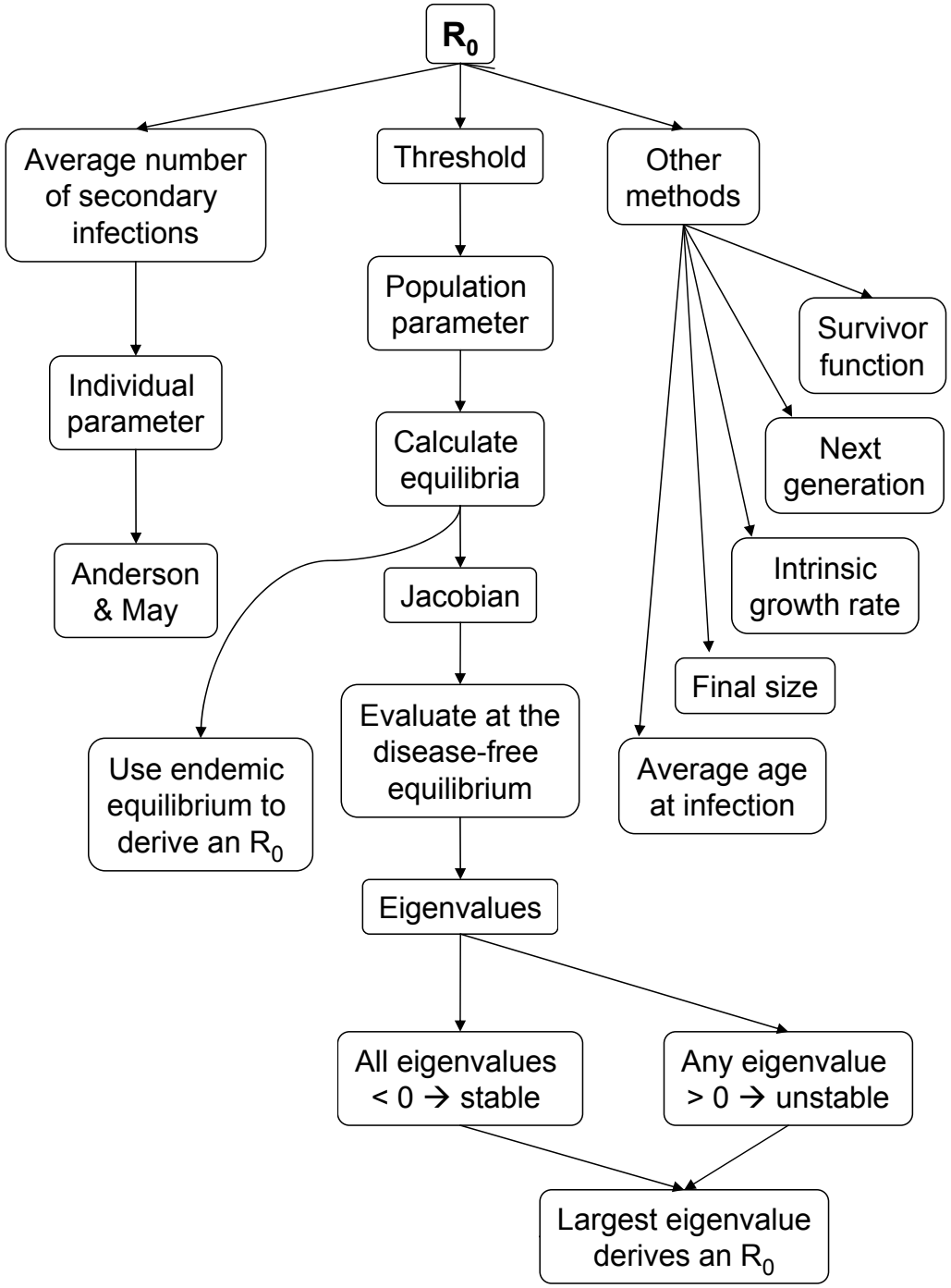
The basic reproductive ratio

- One of the fundamental concepts in mathematical biology
- Defined as “the average number of secondary infections caused by a single infectious individual during their entire infectious lifetime.”


R_0
Average number of secondary infections
Threshold
Other methods
Individual parameter
Population parameter
Survivor function
Calculate equilibria
Next generation
Anderson & May
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Intrinsic growth rate
Final size
Use endemic equilibrium to derive an R_0
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Eigenvalues
All eigenvalues < 0 → stable
Any eigenvalue > 0 → unstable
Largest eigenvalue derives an R_0

A brief history of R_0

- Originally developed for demographics (1886)
- Independently studied for malaria (1911,1927)
- Now widely used for infectious disease (1975+)

"One of the foremost and most valuable ideas that mathematical thinking has brought to epidemic theory"

(Heesterbeek & Dietz, 1996).

