Evolution of pathogens: a within-host approach

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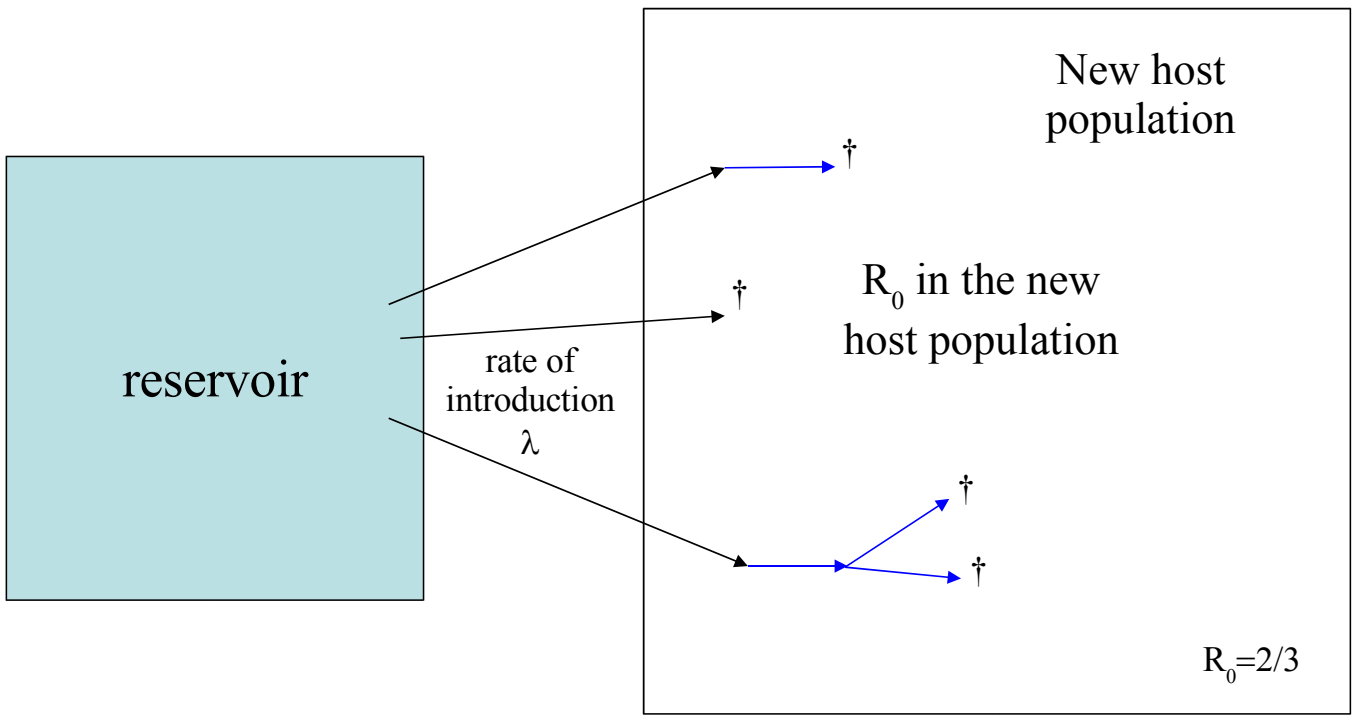
Outline

Emergence of infectious diseases



R_0 equals the average number of secondary infections causes by an infected host introduced into a wholly susceptible population.

Evolution of pathogens in new hosts

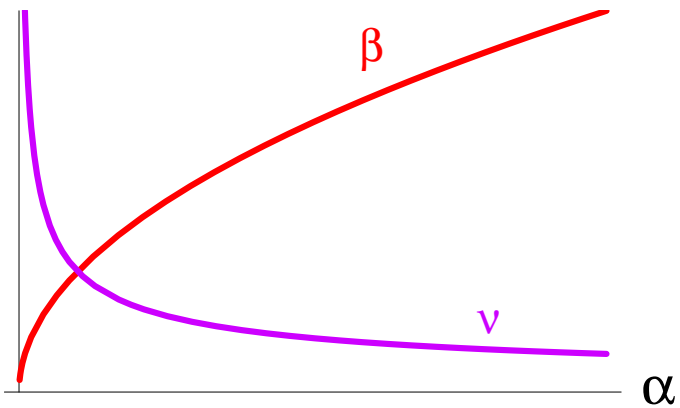
- Once a pathogen has emerged ($R_0 > 1$), the important question is whether it is going to evolve to be benign or virulent.
- The evolution of pathogens is generally considered in terms of the basic reproductive number R_0.
  - Pathogens evolve to maximize R_0 (i.e., their total transmission).
  - Pathogens evolve their virulence, defined as the reduction in host fitness due to infection with the pathogen.
  - In models, virulence is measured by host mortality rate or case mortality.

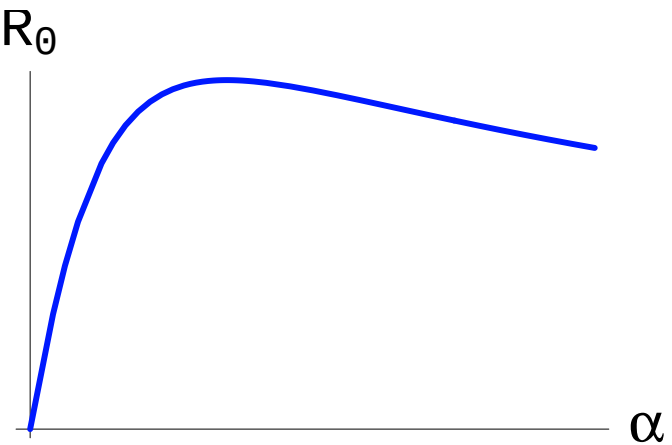
Anderson and May (1982); Bremermann and Thieme (1989)

The basic reproductive number R_0

For directly transmitted diseases

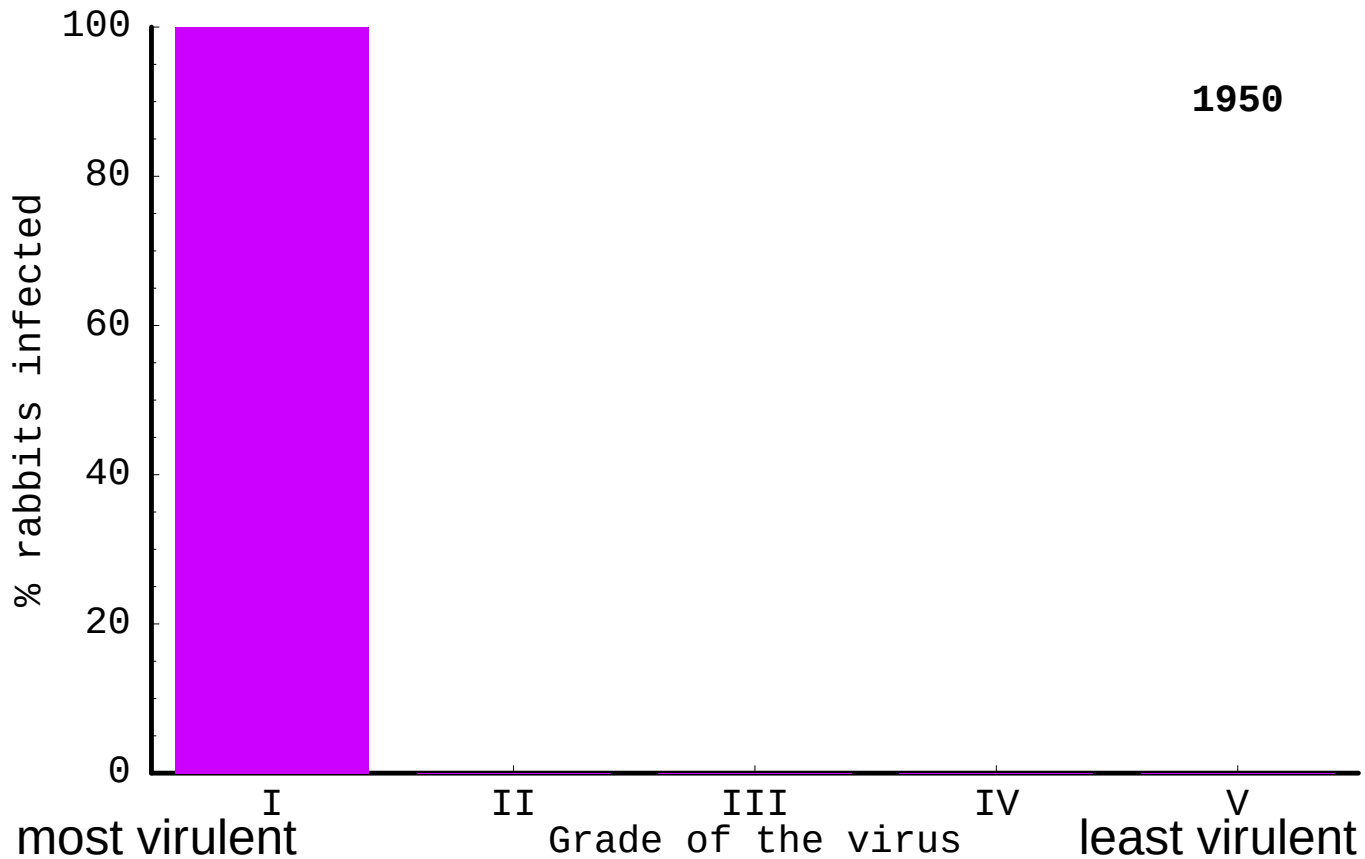
$$R_0 = \underbrace{\beta N}_{\text{infection rate}} \times \underbrace{\frac{1}{\alpha + d + \nu}}_{\text{duration of infection}} = \frac{\boldsymbol{\beta(\alpha)} N}{\boldsymbol{\alpha} + d + \boldsymbol{\nu(\alpha)}}$$





Anderson and May (1982)

Introduced virus strain: 1950



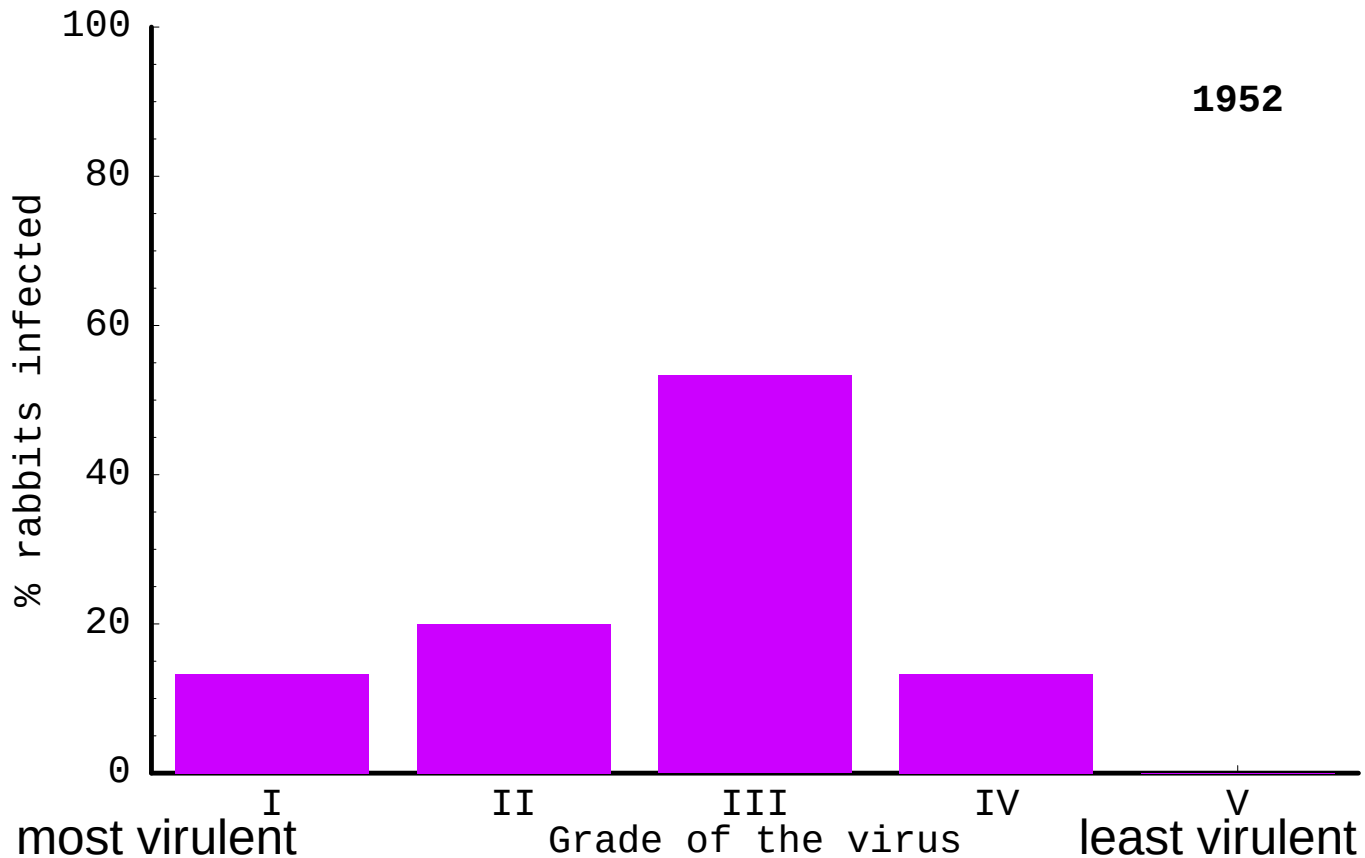
case mortality > 0.99

case mortality ≈ 0.23

Fenner and Fantini (1999);

virulence was measured in laboratory (standard) rabbits.

Virus prevalence: 1952



case mortality > 0.99

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Fenner and Fantini (1999);

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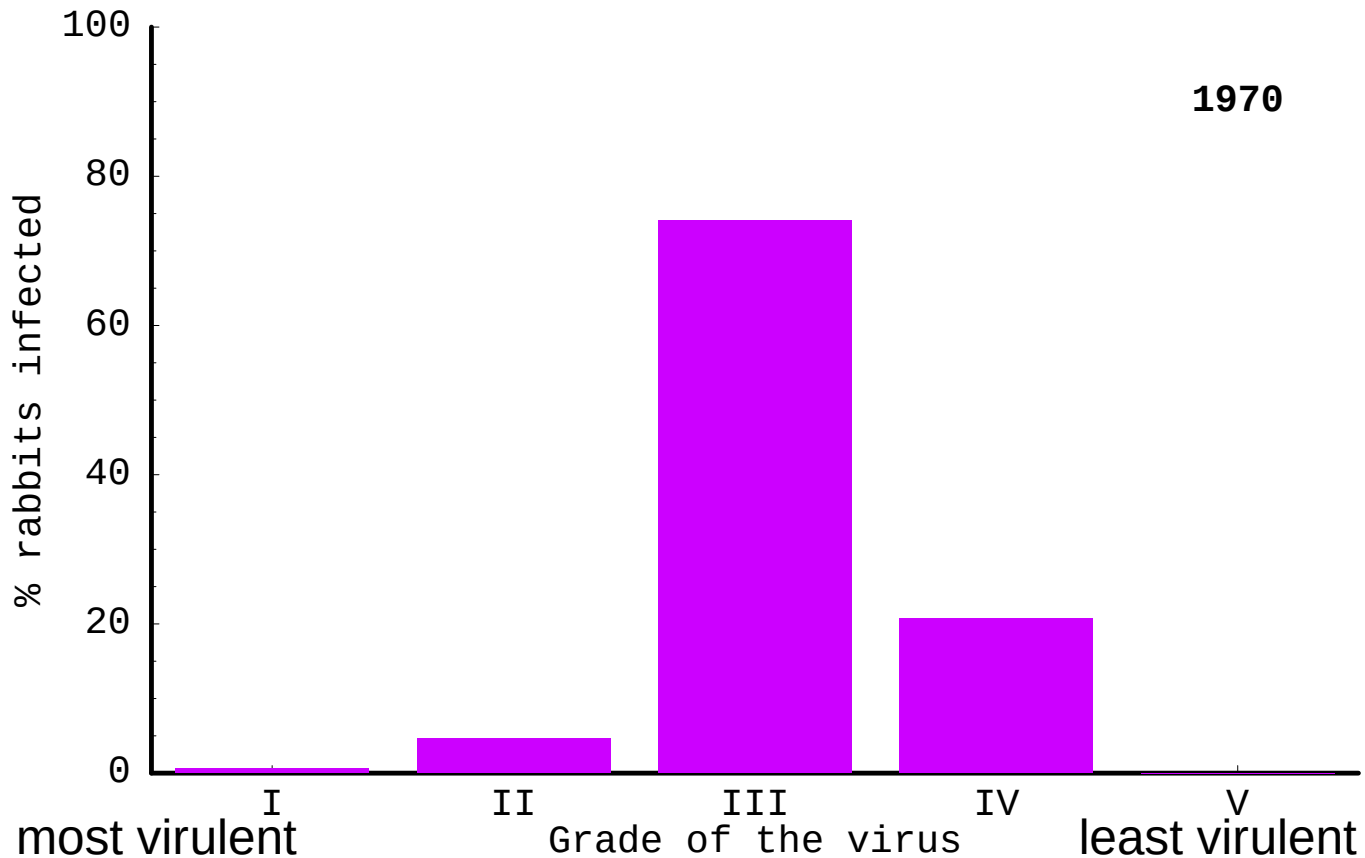
Virus prevalence: 1970



case mortality > 0.99

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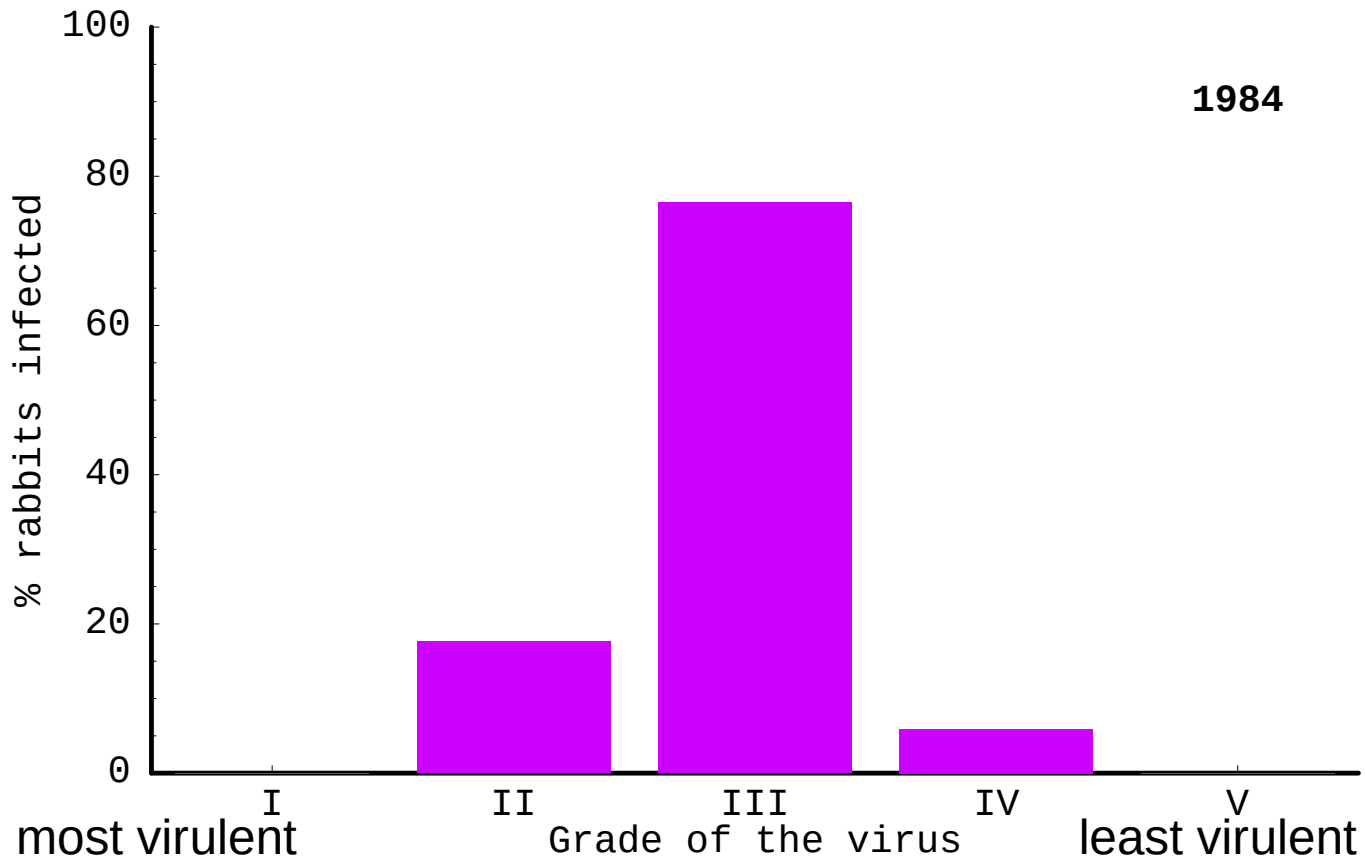
Fenner and Fantini (1999);

virulence was measured in laboratory (standard) rabbits.

