The Importance Of Associative Effects In The Control Of Infectious Disease Through Selection

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Introduction

Control of infectious diseases through selection has proven difficult. Corresponding analysis of disease data tends to interpret variation in disease status in terms of individuals' susceptibility to disease. However, using a stochastic epidemiological model, Nath et al. (2004) identified transmission rate, latent period and recovery period as critical parameters for the control of infectious diseases. In other terms, the impact that individuals have on each other, the time before they can start affecting each other and the time during which they can affect each other are crucial factors for disease prevalence. However, genetic analysis of disease data and subsequent control of diseases through selection currently ignores such effects of individuals on each other.

Over the last forty years, multi-level selection theory has been developed to investigate the impact of group members, or associative effect, on the expression of traits. Given that epidemics depend heavily on interactions among individuals, control of infectious diseases through selection could greatly benefit from the inclusion of such effects. To this effect, a brief description will be given of associative effects and potential applications to disease will be discussed.

What are associative effects?

Classically, the phenotypic trait value of an individual i (P_i) is partitioned into an additive genetic value (A_i), or breeding value, and an environmental deviation (E_i, equation (1); (Falconer and MacKay 1996). The environmental deviation consists of all factors affecting the trait which are external to the individual, such as food or temperature, and non-additive genetic components i.e. dominance and epistasis. Such external factors could be due to interactions with other individuals. In this way, the environmental deviation can be further partitioned into a 'direct' environmental deviation ($E_{D,i}$), which isn't caused by other individuals, and the sum of the effects of each group member j ($P_{S,j}$) (equation (2)) (e.g. Griffing 1967; Bijma *et al.* 2007a). This part of the environmental deviation has been termed 'associative effects', 'indirect genetic effects' (IGE) or 'heritable environment' as it is external to the focal individual but has a genetic component (equation (3); (e.g. Bijma *et al.*

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2007a). Thus an associative effect is a heritable effect of an individual on the trait value of another.

$$P_i = A_i + E_i \tag{1}$$

$$P_i = A_{D,i} + E_{D,i} + \sum_{j=1}^{n} P_{S,j} \qquad j \neq i \tag{2}$$

$$= A_{D,i} + E_{D,i} + \sum_{j=1}^{n} (A_{S,j} + E_{S,j}) \qquad j \neq i \tag{3}$$

How does it apply to disease?

Disease prevalence will be high if individuals are highly liable to become infected and effective at transmitting the infection, e.g. by shedding much pathogen or by remaining infectious for a long time. Describing the time course of infection through an epidemiological SIS model, direct and associative effects on prevalence may be expressed as follows. The impact of an infectious individual on group prevalence depends on (i) the individual's ability to transmit pathogens, which is an associative effect, (ii) the susceptibility of the population's members, which is a direct effect and (iii) the individual's immune response determining duration of its infected status, which again is a direct effect. Hence, the effect of an individual on group prevalence depends on expression of associative and direct effects and their relative importance depends on disease status (Figure 1).

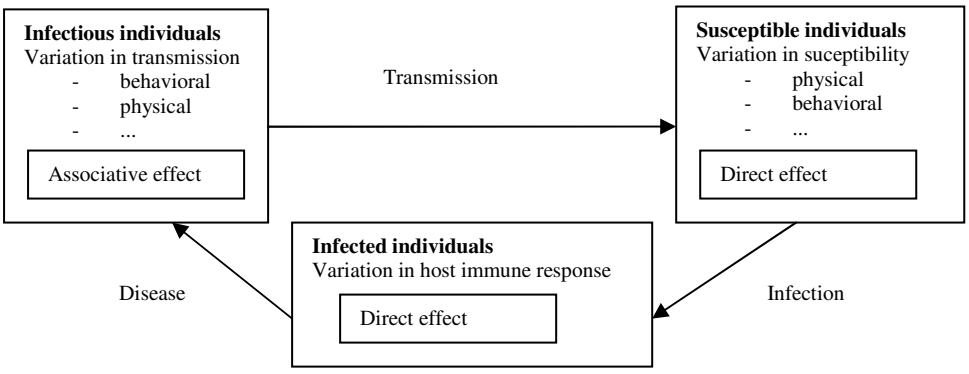

Figure1: Disease dynamics according to an epidemiological SIS model and expression of direct and associative effects.

