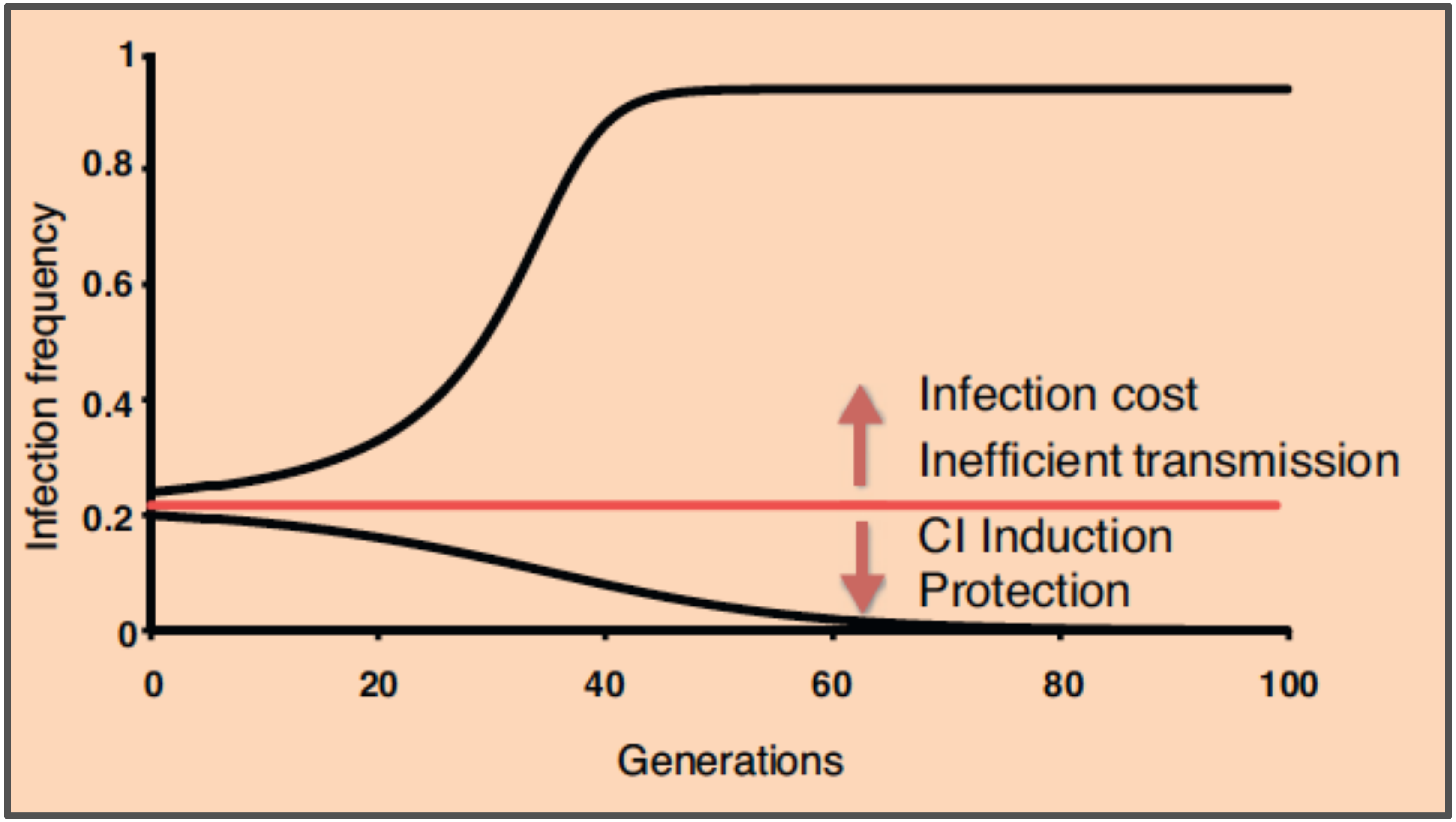
Lecture 2

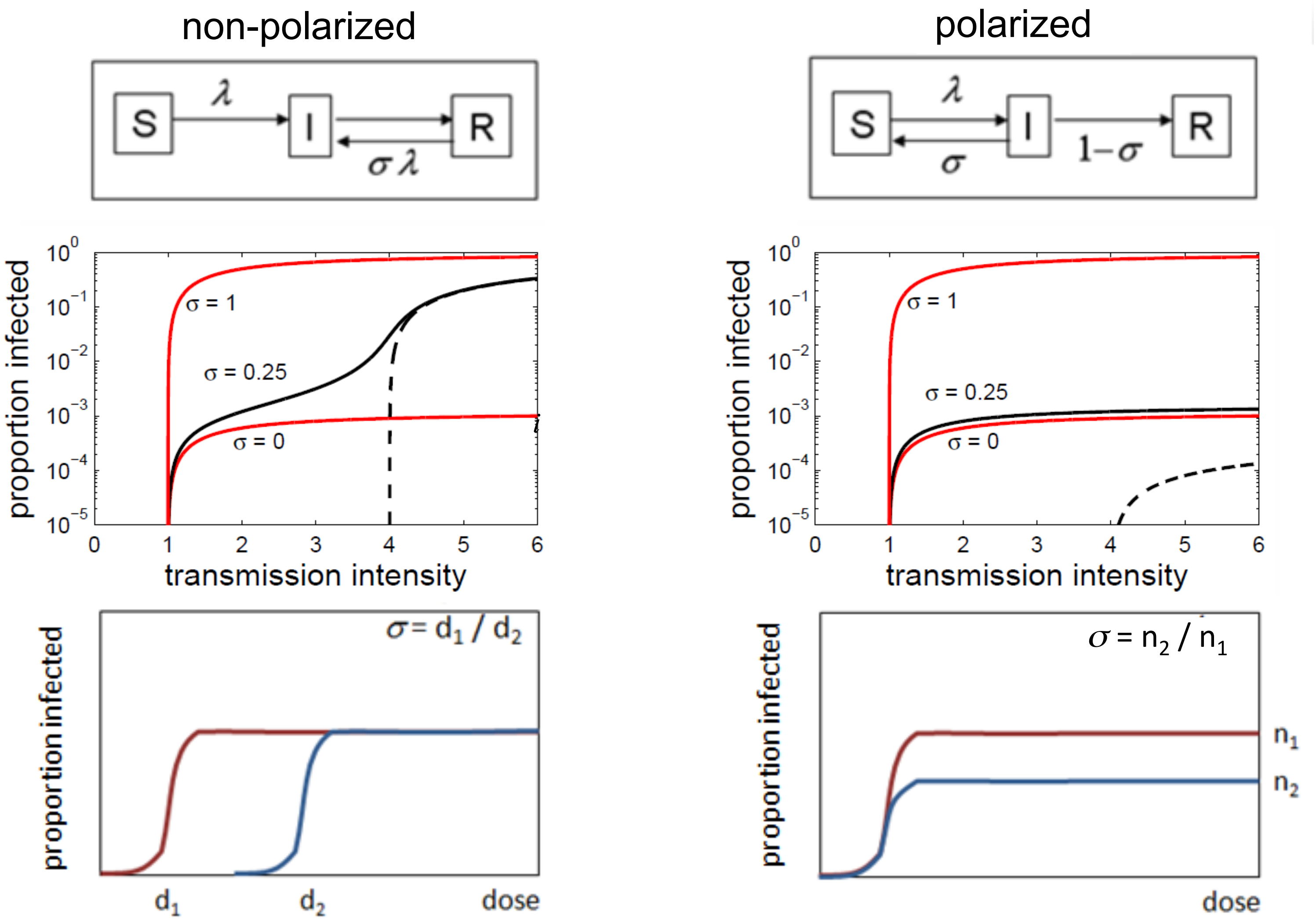
Epidemiological Thresholds and Control Strategies II:

Laboratory

Thresholds in *Wolbachia* transmission



Modes of partial resistance



Model systems

Drosophila melanogaster –
Drosophila C virus (*D*CV)

Aedes aegypti –
Dengue virus (DENV)

Wolbachia

Dose-response model

Under the independent action hypothesis for viral particles, the mean number of infecting particles is:

$$\lambda = p \times dose,$$

where *p* is the probability that each particle causes infection and *dose* is the number of particles the host is challenged with.

If *p* is small and *dose* is large then the number *k* of infectious pathogens per host is Poisson distributed with mean λ:

$$f(k) = \frac{\lambda^k e^{-\lambda}}{k!},$$

and the probability of host infection is: $I = 1 - e^{-\lambda}$

Infer the distribution of induced resistance

Introduce a susceptibility reduction factor distributed according to some probability density function $q(x)$:

$$I = 1 - \int_0^1 e^{-x\lambda} q(x)\, dx$$

For concreteness formalise $q(x)$ as a beta distribution with two shape parameters to be estimated (a and b):

