A model to quantify individual tolerance and resistance to infectious diseases

DEFINITIONS

MECHANISMS

MODELS

COSTS

APPLICATION TO BOVINE MASTITIS

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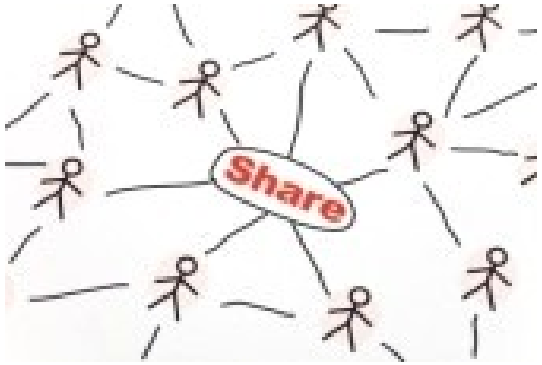
Team work

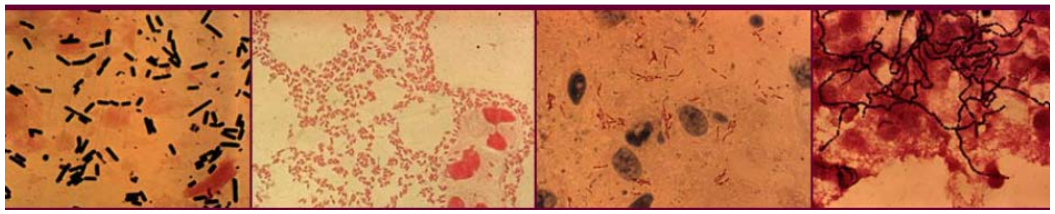


VETERINARY MEDICINE

Université de Liège

Department of infectious and parasitic diseases

LABORATORY OF BACTERIOLOGY



Definitions

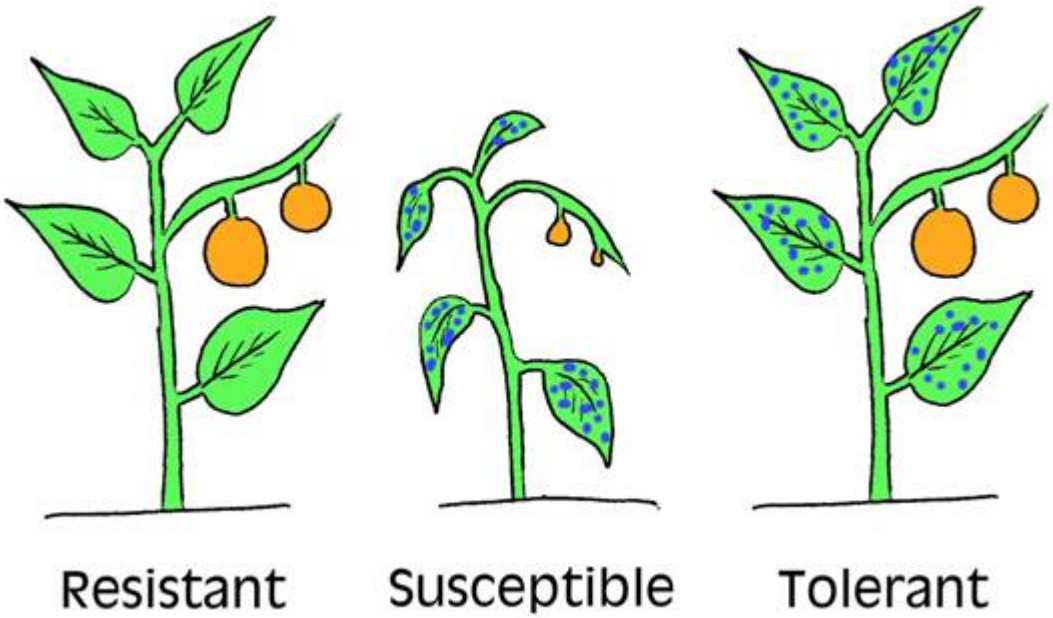
RESISTANCE

TOLERANCE

Definitions

Resistance = ability to reduce pathogen burden

Tolerance = ability to tolerate a certain concentration of pathogen



References: Ayres & Schneider, 2012; Best et al., 2008; Roy & Kirchner, 2000; Raberg et al., 20

Definitions

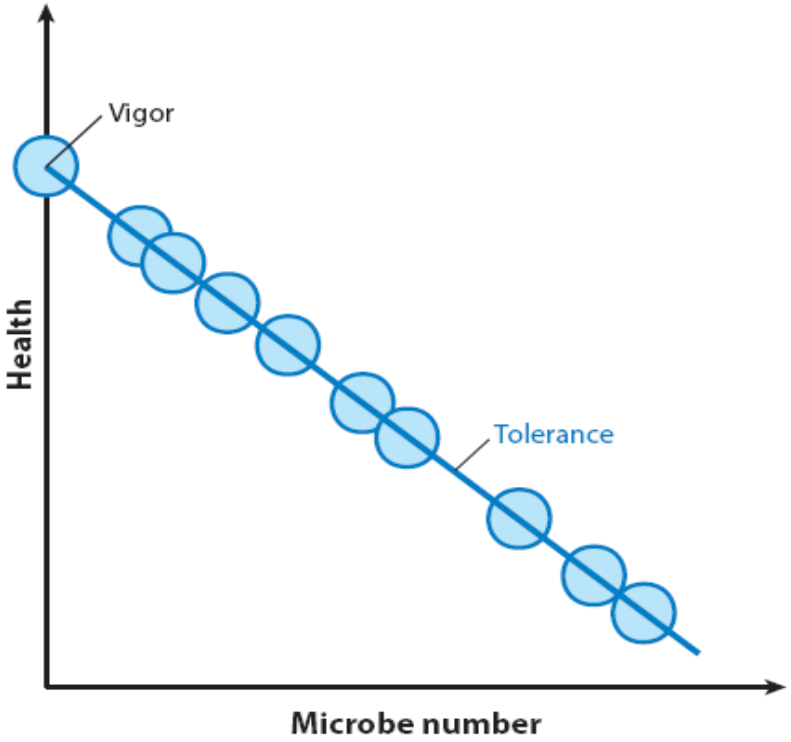
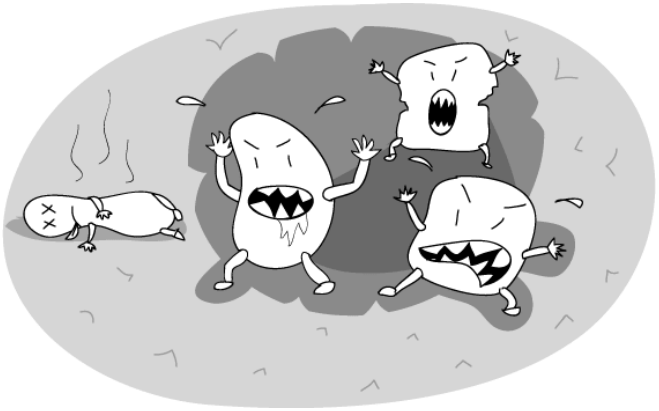


Figure 1

Graphical definitions of resistance and tolerance. Vigor is defined as health at zero parasite load; this may not be the same point that is projected as an intercept by regression (3). Resistance is defined by the inverse of the mean parasite load in the system; more resistant hosts have fewer parasites. Tolerance is defined as the slope of the health-by-microbe curve.

