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THE UNIVERSITY of EDINBURGH
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of Veterinary Studies

Understanding and breeding for resilience traits

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UKRI Biotechnology and Biological Sciences Research Council

- **How does the genetics of animals influence disease prevalence & impact?**
- **How can we use genetics & other control strategies effectively to combat infectious disease?**

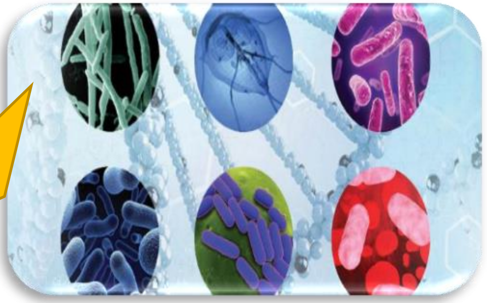
Approach: computational models for data analyses & predictions

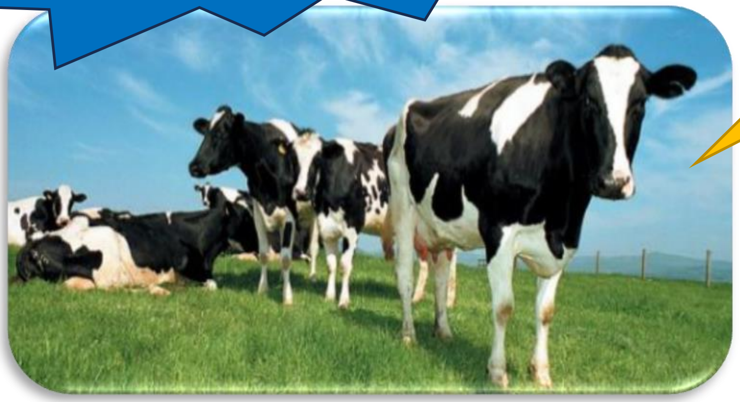
Cattle today face many threats

Cattle today face many threats

RESILIENCE

Infectious pathogens





Breeding approaches to
generate disease-resilient cattle

When, Why and How to breed for disease resilience?

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

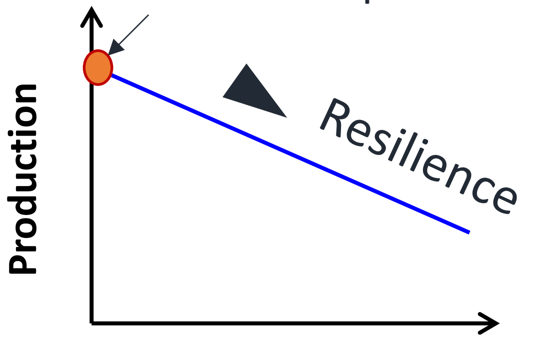
How may future breeding programmes & dairy farmers benefit from recent research in disease resilience?

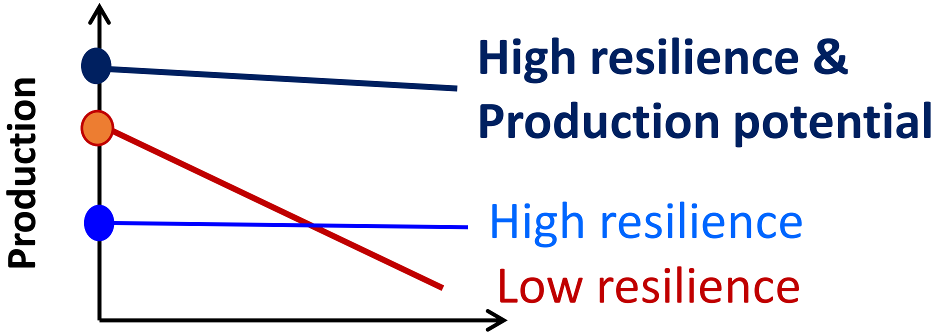
What is disease resilience and how to measure it?

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

Disease resilience as reaction-norm





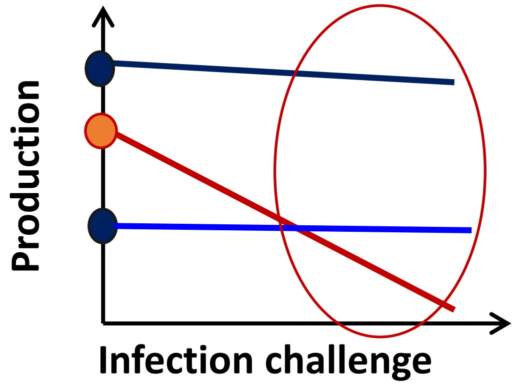
Reaction-norm: change in production with increasing infection challenge

Resilience = reaction-norm **slope**

Production potential = reaction-norm **intercept**

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

When to breed for disease resilience?



High resilience &
Performance potential

High resilience

Low resilience

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

Improvement of disease resilience is 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 achievable genetic gain in productivity

Knap & Doeschl-Wilson: Why breed disease-resilient livestock, and how? GSE 2020

How to breed for disease resilience?

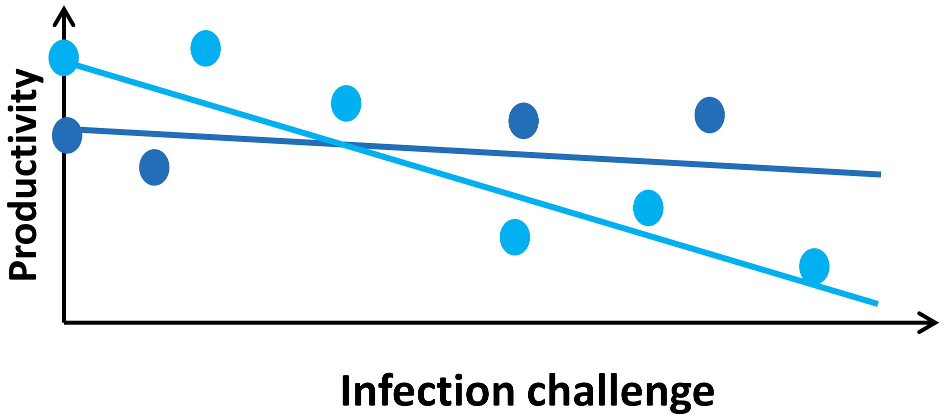
Current (black box) indirect selection on resilience:

- 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

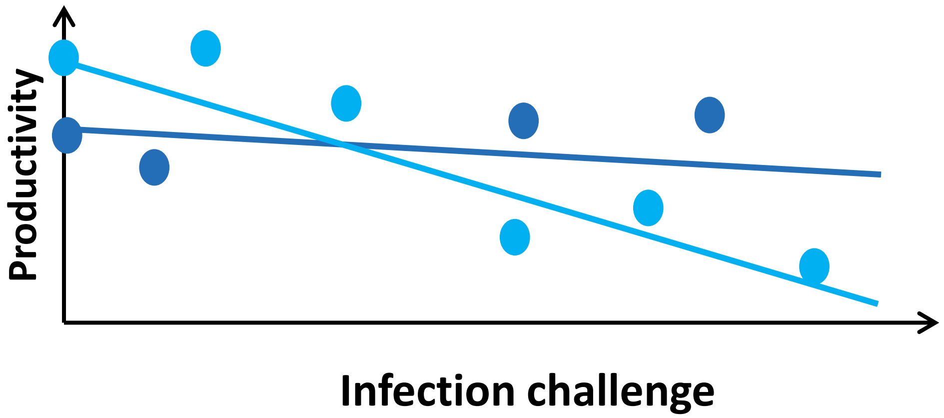
Statistical challenges for estimating resilience

