# Target Reproduction Numbers and Applications to Biological Models

Pauline van den Driessche
University of Victoria BC
Canada
Department of Mathematics and Statistics
vandendr@uvic.ca

CBMS Conference, UCF, May 2022

Thanks to NSF, NSERC, UCF, Collaborators

In population dynamics Threshold Parameters determine population persistence, give insight into control and protection strategies

Examples: net reproductive value (rate)
basic reproduction number...

AIM

To give a general framework for threshold parameters using Target Reproduction Numbers

Key reference: [Lewis, Shuai, vdD, *J Math Biol* 2019]

AGENDA

♦ Algebraic and graphical theories for target reproduction numbers

AGENDA

♦ Algebraic and graphical theories for target reproduction numbers

♦ Protecting salmonoids (ray-finned fish)

University of Victoria

AGENDA

♦ Algebraic and graphical theories for target reproduction numbers

♦ Protecting salmonoids (ray-finned fish)

♦ Resident killer whales

AGENDA

- ⧫ Algebraic and graphical theories for target reproduction numbers
- ⧫ Protecting salmonoids (ray-finned fish)
- ⧫ Resident killer whales
- ⧫ Controlling scentless chamomile (an invasive weed)

AGENDA

- ⧫ Algebraic and graphical theories for target reproduction numbers
- ⧫ Protecting salmonoids (ray-finned fish)
- ⧫ Resident killer whales
- ⧫ Controlling scentless chamomile (an invasive weed)
- ⧫ Modeling cholera control (a bacterial disease)

University of Victoria

- Let $A = [a_{ij}]$ be a nonnegative irreducible $n \times n$ matrix and $S = [s_{ij}]$ be the $n \times n$ target matrix of $A$ i.e., $s_{ij} = a_{ij}$ whenever the entry is targeted, and zero otherwise

- Let $A = [a_{ij}]$ be a nonnegative irreducible $n \times n$ matrix and $S = [s_{ij}]$ be the $n \times n$ target matrix of $A$ i.e., $s_{ij} = a_{ij}$ whenever the entry is targeted, and zero otherwise
- Define the Target Reproduction Number $\mathcal{T}_S$ as

$$\mathcal{T}_S = \rho(S(Id - A + S)^{-1}) \quad \text{provided} \quad \rho(A - S) < 1$$

where $\rho(.)$ denotes the spectral radius and $Id$ denotes an identity matrix

**Theorem**

If $\rho(A - S) < 1$, then the controlled matrix $A_c$, obtained from $A$ by replacing all targeted entries $a_{ij}$ by $a_{ij}/\mathcal{T}_S$, satisfies $\rho(A_c) = 1$

**Theorem**

If $\rho(A - S) < 1$, then the controlled matrix $A_c$, obtained from $A$ by replacing all targeted entries $a_{ij}$ by $a_{ij}/\mathcal{T}_S$, satisfies $\rho(A_c) = 1$

Idea of Proof:
By Perron-Frobenius there exists an eigenvector $x^T \geq 0$ so that

$$x^T S(Id - A + S)^{-1} = \mathcal{T}_S x^T$$

giving

$$x^T(A - S + \frac{S}{\mathcal{T}_S}) = 1x^T$$

# Target Reproduction Number: Special Cases

$$\mathcal{T}_S = \rho(S(Id - A + S)^{-1}) \quad \text{provided} \quad \rho(A - S) < 1$$

An interpretation: $A$ is the next generation matrix of a disease model with basic reproduction number $\mathcal{R}_0$

- Target all entries (i.e., $S = A$): $\mathcal{T}_S = \mathcal{R}_0 = \rho(A)$
  Herd immunity: vaccinate more than $1 - 1/\mathcal{R}_0$ of population

# Target Reproduction Number: Special Cases

$$\mathcal{T}_S = \rho(S(Id - A + S)^{-1}) \quad \text{provided} \quad \rho(A - S) < 1$$

An interpretation: $A$ is the next generation matrix of a disease model with basic reproduction number $\mathcal{R}_0$

- Target all entries (i.e., $S = A$): $\mathcal{T}_S = \mathcal{R}_0 = \rho(A)$
  Herd immunity: vaccinate more than $1 - 1/\mathcal{R}_0$ of population

- Target only one entry $a_{ij}$: $\mathcal{T}_{ij} = a_{ij}(Id - A + S)^{-1}_{ji}$

University of Victoria

# Target Reproduction Number: Special Cases

$$\mathcal{T}_S = \rho(S(Id - A + S)^{-1}) \quad \text{provided} \quad \rho(A - S) < 1$$

An interpretation: $A$ is the next generation matrix of a disease model with basic reproduction number $\mathcal{R}_0$

- Target all entries (i.e., $S = A$): $\mathcal{T}_S = \mathcal{R}_0 = \rho(A)$
  Herd immunity: vaccinate more than $1 - 1/\mathcal{R}_0$ of population

- Target only one entry $a_{ij}$: $\mathcal{T}_{ij} = a_{ij}(Id - A + S)^{-1}_{ji}$

- Target the $i$-th row: $\mathcal{T}_{i*} = \sum_{j=1}^{n} a_{ij}(Id - A + S)^{-1}_{ji}$
  *Type reproduction number* [Heesterbeek, Roberts, 2003, 2007]
  Herd immunity: vaccinate more than $1 - 1/\mathcal{T}_{i*}$ of city $i$

University of Victoria

$$\mathcal{T}_S = \rho(S(Id - A + S)^{-1}) \quad \text{provided} \quad \rho(A - S) < 1$$

An interpretation: $A$ is the next generation matrix of a disease model with basic reproduction number $\mathcal{R}_0$

