Between-host, within-host interactions in simple epidemiological models

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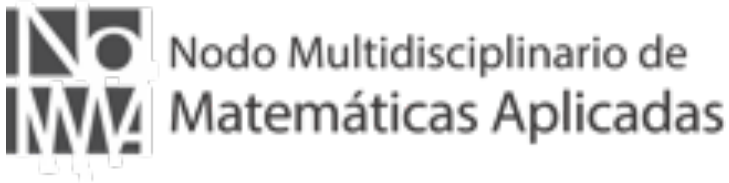
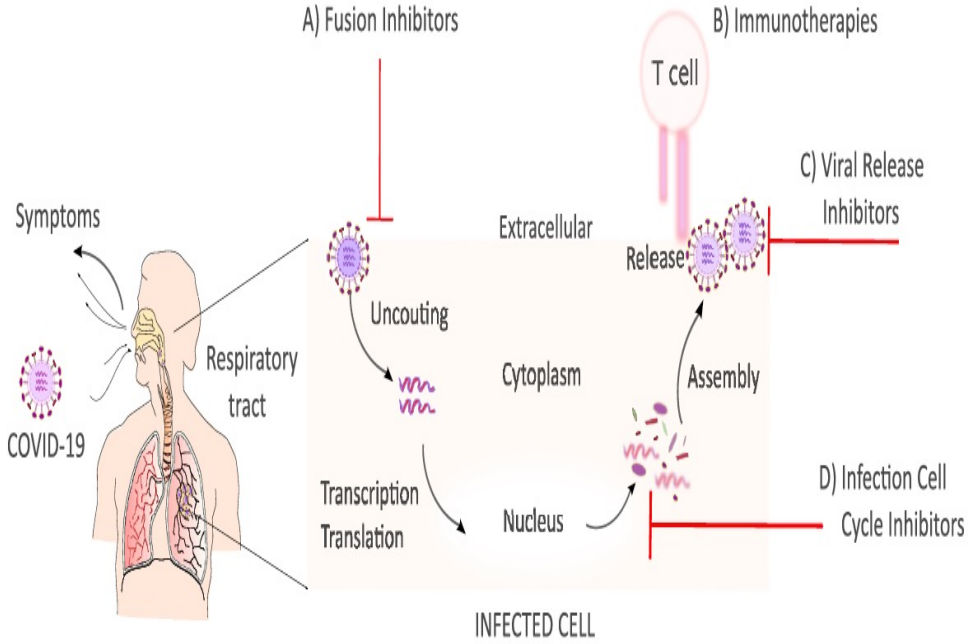
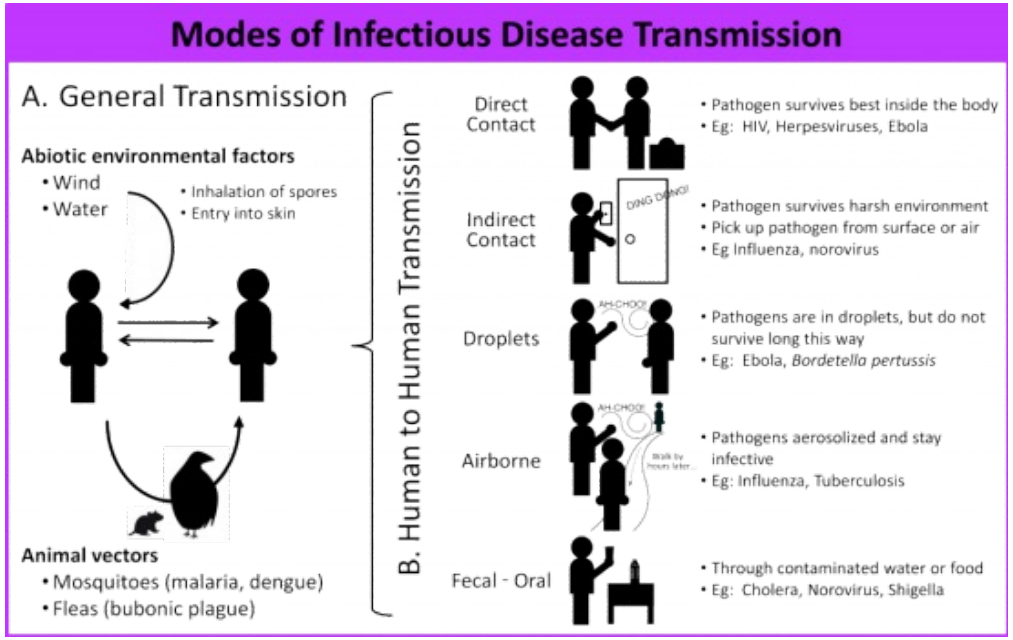
Joint work with Z. Feng



Immunological models consider the within-host dynamics independent of the interactions between hosts (e.g., De Leenheer and Smith,'03; Nowak et al., '97; Perelson et al., '93; Perelson and Nelson, '02; Rong et al., '07)



Epidemiological models consider the between-host transmissions without an explicit link to the within-host dynamics (e.g., standard SI, SIS, SIR, SEIR types of epidemiological models). Feng et al'12, 13, Cen et al'15, Almocera et al,'17, Nuñez-Lopez et al '22



Host-parasite interactions and transmission dynamics:

- The immunological process associated with the pathogen-cell interactions (individual level)

$$\frac{dT}{dt} = \Lambda - kVT - mT$$

$$\frac{dT^*}{dt} = kVT - (m+d)T^*$$

$$\frac{dV}{dt} = pT^* - cV.$$

- The epidemiological process concerning the spread of diseases (population level).

$$\dot{S} = \mu N - \lambda SI - \mu S,$$
$$\dot{I} = \lambda SI - \mu I,$$

Toxoplasma gondii

Obligate intracellular parasite; all warm-blooded vertebrates

- Infections in humans reaches 30% of population and can cause encephalitis in immunocompromised persons.
- Infection during pregnancy may cause severe damage to the fetus.

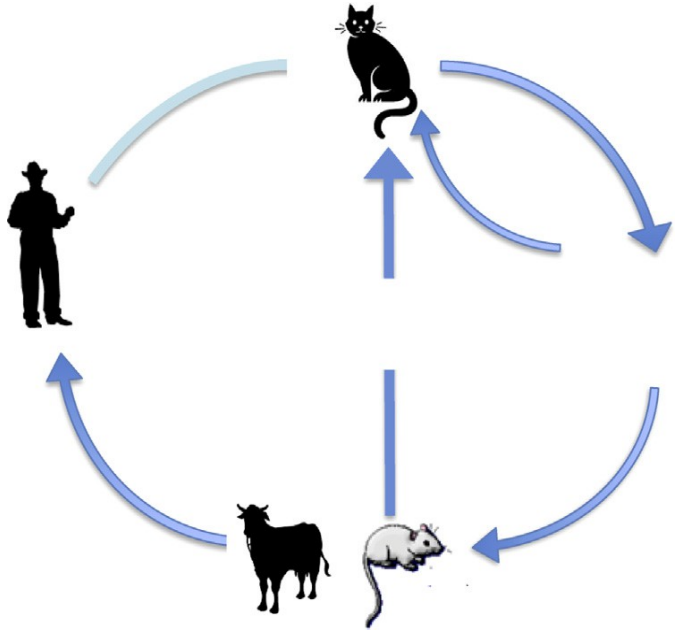
Sexual reproduction only in felines.

