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REVIEW

Disease dynamics in wild populations: modeling and estimation: a review

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Abstract Models of infectious disease dynamics focus on describing the temporal and spatial variations in disease prevalence, and on understanding the factors that affect how many cases will occur in each time period and which individuals are likely to become infected. Classical methods for selecting and fitting models, mostly motivated by human diseases, are almost always based solely on raw counts of infected and uninfected individuals. We begin by reviewing the main classical approaches to parameter estimation, and some of their applications. We then review recently developed methods which enable representation of component processes such as infection and recovery, with observation models that acknowledge the complexities of the sampling and detection processes. We demonstrate the need to account for detectability in modeling disease dynamics, and explore a number of mark–recapture and occupancy study designs for estimating disease parameters while simultaneously accounting for variation in detectability. We highlight the utility of different modeling approaches and also consider the typically strong assumptions that may actually serve to limit their utility in general application to the study of disease dynamics (e.g., assignment of individuals to discrete disease states when underlying state space is more generally continuous; transitions assumed to be simple first-order Markov; temporal separation of hazard and transition events).

Keywords Detection probability · Disease models · Mark–recapture · Multi-state models · Parameterization · Time series · Uncertain states

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Introduction

> "*Disease is a physical process that generally begins that equality which death completes…*"—S. Johnson

Mathematical models play a significant role in our understanding, and management, of the epidemiology and dynamics of parasite–host interactions (hereafter we refer to this interaction generically as 'disease', which we define as an unhealthy state of the host resulting from a micro-parasitic infection, and consider the interaction of host and pathogen in the context of 'disease models'). Despite the importance of such models, their use in the analysis and management of disease in wildlife populations has been limited, relative to their use in the study of human disease (although there are clearly exceptions: Roberts 1996; Smith et al. 2001; Smith and Cheeseman 2002; Ramsey et al. 2002; Schauber and Woolf 2003; Fenichel and Horan 2007;

Wasserberg et al. 2009 are all good examples of the application of mathematical models in the management of wildlife disease; see Delahay et al. 2009 for a recent overview).

In this review, we do not attempt to provide a thorough collation of empirical evidence that disease can significantly impact the dynamics of wild populations. The reader is referred to recent reviews by Grenfell and Dobson (1995) and Hudson et al. (2002). We will accept that, in many cases, disease does impact wild populations. We focus instead on the modeling of disease dynamics, and the estimation of disease model parameters, where the latter is clearly fundamental to any empirical study of the effect of disease. The behavior (and utility) of population dynamics models, including disease models, is potentially affected by both the functional form and the parameters of the model. For disease models, this includes the way in which interactions between infected and susceptible hosts are modeled, and by the accuracy and precision of the estimates used to parameterize the model. (Note: we do not explicitly discuss the use of these models—or models in general—in an adaptive management context, e.g., Wasserberg et al. 2009, or the sensitivity of model-based management to model structure and parameter uncertainty—this has been treated exhaustively elsewhere; Williams et al. 2002.)

Estimation and disease models: the fundamental challenge

Most disease models are constructed by subdividing the population into discrete divisions ('compartments') reflecting the underlying disease 'state' of the individual. The dynamics of such models (see "Appendix A" for a brief review of classical Ross–Kermack–McKendrick compartment models in continuous and discrete time) are governed by the rate of transition between states. Fitting these models to time series data—typically consisting of the relative proportions of the sampled populations in each disease state—is to model and estimate the transitions among disease states, the rate or probability of becoming infected, the odds of recovering if infected, and the effects of infection on fertility and survival.

Some model parameters are generally difficult to estimate, others often more accessible. For example, transmission of the pathogen from one individual to another is almost always inferred rather than seen. How many uninfected individuals will contract the disease, and what factors influence that number? We may see that finch 254 (symptomatic) visits a feeder, that finch 361 (asymptomatic) arrives soon after 254 flies off, and that 361 develops symptoms a few days later. Who infected 361? Our data may let us estimate the odds that it was 254, but we cannot know for sure. For other transitions (e.g., disease progression, mortality, and recovery), more direct and reliable approaches may be available. Plants, invertebrates and "lower" vertebrates (i.e., systems where the probability of 'detecting' the event is generally high—generally because they are sessile or effectively so) can be infected and then monitored for symptoms and their consequences, immune response, and infectivity in controlled conditions. Human diseases are closely monitored once patients enter the health care system. Even patterns of movement and contact (proximity or interactions that could allow transmission) can often be studied by direct observations.

For many wild populations, however, parameter estimation is complicated by the fact that sampling such populations is rarely a census (or, for that matter, random). In most wild populations, sampling and inference are strongly impacted by incomplete observations of the system state. For instance, estimation of demographic parameters from marked individuals often requires estimation of nuisance parameters such as encounter probabilities (Williams et al. 2002).

It is also very rare to have data on all disease states, and there is often considerable uncertainty about those data that are available. As such, information about partially or unobserved states often has to be an output from a fitted model, rather than an input to modeling and estimation. Our goal, then, is to see the invisible, conditioned on data on some states which are somewhat more visible, but subject to some uncertainty about what state we are actually observing.

In the following, we briefly review the fitting of 'classical disease models' to time series data, focussing on the situation where data from marked individuals is unavailable, or where 'detection probability' is either known or assumed not to influence estimation of other parameters. In particular, we consider the generally difficult problem of estimating disease transmission rate. We then discuss recent applications of capture–mark–reencounter (CMR) and related approaches (e.g., occupancy) to estimation when data from marked individuals are available, and where accounting for imperfect detection of individuals in one or more disease states is potentially important. We follow with a review of several challenges in adapting some of these approaches to disease models in particular.

Parameter estimation for disease dynamics models: classical approaches

> "*Like other occult techniques of divination, the statistical method has a private jargon deliberately contrived to obscure its methods from non-practitioners…*"—G.O. Ashley

In 'classical' disease models transmission rate is determined by the contact parameter β.[1] More generally, we want to parameterize a model

$$\text{New case rate}(t) = f(t, \beta, S, I, \ldots), \quad (1)$$

where S are susceptible individuals, I are infected/infectious individuals, and so on.

Two aspects of particular interest are determining patterns of seasonal variation, and identifying "environmental drivers", measurable covariates (rainfall, temperature, or age of the organism) that have predictive power for transmission rates. Drivers point towards mechanisms of transmission, and therefore at possible interventions to reduce transmission. Precise estimation of f has practical value (will culling help? how much? how soon?), but knowing the right form of the model (which covariates matter?) is often far more important both scientifically and practically. Here, we review the diversity of methods that have been applied to estimating f—we focus in particular on necessary conditions and assumptions for these methods to be reasonably robust, given the data.

Trajectory matching

Trajectory matching (also known as *calibration* or the *nonlinear least squares* method) makes the heroic assumptions that the dynamics are deterministic, and that all discrepancies between model and data are due to measurement error. Typically, the observations y_{ij} (of state variable i at observation time t_j) are assumed to be

$$y_{ij} = X_i(t_j; \theta, x_0) + e_{ij} \quad (2)$$

where $X(t; \theta, x_0)$ is the solution at time t of a differential or difference equation model as a function of parameters θ and initial state $x(0) = x_0$, and the errors e_{ij} are *iid* (independent and identically distributed) random Gaussian with zero mean and known variance σ_i^2. This gives an explicitly computable likelihood, $L(y_{ij}|\theta, x_0) = \phi((y_{ij} - X_i(t_j))/\sigma_i)$ where ϕ denotes the Gaussian(0,1) probability density. So even if some state variables are not observed (which is frequently the case), fitting the dynamic model is reduced to a nonlinear regression problem. More mechanistic models for observation error are also possible, for example (in the case of human diseases) assuming that reported new cases are a binomial sample from actual new cases with a (known or estimated) reporting probability p.

The benefits and computational simplicity of trajectory matching for simple ODE (ordinary differential equation) models have made them widely popular. In a recent typical application, Miller et al. (2006) used trajectory matching to fit six *SI*-type models for chronic wasting disease in captive mule deer populations, in order to determine the relative importance of different transmission pathways.

[1] or in structured population models by the contact matrix ($\boldsymbol{\beta}_{ij}$), but for clarity we limit the exposition to unstructured models.

