On the evolutionary dynamics of virulence

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Motivation

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Question.

Is observed virulence an intermediate step in evolution towards avirulence? Can evolution towards nonzero virulence be explained?

Epidemiological dynamics

SI model (S $\equiv$ susceptible, I $\equiv$ infected):

$$\frac{dS}{dt} = b - \beta SI - dS,$$
$$\frac{dI}{dt} = \beta SI - (d + \alpha)I.$$

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Steady states:

- Disease free equilibrium $\bar{I} = 0, \bar{S} = \frac{b}{d}$,
- Endemic equilibrium $\hat{S} = \frac{d+\alpha}{\beta}, \hat{I} = \frac{b}{d+\alpha} - \frac{d}{\beta}$ is biologically meaningful when the **basic reproduction ratio**

$$\mathcal{R}_0 = \frac{b\beta}{d(d+\alpha)} > 1.$$

When the endemic equilibrium exists it is globally asymptotically stable.

The basic notions of Adaptive Dynamics

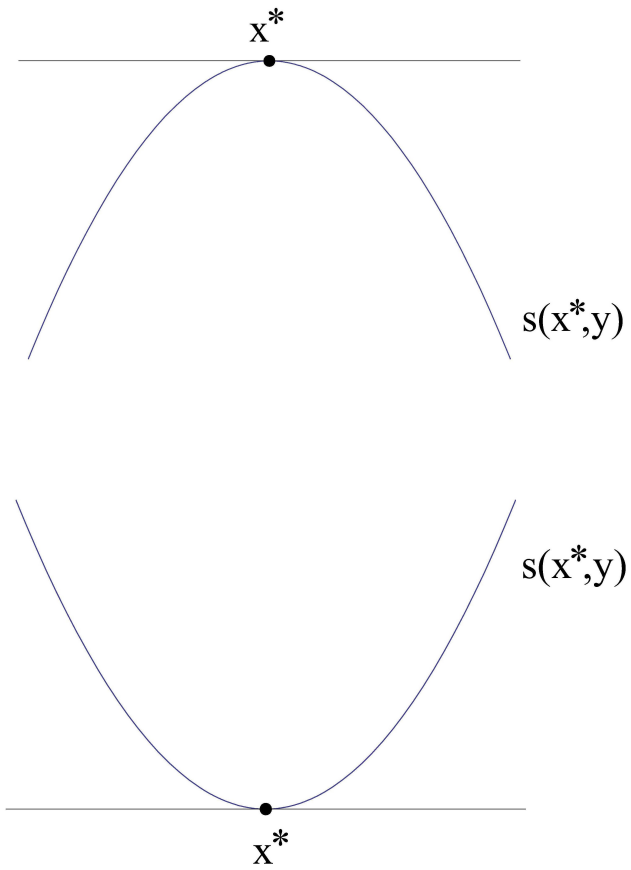
$s(x, y)$:=the growth rate of a mutant with trait y introduced into the environment set by x

Then:

- if $s(x, y) < 0$ the mutant will go extinct,
- if $s(x, y) > 0$ the mutant will grow.

Singular strategy:

$$\frac{\partial s}{\partial y}|_{y=x} = 0.$$



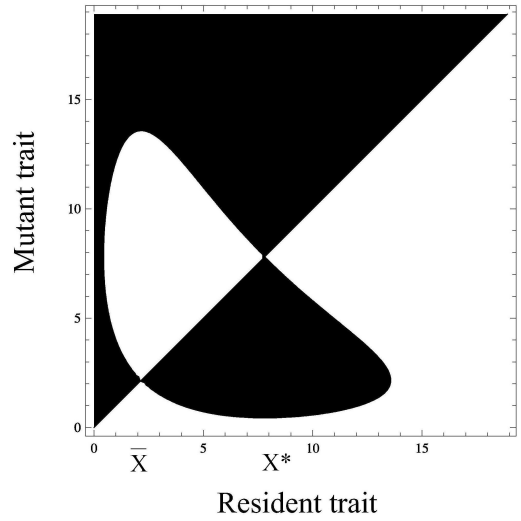
Top: uninvadable SS (ESS)
Bottom: invadable SS

Pairwise invasibility plot (PIP):

Plot the sign of $s(x, y)$ for all feasible pairs (x, y) of (resident, mutant) trait values.