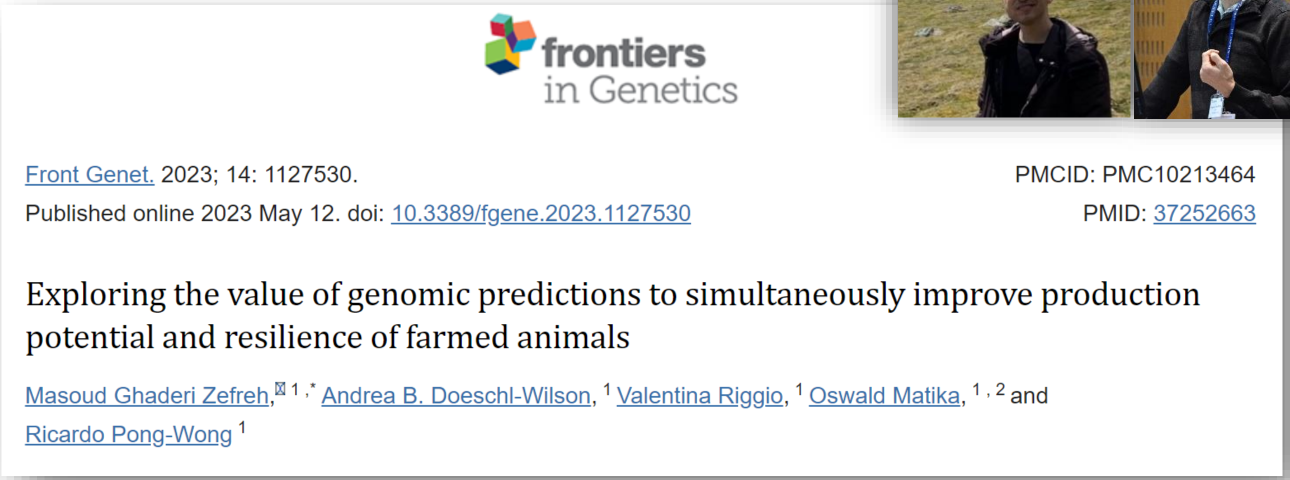


Estimating resilience slopes requires **multiple performance measures** of individuals **across a range of challenge levels**

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

Simulation studies




frontiers in Genetics

Front Genet. 2023; 14: 1127530. PMCID: PMC10213464

Published online 2023 May 12. doi: 10.3389/fgene.2023.1127530 PMID: 37252663

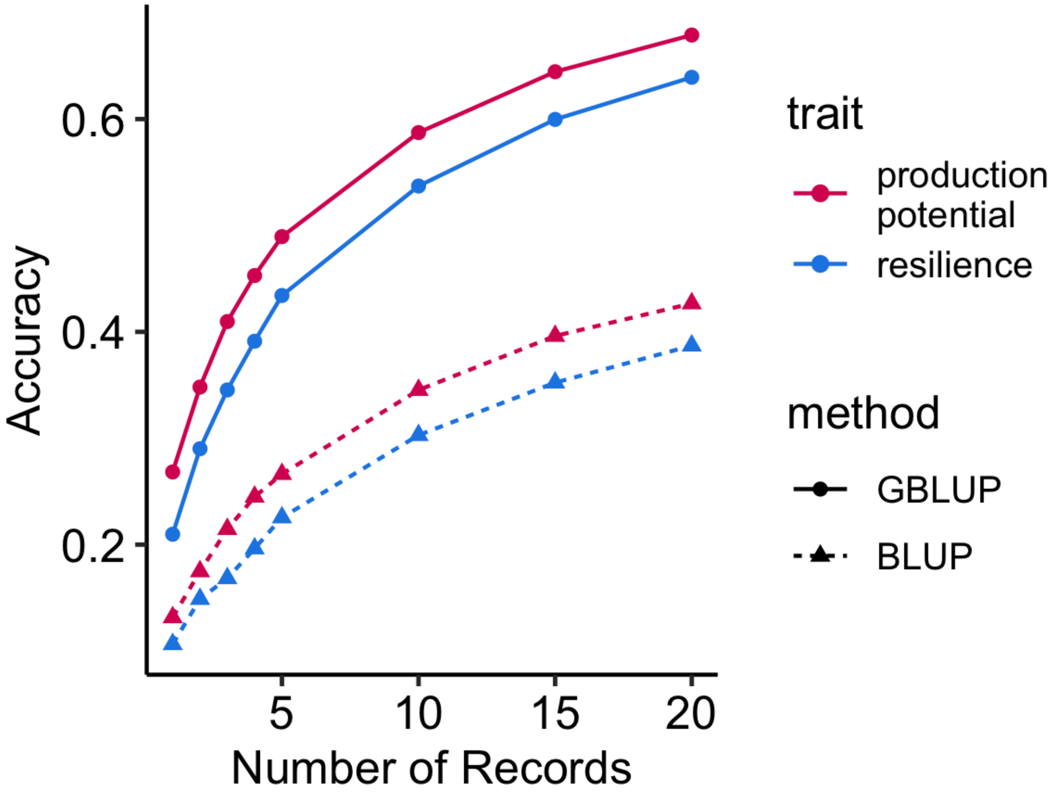
Exploring the value of genomic predictions to simultaneously improve production potential and resilience of farmed animals

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

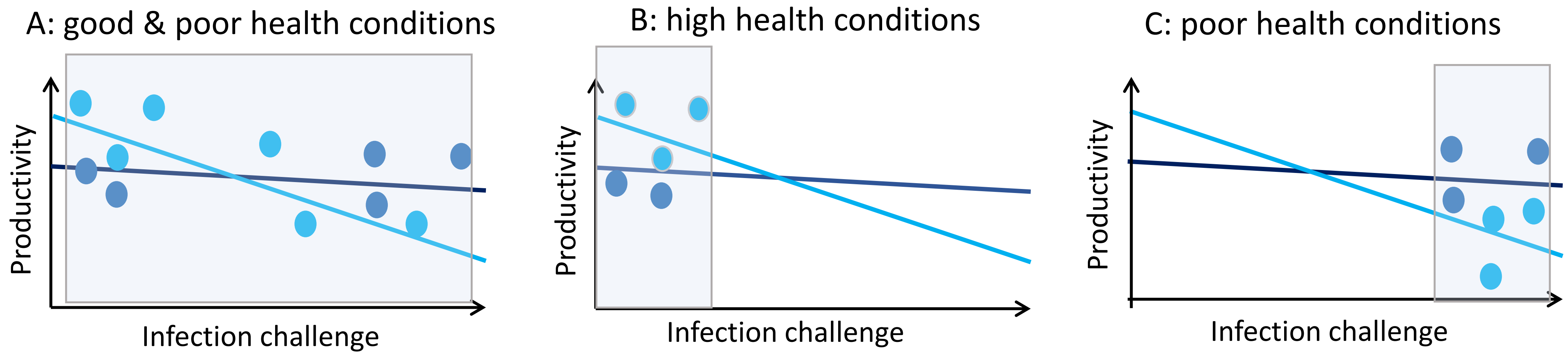


- Prediction accuracies greatly improve with number of records
- Genomic data provide good prediction accuracies even for limited records
- Selection for high production potential & resilience possible with genomic prediction

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

Can we still improve production potential & resilience?

