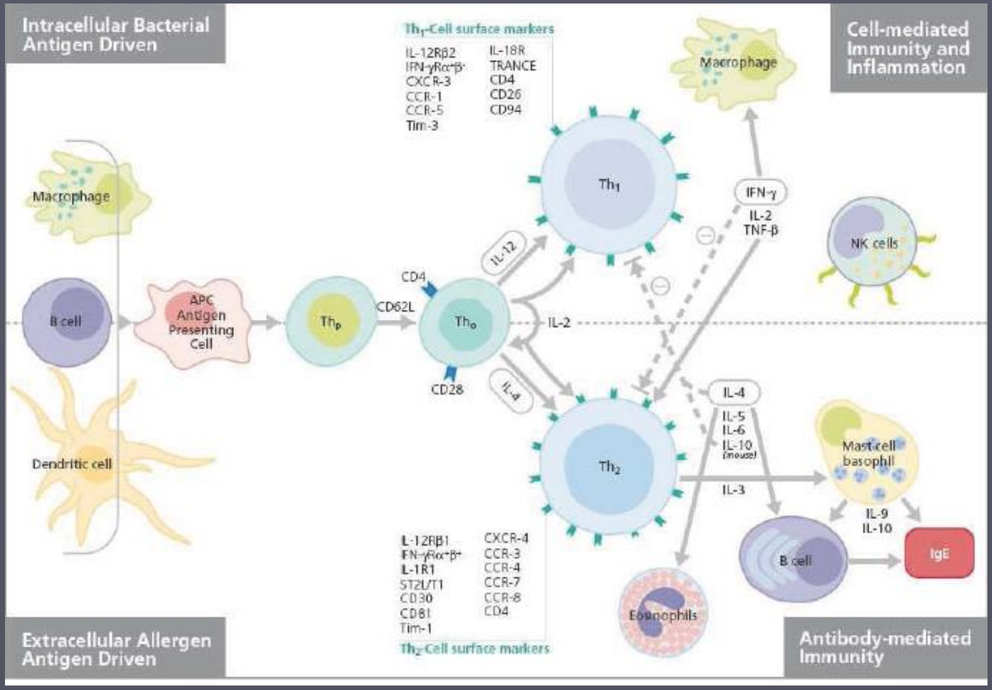
Immunoecology of host-parasite relationships

Immunoecology

- Combining immunity and evolutionary ecology
- It examines variability in the immune response between individuals, populations and species
- It studies the processes that explain this variability and its maintenance
- Seeks trade-offs if immunity is considered a costly component of life history (principle of energy allocation - cost versus benefit)
- Evolutionary adaptation of immunity

Immunity in vertebrates

- **Non-specific** (non-adaptive, innate)
  - dendritic cells, macrophages
- **Specific** (adaptive, acquired)
  cellular and humoral responses
  intracellular parasites, extracellular parasites

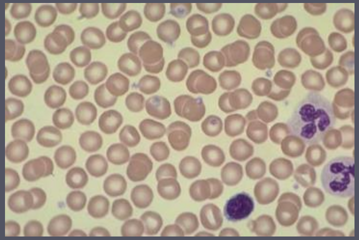


Immunocompetence

- The general ability of an individual to induce an effective immune response in order to minimize losses due to infection

- How to measure immunocompetence?

1. Intensity of parasite infection
   High intensity of parasite infection
   => low immunocompetence
2. Induction of infection
   Resistance to infection => good immunocompetence
   Resistance or susceptibility
3. Serology
   High white blood cell count
   => good immunocompetence



Immunocompetence

- How to measure immunocompetence?

4. Weight of immune organs (spleen, thymus)
5. Injection of mitogens

   Lymphocyte proliferation (T or B)
6. Injection of antigens

   Antibody production
7. Genetic data

   MHC genes

Immunological approaches applied in field studies

Table I. Immunological assays for use in the field[a]

Assay[b]	Component measured	Blood sample or measurement needed	Prediction for invader[c]	Refs
Number of phagocytes	Standing innate defence	Smear collected at capture		[50]
Complement-mediated cell lysis	Standing innate defence	Serum collected at capture		[51]
Bacterial killing	Standing innate defence	Serum collected at capture		[52]
Phagocytosis of bacteria or yeast	Standing innate defence	Whole blood collected at capture		[52]
Acute phase proteins	Systemic inflammation	Serum collected at capture and at 24 hr after LPS injection	Low	[53]
Anorexia and lethargy	Systemic inflammation	Changes in food intake and activity levels 24 hr after LPS injection	Low	[18]
Fever or temperature disregulation	Systemic inflammation	Changes in body temperature during 24 hr following LPS injection	Low	[39]
Natural antibodies levels (IgM)	Standing humoral defence	Whole blood collected at capture	High	[51]
Total IgM and IgG	Standing humoral defence	Blood smear collected at capture	High	[50]
Number of lymphocytes	Standing adaptive defence	Serum collected at capture		[50]
Antibody response to antigen	Induced humoral defence	Immunization followed by serum collected 5 days later	High	[54]
Cutaneous response to PHA	Induced cell-mediated immune response	Skin biopsy for enumeration of lymphocytes taken 24 hr after PHA challenge		[55]
B cell or T cell proliferation	Induced humoral (B cell) or cell-mediated (T cell) immune response	Whole blood collected at capture		[56]

[a]Abbreviations: LPS, lipopolysaccharide; IgM, immunoglobulin M; IgG, immunoglobulin G; PHA, phytohemagglutinin.

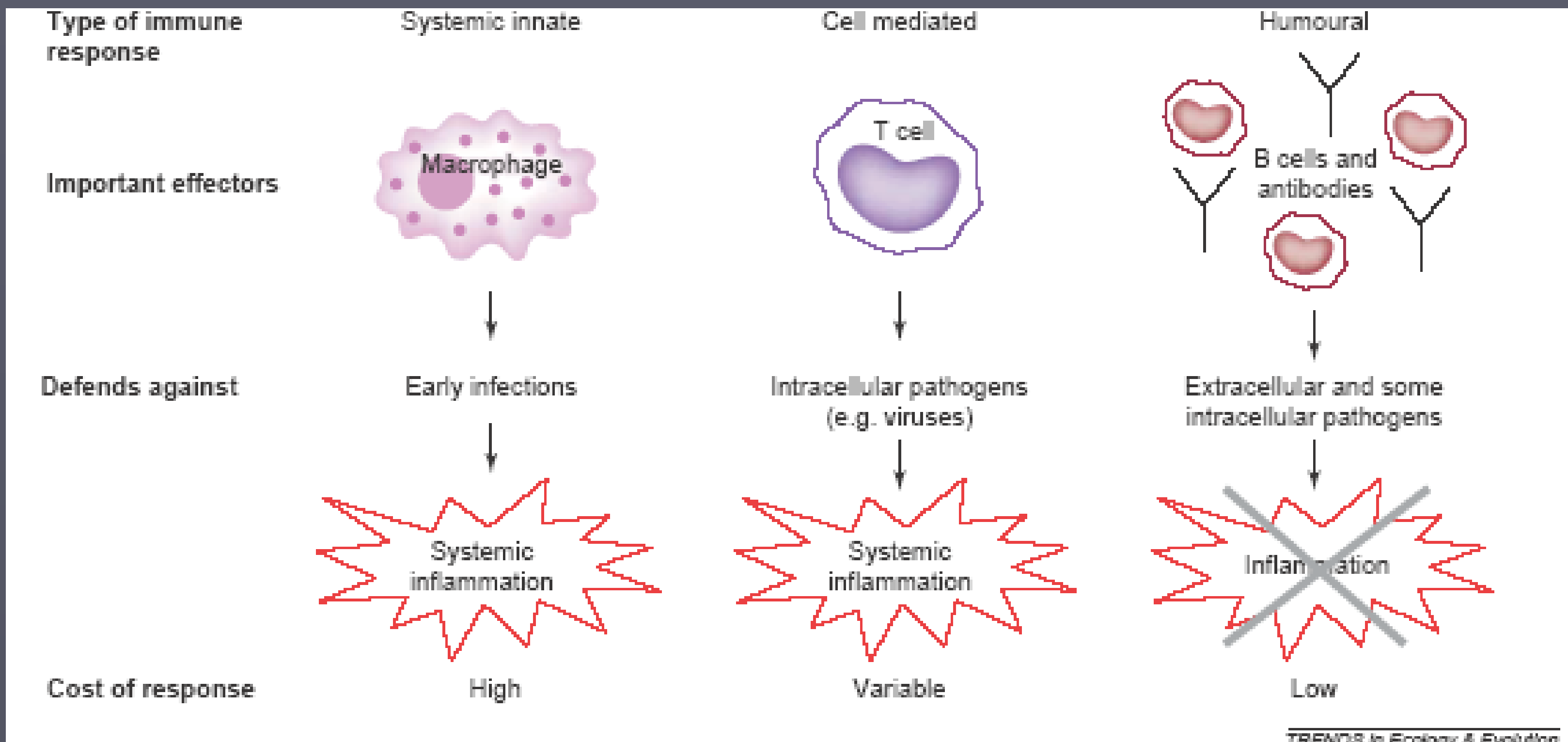
[b]Characteristics of useful assays: (i) Species-neutral: assays should not use reagents or tissue culture media that are species specific (e.g. antibodies, sera, or pathogens); (ii) Utilizes single blood samples: animal capture and recapture is often difficult and always stressful; (iii) Utilizes small blood samples: many species of interest are small and large volumes of blood cannot be taken; and (iv) Adaptable to field conditions: requirements for specialized equipment should be minimal