State reconstruction and 'one-step-ahead' fitting

Fitting also reduces to nonlinear regression if we pretend instead that all discrepancies between model and data are due to stochasticity in the *dynamics*, while the *data* are exact. Additive stochasticity is typically assumed for simplicity, so that

$$y_{ij} = X_i(t_j - t_{j-1}; \theta, y_{j-1}) + e_{ij} \quad (3)$$

and we again have an easily computed likelihood. What we usually do not have is the complete state vector y (since, again, some states are typically unobserved), which would seem to preclude using Eq. 3 for inference.

For some diseases, however, this can be overcome by approximately "reconstructing" unobserved states. Pre-vaccination era childhood diseases are the original and canonical example (Hedrich 1933; Fine and Clarkson 1982). Because every person gets the disease once and only once, the average reporting rate p is given by the ratio between the number of reported cases and the number of births. In the simplest version, the unobserved susceptible state S is assumed to obey a mass balance equation

$$\begin{aligned} \frac{dS}{dt} &= B(t) - C(t)/p \,(\text{continuous time}) \\ S(t+1) &= S(t) - C(t)/p + B(t) \,(\text{discrete time}) \end{aligned} \quad (4)$$

where $B(t)$ is the birth rate [instantaneous, or total for the interval $(t, t+1)$], $C(t)$ is the number of reported cases, and p the reporting rate (assumed known). In effect, a multivariate model such as

$$\begin{aligned} C(t+1) &= f(S(t), C(t), t, \theta) + \text{``noise''} \\ S(t+1) &= S(t) - C(t)/p + B(t) \end{aligned} \quad (5)$$

is turned into a univariate time series model for case reports $C(t)$, by solving the second equation

$$S(t) = S(0) + \sum_{j=0}^{t} B(t-j) - \frac{1}{p}\sum_{j=0}^{t} C(t-j) \quad (6)$$

and substituting this into the first. The initial condition $S(0)$ becomes one more parameter to estimate when fitting the first line of Eq. 5 by maximum likelihood.

Two important features of susceptibles reconstruction are the direct tie between birth rate variability and disease dynamics, and how easy it is to estimate the form of the transmission function f rather than assuming a standard rate equation. Fine and Clarkson (1982) used susceptible reconstruction to show that the contact rate parameter $\beta(t)$ in a mass action transmission model $\beta(t)SI$ showed

similar patterns of variation in years of major and minor measles outbreaks in England and Wales, hence the variation between years was not driven by changes in β. Ellner et al. (1998), using a nonparametric (neural network) estimate for f, showed that the interannual variability in measles that had previously been interpreted as deterministic chaos could be explained by demographic stochasticity and variation in birth rates. Finkenstädt and Grenfell (2000) extended the susceptibles reconstruction method to include variable reporting rates, and fitted a discrete-time model to measles case reports from England and Wales, 1944–1964, with contact rate function $\beta_t S_t^a I_t^b$, β_t being periodic with period 1 year. The model fitted very well the observed biennial pattern in the data, and showed that the previously unexplained episodes of annual cyclicity were caused by increased birth rate during the late 1940s "baby boom". More refined variants have also allowed a possible delay between birth and recruitment into the susceptible class (e.g., if only school-age children are "really" exposed to the possibility of infection), and relaxed the assumption of permanent immunity tacit in Eq. 4.

Living without the likelihood: probe matching, and indirect inference

Once we admit stochasticity in *both* process and observation, epidemic models become state-space models, usually partially observed Markov processes. In this section, we review some of the simpler methods that have been applied effectively to infectious disease dynamics models. (We introduce state-space and related models in more detail in "State-space and hidden Markov models", where we consider the additional complication of imperfect detection.)

Probe matching means that fitting is based on numerical quantities ("probes") that can be computed by analyzing or simulating the model; statisticians would file this under 'Method of Moments'. A classical example is estimation of the basic reproductive ratio R_0 (see "Appendix A") and deriving from this estimates of mean transmission parameter $\beta(t)$ using the steady-state prediction that $R_0 x^* = 1$ where x^* is the fraction of susceptible individuals in the population (e.g., Anderson and May 1992; and "State-space and hidden Markov models"). Statistically "informal" approaches like this abound, e.g., tuning β to match the average number of cases per year. As one recent example, for a model of plague in prairie dogs, Webb et al. (2006) estimated the number of new fleas produced per blood meal by requiring the steady-state flea load on prairie dogs in the absence of plague in the model to match the median flea load in uninfected prairie dog towns. Formal methods are exemplified by martingale methods, in which one or more expressions shown to be zero-mean martingales (under the operative assumptions) are equated to zero, yielding equations that can be solved for unknown parameters (Becker 1989; Andersson and Britton 2000), and inference can be based on Martingale Central Limit Theorems. Similarly, moment equations for stochastic differential equation models can sometimes be derived from the infinitesimal operator (Hansen and Scheinkman 1995), but to our knowledge this approach has not been used on epidemic models.

Indirect inference uses moments derived from an intermediate statistical model. The key references are Brown et al. (1993) and Gouriéroux and Monfort (1996). For example, the "moments" of the data might be the coefficients $\hat{\alpha}_j$ in a Gaussian linear autoregressive (AR) model fitted to case report data. The "moments" of the model are computed by running a long simulation of the model (including process noise, measurement errors, incomplete state observation, and all other presumed features of the real data) and then fitting the same AR model to the simulation output, obtaining coefficients $\bar{\alpha}_j$. The fitting criterion is a quadratic form in the vector of discrepancies $(\hat{\alpha}_j - \bar{\alpha}_j)$, ideally chosen for optimal statistical efficiency based on an estimated Hessian.

The appeal of indirect inference is that if you can simulate the model, then you can fit it, and no computations involving the model's likelihood are needed. The intermediate statistical model does not need to be "right", it just needs to be parameter-rich enough to distinguish between better and worse simulations of the model. Related (and asymptotically equivalent) methods include Efficient Method of Moments (EMM) (Gallant and Tauchen 1996) in which the moments are derived from the score function of the intermediate statistical model fitted to the real data and evaluated on simulated time series from the mechanistic model, and Simulated Quasimaximum Likelihood (SQML; Smith 1993) in which the summary statistic is the likelihood of the observed data under the intermediate model fitted to simulation output. Ellner et al. (1998) applied EMM to measles case report data in order to estimate the magnitude of seasonal variation in $\beta(t)$. An implementation of SQML is available as the function NLF in the R package `pomp` (King et al. 2009).

Working with the likelihood

Working with the likelihood in practice means Monte Carlo methods, typically MCMC or Sequential Importance Sampling (SIS, also called "particle filters"). Ionides et al. (2006), King et al. (2008), Cauchemez and Ferguson (2008), and Newman et al. (2009) represent the state of the art in terms of application to disease models. The appeal of

these methods is the degree of biological detail, and honesty about data insufficiencies and inaccuracies, that the state-space model accommodates. For example, King et al. (2008) were able to parameterize *SI*-type models for cholera with two modes of transmission and multiple disease states representing stages in gradual loss of immunity from time series of only death counts. In contrast to previous studies, they estimated that immunity waned very quickly, within weeks to months.

In concept, Monte Carlo methods solve all our problems. In practice, off-the-shelf methods often require development of customized MCMC samplers to handle new (model × data) set situations. Using off-the-shelf methods (BlackBox Component Builder 1.5 in WinBUGS), New et al. (2009) fitted three alternative state-space models for Red Grouse (*Lagopus l. scoticus*) population cycles, one presuming that the cycles were driven by grouse–parasite interactions. For two of the three models, they noted that diagnostics indicated poor mixing of the MCMC sampler ("only the combined model displayed good mixing for all MCMC chains"; New et al. 2009, p. 410), and cautioned that "posterior densities may not accurately represent the target distribution, leading to questionable inference". Similarly, SIS methods require a careful case-specific fine tuning to avoid "particle depletion", the SIS analog of poor mixing (see, for example, Sect. 3.2 of Newman et al. 2009).

It seems clear that the future belongs to simulation-based methods that work with the full state-space likelihood. It is especially encouraging that the newest methods (SIS, EMM) completely avoid the need for likelihood computations on trajectories—they approach the convenience and versatility of indirect inference methods (which only require the ability to simulate the model), but in theory can achieve the efficiency of maximum likelihood. This bodes well for the development of general-purpose software for nonspecialist users; the `pomp` (King et al. 2009) and `CollocInfer` (Hooker and Xiao 2009) packages in R are small steps in this direction.

