Can we select for both resistance and tolerance of pigs to PRRS?

Graham Lough

H. Rashidi, I. Kyriazakis, J.C.M. Dekkers, N. Deeb, A. Kause, A. Hess, J. Lunney, R.R. Rowland, P.K. Mathur, H. Mulder, A.B. Doeschl-Wilson

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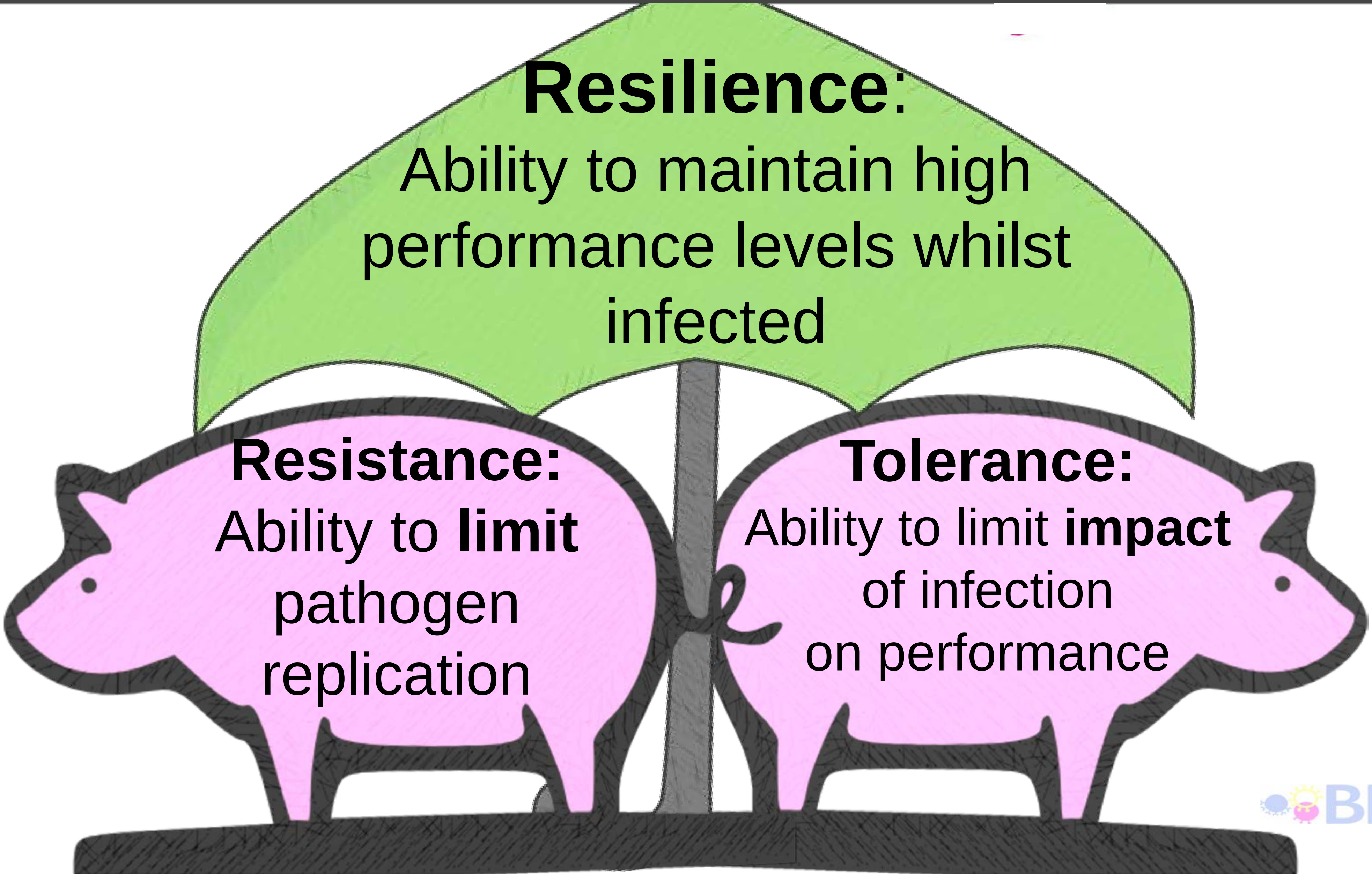
BBSRC bioscience for the future

Alternative strategies to combat infection



Resilience:
Ability to maintain high performance levels whilst infected

Resistance:
Ability to **limit** pathogen replication

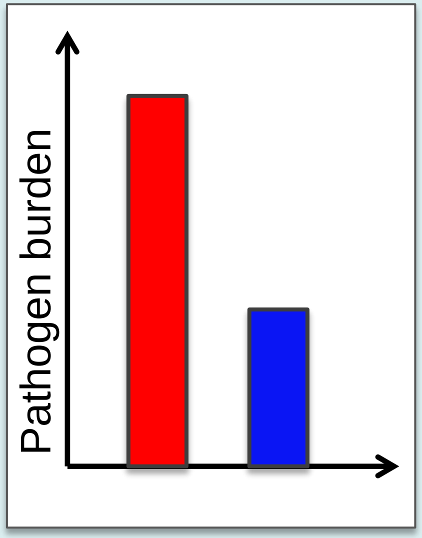
Tolerance:
Ability to limit **impact** of infection
on performance

Alternative strategies to combat infection

- **Improve host**

Resistance:

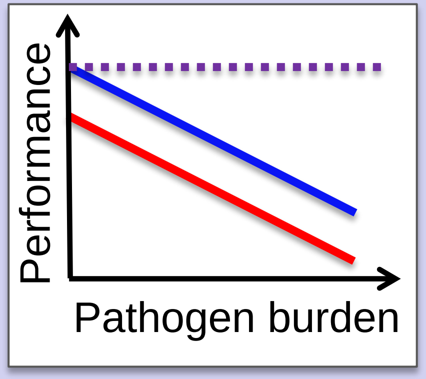
Inverse of pathogen burden



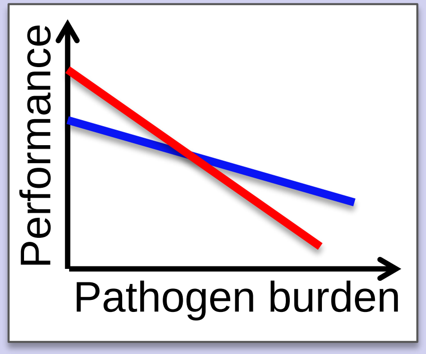
- **Improve host**

Tolerance:

Reaction Norm: change in host performance with change in pathogen burden (**slope**)



Same slope:
Equal



Tolerance can only be estimated at **group** level

Why distinguish between R & T?

Different epidemiological outcomes

- mitigation or eradication?
- e.g. when pathogen difficult to eradicate

Different evolutionary outcomes

- Tolerance may be less pathogen-specific:
- multiple pathogen protection
- may not drive pathogen co-evolution

Porcine reproductive and respiratory syndrome (PRRS)

- Endemic viral disease, causes dramatic losses to pig industry
- Affects **growth rate** and causes mortality of young pigs: variation in host response
- **Host genetic control**:
  - Ample evidence for **genetic variation in resistance** & **resilience** (growth): candidate gene identified
  - But no evidence for genetic variation in **tolerance**

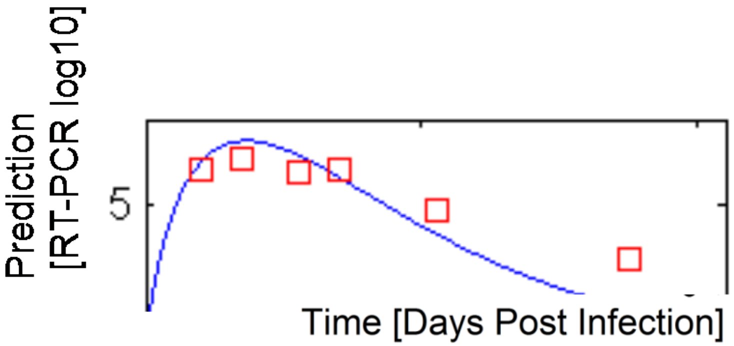
Aims

Is there evidence that pigs differ genetically in tolerance to PRRS?

