AGE, SIZE AND HOST-PATHOGEN INTERACTIONS

Andy Dobson,

SFI Workshop – July 2018

Aging and Disease

TWO THEMES TO THE TALK

1) How does force of infection change with age?

2) Do host-parasite interactions change in hosts with different body sizes?

- Some patterns, some models, some quite huge patterns and lots of wild speculation!

AGE IS DIFFERENT FROM TIME….

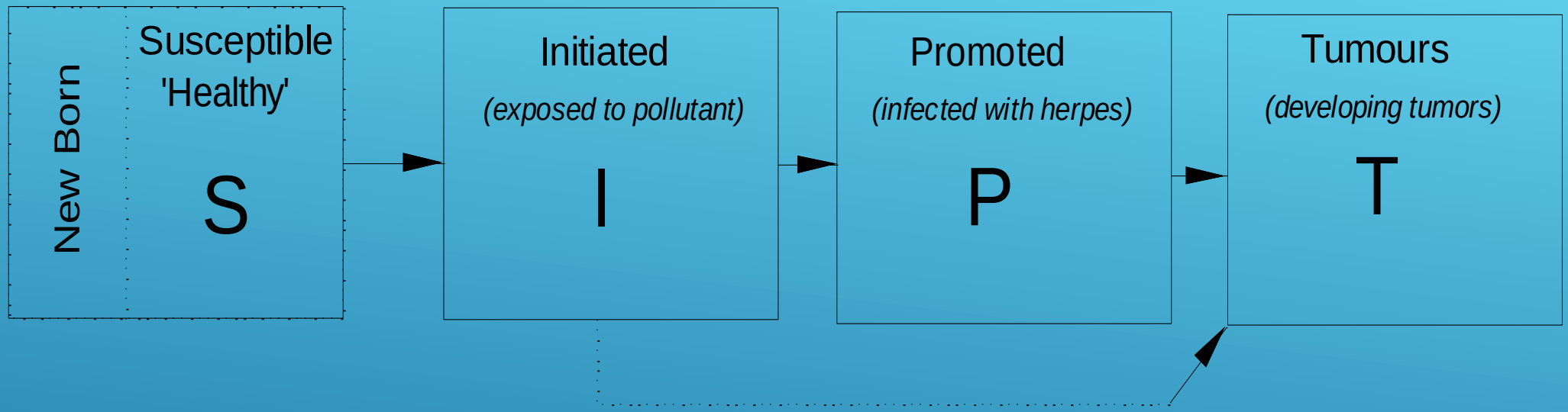
3) GAMMA HERPES IN SEA LIONS
STD THAT IS A PRECURSOR FOR VIRULENT TUMORS

JOINT WORK WITH LINDA LOWENSTEIN, FRANCES GULLAND AND BETH BUCKLES, UC DAVIS AND MARINE MAMMAL CENTER, SAUSALITO…AND WITH SARAH COBEY

STRUCTURE OF BASIC MODEL

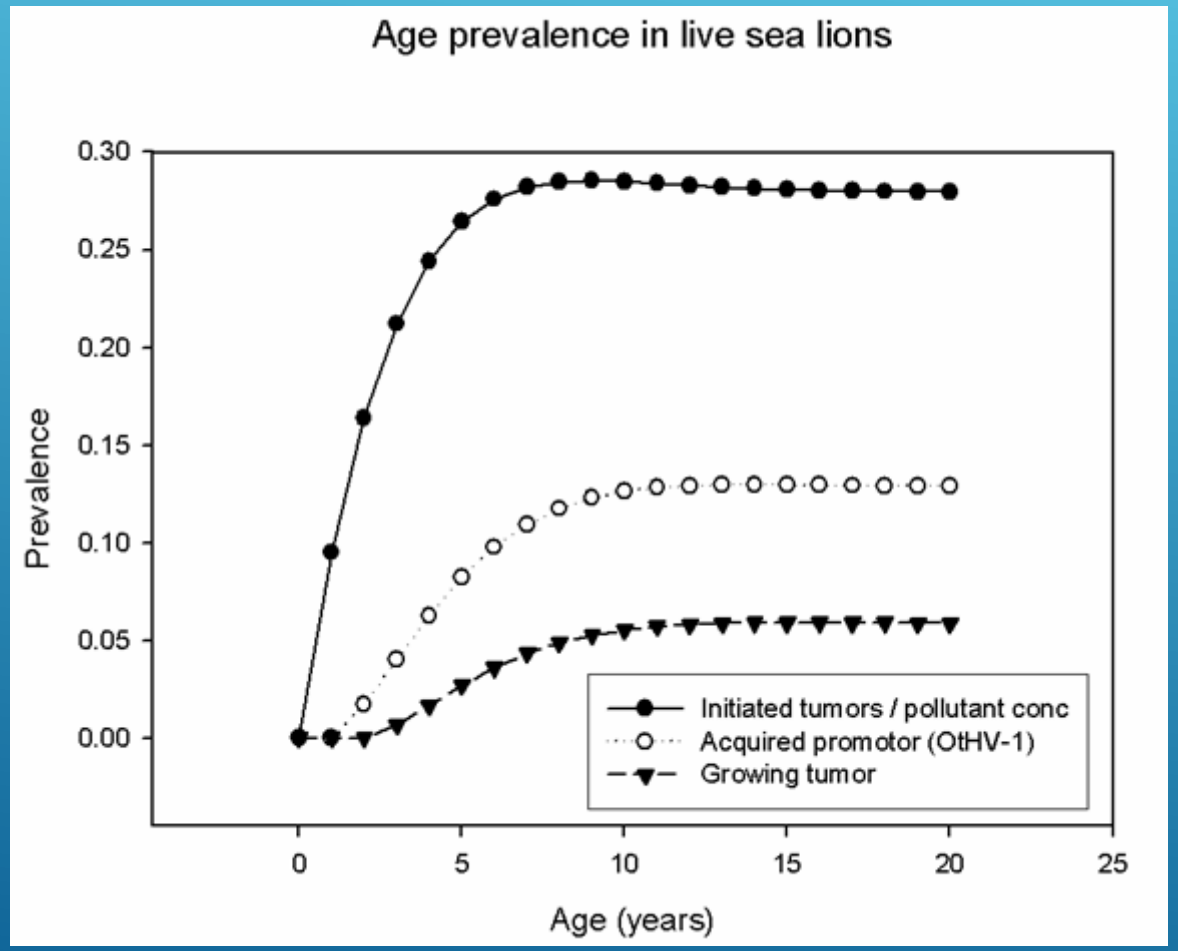
- The models have three major components

- Accumulation and loss of pollutant
  - Mass action through time
- Transmission and impact of pathogen
  - Frequency dependent, STD model.
- Initiation and promotion of tumor development
  - Modified (dynamic) Doll & Armitage (1954).

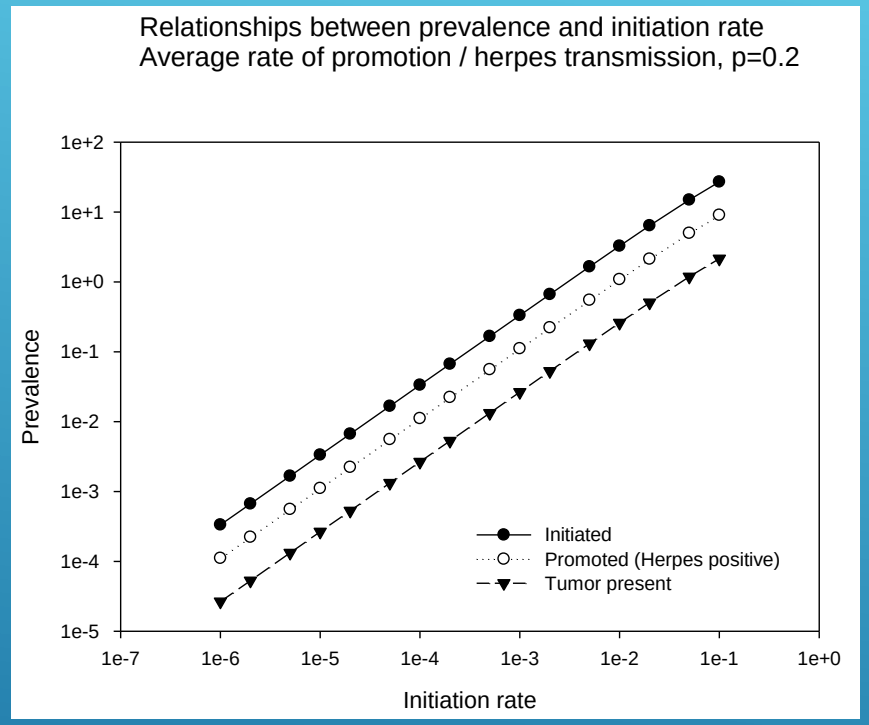


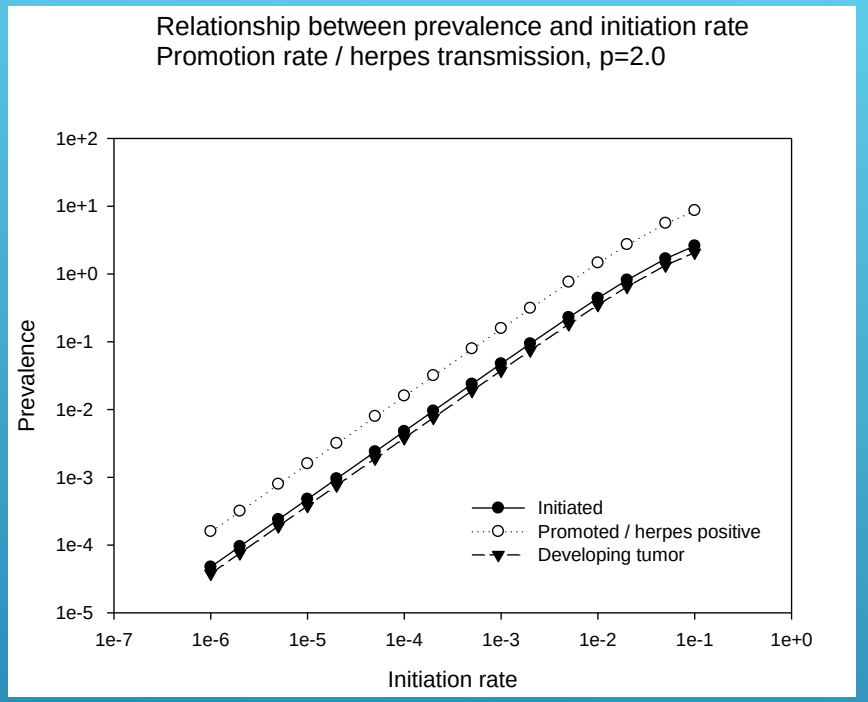
GAMMA HERPES, DDT AND CANCER IN SEA LIONS