 - without explicitly estimating these traits?

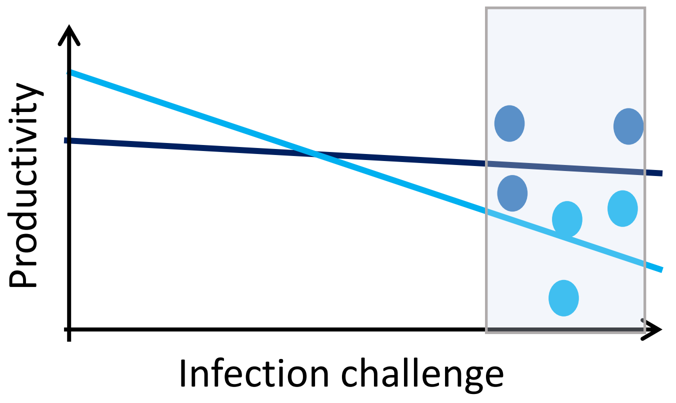


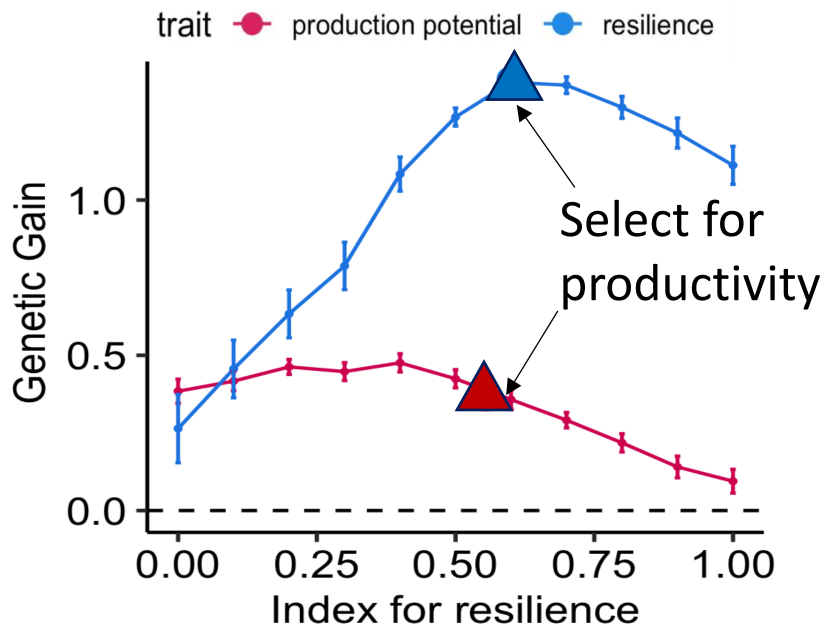
For each phenotyping scenario A-C, simulate 10 generations of selection on

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

Predicted genetic gain after 10 generations of selection

C: **poor health conditions**



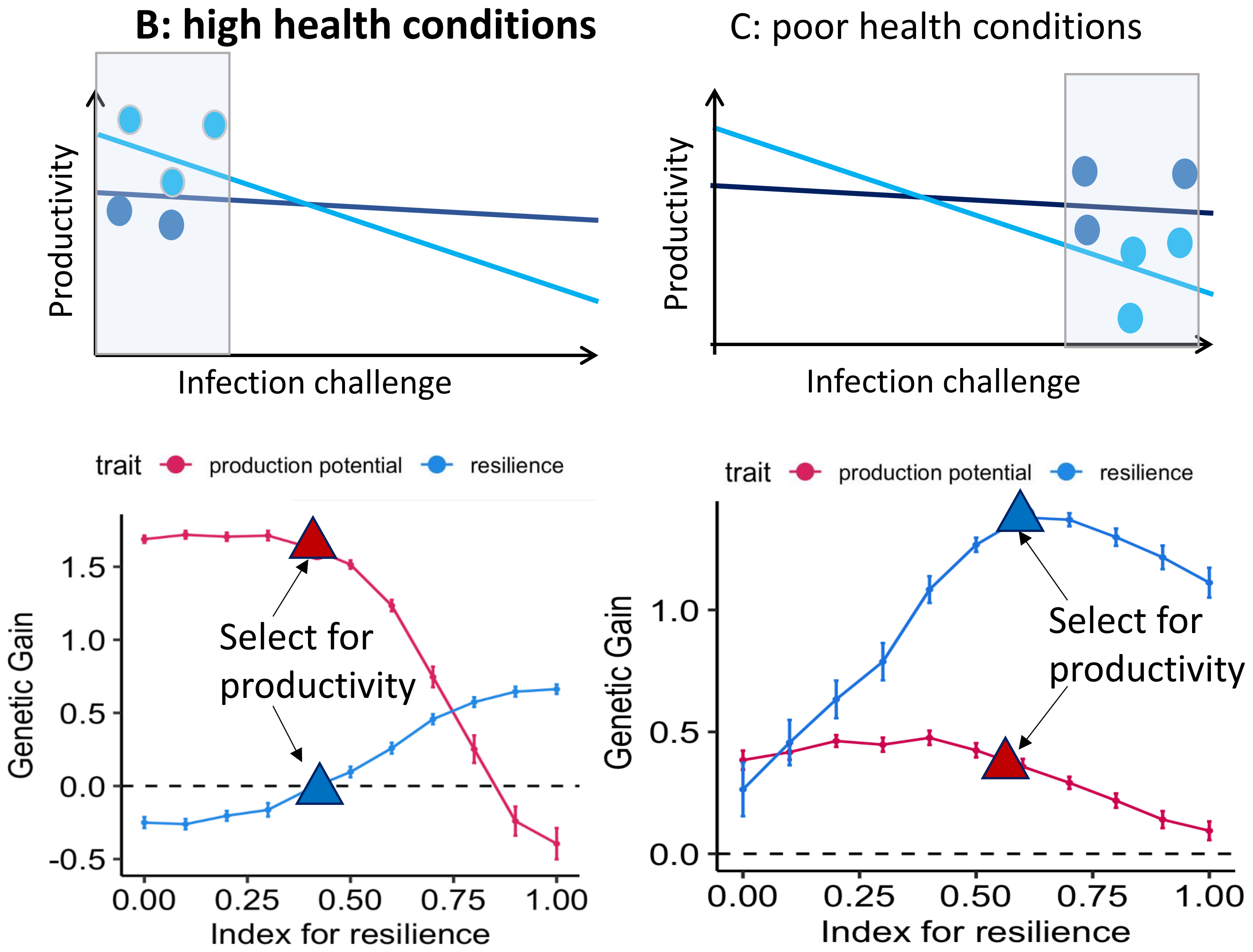


- High genetic gain in resilience
- Limited gain in production potential
- Genetic gain in both traits achieved by selection on productivity alone