Enhancing the signal: estimation from marked individuals

> "*If* $\hat{p} < 0.1$, *you're better off going home, having a beer, and pulling the covers over your head…*"—K.P. Burnham

Disease models are fit to time series of changes in relative abundance of individuals in a given disease state. The canonical estimator for abundance is $\hat{N} = C/\hat{p}$, where C is the count statistic and $\hat{p}$ is the estimated detection probability. When the detection probability is <1, as is generally the case in wild populations, strong inference concerning change in abundance will be generally be conditional on adjusting the observed count statistic for the estimated detection probability.

The need to account for differences in detection probability becomes apparent when examining quantities such as apparent disease prevalence in wild populations. Prevalence is usually defined as the proportion of all individuals in a target population that are infected over some time period (Mausner and Bahn 1974), and time series of prevalence are often 'the data' to which classical disease models are fit (cf. "Parameter estimation for disease dynamics models: classical approaches"). For instance, Senar and Conroy (2004) and Jennelle et al. (2007) considered a simple two-state disease system where individuals were classified as either 'infected', or 'not infected'. The expected count of individuals in a given disease state s at some time i is given as

$$E(C_i^s) = \hat{p}_i^s \hat{N}_i^s \tag{7}$$

where C_i^s is the observed count of individuals in a particular disease state s at time i, $\hat{p}_i^s$ is the estimated detection probability of a individual in disease state s at time i, and $\hat{N}_i^s$ is the estimates population size of individuals in disease state s at time i. Rearranging this expression yields the estimate of $\hat{N}_i^s$ as

$$\hat{N}_i^s = \frac{C_i^s}{\hat{p}_i^s} \tag{8}$$

Since prevalence δ is defined as the proportion of individuals in a disease state s in a population consisting of K possible disease states

$$\delta_i^s = \frac{N_i^s}{\sum_{s=1}^{K} N_i^s} \tag{9}$$

then if the only source of heterogeneity in detection probability is disease state s,

$$\hat{\delta}_i^s = \frac{\hat{N}_i^s}{\sum_{s=1}^{K} \hat{N}_i^s} = \frac{\left(\frac{C_i^s}{\hat{p}_i^s}\right)}{\sum_{s=1}^{K} \left(\frac{C_i^s}{\hat{p}_i^s}\right)} \tag{10}$$

where $\hat{\delta}_i^s$ is the corrected prevalence at time i for a given disease state s (Jennelle et al. 2007). This expression is easily generalized to accommodate other sources of heterogeneity that may be orthogonal to the disease state (Appendix A in Jennelle et al. 2007).

It is straightforward to demonstrate the potential problems in failing to account for detection probability. Consider a situation where true prevalence does not vary over time (say, over a single year), but where there is some seasonal pattern of variation in state-specific detection probability (Fig. 1). The time series of *apparent* disease

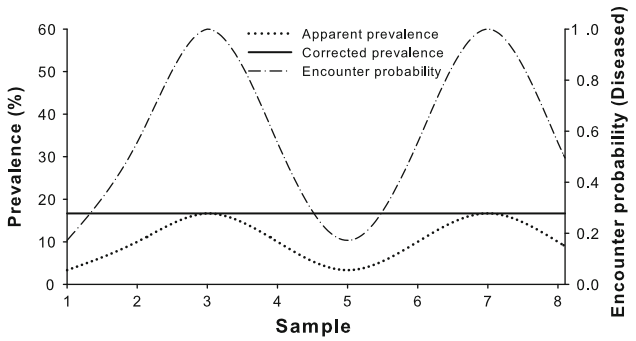

Fig. 1 Illustration showing how cyclic patterns of apparent (observed) prevalence could be an artifact of cyclic patterns in detection probabilities. In this case, only the detection probability of diseased individuals varies over time, while the detection probability of healthy animals (with respect to the condition under study) is time invariant (i.e., $p^{healthy} = 1.0$). In this example, apparent prevalence varies temporally, whereas true prevalence is constant over time. Adapted from Jennelle et al. (2007)

prevalence would suggest a strong seasonal dynamic, whereas, in fact, *true* prevalence is constant. The conclusion of seasonal variation could be readily—and potentially erroneously—accepted because it is well known that seasonal variation in various 'environmental' factors can strongly influence the dynamics of disease in many cases (Altizer et al. 2006; Grassly and Fraser 2006). For example, Hosseini et al. (2004) described a demographic and behavioral model to explain strongly seasonal dynamics in the apparent (uncorrected) prevalence of Mycoplasma infections in House Finches (*Carpodacus mexicanus*) (Altizer et al. 2004). However, Faustino et al. (2004), Jennelle et al. (2007) and Conn and Cooch (2009) found that detection probability of House Finches varied with disease state, and exhibited strong seasonality in state-specific detection probabilities. Similar results have been reported by Senar and Conroy (2004) in another bird species, Ozgul et al. (2009) in tortoises, and Murray et al. (2009) in frogs. Moreover, even if there are no differences in detection probabilities as a simple function of disease state, apparent prevalence can still be biased at the population level in some cases. For example, if there are differences in $\hat{p}_i^s$ as a function of age (or any other single factor), then there will be bias in apparent prevalence if the observed (apparent) proportion of diseased individuals in each of the age-specific classes is different.

Differential detectability of individuals as a function of disease state is perhaps not surprising in some situations. If disease influences one or more factors influencing the encounter process (e.g., a diseased individual might be more or less prone to approach a baited trapping station than a healthy individual, or a diseased individual may be more or less visible in resighting efforts), we might anticipate differences in encounter probabilities. While such differences do not preclude the possibility that temporal or spatial pattern in apparent prevalence reflects factors unrelated to sampling (e.g., Hosseini et al. 2004), it seems prudent to consider the possible role of sampling bias. Failing to account for state-specific differences in detection probability can potentially confound analysis of variation in prevalence. For example, Conner et al. (2000) showed that estimates of prevalence of chronic wasting disease (CWD) in mule deer could be strongly biased by differential susceptibility to harvest sampling between diseased and nondiseased individuals.

Although it is possible to adjust apparent prevalence data for detection probabilities (sensu Jennelle et al. 2007), using such adjusted estimates as 'data' for further analysis amounts to 'doing statistics on statistics'. We instead prefer methods which formally account for state-specific detection probabilities as part of the overall estimation framework. Such methods are the subject of the remainder of this section.

Applications of classic CMR models for disease models

In their recent book on hierarchical modeling and inference, Royle and Dorazio (2008) provide an excellent—and convenient—comparison between two paradigms for ecological inference. On the one hand, they describe inference based on an 'observation-driven' view, which focuses on the observation model. Observation-driven inference is often characterized by complex models of detection (or encounter) probability under some null (generally binomial) sampling model. In contrast, the 'process-driven' view focuses on the process component of the model. Inference under the process-driven paradigm is frequently characterized by densely mathematical treatments of data, often under the assumption that the data are unbiased observations of the underlying process. Many of the methods discussed in "Parameter estimation for disease dynamics models: classical approaches" arguably fall within this 'process-driven' paradigm. In such cases, the role of observation (sampling) bias is generally overlooked as a possible explanation for 'interesting pattern' in apparent prevalence in wild populations. For example, in their comprehensive reviews of seasonal epidemiology, neither Altizer et al. (2006) nor Grassly and Fraser (2006) discussed sampling as important considerations. There is often an implicit assumption that if the pattern of variation in 'disease' is stationary and recurrent over space–time, then detection (reporting) probability is likely to contribute only to the uncertainty in estimates of model parameters, and is unlikely to be a contributing driver to the overall dynamic pattern.

