#ADSA2023

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When, Why & How to breed for disease resilience

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Disease resilience as breeding goal of the future?

What are the key challenges and opportunities for breeding for disease resilience?

How may future breeding programmes benefit from recent research in disease resilience?

What is disease resilience and how to measure it?

1. The ability to **maintain high production & health levels** when challenged by infection
   - **Inferred** from modelling reaction-norms

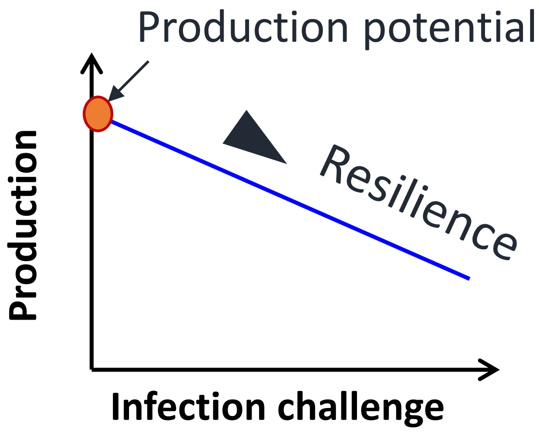
2. The ability to **either maintain or revert quickly** to **high production and health levels** when challenged by infection
   - **Inferred** from modelling trajectories

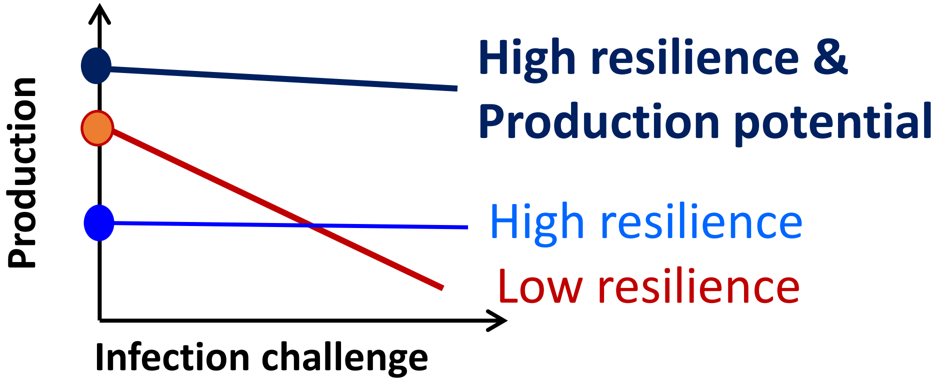
3 take-home messages

Breeding for disease resilience

1. Can be profitable
2. has potential pitfalls one needs to be aware of
3. requires considerable investment into phenotyping

Disease resilience as reaction-norm





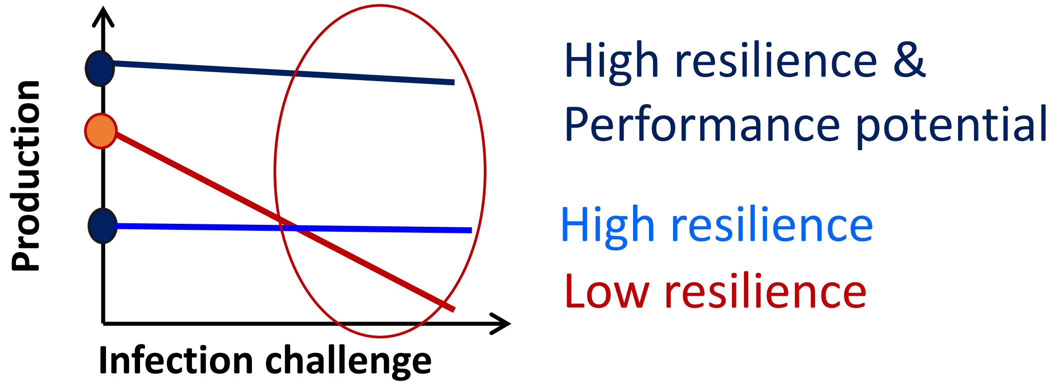
Reaction-norm: change in production with increasing infection challenge

Resilience = reaction-norm **slope**

Production potential = reaction-norm **intercept**

Goal: **high production potential & high resilience**

When to breed for disease resilience?



Consider breeding for disease resilience when animals are frequently exposed to infections that impact productivity & health

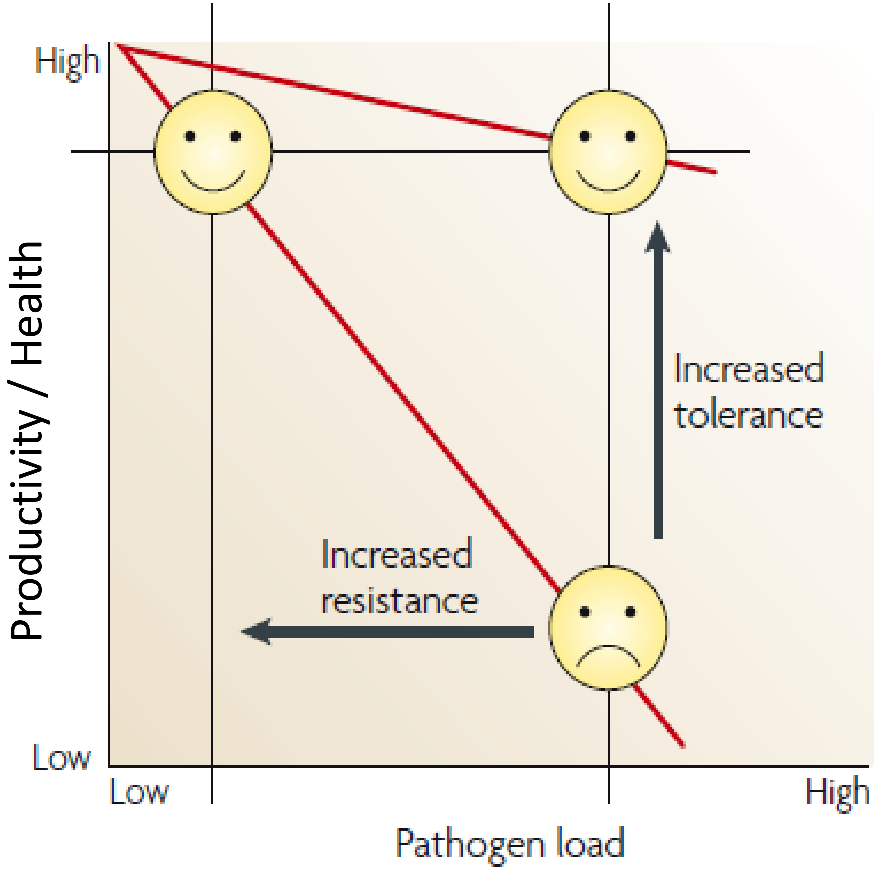
Is breeding for disease resilience profitable?