Resistances

Resistance to infection (avoidance)
= reduction of pathogen transmission at contact



Resistance to disease
= reduction of pathogen growth after infection

Tolerances

Direct tolerance

Indirect tolerance

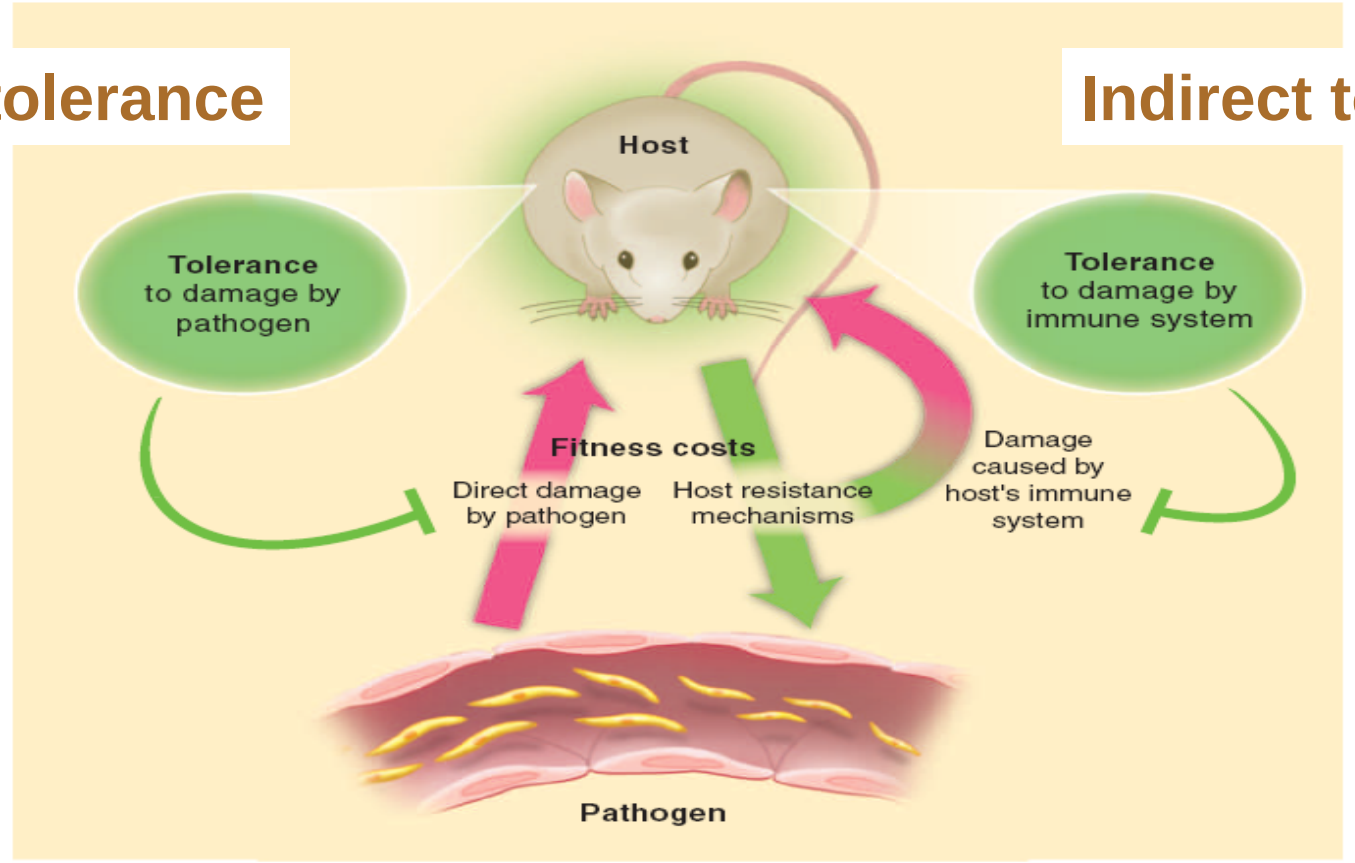


Fig. 1. Two types of fitness costs associated with infections. Pathogens can directly damage the host tissues. The immune system of the host reduces the pathogen burden through the resistance mechanism. The immune response can also damage the host tissues. The host can reduce fitness costs through tolerance mechanisms that reduce both the direct tissue damage by pathogens, and immunopathology.

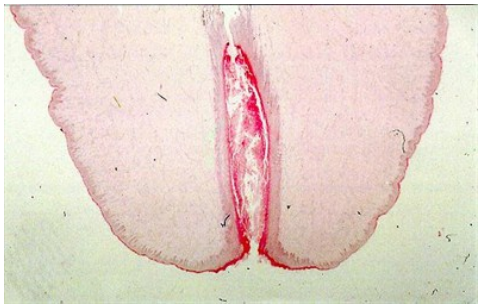
Mechanisms

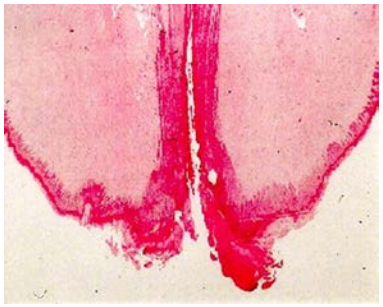
RESISTANCE TO INFECTION
RESISTANCE TO DISEASE
TOLERANCE TO INFECTION
TOLLERANCE TO DISEASE