- Target all entries (i.e., $S = A$): $\mathcal{T}_S = \mathcal{R}_0 = \rho(A)$
  Herd immunity: vaccinate more than $1 - 1/\mathcal{R}_0$ of population
- Target only one entry $a_{ij}$: $\mathcal{T}_{ij} = a_{ij}(Id - A + S)^{-1}_{ji}$
- Target the $i$-th row: $\mathcal{T}_{i*} = \sum_{j=1}^{n} a_{ij}(Id - A + S)^{-1}_{ji}$
  *Type reproduction number* [Heesterbeek, Roberts, 2003, 2007]
  Herd immunity: vaccinate more than $1 - 1/\mathcal{T}_{i*}$ of city $i$
- Target the $i$-th column: $\mathcal{T}_{*i} = \sum_{j=1}^{n} a_{ji}(Id - A + S)^{-1}_{ij}$
  *In fact,* $\mathcal{T}_{*i} = \mathcal{T}_{i*}$ [Moon, Shuai, vdD, *Lin Algebra Appl 2014*]

University of Victoria

$$\mathcal{T}_S = \rho(S(Id - A + S)^{-1}) \quad \text{provided} \quad \rho(A - S) < 1$$

An interpretation: $A$ is the next generation matrix of a disease model with basic reproduction number $\mathcal{R}_0$

- Target all entries (i.e., $S = A$): $\mathcal{T}_S = \mathcal{R}_0 = \rho(A)$
  Herd immunity: vaccinate more than $1 - 1/\mathcal{R}_0$ of population

- Target only one entry $a_{ij}$: $\mathcal{T}_{ij} = a_{ij}(Id - A + S)^{-1}_{ji}$

- Target the $i$-th row: $\mathcal{T}_{i*} = \sum_{j=1}^{n} a_{ij}(Id - A + S)^{-1}_{ji}$
  *Type reproduction number* [Heesterbeek, Roberts, 2003, 2007]
  Herd immunity: vaccinate more than $1 - 1/\mathcal{T}_{i*}$ of city $i$

- Target the $i$-th column: $\mathcal{T}_{*i} = \sum_{j=1}^{n} a_{ji}(Id - A + S)^{-1}_{ij}$
  *In fact,* $\mathcal{T}_{*i} = \mathcal{T}_{i*}$ [Moon, Shuai, vdD, *Lin Algebra Appl 2014*]

University of Victoria

**Theorem** [Moon, Shuai, vdD, *Lin Alg Appl* 2014]
Let $A$ be an $n \times n$ nonnegative irreducible matrix with weighted digraph $D(A)$
A cycle union $\mathcal{U}$ of $D(A)$ is a union of disjoint cycles of $D(A)$
$w(\mathcal{U})$ is the product of weights of arcs of $\mathcal{U}$ and $c(\mathcal{U})$ is the number of cycles

**Theorem** [Moon, Shuai, vdD, *Lin Alg Appl* 2014]
Let $A$ be an $n \times n$ nonnegative irreducible matrix with weighted digraph $D(A)$
A cycle union $\mathcal{U}$ of $D(A)$ is a union of disjoint cycles of $D(A)$
$w(\mathcal{U})$ is the product of weights of arcs of $\mathcal{U}$ and $c(\mathcal{U})$ is the number of cycles

For $1 \leq i, j \leq n$

$$\mathcal{T}_{ij} = \frac{\sum_{\mathcal{U}_{ij}} (-1)^{1+c(\mathcal{U}_{ij})} w(\mathcal{U}_{ij})}{\sum_{\mathcal{V}_{ij}} (-1)^{c(\mathcal{V}_{ij})} w(\mathcal{V}_{ij})}$$

where the sums are over all cycle-unions $\mathcal{U}_{ij}$ and $\mathcal{V}_{ij}$ of $D(A)$ that do and do not contain the arc $ji$, respectively

# Example calculations of $\mathcal{T}_S$

$A = \begin{bmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{bmatrix}$ with weights of cycle unions in $D(A)$ being

$$1, a_{11}, a_{22}, a_{11}a_{22}, a_{12}a_{21}$$

University of Victoria

$$A = \begin{bmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{bmatrix}$$ with weights of cycle unions in $D(A)$ being

$$1, a_{11}, a_{22}, a_{11}a_{22}, a_{12}a_{21}$$

- Take $s_{11} = a_{11}$ as targeted entry

$$\mathcal{T}_{11} = \begin{bmatrix} a_{11} & 0 \\ 0 & 0 \end{bmatrix} \begin{bmatrix} 1 & -a_{12} \\ -a_{21} & 1 - a_{22} \end{bmatrix}^{-1} = \frac{a_{11} - a_{11}a_{22}}{1 - a_{22} - a_{12}a_{21}}$$

- If

$$A = \begin{bmatrix} 0.5 & 0.7 \\ 0.7 & 0.5 \end{bmatrix}$$

then $\mathcal{T}_{11} = 25$, so replacing $a_{11}$ by $0.5/25$ gives $\rho(A_c) = 1$

University of Victoria

$$A = \begin{bmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{bmatrix}$$ with weights of cycle unions in $D(A)$ being

$$1, a_{11}, a_{22}, a_{11}a_{22}, a_{12}a_{21}$$

- Take $s_{11} = a_{11}$ as targeted entry

$$\mathcal{T}_{11} = \begin{bmatrix} a_{11} & 0 \\ 0 & 0 \end{bmatrix} \begin{bmatrix} 1 & -a_{12} \\ -a_{21} & 1 - a_{22} \end{bmatrix}^{-1} = \frac{a_{11} - a_{11}a_{22}}{1 - a_{22} - a_{12}a_{21}}$$

- If

$$A = \begin{bmatrix} 0.5 & 0.7 \\ 0.7 & 0.5 \end{bmatrix}$$

then $\mathcal{T}_{11}$= 25, so replacing $a_{11}$ by $0.5/25$ gives $\rho(A_c) = 1$

- Both first row entries are targeted (type reproduction number)

$$\mathcal{T}_{1*} = \frac{a_{11} + a_{12}a_{21} - a_{11}a_{22}}{1 - a_{22}}$$

Note that $\mathcal{T}_{1*} = 1 \Leftrightarrow \mathcal{T}_{11} = 1$

Age structured population for $x_t$ population vector of ages/stages at time $t$, and $P$ the population projection matrix

$$x_{t+1} = Px_t$$

$\lambda = \rho(P)$ the population growth rate, population grows iff $\lambda > 1$