Definition of R_0

- Expected number of secondary individuals produced by an individual in its lifetime
- However, “secondary” depends on context:
  - mean lifetime reproductive success (demographics and ecology)
  - number of individuals infected within a single infected individual’s entire infectious lifetime (epidemiology)
  - number of newly infected cells produced by a single infected cell (in-host dynamics).

A threshold criterion

- If $R_0<1$, each individual produces, on average, less than one new infected individual...

  ...and hence the disease dies out
- If $R_0>1$, each individual produces more than one new infected individual...

  ...and hence the disease is able to invade the susceptible population
- This allows us to determine the effectiveness of control measures.

R_0 is a threshold

- Predicts whether a disease will become endemic or die out
- If $R_0>1$, then each individual is causing more than one infection, so the disease will take hold
- If $R_0<1$, then the disease will die out
- This threshold is where R_0 is most useful.

R_0 = basic reproductive ratio

Problems with R_0

- R_0 is rarely measured in the field
- R_0 is an individual parameter
- Most models (eg ODEs) deal with populations
- Matching the two $\Rightarrow$ lots of thresholds, not necessarily the true R_0.

Surrogate thresholds

- These surrogate, R_0-like thresholds will also tell us whether a disease will become endemic or die out
- They may be easier to calculate than the true R_0

But…

- We can't compare different diseases.

R_0 = basic reproductive ratio

We can't compare diseases

- Suppose
  - HIV has an R_0 of 3
  - SARS has an R_0 of 5
- Unless they were calculated using the same method, we don't know if SARS is worse than HIV
- All we know is that both will persist
- This is because R_0 is a distance measure and is thus dependent on the metric used.

R_0 = basic reproductive ratio

Anderson & May

$R_0 = \beta\ c\ D$, where

- β = transmission probability
- c = number of contacts
- D = average time spent infectious

  (= $1/b$ if the infection rate is b)

This is the method most commonly used by biologists (not always correctly).

Note: This formula only applies if there is no background death rate

R_0 = basic reproductive ratio

The Jacobian

The Jacobian is

- A matrix of partial derivatives
- Created by differentiating every equation with respect to every variable
- If there are 6 equations and 6 variables, you'll have a 6×6 matrix

This is one of the most useful tools in mathematical biology.

A method for determining stability

1. Calculate the disease-free equilibrium
2. Create the Jacobian matrix
3. Evaluate the Jacobian at the equilibrium
4. Find the eigenvalues
5. If all eigenvalues $< 0 \Rightarrow$ stable

   If even one eigenvalue $> 0 \Rightarrow$ unstable
6. Largest eigenvalue $\Rightarrow R_0$-like threshold.

R_0 = basic reproductive ratio

The SIS Jacobian

$$\frac{dS}{dt} = bI - aSI$$

$$\frac{dI}{dt} = aSI - bI$$

$$J = \begin{bmatrix} \frac{\partial S'}{\partial S} & \frac{\partial S'}{\partial I} \\ \frac{\partial I'}{\partial S} & \frac{\partial I'}{\partial I} \end{bmatrix}$$

S = Susceptible
I = Infected
a = infection rate
b = recovery rate

The SIS eigenvalues

- The disease-free equilibrium is *(S,I)=(N,0)*

$$J\big|_{(N,0)} = \begin{bmatrix} 0 & b - aN \\ 0 & aN - b \end{bmatrix}$$

- The eigenvalues are

$$\lambda = 0,\ aN - b.$$

(See notes: Eigenvalues)

S = Susceptible *I = Infected*
N = total pop. *J = Jacobian*
b = recovery rate *a = infection rate*

Stability from largest eigenvalue

The non-constant eigenvalue is $aN-b$

- $aN-b < 0 \Longrightarrow$ equilibrium is stable
- $aN-b > 0 \Longrightarrow$ equilibrium is unstable.

N = total pop.
a = infection rate
b = recovery rate

Defining an R_0-like threshold

Stability if

$$aN - b < 0$$

$$aN < b$$

$$\frac{aN}{b} < 1$$

$\therefore$ Define

$$R_0^{\mathrm{SIS}} = \frac{aN}{b}.$$

N = total pop.
a = infection rate
b = recovery rate

R_0^{SIS} is a threshold, not R_0

- If $R_0^{SIS} < 1$, we have stability of the DFE and hence the disease dies out
- If $R_0^{SIS} > 1$, we have instability of the DFE and hence the disease persists
- But why isn't this R_0?

R_0^{SIS} = SIS model threshold
R_0 = basic reproductive ratio
DFE = Disease-free equilibrium

Answer

1. It isn't unique:
   - $(R_0^{SIS})^2 < 1 \Rightarrow$ disease dies out
   - $(R_0^{SIS})^2 > 1 \Rightarrow$ disease persists
2. There's no reason the largest eigenvalue would inexorably lead to the average number of secondary infections.

