RTG 2220 EvoPAD

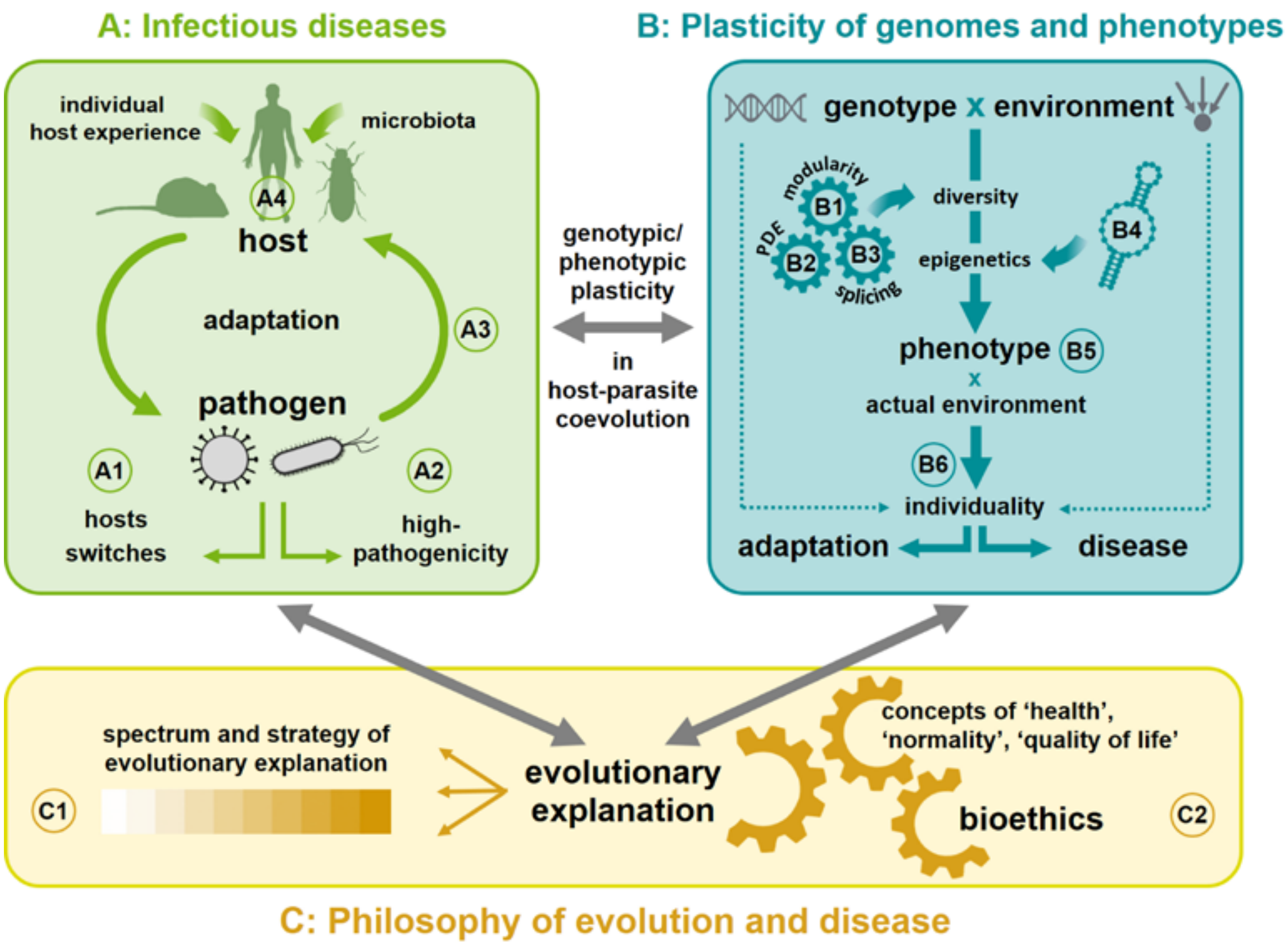
Summer School 2018

Infectious diseases

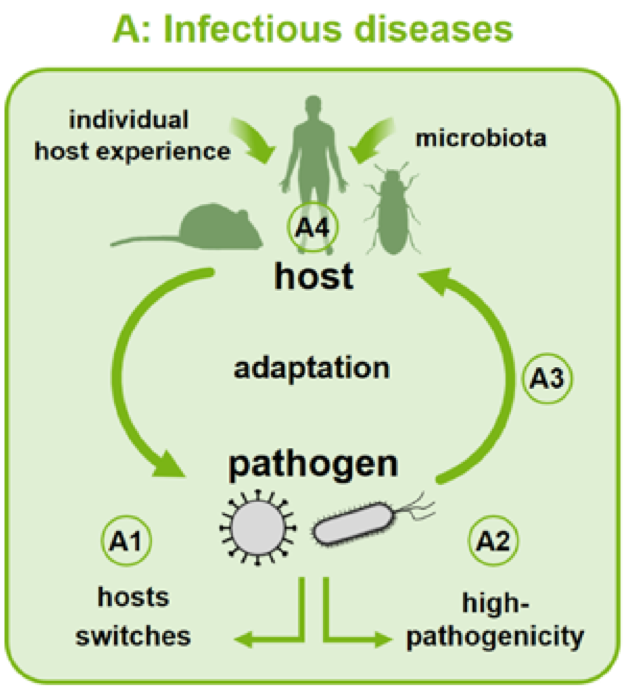
Evolutionary aspects

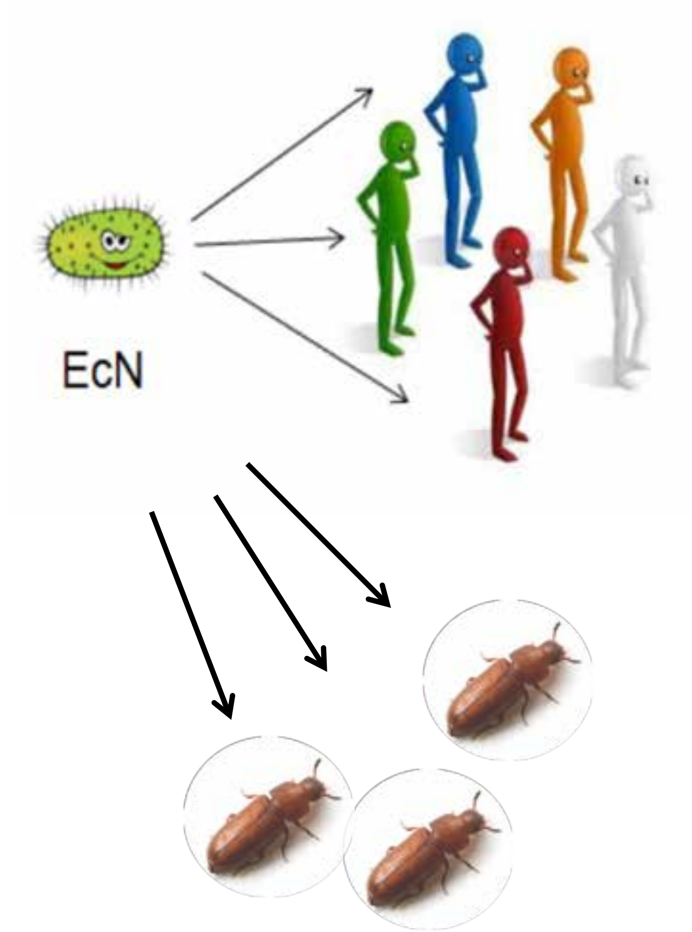
Ulrich Dobrindt & Joachim Kurtz

An important role for infectious diseases in our RTG EvoPAD



Related questions, studied in humans and animals within EvoPAD





Adaptation of *E. coli* Nissle to individual human hosts (Dobrindt project)

… and to flour beetles differing in immune status (Kurtz project)

Most of the species on earth
are parasites!

Windsor (1998)

Parasites everywhere…

Hair follicle mite *Demodex folliculorum*

Fascinating adaptions...

Cymothoa exigua, a parasitic isopod,
replacing the tongue of the fish host

Parasites everywhere...

We can assume that every organism is a host to parasites!

... even worms: bacteria as parasites!

... even bacteria: viruses (phages) as parasites!

... even viruses: selfish genetic elements as parasites!

What is a parasite?

Definition:

A parasite is an organism living in or on another organism, the ***host*** – feeding on it, showing some degree of structural adaptation to it, and causing some harm (i.e. reducing host fitness).

Please note this evolutionary definition includes parasitic viruses, bacteria, fungi, protozoan and metazoan animals.

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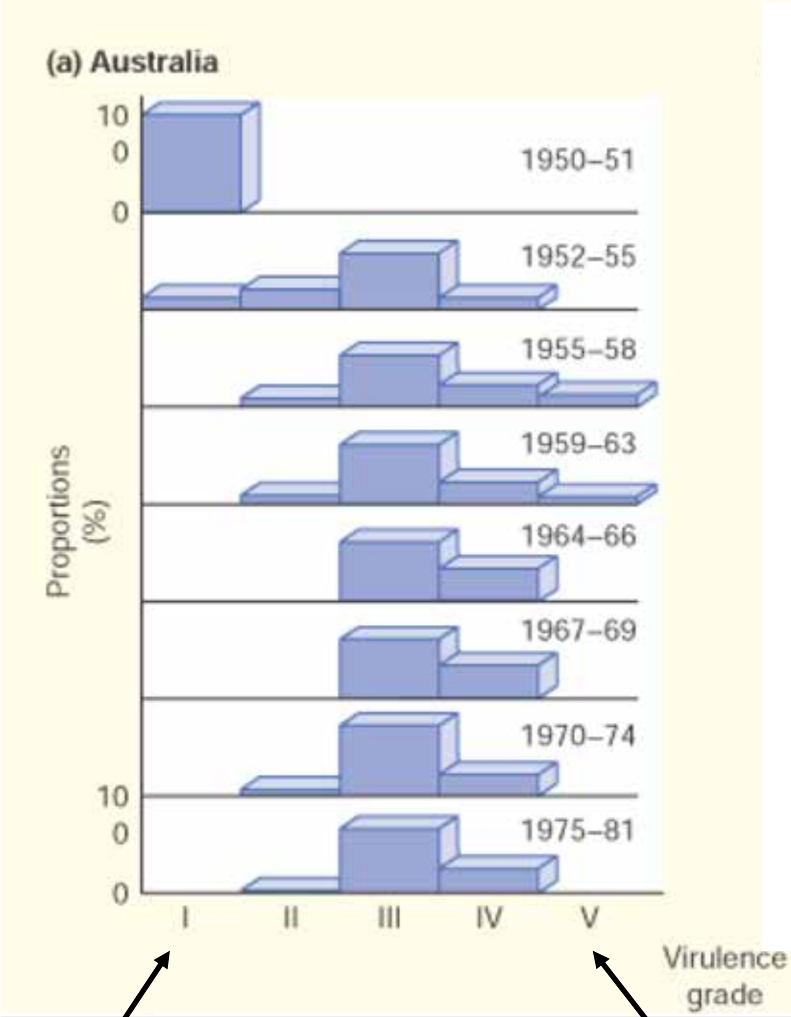
Virulence

Evolutionary Definition:

Reduction in host fitness due to parasite infection.

Evolution of Virulence

Rabbits and *Myxomatosis* virus in Australia



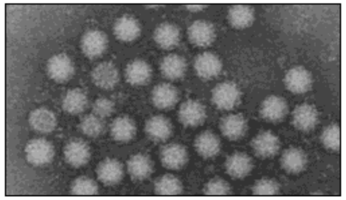


Foto: Dr. von Rhein

Highest virulence decreases virus fitness, since transmission is impaired (rabbits die too fast)!