[c]Although we do not make predictions for all types of immune defence, researchers working with invasive species should be as complete as possible in their characterizations of the immune system until more empirical data are available to support or refute the hypotheses presented here.

Immunity as a component of the life histories of hosts

- role of the immune system as an important component of life history
- the organism makes certain investments in the immune function responsible for resistance to pathogens and parasites
- If the evolution of the immune system is controlled by parasites, then a positive correlation can be expected between parasitic load and the effectiveness of the immune system

Costs associated with immune responses in vertebrates



Investment in reproduction versus investment in immunity

- investment of females and males in reproduction is different
- females - production of oocytes, males - formation of secondary sexual characteristics

- The principle of trade-offs in the distribution of energy - reproduction and immunity
- investment in the development of gonads and investment in the course of reproduction itself energy-costly => reduction of the organism's investment in its immune defenses

Investment in reproduction versus investment in immunity

- Immunocompetence handicap hypothesis
- energy devoted to reproduction => increased production sex hormones at the expense of reduced immune function (immunosupresive role of testosterone)

- Sperm protection hypothesis (Folstad & Skarstein 1997)

- immunosuppressive effect of testosterone leads to protection of sperm as sperm are recognized as antigenic, attacked by autoimmune system

- better males (= better tolerating costs associated with the negative effect of testosterone) - more pronounced secondary sexual characteristics and sperm of better quality

Gender-differences in immunity

Risk of infection	Males > Females
Cellular response Humoral response Inflammation	Males < Females
Auto-immune disease	Males < Females

Proximal causes

testosterone

immunosuppression

reproductive success of males

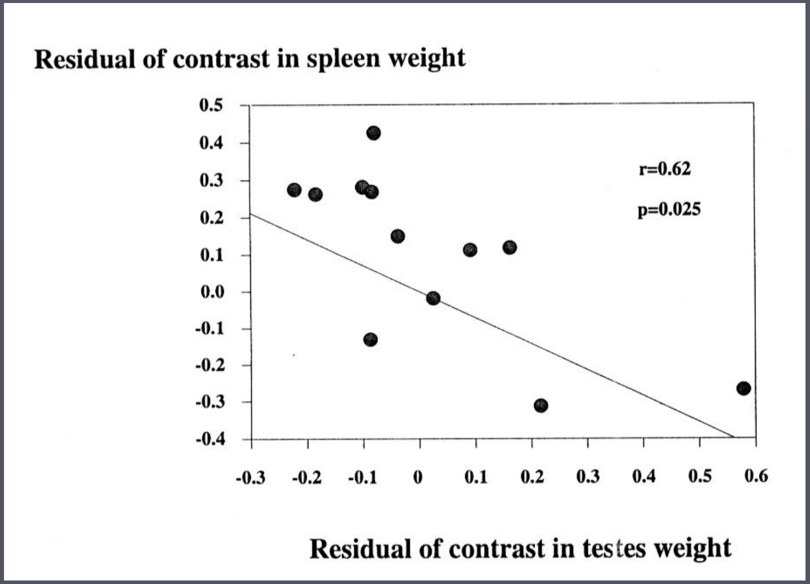
behavior (aggressive, dispersion)

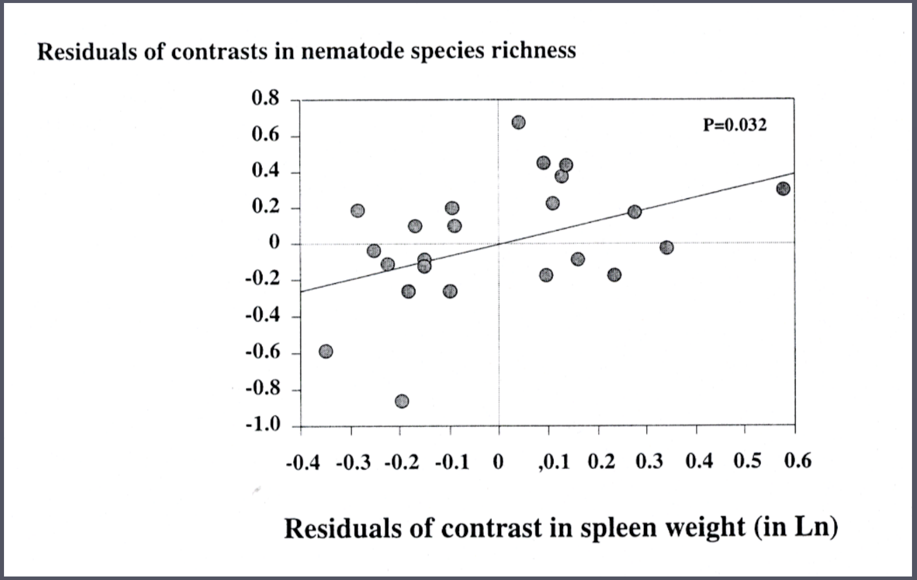
Estrogen = increasing the expression of MHC genes

Investment in reproduction versus investment in immunity - an interspecific study

- Ex. Interspecies study in birds

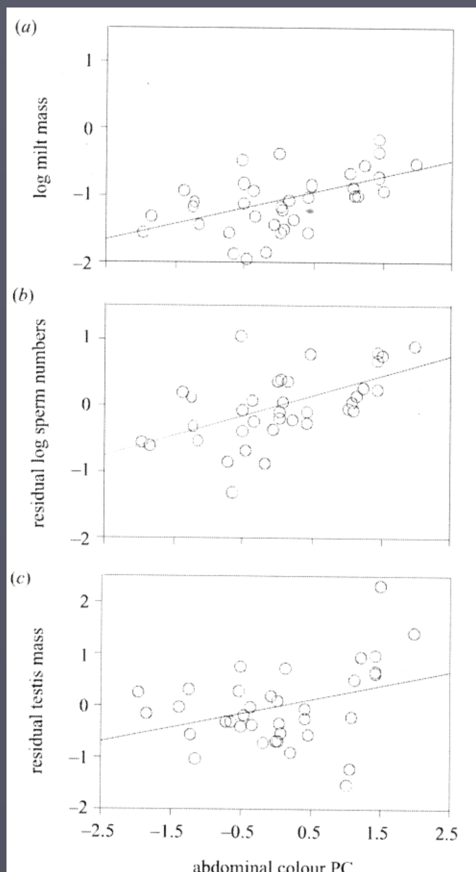
1. Males with larger gonads invest more in the production of sex hormones, which is compromised with immune function, the evolution of the size of testes may be the result of sexual selection
2. Birds affected by higher pressure from parasites invest more in immunocompetence