Here, we consider estimation methods that explicitly account for differences in detection probability, using data from multiple encounters of known individuals. We

refer to this class of models as CMR (capture–mark–reencounter) models, which we take to include models using multiple encounter types, including live recapture or resights, dead recoveries, or both (we consider occupancy models as a special case of the general CMR modeling framework). We consider these methods in terms of three objectives: (1) accurate estimation of the system state (in particular, the number of individuals in the sampled population in each disease state at a given point of time), (2) assessment of the impacts of the pathogen on the demography of the host, and (3) estimation of disease transmission. We distinguish between closed population and open population models, where interest in the former has generally focused on estimation of abundance. In the disease context, the use of closed abundance estimators would be useful for calculating prevalence (within the closed sampling period; objective 1) and for modeling disease transmission between successive closed samples (e.g., in a robust design framework) as a function of abundance or density of each disease state. Closed abundance estimation has been thoroughly reviewed by Borchers et al. (2002), Williams et al. (2002), and Chao and Huggins (2005). The fairly common use of 'list-matching' abundance estimators in human disease studies, where individual patient identification/records are the identifying 'markers', is introduced and reviewed by Yip et al. (1995a, b) and Chao et al. (2004). Here, we consider only open-population and related models.

Open models: single-state

There has been growing adoption of single-state, open CMR models (which we take to include live encounter and dead recovery models in various combinations, as well as patch occupancy models) to the study of disease in wild populations. Such models allow for direct estimation of the possible acute (immediate) effects of disease on one or more demographic components (e.g., survival, population growth rate), while accounting for variation in detection probability. The most common application of this class of models has been in establishing 'single-factor' effects: typically, the morbidity impacts of disease (e.g., Telfer et al. 2002; McCallum et al. 2007; Burthe et al. 2008). In most cases, such analysis takes the form of a quasi-experiment (Schwarz 2002), where individual disease status ('diseased', 'healthy') is used as a classification variable in an ANOVA-type analysis, where differential survival and encounter probabilities between disease states are modeled as linear functions of one or more environmental or demographic covariates. Formal experiments are less common. Notable exceptions are studies by Samuel et al. (1999) and Slattery and Alisauskas (2002).

While the utility of classical open single-state models for establishing impacts of disease on wild populations is clear, there has been a surprising lack of application of models which more fully describe the duration and breadth of demographic impacts of disease. For example, disease may have acute or chronic effects, or both. Construction of models to differentiate between acute (transitory) and chronic (permanent) effects on one or more parameters is straightforward (e.g., Schwartz et al. 2006). While common in human disease studies, we are unaware of an application of such models to study of disease in wild populations. One reason might be the need to condition on known time-of-infection. In an experimental (clinical setting), time-of-infection may be known (established by the investigator). In the wild, time of infection may generally be unknown (discussed in "History matters: memory models, sojourn time, and related issues").

In addition, open CMR models could be used to assess the broader impacts of disease on the demography of the host as a whole. One approach is to consider estimates of population growth as a parameter integrating the combined effects of disease on the demographic processes (net additions and subtractions) of the host population. Two important frameworks for characterizing realized growth of the host population are the temporal symmetry approach (Pradel 1996; see also Link and Barker 2005) and the 'super-population' approach (Schwarz et al. 1993; Schwarz and Arnason 1996).[2] In these models, population growth rate is an estimated parameter, which can be modeled using standard linear models approaches (however, models involving constraints on growth need to be considered carefully. Since growth $\lambda_i = \phi_i + f_i$, then constraining λ as a function of a covariate, like apparent disease prevalence, imposes a structure on the other two parameters which may not be biologically plausible; Barker et al. 2002). Methods for partitioning variation in realized population growth between survival and recruitment have been reviewed by Schwarz and Arnason 1996, Nichols et al. (2000), and Nichols and Hines (2002). The only application of these approaches to study of disease in a wild population we are aware of is a recent study of facial tumor disease in Tasmanian devils (*Sarcophilus harrisii*; Lachish et al. 2007), which used the Pradel (1996) temporal symmetry approach to demonstrate that incidence of facial tumor disease corresponded to a decline in the growth rate of a previously stable population.

Another open population approach which appears to have some potential for application to disease studies is the use of mark–resight models (McClintock and White 2009;

[2] In fact, the two approaches are conceptually equivalent, with the primary differences being (1) the handling of losses on capture, and (2) whether the estimation conditions on first encounter (e.g., Link and Barker 2005) or not (e.g., Schwarz and Arnason 1996).

McClintock et al. 2009a, b). Mark–resight models use encounters (resightings) of marked individuals, but they also incorporate additional data via sightings of unmarked individuals into the estimation framework. Mark–resight data may be used to estimate abundance analogous to the classical closed capture models, but often assume sampling is with replacement. When sampling is under the robust design (Kendall et al. 1995), mark–resight data may be used to estimate abundance, apparent survival, and transition rates between observable and unobservable states in a fashion analogous to the closed capture robust design models. If one wished to estimate abundance separately for infected and uninfected subpopulations, then individuals would need to be diagnosed by sight. These models assume some individuals have been marked prior to sampling, and sampling occasions consist of sighting surveys (instead of capture periods). The mark–resight approach can be applied when the number of marked individuals over some time interval is unknown. The main advantage of the mark–resight approach is that, because costs associated with recapturing individuals can be minimized, it can in many circumstances be a less expensive (and less invasive) alternative to traditional mark–recapture as a means for monitoring.

Open models: multi-state

In the general case where assigned disease state is discrete, multi-state estimation models would appear to be particularly well-suited. Given encounter data from known individuals and when sampling occurs at discrete intervals, multi-state mark–reencounter (MSMR) models (Arnason 1973; Brownie et al. 1993; Schwarz et al. 1993; Kendall et al. 1995) which account for possible state-specific differences in detection probability have seen increasing use in study of diseases in wild populations (see Viallefont and Auget 1999 and Schmidtmann 2008 for applications to human clinical studies). Because of the conceptual consistency of MSMR with analysis of systems where state changes dynamically (such as disease models), we consider MSMR models in more depth (for a thorough review, including extensions to continuous space-time models, see Schwarz 2009). We note that many models which combine open and closed estimation models (e.g., robust design; Kendall et al. 1995; joint live encounter-dead recovery models; Burnham 1993) can be derived as a special case of a MSMR model (Lebreton and Pradel 2002).

MSMR models typically use encounter data from k discrete sampling occasions over s discrete 'states' (where state could be geophysical location, behavioral state, etc). Encounter histories specifying the occasion of the encounter, and the state of the animal at each encounter, provide the data for MSMR models. In addition to common assumptions of capture–mark–reencounter models (Williams et al. 2002), the standard Arnason–Schwarz MSMR model assumes state transitions are first-order Markov—that is, a transition between states between time i and $i + 1$ depends only on the state at time i.

The standard parameterization of the Arnason–Schwarz model consists of

ϕ_i^{dr}, the probability that an individual alive in state d (donor) at time i is alive and in state r (recipient) at time $i + 1$.
p_i^r, the probability that a marked individual alive in state r at time i is encountered.

Clearly, the parameter ϕ_i^{dr} is a compound probability of multiple events. Typical modeling simplifications, often rationalized by the ability of the investigator to tinker with sampling designs, are that (1) survival and other state transitions are temporally separated, and (2) at most one state transition can occur between encounter events. In the case where survival from time i to $i + 1$ does not depend on stratum at time $i + 1$, and assuming that mortality occurs prior to other state transitions, we can write

$$\phi_i^{dr} = S_i^d \psi_i^{dr}$$

where

$S_i^d = \sum_{\forall d} \phi_i^{dr}$, the probability that an animal alive in state d at time i survives and remains in the superpopulation (i.e., does not permanently emigrate) until time $i + 1$
ψ_i^{dr}, the probability of making a state transition (moving) from state d at time i to state r at time $i + 1$, conditional on surviving from i to $i + 1$

Individual model parameters can be modeled as linear functions of one or more covariates of interest, using the appropriate link functions and design matrices.

MSMR methods appear to provide a natural framework for analysis of disease dynamics, and a growing number of studies have applied classical MSMR models to the study of disease dynamics in wild populations (e.g., Faustino et al. 2004; Senar and Conroy 2004; Lachish et al. 2007; Murray et al. 2009; Ozgul et al. 2009). Construction of an MSMR model analogous to a classical compartment disease model (e.g., the sequential *SIR* model; "Appendix A") proceeds naturally: transitions between disease states[3]

[3] Most studies that have used MSMR models have referred to finite state transition probabilities from susceptible to infected states as *force of infection*, either explicitly (Lachish et al. 2007; Ozgul et al. 2009) or implicitly (Faustino et al. 2004). However, Arnason–Schwarz MSMR models estimate the *probability* that an individual will be infected at time $t + 1$ given that it was not infected (susceptible) at time t and survived from $t \rightarrow t + 1$. This interpretation differs from the usual definition of FOI as an instantaneous *rate* (vs. "Appendix A"). It is possible to write MSMR models in terms of instantaneous rates (see the paper by Conn et al., this issue)

are determined by the joint probability of surviving and moving between successive disease states (Fig. 2). Kendall et al. 2004 have shown that it is possible to directly estimate population prevalence under a multi-state robust design.