-> Evolution to intermediate level of virulence

Theory of optimal virulence

Virulence grade I: 99% lethal

Virulence grade V: 50% lethal

Evolution of virulence

In epidemiology, the **basic reproductive number** (or ratio, or rate) **R_0** of an infection gives the number of infected cases that one case generates over the course of its infectious period, in an otherwise uninfected population.

When $R_0 > 1$ the infection will be able to spread in the population.

Examples of R_0 :

- Measles (airborne): 12-18
- Diphtheria (saliva): 6-7
- Polio (fecal-oral): 5-7
- HIV/AIDS: 2-5
- Influenza, 1918 pandemic (airborne): 2-3
- Ebola, 2014 outbreak: 1.5-2.5

From: Wikipedia, mostly after WHO

Evolution of virulence

Parasites face a ***trade-off*** between within-host and between-host components of fitness, i.e. more growth or replication within a host is often associated with higher host mortality and thus reduced transmission to the next host.

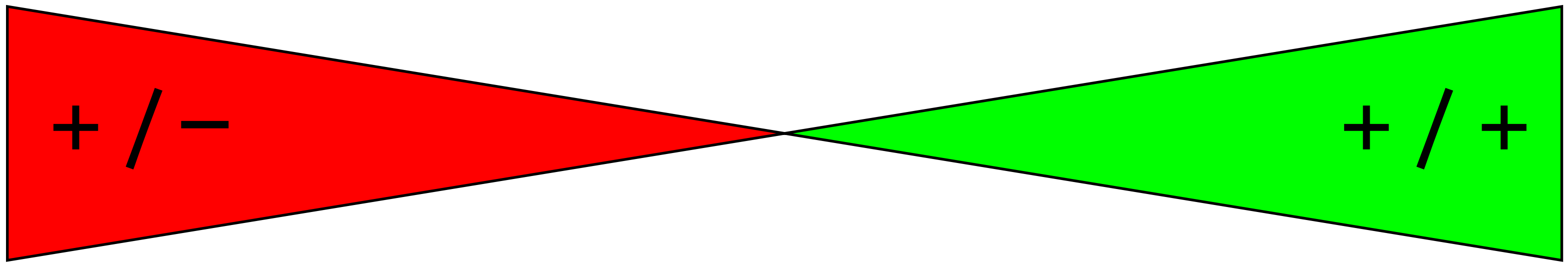
$$R_0 = \frac{\beta(\alpha) \times N}{\mu + \alpha + \nu}$$

R_0 basic reproductive rate of parasite
β transmission
N host pop. size
μ background mortality
α parasite-induced mortality
ν host recovery rate

Virulence is expected to be higher...

- for horizontal than vertical transmission.
- when unrelated parasites compete within hosts.

A continuum between parasitism und mutualism



Antagonism

Mutualism

Parasitism

Symbiosis = “living together”
(both antagonistic and mutualistic relationships)

Parasite transmission

horizontal

among hosts within
a population

vertical

from parent to offspring
(normally mother-to-child
via placenta or milk)

Examples:

many viruses many bacteria many macroparasites Plasmodium, Dengue Fever, Rikettsia

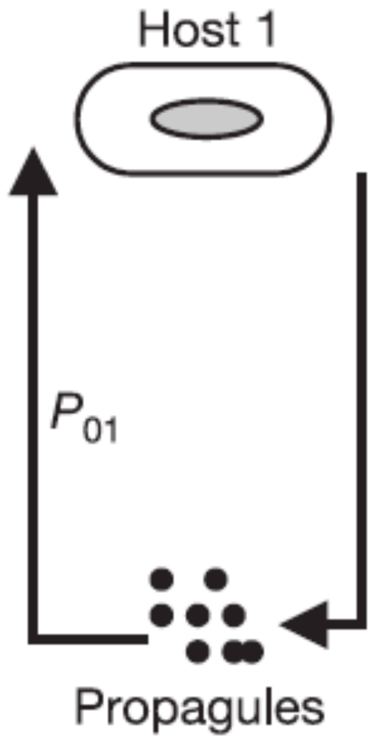
some microsporidia sigma virus Wolbachia

HIV, hepatitis B & C, microsporidia, Toxoplasma, Salmonella, Listeria, Babesia

Parasite transmission

direct

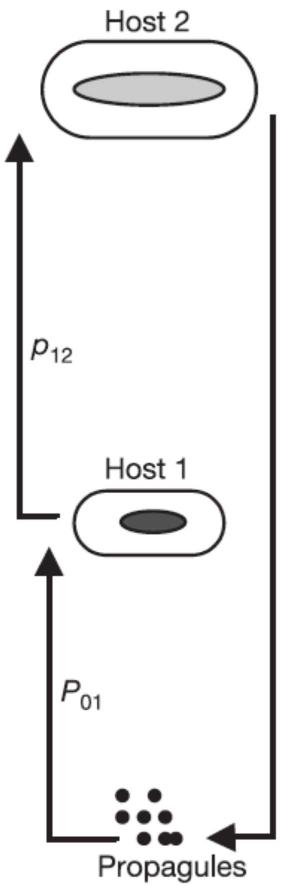
only 1 host species



indirect

with intermediate host(s)

(i.e., with host change)

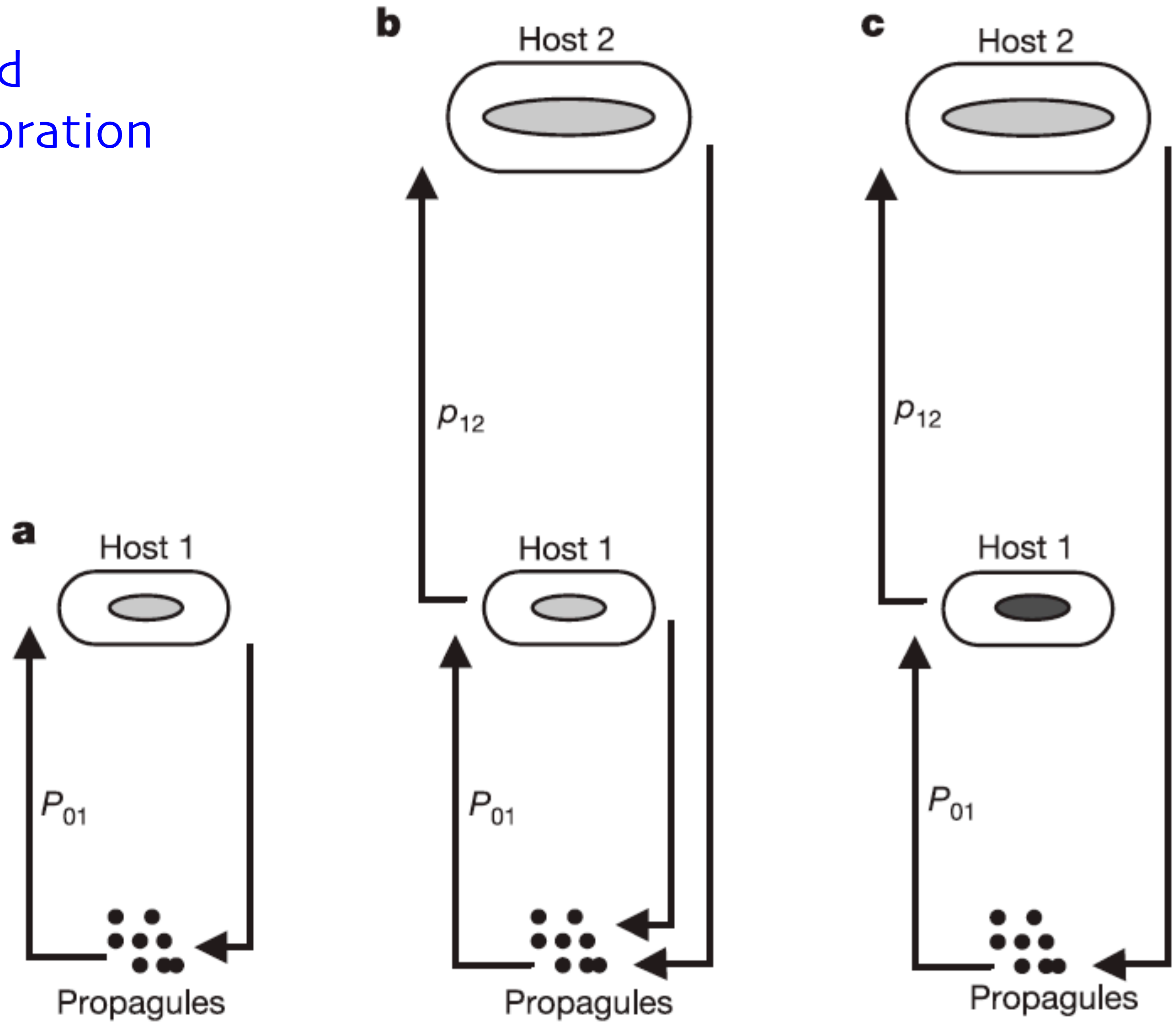


definitive or final host (reproduction)