Once a cat becomes infected, it sheds oocysts, which contaminate the environment.

Oocysts ingested by mammals and birds.

Predation may also infect the secondary hosts

(Sullivan et al.'12)



Life history of *Toxoplasma gondii*

Life cycle of Toxoplasma comprises three distinct time scales.

1. Transmission times between individuals, according to the contacts of cats and infectious agents or reservoirs.
2. Infection times at individual level. Reproductive cycle within the host and its interaction with the host immune system.
3. Environmental times for oocysts. Oocysts may survive in the environment for a long time.

As in many other diseases that are transmitted through the environment, the size of the inoculum is important in the likelihood of infection in any given host

Biological time scales

Biological system with three clearly defined time scales:

- The slow scale: epidemiological and between-host transmission process
- The fast scale: the immunological and within-host infection process
- The intermediate scale: the environmental reservoir

$$\frac{dT}{dt} = \Lambda - kVT - mT$$

$$\dot{S} = \mu N - \lambda SI - \mu S,$$
$$\dot{I} = \lambda SI - \mu I$$

$$\frac{dE}{dt} = \theta IV(1-E) - \gamma E,$$

$$\frac{dT^*}{dt} = kVT - (m+d)T^*$$

$$\frac{dV}{dt} = pT^* - cV.$$

Basic reproduction numbers (isolated systems)

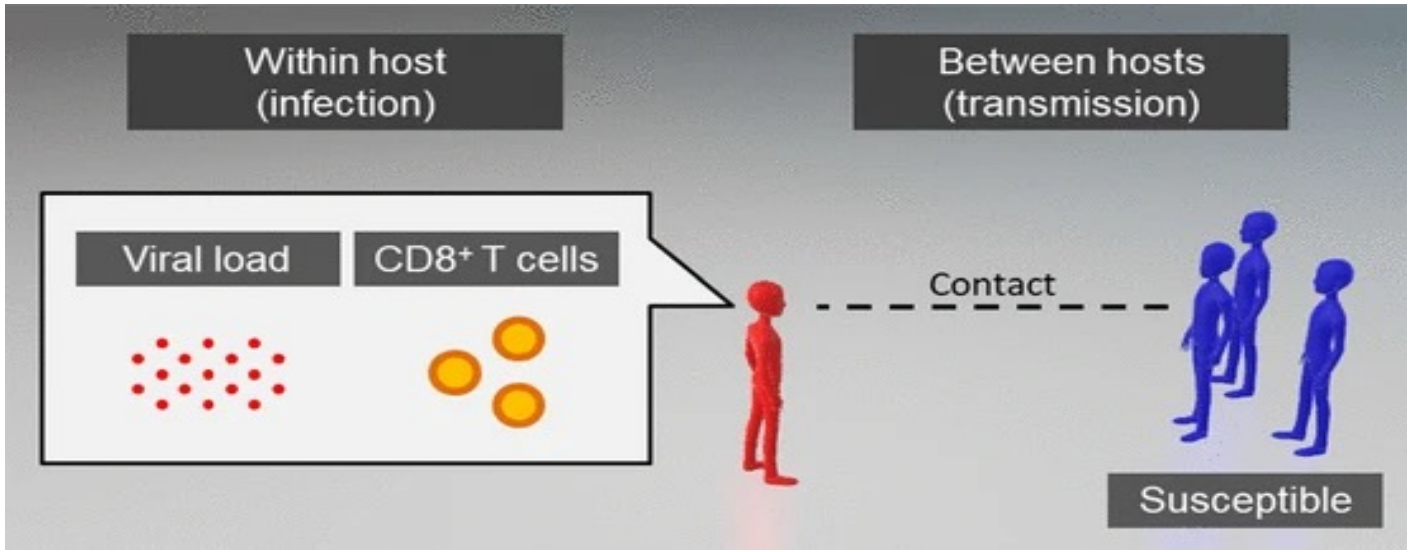
$$R_0 = \frac{\lambda N}{\mu}$$

$$\mathcal{R}_0 = \frac{\Lambda kp}{m(m+d)c}$$

Feng et al‘12, 13, Cen et al’15, Almocera et al,’17, Nuñez-Lopez et al ‘22

Questions

- How does the within-host dynamics influence transmission from individual to individual?
- What is the effect of disease transmission on the viral dynamics at the individual level?
- Will the model predictions in terms of the virulence and basic reproduction number of the pathogen be altered if the two process are dynamically linked?



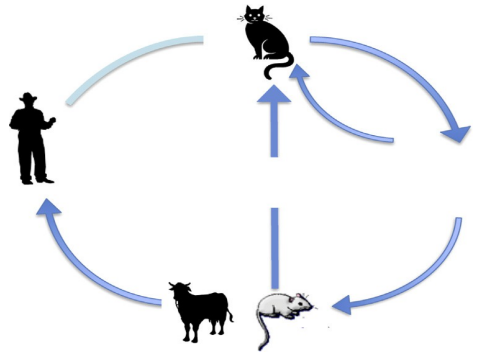
Almocera et al, JMB'18

Basic model BH-WH dynamics

$$\dot{I} = \lambda E(N - I) - \mu I,$$
$$\dot{E} = \theta I V(1 - E) - \gamma E$$
$$\dot{T} = \Lambda - kVT - mT$$
$$\dot{T}^* = kVT - (m + d)T^*$$
$$\dot{V} = g(E) + pT^* - cV.$$

$$g(E) = aE$$

λ	effective contact rate
μ	mortality rate
θ	virus shedding rate
γ	environmental cleaning rate
Λ	target cells recruitment rate
k	virus-cell contact rate
m	target cell mortality rate
p	viral production rate (bursting rate)
c	viral clearance rate



Between-host dynamics at slower time scale than within-host dynamics.

- Ignore the transient dynamics of the pathogen-cell interaction

- Focus only on the steady state of the WH equations while treating *E* and *I* as constants.

- Steady state input for between-host system.

- Consider systems WH and BH at two time scales in the analysis (fast and slow systems).

Isolated WH

WH in isolation $g(0) = 0$, behavior determined by the within-host baseline reproduction number

$$R_{w0} = \frac{kpT_0}{c(m+d)}$$

$$\begin{aligned} T' &= \lambda - kvT - mT, \\ T^{*'} &= kvT - (m+d)T^*, \\ v' &= pT^* - cv + g(E). \end{aligned}$$

$T_0 = \frac{\Lambda}{\mu}$ target cells in the absence of infection.

$R_{w0} < 1, U_0 = (\frac{\Lambda}{\mu},0,0)$ is globally asymptotically stable.

$R_{w0} > 1$ then the unique positive equilibrium U_1.