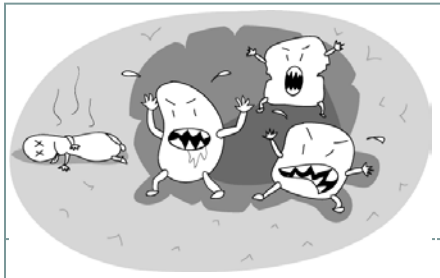
Resistance to infection

Behavioral immunity

Innate constitutive protective barriers



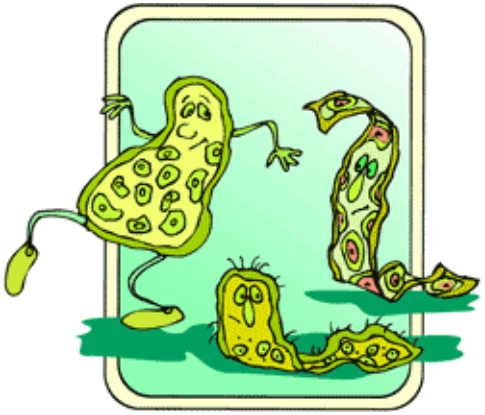


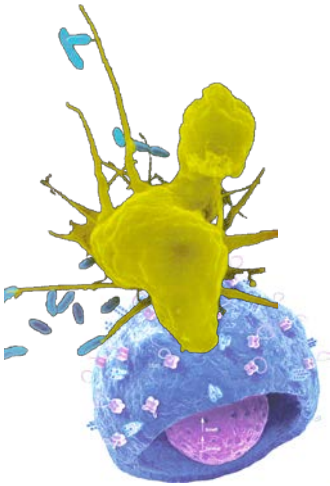


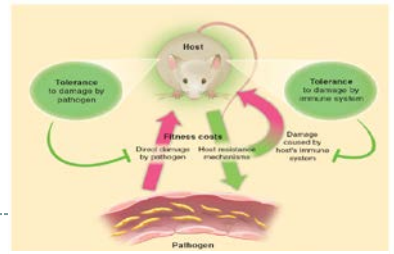
Resistance to disease

Infection

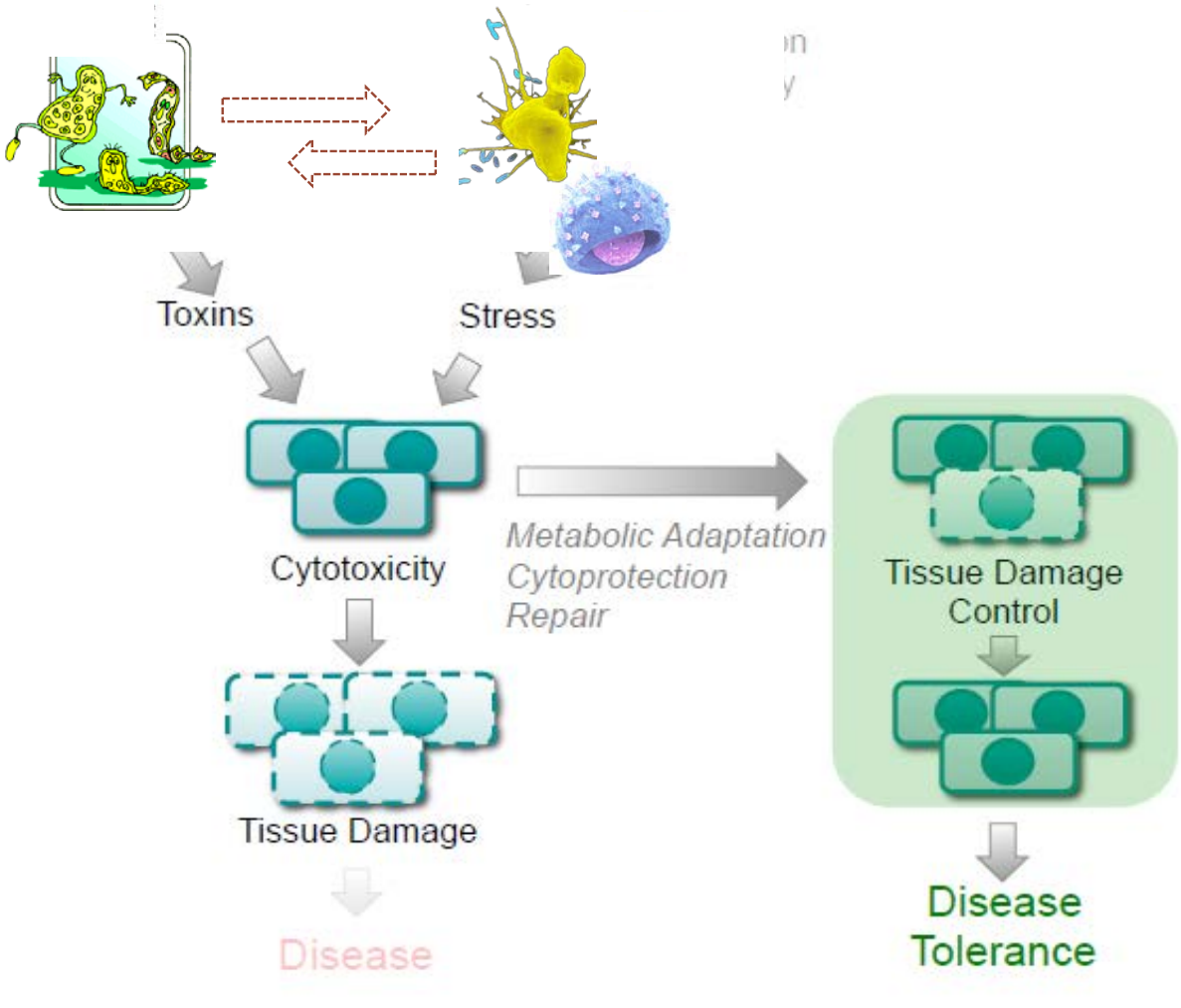
Inflammation
Immune response







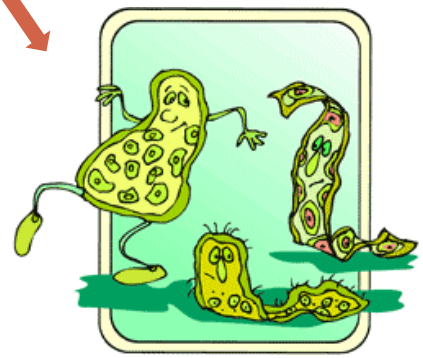
Tolerance to infection and disease



All together

Resistance to infection

Infection



Immune response

Resistance to disease

Inflammation
Immunity

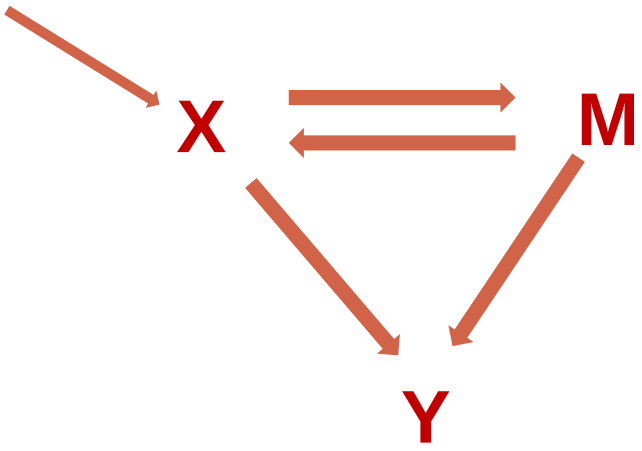
Direct damage

Indirect damage

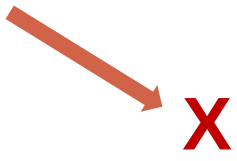
Performance

Models

X = PATHOGEN LOAD
M = IMMUNE INDEX
Y = PERFORMANCE



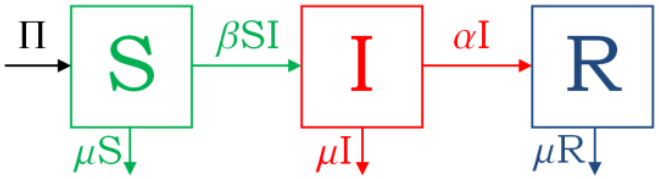
Resistance to infection



Resistance to infection

- Basic reproduction rate (R_0)

= number of new cases created by a single primary case in a susceptible population