Virus prevalence: 1984



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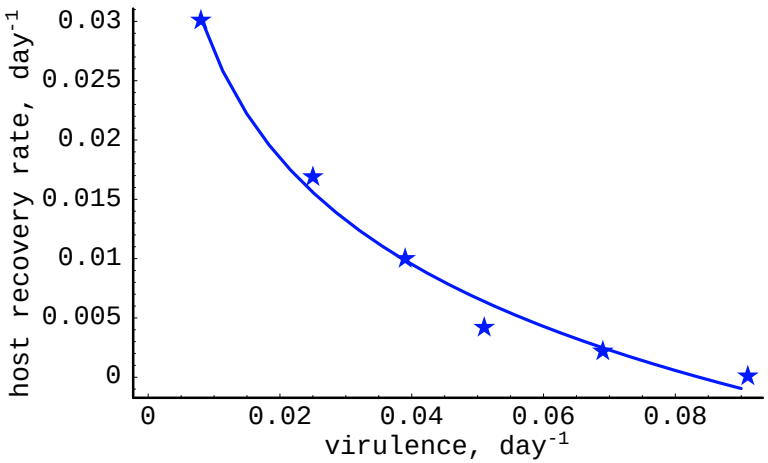
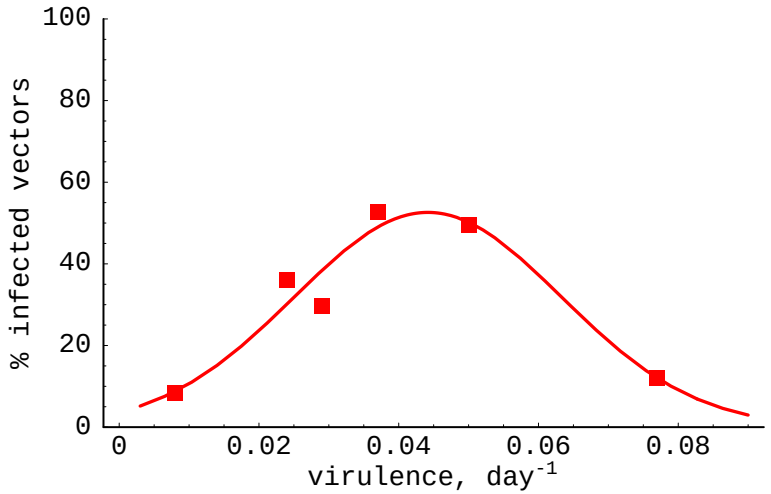
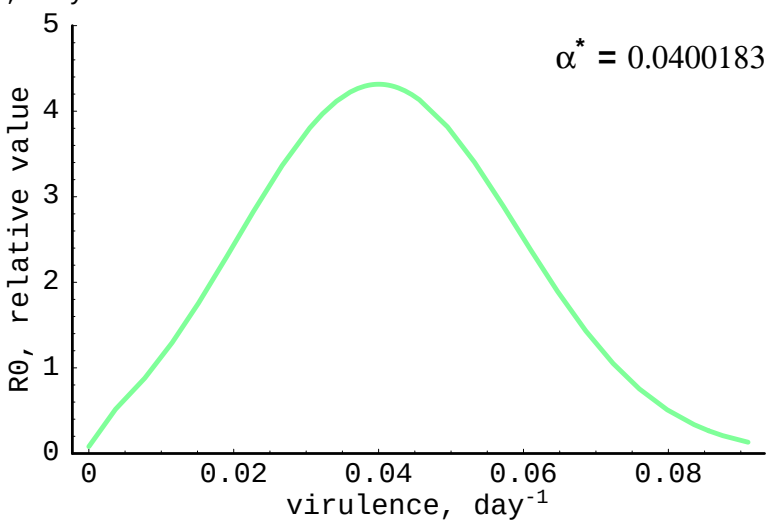
Trade-offs for the myxoma virus infection of rabbits



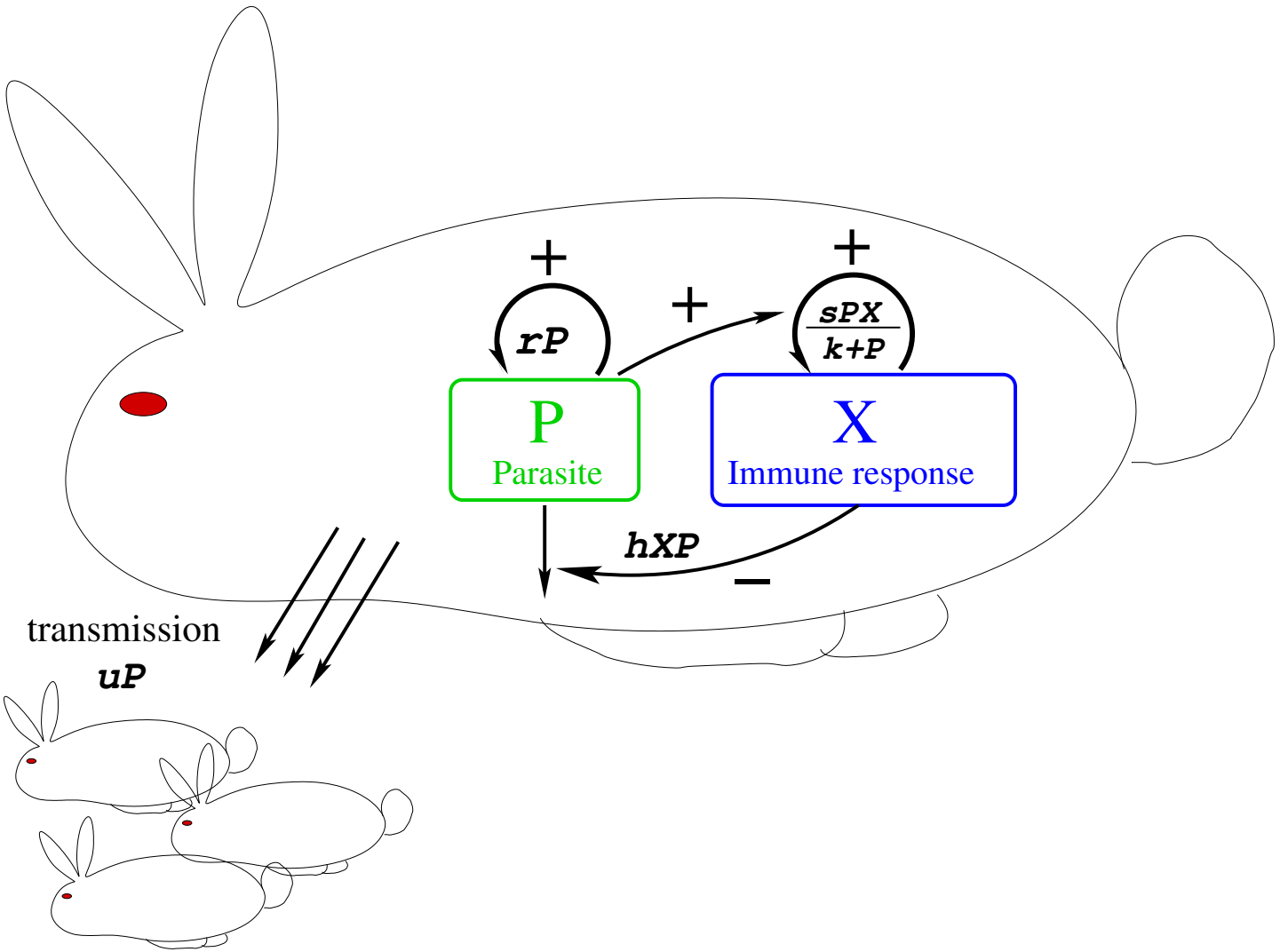


$\alpha^* = 0.0400183$



Fenner et al. 1956; Mead-Briggs et al. 1975; Anderson and May 1982*

Within-host dynamics of pathogens



Dynamics of the pathogen and the immune response

$$
\begin{aligned}
\dot{P} &= rP - hPX, \\
P &= 0, \text{ if } P(t) \geq D, \\
\dot{X} &= \frac{sXP}{k+P}, \\
l(r) &= u \int_0^{\Delta} P(t)\, dt.
\end{aligned}
$$

- Pathogen kills the host if it reaches a lethal density D;
- There is no transmission from a dead host;
- Pathogens evolve to maximize their total transmission.

P – pathogen, X – immune response, l – total transmission, Δ – duration of infection.

Parameters: $P(0) = 1, X(0) = 1, h = 10^{-3}, k = 10^3, s = 1, D = 10^9, r = 2.08.$

Antia et al. 1994

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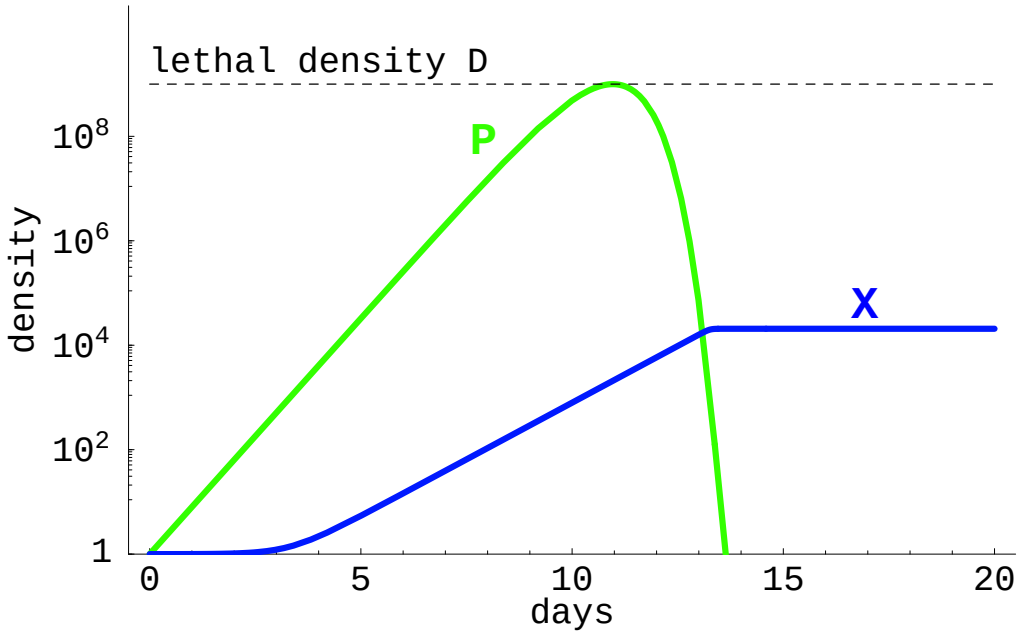

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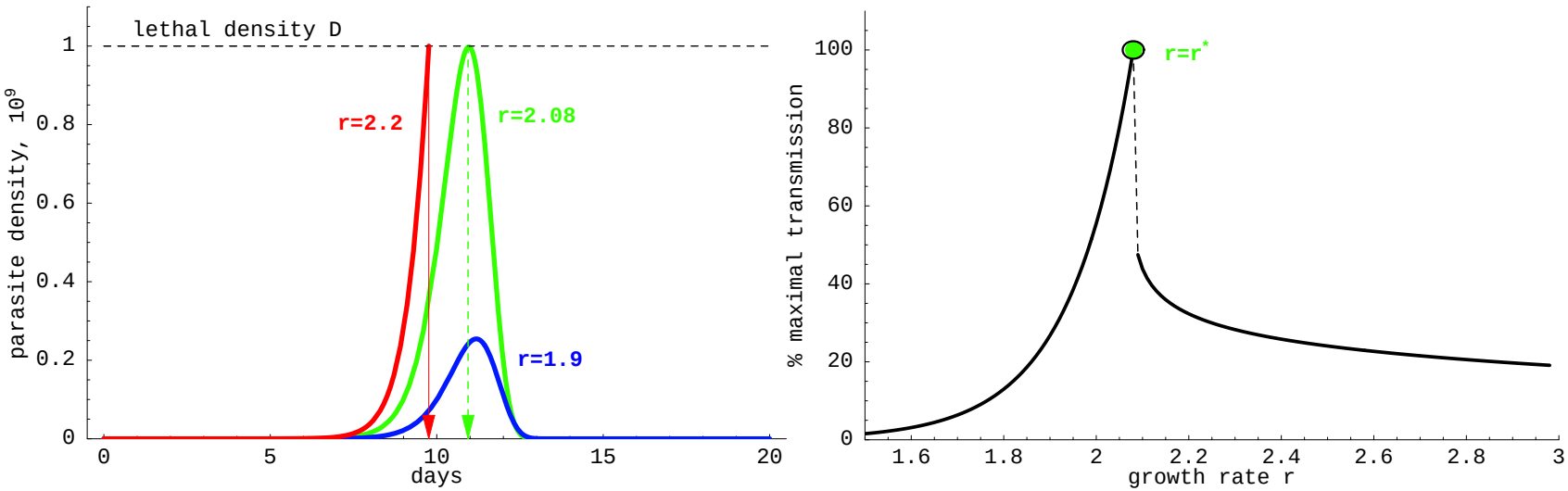
Antia et al. 1994

Total transmission of pathogens



where total transmission

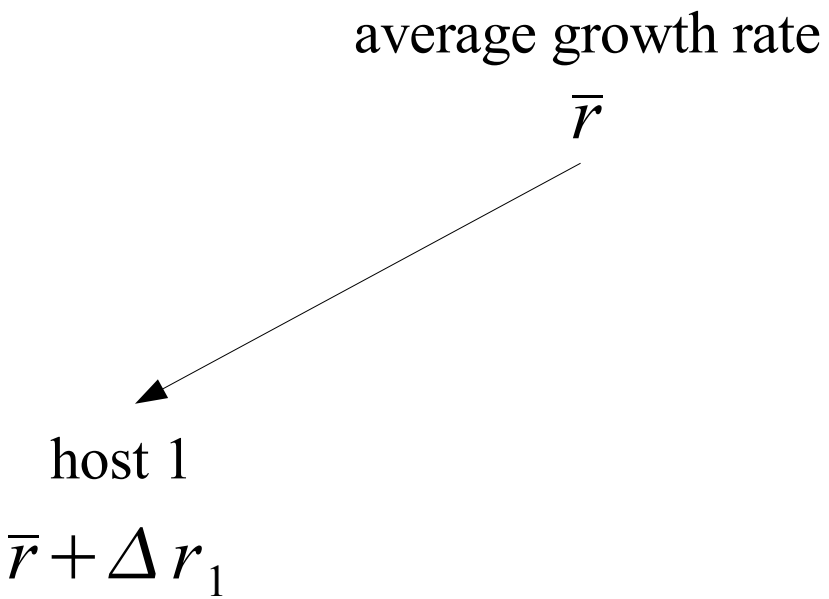
$$l(r) = \int_0^{\Delta} P(t)\, dt.$$

Stochastic heterogeneity in r

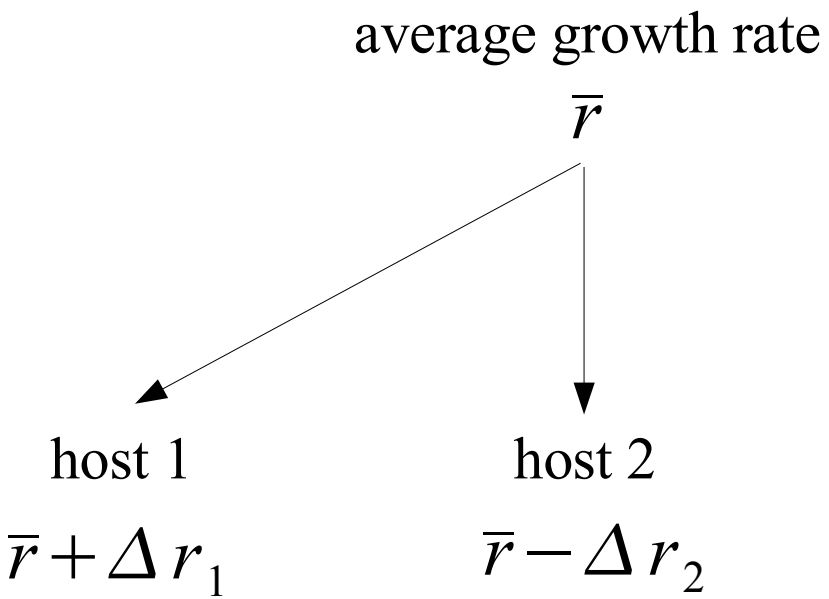
average growth rate

$\overline{r}$

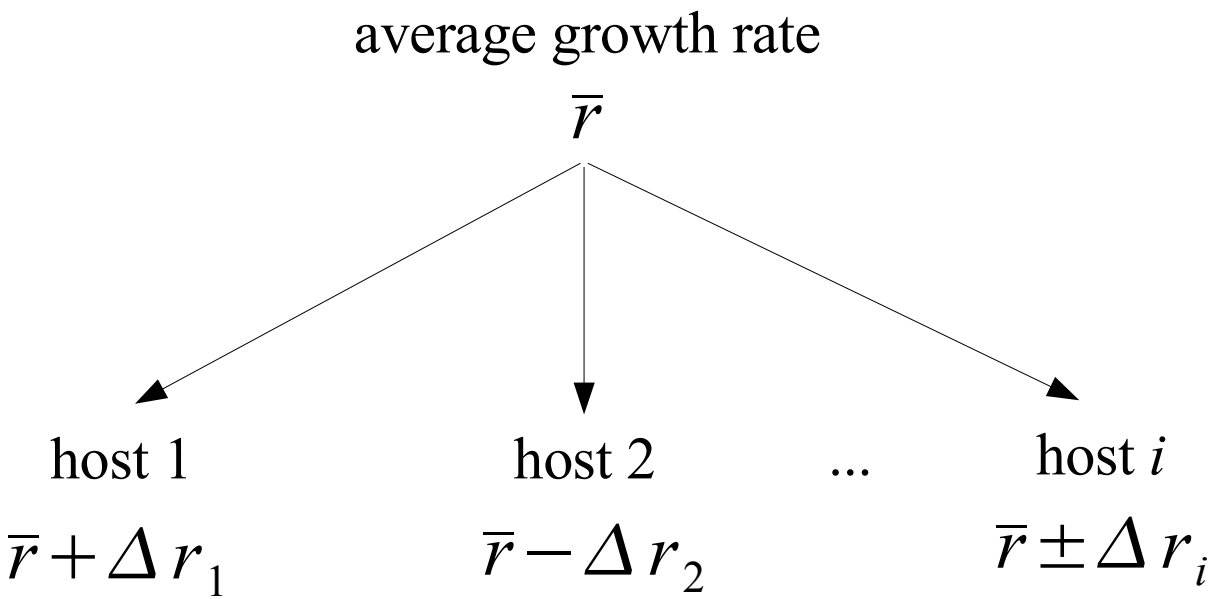
Stochastic heterogeneity in r



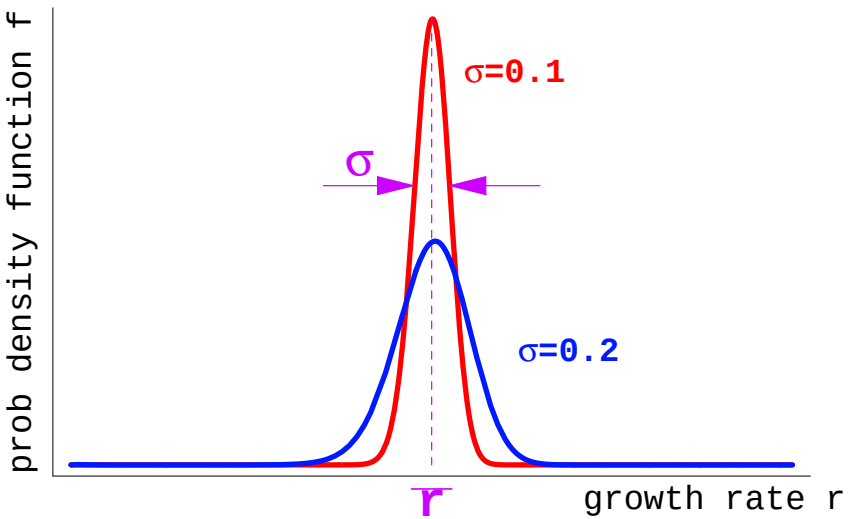
Stochastic heterogeneity in r



Stochastic heterogeneity in r



Stochastic heterogeneity in r

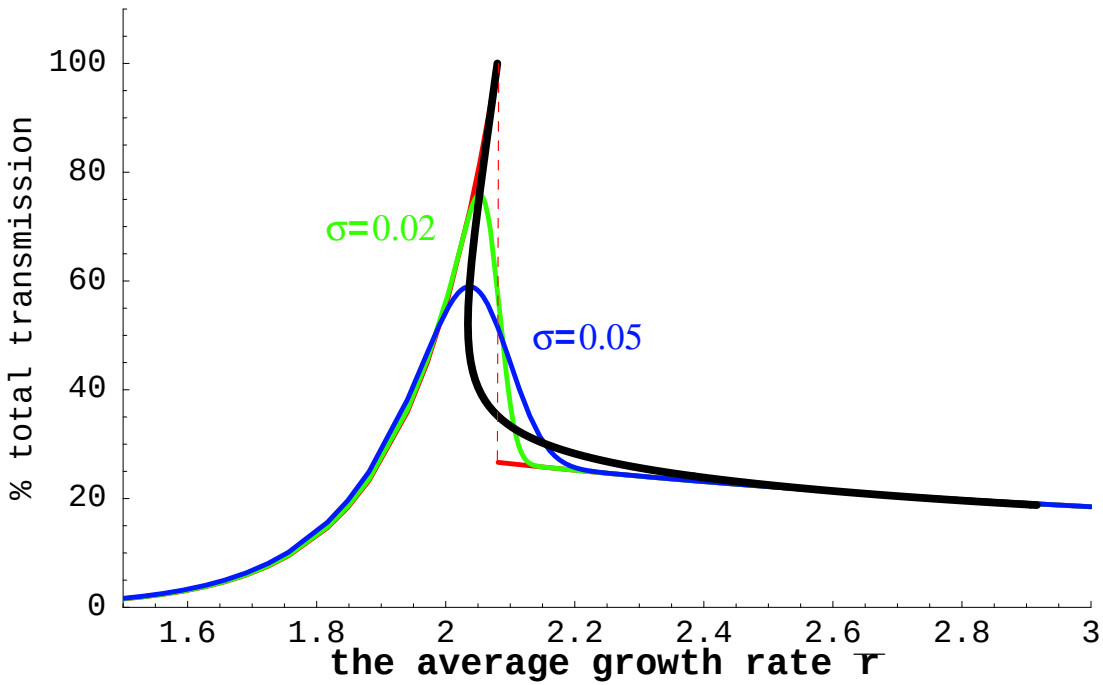


$$f(r,\overline{r}) = \frac{\overline{r}/\sigma^2}{\Gamma(\overline{r}^2/\sigma^2)} \left(\frac{\overline{r}r}{\sigma^2}\right)^{\overline{r}^2/\sigma^2-1} \times \exp\left[-\frac{\overline{r}r}{\sigma^2}\right],$$