$$q(x) = \frac{(1-x)^{b-1} x^{a-1}}{B(a,b)}$$

Insert the distribution of induced resistance into a transmission model

Non-intervention group

$$\frac{dS(t)}{dt} = (1-v)\mu - \lambda S(t) - \mu S(t)$$

$$\frac{dI(t)}{dt} = \lambda S(t) - \mu I(t)$$

Intervention group with distribution of effects $q(x)$

$$\frac{\partial X(x,t)}{\partial t} = vq(x)\mu - x\lambda X(x,t) - \mu X(x,t)$$

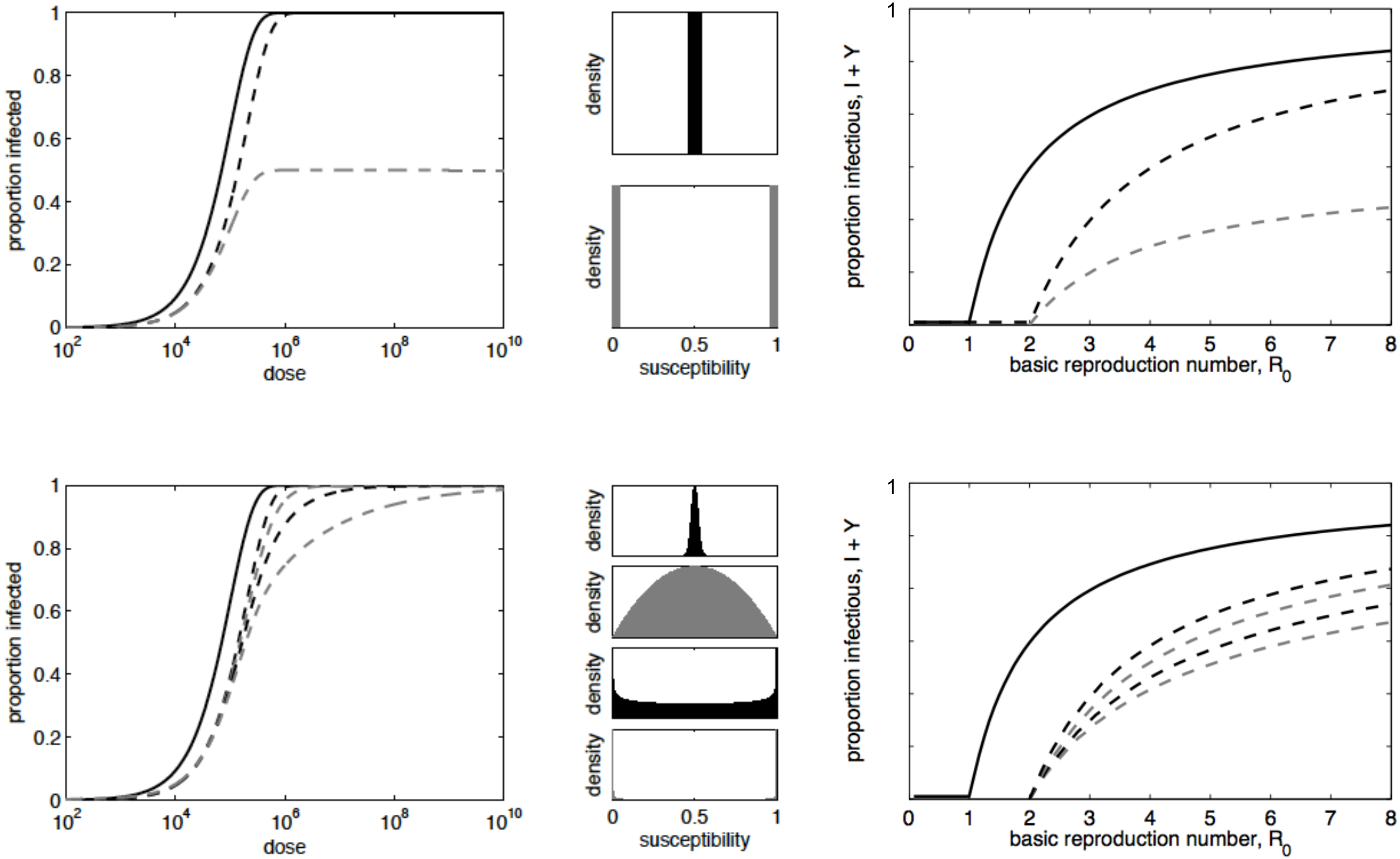
$$\frac{\partial Y(x,t)}{\partial t} = x\lambda X(x,t) - \mu Y(x,t)$$

where $\lambda = \beta\left(I + \hat{Y}\right)$ and $\hat{Y} = \int_0^1 Y(x)dx$

$$R_0(v) = \frac{\beta}{\mu+\gamma}\left(1-(1-\bar{x})v\right)$$

R_0 decreases with mean susceptibility, but does not depend on the variance.

The effects of susceptibility distributions



For fixed mean susceptibility, infection decreases with variance.