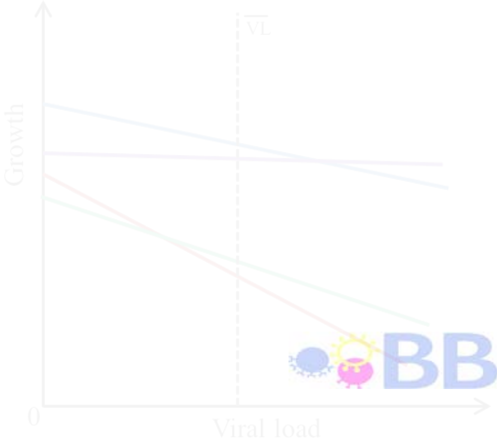
- Estimate **additive genetic variance in tolerance** using **random regression models**

PRRS Host Genetics Consortium Data

- 1320 growing pigs of known pedigree challenged with virulent strain of PRRSv over 9 trials
- Measures of body weight and viremia in blood for 0-6 weeks post-infection
  - **Resistance**: inverse of viral load (VL)
    - Used to identify candidate gene for resistance



  - **Tolerance**: Average Daily Gain (ADG) regressed on VL
    - **1 slope per sire**



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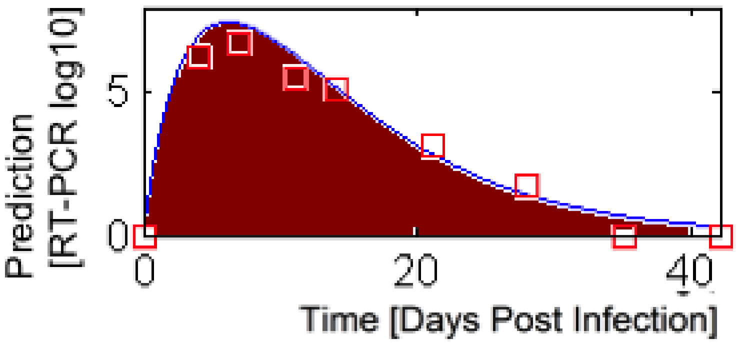

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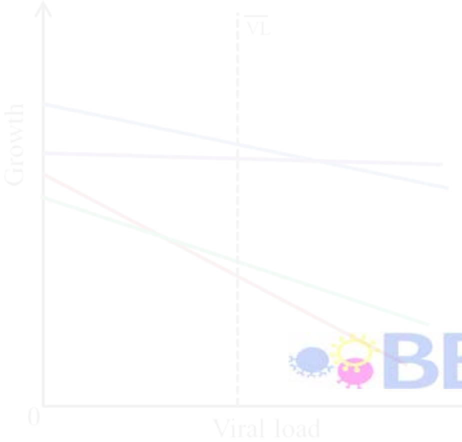

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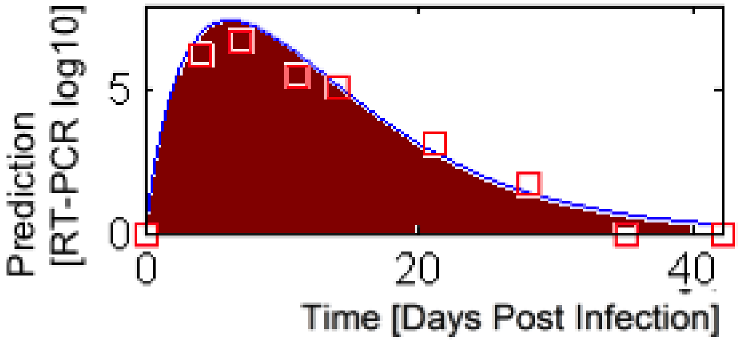
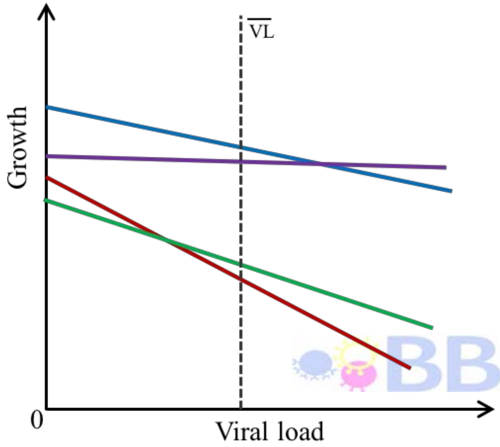
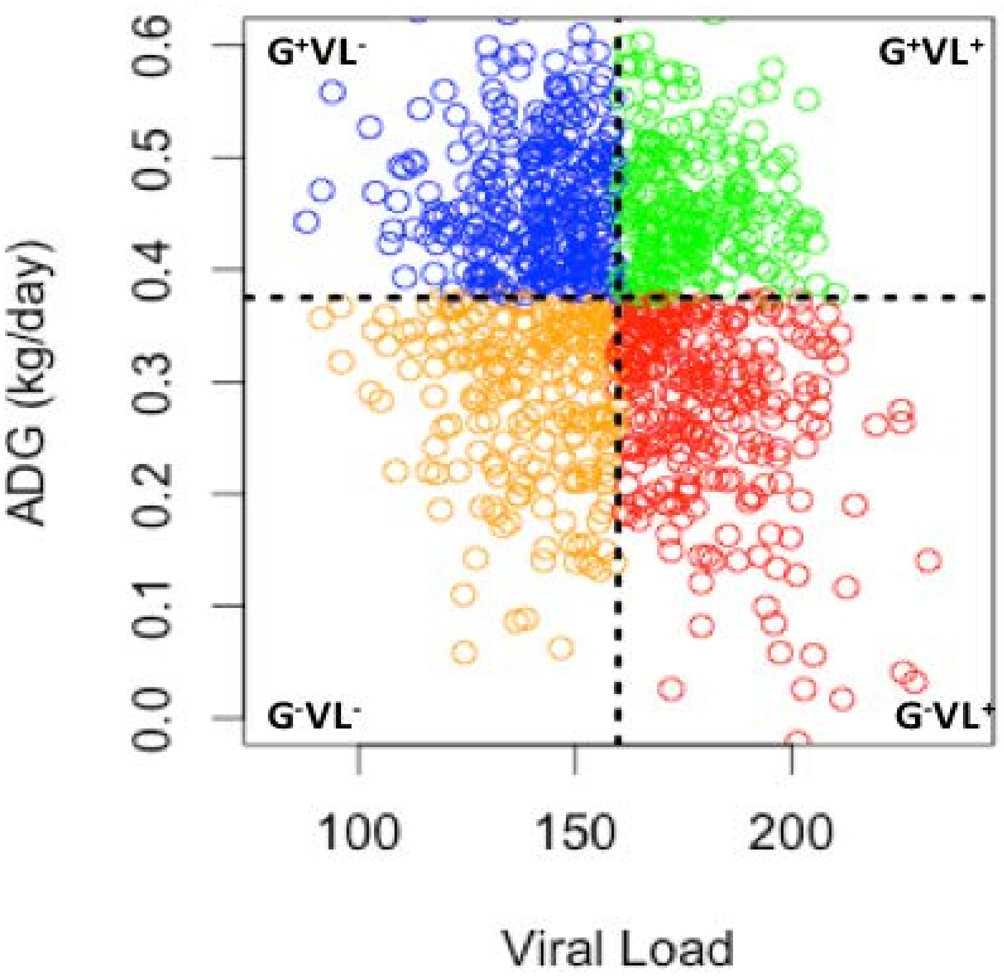
  - **Tolerance**: Growth (Average Daily Gain (ADG)) regressed on Viral Load
    - **1 slope per sire**





