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Inferring genetic resilience of animals to infectious pathogens – opportunities and pitfalls

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Abstract

Farm animals suffer constant bombardment with cocktails of infectious pathogens present in the environment. Eliminating these pathogens from farms is not always feasible. Therefore, improving the resilience of animals, i.e. their ability to maintain high production levels whilst infected, may constitute a desirable defence strategy. Despite compelling evidence for genetic variation in host resilience for some types of infections, genetic studies of this trait face a number of theoretical and practical issues. The aim of this article is to bring these issues to light and to propose potential approaches that may help to overcome these in future research. In particular, we demonstrate how alternative definitions of resilience give rise to different statistical methods and data requirements, and may produce different outcomes of selection. We examine the relationship between resilience, resistance and tolerance and the necessary data requirements for disentangling these traits. Using a recent large scale infection experiment in controlled environmental settings as a case study, we illustrate why resilience is not synonymous to tolerance, as often suggested. We address potential pitfalls and solutions for situations when pathogen challenge cannot be specified, or varies over time, and conclude with some practical considerations for inferring resilience genetics from field data.

Introduction

Infectious disease constitutes a major threat to livestock production worldwide. In addition to the direct impact on animal health and welfare, it has a massive economic impact with estimated costs of 20% of turnover in developed countries and up to 50% of turnover within the livestock sector in developing countries (Bennet and IJpelaar, 2005). Given the ubiquitous, manifold and persistent nature of pathogens, direct elimination of the pathogens from farms is not always possible. Improving the resilience of domestic livestock, i.e. the ability of animals to maintain production at a given level of infection (Hermesch, 2014 this publication), would therefore constitute a highly desirable breeding goal to ensure sustainable livestock production. However, in practice, breeding for resilience faces a number of issues concerning the inference of accurate, unbiased parameter estimates for this trait that arise from ambiguous definitions

and lack of appropriate data and statistical tools. The aim of this paper is to highlight some of these issues and to propose avenues for future progress.

Alternative definitions of resilience and associated data requirements

Estimating genetic parameters for genetic selection requires precise and quantifiable trait definitions that lead to reliable phenotypes. As pointed out by Bisset and Morris (1996), the common definition of resilience as 'the ability of animals to maintain relatively undiminished performance levels whilst subjected to pathogen challenge' lends itself to a number of interpretations associated with different resilience phenotypes. For example, resilience may be defined as the relative performance of an individual compared to that of peers in relation to a standard pathogen challenge assumed to be equal to all peers (Bisset and Morris, 1996). This interpretation has the practical advantage that it only requires one performance measurement per animal and does not require a measure of pathogen challenge, and it can easily be analysed with standard linear mixed models. However, this interpretation suffers from confounding between the ability to withstand the impact of infection and the performance potential in the absence of infection. Thus, an animal with a relatively high performance level compared to its peers could be classified as resilient, even if its performance has dropped by several factors of magnitude as a cause of infection. Comparing performance levels between peers at a particular pathogen challenge is not informative about the relative ability of animals to cope with pathogens. Selection according to this first definition of resilience may thus lead to poor ranking and thus inferior performance in improved environmental conditions.

To avoid confounding between performance potential and ability to cope with infections, resilience needs to be assessed in terms of depression in performance of an individual or a group (e.g. sire family) associated with a change in pathogen challenge (Bisset and Morris, 1996). This definition requires individual performance measures in at least two different pathogenic environments (e.g. low and high pathogen challenge). Although establishment of genetic variation in resilience according to this definition does not necessarily require measures of pathogen challenge per se, it is important to note that comparison between animals is only possible if all animals are assumed to be exposed to the same levels of pathogen challenge. The stringency of this assumption is often overlooked in practice. For example, the assumption does not hold if exposure varies over time and infection duration varies between individuals, which is often the case in natural farming conditions (see section below). However, if equal pathogen challenge can be assumed, traditional models for the analysis of GxE interactions, such as the interaction term or multi-trait models (Strandberg, 2006) can be used to assess whether differences in resilience give rise to re-ranking of animals in different pathogenic environments. If pathogen challenge can be considered as a quantifiable, continuous variable, reaction norm models (Lynch and Walsh, 1998) can quantify the responses to changes in pathogen challenge in greater detail. In particular, when implemented as random regression models, reaction norms provide estimates for genetic variance in resilience as well as breeding values (Strandberg, 2006).