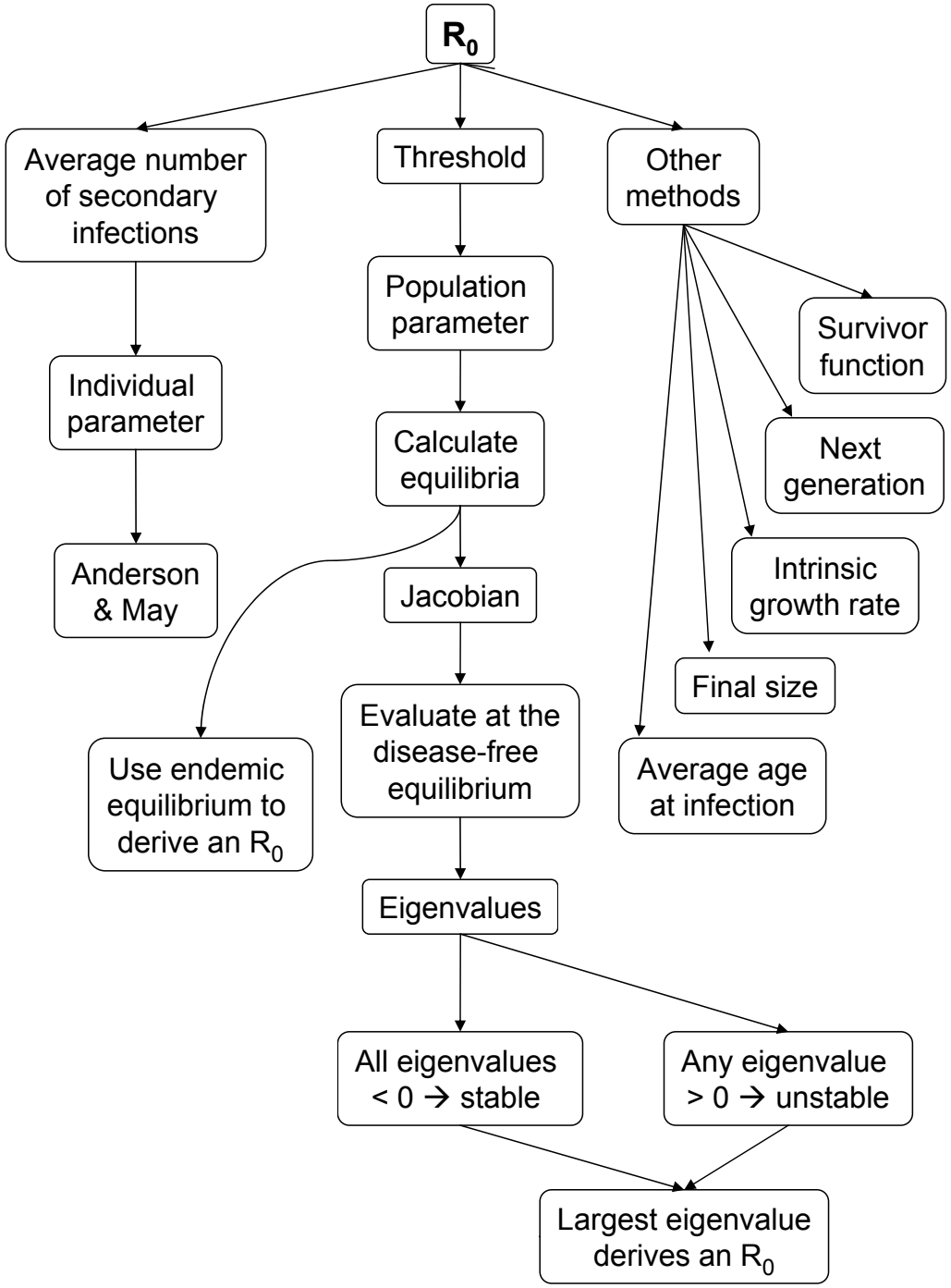
(See notes: R_0 sleight of hand)

R_0^{SIS} = SIS model threshold

What does this mean?

- R_0 is not well defined for ODEs
- But if all we want is a threshold, then this is acceptable
- We have lots of methods of calculating R_0-like thresholds.

R_0 = basic reproductive ratio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SIS endemic equilibrium

- The endemic equilibrium for the SIS model is *(b/a,N-b/a)*
- This only exists if $N-b/a > 0$

$$N > b/a$$

$$aN/b > 1$$

- $\therefore$ Define $R_0^{end} = aN/b$ as before (since if $R_0^{end} > 1$, the disease persists).