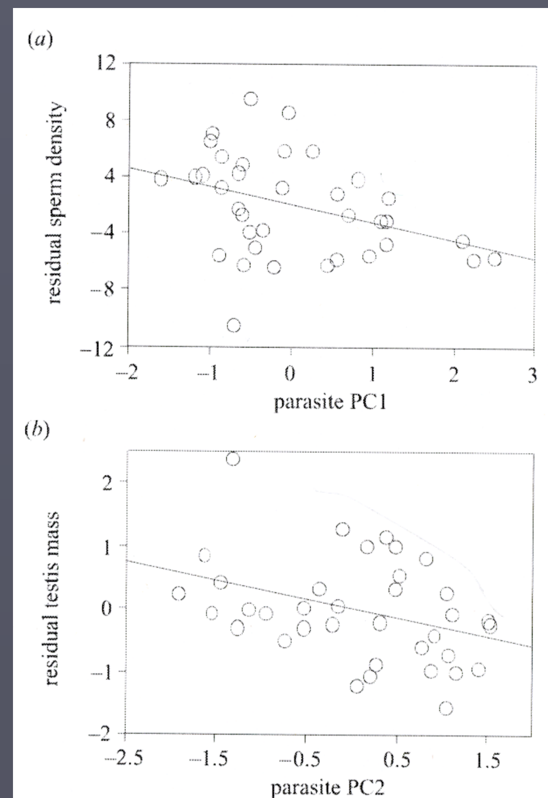




Investment in reproduction versus investment in immunity - intraspecific studies

- Ex. analysis of trade-offs between investments in immunity and reproduction





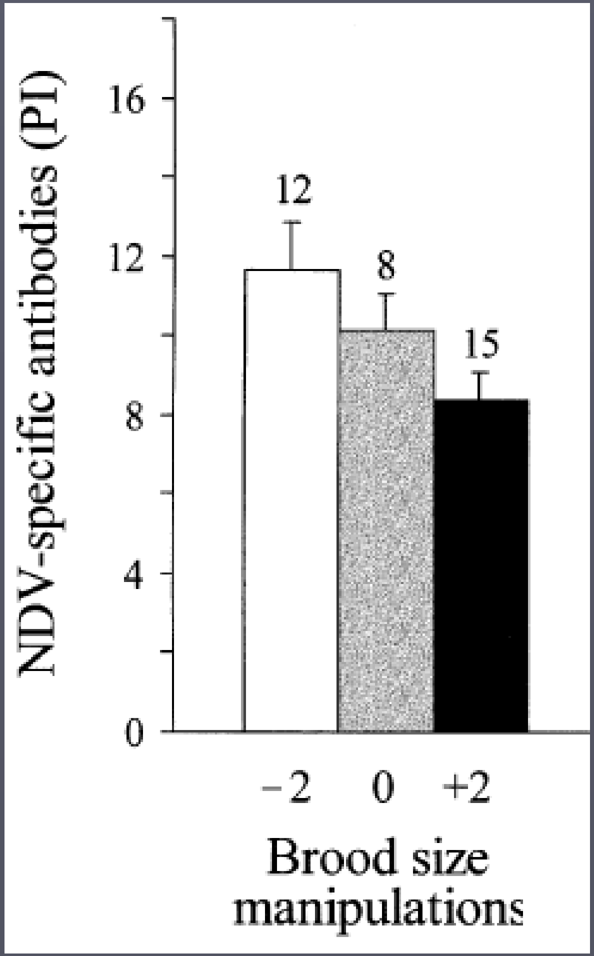
Arctic char
(*Salvelinus alpinus*)

=> trade-off between parasite resistance and the expression of primary sexual characteristics

Reproduction versus immunity

Relationship between reproduction and specific immunity

Females immunized with NDV (Newcastle disease virus)



Ficedula albicollis

Nordling et al. 1998

1. Increasing investment in reproduction reduces humoral immunity
2. Increasing reproductive effort increases the intensity of *Haemoproteus* infection - associated with higher mortality

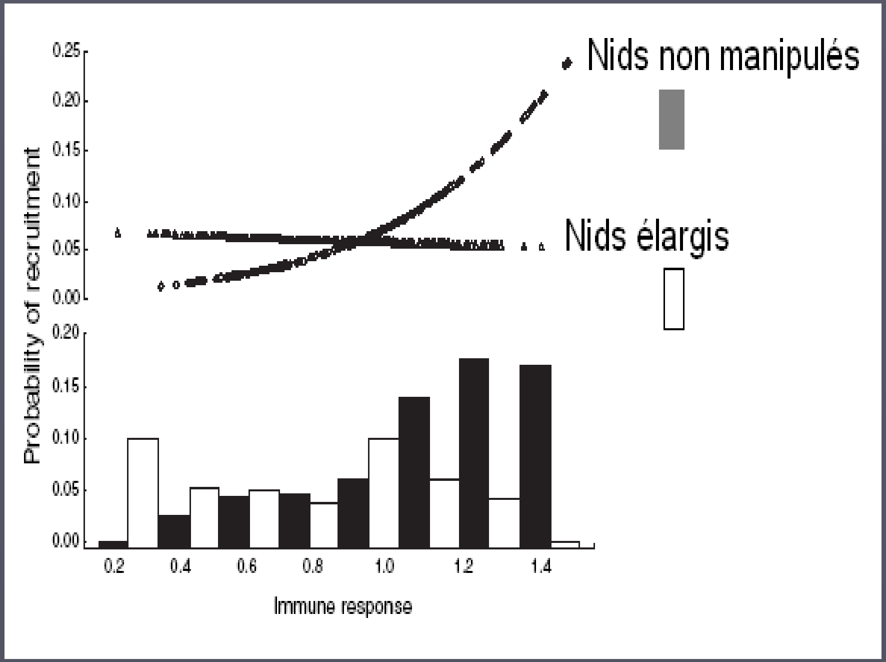
Pup success and immunocompetence

Manipulation with increasing offspring in nests
T cell mediated immunity - response to PHA

Positive relationship between immunity and offspring success → predicted probability of admission of young to the population

