The Overlooked Implications of Density Dependence in Evolutionary Epidemiology

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Overview

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2. Adaptive Dynamics Theory
3. Invasion Analysis of SI Models
4. Causes of Density Dependence
5. Analysis of Pathogen Evolution
6. Summary

Limitations of R_0 Maximization

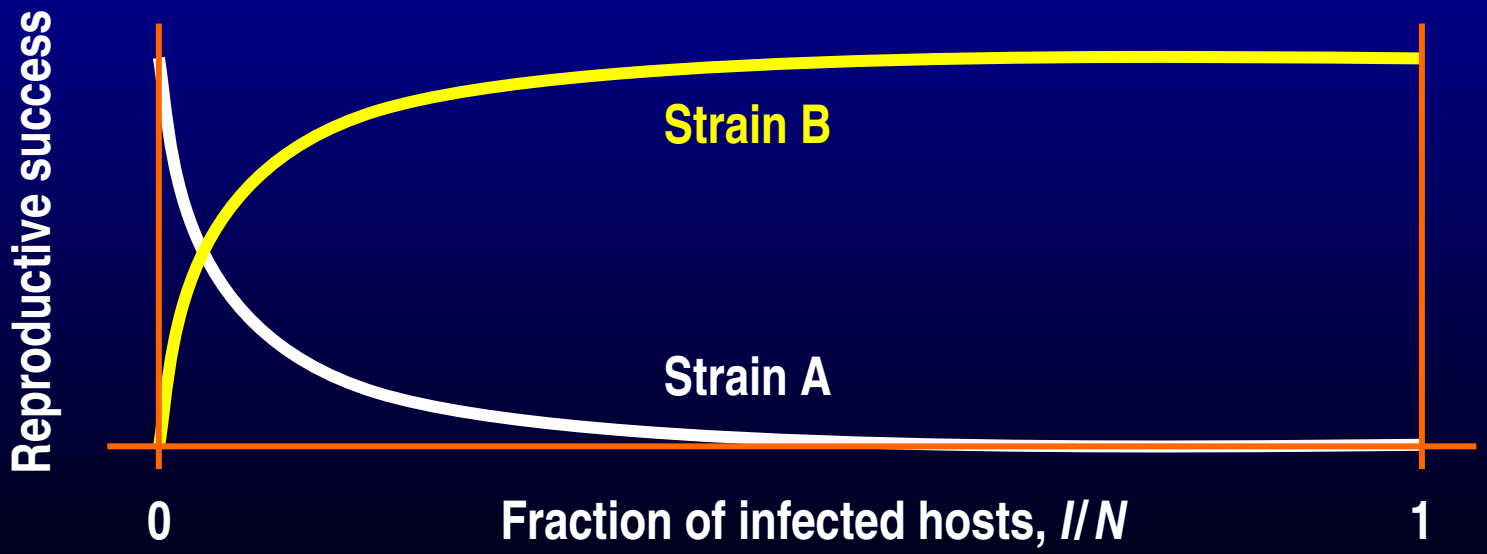
R_0 Maximization

- The basic reproduction ratio of a pathogen, R_0, is defined as the expected number of infections produced by a single infected host individual *in an otherwise uninfected host population*.
- Analyses of relatively simple epidemiological models led to a widespread understanding that R_0 is maximized in the course of pathogen evolution.
- Since the basic reproduction ratio is a measure of effective transmissibility, maximizing a pathogen's R_0 is equivalent to maximizing its transmissibility.

Limitations of R_0 Maximization 1

- **Density-dependent Selection:**

  The reproductive success of a pathogen strain in an environment of uninfected hosts may not be indicative of its reproductive success in a partially infected host population.



Limitations of R_0 Maximization 2

- **Frequency-dependent Selection:**

  The reproductive success of a pathogen may critically depend on the frequency and phenotype of other strains prevalent in the host population.

R(A) max. in E_0

R(B) max. in E_A

R(C) max. in E_B

R(A) max. in E_C

Limitations of R_0 Maximization 3

- **Pathogen-Host Coevolution:**

  The reproductive success of a pathogen may critically depend on the prevalent phenotypes of hosts. Accordingly, pathogens and hosts may be engaged in Red Queen evolution, resulting in continual evolutionary change.

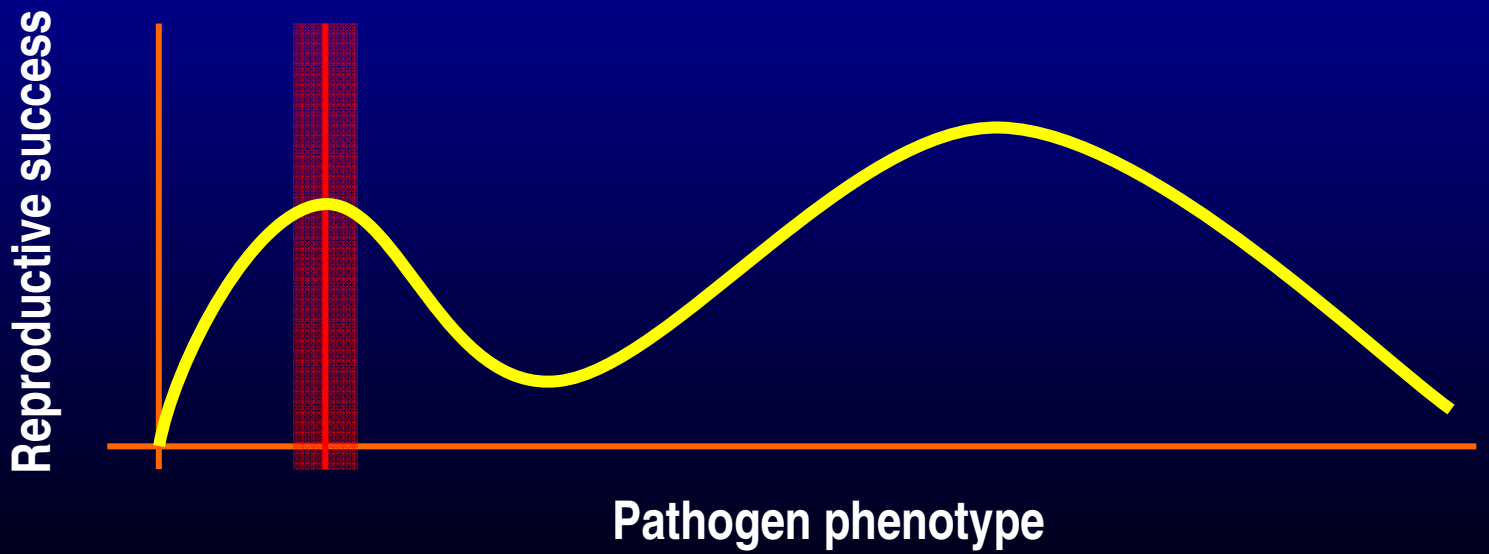
R_0(A) max. in E(Host trait 1)

