ROSLIN

Unravelling the Contribution of Host Genetics to Infectious Disease Outbreaks in Livestock Populations

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Hypotheses

- Host genetics has a huge influence on infectious disease spread

- **We are currently NOT capturing ALL of the host genetic variation in infectious disease data**

Outline

1. **Why don't we capture all genetic variation in infectious disease data?**
   - **What does it take to correct this?**
2. **An example from fish data**
3. **A new statistical method to estimate genetic parameters for host susceptibility & infectivity from outbreak data**
4. **Potential application to cattle**

Breeding goals for combatting infectious disease

Reduce Prevalence

- **Improve host Resistance:**
  Ability to restrict pathogen reproduction
- **Reduce host Infectivity:**
  Ability to transmit the infection

Reduce Impact

- **Improve host Tolerance:**
  Ability to limit impact of infection on health or fitness

Breeding goals for combatting infectious disease

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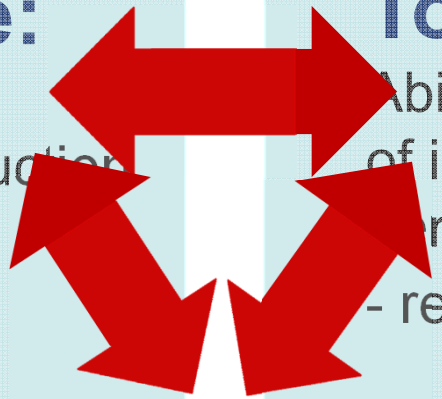
Reduce Prevalence

- Improve host **Resistance:**
  Ability to restrict pathogen reproduction
- Reduce host **Infectivity:**
  Ability to transmit the infection

Mitigate Impact

- Improve host **Tolerance:**
  Ability to limit impact of infection on health or performance
  - related to **Resilience**



All host traits may harbour genetic variation & may be related: "Tolerant superspreader"

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How to measure Resistance

- Did it become infected?
  - **Binary infection status (infected / not infected)**
- When did it become infected?
  - **Time of infection**
- How severe is the infection?
  - **Pathogen load**
  - **Immune response**

Much known about genetic resistance

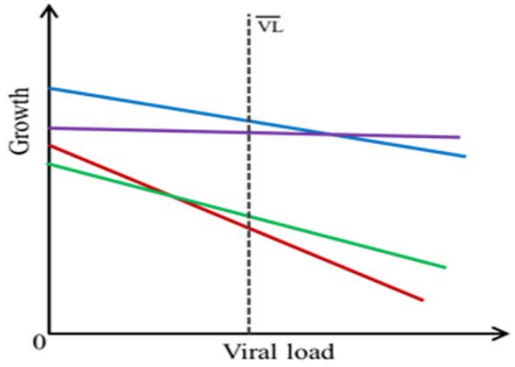
How to measure Tolerance

- Did the host survive the infection?
  - **Time to death**
  - *Requires knowledge of presence of infection*
  - *Only suitable for infections that kill*

Relatively little known about tolerance genetics

- How did host performance change with increasing pathogen burden?
  - **Reaction norms**

See presentation by G. Lough
Session 31, Tuesday 16.45pm

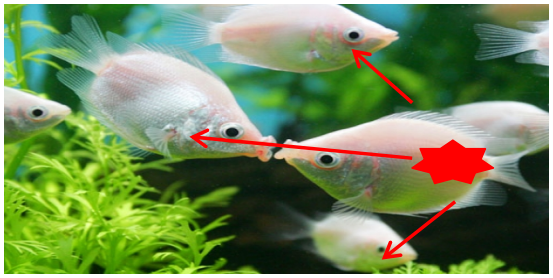


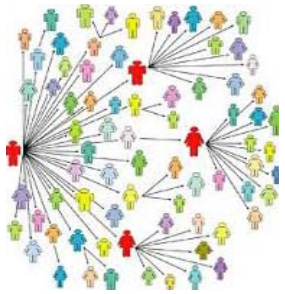
How to measure Infectivity

Infectivity is an indirect genetic effect (IGE):
Individual's genes affect the (disease) phenotype of group members