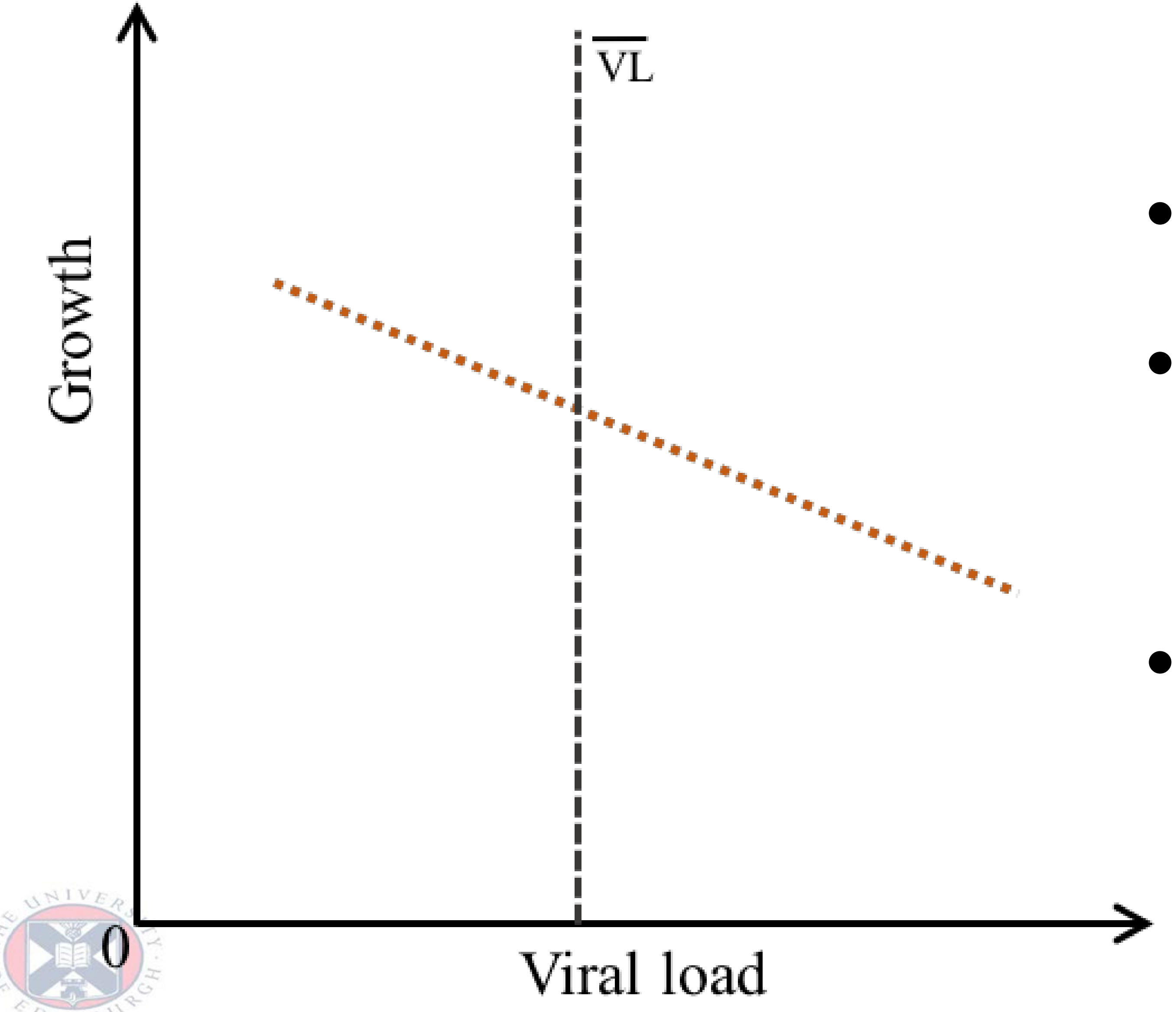
Evidence of phenotypic variation in tolerance