- Individual probability to get infected

$$b_i = h^2 (1 - b_0) a_i + b_0$$

b_i = probability to become infected after contact with an infective

h^2 = heritability of the resistance to infection

a_i = degree of relationship between cows in contact

b_0 = average population transmission probability

Sources: Detilleux, 2005; Dieckmann & Heesterbeek 2000; Heffernan & al., 2005; …

Resistance to disease

Resistance to disease

Differential equations

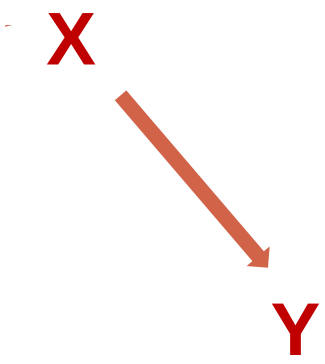
$$\left(\begin{array}{l}\text{Pathogen load}\\ \text{rate of change}\end{array}\right) = \left(\begin{array}{l}\text{Pathogen}\\ \text{growth rate}\end{array}\right) - \left(\begin{array}{l}\text{Pathogen}\\ \text{killing rate}\end{array}\right)$$

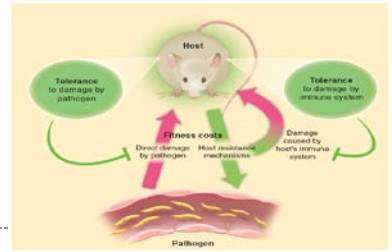
$$\left(\begin{array}{l}\text{Immune index}\\ \text{rate of change}\end{array}\right) = \left(\begin{array}{l}\text{Immune index}\\ \text{entry rate}\end{array}\right) - \left(\begin{array}{l}\text{Immune index}\\ \text{exit rate}\end{array}\right)$$

Differents models for rates: Holling functional response, saturation term, logistic/exponential growth,

References: Doeschl-Wilson, 2011; Detilleux, 2009; Pugliese and Gandolfi, 2007; …

Direct tolerance





Direct tolerance

Random regression models

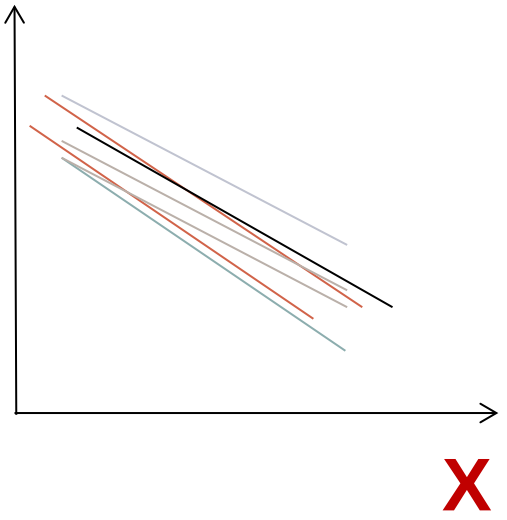
$$E(Y_{ij} \mid b_{i0}, b_{i1}) = b_{i0} + b_{i1} X_i$$
$$\text{with } b_{i0} \sim N(\beta_0 , \sigma_0^2) \text{ and } b_{i1} \sim N(\beta_1 , \sigma_1^2)$$

b_{i0} = vigour

b_{i1} = tolerance

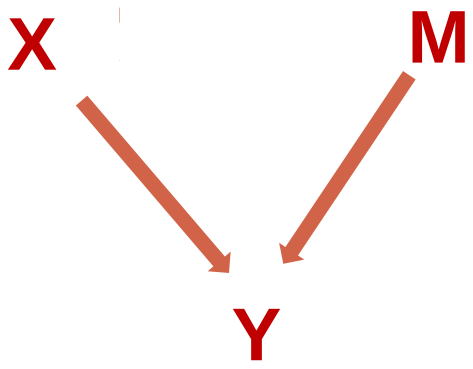
X_i= pathogen load

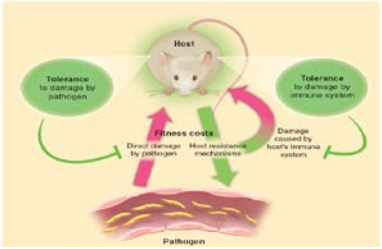
Y_{ij} = host infected



References: Kause and Odegard, 2012; Little et al., 2010; …

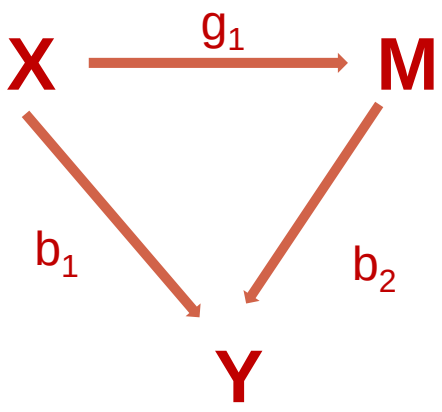
Direct & indirect tolerances





Tolerances

Structural equation models



Direct tolerance
$= b_1$

Indirect tolerance
$= g_1 b_2$

$$E(M_{ij} \mid b_{i0}, b_{i1}) = g_{i0} + g_{i1} X_{ij}$$

with $g_{i0} \sim N(g_0, \tau_0^2)$ and $g_{i1} \sim N(g_1, \tau_1^2)$

$$E(Y_{ij} \mid b_{i0}, b_{i1}, b_{i2}) = b_{i0} + b_{i1} X_{ij} + b_{i2} M_{ij}$$

with $b_{i0} \sim N(\beta_0, \sigma_0^2)$, $b_{i1} \sim N(\beta_1, \sigma_1^2)$ and $b_{i2} \sim N(\beta_2, \sigma_2^2)$

References: Baron et Kenny, 1986; Iacobucci et al., 2007; …

Tolerances

Counterfactual interpretation

Y(x,m) = potential performance observed in an individual with infection levet set at the value x and immune index set at the value m

m_0 = level of immune index under health

m_1 = level of immune index under infection

Natural direct effect

$$E[Y(\text{infection}, m_0)-Y(\text{health},m_0)]$$

Natural indirect effect

$$E[Y(\text{infection}, m_1)-Y(\text{infection},m_0)]$$

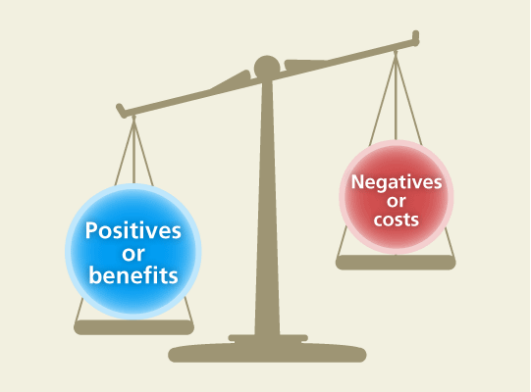
References: Lange et al., 2012; Vansteelandt, 2012;

