The Population Genetics of Pathogen Virulence

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Ecology and evolutionary biology, deterministic and stochastic models
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Outline

VIRULENCE (READ, 1994)

- The term virulence is used to describe two closely intertwined aspects of a pathogen's disease-producing capacity:
  - infectivity: the ability to colonise and to invade a host, and
  - the severity of the disease produced
- In most mathematical models (including those I'll present)

  virulence = increase in host mortality rate.
- Why is there variation in the virulence of infectious diseases?

  common cold $\longleftrightarrow$ ebola
- Natural selection acts on virulence:
  - Virulence has major effects on host & pathogen fitness
  - Standing genetic variation (polymorphisms, phage, plasmids, transposons)
  - Artificial selection can maintain or reduce virulence
- Examples of evolution towards reduced virulence, *e.g.*, myxomatosis, SIV *vs.*, HIV, *etc.*

WHY IS THERE VARIATION IN THE VIRULENCE OF INFECTIOUS DISEASES?

- For along time, group selection was used to argue evolution to avirulence:

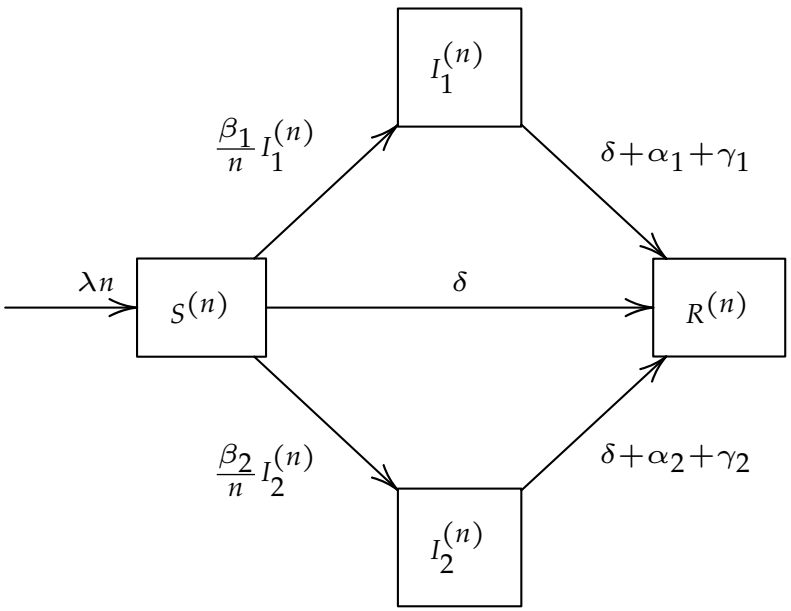
  > *"[without] the early appearance and dominance of strains of virus which caused a lower mortality [...] rabbits would have been eradicated or greatly reduced in numbers, and the rabbit itself would have disappeared from such localities"*
  >
  > *Fenner & Ratcliffe. Myxomatosis. Cambridge University Press, 1965.*

- But deterministic models quickly dismissed this thinking:

  > *"The 'conventional wisdom' that successful parasites have to become benign is not based on exact evolutionary thinking. Rather than minimizing virulence, selection will work to increase a parasite's reproductive rate."*
  >
  > *Nowak & May (1994) Proc. R. Soc. Lond. B 255 (4): 81–89*

- But this doesn't explain the observed evolution to reduced virulence.
- Can including demographic stochasticity tell us anything?

A HOST-PATHOGEN MODEL: TWO STRAIN SIR MODEL WITH DEMOGRAPHY



λn	immigration rate for susceptibles
δ	base mortality rate
β_i	contact rate for strain i
α_i	excess mortality for strain i
γ_i	recovery rate for strain i

- Population is grouped into *susceptibles*, $S^{(n)}(t)$, *infectives*, $I_i^{(n)}(t)$, and *removed* individuals, $R^{(n)}(t)$.
- Assume cross-immunity between strains, no co-infection.
- Model is completely described by $(S^{(n)}(t), I_1^{(n)}(t), I_2^{(n)}(t))$ – can ignore removed individuals.

CONTINUOUS TIME MARKOV CHAIN FORMULATION

- This is a continuous-time Markov chain taking values in $\mathbb{N}_0^3$ with jump rates

$$
\begin{aligned}
q_{(s,i_1,i_2),(s+1,i_1,i_2)} &= \lambda n \\
q_{(s,i_1,i_2),(s-1,i_1,i_2)} &= \delta s \\
q_{(s,i_1,i_2),(s-1,i_1+1,i_2)} &= \frac{\beta_1 s i_1}{n} \\
q_{(s,i_1,i_2),(s-1,i_1 1,i_2+1)} &= \frac{\beta_2 s i_2}{n} \\
q_{(s,i_1,i_2),(s,i_1-1,i_2)} &= (\delta + \alpha_1 + \gamma_1) i_1 \\
q_{(s,i_1,i_2),(s,i_1 1,i_2-1)} &= (\delta + \alpha_2 + \gamma_2) i_2
\end{aligned}
$$

- The parameter n is a "system-size", proportional to the *average* host population size. The actual number of individuals fluctuates stochastically.
- Crucially, it allows us to consider our host-pathogen model as a *density dependent population process*.