Reverse-time and MSMR models

Nichols et al. (2000) described application of the reverse-time CMR approach (sensu Pradel 1996; vs. "Introduction", and references therein) to a multi-state situation. If we imagine two discrete states (healthy, diseased), then it is possible to partition variation in growth rate of either state, or both. Consider the case where individuals are marked and recaptured in one of two disease states, with individuals able to make the transition between the two states (we assume here that both infection and recovery transitions are possible). In the case where interest concerns only a single state (say, diseased), relative contributions of both states to the growth of the diseased state can be analyzed. For example, this approach would allow direct assessment of how the rate of increase of the diseased state might be mitigated by some proportional reduction in the contribution from the healthy state, perhaps by a vaccination or similar public health program aimed at reducing the probability of becoming diseased. Alternatively, interest could be on the entire population representing the sum of contributions from the animals in the two states. This approach could be further extended to allow for different disease states in different physical locations. However, because population growth here is defined in terms of both states, the influence of a demographic component on the growth of the population as a whole between two time steps requires additional information on the state composition at the initial step (in reverse time). Estimation of temporal symmetry parameters follows Pradel (1996). Estimation of the state composition involves the counts of individuals in each state corrected for the estimated state-specific encounter probabilities. In theory, it should be possible to construct a robust design multi-state reverse-time model, which would allow for simultaneous estimation of both population growth and the state composition (which in turn would allow for direct estimation of prevalence, rate of change in prevalence, and relative contributions of various factors to such change). Such a model has not yet been developed (although separate robust design multi-state and robust design reverse-time models are currently available). Schofield and Barker (2009) have suggested such a model as a particular set of constraints applied to the complete data likelihood ('mother-of-all-models') proposed by Barker and White (2004).

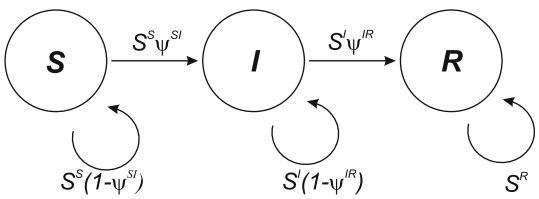

Fig. 2 Simple *SIR* model (see "Appendix A") parameterized as Arnason–Schwarz MSMR model. See text for definition of transition parameters. Here, we assume $\psi^{RR} = 1.0$. Note that the model as presented does not consider fertility contributions among nodes (e.g., for pure horizontal transmission, we might imagine that states *I* and *R* might contribute to state *S*; "Appendix A", Fig. 5.)

Occupancy models: considerations of space and time

Kendall (2009) and McClintock et al. (2010) have described the use of occupancy modeling (MacKenzie et al. 2005) to infer disease dynamics over space and time. Occupancy modeling considers the detection or non-detection of a group of interest over some collection of well defined units—typically spatial, but that is not a strict requirement. Occupancy is a proxy for abundance, and the relative ease and cost-effectiveness of data collection has prompted consideration of occupancy modeling as a robust framework for monitoring system dynamics at very large spatial scales where traditional CMR-based methods might be impractical (MacKenzie 2009).

While occupancy models have most commonly been applied to the estimation of the proportion of spatially discrete sampling units occupied, the approach is general, and can be extended to estimation of the proportion of any discrete sampling class that is 'occupied', or in some specified state. In that context of disease models, the estimated 'proportion occupied' appears strictly analogous to disease prevalence. Recent extensions enable estimation of occupancy as a dynamic state-variable (MacKenzie et al. 2003), and direct estimates of increase or decrease in occupancy by the pathogen are potentially quite useful in the disease context.

Occupancy modeling can also accommodate species co-occurrence dynamics (MacKenzie et al. 2004), which has potential application for evaluating the impact of multispecies interactions on disease (e.g., multiple hosts reservoir systems; Craft et al. 2008). Recently, Nichols et al. (2007) and MacKenzie et al. (2009) have extended occupancy modeling to account for multiple occupancy states. Kendall (2009) described an application of a multi-state occupancy model to disease in the Spotted Owl (*Strix occidentalis*). A general application might involve evaluating multiple disease states; for example, consider two different disease states: symptomatic, and asymptomatic. Here, there is a potential hierarchy of states, such that an individual which is asymptomatic is either not infected (not occupied), or is infected (occupied), but not expressing symptoms

(occupied, not detected), and therefore not detected. In contrast, a symptomatic individual must be infected (occupied).

Multi-state occupancy modeling also makes it possible to estimate the extinction probability as a function of proportion of patches that are suitable—this is particularly relevant to disease modeling where the dynamics of transmission are often strongly influenced by the proportion of the population in a given state. In the simplest case, we might characterize a host as either susceptible, or not (analogous to, say, specifying a habitat or territory as suitable or unsuitable; sensu Lande 1987). The disease state of the system is then characterized by the proportion of hosts that are susceptible, and the proportion of the susceptible hosts that are infected (occupied) by the pathogen. This would allow direct estimation of state-specific transition probabilities—the extinction and colonization parameters now depend on proportions of susceptible individuals in the population. Estimation of 'extinction threshold' relationships is also possible, as is the incorporation of changes in the disease state in the population (i.e., by vaccination, or culling/removal of infected individuals). This modeling is not straightforward in a ML context, but is readily handled using Monte Carlo methods (cf. "Disease models, unobservable states and state uncertainty").

While we believe there are clear opportunities for application of occupancy modeling in the study of disease dynamics, there are some important sampling issues which we believe require careful consideration prior to application to disease studies. First, it is important to think carefully about the appropriate scale of the analysis. McClintock et al. (2010) discuss application of occupancy models to hierarchical spatial models of disease, where the sampling unit was generally spatially discrete and aggregated over individuals in the patch (at least at some scale). While they considered the estimation of prevalence over a hierarchy of organization scales (e.g., ponds within refuges, flocks of birds within ponds), they did not consider individuals as the 'patch'. It might seem that estimation of $\hat{\psi}$ over all hosts sampled (i.e., considering the host individual as the patch) should provide a robust estimate of proportion of hosts that are occupied by the pathogen (i.e., prevalence; e.g., Thompson 2007).

However, would such an estimate might potentially be biased at the population level if the probability of encountering (sampling) an individual is a function of its latent occupancy (disease) state. If infected individuals (say) are less likely to be encountered than uninfected individuals in the initial sampling process, then infected individuals will be under-represented in the sample relative to the larger population; $\hat{\psi}$ will be biased low. In the majority of the literature on occupancy modeling, patches are fixed in space–time, and there is assumed to be little to no heterogeneity of encounter with the patch (which in fact is not modeled). Magle et al. (2007) have discussed a similar problem for estimating population densities for prairie dogs based on aerial surveys, where the probability of detecting dens is partially determined by their occupancy state. The problem clearly arises whenever the probability of encounter with the individual organism is a function of disease state, which is frequently the case. Kendall et al. (this volume) discuss combining occupancy and mark–recapture models—their approach could be modified to address the complication we have presented here. Such hybrid models should also enable the decomposition of ambiguous colonization or extinction events (e.g., non-extinction due either to (1) survival of individuals in the patch, without dispersal, or (2) death or dispersal followed by colonization; i.e., demographic rescue). We can see several clear applications of these methods, especially for vector-transmitted pathogens, with mobile hosts.

Another important point concerns distinguishing between 'prevalence' and 'presence'—at anything other than the level of the individual host, presence is not generally a robust indicator of prevalence (except in the extreme case where presence—and thus prevalence—is estimated to be zero). Further, occupancy modeling minimizes resolution—prevalence could decrease, but this may not be detected by an occupancy model. For example, prevalence may vary widely over space or time, but may not approach either [0,1] boundary. As such, all patches may be occupied, even though the true prevalence may differ widely (since a patch with prevalence of 0.1 and another patch with prevalence of 0.9 are both equally 'occupied').