Tolerant pigs

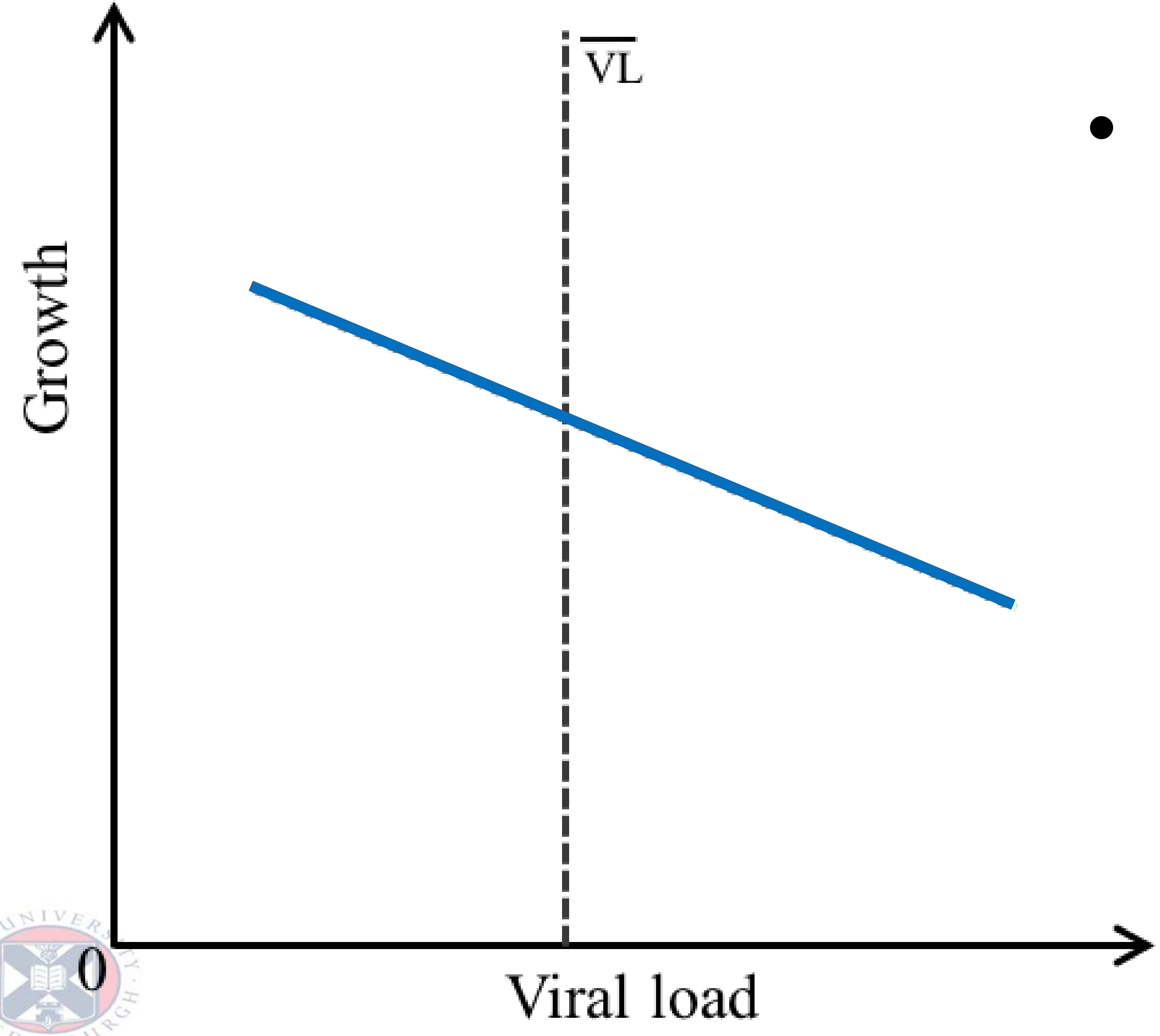
Non-Tolerant pigs

A) Null model



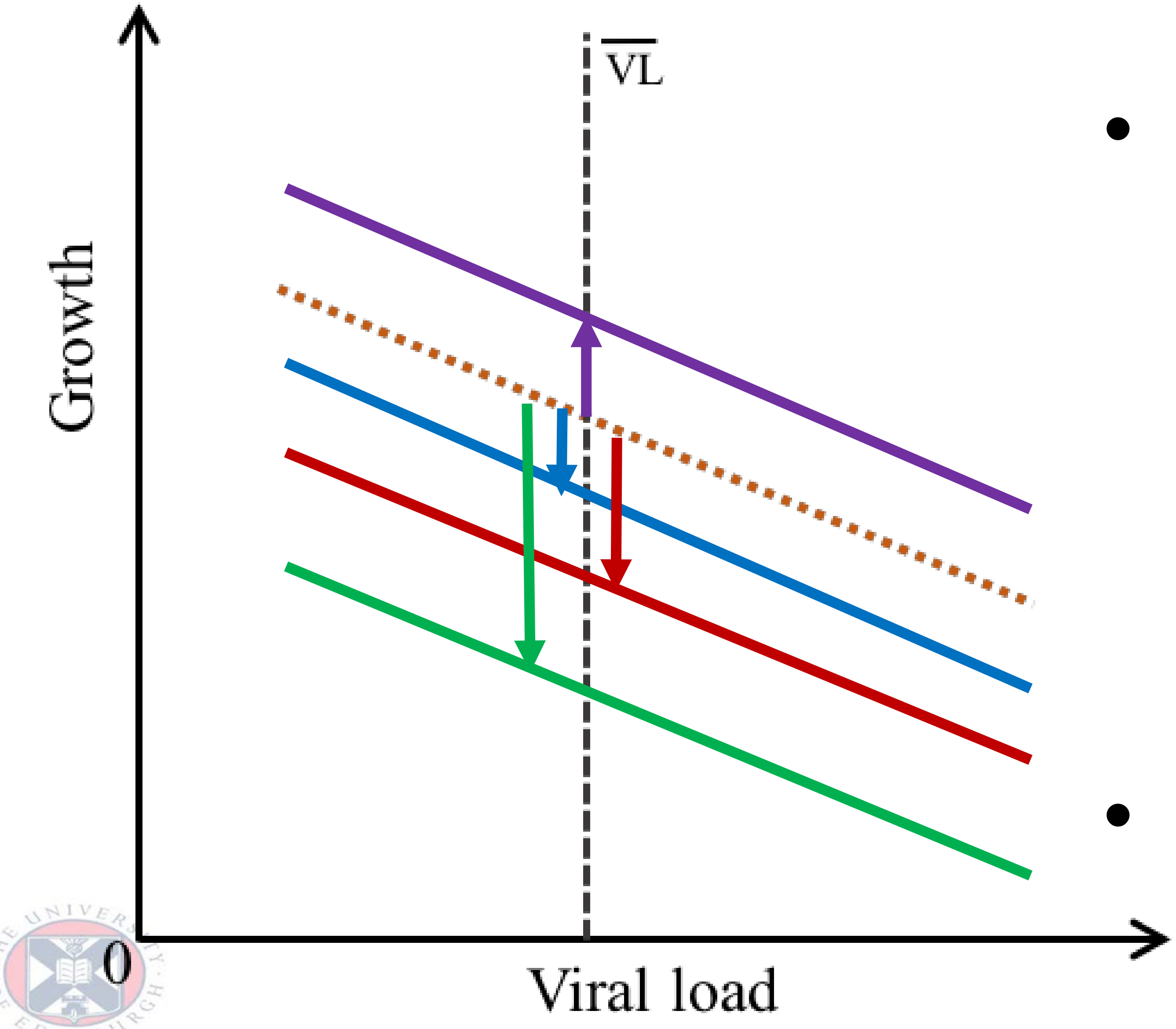
- 1 **average slope** fitted
- No genetic variation in resilience
- No genetic variation in tolerance

B) Resilience model



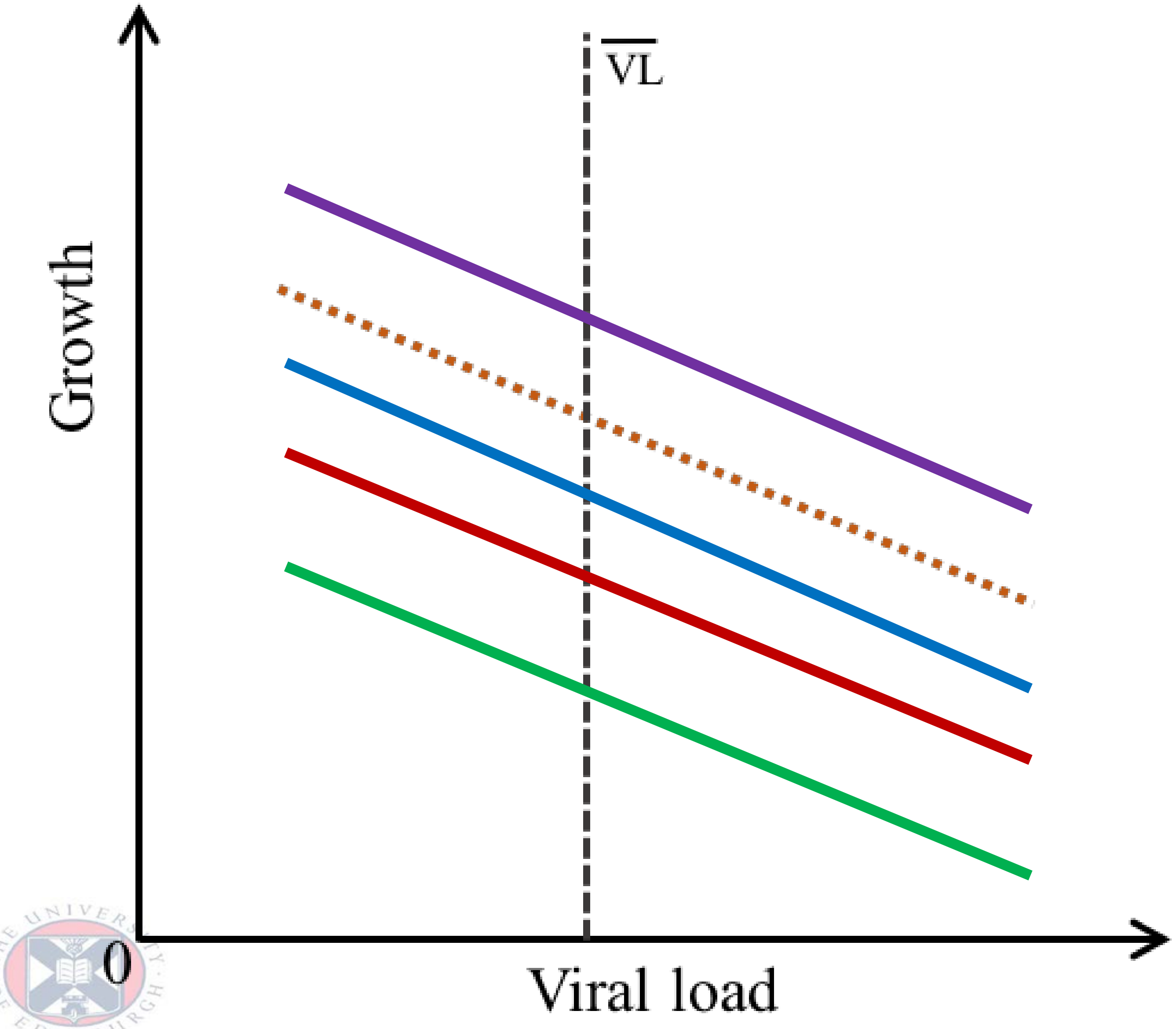
- **Genetic variation in resilience** (growth for a given Viral Load)

