Eco-evolutionary dynamics of pathogen virulence

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Outline

1. Overview
   - The evolution of host-pathogen theory
   - Toy models
2. Transient virulence and emerging diseases
   - Overview
   - Toy model
   - Myxomatosis data
3. Transient virulence of HIV
   - abc
4. Conclusions

Acknowledgements

People Arjun Nanda and Dharmini Shah; Christophe Fraser; Marm Kilpatrick; Anson Wong

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Host-pathogen evolutionary biology

Why is it interesting?

- Intellectual merit
  - Coevolutionary loops
  - Cryptic effects
  - Eco-evolutionary dynamics (Luo and Koelle, 2013)
  - Cool stories
  - Lots of data (sometimes)
- Broader applications
  - Medical
  - Conservation and management
  - Outreach

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Virulence: definitions

- General public: badness
- Plant biologists: infectivity
- Evolutionists: loss of host fitness
- Theoreticians: *rate* of host mortality
  (mortality rate vs. case mortality vs. clearance)

Evolution of virulence evolution theory

Classical dogma monotonic trend toward avirulence

Ewald era virulence as an evolved (adaptive) trait. Tradeoff theory, modes of transmission.

post-Ewald more formal tradeoff models, mostly based on $\mathcal{R}_0$ optimization. Adaptive dynamics

Now
- tradeoff backlash
- within-host dynamics/multi-level models
- eco-evolutionary dynamics
- host effects: resistance vs tolerance vs virulence

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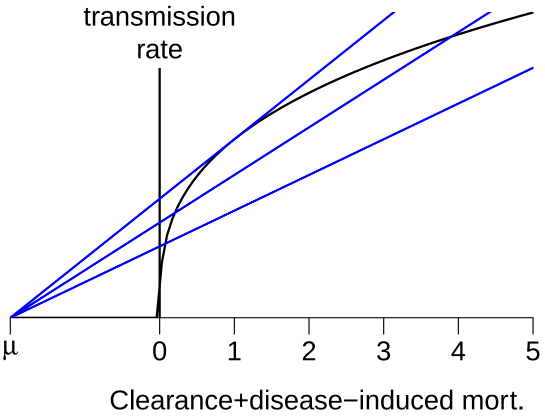
Basic tradeoff theory: assumptions

- Homogeneous, non-evolving hosts
- No superinfection/coinfection
- Horizontal, direct transmission
- Tradeoff between *rate* of transmission and length of infectious period
- Infectious period $\propto$ 1/clearance (= recovery+disease-induced mortality+natural mortality)

Tradeoffs, $\mathcal{R}_0$, and r



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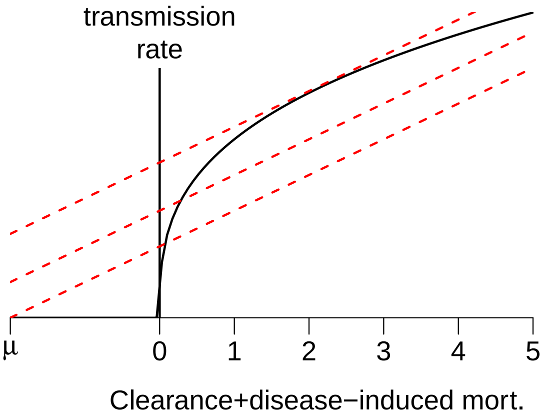

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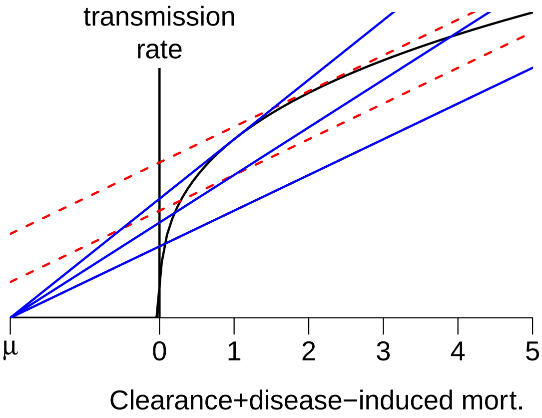