intermediate host

Evolution of complex life cycles

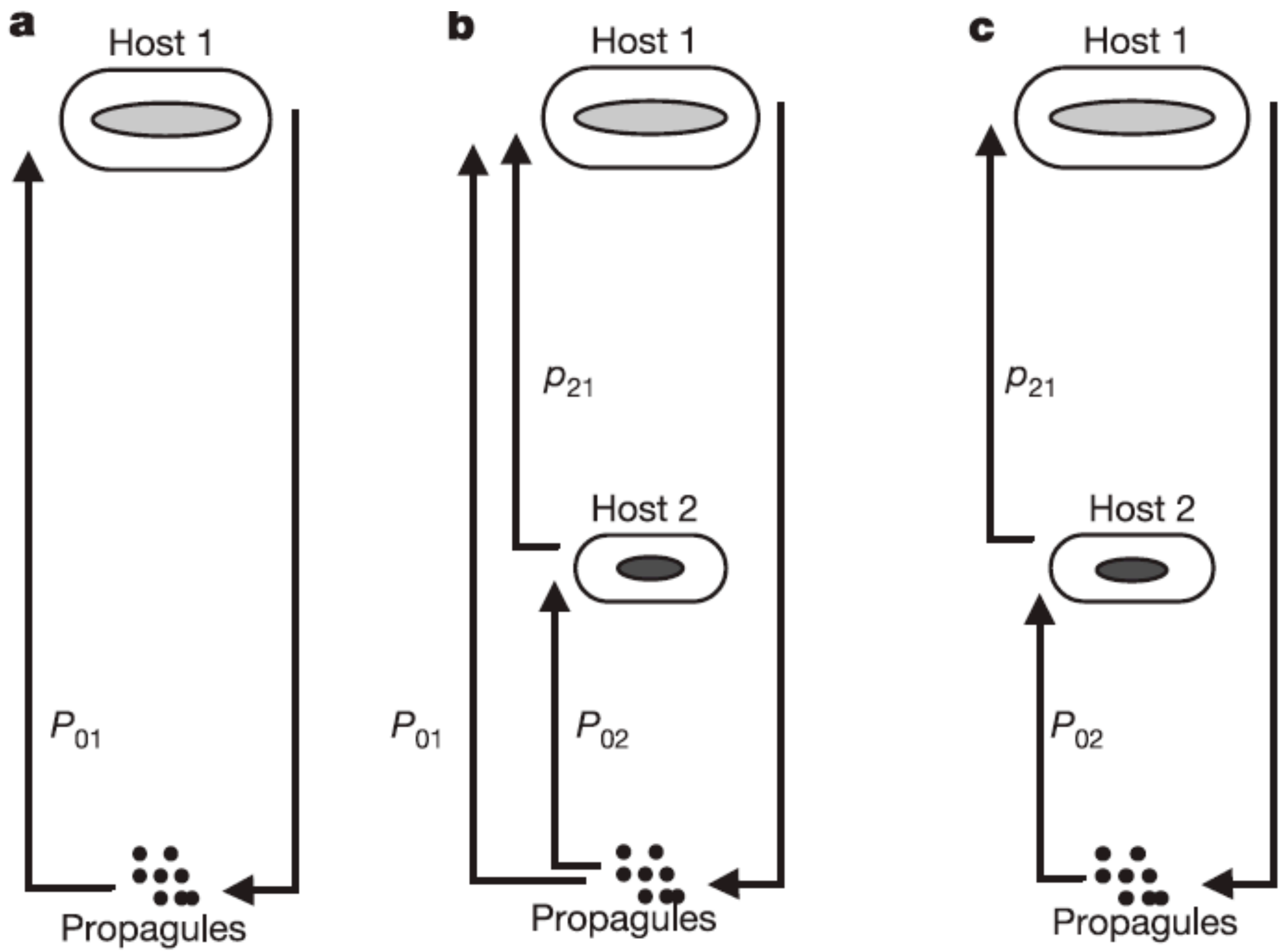
Upward incorporation



Parker et al
Nature 2003

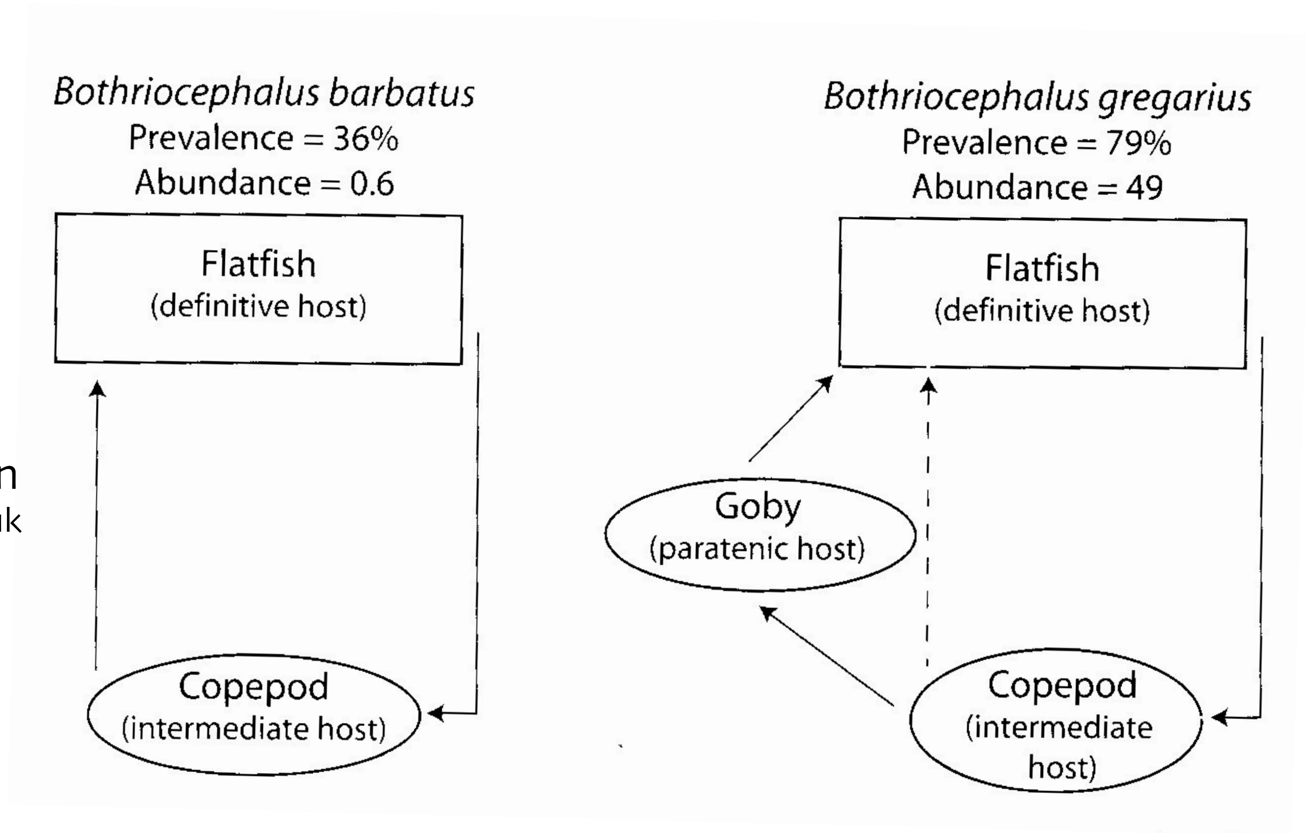
Evolution of complex life cycles

Downward
incorporation



Downward incorporation of a paratenic hosts?

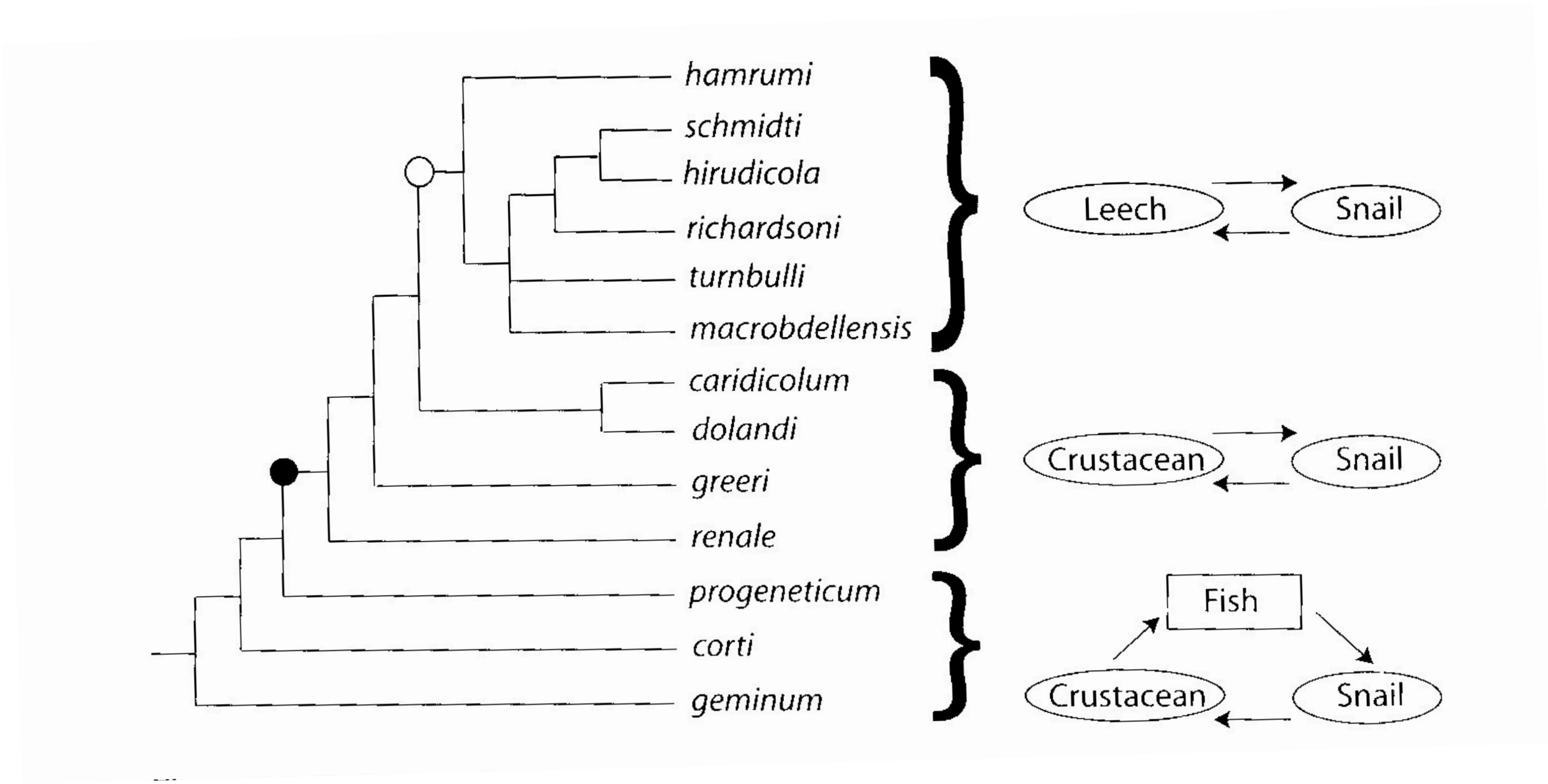
Fish intestine with heavy *Bothriocephalus* infestation



Larger proportion of infective stages might reach the definitive host when a paratenic host is used.

after Poulin (2007), from Robert et al. (1988)

Life cycle might also get simpler!



The phylogeny of the Digenean genus Alloglossidium indicates that the three-host cycle is the ancestral condition, and the fish host was lost.

after Poulin (2007), from Smyth & Font (2001)

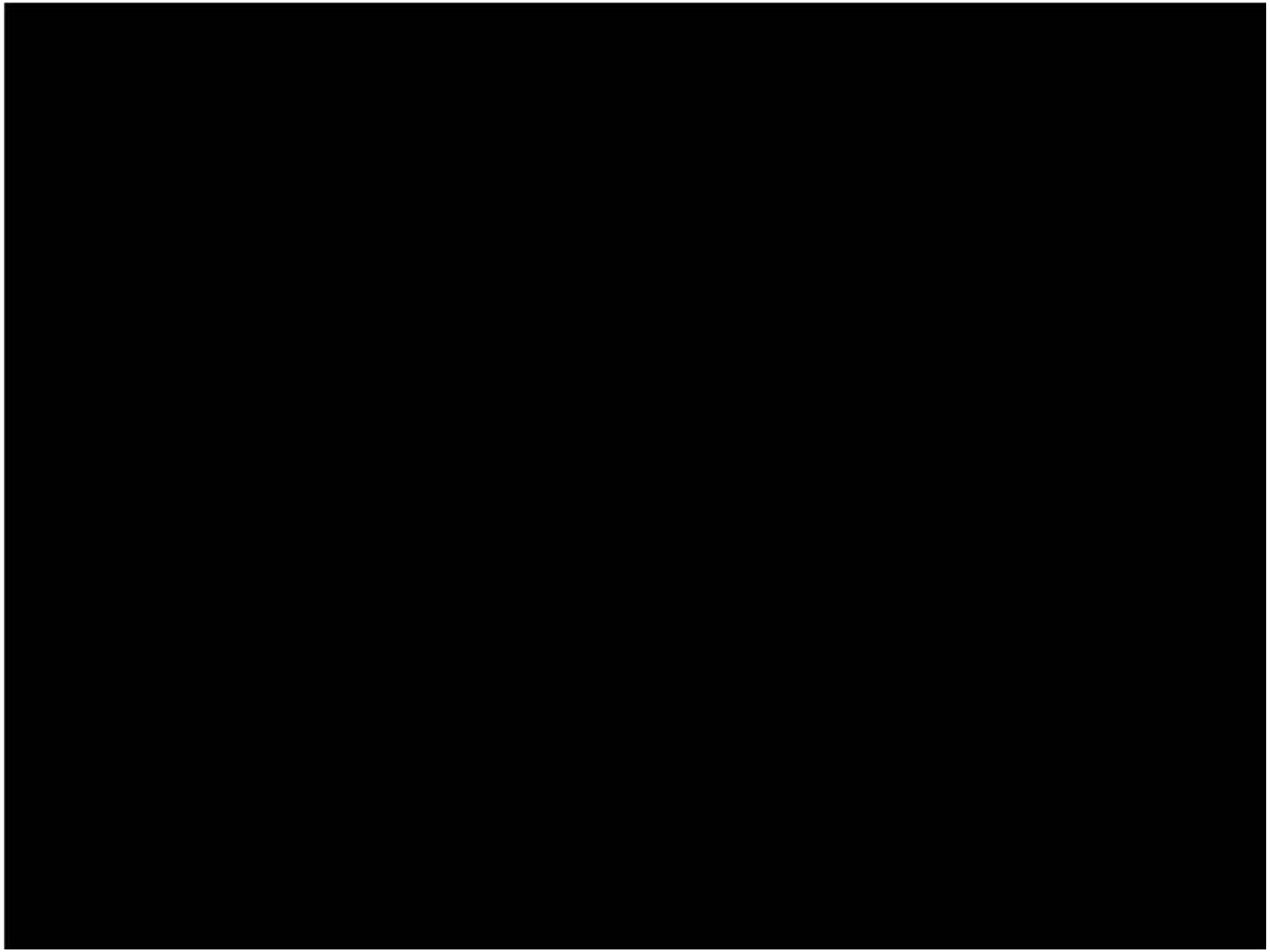
Enhancing Transmission

- Producing huge amounts of infective stages
- Precisely timed release of infective stages
- Use of chemical cues for host searching
- Manipulation of intermediate host behaviour