Costs

RESISTANCES
TOLERANCES

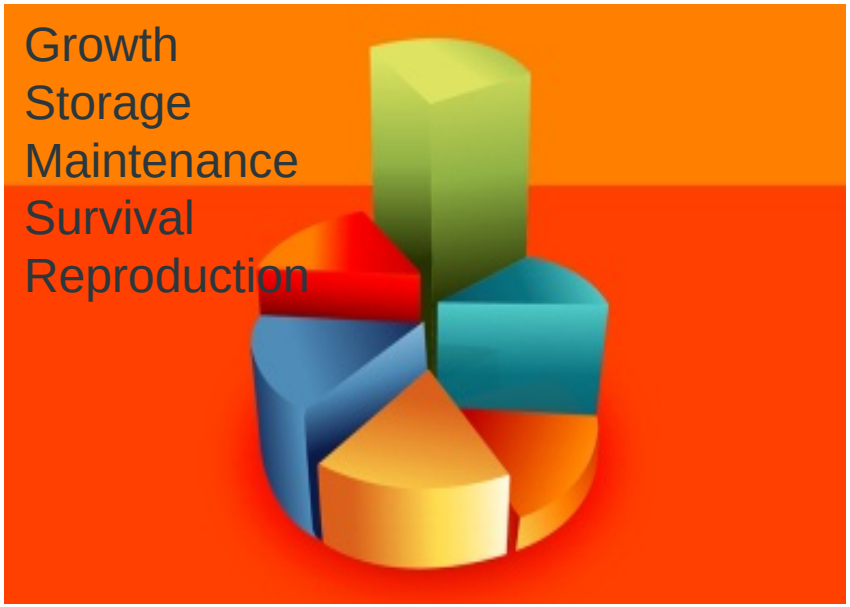
Mechanisms

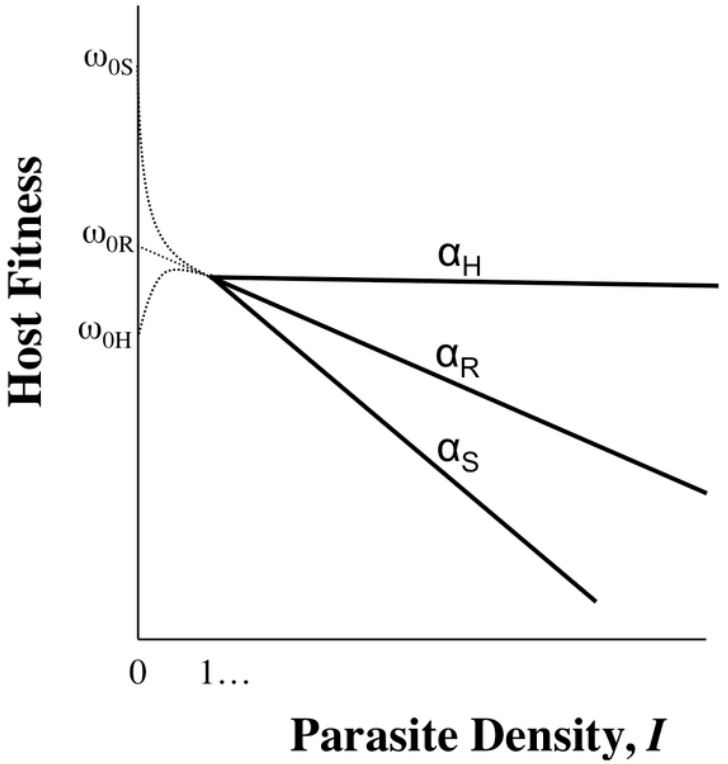
- Innate constitutive protective barriers: low
  - lack of diversification process
  - low rates of cell turnover
  - small tissue mass in innate response
- Inflammation: high
  - increased production of acute phase protein
  - changes in energy and nutrient metabolism
  - anorexia, fever
- Immune response:
  - high for cell-mediated response, low for humoral response
  - innate more costly than adaptive response
  - reduced tolerance
- Tissue damage repair



References: Horns & Hood, 2012; Romanyukha et al., 2006; Medzhitov, 2009; …

Life-history traits theory



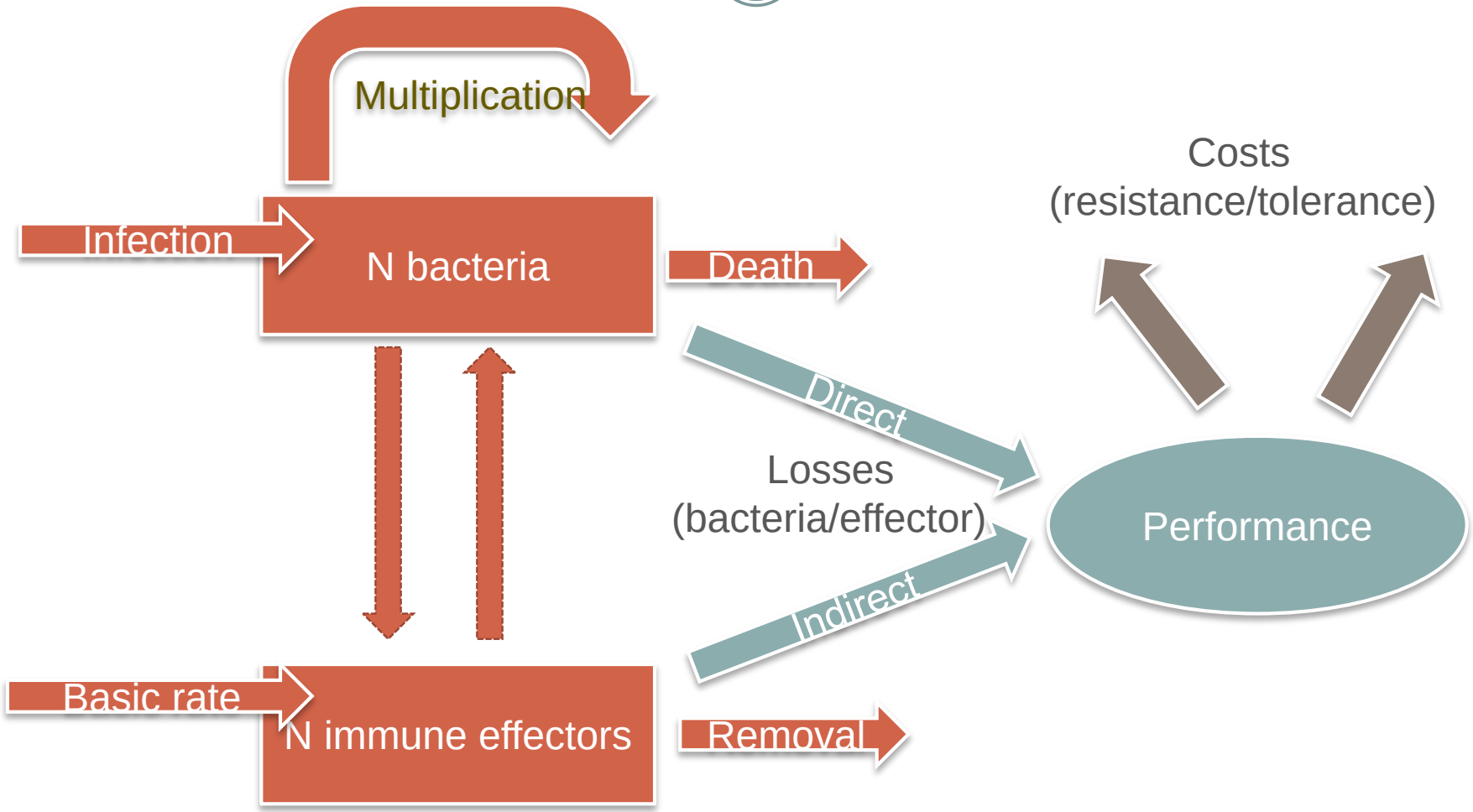


References: Baucom & de Roode, 2011;Little & al., 2010; Rauw, 2012;