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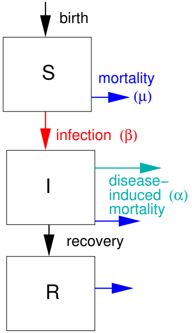
Epidemiological model

- SIR model
- Constant population size (birth=death)
- Ignore recovery
- Rescale: $\mu = 1$, $N = 1$ (time units of host lifespan)



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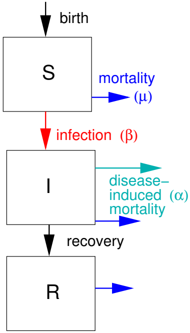

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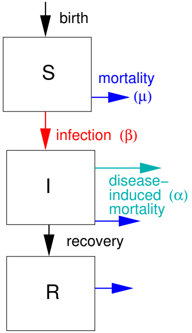

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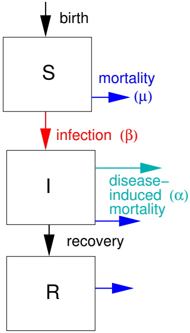

The model (2): evolutionary dynamics

Incorporate *trait dynamics*
Standard quantitative genetics model (Abrams, 2001):

- Fitness depends on mean trait value ($\bar{\alpha}$) and ecological context (proportion susceptible)
- Constant additive genetic variance V_g
- Trait evolves toward increased fitness: rate proportional to Δfitness/Δtrait

Alternatives:
multi-strain, adaptive dynamics, PDEs, agent-based models . . .

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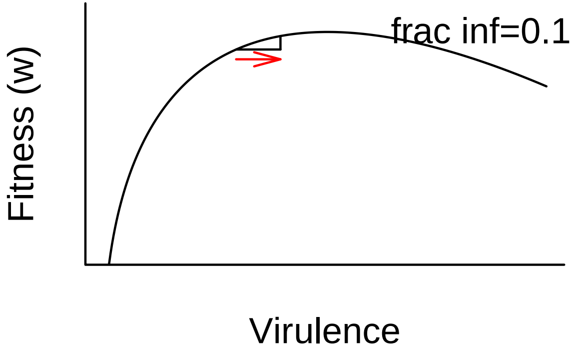

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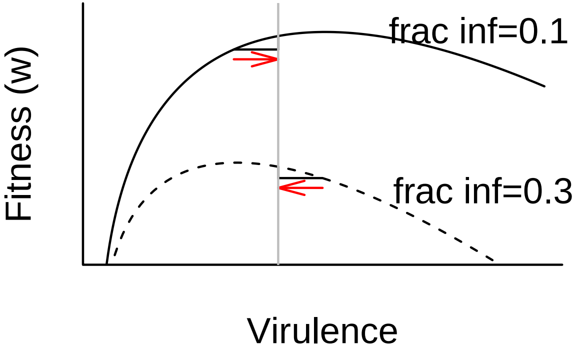
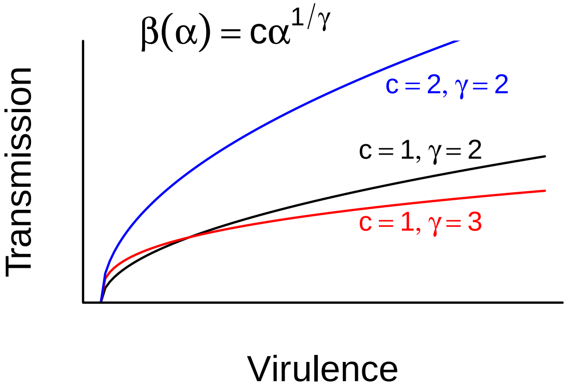


Power-law tradeoff curves



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(Why) are emerging pathogens more virulent?