Prevalence table

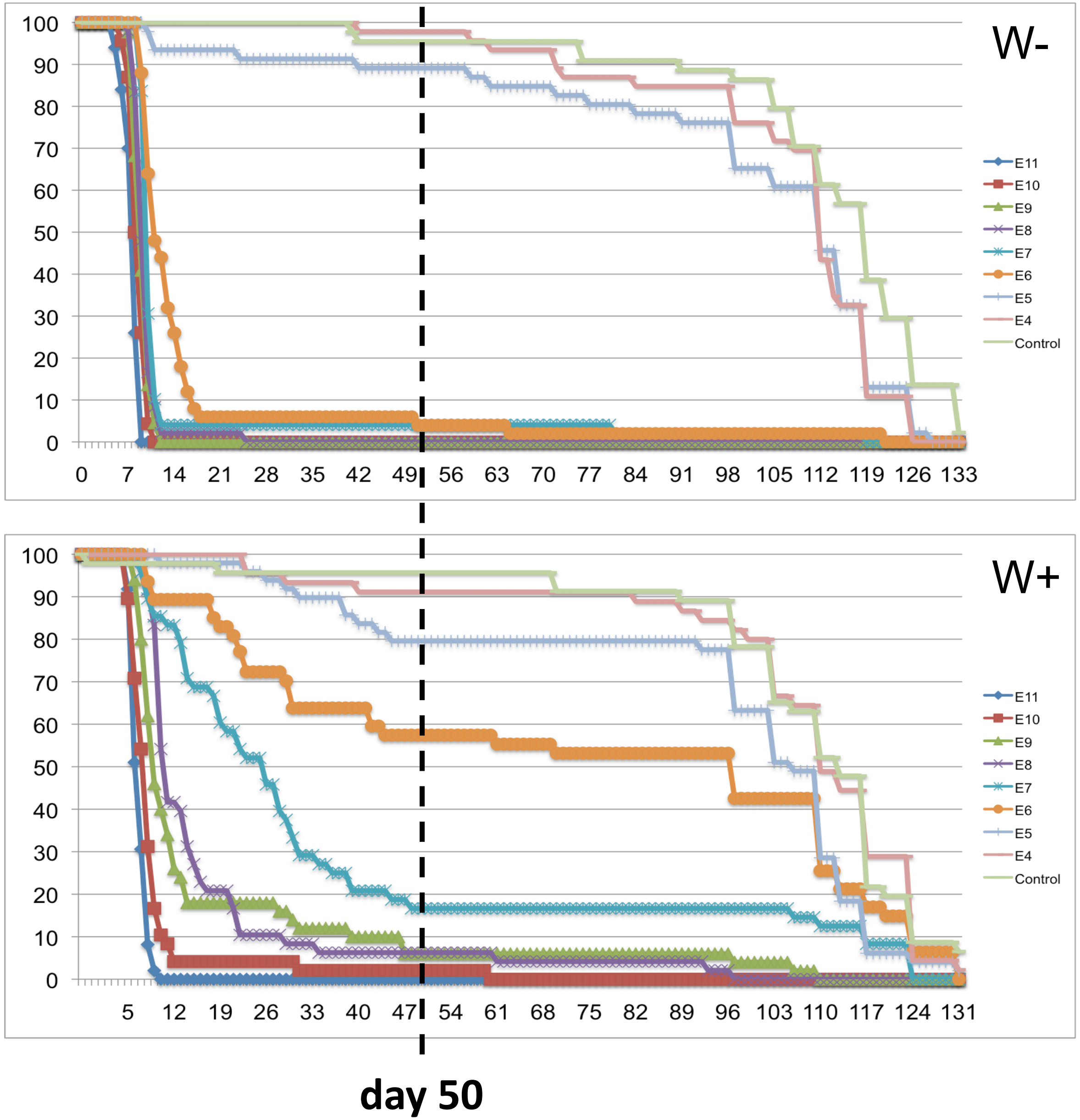
No intervention	Homogeneous resistance	All-or-none resistance
$I = \frac{R_0 - 1}{R_0}$	$\hat{Y} = \frac{\bar{x} R_0 - 1}{\bar{x} R_0}$	$\hat{Y} = \frac{\bar{x} R_0 - 1}{R_0}$

The formula for R_0 in terms of model parameters is not affected by heterogeneity.

However, given a fixed mean susceptibility, the prevalence decreases with heterogeneity.

How does this affect data interpretation?

Experimental survival curves

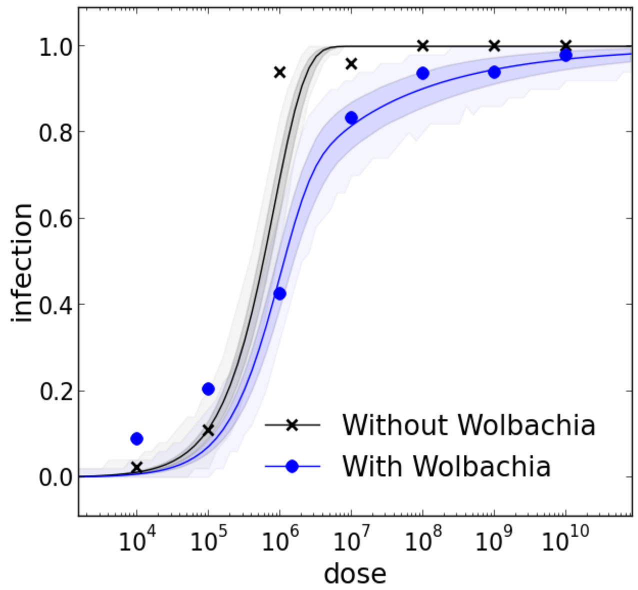


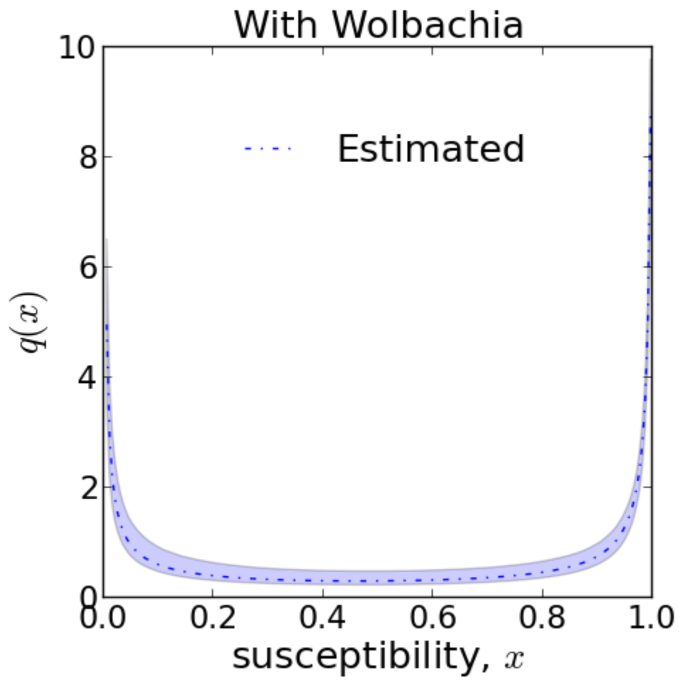
Model fitting and parameter estimation

p = 1.2 x 10^{-6} [9.8 x 10^{-7}, 1.4 x 10^{-6}]