N = total pop.
a = infection rate
b = recovery rate

The SIR Jacobian

$$\begin{aligned}
\frac{dS}{dt} &= \pi - aSI - \mu S \\
\frac{dI}{dt} &= aSI - bI - \mu I \\
\frac{dR}{dt} &= bI - \mu R
\end{aligned}$$

$$J = \begin{bmatrix} \frac{\partial S'}{\partial S} & \frac{\partial S'}{\partial I} & \frac{\partial S'}{\partial R} \\ \frac{\partial I'}{\partial S} & \frac{\partial I'}{\partial I} & \frac{\partial I'}{\partial R} \\ \frac{\partial R'}{\partial S} & \frac{\partial R'}{\partial I} & \frac{\partial R'}{\partial R} \end{bmatrix}$$

$$= \begin{bmatrix} -aI - \mu & -aS & 0 \\ aI & aS - b - \mu & 0 \\ 0 & b & -\mu \end{bmatrix}.$$

S = Susceptible *I = Infected*
R = Recovered *J = Jacobian*
π = birth rate *a = infection rate*
b = recovery rate *μ = death rate*

Jacobian at the DFE

$$J\big|_{(\frac{\pi}{\mu},0,0)} = \begin{bmatrix} -\mu & -\frac{a\pi}{\mu} & 0 \\ 0 & \frac{a\pi}{\mu} - b - \mu & 0 \\ 0 & b & -\mu \end{bmatrix}$$

J = Jacobian *DFE = Disease-free equilibrium*
π = birth rate *a = infection rate*
b = recovery rate *μ = death rate*

Calculating eigenvalues

$$\det(J - \lambda I) = \begin{bmatrix} -\mu - \lambda & -\frac{a\pi}{\mu} & 0 \\ 0 & \frac{a\pi}{\mu} - b - \mu - \lambda & 0 \\ 0 & b & -\mu - \lambda \end{bmatrix}$$

$$= (\mu + \lambda)^2 \left(\frac{a\pi}{\mu} - b - \mu - \lambda \right) .$$

(See notes: Eigenvalues)

J = Jacobian *I = identity matrix*
π = birth rate *a = infection rate*
b = recovery rate *μ = death rate*

A 3×3 matrix has 3 eigenvalues

- The eigenvalues are thus

$$\lambda = -\mu, -\mu, \frac{a\pi}{\mu} - b - \mu$$

- Rearrange the largest eigenvalue to find

$$R_0^{\mathrm{SIR}} = \frac{a\pi}{\mu(b+\mu)}\,.$$

π = birth rate *a = infection rate*
b = recovery rate *μ = death rate*

SIR endemic equilibrium

- The endemic equilibrium for the SIR model is

$$(\bar{S}, \bar{I}, \bar{R}) = \left(\frac{b+\mu}{a}, \frac{\pi}{b+\mu} - \frac{\mu}{a}, \frac{b\pi}{\mu(b+\mu)} - \frac{b}{a} \right)$$

- The disease persists when $\bar{I} > 0$.

S = Susceptible *I = Infected* *R = Recovered*
π = birth rate *a = infection rate*
b = recovery rate *μ = death rate*

Endemic equilibrium > 0 → $R_0^{end}>1$

- $\bar{I} > 0$:

