Eco-evolutionary virulence of pathogens: models and speculations

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Outline

Acknowledgements

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

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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 and seasonality
   - Overview
   - Toy model
   - WNV data
4. More on theory vs. data
   - Tradeoff curves
   - Conclusions

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 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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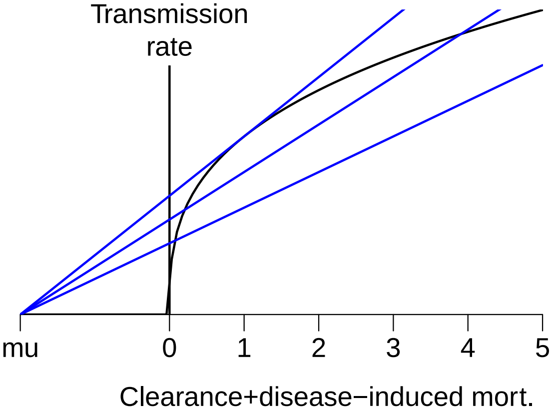
Basic tradeoff theory: assumptions

- 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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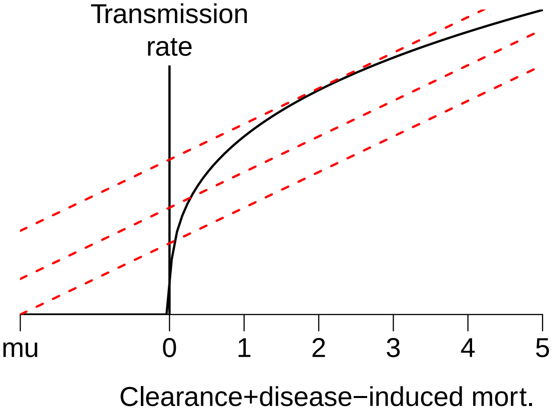

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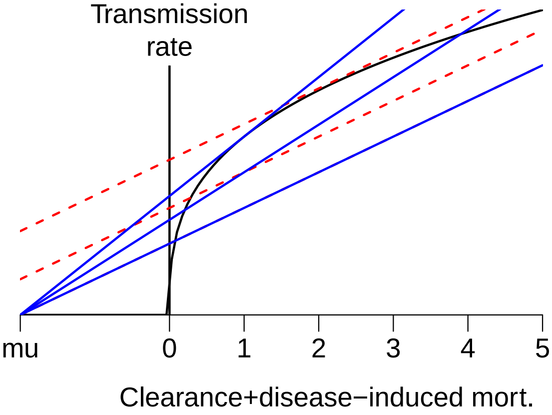

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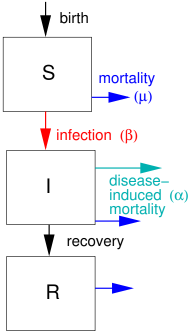
Epidemiological model

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



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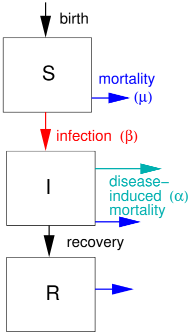

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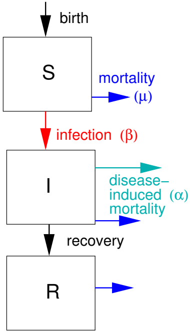

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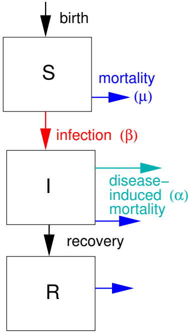