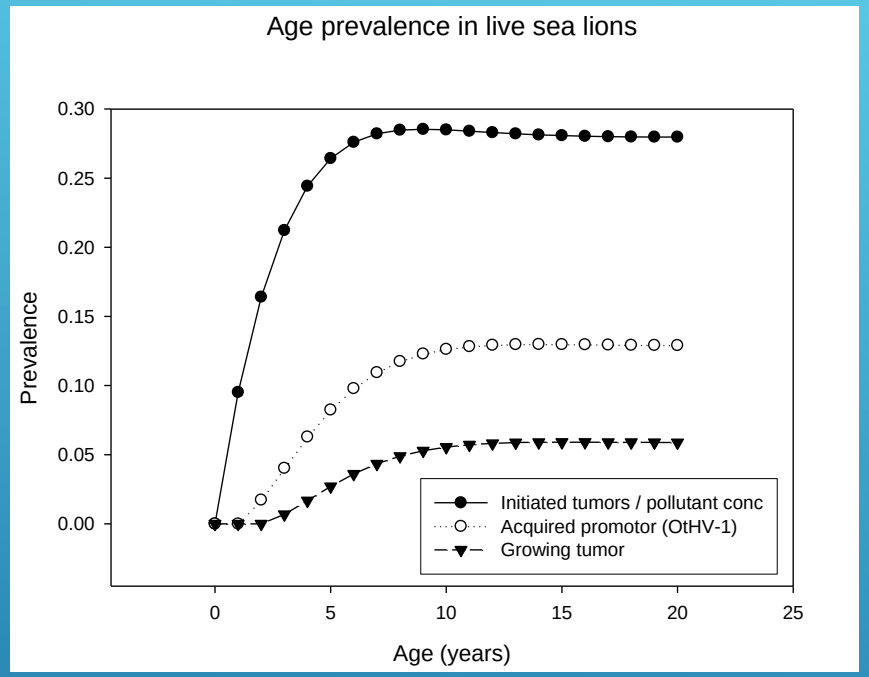
GAMMA HERPES & TUMORS IN SEA LIONS

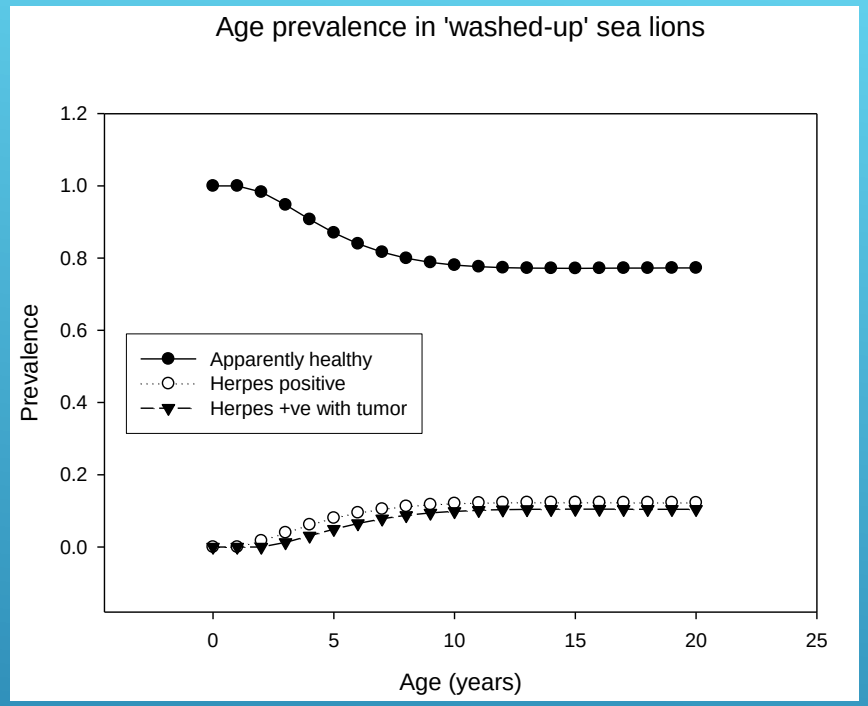


PREVALENCE AND INITIATION RATE





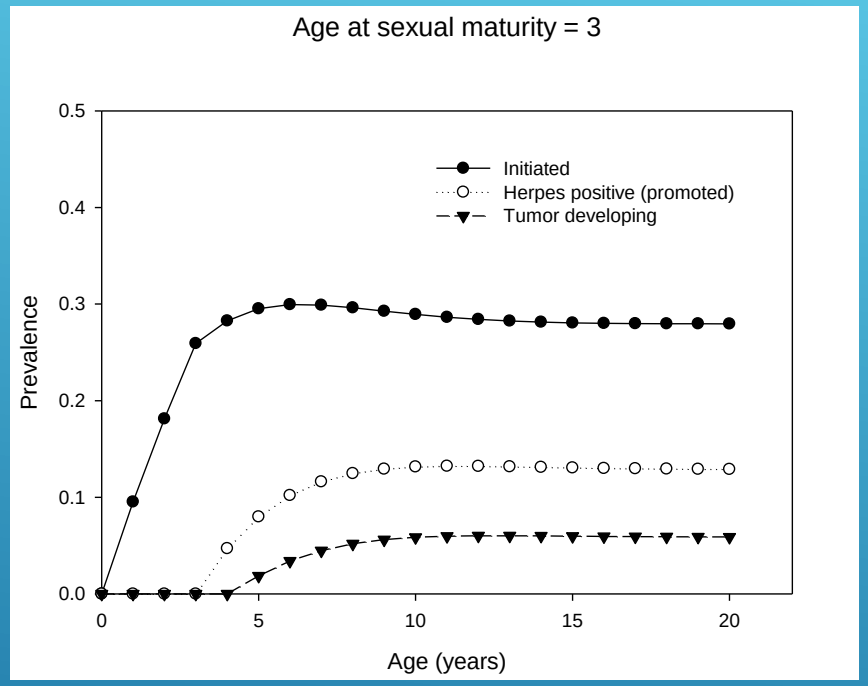




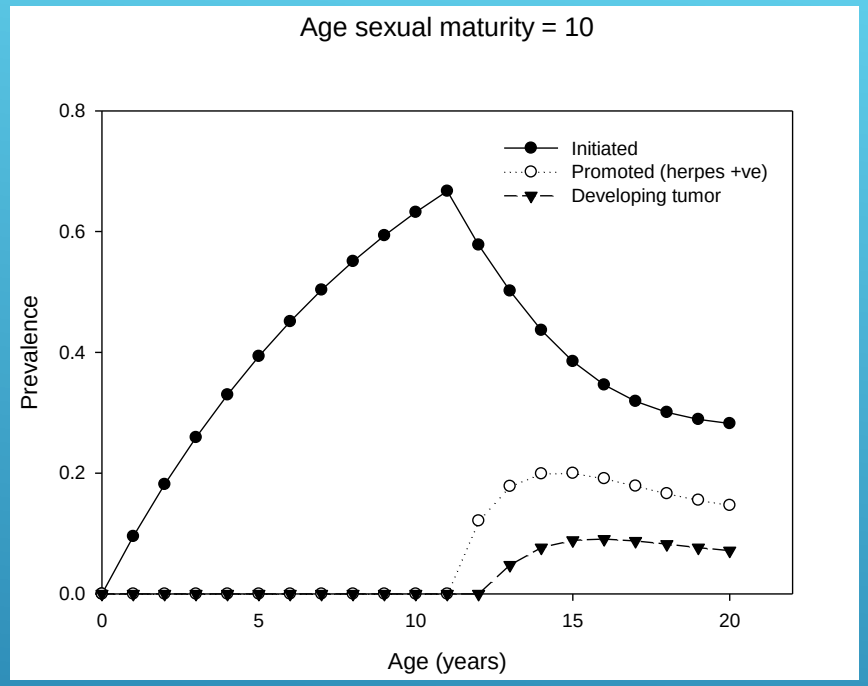
AGE-PREVALENCE IN BASIC MODEL

The proportion of sea lions with tumors is twice as high in the ‘washed ashore’ sample than in the ‘live’ population

Females



Males

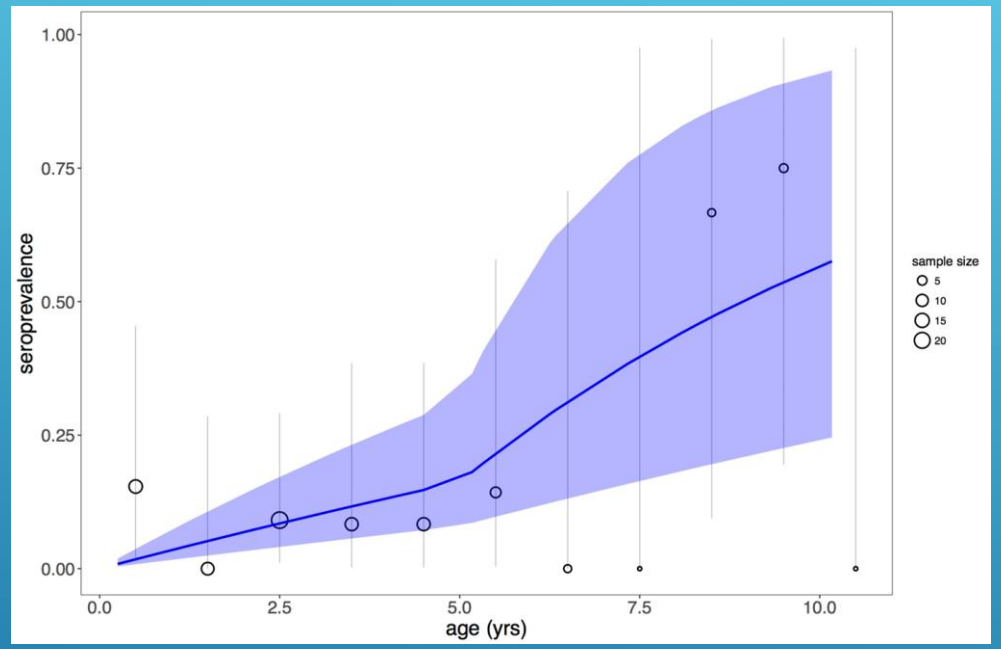


AGE PREVALENCE & SEX

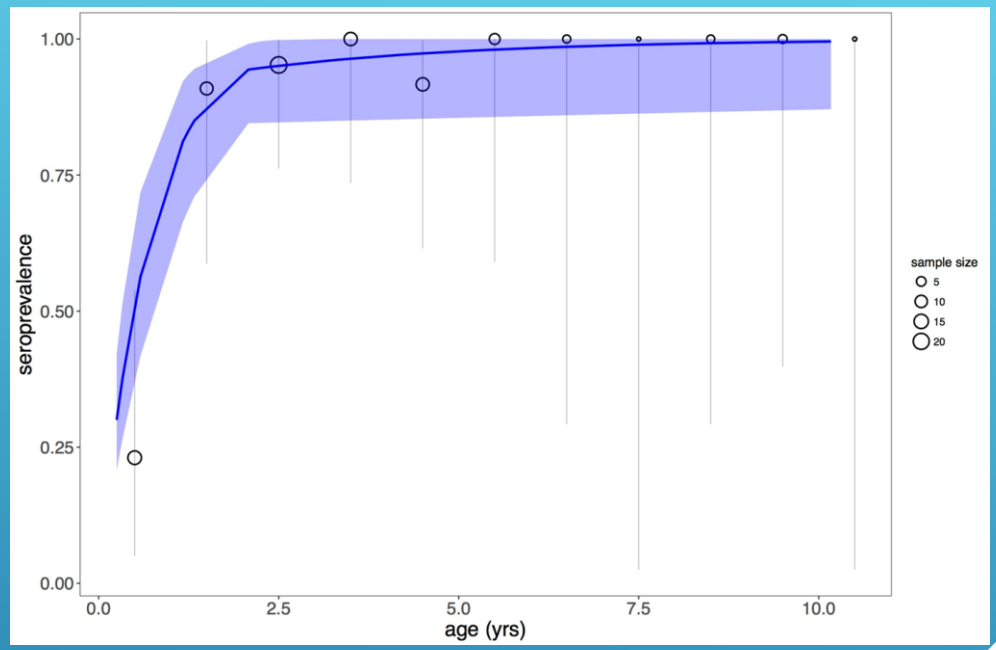
AGE PREVALENCE CURVES

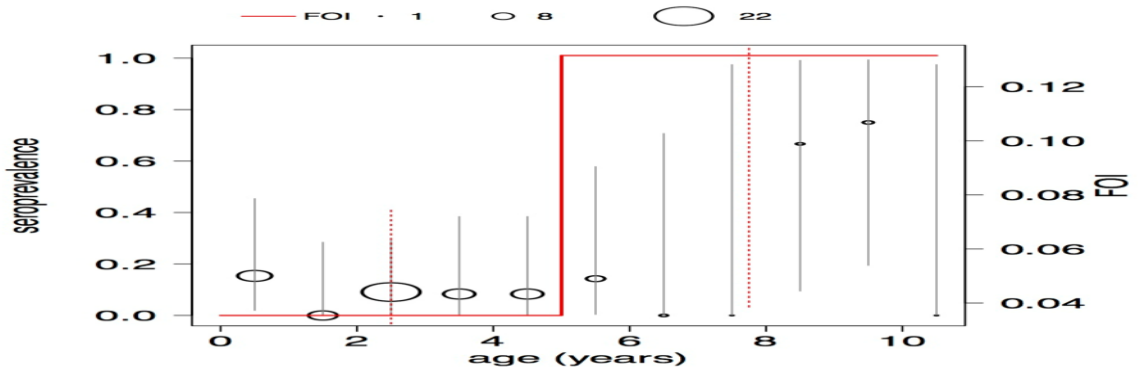
- Data from many human and wildlife diseases can be collected and presented in this fashion
- More characteristic of SIR pathogens
  - Also called a serology profile
- Less common for SEI pathogens
- How do we interpret these patterns?