Bovine mastitis

RESISTANCES
TOLERANCES
COSTS

Model



References: Detilleux, 2013

B = N bacteria
C = N immune effectors
P = Performance

Contact rate

Resistance to infection

Logistic growth

Infection: $D_{t+\Delta t} = \sum_i c\ \nu\ \beta^i\ B^i_t \quad \text{for } i = 1, 2, \ldots I,$

Resistance to disease

Multiplication: $N_{t+\Delta t} \sim \text{Poisson}[\gamma\ B_t\ (1 - B_t/K_B)]$

Bacteria killing: $K_{t+\Delta t} \sim \text{Poisson}[\alpha\ C_t\ B_t\ \rho/(1 + (\tau\ \alpha\ B_t))]$

Costs

Basic flow: $M_{t+\Delta t} \sim \text{Poisson}\ [\omega\ (C_1 - C_t)]$

Extra-recruitement: $G_{t+\Delta t} \sim \text{Poisson}\ [\mu\ B_t\ C_t/(K_m + B_t)]$

Extra-removal: $S_{t+\Delta t} \sim \text{Poisson}\ [\alpha\ C_t\ B_t\ \rho/\theta\ (1 + (\tau\ \alpha\ B_t))]$

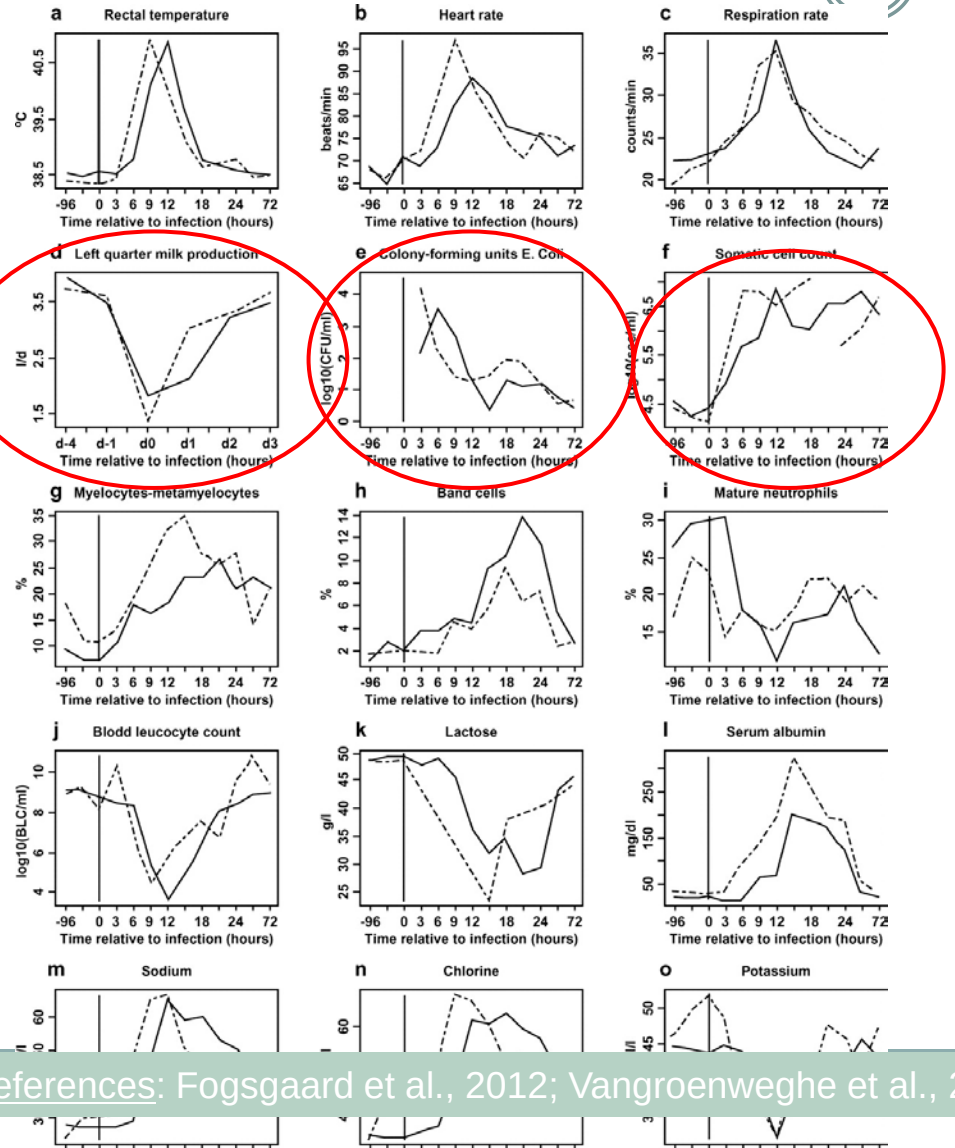
Direct tolerance

Costs: $P_1 = P^{Max}\ (1 - \rho\ c_\rho - \lambda_b\ c_b - \lambda_c\ c_c)$

Losses: $P_t = P_1 - [B_t\ L_B\ (1 - \lambda_b) + C_t\ L_C\ (1 - \lambda_c)]$

Indirect tolerance

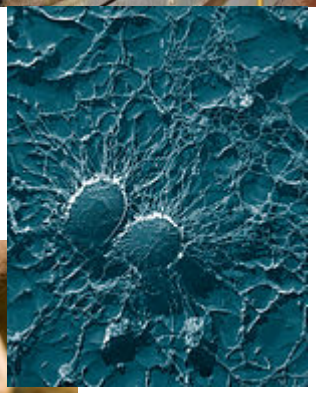
Data



Experimental studies

References: Fogsgaard et al., 2012; Vangroenweghe et al., 2005; …

Data



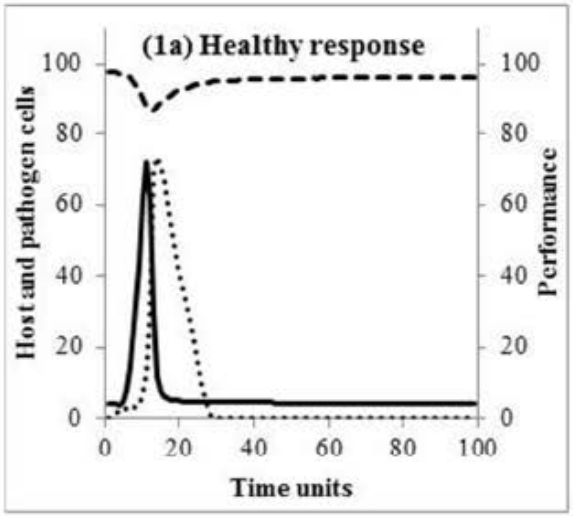
Field data

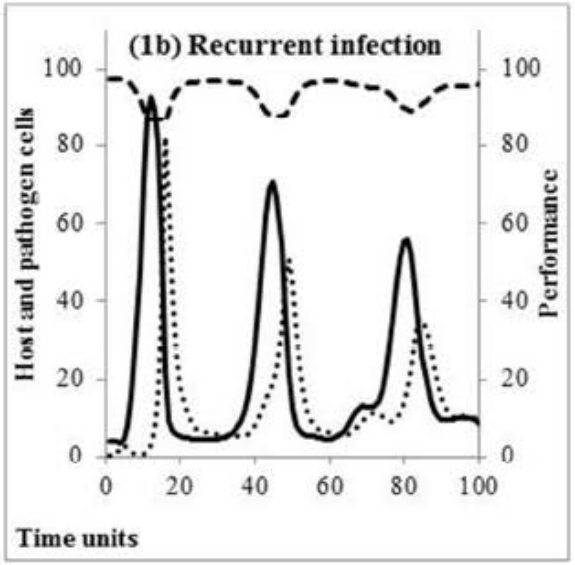
References: Barkema et al.,1998 ; Grohn et al., 2004; Reding et al., 2013; ….

