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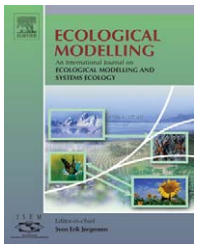

Population dynamics of infectious diseases: A discrete time model

Madan K. Oli[a,*], *Meenakshi Venkataraman*[a], *Paul A. Klein*[b], *Lori D. Wendland*[c], *Mary B. Brown*[c]

[a] *Department of Wildlife Ecology and Conservation, 110 Newins-Zeigler Hall, University of Florida, Gainesville, FL 32611-0430, United States*

[b] *Department of Pathology, Immunology, and Laboratory Medicine, College of Medicine, University of Florida, Gainesville, FL 32610-0275*

[c] *Department of Infectious Diseases and Pathology, College of Veterinary Medicine, University of Florida, Gainesville, FL 32610-0880, United States*

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ABSTRACT

Mathematical models of infectious diseases can provide important insight into our understanding of epidemiological processes, the course of infection within a host, the transmission dynamics in a host population, and formulation or implementation of infection control programs. We present a framework for modeling the dynamics of infectious diseases in discrete time, based on the theory of matrix population models. The modeling framework presented here can be used to model any infectious disease of humans or wildlife with discrete disease states, irrespective of the number of disease states. The model allows rigorous estimation of important quantities, including the basic reproduction ratio of the disease (R_0) and growth rate of the population (λ), and permits quantification of the sensitivity of R_0 and λ to model parameters. The model is amenable to rigorous experimental design, and when appropriate data are available, model parameters can be estimated using statistically robust multi-state capture-mark-recapture models. Methods for incorporating the effects of population density, prevalence of the disease, and stochastic forces on model behavior also are presented.

1. Introduction

Infectious diseases have been one of the most influential causes of morbidity and mortality throughout the history of mankind. An estimated 25 million Europeans died of bubonic plague in the 14th century, and about 1.5 million Aztecs succumbed to smallpox in 1520 (Anderson and May, 1991; Ewald, 1994). Infectious diseases such as plague, smallpox, measles, and tuberculosis have had a devastating effect on human populations in the past, and some of these diseases continue to be a major cause of morbidity and mortality in developing countries (Anderson, 1994). The AIDS epidemic, SARS, West Nile Virus encephalitis, and other emerging infectious diseases suggest that diseases remain an important public health concern even in developed countries (Low and McGeer, 2003; Enserink, 2004; Gould and Fikrig, 2004; Watson and Gerber, 2004).

An important development in the study of infectious diseases has been the application of mathematical models to understand the interplay between various factors that deter-

* *Corresponding author*. Tel.: +1 352 846 0561.
E-mail addresses: olimadan@wec.ufl.edu, olim@ufl.edu (M.K. Oli).
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mine the epidemiological processes, course of infection within a host, and transmission dynamics in a host population (Anderson and May, 1991; Anderson, 1994). Mathematical models of infectious diseases range from the early models of Ross (1911) and Kermack and McKendrick (1927), to more recent models of HIV-AIDS (Anderson and May, 1988, 1991; Anderson, 1991a,b, 1994; Levin et al., 2001; May, 2004), cholera (Pascual et al., 2002), and measles (Bolker and Grenfell, 1993; Grenfell et al., 2002). Mathematical models have been used to formulate and test hypotheses of disease transmission; to explore transmission dynamics of pathogens; to investigate the evolution of resistance to antibiotics and the evolutionary cost of resistance; and to design programs for disease control (Anderson and May, 1991; Anderson, 1994; Wilson et al., 1994; Barlow and Kean, 1998; Grossman, 2000; Kristinsson, 2001; Levin, 2001; Smith and Cheeseman, 2002; Scherer and McLean, 2002; Spear et al., 2002; Woolhouse, 2002; May, 2004; van Boven and Weissing, 2004).

In the past, wildlife diseases received attention only if they posed zoonotic threats or impacted livestock. However, the loss and fragmentation of wildlife habitat has led to more direct contact between humans and wildlife. Because many wildlife species serve as reservoirs, or intermediate or secondary hosts for diseases of humans and domestic livestock (Low and McGeer, 2003; Enserink, 2004), an understanding of diseases in wildlife populations has become important from a public health perspective. From a conservation perspective, habitat fragmentation coupled with small population sizes may make wildlife populations vulnerable to extinction from diseases (Saunders and Hobbs, 1991; Jacobson, 1994; Hudson et al., 2001). For example, recent declines in populations of Ethiopian wolves are attributed to rabies transmitted by domestic dogs, canine distemper virus (CDV) from other carnivore species is threatening populations of black-footed ferrets, and measles from humans poses a serious threat to mountain gorillas (Cleaveland et al., 2001; Dobson and Foufopoulos, 2001). As wildlife populations diminish and the interest in their conservation increases, it becomes essential to investigate the importance of the impact of diseases at the population level (Daszak et al., 2000; Dobson and Foufopoulos, 2001). Thus, studies of wildlife diseases are important from public health, economic as well as conservation perspectives.

Most existing disease models are continuous time (differential or partial differential equation) models. Discrete time epidemiological models have received little attention (see van Boven and Weissing, 2004 for an exception) due, at least in part, to the lack of a unified framework. Within the past two decades, substantial progress has been made in the theory of matrix population models (Caswell, 2001), and these powerful tools can be used to model the dynamics of infectious diseases with discrete disease states. When appropriate data are available, parameters for matrix-based disease models can be estimated using statistically sound multi-state mark-recapture methods (Williams et al., 2002). Finally, disease models based on the theory of matrix population models not only allow asymptotic analyses (e.g., estimation of net reproduction rate of the disease and growth rate of the population, sensitivity analyses), but also provide a flexible framework for modeling stochastic influences and frequency- or density-dependence of the disease and population dynamics.

In this paper, we provide a unified framework for modeling disease dynamics in discrete time within the framework of matrix population models (Caswell, 2001; Oli, 2003; Yearsley, 2004). First, we outline methods for determining model structure for infectious diseases with any number of disease states, and present methods for asymptotic analyses of the model. We then describe methods for estimating model parameters using rigorous statistical techniques. Transmission dynamics of diseases can be influenced by population density of the host, prevalence of the disease, and by stochastic influences. Thus, a framework for modeling the effects of disease prevalence, population density, and stochastic forces also are presented.