R_0(B) max. in E(Host trait 2)

Limitations of R_0 Maximization 4

- **Gradual Evolution:**

  Even in pathogens, adaptation can often only explore the small range of variation that is accessible by small evolutionary steps.



Adaptive Dynamics Theory

Adaptive Dynamics

Adaptive dynamics theory extends evolutionary game theory:

- Frequency- und density-dependent selection
- Stochastic and nonlinear population dynamics
- Continuous strategies or metric characters
- Evolutionary dynamics and outcomes
- Derivation of fitness from underlying population dynamics

Characteristic tools:

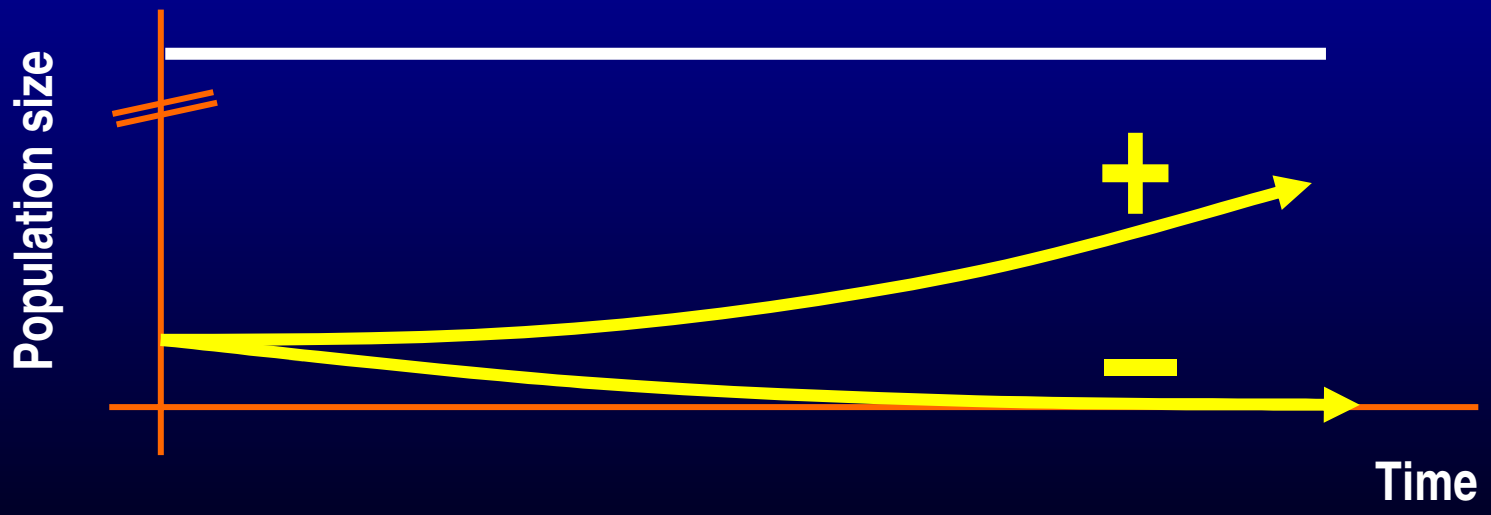
- Invasion fitness
- Pairwise invasibility plots
- Canonical equation

Invasion Fitness

Metz *et al.* (1992)

- **Definition**

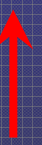
  Initial per capita growth rate of a small **mutant** population within a resident population at ecological equilibrium.



Invasion Fitness

- Fitness is a function of two variables:

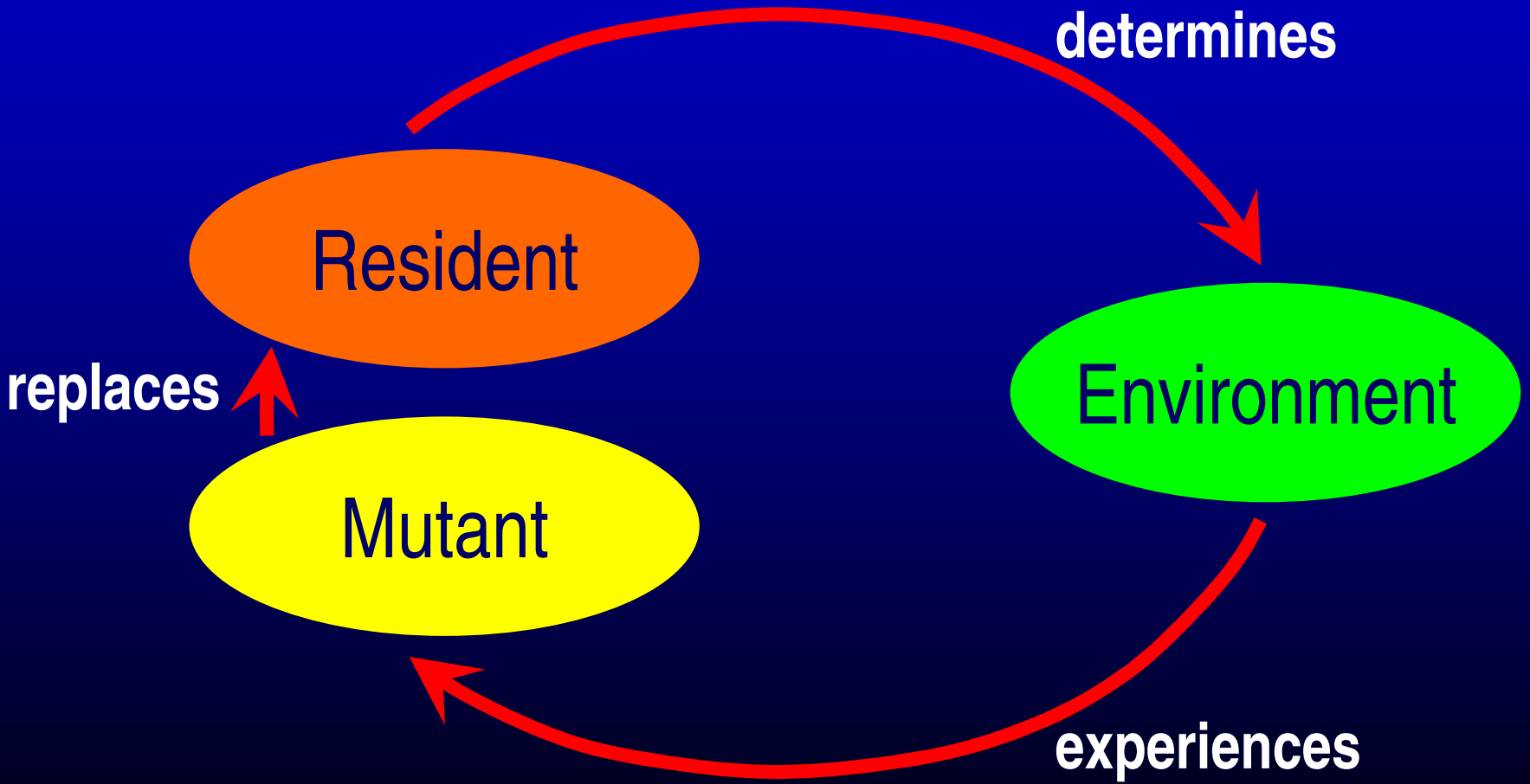
$$f(x', x)$$



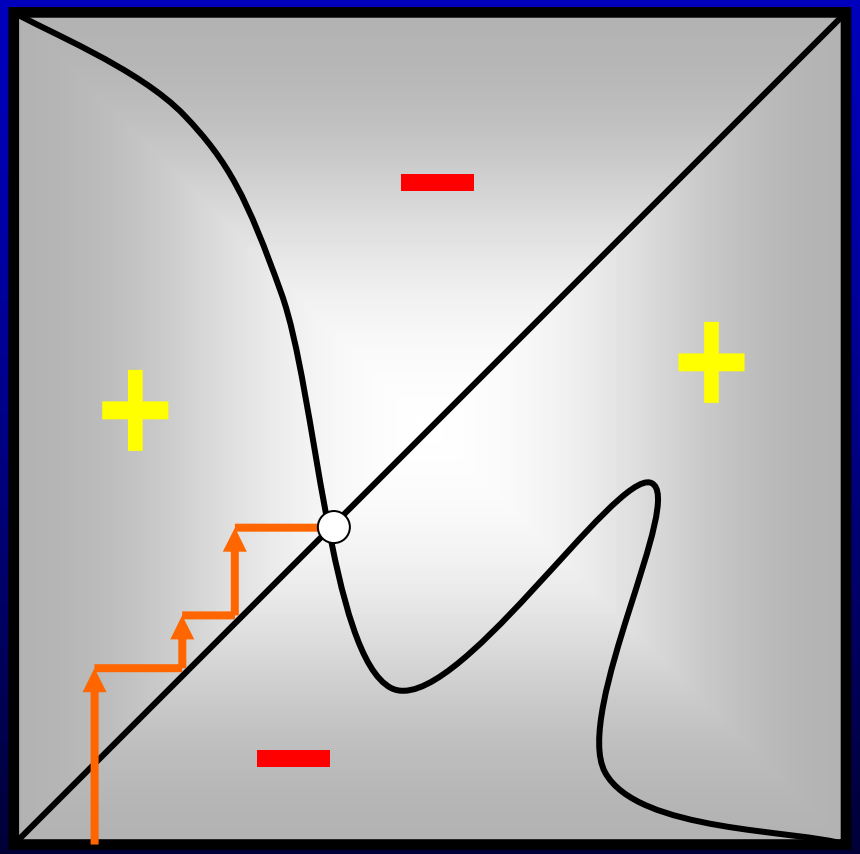
mutant trait

resident trait: determines environment

Environmental Feedback



Pairwise Invasibility Plots (PIPs)