Disease models, unobservable states and state uncertainty

> "*As we know, there are 'known knowns'. There are things we know we know. We also know there are 'known unknowns'. That is to say, we know there are some things we do not know. But there are also 'unknown unknowns', the ones we don't know we don't know…*" – D. Rumsfeld

Disease models consider the dynamics of individuals classified by disease 'state'. Uncertainty in assignment of individuals to a particular disease state is a general problem, which we consider here in detail with respect to the Arnason-Schwarz MSMR model (see "Open models: multi-state").

Classical MSMR models make several assumptions. Two we consider here are that (1) the true state of each

sampled individual is known, and (2) that all states are observable. In practice, however, these assumptions are frequently not met. This is especially true in many studies of disease in wild populations. Imperfect state assignment can arise from at least two, not mutually exclusive, sources. In some cases, all encountered individuals are assigned a state, but the state assignment process is subject to error. This is generally referred to as 'misclassification error'. For example, suppose that disease state is assigned based on identification of a visible marker (a common approach in wildlife disease studies), and that the marker is fixed (does not evolve) over the course of the sampling interval. Thus, the observation uncertainty would consist of the possibility of misclassifying state, either by (1) misreading the symptomatic marker where the marker indicates true disease state without error, or (2) reading the marker correctly, but where the underlying probability that the marker accurately indicates the underlying disease state is <1, or both. When an animal that is captured is misclassified, the potential for bias in the estimation of transition probabilities as well as all other parameters arises. Estimated differences in survival between states could be underestimated. Lebreton and Pradel (2002), Kendall (2009), and Pradel (2009) provide comprehensive reviews of the problem of misclassified states. In addition to potential for biased parameter estimates, they also pointed out that, without additional information, state misclassification can lead to parameter redundancy problems in some cases.

Alternatively, individual state may be only 'partially observable' for a fraction of the individuals encountered at a given sampling period. In such cases, the individual is encountered, but state is not observed directly. For example, Faustino et al. (2004) and Senar and Conroy (2004) considered situations where determination of disease state was based on a single visible marker (presence of a visible symptom). As such, the susceptible (S) and removed (R) (recovered) states (which are both asymptomatic) were confounded. Both studies also encountered some fraction of marked individuals where the classifying symptom was not observed, and thus state could not be assigned. Finally, even for situations where the individual symptom was noted, there was uncertainty between the mapping of symptom and true underlying state (e.g., diseased individuals which did not express the visible symptom). We distinguish 'partial observability' from truly 'unobservable states', which strictly applies only to individuals that are not encountered, either because they are not available for encounter (encounter probability equals 0 for individuals in a given state) or because of imperfect detection of available individuals (encounter probability <1 for individuals in a given state).

The distinction between 'misclassification' and 'partial observability' is not a sharp one, and many (if not most) systems will have both sources of uncertainty to some degree. For example, consider a system where states are unobservable, and that the only indication of underlying state is some discrete covariate which maps to the true state with some probability. This would represent a classical partially observable system. Generally, in such cases, we assume that the covariates which 'predict' state are recorded without error (i.e., that there is no misclassification error for the covariate), and that all encountered individuals are assigned to a particular covariate. It is relatively easy to imagine a situation where one or both assumptions are relaxed.

Some of the difficulties with both misclassification and partially observable states can in some instances be mitigated through use of ancillary information (e.g., where the sensitivity and specificity of the diagnostic criterion is known), or robust sampling approaches (generally under strong constraints; Kendall et al. 2004; Kendall 2009). A more general approach is to explicitly model the uncertainty between observation and underlying process. Recently, Pradel (2005, 2009) suggested that MSMR models could be generalized to account for state uncertainty using extended Markov chain models which allow for 'hidden' states. These approaches are very general and highly flexible, and can be adapted to apply to a number of situations where state uncertainty exists (Pradel 2009). We briefly introduce and review the application of these methods to disease models in the following section.

State-space and hidden Markov models

> "*It's not what you look at that matters, it's what you see…*"—H.D. Thoreau

> "*The only thing that makes hidden Markov models interesting is their name—there's something 'hidden', and a Russian is involved…*"—D. Lipman

When one or more states of a dynamic (say, disease) process are not directly observable, the state(s) is then said to be 'hidden'. In some cases where one or more states are hidden, we may be able to instead observe the state of entities which are influenced by the hidden state. The problem of imperfect state assignment is very general. Failure to account for state uncertainty can have significant consequences for modeling the disease dynamic (for example, King et al. (2008) showed that asymptomatic infections—an unobservable state—with short-term immunity could have important epidemiological consequences). State-space and hidden Markov models (hereafter, SSM and HMM, respectively—SS/HM when referred to jointly) originate from control theory, and are increasingly used by ecologists (de Valpine 2004; Buckland et al. 2004; Clark and Bjørnstad 2004; Besbeas et al. 2005; de

Valpine and Hilborn 2005; Pradel 2005, 2009; Clark and Gelfland 2006). SS/HM models typically consists of two primary elements: the system equations ('process model') and the observation equations ('observation model'). Process models can be either continuous- or discrete-time Markov. The system (dynamic) equations model the dynamics of state variables and the observation (output) equations model the observed state variables. In fact, a HMM is simply a special case of a more general SSM, with the key difference being that the hidden (or partially observed) state variables in SSM can take values in a continuous space, whereas the state space is discretized in the classical HMM. This difference is most significant in terms of the implications for estimating model parameters (where the discretization of the states in the HMM simplifies things considerably; parameter estimation for SS/HM models is discussed in "SS/HMM: estimation and computation").

We introduce the conceptual basis for these methods by means of a simple example. Consider a Markov chain consisting of two discrete disease states ($\mathbf{Q} = D, U$). When both states are observed directly, the elements of the transition matrix are determined by the time-specific transition probabilities ψ^{ij} (as might be estimated by a MSMR model). However, what if instead of observing the states $\mathbf{Q}$ we instead observe with some probability only some 'event' associated with the disease state. For example, suppose there is a visible marker (i.e., a visible 'symptom') which might indicate disease state. We imagine this marker as being discrete (S = symptomatic; N = not symptomatic); thus, in this example, we are considering a HMM (a brief summary of HMM is provided in "Appendix B" . For a more complete but very accessible introduction to HMM, see Rabiner 1989). We assume for the moment that there is no observation error in classifying individuals as S or N. If the mapping of the visible marker 'state' with the underlying disease state is one-to-one, then the system is a simple Markov chain in discrete time. Here we consider the situation where the visible markers are not perfectly mapped to disease states—this is most easily described by means of a fixed probability distribution (commonly referred to as 'emission' distributions; see "Appendix B"), where $Pr(S|D)$, $Pr(N|(U) < 1$. In the disease context, the 'event' distributions might be based on estimates of sensitivity and specificity of diagnostic procedures. The relationship between unobserved disease states and observed 'events' described in this example is shown in Fig. 3.

Suppose that, over two sampling occasions, we observe an individual 'event' history as $O = \{SN\}$; at the first sampling occasion, the individual was 'symptomatic' (event S, symptomatic), whereas on the second sampling occasion, the individual was 'asymptomatic' (N, no visible symptoms). Given O, we calculate the probability of