2. Model formulation

We first consider the classical SIR disease model (e.g., Anderson and May, 1991), where the host population is composed of susceptible (S), infective (I), or recovered (R) individuals such that the total population size at any given time $N(t)$ is given by

$$N(t) = S(t) + I(t) + R(t). \tag{1}$$

We assume that the population is sampled at discrete time $t = 1, 2, 3, \ldots, T$, and the disease states are accurately identified. Each individual in the population is assigned to one of the disease states, namely, S, I or R. Susceptible individuals survive with the probability p_s and become infective with the probability β ($0 < \beta \leq 1$) per unit time. Infective individuals survive with the probability p_i, and recover with the probability γ ($0 < \gamma \leq 1$) per unit time. Recovered individuals remain at the same disease state throughout their lives, and survive with the probability p_r per unit time. Finally, let F_s, F_i, and F_r be the fertility rates of susceptible, infective and recovered individuals, respectively, and assume that all juveniles (i.e., new born individuals) are susceptible. The dynamics of the population can be graphically portrayed by a life cycle graph (Fig. 1), from which a population projection matrix can be derived (Caswell, 2001):

$$\mathbf{A} = \begin{pmatrix} F_s + (1-\beta)p_s & F_i & F_r \\ p_s\beta & (1-\gamma)p_i & 0 \\ 0 & \gamma p_i & p_r \end{pmatrix}. \tag{2}$$

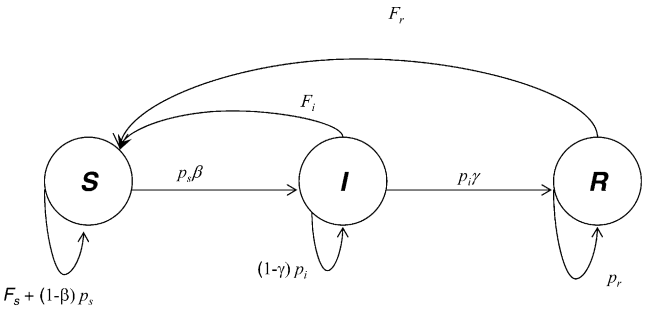
The dynamics of the model is determined by the recurrence equations:

$$\mathbf{n}(t+1) = \mathbf{A}\mathbf{n}(t), \tag{3}$$

where the population state vector $\mathbf{n}(t)$ gives the number of susceptible, infected and recovered individuals at time t:

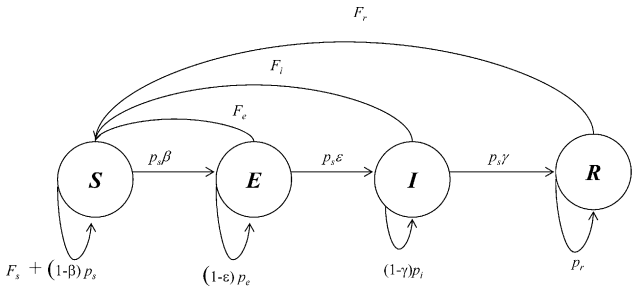
$$\mathbf{n}(t) = \begin{pmatrix} S(t) & I(t) & R(t) \end{pmatrix}^{T}. \tag{4}$$

We note that the parameter β differs from the transmission rate parameter commonly used in continuous time models (which is difficult to estimate; see McCallum et al., 2001;



$$\mathbf{A} = \begin{pmatrix} F_s + (1-\beta)p_s & F_i & F_r \\ \beta p_s & (1-\gamma)p_i & 0 \\ 0 & \gamma p_i & p_r \end{pmatrix}$$

Fig. 1 – Life cycle graph for a SIR-type disease, and a corresponding projection matrix. Disease states are: *S* = susceptible, *I* = infective, and *R* = recovered. Model parameters are: F_k = fertility rate of individuals in disease state *k*, p_k = survival probability of individuals in disease state *k* (where *k* = S, *I* or R), β = infection rate (probability that a susceptible individual becomes infective between time *t* and *t* + 1), and γ = recovery rate (probability that an infective individual recovers between time *t* and *t* + 1).



$$\mathbf{A} = \begin{pmatrix} F_s + (1-\beta)p_s & F_e & F_i & F_r \\ \beta p_s & (1-\varepsilon)p_e & 0 & 0 \\ 0 & \varepsilon p_e & (1-\gamma)p_i & 0 \\ 0 & 0 & \gamma p_i & p_r \end{pmatrix}$$

Fig. 2 – Life cycle graph for a SEIR-type disease. A corresponding projection matrix A also is given. Disease states are: *S* = susceptible, *E* = exposed, *I* = infective, and, *R* = recovered. Model parameters are: F_k = fertility rate of individuals in disease state *k*, p_k = survival rate of individuals in disease state *k* (where *k* = S, E, *I* or R), β = exposure rate (probability that a susceptible individual becomes exposed to infection between time *t* and *t* + 1), ε = infection rate (probability that an exposed individual becomes infective between time *t* and *t* + 1), and γ = recovery rate (probability that an infective individual recovers between time *t* and *t* + 1).

Begon et al., 2002) in that β is clearly defined as the probability that a susceptible individual becomes infective between time *t* and *t* + 1 and can be easily estimated as described below. Also, density- or frequency-dependence in disease transmission in not considered in this formulation (but see below); consequently, model structure in Eq. (3) differs slightly from the equivalent continuous time model based on the law of mass action (McCallum et al., 2001; Begon et al., 2002).