Species	Disease	Cost per animal ($)	Genetic gain per animal ($)	Cost / Gain
Sheep	Parasites	6.2	0.8	**7.6**
Ruminants	Bluetongue	37.3	14.0	**2.7**
Cattle	bTB	19.9	3.8	**5.2**
Pigs	PRRS	10.2	2.2	**4.7**

Pieter Knap: Genetic Strategy Manager, Genus-PIC

The cost of combatting disease exceeds any genetic gain

Disease resilience is the composite of host disease resistance & tolerance



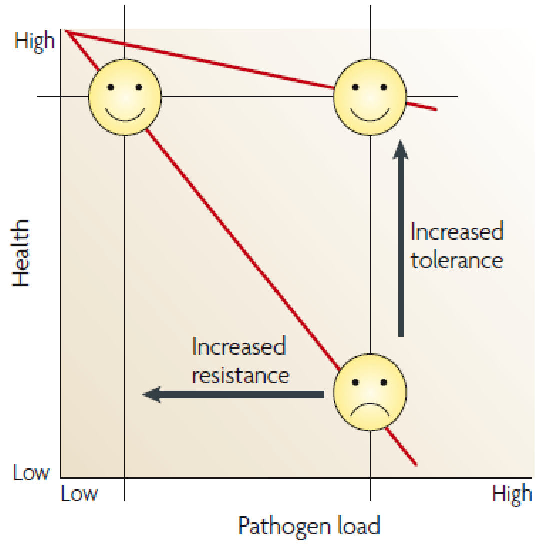
Resistance:
Ability to reduce within-host pathogen load

Tolerance:
Ability to limit the loss caused by a given within-host pathogen load

The economic value of disease resilience

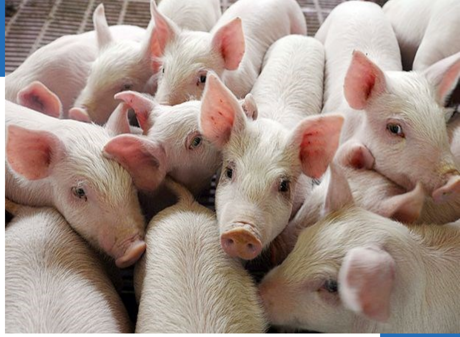
The marginal economic value (MEV) of disease resilience is the value of productivity (P) that is recaptured by improvement in Resistance (R) or Tolerance (T):

$$\Delta P \times MEV(P) \sim \Delta T \times MEV(T) + \Delta R \times MEV(R)$$



- Depends equally on economic value of resistance & tolerance
  - Weighted by their improvement
- Cannot be estimated without knowledge of the R & T contributions

Case Study: economic value of PRRS resilience in pigs



- Resistance and tolerance estimates from data of pathogen load and growth rate from large scale PRRS challenge experiments
- Economic value of productivity (growth rate in absence of PRRS) known

Results: The economic value of increasing productivity by improving resistance & tolerance can be more than 3 times higher than that achieved by selecting for productivity in high health conditions.

Breeding for disease resilience is profitable

How to breed for disease resilience?

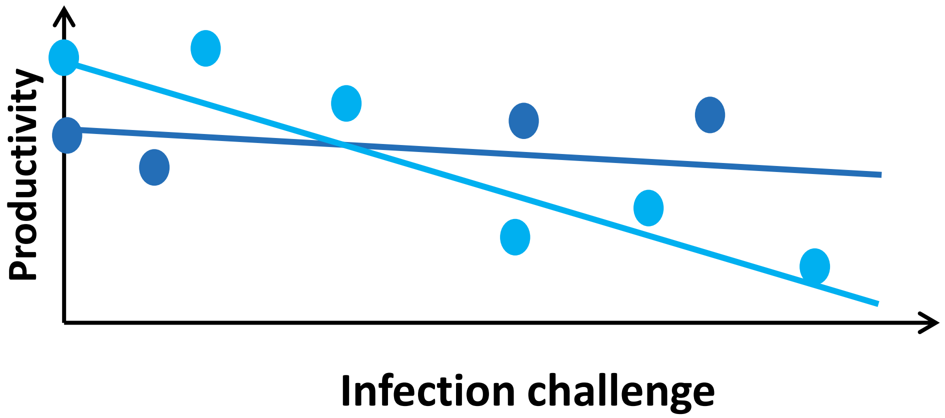
Current (black box) indirect selection on resilience:

- Select for high productivity in infectious conditions
- Good enough?

Key challenges for explicitly selecting for resilience :

- Reliable resilience phenotypes for genetic evaluations
- Identifying and managing trade-offs between resilience and other traits

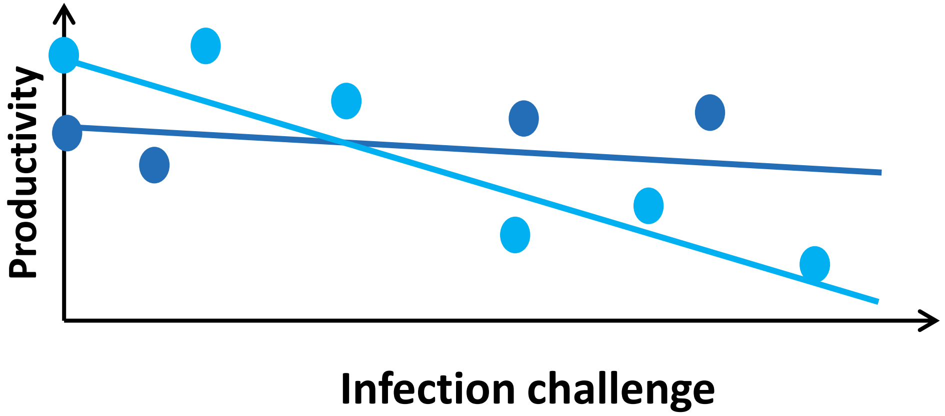
Statistical challenges for estimating resilience



Estimating resilience slopes requires **multiple performance measures** of individuals **across a range of challenge levels**

- Do genomic data help?
- How sensitive are resilience estimates to phenotyping strategies?