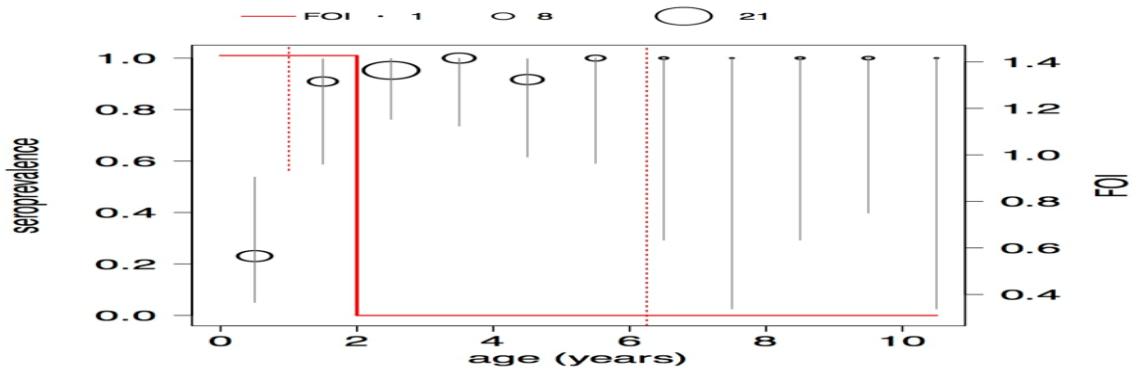
CDV in Minnesota Wolves



CPV in Minnesota Wolves

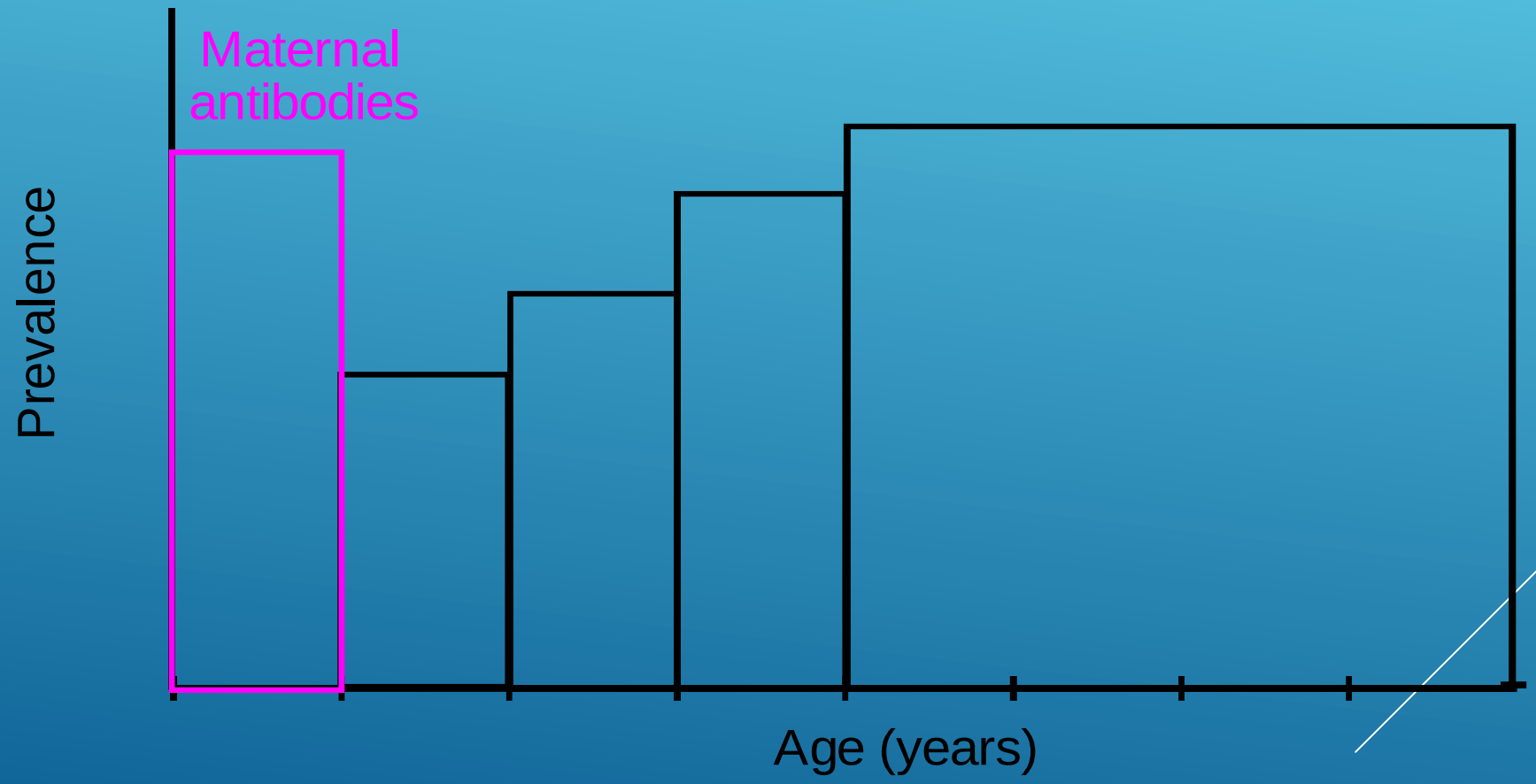






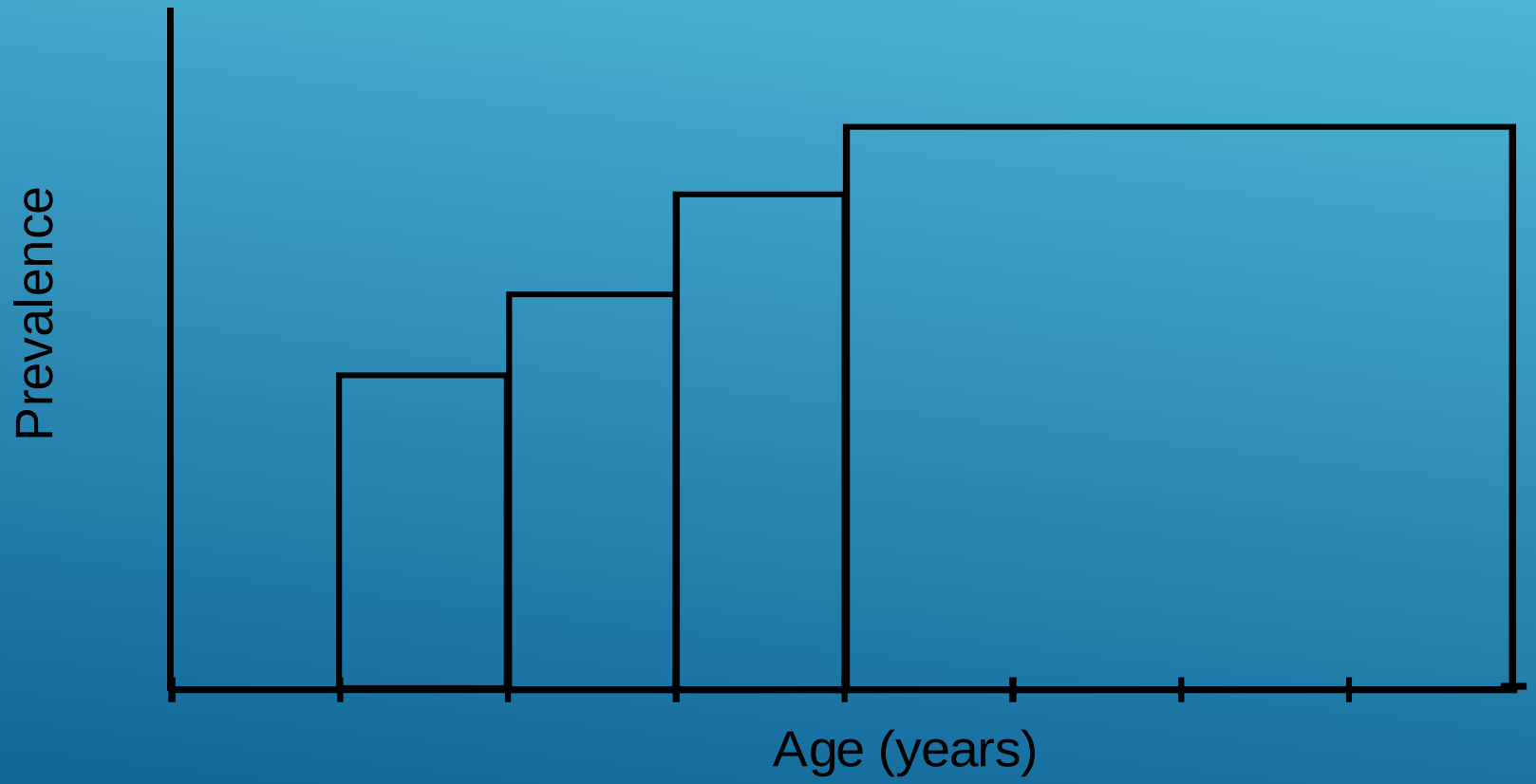
Marie L.J. Gilbertson[1], Ellen Brandell[2], L. David Mech[3], Shannon Barber-Meyer[3], Cara E. Brook[4], Paul C. Cross[5], Andrew P. Dobson[6], Meggan E. Craft[1] (in prep)

HYPOTHETICAL AGE-PREVALENCE CURVE

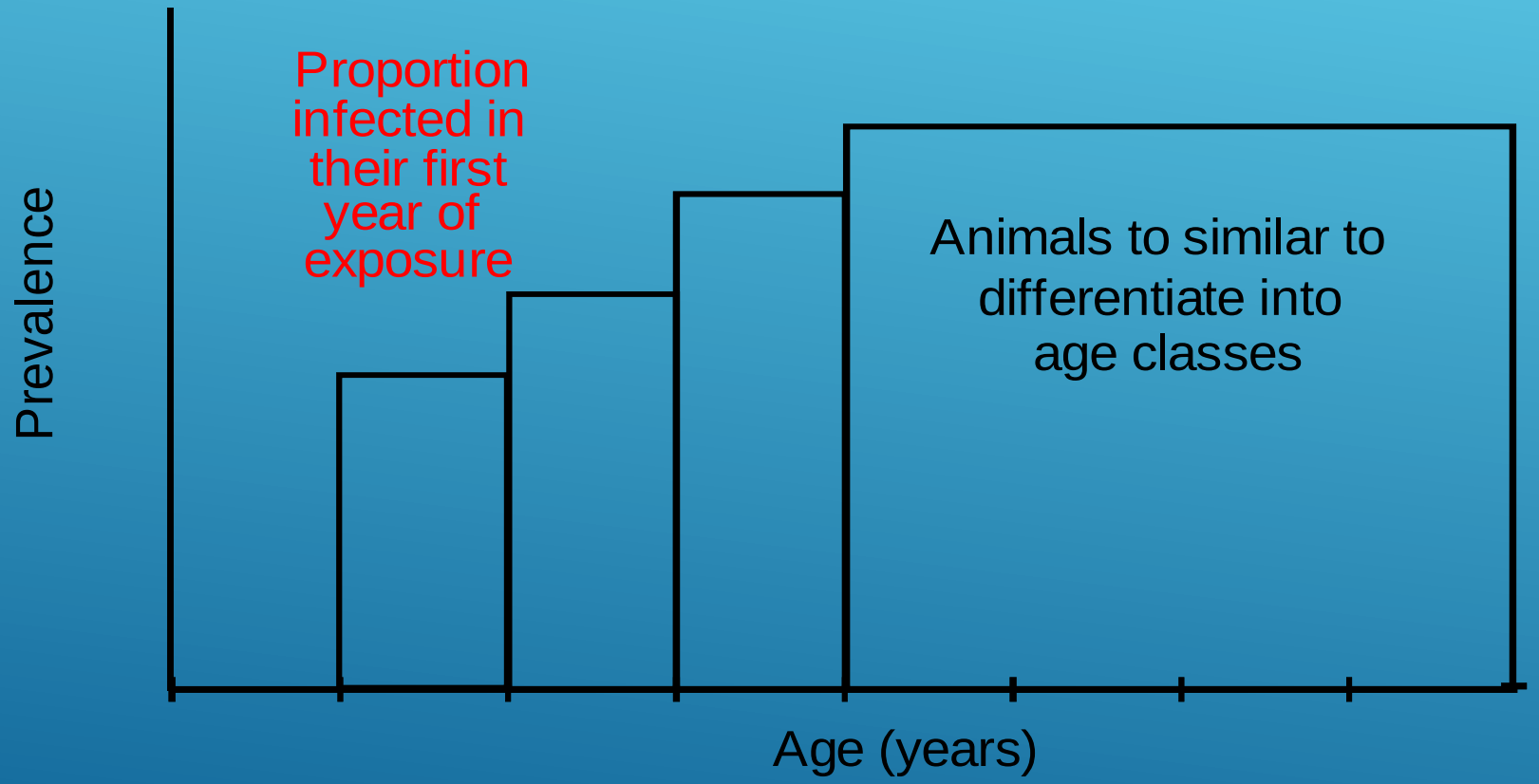


HYPOTHETICAL AGE-PREVALENCE CURVE

Let's initially ignore maternal antibodies….