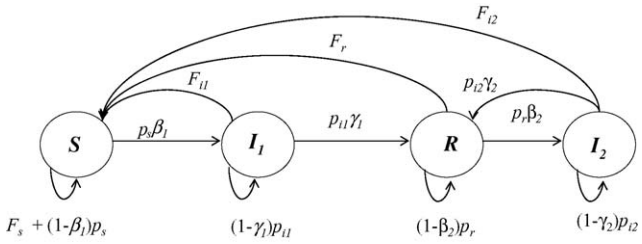
Within the framework provided above, life-cycle graphs and corresponding projection matrices can be derived for any disease with discrete disease states. Examples of life-cycle graphs and corresponding projection matrices are given for the classical SEIR (susceptible, exposed, infected, recovered; Fig. 2) model, SI_1RI_2 (susceptible, infected$_1$, recovered, infected$_2$; Fig. 3) model, and for a modified SIR model with multiple infection and recovery states ($SI_1R_1R_2R_3I_2$; Fig. 4) for horizontally transmitted diseases. The life-cycle graphs (and projection matrices) can be easily modified to model diseases that are transmitted vertically or both vertically and horizontally.

In this paper we have used the SIR model (Fig. 1) as an example for detailed analyses. However, once the projection matrix appropriate for a particular disease is derived, the same principles of analysis apply to all disease models regardless of the number of disease states or model structure.

2.1. *Estimation of population growth rate (λ) and basic reproduction ratio (R_0)*

If the model parameters remain constant, the population will ultimately converge to the stable state distribution, and each of the disease states as well as the entire population will grow with a projected population growth rate, λ (Fig. 5A) The projected population growth rate λ is estimated as the dominant eigenvalue of the projection matrix **A**, and can be obtained numerically (Caswell, 2001). The long-term behavior of the model is determined by λ such that each disease state as well as the entire population grows exponentially when $\lambda > 1$, and declines exponentially when $\lambda < 1$. Transient dynamics of the model depend on initial conditions and relative magnitudes of the eigenvalues of **A**, and are described in detail by Caswell (2001). The right and left eigenvectors corresponding to the dominant eigenvalue quantify the stable state distribution, and state-specific reproductive values, respectively.

The basic reproduction ratio (R_0) is an important statistic in models of infectious diseases, and has been frequently used for establishing disease control strategies, vaccination programs, and in evolutionary studies (Anderson and May, 1991; Keeling, 1997; van Boven and Weissing, 2004). In disease models, R_0 is defined as the expected number of new infections in a population of susceptible hosts by the introduction of a single infective individual (Anderson and May, 1991; Hethcote, 2000; Heesterbeek, 2002). In practice, however, R_0 has been estimated using various methods. For continuous time models, Dieckmann and Heesterbeek (2000) and Heesterbeek (2002) have shown that R_0 is best estimated as the spectral radius of the next generation operator. Here, we present an equivalent method for estimating R_0 for discrete time models such as that represented by the SIR model (Eq. (2)). The concept of basic reproduction ratio in models of disease dynamics is sim-



$$\mathbf{A} = \begin{pmatrix} F_s + (1-\beta_1)p_s & F_{i1} & F_r & F_{i2} \\ \beta_1 p_s & (1-\gamma_1)p_{i1} & 0 & 0 \\ 0 & \gamma_1 p_{i1} & (1-\beta_2)p_r & \gamma_2 p_{i2} \\ 0 & 0 & \beta_2 p_i & (1-\gamma_2)p_{i2} \end{pmatrix}$$

Fig. 3 – Life cycle graph for a SIRI-type disease with two infective states. A corresponding projection matrix A also is given. Disease states are: S = susceptible, I_1 = primary infective (i.e., susceptible individuals that become infective), R = recovered, and I_2 = secondary infective (i.e., due to reinfection of recovered individuals). Model parameters are: F_k = fertility rate of individuals in disease state k, p_k = survival rate of individuals in disease state k (where k = S, I_1, R, or I_2), β_1 = primary infection rate (probability that a susceptible individual becomes infective between time t and $t+1$), γ_1 = primary recovery rate (probability that an infective individual recovers from the primary infection between time t and $t+1$), β_2 = secondary infection rate (probability that a recovered individual succumbs to secondary infection between time t and $t+1$), γ_2 = secondary recovery rate (probability that an infective individual recovers from the secondary infection between time t and $t+1$).

ilar to that of net reproductive rate in stage-structured models of population dynamics. In population ecology, net reproductive rate (R_0) is defined as the average number of offspring produced by a newborn individual during its lifetime.

We begin with a brief review of relevant concepts in matrix population theory as they apply to stage-structured populations (Cushing and Yicang, 1994; Caswell, 2001). In matrix models of stage-structured populations, stage-specific transition probabilities and reproductive parameters are summarized in a population projection matrix **A**, which can be written in terms of the transition matrix **T** (where the element t_{ij} is the probability that an individual in stage j at the time t is alive and in stage state i at time $t+1$), and the fertility matrix **F** which describes the reproduction (where the element f_{ij} is the expected number of i-type offspring of an individual in stage j):

$$\mathbf{A} = \mathbf{T} + \mathbf{F}. \tag{5}$$

The fundamental matrix **N** is defined as

$$\mathbf{N} = (\mathbf{I} - \mathbf{T})^{-1}, \tag{6}$$

where **I** is the identity matrix. The fundamental matrix provides information about the expected number of time steps spent in each state and expected time to death or absorption. Finally, the matrix **R** is given by

$$\mathbf{R} = \mathbf{FN}. \tag{7}$$

The entries r_{ij} of matrix **R** quantify the expected lifetime production of offspring of type i by an individual starting life in stage j (Cushing and Yicang, 1994; Caswell, 2001). The dominant eigenvalue of matrix **R** is the net reproductive rate R_0 as defined in population ecology.