$$\frac{\pi}{b+\mu} - \frac{\mu}{a} > 0$$

$$\frac{\pi}{b+\mu} > \frac{\mu}{a}$$

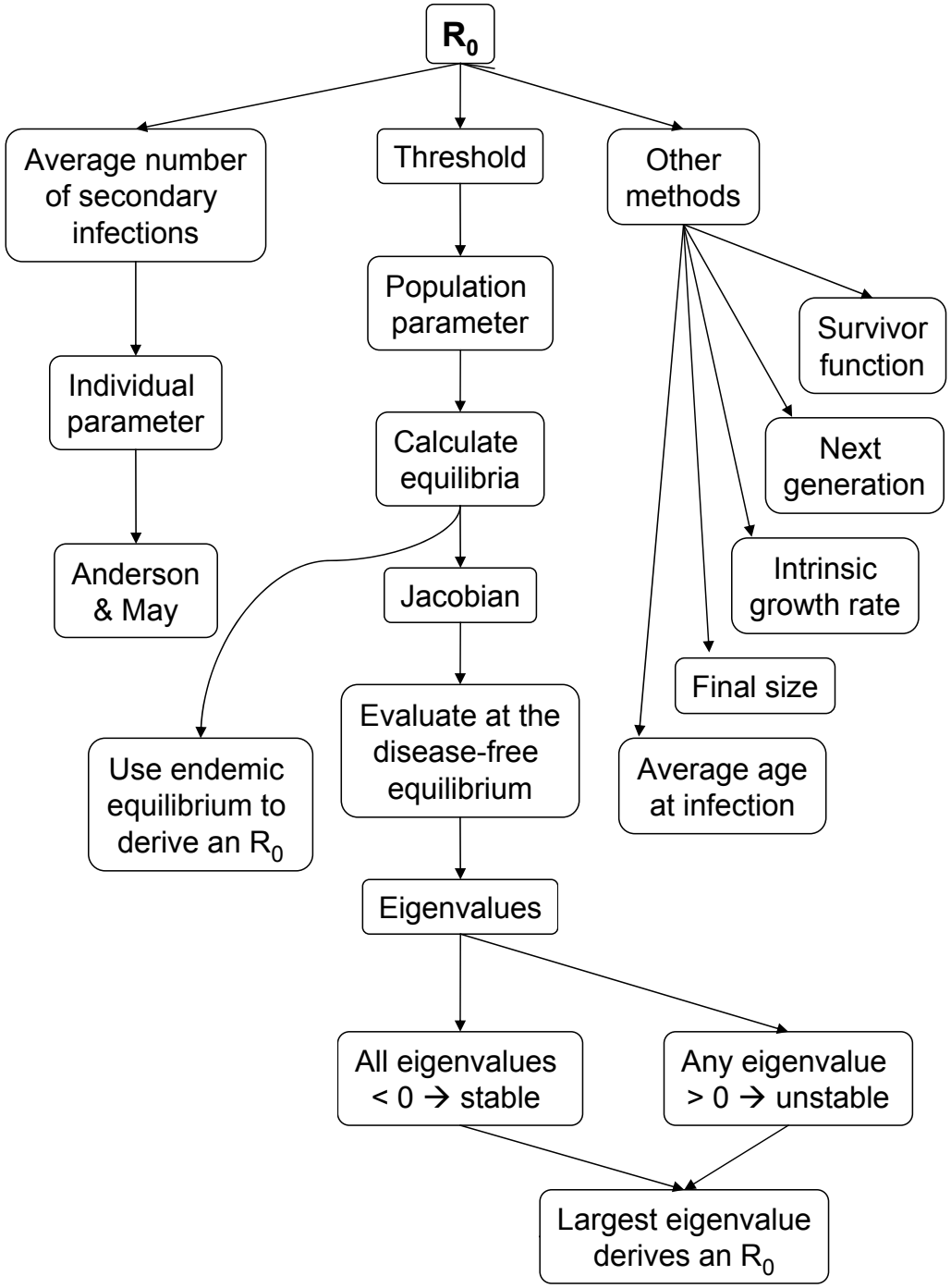
$$\frac{a\pi}{\mu(b+\mu)} > 1$$

Note: In general, these two methods produce *different* R_0s.

I = Infected
π = birth rate
b = recovery rate
R_0^{end} = endemic threshold
a = infection rate
μ = death rate

Usefulness of the Jacobian

- The Jacobian can determine stability of equilibria
- It can also lead us to R_0-like thresholds
- These determine whether an epidemic will persist or die out.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Other methods

- There are many other methods used to calculate R_0
- Few of them agree with each other
- Even fewer calculate the true R_0.

Survival function

$$R_0 = \int_0^\infty b(a)F(a)da$$

where

- *b(a)* is the average number of newly infected individuals an infectious individual produces per unit time when infected for total time *a*
- *F(a)* is the probability that a newly infected individual remains infectious for at least time *a*.

Infection cycle

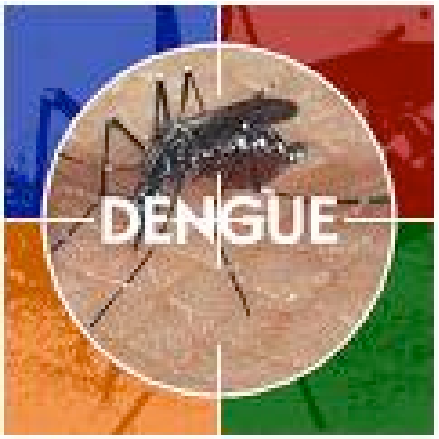
Eg malaria:

- $$F(a) = \int_0^a \text{prob(human infected at time 0 exists at time t)} \times \text{prob(human infected for tot. time } t \text{ infects mosquito)} \times \text{prob(infected mosquito lives to be age } a - t) dt$$
- *b(a)* = average number of humans newly infected by a mosquito which has been infected for time *a*
- This yields the total number of humans produced by one infected human.

The “gold standard” of R_0

- Takes into account the complete cycle
- Not restricted to ODEs
- But can get cumbersome for multiple states (eg schistosomiasis)

Recent uses: Scrapie in Cyprus (Gravenor *et al.*, 2004), Dengue in Brazil (Luz *et al.*, 2003).



The next-generation method

- A general method for deriving R_0 when the population is divided into discrete, disjoint cases
- Can be used for models with underlying age structure or spatial structure.