Invasion of the mutant into the resident population possible

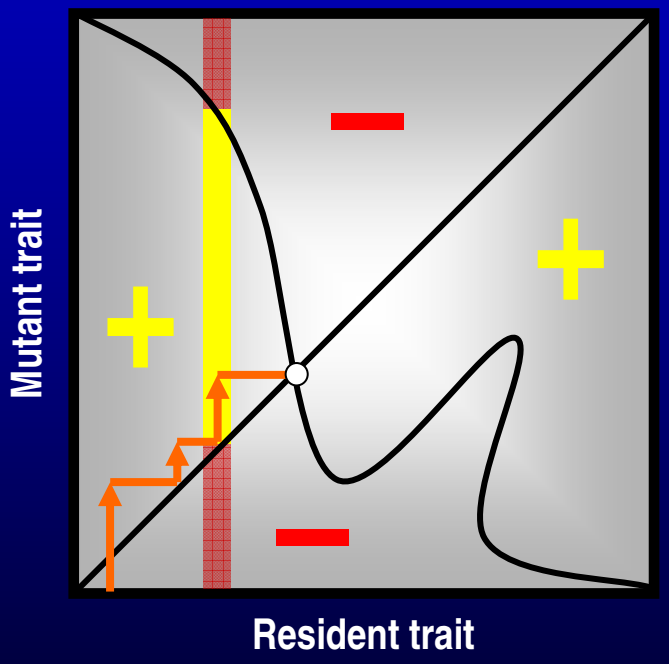
Invasion impossible

One trait substitution

Singular phenotype

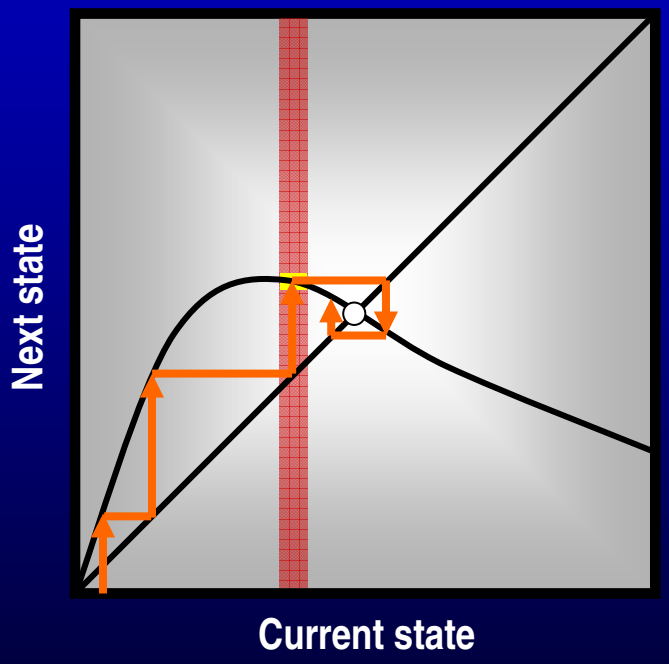
Reading PIPs: Comparison with Recursions

- Trait substitutions



Size of vertical steps probabilistic

- Recursion relations

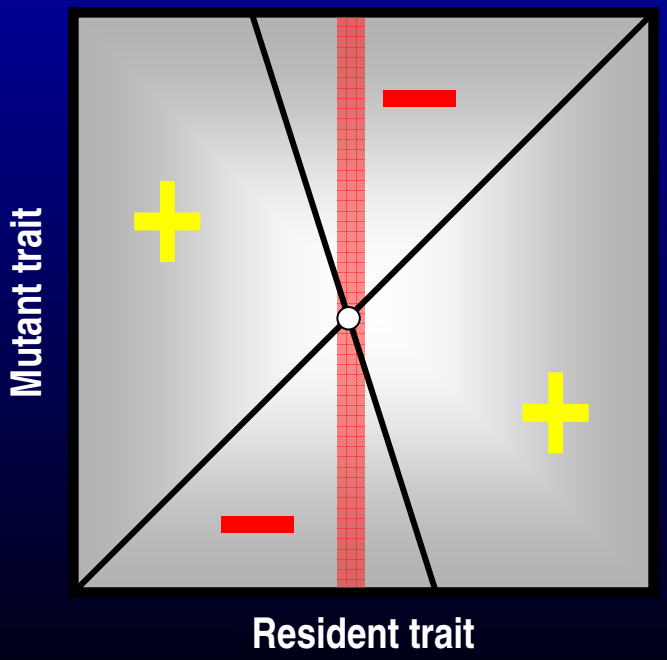


Size of vertical steps deterministic

Reading PIPs: Evolutionary Stability

- Is a singular phenotype immune to invasions by neighboring phenotypes?

Yes:



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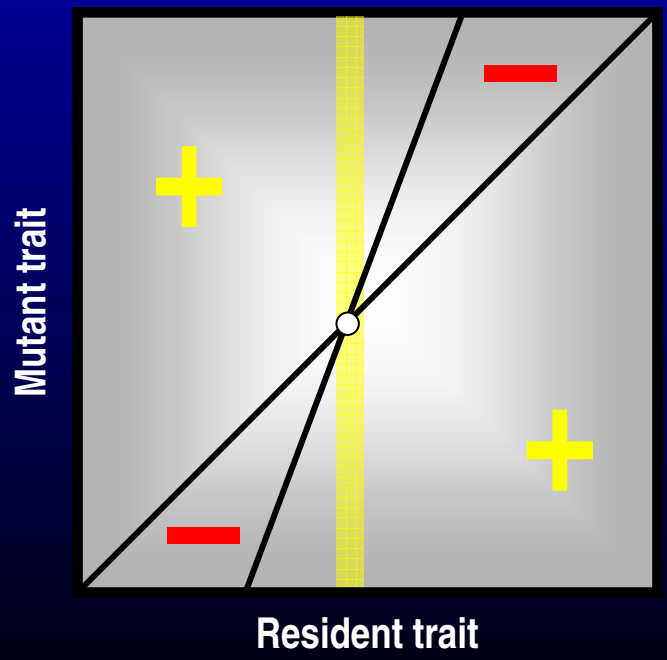
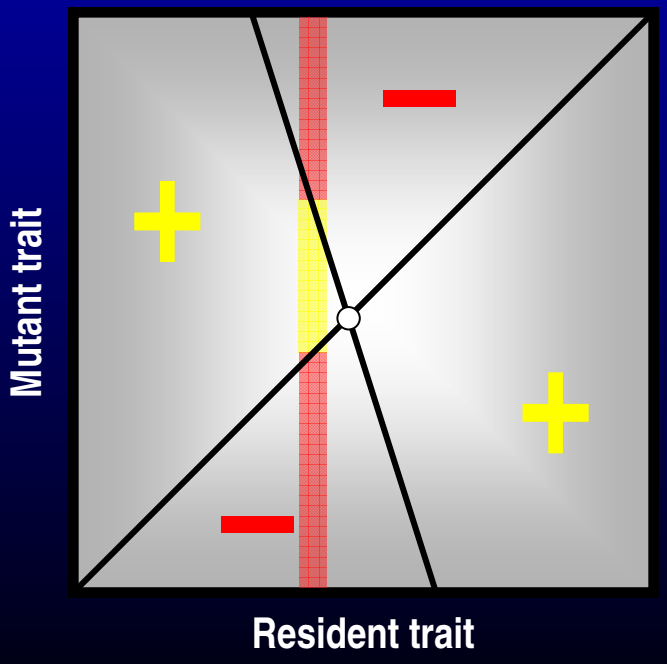


Reading PIPs: Convergence Stability

- When starting from neighboring phenotypes, do successful invaders lie closer to the singular one?