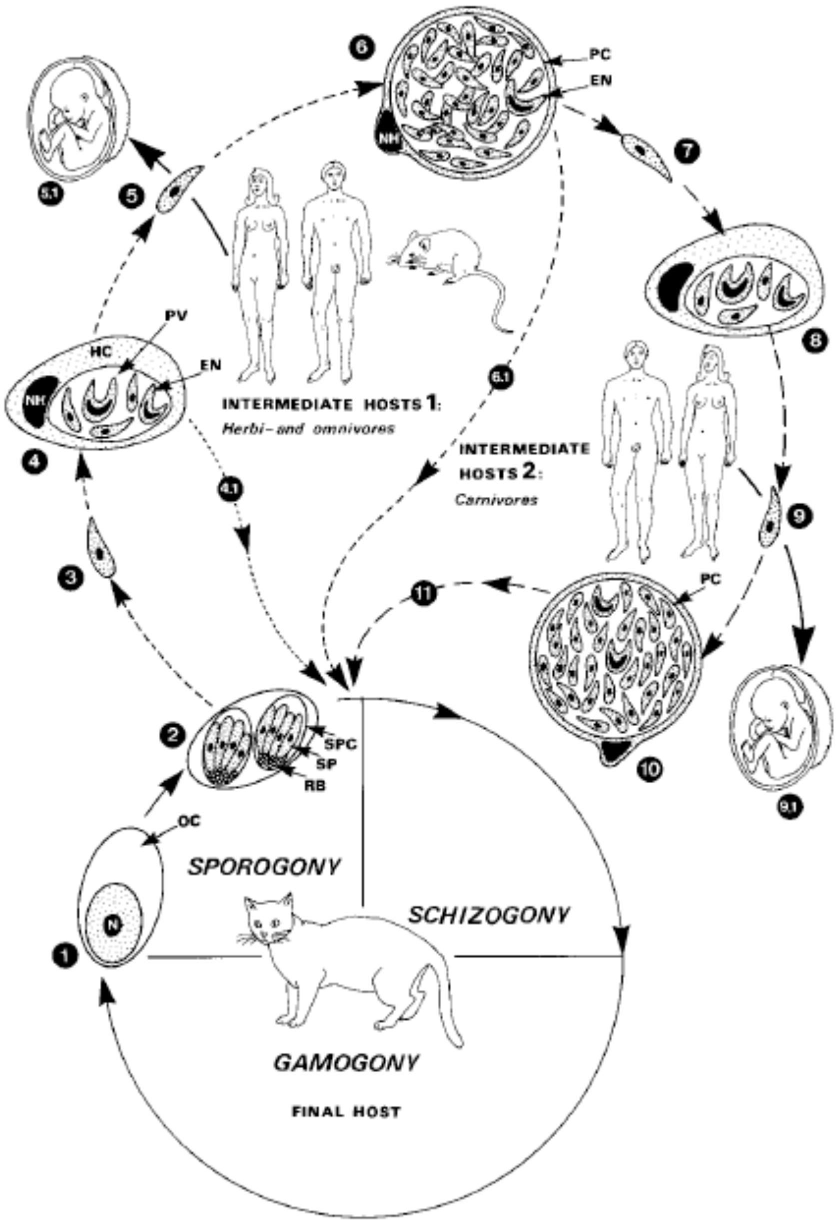
cercaria

Diplostomum pseudospathaceum
(photo M. Kalbe)

Nematomorphs manipulate host behaviour



Manipulation of host behaviour



Mehlhorn: Encyclopedic Reference of Parasitology

Toxoplasma gondii manipulates the behaviour of the intermediate host (rat) to enhance transmission to the cat final host.

Maybe also human behaviour!

Wenn aus Tieren Zombies werden

Neuroparasiten scheinen einem Albtraum entsprungen: Sie entern das Nervensystem ihrer Wirte, manipulieren **deren Verhalten und treiben sie in den Selbstmord. Auch Menschen sind nicht vor ihnen gefeit**

VON FRITZ HABEKUSS

Fremdbestimmt: Der Stichling wird zur leichten Beute, weil ein Parasit ihn nah an die Oberfläche treibt

Parasites and population dynamics

First, we need some basic knowledge of population dynamics!

Basic formula:

without competition: exponential growth

$$\frac{dN}{dt} = rN$$

r = intrinsic rate of increase (theoretical maximum rate of increase of a population per individual, therefore sometimes denoted r_{max})

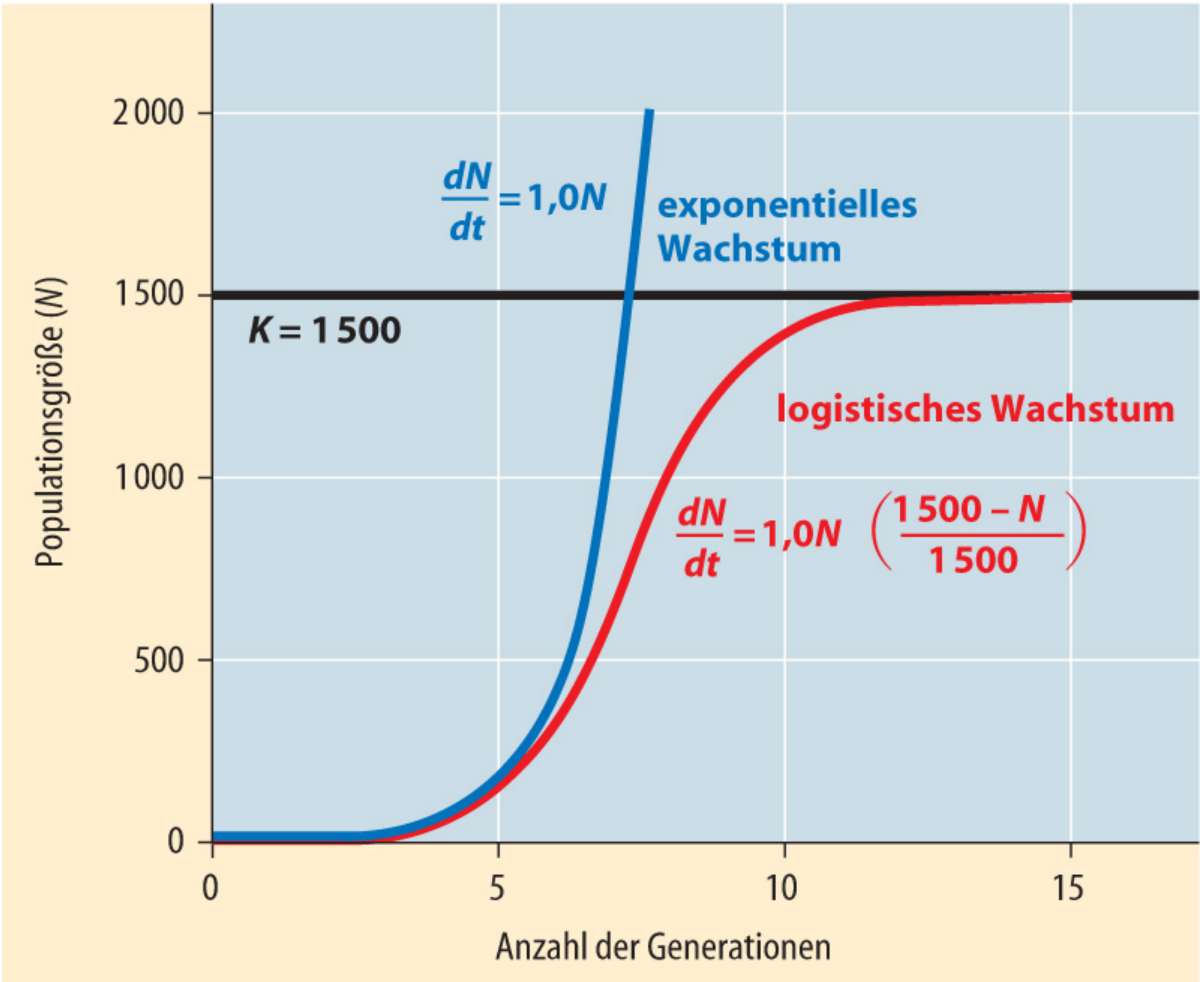
with intra-specific competition: logistic growth curve

$$\frac{dN}{dt} = rN\frac{(K-N)}{K}$$

K = carrying capacity

Population growth

$$\frac{dN}{dt} = rN\frac{(K-N)}{K}$$



Epidemiology

- Epidemiology is the study and analysis of the patterns, causes, and effects of health and disease conditions in defined populations.
- SIR models:
  Susceptible -> Infected/ious -> Recovered/resistant

$$\frac{dS}{dt} + \frac{dI}{dt} + \frac{dR}{dt} = 0 \qquad S(t) + I(t) + R(t) = \text{Constant} = N$$

$$\frac{dS}{dt} = -\frac{\beta I S}{N},$$
$$\frac{dI}{dt} = \frac{\beta I S}{N} - \gamma I,$$
$$\frac{dR}{dt} = \gamma I.$$