$$L(\overline{r}) = \int_0^\infty l(r) f(r,\overline{r}) dr.$$

Optimal growth rate and total transmission

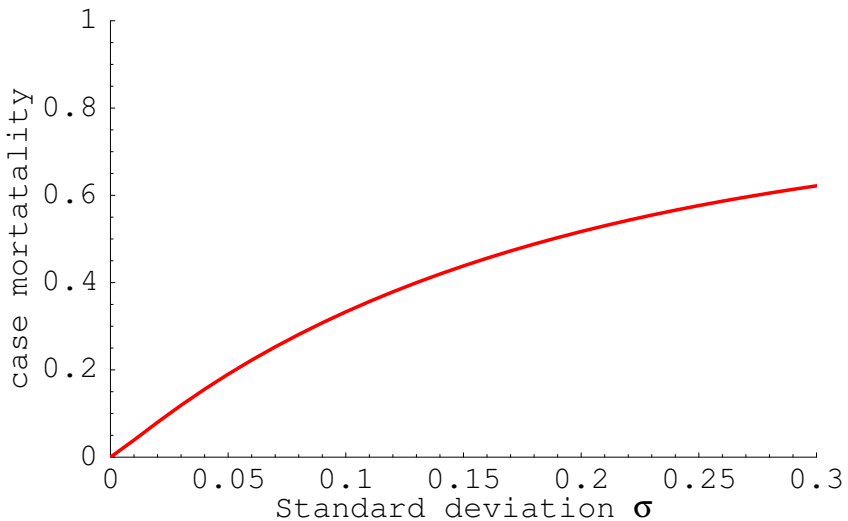
$$L(r) = \int_0^\infty l(r,x)\, f(x)\, dx.$$



where $f(x)$ is given by a gamma distribution of r with standard deviation σ.

Changes in virulence

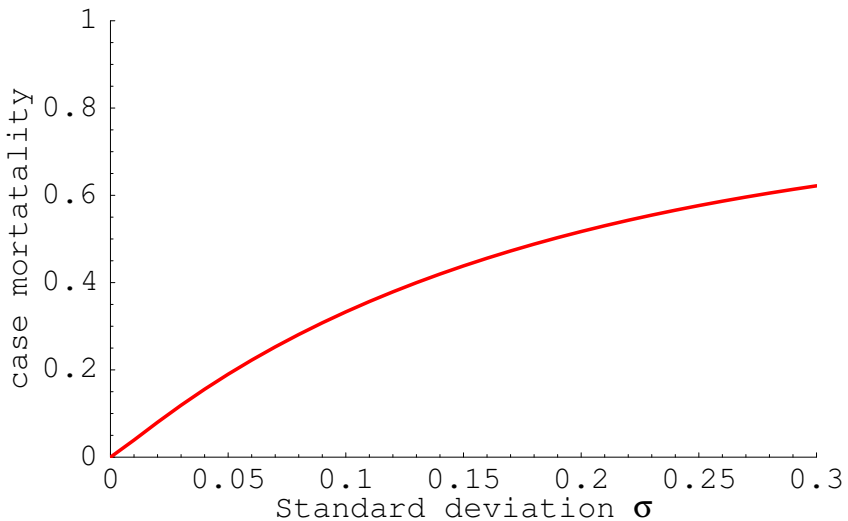
$$M(\overline{r}) = \int_{r^*}^{\infty} f(r, \overline{r}) dr$$

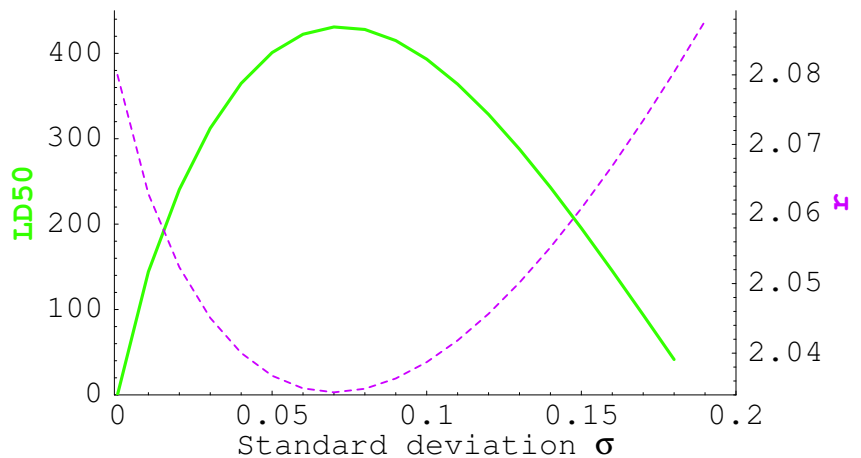


Changes in virulence

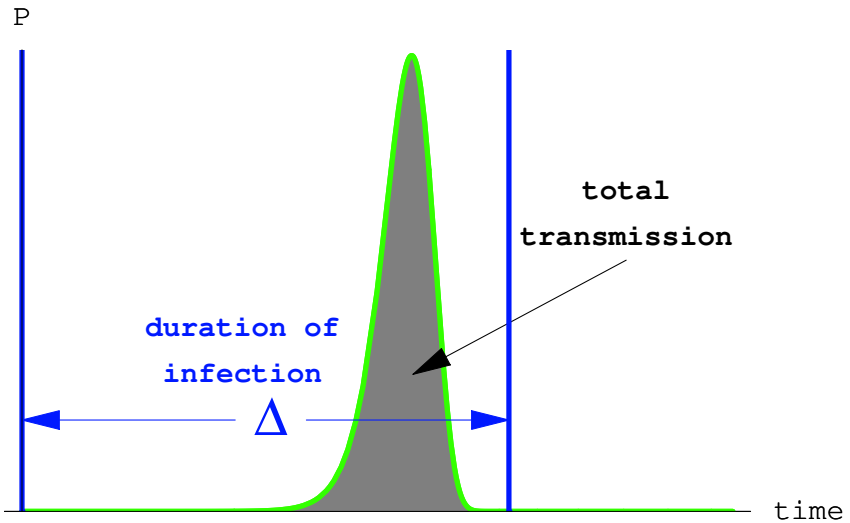
$$M(\overline{r}) = \int_{r^*}^{\infty} f(r, \overline{r}) dr$$

$$LD_{50}(\overline{r}) = P_0 : \int_{r^*[P_0]}^{\infty} f(r, \overline{r}) dr = 0.5$$





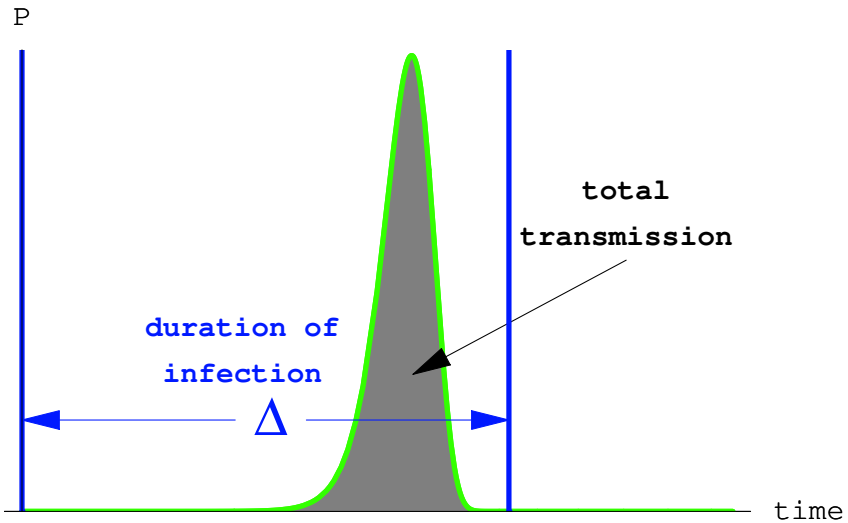
Estimating epidemiological parameters and trade-offs



$$\hat{\beta}(r) = \frac{l(r)}{\Delta(r)}$$

$$\beta(\overline{r}) = \int_0^\infty \hat{\beta}(r) f(r, \overline{r})\, dr$$

Estimating epidemiological parameters and trade-offs



$$\hat{\beta}(r) = \frac{l(r)}{\Delta(r)}$$

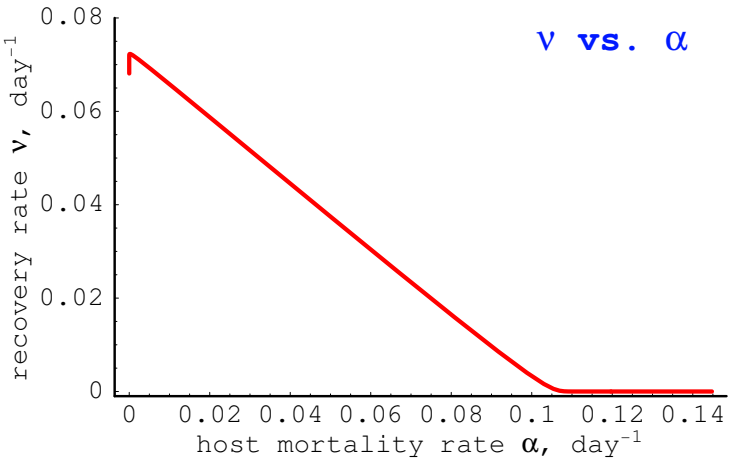
$$\beta(\overline{r}) = \int_0^\infty \hat{\beta}(r) f(r,\overline{r})\, dr$$

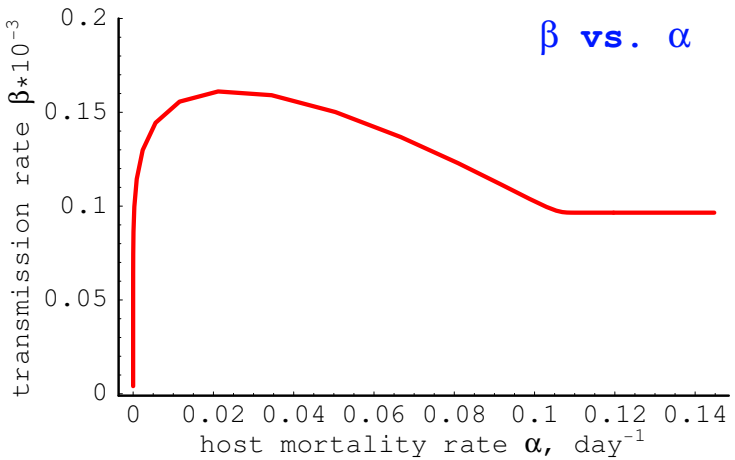
$$\alpha(\overline{r}) = \int_0^\infty \frac{m(r)}{\Delta(r)} f(r,\overline{r})\, dr$$

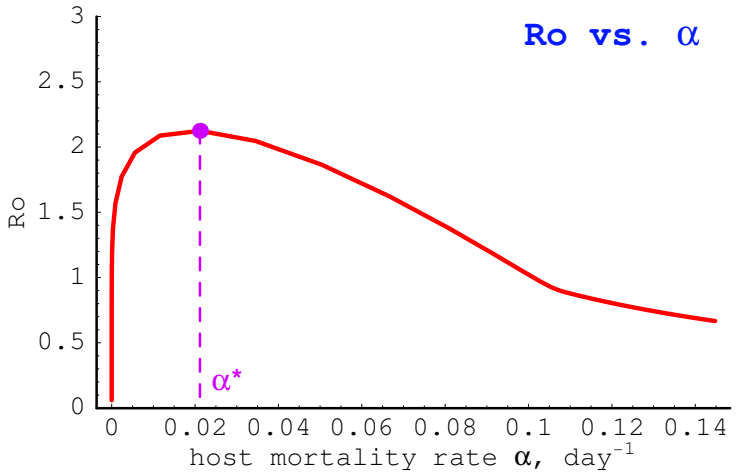
$$\nu(\overline{r}) = \int_0^\infty \frac{1-m(r)}{\Delta(r)} f(r,\overline{r})\, dr$$

where $m(r)$ is the probability of host’s death following infection.

Trade-offs emerging from the within-host dynamics







To myxoma trade-offs

Ganusov et al 2002

Short summary

- Within-host and between host dynamics of pathogens are inherently linked.
- Trade-offs for the myxoma virus infection can be originated from simple properties of the within-host dynamics.
  - **but**: other explanations may work too.
- Prediction on the evolution of pathogen virulence may depend on the definition of virulence used.

Ganusov et al. 2002; Gilchrist and Sasaki 2002; André et al. 2003; André and Gandon (2006); Ganusov and Antia 2003, 2006

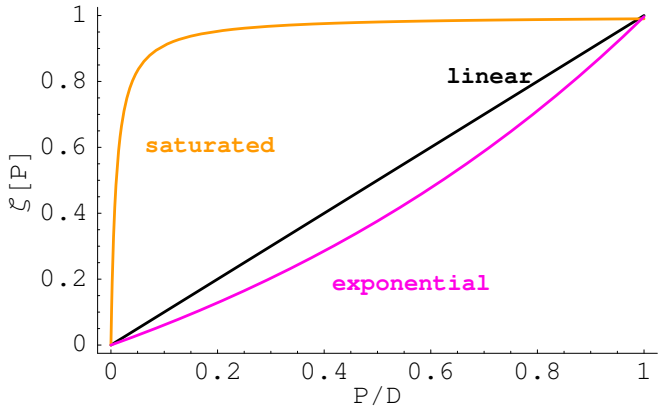
Can virulence be predicted from a single factor?

Table 1 Mortality associated with parasites transmitted with and without vectors

	Transmission[a]	
Mortality	Without vectors	With vectors
>1%	Kuru	Yellow fever virus
	Variola	*Bartonella bacilliformis*
	Corynebacterium diphtheriae	*Rickettsia prowazekii*
	Mycobacterium tuberculosis (35)	*Borrelia recurrentis*
	Treponema pallidum	*Leishmania donovani*
		Plasmodium falciparum
		P. malariae (57)
		P. vivax (47)
		Trypanosoma cruzi
		T. brucei
<1%	Adenovirus	Chikungunya
	Coronavirus	Dengue (41)
	Cytomegalovirus	O'nyong-nyong
	Epstein-Barr	Oropouche
	Herpes simplex	Phlebotomus fever virus
	Influenza	*Rochalimaea quintana*
	Mumps	*Plasmodium ovale*
	Papillomavirus	*Leishmania tropica*
	Parainfluenza	
	Respiratory syncytial virus	
	Rhinovirus	
	Rubella	
	Rubeola (23)	
	Varicella-zoster	
	Bordetella parapertussis	
	B. pertussis (18)	
	Branhamella catarrhalis	
	Calymmobacterium granuloma	
	Chlamydia trachomatis	
	Gardnerella vaginalis	
	Hemophilus ducreyi	
	H. influenzae (90)	
	Hemophilus spp. (104)	
	Moraxella spp. (88)	
	Mycobacterium leprae (1)	
	Mycoplasma hominis	
	M. pneumoniae (64)	
	Neisseria gonorrhea	
	N. meningitides (8)	
	Neisseria spp. (88)	
	Staphylococcus aureus	
	S. epidermidis	
	S. saprophyticus	