Age structured population for $x_t$ population vector of ages/stages at time $t$, and $P$ the population projection matrix

$$x_{t+1} = Px_t$$

$\lambda = \rho(P)$ the population growth rate, population grows iff $\lambda > 1$

Let $P = T + F$: transition matrix $T \geq 0$, fecundity matrix $F \geq 0$
The next generation matrix is $F(Id - T)^{-1}$
The net reproductive value $R_0 = \rho(F(Id - T)^{-1})$
[Allen & vdD, 2008, Cushing & Zhou, 1994, Li & Schnieder, 2002]

University of Victoria

Age structured population for $x_t$ population vector of ages/stages at time $t$, and $P$ the population projection matrix

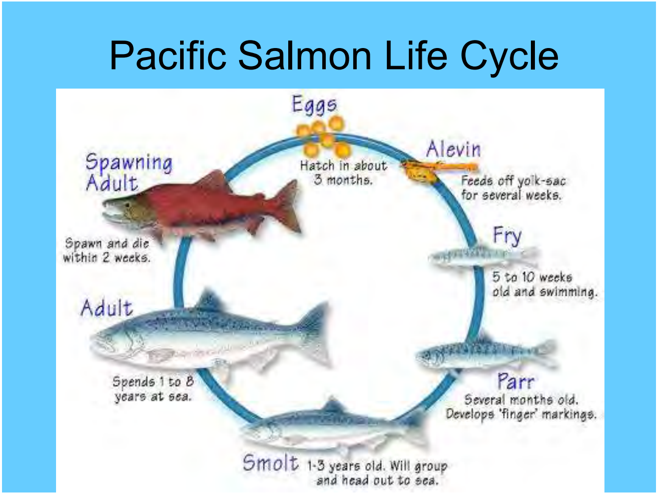
$$x_{t+1} = Px_t$$

$\lambda = \rho(P)$ the population growth rate, population grows iff $\lambda > 1$

Let $P = T + F$: transition matrix $T \geq 0$, fecundity matrix $F \geq 0$
The next generation matrix is $F(Id - T)^{-1}$
The net reproductive value $R_0 = \rho(F(Id - T)^{-1})$
[Allen & vdD, 2008, Cushing & Zhou, 1994, Li & Schnieder, 2002]

If $\rho(T) < 1$ then $R_0$ is the target reproduction number for $A = P$ corresponding to the target matrix $S = F$

If the target matrix is $S = P$ then $\mathcal{T}_P = \rho(P) = \lambda$




Credit: http://kingcd.org/wp-content/uploads/2014/12/pacific-salmon-life-cycle

Lefkovitch matrix with 4 life stages: egg, fry, juvenile, adult
[Huang & Lewis, *Theor Ecol* 2015]

$$P = \begin{bmatrix} 0 & 0 & 0 & b_4 \\ t_1 & 0 & 0 & 0 \\ 0 & t_2 & s_3 & 0 \\ 0 & 0 & t_3 & s_4 \end{bmatrix}$$

The order of events: production of $b_4$ offspring per survivor, survival probability $p_i$, proportion $1 - q_i$ moving to the next class

$s_i = p_i q_i \geq 0$ is the probability of staying
$t_i = p_i(1 - q_i)$ is the probability of transition

University of Victoria

# Control to Protect Endangered Salmonoids

[Lewis, Shuai, vdD, *JMB* 2019]

$$P = \begin{bmatrix} 0 & 0 & 0 & b_4 \\ t_1 & 0 & 0 & 0 \\ 0 & t_2 & s_3 & 0 \\ 0 & 0 & t_3 & s_4 \end{bmatrix}$$

Assume that the net reproductive value $R_0 < 1$

The first row/column of $P$ each contain 1 nonzero entry

$R_0 = \mathcal{T}_{1*} = \mathcal{T}_{14} = \mathcal{T}_{21} = \frac{t_1 t_2 t_3 b_4}{(1-s_3)(1-s_4)}$

To protect endangered salmonoids increase number of eggs per adult $b_4$ to $> b_4/R_0$ or the proportion of eggs that hatch to the fry stage $t_1$ to $> t_1/R_0$

University of Victoria

[Lewis, Shuai, vdD, *JMB* 2019]

$$P = \begin{bmatrix} 0 & 0 & 0 & b_4 \\ t_1 & 0 & 0 & 0 \\ 0 & t_2 & s_3 & 0 \\ 0 & 0 & t_3 & s_4 \end{bmatrix}$$

Assume that the net reproductive value $R_0 < 1$
The first row/column of $P$ each contain 1 nonzero entry
$R_0 = \mathcal{T}_{1*} = \mathcal{T}_{14} = \mathcal{T}_{21} = \frac{t_1 t_2 t_3 b_4}{(1-s_3)(1-s_4)}$

To protect endangered salmonoids increase number of eggs per adult $b_4$ to $> b_4/R_0$ or the proportion of eggs that hatch to the fry stage $t_1$ to $> t_1/R_0$

From the second row/column $\mathcal{T}_{2*} = \mathcal{T}_{21} = \mathcal{T}_{32} = R_0$
Increase $t_2$ proportion of fry that survive to juveniles to $t_2/R_0$

University of Victoria

[Lewis, Shuai, vdD, *JMB* 2019]

$$P = \begin{bmatrix} 0 & 0 & 0 & b_4 \\ t_1 & 0 & 0 & 0 \\ 0 & t_2 & s_3 & 0 \\ 0 & 0 & t_3 & s_4 \end{bmatrix}$$

Assume that the net reproductive value $R_0 < 1$
The first row/column of $P$ each contain 1 nonzero entry
$R_0 = \mathcal{T}_{1*} = \mathcal{T}_{14} = \mathcal{T}_{21} = \frac{t_1 t_2 t_3 b_4}{(1-s_3)(1-s_4)}$

To protect endangered salmonoids increase number of eggs per adult $b_4$ to $> b_4/R_0$ or the proportion of eggs that hatch to the fry stage $t_1$ to $> t_1/R_0$

From the second row/column $\mathcal{T}_{2*} = \mathcal{T}_{21} = \mathcal{T}_{32} = R_0$
Increase $t_2$ proportion of fry that survive to juveniles to $t_2/R_0$