What might explain initially high, but rapidly decreasing, virulence of emerging pathogens?

- Sampling bias
- Lower host resistance/tolerance
- High transmission $\rightarrow$ frequent coinfection $\rightarrow$ selection for virulence
- Disease-induced decrease in host density $\rightarrow$ selection for lowered virulence (Lenski and May, 1994)

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Transient virulence

Selection differs between the **epidemic** and **endemic** phases of an outbreak (Frank, 1996; Day and Proulx, 2004)

endemic phase selection for per-generation offspring production: maximize $\mathcal{R}_0$, $\beta N/(\alpha+\mu)$

epidemic phase selection for per-unit-time offspring production: maximize r, $\beta N-(\alpha+\mu)$

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epidemic phase
: selection for per-unit-time offspring production: maximize r, $\beta N-(\alpha+\mu)$

Transient emerging virulence

When a parasite previously in eco-evolutionary equilibrium emerges in a new host population (at low density) it will show a transient peak in virulence as it spreads

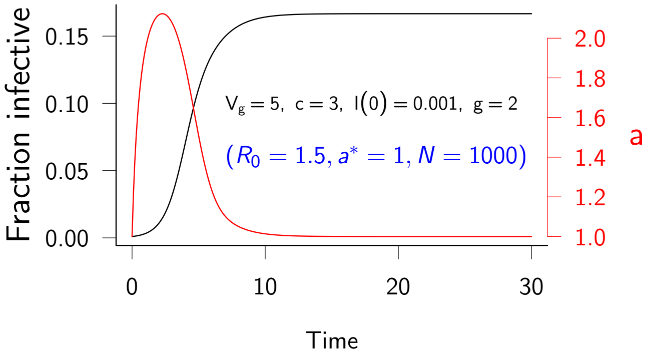
How big is the peak? Does it matter?

Outline

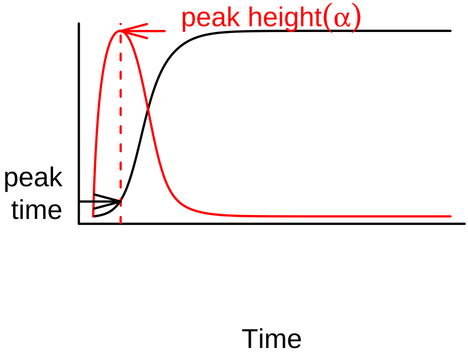
Model parameters

Parameter		Alternative	
c	Transmission scale	$\mathcal{R}_0^*$	Equilibrium $\mathcal{R}_0$
γ	Transmission shape	α^*	Equilibrium virulence
$I(0)$	Initial epidemic size	$1/N_0$	Inverse population size
V_g	Genetic variance		

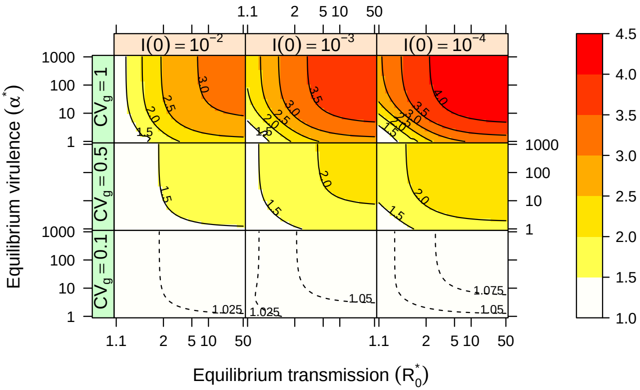
Example


Fraction infective
0.15
0.10
0.05
0.00
0
10
20
30
Time
2.0
1.8
1.6
1.4
1.2
1.0
a
$V_g = 5$, $c = 3$, $I(0) = 0.001$, $g = 2$
$(R_0 = 1.5, a^* = 1, N = 1000)$

