SPREAD OF INFECTIOUS DISEASES AMONG DIFFERENT DEGREES OF RELATIVES

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Introduction

The distribution of an infectious disease over an animal population and its evolution through time are the results of the dynamic interactions of the host and pathogen systems. These interactions may be represented in the form of mathematical functions specified by parameters that quantify the rates at which processes evolve. Various types of epidemic models have been formulated depending upon the characteristic of the infection (3). Among others, the SIS model is appropriate for infectious disease for which no permanent immunity occurs after recovery. The initials SIS refer to the movement of a typical animal through the two states of the disease: Susceptible – Infectious. An animal in the state *S* is healthy but susceptible to become infected with the disease upon exposure to the contagious agent. Upon infection, it enters the state *I* and remains in it until recovery to the *S* state.

Usually, SIS models treat populations as homogeneous in the sense that an *I* animal is equally likely to infect any *S* animal and all *S* animals are equally susceptible to infection by any *I* animal. However, it must be recognized that animals are more or less resistant to a same infective dose because of genetic and non-genetic differences. It seems likely that the genetic factor behind resistance to infectious disease is a combination of a number of genes, each having a small contribution to the disease relative risk (8).

Both, deterministic and stochastic modeling approaches exist. Deterministic models are based on ordinary differential equations and capture the essential relationships among the different components. However, an infection may be initiated in a small population, and under such conditions, a stochastic model that allows for inherent fluctuations may yield qualitatively different behavior.

In this paper, we extend homogeneous deterministic and stochastic SIS models to investigate the impact of genetic heterogeneity in the spread of a bacterial infectious disease.

Material and Methods

Let a population of density N constituted of g groups of cows sharing the same kinship degree i such that $N = \Sigma_i N_i$ (i = 1, 2, … g) and $p_i = N_i / N$ is the proportion of pairs of relatives of the i^{th} kinship degree ($\Sigma_i p_i = 1$). Each i^{th} group is constituted of S_i susceptible cows and I_i infected ones, with $S_i + I_i = N_i$. The initial conditions (t = 0) are specified by $S_i(0) = s_0$ and $I_i(0) = i_0$.

The deterministic form of the SIS model is for the i^{th} group of relatives:

$$dS_i/dt = \Delta - \mu S_i + \gamma I_i - \lambda_i k [SI_i]$$
$$dI_i/dt = \lambda_i k [SI_i] - (\gamma + \mu + \varepsilon) I_i$$
$$dN_i/dt = \Delta - \mu N_i - \varepsilon I_i$$

where Δ is the constant replacement rate, μ is the natural culling rate, γ is the recovery rate, ε is the culling rate due to the infection, k is the contact rate between cows, λ_i is the probability that any one contact will transmit infection and $[SI_i]$ is number of encounters between an infected cow and a susceptible one. As a measure of the susceptibility of a cow to infection, λ_i is a function of the degree of relatedness between cows in contact within the i^{th} group (a_i), the heritability of the resistance to infection (h^2), and the average population transmission probability (λ_0): $\lambda_i = h^2 (1 - \lambda_0) a_i + \lambda_0$.

In the stochastic framework, the spread of a SIS infectious disease is modelled as a Markovian continuous-time model (1). The infinitesimal transition probabilities in the interval (t, t + dt) are defined by:

$Pr[(S_i, I_i)_{t+dt} = (s + 1, i) \mid (S_i, I_i)_t = (s, i)] \sim \Delta\, dt$
$Pr[(S_i, I_i)_{t+dt} = (s - 1, i) \mid (S_i, I_i)_t = (s, i)] \sim \mu\, s\, dt$
$Pr[(S_i, I_i)_{t+dt} = (s, i - 1) \mid (S_i, I_i)_t = (s, i)] \sim (\mu + \varepsilon)\, i\, dt$
$Pr[(S_i, I_i)_{t+dt} = (s + 1, i - 1) \mid (S_i, I_i)_t = (s, i)] \sim \gamma\, i\, dt$
$Pr[(S_i, I_i)_{t+dt} = (s - 1, i + 1) \mid (S_i, I_i)_t = (s, i)] \sim \lambda_i\, k\, [si]_i\, dt$

where Δ, μ, ε, γ, λ and k have the same meanings as in the deterministic model. The Gillespie algorithm was selected for the stochastic simulation. This discrete-event simulation technique makes time steps of variable length, based on the transition probabilities and numbers s and i . In each iteration, random numbers are generated to determine the time and the type of the next transition. Upon the execution of the selected transition, the populations are altered accordingly and the process is repeated (6).