The model (2): evolutionary dynamics

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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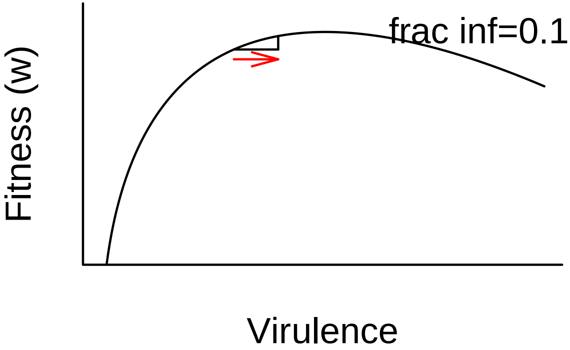
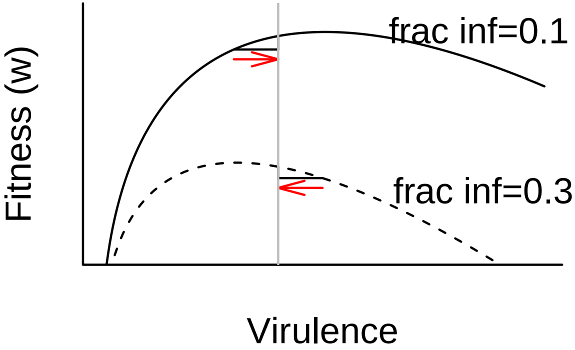
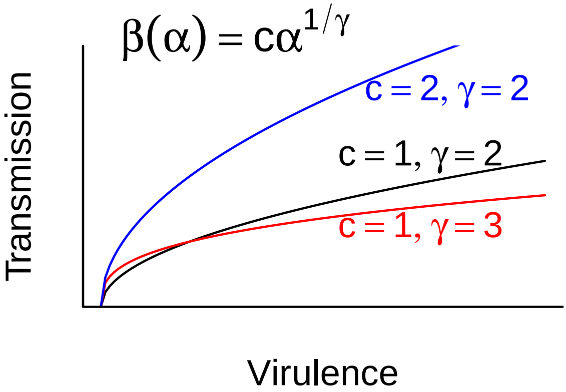


Evolutionary dynamics, cont.



Power-law tradeoff curves



Outline

(Why) are emerging pathogens more virulent?

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

- Pathogens with low virulence go unnoticed
- Hosts less resistant to / tolerant of novel parasites
- High transmission $\rightarrow$ frequent coinfection $\rightarrow$ selection for virulence
- Disease-induced drop in population density decreases selection for 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 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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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

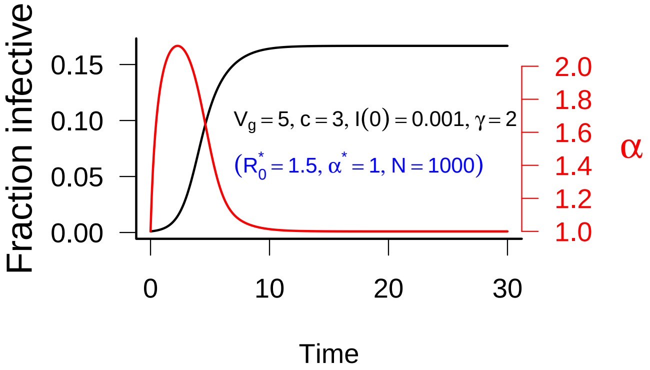
How big is the peak? Does it matter?

Outline

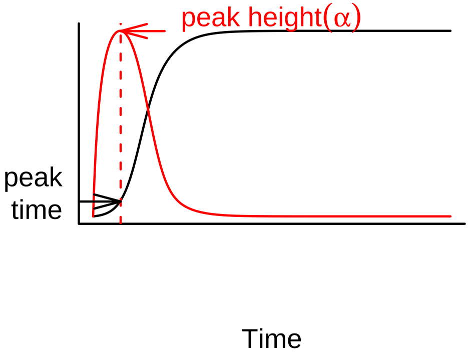
Model parameters

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

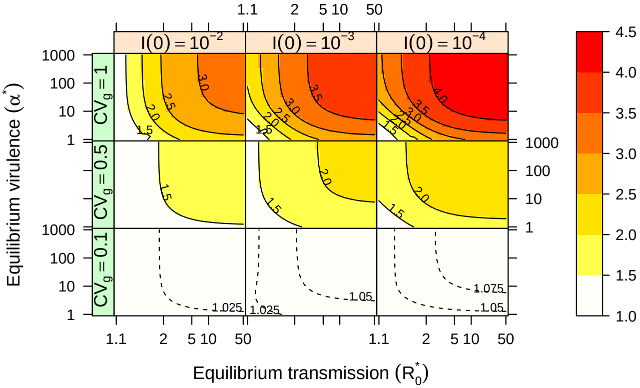
Example


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
α
$V_g = 5, c = 3, I(0) = 0.001, \gamma = 2$
$(R_0^* = 1.5, \alpha^* = 1, N = 1000)$

Response variables



Peak height


I(0) = 10^−2
I(0) = 10^−3
I(0) = 10^−4
CV_g = 1
CV_g = 0.5
CV_g = 0.1
Equilibrium virulence (α*)
Equilibrium transmission (R*_0)
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
1.0
4.5