Nothing known about infectivity genetics

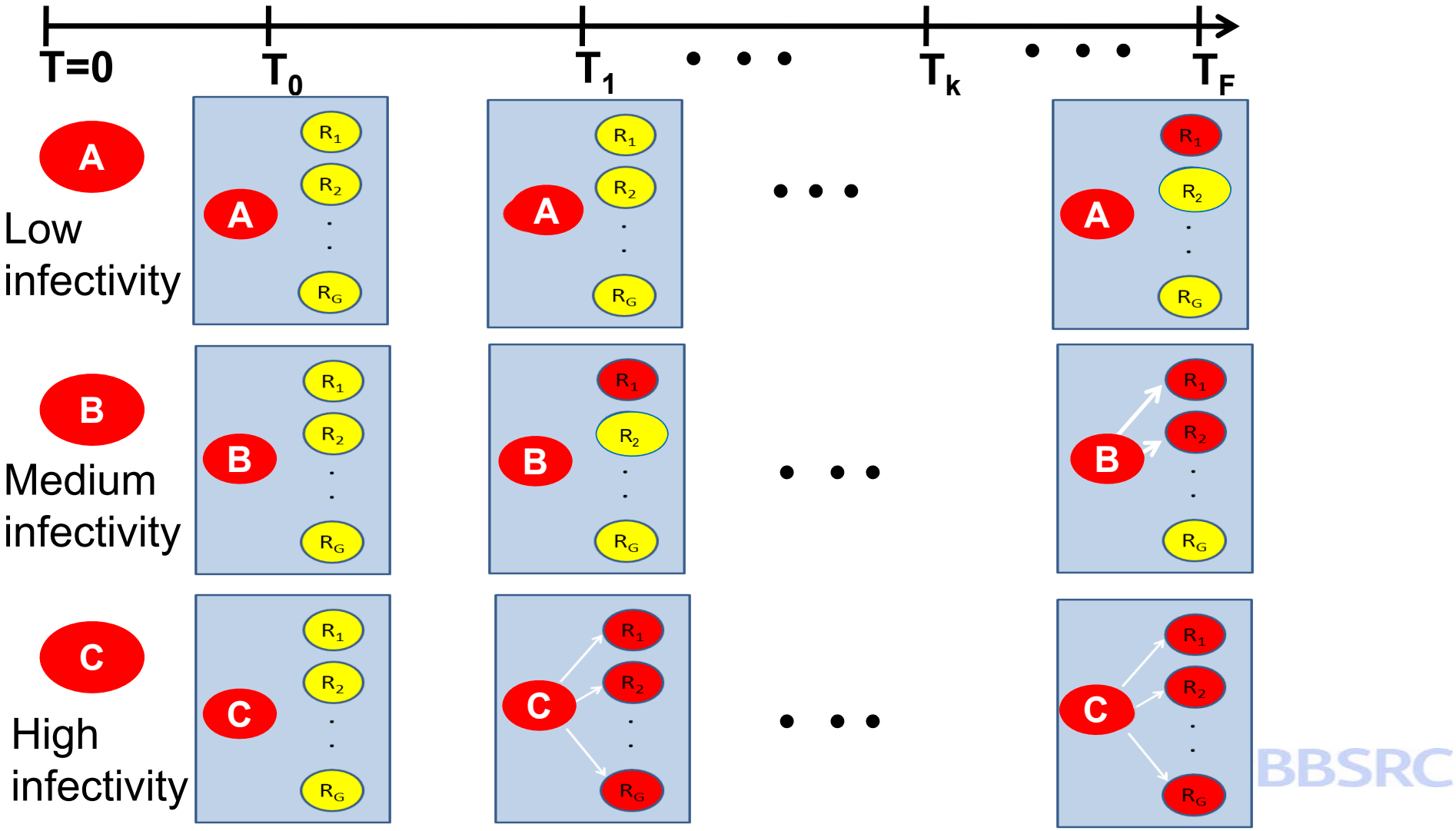
- Requires measurement of infection status of contact individuals
- Difficult to capture with current genetic models





Lipschutz-Powell et al. PLoS ONE 2012; Front. Gene. 2012; Anche et al. (Heredity 2014)

How to infer differences in infectivity?



Application: Scuticociliatosis in Turbot

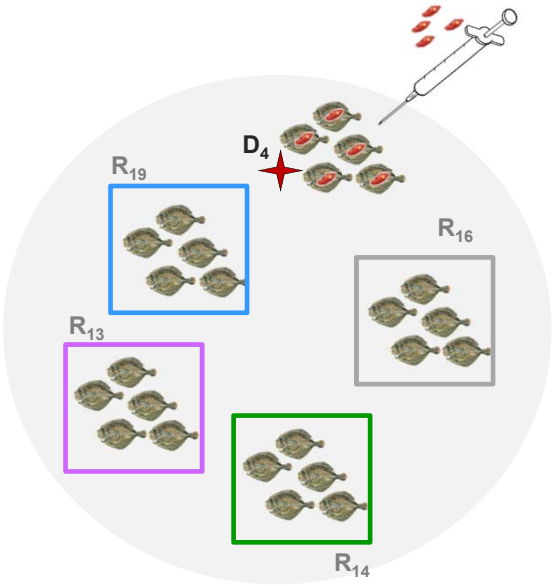
- Infectious disease caused by protozoa *Philisterides Dicentrarchi*
- Symptoms: Colour change, skin lesions … death

➢ Unique model for disentangling resistance / tolerance / infectivity

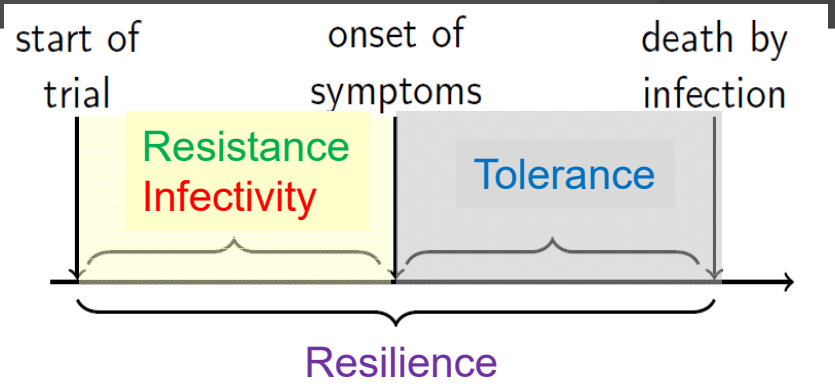
Transmission experiment

Carefully designed transmission experiment to determine genetic (co-)regulation of resistance, tolerance & infectivity