HYPOTHETICAL AGE-PREVALENCE CURVE



So what is force of infection on animals in first age class to be exposed?

HYPOTHETICAL AGE-PREVALENCE CURVE

- Proportion in age class 1 p
- Age class 2 $2p - p^2$
- Age class 3 $3p - 3p^2 + p^3$
- Age class 4 $4p - 6p^2 + 4p^3 - p^4$
- Age class 5 $5p - 10p^2 + 10p^3 - 5p^4 + p^5$

Note that this begins to form a predictable series…..
Pascal's triangle…

HYPOTHETICAL AGE-PREVALENCE CURVE

- Newly infected in each class.
- Age class 1
- Age class 2
- Age class 3
- Age class 4
- Age class 5

$$p$$

$$p - p^2$$

$$p - 2p^2 + p^3$$

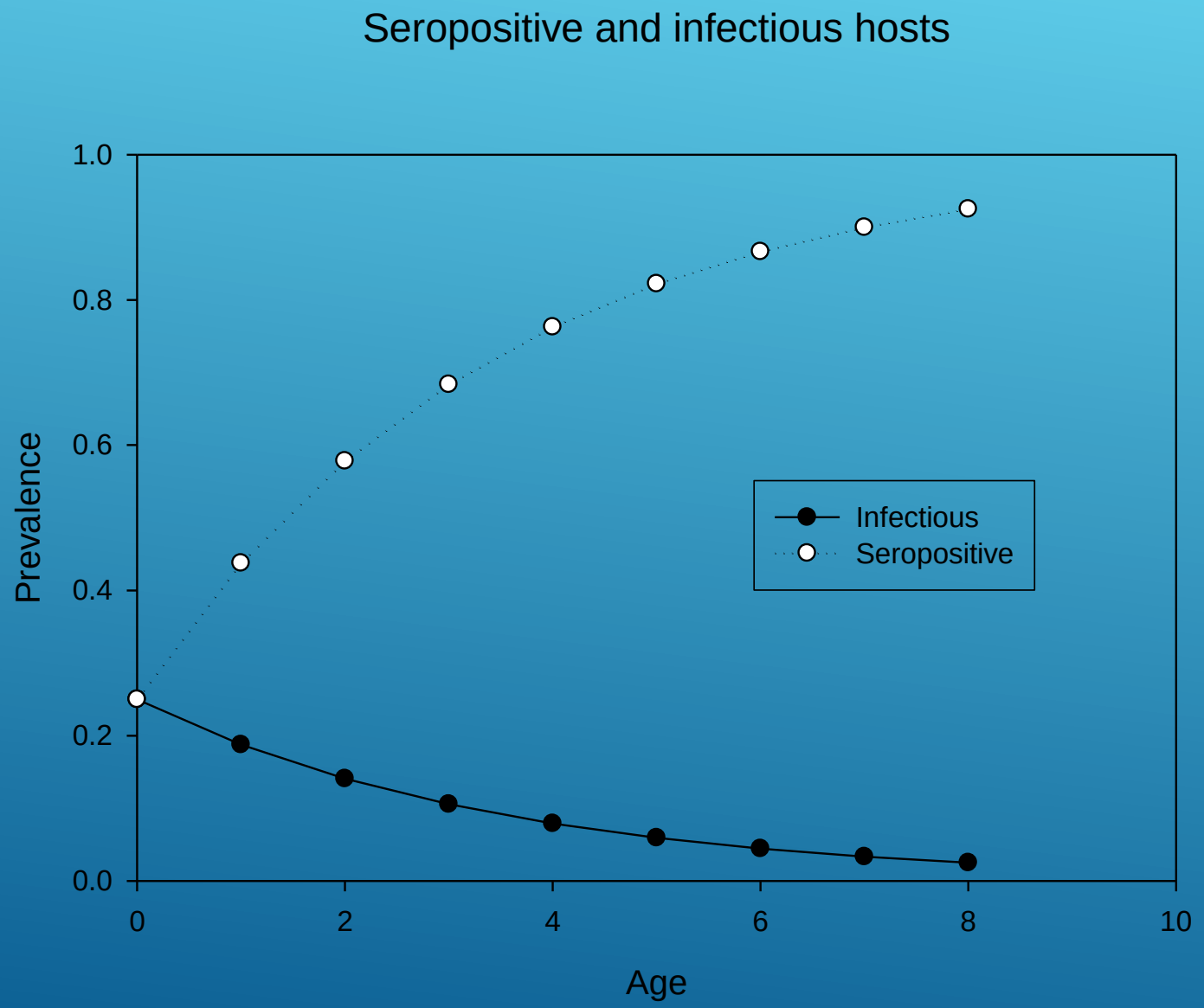
$$p - 3p^2 + 3p^3 - p^4$$

$$p - 4p^2 + 6p^3 - 4p^4 + p^5$$

Note that this corresponds to the relative risk of handling an animal of each age.
AND Actual numbers of infected have to have rescaled by
ratio of period of infectious to sampling period

Now let's plot these out…

EXPECTED AGE-PREVALENCE CURVE



FORCE OF INFECTION ON ANIMALS IN FIRST AGE CLASS TO BE EXPOSED?

- So what is 'pi'?
- Well if transmission if 'true mass-action', then (in the absence of virulence)
- Probability of infection

$$p_1 = \frac{\beta I}{N}$$

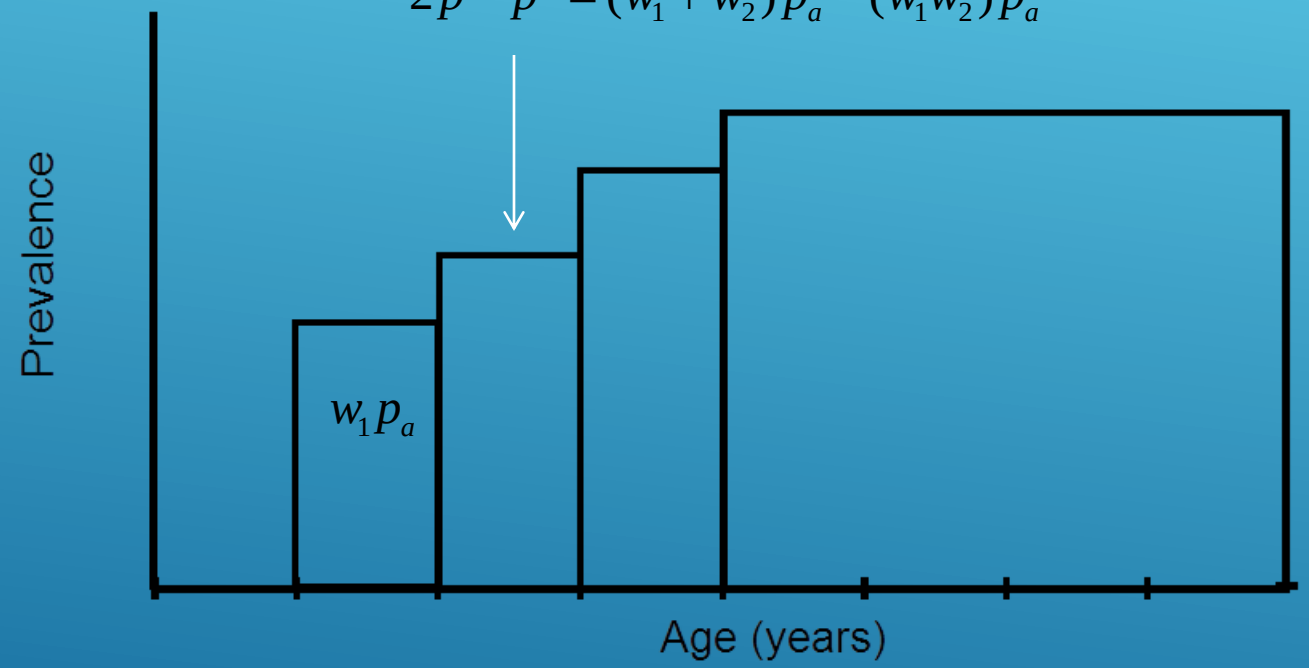
- Force of infection,

$$\lambda_i = 1 - e^{-p_i}$$

- So if we know age-prevalence, we can estimate Ro?

WHAT ABOUT DIFFERENCES IN SUSCEPTIBILITY BETWEEN AGE-CLASS?

$$2p - p^2 = (w_1 + w_2)p_a - (w_1 w_2)p_a^2$$



Assume there is an average probability of infection, p_a and this is modified in each age class by an age-class specific relative rate of infection, w_i.

HYPOTHETICAL AGE-PREVALENCE CURVE

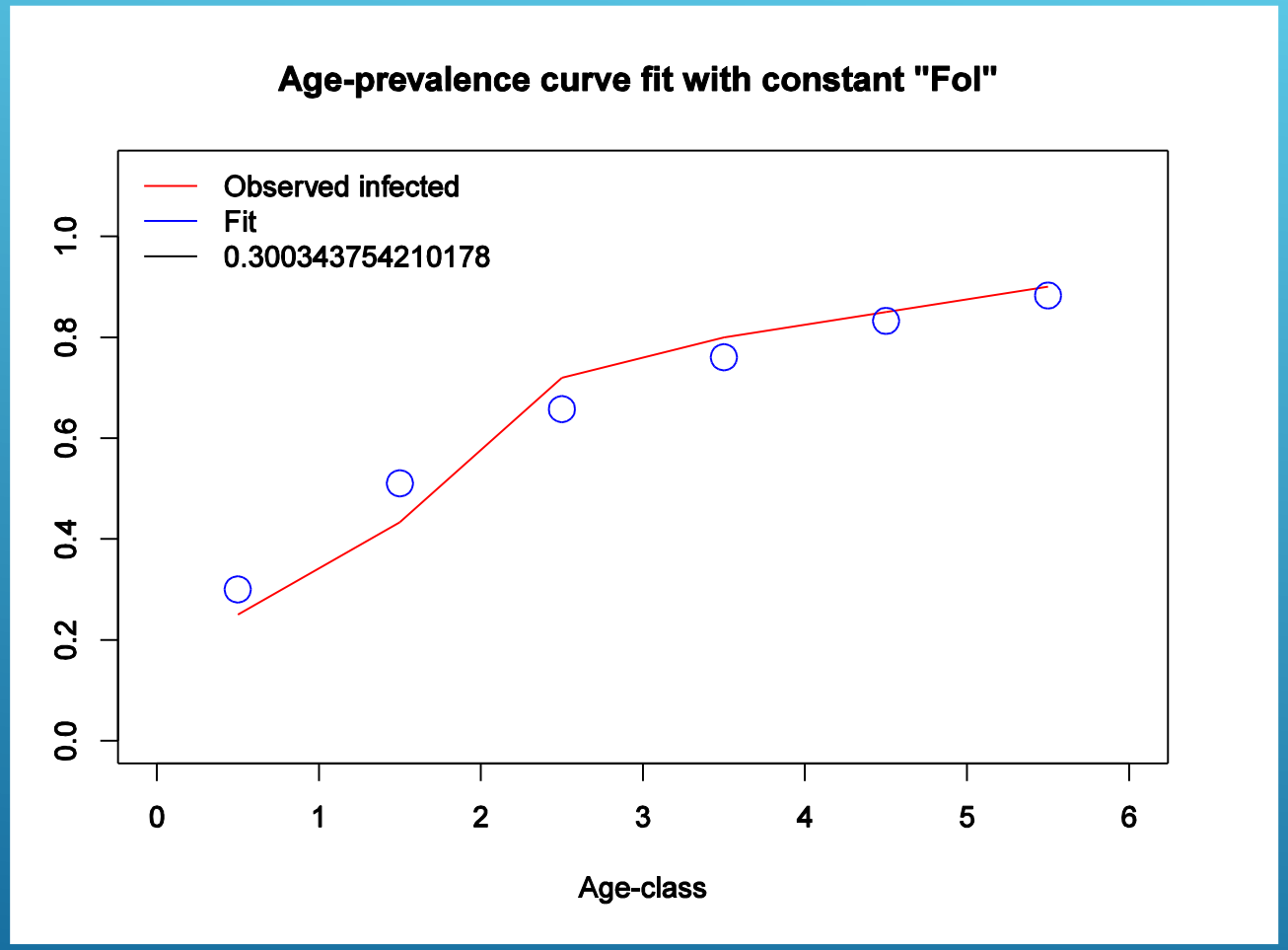
- Proportion in age class 1 p
- Age class 2 $2p - p^2$
- Age class 3 $3p - 3p^2 + p^3$
- Age class 4 $4p - 6p^2 + 4p^3 - p^4$
- Age class 5 $5p - 10p^2 + 10p^3 - 5p^4 + p^5$