Much of this theory also applies to models of disease dynamics, except that the reproductive matrix **F** is defined differently. This is because of the differences in the definition of R_0 in population and disease models. In disease models, "reproduction" of a disease quantifies the number of new infections, which may not include neonates if disease transmission is strictly horizontal. When we speak of R_0 in case of a disease, it is the number of infections that a single "infective" individual produces in a population of susceptible hosts during the infectious period. If transmission of a disease is strictly horizontal, all newborn babies are infection-free, regardless of their parentage. On the other hand, if transmission is strictly vertical, only offspring of infective individuals are born as infectives. If transmission occurs horizontally as well as vertically, newly infected individuals may comprise of neonates and adults. For the SIR model with strictly horizontal transmission of the disease, only one type of infection is produced. Thus, only f_{22} entry of the reproductive matrix **F** will be nonzero:

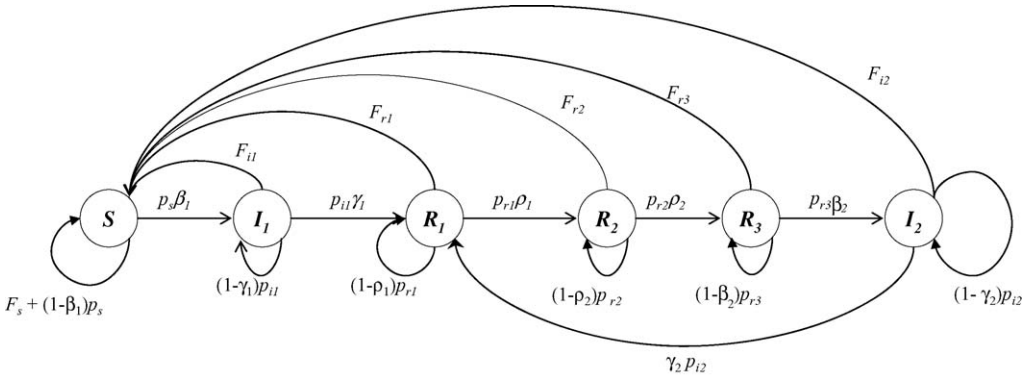
$$f_{ij} = \begin{cases} \beta p_s & \text{if } i = j = 2, \\ 0, & \text{otherwise.} \end{cases} \tag{8}$$

Once the "reproductive" matrix **F** is constructed, the fundamental matrix **N** is derived as above. Then, **R** = **FN**. We refer to **R** as the *next generation matrix* of the disease. The basic reproduction ratio, R_0, of the disease is estimated as the dominant eigenvalue of the next generation matrix **R**. Once the next generation matrix **R** is constructed, R_0 can be estimated numerically for a disease with any number of disease states or model structure. Although numerical estimation of R_0 is preferable for complex models, analytical expressions for the computation of R_0 can be derived for simple models, such as the SIR model (Appendix I).

The transmission dynamics of the disease is determined by the value of R_0. Persistence or spread of the infection occurs if $R_0 \geq 1$; the disease is expected to die out if $R_0 < 1$. For this reason, R_0 is also called the *threshold quantity* in that it determines whether a disease will persist in the population (Dieckmann and Heesterbeek, 2000; Hethcote, 2000; Heesterbeek, 2002).

2.2. *Sensitivity and elasticity analyses*

It is of interest to know how λ or R_0 respond to perturbations in model parameters. Likely responses of λ or R_0 to changes in model parameters can be investigated using the sensitivity analysis (Caswell, 2001). Given that the growth rate λ and the basic reproduction ratio R_0 are estimated as the dominant eigenvalue of the matrix **A** and **R**, respectively, the theory



$$\mathbf{A}=\begin{pmatrix} F_s+(1-\beta_1)p_s & F_{i1} & F_{r1} & F_{r2} & F_{r3} & F_{i2} \\ p_s\beta_1 & (1-\gamma_1)p_{i1} & 0 & 0 & 0 & 0 \\ 0 & p_{i1}\gamma_1 & (1-\rho_1)p_{r1} & 0 & 0 & \gamma_2 p_{i2} \\ 0 & 0 & p_{r1}\rho_1 & (1-\rho_2)p_{r2} & 0 & 0 \\ 0 & 0 & 0 & p_{r2}\rho_2 & (1-\beta_2)p_{r3} & 0 \\ 0 & 0 & 0 & 0 & p_{r3}\beta_2 & (1-\gamma_2)p_{i2} \end{pmatrix}$$

Fig. 4 – Life cycle graph for a SIR-type disease with multiple infective and recovery states. A corresponding projection matrix A also is given. Disease states are: S = susceptible, I_1 = primary infective (i.e., susceptible individuals that become infective), R_1, R_2, R_3 = early, mid, and late recovery states, respectively, and I_2 = secondary infective (i.e., due to reinfection of recovered individuals). Model parameters are: F_k = fertility rate of individuals in disease state k, p_k = survival rate of individuals in disease state k (where k = S, I_1, R_1, R_2, R_3 or I_2), β_1 = primary infection rate (probability that a susceptible individual becomes infective between time t and $t+1$), β_2 = secondary infection rate (probability that an individual in disease state R_3 becomes infective between time t and $t+1$), γ_1 = primary recovery rate (probability that an infective individual in disease state I_1 recovers from the primary infection and is in disease state R_1 between time t and $t+1$), β_2 = secondary infection rate (probability that a recovered individual in disease state R_3 succumbs to secondary infection between time t and $t+1$), ρ_1 = probability that an individual in disease state R_1 at time t is in disease state R_2 at time $t+1$, and ρ_2 = probability that an individual in disease state R_2 at time t is in disease state R_3 at time $t+1$.

of sensitivity analysis developed for the matrix population models (see Caswell, 2001 for details) can be extended to the disease models. The sensitivity of the growth rate λ to changes in a_{ij} (i.e., i, j-th entry of **A**) is given by the partial derivative of λ with respect to a_{ij}:

$$\frac{\partial\lambda}{\partial a_{ij}} = \frac{v_i w_j}{\langle \mathbf{w}, \mathbf{v}\rangle}, \tag{9}$$

where **w** and **v** are the right and left eigenvectors, respectively, corresponding to the dominant eigenvalue of the projection matrix **A**, and the denominator is the scalar product of **w** and **v**. Many entries of **A**, however, are functions of other lower-level parameters, such as transmission rate (β) and recovery rate (γ). One might apply the chain rule to estimate the sensitivity of λ to changes in any model parameter X as

$$\frac{\partial\lambda}{\partial X} = \sum_{i,j}\frac{\partial\lambda}{\partial a_{ij}}\frac{\partial a_{ij}}{\partial X}. \tag{10}$$