Black: $s(x, y) < 0$

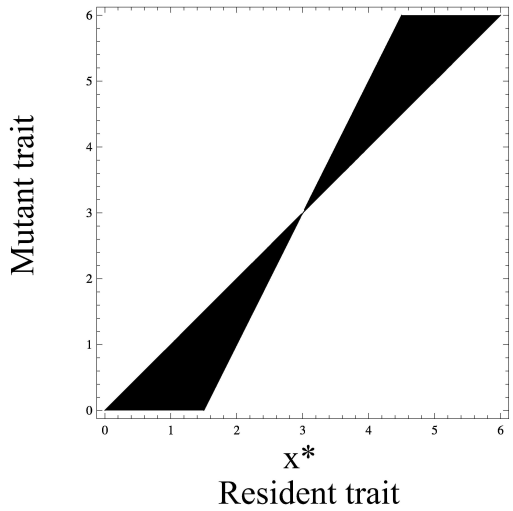
White: $s(x, y) > 0$



Examples:
Top:

- x^* is a CSS (convergent stable ESS),
- $\bar{x}$ is an invadable repellor

Bottom: x^* is a branching point.



Evolution of virulence: single infection model

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Invasion exponent

$$s(\alpha_r, \alpha_m) = \beta \hat{S}(\alpha_r) - (d + \alpha_m)$$

determines the fate of a mutant:

- if $s(\alpha_r, \alpha_m) < 0$, the mutant will go extinct,
- if $s(\alpha_r, \alpha_m) > 0$, the mutant will grow.

Since $\hat{S}(\alpha) = \frac{d+\alpha}{\beta}$ and $\mathcal{R}_0(\alpha) = \frac{b\beta}{d(d+\alpha)}$ we find

$$s(\alpha_r, \alpha_m) > 0 \iff \hat{S}(\alpha_r) > \hat{S}(\alpha_m) \iff \mathcal{R}_0(\alpha_r) < \mathcal{R}_0(\alpha_m).$$

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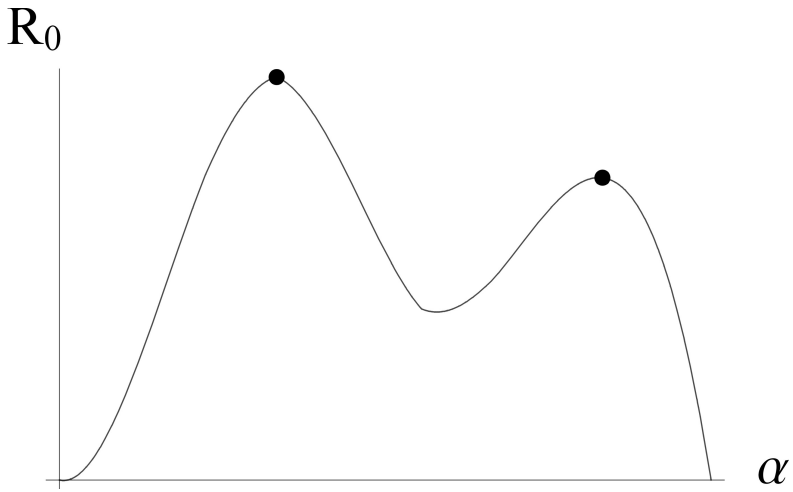
Strategies that (locally) maximize