Reduce the harvest of adult salmonoids, increase $s_4$ to $s_4/\mathcal{T}_{44}$ where $\mathcal{T}_{44} = s_4(1-s_3)/(1-s_3-t_1 t_2 t_3 b_4)$

University of Victoria

# Population of Resident Killer Whales

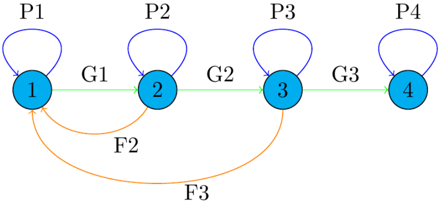
[Brault, Caswell, 1993] Bronwyn Hobson report, istockphoto.com

Four life stages for female resident killer whales: calf (1), juvenile (2), reproductive adult (3), and post reproductive adult (4)

$$P_{BC} = \begin{bmatrix} 0 & F_2 & F_3 & 0 \\ G_1 & P_2 & 0 & 0 \\ 0 & G_2 & P_3 & 0 \\ 0 & 0 & G_3 & P_4 \end{bmatrix}$$

$\sigma_i$ = stage specific survival, $\gamma_i =$ transition probability
$m_i =$ mean reproductive output

$G_i$ gives the probability of survival and transfer into stage $i+1$
$F_i$ gives the number of offspring at $t+1$ from a female at $t$




$P_1 = 0$, $P_2 = (1-\gamma_2)\sigma_2$ , $P_3 = (1-\gamma_3)\sigma_3$, $P_4 = \sigma_4$, $G_1 = \sigma_1^{1/2}$ ,
$G_2 = \gamma_2\sigma_2$ , $G_3 = \gamma_3\sigma_3$, $F_2 = \sigma_1^{1/2} G_2 m_3/2$, $F_3 = \sigma_1^{1/2}(1+P_3)m_3/2$

Using data for BC Resident killer whales from 1973-1987 provided by Brault and Caswell

$$1 < \lambda_{BC} = \mathcal{T}_{\mathcal{P}} = 1.03 < \mathcal{R}_{0BC} = \mathcal{T}_F = 2.01$$

# Sensitivities for Killer Whales

Using data for BC Resident killer whales from 1973-1987 provided by Brault and Caswell

$$1 < \lambda_{BC} = \mathcal{T}_{\mathcal{P}} = 1.03 < \mathcal{R}_{0BC} = \mathcal{T}_F = 2.01$$

Both $\lambda_{BC}$ and $\mathcal{R}_{0BC}$ are most sensitive to $\gamma_3$ and $\sigma_3$, that is transition from and survival in the reproductive stage

[Lewis, Shuai, vdD, *JMB*2019]

Photo Credit: Daniel Laubhann

A weed in north America that invades agricultural farmland

One plant can produce up to 1 million seeds that remain viable for up to 15 years in the soil

It has 3 stages: (1) seed bank (in the ground), (2) rosettes, and (3) flowering plants

[de-Camino-Beck & Lewis, *Bull Math Biol* 2007]

The projection matrix for the growth of scentless chamomile with stages of seeds, rosettes and flowers is

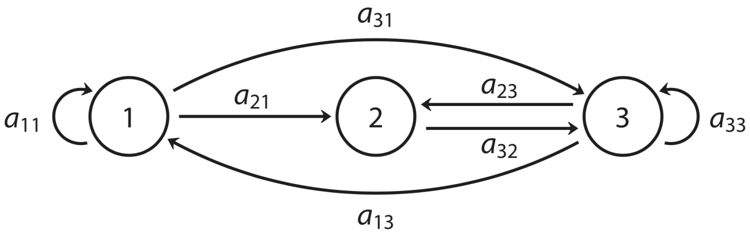
$$P = \begin{bmatrix} a_{11} & 0 & a_{13} \\ a_{21} & 0 & a_{23} \\ a_{31} & a_{32} & a_{33} \end{bmatrix}$$

In a year seeds remain in the seed bank with probability $a_{11}$, germinate into a rosette with probability $a_{21}$, into a flower with probability $a_{31}$, die with probability $1 - a_{11} - a_{21} - a_{31}$

Rosettes transform into flowers with probability $a_{32}$

Flowers contribute to all fecundities in each of the stages

# Control affecting fecundity (seed production), e.g., by seed weevils




Target matrix $S$ has nonzero entries $s_{i3} = a_{i3}$ for $i = 1, 2, 3$ the fecundity matrix with rank 1, so assuming $a_{11} < 1$

$$\mathcal{T}_{*3} = \frac{a_{33} + a_{13}a_{31} + a_{23}a_{32} + a_{13}a_{21}a_{32} - a_{11}a_{33} - a_{11}a_{23}a_{32}}{1 - a_{11}}$$

Here $\mathcal{T}_{*3} = R_0$ the net reproductive value

University of Victoria

Target matrix $S$ has nonzero entries
$s_{21} = a_{21}, s_{31} = a_{31}, s_{32} = a_{32}$ so $\mathcal{T}_S$ has rank 2 (harder!)

Take controlled matrix Let $\tilde{A} = \begin{bmatrix} a_{11} & 0 & a_{13} \\ a_{21}/\sigma & 0 & a_{23} \\ a_{31}/\sigma & a_{32}/\sigma & a_{33} \end{bmatrix}$

$\mathcal{T}_S$ is the value of $\sigma$ such that $\rho(\tilde{A}) = 1$

Target matrix $S$ has nonzero entries
$s_{21} = a_{21}, s_{31} = a_{31}, s_{32} = a_{32}$ so $\mathcal{T}_S$ has rank 2 (harder!)