The concept of elasticity (proportional sensitivity) has received substantial attention in population ecology and conservation biology (Caswell, 2001; de Kroon et al., 1986) but not in epidemiological models. The elasticity of λ to changes in a_{ij} quantifies responses of λ to proportional changes in i, j-th entry of the matrix (de Kroon et al., 1986; Caswell, 2001):

$$e_{ij} = \frac{\partial \log\lambda}{\partial \log a_{ij}} = \frac{a_{ij}}{\lambda}\frac{\partial\lambda}{\partial a_{ij}}. \tag{11}$$

Finally, elasticity of λ to changes in a lower-level parameter X is given by

$$e(X) = \frac{X}{\lambda}\frac{\partial\lambda}{\partial X} = \frac{X}{\lambda}\sum_{i,j}\frac{\partial\lambda}{\partial a_{ij}}\frac{\partial a_{ij}}{\partial X}. \tag{12}$$

The sensitivity and elasticity of R_0 to changes in model parameters are estimated similarly, except that we now seek to quantify the sensitivity of R_0 to changes in r_{ij} (i.e., i, j-th entry of the next generation matrix **R**) or a lower-level parameter X:

$$\frac{\partial R_0}{\partial r_{ij}} = \frac{v_i w_j}{\langle \mathbf{w}, \mathbf{v}\rangle}, \tag{13}$$

$$\frac{\partial R_0}{\partial X} = \sum_{i,j}\frac{\partial R_0}{\partial r_{ij}}\frac{\partial r_{ij}}{\partial X}, \tag{14}$$

$$e_{ij} = \frac{r_{ij}}{R_0}\frac{\partial R_0}{\partial r_{ij}} \tag{15}$$

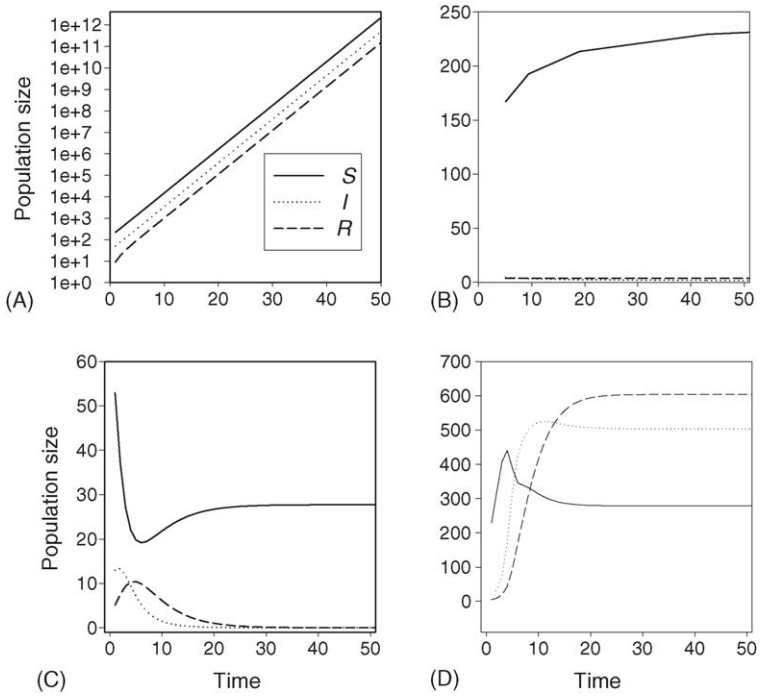


Fig. 5 – (A) Density-independent dynamics of the discrete time SIR model. Parameter values were: $p_s = p_i = p_r = 0.8$, $\beta = 0.3$, and $\gamma = 0.3$. Fecundity rate (m) was assumed to be 1.0 for all disease states. Initial population sizes were 100, 10, and 0 for susceptible, infective, and recovered states, respectively. (B–D) Depict the dynamics of SIR model with density-dependent β and fecundity rates. Density of infective individuals was assumed to influence β such that $\beta(N) = 1 - \exp(-kI)$, where k quantifies the strength of density-dependence and I is the density of infective individuals. Ricker function was used to incorporate density-dependence in fecundity rates, which was assumed to be influenced by total population size ($N(t) = S(t) + I(t) + R(t)$): $m(N) = m \times \exp(-cN)$, where c quantifies the strength of density-dependence. Values of density-dependence parameters were (B) $k = 0.001$, $c = 0.005$, (C) $k = 0.01$, $c = 0.05$, and (D) $k = 0.01$, $c = 0.001$.

and

$$e(X) = \frac{X}{R_0} \sum_{i,j} \frac{\partial R_0}{\partial r_{ij}} \frac{\partial r_{ij}}{\partial X}, \quad (16)$$

where **w** and **v** are the right and left eigenvectors, respectively, corresponding to the dominant eigenvalue R_0 of the next generation matrix **R**.

Sensitivities and elasticities can be estimated numerically for a disease with any number of disease states or model structure. Although numerical methods should be preferred for estimating R_0 for complex models, analytical expressions can be derived for simple models (Appendix II).

3. Parameter estimation

Reliability of the results of a modeling process depends on the robustness of the model parameters. Because disease models are frequently used in the formulation or implementation of disease control programs with far reaching public health or conservation consequences, it is imperative that parameters of disease models are estimated using rigorous and statistically sound techniques. In this section, we outline methods for estimating parameters for the discrete time model outlined above.

We envisage a study in which a population is sampled at discrete time $t = 1, 2, 3, \ldots, T$. During each sampling occasion, unmarked individuals are uniquely marked, disease states accurately identified, and each individual in the population is assigned to one of the disease states, k ($k = 1, 2, \ldots, K$). Resulting data from this type of capture-mark-recapture (CMR) study include capture history, disease state of each individual in the population during each sampling occasion, and individual attributes of the host (e.g., mass, sex, reproductive status, clinical signs of the disease, morphometric measurements) and of the pathogen (e.g., strains, virulence) that are deemed important. Environmental covariates (e.g., temperature, rainfall, population density) that are likely to influence transmission dynamics of the disease may also be recorded. Multi-state CMR models can be applied to these data to obtain maximum likelihood estimates of state-specific survival and disease state transition probabilities. Multi-state CMR models are described elsewhere in detail in the context of estimating demographic parameters (Nichols and Kendall, 1995; Fujiwara and Caswell, 2002; Williams et al., 2002). Here, we provide a brief overview of this technique as it relates to estimating disease model parameters using the SIR model as an example.

