

**EADGENE** European Animal Disease Genomics Network of Excellence for Animal Health and Food Safety

**Genomics for Animal Health: Outlook for the Future**  
 13- 14th October 2009, Muséum National d'Histoire Naturelle, Paris, France

**Genetic-epidemiological models**  
 Detilleux J. – Quantitative Genetics – FMV

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**Two applications**

- Effects of individual levels of resistance and tolerance to infection
- From association to causation

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**GE model 1**

Resistance to infection  $\beta^i = \sum_{j=1}^{nI} [\beta + h^2(1-\beta)a^{ij}]$

Resistance to growth  $C_{t+1}^i = C_t^i \exp\{[\gamma(1 - (C_t^i/K^i))] - \rho_i \mu\}$

Tolerance  $P_t^i = P_{t=0}^i - C_t^i \omega(1 - \lambda^i)$

Costs:  $P_{t=0}^i = P^{\text{Max}}(1 - c_\rho \rho - c_\lambda \lambda)$

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**Resistance**

Host resistance may act at different steps of parasite life cycle

Anti-infection      Anti-growth      Anti-transmission

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The basic reproductive ratio  $R_0 = 3$

Nowak, M.A., Evolutionary Dynamics, Harvard

SIR:  $S \xrightarrow{\lambda} I \xrightarrow{r} R$

SIS:  $S \xrightarrow{\lambda} I \xrightarrow{r} S$

SEIR:  $S \xrightarrow{\lambda} E \xrightarrow{\sigma} I \xrightarrow{r} R$

SEIS:  $S \xrightarrow{\lambda} E \xrightarrow{\sigma} I \xrightarrow{r} S$

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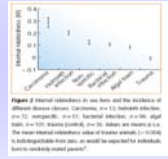
**Hypothesis**

Animals are heterogeneous in resistance to infection ( $r_1$ )

Resistance/susceptibility is genetic → Relatives share genes in common, including resistance genes

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Nature Genetics (November 2006)  
 'In humans, there is growing evidence for adverse effects of inbreeding on resistance to infectious diseases ....'

Inbred sea lions' increased susceptibility to disease could pose a risk to their fellows as well as themselves (Acevedo-Whitehouse et al., Nature, 2003)

« If resistance/susceptibility to infection is genetic, then the probability that a relative of a proband is diseased is a function of its degree of genetic relationship with the proband » Schliekelman et al., 2007.

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Individual probability to get infected is:

$$\beta_i = \sum_j [\beta + h^2 (1 - \beta) a_{ij}]$$

$\beta_i$  = probability to become infected after contact with an infective  
 $h^2$  = heritability of the resistance to infection  
 $a_{ij}$  = degree of relationship between cows in contact  
 $\beta$  = 'average' population transmission probability  
 $\gamma$  = probability of recovery

→  $R_0 \# R_{non\ gene} + R_{gene}$

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Data + Results

Mastitis in heifers (quarter)

Parameters (per quarter-day at risk)

Literature (Lam et al., 1996; Zadoks et al., 2002)

$\beta = 2 \cdot 10^{-2}$        $h^2 = 5\%$

2 management strategies:      controlled      uncontrolled

$\gamma = 0.040$        $\gamma = 0.007$

	$R_{non\ gene}$		$R_{gene}$	
Controlled	0.42	+	0.19	= 0.61
Uncontrolled	1.43	+	0.66	= 2.09

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Resistance


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Anti-infection      Anti-growth      Anti-transmission

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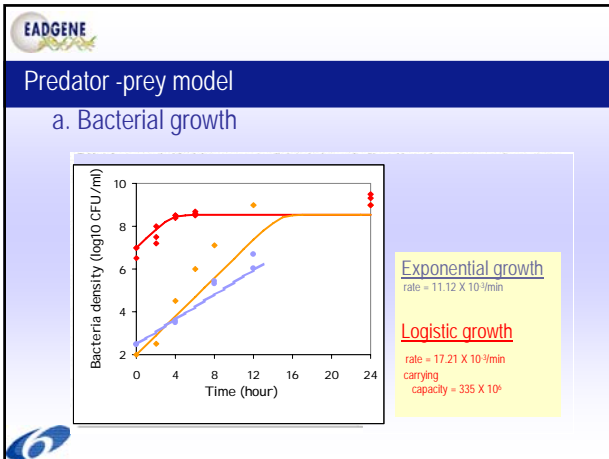
Hypothesis