Take controlled matrix Let $\tilde{A} = \begin{bmatrix} a_{11} & 0 & a_{13} \\ a_{21}/\sigma & 0 & a_{23} \\ a_{31}/\sigma & a_{32}/\sigma & a_{33} \end{bmatrix}$

$\mathcal{T}_S$ is the value of $\sigma$ such that $\rho(\tilde{A}) = 1$

Solving this gives a quadratic equation in $\sigma^{-1}$

$$u(\sigma^{-1})^2 + v\sigma^{-1} + w = 0$$

$w = -1 + a_{11} + a_{33} - a_{11}a_{33}$ is weight of cycle unions in $D(\tilde{A})$ containing no target entries
$v = a_{13}a_{31} + a_{23}a_{32} - a_{11}a_{23}a_{32}$ containing 1 target entry
$u = a_{13}a_{21}a_{32}$ containing 2 target entries, starts with flowers goes to seed bank $a_{13}$, to rosettes $a_{21}$ then back to flowers $a_{32}$

University of Victoria

To determine the minimum cost control effort take the controlled matrix $\tilde{A} = \begin{bmatrix} a_{11} & 0 & a_{13}/\tau \\ a_{21}/\sigma & 0 & a_{23}/\tau \\ a_{31}/\sigma & a_{32}/\sigma & a_{33}/\tau \end{bmatrix}$ with $\tau, \sigma > 1$

Setting $\rho(\tilde{A}) = 1$ gives $\tau = f(\sigma)$

$$\tau = \frac{a_{13}a_{21}a_{32}}{1 - a_{11}}\sigma^{-2} + \left(a_{23}a_{32} + \frac{a_{13}a_{31}}{1 - a_{11}}\right)\sigma^{-1} + a_{33} = f(\sigma)$$

To determine the minimum cost control effort take the controlled matrix $\tilde{A} = \begin{bmatrix} a_{11} & 0 & a_{13}/\tau \\ a_{21}/\sigma & 0 & a_{23}/\tau \\ a_{31}/\sigma & a_{32}/\sigma & a_{33}/\tau \end{bmatrix}$ with $\tau, \sigma > 1$

Setting $\rho(\tilde{A}) = 1$ gives $\tau = f(\sigma)$

$$\tau = \frac{a_{13}a_{21}a_{32}}{1-a_{11}}\sigma^{-2} + \left(a_{23}a_{32} + \frac{a_{13}a_{31}}{1-a_{11}}\right)\sigma^{-1} + a_{33} = f(\sigma)$$

Assume the costs per unit effort for fecundity, growth control strategy are $d_1, d_2$ and that the total cost function

$$D = d_1(\tau - 1) + d_2(\sigma - 1)$$

Minimum cost $D(\sigma^*)$ achieved where $\sigma^*$ is the unique positive root of $D'(\sigma) = 0$ giving a cubic for $\sigma^*$ in terms of $d_1/d_2$ and $a_{ij}$

To determine the minimum cost control effort take the controlled matrix $\tilde{A} = \begin{bmatrix} a_{11} & 0 & a_{13}/\tau \\ a_{21}/\sigma & 0 & a_{23}/\tau \\ a_{31}/\sigma & a_{32}/\sigma & a_{33}/\tau \end{bmatrix}$ with $\tau, \sigma > 1$

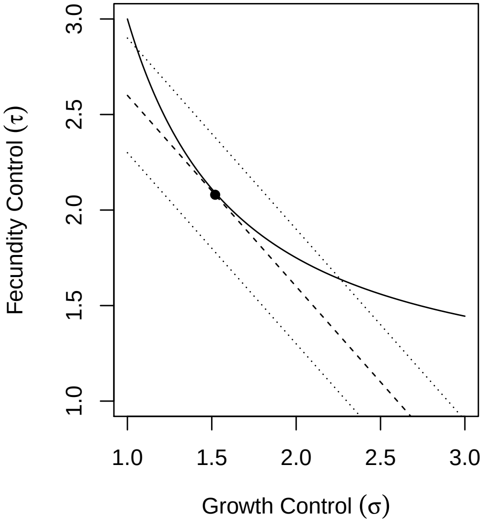
Setting $\rho(\tilde{A}) = 1$ gives $\tau = f(\sigma)$

$$\tau = \frac{a_{13}a_{21}a_{32}}{1-a_{11}}\sigma^{-2} + \left(a_{23}a_{32} + \frac{a_{13}a_{31}}{1-a_{11}}\right)\sigma^{-1} + a_{33} = f(\sigma)$$

Assume the costs per unit effort for fecundity, growth control strategy are $d_1, d_2$ and that the total cost function

$$D = d_1(\tau - 1) + d_2(\sigma - 1)$$

Minimum cost $D(\sigma^*)$ achieved where $\sigma^*$ is the unique positive root of $D'(\sigma) = 0$ giving a cubic for $\sigma^*$ in terms of $d_1/d_2$ and $a_{ij}$
E.g. Coefficients for each power in $f(\sigma)$ equal 1 and $d_2/d_1 = 1$




Control for points $(\sigma, \tau)$ lying above curve $\tau = f(\sigma)$
Dashed line $D = 1.6d_1$ shows cost function for min cost at $(\sigma^*, \tau^*)$ given by the dot
Lower (higher) dotted line $D = 1.3d_1(1.9d_1)$

- An infection of the small intestine caused by the bacterium *Vibrio cholerae* that can persist for extended time outside the human host

# What is Cholera?

- An infection of the small intestine caused by the bacterium *Vibrio cholerae* that can persist for extended time outside the human host
- SIR model with a second route of infection from contaminated water

University of Victoria

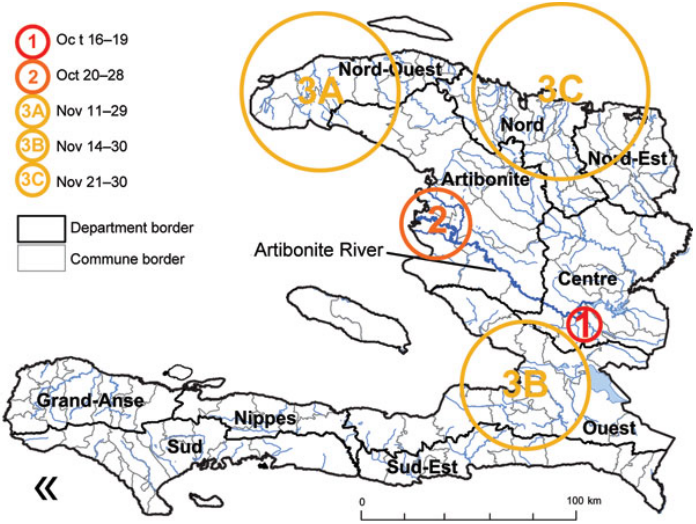
- An infection of the small intestine caused by the bacterium *Vibrio cholerae* that can persist for extended time outside the human host
- SIR model with a second route of infection from contaminated water
- Infection causes mild diarrhea in most cases