Isolated BH

BH system is in isolation, i.e V constant, dynamics determined by the between-host reproduction number:

$$\hat{R}_{b0} = \frac{\theta \tilde{V}}{\gamma} \frac{\lambda N}{\mu}$$

$$\dot{I} = \lambda E(N - I) - \mu I,$$

$$\dot{E} = \theta I \tilde{V}(E)(1 - E) - \gamma E$$

DFE $W = (0,0)$

If $\hat{R}_{b0} > 1$ endemic equilibrium exists

$$W_1 = \left(\frac{\gamma\mu(\hat{R}_{b0} - 1)}{\theta(\lambda + \mu)V}, \frac{\gamma\mu(\hat{R}_{b0} - 1)}{\lambda(\gamma + \theta N V)} \right)$$

BH-WH interactions: fast system

The WH coupled unique positive equilibrium, existence independent of R_{w0}

$$\tilde{U}(E) = (\tilde{T}(E), \tilde{T}^*(E), \tilde{V}(E))$$

$$\tilde{V} = \frac{1}{c}(g(E) + p\tilde{T}^*(E),$$
$$\tilde{T}^*(E) = \frac{m}{m+d}(T_0 - \tilde{T}(E),$$
$$\tilde{T}(E) = \frac{1}{2}(a_1 - \sqrt{a_1 - 4a_2}),$$

$$a_1 = \frac{(m+d)g(E)}{pm} + T_0\left(1 + \frac{1}{R_{w0}}\right) > 0,$$
$$a_2 = \frac{T_0^2}{R_{w0}}.$$

The virus free equilibrium does not exist and the equilibrium with positive densities of virus is stable.

Behavior of viral load environmental contamination declines

$$\tilde{V}(0) = \lim_{E \to 0} \tilde{V}(E) \begin{cases} 0, & \text{if } R_{w0} \leq 1 \\ \frac{m(R_{w0}-1)}{k}, & \text{if } R_{w0} > 1. \end{cases}$$

BH-WH interactions: slow system

$$\dot{I} = \lambda E(N - I) - \mu I,$$
$$\dot{E} = \theta I \tilde{V}(E)(1 - E) - \gamma E$$

$$\tilde{V}(E) = \frac{1}{c}(g(E) + \frac{pm}{m+d}(T_0 - \tilde{T}(E))$$

$R_{w0} > 1,$

$\tilde{V}(0) = \frac{m(R_{w0} - 1)}{k}$ Initial viral density

$R_{b0} = \frac{\theta \tilde{V}(0)}{\mu} \frac{\lambda N}{\gamma}$ (new) between-host reproduction number

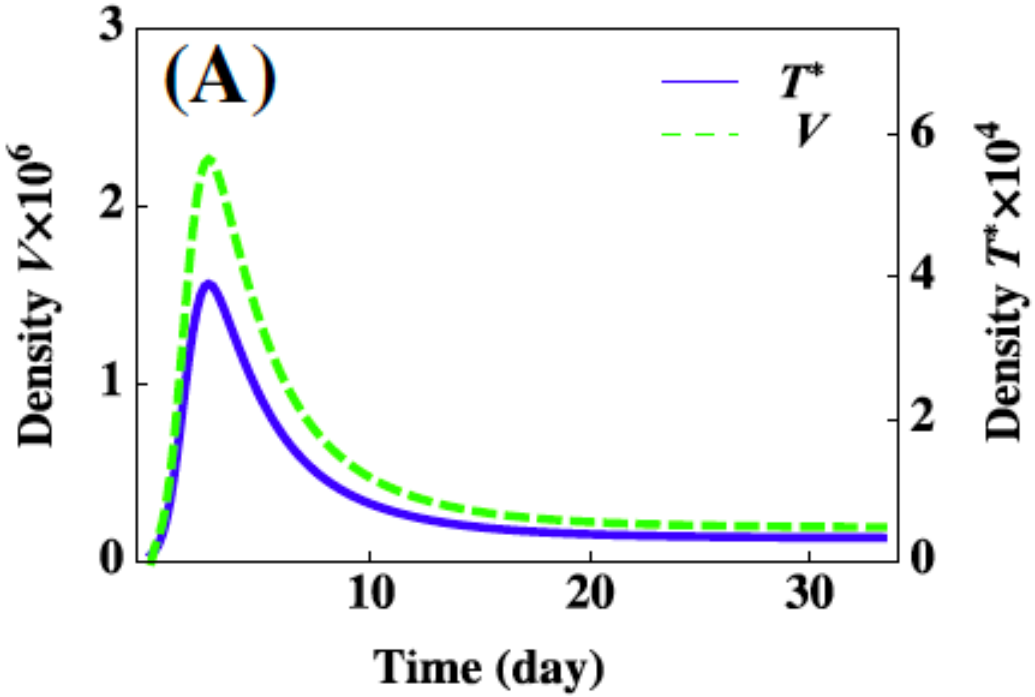
Expected amount of viral contamination in a clean environment by a typical infected host while shedding virus

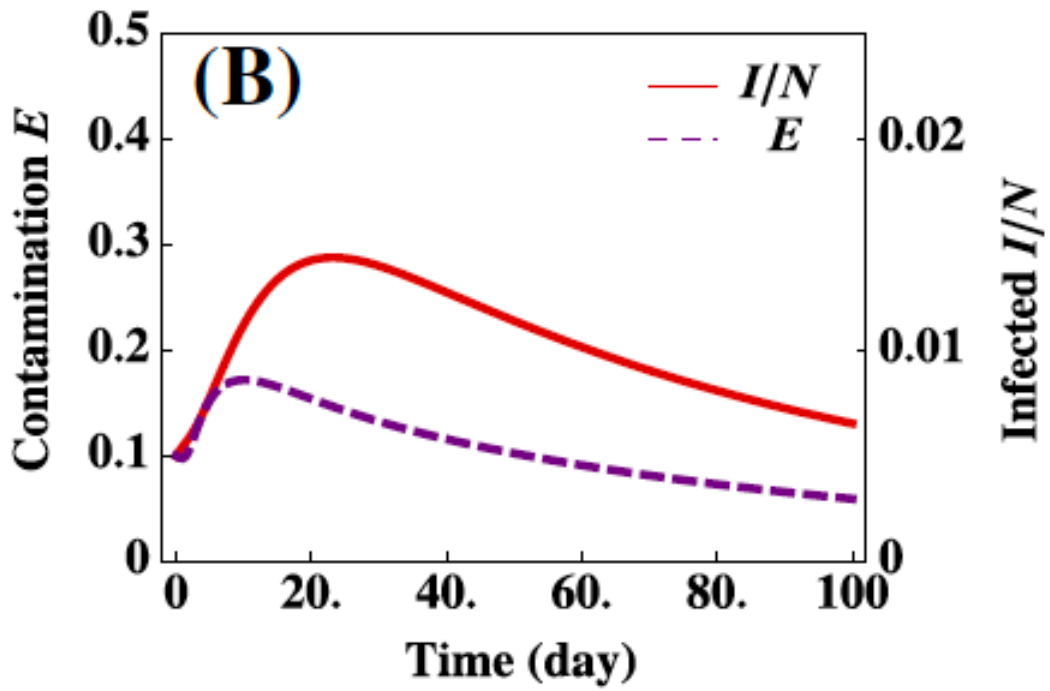
Expected number of host infected through the environment while contaminated

R_{b0}: expected number of secondary infections from a typical infectious individuals (while infectious) in a completely susceptible and uncontaminated environment

$W_0 = (0,0)$ infection-free equilibrium of BH system.

- When $R_{w0} > 1, W_0$ is L.A.S. if $R_{b0} < 1$ and unstable if $R_{b0} > 1$.
- When $R_{w0} < 1, W_0$ is L.A.S.