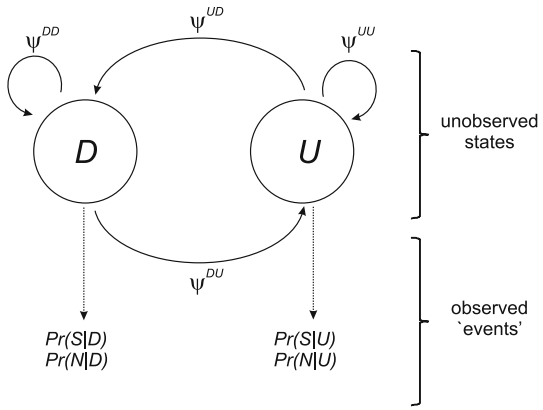

Fig. 3 Simple hidden Markov model representing transitions between two discrete unobserved disease states: D (diseased, infected), U (not diseased, not infected), and associated 'events' (S symptomatic, N not symptomatic). Time-specific transition probabilities ψ^{ij} between disease states (represented by the nodes of the graph) are indicated along the directed arcs (edges) connecting the nodes. The probability of observing 'event' i given disease state j is given as $Pr(i|j)$

observing this sequence of events given an unknown parameter vector. Clearly, the problem in this calculation consists of accounting for the uncertainty between the unobserved state and the observed 'event'. (We note that this is strictly analogous to accounting for the different possible sample paths which might result in a '0' (not detected) in a traditional CMR encounter history based on only two sampling occasions—the only difference is conditioning the first 'event' on a prior probability of the system being in a given state; i.e., π.) Assuming time homogeneity and a survival probability of 1.0, we can write the probability expression corresponding to this event history as

$$\begin{aligned} Pr(SN) = {} & [\pi^D b_D^S][\psi^{DU} b_U^N] + [\pi^D b_D^S][(1-\psi^{DU}) b_D^N] \\ & + [(1-\pi^D) b_U^S][(1-\psi^{UD}) b_U^N] \\ & + [(1-\pi^D) b_U^S][\psi^{UD} b_D^N] \end{aligned}$$

where π^i is the probability the system is initially in state i, $b^i{}_j$ is the probability of event i conditional on being in state j, and ψ^{ij} is the probability of transition from state i to j. The top line of the RHS sums the probabilities of the two sample paths given that the initial state was D (with probability π^D). The first term is the probability of the event history given the true unobserved state sequence $Q = \{DU\}$, while the second term is the probability of the event history given $Q = \{DD\}$. The second two lines of the RHS are the equivalent terms conditional on the initial state of the system being U (with probability $1 - \pi^D$).

Recently, Conn and Cooch (2009) analyzed a situation where the true disease state for some encountered individuals in a wild disease study was ambiguous—the

individual was observed alive, but disease state could not be assigned. This is a very common problem in field studies of disease in wild populations, where disease status may be determined only by visual examination. In such cases, the investigator has at least two options for handling encounter data from such individuals: (1) the encounters where disease state could not be assigned could be dropped from the analysis, or (2) a novel third state representing 'unknown' disease states could be added (Faustino et al. 2004). As noted by Conn and Cooch (2009), the first approach is deficient in the sense that one is throwing away data, which almost invariably leads to decreased precision on parameter estimates. The second approach is deficient because it results in biased estimates of infection and recovery rates (although estimates of survival and encounter probability will typically remain unbiased; Faustino et al. 2004). Adding a dummy state to the model means that transitions to/from that state have to be taken away from 'true' transitions. The situation is further complicated whenever the probability that the state of the animal being observed differs between disease states.

Conn and Cooch (2009) adopted a HMM approach to this problem by developing a novel multi-state model which mapped the two underlying disease states (asymptomatic and symptomatic) to 3 observation 'events' (sensu Pradel 2005) or 'attributes' ('symptomatic', 'asymptomatic', 'unknown symptom state'). Since the analysis was based on live encounter data, an absorbing unobservable 'dead' state was included in the model structure. The vector specifying the probability of initial encounter at time t (see "Appendix B") was

$$\pi_{\mathbf{i}} = \begin{pmatrix} \pi_t^A & 1 - \pi_t^A & 0 \end{pmatrix}$$

where the columns left-to-right represent the probability of initial encounter in the asymptomatic state, probability of initial encounter in the symptomatic state, and the probability of the initial encounter in the dead state, respectively. It is worth noting that $\boldsymbol{\pi}$ does not represent *population* prevalence, and applies only to the newly encountered unmarked individuals. If, however, we assume similar encounter probabilities of newly marked and previously marked individuals, then the initial-state probabilities $\boldsymbol{\pi}$ could be rewritten so as to yield proportions in each state in the unmarked population as well (Pradel 2005), although this would be complicated by possible state-specific differences in initial encounter probability (Pradel 2009).

There are two important points to make here. First, Conn and Cooch (2009) showed that applying the HMM approach led to significantly improved parameter precision. Second, in the HMM approach, process dynamics are considered for two states only: symptomatic and asymptomatic. Individuals of unknown state were assumed to be a member of one of the two groups; the uncertainty arose in not knowing which state they belonged to. The HMM approach considers the probabilistic mapping of the observed event vector given the true process vector which is only partially observed. In contrast, MSMR analysis using an additional 'unknown' state (Faustino et al. 2004) effectively treats those individuals assigned to that state has having potentially different dynamics from symptomatic and asymptomatic individuals, when in fact the 'unknown' state consists of some unknown mixture of both.

We also note that Conn and Cooch (2009) considered partial observability only—they assumed that the classification as 'symptomatic' or 'asymptomatic' was made without error. While it would be straightforward to account for misclassification uncertainty by making the probability of assignment conditional on the joint probability of correctly assigning a 'symptom state' (given estimates of sensitivity and specificity of 'diagnosis'; i.e., state-assignment), conditional on the true underlying state, introducing misclassification in addition to partial state observability can result in multi-modal solutions (Pradel et al. 2008). Such technical problems of parameter estimation for misclassified Markov data has been recently considered in a Bayesian context by Rosychuk and Islam (2009).

The SS/HM modeling approach enables a robust integration of two primary elements of modeling and analysis. First, by explicitly specifying the observation model, SS/HM models allow for inferences explicitly accounting for uncertainties. In the context of data from marked individuals, one clear source of uncertainty concerns the detection probability when $p < 1$. In fact, SS/HM models handle this source of uncertainty in a natural fashion. Consider a simple single- or multi-state CJS mark–recapture model, where the state (alive or dead) is only partially observed by the encounter process (encountered alive, or not encountered—dead encounters are an unobservable state). Gimenez et al. (2007) and Royle (2008) show how CJS models can be specified generally as a SSM. Second, the SSM allows for estimation of probability of state at any point in time (or space; see Patterson et al. 2008 for a recent review of SSM applied to spatial problems), as well as joint estimation of the process and observation model parameters (see Wang 2007 and Tavecchia et al. 2009 for recent reviews). An extremely useful application involves the integration of different 'observation' vectors into the estimation of the underlying process model. For example, it is now relatively straightforward to combine census data (counts) with dead recovery data to provide estimates of process parameters which would not be available from either type of data alone (e.g., Besbeas et al. 2002). The two data sources (observation vectors) are coupled to an underlying process model, which can take the form of a classical matrix projection model (the structure of the model is arbitrary). As such, it would seem to be relatively

straightforward to use point counts of individuals observed in a particular disease state to augment a discrete-time disease model (e.g., Oli et al. 2006; see also "Appendix A") in a SSM. Recent SSM integration of multisite recruitment, census, and mark–recapture–recovery data (Borysiewicz et al. 2009) could conceptually be extended to accommodate multiple disease states in the same way. While there have been relatively few applications of SS/HM models to studies of disease in wild populations (Streftaris and Gibson 2004; Marcos et al. 2008; and Conn and Cooch 2009 are notable exceptions), we anticipate that this situation will change quickly as researchers become aware of these methods.

SS/HMM: estimation and computation

The method(s) used for estimation of SSM and HMM parameters are generally determined by whether or not the process and/or the mapping between the process and observation is linear and Gaussian. For a linear Gaussian state-space model, the well-known Kalman filter (Roweis and Ghahramani 1999; Morgan 2007) provides optimal estimates for state variables based on the information from the two sources, the dynamic equations and the observations. Kalman filters are based on linear dynamical systems discretized in the time domain. They are modeled on a Markov chain built on linear operators perturbed by Gaussian noise. As with the HMM, the state of the system is represented as a vector of real numbers. At each discrete time increment, a linear operator is applied to the state to generate the new state, with some noise mixed in, and optionally some information from the controls on the system if they are known. Then, another linear operator mixed with more noise generates the visible outputs from the hidden state. For non-linear and/or non-Gaussian SSM, Bayesian methods such as sequential importance sampling ('particle filtering'; Thomas et al. 2005; Ionides et al. 2006) and Markov Chain Monte Carlo approaches (Newman et al. 2006; Buckland et al. 2007; Sisson et al. 2007; Newman et al. 2009) are increasingly being used.