LAW OF LARGE NUMBERS (KURTZ 1978)

Let

$$\bar{S}^{(n)}(t) = \frac{1}{n}S(t),\ \bar{I}_1^{(n)}(t) = \frac{1}{n}I_1(t),\ \text{and}\ \bar{I}_2^{(n)}(t) = \frac{1}{n}I_2(t).$$

Then, for any fixed $T > 0$,

$$\lim_{n\to\infty} \sup_{t\le T} \left| \left(\bar{S}^{(n)}(t), \bar{I}_1^{(n)}(t), \bar{I}_2^{(n)}(t)\right) - \left(\bar{S}(t), \bar{I}_1(t), \bar{I}_2(t)\right) \right| = 0 \quad \text{a.s.}$$

where $\bar{S}(t)$, $\bar{I}_1(t)$ and $\bar{I}_2(t)$ satisfy

$$\begin{aligned}
\frac{d}{dt}\bar{S}(t) &= \lambda - \left(\beta_1\bar{I}_1(t) + \beta_2\bar{I}_2(t) + \delta\right)\bar{S}(t) \\
\frac{d}{dt}\bar{I}_1(t) &= \left(\beta_1\bar{S}(t) - (\delta + \alpha_1 + \gamma_1)\right)\bar{I}_1(t) \\
\frac{d}{dt}\bar{I}_2(t) &= \left(\beta_2\bar{S}(t) - (\delta + \alpha_2 + \gamma_2)\right)\bar{I}_2(t)
\end{aligned}$$

with initial condition

$$\left(\bar{S}(0), \bar{I}_1(0), \bar{I}_2(0)\right) = \lim_{n\to\infty}\left(\bar{S}^{(n)}(0), \bar{I}_1^{(n)}(0), \bar{I}_2^{(n)}(0)\right).$$

- One can improve on Kurtz's result: for all $r < s < 1$, there exists $C_{r,s,\mathbf{x}}$ such that

$$\mathbb{P}\left\{\sup_{t<C_{r,s,\mathbf{x}}\ln n}\left|\left(\bar{S}^{(n)}(t),\bar{I}_1^{(n)}(t),\bar{I}_2^{(n)}(t)\right)-\left(\bar{S}(t),\bar{I}_1(t),\bar{I}_2(t)\right)\right|>N^{-r}\right\}<N^{-s}.$$

- The Law of Large Numbers tells us that we can neglect stochasticity
  - when the number of individuals of the pathogen or host are already proportional to n, and
  - over sufficiently slow time scales
- When either of these conditions is violated, stochasticity can be important.
- Nonetheless, the deterministic approximation will guide our investigation of the stochastic model.

THE BASIC REPRODUCTION NUMBER & EQUILIBRIA

The i^{th} *basic reproduction number*,

$$R_{(0,i)} = \frac{\beta_i}{\delta + \alpha_i + \gamma_i}$$

is the total number of new infections caused by a single infective with strain i entering a disease free population. It is a bifurcation parameter for the Law of Large Numbers, which has equilibria at the points $(S^\star, I_1^\star, I_2^\star)$,