$$\mathcal{R}_0(\alpha) = \frac{b\beta}{d(d+\alpha)}$$

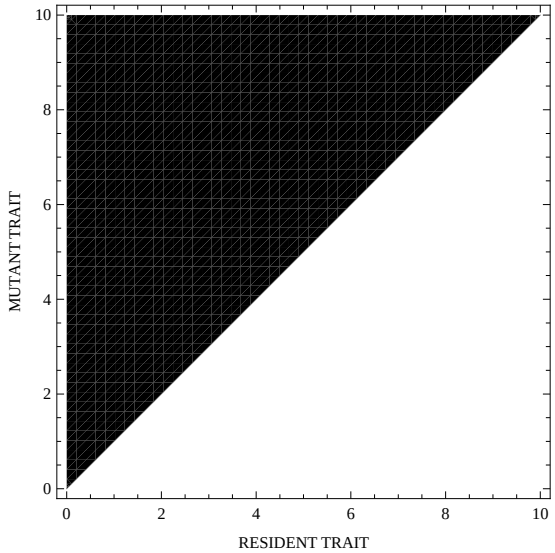
are convergent stable and uninvadable (CSS).



Top: If α and β independent

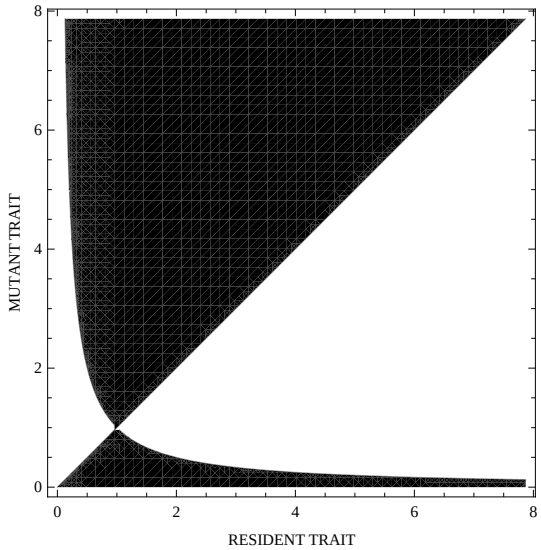
$$s(\alpha_r, \alpha_m) = \alpha_r - \alpha_m \Rightarrow$$

mutant successful if it decreases virulence
$\Rightarrow$ evolution towards avirulence
(conventional evolutionary wisdom)



Bottom: Trade-off hypothesis
pathogens aim to increase transmission to new hosts but cannot do so without harming the host, $\beta = \beta(\alpha)$.
$\Rightarrow$ CSS at a (local) maximum of

$$\mathcal{R}_0 = \frac{b\beta(\alpha)}{d(\alpha + d)}.$$



Multiple infections: coinfection vs. superinfection

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Superinfection: Assumes fast within-host dynamics. Immediately after the introduction of a mutant, the system is in an attractor. For example, if competitive exclusion applies and mutant is the better competitor, the mutant replaces the resident immediately.

Evolution of virulence: superinfection model

$$\frac{dS}{dt} = b - \beta(\alpha_r)SI_r - \beta(\alpha_m)SI_m - dS$$
$$\frac{dI_r}{dt} = \beta(\alpha_r)SI_r - (d + \alpha_r)I_r$$
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where

$$\Phi(\alpha_r,\alpha_m) = \beta(\alpha_m)\phi(\alpha_r,\alpha_m) - \beta(\alpha_r)\phi(\alpha_m,\alpha_r).$$

The **superinfection function** $\phi(\alpha_r,\alpha_m)$ describes the ability of strain α_m to 'take over' a host that is already infected with α_r.