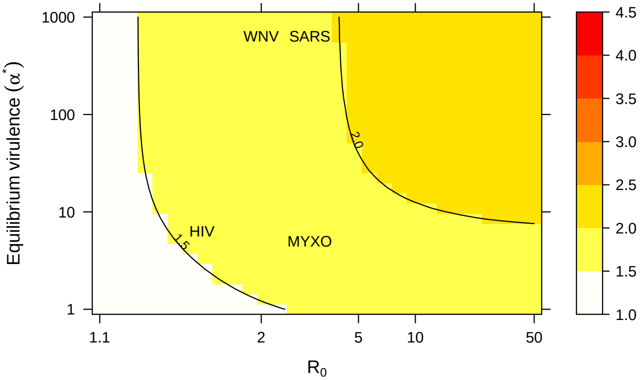
Estimates for emerging pathogens

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

Pathogen	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):

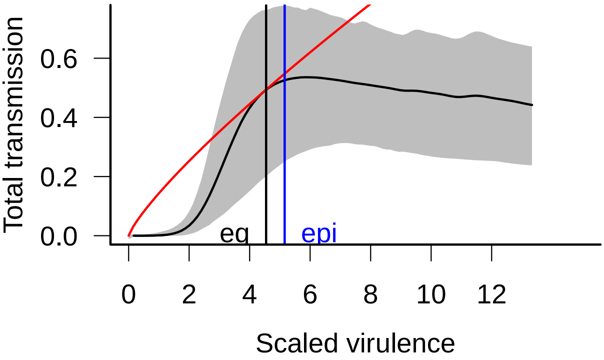


Outline

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, 1999a)

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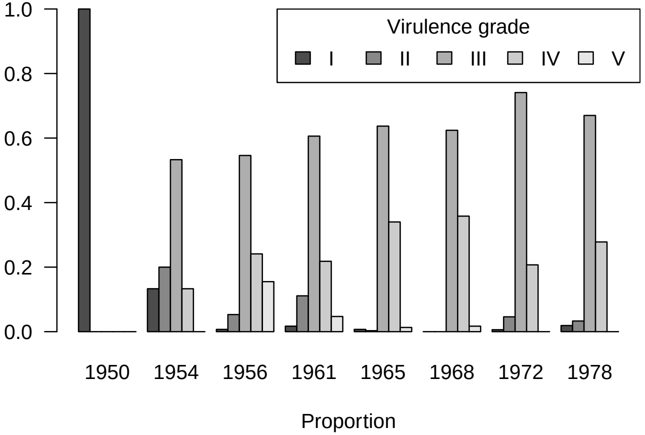
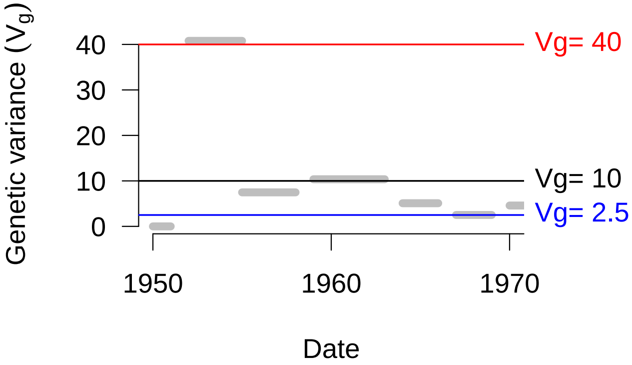
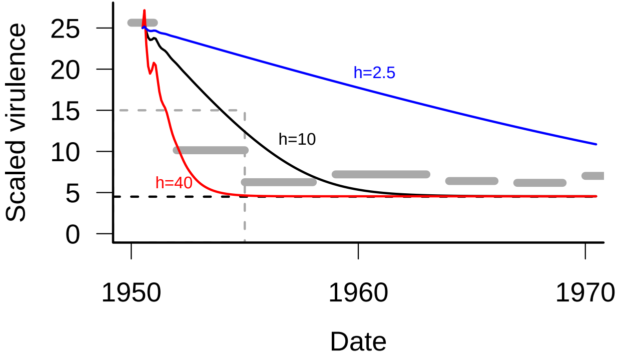
Myxomatosis grades vs. time