Resilience conflates resistance and tolerance

Both of the above resilience definitions build upon the assumption that animals are exposed to a given (equal) environmental pathogen challenge that causes potential loss in performance. However, it could be argued that depression in performance is caused by the within host pathogen burden rather than by the environmental pathogen challenge. These are two different quantities, with the former depending on the host ability to inibit or reduce pathogen establishment or replication, i.e. its *resistance* to infectious pathogens (Råberg *et al.,* 2007). The ability to maintain performance by counteracting the damage that established replicating pathogens can inflict, is defined as *tolerance* (Råberg *et al*., 2007; Doeschl-Wilson *et al*., 2012b). More precisely, resistance is typically described as an inverse measure of within host pathogen burden (Råberg *et al*., 2007), whilst tolerance is described in terms of change of host performance as a result of change in within host pathogen burden (Simms, 2000). Resilience and tolerance are both concerned with the impact of infection on performance, but resilience conflates resistance and tolerance. As illustrated in Figure 1, an animal can be resilient because of either high resistance or high tolerance. Decomposing resilience into its two distinct components can be crucial for developing effective long-term selection strategies in case of a trade-off between resistance and tolerance, which may handicap genetic gain in resilience (Read *et al*., 2008).

Distinguishing between resistance and tolerance is also important for epidemiological reasons, as each trait has a different effect on the epidemiology of infectious diseases and host-pathogen co-evolution (Råberg *et al*., 2007). Furthermore, resistance and tolerance are likely to relate to different immunological processes and pathways, which must be considered for identifying novel genetic loci (Medszhitov *et al*., 2012). Similar to resilience, tolerance is usually assessed as the slope of reaction norms (Simms, 2000; Kause, 2011). However, estimation of tolerance requires actual measures of within-host pathogen burden of individuals, rather than measures of environmental pathogen challenge (Doeschl-Wilson *et al*., 2012b). Within-host pathogen burden, in turn, is also a useful measure to infer resistance (Kause, 2011). We refer to the special issue "Should we aim for genetic improvement in host resistance or tolerance to infectious pathogens" (Doeschl-Wilson and Kyriazakis, 2012) for a more detailed investigation of resistance and tolerance.

Accounting for dynamic aspects of infectious disease

As mentioned above, an intrinsic assumption in the above definitions of resilience is that both pathogen challenge and performance are considered as constants during the observation period. However, in field conditions where the pathogen spreads through the population, pathogen challenge is likely to change over time. As more and more individuals become infected, environmental pathogen load is expected to increase. Thus individuals that are infected at the early stage of an epidemic are likely to experience lower pathogen challenge than individuals at later stages. Bishop and Woolliams (2010) have shown that differences in exposure to pathogen load can produce a severe bias in the genetic parameter estimates of disease traits. In particular, in cases where only a fraction of individuals has been exposed to infectious pathogens a

substantial downward-bias in the heritability of disease resistance (based on binary measures of infection status and an underlying threshold model) is expected. They also proposed a formula for adjusting the estimates with regards to incomplete exposure, but this formula refers to static rather than dynamic conditions (i.e. it is assumed that the proportion of non-exposed susceptible individuals is constant over time). Clearly more research is needed to incorporate epidemiological principles of infection dynamics into genetic models of epidemiological data.

In the meantime, the complications arising from dynamic exposure may be avoided by focusing on infections with a relatively constant level of prevalence over the period of interest. An example for such an infection type is gastro-intestinal parasitism in ruminants, which may reach a prevalence of close to 100%. Readily available faecal egg count (FEC) measures not only provide a quantitative estimate of pathogen challenge for reaction-norm approaches, but also allow dissecting resilience into resistance and tolerance (Bishop, 2012). Thus, they constitute an ideal candidate for resilience studies, and it is therefore not surprising that the majority of resilience studies for domestic livestock to date are associated with this disease (e.g. Albers *et al*., 1987; Bisset and Morris, 1996; Jackson and Miller, 2006).

Dynamic exposure also does not occur in challenge experiments in which all individuals get infected with the same challenge dose at the same time. An example for such an experiment is presented below. However, large scale infection models that produce sufficient phenotypes for quantitative genetic analyses are extremely costly and thus not always feasible. Furthermore, results arising from these studies still require validation in the field, where dynamic exposure will eventually need to be accounted for.