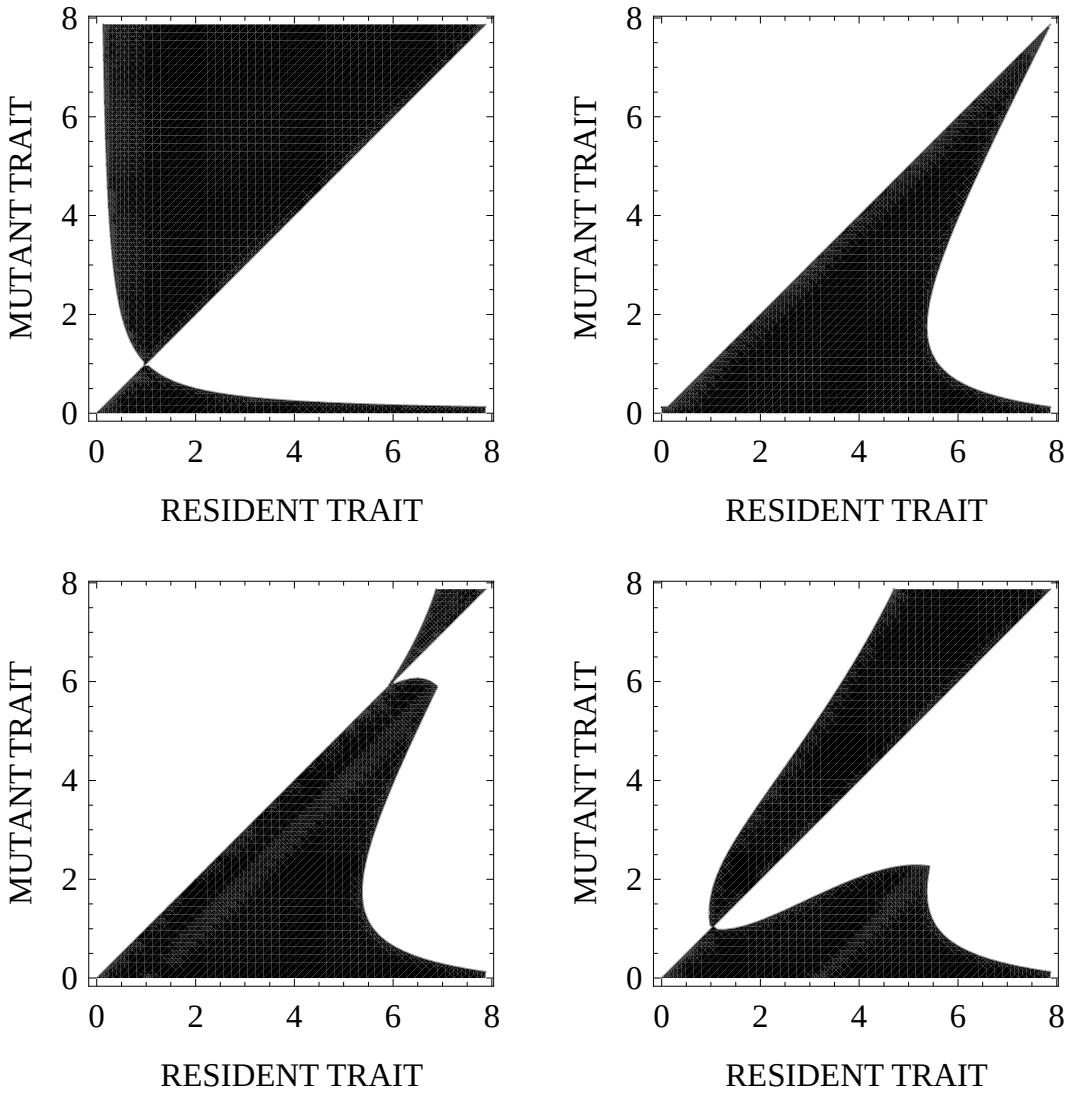
AD depends on the smoothness of $q \mapsto \phi(p, q)$ in $q = p$:

Top left:
Single infection model

Top right:
Discontinuous SF

Bottom left:
Continuous SF

Bottom right:
Differentiable SF



Observations:

- possible branching points, coexistence of strains
- superinfections push virulence beyond the value that maximizes $\mathcal{R}_0$.
  Indeed, invasion exponent is given by :

$$\begin{aligned} r(\alpha_r, \alpha_m) &= \beta(\alpha_m)\hat{S}(\alpha_r) - (d + \alpha_m) + \Phi(\alpha_r, \alpha_m)\hat{I}_r(\alpha_r) \\ &= s(\alpha_r, \alpha_m) + \Phi(\alpha_r, \alpha_m)\hat{I}_r(\alpha_r) \end{aligned}$$

singular strategies satisfy

$$\frac{\partial r}{\partial \alpha_m}|_{\alpha_m=\alpha_r=\alpha^*} = \frac{\partial s}{\partial \alpha_m}|_{\alpha_m=\alpha_r=\alpha^*} + \frac{\partial \Phi}{\partial \alpha_m}|_{\alpha_m=\alpha_r=\alpha^*}\hat{I}(\alpha^*)$$

and so

$$s'(\alpha^*) < 0.$$

But ...