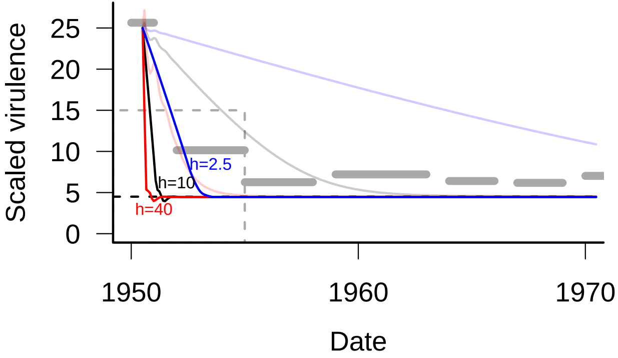
Myxomatosis variance vs. time



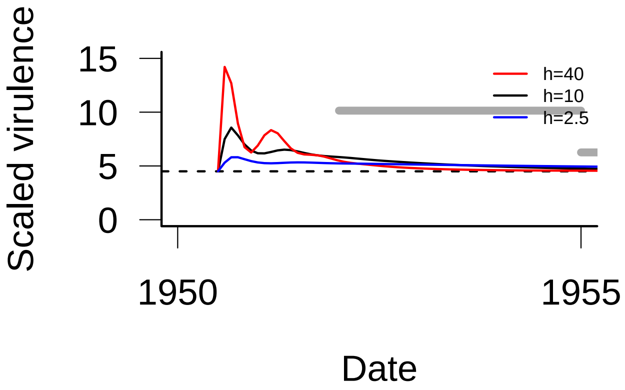
Myxomatosis virulence dynamics: power-law tradeoff



Myxomatosis virulence dynamics: realistic tradeoff



Myxo virulence: equilibrium start, power-law tradeoff



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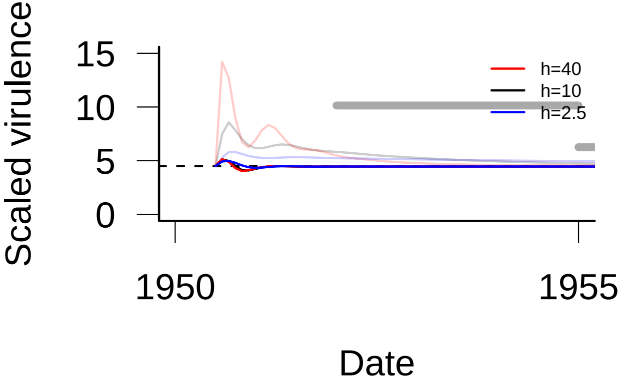


Outline

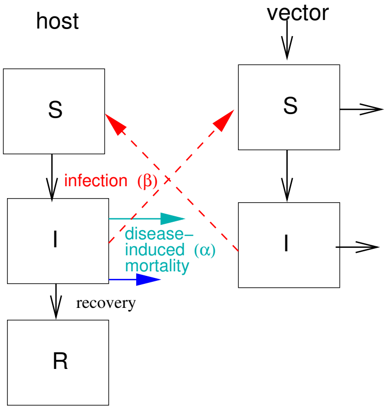
Seasonality

- Many pathogens fluctuate annually
  - Host contact/aggregation patterns
  - Host (or vector) demography
  - Climatic effects on transmissibility
- Fluctuating incidence = fluctuating selection
- Seasonal variation *or* latitudinal variation?

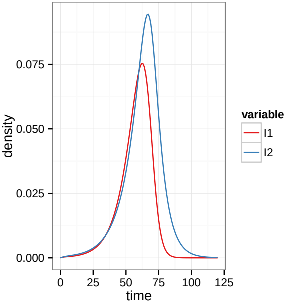
Outline

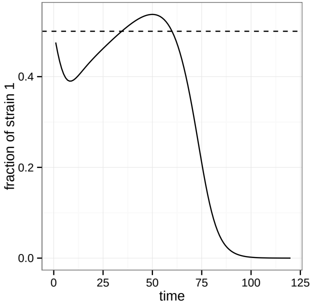
Toy model

- Basic Ross-MacDonald vector-host model
- Simple vector (mosquito) demography
- No host demography
- Two pathogen strains

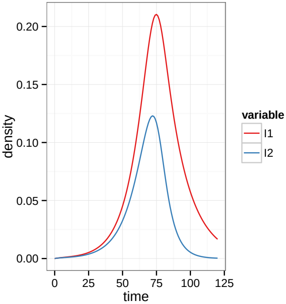


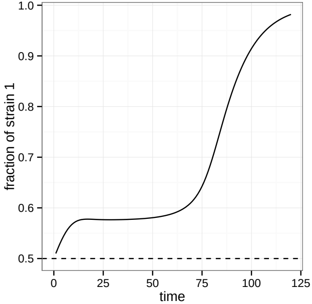
Case I: $r_1 > r_2$, equal $\mathcal{R}_0$