Simulation studies




frontiers in Genetics

Front Genet. 2023; 14: 1127530.
Published online 2023 May 12. doi: 10.3389/fgene.2023.1127530
PMCID: PMC10213464
PMID: 37252663

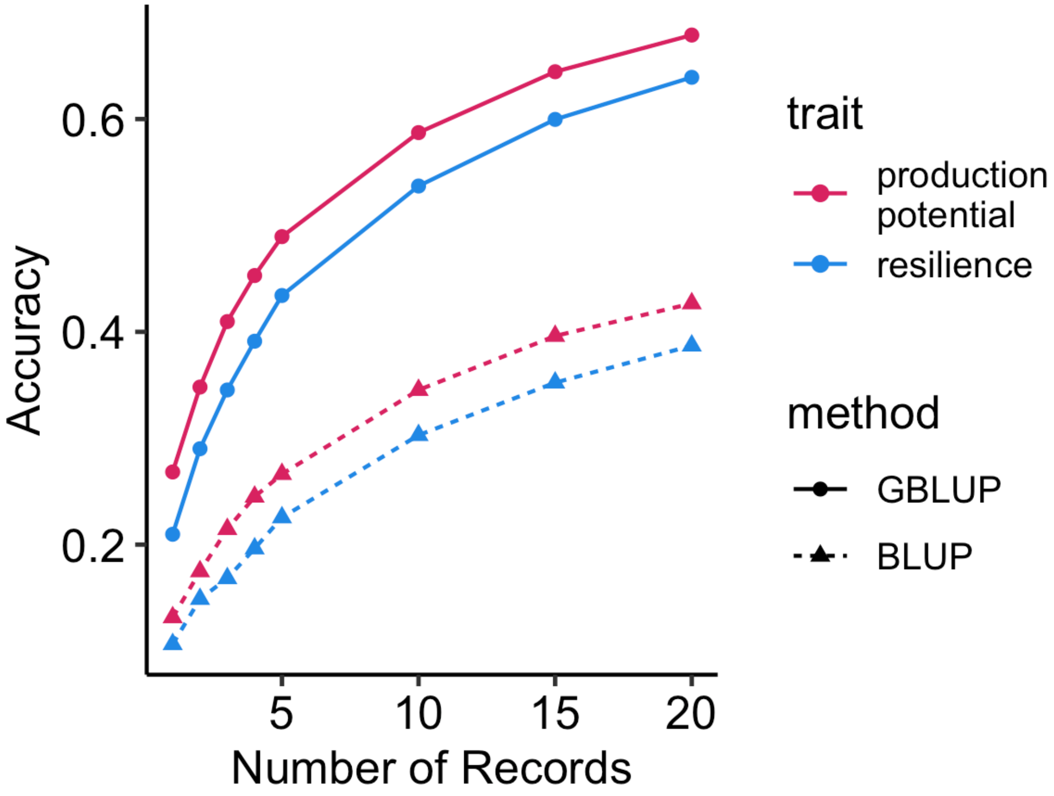
Exploring the value of genomic predictions to simultaneously improve production potential and resilience of farmed animals

Masoud Ghaderi Zefreh,[1,*] Andrea B. Doeschl-Wilson,[1] Valentina Riggio,[1] Oswald Matika,[1,2] and Ricardo Pong-Wong[1]

- Simulate reaction-norms of a population of genotyped animals exposed to different challenge levels
    - Assume potential trade-off between production potential & resilience
- Evaluate how prediction accuracies & response to selection depend on genotyping and phenotyping strategies

Ghaderi-Zefreh et al., Front. Gene. 2023

Much improvement in prediction accuracies with genomic data & repeated records

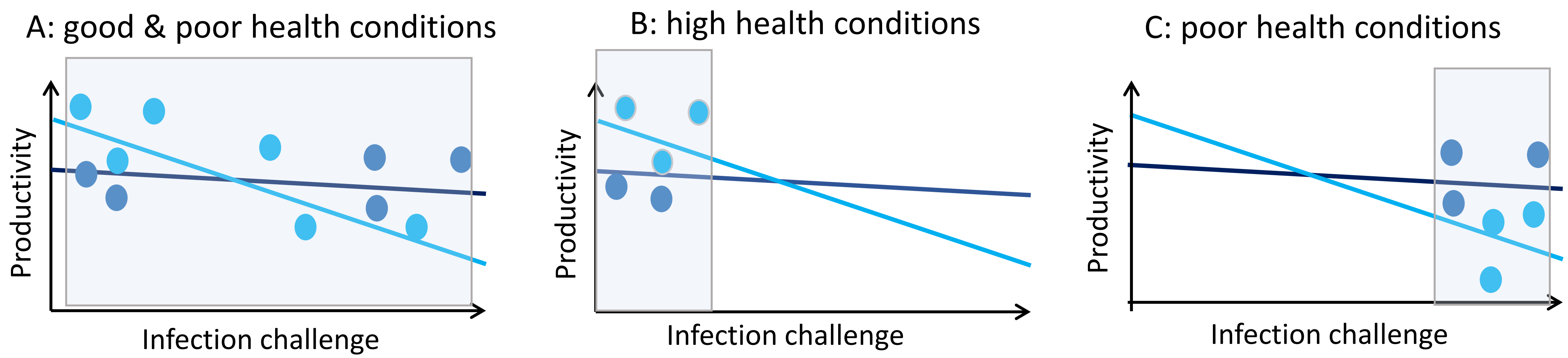


- Prediction accuracies greatly improve with number of records
- Genomic data provide good prediction accuracies even for limited records
- Selection for high production potential & resilience possible with genomic prediction

What if we only have data from good or poor conditions?

Can we still improve production potential & resilience?

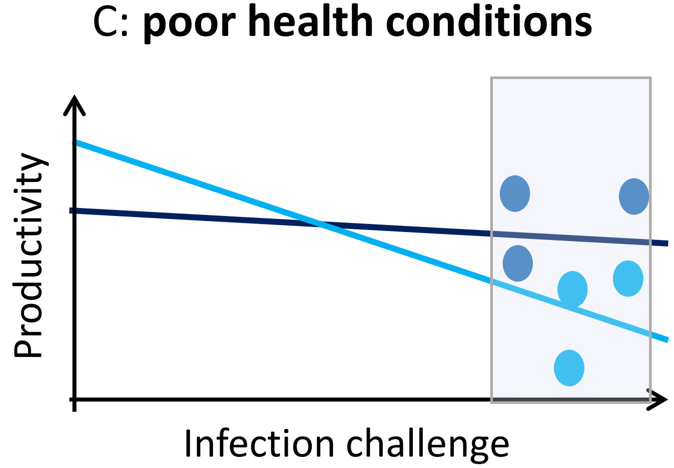
- without explicitly estimating these traits?