(A)
T*
V
Density V×10^6
Density T*×10^4
Time (day)
0
1
2
3
0
2
4
6
10
20
30


(B)
I/N
E
Contamination E
Infected I/N
Time (day)
0
0.1
0.2
0.3
0.4
0.5
0
0.01
0.02
0
20.
40.
60.
80.
100

Multiple endemic equilibria

$$\dot{I} = \lambda E(N - I) - \mu I,$$
$$\dot{E} = \theta I \tilde{V}(E)(1 - E) - \gamma E$$

$$W = (\hat{I}, \hat{E}), \quad \hat{I} = \frac{\lambda N \hat{E}}{\lambda \hat{E} + \mu}.$$

$\hat{E}$ solution of $H(E) = F(E) - G(E) = 0$.

$R_{w0} > 1, R_{b0} < 1$

$H_{max} > 0, W_1 \neq W_2$ exist
$H_{max} = 0, W_1 = W_2$ unique
$H_{max} < 0$, no equilibria exist

$R_{w0} > 1, R_{b0} > 1, W$ is unique

$R_{w0} < 1$

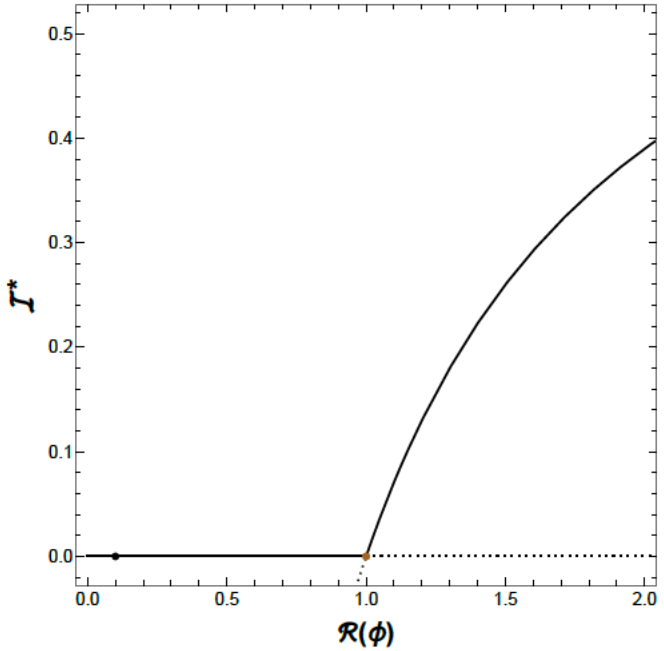
$H_{max} > 0, W_1 \neq W_2$ exist
$H_{max} = 0, W_1 = W_2$ unique
$H_{max} < 0$, no equilibria exist

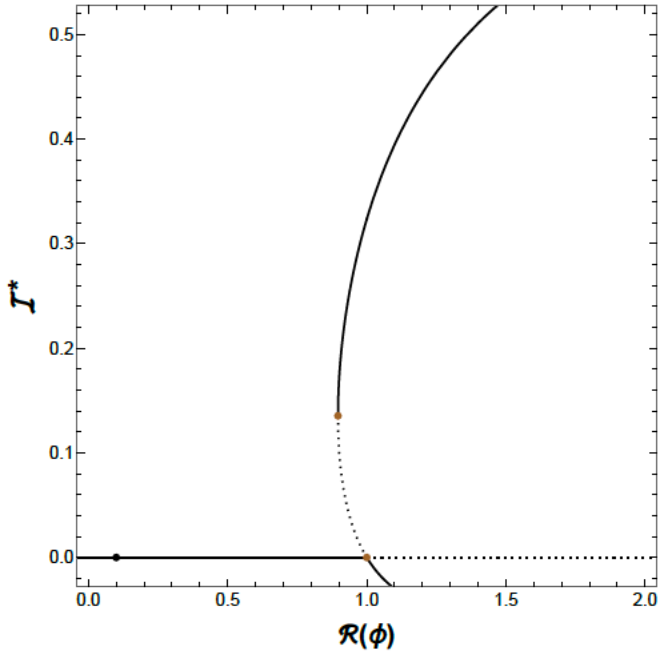
$H_{max} > 0$, requires $H'(0) > 0$, equivalent to $g'(0) > C(R_{w0})$.

Remark. The slow BH system can have up to two interior equilibria even $R_{b0} > 1$ or $R_{w0} < 1$, implying the existence of backward bifurcations.

Remark. The number of interior equilibria of BH system depends on the two reproduction numbers R_{b0} and R_{w0}.