# What is Cholera?

- An infection of the small intestine caused by the bacterium *Vibrio cholerae* that can persist for extended time outside the human host
- SIR model with a second route of infection from contaminated water
- Infection causes mild diarrhea in most cases
- But some cases develop severe diarrhea and vomiting which if untreated may lead to death within a few hours due to dehydration and electrolyte imbalance

University of Victoria

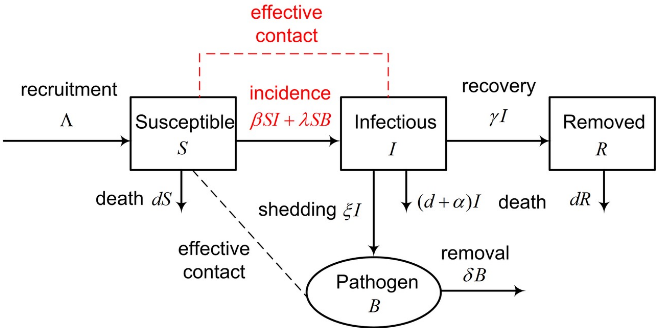
# Cholera outbreak in Haiti as of November 2010



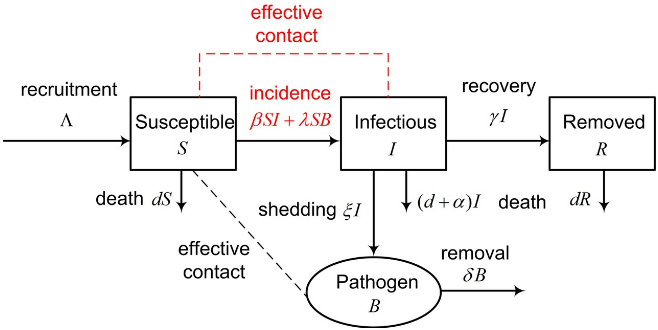

Piarroux et al., *Emerging Infectious Diseases* 2011

University of Victoria

# Application to cholera modeling: One patch ODE model




University of Victoria




$$\frac{dI}{dt} = \beta SI + \lambda SB - (d + \alpha + \gamma)I$$

$$\frac{dB}{dt} = \xi I - \delta B$$

[Tien & Earn, *Bull Math Biol* 2010]

Taking shedding as a new infection
the Jacobian matrix at the disease-free equilibrium $(S_0, 0, 0)$ is

$$J = \begin{bmatrix} \beta S_0 - (d + \alpha + \gamma) & \lambda S_0 \\ \xi & -\delta \end{bmatrix}$$

Taking shedding as a new infection
the Jacobian matrix at the disease-free equilibrium $(S_0, 0, 0)$ is

$$J = \begin{bmatrix} \beta S_0 - (d+\alpha+\gamma) & \lambda S_0 \\ \xi & -\delta \end{bmatrix}$$

The next-generation matrix method decomposition gives

$$F = \begin{bmatrix} \beta S_0 & \lambda S_0 \\ \xi & 0 \end{bmatrix} \qquad V = \begin{bmatrix} d+\alpha+\gamma & 0 \\ 0 & \delta \end{bmatrix}$$

# Threshold for ODE cholera model

Taking shedding as a new infection
the Jacobian matrix at the disease-free equilibrium $(S_0, 0, 0)$ is

$$J = \begin{bmatrix} \beta S_0 - (d+\alpha+\gamma) & \lambda S_0 \\ \xi & -\delta \end{bmatrix}$$

The next-generation matrix method decomposition gives

$$F = \begin{bmatrix} \beta S_0 & \lambda S_0 \\ \xi & 0 \end{bmatrix} \qquad V = \begin{bmatrix} d+\alpha+\gamma & 0 \\ 0 & \delta \end{bmatrix}$$

The next-generation matrix and basic reproduction number

$$A = FV^{-1} = \begin{bmatrix} \frac{\beta S_0}{d+\alpha+\gamma} & \frac{\lambda S_0}{\delta} \\ \frac{\xi}{d+\alpha+\gamma} & 0 \end{bmatrix}, \quad \mathcal{R}_0 = \rho(A)$$

University of Victoria

# Threshold for ODE cholera model

Taking shedding as a transition, a different decomposition gives

$$\widetilde{F} = \begin{bmatrix} \beta S_0 & \lambda S_0 \\ 0 & 0 \end{bmatrix} \qquad \widetilde{V} = \begin{bmatrix} d+\alpha+\gamma & 0 \\ -\xi & \delta \end{bmatrix}$$

Taking shedding as a transition, a different decomposition gives

$$\widetilde{F} = \begin{bmatrix} \beta S_0 & \lambda S_0 \\ 0 & 0 \end{bmatrix} \qquad \widetilde{V} = \begin{bmatrix} d+\alpha+\gamma & 0 \\ -\xi & \delta \end{bmatrix}$$

$$\widetilde{\mathcal{R}_0} = \rho(\widetilde{F}\widetilde{V}^{-1}) = \underbrace{\frac{\beta S_0}{d+\alpha+\gamma}}_{\text{direct}} + \underbrace{\frac{\lambda S_0 \xi}{\delta(d+\alpha+\gamma)}}_{\text{indirect}} \qquad \text{with } S_0 = \Lambda/d$$

Taking shedding as a transition, a different decomposition gives

$$\widetilde{F} = \begin{bmatrix} \beta S_0 & \lambda S_0 \\ 0 & 0 \end{bmatrix} \qquad \widetilde{V} = \begin{bmatrix} d+\alpha+\gamma & 0 \\ -\xi & \delta \end{bmatrix}$$

$$\widetilde{\mathcal{R}_0} = \rho(\widetilde{F}\widetilde{V}^{-1}) = \underbrace{\frac{\beta S_0}{d+\alpha+\gamma}}_{\text{direct}} + \underbrace{\frac{\lambda S_0 \xi}{\delta(d+\alpha+\gamma)}}_{\text{indirect}} \qquad \text{with } S_0 = \Lambda/d$$