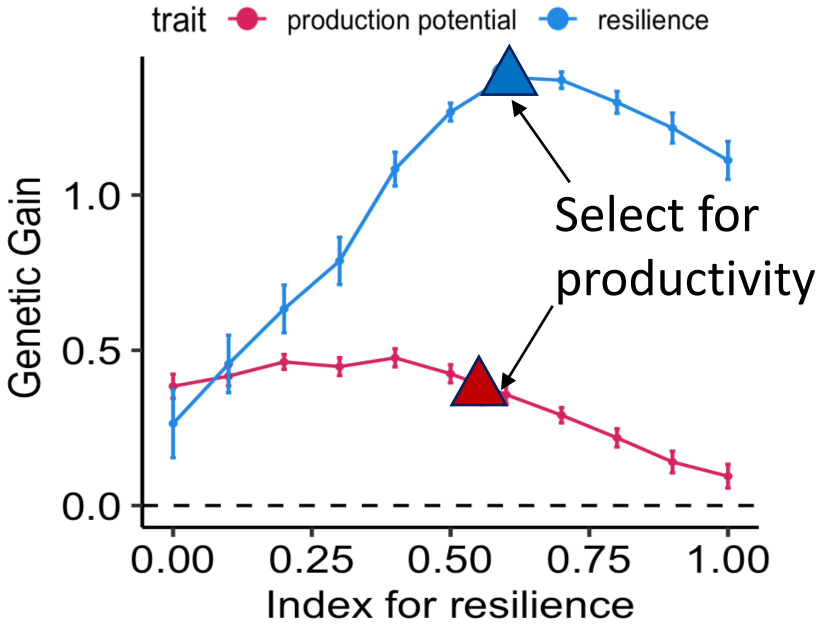


For each phenotyping scenario A-C, simulate 10 generations of selection on

- (i) production (GEBV) or
- (ii) index of estimated production potential & resilience

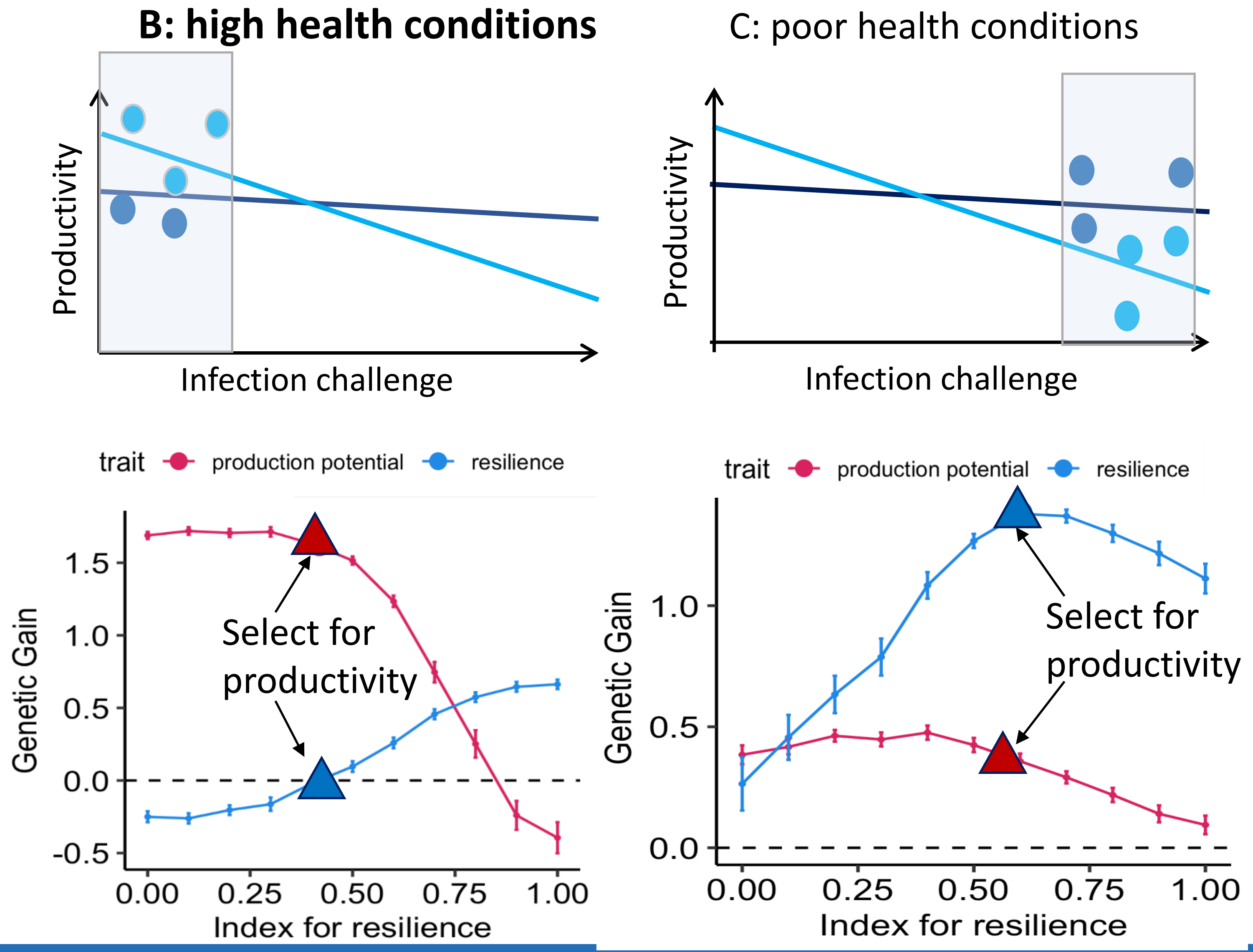
Predicted genetic gain after 10 generations of selection





- High genetic gain in resilience
- Limited gain in production potential
- Genetic gain in both traits achieved by selection on productivity alone

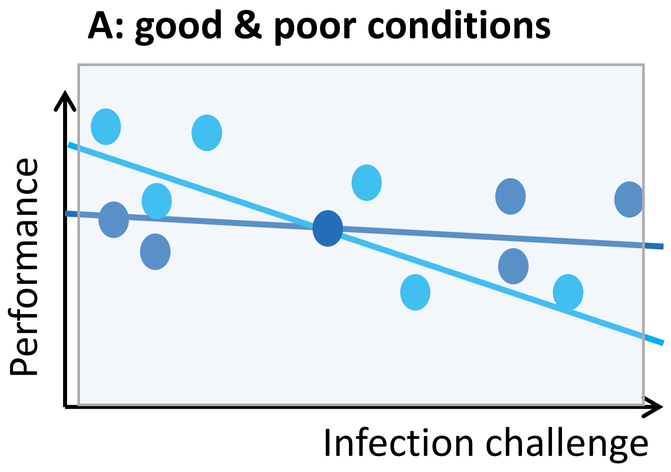
Predicted genetic gain after 10 generations of selection