β = probability of contact between infected and uninfected individual
γ = rate with which infected individuals become resistant

$$R_0 = \frac{\beta}{\gamma}$$

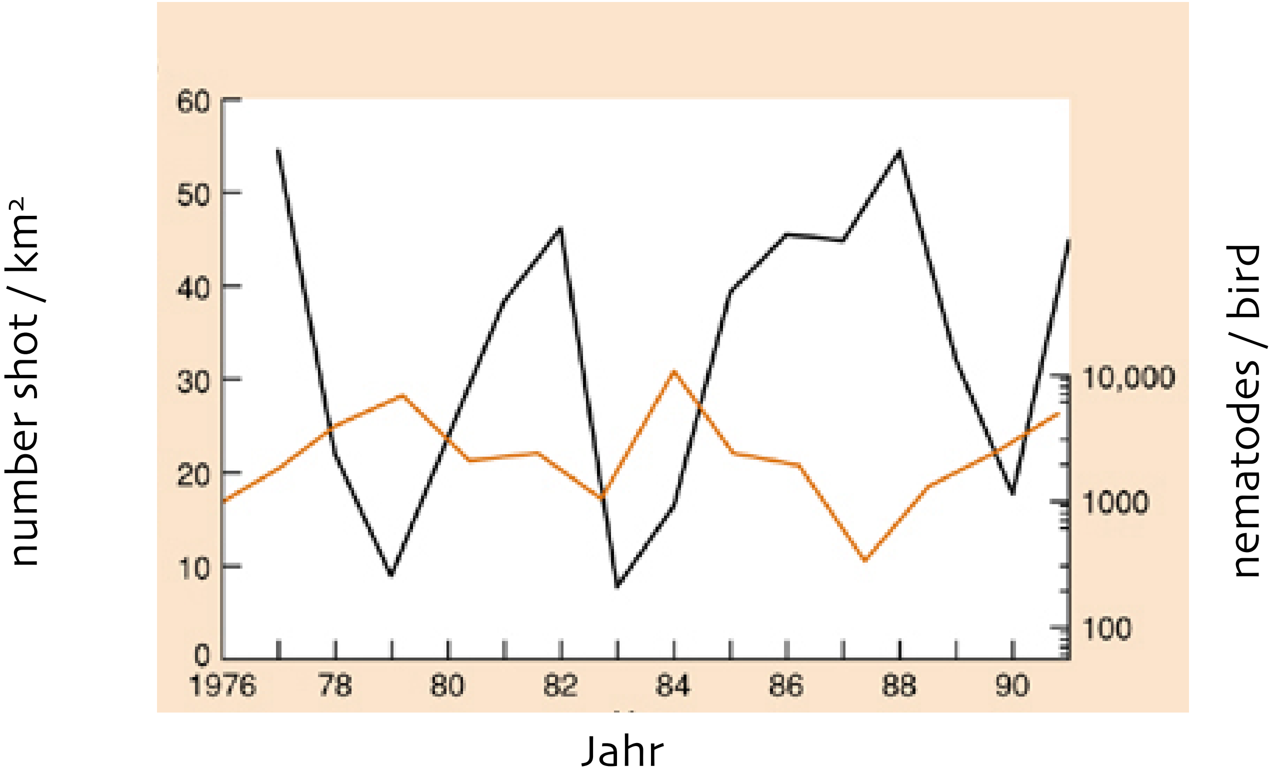
R_0 = basic reproduction number (also called basic reproduction ratio).

Effects of parasites on the population level



Red grouse
Lagopus lagopus
Royal Sco Prot Birds UK

Treatment with antihelminthic drug showed that population cycles are caused by parasites.

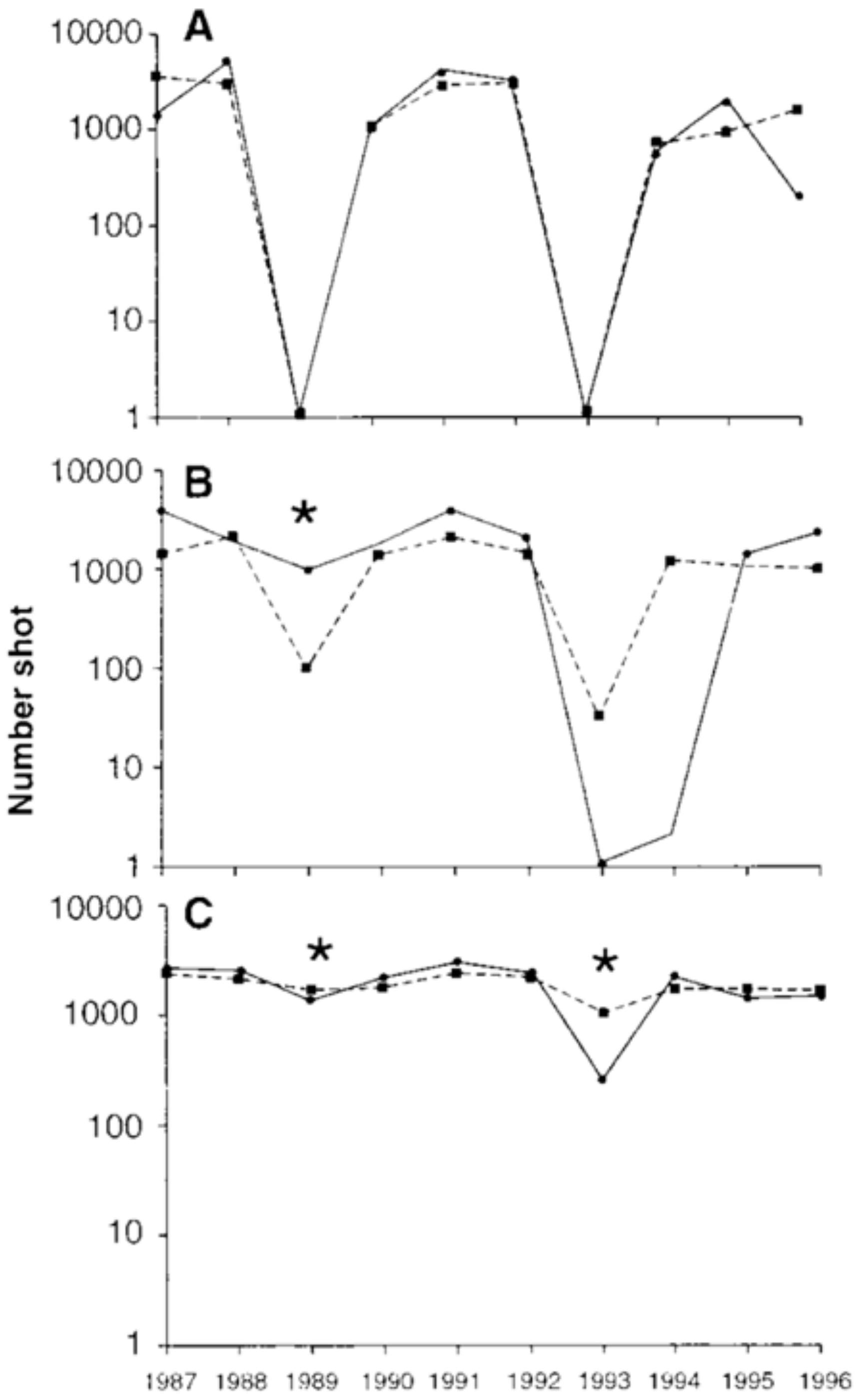


Hudson et al. Science 1998
Fig. adapted from Begon et al. Ecology

Prevention of Population Cycles by Parasite Removal

Peter J. Hudson,* Andy P. Dobson, Dave Newborn

★ = antihelminthic treatment

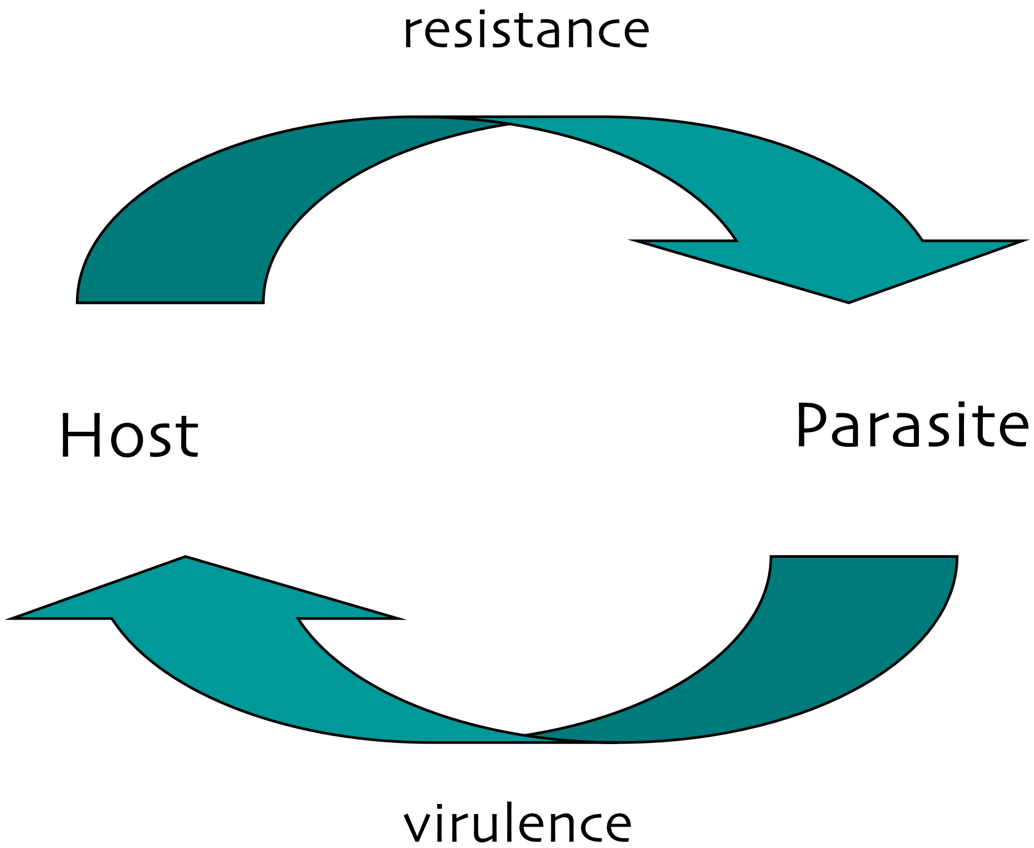


Hudson et al. Science 1998

Host-Parasite Coevolution

Reciprocal genetic change in hosts and parasites, owing to natural selection imposed by each on the other.

Coevolution: The „Red Queen"



Red-Queen model (van Valen 1973)

"In this place it takes all
the running you can do,
to keep in the same place."

Lewis Caroll
Through the looking glass

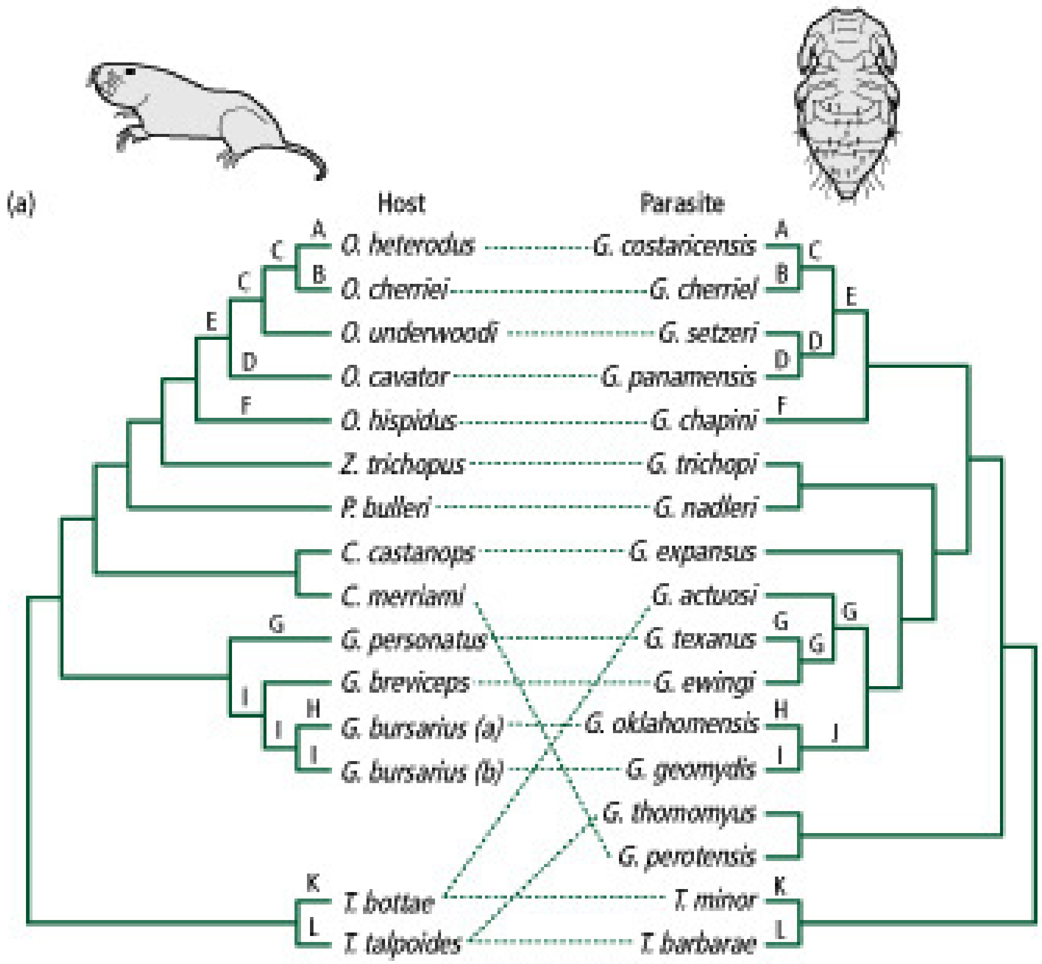
The difficulties to demonstrate coevolution

But: Population cycles do not necessarily mean that there is coevolution (i.e. reciprocal adaptation).