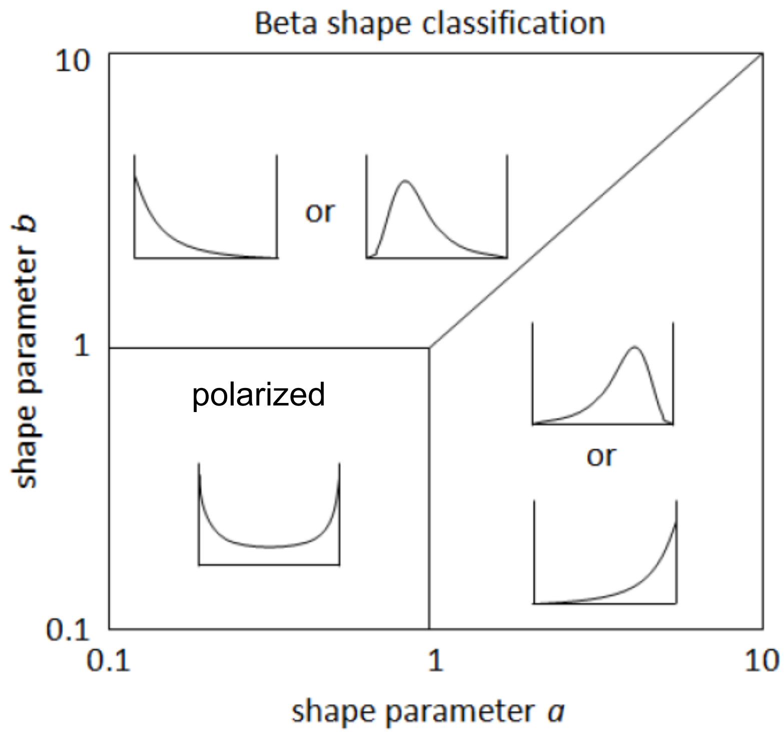
a = 0.25 [0.19, 0.34]

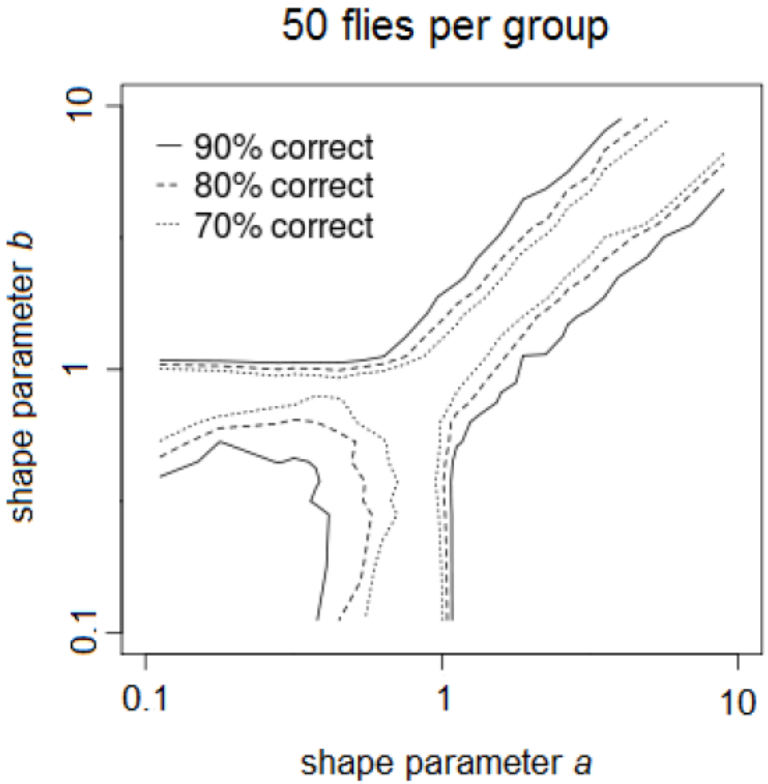
b = 0.14 [0.10, 0.22]