Response variables



Peak height



I(0) = 10^−2
I(0) = 10^−3
I(0) = 10^−4
CVg = 1
CVg = 0.5
CVg = 0.1
Equilibrium virulence (α*)
Equilibrium transmission (R0*)
1.1
2
5 10
50
1
10
100
1000
1.5
2.0
2.5
3.0
3.5
4.0
1.025
1.05
1.075
4.5
1.0

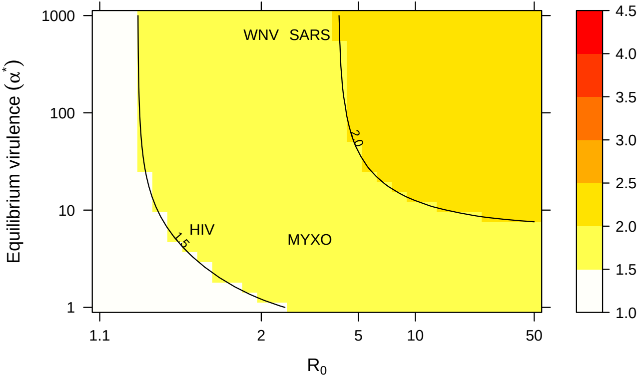
Estimates for emerging pathogens

Order of magnitude estimates for some emerging high-virulence pathogens:

Pathogen	$\mathcal{R}_0^*$	α^*	**Reference**
SARS	3	640	Anderson et al. (2004)
West Nile	1.61–3.24	639	Wonham et al. (2004)
HIV	1.43	6.36	Velasco-Hernandez et al. (2002)
myxomatosis	3	5	Dwyer et al. (1990)

Emerging pathogens: where are we?

$CV_g = 0.5$, $I(0) = 10^{-3}$ (middle panel):



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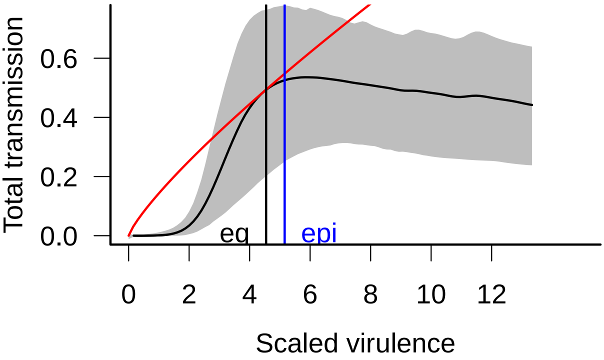
Overview

- Mosquito-borne viral disease of rabbits
- Benign in South American rabbits,
  quickly fatal in European rabbits
- Well characterized (Fenner et al., 1956; Dwyer et al., 1990)

Myxomatosis tradeoff curve



Estimating evolvability (V_g)

- Key parameter: genetic variance in virulence (evolvability)
- Despite case studies of rapid pathogen evolution:
  - myxomatosis (Dwyer et al., 1990)
  - syphilis (Knell, 2004)
  - serial passage experiments (Ebert, 1998)
  - *Plasmodium chabaudi* (Mackinnon and Read, 1999)