B) Resilience model



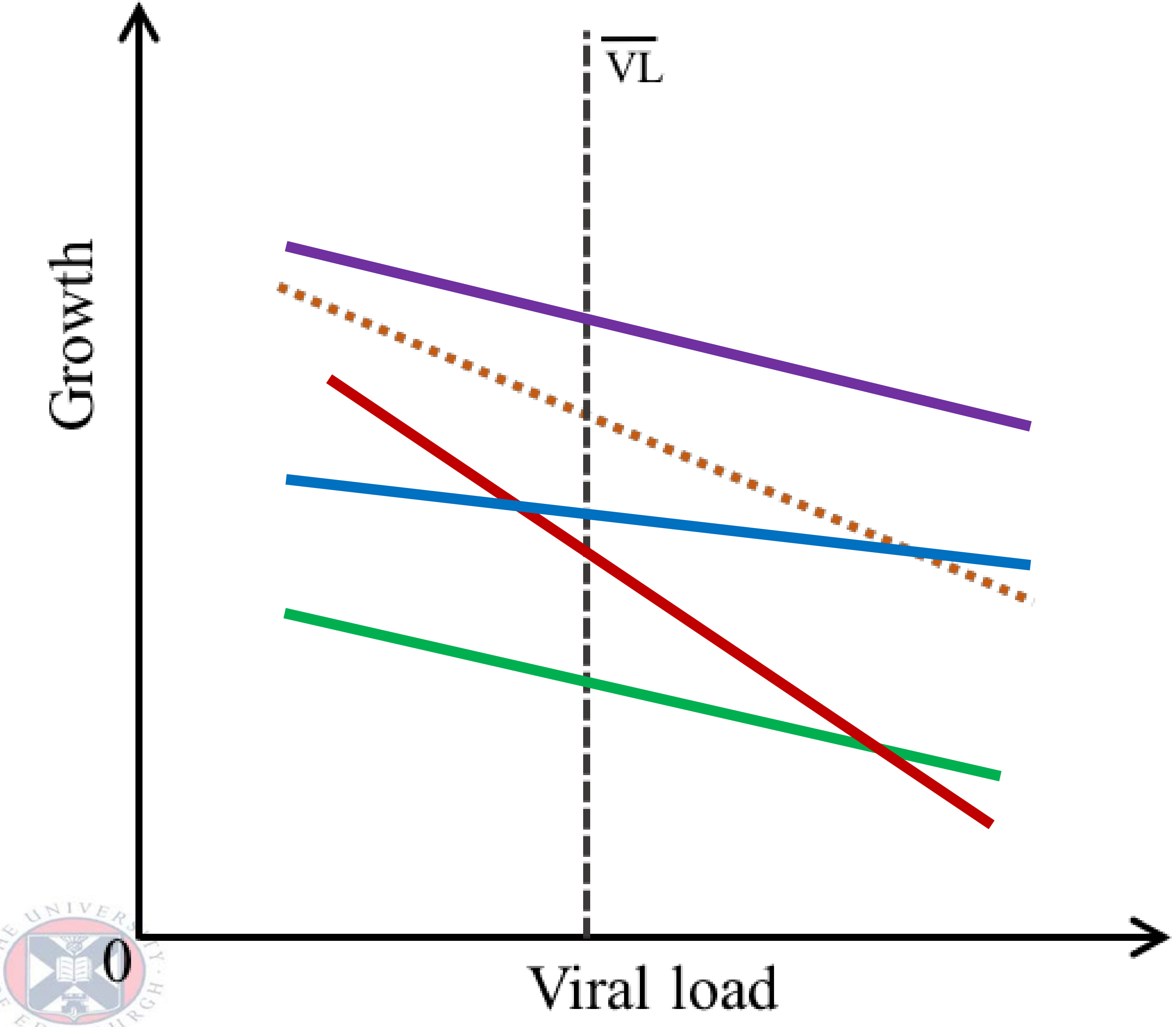
- **Genetic variation in resilience** (growth for a given Viral Load)
  - **Purple** sire most resilient
  - **Green** sire least resilient
- No genetic variation in tolerance (equal slope)

C) Tolerance model



- Genetic variation in **resilience** (growth)
- Also genetic variation in **tolerance slope**

C) Tolerance model



- Genetic variation in **resilience** (growth)
- Also genetic variation in **tolerance slope**

  - **Blue** sire most tolerant
  - **Red** sire least tolerant

A) Null model

$$\mathbf{y} = \mathbf{Xb} + \mathbf{Za_g} + \mathbf{Z_{VL}a_s} + \mathbf{Up} + \mathbf{Ml} + \mathbf{e}$$

$\mathbf{y}$ = Cumulative average daily gain (ADG)

$\mathbf{b}$ = fixed-effect coefficients (BW0, VL, sex, rebound, age, trial*parity)

$\mathbf{a_g}$ = additive genetic-effect coefficients for **resilience**

$\mathbf{a_s}$= additive genetic-effect coefficients for **slope**

$\mathbf{p}$ & $\mathbf{l}$= additional random (pen & litter effects)

$\mathbf{e}$ = error term

$$\mathrm{Var}\begin{bmatrix}\mathbf{a_I}\\ \mathbf{a_s}\end{bmatrix} = \frac{1}{4}\mathbf{G_{RN}} \otimes \mathbf{A}, \quad \begin{bmatrix}\sigma^2_{a_I} & \sigma_{a_I a_s}\\ \sigma_{a_I a_s} & \sigma^2_{a_s}\end{bmatrix}$$

B) Resilience model

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$$\mathrm{Var}\begin{bmatrix}\mathbf{a_l}\\ \mathbf{a_s}\end{bmatrix} = \frac{1}{4}\mathbf{G_{RN}} \otimes \mathbf{A}, \quad \mathbf{G_{RN}} = \begin{bmatrix}\sigma^2_{a_l} & \sigma_{a_l a_s}\\ \sigma_{a_l a_s} & \sigma^2_{a_s}\end{bmatrix}$$

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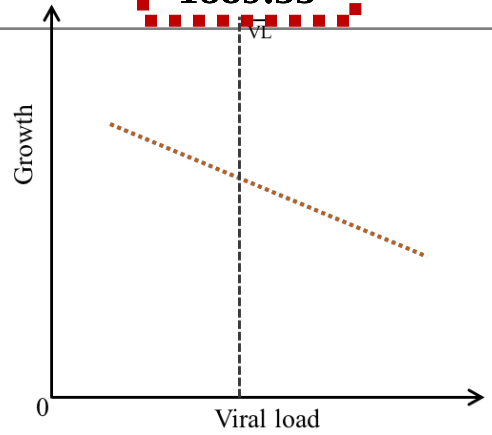
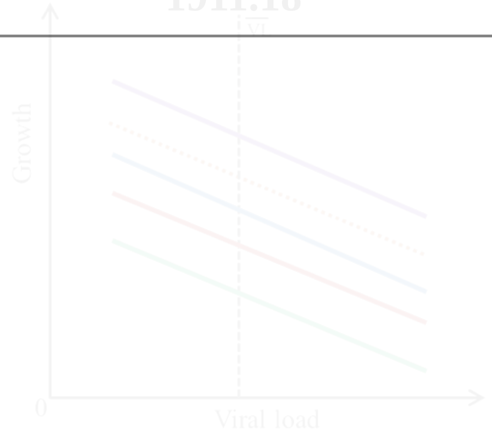
Model results

	Null model	**Resilience model**	**Tolerance model**
	Estimate (SE)	Estimate (SE)	Estimate (SE)
Level	.	**2.32E-03 (1.02E-03)**	**2.33E-03 (1.03E-03)**
Covariance	.	.	**-3.95E-15 (2.04E-16)**
Slope	.	.	**3.41E-07 (5.94E-07)**
Residual	5.39E-03 (3.03E-04)	5.33E-03 (2.99E-04)	5.30E-03 (3.02E-04)
LogLikelihood	**1889.55**	**1911.18**	**1911.35**





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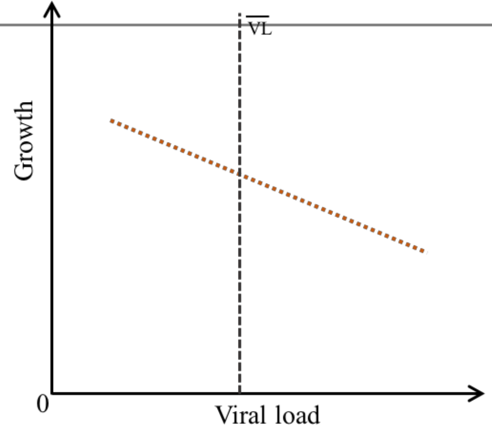

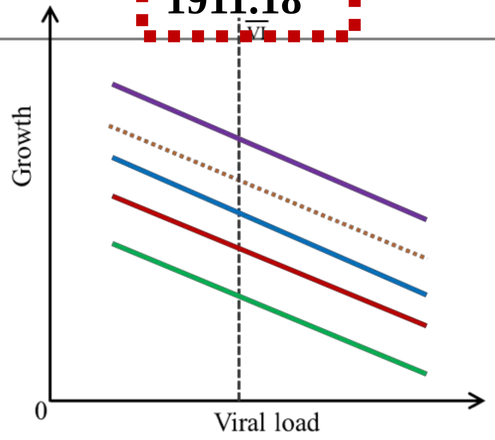

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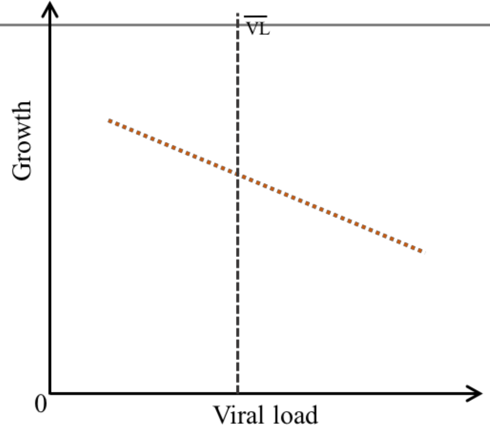