If $\widetilde{\mathcal{R}_0} < 1$ ($> 1$ ) then cholera dies out (persists)
Both routes of infection must be controlled for $\widetilde{\mathcal{R}_0} < 1$

Note that $\mathcal{R}_0 = 1 \Leftrightarrow \widetilde{\mathcal{R}_0} = 1$, giving the same threshold

Taking shedding as a transition, a different decomposition gives

$$\widetilde{F} = \begin{bmatrix} \beta S_0 & \lambda S_0 \\ 0 & 0 \end{bmatrix} \qquad \widetilde{V} = \begin{bmatrix} d+\alpha+\gamma & 0 \\ -\xi & \delta \end{bmatrix}$$

$$\widetilde{\mathcal{R}_0} = \rho(\widetilde{F}\widetilde{V}^{-1}) = \underbrace{\frac{\beta S_0}{d+\alpha+\gamma}}_{\text{direct}} + \underbrace{\frac{\lambda S_0 \xi}{\delta(d+\alpha+\gamma)}}_{\text{indirect}} \qquad \text{with } S_0 = \Lambda/d$$

If $\widetilde{\mathcal{R}_0} < 1$ ($> 1$) then cholera dies out (persists)
Both routes of infection must be controlled for $\widetilde{\mathcal{R}_0} < 1$

Note that $\mathcal{R}_0 = 1 \Leftrightarrow \widetilde{\mathcal{R}_0} = 1$, giving the same threshold

Aside: A simple model for COVID-19 includes asymptomatic and symptomatic transmission, to control the virus both routes of infection must be controlled

# Different decompositions

In general different decompositions of the Jacobian matrix lead to different $\mathcal{R}_0$, and they are target reproduction numbers with different target matrices

University of Victoria

In general different decompositions of the Jacobian matrix lead to different $\mathcal{R}_0$, and they are target reproduction numbers with different target matrices

<u>**Theorem**</u> [Lewis, Shuai, vdD, *J Math Biol* 2019]
Let $J = F - V = \widetilde{F} - \widetilde{V}$ with $F, \widetilde{F}, V^{-1}, \widetilde{V}^{-1} \geq 0$
If $F > \widetilde{F} \geq 0$ and $\rho((F - \widetilde{F})V^{-1}) < 1$, then $\rho(\widetilde{F}\widetilde{V}^{-1})$ is a target reproduction number of $A = FV^{-1}$ with target matrix $\widetilde{F}V^{-1}$

# Different decompositions

In general different decompositions of the Jacobian matrix lead to different $\mathcal{R}_0$, and they are target reproduction numbers with different target matrices

**Theorem** [Lewis, Shuai, vdD, *J Math Biol* 2019]
Let $J = F - V = \widetilde{F} - \widetilde{V}$ with $F, \widetilde{F}, V^{-1}, \widetilde{V}^{-1} \geq 0$
If $F > \widetilde{F} \geq 0$ and $\rho((F - \widetilde{F})V^{-1}) < 1$, then $\rho(\widetilde{F}\widetilde{V}^{-1})$ is a target reproduction number of $A = FV^{-1}$ with target matrix $\widetilde{F}V^{-1}$

One of the following holds:

$$1 < \rho(FV^{-1}) < \rho(\widetilde{F}\widetilde{V}^{-1})$$
$$\rho(FV^{-1}) = \rho(\widetilde{F}\widetilde{V}^{-1}) = 1$$
$$\rho(\widetilde{F}\widetilde{V}^{-1}) < \rho(FV^{-1}) < 1$$

Other authors have noticed this, for example:
[Cushing & Diekmann, *J Theor Biol* 2016
The many guises of $R_0$, a didactic note]

$$A = \begin{bmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{bmatrix} = \begin{bmatrix} \frac{\beta S_0}{d+\alpha+\gamma} & \frac{\lambda S_0}{\delta} \\ \frac{\xi}{d+\alpha+\gamma} & 0 \end{bmatrix}$$

# Calculating target reproduction numbers for ODE cholera model

$$A = \begin{bmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{bmatrix} = \begin{bmatrix} \frac{\beta S_0}{d+\alpha+\gamma} & \frac{\lambda S_0}{\delta} \\ \frac{\xi}{d+\alpha+\gamma} & 0 \end{bmatrix}$$

- Isolation reduces effective human-human contact (decreasing $\beta$) $\mathcal{T}_{11} = \frac{a_{11} - a_{11}a_{22}}{1 - a_{22} - a_{12}a_{21}} = \frac{\beta S_0 \delta}{\delta(d+\alpha+\gamma) - \lambda S_0 \xi}$
  If a fraction at least $1 - \frac{1}{\mathcal{T}_{11}}$ can be isolated then cholera can be eradicated

University of Victoria

$$A = \begin{bmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{bmatrix} = \begin{bmatrix} \frac{\beta S_0}{d+\alpha+\gamma} & \frac{\lambda S_0}{\delta} \\ \frac{\xi}{d+\alpha+\gamma} & 0 \end{bmatrix}$$

- Isolation reduces effective human-human contact (decreasing $\beta$) $\mathcal{T}_{11} = \frac{a_{11}-a_{11}a_{22}}{1-a_{22}-a_{12}a_{21}} = \frac{\beta S_0 \delta}{\delta(d+\alpha+\gamma)-\lambda S_0 \xi}$
  If a fraction at least $1 - \frac{1}{\mathcal{T}_{11}}$ can be isolated then cholera can be eradicated
- Providing clean water reduces water-human transmission (decreasing $\lambda$) $\mathcal{T}_{12} = \frac{a_{12}a_{21}}{1-a_{11}-a_{22}+a_{11}a_{22}} = \frac{\lambda S_0 \xi}{\delta(d+\alpha+\gamma)-\beta S_0 \delta}$