To demonstrate coevolution, we need to show that there is reciprocal adaptation.

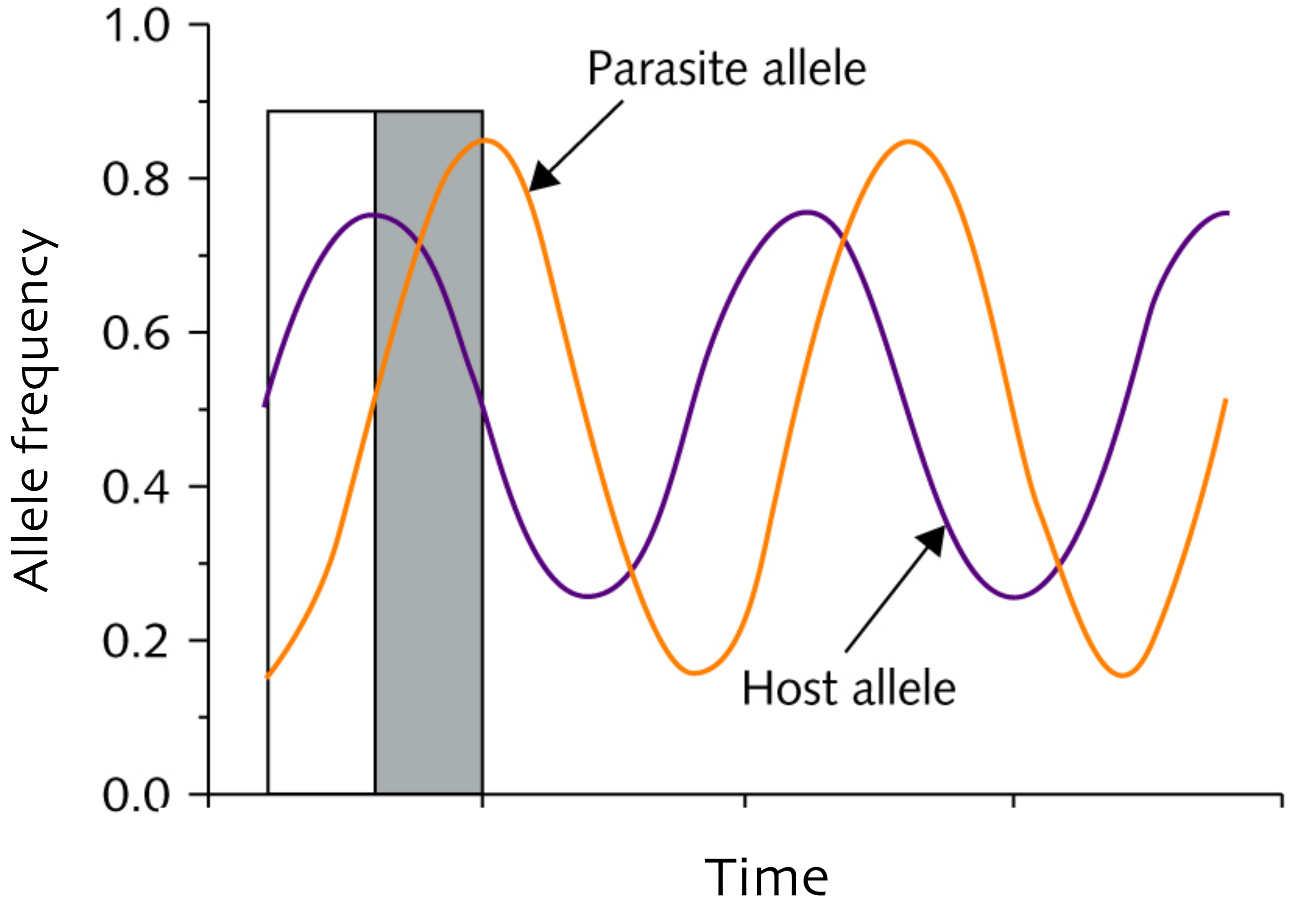
But how?

Pocket gophers and louse:
Cophylogeny as evidence for coevolution



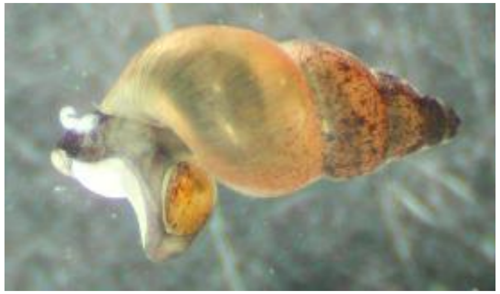
Haffner et al. 1994

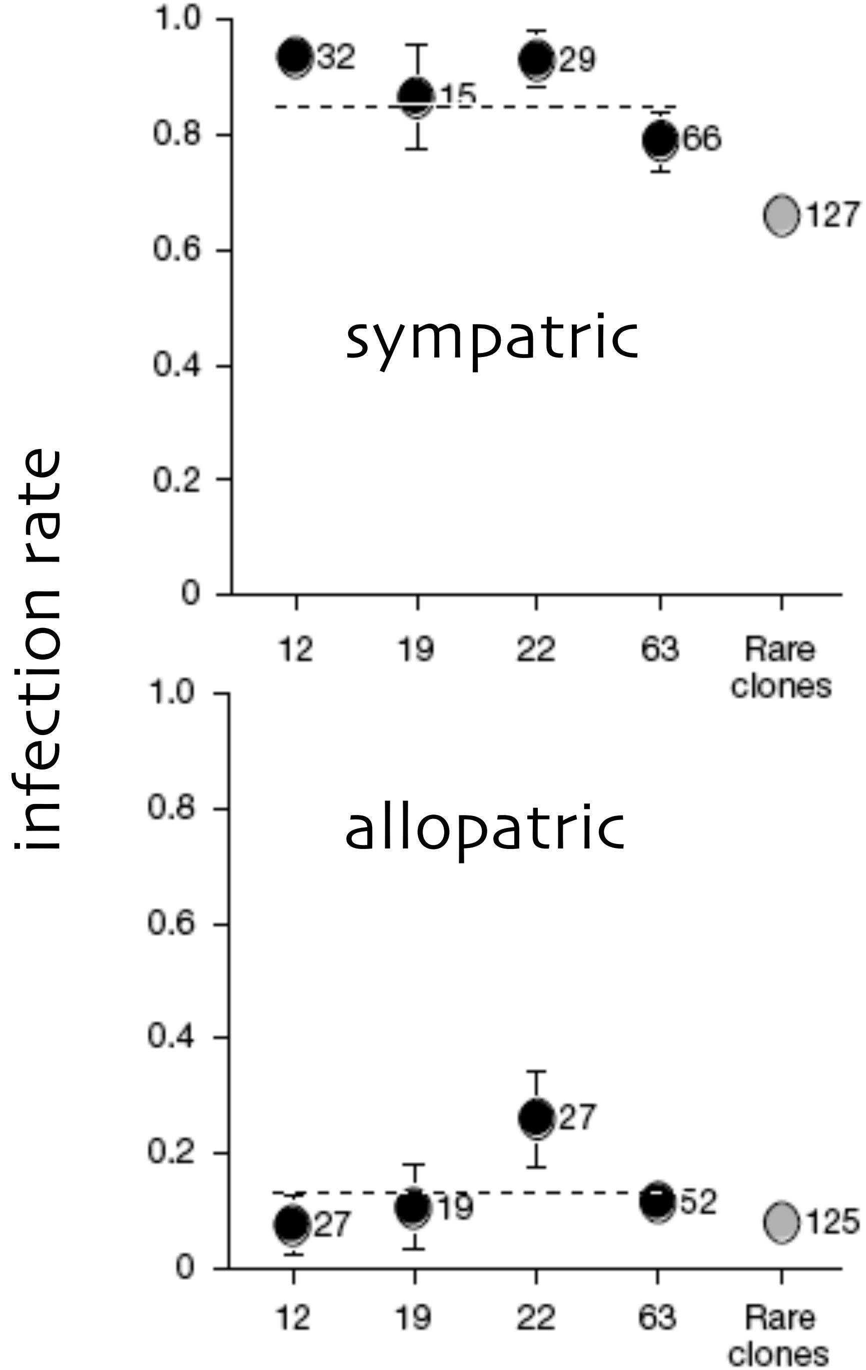
Types of coevolutionary genetic changes



Coadaptational cycles of parasite and host allele frequencies can be based on frequency-dependent selection.

Advantage of rare host clones, as expected under frequency-dependent selection





Lively & Dybdahl *Nature* 2000

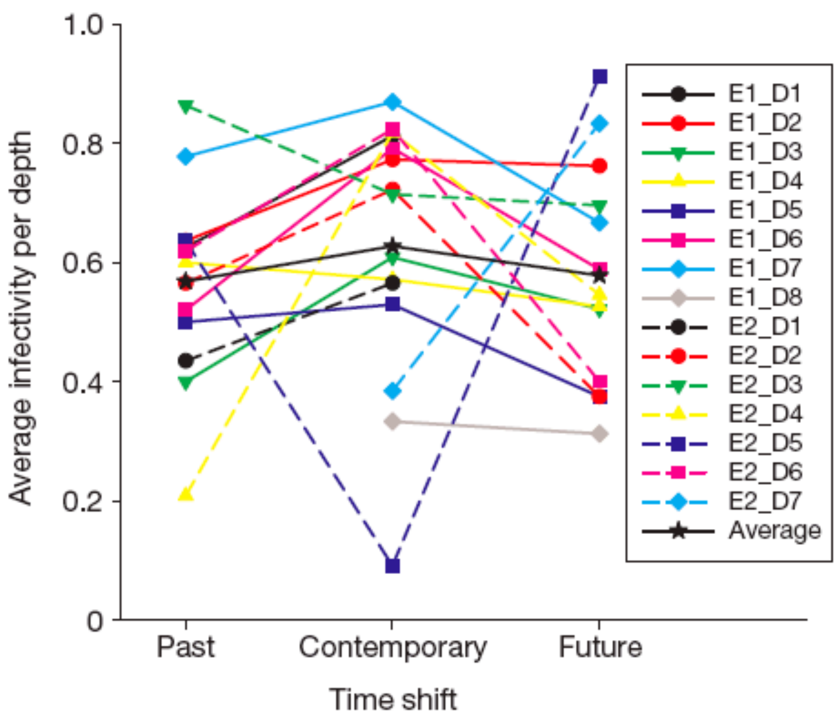
Temporal dynamics: Tracing the history

nature Vol 450|6 December 2007|doi:10.1038/nature06291

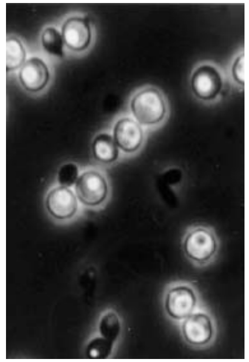
LETTERS

Host–parasite 'Red Queen' dynamics archived in pond sediment

Ellen Decaestecker[1,3], Sabrina Gaba[4,5], Joost A. M. Raeymaekers[1,2], Robby Stoks[1], Liesbeth Van Kerckhoven[1], Dieter Ebert[4]* & Luc De Meester[1]*