Note that this begins to form a predictable series…..

$$3p - 3p^2 + p^3 \Rightarrow (w_1 + w_2 + w_3)p - (w_1w_2 + w_2w_3 + w_1w_3)p^2 + w_1w_2w_3p^3$$

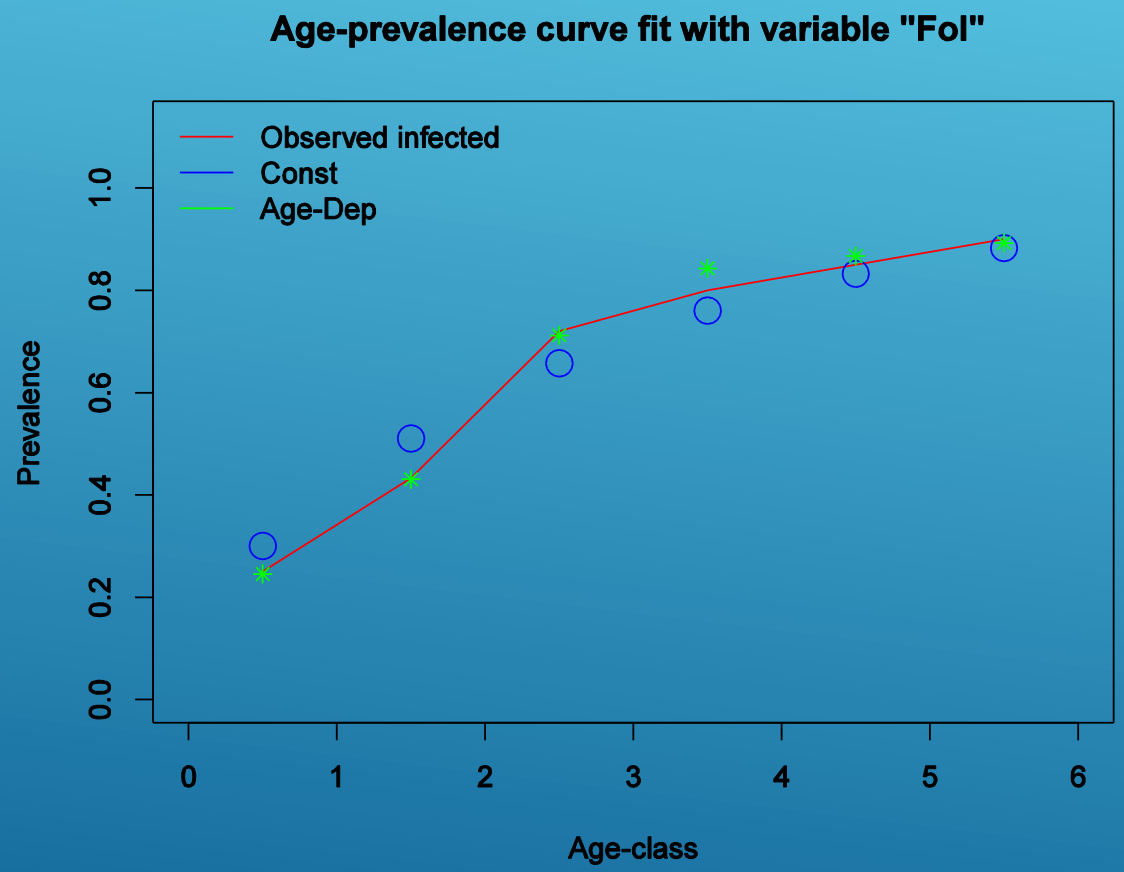
Etc…

RELATIVELY EASY TO FIT TO AGE-PREVALENCE DATA



Chagas disease in Venezuela, 1960-69.

AVERAGE P AND TWO ESTIMATED W'S.



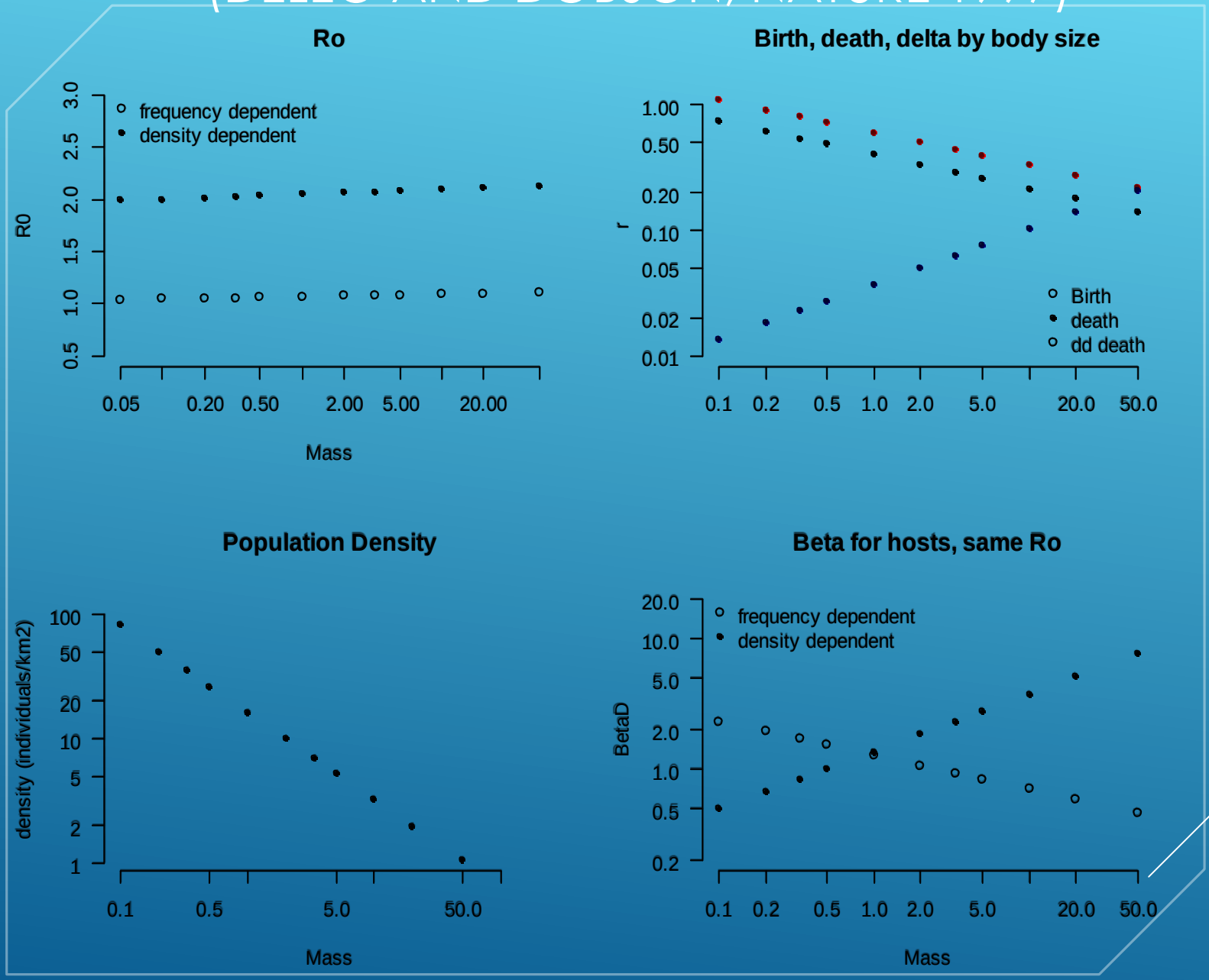
W3,w4,w5>>w1,w2

BUT WHAT DETERMINES THE AVERAGE RATE OF INFECTION FOR DIFFERENT HOST SPECIES?

All sorts of subtle local climate, habitat, behavioral, genetic differences…

Or, one general thing?

UNDERLYING DEMOGRAPHY BASED ON ALLOMETRIC SCALING WITH BODY SIZE (DELEO AND DOBSON, NATURE 1997)



BASIC MULTI-HOST MODEL STRUCTURE..

Susceptibles

Allometric scaling of all birth and death rates

$$dS_i/dt = (b_i - d_i - \Delta_i(S_i + I_i))S_i - (\beta_{ii} I_i + \sum \beta_{ij} I_i)S / (\sum_{j=1,n} N_n)^c$$

Within

Between

Infecteds

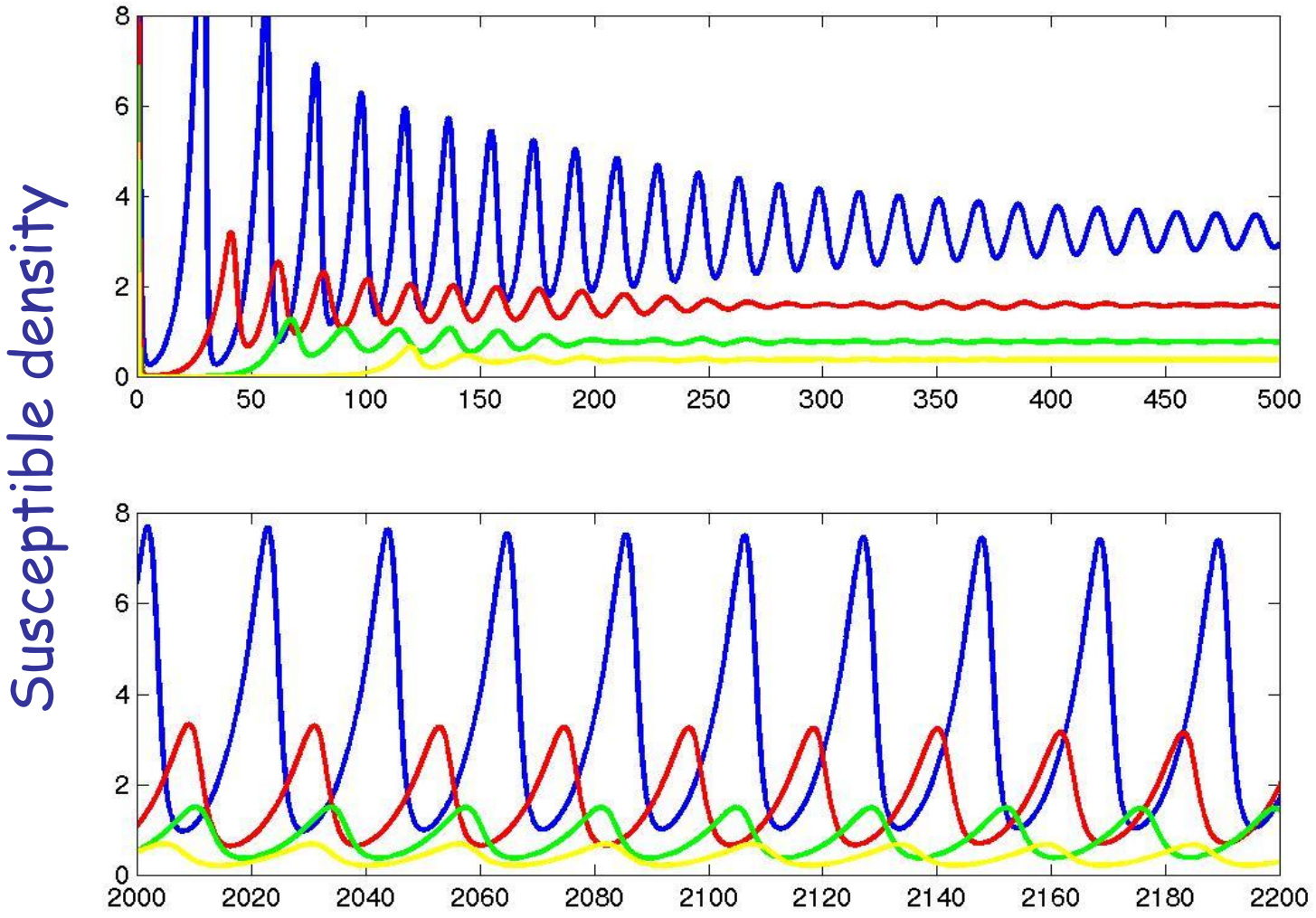
$$dI_i / dt = (\beta_{ii} I_i + \sum \beta_{ij} I_i)S / (\sum_{j=1,n} N_n)^c - d_i(1+\alpha_i)I_i$$