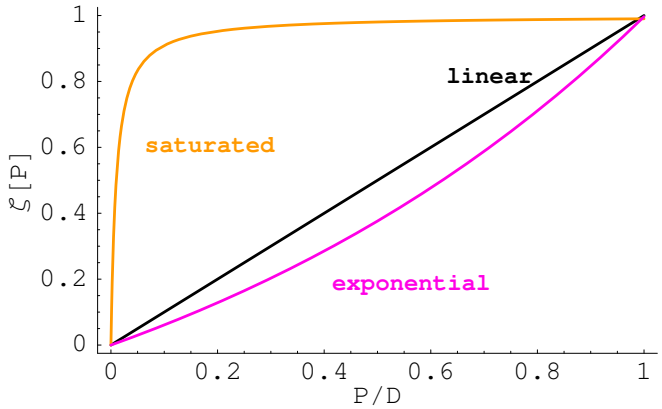
Ewald 1983

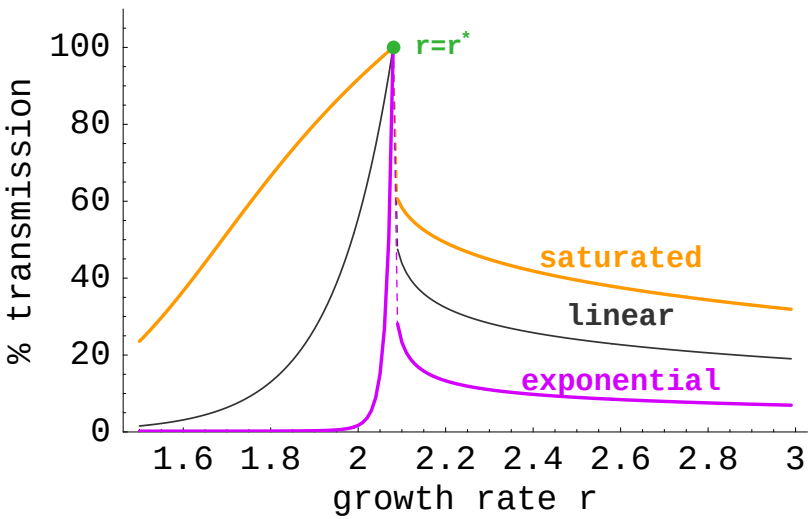
Changing pathogen transmissibility

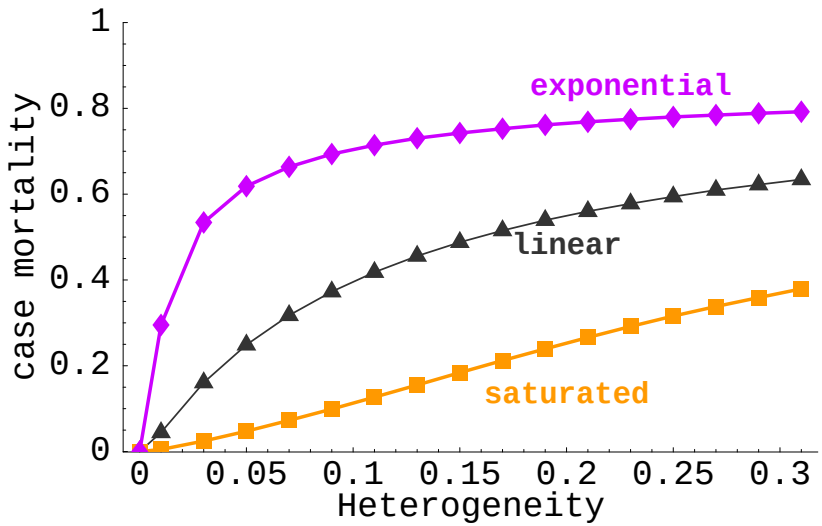


Ganusov and Antia 2003

Changing pathogen transmissibility

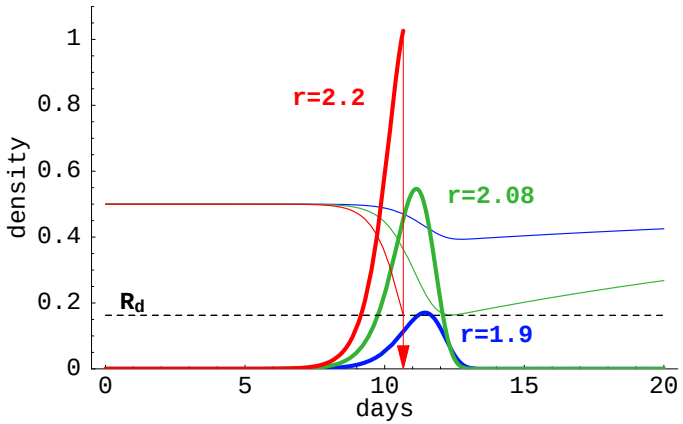






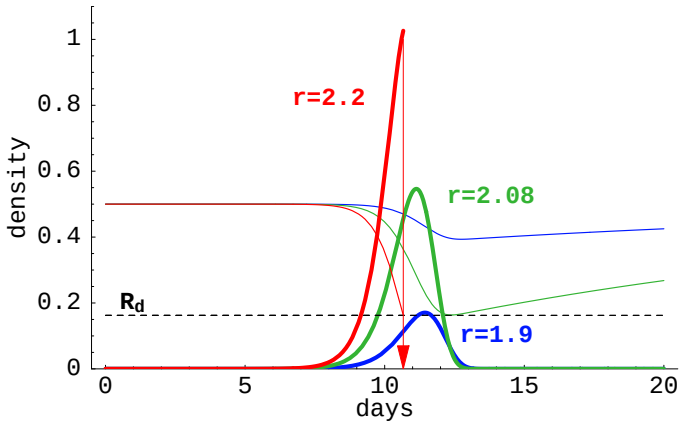
Ganusov and Antia 2003

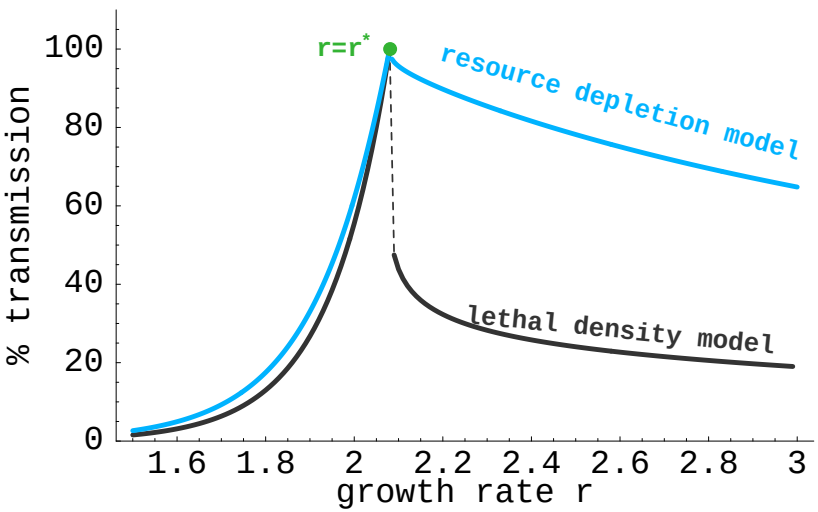
Changing mechanism of pathogenesis

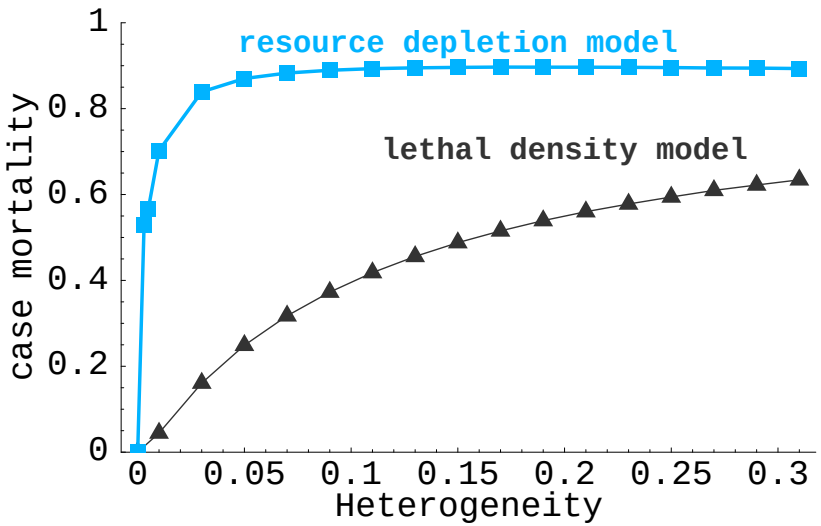


$P(0) = 1$, $R(0) = R_0 = 10^4$, $X(0) = 1$, $h = 10^{-3}$, $k = 10^3$, $s = 1$, $R_d = 3.25 \times 10^3$, $c = 10^3$, $y = 10^5$, $d = 0.05$. Heterogeneity is modelled by a normal distribution of r.

Changing mechanism of pathogenesis







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$y = 10^5, d = 0.05$. Heterogeneity is modelled by a normal distribution of r.

Details do matter!

- Changing the structure of the model may dramatically affect the optimal level of virulence.
- It seems unlikely that a single factor can determine virulence of diverse pathogens.

Vaccines and pathogen evolution

- Escape from vaccines

Vaccines and pathogen evolution

- Escape from vaccines
- Evolution of pathogen virulence in response to vaccination

Imperfect vaccines and the evolution of pathogen virulence

Sylvain Gandon*†, Margaret J. Mackinnon*†, Sean Nee* & Andrew F. Read*

NATURE | VOL 414 | 13 DECEMBER 2001 | www.nature.com

Imperfect vaccines and evolution of pathogens

- Epidemiological approach and R_0

$$R_0[\alpha^*, \alpha] = \frac{\beta^*(\hat{x} + \sigma\hat{y})}{d + \alpha^* + \nu^* + \sigma\beta\hat{y}}$$

where * and $\hat{\cdot}$ denote mutant and resident, and σ is superinfection parameter.

Imperfect vaccines and evolution of pathogens

- Epidemiological approach and R_0

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where * and $\hat{\cdot}$ denote mutant and resident, and σ is superinfection parameter.

- Both virulence α and transmissibility β are reduced in vaccinated hosts.

$$\begin{aligned} \alpha_V &= (1 - r_2)(1 - r_4)\alpha_U, \\ \beta_V &= (1 - r_3)\beta_U[(1 - r_2)\alpha_U], \end{aligned}$$

where r_2, r_3, and r_4 are the efficacies of vaccines blocking replication, transmission and virulence, respectively.

Imperfect vaccines and evolution of pathogens

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where r_2, r_3, and r_4 are the efficacies of vaccines blocking replication, transmission and virulence, respectively.

- Vaccination does not affect trade-offs $\beta = \beta(\alpha)$ and $\nu = \nu(\alpha)$.

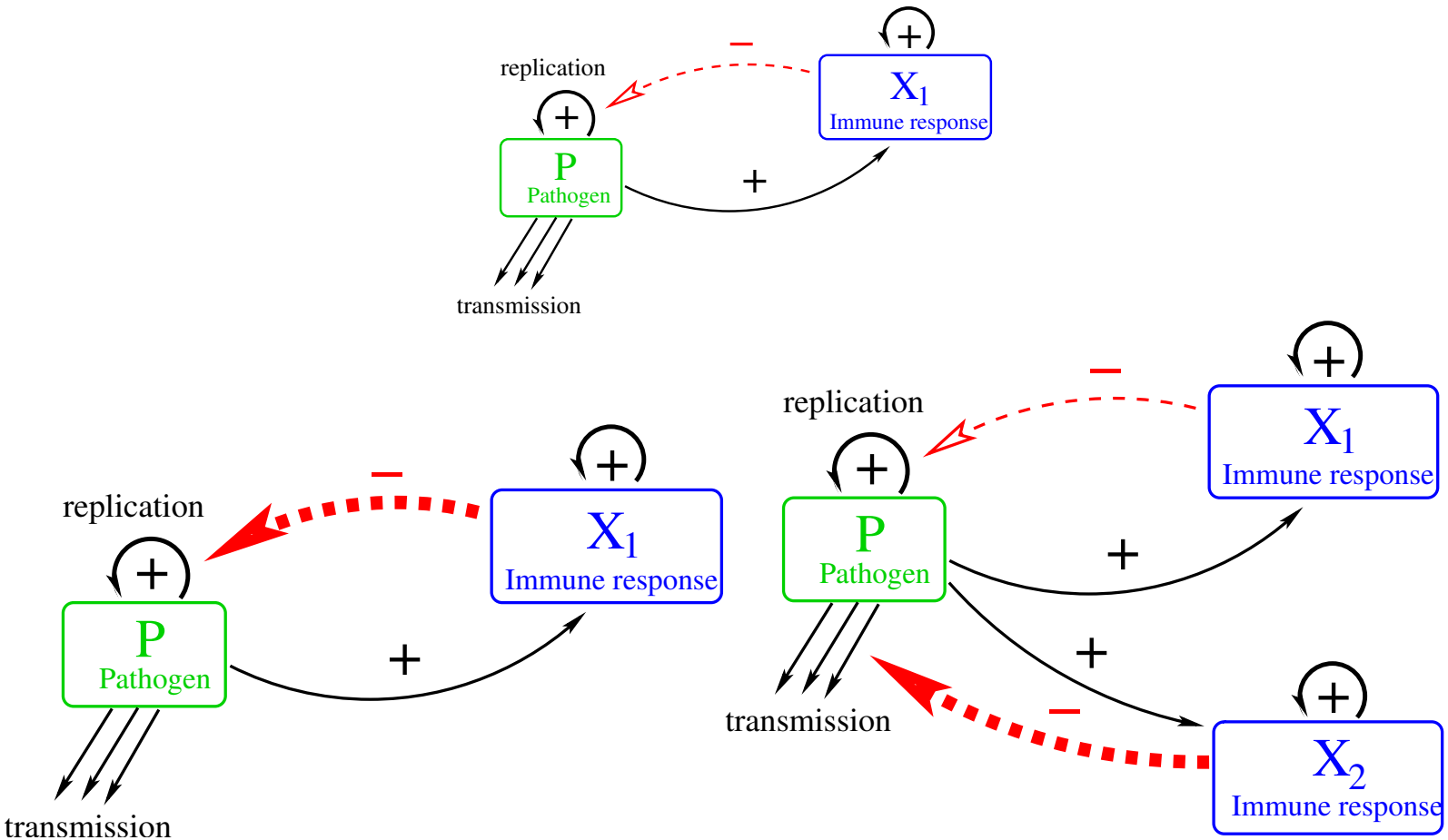
Gandon et al. 2001

Imperfect vaccines: Gandon et al. conclusions

- Anti-growth and anti-virulence vaccines are expected to select for pathogens with high virulence.
- Anti-transmission vaccines are expected to select for pathogens with low virulence.

Gandon et al. 2001

Within-host approach



Model

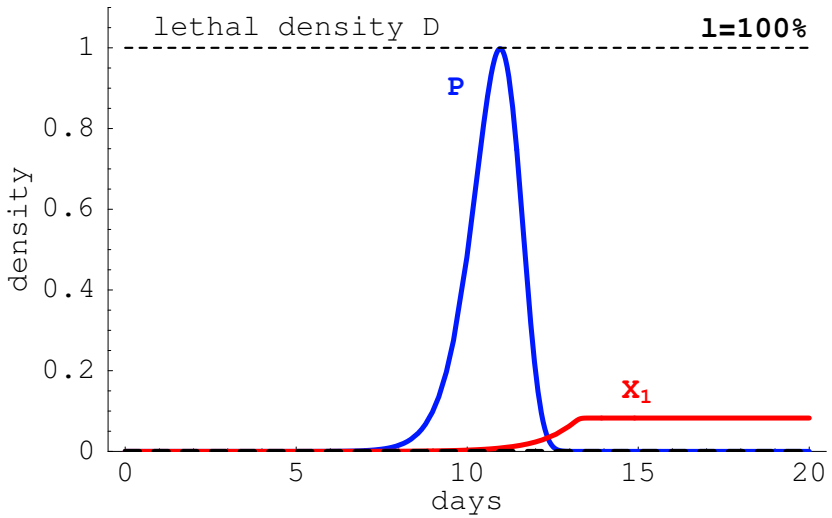
- response X_1 reduces the rate of expansion of the pathogen population within the host;
- response X_2 reduces the rate of pathogen transmission from infected hosts.

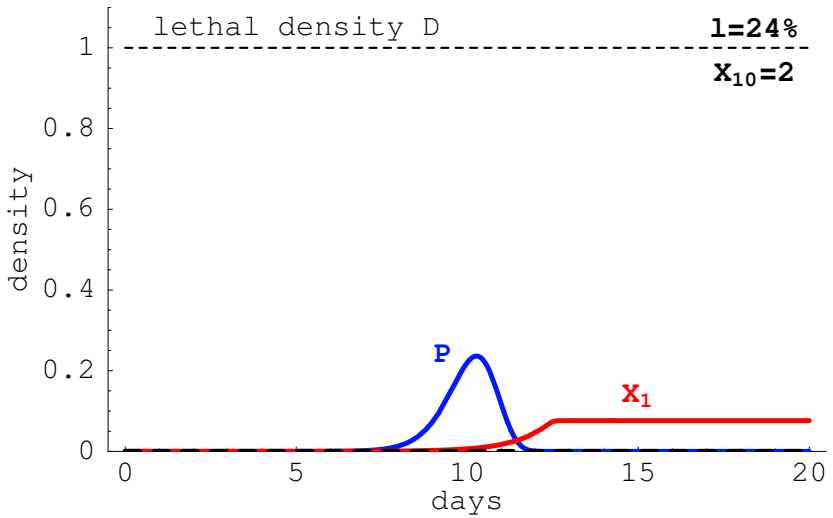
$$\begin{aligned} \dot{P} &= (r - h_1 X_1)P, \\ \dot{X}_i &= \frac{sX_i P}{k + P}, \qquad i = 1, 2, \\ l(r) &= \int_0^{\Delta} \frac{P(t)dt}{1 + h_2 X_2(t)}. \end{aligned}$$

Vaccination results in an increase in the number of pathogen-specific immune cells (precursor numbers) existing prior to infection.

Ganusov and Antia 2006

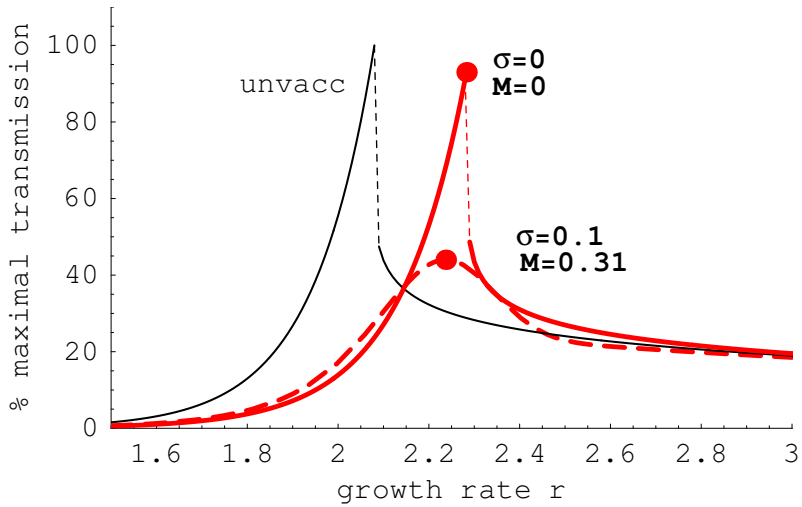
Within-host dynamics: anti-growth vaccines

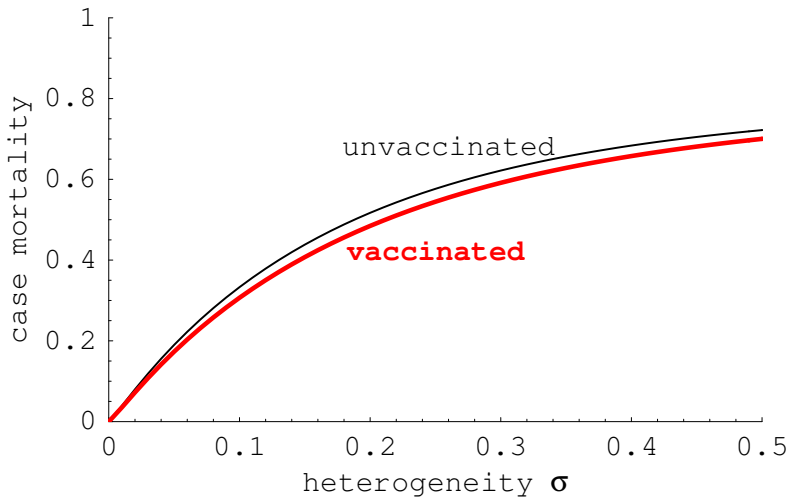




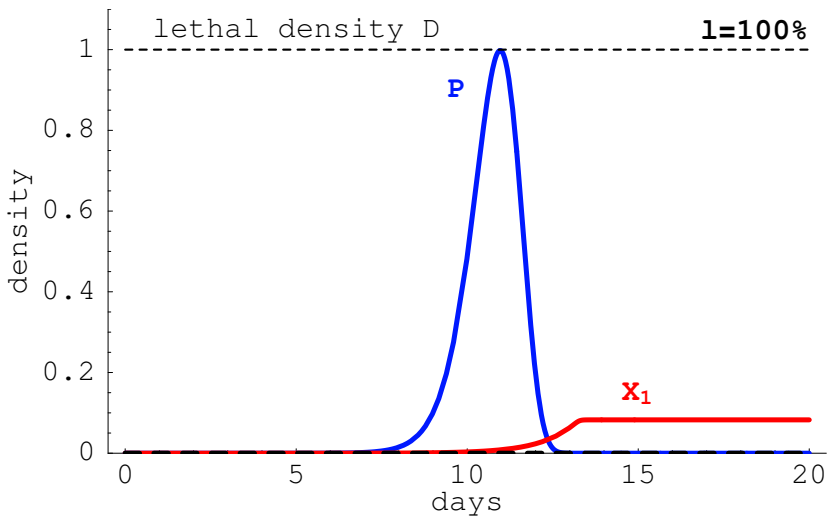
$P(0) = 1$, $h_1 = 10^{-3}$, $h_2 = 10^{-4}$, $k = 10^3$, $s = 1$, $D = 10^9$, $r = 2.08$, pathogen density is multiplied by 10^{-9}, the immune response densities are multipled by 4×10^{-6}.