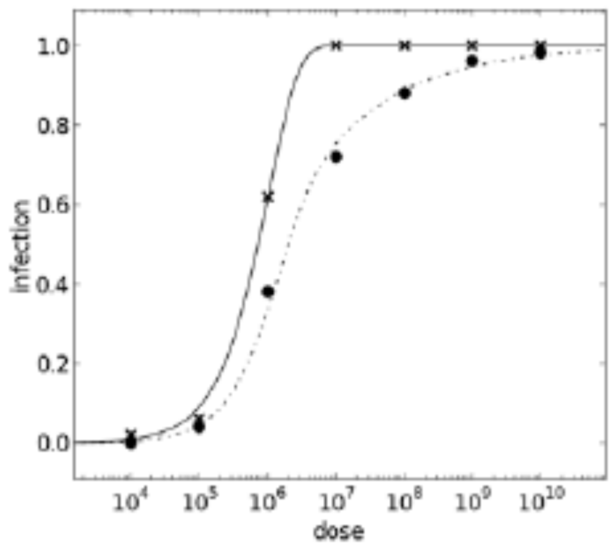


Classification of distribution shapes

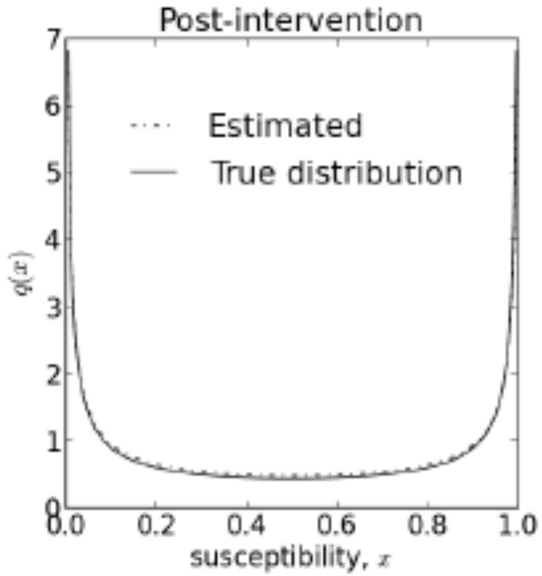


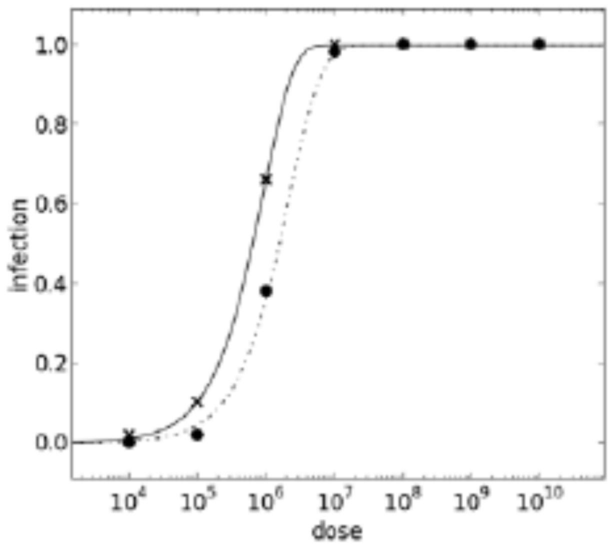


Simulated data

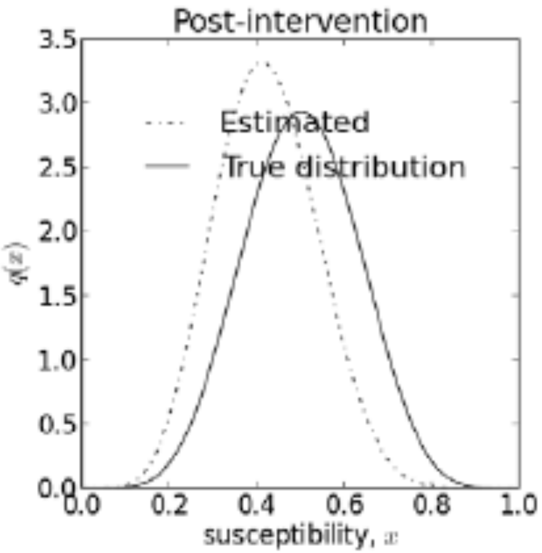


a = 0.3
b = 0.3





a = 7
b = 7



Wolbachia spread in the presence of environmental pathogens

$$\frac{dU}{dt} = U\,a\left[\frac{U + W\left(1 - s_h\right)}{N}\right] - U\left(b + k\,N\right) - \lambda U$$

$$\frac{dW}{dt} = W\,a\left(1 - s_f\right) - W\left(b + k\,N\right) - \sigma\lambda W$$

U: Insects without *Wolbachia*
W: Insects to whom *Wolbachia* confers partial protection

Invasion threshold:

$$\hat{p} = \frac{s_f}{s_h} - \frac{\lambda\left(1 - \sigma\right)}{a\,s_h}$$

Table 1: Parameters, values and references

Symbol	Definition	Value	Reference
a	Reproduction or birth rate of insect host	10	(Hassell et al. 1976)
b	Density-independent death rate of insect host	1	(Hassell et al. 1976; Maciel-de-Freitas et al. 2011)
s_h	Proportion of offspring in incompatible crosses not viable	0.8, 0.9	(Blagrove et al. 2011; Yeap et al. 2011)
s_f	Relative fecundity reduction of *Wolbachia* carrying hosts	0.6	(Walker et al. 2011; Yeap et al. 2011)
s_l	Relative lifespan reduction of *Wolbachia* carrying hosts	0, 0.4	(Walker et al. 2011; Yeap et al. 2011)
λ	Infection-induced mortality	0 – 10	This study
σ	Mean susceptibility to infection	0 – 1	This study