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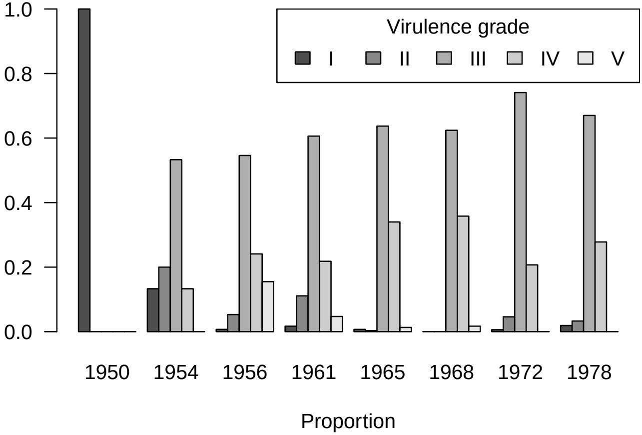
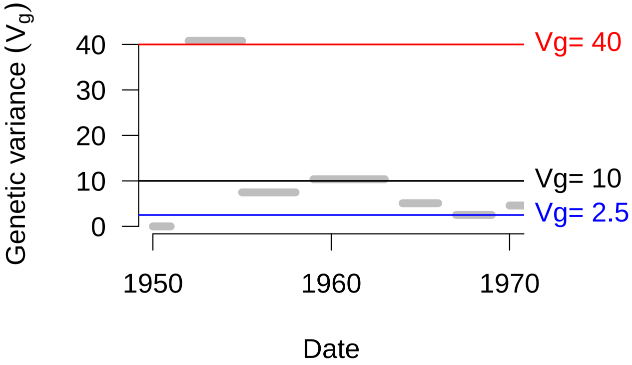
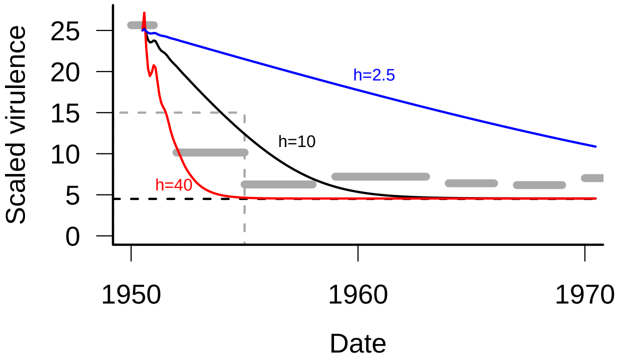
Myxomatosis grades vs. time



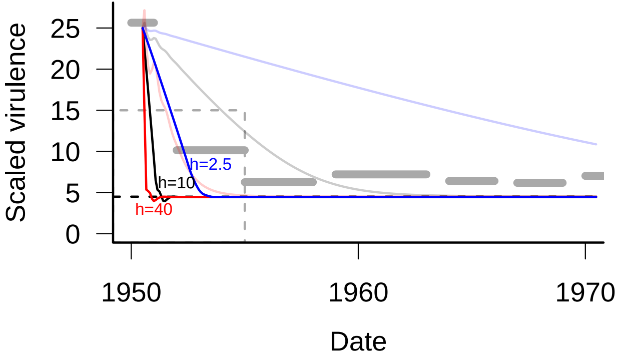
Myxomatosis variance vs. time



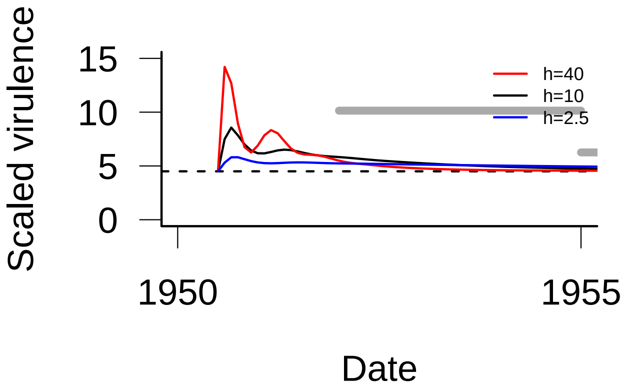
Myxomatosis virulence dynamics: power-law tradeoff