Yes:



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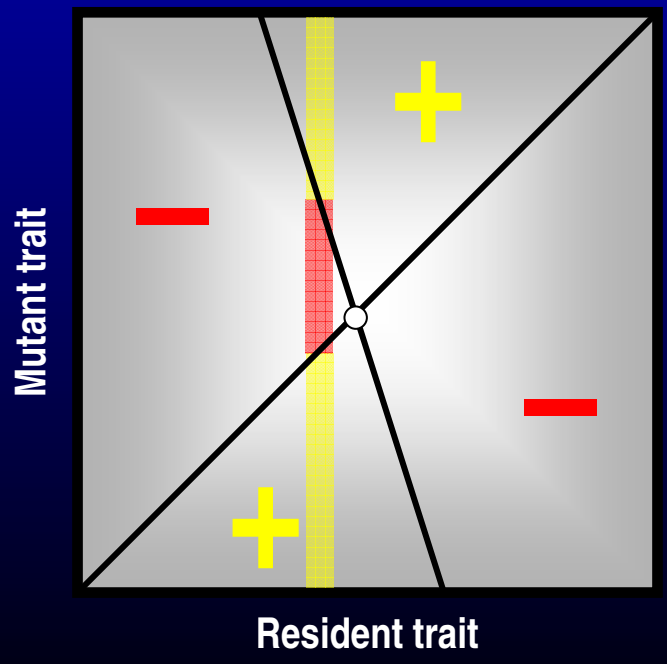
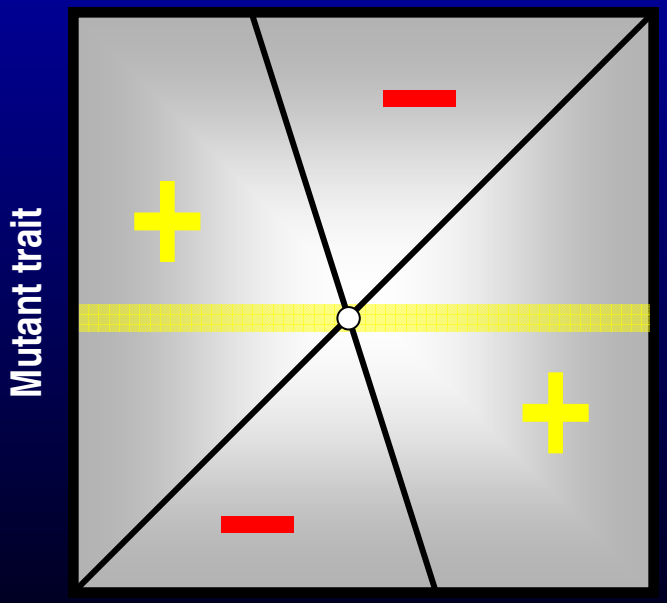


Reading PIPs: Invasion Potential

- Is the singular phenotype capable of invading into all its neighboring types?

Yes:



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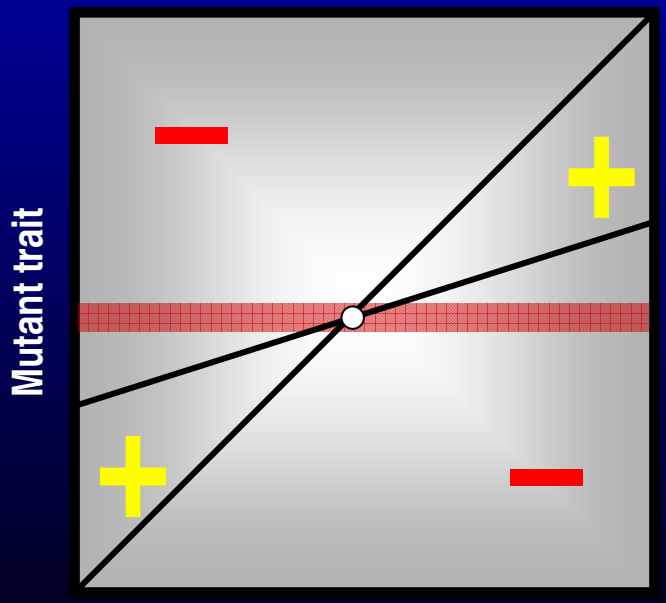
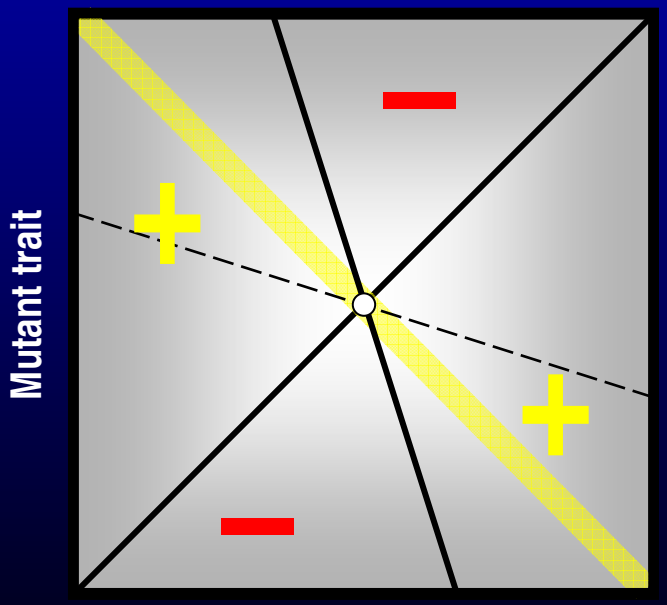


Reading PIPs: Mutual Invasibility

- Can a pair of neighboring phenotypes on either side of a singular one invade each other?