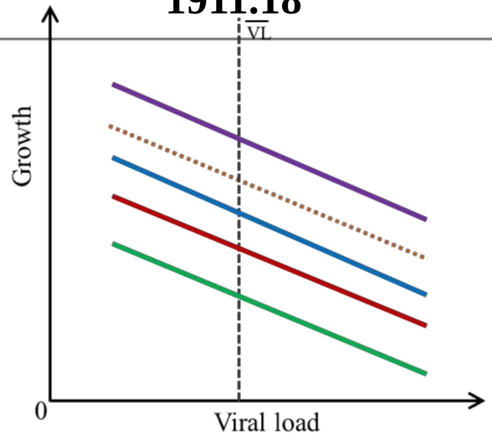

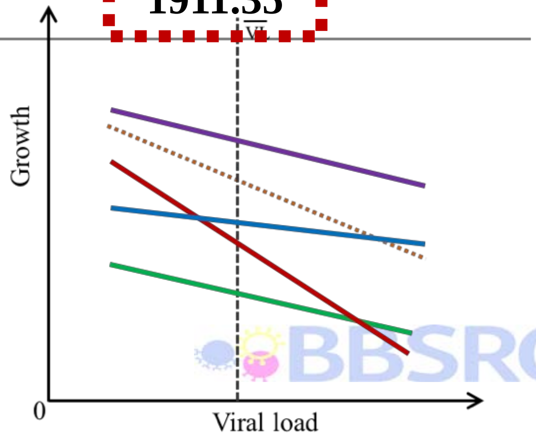

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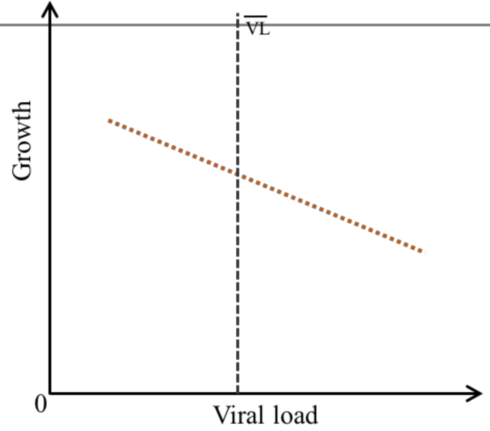
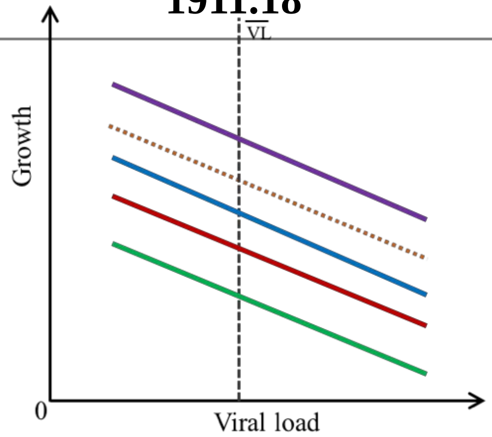
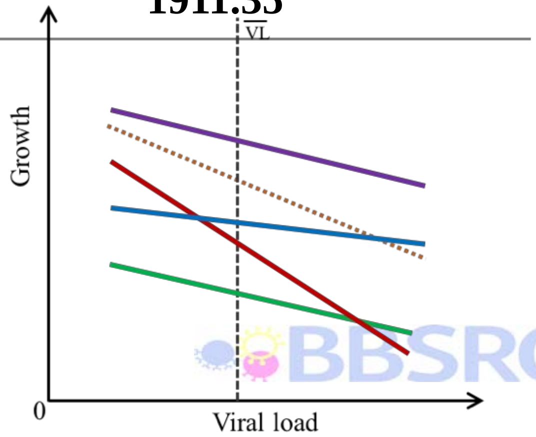
No statistical evidence for genetic variation in tolerance



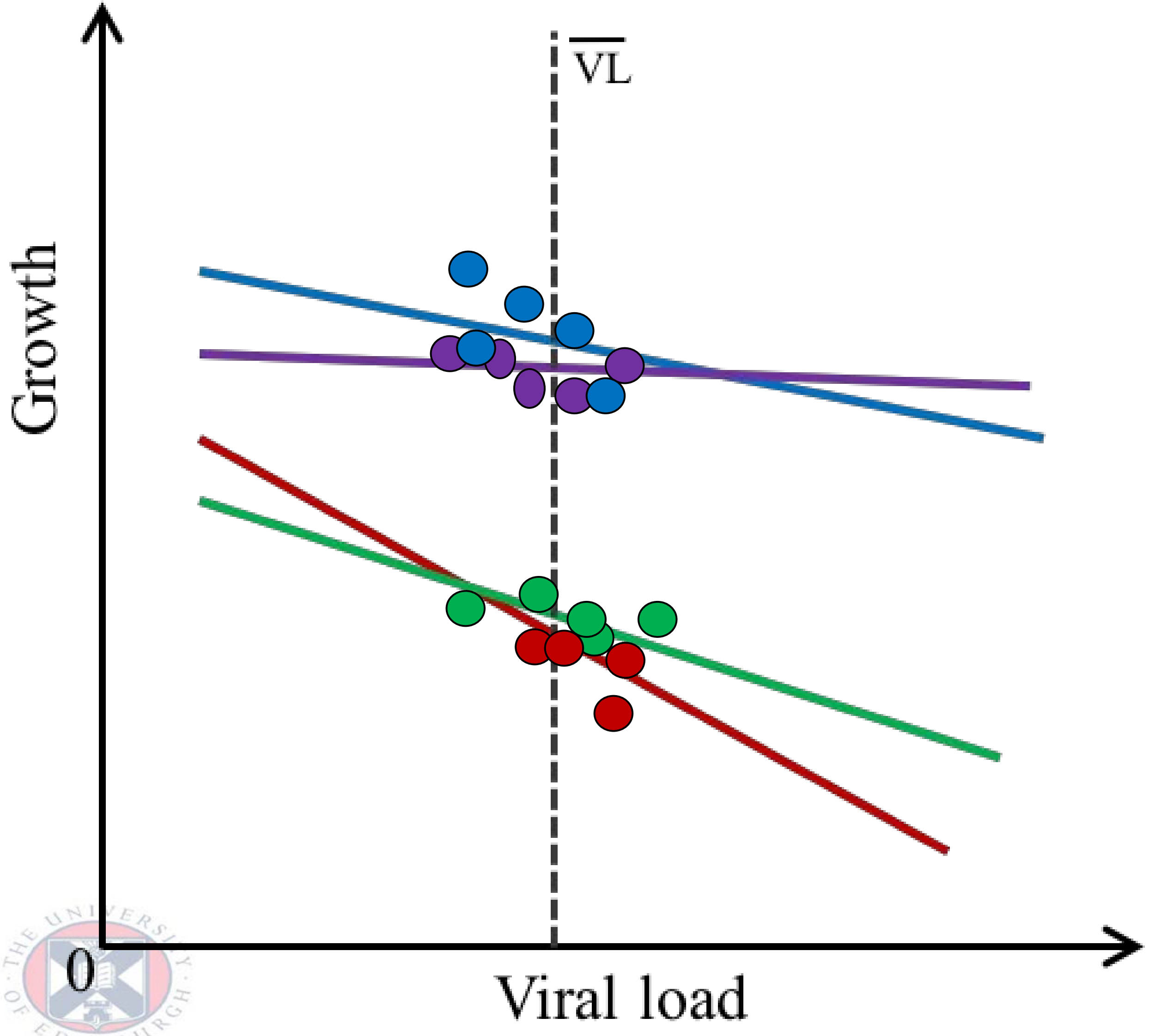




No genetic variation in tolerance?