Myxomatosis virulence dynamics: realistic tradeoff



Myxo virulence: equilibrium start, power-law tradeoff



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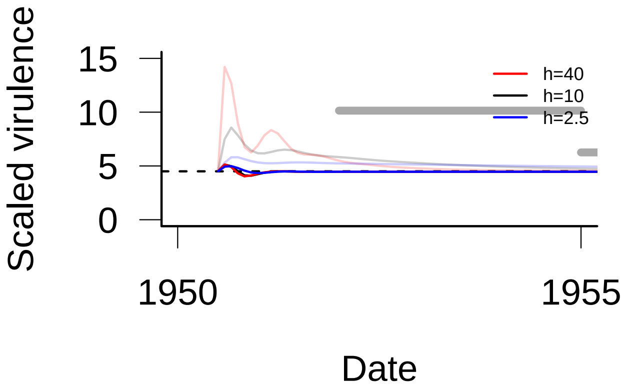
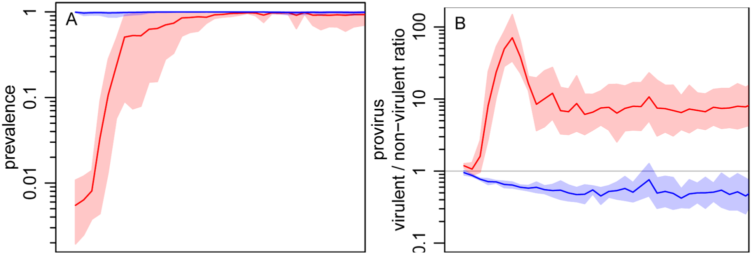


Myxomatosis: conclusions

- eco-evo virulence dynamics are at least in the ballpark of what we would expect
- detailed shape of virulence curve very important ...
- ... as is genetic variance
- more realistic models (esp. of variance) needed?

Phage dynamics (Berngruber et al., 2013)



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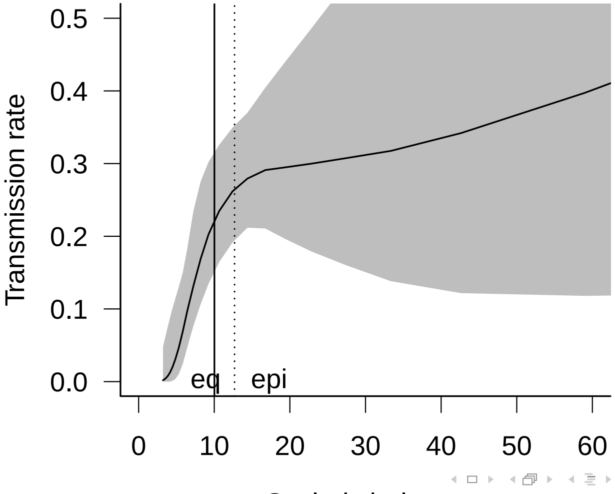
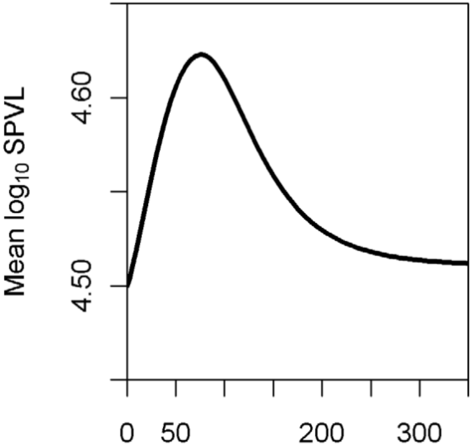
HIV tradeoff curve (Fraser et al., 2007)



HIV virulence dynamics (Shirreff et al., 2011)

- virulence/transmission from set-point viral load (SPVL)
- Fraser et al. (2007) : plausible tradeoff observed from Rakai data
  - SPVL heritable
  - correlated with rate of progression to AIDS
  - correlated with probability (rate) of within-couple transmission

Model results



(Shirreff et al., 2011; Herbeck et al., 2014)

Shirreff et al. (2011): within-host assumptions

- generally based on Rakai estimates
- Normally distributed mutation of SPVL between hosts
- Normally distributed phenotypic variation
- different infectivity for early, mid, late stages of HIV
- tradeoff applies in mid stage:
  Hill functions $(x^d/(a + bx^d))$
- Weibull-distributed time in mid stage