Yes:



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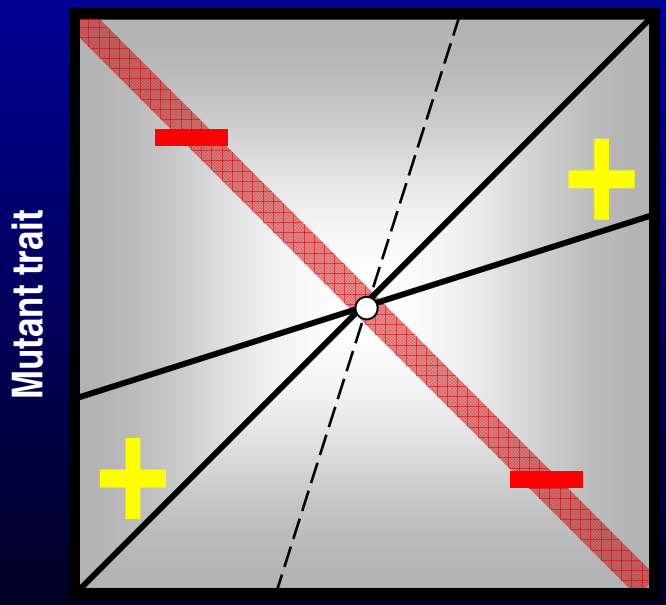
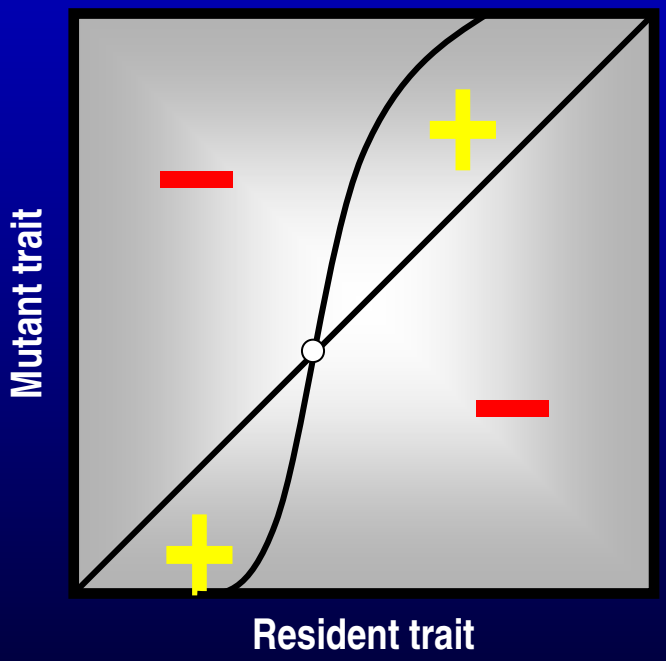