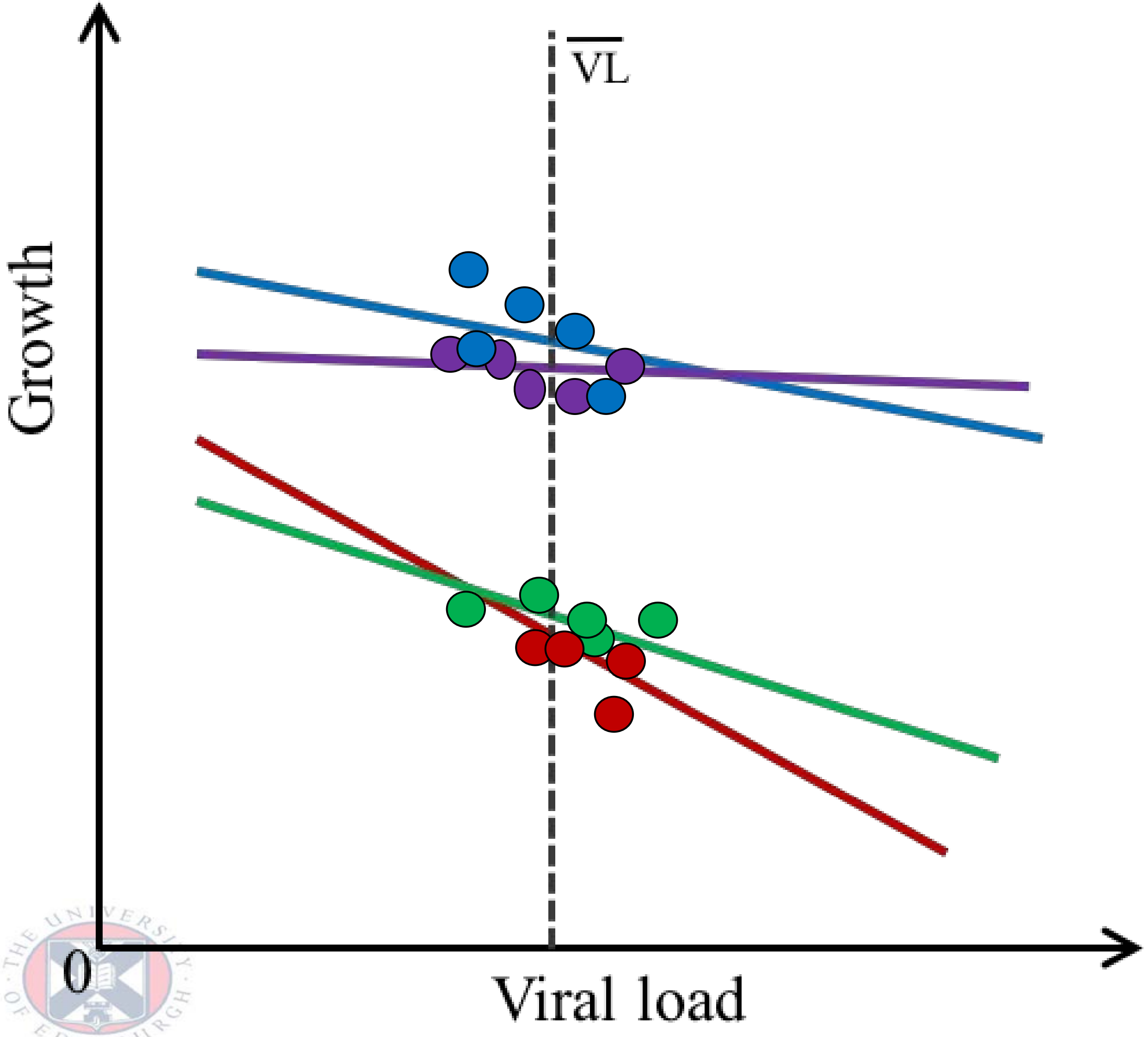
- Is genetic variance too **small** to detect?
- Is there potential **confounding** problem?
- Previous simulation studies show unbiased slope estimate only if **growth in absence of infection** is known
  - Sib-challenge tests

Simulating growth for uninfected individuals



- Data around average VL
- Growth in absence of infection unknown
- Simulate for **paternal half-sibs** for **non-infected** individuals

Simulating growth for uninfected individuals



- Based on **genetic correlation** with growth under infection
- **No assumptions** made about tolerance

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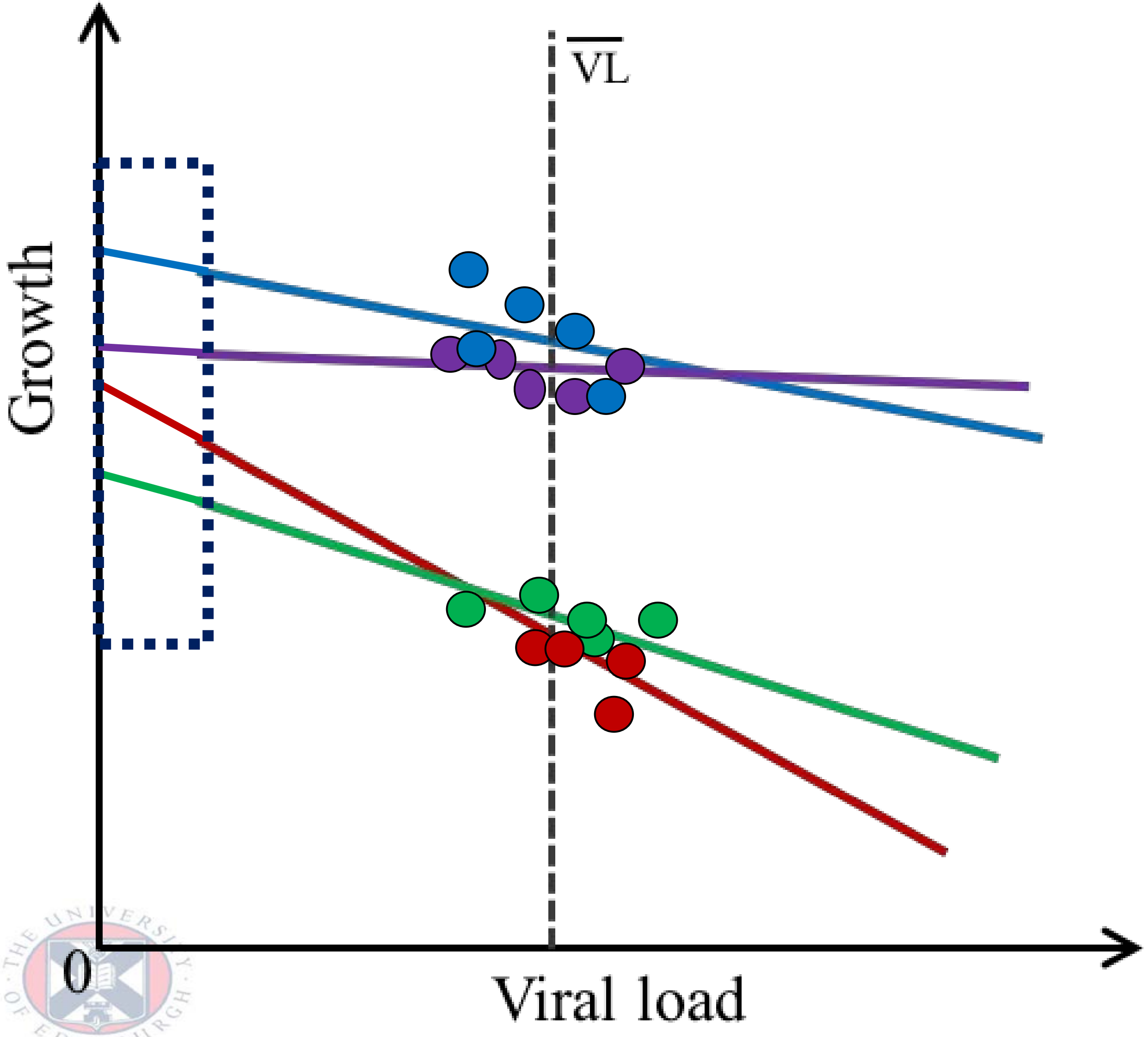

