal{T}_i(0, y_\infty)}{\partial x_j}\right]$$

$F \geq 0$ is the matrix of new infections, T is the transition matrix

The Jacobian matrix $J = F + T$, LAS if $\rho(J) < 1$, unstable if $\rho(J) >$

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Next Generation Matrix for a Discrete-Time System

Since some of the population may die $\rho(T) < 1$ with $(Id - T) \in \mathcal{M}$

$$(Id - T)^{-1} = Id + T + T^2 + \cdots + T^n + \cdots,$$

assuming that $T \geq 0$ and $\rho(T) < 1$ implying $(Id - T)^{-1} \geq 0$
$F(Id - T)^{-1}$ has (i, j) entry equal to the expected number of secondary infections in compartment i produced by an infected individual introduced in compartment j; it is the *next generation matrix*
The basic reproduction number for the discrete-time system is

$$\mathcal{R}_0 = \rho\left(F(Id - T)^{-1}\right)$$

Proof of the next theorem uses the Perron-Frobenius Theorem

Theorem

If $(0, y_\infty)$ *is DFE of the system*
$x(t+1) = \mathcal{F}(x(t), y(t)) + \mathcal{T}(x(t), y(t)), \quad y(t+1) = \mathcal{G}(x(t), y(t))$
then $(0, y_\infty)$ *is LAS if* $\mathcal{R}_0 = \rho\left(F(Id - T)^{-1}\right) < 1$ *but unstable if* $\mathcal{R}_0 > 1$

Computation of $\mathcal{R}_0$ for the Discrete-Time SEIR Model

$$\begin{aligned} e_{t+1} &= (1-d)\, s_t \left(\theta \widehat{\varphi}\,(i_t) + (1-\theta)\, \widehat{\psi}\,(\varepsilon e_t)\right) + (1-\kappa)\,(1-d)\, e_t \\ i_{t+1} &= \kappa\,(1-d)\, e_t + (1-\gamma)\,(1-d)\, i_t \\ r_{t+1} &= \gamma\,(1-d)\, i_t + (1-d)\, r_t \end{aligned}$$

with disease-free equilibrium (DFE) $(e, i, r) = (0, 0, 0)$

Write the Jacobian at the DFE as $F + T$ assuming a new infection means entry into the mildly infectious exposed class

$$F = \begin{bmatrix} -(1-d)\,(1-\theta)\,\varepsilon\psi'(0) & -(1-d)\,\theta\varphi'(0) \\ 0 & 0 \end{bmatrix}$$

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Computation of $\mathcal{R}_0$ for the Discrete-Time SEIR Model

$$\begin{aligned} e_{t+1} &= (1-d)\, s_t \left(\theta \widehat{\varphi}\,(i_t) + (1-\theta)\, \widehat{\psi}\,(\varepsilon e_t)\right) + (1-\kappa)\,(1-d)\, e_t \\ i_{t+1} &= \kappa\,(1-d)\, e_t + (1-\gamma)\,(1-d)\, i_t \\ r_{t+1} &= \gamma\,(1-d)\, i_t + (1-d)\, r_t \end{aligned}$$

with disease-free equilibrium (DFE) $(e, i, r) = (0, 0, 0)$

Write the Jacobian at the DFE as $F + T$ assuming a new infection means entry into the mildly infectious exposed class

$$F = \begin{bmatrix} -(1-d)\,(1-\theta)\,\varepsilon\psi'(0) & -(1-d)\,\theta\varphi'(0) \\ 0 & 0 \end{bmatrix}$$

The transition matrix $T \geq 0$ with spectral radius $\rho(T) < 1$

$$T = \begin{bmatrix} (1-\kappa)\,(1-d) & 0 \\ \kappa\,(1-d) & (1-\gamma)\,(1-d) \end{bmatrix}$$

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Local stability of DFE

These matrices give

$$\mathcal{R}_0 = \rho\left(F\left(Id - T\right)^{-1}\right) = \mathcal{R}_{0E} + \mathcal{R}_{0I}$$

where

$$\mathcal{R}_{0E} = \frac{-\left(1-d\right)\left(1-\theta\right)\varepsilon\psi'\left(0\right)}{1-\left(1-\kappa\right)\left(1-d\right)}$$

$$\mathcal{R}_{0I} = \frac{-\kappa\left(1-d\right)^2\theta\phi'\left(0\right)}{\left(1-\left(1-\gamma\right)\left(1-d\right)\right)\left(1-\left(1-\kappa\right)\left(1-d\right)\right)}$$

$\mathcal{R}_{0I}$ gives contributions from the infectious compartment I
$\mathcal{R}_{0E}$ gives contributions from the mildly infectious compartment E, increasing $\mathcal{R}_0$

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Under the asymptotically constant growth assumption the DFE $(1,0,0,0)$ is LAS if $\mathcal{R}_0 < 1$ and unstable if $\mathcal{R}_0 > 1$

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Concluding remarks

- The next generation matrix method (derived using results from linear algebra including Perron Frobenius, M-matrices, stability...) works well in continuous-time and discrete-time models
- It is especially useful if F has low rank (preferably rank 1), and has biological meaning

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Concluding remarks

- The next generation matrix method (derived using results from linear algebra including Perron Frobenius, M-matrices, stability...) works well in continuous-time and discrete-time models
- It is especially useful if F has low rank (preferably rank 1), and has biological meaning
- Usually the threshold 1 distinguishes between the DFE being stable or unstable, and another endemic (positive) equilibrium appearing and being LAS. But in some models there is a *backward bifurcation* when an endemic equilibrium can also occur if $\mathcal{R}_0 < 1$. Linear algebra then helps to determine local stability, which can be initial value dependent
- What about global stability? Linear algebra and combinatorial ideas can help in the construction of Lyapunov functions

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HAIKU FOR $\mathcal{R}_0$

To control disease

Stop spots, coughs and a sneeze:

$\mathcal{R}_0$'s a breeze

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