Finally, it should be noted that dynamic aspects not only affect environmental pathogen challenge, but also the relationship between host and pathogen. For many infections – in particular infections by micro-parasites - both the within-host pathogen burden and the impact of infection on performance can vary considerably over the time course of infection (Schneider and Ayres, 2008; Doeschl-Wilson *et al*., 2012b). Measurements taken of an individual at different stages of infection may therefore give rise to different resistance, tolerance and resilience estimates. This is likely to be exacerbated in field conditions when individual infection times are not known and are therefore difficult to account for. The bias due to time of sampling can be minimised by taking repeated measurements of host performance (and ideally also of within-host pathogen burden for estimating resistance and tolerance) over a sufficiently long time period to capture the full impact of infection on performance. Repeated measurements may be combined into meaningful summary measures capturing the full impact of infection over the period of interest (e.g. cumulative or peak levels of pathogen burden and performance) for the conventional statistical models described above. Alternatively, detailed insight about the interaction of host resistance and tolerance over time and the genetic footprint on these interactions may be obtained by analysing trajectories based on longitudinal measures of within-host pathogen burden and performance (Doeschl-Wilson *et al*., 2012a; Doeschl-Wilson, 2014, Lough *et al*., 2014).

Lessons from a recent disease challenge experiment with detailed disease phenotypes

The porcine reproductive and respiratory syndrome virus (PRRSV) causes infections in pigs that lead to reproductive failure in breeding females and growth reduction and mortality in growing piglets. It constitutes one of the biggest health problems and economic challenges to the global pig industry, and conventional methods to control this devastating disease have so far shown limited success (Zimmerman *et al*., 2007). There is plenty of evidence that pigs vary genetically in their response to PRRSV, but estimates of genetic parameters vary substantially between studies (Lunney and Chen, 2010). Infectious challenge experiments in which individuals are subjected to the same pathogen challenge not only eliminate the bias from dynamic exposure, but also many other uncontrollable variations inherent in field studies that may be difficult to account for. For this reason the PRRS Host Genetics Consortium (PHGC) set up a large scale challenge experiment with the aim to establish the genetic basis of host response to PRRSV infections (Rowland *et al*., 2012). The study consisted of a number of trials (currently 16), in which approximately 200 commercial cross-bred piglets per trial between 3-4 weeks of age were orally infected with PRRSV. Besides a well-defined pathogen challenge, the PHGC experiments have the additional benefit that they provide repeated measurements of within-host pathogen burden and performance, thus facilitating genetic analyses of host resilience, resistance and tolerance. In particular, repeated measures of viral load in blood (twice a week) and weekly body weights were recorded for a period of 42 days as measures of within-host pathogen burden and growth performance, respectively. For all pigs in this study pedigree information was available and pigs were genotyped with the Illumina Porcine 60K Beadchip for genome wide association studies.

The experiments revealed a large variation in (log transformed) virus load and body weight profiles over the 42 day infection period (Boddicker *et al.*, 2012). Using cumulative virus load (VL, calculated as the area under the curve of the log-transformed virus load profiles) as a measure of resistance, Boddicker *et al*. (2013) reported a relatively high heritability of 39% based on data from the first five trials, and similar heritability estimates for net weight gain (WG). Estimated genetic correlations between VL and WG were favourable (approximately -0.3). Moreover, a QTL was identified on chromosome four that influenced both VL and WG, with corresponding estimated genomic breeding values for this 1–Mb region being favourably and almost perfectly correlated (Boddicker *et al*., 2012, 2013). Together these results suggest that marker assisted selection for host resistance to PRRSV may be feasible to reduce both infection severity and impact of PRRSV in individual hosts and thus in pig populations. Current efforts concentrate on validating these markers in field conditions for different PRRSV strains.