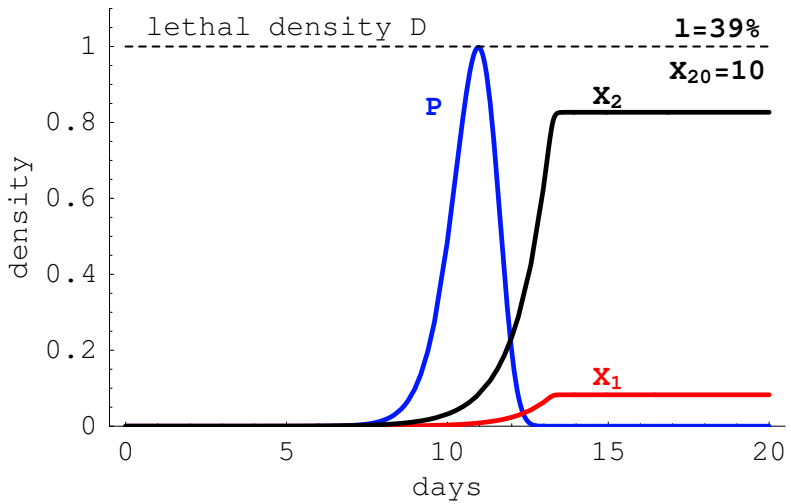
Transmission and virulence: anti-growth vaccines



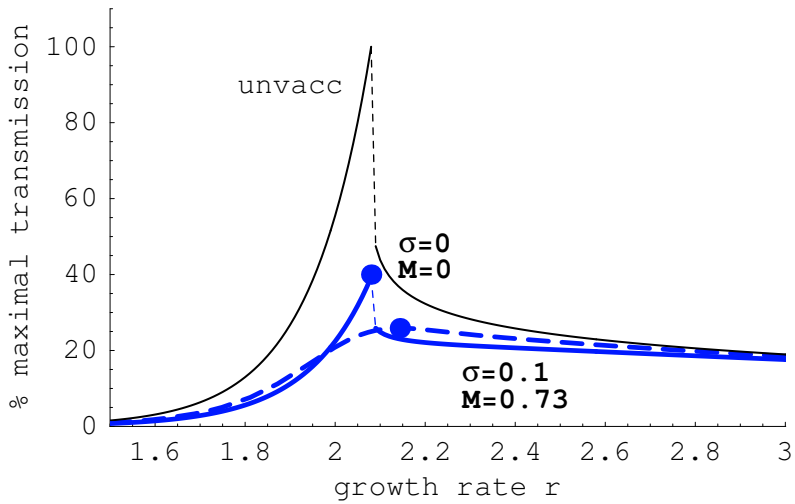


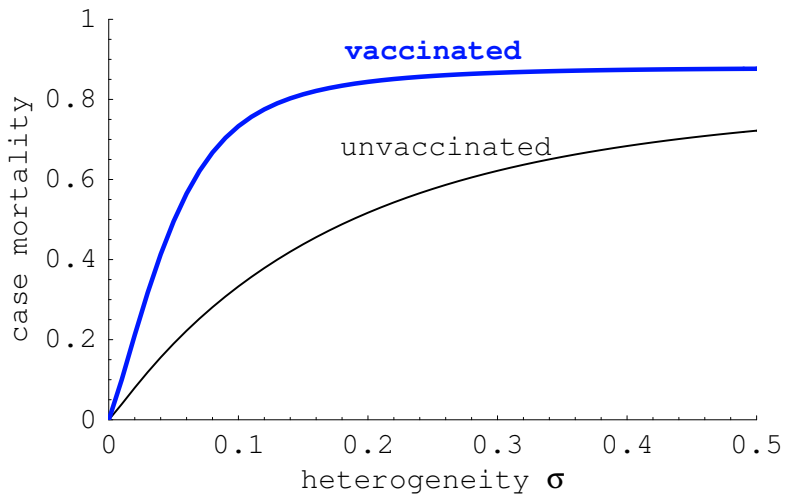
Within-host dynamics: anti-transmission vaccines



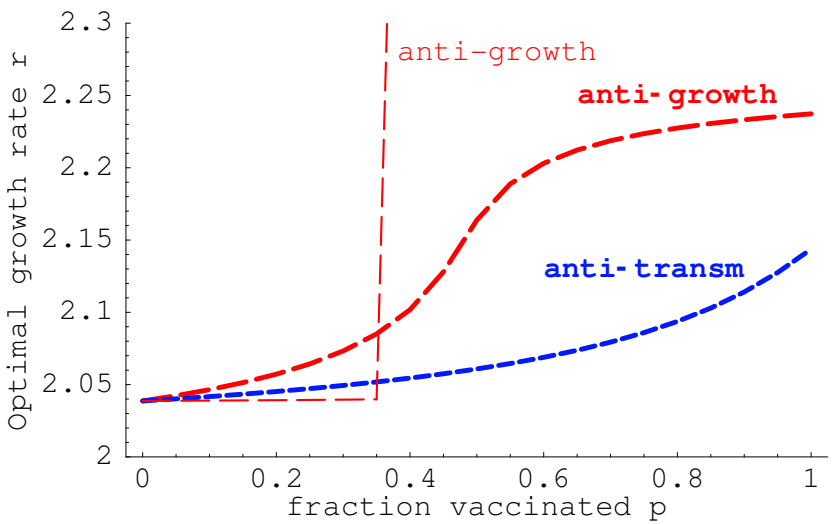


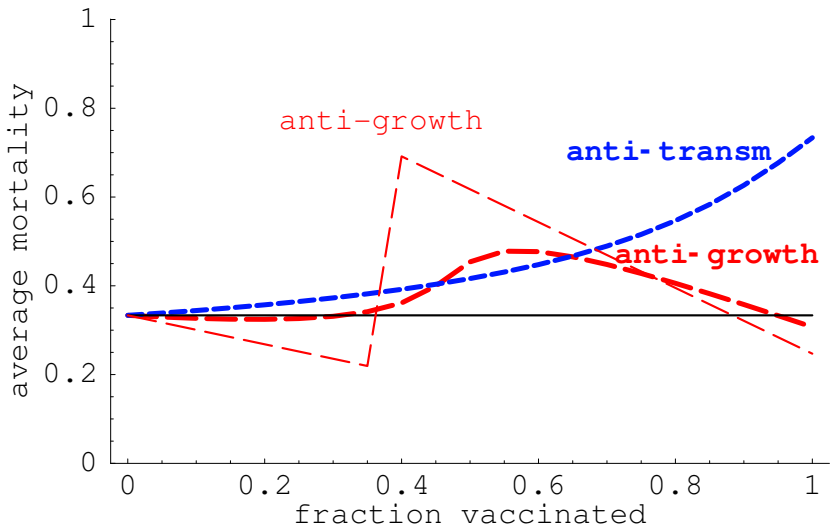
Transmission/virulence: anti-transmission vaccines





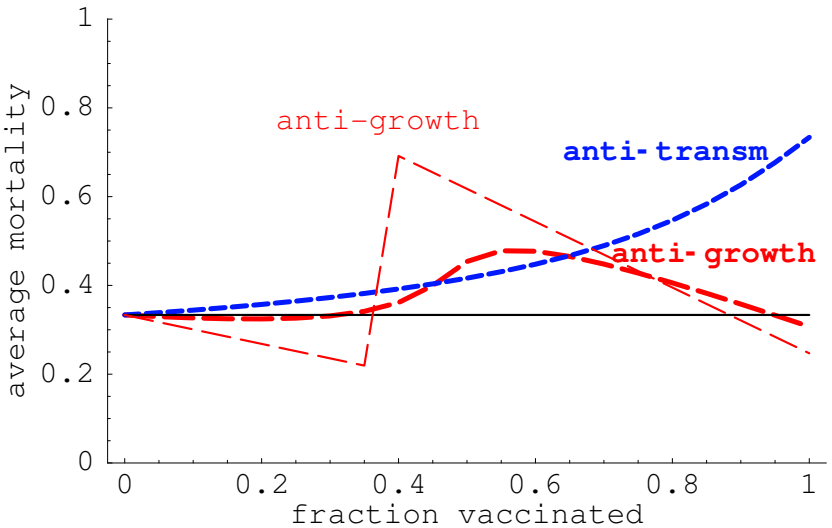
ES growth rate and virulence: partially vaccinated

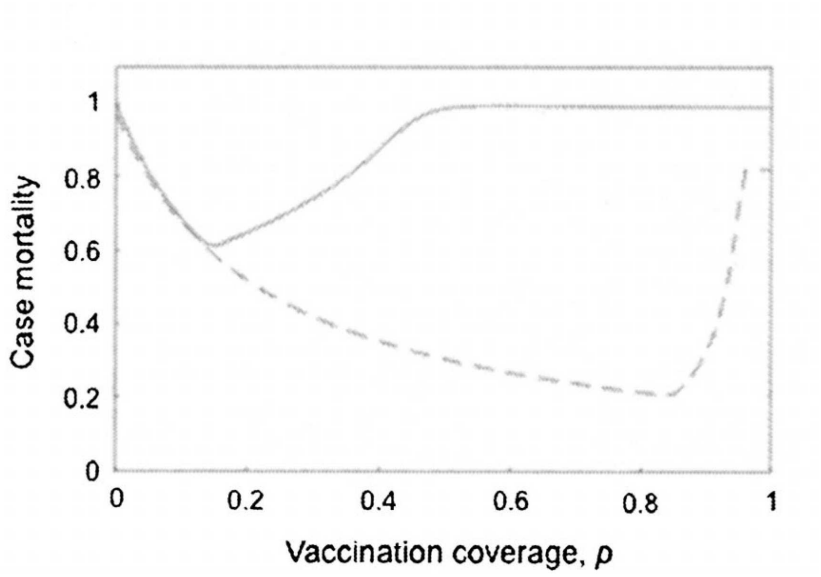




For anti-growth vaccines, the precursor number increases from $X_{10} = 1$ to $X_{10} = 2$ (bold red lines) or to $X_{10} = 10$ (plain red lines). For anti-transmission vaccines, the precursor number increases from $X_{20} = 0$ to $X_{20} = 10$ (bold blue lines).

Do results depend on the model?





- In these models, the difference arises due to different description of pathogenesis and as the result, due to high ES virulence in unvaccinated hosts in the right panel (at $p = 0$).

Ganusov and Antia 2006; André and Gandon 2006

Implications for epidemiology

- Epidemiological models can include the within-host dynamics:

$$\begin{aligned}
\frac{dS(t)}{dt} &= \lambda - dS(t) - h(t)S(t), \\
\frac{\partial I(t,\tau)}{\partial t} + \frac{\partial I(t,\tau)}{\partial \tau} &= -(d + \alpha(\tau) + \nu(\tau))I(t,\tau), \\
\frac{dR(t)}{dt} &= \int_0^t I(t,\tau)\nu(\tau)\,\mathrm{d}\tau - dR(t), \\
I(t,0) &= h(t)S(t) = S(t)\int_0^t I(t,\tau)\beta(\tau)\,\mathrm{d}\tau.
\end{aligned}$$

- Future studies may investigate the role of mutation, co- and super-infection in determining evolution of pathogens using within-host models.

André and Gandon 2006

More implications for epidemiology

- Predictions on the evolution of pathogens may depend on the model used as well on the model parameters, and therefore, building of proper models requires better understanding of the biology of pathogen-host interactions.
- Other factors may further complicate the picture: within-host evolution of pathogens, co- and super-infection, locality of transmission, host evolution, etc.

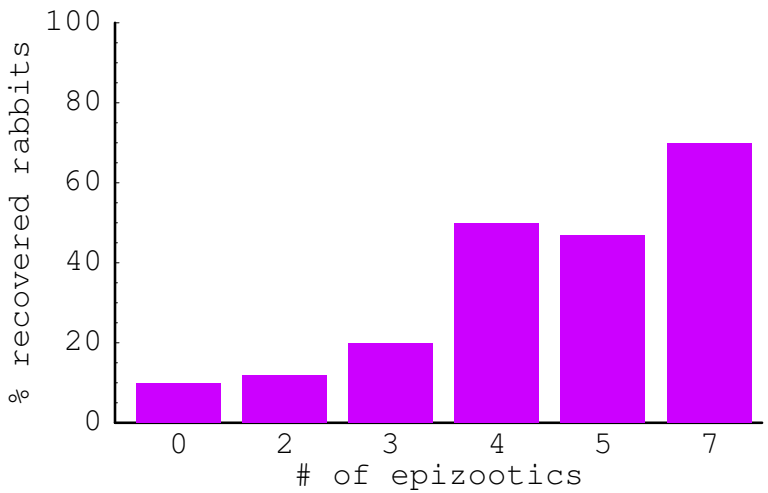
Acknowledgements

- Rustom Antia and Carl Bergstrom
- Theoretical Biology group at Utrecht University
- Marie Curie Incoming International Fellowship (Framework Programme 6)

Testing model predictions?

- Higher levels of (host) heterogeneity select for more virulent pathogens.
  - High mutation rate of Neisseria meningitidis helps escaping immune response.
  - Malaria (P. falciparum) infecting resistant adults and nonimmune infants.
- Transmission-blocking vaccines may select for more rapidly growing pathogens
  - ?
- Testing both predictions in serial passage experiments?

Coevolution of the myxoma virus and rabbits



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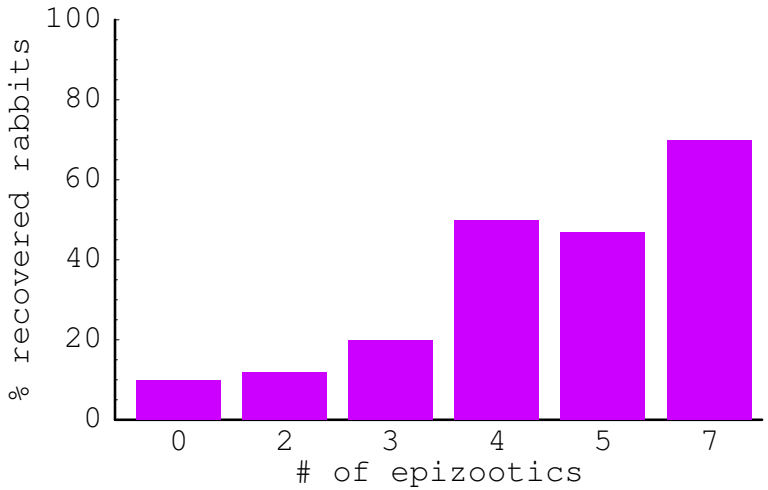
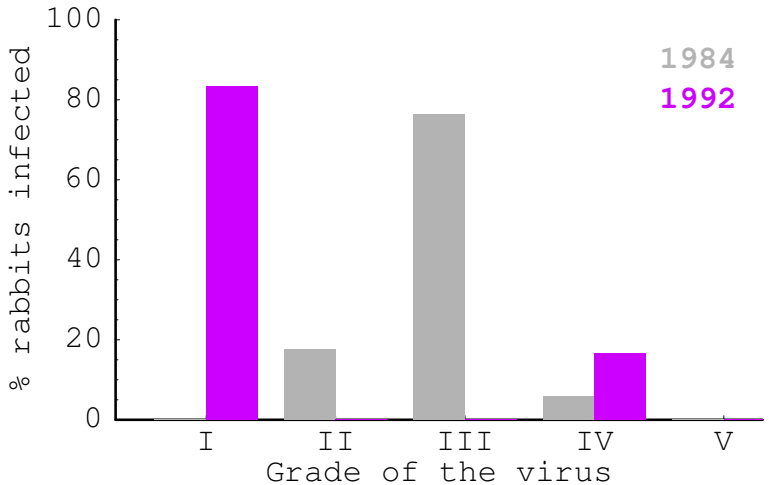
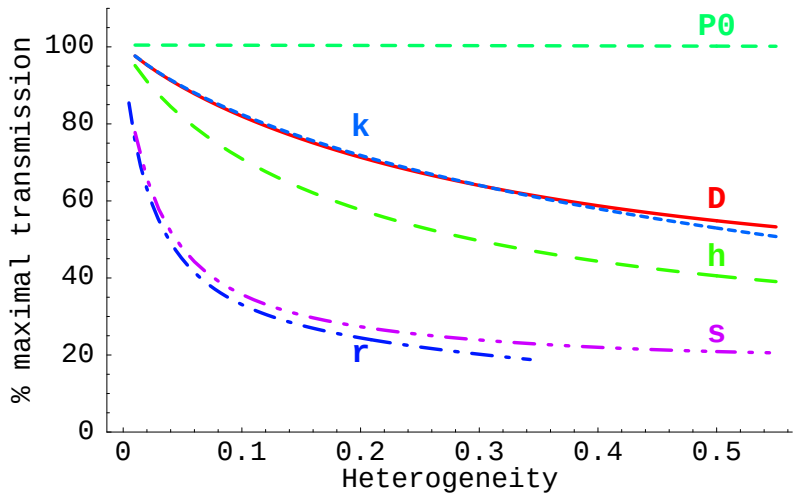
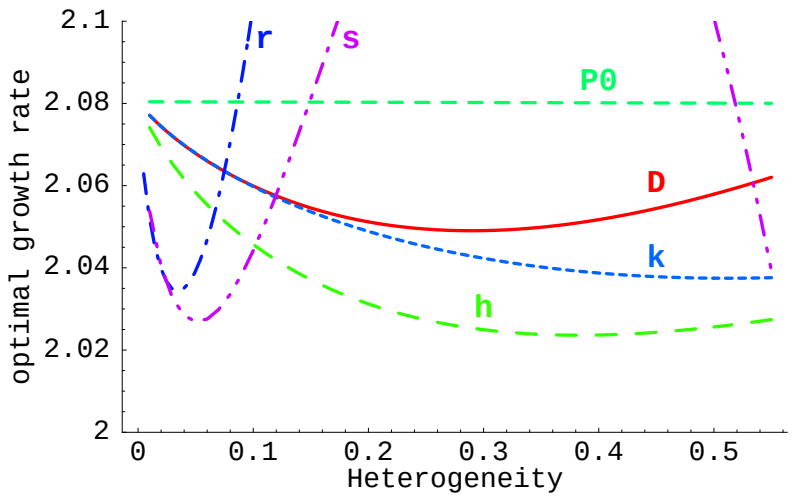
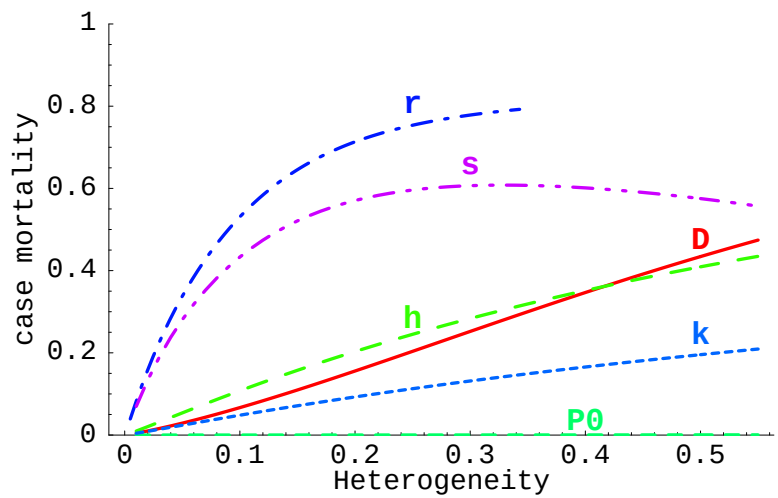


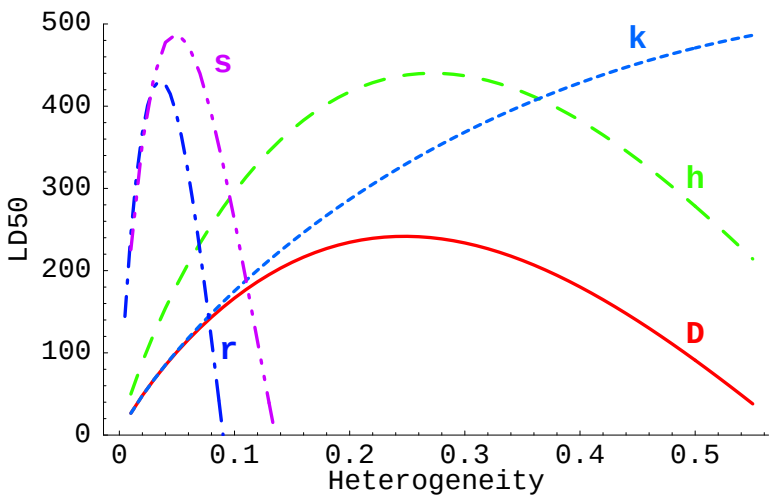


Heterogeneity in other parameters



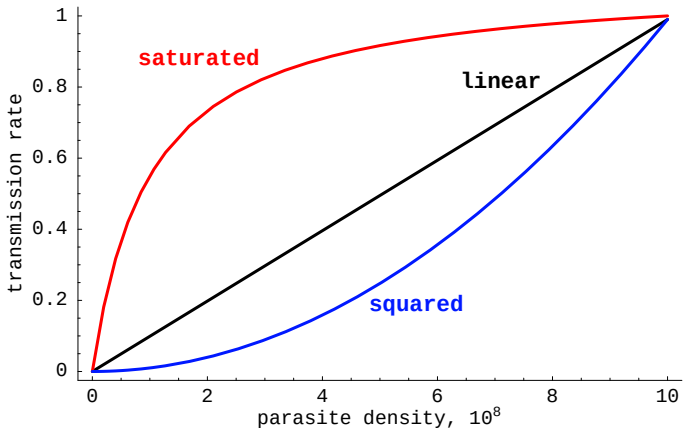


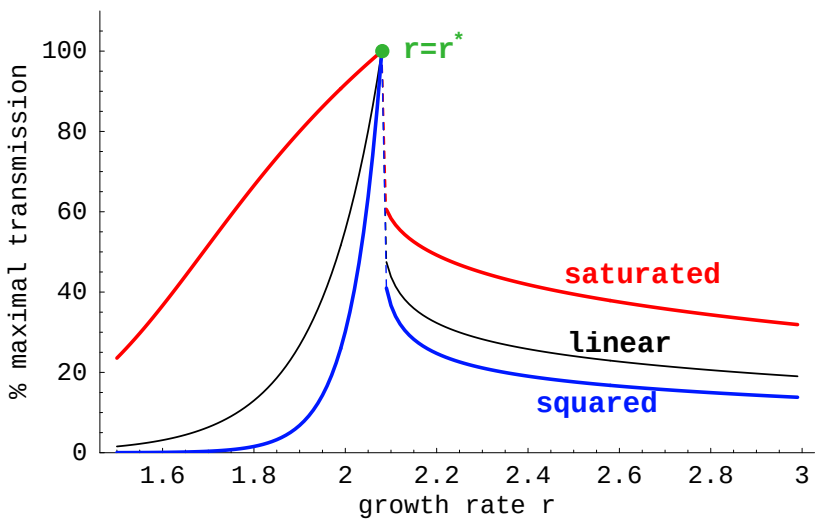


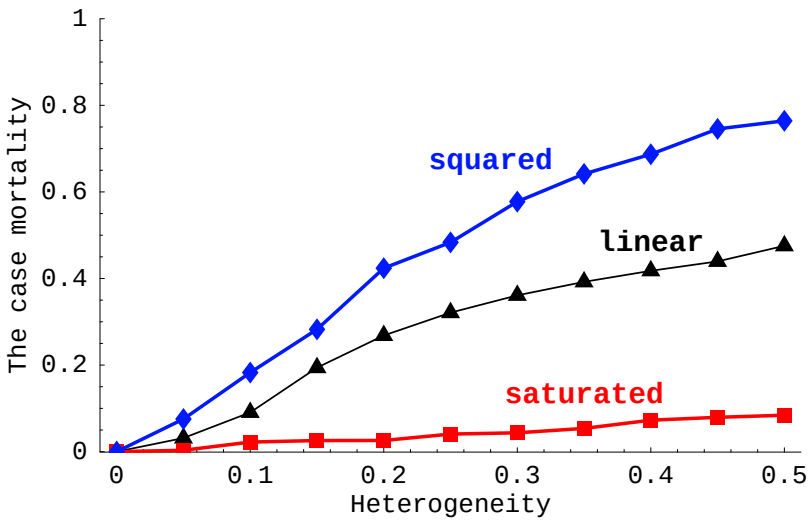


heterogeneity = σ / mean.