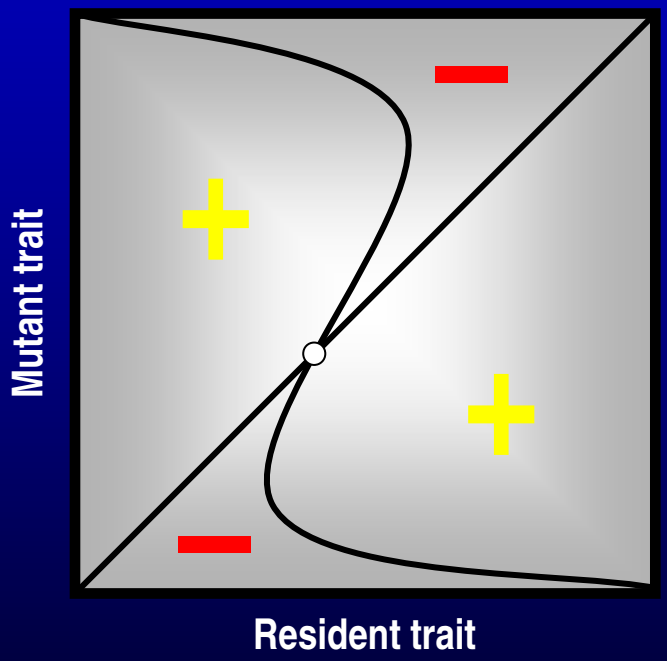
Two Especially Interesting Types of PIP

- Garden of Eden



Evolutionarily stable,
but not convergence stable

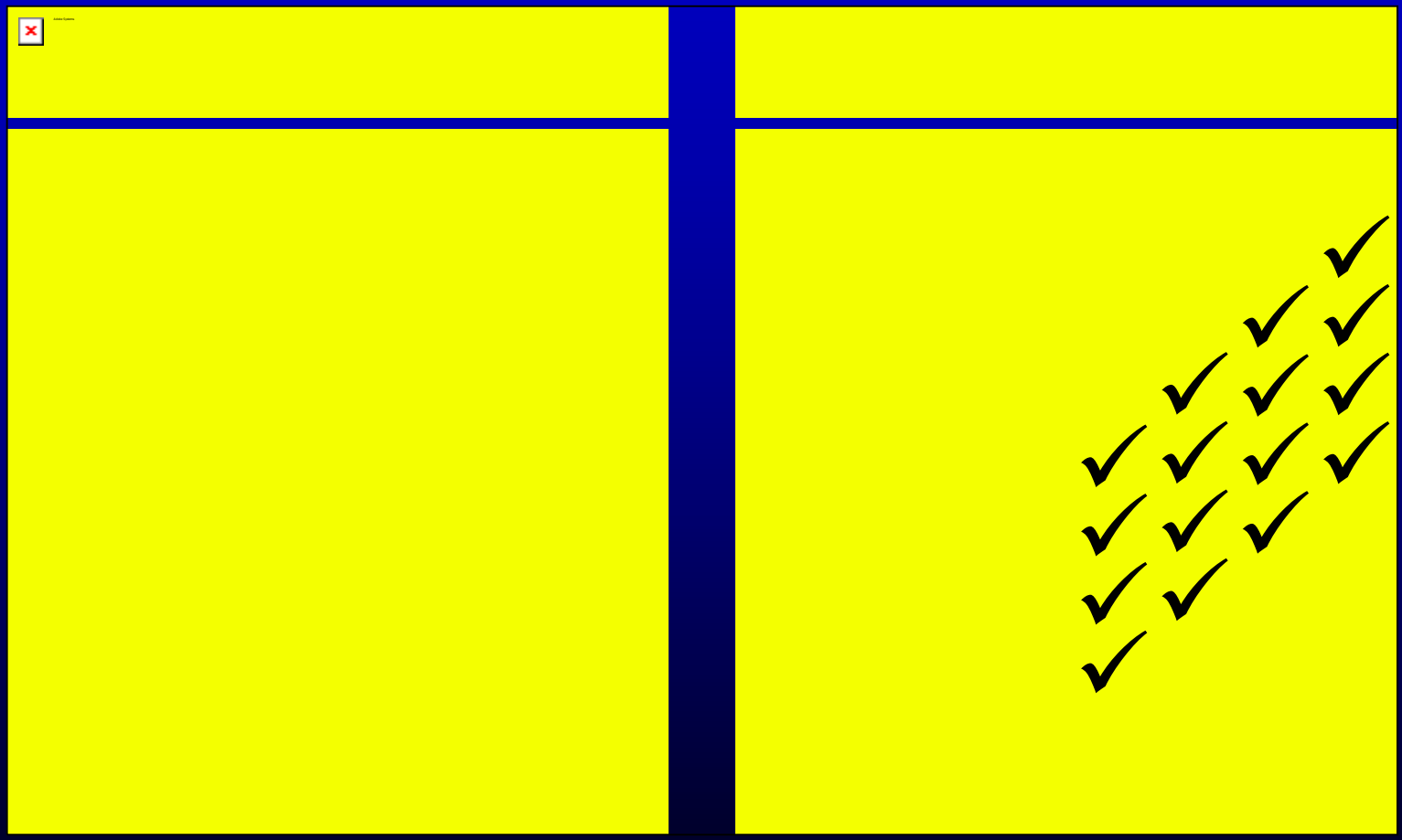
- Branching Point



Convergence stable,
but not evolutionarily stable

Eightfold Classification

Geritz *et al.* (1997)



(1) Evolutionary stability, (2) Convergence stability, (3) Invasion potential, (4) Mutual invasibility.

Canonical Equation

Dieckmann & Law (1996)

$$\frac{d}{dt} x_i = \frac{1}{2} \mu_i n_i \sigma_i^2 \frac{\partial}{\partial x_i'} f_i(x_i', x)\Big|_{x_i' = x_i}$$

- $\frac{d}{dt} x_i$: evolutionary rate in species *i*
- μ_i: mutation probability
- n_i: population size
- σ_i^2: mutation variance-covariance
- $\frac{\partial}{\partial x_i'}$: local selection gradient
- $f_i(x_i', x)$: invasion fitness

Result is formally similar to Lande's (1979) approximation based on quantitative genetics.

Invasion Analysis of SI Models

Generalized SI Models

- **Population Dynamics**

$$\frac{dS}{dt} = +b_S(x,S,I)S + b_I(x,S,I)I - d_S(x,S,I)S - \beta(x,S,I)SI + \theta(x,S,I)I$$

$$\frac{dI}{dt} = -d_I(x,S,I)I + \beta(x,S,I)SI - \theta(x,S,I)I$$

- **Demographic and Epidemiological Rates**

b_S	Disease-free fertility
d_S	Disease-free mortality
$b_S - b_I$	Disease-induced loss of fertility (virulence)
$d_I - d_S$	Disease-induced mortality (virulence)
β	Transmission rate
θ	Recovery rate

Evolutionary Measures

- **Invasion Fitness**

$$f(x',x) = -d_I(x',S^*(x),I^*(x)) + \beta(x',S^*(x),I^*(x))S^*(x) - \theta(x',S^*(x),I^*(x))$$

- **Lifetime Reproductive Success**

$$R(x',x) = \beta(x',S^*(x),I^*(x))S^*(x)/[d_I(x',S^*(x),I^*(x)) + \theta(x',S^*(x),I^*(x))]$$

- **Basic Reproduction Ratio**

$$R_0(x') = \beta(x',S_0,0)S_0/[d_I(x',S_0,0) + \theta(x',S_0,0)]$$

Relations between Evolutionary Measures

- **Invasion Fitness & Lifetime Reproductive Success**

$$f(x', x) > 0 \Leftrightarrow R(x', x) > 1$$

- **Lifetime Reproductive Success & Basic Reproduction Ratio**

$$R(x', x) > 1 \Leftrightarrow R_0(x') > R_0(x)$$

This holds, if all three rates d_I, β, and θ are density-independent. Otherwise, such a simple relation cannot be taken for granted.

Causes of Density Dependence

Density-dependent Demographic Rates

- Density dependence of demographic rates is assumed in all simple *non-epidemiological* population models and is needed to prevent the density of susceptible hosts to diverge without bounds in the absence of the disease.
- An often invoked justification for neglecting such dependence in simple SI models is the assumption that the disease itself is fully responsible for regulating the host population density. However, even for the severest of diseases this must remain an approximation, whereas for most other infections the assumption is plainly wrong.
- An alternative justification for not having to consider density-dependent demographic rates is to assume that the total host population size stays strictly constant – independent of the virulence of the resident strain. Obviously, also this is an approximation at best and is likely to apply to very benign diseases only.
- As usual, reality lies in between these mathematical extremes, and density regulation in an infected population is partially due to disease-independent factors and partially to the disease itself.

Density-dependent Epidemiological Rates 1

- There is a plethora of mechanisms that cause epidemiological rates to be density-dependent. Six illustrative classes of mechanism are listed below:
- The number of patients a doctor must attend to may rise with the density of infected hosts. This can affect disease-induced mortality and loss of fertility, as well as transmission and recovery rates.
- The nutritional status of hosts, and thus their resistance against disease symptoms, may deteriorate with increases in total population density or in the population's morbidity level. Again, this can affect all four epidemiological rates.
- The quality of medical services in terms of diagnostic and therapeutic options may improve with the wealth of a population. Such wealth may either increase or decrease with total population density and is likely to deteriorate with the density of infecteds. As before, this can influence all four epidemiological rates.

...

Density-dependent Epidemiological Rates 2

- Awareness about potential transmission routes is expected to grow under conditions of high incidence. Through this effect, transmission rates are predicted to decrease when the density of infecteds is growing.
- The density of infecteds changes the ambient density of infectious propagules to which susceptible hosts are exposed. Through the operation of the host's immune system, this propagule density may not translate linearly into the rate at which susceptible hosts acquire infections, and transmission rates then become dependent on the density of infecteds.
- Changes in total population density are known to reshape social contact networks and thereby to affect chances for disease transmission.

Analysis of Pathogen Evolution

Example 1: S-dependent Mortality

- **Rates**

  $d_S = d + S/K \qquad d_I - d_S = x \qquad \beta = x/(x + c) \qquad b_S = b_I = b \qquad \theta$

- **Motivation**

  Logistic density regulation through mortality.