What does this study tell us about genetic variation in resilience of growing pigs to PRRSV? Does the favourable genetic correlation between VL and WG imply that the genetically most resistant pigs are also likely the most resilient to the infection? And what about tolerance – is there genetic variation in tolerance too? Note that a negative correlation between VL and WG implies that pigs with relatively high resistance (low VL) tend to grow faster compared to pigs

with low resistance. However, as outlined above, resilience is more accurately described by the reduction in individual weight gain due to infection relative to the weight gain that the individual would have achieved in the absence of infection. Thus, the actual measure of resilience would require knowledge how the pig would have grown if it hadn't been infected. This is, of course, infeasible, and assumptions based on growth rates or body weights of non-infected siblings or of the challenged individuals prior to infection would therefore need to be made. Similar considerations hold when inferring tolerance from the data. At first glance, one may infer that pigs experience both high VL and high WG are the most tolerant to infection, as they manage to gain weight despite high virus load. However, similar to resilience, the true measure of tolerance would require knowledge of weight gain relative to the expected gain without pathogen challenge.

Unfortunately, measures of weight gain of siblings or challenged individuals prior to infections were not available in this study. Instead, body weights at the start of infection (BW0) may be used as (crude) indicators for growth in the absence of infection and fitted as covariates into statistical models for WG to infer genetic variation in resilience and tolerance. Using data from the first eight trials and the same single-trait animal model for WG as outlined in Boddicker *et al*. (2012 & 2013) with sex and trial by parity interaction as fixed effects and pen within trial, animal and litter as random effects, but including BW0 as additional covariate, resulted in genetic variance estimates for resilience (here defined as genetic variance in weight gain adjusted for BW0, in accordance with concepts illustrated in Figure 1) significantly different from zero (Table 1), and a heritability estimate for resilience of 0.31 (std. error 0.06). To infer genetic variation in tolerance, the following mixed sire model was fitted to records from sires with ten or more offspring:

$$WG = mean + Sex + Trial \times Parity + Pen\ (Trial) + \beta_0 BW0 + \beta_1 VL + b_{0,Sire} + b_{1,Sire}\ VL + residual$$

where sex and trial-by-parity interaction are the fixed effects, pen within trial is a random effect, BW0 and VL were fitted as covariates to account for differences in WG prior to infection (in this case corresponding to VL= 0) and mean tolerance slope, respectively, and $b_{0,Sire}$ and $b_{1,Sire}$ refers to the random effect of sire on WG and tolerance slope, respectively. Genetic variance in tolerance was estimated as four times the variance of $b_{1,Sire.}$ As this model does not produce a residual variance for tolerance, a heritability estimate for tolerance could not be inferred.

The above reaction-norm model for tolerance provided an estimate for genetic variance in tolerance (Table 1), which was not significantly different from zero ($p<0.05$), and also reported convergence issues. The results suggest that there is no significant genetic variation in tolerance of pigs to PRRSV, and demonstrate the high data demand for estimating genetic parameters for tolerance with reaction norm models.

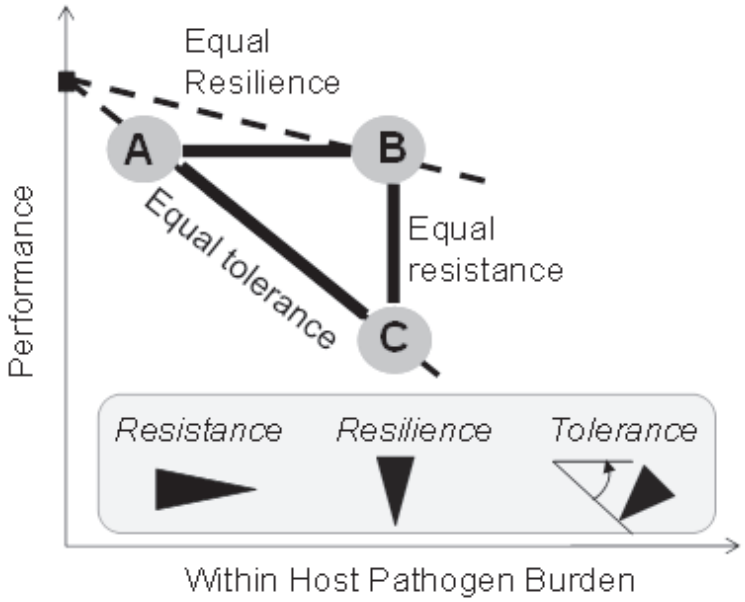

Figure 1. Graphical illustration of the relationship between resilience, resistance and tolerance to infectious pathogens. In this graph points A, B and C refer to three individuals exposed to the same pathogen challenge. Individual A suffers less within host pathogen burden for the same external pathogen exposure and is thus more resistant than individuals B and C. Individuals A and B are equally resilient as they have the same performance level after pathogen challenge, but individual A has higher resistance whereas individual B has higher tolerance as indicated by the flatter slope when regressing pathogen burden against performance. Individual C is less resilient than A and B, but has the same tolerance as individual A, and equal resistance to individual B.