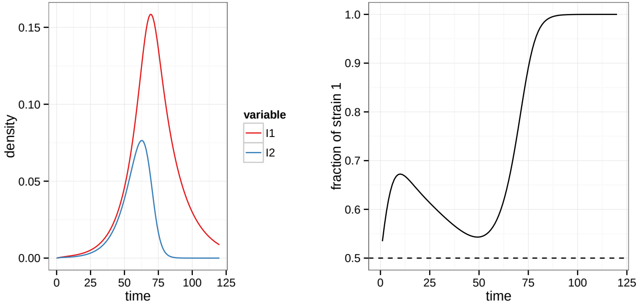


Case II: $\mathcal{R}_{0,1} > \mathcal{R}_{0,2}$, equal r





Case III: $\mathcal{R}_{0,1} > \mathcal{R}_{0,2}$, $r_2 > r_1$



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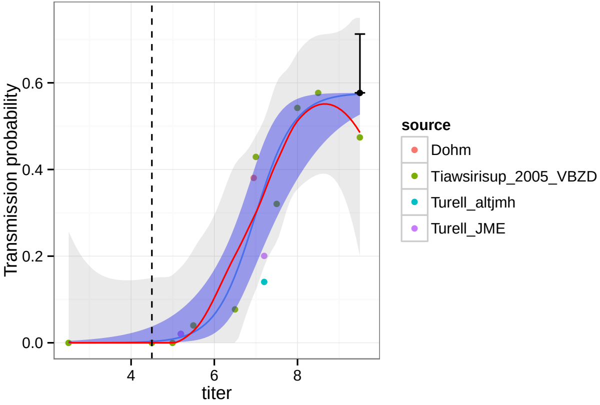
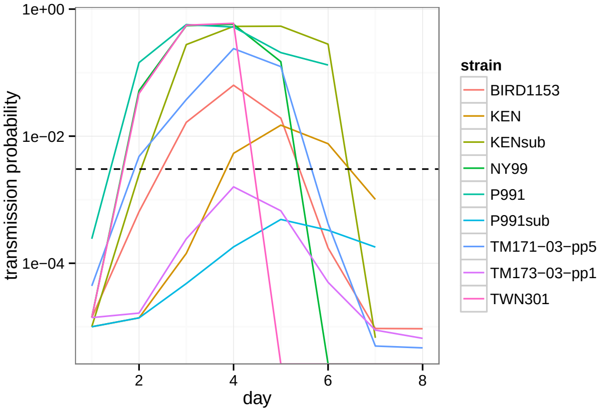
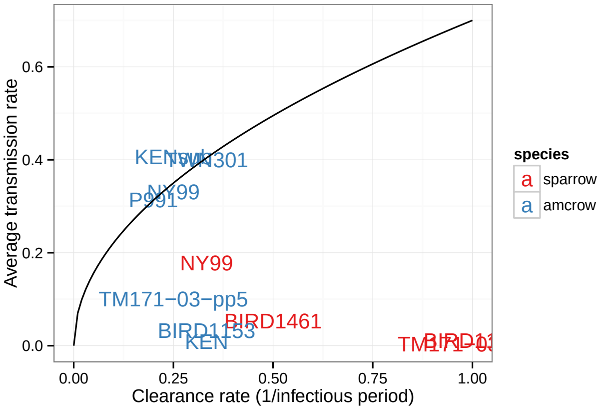
Titer vs infectiousness



Titer curves (American crows)



Transmission vs clearance for WNV



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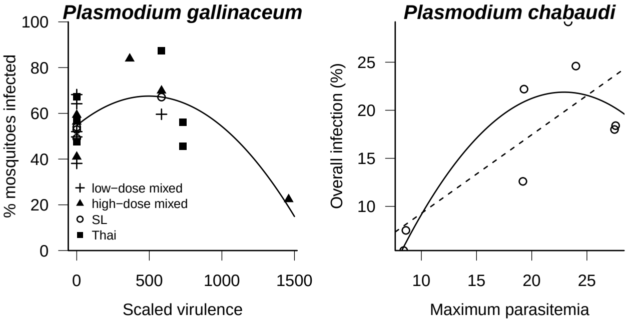
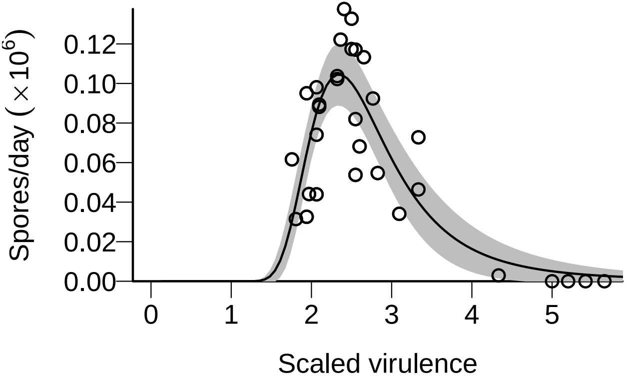
Estimating tradeoff curves