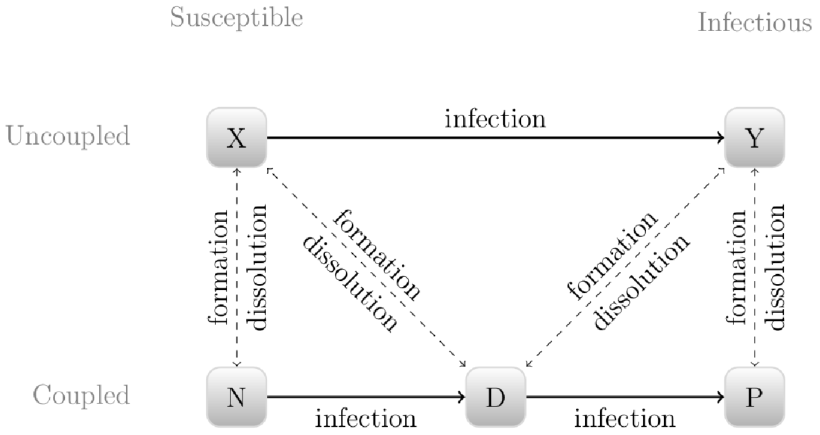
Shirreff et al. (2011) epidemiological assumptions

- implicit partnership-formation model

$$\mathrm{foi} = \frac{\beta c}{\beta + c + 1/d}$$

- derived from $\mathcal{R}_0$ for an instantaneous-partnership-formation model, e.g. Hollingsworth et al. (2008); Diekmann and Heesterbeek (2000)

Epidemiological models for HIV Champredon et al. (2013)



Model modifications

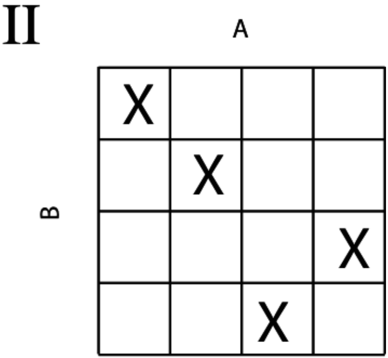
- need to track $\{S, SS, I(\alpha), SI(\alpha), II(\alpha, \alpha')\}$
- simplifications:
  - single-stage, exponential infectious period ($\beta =$ time-weighted average of β_1, $\beta_2(\alpha)$, β_3)
  - no phenotypic variation

Model variations

- 6 models:
  - extra-pair contact (yes/no) $\times$
  - instantaneous partnership formation (yes/no)
- implicit (Shirreff/Hollingsworth) model
- random-mixing model

Latin hypercube sampling

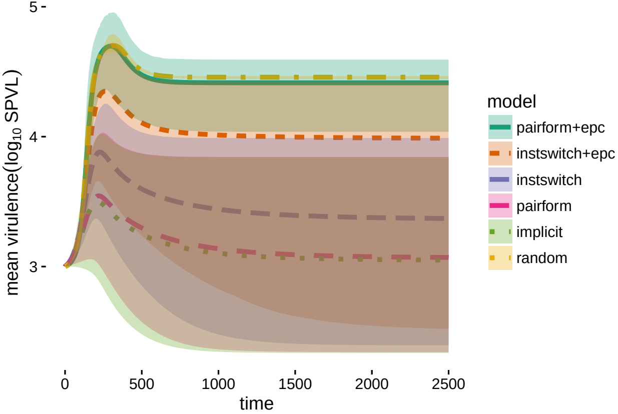
- sample evenly, randomly across (potentially many) uncertain parameters
- following Champredon et al. (2013), earlier Blower et al. (1991)