Parus caerulus

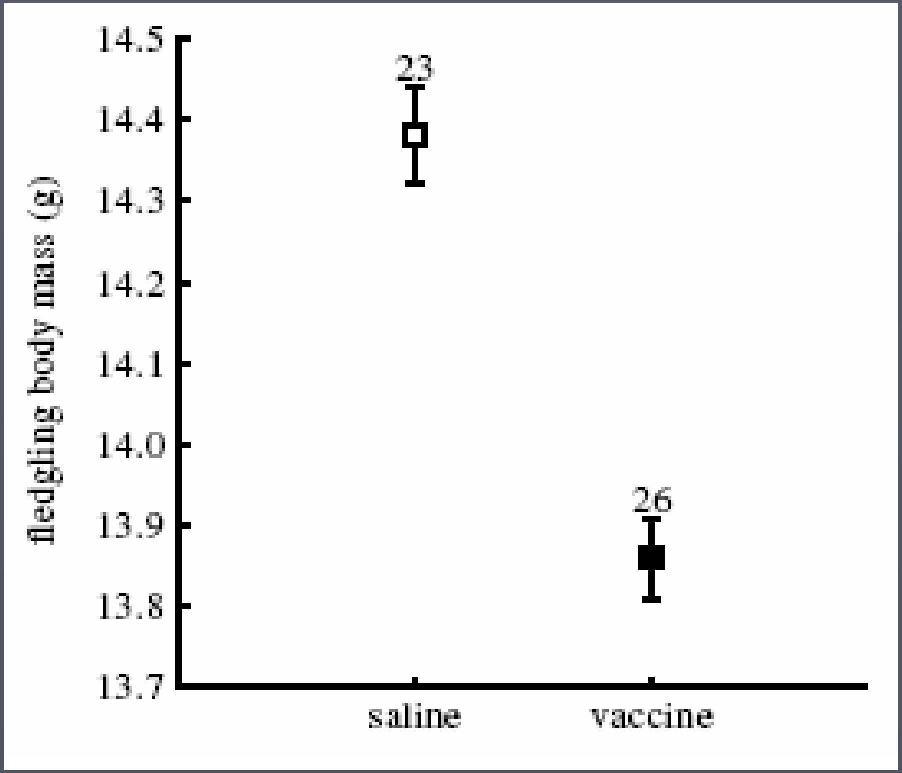
Cichon & Dubiec 2005



The immune response doesn't play a role in unfavourable breeding conditions
Local recruitement is dependent on immunity, but also on environmental factors

Offspring size and activation of humoral immunity

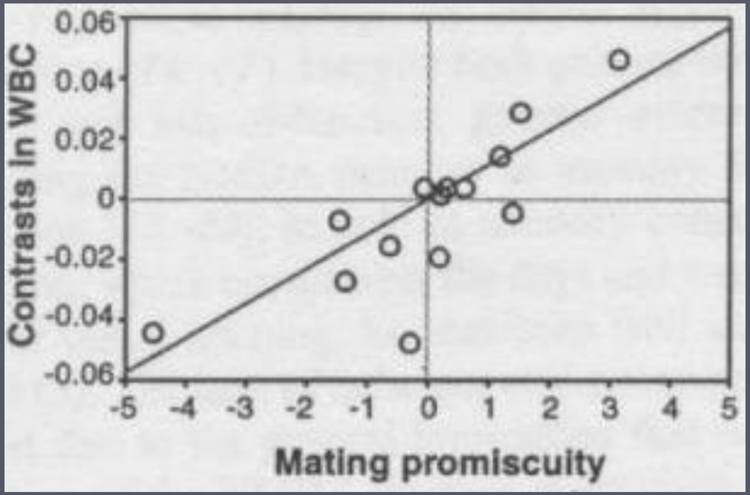
Females immunized with non-pathogenic antigen (diphtheria-tetanus vaccine)
Test of activation of the immune response to investment in reproduction



Ficedula hypoleuca
Ilmonen et al. 2000

Activation of the immune system decreases reproductive success (number and size of offspring)

White blood cells and sexual promiscuity in primates

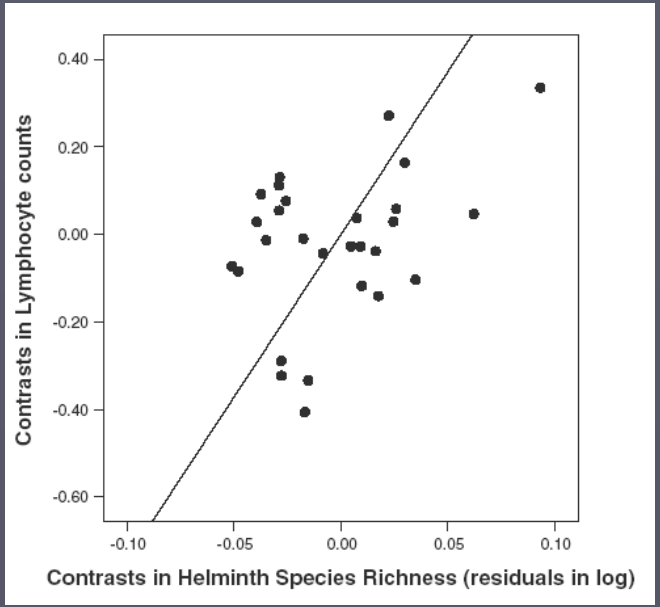


Nunn et al. 2000

Mating promiscuity: gestation time and size of testes

Relationship between white blood cell count and number of sexual partners => potential relationship to sexually transmitted diseases

Multiple helminth infections and basic investment in immunity



Increasing the number of helminth species is positively correlated with increasing the basic investment in immunity in mammals

Dependent variables	WBC counts			
	Leucocytes (F, P)	Lymphocytes (F, P)	Neutrophils (F, P)	Monocytes (F, P)
Helminth species richness (residuals in log)	**6.048 (0.02)**	**5.202 (0.03)**	1.958 (0.17)	3.172 (0.09)
Host body mass (in log)	0.544 (0.46)	1.357 (0.11)	3.433 (0.08)	1.754 (0.20)
Latitude	2.138 (0.16)	2.710 (0.11)	**8.279 (<0.01)**	0.046 (0.83)
Host longevity (month^{-1} in log)	**7.883 (<0.01)**	0.676 (0.42)	**7.096 (0.01)**	**22.984 (<0.001)**

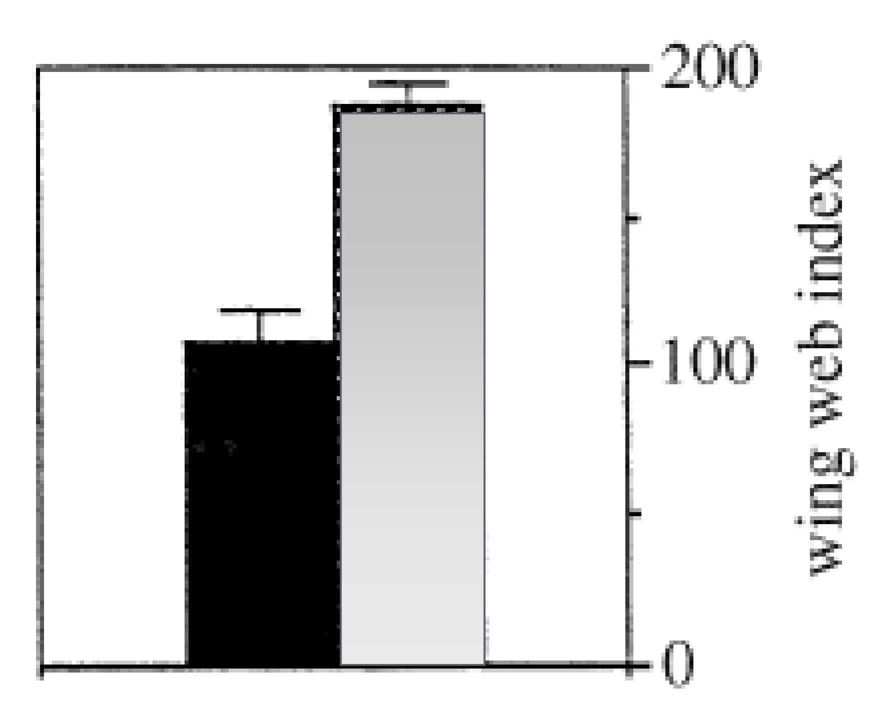
Significance of P value is in bold

Bordes & Morand, 2009, Par Res

Food resources and immunocompetence

Effect of brood nutrition on growth and T cell immunity (reaction to mitogen)