For the SIR model, the capture and disease transition history may consist of N and I to indicate the disease states (not infected and infected, respectively) when an individual was captured, and 0 if it was not captured during a sampling occa-

sion. Thus, capture and disease transition history for each individual will consist of a string of *I*, *N*, and 0 (and appropriate covariates). Let φ_t^{NI} be the combined probability that a susceptible individual alive at sample *t* is alive and is infective at sample $t+1$. Assuming that survival between two sampling occasions depends only on the disease state at sample *t*, φ_t^{NI} can be written as (Williams et al., 2002):

$$\phi_t^{NI} = p_s\beta, \tag{17}$$

where β is the probability that a susceptible individual at sample *t* is infective at sample $t+1$ given that it is alive at sample $t+1$, and p_s is the probability that a susceptible individual alive at sample *t* survives and remains in the population at sample $t+1$. Likewise, define φ_t^{IN} as the combined probability that an infective individual alive at sample *t* is alive and is recovered at sample $t+1$. With the assumption stated previously, φ_t^{IN} can be written as

$$\varphi_t^{IN} = p_i\gamma, \tag{18}$$

where φ_t^{IN} is the combined probability that an infective individual alive at sample *t* is alive and in recovered state at sample $t+1$, p_i the survival probability of an infective individual and γ is the probability that an infective individual recovers during the interval *t* and $t+1$ given that it is alive at time $t+1$. Maximum likelihood estimates of these parameters (and of state-specific capture probabilities) can be obtained using software packages such as MARK (White and Burnham, 1999) or MSSURVIV (Hines, 1994).

The survival and disease state transition probabilities can differ between sexes or vary over time or space. These may also be influenced by other individual or environmental covariates. A particularly useful feature of estimating model parameters within the multi-state CMR framework is that it allows modeling parameters of interest as functions of individual or environmental covariates, and permits an objective evaluation of the effect of individual or environmental covariates using either a likelihood ratio test (LRT) or an information theoretical approach (Williams et al., 2002). For example, a parameter (e.g., p_s) can be modeled as function of one or more covariates (x_i) that are hypothesized to influence the parameter of interest. The parameter p_s may be modeled as a function of environmental covariates using a logit-link function (Williams et al., 2002):

$$\hat{p}_s = \frac{\exp\left(\hat{\alpha}_0 + \sum_j \hat{\alpha}_j x_{ji}\right)}{1 + \exp\left(\hat{\alpha}_0 + \sum_j \hat{\alpha}_j x_{ji}\right)}, \tag{19}$$

where α's are regression coefficients and are estimated directly from maximum likelihood. Likewise, individual covariates can be modeled directly using logit (or other appropriate) link functions (Nichols and Kendall, 1995; Fujiwara and Caswell, 2002; Williams et al., 2002). Akaike's information criterion (AIC) or estimates of slope parameters can be used to select models or test hypotheses about the influence of environmental or individual covariates on model parameters (Burnham and Anderson, 2002). Programs MARK and MSSURVIV provide a flexible framework for estimation and modeling of parameters for multi-state CMR models, and for hypothesis testing and model selection (Hines, 1994; White and Burnham, 1999). Faustino et al. (2004) is a good example of the way multi-state mark-recapture approach can be used to estimate disease transition probabilities in a natural population.

State-specific fertility rates, F_k (*sensu* Caswell, 2001), can be estimated as $F_k = p_k m_k$, where p_k and m_k are the survival probability and fecundity, respectively, of individuals in disease state *k*. If reproductive data are collected using pre-breeding censuses and if separate estimates of survival of young are available, p_k should be replaced by survival of juveniles produced by individuals in state *k* (Caswell, 2001).

4. Model modification

4.1. *Density- and frequency-dependence*

Dynamics of many diseases are heavily influenced by density of hosts and prevalence of the disease because densities of susceptible or infective hosts can influence state-specific survival and transition probabilities, and/or reproductive rates (Hochachka and Dhondt, 2000; Begon et al., 2002). In many situations, the probability of infection increases as the density of infective hosts or prevalence of the infection increases (Wilson et al., 2002; Cotter et al., 2004). Thus, it is essential to consider the influence of density- and frequency-dependent processes on disease transmission dynamics.

The effect of population density can be incorporated into the model by letting one or more model parameters to be functions of population density such that (Caswell, 2001):

$$\boldsymbol{n}(t+1) = \mathbf{A}_n(t), \tag{20}$$

where the subscript *n* indicates that one or more entries (or components thereof) of the projection matrix depend on the population density, which may be the total density of the population or the density of one or more of the disease states. The relationship between overall or state-specific population density and a model parameter can take many forms, but it must satisfy the constraint that transition from any disease state to all other states should be bounded by 0 and 1. One can use existing (e.g., McCallum et al., 2001) or empirically derived functions to model the probability of disease transmission (and/or recovery if appropriate) as a function of overall or state-specific population density. Survival and reproductive rates may be modeled as function of total or state-specific population density using the logistic, Beverton–Holt, Ricker or empirically derived functions (Caswell, 2001). Likewise, frequency- or prevalence-dependence in the disease transmission and/or recovery parameters may be incorporated into the model by letting β and/or γ to be functions of density of infective individuals relative to the total population size (i.e., *I*/*N*).

It is well known that density-dependent models of population dynamics exhibit a variety of non-linear dynamics (May, 1974; Caswell, 2001). Likewise, dynamics of density- or frequency-dependent models are essentially non-linear, and may exhibit a variety of behaviors (Fig. 5B–D). Depending on the functional form of density-dependence and initial param-

eter values, the disease can die out in the long run, invade the population and persist indefinitely, or the population may ultimately recover from the infection. It is advisable to test for the presence of frequency- or density-dependence in parameter(s) of interest. This can be easily achieved by modeling, for example, β and γ as functions of current or past density of individuals in a given state, total population size, or I/N as described above. If density- or frequency-dependence is detected, an appropriate functional form of such relationship should be determined, preferably empirically. Behaviors of some continuous time frequency- or density-dependent disease models have been examined by Tapaswi et al. (1995), Thrall et al. (1995), Gao and Hethcote (1992), Allen et al. (2003), Chattopadhyay et al. (2003), and Greenhalgh et al. (2004).