Disgression on backward bifurcations



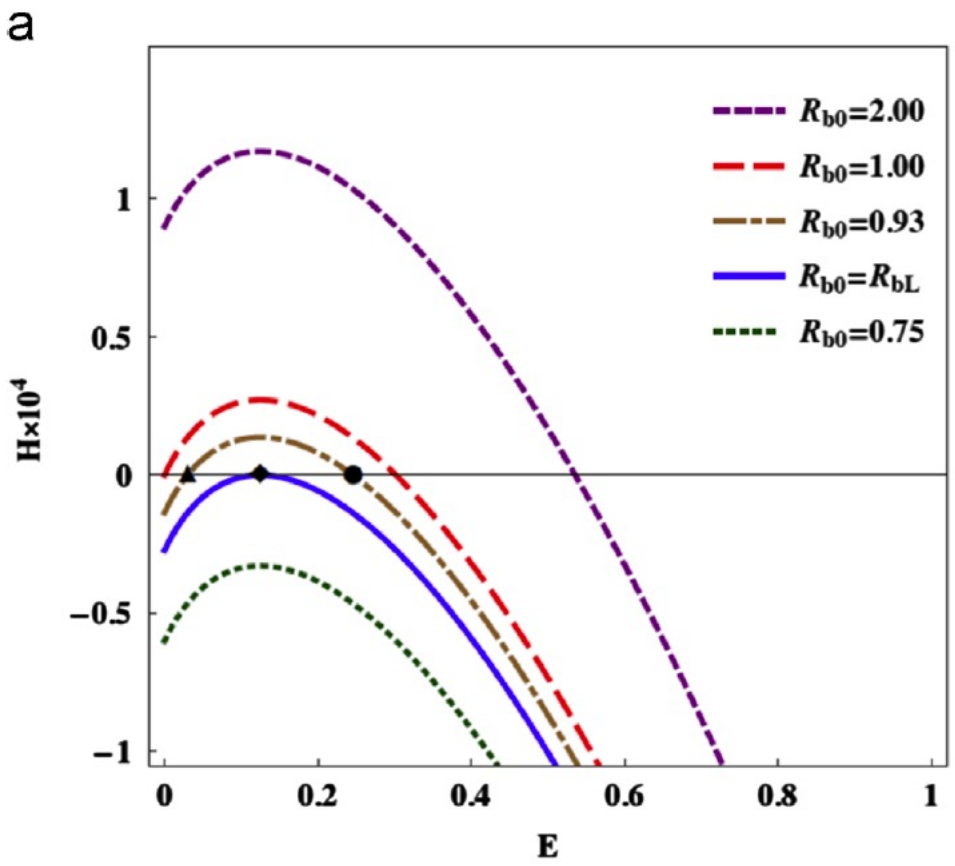


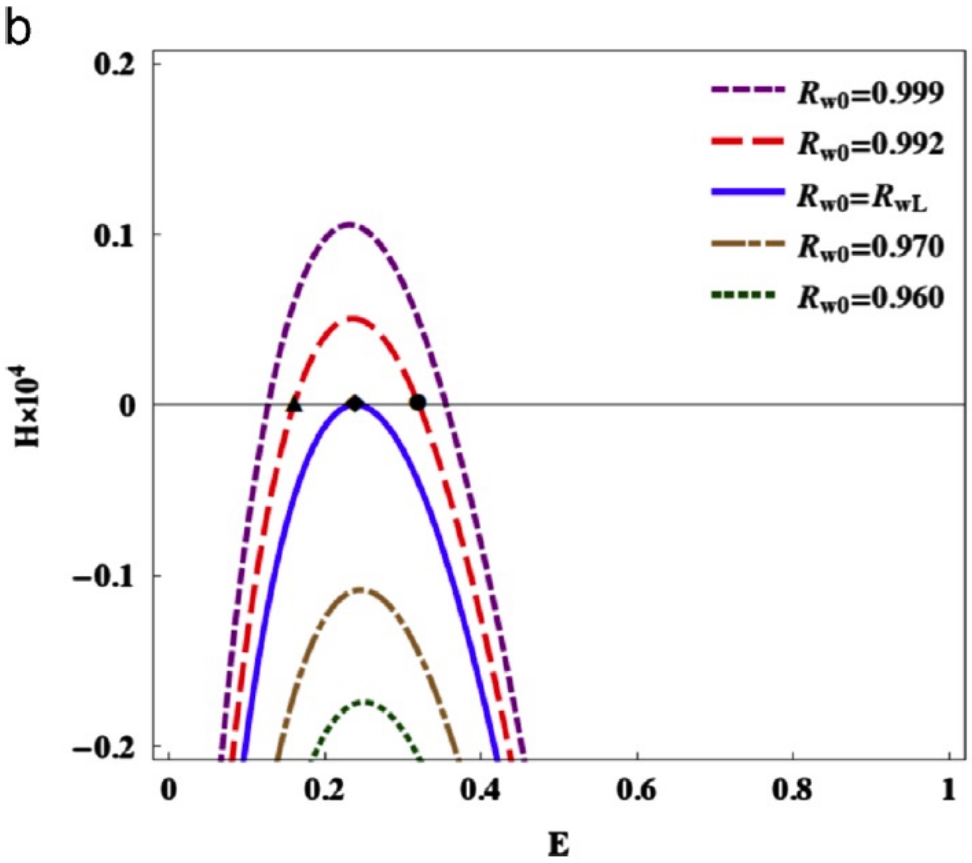
$$R_* = R_0 \Phi(\psi)$$

ψ vector of parameters (vaccine related coverage, efficacy, waning….)

Kribs & VH, MBS 2000

$\hat{E}$ solution of $H(E) = F(E) - G(E) = 0$.

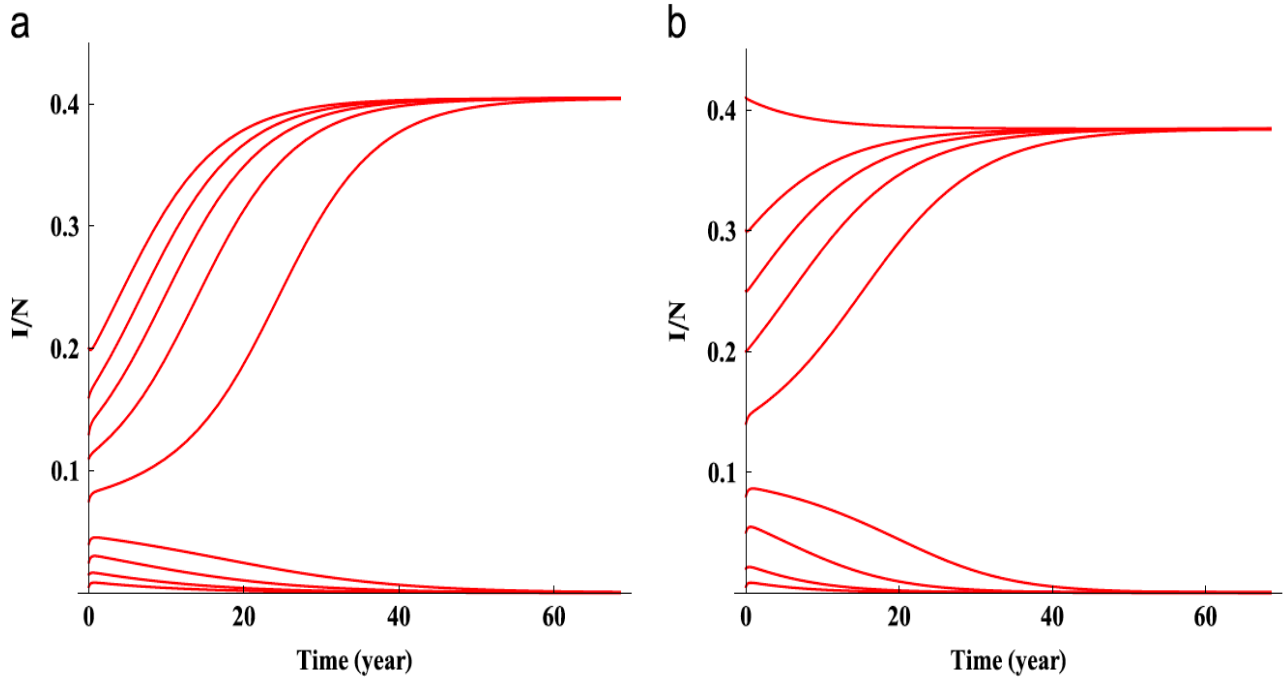




Stability of endemic equilibria

$W = (\hat{I}, \hat{E}), \quad \hat{I} = \frac{\lambda N \hat{E}}{\lambda \hat{E} + \mu}.$

$\hat{E}$ solution of $H(E) = F(E) - G(E) = 0$.
When two exist $E_1 < E_2$ (will say $W_1 < W_2$)