Daphnia magna



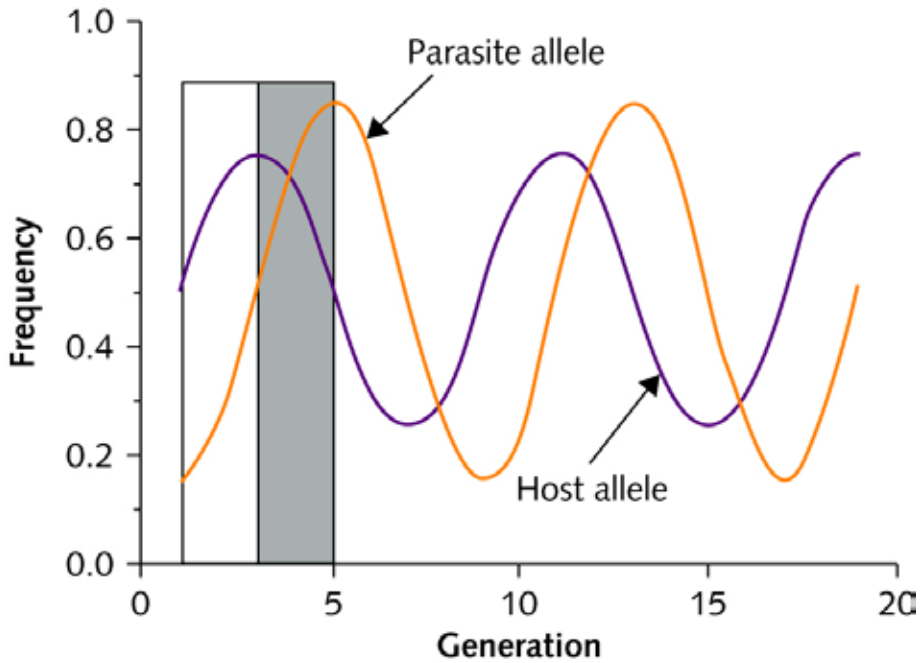
Pasteuria ramosa

Who leads, host or parasite?

The interacting species with...

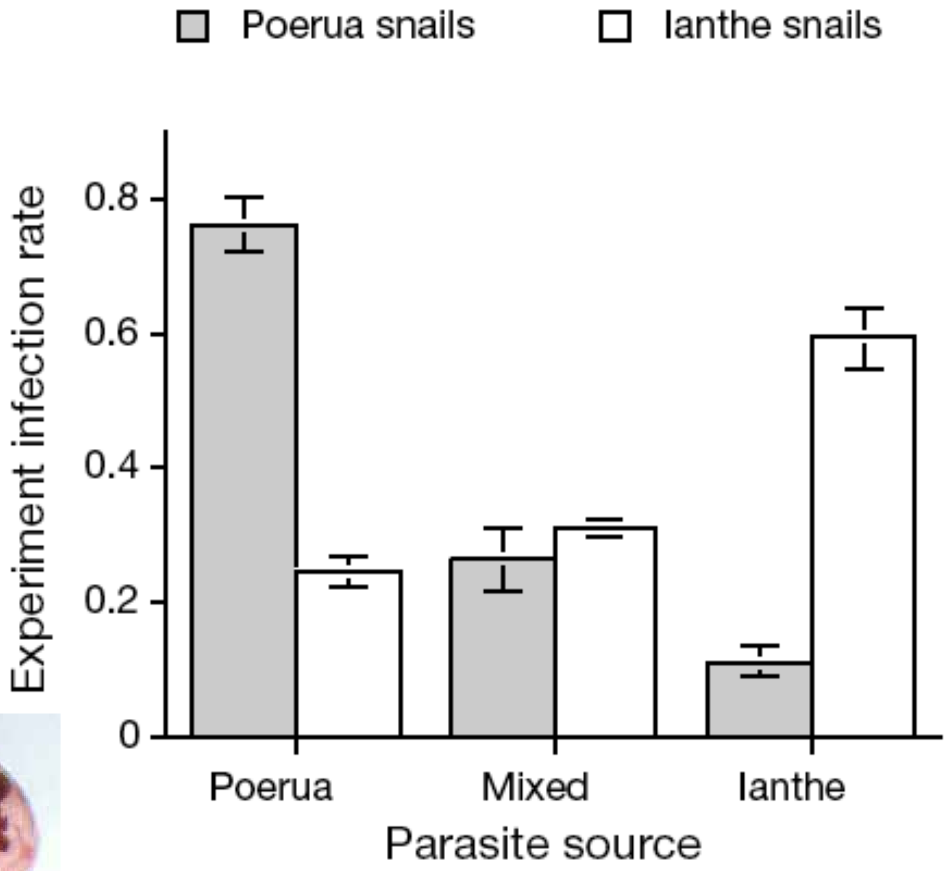
1. the stronger selection pressure
2. the shorter generation time
3. more genetic variation for the interaction trait
4. sexual reproduction

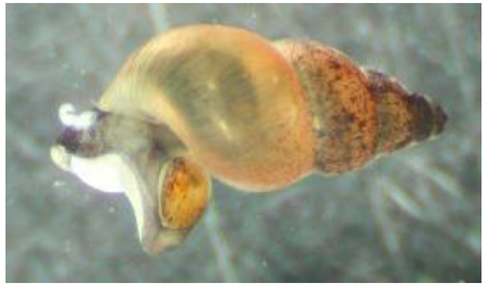
... will normally evolve more rapidly.



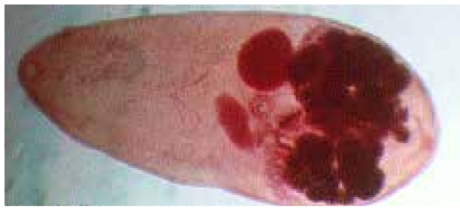
Most often, this will be the parasite!

Local adaptation: Correlative evidence of coevolution





Potamopyrgus antipodarum

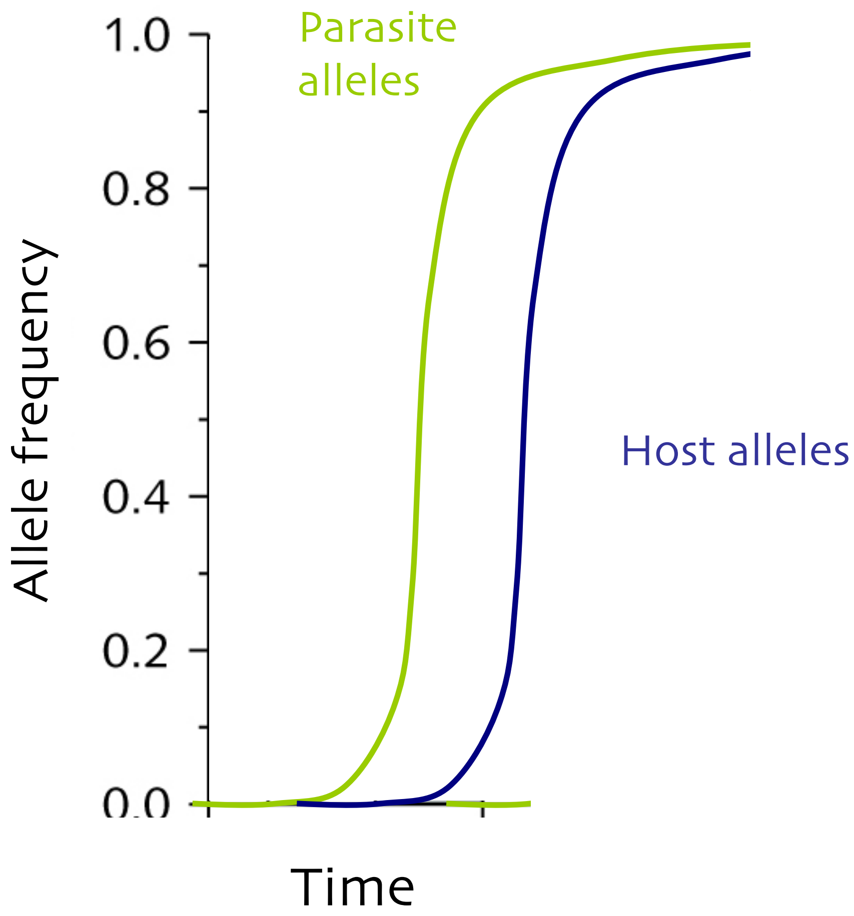


Microphallus spec.

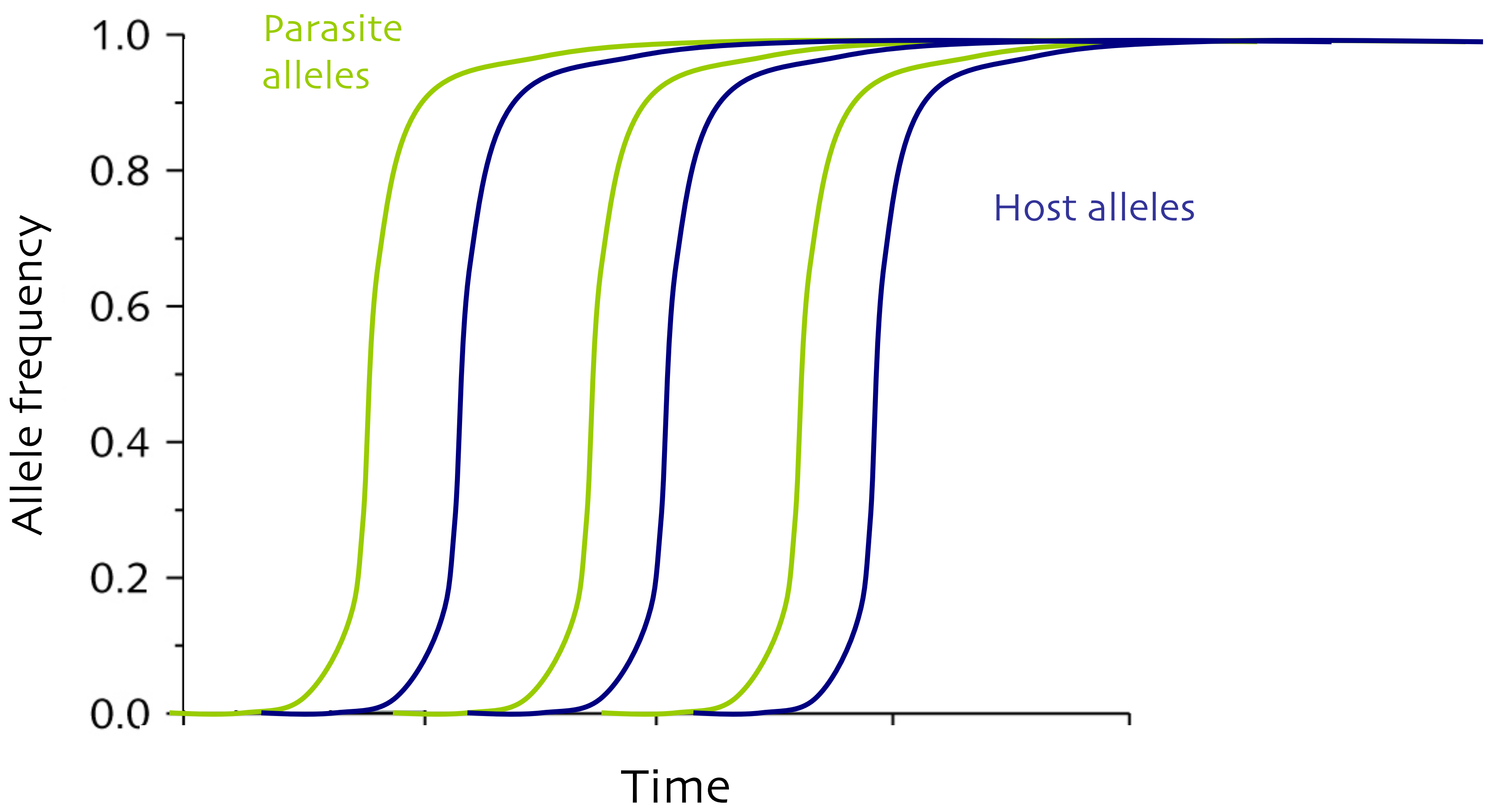
Lively & Dybdahl *Nature* 2000

If parasites are ahead in the arms race, then sympatric (i.e. local) parasites should be superior to allopatric ones, which was the case here.