- **Results**

  - With $R_0(x') = x'S_0/[(x' + d + \theta + S_0/K)(x' + c)]$, R_0 maximization cannot even be applied.
  - Evolutionary invasion analysis yields $x^* = [c + \sqrt{c^2K + cK(K-1)(d+\theta)}]/(K-1)$.
  - An alternative optimization principle exists $\Phi(x') = [x'(K-1) - c]/[K(x' + d + \theta)(x' + c)]$.

Example 2: S-dependent Transmission

- **Rates**

  $d_S = d$ $\quad$ $d_I - d_S = x$ $\quad$ $\beta = x/(x + c/S)$ $\quad$ $b_S = b_I = b$ $\quad$ θ

- **Motivation**

  Gain in transmission resulting from a rise in virulence increases with the density of susceptible hosts.

- **Results**
  - Again, R_0 maximization cannot even be applied.
  - Evolutionary invasion analysis yields $x^* = \sqrt{d+\theta}[\sqrt{d+\theta+4\sqrt{c}} - \sqrt{d+\theta}]/2$.
  - Also for this example, an alternative optimization principle exists $\Phi(x') = x'/[z + \sqrt{z(z+4c)}]$ with $z = x'(x' + d + \theta)$.

Example 3: I-dependent Transmission

- **Rates**

  $d_S = d$ $\quad$ $d_I - d_S = x$ $\quad$ $\beta = xI/(x + c)$ $\quad$ $b_S = b_I = b$ $\quad$ θ

- **Motivation**

  A host's immune system is more likely to succumb to a disease if the ambient density of pathogens is high.

- **Results**

  - With $R_0(x') = 0$, R_0 maximization erroneously suggests that virulence is selectively neutral.
  - Evolutionary invasion analysis yields $x^* = \sqrt{c(d+\theta)}$.
  - Also for this example, an alternative optimization principle exists $\Phi(x') = x'/[(x' + d + \theta)(x' + c)]$.

Example 4: I-dependent Recovery

- **Rates**

$$d_S = d \qquad d_I - d_S = x \qquad \beta = x/(x + c) \qquad b_S = b_I = b \qquad \theta = \theta_0/(1 + I/K)$$

- **Motivation**

  The care extended to individual infecteds declines with their overall density.

- **Results**
  - R_0 maximization completely misses out on predicting the dependence of the evolutionarily stable virulence on *K* and *b*.
  - Also quantitatively, R_0 maximization gives erroneous results, compared to the correct predictions of evolutionary invasion analysis.

Example 5: I-dependent Disease-induced Mortality

- **Rates**

$d_S = d$ $\quad$ $d_I - d_S = x(1 + I/K)$ $\quad$ $\beta = x/(x + c)$ $\quad$ $b_S = b_I = b$ $\quad$ θ

- **Motivation**

  Virulence increases with the density of infecteds, taking off from *x*. This could result, for instance, from the diminished care available to each infected host.

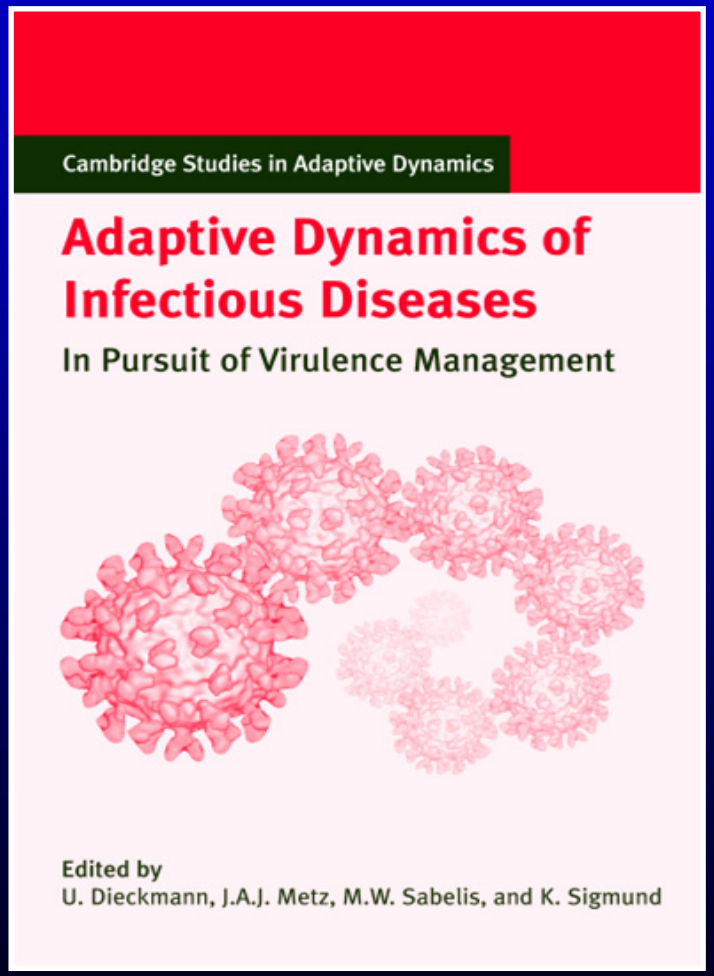
- **Results**
  - R_0 maximization completely misses out on predicting the dependence of the evolutionarily stable virulence on *K* and *b*.
  - Also quantitatively, R_0 maximization gives erroneous results, compared to the correct predictions of evolutionary invasion analysis. Predictions are easily off by a factor of 10.

Summary

Summary

- R_0 maximization must be applied with great care if erroneous conclusions are to be avoided.
- Failures of R_0 maximization can occur when demographic or epidemiological rates are density-dependent. Such failures may easily go unnoticed.
- These conclusions apply to pathogen evolution, as well as to pathogen-host coevolution (results not shown).
- Evolutionary invasion analysis of epidemiological models offers a reliable and widely applicable alternative to the traditional approach of R_0 maximization.

Further Reading



Adaptive Dynamics of Infectious Diseases: In Pursuit of Virulence Management

Edited by U Dieckmann, JAJ Metz, MW Sabelis & K Sigmund

Cambridge University Press, 2002