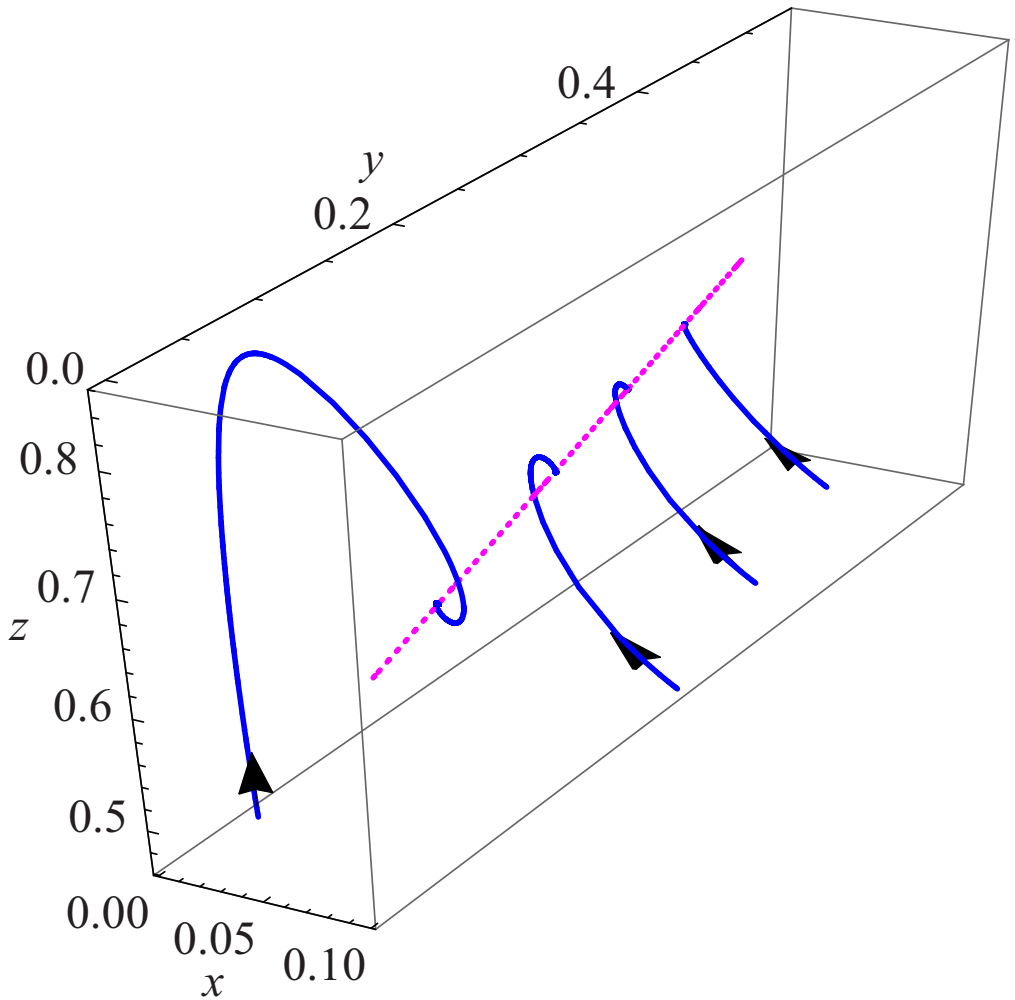
$$\left(\frac{\lambda}{\delta}, 0, 0\right), \left(\frac{1}{R_{(0,1)}}, \frac{1}{\beta_1}\left(\frac{\lambda}{R_{(0,1)}} - \delta\right), 0\right), \text{ and } \left(\frac{1}{R_{(0,2)}}, 0, \frac{1}{\beta_2}\left(\frac{\lambda}{R_{(0,2)}} - \delta\right)\right).$$

- The first is stable if $R_{(0,1)}, R_{(0,2)} < \frac{\delta}{\lambda}$.
- The second is stable if $\max\{\frac{\delta}{\lambda}, R_{(0,2)}\} < R_{(0,1)}$.
- If $R_{(0,1)} = R_{(0,2)} \left(> \frac{\delta}{\lambda}\right)$, then coexistence at any point on the *slow manifold* of points $(S^\star, I_1^\star, I_2^\star)$ such that

$$S^\star = \frac{1}{R_{(0,1)}} = \frac{1}{R_{(0,2)}}, \quad \beta_1 I_1^\star + \beta_2 I_2^\star = \frac{\lambda}{S^\star} - \delta.$$

- Today I'll focus on the latter...

CRITICAL MANIFOLD



Kogan *et al.* (2014)