Between species transmission

$$\beta_{ij} = c\sqrt{\beta_{ii}\beta_{jj}}$$

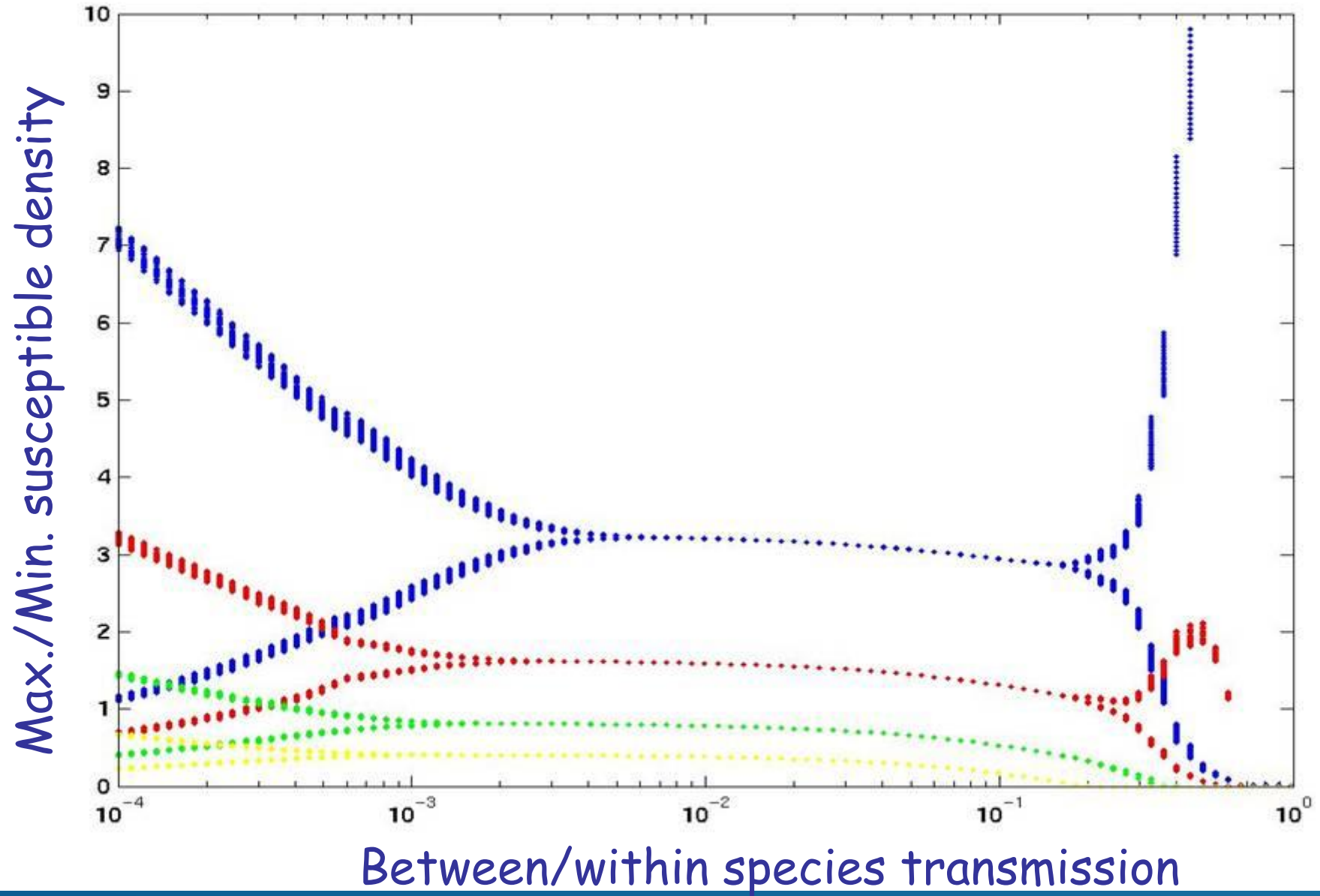
Scale virulence as a proportion of life expectancy

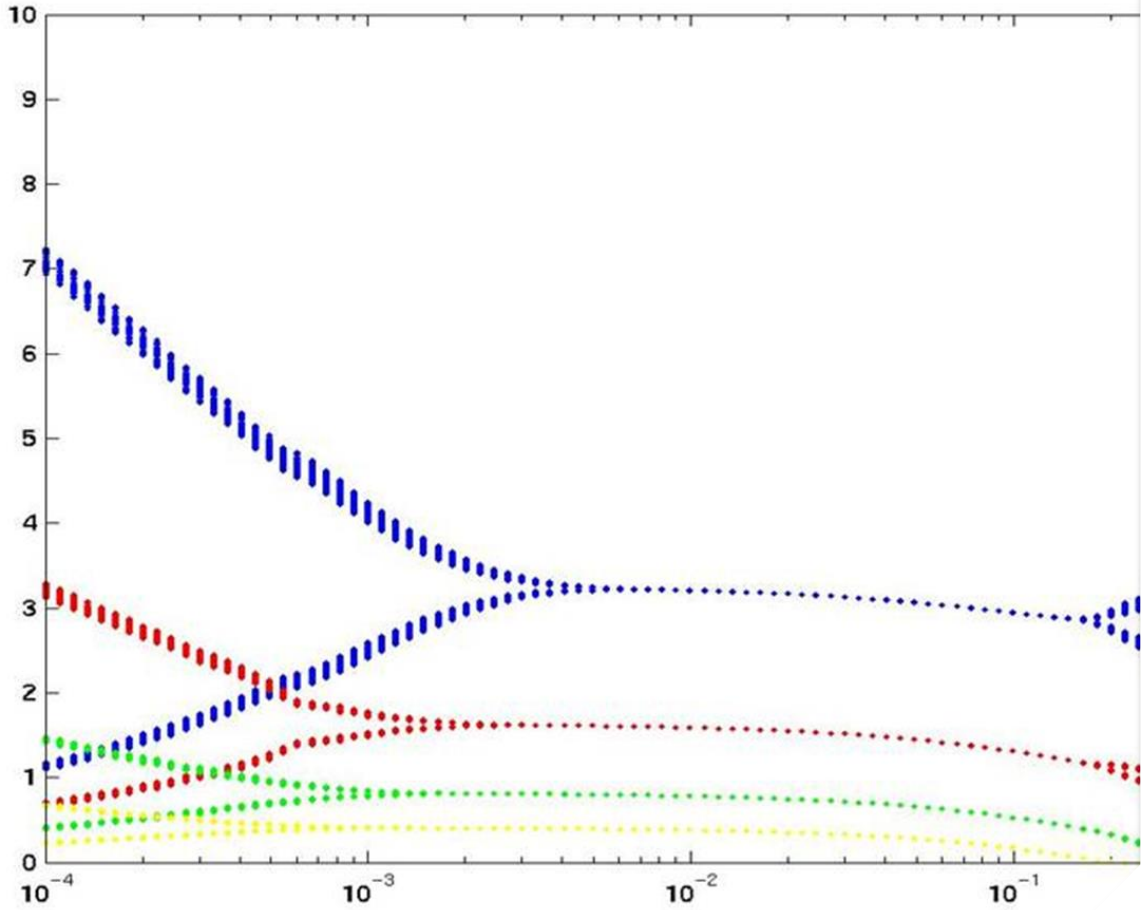
Buffering: dynamics in DD case



Between sps. transmission

BUFFERING: DYNAMICS IN DD CASE





Between age class transmission

- Would we see similar effects if Hosts of Different AGES illustrate different durations of incubation and Infectivity?

Prepatent period x size

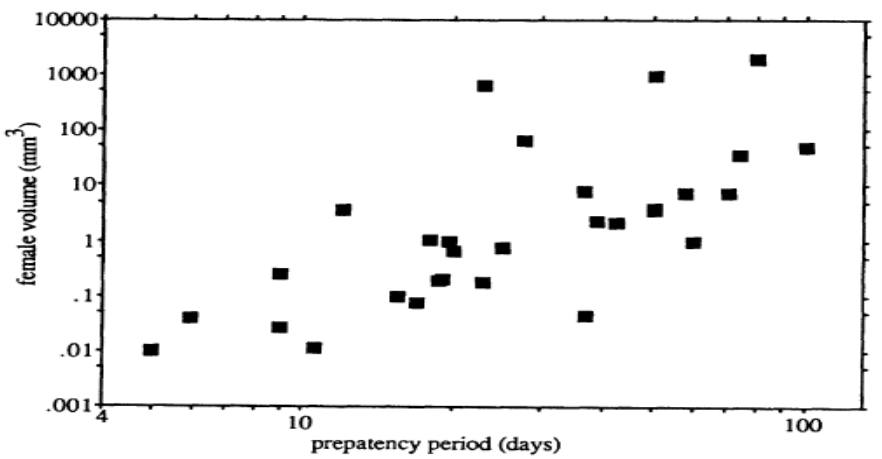


Fig. 1. Log-log plot of the association between prepatency period and female body volume across generic means. r = 0.70, β = 2.61, p < 0.0001, n = 31 genera, based on 49 species.

Fecundity x size

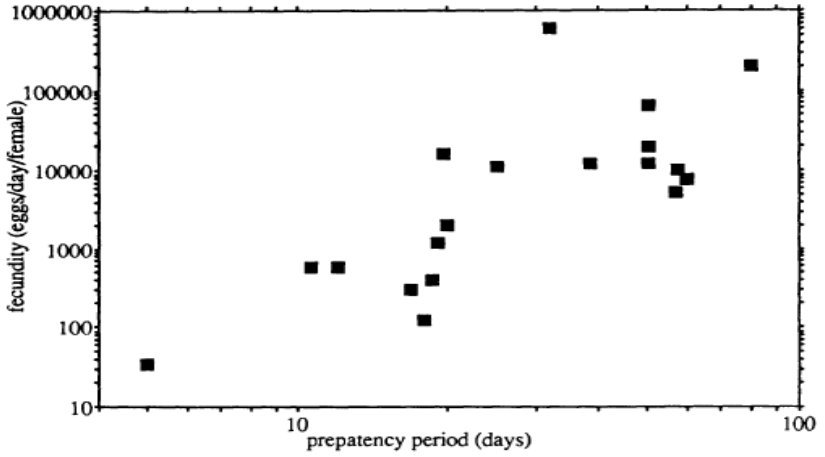


Fig. 2. Log-log plot of the associations between prepatency period and fecundity across generic means. r = 0.77, β = 2.66, p < 0.0001, n = 19 genera, based on 28 species.

WHAT ABOUT ALLOMETRIC SCALING OF BOTH HOST AND PARASITE?