Table 1. Estimates for genetic variance (std. error) for resilience, resistance and tolerance of growing pigs to PRRSV, based on data from 8 infectious challenge trials of the PRRS host genetics consortium (Rowland et al., 2012). The term 'dpi' refers to days post infection. Note that no heritability estimates for tolerance could be obtained due to the lack of phenotypic variance estimates for tolerance slopes (Kause, 2011).

Trait	Measure used	Genetic variance (std. error)	Heritability (std. error)
Resilience	WG between 0-21 dpi, adjusted for BW at 0 dpi	0.02(0.004)	0.30 (0.07)
Resistance	VL between 0-21dpi	17.88 (7.64)	0.22 (0.09)
Tolerance	Sire slope of WG regressed against VL	0.000007 (0.000005)	Not applicable

Practical considerations for inferring resilience from field data

One of the hallmarks in real farming conditions is that animals are usually exposed to a wide range of infectious pathogens, not all of which are identifiable. Random regression reaction-norm models have proved powerful to assess genetic resilience of animals to all kinds of environmental stressors, even if these are not explicitly specified. Although the definition of the environmental scale has been identified as one of the main hurdles with these models (Strandberg, 2006), the conventional approach is to substitute the actual environmental scale with average performance measures, such as herd-year or contemporary group estimates of the phenotypes studied (Kolmodin *et al*., 2002; Cardoso and Tempelman, 2012). These averages may be useful indicators for different types of environments, but caution is advised when interpreting the model results, as the direct relationship between the environmental scale and the phenotype as dependent variable is prone to introduce bias in the variance estimates of the resilience slopes (Strandberg, 2006). These may be overcome by replacing phenotypic averages with random effects, but this requires large amount of data covering a wide environmental range (Su *et al*., 2006; Knap and Su, 2008). Furthermore, it cannot be guaranteed that animals would be equally ranked if the actual environmental scale (i.e. defined by variables that have a causative effect on performance) was used (Strandberg, 2006). Thus, appropriate choice of the environmental scale is crucial for reaction-norm models, as exemplified by Rashidi *et al*. (2014), who identified herd-year-week estimates of number of piglets born alive as valid indicators for pathogen challenge when assessing the resilience of sows to PRRS in commercial settings, where the actual pathogen challenge was unknown.

Despite the power and versatility of reaction norms, applying these models to estimate genetic resilience remains a major problem in cases where infectious pathogens cause epidemic outbreaks with large temporal variation in prevalence and consequently also in pathogen chal-

lenge. To date quantitative genetic models cannot account for these dynamic aspects. These are usually captured by epidemiological models. Approaches for integrating dynamic aspects captured by epidemiological models into quantitative genetics models are currently under way (e.g. Lipschutz-Powell *et al*., 2014), but so far these have not been applied to address resilience of livestock to infectious pathogens.

Finally, it should be emphasized that even in situations where pathogen challenge can be appropriately specified, many other factors may influence performance, and thus must not be ignored in the statistical analyses. As Guy *et al*. (2012) point out "… resistance and tolerance" [and therefore also resilience] "cannot simply be modelled as a one dimensional reaction norm, with pathogen burden as the only explanatory variable. In order to objectively model and predict these traits, we need to take into account a number of factors simultaneously, including not only genotype and disease variables, but also descriptors of the environment, as well as any possible interactions."

Without doubt, the data-hungry nature of random regression reaction-norm models, the need for repeated measurements to capture dynamic aspects and the influence of non-infectious environmental factors on performance will have strong implications for data collection on farm. This rising demand may be met by recent advances in real-time technologies (e.g. feed intake recorders, GPS tracking systems, better and cheaper diagnostics for measuring pathogen burden).In the face of continuing threats of epidemics with potentially devastating consequences to livestock production, the costs associated with intense data recording need to be weighted carefully against the potential benefits to livestock production arising from improved ability to identify animals with high genetic resilience to a range of pathogens.

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