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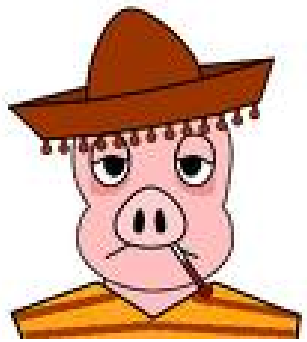
- Phenomenological superinfection functions, not clear how they relate to within-host competition of strains.

Suggestion: Instead of

$$\beta \longleftrightarrow \alpha$$

assume

$$\beta \longleftrightarrow \quad \longleftrightarrow \alpha$$



WH dynamics

Relating within- and between-host dynamics

Model of within-host dynamics:

$$\frac{dT}{dt} = \lambda - kVT - \delta T$$
$$\frac{dT^*}{dt} = kVT - (\mu(p) + \delta) T^*$$
$$\frac{dV}{dt} = pT^* - kVT - cV.$$

Here,

$T \equiv$ uninfected target cells
$T^* \equiv$ infected target cells
$V \equiv$ free pathogens

Evolutionary dynamics in a single infected host

WH model has two equilibria:

- infection free steady state $(\bar{T}, \bar{T}^*, \bar{V}) = (\frac{\lambda}{\delta}, 0, 0)$
- a unique nontrivial equilibrium $(\hat{T}, \hat{T}^*, \hat{V})$.

The nontrivial steady state is globally stable when

$$\mathcal{R}_0^w(p) = \frac{k\lambda}{k\lambda + \delta c} \frac{p}{\mu(p) + \delta} > 1.$$

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Adaptive dynamics of p:

$$p_m \text{ invades } p_r \iff \mathcal{R}_0^w(p_m) > \mathcal{R}_0^w(p_r) \iff \hat{T}(p_m) < \hat{T}(p_r).$$

$\Rightarrow$ evolution in a single infected host minimizes $\hat{T}$, maximizes $\mathcal{R}_0^w$.

Describing the dynamics at host population level

$$\frac{dS}{dt} = b - \beta(p)SI_p - \beta(q)SI_q - dS$$
$$\frac{dI_p}{dt} = \beta(p)SI_p - (d + \alpha(p))I_p + \Phi(q,p)I_pI_q$$
$$\frac{dI_q}{dt} = \beta(q)SI_q - (d + \alpha(q))I_q + \Phi(p,q)I_pI_q,$$

where

$$\Phi(p,q) = \beta(q)\phi(p,q) - \beta(p)\phi(q,p)$$

and

$\phi(p,q) =$ the probability with which the trait q, upon transmission to a host already infected by trait p, eliminates p.

Invasion exponent

$$r_p(q) = \beta(q)\hat{S}(p) - (d + \alpha(q)) + \Phi(p, q)\hat{I}(p).$$

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- ϕ differentiable: singular strategies are the same as in SIM, attracting (repelling) SS in SIM remain attractors (repellors), invadability may change.

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- ϕ continuous (but not differentiable): SS inbetween SIM and WHM.