Only seeds ■
Seeds and supplementary diet □

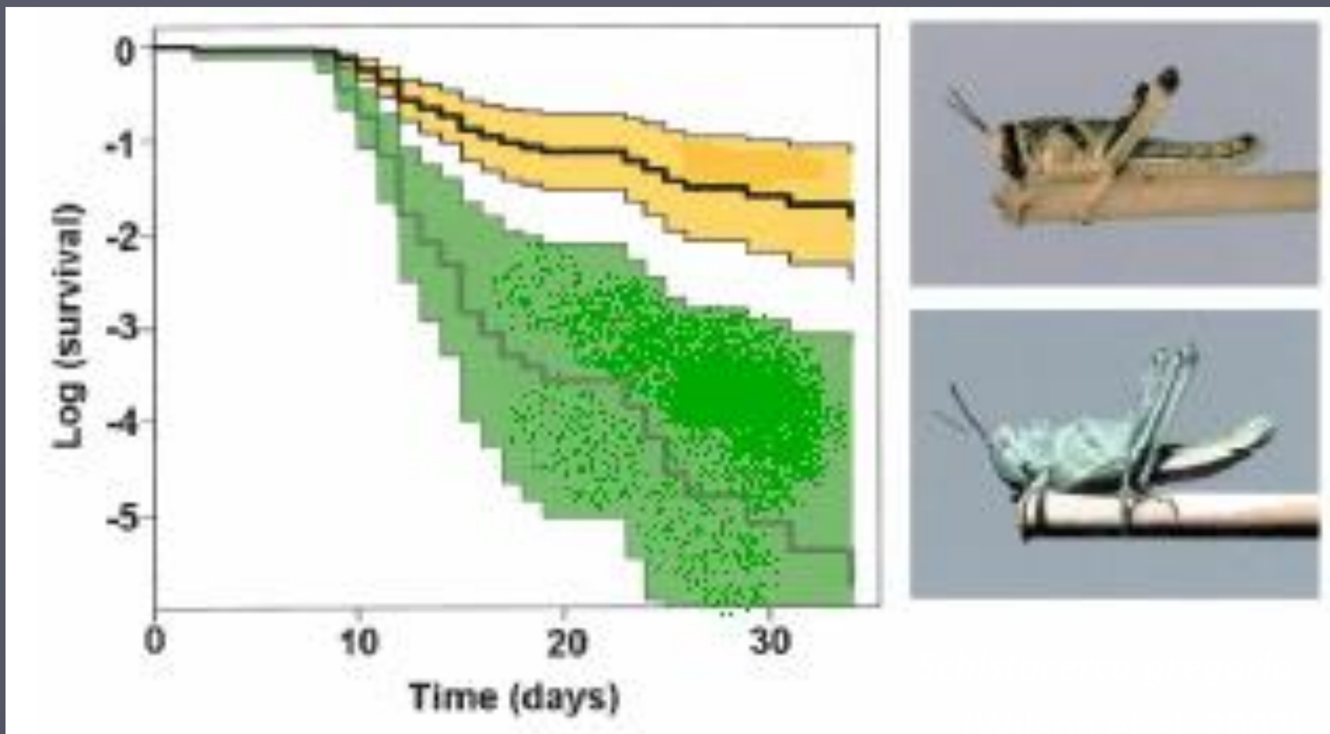


Taeniopygia guttata

Birkhead et al. 1999

Improving food quality accelerates growth and increases immunocompetence (cellular response)

Sociability and immunocompetence



Larvae

social

Solitary

The survival of social crickets is higher than that of solitary crickets ⇨ increasing density through phenotypic changes associated with better immunity

The effect of stress on immunity

Stress = an event that disrupts homeostasis, increasing energy use

stress

↓

hypothalamus - pituitary gland - adrenal gland

↓

corticoids

↓

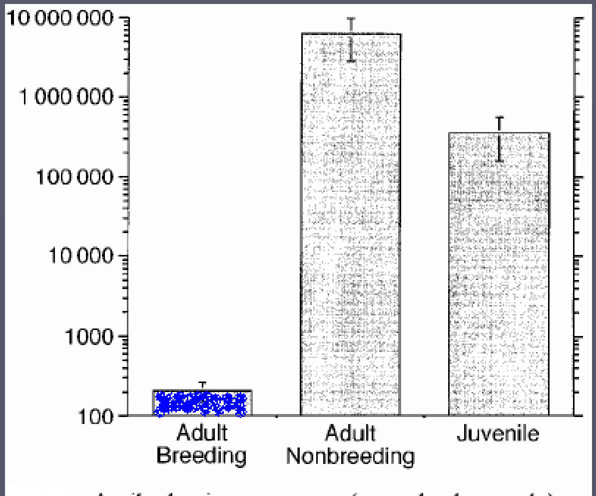
adaptive response

mobilizing energy for organs that need it

suppression of cost functions (immunity)

Sexual competition and social stress

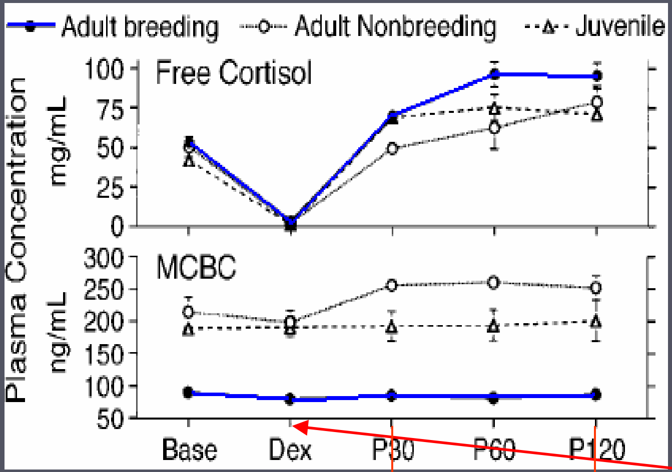
Adaptive response to stress during reproduction



Antibody titer response (note the log scale) to injected sheep red blood cells

Excitation of immunity

Arctic ground squirrel
Spermophilus parryii
Boonstra et al. 2001



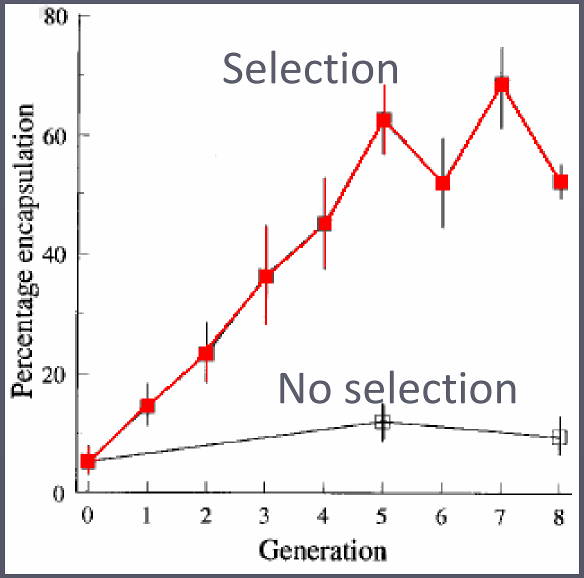
Hormonal induction

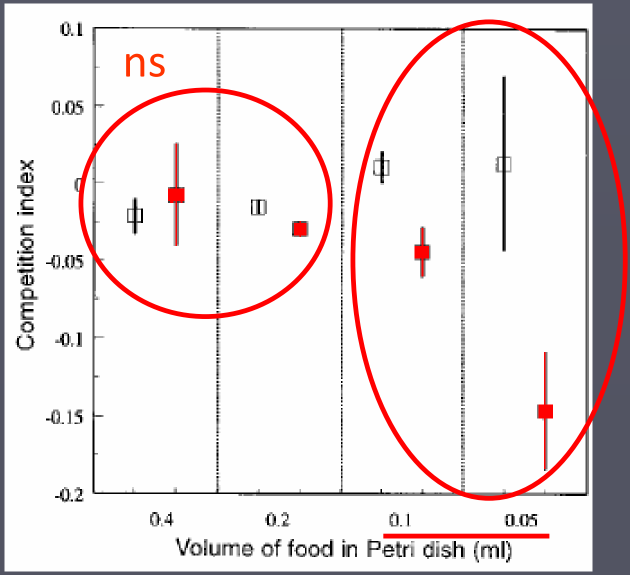
Chronic stress in reproductive adults - high cortisol levels, low ability to bind corticosteroids, low resistance to dexamethoson, low haematocrit, low white blood cell count, low ability to respond to immune stimulation