Calculating the next generation R_0

Let

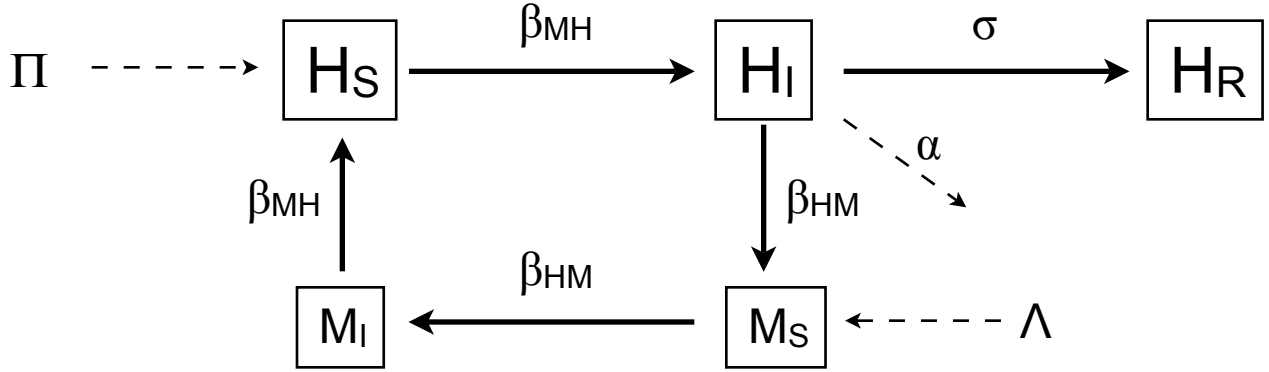
- F_i be the rate of appearance of new infections in compartment *i*
- V_i be the transfer of individuals out of compartment *i* by all other means
- x_0 be the disease-free equilibrium
- R_0 is the largest eigenvalue of

Matrix of partial derivatives

$$\left[\frac{\partial F_i(x_0)}{\partial x_j}\right] \cdot \left[\frac{\partial V_i(x_0)}{\partial x_j}\right]^{-1}$$

Matrix of partial derivatives.

A malaria model



$$
\begin{aligned}
H_S' &= \Pi - \beta_{MH} M_I H_S - \mu_H H_S \\
H_I' &= \beta_{MH} M_I H_S - (\mu_H + \alpha + \sigma) H_I \\
H_R &= \sigma H_I - \mu_H H_R \\
M_S' &= \Lambda - \beta_{MH} M_S H_I - \mu_M M_S \\
M_I &= \beta_{HM} M_S H_I - \mu_M M_I
\end{aligned}
$$

Infected humans

Infected mosquitos.

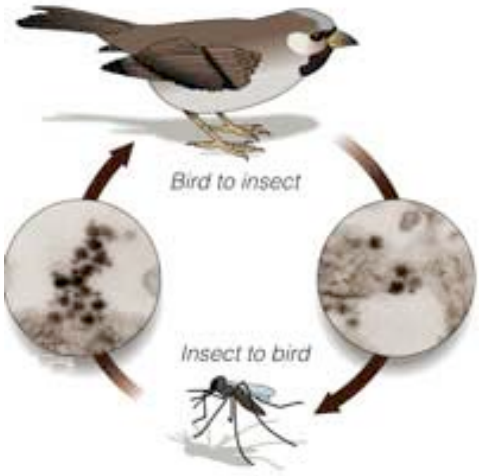
Eg malaria

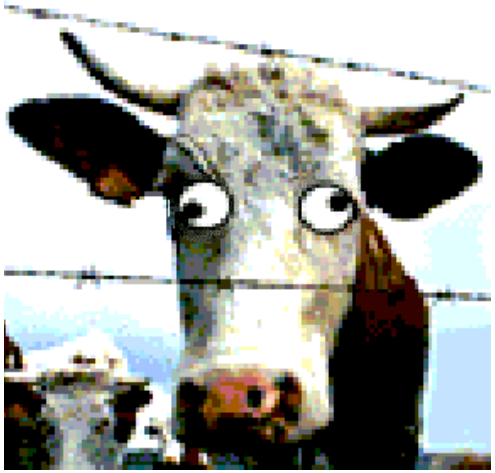
$$
\begin{aligned}
H_I' &= \beta_{MH} M_I H_S - (\mu_H + \alpha + \sigma) H_I \\
M_I' &= \beta_{HM} M_s H_I - \mu_M M_I \\
F &= \begin{pmatrix} 0 & \beta_{MH} H_S(0) \\ \beta_{HM} M_S(0) & 0 \end{pmatrix} \\
V &= \begin{pmatrix} \mu_H + \alpha + \sigma & 0 \\ 0 & \mu_M \end{pmatrix} \\
R_{0,N} &= \sqrt{\frac{\beta_{MH}\beta_{HM} H_S(0) M_S(0)}{(\mu_H + \alpha + \sigma)\mu_M}} \\
&= \sqrt{R_{0,S}} \text{ (the } R_0 \text{ from the survival method).}
\end{aligned}
$$

Difference: definition of a “generation”

- Survival method: the number of infected humans produced by a single infected human
- Next-generation: the number of infected *mosquitos* produced by a single human

Recent uses: West Nile virus (Wonham *et al.*, 2004),
Mad cow (de Koeijer *et al.*, 2003).





Threshold criterion

- The true R_0 is clearly a threshold
- Other expressions are also thresholds
- eg $(R_0)^k$ for $k > 0$
- However, these thresholds are not necessarily the average number of secondary infections

Q. Does this matter?

Does the emperor have no clothes?