- 1800 recipient fish from 60 families
- Distributed (optimally) into 72 tanks (25 fish / tank); 2 trials
- Epidemics seeded by infected donor fish from one of 8 families
- Daily measurements of infection status of each individual; genotypes

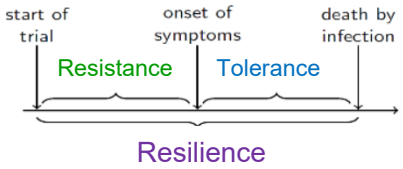


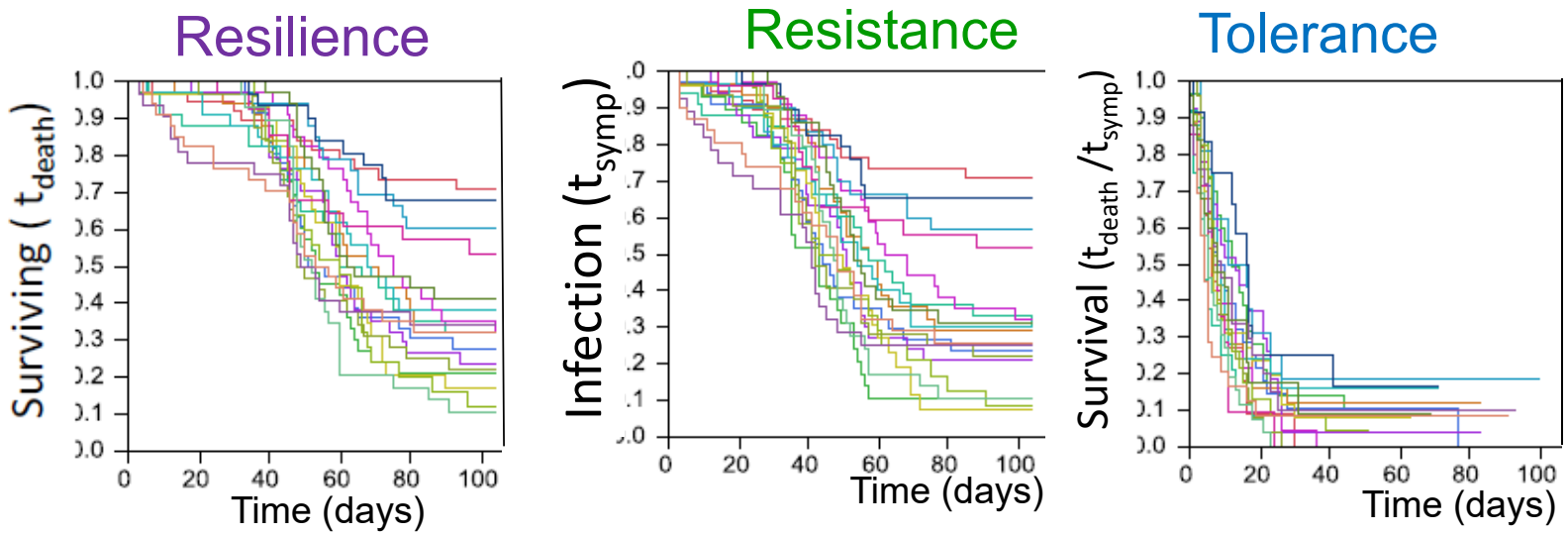
Trait definitions & data



- **RESILIANCE**
  Ability to survive after exposure
  Time (days) to death
- **RESISTANCE**
  Ability to avoid infection
  Time (days) to onset of first symptoms
- **TOLERANCE**
  Ability to survive despite being infected
  Time (days) from onset of first symptoms to time to death
- **INFECTIVITY**
  Ability to transmit infection
  Time (days) to onset of first symptoms of tank mates

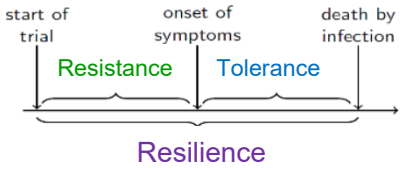
Kaplan Meier survival / infection curves for recipient families