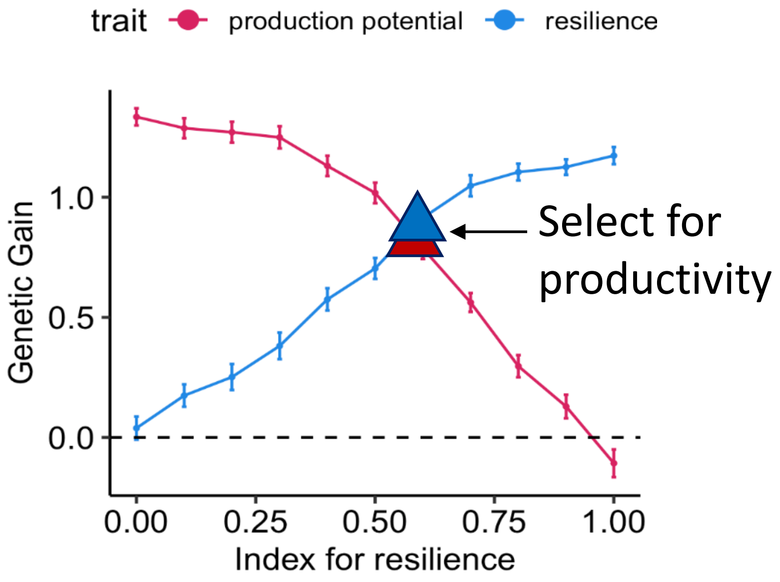


High genetic gain in production potential

No improvement in resilience unless one explicitly selects for it!

Predicted genetic gain after 10 generations of selection





- Best scope for genetic improvement in production potential & resilience
  - And managing trade-offs
- Selection on productivity alone improves both traits

Key messages from simulation studies

1. Genetic improvement of both production potential and resilience is possible even if there is a trade-off

   – Much more improvement with genomic data & more phenotypes

2. Genetic gain in either trait depends strongly on the environment in which data are collected

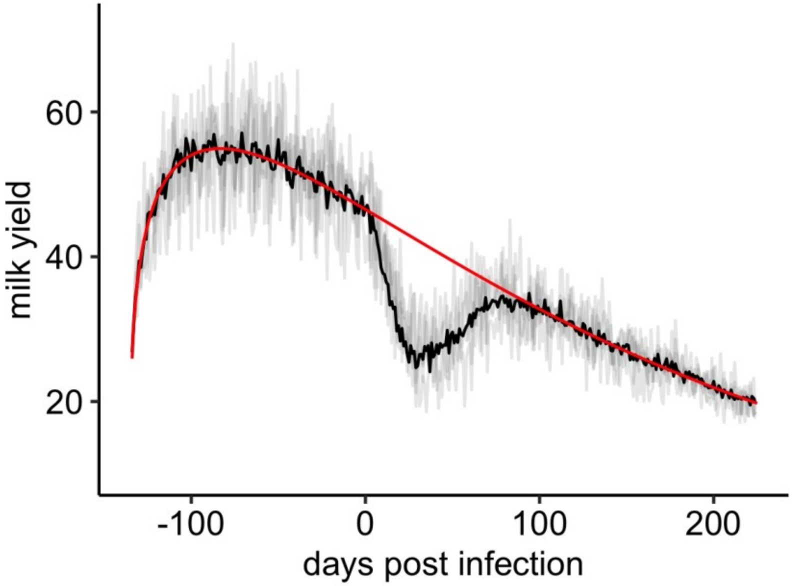
   - Best results when genotypes and phenotypes are collected across a wide range of challenge conditions

3. Selecting on productivity alone can indirectly improve resilience, but only if data are collected in infectious conditions

Resilience trajectories

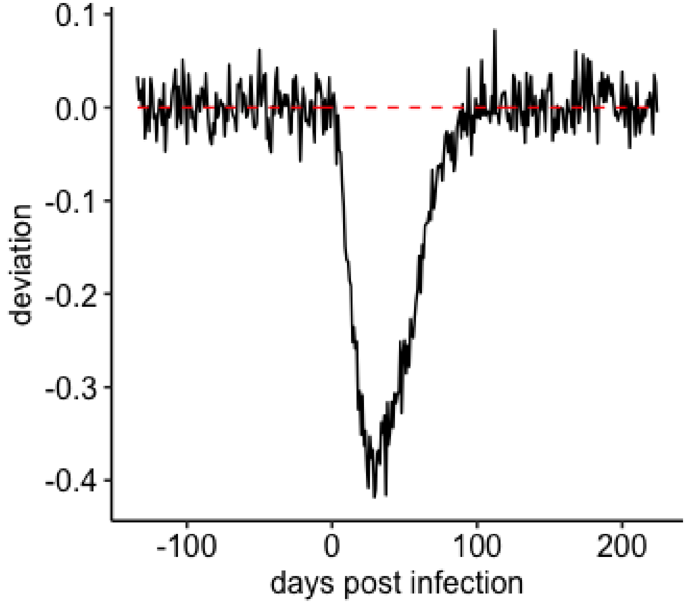
Disease resilience:

The ability of an animalto either **maintain or revert quickly** to high production and health status when exposed to challenges



- Characterise animals by their **deviations in the performance trajectory**
- **Resilient animals deviate less from their optimal trajectory & recover faster**
- What is an **appropriate resilience phenotype** to include into breeding goals?

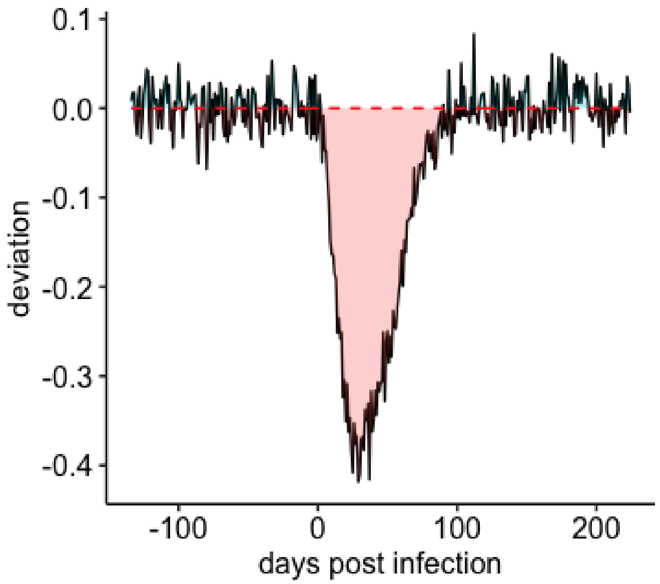
Statistical resilience indicators based on deviations from a target trajectory



Proposed resilience indicators (RI):

- Mean (square) deviation
- Variance of deviations
- Area under the curve (AUC)
- Lag-1 Autocorrelation
- Skewness