Wolbachia spread in the presence of environmental pathogens

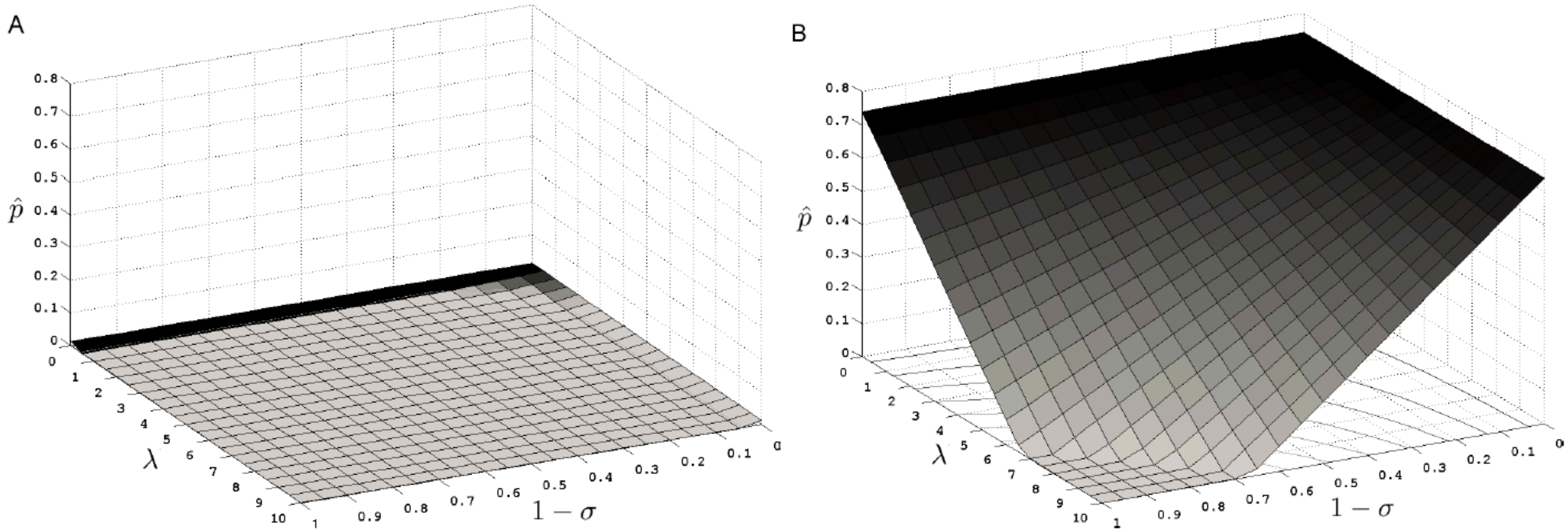


Figure 2: Critical frequency for invasion by *Wolbachia*-carrying insects as a function of both force of infection and level of resistance under the homogeneous model. Parameters values are $s_f = 0.0, s_l = 0.1, s_h = 0.9$ (A), and $s_f = 0.6, s_l = 0.4, s_h = 0.9$ (B).

Resistance to environmental pathogens lowers the threshold for *Wolbachia* invasion, and this effect increases with the force of infection.

Wolbachia spread in the presence of environmental pathogens

$$\frac{dU}{dt} = U\,a\left[\frac{U + W\left(1 - s_h\right)}{N}\right] - U\left(b + k\,N\right) - \lambda U$$

$$\frac{dW_0}{dt} = \left(1 - \sigma\right)W\,a\left(1 - s_f\right) - W_0\left(b + k\,N\right)$$

$$\frac{dW_1}{dt} = \sigma W\,a\left(1 - s_f\right) - W_1\left(b + k\,N\right) - \lambda W_1$$

U: Insects without *Wolbachia*
W_0: Insects to whom *Wolbachia* confers total protection
W_1: Insects to whom *Wolbachia* confers no protection