4.2. *Stochasticity*

Unpredictable variation in the environment is a rule rather than an exception in the natural world. Such environmental changes can influence characteristics of the host as well as the pathogen, and therefore, the dynamics of the disease. Studies of childhood diseases indicate that stochasticity can profoundly influence disease epidemiology at the population level. Consequently, it is often necessary to incorporate the effect of stochastic forces into disease models (Lloyd, 2001; Keeling et al., 2001; Keeling and Grenfell, 2002; Keeling and Rohani, 2002). Recent examples of continuous-time stochastic models of disease dynamics include Dexter (2003), McCormack and Allen (2005), and Tornatore et al. (2005). Here, we present methods for incorporating effects of environmental stochasticity into the matrix-based epidemiologic models (Tuljapurkar, 1990; Caswell, 2001).

The main components of stochastic model formulation include a model of environmental states, a function to associate a matrix to each of the environmental states, and the sequence of population vectors $\mathbf{n}(t)$ that result from applying the matrices to initial population vector $\mathbf{n}(0)$ (Caswell, 2001). The three commonly used models to describe stochastic environments are independent and identically distributed sequences depicting the environment, discrete state Markov chains assuming a finite number of states, or the environmental state as an autocorrelated continuous state variable (autoregressive moving average models). Once the model is chosen, the model of the environment is then linked to the vital rates by selecting a projection matrix (or entries of the matrix) associated with a particular environmental state. Linking vital rate and the environment is followed by projection of the initial population vector $\mathbf{n}(0)$ as (Caswell, 2001):

$$\mathbf{n}(t+1) = \mathbf{A}_t\mathbf{A}_{t-1}, \ldots, \mathbf{A}_0\mathbf{n}(0). \tag{21}$$

Many aspects of stochastic models can be studied using simulations, but analytical approximations may also be used (Tuljapurkar, 1990; Caswell, 2001). For example, to estimate the stochastic population growth rate, one may assume a stochastic sequence generated by a stationary stochastic process and select $\mathbf{A}_t$ from an ergodic matrix set. When $t=0$, the initial population vector $\mathbf{n}(0)=\mathbf{n}_0$, with the population size at time t given by (Tuljapurkar, 1990; Caswell, 2001):

$$N(t) = ||\mathbf{A}_{t-1}\mathbf{A}_{t-2}, \ldots, \mathbf{A}_0\mathbf{n}_0||. \tag{22}$$

The stochastic growth rate is then approximated as

$$\log \lambda_s = \lim_{t\to\infty}\frac{1}{t}\log N(t) = \lim_{t\to\infty}\frac{1}{t}\log ||\mathbf{A}_{t-1}, \ldots, \mathbf{A}_0 n_0||. \tag{23}$$

The analytical solution, though feasible for small matrices, is an impractical task for diseases with may disease states, and simulations of the average growth rate over a long time provide the maximum likelihood estimate of λ_s (Caswell, 2001); stochastic net reproductive ratio R_0 can be estimated similarly. The sensitivity and elasticity of the stochastic growth rate and net reproductive ratio to model parameters can be estimated via stochastic simulations (Caswell, 2001).

5. Discussion

Effective management of infectious diseases necessitates an understanding of factors or processes that determine the course of infection within a host and transmission dynamics of the disease in a host population. Although controlled laboratory infection studies provide critical information regarding infectious disease pathogenesis, such studies by themselves are not sufficient to understand or predict the transmission dynamics of a disease in a host population. To this end, mathematical models have played a pivotal role (Anderson and May, 1991; Riley et al., 2003; Rohani et al., 2003). For example, models of AIDS (Anderson and Garnett, 2000; Coutinho et al., 2001; Levin et al., 2001), SARS (Enserink, 2004; Weinstein, 2004), and measles (Bolker and Grenfell, 1993; Keeling, 1997; Grenfell et al., 2002; Keeling and Grenfell, 2002) have provided valuable insights regarding the processes governing disease dynamics, and have contributed substantially to the formulation and implementation of disease control programs.

Although infectious diseases of humans and domestic livestock have been the focus of epidemiological modeling in the past, infectious diseases of wildlife have recently received much attention (Cleaveland et al., 2001; Grenfell et al., 2001; Swinton et al., 2001). This is because many wildlife populations serve as reservoir or secondary hosts for many infectious diseases of humans and domestic animals (De Leo et al., 2002; Low and McGeer, 2003; Enserink, 2004), and also because infectious diseases have been found to be responsible for the decline or demise of some wildlife populations (Cleaveland et al., 2001; De Leo et al., 2002). In addition to the conservation implications of wildlife disease research, the economic and public health ramifications of transmission of the disease from this interface makes the understanding and management of wildlife diseases critical. Thus, a better integration of empirical data, parameter estimation and epidemiological models is of paramount importance.

In this paper, we have presented a framework for modeling the dynamics of infectious diseases in discrete time. The framework of the model is based on the well-founded theory of matrix population models (Caswell, 2001), and is appropriate for modeling infectious diseases of humans, wildlife or domestic livestock. Our model has several desirable properties. First, this model can be applied to any disease, regardless of the number of diseases states. Second, the model is amenable to rigorous parameterization within the framework of multi-state capture-mark-recapture (CMR) modeling. Third,

our model allows rigorous estimation of important quantities such as the net reproductive ratio (R_0) of the disease and growth rate of the population (λ). Fourth, our model allows quantification of the sensitivity and elasticity of R_0 and λ to changes in model parameters using standard techniques. Fifth, our model provides a flexible framework for incorporating the density- or frequency-dependence and stochastic influences into the model. Finally, analysis of this model is straightforward, and does not require advanced mathematical training. We believe that the aforementioned advantages of our model will help integrate theoretical and empirical studies of infectious diseases, and in so doing, will contribute to the understanding of factors and processes influencing the disease dynamics.