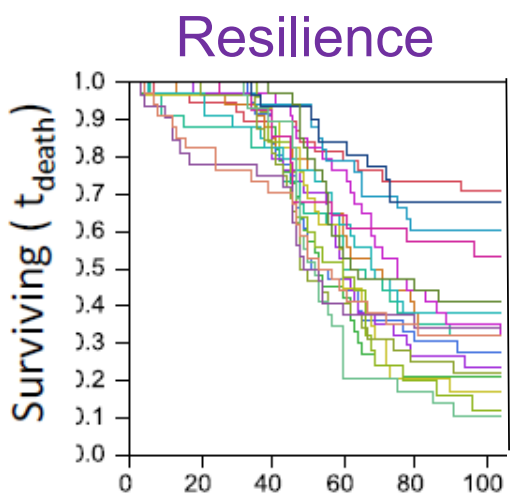


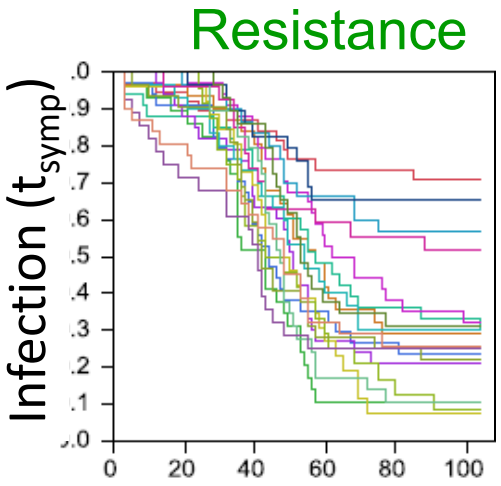


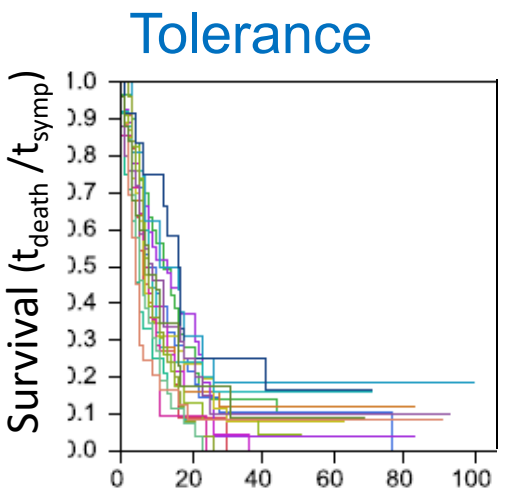
- High variation in recipient family resistance
- Variation in tolerance much smaller
- Most variation in resilience explained by variation in resistance

Genetic analysis – proportional hazard models



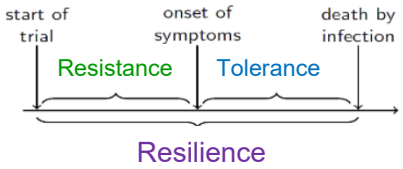


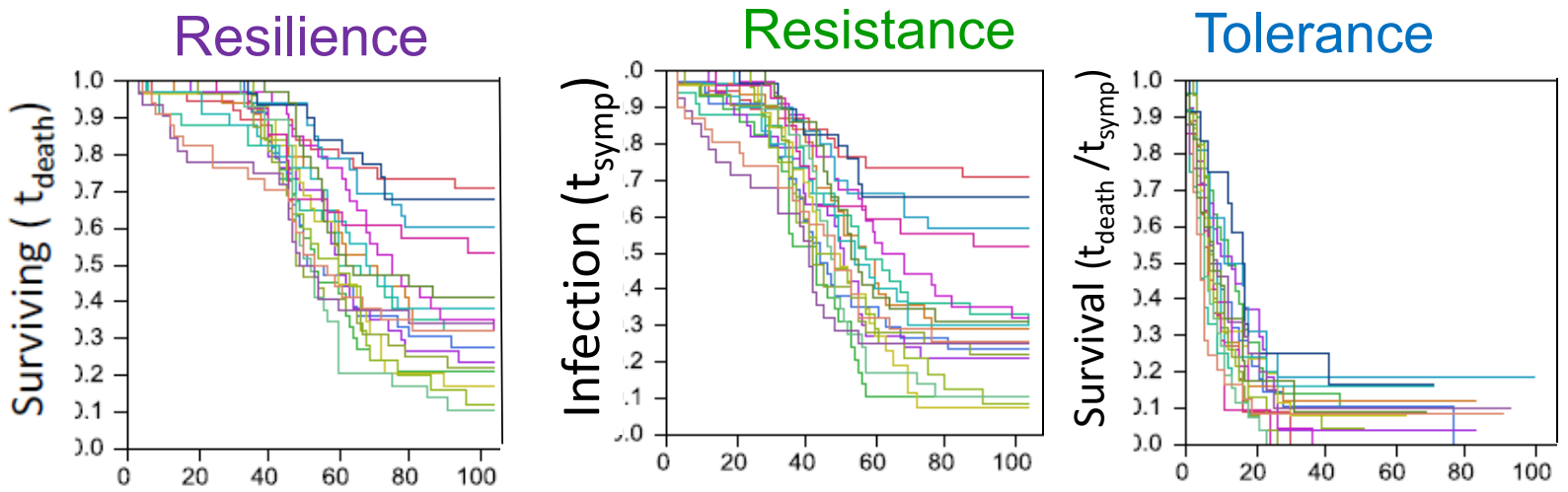




	Resilience	Resistance	Tolerance
Genetic var	0.09	0.14	0.11
Heritability	0.04	0.08	0.09

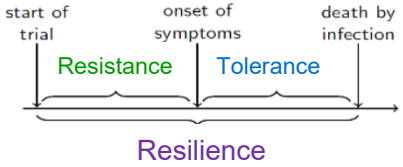
Genetic analysis – proportional hazard models





	Resilience	Resistance	Tolerance
Genetic var	0.09	0.14	0.11
Tank var.	**0.58**	**0.65**	**0.0001**
Heritability	0.04	0.08	0.09