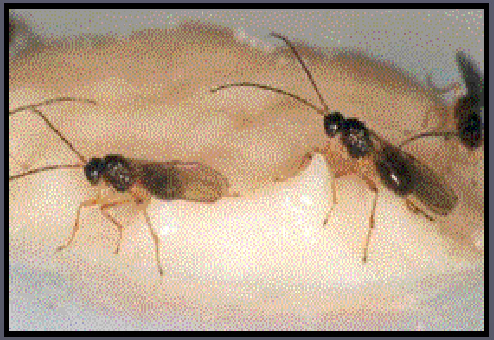
Response to adrenocorticotropic hormone

Dexamethosone injection - steroid immunosuppressor

Immune response and competition



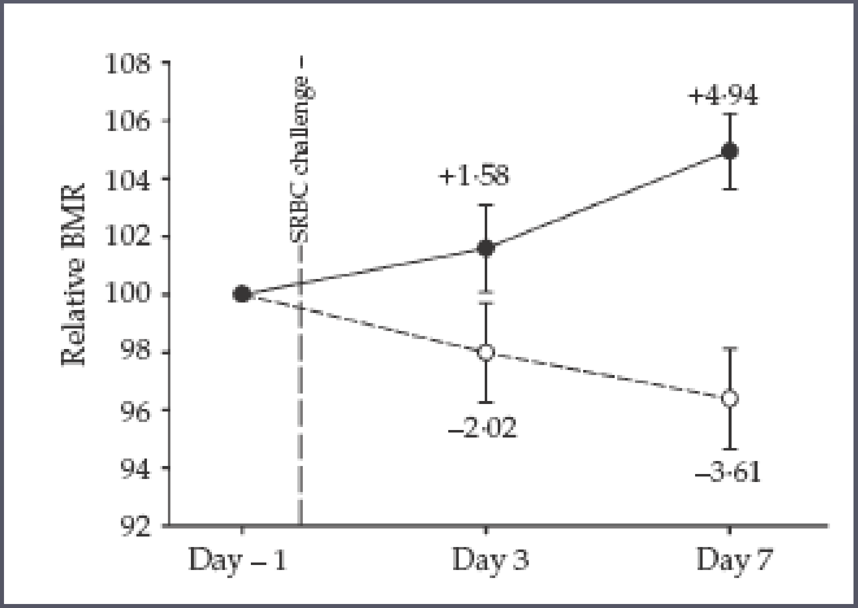




Kraaijeveld & Godfray, 1997

Selection of *Drosophila melanogaster* lines resistant to parasitoids (encapsulation) leads to reduced competitiveness

Immune response and metabolism



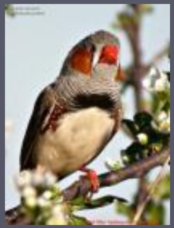
Pigeons were injected with sheep red blood cell suspension (SRBC) or injected with saline (control)

Effect of immune activation on the relative rate of basal metabolism in pigeons

Individuals with a strong immune response relative to a control that showed a low immune response (Eraud et al. 2005)

Costs associated with the immune response

protocol	organism	effect of treatment	references
clipping wings to prevent foraging and flying	free-flying bumble-bee (*Bombus terrestris*)	foraging bees show reduced encapsulation response	König & Schmid-Hempel (1995) and Doums & Schmid-Hempel (2000)
experimental increase of parental effort by increasing brood size, and increasing daily work effort by different reward schedules	captive zebra finch (*Taeniopygia guttata*)	increased parental effort and workload reduce antibody titre against sheep red blood cells	Deerenberg *et al.* (1997)

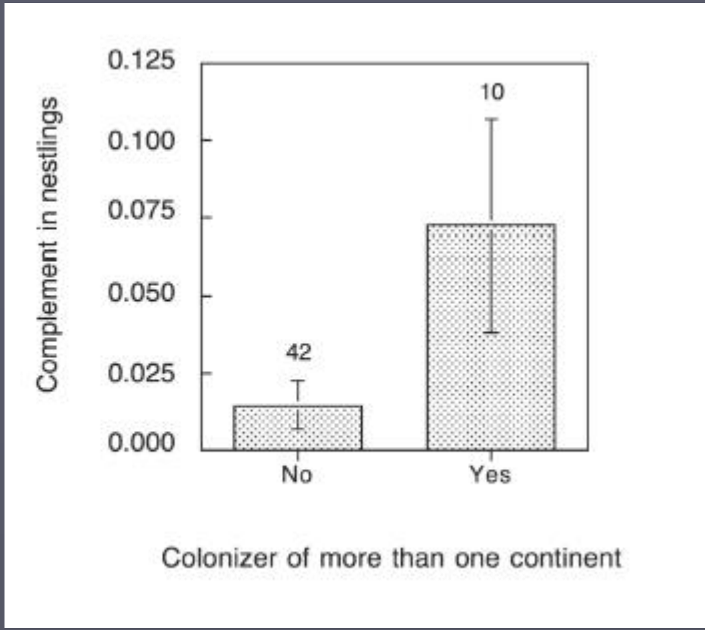


Increasing activity (e.g. flying, reproduction) reduces immune response => trade-off in energy and resource allocation

Immunity and successful invasion

Fixed effect	Parameter estimate	Standard error	*t* statistic
Life history			
Log_{10}(Body mass)	0·40	0·69	0·59
Log_{10}(Annual fecundity)	1·55	1·77	0·88
Ecology			
Habitat generalism	1·11	0·25	4·39**
Migratory habit	−0·40	0·33	−1·21
Sexual monochromatism	0·30	0·59	0·51
Introduction event			
Log_{10}(no. of propagules)	0·73	0·18	4·15**
Immune response			
Nestling T-cell response	0·75	0·40	1·88*
Adult T-cell response	2·96	4·35	0·68

$^*P < 0{\cdot}05$, $^{**}P < 0{\cdot}01$.



T cell - mediated immune response in young (measured in response to mitogenic lectin PHA) determines the success of population establishment

The immunity of young birds increases expansion of the introduced populations or the colonization of continents

Moller and Cassey, 2004

Costs associated with immune responses

Table 1. Examples of experimental studies of the cost associated with the evolution of an immune defence component.

selective regime	organism	effect on other fitness components	references
earlier or later age at pupation (i.e. age at reproduction)	mosquito (*Aedes aegyptii*)	earlier reproduction correlates with lower encapsulation response, the opposite for later reproduction	Koella & Boete (2002)
increased resistance to nematode infections	mosquito (*Aedes aegyptii*)	reduced reproductive success	Ferdig *et al.* (1993)
increased encapsulation response to common larval parasitoids (*Asobara tabida*)	fruitfly (*Drosophila melanogaster*)	reduced competitive ability	Kraaijeveld & Godfray (1997)
increased encapsulation response to virulent larval parasitoids (*Leptopilina boulardi*)	fruitfly (*Drosophila melanogaster*)	lower survival rate of larvae	Fellowes *et al.* (1998)
increased resistance to bacterial disease	honeybee (*Apis mellifera*)	slower larval growth	Sutter *et al.* (1968)
increased resistance to bacterial disease	honeybee (*Apis mellifera*)	higher larval mortality	Rothenbuhler & Thompson (1956)
increased resistance to granulosis virus	Indian meal moth (*Plodia interpunctella*)	slower development, lower egg viability, but increased pupal mass	Boots & Begon (1993)
increased resistance or susceptibility to *Schistosoma* infections	snail (*Biomphalaria glabrata*)	susceptible lines produce more offspring, irrespective of infection status	Webster & Woolhouse (1998)
increased body mass	turkey (*Meleagris gallopavo*)	reduced immune function	Bayyari *et al.* (1997) and Nestor *et al.* (1996)