The Jacobian method again

- Stability of the disease-free equilibrium is determined by the largest eigenvalue of the Jacobian
- This is a threshold condition that can derive an $R_{0,J}$
- May not produce a biologically meaningful value

Recent use: malaria immunology (Tumwiine et al, 2007).

Eg malaria again, using the Jacobian

$$J(x_0) = \begin{bmatrix} -(\mu_H + \alpha + \sigma) & \beta_{MH} H_S(0) \\ \beta_{HM} M_S(0) & -\mu_M \end{bmatrix}$$

$$\lambda_{\max} = \frac{1}{2}\Bigg\{ -\mu_M - \mu_H - \alpha - \sigma + \sqrt{\left[\mu_M - (\mu_H + \alpha + \sigma)\right]^2 + \frac{4\beta_{HM}\beta_{MH} H_S(0) M_S(0)}{\mu_H \mu_M}} \Bigg\}$$

$$R_{0,J} = \sqrt{\frac{\left[\mu_M - (\mu_H + \alpha + \sigma)\right]^2 + \frac{4\beta_{HM}\beta_{MH} H_S(0) M_S(0)}{\mu_H \mu_M}}{(\mu_M + \mu_H + \alpha + \sigma)^2}}$$

$$\neq R_{0,S},\ R_{0,N}.$$

Constant term of the characteristic polynomial

- Malaria again:

$$J(x_0) = \begin{bmatrix} -(\mu_H + \alpha + \sigma) & \beta_{MH} H_S(0) \\ \beta_{HM} M_S(0) & -\mu_M \end{bmatrix}$$

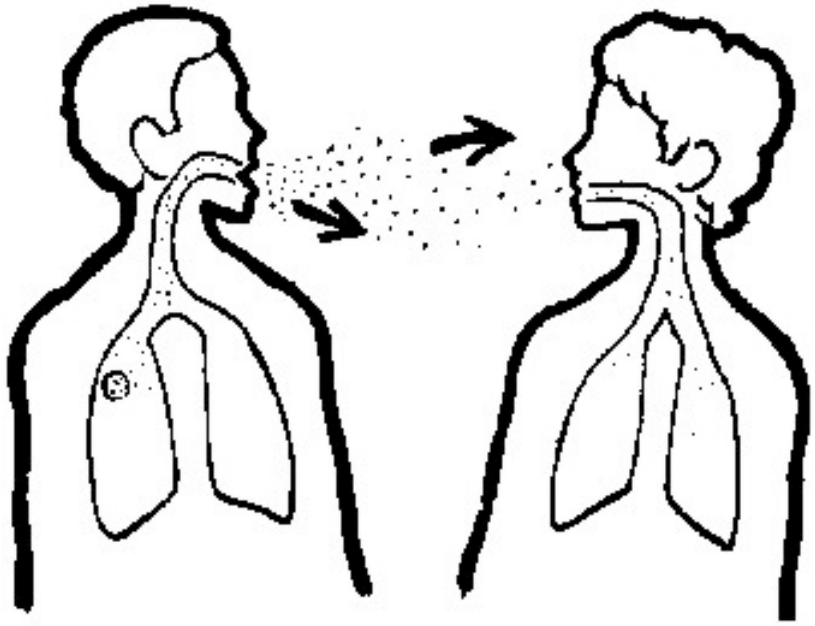
$$\begin{aligned} \det(J - \lambda I) &= \lambda^2 + (\mu_M + \mu_H + \alpha + \sigma)\lambda \\ &\quad + \mu_M(\mu_H + \alpha + \sigma) - \beta_{MH}\beta_{HM} M_S(0) H_S(0) \end{aligned}$$

$$\begin{aligned} R_{0,C} &= \frac{\beta_{MH}\beta_{HM} M_S(0) H_S(0)}{\mu_M(\mu_H + \alpha + \sigma)} \\ &= R_{0,S} \\ &\neq R_{0,J}, R_{0,N}. \end{aligned}$$

Constant term

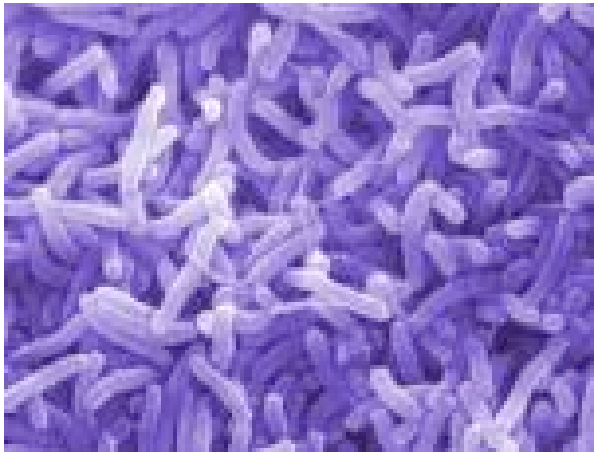
- Easier to calculate than most other methods
- Especially useful for calculating different R_0s corresponding to different strains of a disease

Recent use: tuberculosis in hot zones (Blower & Chou, 2004).