$R_{w0} > 1, R_{bL} < R_{b0} < 1$

$R_{wL} < R_{w0} < 1$

$R_{w0} > 1, R_{b0} < 1$

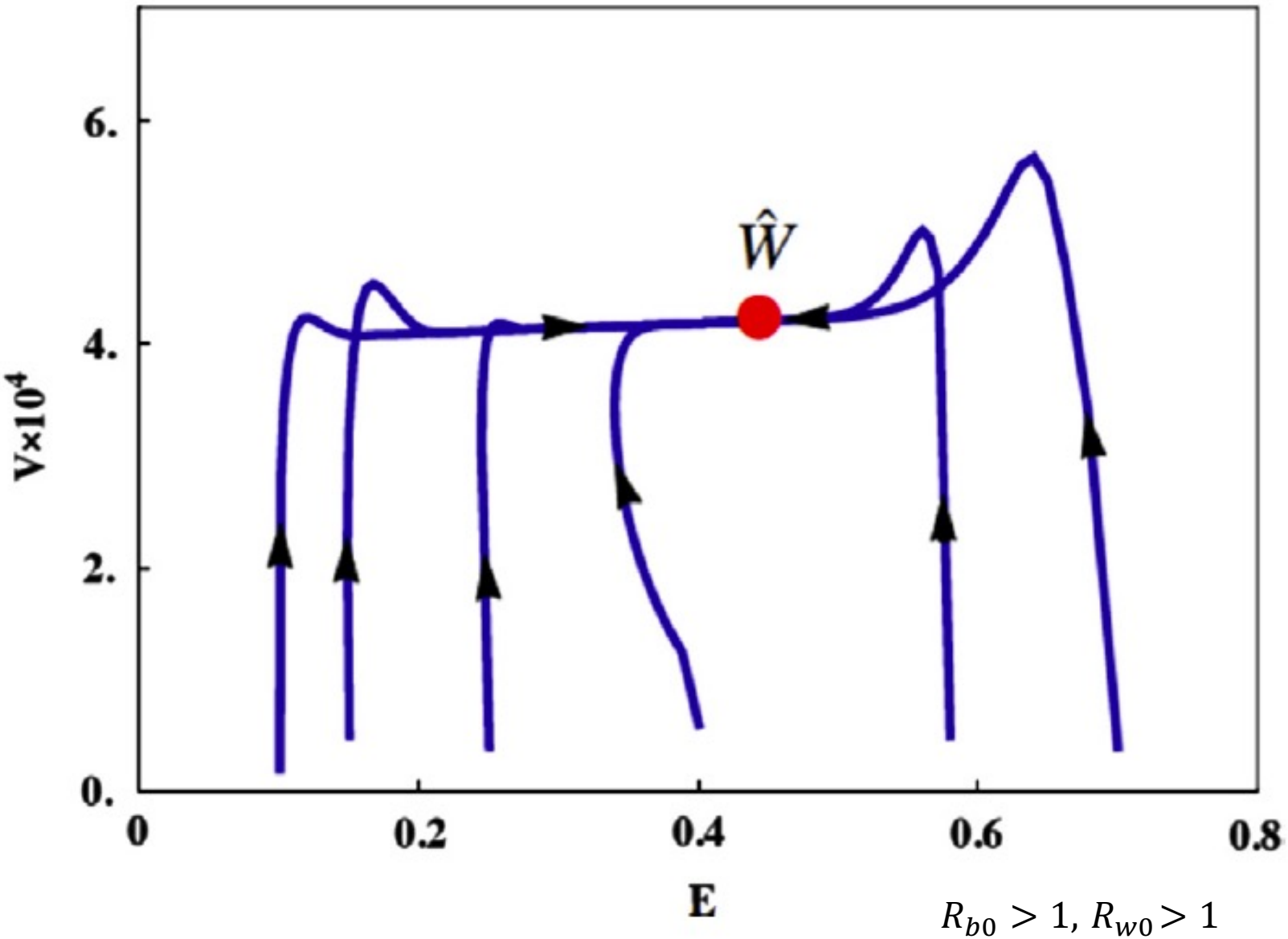
$H_{max} > 0, W_1$ unstable, W_2 L.A.S.
$H_{max} = 0, W_1 = W_2$ saddle-node

$R_{w0} > 1, R_{b0} > 1, W$ L.A.S.

$R_{w0} < 1$

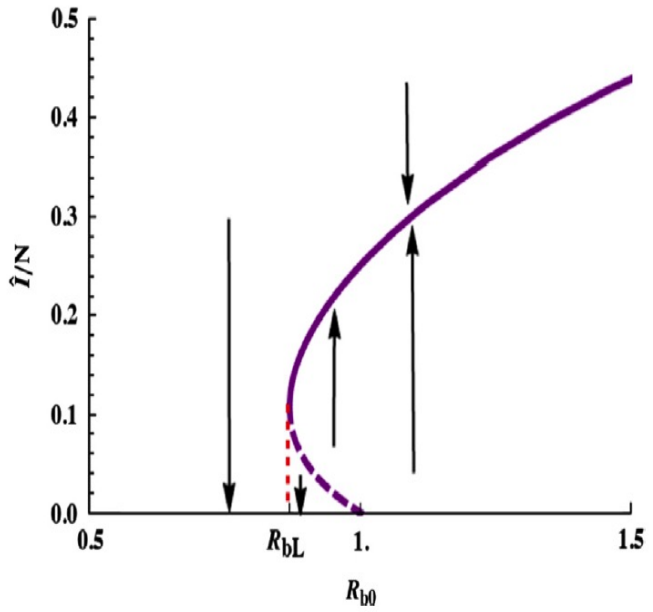
$H_{max} > 0, W_1$ unstable, W_2 L.A.S.
$H_{max} = 0, W_1 = W_2$ saddle-node

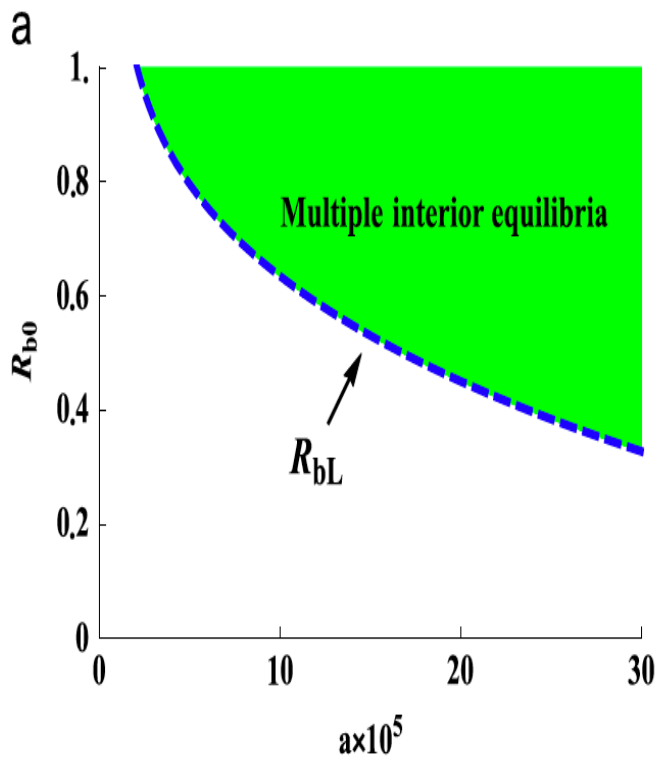
Full system

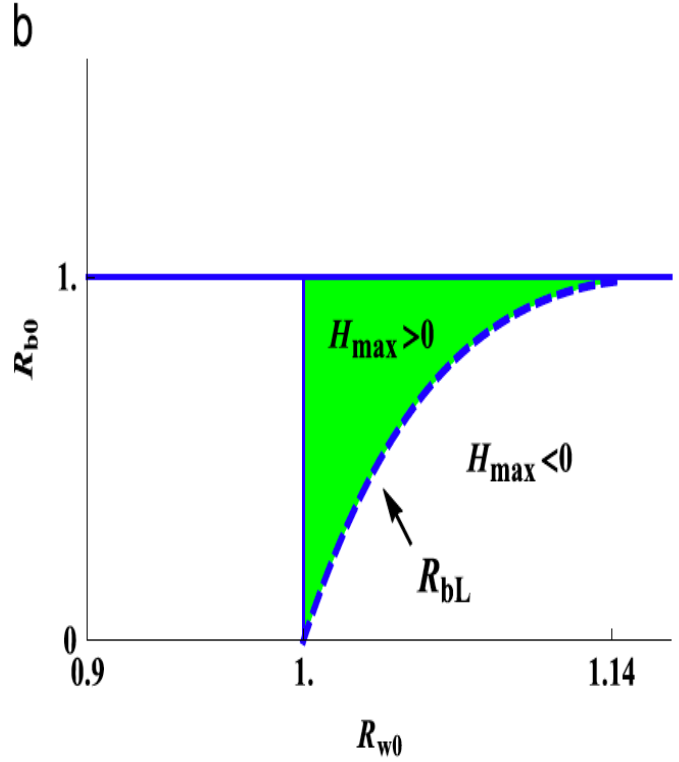


$R_{b0} > 1, R_{w0} > 1$

$R_{w0} > 1, R_{b0} < 1$


0.5
0.4
0.3
0.2
0.1
0.0
$\hat{I}/N$
0.5
R_{bL}
1.
1.5
R_{b0}


a
1.
0.8
0.6
0.4
0.2
0
R_{b0}
Multiple interior equilibria
R_{bL}
0
10
20
30
a×10^5