Relation bacteria - PMN = prey - predator



PMN = predator

Bacteria = prey

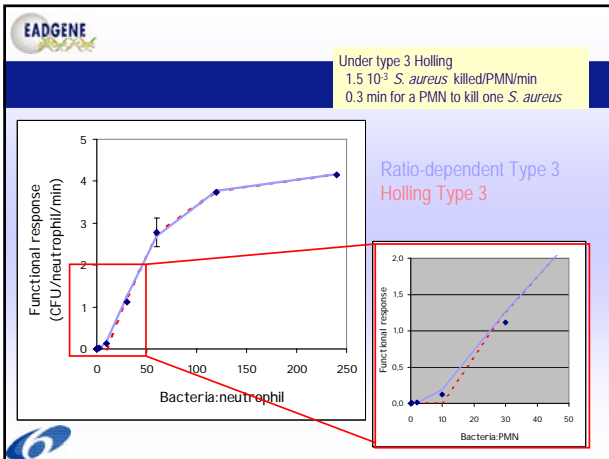


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### b. Killing → Functional response

Table 2. Results of a literature search on in vitro co-cultures of different strains of *Staphylococcus aureus* with blood neutrophils from bovine or human origins.

S. aureus strains	Origin	Time of in-culture (min)	Initial bacterial load (cfu × 10 <sup>6</sup> /mL)	Initial bacteria neutrophil ratio	Average number of bacteria killed (SE) per neutrophil (cfu × 10 <sup>6</sup> /min)	Reference
187 strains	Bovine	60	not available	10:1	86.44 (11.83)	Aarstrup et al., 1994
Newbold 305	Bovine	60	5	2:1	9.17 (2.17)	Berrio et al., 2000
M 40	Bovine	60	0.6	1:3	2.75	Cervera et al., 1998
Newbold 305	Bovine	60	5	2:1	17.00 (2.71)	Dougner et al., 2001
502b	Bovine	30 to 120	0.2	1:5	1.41 (0.34)	Hartford et al., 1975
238 strains	Bovine	60	1	1:10	0.79 (0.09)	Mallory et al., 2001
Mandira case	Bovine	10	150	15:1 to 240:1	1.75 (0.43)	Roth and Kuebler, 1981
Not available	Bovine	60	5	10:1	0.125	Stevens et al., 1991
Newbold 305	Bovine	60	0.003	1:10 to 1:500	0.003, 0.0145, 0.0034	Tomita et al., 2000
M66	Bovine	90	0.6	1:2	4.49 (0.81)	Williams et al., 1984
M66	Bovine	90	0.6	1:3	3.13 (0.18)	Williams et al., 1985
ATCC 27217	Human	5 to 45	not available	2:1	71.78 (27.96)	Alajoudi et al., 1999
ATCC 27217	Human	20	100	20:1	709	Chapman et al., 2002
ATCC 27217	Human	10 to 30	10	1:1	30.99 (2.12)	Hampton and Waterbourn, 1999
NYC14971	Human	30, 60	1	1:5	20.68 (27.26)	Hu et al., 1999
DOC	Human	120, 1440	5	10:1	28.55 (14.7)	Kaplan et al., 1999
SGR11	Human	20	5	10:1	319.98 (55.07)	Pockhronsky et al., 1996
Sa113	Human	30 to 180	0.085	1:12	0.074 (0.005)	Peschel et al., 2001
NCTC12981	Human	2, 4, 8, 16	5	5:28	121.71 (99.56)	Reeves et al., 2002
ATCC 20923	Human	4 to 60	70	50:1	1345 (117)	Saiki et al., 2000
ATCC 30548	Human	180	9.375	0:1	23.81	Schryder et al., 1998
ATCC	Human	90	0.33	3:1	3.15 (0.13)	Wolach et al., 1998



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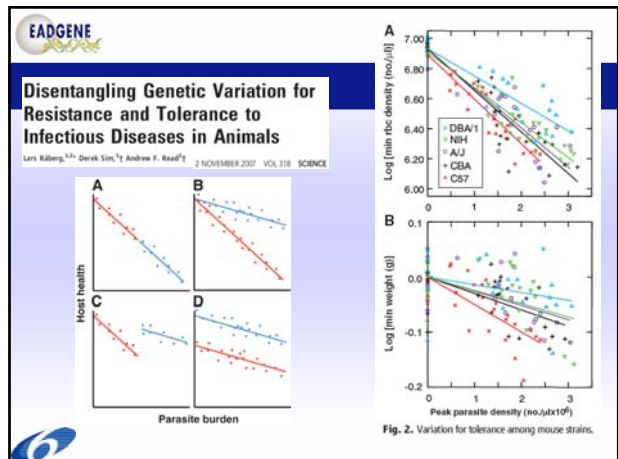
### GE model 1