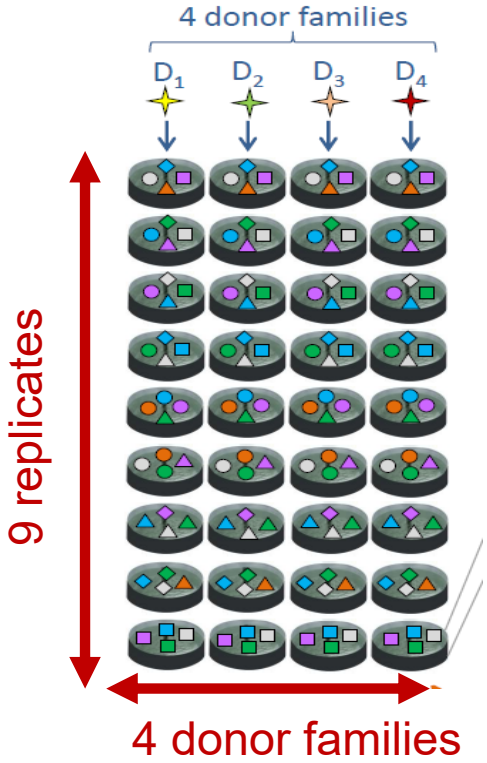
Genetic analysis – proportional hazard models



- **(Genetic) Variation in infectivity is fully absorbed in tank effects**
- **Are we missing an important host genetic component affecting disease prevalence?**

	Resilience	Resistance	Tolerance
Genetic var	0.09	0.14	0.11
Tank var.	**0.58**	**0.65**	**0.0001**
Heritability	0.04	0.08	0.09

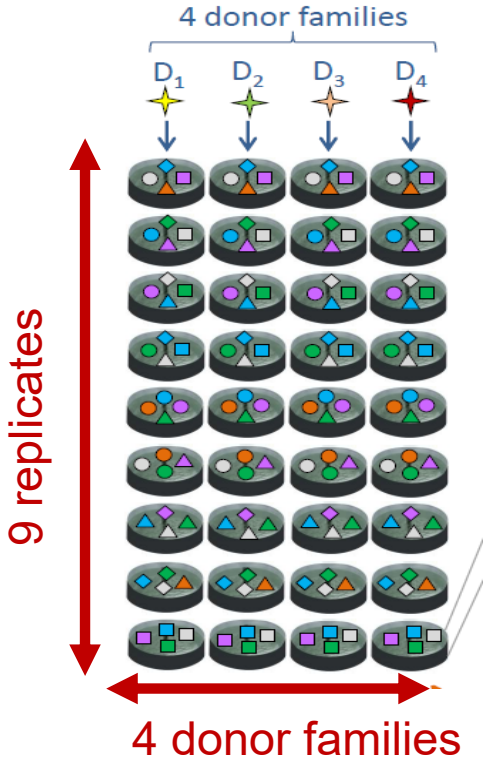
First evidence for genetic variation in infectivity

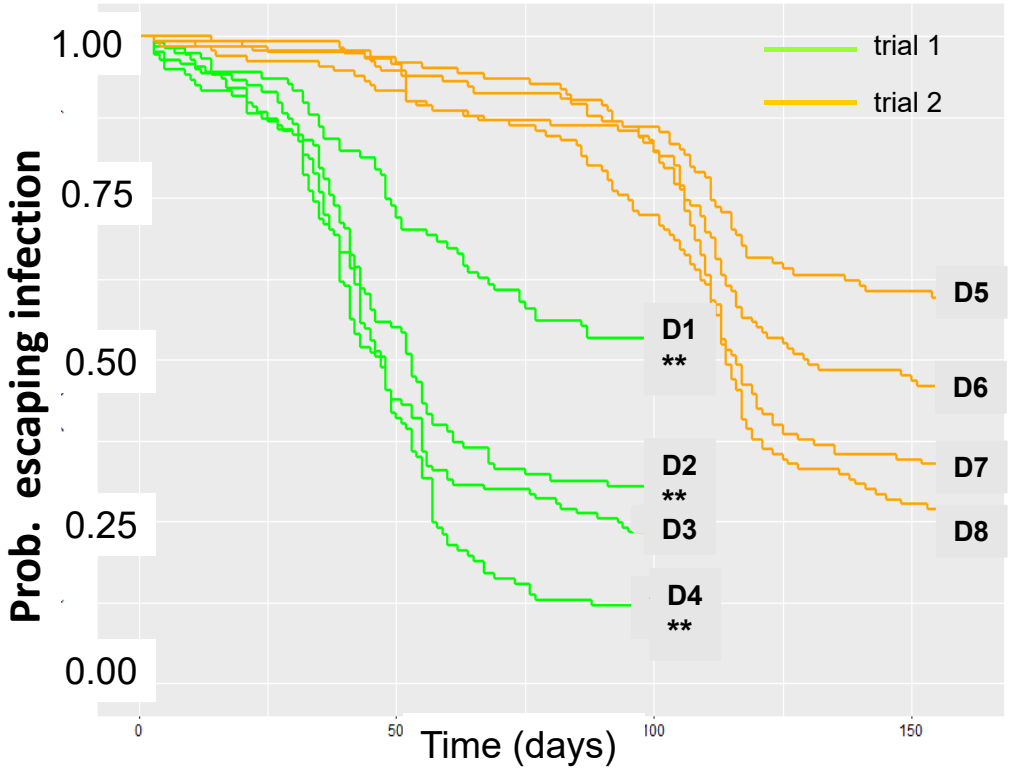


Does infection spread equally fast for each donor family?