- Usually *assume* a tradeoff between virulence and transmission
- Positive *correlation* virulence and transmissibility (or proxies) known from many systems (Lipsitch and Moxon, 1997)
- *shape* of tradeoff curves is largely unknown

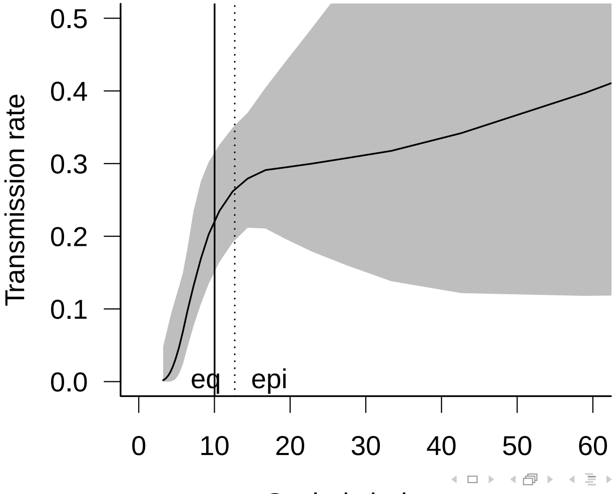
Malaria (Mackinnon and Read, 1999b; Paul et al., 2004)



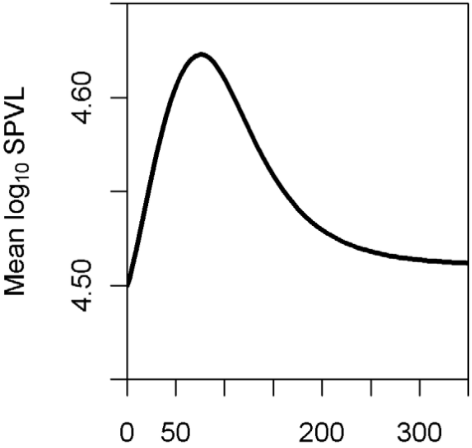
Pasteuria ramosa (Jensen et al., 2006)



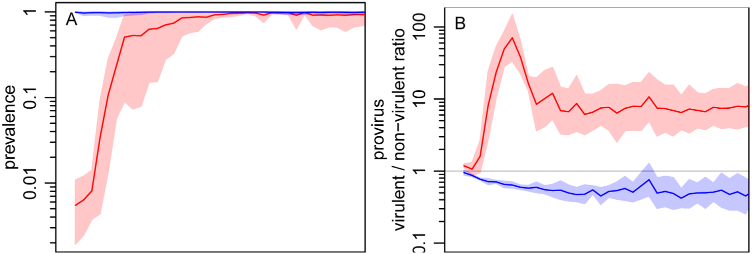
HIV (Fraser et al., 2007)



HIV dynamics (Shirreff et al., 2011)

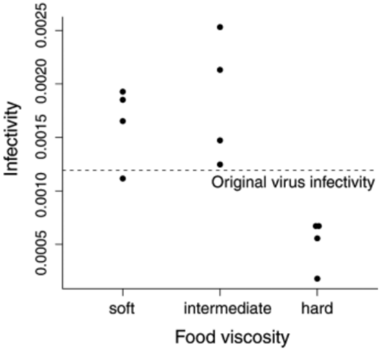


Phage dynamics (Berngruber et al., 2013)



What about space?

- Theory: spatial structure should select for decreased virulence
- Experiment: viscosity decreases *infectivity* in *Plodia* (Boots and Mealor, 2007)
- Are we ready for space?



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Conclusions

- Eco-evolutionary dynamics of virulence are still plausible (Alizon et al., 2009; Luo and Koelle, 2013)
- Sensitive to genetic variance and shape of tradeoff curve
- Theory meets molecular biology: mutations of large effect vs. quantitative variability

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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 . . .

References

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