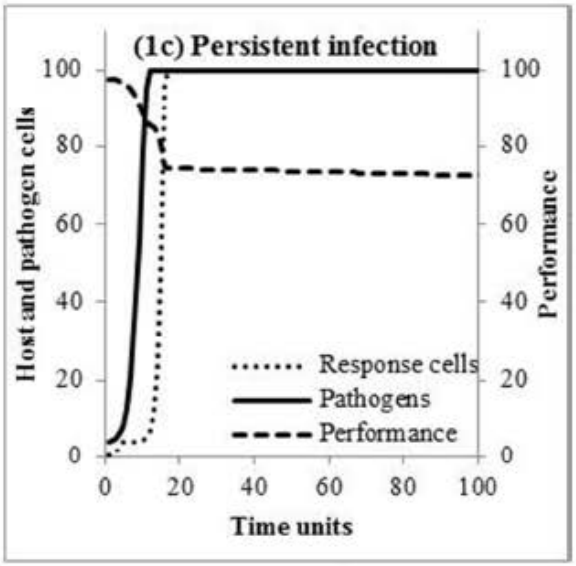
Results

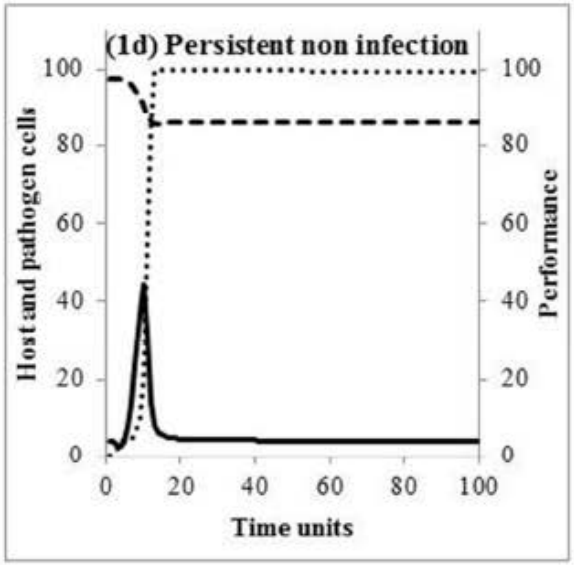
- Healthy response
- Recurrent infection
- Persistent response without infection
- Persistent response and infection
- Severe immunodeficiency

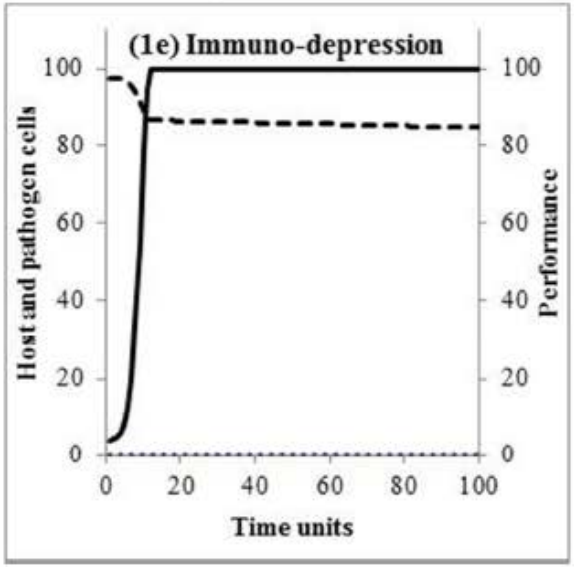
Results


(1a) Healthy response
Host and pathogen cells
Performance
Time units
0
20
40
60
80
100


(1b) Recurrent infection
Host and pathogen cells
Performance
Time units
0
20
40
60
80
100

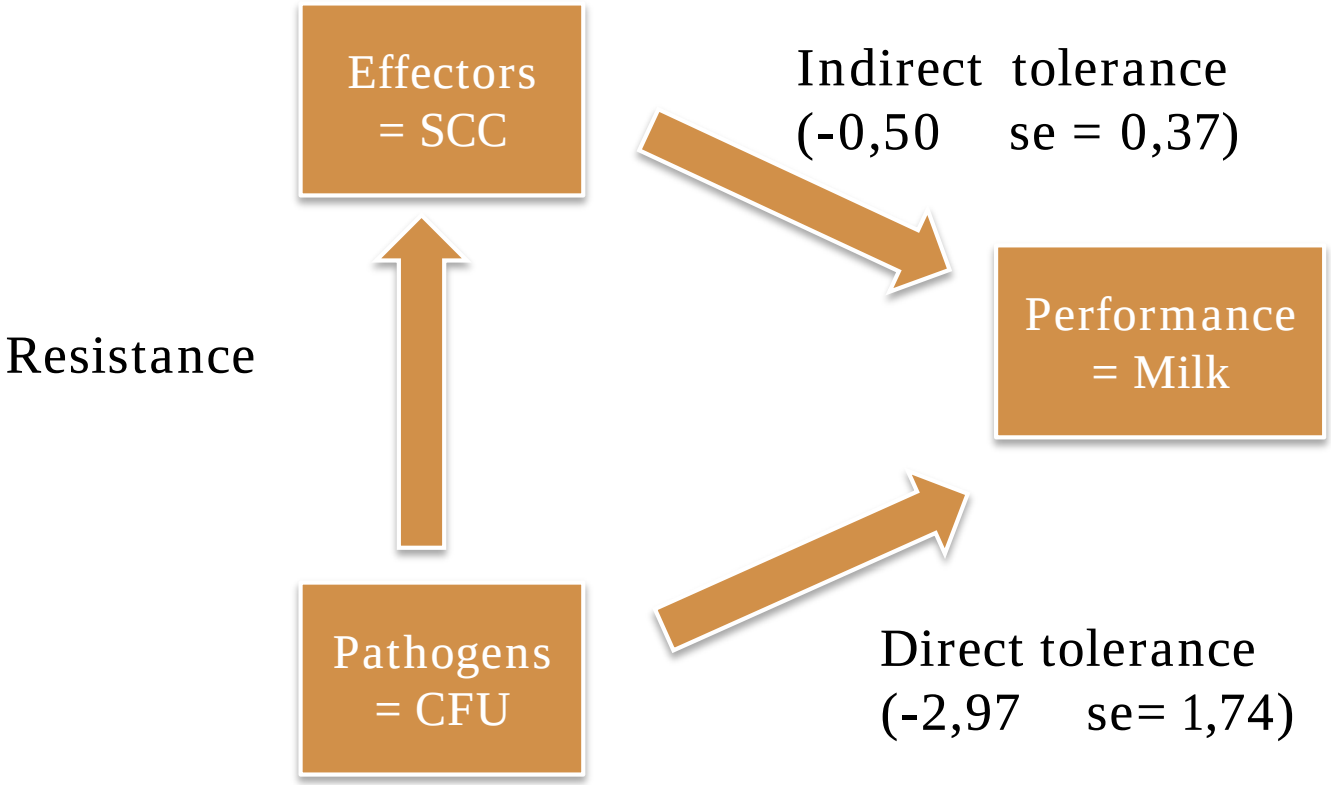

(1c) Persistent infection
Host and pathogen cells
Performance
Time units
Response cells
Pathogens
Performance
0
20
40
60
80
100