One of the most difficult challenges in modeling wildlife diseases is the estimation of model parameters from field data (Begon et al., 1998). Most existing models of wildlife diseases have been parameterized inconsistently, frequently with the best guess estimates of parameter values. Many studies of wildlife populations utilize mark-recapture methodologies, and such studies can provide data that are amenable to multi-state capture-mark-recapture (CMR) models. Multi-state CMR models allow rigorous estimation of many of parameters required by the disease model presented here. Additionally, these parameters can be modeled as functions of environmental and individual covariates, and this permits rigorous testing of hypotheses regarding the influence of individual or environmental covariates on model parameters. The implementation of the information-theoretic approach within the CMR modeling framework allows multi-model comparison, and selection of the most parsimonious model using the Akaike's information criterion (AIC). Finally, software packages such as program MARK provide a flexible architecture for the implementation of multi-state CMR models for parameter estimation and modeling (White and Burnham, 1999; Williams et al., 2002).

Despite their enormous potential for providing rigorous estimates of parameters for models of infectious diseases, multi-state CMR models have received little attention in the epidemiological literature. Faustino et al.'s (2004) study is an excellent example of the application of CMR framework for estimating disease transmission and recovery rates from field data. They investigated the seasonal variation in survival probability, the encounter rate, and transmission and recovery rates of *Mycoplasma gallisepticum* infection in a house finch population over 3 years. Effects of sex and temperature were also examined, and parameters were estimated using the most parsimonious model selected from a candidate model set (Faustino et al., 2004).

In summary, the model presented here provides a flexible framework for modeling the dynamics of infectious diseases with discrete disease states. The disease model is effectively integrated with parameter estimation using multi-state CMR models, and allows rigorous estimation of important quantities such as net reproductive ratio R_0 of the disease and growth rate of the population, and permits estimation of the sensitivity and elasticity of R_0 and λ to model parameters. Moreover, the model allows a flexible framework for incorporating influences of overall or state-specific density of the population, prevalence of the disease, and vegaries of stochastic influences. With the growing demand for robust estimates of model parameters and the need for a unified protocol in epidemiological modeling (Koopman, 2004), the modeling framework outlined in this paper provides the much needed impetus towards the effective integration of theoretical and empirical epidemiological research.

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Appendix I

A.1. *Estimating R_0 for the SIR model*

For the SIR model in (Eq. (2)), the transition matrix **T** is

$$\mathbf{T} = \begin{pmatrix} p_s(1-\beta) & 0 & 0 \\ p_s\beta & (1-\gamma)p_i & 0 \\ 0 & p_i\gamma & p_r \end{pmatrix}, \tag{A.1}$$

where the element t_{ij} quantifies the probability that an individual in disease state j at time t is alive and in state i at time $t+1$. The entry f_{ij} of the reproductive matrix **F** in a disease model dynamics is the rate at which i-type new infections are produced by infective individuals in stage j. Because there is only one infective state in the SIR model, only one type of infection is produced by only one type of infectives; consequently, only the entry f_{22} is nonzero. If transmission of the disease is strictly horizontal, the fertility matrix is

$$\mathbf{F} = \begin{pmatrix} 0 & 0 & 0 \\ 0 & p_s\beta & 0 \\ 0 & 0 & 0 \end{pmatrix}. \tag{A.2}$$

Note that this definition of f_{22} is based on the assumption that infection occurs toward the end of the interval (t to $t+1$); this assumption can be relaxed or modified as desired. The fundamental matrix **N** is (Caswell, 2001):

$$\mathbf{N} = (\mathbf{I}-\mathbf{T})^{-1} = \begin{pmatrix} \dfrac{1}{-p_s+p_s\beta+1} & 0 & 0 \\ \dfrac{p_s\beta}{(-p_s+p_s\beta+1)(-p_i+p_i\gamma+1)} & \dfrac{1}{(-p_i+p_i\gamma+1)} & 0 \\ \dfrac{-p_ip_s\beta\gamma}{(-p_s+p_s\beta+1)(-p_i+p_i\gamma+1)(p_r-1)} & \dfrac{-p_i\gamma}{(-p_i+p_i\gamma+1)(p_r-1)} & \dfrac{-1}{p_r-1} \end{pmatrix}. \tag{A.3}$$

The next generation matrix **R** is the product of the fertility and the fundamental matrices:

$$\mathbf{R}=\mathbf{FN}=\begin{pmatrix} 0 & 0 & 0 \\ \dfrac{p_s^2\beta^2}{(-p_s+p_s\beta+1)(-p_i+p_i\gamma+1)} & \dfrac{p_s\beta}{(-p_i+p_i\gamma+1)} & 0 \\ 0 & 0 & 0 \end{pmatrix}, \tag{A.4}$$

where r_{ij} (ij-th entry of the matrix **R**) quantifies the expected number of i-type new infections produced by an infective individual starting life in state j over the duration of the infection (i.e., lifetime of the infection). The dominant eigenvalue of the matrix, **R** is an estimate of the basic reproduction ratio R_0 of the disease:

$$R_0 = \frac{p_s\beta}{(1-p_i+p_i\gamma)}. \tag{A.5}$$

Appendix II

B.1. Sensitivity of R_0 to the SIR model parameters

The sensitivity of R_0 to changes in model parameters is obtained by differentiating R_0 with respect to each variable in Eq. (A.5):

$$\frac{\partial R_0}{\partial \beta} = \frac{p_s}{-p_i+p_i\gamma+1}, \tag{B.1}$$

$$\frac{\partial R_0}{\partial \gamma} = \frac{-p_s p_i \beta}{(-p_i+p_i\gamma+1)^2}, \tag{B.2}$$

$$\frac{\partial R_0}{\partial p_s} = \frac{\beta}{-p_i+p_i\gamma+1}, \tag{B.3}$$

$$\frac{\partial R_0}{\partial p_i} = \frac{p_s\beta(\gamma-1)}{(-p_i+p_i\gamma+1)^2}. \tag{B.4}$$

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