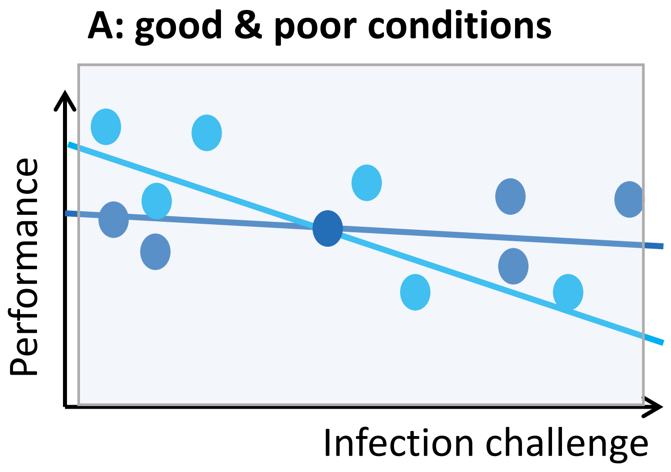
Predicted genetic gain after 10 generations of selection

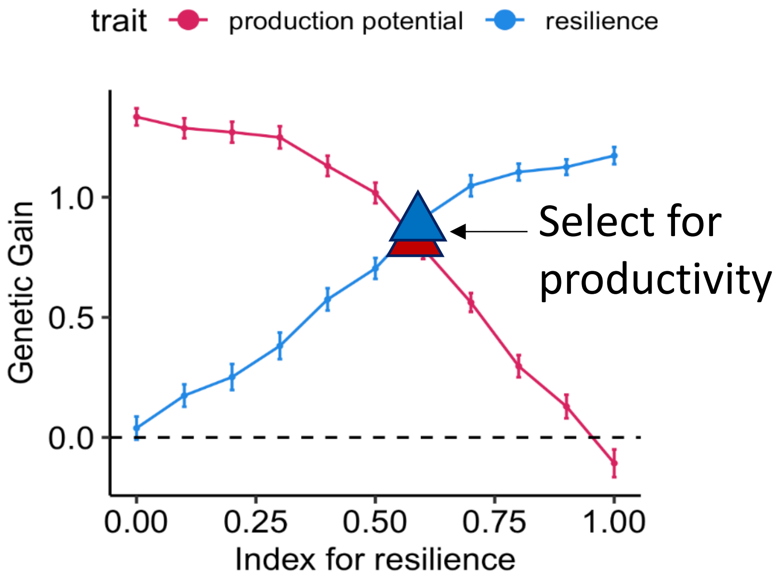
High genetic gain in production potential

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 measurements

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

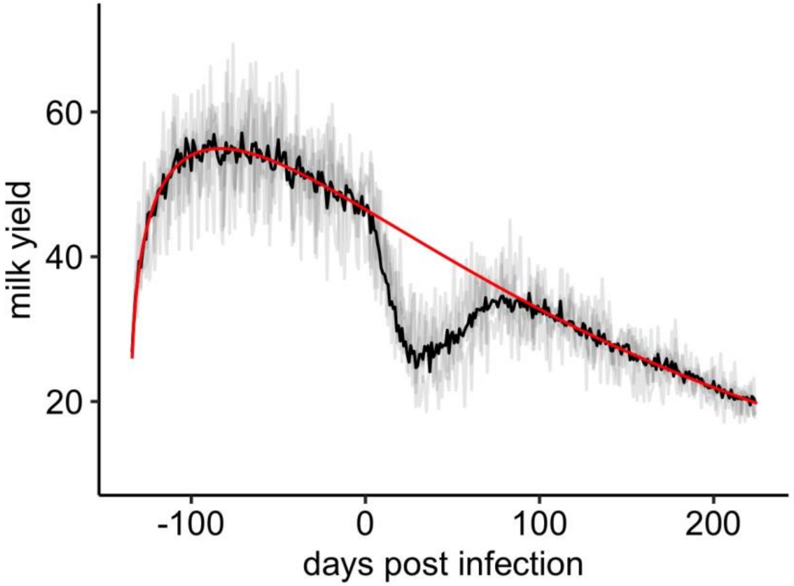
3. Selecting on productivity alone can indirectly improve resilience, but only if data are collected in infectious conditions

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

Resilience trajectories

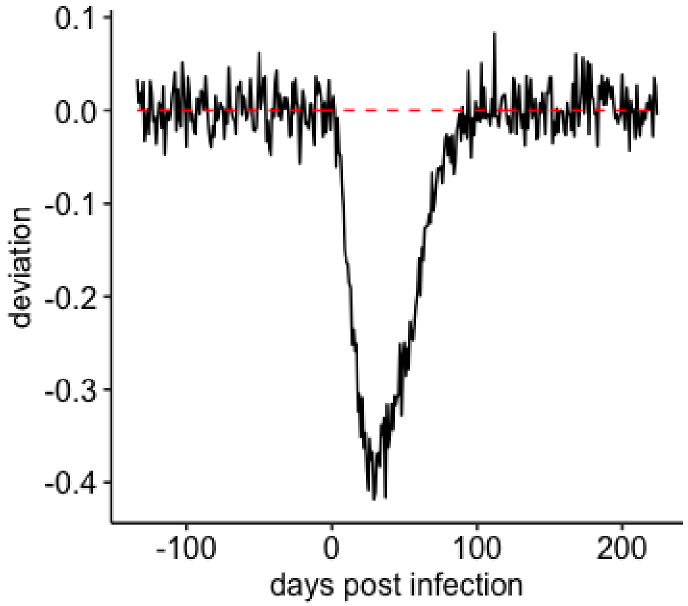
Disease resilience:

The ability of an animal to 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?