b
1.
0
R_{b0}
$H_{max}>0$
$H_{max}<0$
R_{bL}
0.9
1.
1.14
R_{w0}

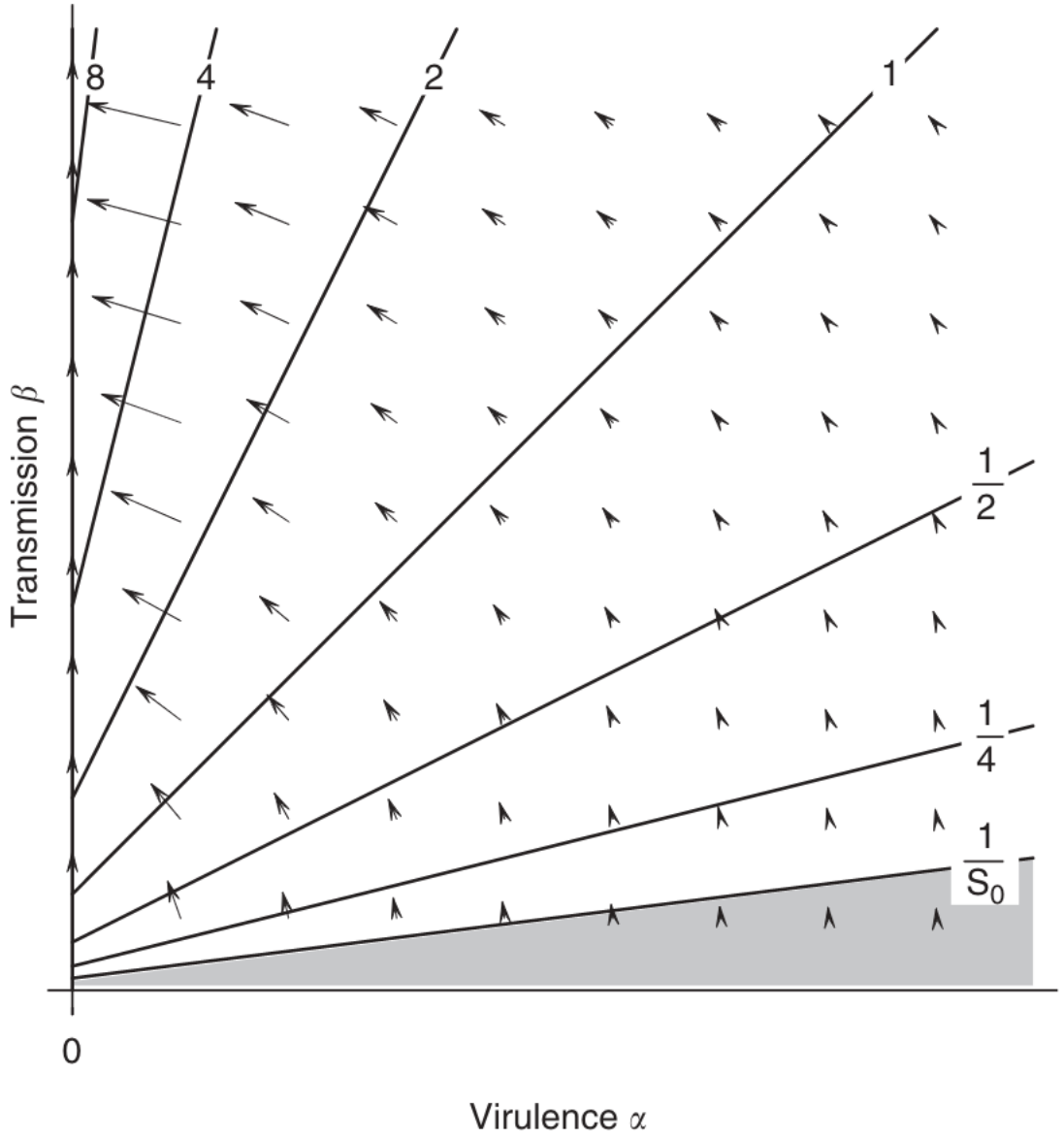
Evolution of virulence

Evolution of virulence population level: Optimum virulence rate for a pathogen is determined by the relationship between the rates of disease transmission and virulence.

Evolution of virulence individual level:
Optimal pathogen trade-off between intra-cellular virulence and inter-cellular transmission.

However, success of a parasite within a single host does not necessarily lead to optimal exploitation of the population of uninfected hosts.

Gilchrist & Coombs



$$R_0 = \frac{\beta}{\alpha + \delta}$$

α disease induced death rate (virulence)
δ natural or background mortality rate
β effective contact rate

Evolution of virulence

Incorporating disease induced death rate δ:
transmission-virulence trade-off, selection characteristics at BH and WH.

$$S' = \mu N - \lambda EI - \mu S,$$
$$I' = \lambda EI - (\mu + \delta) I,$$
$$E' = \theta(v) I(1 - E) - \eta E$$

$\Phi(p) = \frac{p}{m + d(p)}$, burst size

$R_{w0} = \frac{\Phi(p) k T_0}{c}$

WH measures of fitness
(optimized for *p*)

Example

$$\theta(V) = a_1 V^z, z > 0, \qquad \delta(T) = a_2(\frac{1}{\hat{T}} - \frac{1}{T_0})$$

To determine optimal p (WH) and associated δ (BH)

$$T' = \lambda - kvT - mT,$$
$$T^{*'} = kvT - (m + d)T^*,$$
$$v' = pT^* - cv + g(E).$$

If $d(p) = d_0 p^2$, R_{w0} has critical point $p_c = \sqrt{\frac{m}{d_0}}$.

$p^* = \min(p_{max}, p_c)$.

p_{max} (maximal virion production rate) imposes δ_{max}

BH measure of fitness, optimized for δ through R_{b0}.