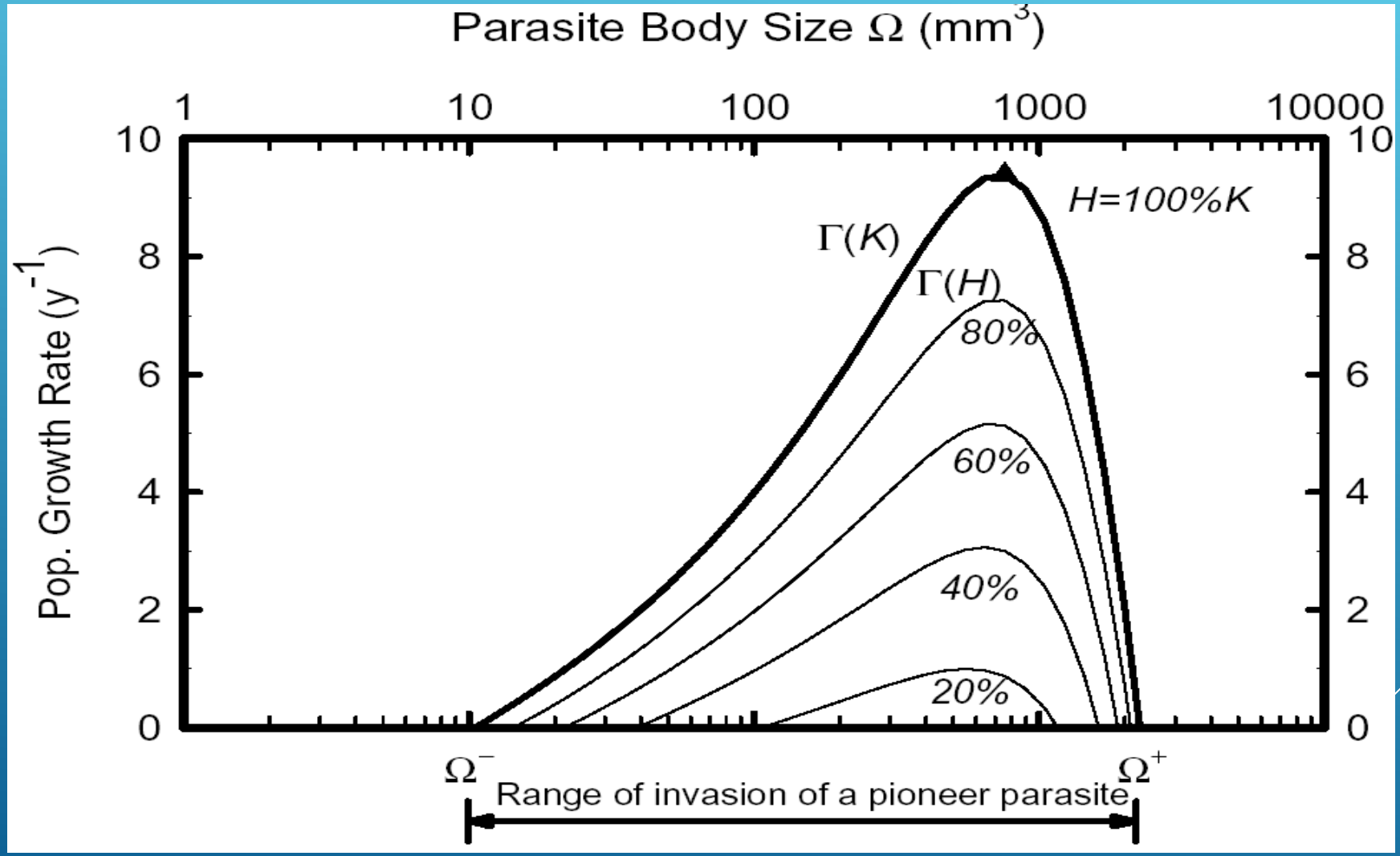
(From Skorping, Read and Keymer, Oikos, 1991)

Table 1. Summary of main model parameters and their allometric relationship with body size, along with unit of measure, the corresponding reference and the formula used to compute them. W [kg] is host body size and Ω [mm^3] is parasite body size. Data for prepatent and patent period were extracted from Fig. 3 of Skorping *et al.* (1991) and analysed with Ranged Major Axis Regression on the log-log transformed data with LMODEL2 in R: slope = 1·498, confidence interval [0·839, 2·405]; intercept = 0·142, confidence interval [−2·706, 2·211]; $n = 24$, $r = 0·66$, $P < 0·001$

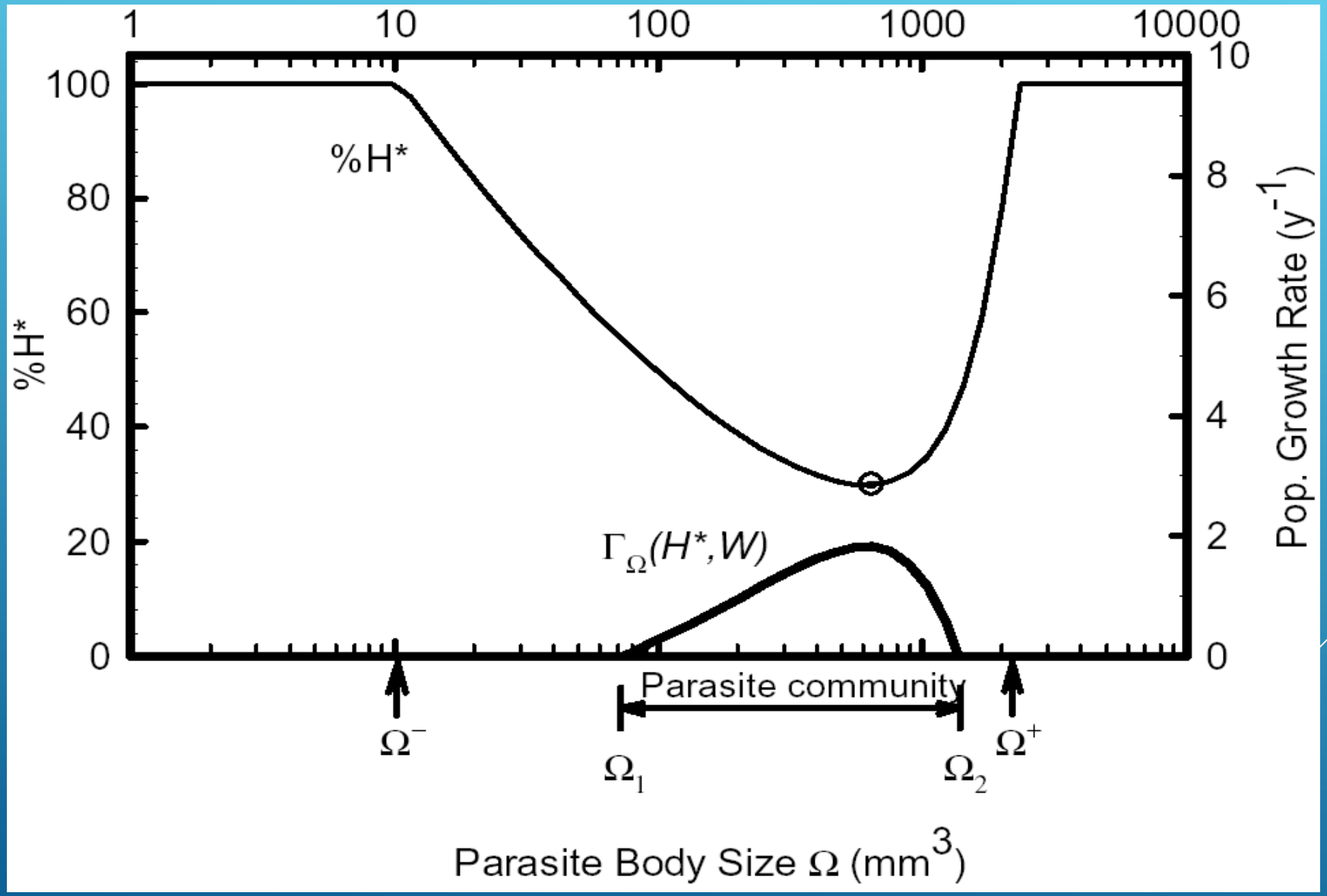
Host				
	Parameters	Units	Function/value	References
K	Parasite-free carrying capacity for mammalian herbivores	No. km^{-2}	$=103\ W^{-0·93}$	Peters (1983, p. 167)
r	Per-capita growth rate		$=0·9\ W^{-0·27}$	Damuth (1981), Peters (1983)
B	Per-capita mortality rate		$=0·4\ W^{-0·26}$	Peters (1983), Calder (1984), Schmidt-Nielsen (1984).
Parasite				
	Parameters	Units	Relationships	References
λ	Per-capita fecundity	Eggs·day^{-1}	$=10^{3·5}\ \Omega^{0·79}$	Hechinger *et al.* (2012)
T	Time to maturity	Days	$=10^{1·4}\ \Omega^{0·24}$	Hechinger *et al.* (2012)
Pat	Patent period	Days	$=1·15\ T^{1·498}=1·15·(10^{0·14}\ \Omega^{0·24})^{1·498}=144\ \Omega^{0·359}$	RMA regression on Skorping *et al.*'s (1991) data digitized from Fig. 3
μ	Mortality rate of adult parasites	Day^{-1}	$=1/\text{Pat}=0·00693\ \Omega^{-0·359}$	
σ	Maturation rate	Day^{-1}	$=1/T=0·0398\ \Omega^{-0·24}$	
S	Fraction of worms surviving to age at maturity		$=\sigma(\Omega)/[\sigma(\Omega)+\mu(\Omega)+b(W)]$	As in Morand and Poulin (2002)
k	Clumping parameter	A dimensional	Between 0·01 and 1	Shaw *et al.* (1998)
H_o	Seminaturation constant	No. km^{-2}	Set up for any host body size W so that $R_o \leqslant 10$	
α	Per-capita, per-worm, parasite induced mortality	# of host · # of parasite^{-1} · time^{-1}	$=\varepsilon\ \Omega^{q}/W^{0·75}$	This study. Parameters q and ε set so that the resulting allometric relationship between host body size (kg) and parasite body size (mm^3) coincides with that estimated empirically by Morand and Poulin (2002).

DeLeo, Gatto and Dobson, Parasitology, 2015

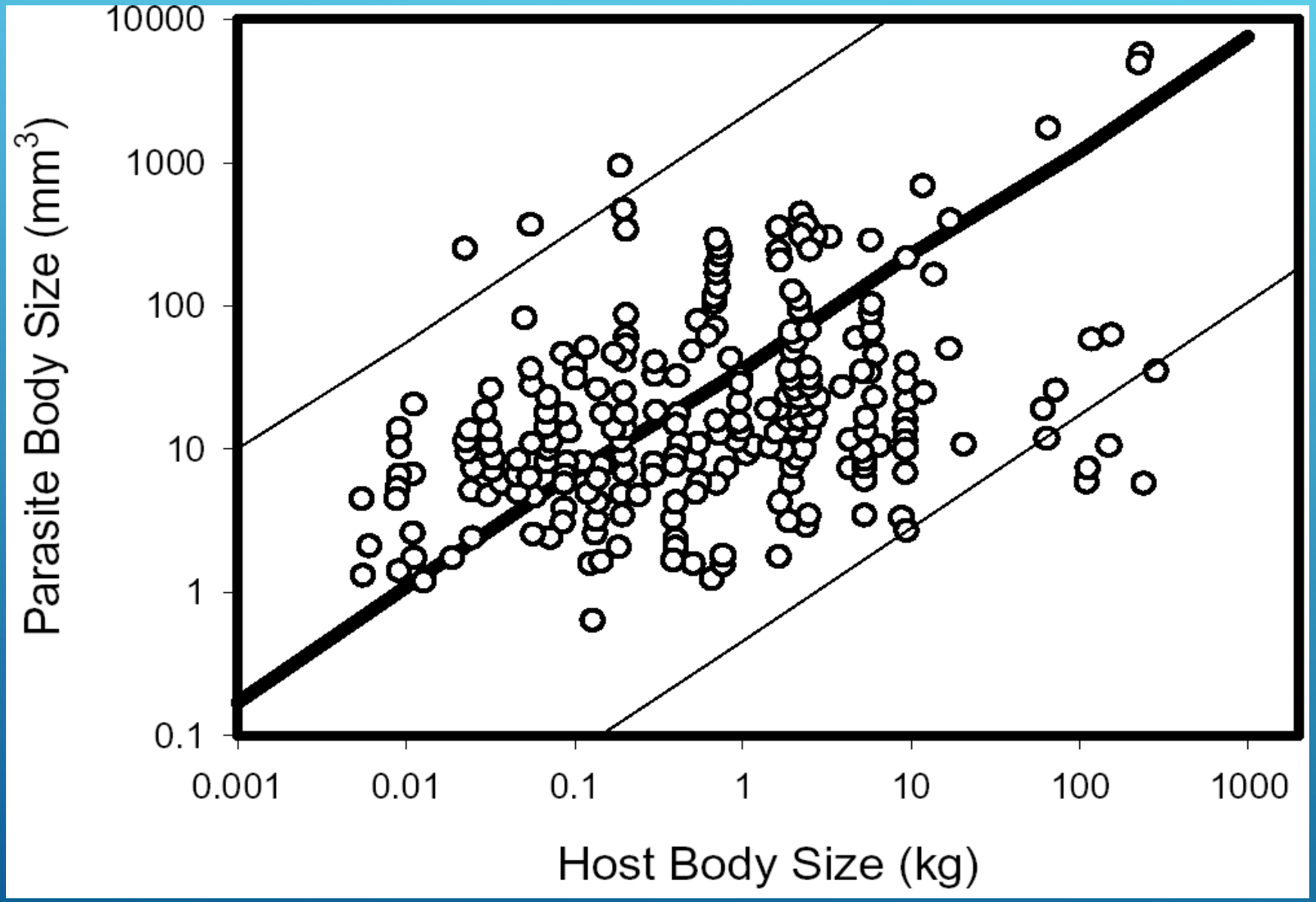
ALLOMETRIC SCALED DYNAMIC MODELS FOR PARASITIC NEMATODES AND THEIR HOSTS



INVASION CRITERIA VERSUS EQUILIBRIUM COMMUNITY



MODEL FIT AND OBSERVED DATA



What is the slope?