Measuring R_0 in the field

- R_0 is usually calculated from readily estimated parameters
- eg death and recovery rates
- But not contact rates
- Thus, other methods are needed to produce R_0, using simple estimates.



Susceptibles at endemic equilibrium

- The number of successful contacts for an individual is $R_0\pi_s$
- π_s is the probability that a given contact is with a susceptible
- At equilibrium, $R_0=1/\pi_s$
- Assumes homogenous mixing and mass action transmission

  (ie number of contacts per infective is independent of the number of infectives).

Relaxing mass-action assumption

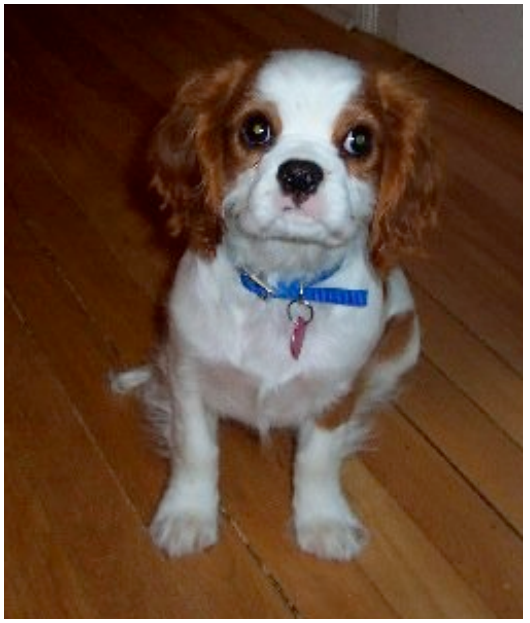
- When the assumption of mass-action transmission is relaxed, a backward bifurcation may occur at $R_0=1$
- Thus, diseases with $R_0<1$ may persist

Recent uses: foot and mouth disease (Ferguson *et al.*, 2001), avian flu in seabirds (Clancy *et al.*, 2006).

Average age at infection

- $R_0 = L/A$
- L=mean lifetime
- A=average age of acquiring disease
- Assumes population is well mixed among different age groups

Recent use: canine pathogens (Laurenson *et al.*, 1998).

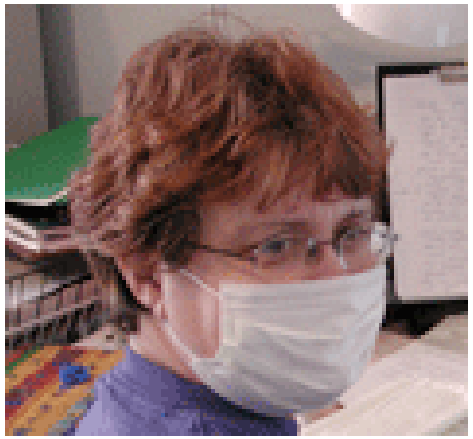


Final size equation

- Only applicable to closed populations
- ie infection leads to either immunity or death
- Thus, the number of susceptibles decreases to *s(∞)*

$$R_{0,F} = \frac{\ln s(\infty)}{s(\infty) - 1}$$

Recent use: SARS (Lipsitch *et al.*, 2003).



Intrinsic growth rate

- r_0 is the rate at which infections grow such that $I' = r_0 I$
- R_0 can be estimated from r_0
- This is an implicit definition, so seldom elegant

Recent use: Hepatitis C
(Pybus *et al.*, 2001).

R_0 in disease control policy

- How has R_0 been used in policy?
- Can it determine useful outcomes in the field?

R_0 in disease control policy

SARS: R_0 used to determine when intervention measures had Hong Kong epidemic under control (Riley *et al.*, 2003)

Mad Cow: Effect of ban on recycling animals into bonemeal showed that disease spread could be controlled in the UK (Ferguson *et al.*, 1999)

Foot and Mouth: Slaughter of animals within 24h would not reduce R_0 below one, but ring vaccination and ring culling would be effective (Ferguson *et al.*, 2001).

R_0 in disease control shocker!

Malaria: Low R_0 used to justify possibility of elimination from an island in the Gulf of Guinea (Hagmann *et al.*, 2003)

West Nile Virus: R_0 used to evaluate public health policies of mosquito vs bird control, concluding that bird control would actually enhance transmission (Wonham *et al.*, 2004).

Limitations

- Models used “in the field” are usually simple, deterministic and non-structured
- R_0 typically quantified after epidemic has run its course
- R_0 values usually used to justify severe or costly control measures, rather than affecting public health measures directly.

Summary

- Many threshold parameters
- Few of these reliably calculate the average number of secondary infections
- R_0 can't be used to compare different diseases
- However, multiple methods provide a variety of ways to determine thresholds.

Answering our question

- R_0's methods aren't consistent and don't give the average number of secondary infections

Q. Does this matter?

A. Not if we only want a threshold

The emperor doesn't need clothes to reign.