WEAK SELECTION

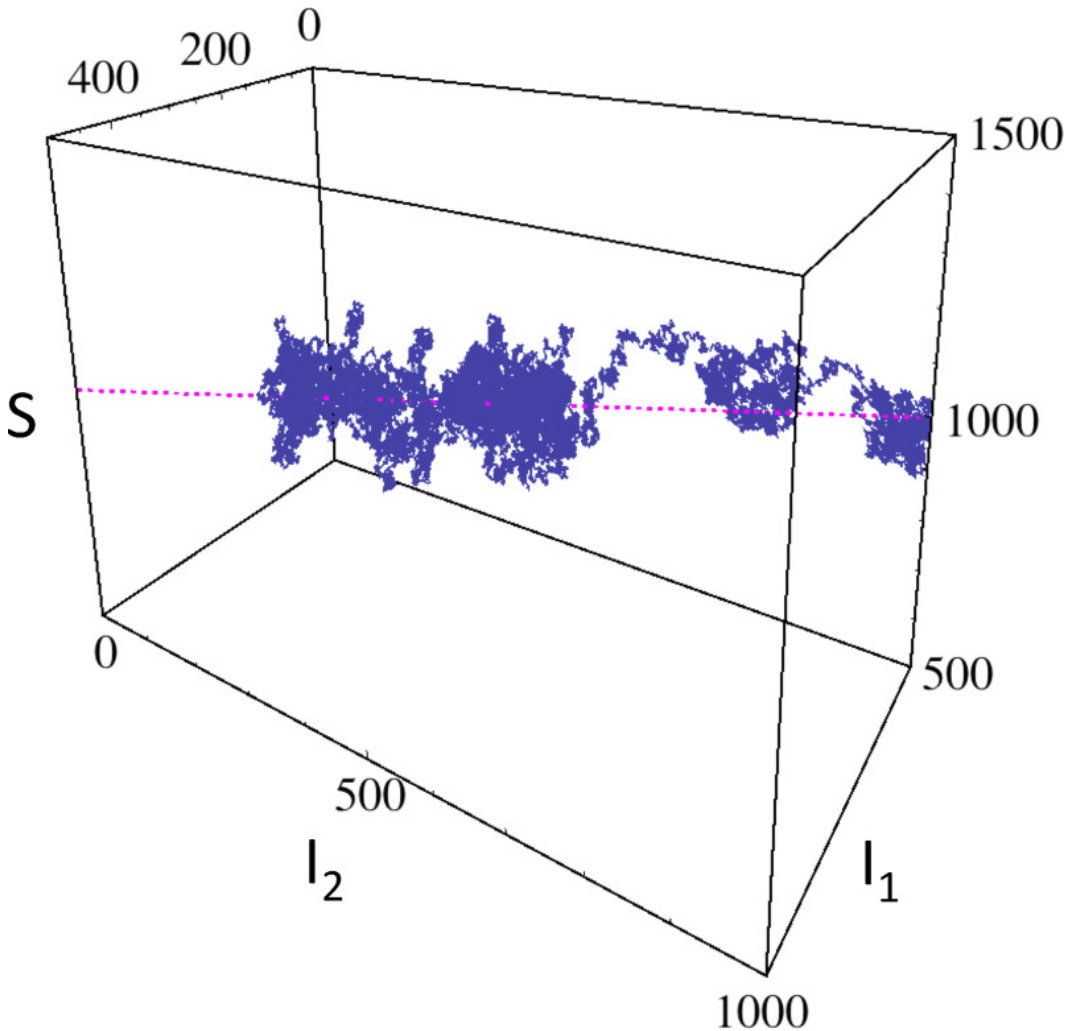
- To understand what happens when $R_{(0,1)} \approx R_{(0,2)}$, we'll borrow an idea from population genetics: *weak selection*.
- Consider the case when the rates depend on n, to order $\mathcal{O}\left(\frac{1}{n}\right)$:

$$\beta_i^{(n)} = \beta_i + \mathcal{O}\left(\tfrac{1}{n}\right),\ \gamma_i^{(n)} = \gamma_i + \mathcal{O}\left(\tfrac{1}{n}\right),\ \delta^{(n)} = \delta + \mathcal{O}\left(\tfrac{1}{n}\right),\ \text{and } \alpha_i^{(n)} = \alpha_i + \mathcal{O}\left(\tfrac{1}{n}\right).$$

- We then have

$$R_{(0,1)}^{(n)} = \frac{\beta_i^{(n)}}{\delta^{(n)} + \alpha_i^{(n)} + \gamma_i^{(n)}} = R_0^\star \left(1 + \frac{r_i}{n}\right) + o\left(\tfrac{1}{n}\right)$$

STOCHASTIC SLOW MANIFOLD



Kogan *et al.* (2014)

DIFFUSION APPROXIMATION / DIMENSION REDUCTION

- Consider the process in "generation time", *i.e.*, time rescaled by n. Then,

$$\left(S^{(n)}(nt), I_1^{(n)}(nt), I_2^{(n)}(nt)\right) \overset{w}{\Longrightarrow} \left(S^\star, \hat{I}_1(t), \hat{I}_2(t)\right),$$

  where $S^\star = \frac{1}{R_0^\star}$ is the equilibrium number of susceptibles and $(\hat{I}_1(t), \hat{I}_2(t))$ is a diffusion trapped on the slow manifold *i.e.*,

$$\beta_1 \hat{I}_1(t) + \beta_2 \hat{I}_2(t) = \frac{\lambda}{S^\star} - \delta.$$

  that can be explicitly calculated (Katzenberger, 1992, Parsons & Rogers, 2017).