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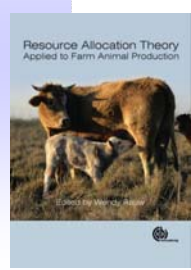

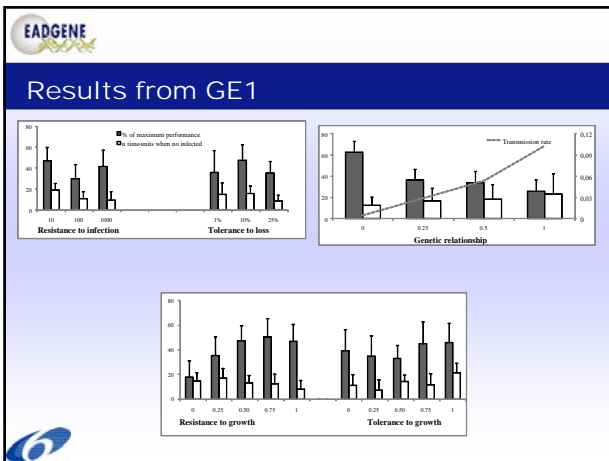
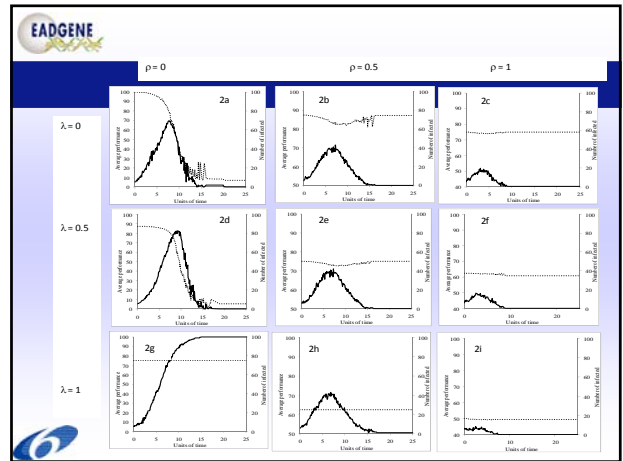
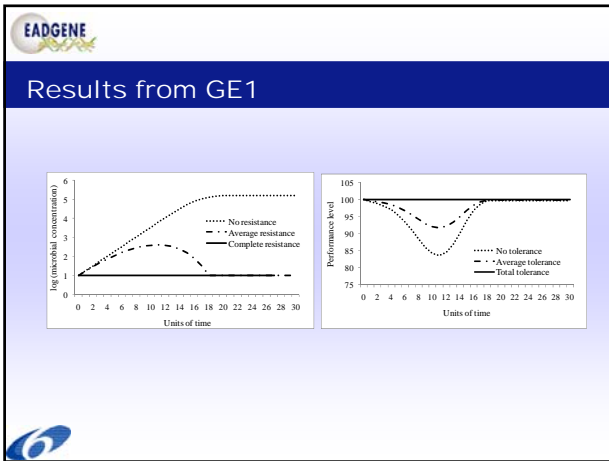


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## Resource allocation




Olteneacu, 2005


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## GE model 2

- Association and causation



... association = cause ...  
 Only in an ideal randomised experiment, but  
 disequilibrium is the problem!



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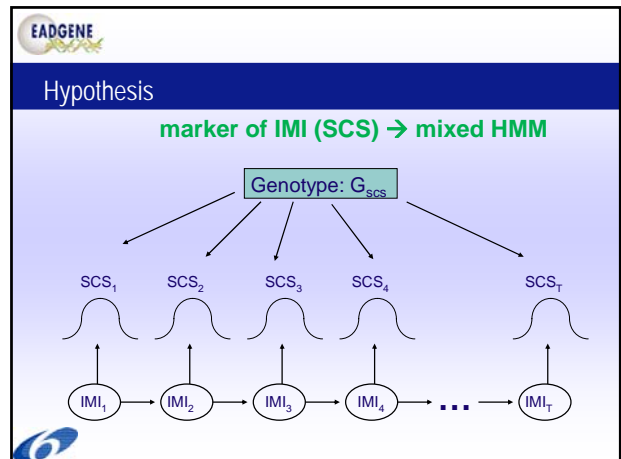
Invited Editorial  
 "Are We There Yet?": Deciding When One Has Demonstrated Specific Genetic Causation in Complex Diseases and Quantitative Traits  
 Grier P. Page,<sup>1</sup> Varghese George,<sup>1,2</sup> Rodney C. Go,<sup>3</sup> Patricia Z. Page,<sup>4</sup> and David B. Allison<sup>1,5</sup>