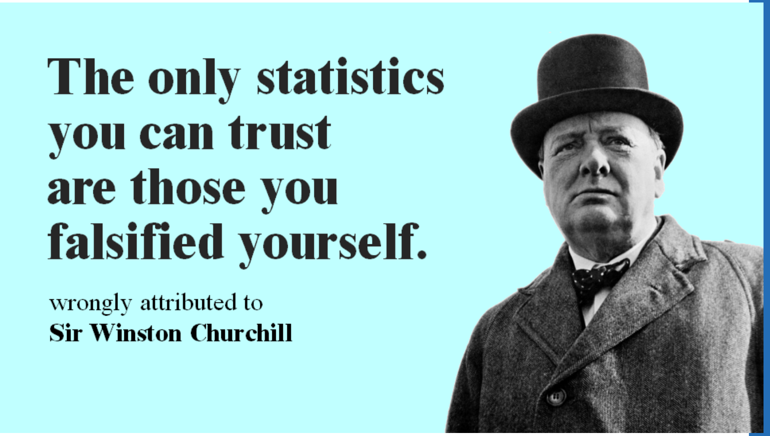
Area under the curve



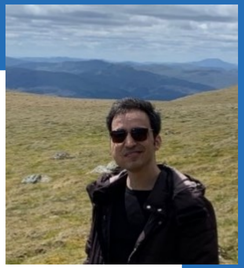
More resilient animals have RI values closer to zero

Can we trust these resilience indicators?

- **Various studies** applied to short-term disturbances in milk yield in dairy cattle, feed intake & growth in pigs & chicken
- **Generally promising results**:
  E.g. heritable, positively associated with good health & longevity, repeatable, complementary
- **But many potential pitfalls**:
  - Unknown target trajectory
  - Dependence on data features poorly understood
  - Unknown impact on animals' physiology

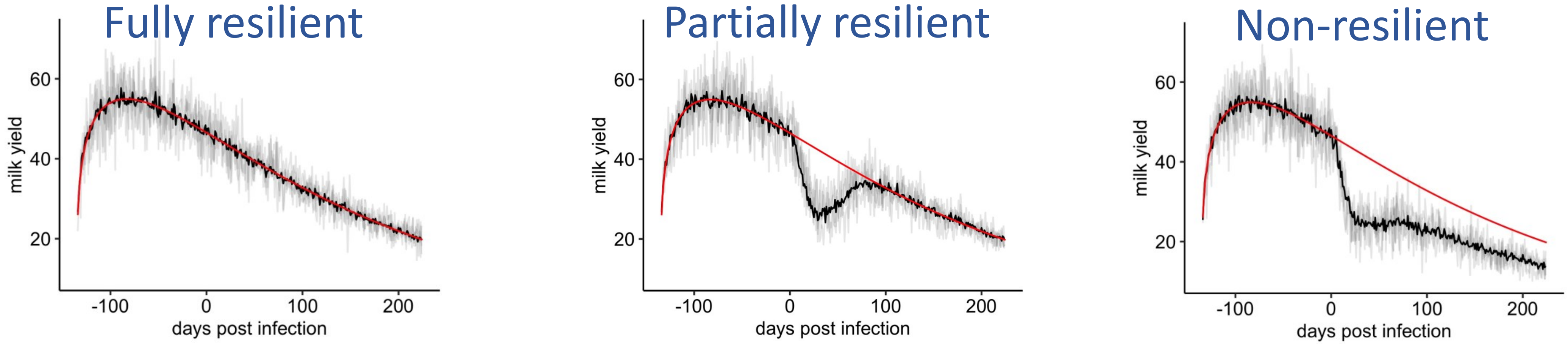


Putz et al., 2019; Berghof et al., Front. Gene. 2019-21; Poppe et al., 2020-22; Wang et al., Front. Gene. 2023



Simulation studies to validate resilience indicators

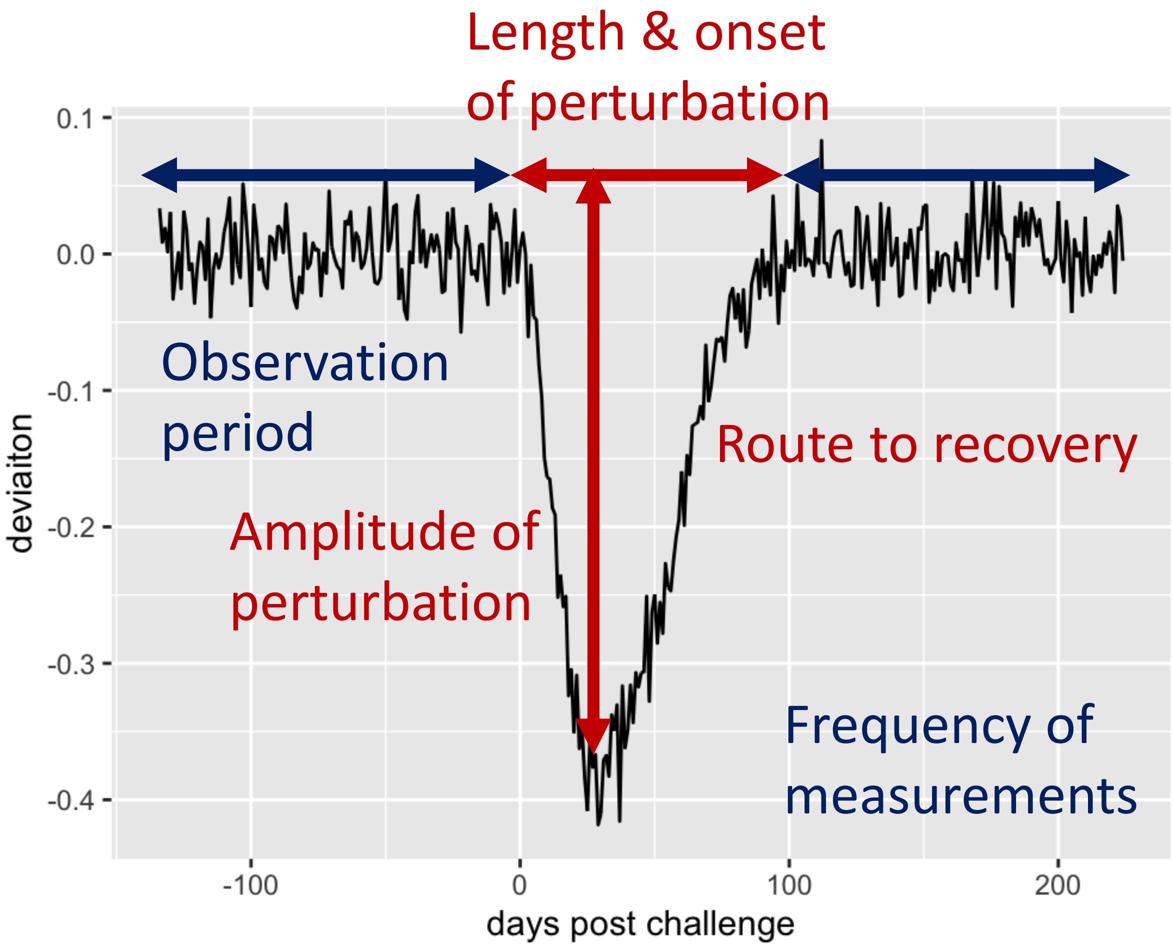
Simulated milk yield profiles under short-term challenge for 3 response types:



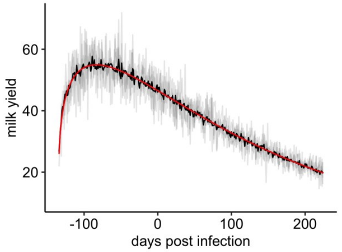
Objectives for validating the statistical resilience indicators

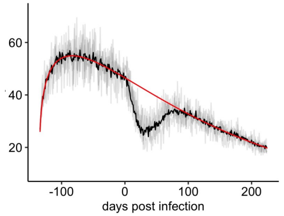
1. Can the RI correctly distinguish between the 3 response types?
2. How dependent are RI to the methods for estimating individuals’ target trajectories?
3. How sensitive are the RIs to individuals’ response and data features?

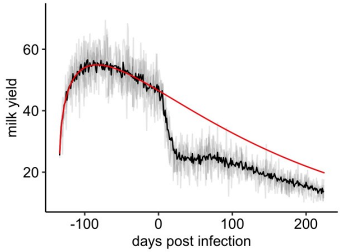
Sensitivity of resilience indicators to data features



Not all resilience indicators can distinguish non-resilient from partially resilient animals







Resilience indicators	Fully vs non-resilient	Fully vs partially resilient	Non-Resilient vs partially resilient
Log-variance deviation	1.00	0.99	**0.87**
Mean square deviation	1.00	1.00	**0.87**
Area under the Curve	1.00	0.99	**0.81**
Lag-1 autocorrelation	0.99	1.00	0.15
Skewness	**0.71**	0.98	0.09

Strong tendency to mis-classify

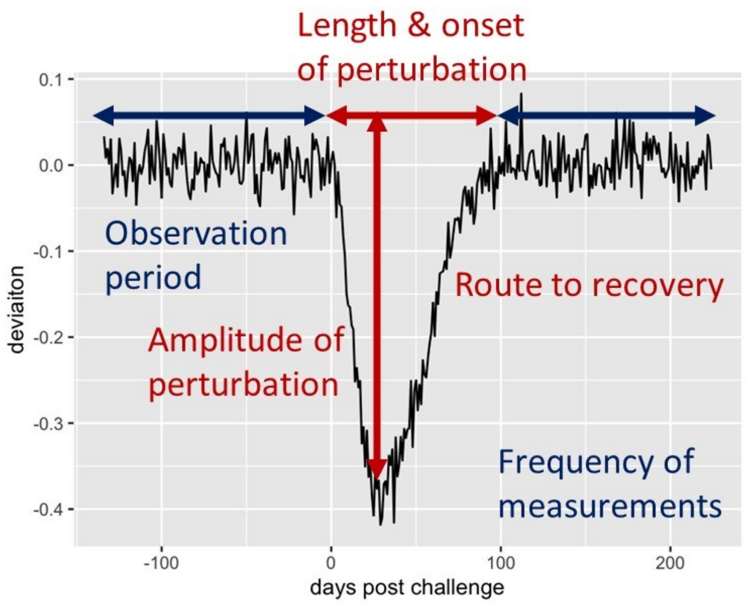
Area under the Receiver-Operator-Curve (ROC) for classifying response types based on resilience indicators

Similar results across different methods for estimating target trajectories

Sensitivity of resilience indicators to data features

Skewness is generally a poor resilience indicator

Most other resilience indicators are reliable if
- individual performance is recorded frequently & regularly
- sufficient pre- and post-perturbation data exist
- onset of perturbation is known



Sensitivity of resilience indicators to data features

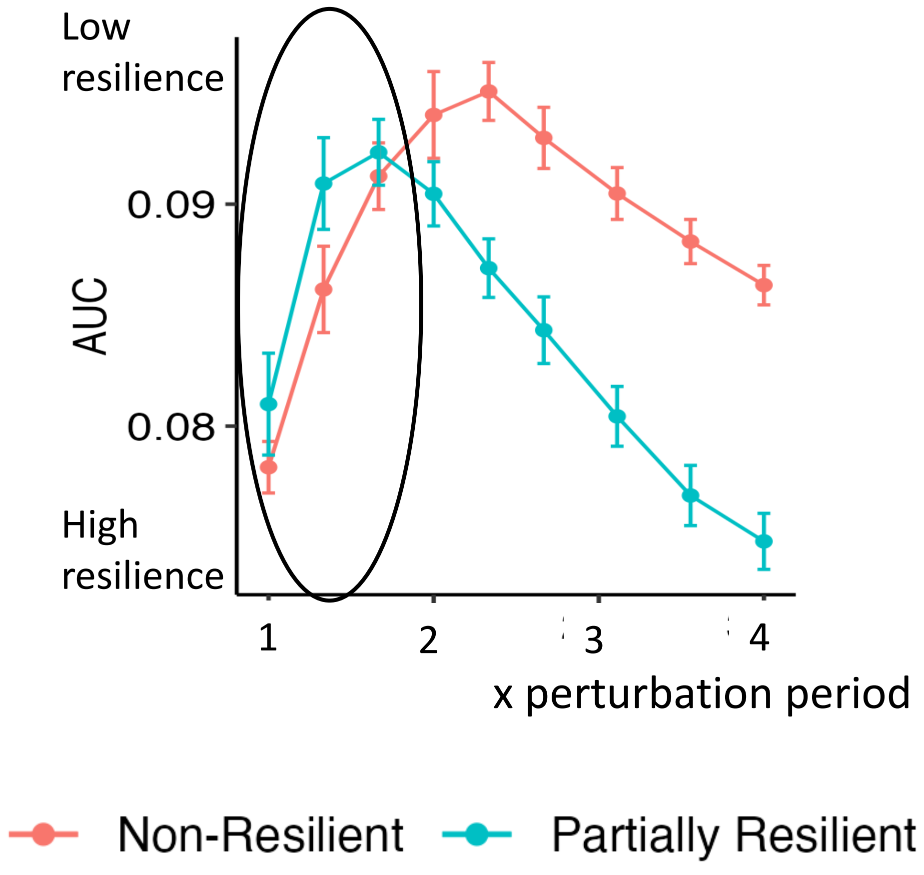
Skewness is generally a poor resilience indicator