- This is a one-dimensional problem that is completely characterised by the frequency of strain 2,

$$P(t) = \frac{\hat{I}_2(t)}{\hat{I}_1(t) + \hat{I}_2(t)}.$$

GENERATOR

$P(t)$ has generator

$$\mathbb{A}f(p) = b(p)f'(p) - \frac{1}{2}a(p)f''(p),$$

where

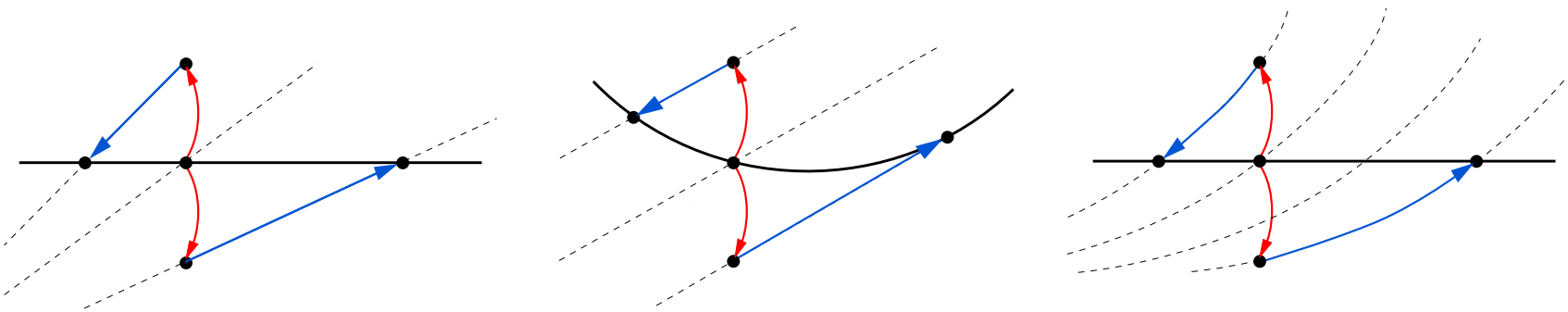
$$b(p) = \frac{1}{R_0^\star}\frac{\beta_1\beta_2}{i_e(p)}\left((r_1 - r_2) - (\beta_1 - \beta_2)\frac{\beta_1 p + \beta_2(1-p)}{\left(\beta_1^2 p + \beta_2^2(1-p)\right)^2}\right)p(1-p)$$
$$\times\left((\beta_1(1-p) + \beta_2 p) - (\beta_1 p + \beta_2(1-p)) + \frac{\beta_1\beta_2\left(\beta_1 p + \beta_2(1-p)\right)}{\beta_1^2 p + \beta_2^2(1-p)}\right),$$

$$a(p) = 2\frac{1}{R_0^\star}\frac{\beta_1\beta_2}{i_e(p)}\frac{\left(\beta_1 p + \beta_2(1-p)\right)^3}{\left(\beta_1^2 p + \beta_2^2(1-p)\right)^2}p(1-p),$$

and $i_e(p) = \frac{\lambda R_0^\star - \delta}{\beta_1 p + \beta_2(1-p)} \sim \frac{\text{total number of infectives}}{n}$.

UNDERSTANDING INDUCED DRIFT

We got an odd new drift term, proportional to $\beta_1 - \beta_2$. Where does it come from?



Parsons & Rogers (2017)

The geometry of the flow lines and of the manifold cause the restoring action to transform variability transverse the manifold into drift along the manifold.

FIXATION PROBABILITY

As this is one dimensional, we can explicitly solve the Dirichlet problem for the corresponding backwards equation to obtain the fixation probability of strain 2:

$$h(p) := \mathbb{P}\left\{\lim_{t\to\infty} P(t) = 1 \middle| P(0) = p\right\} = \frac{\psi(p) - \psi(0)}{\psi(1) - \psi(0)}$$

where

$$\psi(p) := \int e^{-2\int^p \frac{b(q)}{a(q)}\,dq}\,dp$$

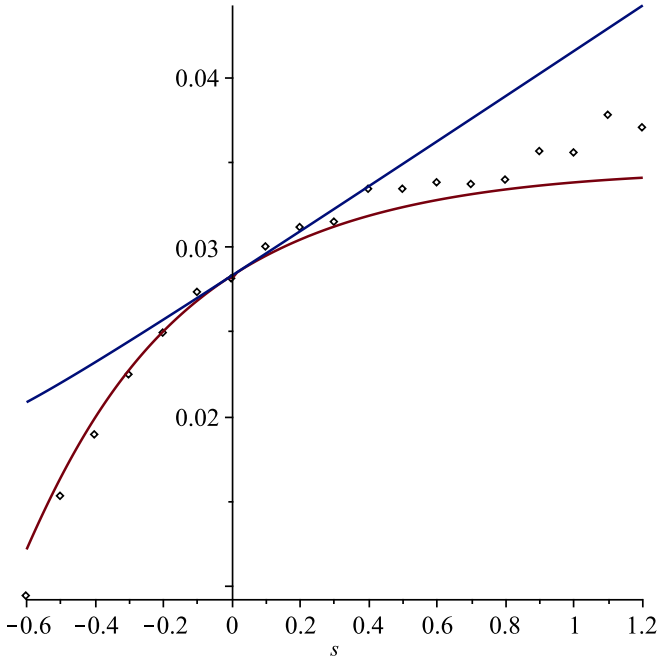
is the scale function for $P(t)$. For the SIR model, if $r_1 = r_2$, then