An association between a polymorphism and a complex disease or quantitative trait can exist for four reasons:

1. The polymorphism is actually causative for the disease or trait.
2. The association is a false positive due to random chance.
3. The polymorphism is in disequilibrium with the true causative allele.
4. The polymorphism is associated because of some systematic bias in the biology, study, samples, or analysis.



→ 'Phenotype'



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Data + Results

$$p(\underline{y} | \underline{\mu}_0, \underline{\mu}_1, \sigma_0^2, \sigma_1^2, \underline{a}, \underline{z}) \sim N(M_0 \underline{\mu}_0 + M_1 \underline{\mu}_1 + Z \underline{a}, R)$$

$\underline{y}$  = (NT X 1) vector of data (SCS)  
 $\underline{z}$  = (NT X 1) vector of hidden states (IMI)  
 $\underline{\mu}_0$  = (T X 1) vector of fixed effects for data on a IMI- cow  
 $\underline{\mu}_1$  = (T X 1) vector of fixed effects for data on a IMI+ cow  
 $\underline{a}$  = (N X 1) vector of random additive genetic effects ( $G_{SCS}$ )

$M_0$  = (NT X T) matrix with elements = 1 if  $z_k^i = 0$   
 $M_1$  = (NT X T) matrix with elements = 1 if  $z_k^i = 1$   
 $Z$  = (NT X N) incidence matrix relating  $\underline{a}$  to  $\underline{y}$ .

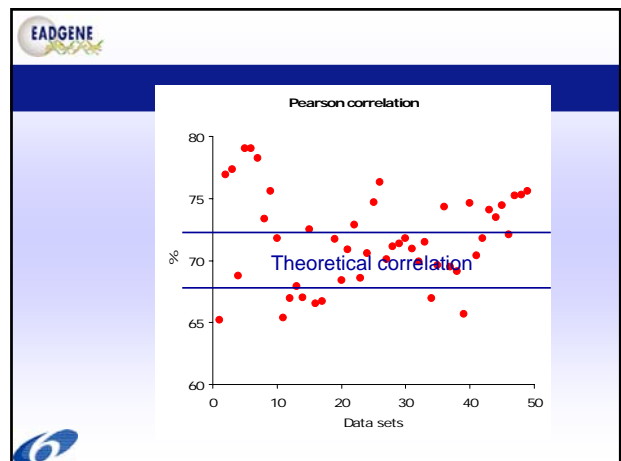
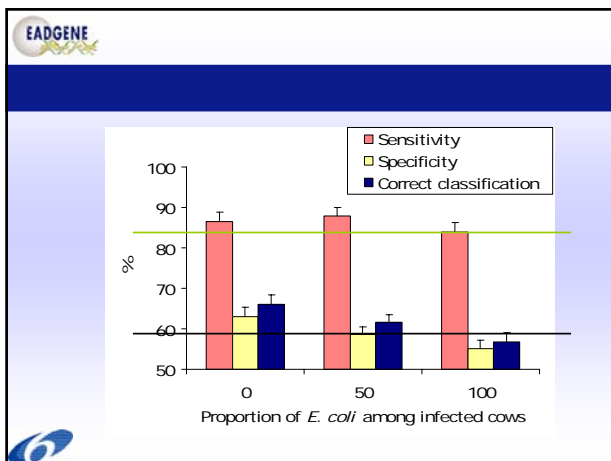
$$R \sim J_0 \sigma_0^2 + J_1 \sigma_1^2 \quad J_i = (NT \times NT) \text{ matrix with elements } = 1 \text{ if } z_k^i = i$$

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Simulated data sets:  
 % infected cows = 20, 50%  
 % *E. coli* among infected cows = 0,50,100%  
 high and moderate responders:  
 → residuals IMI-  $\sim N(0, \sigma_a^2)$

Gibbs sampler  
 1000 iterations  
 200 burn-in  
 10 replications

de Haas et al., 2002, 2004



**Hypothesis**

marker of IMI (Immune assay) → ODE

$$\begin{aligned} dB/dt &= \sigma CB - \nu CB \\ dM/dt &= \nu BC - \rho MC \\ dC/dt &= [\beta - \epsilon M]C \end{aligned}$$

Ordinary differential equation to describe the rates of changes in cell numbers

Figure 29-3 Cellular phase of acute inflammation. Neutrophil migration, emigration, chemotaxis, and phagocytosis.