Deterministic and stochastic models were illustrated by modelling bovine mastitis spread on a dairy farm with 5 different groups, each composed of 20 relatives of the i^{th} degree with a_i = 0, ½, ½², ½³ and ½⁴. Models were implemented by introducing a single infected cow in each group and typical proportion of infected quarters was computed. Default values for the parameters were derived from the literature on *S. aureus* quarter infection and on culling strategies in dairy cattle (4, 7, 9,10): $\lambda_0 = 2 * 10^{-2}$, $\gamma = 4 * 10^{-3}$, $\varepsilon = 0.005$, $\mu = 7 * 10^{-4}$, $h^2 = 0.05$. The replacement rate was chosen to insure the initial disease-free equilibrium: $\Delta = \mu S_{i(t=0)}$. As no information was available on the average number of contacts per unit of time made by a quarter, it was assumed constant and directly proportional to the number of quarters initially present in each group of relatives.

Results

For each group of relatives, the deterministic model has two equilibrium points: the disease-free equilibrium with $I_i = 0$ and $S_i = \Delta/\mu$ and the endemic-disease equilibrium with $S_i = (\gamma + \mu + \varepsilon)/(\lambda_i k)$ and $I_i = [(\Delta \lambda_i k) - \mu (\gamma + \mu + \varepsilon)]/(\mu + \varepsilon) \lambda_i k$. The Jacobian matrix evaluated at both equilibria showed the endemic-disease equilibrium is always stable but the disease-free equilibrium is stable if $R_{0i} < 1$ with $R_{0i} = [\lambda_i \Delta k]/[\mu (\gamma + \mu + \varepsilon)] < 1$. As the same

set of coupled equation was applied to all groups of relatives, the R_0 for the whole population is $R_0 = \Sigma_i\ p_i\ R_{0i}$ for i = 1, 2, … g. This global R_0 gives the total average number of new infective cows in the population produced by one infective during the mean (death-adjusted) infective period (5).

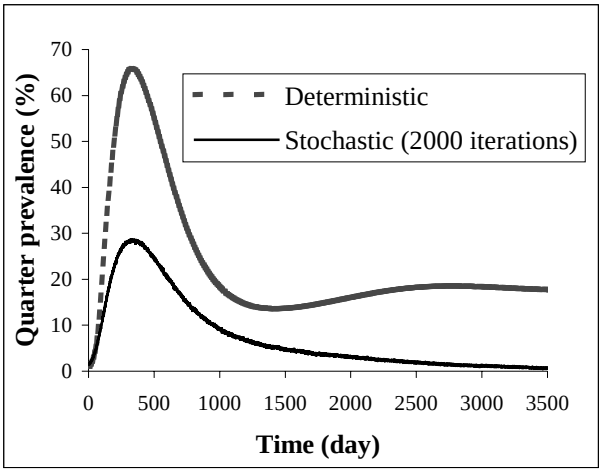
The relationship between R_0 and the proportion of relatives is given by

$$R_0 = [\Delta/\mu]\ [k/(\gamma + \mu + \varepsilon)]$$
$$[\lambda_0\ (1 - h^2\ \Sigma_{i=1}\ a_i\ p_i) + h^2\ \Sigma_{i=1}\ a_i\ p_i].$$

Then, in a population composed of unrelated and relatives of one type (a_i>0), the maximum proportion of relatives tolerable to have no or minor epidemics (R_0<1) is:

$$p_{Max} = \{1 - \lambda_0\ [\Delta/\mu]\ [k/(\gamma + \mu + \varepsilon)]\}/$$
$$\{(1 - \lambda_0)\ a_i\ h^2\ [\Delta/\mu]\ [k/(\gamma + \mu + \varepsilon)]\}$$

The results of the simulation with the deterministic and stochastic models for the *S. aureus* infection are illustrated in the following figure:



Discussion

The central question is whether or not, and under which conditions, an infectious disease will spread in a population when the degree of susceptibility is related to the degree of relationship between susceptible and infected animals. Given the assumption of fitness declining with increased inbreeding, the probability of an epidemic will be minimized if the population is composed only of unrelated animals but this is not an absolute constraint (2). Indeed, the global R_0 can be made less than 1 for different population structures. For example, in a population composed of related and unrelated of the i^{th} type, the maximum proportion of related cows (p_{Max}) admissible to keep R_0<1 can be computed and will increase if h^2 decreases. This is particularly interesting for the control of infectious disease for which h^2 is usually low.

Other assumptions underline the model such as equal contact amongst animals of different genotypes and constant average infectiousness per infective animal. But these are an obvious starting point for developing any general theory and more realistic models may be developed.

Conclusion

Methodologies exist to help breeders to make appropriate breeding choices to limit the transmission of an infectious disease based on the knowledge of parameters characterizing the infection (γ, ε), the population demography (Δ, μ) and the genetic composition (λ_0, a_i, h^2) of the population.

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