$$h(p) = p + \frac{\beta_2^2 p e^{-\frac{\beta_2+\beta_1}{\beta_2}} + \beta_1^2(1-p)e^{-\frac{\beta_2+\beta_1}{\beta_1}}}{\beta_2^2 e^{-\frac{\beta_2+\beta_1}{\beta_2}} + \beta_1^2 e^{-\frac{\beta_2+\beta_1}{\beta_1}}} + \frac{\left(\beta_2^3 p + \beta_1^3(1-p)\right) e^{-\frac{\beta_2+\beta_1}{\beta_2 p+\beta_1(1-p)}}}{(\beta_2 p + \beta_1(1-p))\left(\beta_2^2 e^{-\frac{\beta_2+\beta_1}{\beta_2}} + \beta_1^2 e^{-\frac{\beta_2+\beta_1}{\beta_1}}\right)}.$$

INTERPRETING THE FIXATION PROBABILITY

- This isn't terribly illuminating, but inspection shows it only depends on the ratio $\frac{\beta_1}{\beta_2}$; set
$$\beta_1 = \beta_2(1+s).$$
- Because ratios $R_{(0,1)} = R_{(0,2)}$ are fixed, this means (wild-type) strain 1 has higher contact rate *and* higher virulence.
- Taylor expansion gives fixation probability for (mutant) strain 2 is
$$p + \frac{s}{2}p(1-p) + \mathcal{O}(s^2).$$
- If a mutation conveys no benefit, it's fixation probability is just its initial frequency p.
- Get advantage to type with lower contact rate/virulence (at least for small values of s).

FIXATION PROBABILITIES FOR A SINGLE INVADER, $\rho = 0$, s VARYING



Simulations, $h(p)$, $p + \frac{s}{2}p(1-p)$

Parameters: $n = 100$, $\beta_1 = \beta_2(1+s)$, $\alpha_1 = \frac{\delta+\alpha_2+\gamma}{1+s} - \delta - \gamma$, $\lambda = 2$, $\delta = 1$, $\beta_1 = 20$, and $\alpha_2 = 3$, $R^{(n)}_{(0,2)} = R^{(n)}_{(0,1)} = R^{\star}_0 = 4$.

FIXATION PROBABILITY WITH SELECTION

- If $r_1 \neq r_2$, we can no longer get a completely closed form for the scale function, but we can still express it as an integral:

$$\psi(p) = \int \frac{\beta_1^2 p + \beta_2^2(1-p)}{(\beta_1 p + \beta_2(1-p))^3} \times e^{-\frac{\beta_1+\beta_2}{\beta_1 p+\beta_2(1-p)}p - i_e(p)\frac{(r_1-r_2)}{(\beta_2-\beta_1)}\left(\beta_1+\beta_2-\frac{1}{2}\frac{\beta_1\beta_2}{\beta_1 p+\beta_2(1-p)}\right)} dp$$

- If we set $\rho := r_1 - r_2$ and $\beta_1 = \beta_2(1+s)$ as before, then Taylor expansion gives

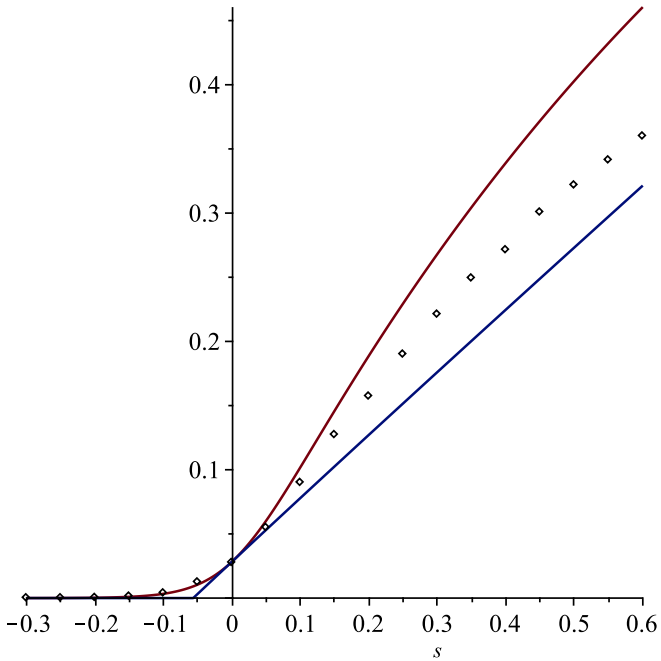
$$h(p) = \frac{\psi(p) - \psi(0)}{\psi(1) - \psi(0)} = p + \frac{1}{2}\left(s - i_e(p)\rho\right) p(1-p) + \mathcal{O}\left(s^2, \rho^2\right).$$