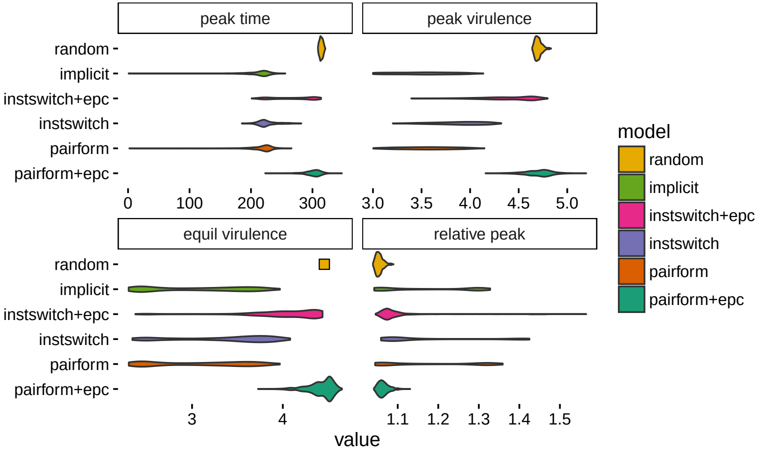
Details

- r varies widely across parameters/model sets
- scale parameters to a common r
- scale both uncoupled and extra-coupled rates relative to within-coupled rate
- response variables:
  - equilibrium virulence
  - peak virulence time (years)
  - peak virulence
  - relative peak virulence (peak/eq)

Virulence trajectories



Univariate distributions



~~Conclusions~~ Open questions

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- need to know: genetic variance, shapes of tradeoffs
- theory meets molecular biology: mutations of large effect vs. quantitative variability
- next steps in connecting with data? general theory?

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Crome (1997) on theory

When we regard theories as tight, real entities and devote ourselves to their analysis, we can limit our horizons and, worse, attempt to make the world fit them. A lot of ecological discussion is not about nature, but about theories, generalizations, or models supposed to represent nature ...

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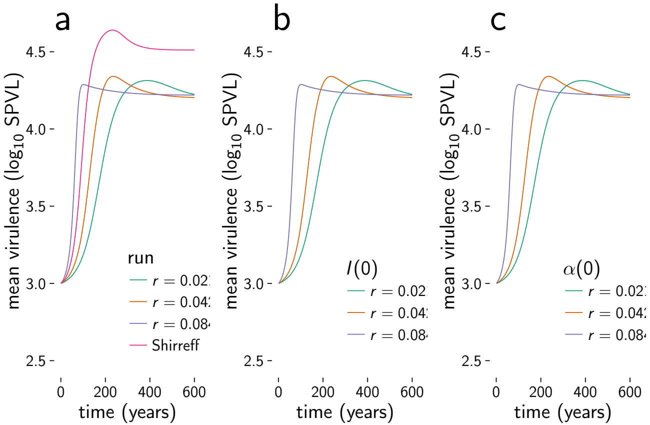
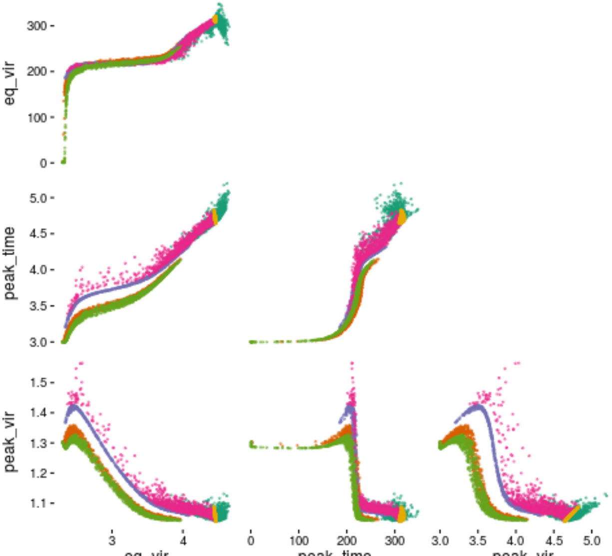
extras

Baseline results



Pairs plots


eq_vir
peak_time
peak_vir
300
200
100
0
5.0
4.5
4.0
3.5
3.0
1.5
1.4
1.3
1.2
1.1
3
4
0
100
200
300
3.0
3.5
4.0
4.5
5.0

Sensitivity