# Calculating target reproduction numbers for ODE cholera model

$$A = \begin{bmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{bmatrix} = \begin{bmatrix} \frac{\beta S_0}{d+\alpha+\gamma} & \frac{\lambda S_0}{\delta} \\ \frac{\xi}{d+\alpha+\gamma} & 0 \end{bmatrix}$$

- Isolation reduces effective human-human contact (decreasing $\beta$) $\mathcal{T}_{11} = \frac{a_{11} - a_{11}a_{22}}{1 - a_{22} - a_{12}a_{21}} = \frac{\beta S_0 \delta}{\delta(d+\alpha+\gamma) - \lambda S_0 \xi}$
  If a fraction at least $1 - \frac{1}{\mathcal{T}_{11}}$ can be isolated then cholera can be eradicated

- Providing clean water reduces water-human transmission (decreasing $\lambda$) $\mathcal{T}_{12} = \frac{a_{12}a_{21}}{1 - a_{11} - a_{22} + a_{11}a_{22}} = \frac{\lambda S_0 \xi}{\delta(d+\alpha+\gamma) - \beta S_0 \delta}$

University of Victoria

# Calculating target reproduction numbers for ODE cholera model

$$A = \begin{bmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{bmatrix} = \begin{bmatrix} \frac{\beta S_0}{d+\alpha+\gamma} & \frac{\lambda S_0}{\delta} \\ \frac{\xi}{d+\alpha+\gamma} & 0 \end{bmatrix}$$

$$A = \begin{bmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{bmatrix} = \begin{bmatrix} \frac{\beta S_0}{d+\alpha+\gamma} & \frac{\lambda S_0}{\delta} \\ \frac{\xi}{d+\alpha+\gamma} & 0 \end{bmatrix}$$

- Vaccine reduces both direct and indirect transmission (decreasing $S_0$)
  $\mathcal{T}_{1*} = \frac{a_{11}+a_{12}a_{21}-a_{11}a_{22}}{1-a_{22}} = \frac{\beta S_0}{d+\alpha+\gamma} + \frac{\lambda S_0 \xi}{\delta(d+\alpha+\gamma)} = \rho(\widetilde{F}\widetilde{V}^{-1})$
  If a proportion more than $1 - 1/\mathcal{T}_{1*}$ is successfully vaccinated then cholera can be eradicated

$$A = \begin{bmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{bmatrix} = \begin{bmatrix} \frac{\beta S_0}{d+\alpha+\gamma} & \frac{\lambda S_0}{\delta} \\ \frac{\xi}{d+\alpha+\gamma} & 0 \end{bmatrix}$$

- Vaccine reduces both direct and indirect transmission (decreasing $S_0$)
  $\mathcal{T}_{1*} = \frac{a_{11}+a_{12}a_{21}-a_{11}a_{22}}{1-a_{22}} = \frac{\beta S_0}{d+\alpha+\gamma} + \frac{\lambda S_0 \xi}{\delta(d+\alpha+\gamma)} = \rho(\widetilde{F}\widetilde{V}^{-1})$
  If a proportion more than $1 - 1/\mathcal{T}_{1*}$ is successfully vaccinated then cholera can be eradicated
- Sanitation reduces the shedding of pathogen into water (decreasing $\xi$) $\mathcal{T}_{21} = \mathcal{T}_{12}$

University of Victoria

$$A = \begin{bmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{bmatrix} = \begin{bmatrix} \frac{\beta S_0}{d+\alpha+\gamma} & \frac{\lambda S_0}{\delta} \\ \frac{\xi}{d+\alpha+\gamma} & 0 \end{bmatrix}$$

- Vaccine reduces both direct and indirect transmission (decreasing $S_0$)
  $\mathcal{T}_{1*} = \frac{a_{11}+a_{12}a_{21}-a_{11}a_{22}}{1-a_{22}} = \frac{\beta S_0}{d+\alpha+\gamma} + \frac{\lambda S_0 \xi}{\delta(d+\alpha+\gamma)} = \rho(\widetilde{F}\widetilde{V}^{-1})$
  If a proportion more than $1 - 1/\mathcal{T}_{1*}$ is successfully vaccinated then cholera can be eradicated
- Sanitation reduces the shedding of pathogen into water (decreasing $\xi$) $\mathcal{T}_{21} = \mathcal{T}_{12}$

We have also used target reproduction numbers in a network model of cholera [Li, Ma, vdD, *JMB* 2015]

Need estimates of parameter values from data to evaluate different control strategies

University of Victoria

In some biological models it may be appropriate to target part of a term in the projection matrix, and the target reproduction can be adapted to such situations
For example consider a 4-stage Lefkovitch model with projection matrix

$$P = \begin{bmatrix} s_1 + b_1 & b_2 & b_3 & b_4 \\ t_1 & s_2 & 0 & 0 \\ 0 & t_2 & s_3 & 0 \\ 0 & 0 & t_3 & s_4 \end{bmatrix}$$

where $s_i = p_i q_i$ is the probability of staying in stage $i$
$t_i = p_i(1 - q_i)$ is the probability of leaving stage $i$
and $b_i$ is the fertility of stage $i$ with $b_4 > 0$

Controlling the survival probability in stage 1, $p_1$ means that the target matrix has nonzero entries $s_1$ and $t_1$

- Target reproduction numbers unify several threshold quantities used in biological models

# Concluding remarks

- Target reproduction numbers unify several threshold quantities used in biological models
- Target reproduction numbers can give guidance for control or enhancement of biological populations modeled with either continuous or discrete time

# Concluding remarks

- Target reproduction numbers unify several threshold quantities used in biological models
- Target reproduction numbers can give guidance for control or enhancement of biological populations modeled with either continuous or discrete time
- They can include multiple controls and can be combined with economic factors

# Concluding remarks

- Target reproduction numbers unify several threshold quantities used in biological models
- Target reproduction numbers can give guidance for control or enhancement of biological populations modeled with either continuous or discrete time
- They can include multiple controls and can be combined with economic factors
- Examples considered are simple biological models but we hope to apply the methods to more realistic biological models, and to incorporate data

THANK YOU

QUESTIONS and COMMENTS???

University of Victoria