Given

$$\hat{V} = \frac{\Lambda\Phi}{c} - \frac{m}{k}$$

$$\hat{T} = \frac{c}{k\Phi}$$

Population level: selection will favour *p* that maximizes R_{b0}

WH perspective: optimize *p*

$$\theta(p) = \theta_0\left(\frac{\Lambda\Phi(p)}{c} - \frac{m}{k}\right)^z$$

$$\delta(p) = a_2\left(\frac{k\Phi(p)}{c} - \frac{m}{\Lambda}\right)$$

$$R_{b0}(p) = \frac{\theta(p)}{\mu + \delta(p)}\frac{\lambda N}{\gamma}$$

BH perspective: optimize δ

$$\theta(\delta) = \theta_0\left(\frac{\Lambda\delta}{a_2 k}\right)^z$$

$$R_{b0}(\delta) = \frac{\lambda N\theta_0}{\gamma(\mu+\delta)}\left(\frac{\Lambda\delta}{a_2 k}\right)^z$$

δ^* optimal from $R_{w0}(\delta)$, $\delta^* = \delta(p^*) = \delta_{max}$. (WH)

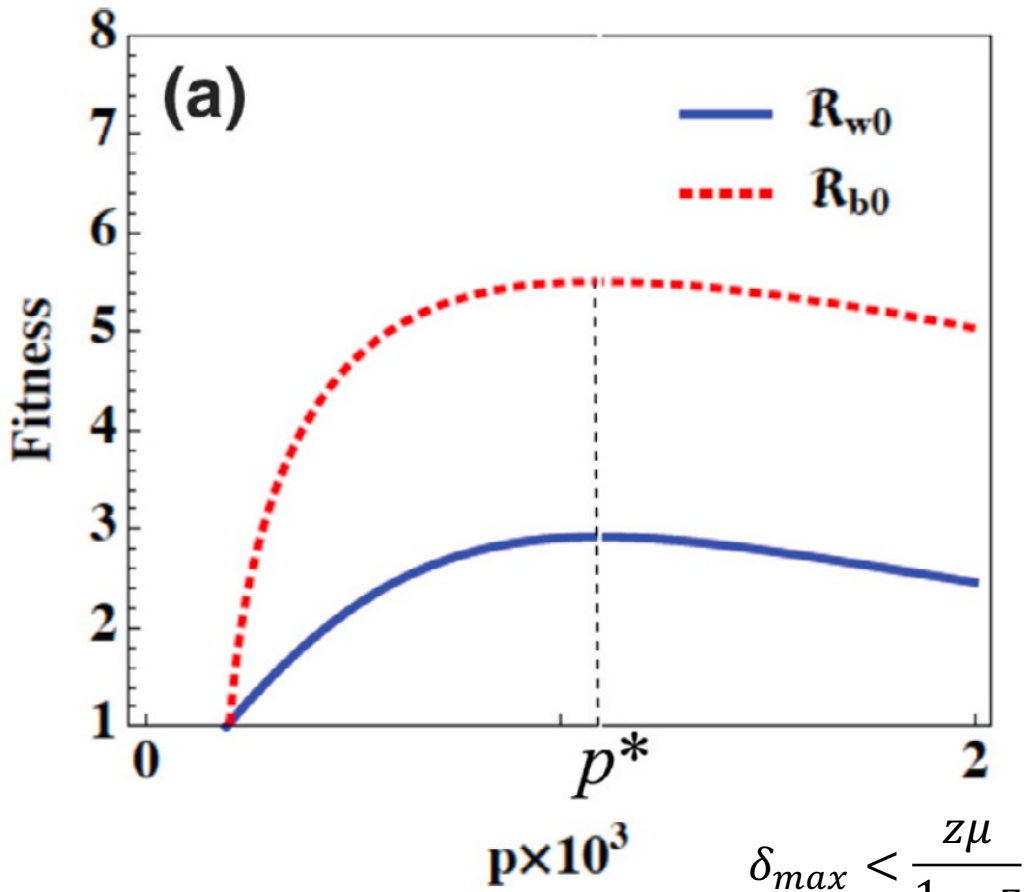
p^+, δ^+ optimal from BH dynamics $(R_{b0}(p), R_{b0}(\delta))$, case: $z < 1$.

δ_c optimum of $R_{b0}(\delta)$, $\delta_c = \frac{z\mu}{1-z}$

$\delta^+ = \min\{\delta_{max}, \delta_c\}$

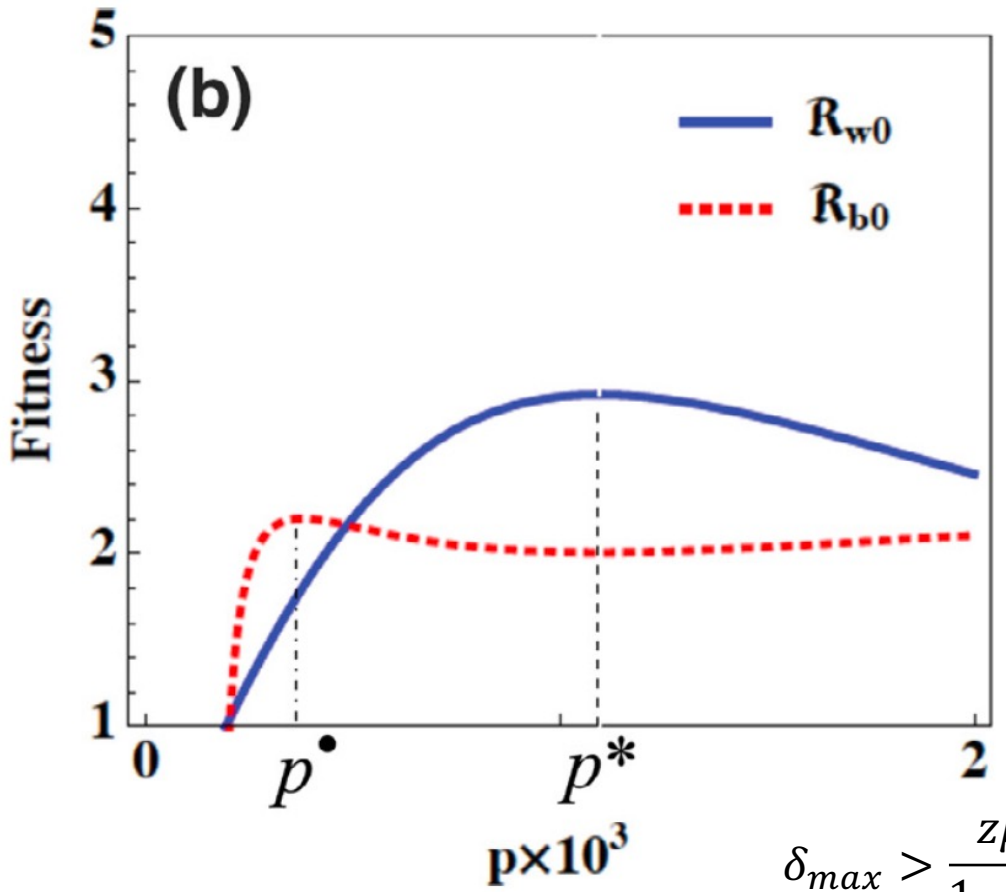
If $\delta_{max} < \delta_c$, then $p^* = p^+$. (WH selection = BH selection)

If $\delta(p^*) = \delta_{max} > \delta_c$, then $p^+ < p^*$. (WH selection ↔ BH selection)



$\delta_{max} < \frac{z\mu}{1-z}$

$p^+ = p^*$



$\delta_{max} > \frac{z\mu}{1-z}$

$p^+ < p^*$

Concluding remarks: vector-transmitted diseases

Ross-Macdonald model

$$i' = \alpha_v(1-i)y - (\mu+\gamma)i,$$
$$y' = \beta(v)(1-y)i - \delta y$$

i: proportion of infected hosts
y: proportion of infected mosquitoes

$$T' = \lambda - kvT - mT,$$
$$T^{*'} = kvT - (m+d)T^*,$$
$$v' = pT^* - cv + g(y).$$

Biting rates

$$\alpha_v = a_v q \qquad \beta(v) = \frac{b_0 v}{s_2 + v}$$

$$g(y) = rye^{-\zeta y}.$$

Thank you