(1d) Persistent non infection
Host and pathogen cells
Performance
Time units
0
20
40
60
80
100


(1e) Immuno-depression
Host and pathogen cells
Performance
Time units
0
20
40
60
80
100

Results

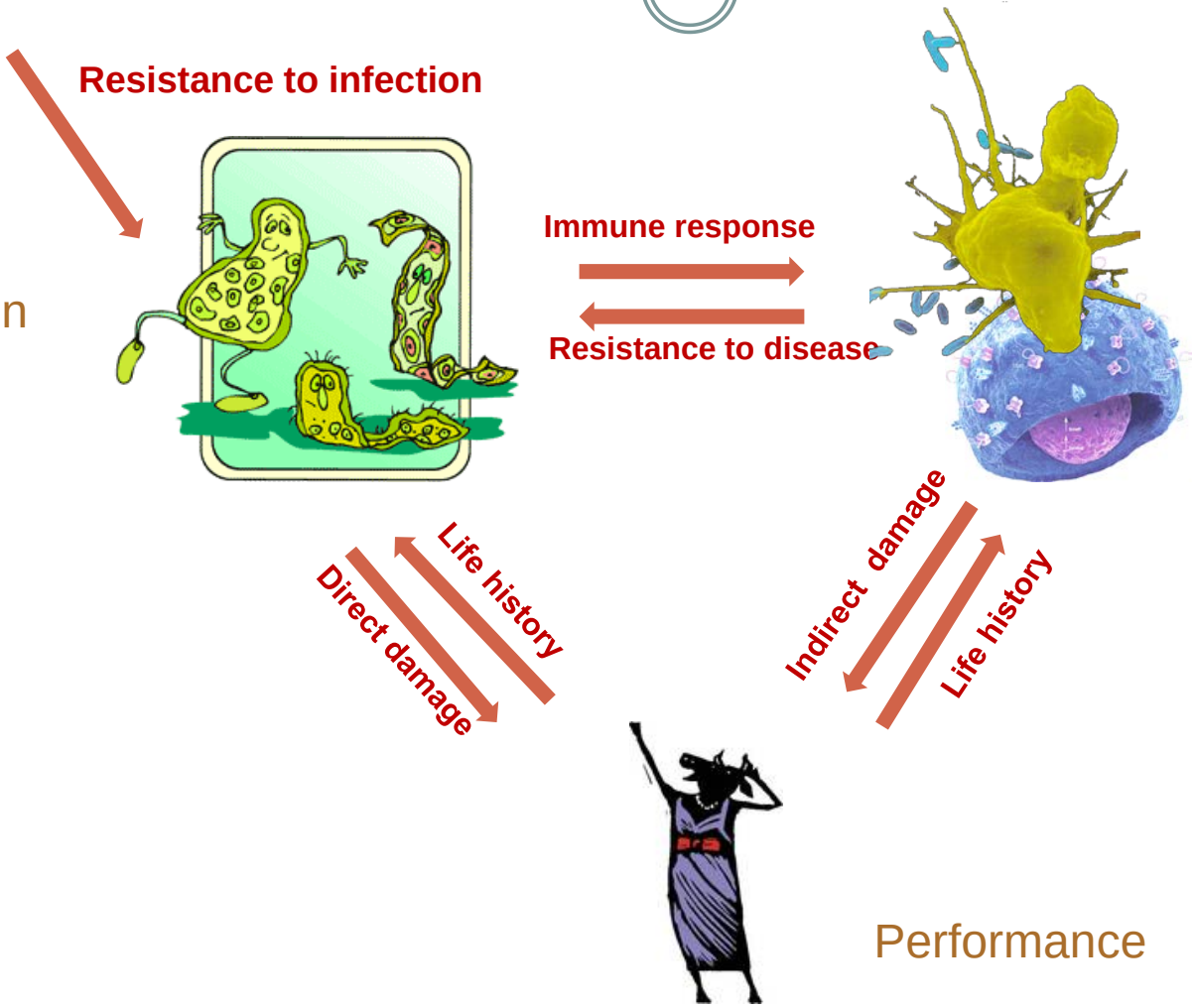
Structural equation model



Conclusions

	Mechanisms	Costs	Models
Resistance			
- infection	Behavior Inflammation Immunity	++	R_O
- disease			ODE
Tolerance			
- direct	Immuno-regulation Tissue damage control and repair	++	RRM
- indirect			SEM

Further work



Results

E. coli bovine mastitis

Symbol	Signification	Values
	Parameters with the same values in all simulations	
K_B	Maximum concentration of pathogens	10^6/µL
K_C	Maximum concentration of response cells	10^7/µL
P^{Max}	Maximum performance	100 units
γ	Pathogen logistic growth rate	1 pathogen /µL/h
τ	Time for a response cell to capture and kill pathogens	1 h/cell
θ	Pathogen concentration killed per response cell	10 pathogens/cell
c	Contact rate between hosts	0.1/h
	Parameters for the different response scenarios	
K_M	Pathogen concentration such that response cells reach the infection site in 1 time unit Healthy response Recurrent infection	 10 cells/µL 10 000 cells/µL
α	Pathogen clearance rate Healthy response Persistent infectious response	 0.005 pathogen/cell/h 0 pathogen /cell/h
ω	Recruitment rate of response cells during health Healthy response Persistent non-infectious response	 0.5 cells/h 0.01 cells/h
μ	Extra-recruitment rate of response cells during infection Healthy response Immuno-depression	 2 cells/µL/h 0 cells/µL/h

References: Barlow et al., 2009; Detilleux, 2013 ; Reynolds et al., 2006; White et al., 2010; …

Resistance/Tolerance

	Parameters with uniform distributions	
β	Infectiousness	U[0;0.01]
L_C	Loss associated with each response cell	U[0; 25/K_C]
L_B	Loss associated with each pathogen	U[0; 25/K_B]
c_ρ, c_b, c_c	Resistance, direct and indirect tolerance costs	U[0; 0.1]
ν	Resistance to infection Low Average High	 U[0; 0.001] U[0; 0.01] U[0.009; 0.01]
ρ λ_b, λ_c	Resistance to disease Direct and indirect tolerances Low Average High	 U[0; 0.1] U[0; 1] U[0.9; 1]