- In particular, for a single invader, expressed in the original variables, this is

$$\frac{1}{I_e(0)} + \frac{1}{2}\left(1 - \frac{R^{(n)}_{(0,1)}}{R^{(n)}_{(0,2)}} + \frac{1}{I_e(0)}\left(\frac{\beta_1^{(n)}}{\beta_2^{(n)}} - 1\right)\right) + o\left(\frac{1}{n}\right),$$

where $I_e(p) = n i_e(p) \sim$ total number of infectives.

FIXATION PROBABILITIES FOR A SINGLE INVADER, ρ, s VARYING



Simulations, $h(p)$, $p + \frac{1}{2}\left(s - i_e(p)\rho\right)p(1-p)$

Parameters: $n = 100$, $\beta_1 = \beta_2(1+s)$, $R^{(n)}_{(0,1)} = R^{(n)}_{(0,2)}(1+s)$. $R^{(n)}_{(0,2)} = R^{\star}_0 = 4$, $\lambda = 2$, $\delta = 1$, $\beta_1 = 20$, and $\alpha_1 = 3$.

TRANSMISSION/VIRULENCE TRADEOFFS

Consider the long term evolution of the virulence in the framework of *adaptive dynamics*.

- Assume that the transmissibility of the strain depends on the virulence according to some function $\beta(\alpha)$. Then the reproductive number is a function of the virulence:

$$R_0(\alpha) = \frac{\beta(\alpha)}{\delta + \alpha + \gamma}$$

  Assume that R_0 is maximized at α_0.
- Under these assumptions, there are approximately

$$I^\star(\alpha) = n\frac{\lambda R_0(\alpha) - \delta}{\beta(\alpha)}$$

  individuals infected with the resident strain at the endemic equilibrium.
- $I^\star(\alpha)$ is non-zero on a range $(\alpha_{min}, \alpha_{max})$; outside of this range, the pathogen goes extinct.

MUTATIONAL DYNAMICS

Further, assume that

- the mutation rate $\eta \ll 1$ is sufficiently low that fixation occurs before a second novel mutation can arise, and that
- mutational effects are small and unbiased. A mutation in a strain with virulence α gives rise to a new strain with virulence α', with probability $K(\alpha, \alpha')$:

$$\int_{\alpha_{min}}^{\alpha_{max}} (\alpha - \alpha')K(\alpha, \alpha')\, d\alpha' = 0$$
$$\int_{\alpha_{min}}^{\alpha_{max}} (\alpha - \alpha')^2 K(\alpha, \alpha')\, d\alpha' = \varepsilon\nu.$$

Then, from before, an invader of virulence α' invading a resident population of virulence α has fixation probability (to lowest order in n)

$$f(\alpha, \alpha') = \frac{1}{I^\star(\alpha)} + \frac{1}{2}\left(1 - \frac{\beta(\alpha)(\delta + \alpha' + \gamma)}{\beta(\alpha')(\delta + \alpha + \gamma)} + \frac{1}{I^\star(\alpha)}\frac{\beta(\alpha) - \beta(\alpha')}{\beta(\alpha')}\right).$$

TRAIT SUBSTITUTION SEQUENCE & CANONICAL DIFFUSION

The virulence of the population at time t, $A_\varepsilon(t)$ is then a jump process with generator

$$\mathbb{B}_\varepsilon \phi(\alpha) = \int_{\alpha_{min}}^{\alpha_{max}} \eta K(\alpha', \alpha) f(\alpha', \alpha) \left(\phi(\alpha') - \phi(\alpha)\right) \, d\alpha'$$

The rescaled process $A_\varepsilon\left(\frac{t}{\varepsilon}\right)$ then converges to a diffusion process with generator

$$\mathbb{B}\phi(\alpha) = \eta\nu \left(\frac{R_0'(\alpha)}{R_0(\alpha)} - \frac{1}{I^\star(\alpha)} \frac{\beta'(\alpha)}{\beta(\alpha)} \right) \phi'(\alpha) + \frac{1}{2} \eta\nu \phi''(\alpha)$$

to lowest order in n.