On the mechanistic derivation of superinfection functions

Explicit submodel of WH dynamics allows us to calculate invasion probability of a mutant strain:

- Suppose trait q introduced into environment $\hat{T}(p)$. Probability that strain q produces n new pathogens is

$$\pi_n = \frac{k\hat{T}(p)}{k\hat{T}(p)+c} \int_0^\infty (\mu(q)+\delta) e^{-(\mu(q)+\delta)t} e^{-qt} \frac{q^n t^n}{n!} dt.$$

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- Probability of clan extinction is given as the smallest root of the generating function

$$G(z) = \frac{c}{k\hat{T}(p)+c} + \sum_{n=0}^{\infty} \pi_n z^n$$

- Probabilty of clan survival, following an introduction of a single mutant

$$\phi_1(p,q) = \begin{cases} \dfrac{k\hat{T}(p)}{c+k\hat{T}(p)} - \dfrac{k\hat{T}(q)}{c+k\hat{T}(q)}, & \hat{T}(q) < \hat{T}(p) \\ 0, & \text{otherwise} \end{cases}$$

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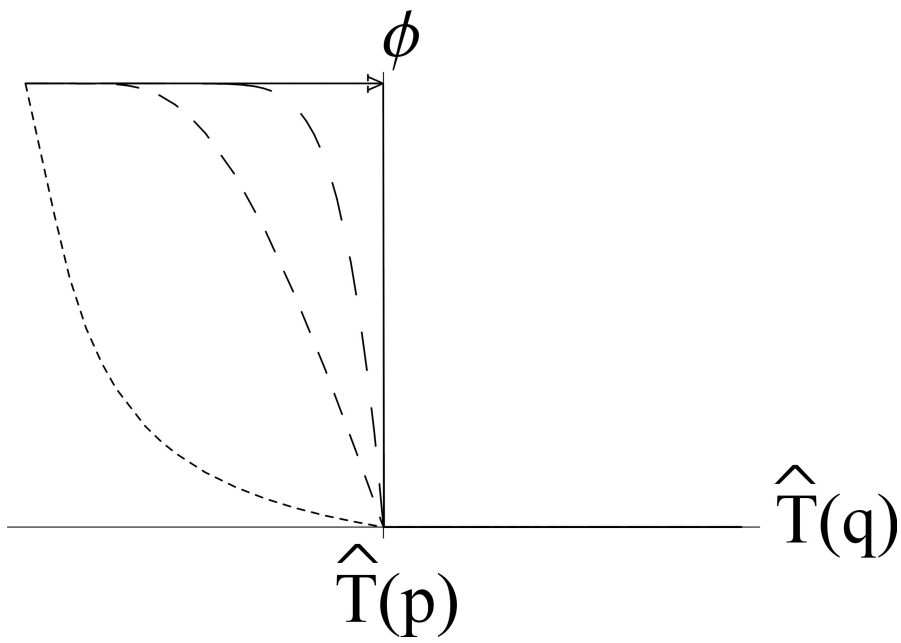
- When n particles are introduced, the probability of survival equals

$$\phi_n(p,q) = \begin{cases} 1 - \Big(1 - \phi_1(p,q)\Big)^n, & \hat{T}(q) < \hat{T}(p) \\ 0, & \text{otherwise} \end{cases}$$

Mechanistically derived SFs have the following properties:

- $q \mapsto \phi_n(p, q)$ continuous in $q = p$,
- $q \mapsto \phi_n(p, q)$ differentiable in $q = p$ from the left, $\phi'_{n+} = n$,
- $\{q \mapsto \phi_n(p, q)\}_n$ increasing sequence of functions,
-



$$\lim_{n\to\infty} \phi_n(p, q) = \begin{cases} 1, & \hat{T}(q) < \hat{T}(p) \\ 0, & \text{otherwise.} \end{cases}$$

Concluding remarks

- Mathematical models give insight into pathogen evolution.
- Simple single infection model $\Rightarrow$ optimization principle. This is also due to simple demography of the underlying SI model. If density dependence in birth & death rates included, evolution no longer acts as optimization.
- Superinfection model: no optimization, coexistence of two or more strategies found. Critical function analysis can be used to study in which parameter regions branching possible.
- Nested models:
  1. more easily tested relationships between transmissibility, virulence and WH dynamics,
  2. mechanistic derivation of mutant invasion probabilities (superinfection functions).

Thank you!