Types of coevolutionary genetic changes



Types of coevolutionary genetic changes



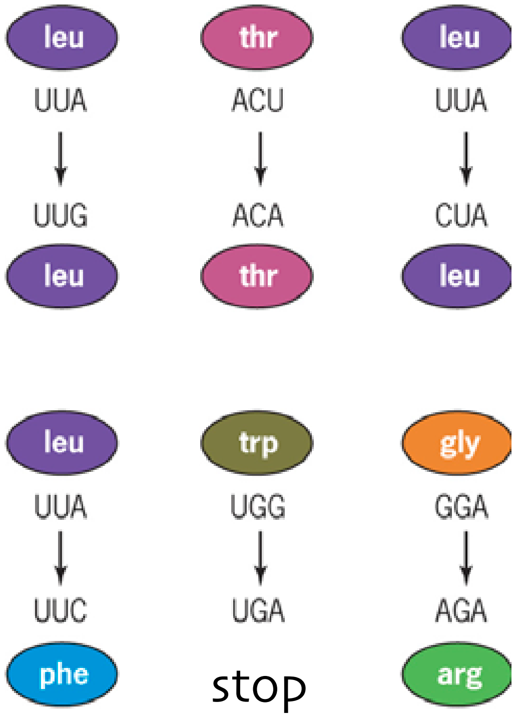
Arms races between parasite and host can be based on rapid fixation (selective sweeps) of beneficial alleles.

Synonymous *vs.* non-synonymous substitutions

examples:

neutral mutations
-> synonymous substitutions

non-neutral mutations
-> non-synonymous substitutions



Since most mutations are neutral or (slightly) negative, we normally expect more synonymous than non-synonymous substitutions to accumulate over time.

Normally, more synonymous than nonsynonymous substitutions accumulate over time

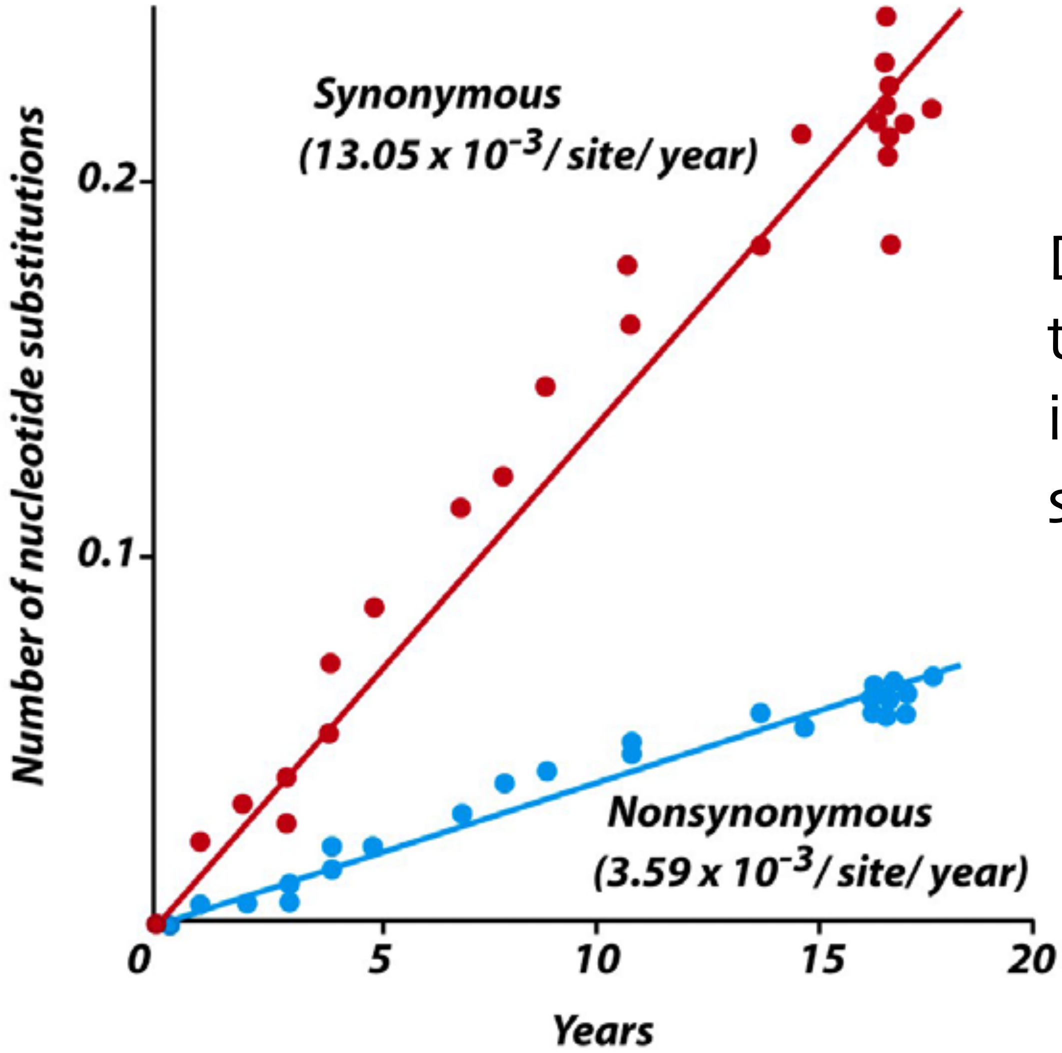


Figure 7-21c Evolutionary Analysis, 4/e

Deviations from this pattern are indicative of selection.

Fig. from Freeman & Herron (2004), adapted from Gojoburi et al. (1990)

Testing for selection

The relationship of synomous vs. non-synonymous substitutions can indicate whether selection has been acting on a gene.

$d_N < d_S$ -> negative (purifying) selection
$d_N = d_S$ -> no selection (neutral)
$d_N > d_S$ -> positive (directional) selection

d_N rate of non-synonymous substitutions

d_S rate of synonymous substitutions

d_N/d_S (also denoted K_a/K_s) can be calculated and tested for a deviation from the neutral expectation $d_N/d_S = 1$

Immunity genes show signs of positive selection

Open access, freely available online PLoS BIOLOGY

A Scan for Positively Selected Genes in the Genomes of Humans and Chimpanzees

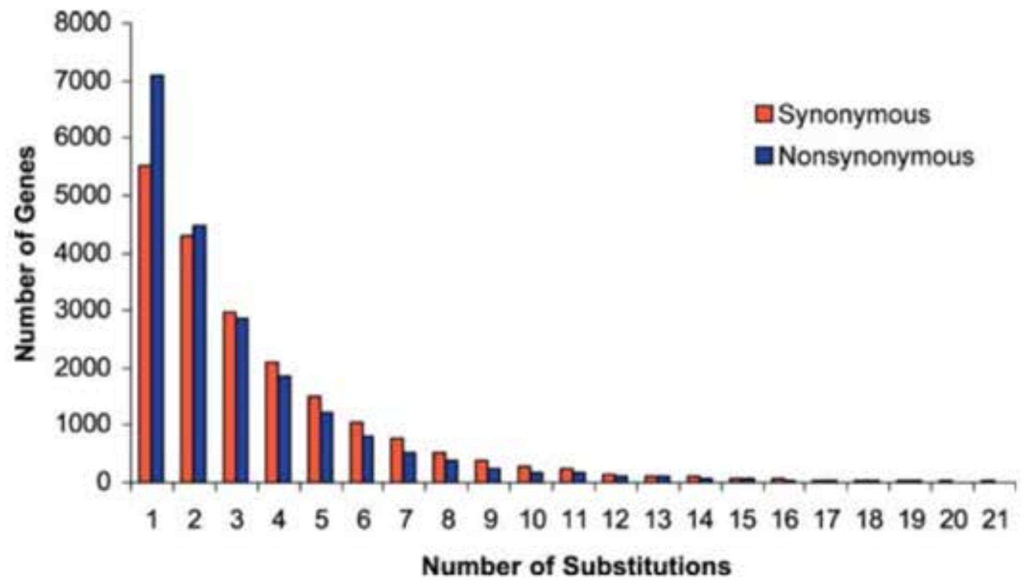
Rasmus Nielsen[1,2*], Carlos Bustamante[1], Andrew G. Clark[3], Stephen Glanowski[4], Timothy B. Sackton[3], Melissa J. Hubisz[1], Adi Fledel-Alon[1], David M. Tanenbaum[5], Daniel Civello[6], Thomas J. White[6], John J. Sninsky[6], Mark D. Adams[5¤], Michele Cargill[6]

1 Biological Statistics and Computational Biology, Cornell University, Ithaca, New York, United States of America, **2** Center for Bioinformatics, University of Copenhagen, Denmark, **3** Molecular Biology and Genetics, Cornell University, Ithaca, New York, United States of America, **4** Applied Biosystems, Rockville, Maryland, United States of America, **5** Celera Genomics, Rockville, Maryland, United States of America, **6** Celera Diagnostics, Alameda, California, United States of America

PLoS Biology 2005

Analysis based on comparison between species.

Number of substitutions per gene



Biological Process Categories with an Excess of Putatively Positively Selected Genes

Biological Process	Number of Genes	*p*-Value
Immunity and defense	417	0.0000
T-cell-mediated immunity	82	0.0000
Chemosensory perception	45	0.0000
Biological process unclassified	3,069	0.0000
Olfaction	28	0.0004
Gametogenesis	51	0.0005
Natural killer-cell-mediated immunity	30	0.0018
Spermatogenesis and motility	20	0.0037
Inhibition of apoptosis	40	0.0047
Interferon-mediated immunity	23	0.0080
Sensory perception	133	0.0160
B-cell- and antibody-mediated immunity	57	0.0298

Which inmune pathways/genes show signs of selection?

OPEN ACCESS Freely available online PLoS GENETICS

Quantifying Adaptive Evolution in the *Drosophila* Immune System

Darren J. Obbard[1]*, John J. Welch[1], Kang-Wook Kim[1,2], Francis M. Jiggins[3]

1 Institute of Evolutionary Biology, University of Edinburgh, Edinburgh, United Kingdom, 2 Department of Animal and Plant Sciences, University of Sheffield, Sheffield, United Kingdom, 3 Department of Genetics, University of Cambridge, Cambridge, United Kingdom

PLoS Genetics 2009

Estimates of the proportion of adaptive non-synonymous substitutions (α) between *D. melanogaster* and *D. simulans*.