Thus, variation in associative and direct effects are expected to change over the time course of infection. As change in number of infected individuals over time is proportional to the number of infected and susceptible individuals, $dI/dt \propto IS$, and the variation in transmission is expected to be expressed in infected individuals (Figure 1), we can expect the variation in associative effects to be scaled by $S^2 = (1 - I)^2$. Similarly, ignoring

direct effects representing the immune response in infected animals for simplicity, the variation in direct effects is expected to be expressed in susceptible individuals and will therefore be scaled by I^2 (Figure 2). Hence, this illustrates the need to take disease dynamics into account.

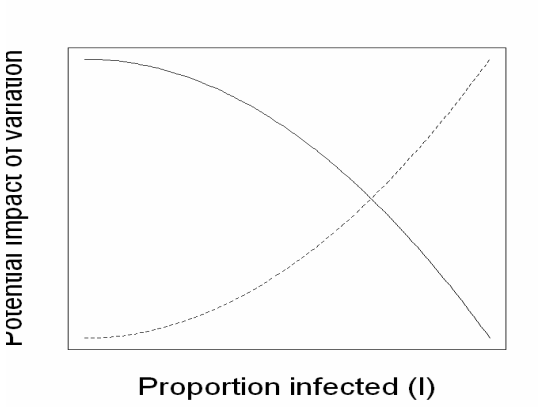

Figure 2: Potential impact of individuals' direct and associative variation depending on the proportion of infected individuals in the population. __Associative, -- Direct (susceptibility)

Including associative effects into classical genetic models

The concepts described above can be incorporated into the classical genetic models for disease that assume an underlying normally distributed threshold trait called liability (Falconer and MacKay 1996). In this way, liability will depend on variation in transmission, susceptibility and immune response, and time. Therefore, liability could be expressed as:

$$P_i(t) = A_{D,i}(t) + E_{D,i}(t) + c(n)\xi_i \sum_{j=1}^{n=1} A_{S,j}(t) + c(n)\xi_i \sum_{j=1}^{n-1} E_{S,j}(t), \qquad i \neq j. \qquad (4)$$

where the first two terms represent the individual's immune response, and the second two the capacity of others to infect the individual. The latter are a function of the individuals' susceptibility to infection ξ, a density dependent contact rate c(n), and the net amount of pathogens contributed by each conspecific $A_{S,j}(t) + E_{S,j}(t)$. It has been noted that susceptibility ξ is a direct effect in itself and could also be partitioned into additive genetic and environmental components.

The prevalence data required to estimate the variance components of liability would be obtained from relevant epidemiological models of the disease in question. Estimation of response to selection would then in turn provide knowledge about the impact of genetic selection on disease dynamics.

What are the potential implications?

Response to selection depends on the covariance between the direct and associative effect (e.g. Bijma *et al.* 2007a). When the direct effects and associative effects are positively correlated, response to selection will exceed expectations from the classical model without associative effects. Such discrepancies have been observed by Bishop et al. (1997) in a model of gastro-intestinal parasitism in sheep, where selection for reduced feacal egg count resulted in an observed response 1.7 times greater than expected.

When direct and associative effects are sufficiently negatively correlated, on the other hand, response to selection could be going in the opposite direction of selection. In disease terms, a negative covariance would occur if less susceptible individuals are more infectious, e.g. by exhibiting a prolonged asymptomatic carrier phase.

Better knowledge of associative effects on disease prevalence would allow for better design of breeding programmes. For example, relatedness between group members and/or selection based on group performance was shown in theory to reduce the importance of the correlation of effects, and therefore reduce the risk of response in the wrong direction (Griffing 1981b; Bijma and Wade 2008). These results were corroborated in a fourteen year selection study on broiler behavioral traits by Muir and associates, reviewed by Muir & Craig (1998).

Conclusion

The spread of infectious diseases depends heavily on the disease states of individuals and on interactions between them. The importance of variation due to such interactions for the control of infectious disease through selection should therefore be tested. Multi-level selection theory provides a promising framework to pick up on this variation, and to optimize the design of breeding strategies aiming to reduce disease prevalence.

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