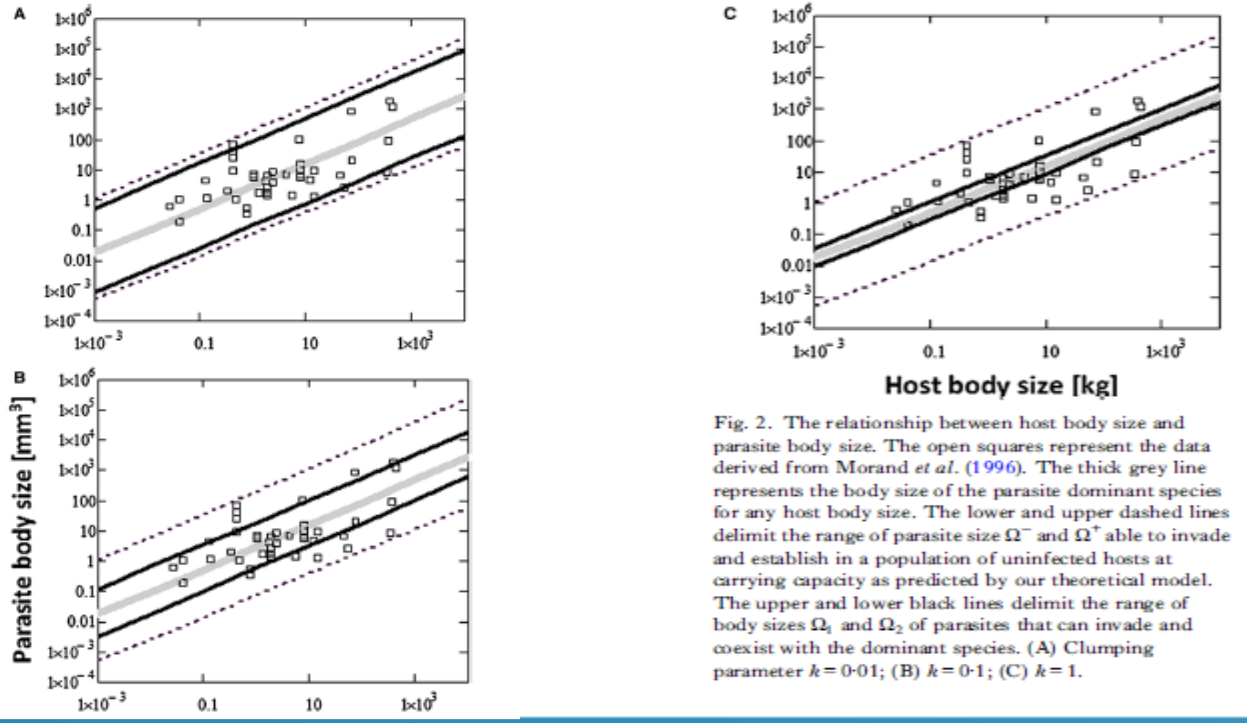


Fig. 2. The relationship between host body size and parasite body size. The open squares represent the data derived from Morand *et al.* (1996). The thick grey line represents the body size of the parasite dominant species for any host body size. The lower and upper dashed lines delimit the range of parasite size Ω^- and Ω^+ able to invade and establish in a population of uninfected hosts at carrying capacity as predicted by our theoretical model. The upper and lower black lines delimit the range of body sizes Ω_1 and Ω_2 of parasites that can invade and coexist with the dominant species. (A) Clumping parameter $k = 0{\cdot}01$; (B) $k = 0{\cdot}1$; (C) $k = 1$.

RELATIONSHIP BETWEEN HOST BODY SIZE AND NEMATODE PARASITE BODY SIZE (SLOPE ~ 2, LARGER HOSTS HAVE DISPROPORTIONATELY LARGER PARASITES HOSTS LIVE LONGER, SO PARASITES CAN GROW BIGGER AND BE MORE FECUND?)

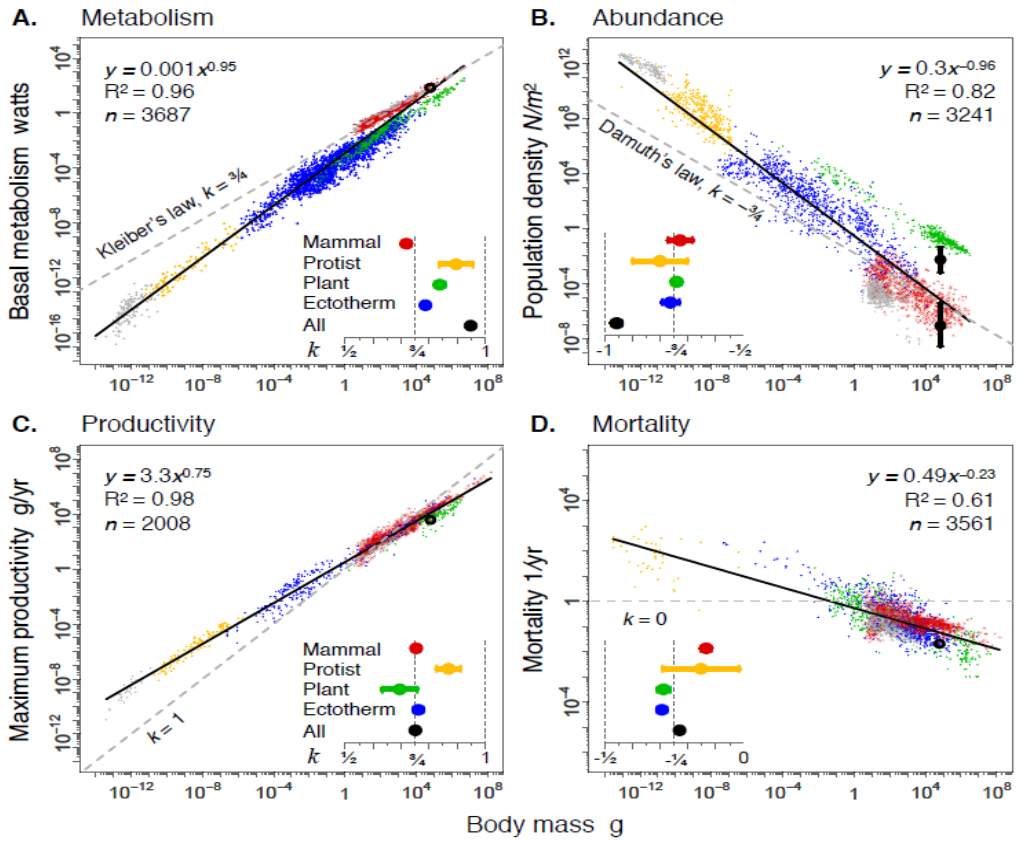


Fig. 1. Scaling of ecological variables with body mass across taxa. Points are separate species average values or minimum values in the case of basal metabolism, except for plants and data unresolved to species level. The number of data points is *n*. Scaling exponents *k* and 95% confidence intervals are shown in the insets, except for birds and bacteria, shown in grey (birds are mostly masked by mammals). Black circles are humans, with range shown in B for the 1000 largest cities and 300 hunter-gatherer communities (not included in *n*). Regressions are in SI.

Hatton, Dobson, et al, submitted.

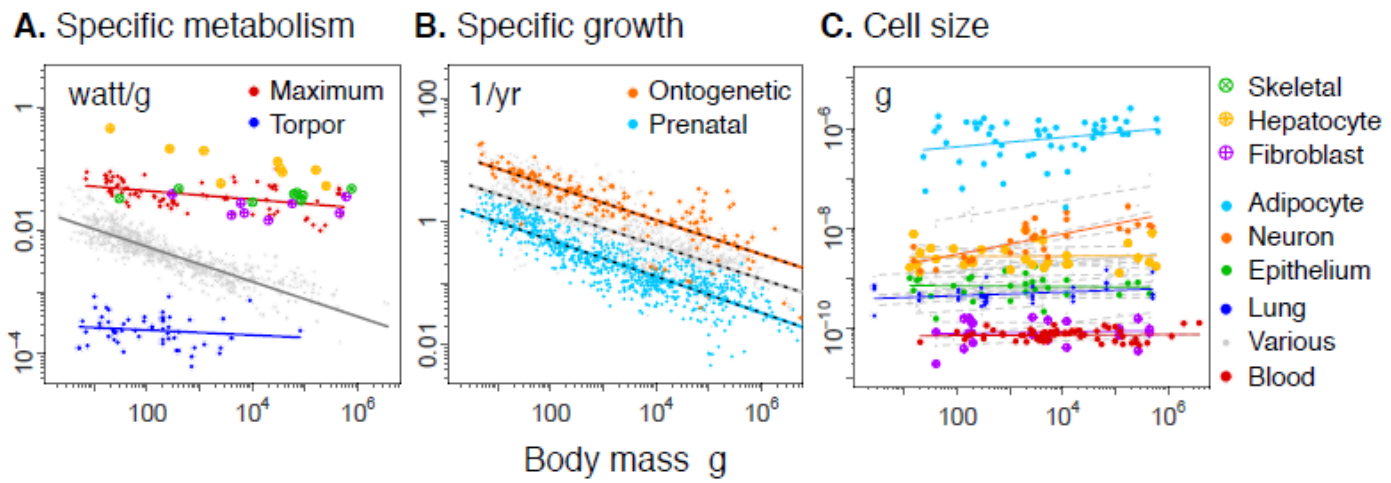


Fig. 3. Mammal range in specific metabolism, growth and cell size. Mammal basal metabolism and reproductive growth are shown as grey points in A and B, corresponding to the red points in Fig. 2 A and D, respectively. Regressions are in SI.

A. Mammal specific metabolism across different activity states. Maximum (k = –0.07) and minimum torpor (k = –0.04) are compared with basal rates (grey points; k = –0.28), and three types of experimental cell cultures: skeletal, hepatocyte and fibroblast, where the sizes of the latter two are shown in C. Data are not temperature corrected for reasons outlined in Methods, but would shift torpor closer to basal rates.

B. Mammal specific growth across different life stages. Ontogenetic growth (k = –0.28) and prenatal growth (k = –0.29) are compared with reproductive growth (grey points; k = –0.28).

C. Mammal average cell sizes. Cell volume was converted to mass assuming 1 gram=10^{12} μm^3. Sperm and egg cells are excluded and are typically the smallest and largest cells, respectively. Grey dashed lines are regressions for other specific cell types not listed. In total, only six of 28 cell types show significant positive relations: adipocyte, epidermis, alveolar macrophage, and three types of neurons, all with shallow slopes of $k < 0.2$.

EMERGING QUESTIONS

- Do the dynamics of the Immune Systems Scale with Size/Mass of its Constituents. Can we use this to make next generation models of immune systems (as food-webs)

- Do incubation periods and durations and infectivity change with host age? Do these also change as virus and bacteria ‘age’

- How can we tease apart background rates of infection from age-dependent changes in susceptibility and transmission efficiency