Wolbachia spread in the presence of environmental pathogens

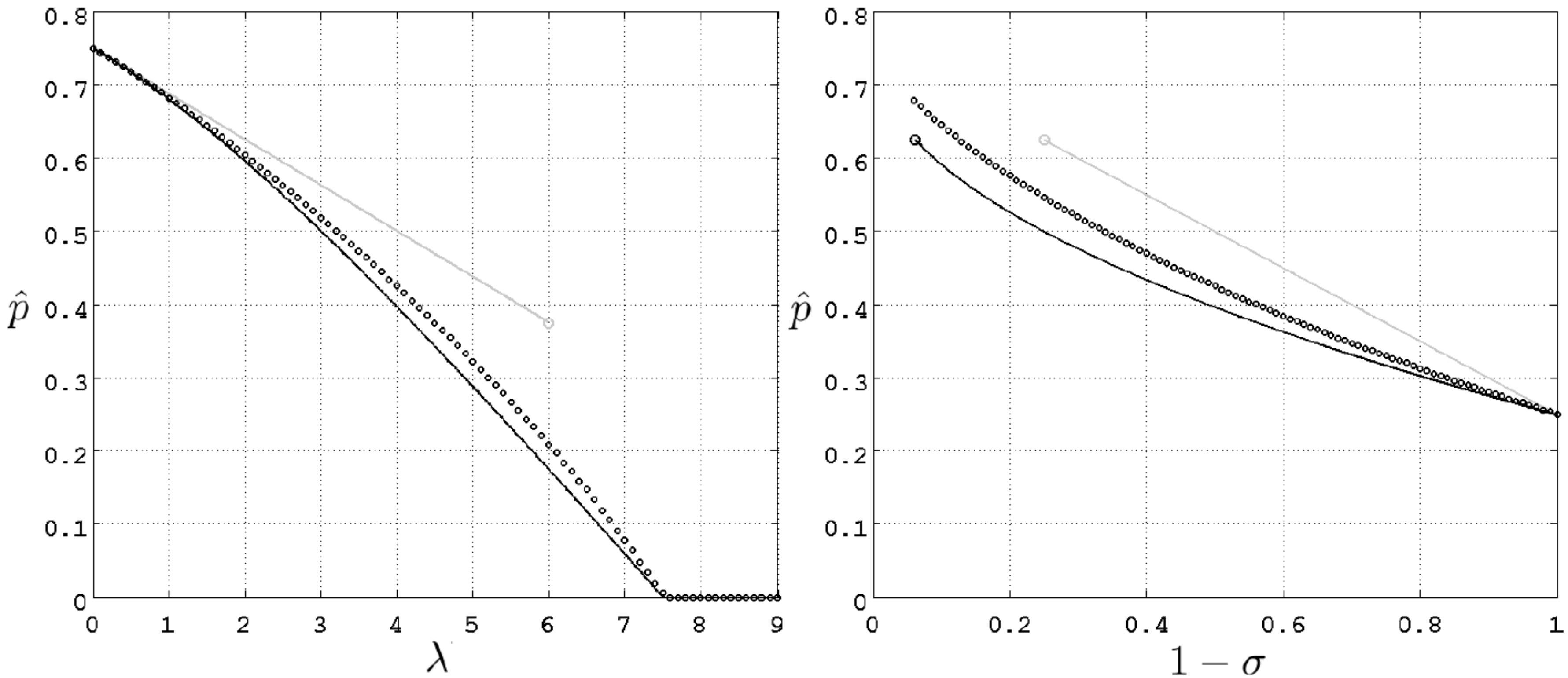


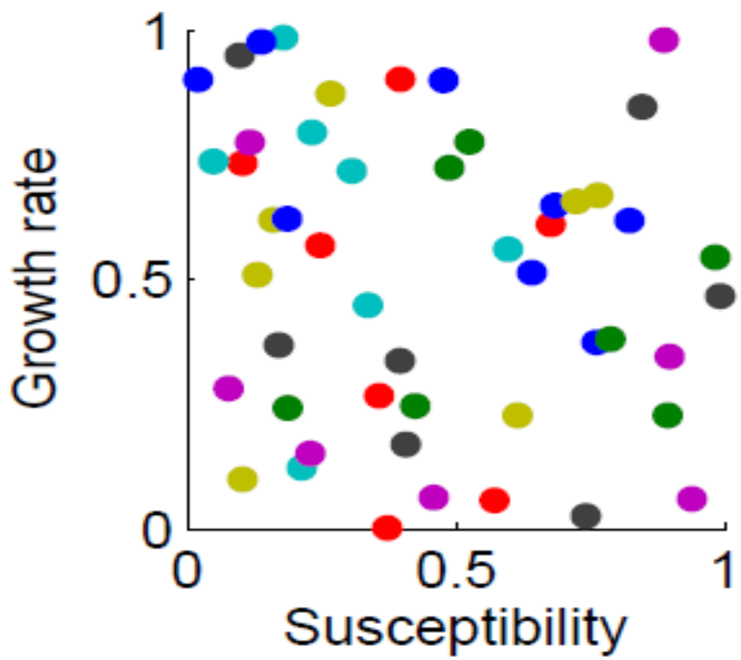
Figure 3: $\hat{p}$ of the all-or-none resistance model as a function of: the force of infection λ (fixing $\sigma = 0.5$) (A); and mean resistance σ (fixing λ=4) (B). Full light gray lines (higher) give $\hat{p}$ under the homogeneous model for comparison.

All else being fixed, heterogeneity in resistance lowers the threshold for *Wolbachia* invasion!

Variability on multiple traits

$$\frac{dU}{dt} = U\,a\left[\frac{U + W_T\left(1 - s_h\right)}{N}\right] - U\left(b + kN\right) - \lambda U$$

$$\frac{dW_i}{dt} = \underbrace{\gamma_i W_i\, a\left(1 - s_{f_i}\right)}_{\text{growth}} - \underbrace{W_i\left(b + kN\right)}_{\text{natural mortality and crowding}} - \underbrace{x_i \lambda W_1}_{\text{loss due to infection by environmental pathogens}} \overbrace{- \eta W_i + \eta \sum_j m_{ji} W_j}^{\text{mutation}}$$



Evolution to minimum susceptibility and maximum growth rate unless constrained by trade-offs.

Bibliography

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