Changing pathogen transmissibility





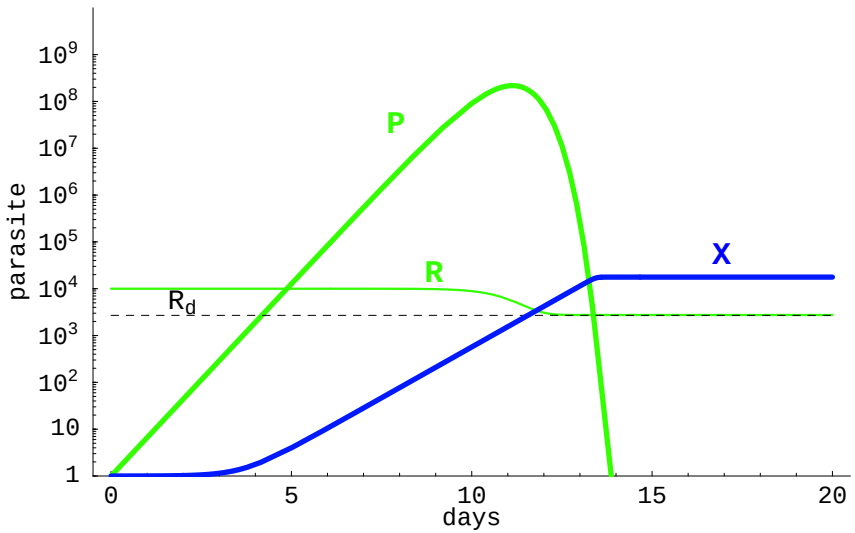


Heterogeneity ($CV = \sigma / D$) is modelled by a gamma distribution of the lethal density D.

Ganusov and Antia 2003

Dynamics of the pathogen, resource and the immune response

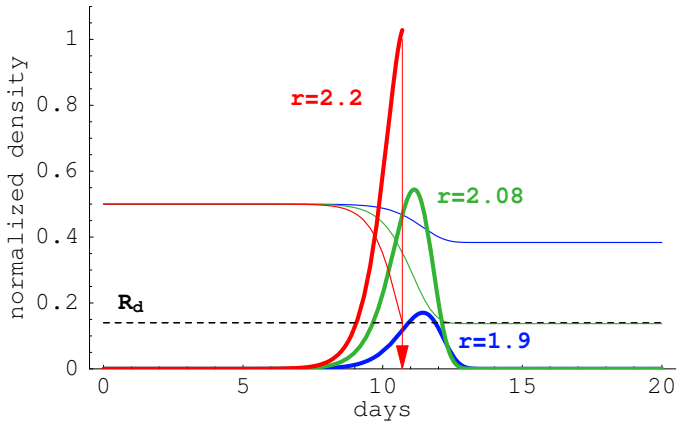
$$\begin{aligned}\dot{P} &= \frac{rPR}{c+R} - hPX,\\ \dot{R} &= d(R_0 - R) - y^{-1}\frac{rPR}{c+R},\\ \dot{X} &= \frac{sXP}{k+P},\end{aligned}$$



P – pathogen, R – resource, X – immune response.

Parameters: $P(0) = 1$, $R(0) = R_0 = 10^4$, $X(0) = 1$, $h = 10^{-3}$, $k = 10^3$, $s = 1$, $R_d = 2.7 \times 10^3$, $c = 10^3$, $y = 10^5$, $d = 0$, $r = 2.08$.

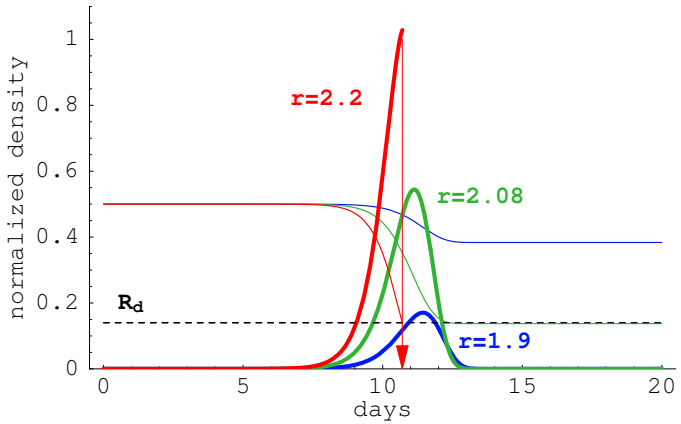
Changing mechanism of pathogenesis

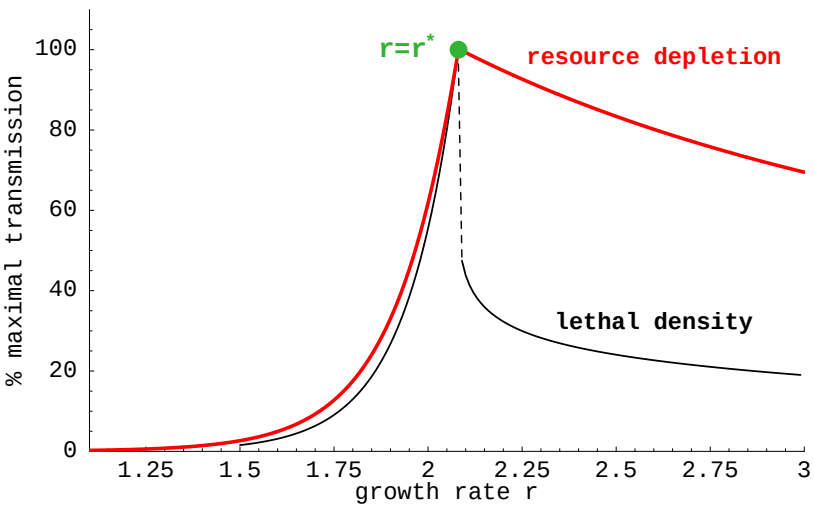


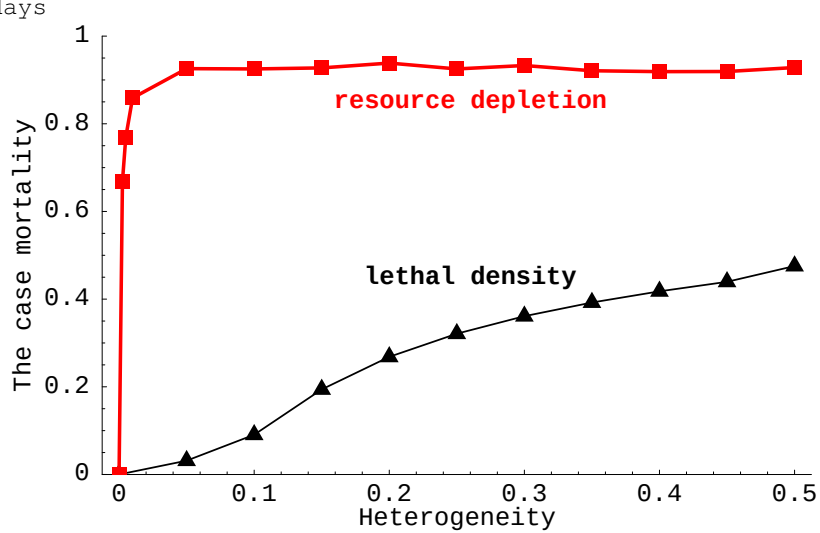
Heterogeneity ($CV = \sigma / R_d$) is modelled by a gamma distribution in the minimal resource density R_d.

$P(0) = 1$, $R(0) = R_0 = 10^4$, $X(0) = 1$, $h = 10^{-3}$, $k = 10^3$, $s = 1$, $R_d = 2.7 \times 10^3$, $c = 10^3$, $y = 10^5$, $d = 0$.

Changing mechanism of pathogenesis







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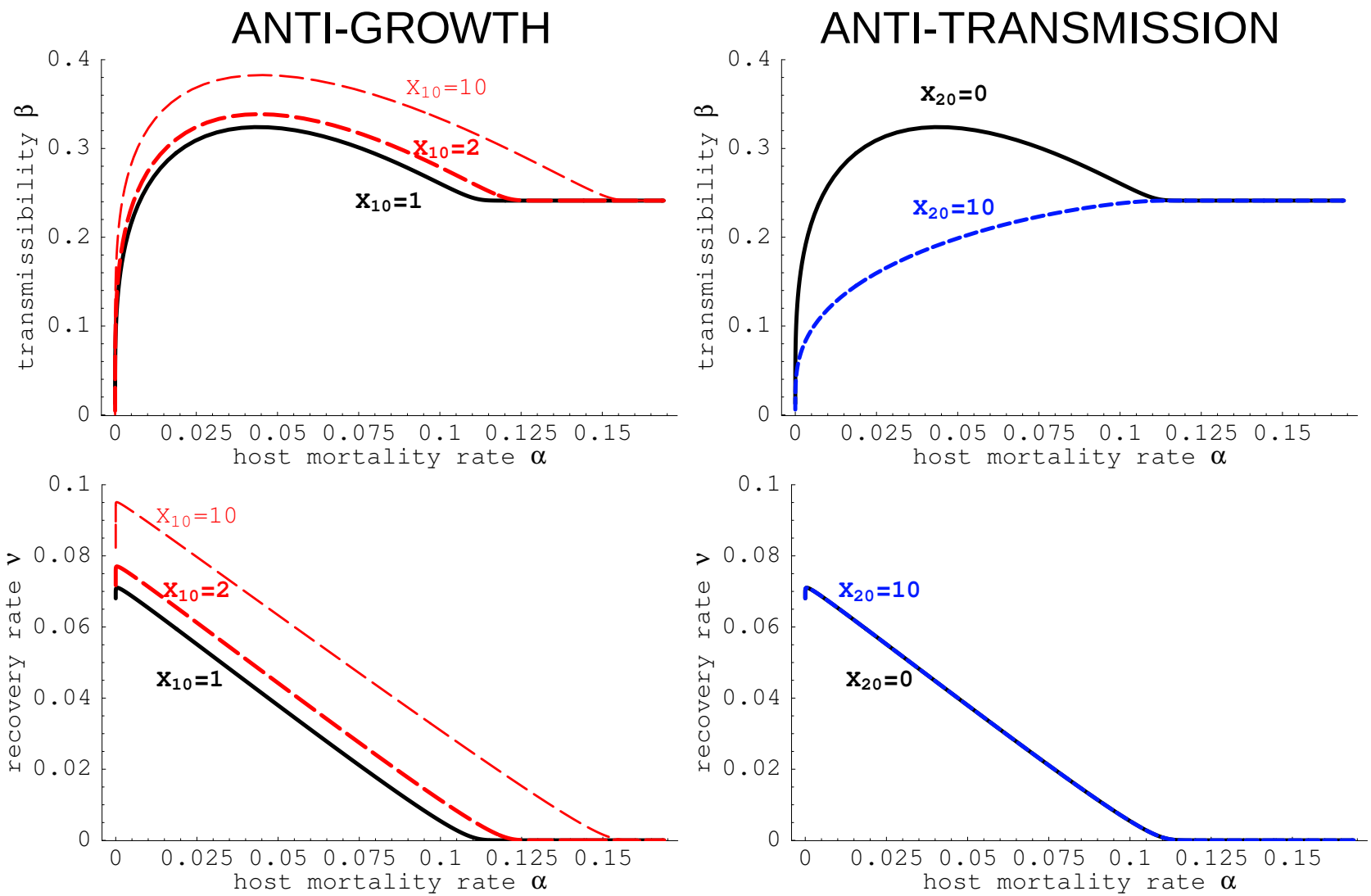
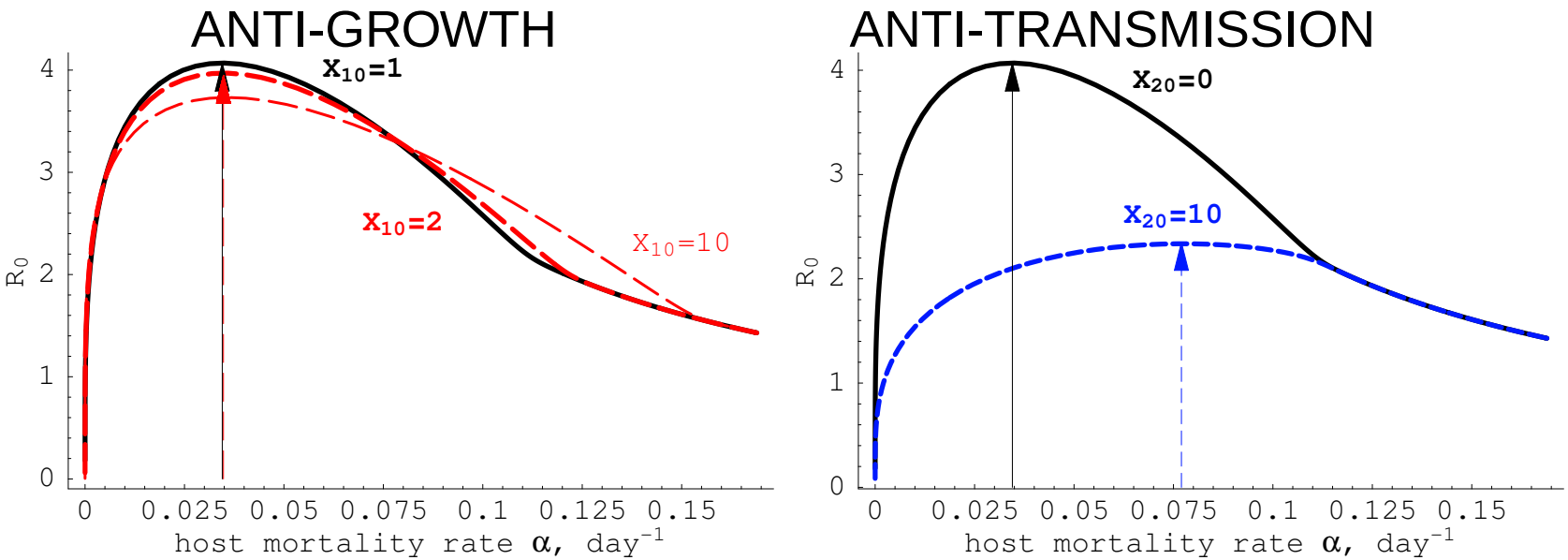
$y = 10^5, d = 0.$

Changes in trade-offs with vaccination

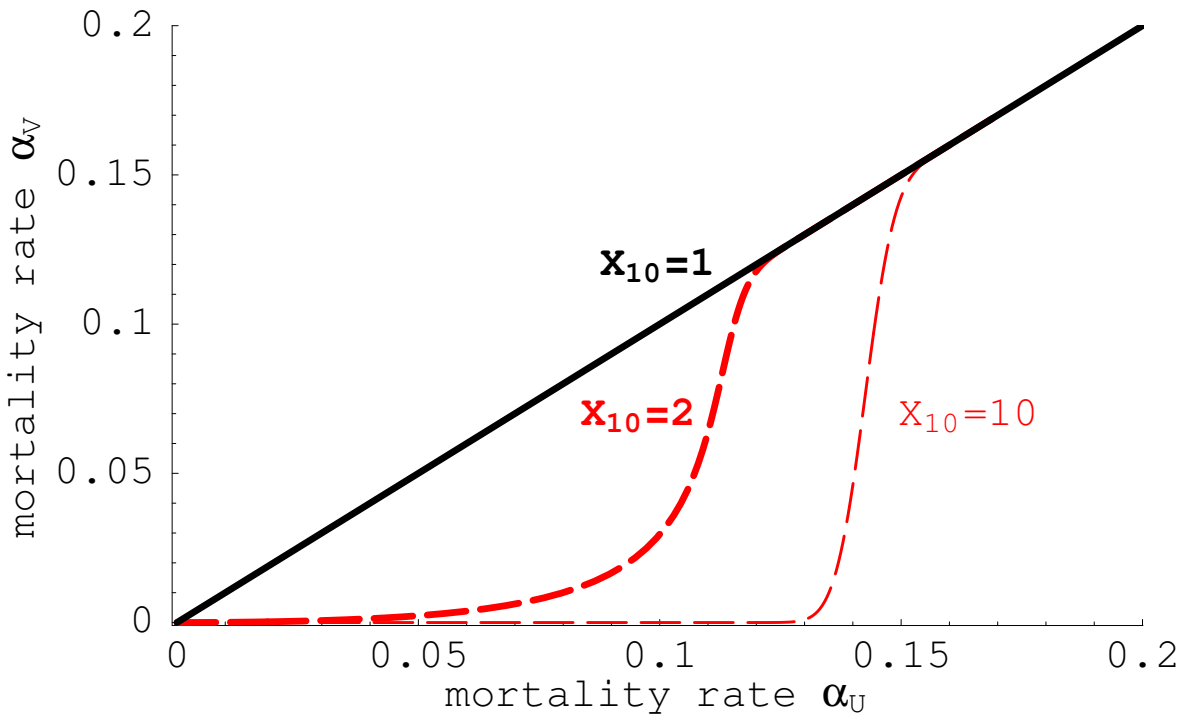


Changes in R_0 with vaccination



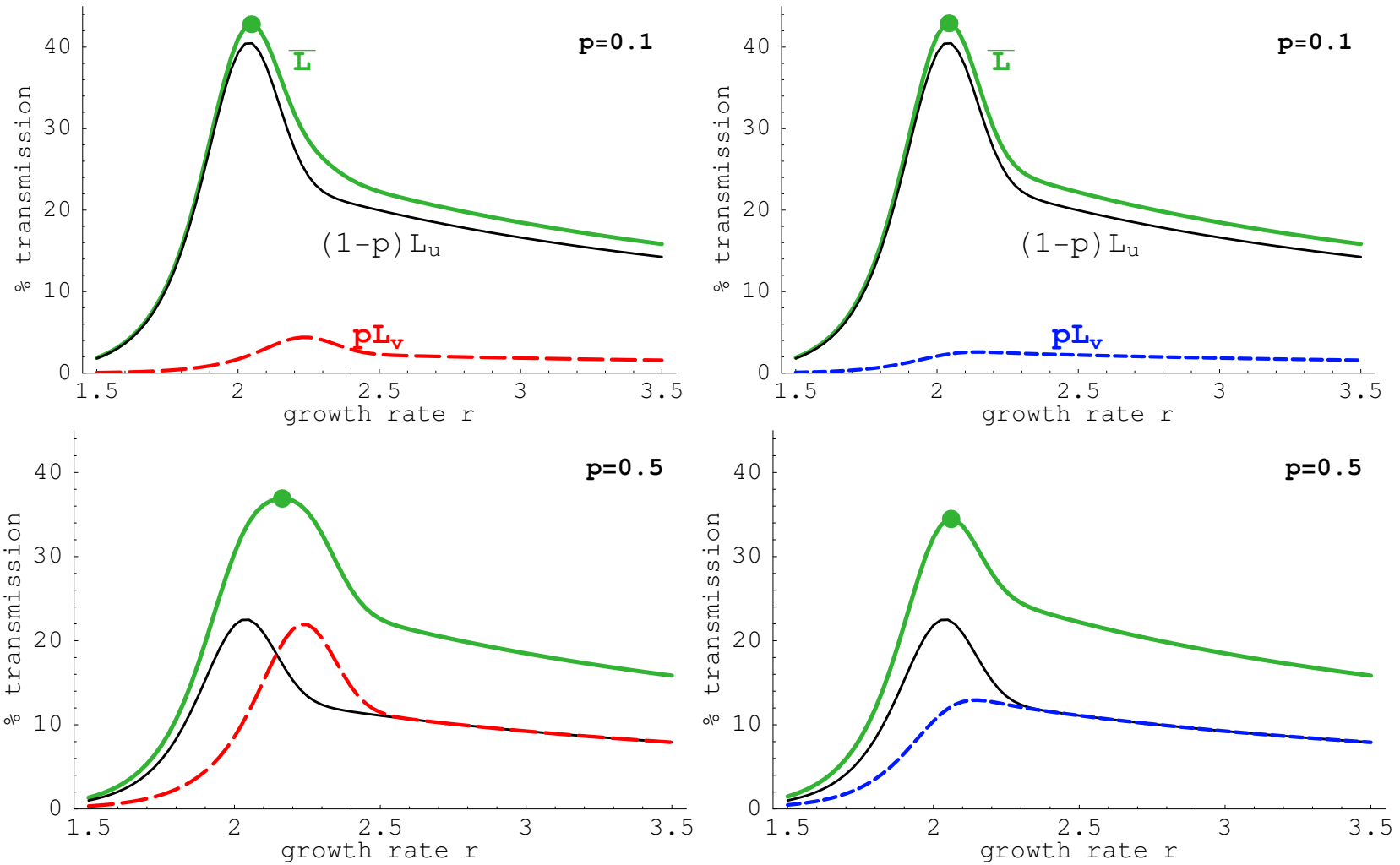
- Trade-offs do change with vaccination although changes may be small at low efficacy of vaccines (small increase in X_{10} and X_{20}).
- Anti-transmission vaccines may select for more virulent pathogens.