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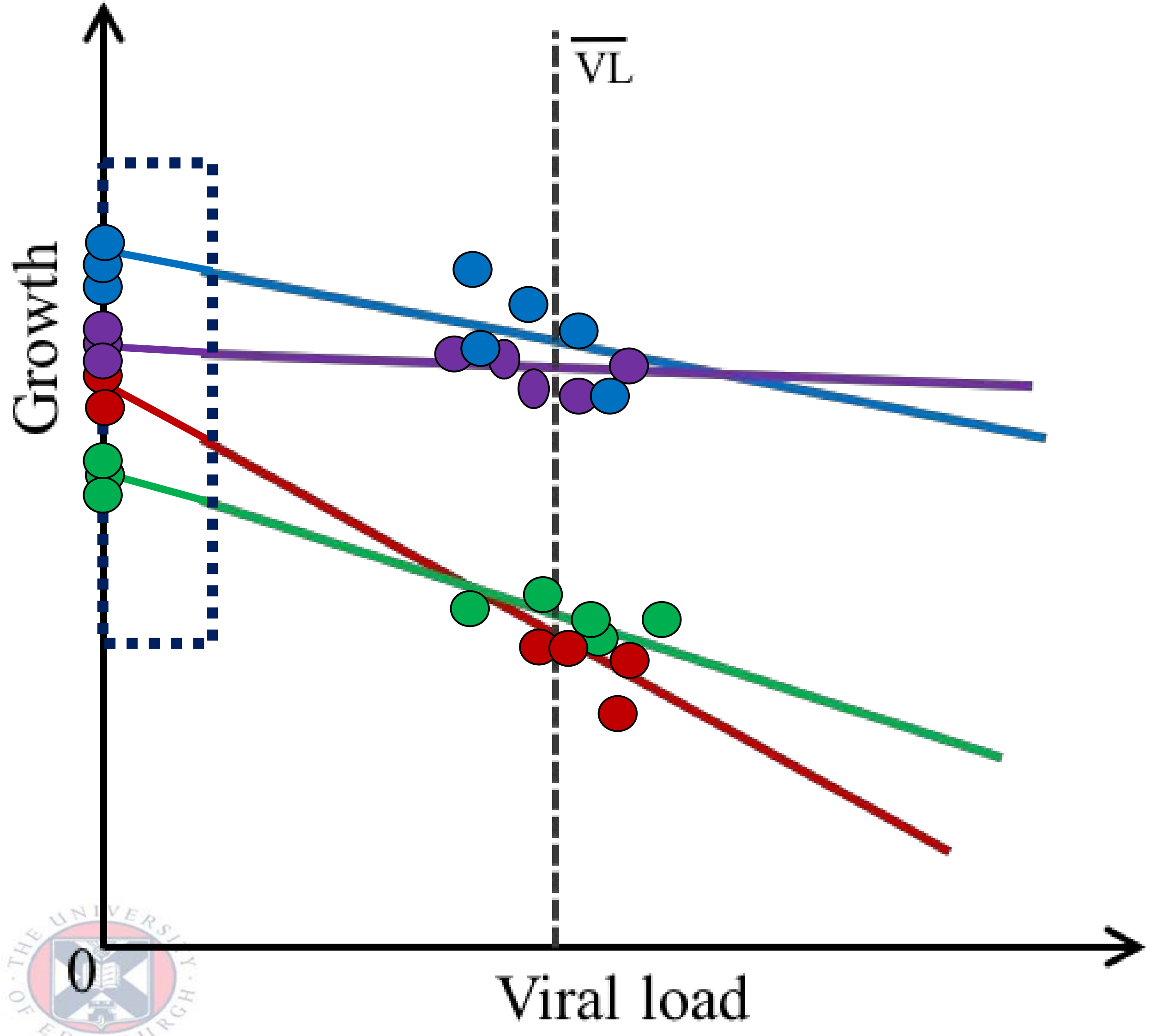
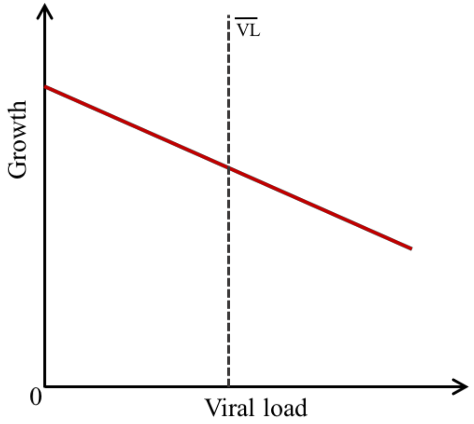
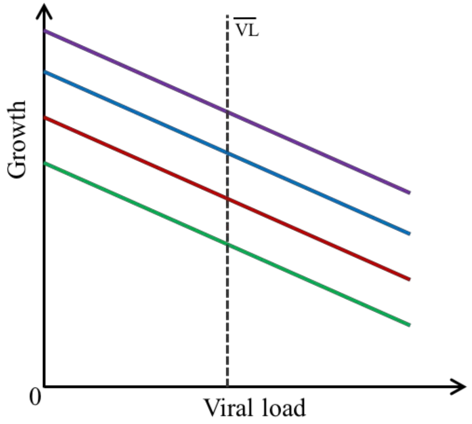


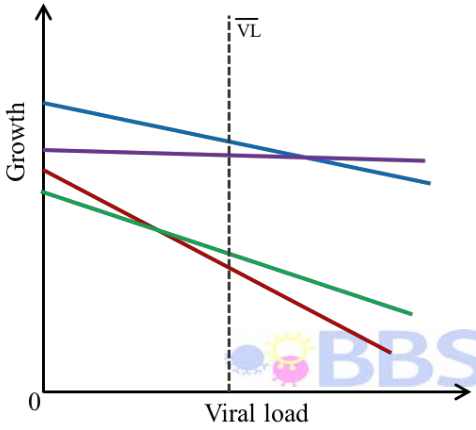
- Use **same model**, but estimate true intercept i.e. when VL=0

Results

	Null model	**Resilience model**	**Tolerance model**
	Estimate (SE)	Estimate (SE)	Estimate (SE)
Intercept	.	8.30E-03(3.19E-04)	1.00E-01(2.33E-02)
Covariance	.	.	-6.14E-04 (1.37E-04)
Slope	.	.	4.09E-06 (8.31E-07)
Residual1	2.62E+00 (4.84E-01)	2.52E+00 (4.84E-01)	2.60E+00 (4.84E-01)
Residual2	7.38E-03 (0.00E-00)	7.39E-03 (4.72E-06)	7.06E-03 (3.43E-05)
LogLikelihood	**480.63** (123.00)	**504.54** (123.00)	**515.08** (123.11)







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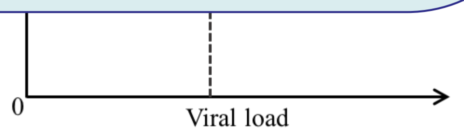
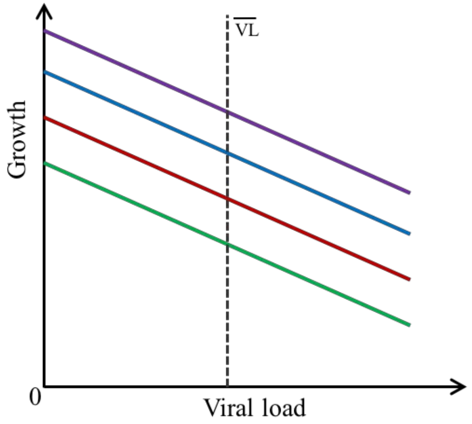
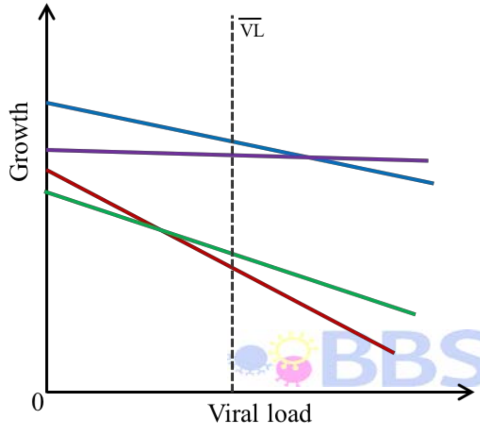
		7.39E-03 (4.72E-06)	7.06E-03 (3.43E-05)
		504.54 (123.00)	**515.08** (123.11)

1) Additional data give additional statistical power to disentangle
2) Under assumptions made, could detect genetic variation in tolerance







Conclusions

- **Little statistical evidence for significant genetic variation of pigs in tolerance to PRRS, based on the data alone**
  - Potentially due to statistical limitations
- **Augmenting data with simulated growth data of non-infected relatives overcomes statistical limitations**
  - Simulations suggest that there may be significant genetic variation in tolerance of pigs to PRRS
  - Need to confirm with real data
- **Genetic variance in tolerance is much harder to detect than for resistance and resilience**

Acknowledgements

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Han Mulder
Hamed Rashidi

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Cheers!