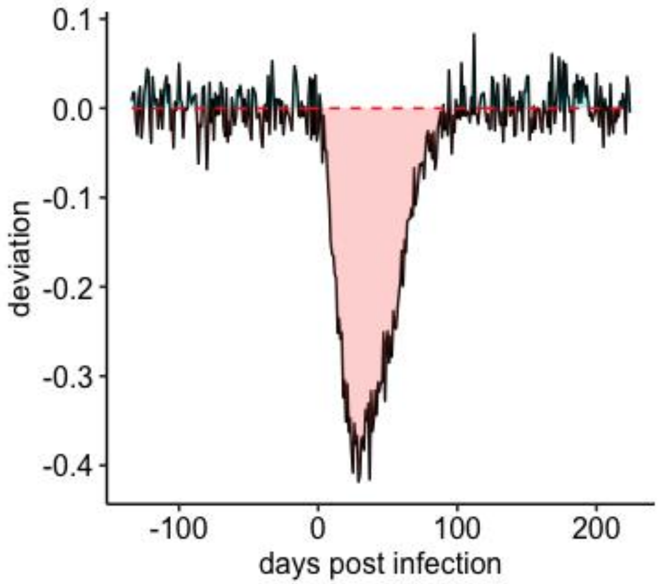
Statistical resilience indicators based on deviations from a target trajectory



Proposed resilience indicators (RI):

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

Area under the curve



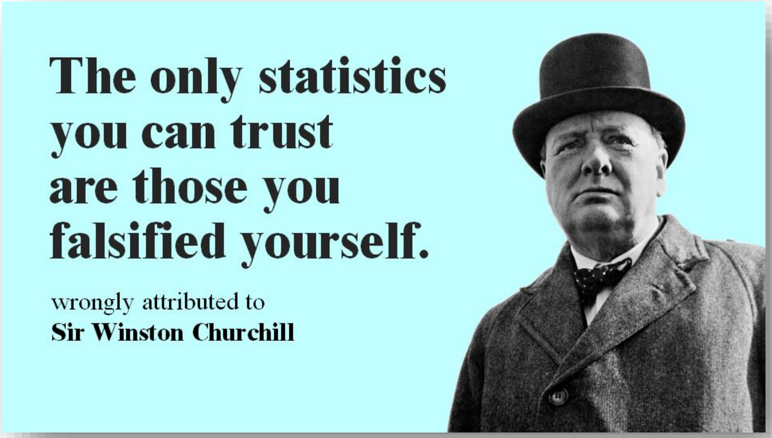
More resilient animals have RI values closer to zero

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



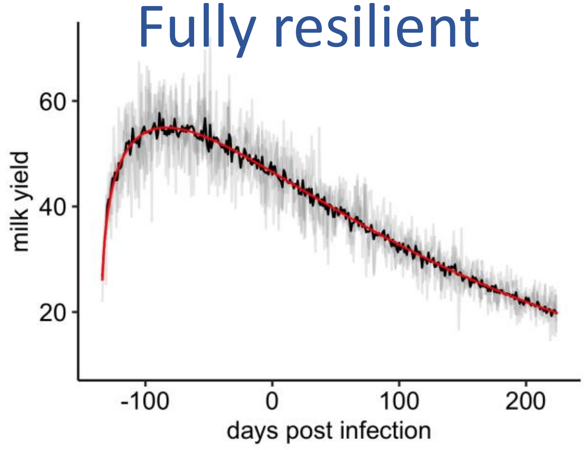
Putz et al., 2019; Berghof et al., Front. Gene. 2019-21; Poppe et al., 2020-22; Wang et al., Front. Gene. 2023