Costs associated with immune responses

Table 2. Examples of studies of the cost associated with the use of immune defence components.

protocol	organism	effect of treatment	references
(*a*) nutrition and general stress			
restricted access to food	captive bumble-bee (*Bombus terrestris*)	reduces reproductive success but has no effect on encapsulation response	Schmid-Hempel & Schmid-Hempel (1998)
mechanical disturbance of 15 min duration	oyster (*Crassostrea gigas*)	various immune parameters down-regulated during stress, but stimulated for 30–40 min afterwards	Lacoste *et al.* (2002)
birds raised on supplemented diet or seeds only	captive zebra finch (*Taeniopygia guttata*)	seed-only diet reduces survivorship, and leads to reduced cell-mediated immune function in nestlings. No difference in adult birds, perhaps owing to compensation	Birkhead *et al.* (1999)
protein-rich or protein-poor diet	captive house sparrow (*Passer domesticus*)	protein-rich diet leads to higher cellular but lower humoral response	Gonzalez *et al.* (1999)
food deprivation or excess food	chicken (*Gallus domesticus*)	excess food decreases and deprivation increases various immune response parameters	Klasing (1988)

Evolution of immune genes

- Major histocompatibility system (MHC) genes
- Evolution of MHC genes and selective factors
- capture peptides and fragments (antigens) and immerse them in the cell surface => cells offering antigen, fragments of which are recognized by the T-cell receptor for antigen
- PBR sites (peptide binding regions) - binding sites of MHC glycoproteins

Glycoproteins MHC I and MHC II

- MHC class I glycoproteins - present on all nuclear cells of the organism

- To ensure the presentation of intracellularly derived peptides formed by the breakdown of proteins derived from viruses and some species of bacteria

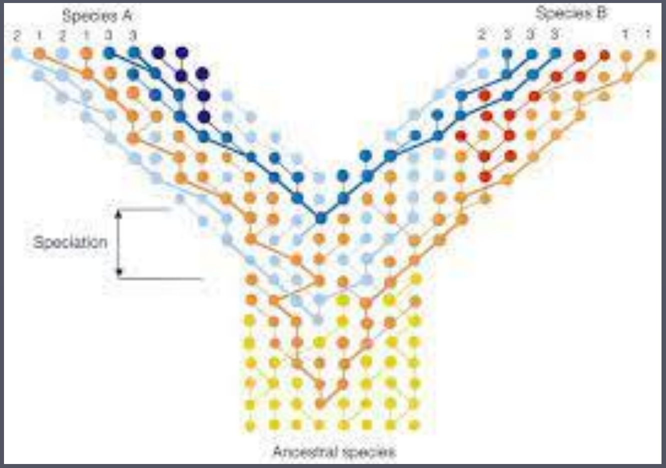
- MHC class II glycoproteins - occur on antigen-presenting cells - B lymphocytes, monocytes, macrophages and dendritic cells

- To present peptide fragments derived from extracellular parasites, e.g. some species of bacteria or metazoan parasites

MHC polymorphism

- found in all jawed vertebrates from fish to mammals

- highly polymorphic genes
- high number of alleles that provide functional loci
- high number of nucleotide substitutions between individual alleles
- trans-species polymorphism



Selection leading to high polymorphism of MHC genes

- Two non-exclusive mechanisms:

1. parasite-mediated selection
2. sexual selection

- Parasite-mediated selection
- 1. advantage of rare MHC genotypes (theory of advantage of rare allele)
- 2. advantage of MHC heterozygotes (heterozygote advantage theory)

Heterozygote advantage theory

- heterozygote has a higher ability to distinguish a wide range of antigenic peptides derived from parasites or pathogens than homozygote
- heterozygote resistence > homozygote resistance

- Ex. female salmon choose males in terms of increasing the MHC heterozygosity of their offspring
- Ex. relationship between MHC IIB heterozygosity and Gyrodactylus (Monogenea) infection in *Poeciliopsis occidentalis*
- Ex. advantage of mice MHC heterozygotes in infection with *Salmonella* strains

Rare allele advantage theory

- Frequency-dependent selection
- Assumption: host individuals with a rare allele respond better to the presence of new parasite
- Increasing the frequency of the rare allele in the host population leads to the allele becoming the target of parasitic adaptation

- Ex. the relationship between the specific allele of the MHC IIβ system and parasitism in salmonid fish

The average number of alleles is advantageous for individuals

- Nowak et al. 1992 – mathematical model

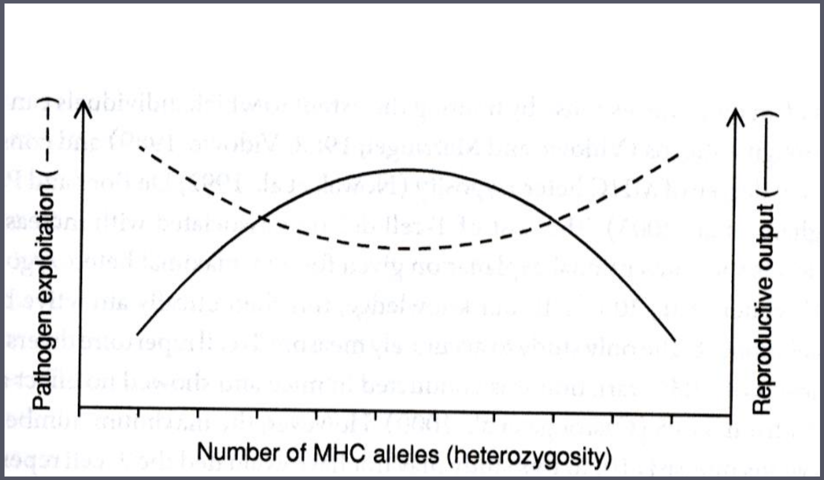
  High diversity of MHC alleles in an individual is not advantageous

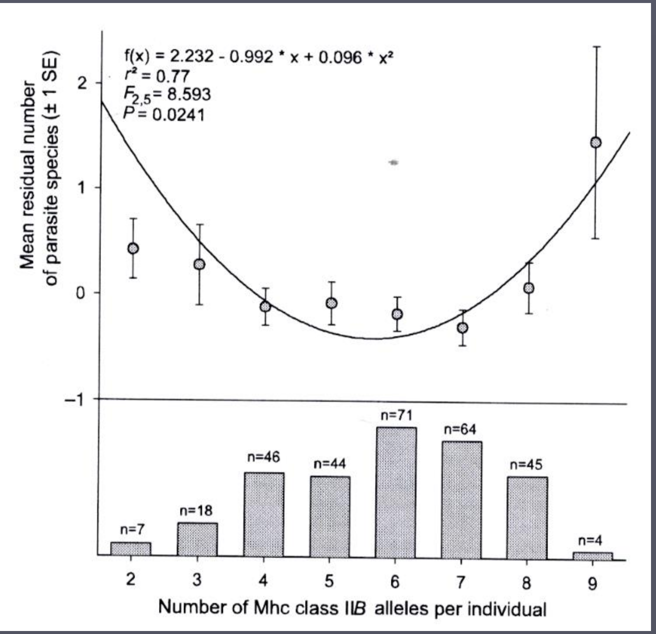
  - recognition of a wide range of antigenic peptides