**Data + Results**

Model applied on experimental data:

Groups	Inoculation	Vaccination
A	1 x 10 <sup>4</sup> cfu	
B	1 x 10 <sup>6</sup> cfu	
C	1 x 10 <sup>4</sup> cfu	<i>E. coli J5 bacterin</i>
D	1 x 10 <sup>6</sup> cfu	<i>E. coli J5 bacterin</i>

**Moderate Inflammatory Reaction During Experimental *Escherichia coli* Mastitis in Primiparous Cows**  
 F. Vanrooyenweghe, L. Duchateau, and C. Burvenich

Data on infected quarters or blood from primiparous cows infused with 1 x 10<sup>4</sup> (—) and 1 x 10<sup>6</sup> (---) cfu of *E. coli*

10<sup>4</sup> cfu  $\sigma, \nu, \rho = 0 \rightarrow$  no extra-stimulation  
 n cells in milk enough to jugulate IMI

10<sup>6</sup> cfu  $\sigma, \nu, \rho > 0 \rightarrow$  extra-stimulation

No differences  
 Same bacterial strain

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**Sensitivity analyses**

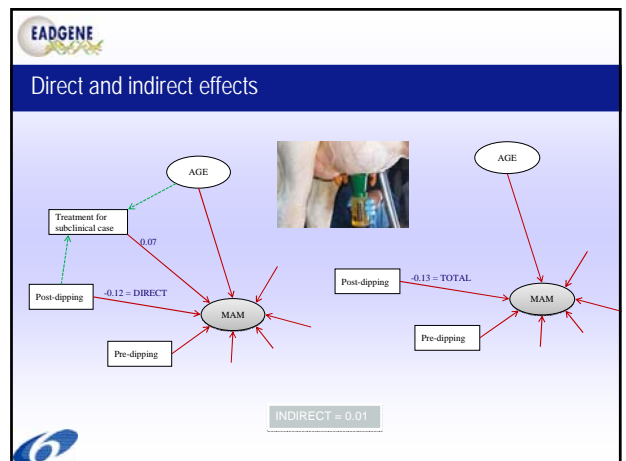
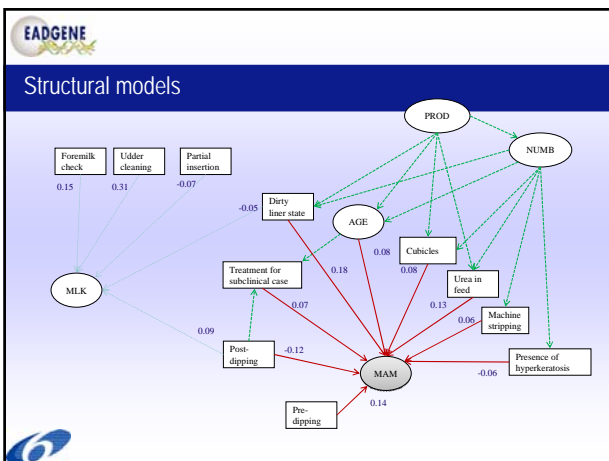
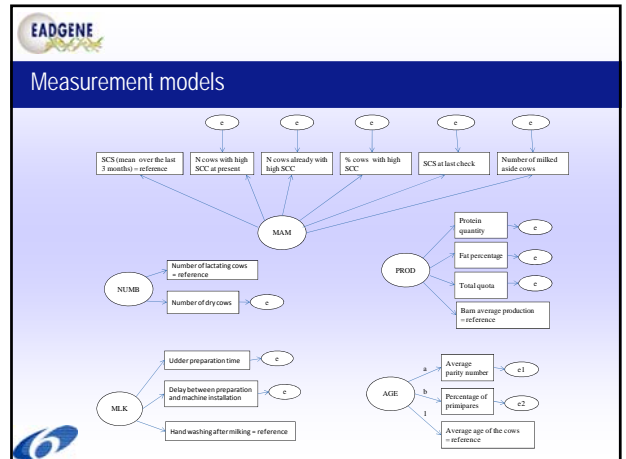
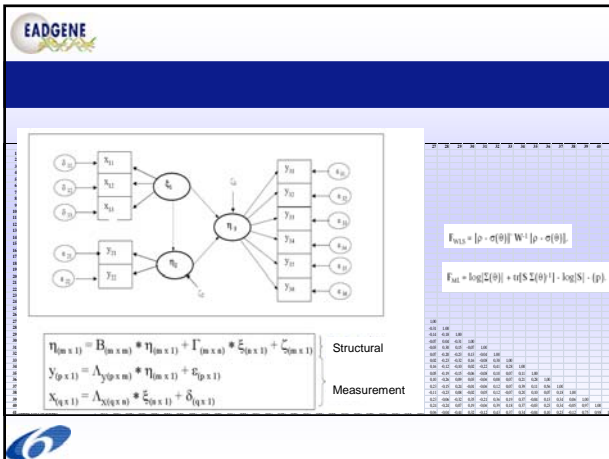
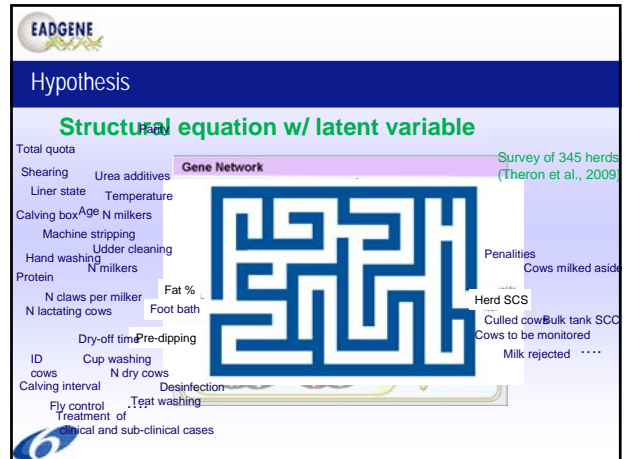
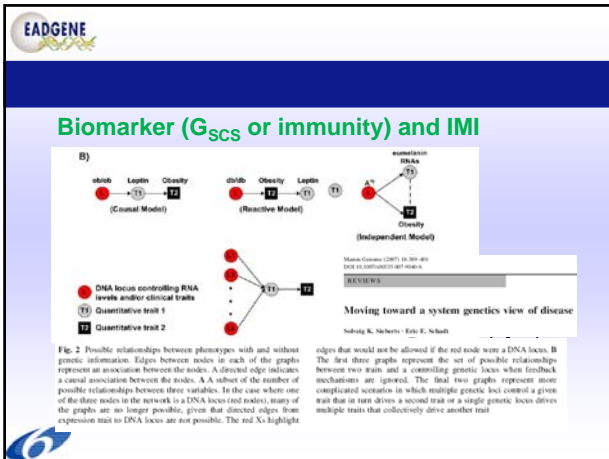
To identify parameters influencing most the outcomes of the AIR

Tornado graph: highest bar = most influential parameters → candidates for selection

**GE model 2**

• Association and causation

CONFOUNDER (C) → EXPOSURE (E) → DISEASE (D)  
 CONFOUNDER (C) → DISEASE (D)  
 CONFOUNDER (C) → DISEASE (D) (dashed arrow with question mark)



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**Modeling the complex gene x environment interplay in the simulated rheumatoid arthritis GAW15 data using latent variable structural equation modeling**  
 Nora I. Nock\*, Emma K. Larkin, Nathan J. Morris, Yali Li and Catherine M. Stein

**Figure 1**  
 Evaluation of the GAW15 simulated rheumatoid arthritis (RA) model. Measurement model loadings depict relationships between observed variables (rectangles) and latent variables (ovals) and structural model paths (double-headed arrows) between latent variables. Correlations in parentheses are shown in grey shaded areas. Correlations are shown double-headed arrows. Red arrows indicate the simulated true location (parameter)  $\gamma$  (0.5).

**6**

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## Back to the future

Models  
 = tools for better understanding  
 = simplification of reality  
 → Models must evaluate and be validated

**6**

IMD

Thank you  
 for your attention !