Simulation studies to validate resilience indicators

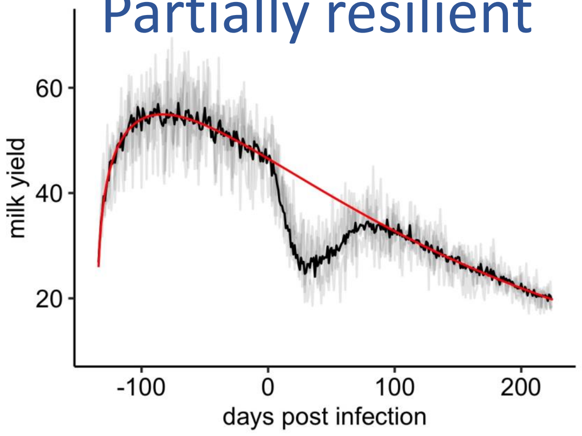
Masoud Ghaderi-Zefreh

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

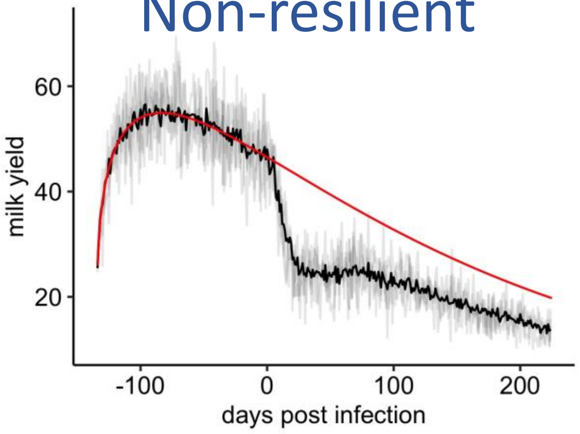
Fully resilient



Partially resilient



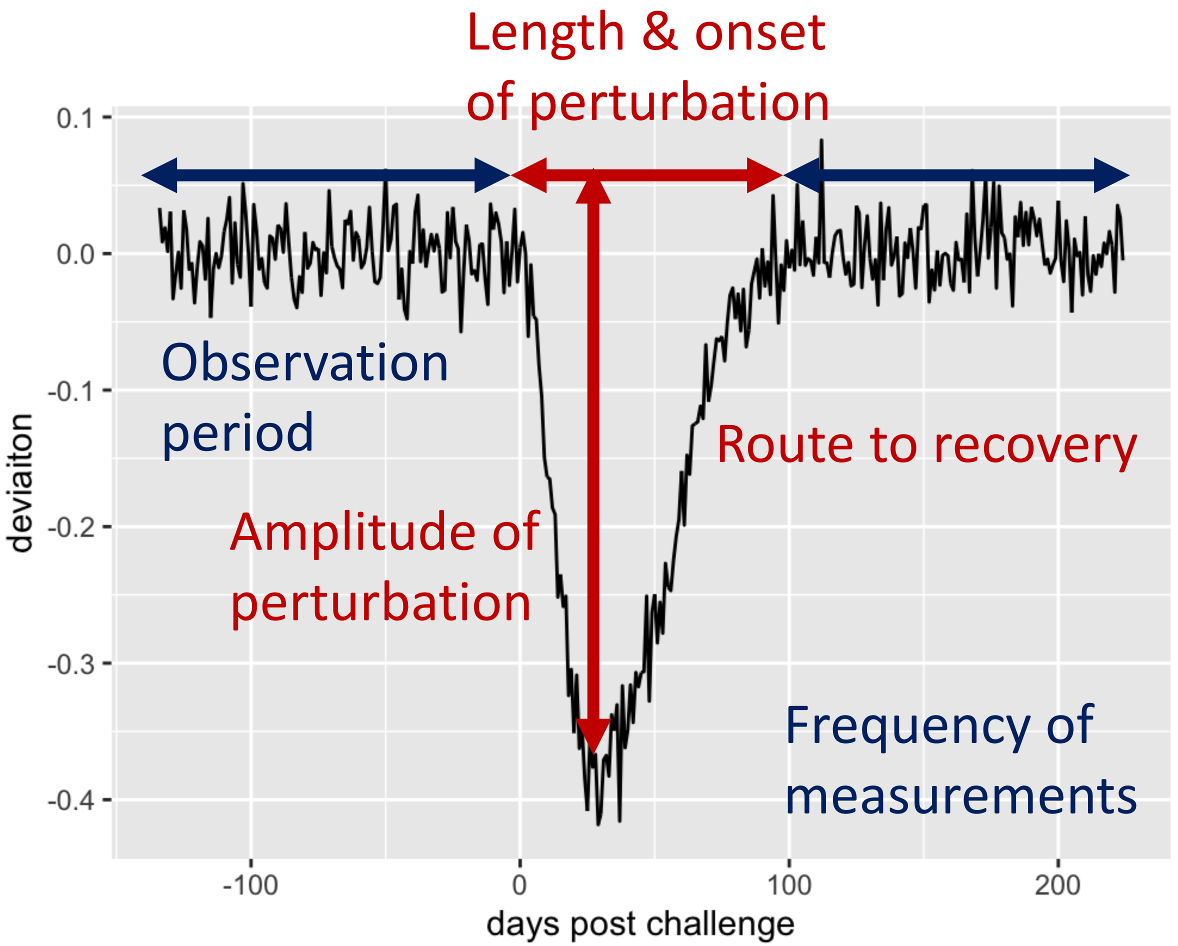
Non-resilient



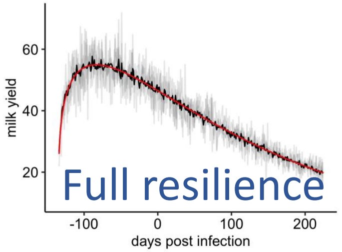
Objectives for validating the statistical resilience indicators

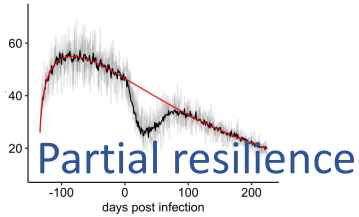
1. Can the RI correctly distinguish between the 3 response types?
2. How sensitive are the RIs to individuals' response and data features?
3. How dependent are RI to the methods for estimating individuals' target trajectories

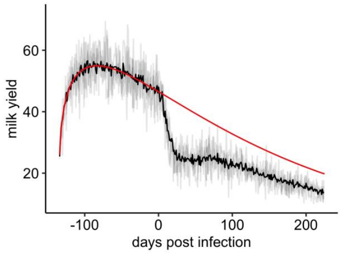
Sensitivity of resilience indicators to data features



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







Non-resilient

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

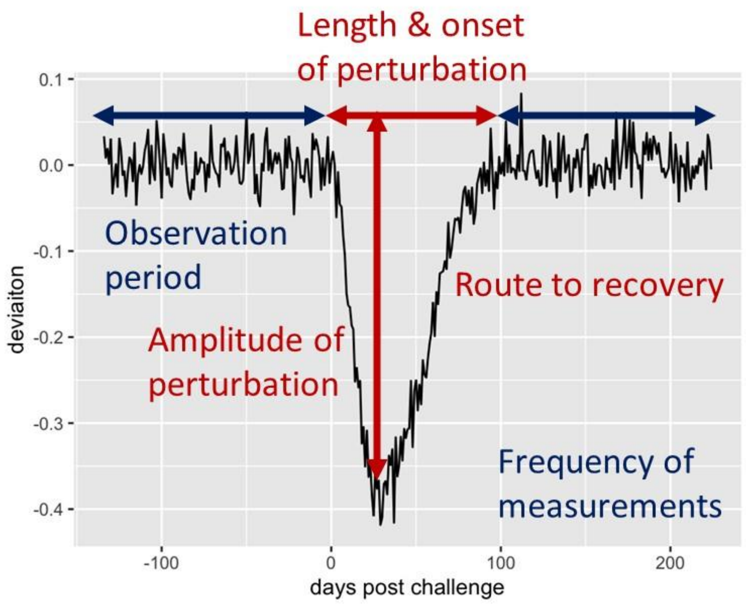
Area under the Receiver-Operator-Curve (ROC) for classifying response types based on resilience indicators

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



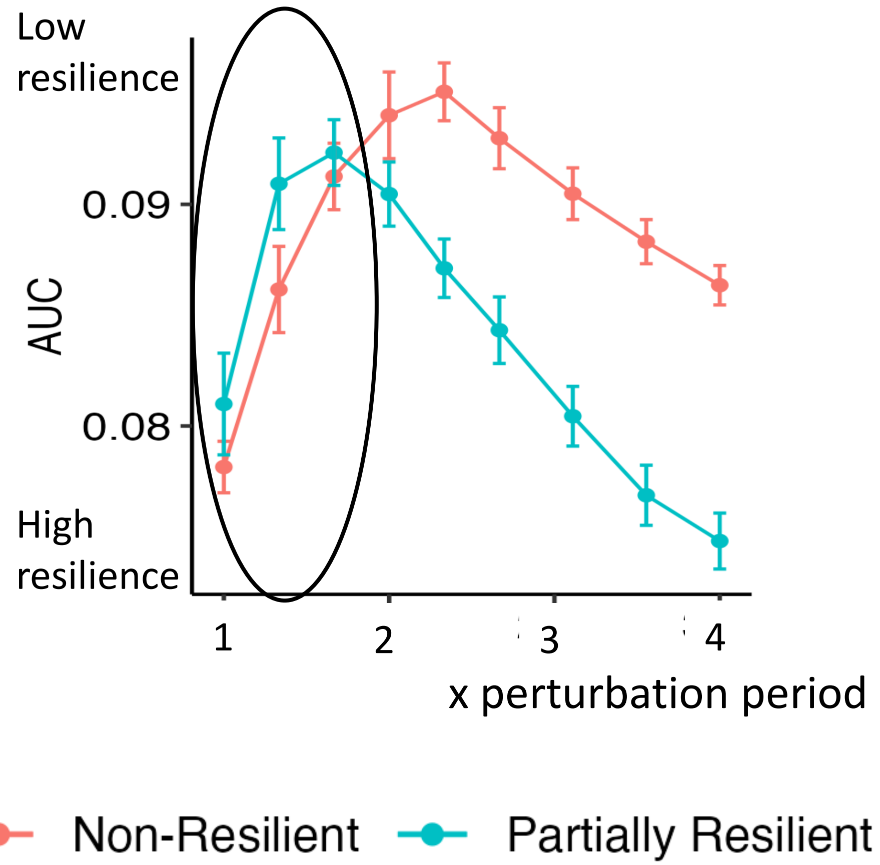
Sensitivity of resilience indicators to data features

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



Summary of results

1. Can the RI correctly distinguish between the 3 response types?

   Generally yes (apart from skewness)

   Risk for mis-classifying non-resilient animals

2. How sensitive are the RIs to individuals’ response and data features?

   Risk for mis-classifying non-resilient animals if data are sparse or only collected during challenge period

3. How dependent are RI to the methods for estimating individuals’ target trajectories

   Risk for downward bias in target trajectory estimate, especially for non-resilient animals → cause of mis-classification

Ghaderi-Zefreh et al., Validating statistical properties of resilience indicators derived from simulated longitudinal performance measures of farmed animals, Animal 2024

Case study: Bovine Mastitis

The problem:

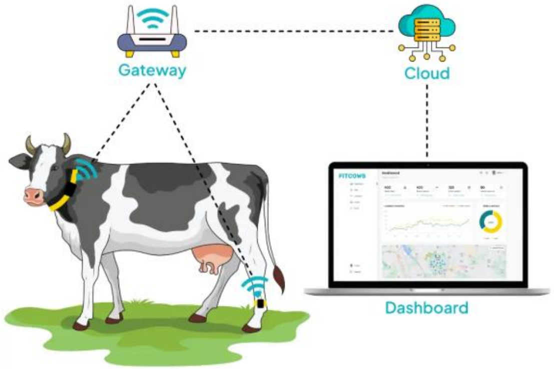
Endemic disease in dairy cattle, causing massive economic losses

Difficult to control (multiple pathogens; sub-clinical mastitis)

The opportunity:

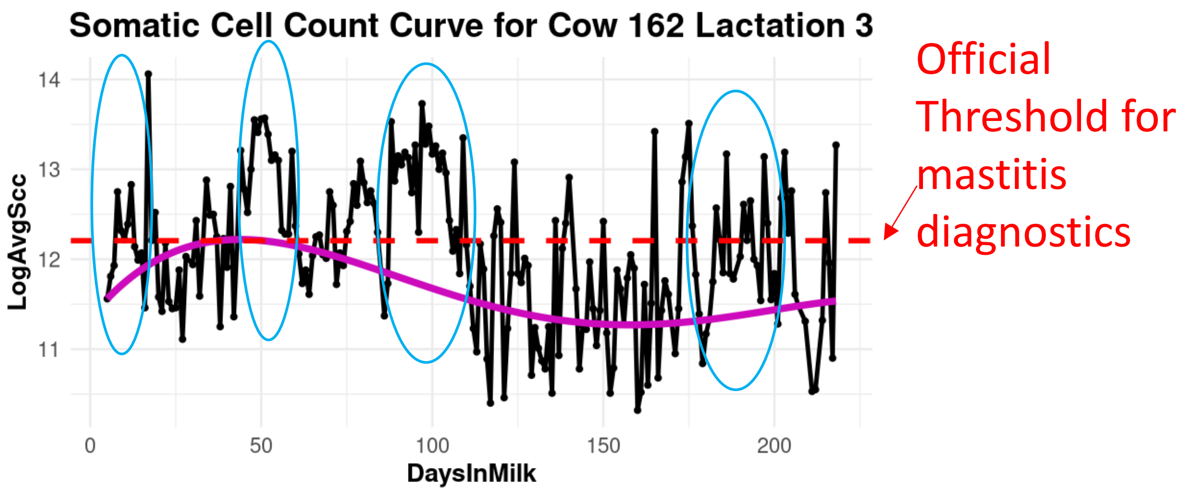
Construct novel indicators for resilience to mastitis from longitudinal records of milk yield and somatic cell counts from milk robotic data

SLU **Gigacow**



repeated milk & SCC records (from automated milking systems) from >1000 cows, 6 farms

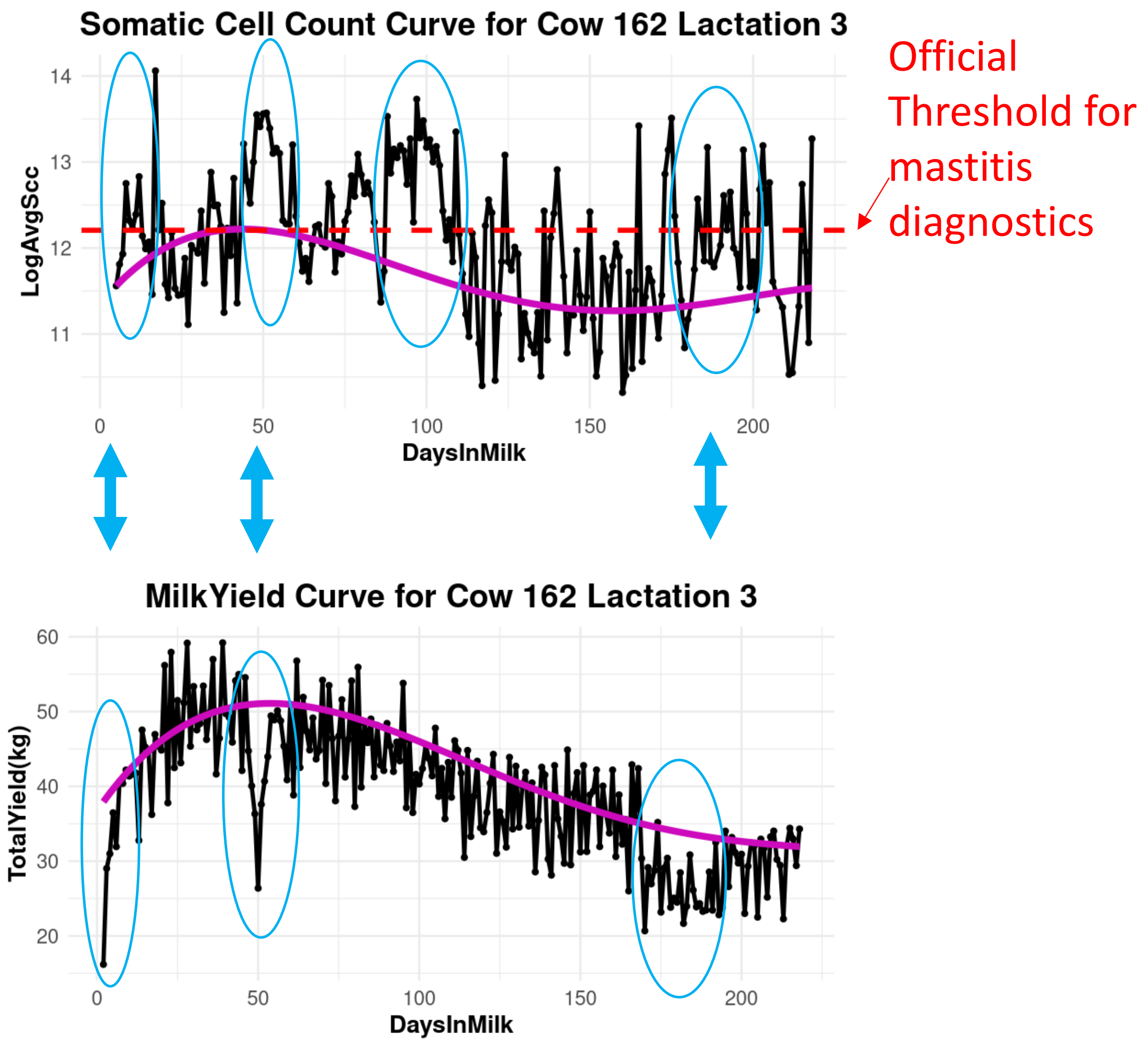
Case study: Bovine Mastitis



Tijesunimi Ojo

- Official SCC threshold for mastitis poor diagnostics
- Can we construct individual SCC target trajectories and identify & characterise potential mastitis events for each cow?

Case study: Bovine Mastitis



Tijesunimi Ojo

- Official SCC threshold for mastitis poor diagnostics
- Can we construct individual SCC target trajectories and identify & characterise potential mastitis events for each cow?