Most other resilience indicators are reliable if

- individual performance is recorded frequently & regularly
- sufficient pre- and post-perturbation data exist
- onset of perturbation is known

But serious risk of mis-classifying animal if these criteria are not met

Sensitivity to length of recording interval



Identifying and managing resilience trade-offs

"When the breeding goal is a composite trait, all components must be kept under control. Otherwise selection may come to nothing or make things worse" (Knap 2020)

Potential resilience trade-offs:

- resistance & tolerance (affecting individual's resilience)
- resilience & productivity in disease-free conditions (affecting productivity)
- tolerance & host infectivity (affecting herd resilience)

Identifying and managing resilience trade-offs

Knap and Doeschl-Wilson *Genet Sel Evol* (2020) 52:60
https://doi.org/10.1186/s12711-020-00580-4

Genetics Selection Evolution

REVIEW — Open Access

Why breed disease-resilient livestock, and how?

Pieter W. Knap[1*] and Andrea Doeschl-Wilson[2]

ELSEVIER

Animal

Volume 15, Supplement 1, December 2021, 100286

Review: Livestock disease resilience: from individual to herd level

A. Doeschl-Wilson [a], P.W. Knap [b], T. Opriessnig [a], S.J. More [c]

- It is possible to identify and manage resilience trade-offs (e.g. by selecting for resistance rather than resilience)
- But this requires serious investment into phenotyping

Take-home messages

Breeding for disease resilience

1. **Is profitable**

   Especially for endemic diseases

2. **has potential pitfalls one needs to be aware of**

   Modelling studies can help identify these & test potential solutions

3. **requires considerable investment into phenotyping**

   Big opportunities with non-invasive diagnostics & automated data

Acknowledgements

Roslin students / post-docs & colleagues

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- Steve Bishop

External

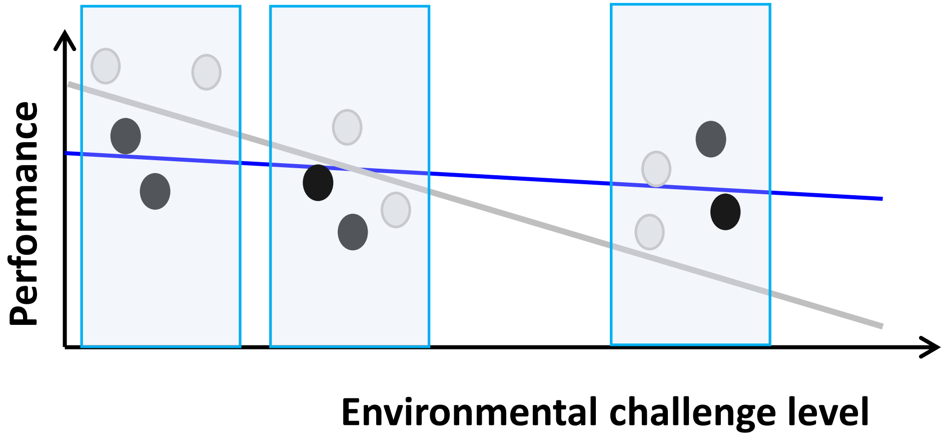
- **Pieter Knap** (Genus PIC)
- **EU H2020 Smarter consortium**
- Ilias Kyriazakis (Newcastle University)
- PRRS Host Genetics consortium

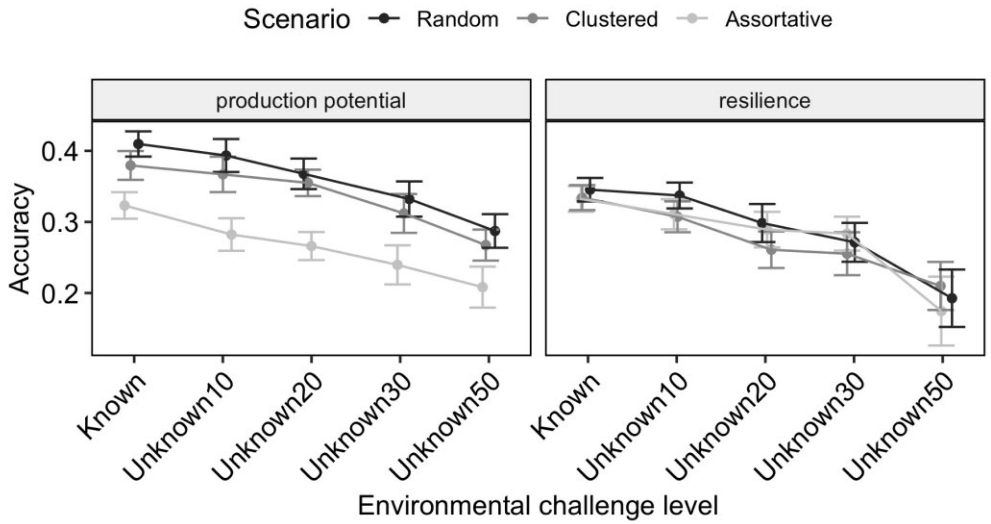
SMAll RuminanTs breeding for Efficiency and Resilience

THANK YOU

Questions & Comments?

Unknown infection levels





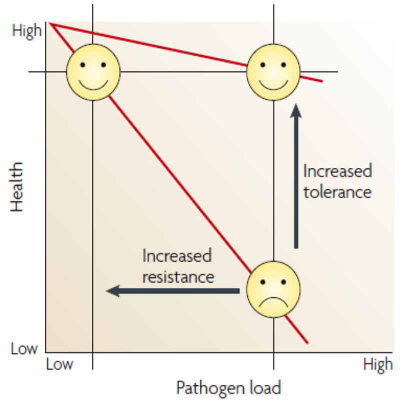
Not a problem – the contemporary group mean performance is a good proxy

- as long as there are sufficient groups spanning a range of environments
- & challenge levels are similar for animals in the same group

The economic value of disease resistance & tolerance

$$\mathrm{MEV(Resistance)} = 1/\mathrm{Tolerance} \times \mathrm{MEV(Productivity)}$$

Improving resistance is worth more if tolerance is low



$$\mathrm{MEV(Tolerance)} = \frac{\text{Infection Challenge} - \text{Resistance}}{\text{Tolerance}^2} \times \mathrm{MEV(Productivity)}$$

Improving tolerance is worth more if infection challenge is high and resistance / tolerance are low

Economic values require estimates of resistance and tolerance