- Significant difference in recipient infection profiles between the 4 donor families would indicate genetic variation in infectivity

First evidence for genetic variation in infectivity





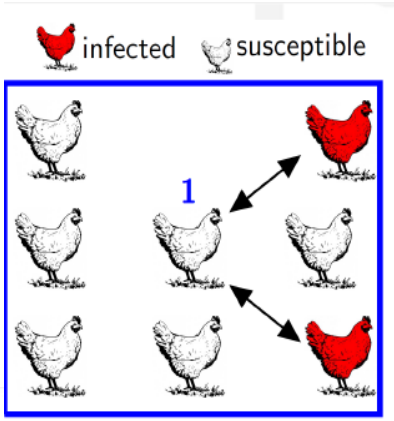
- Significant difference in infectivity between donor families
- **But how to account for differences in recipients' infectivity?**
- **How to apply these principles to field data?**

Estimating genetic susceptibility & infectivity for natural disease outbreaks

Dynamic non-linear Indirect Genetics Effects method (DnIGE)

What is it?

- **A Bayesian computational method that estimates genetic parameters for susceptibility & infectivity from disease outbreak data**
  - Embeds principles from epidemiological models
  - Incorporates genetic variation in host susceptibility & infectivity
    - Assumes that susceptibility & infectivity are controlled by many genes (**polygenic effects**)



rate of infection of animal 1 at time t

$$\lambda_1(t) = \underbrace{g_1}_{\text{susceptibility of animal 1}} \times \underbrace{\beta}_{\text{mean transmission rate}} \times \underbrace{\sum f_k I_k(t)}_{\text{infectivity of animals infected before } t_j}$$

Anacleto et al. Genetics, 2015

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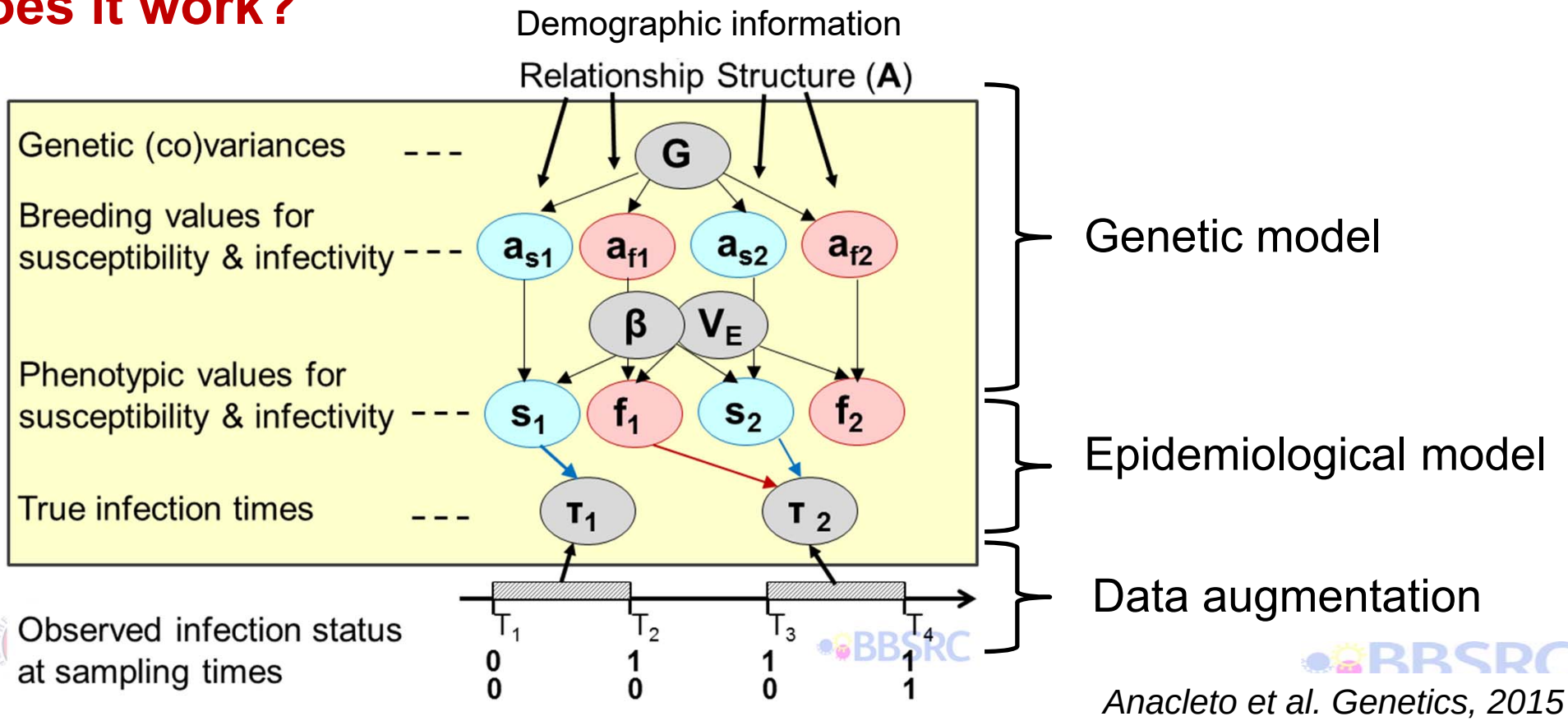
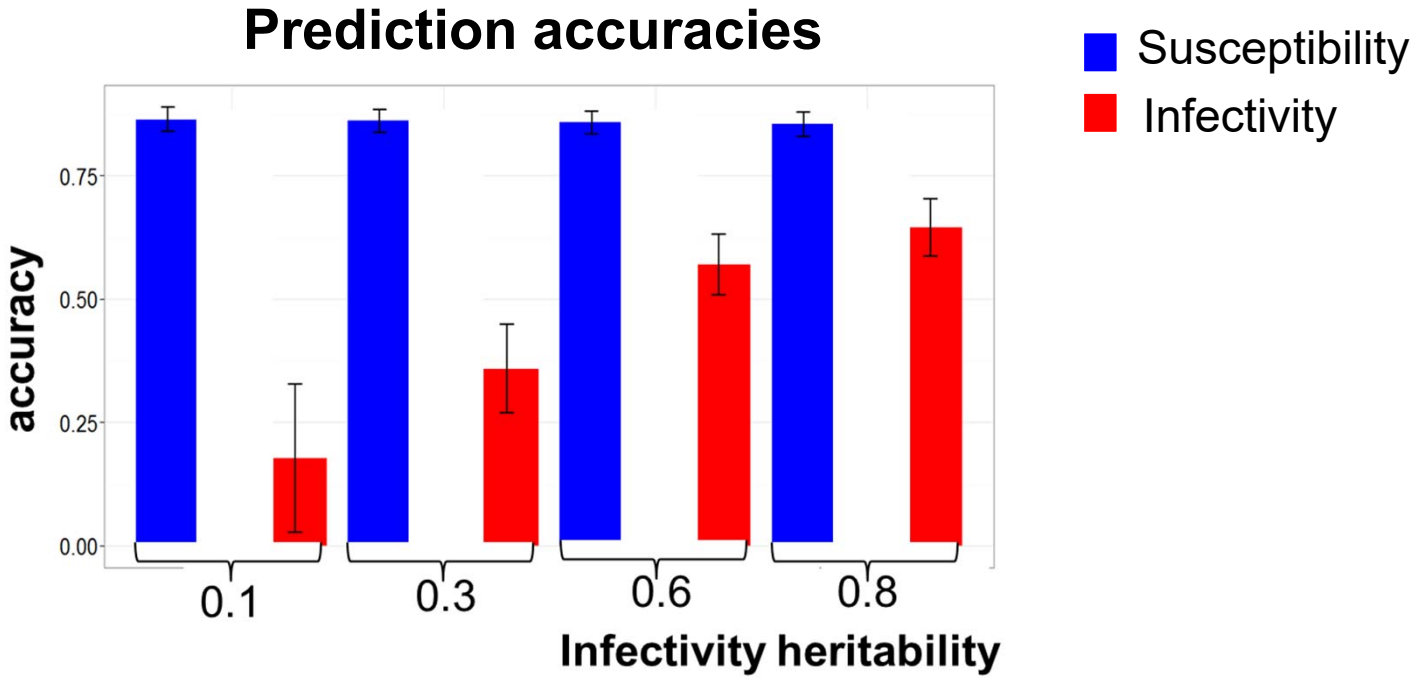
Dynamic non-linear Indirect Genetics Effects method (DnIGE)