QUASI-STATIONARY DISTRIBUTION

We can use this to analytically compute quasi-stationary distribution of the virulence conditioned on non-extinction. For large values of n, Laplace's method gives a simple approximation:

$$\frac{\beta(\alpha_0)}{\beta(\alpha)} N(\alpha_0, \sigma^2),$$

where $N(\alpha_0, \sigma^2)$ is the Gaussian distribution with mean α_0 and variance

$$\sigma^2 = \frac{1}{I_{eq}(\alpha_0) \frac{\left|R_0''(\alpha_0)\right|}{R_0(\alpha_0)}}.$$

The pre-factor $\frac{\beta(\alpha_0)}{\beta(\alpha)}$ biases the probability distribution towards reduced virulence.

SUMMARY STATISTICS

The full distribution has mode and mean

$$\alpha_{\text{mean}} = \alpha_0 - \sigma^2 \left(\frac{1}{\delta + \alpha_0 + \gamma} + \frac{I'_{\text{eq}}(\alpha_0)}{I_{\text{eq}}(\alpha_0)} - \frac{R_0'''(\alpha_0)}{|R_0''(\alpha_0)|} \right) + o\left(\tfrac{1}{n}\right)$$

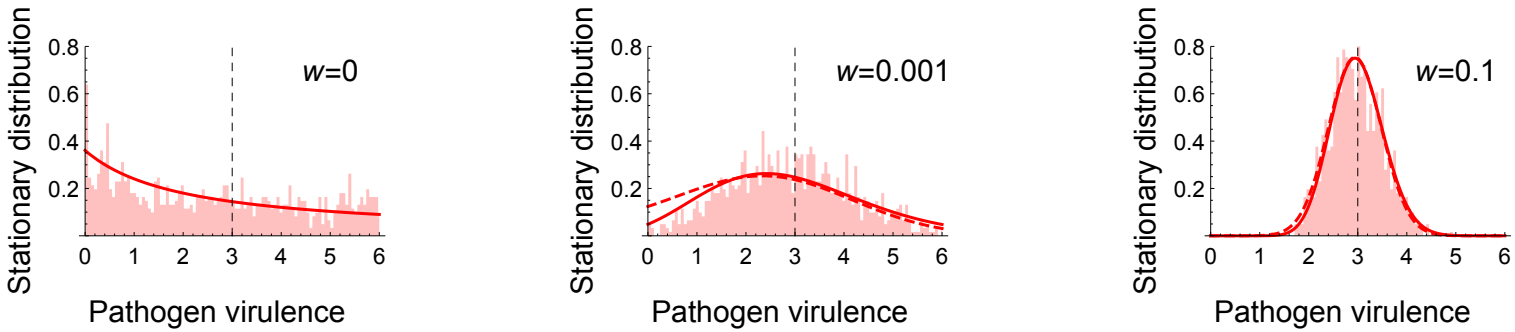
and

$$\alpha_{\text{mode}} = \alpha_0 - \frac{\sigma^2}{\delta + \alpha_0 + \gamma} + o\left(\tfrac{1}{n}\right),$$

which reflect a bias towards reduced virulence in finite populations, but one that is confounded by the effects of asymmetry in the fitness landcape.

THE DISTRIBUTION OF VIRULENCE IN DIFFERENT FITNESS LANSCAPES

Take $\beta(\alpha) = (\delta + \alpha + \gamma)(R_{max} - w(\alpha - \alpha_0)^2)$; w determines the "flatness" of the fitness landscape.



Simulations (histogram) Stationary Distribution (solid) Laplace Approximation (dashed)

Stationary distribution for symmetric fitness landscapes with increasing strength of selection around the optimum ($w = 0$, 0.001 and 0.1). The dashed vertical line indicates the position of α_0.

Parameters: $n = 200$, $R_{0,max} = 4$, $d = 1$, $\alpha_0 = 3$, $\gamma = 1$, $\lambda = 2$, $\mu = 0.01$.

SUMMARY

Population genetic approaches can give insight into pathogen evolution:

- Not all R_0 are created equal!
- When two strains with approximately the same R_0 compete, the one with lower virulence has a competitive advantage.
- In the long term, this can lead to distributions of virulence through time that are biased away from the maximal R_0 towards reduced virulence.
- This effect can become significant as the adaptive landscape becomes flatter.
- In finite populations, we would expect to see considerable variation in virulence on evolutionary timescales.
- Perhaps the 'conventional wisdom' isn't completely lacking...

THANK YOU!

- For your attention!
- For the opportunity to speak today!
- And your questions…