- Aim: construct mastitis resilience indicators

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:

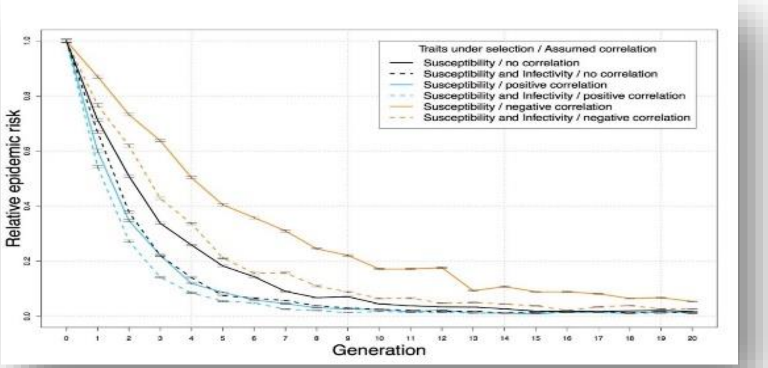
- resilience & productivity in disease-free conditions (affecting productivity)
- resistance & tolerance to disease
- resilience & host infectivity (affecting herd resilience)

Resilient Super-spreaders compromise herd resilience

→ Improve resilience & decrease infectivity

Case study : Bovine Tuberculosis

- Persistent zoonotic disease in many countries
- Costly eradication programmes
  - Cattle: Stringent testing & culling; movement restrictions
- TBAdvantage selection index (UK): enables farmers to select bulls with high genetic bTB resistance
- Modelling studies: selection for resistance alone may not be enough



Raphaka et al. Front. Vet. Sci 2021 & Tsairidou et al. Front. Vet. Sci. 2018

Duygu Madenci

Enrique Sanchez-Molano

Can / should one breed cattle for low bTB infectivity, in addition to high bTB resistance?

Objective:

- Detect genetic variance in cattle infectivity from UK national surveillance data
- Assess potential trade-off with bTB resistance and other health and production traits

Approach

DATA:

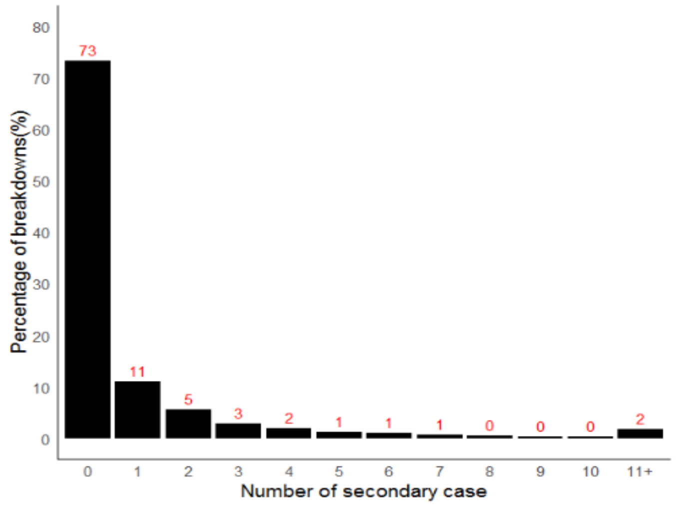
- Same as used in UK national genetic evaluation of bTB resistance
- After filtering: Individual test records of >1Mio Holstein-Friesian cows from >4000 bTB outbreaks (GB, 2000-2021) + pedigree (7 generations, >70K records)

INFECTIVITY PHENOTYPE (index cases only):

- **Number of secondary cases associated with each index case**

Index case: first identified bTB positive cow in a breakdown

Secondary case: identified bTB positive cows at the follow up test



GENETIC VARIANCE ESTIMATION:

- Generalized linear mixed models implemented in MCMCglmm R package

Madenci et al., J. Dairy Sci. In press

Infectivity variance estimates

Model					
	Hurdle[1]		**Zero Inflated Poisson**		**Geometric**
Variance	Binary[2]	Poisson	Binary[2]	Poisson	
σ_s^2	$<10^{-5}$	**0.0328*** (0.0004 , 0.1021)	$<10^{-5}$	**0.0197*** (0.0002, 0.0715)	**0.0288*** ($<10^{-5}$, 0.0979)
σ_e^2	1.000	1.2990 (1.128 , 1.481)	1.000	3.884 (3.513 , 4.326)	3.046 (2.692,3.383)

[1] Best model fit

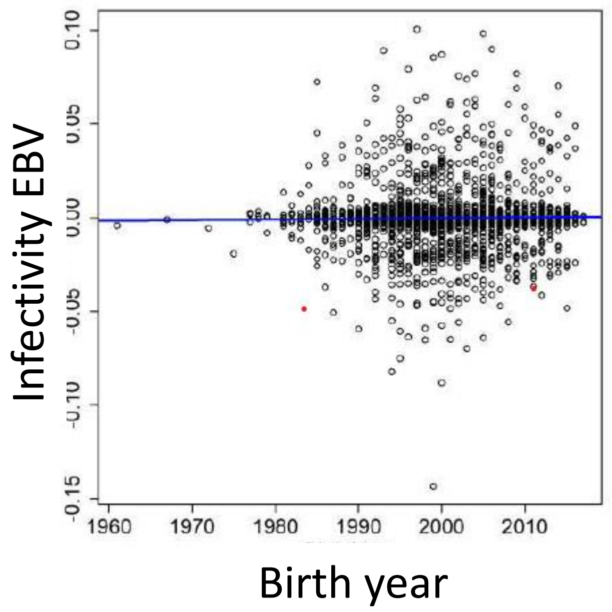
[2] The residual variance, σ_e^2, for the zero-part in both ZIP and Hurdle models fixed at 1

***Infectivity EBV of - 1σ_A below average ≈ 32% - 44% fewer secondary cases**

Madenci et al., J. Dairy Sci. 2025

Infectivity breeding value correlations

Trait	All sires	Most informative sires
TB Advantage (bTB resistance)	0.008	0.055
Mastitis	-0.029	-0.124
Lameness	0.037	0.182*
Milk yield	-0.012	-0.023
Fat yield	0.012	0.085
Protein yield	0.002	0.091
Lifespan	0.029	0.089
Fertility index	0.006	0.027
Calving interval	-0.004	-0.074



No indirect selection for infectivity

Key Lessons – bovine Tuberculosis

1. Strong evidence for genetic variation in infectivity
   - likely under-estimated
2. No evidence that current selection for bTB resistances also reduces bTB transmission
3. Scope for breeding cattle that are both resistant to bTB and less likely to transmit bTB

Take-home messages

Breeding for disease resilience

1. **Is possible and 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

- **Masoud Ghaderi-Zefreh**
- **Ricardo Pong-Wong**
- **Tijesunimi Ojo**
- **Duygu Madenci**
- **Enrique Molano-Sanchez**
- Georgios Banos (SRUC)
- Mike Coffey (SRUC)
- Wilson group members

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THANK YOU

Questions & Comments?