How does it work?



Anacleto et al. Genetics, 2015

Good prediction accuracies for genetic risk for susceptibility & infectivity

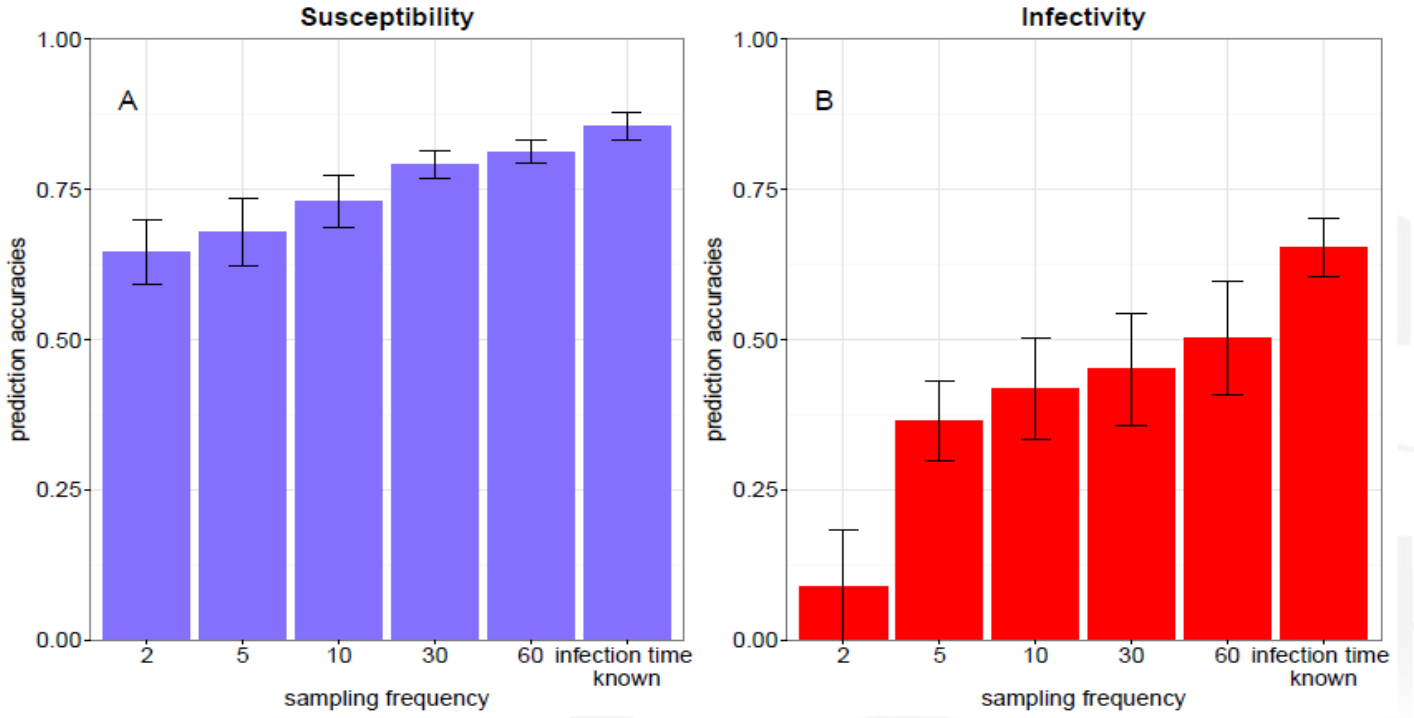


Estimating genetic risk for infectivity is more difficult than for susceptibility, but possible

Anacleto et al. Genetics, 2015

How often do we need to sample?

N=2000, 100 sires, 20 dams/sire, group size 10, $h^2 = 0.8$ (10 replicates)



Estimating infectivity BVs requires repeated measurements

Reasonable predictions even for low sampling frequencies

Anacleto et al. Genetics, 2015

Potential applications in cattle

Bovine Tuberculosis & mastitis

Relevant?

- **Devastating effects on cattle industry**
- **Much known about genetics underlying disease resistance & some understanding about tolerance** (see talks in this session)
- **Evidence for variation in infectivity – supers-spreaders!**
- **Are genetically more resistant / tolerance animals also less infectious?**

Feasible?

- **Large datasets with appropriate populations structure and required genetic & epidemiological information**

Conclusion

Opportunities:

1. Much scope for genetic disease control
2. Make better use of epidemiological data
   - Consider more traits that harbour genetic variation (e.g. tolerance, infectivity)
   - Utilize epidemiological models and latest Bayesian inference methods to obtain

➢ Better estimates of underlying genetic effects

➢ More effective selection

Acknowledgements

Roslin Colleagues

- Doeschl-Wilson group
  - O. Anacleto, G. Lough, S. Tsairidou
- S.Bishop, J. Woolliams,
- R. Houston, A. Archibald

External

- M. Saura, B. Villanueva, M. Carabano, A. Garcia-Cortes (INIA, Spain)
- S. Cabaleiro (Cetga, Spain)
- P. Bijma, H. Mulder (WUR)

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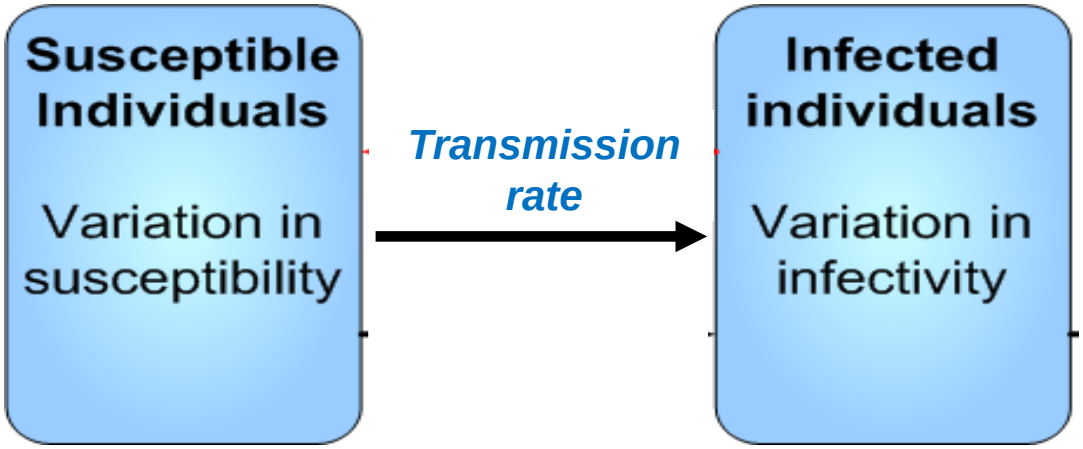
Genus

Cobb

Validation with simulated data



Stochastic epidemiological SI model

2000 half-sibs (100 sires x 20 dams)

- Distributed randomly into closed groups of equal size
- No between group transmission
- Each epidemic starts with1 (randomly) infected individual
- Individual infection status recorded at regular sampling times

Estimating genetic susceptibility & infectivity for natural disease outbreaks

Dynamic non-linear Indirect Genetics Effects method (DnIGE)

What data does it require?

- Repeated measures of binary infection status (infected / not infected) of individuals during a disease outbreak
- From related individuals spread across different outbreak herds