  - elimination of own T cells

- the optimal (= intermediate) number of MHC alleles determines the best immune response

Ex. Mean number as the optimum of MHC alleles and the lowest parasitism at the level of the individual in three-spined stickleback

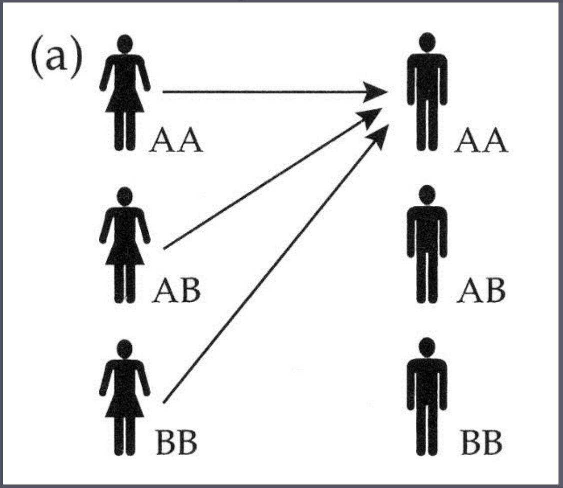




The role of sexual selection in increasing MHC polymorphism

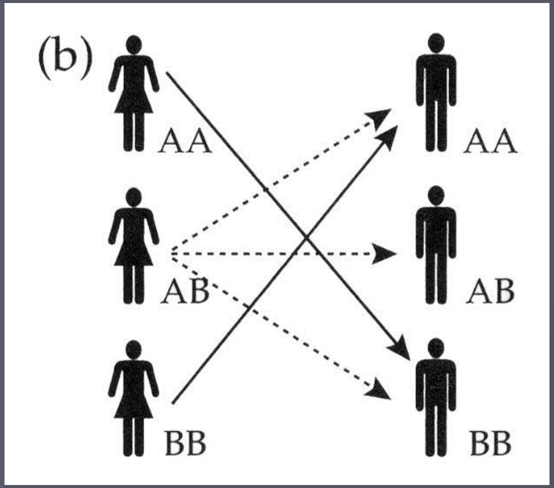
- the relationship between MHC genotype and sexual selection
- MHC genes = resistance genes - good or compatible genes

- Hypothesis of good genes
- vitale males with genetic predisposition for high resistance to parasites have strong sexual ornamentation
- the female selects her partner in terms of selecting good genes for offspring
- the relationship between MHC genotype and fitness-dependent character
- Good genes of males – parasite load, secondary sexual traits (body colaration, breeding tubercles in fish)

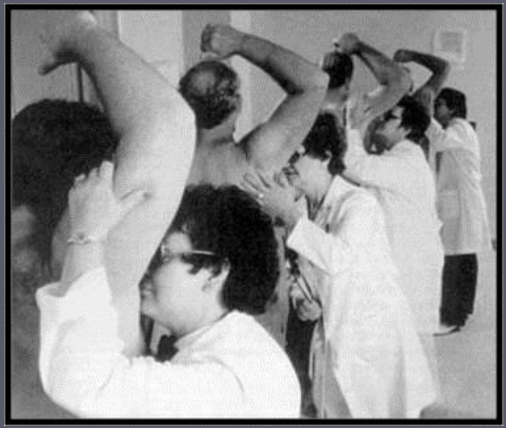


The role of sexual selection in increasing MHC polymorphism

- Genetic compatibility hypothesis
- MHC as a genetically incompatible system - prevents inbreeding, individuals with a similar MHC genotype = related individuals
- the female directs her choice of partner depending on her own MHC genotype, i.e. she selects a male with a different MHC genotype = complementary to her MHC genotype = high MHC variability for offspring
- Ex. three-spined stickleback

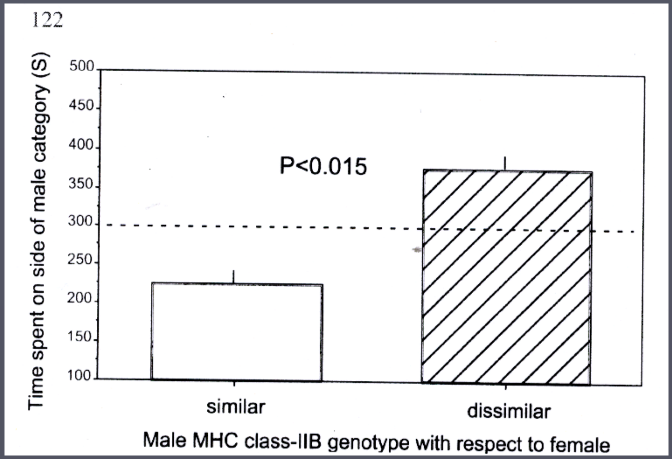


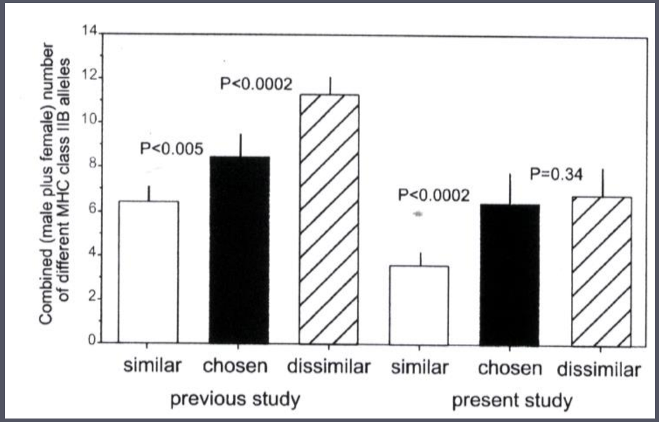
The role of sexual selection in increasing MHC polymorphism



- How can a female recognize a different or complementary MHC genotype?

- the choice of a partner is based on olfactory perceptions
- Studies in humans, mice, also documented in fish





Sexual selection and MHC

- Two levels of sexual selection in relation to MHC
- at the level of individuals - certain males with better condition bound traits
- at the gamete level - the sperm of a certain individual are selected by female oocytes more than the sperm of another individual

e.g. Arctic char - sperm of MHC heterozygotes have higher success in fertilization

Arctic char
(*Salvelinus alpinus*)

MHC and extinction of species

desert bighorn sheep
(Ovis canadensis nelsoni)

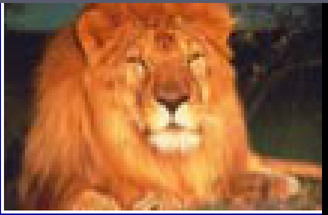
Arabian oryx
Oryx leucoryx

FIG. 2. A neighbor-joining tree with the three class II *DRB* Arabian oryx alleles indicated by triangles and related sequences from other ruminants.

Protection program
= maintain all 3 variants

MHC and extinction of species

Correlations of Genetic Variation and Reproductive Parameters in Three Lion Populations



Parameter	Serengeti Tanzania	Ngorongoro Crater Tanzania	Gir Forest India
Genetic Properties			
Heterozygosity (%)	3.1	1.5	0.0
% diff. in MHC Loci	21.8	8.0	0.0
Reproductive Measures			
Sperm count (x 10^{-6})	34.4 ± 12.8	25.8 ± 11.0	3.3 ± 2.8
% sperm abnormality	24.8 ± 4.0	50.5 ± 6.8	66.2 ± 3.6
Motile sperm/ejac.	228.5 ± 65.5	236.0 ± 93.0	45.3 ± 9.9
Testosterone (ng/ml)	1.3 to 1.7	0.5 to 0.6	0.1 to 0.3