Virulence in unvaccinated and vaccinated hosts

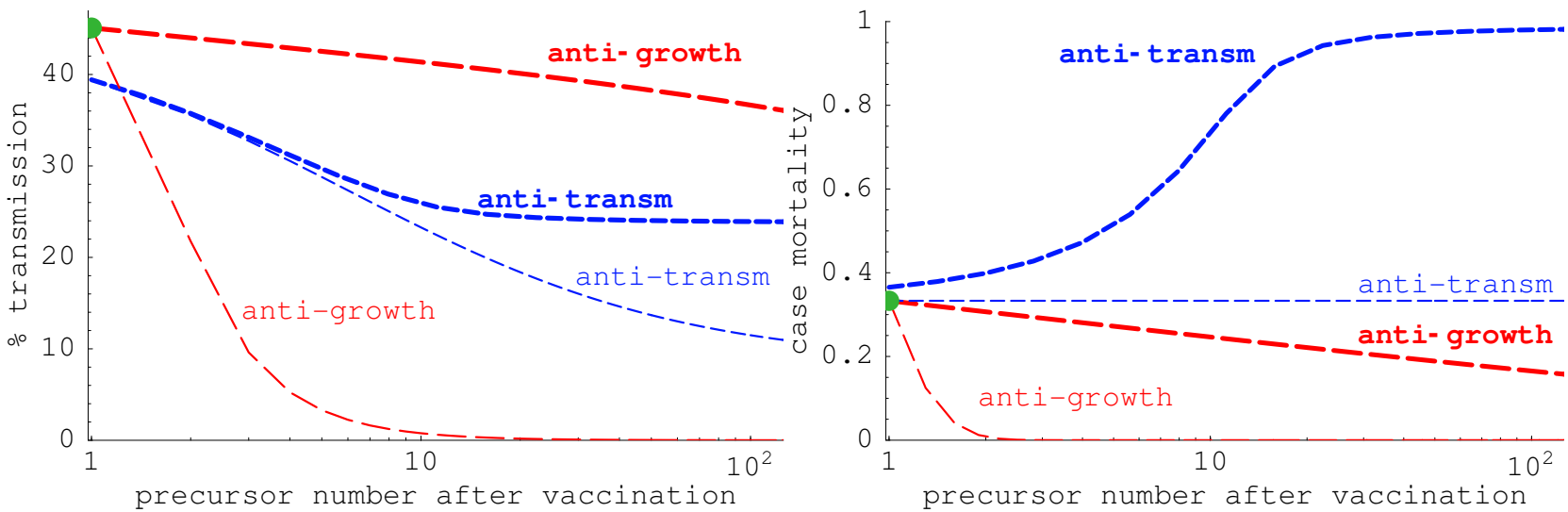


- The relationship between virulence of a pathogen with a fixed growth rate r in vaccinated α_V and unvaccinated α_U hosts is nonlinear.
- Note that in the study by Gandon et al. 2001, $\alpha_V = (1 - r_2)(1 - r_4)\alpha_U$.

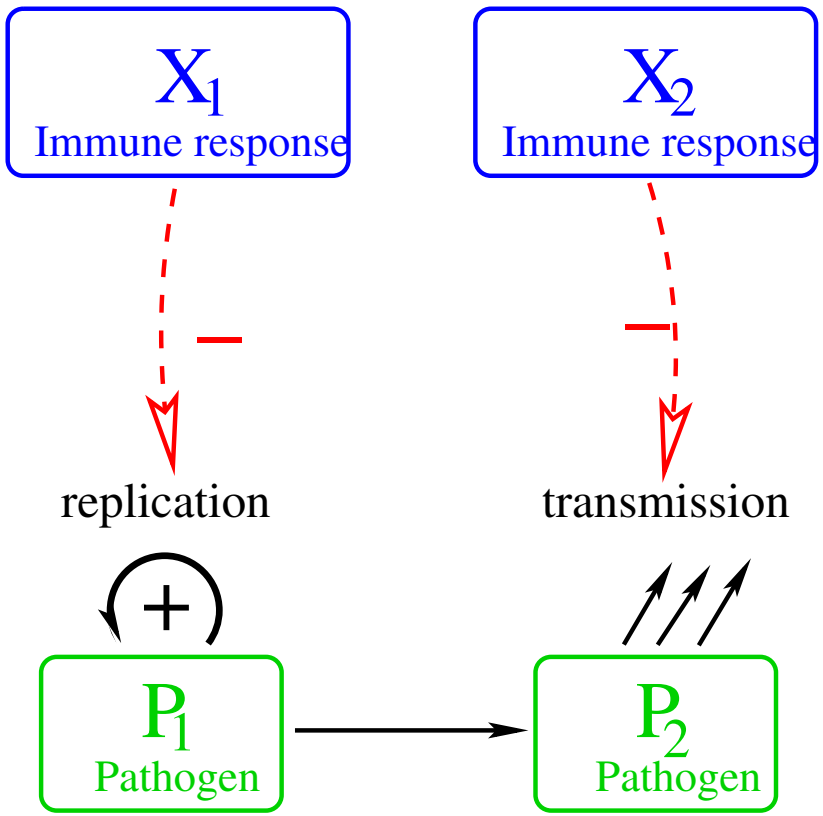
Total transmission vs. r



Total transmission and virulence vs vaccine efficacy



Two stages


X_1
Immune response
X_2
Immune response
replication
transmission
P_1
Pathogen
P_2
Pathogen

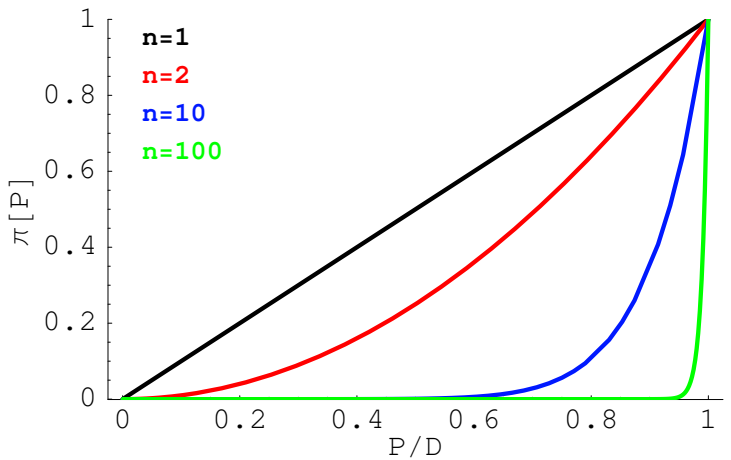
Pathogenesis and transmission

- The probability of host survival $S(t)$ until time t is the solution of

$$\dot{S}(t) = -\pi[r, P(t)]S(t)$$

where $\pi(r, P)$ is the rate of host's death due to pathogen.

$$\pi[r, P] \sim (P/D)^n$$



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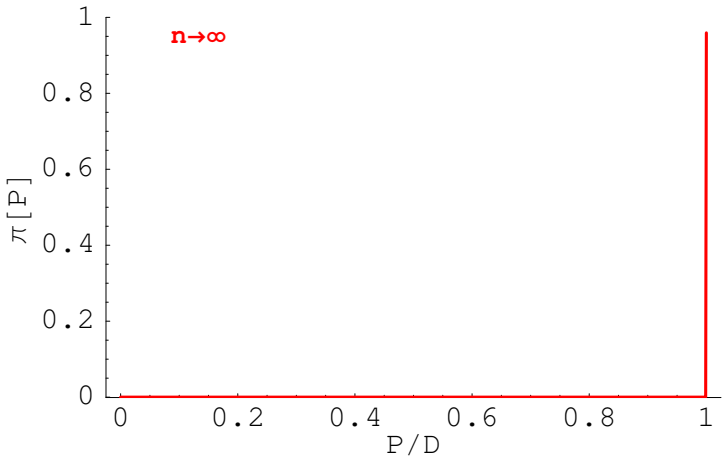

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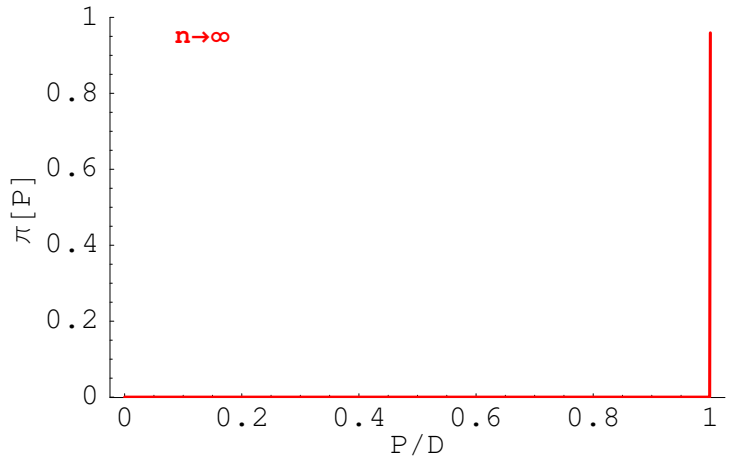
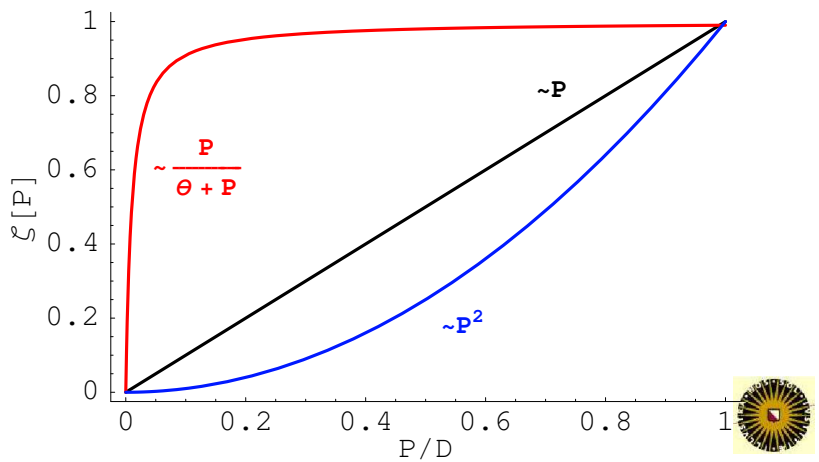
- The total transmission of the pathogen during the infection is

$$l = \int_0^{\Delta} \zeta[P(t)]S(t)\, dt$$

where $\zeta(P)$ is the rate of pathogen transmission.

$$\pi[r, P] = \lim_{n\to\infty}(P/D)^n$$





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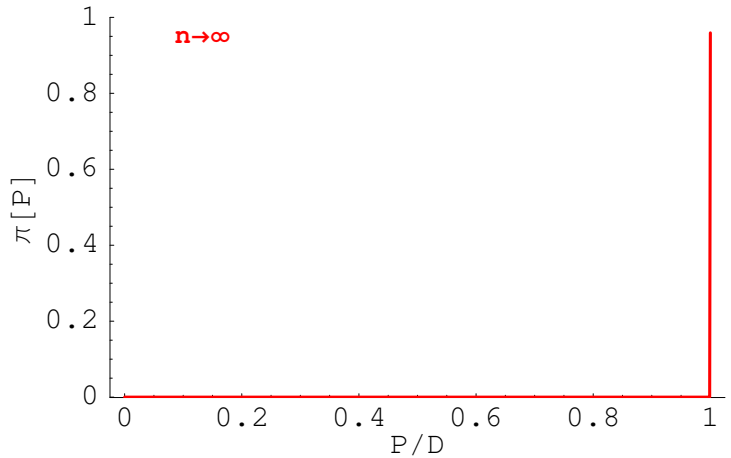

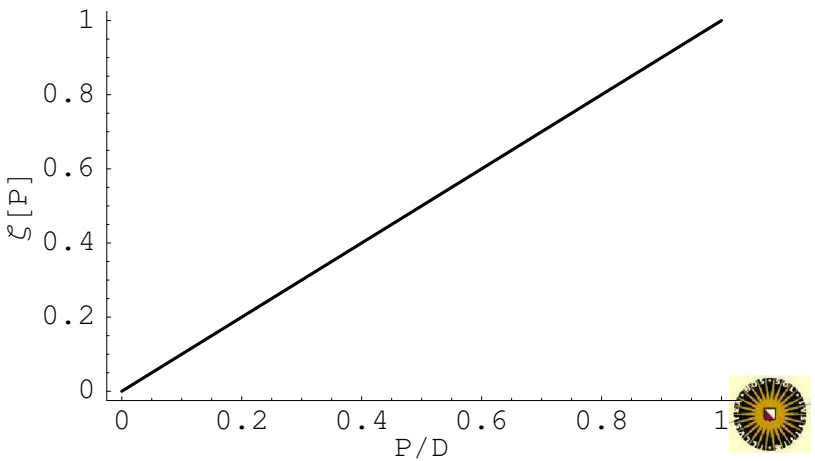

Back to a more general “stochastic” approach

- Host survival during an infection is a stochastic process

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$$l(r) = \int_0^{\Delta} \zeta[P(t)]S(t)\, dt$$

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- Consider a particular case when $\pi \sim P^n$ and $\zeta \sim P$:

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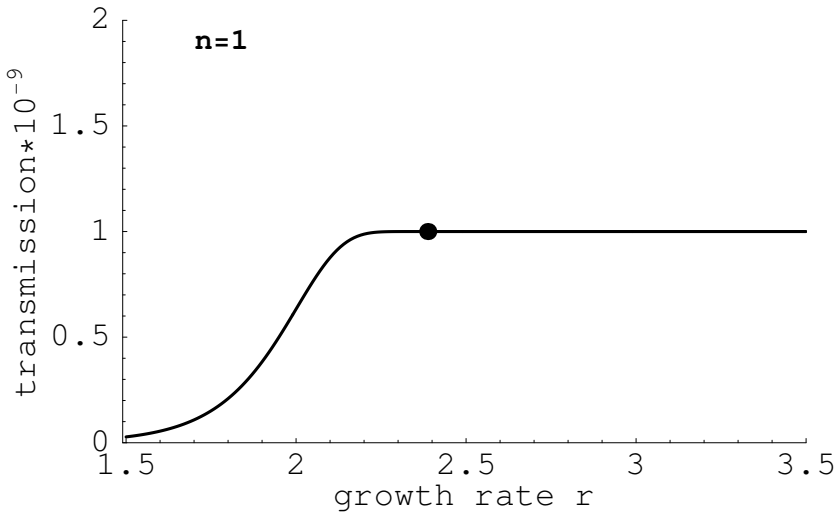
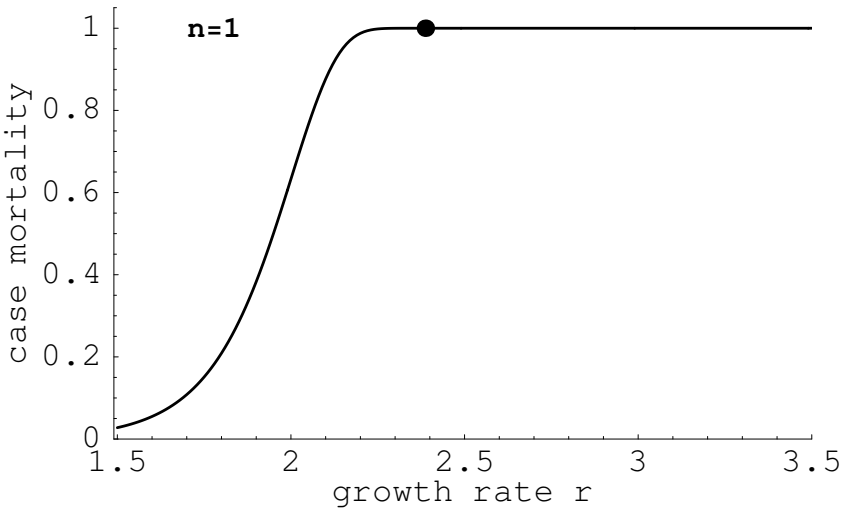
$$\pi(r, P) = \left[\frac{P}{D}\right]^1$$





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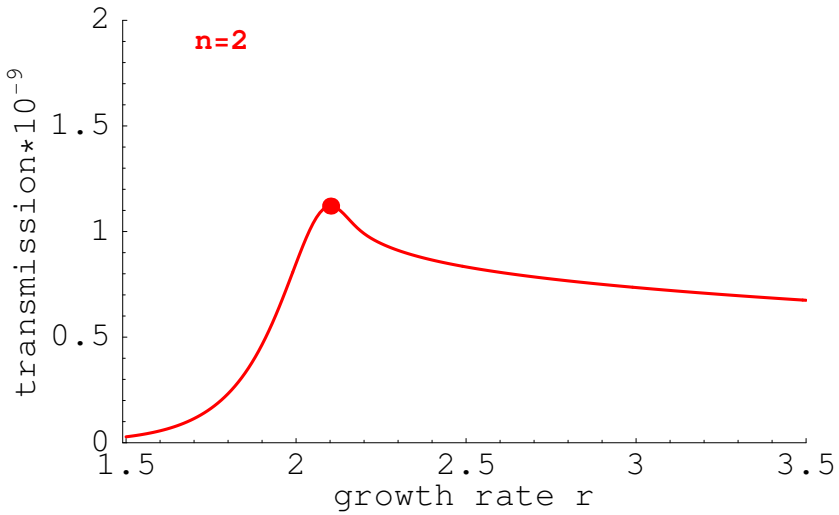
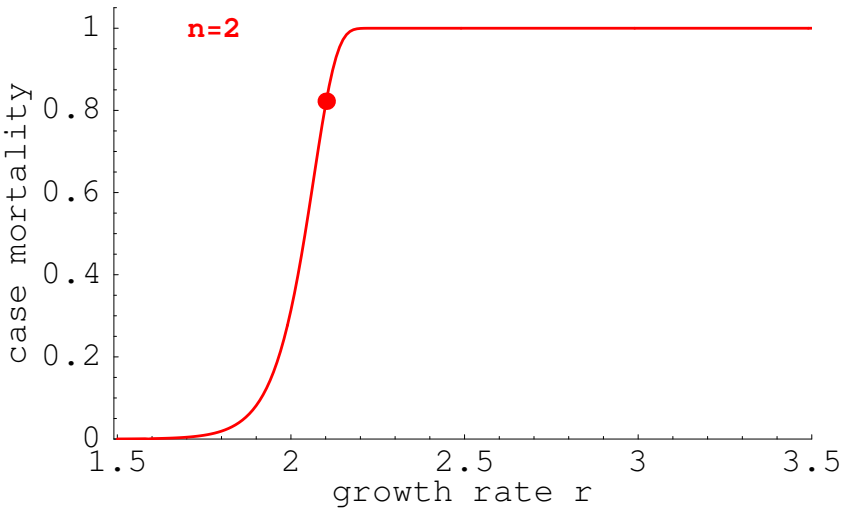
$$\dot{S}(t) = -\pi[r, P(t)]S(t)$$

$$l(r) = \int_0^{\Delta} \zeta[P(t)]S(t)\, dt$$

- Consider a particular case when $\pi \sim P^n$ and $\zeta \sim P$:

$$\pi(r, P) = \left[\frac{P}{D}\right]^2$$





Back to a more general "stochastic" approach

- Host survival during an infection is a stochastic process

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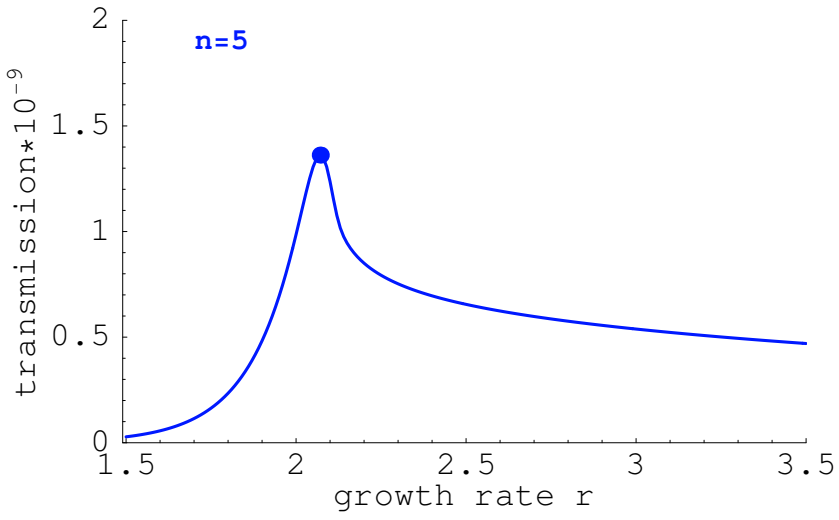
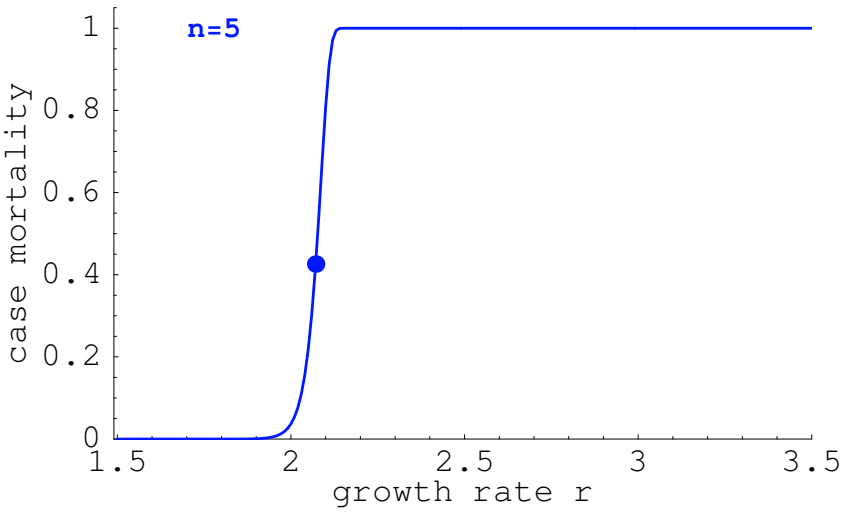
$$l(r) = \int_0^{\Delta} \zeta[P(t)]S(t)\, dt$$

- Consider a particular case when $\pi \sim P^n$ and $\zeta \sim P$:

$$\pi(r, P) = \left[\frac{P}{D}\right]^5$$





Back to a more general "stochastic" approach

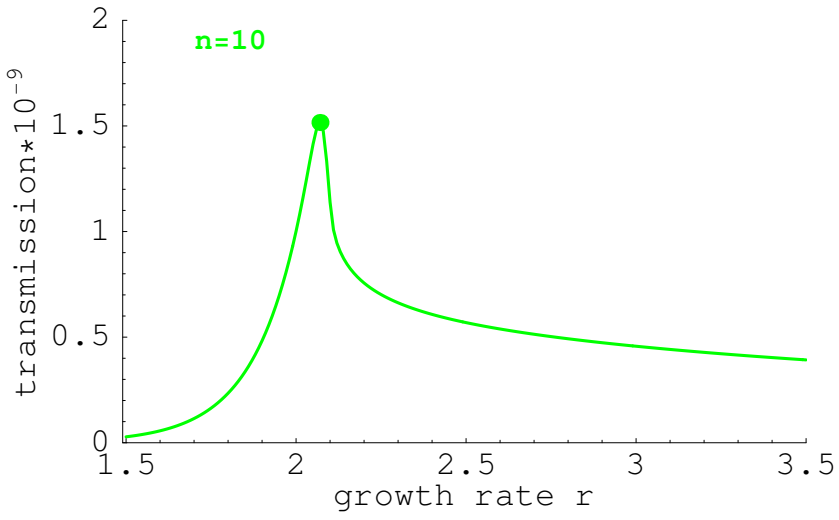
- Host survival during an infection is a stochastic process

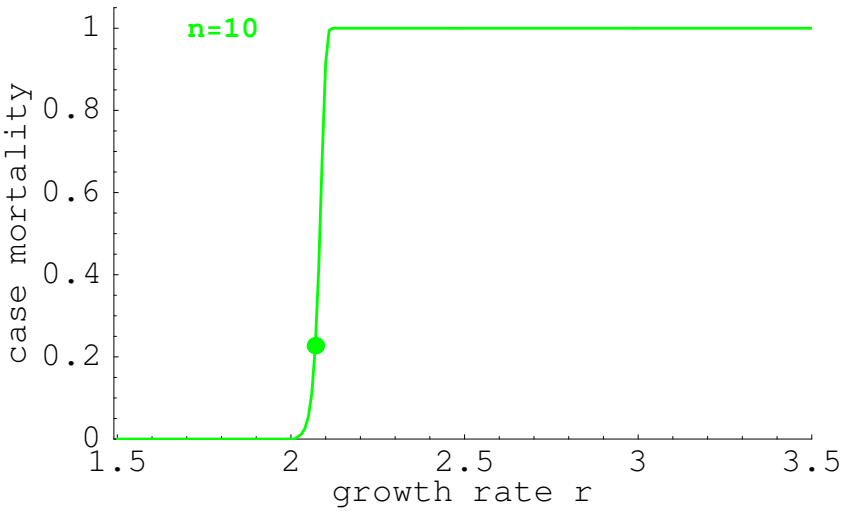
$$\dot{S}(t) = -\pi[r, P(t)]S(t)$$

$$l(r) = \int_0^{\Delta} \zeta[P(t)]S(t)\, dt$$

- Consider a particular case when $\pi \sim P^n$ and $\zeta \sim P$:

$$\pi(r, P) = \left[\frac{P}{D}\right]^{10}$$





Back to a more general “stochastic” approach: II

- Basic formulas

$$\dot{S}(t) = -\pi[r, P(t)]S(t)$$

$$l(r) = \int_0^{\Delta} P(t)S(t)\,dt$$

$$M(r) = 1 - S(\Delta)$$

- Traditionally, stochastic host survival is modelled differently, $\pi = \lambda r^m P$.

Sasaki and Iwasa 1991; Gilchrist and Sasaki 2002; André et al. 2003.

Back to a more general “stochastic” approach: II

- Basic formulas

$$\dot{S}(t) = -\pi[r, P(t)]S(t)$$

$$l(r) = \int_0^{\Delta} P(t)S(t)\,dt$$

$$M(r) = 1 - S(\Delta)$$

- Traditionally, stochastic host survival is modelled differently, $\pi = \lambda r^m P$.

$$\pi(r, P) = \lambda r^1 P$$

Sasaki and Iwasa 1991; Gilchrist and Sasaki 2002; André et al. 2003.

Back to a more general "stochastic" approach: II

- Basic formulas

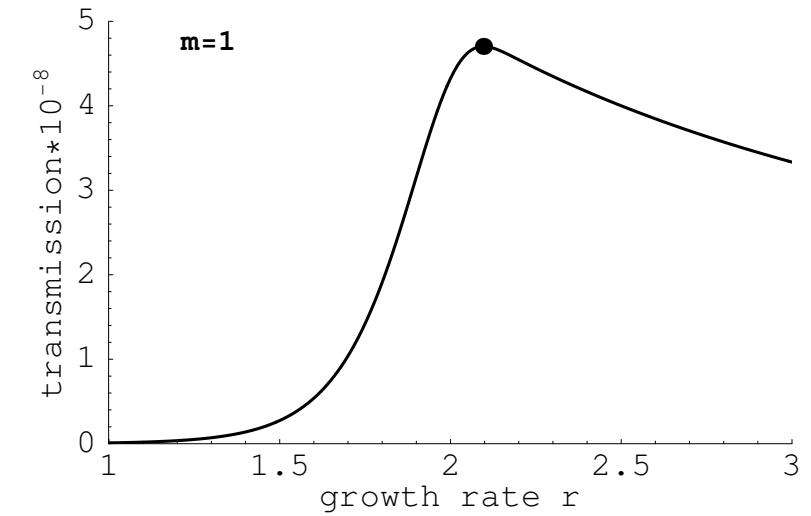
$$\dot{S}(t) = -\pi[r, P(t)]S(t)$$

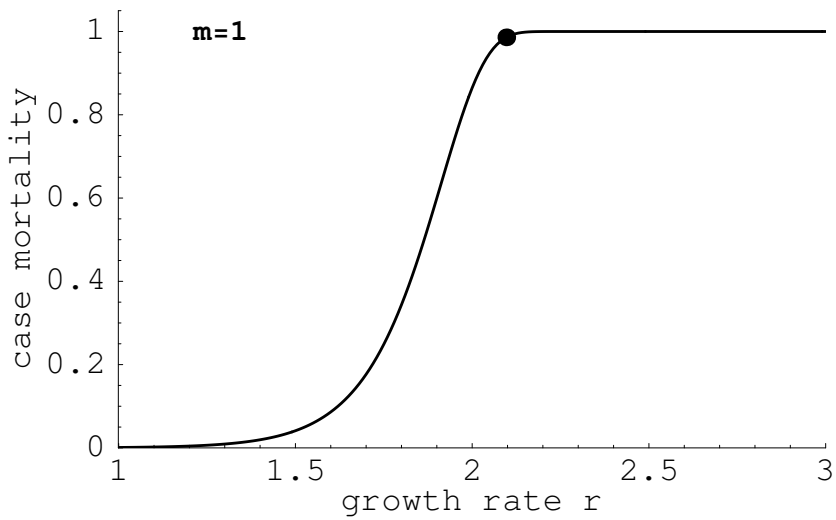
$$l(r) = \int_0^{\Delta} P(t)S(t)\,dt$$

$$M(r) = 1 - S(\Delta)$$

- Traditionally, stochastic host survival is modelled differently, $\pi = \lambda r^m P$.

$$\pi(r, P) = \lambda r^1 P$$





Sasaki and Iwasa 1991; Gilchrist and Sasaki 2002; André et al. 2003.

Back to a more general "stochastic" approach: II

- Basic formulas

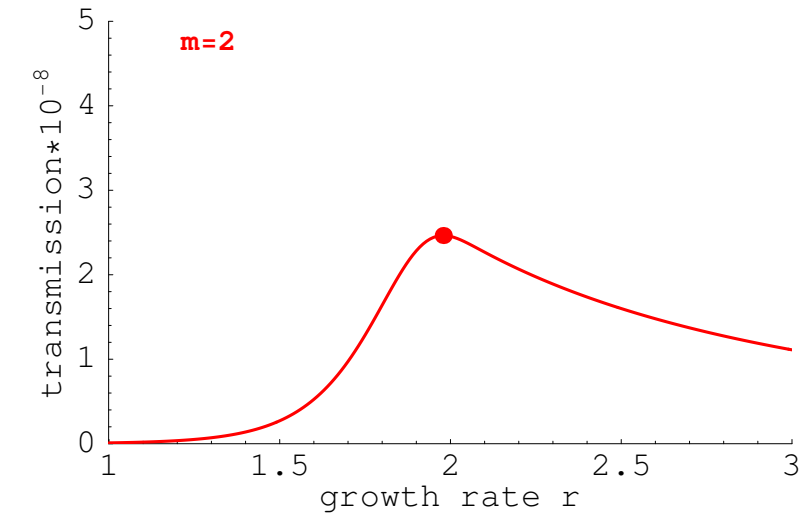
$$\dot{S}(t) = -\pi[r, P(t)]S(t)$$

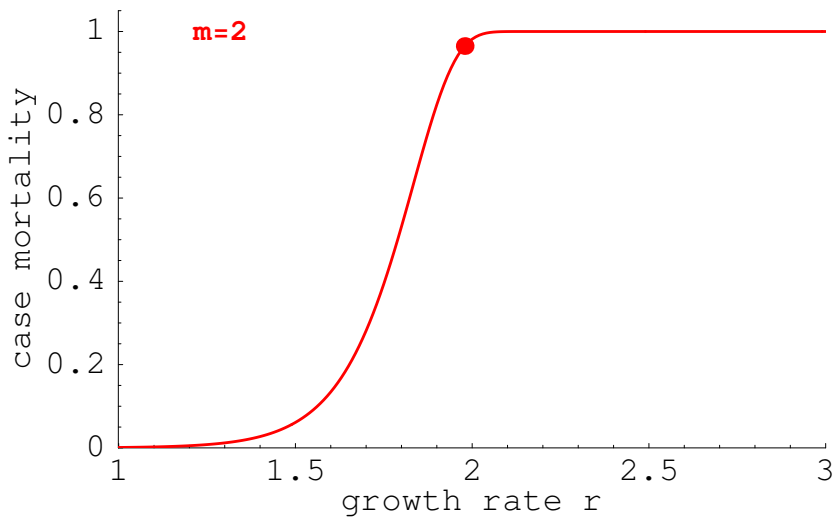
$$l(r) = \int_0^{\Delta} P(t)S(t)\,dt$$

$$M(r) = 1 - S(\Delta)$$

- Traditionally, stochastic host survival is modelled differently, $\pi = \lambda r^m P$.

$$\pi(r, P) = \lambda r^2 P$$





Sasaki and Iwasa 1991; Gilchrist and Sasaki 2002; André et al. 2003.

Back to a more general "stochastic" approach: II

- Basic formulas

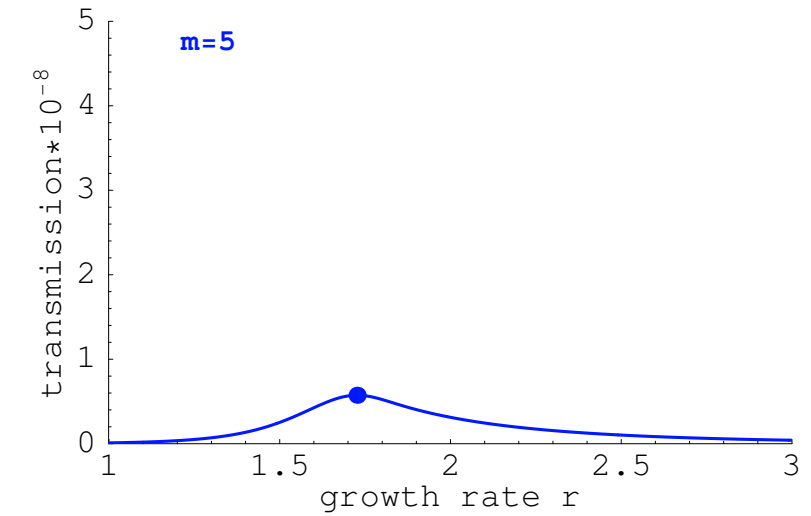
$$\dot{S}(t) = -\pi[r, P(t)]S(t)$$

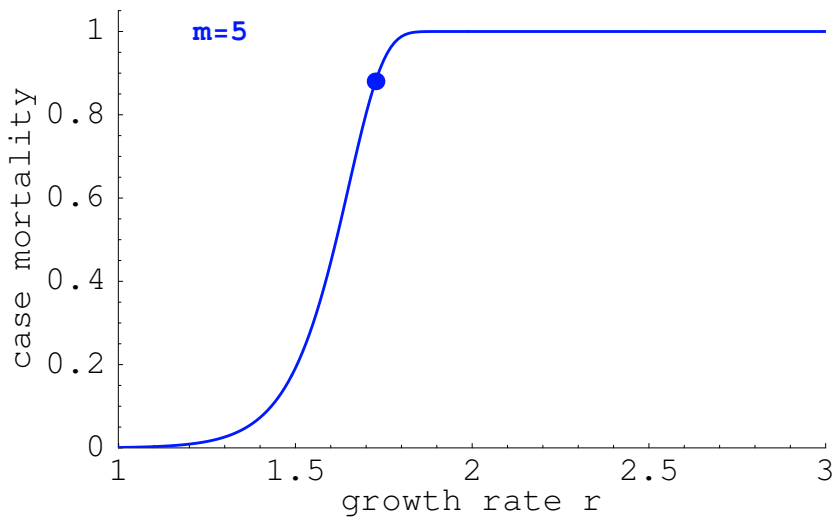
$$l(r) = \int_0^{\Delta} P(t)S(t)\,dt$$

$$M(r) = 1 - S(\Delta)$$

- Traditionally, stochastic host survival is modelled differently, $\pi = \lambda r^m P$.

$$\pi(r, P) = \lambda r^5 P$$





Sasaki and Iwasa 1991; Gilchrist and Sasaki 2002; André et al. 2003.

Back to a more general "stochastic" approach: II

- Basic formulas

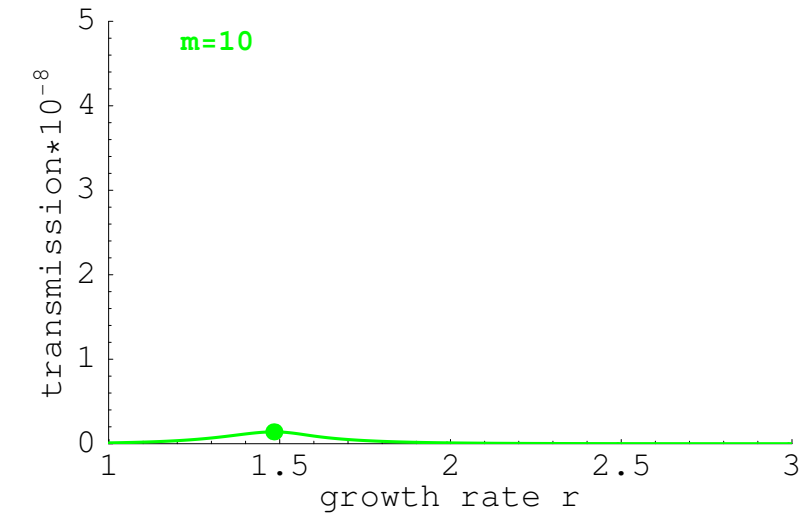
$$\dot{S}(t) = -\pi[r, P(t)]S(t)$$

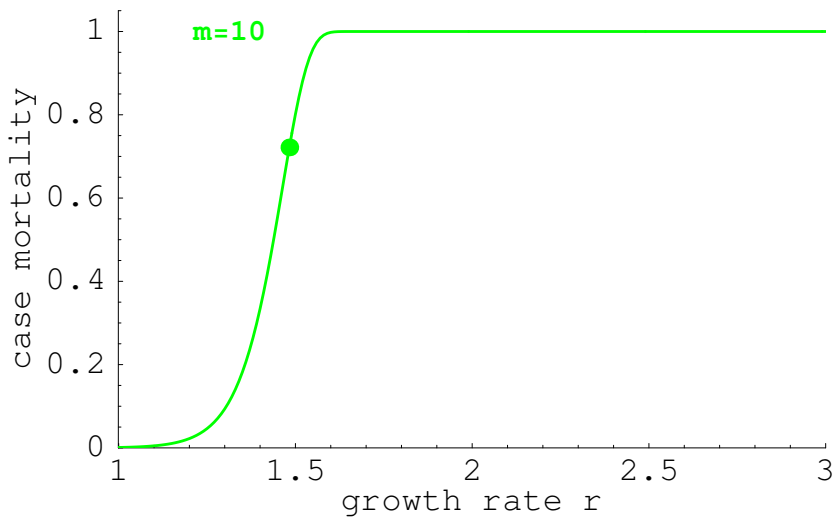
$$l(r) = \int_0^{\Delta} P(t)S(t)\,dt$$

$$M(r) = 1 - S(\Delta)$$

- Traditionally, stochastic host survival is modelled differently, $\pi = \lambda r^m P$.

$$\pi(r, P) = \lambda r^{10} P$$





Sasaki and Iwasa 1991; Gilchrist and Sasaki 2002; André et al. 2003.

Summary

- Even in simple “within-host” models, a variety of methods exist to describe pathogenesis.
- Moderate levels of virulence (case mortality) can evolve if rate of pathogenesis $\pi \sim P^n$.
- When $\pi \sim r^m P$, saturation in the transmission rate may help to reduce the case mortality.

Introducing heterogeneity in parameters

- For a parameter X, $f(x)\,dx$ is the probability that a during a given infection, the parameter X will be in the range $(x, x + dx)$.
- Then total transmission of the pathogen with the growth rate r in a heterogeneous population is calculated as

$$L(r) = \int_0^\infty l(r, x)\, f(x)\, dx.$$

- Thus, such heterogeneity may arise due to stochasticity in pathogen-host interactions.
- We illustrate the results with heterogeneity in the growth rate r described by a gamma distribution.