One potential complication is the need to specify the structure of the model in advance—in other words, specifying the number (or distribution) of hidden states. For example, the Baum–Welch and related EM estimation algorithms commonly used in fitting HMM (see "Appendix B") do not estimate the number of states. It is unclear to us at present how uncertainty in the specification of the number of states in the process model should be handled in the context of multi-model inference. Beal et al. (2002) (see also Mochihashi and Sumita 2008) have proposed using a hierarchical Dirichlet process to implicitly integrate out the full set of transition parameters when the number of hidden states is countable infinite (such that the number of states is not specified).[4] This leaves only a set of hyperparameters which control the time scale of the dynamics of the system, the sparseness of the underlying state-transition matrix, and the expected number of distinct hidden states.

A key step in the wider adoption of SS/HMM approaches are the computational challenges of fitting the models to data. HMM models can be fit to data in a very flexible manner using E-SURGE (which was written specifically to accommodate encounter data from marked individuals; Pradel 2005; Choquet et al. 2009), or more generally (albeit with an arguably steeper learning curve than E-SURGE) using (1) the R packages `pomp` (King et al. 2009) and `msm` (Jackson 2009) for multi-state Markov and hidden Markov models (the `msm` package also includes diagnostics for assessing goodness of fit; for a general review of model diagnostics for multi-state and hidden Markov models, see Titman and Sharples 2008; Titman and Sharples 2009), or (2) WinBUGS (noted earlier in the context of the Kalman filter and integrated models). Smith and Vounatsou (2003) used a Bayesian hierarchical model developed using WinBUGS for estimating parasitic infection dynamics for highly polymorphic parasites when detectability of the parasite using standard tests is imperfect. The parasite dynamics were modeled as a non-homogeneous hidden two-state HMM, where the observed process is the detection or failure to detect a parasitic genotype. HMM models (with or without misclassification error) are also a special constrained case of the complete data likelihood proposed by Barker and White (2004). Schofield et al. (2009) has discussed implementation of elements of the complete likelihood in WinBUGS, and it is conceivable that a completely general approach to handling state uncertainty could be implemented, although there are likely significant computational barriers to a full implementation (Schofield and Barker 2009).

For linear Gaussian SSM models, parameter estimation proceeds by maximum likelihood (Morgan 2007). Specialized routines for fitting the Kalman filter to observation data are available in several statistical packages; IML, ETS and STATESPACE procedures in SAS, the `sspir` (Dethlefsen et al. 2009) package in R, and as specialized packages in MATLAB and other symbolic mathematics software. For non-linear SSM, general particle filters can be implemented using the `pomp` package (King et al. 2009) in R. Application of MCMC to fitting SSM to CMR data has been described for WinBUGS (Brooks et al. 2004; Gimenez et al. 2007; Royle, 2008) and AD Model Builder (Maunder et al. 2009). MacKenzie et al. (2009) have developed SSM approaches to multi-state occupancy models using WinBUGS. See Newman et al. (2009) for a

[4] see Dupuis (1995) for a similar analysis of a multi-stare mark–reencounter model with a specified number of hidden states.

recent review of Bayesian computation for SSM for modeling the dynamics of wild populations.

Challenges and limitations

"*The combination of some data and an aching desire for an answer does not ensure that a reasonable answer can be extracted from a given body of data…*"—J. Tukey

Despite the number of statistical methods which are available which account for both state uncertainty, and imperfect detection, estimation of disease model parameters is rarely straightforward. The following reviews several current challenges and opportunities for further research. We structure our discussion in terms of state-structured capture-mark–encounter models (which are the most commonly applied), and assume that the structure of the disease model is fixed during the time of study. In SS/HM models (cf. "State-space and hidden Markov models") this means that the number of host states (e.g., S or I) and (generally) the transition or detection relationships (parameters or functions) between states do not change fundamentally during the course of the study.[5]

Time scale

Many of the models we have discussed are discrete-time approximations to continuous dynamic systems. While such approaches are useful, especially pedagogically, justification of the time step used is an important consideration. In a great many studies, the time step is selected based on the timing of data collection, and not the 'biology' of the system. This can create significant problems. For example, consider a situation where sampling is done on a bi-weekly basis, but where the underlying transmission-recovery rate is 1 week. This would mean that an individual that is observed healthy in week 1 (sampling period 1) and also in week 4 (sampling period 2) could have experienced 0 or 1 infections and 'recoveries' in the intervening interval, but no more (that is, it could have passed through a number of transient states, before arriving at its final state in week 4). Clearly, interpretation of state transition probabilities is difficult in this case. Such probabilities are much easier to interpret when the sampling schedule is strongly determined by consideration of the underlying biology of the disease. This requires at minimum some assessment of the time-scale of the transmission process, which is often strongly influenced by a variety of factors at both the individual and group/aggregate level, and the rate of removal. For some species, this information might be accessible from laboratory studies of controlled infection of captive populations. Clearly, this will not always be practical in some cases. In the absence of such data from a companion laboratory study, every effort must be made, perhaps during a pilot study, to determine the appropriate time scale.

Although discrete time approximations are useful for disease dynamics (not least because accessible software is available), we believe the classical focus on discrete probabilities (i.e., survival and/or transition probabilities) is actually an impediment to a broader understanding of population dynamics (including disease). Disease dynamics ultimately occur on a continuous time scale, and in many cases it may make sense to parameterize them with continuous time–hazard rates. This is frequently done when modeling fish survival for instance, where the discrete time survival probability S_t may be written as $S_t = \exp(-Z)$ where Z represents a cumulative mortality rate. For instance, when both natural and fishing mortality occur, one often writes $Z = F + M$, where F is a fishing mortality rate and M is a natural mortality rate. This specification actually assumes that there are constant forces of fishing and natural mortality over the time interval of interest (i.e., constant hazard rates). In a similar manner, it may be more natural to write models for disease dynamics in terms of forces in and out of different disease states (see paper by Conn et al., this issue). Even when infection and mortality hazards vary over time, they can often be approximated with a large number of time intervals which themselves are assumed to have constant hazards.

Discrete disease states

When is an encountered individual 'sick'? While such a question seems almost trivial, it is perhaps one of the more challenging problem faced by disease modelers. In the simplest case, an individual is discretely classified as either 'sick' (which might mean symptomatic, or infectious), or 'healthy'. However, in many cases, the immune response of an individual host to a pathogenic challenge is one possible realization of a *continuous* norm of reaction, and classification of an individual as either 'sick' or 'healthy' is clearly an approximation to the continuous distribution of possible diseases 'states'.

One approach to accommodating such a continuous structure of host–pathogen dynamics is to use methods which do not use discrete classes. Easterling et al. (2000), Childs et al. (2004) and Ellner and Rees (2006, 2007) have described methods based on integral projections (IPM) which avoid the strict need for discrete classes and the potential artifacts from arbitrary class divisions. In this

[5] However, as rapid evolution and coevolution in host and pathogen populations become more widely recognized, e.g., Altizer et al. 2003, these assumptions are increasingly questionable in many systems. In particular, for pathogens with short generation times and high mutation rates, changes can occur very rapidly.

approach, the population vector is replaced by a distribution function $n(x, t)$, where $n(x, t)dx$ is the number of individuals with their state variable in the range $[x, x + dx]$. The standard projection matrix **A** is in turn replaced by a projection kernel $K(y, x) = P(y, x) + F(y, x)$, where P represents the transition from state x to state y and F represents the production of state y offspring by state x parents. The population dynamics are then

$$n(y, t+1) = \int_U^L K(y, x)n(x, t)dx,$$

where $[L, U]$ is the range of possible states (Ellner and Rees 2007). This is the continuous analogue of the matrix projection $n_i(t+1) = \sum_j a_{ij}n_j(t)$, where a_{ij} is the (i, j)th entry in the projection matrix **A**. The IPM approach can readily accommodate heterogeneity in individual latent parameters (sensu Cam et al. 2002; Link et al. 2002). Ellner and Rees (2007) cite several studies which show how the projection kernel can be estimated from the same data as a matrix model. Such simple 'structured' (compartment, matrix) models are often used as a 'solution' to limited data—low-dimensional matrix models are often the result of data which are not sufficient to classify individuals by more than a single state variable. IP models often make more parsimonious use of limited data.

We predict that IPM will likely have an important role in disease models, since they provide a rigorous and concise solution to the general problem of discretizing continuous disease states. It is straightforward to parameterize the dynamics equation in terms of a continuum of 'disease states' (rather than, say, size-classes). Recently, IPM have been applied to analysis of coral disease, where infected individuals are classified by a continuum of disease states (specifically, the amount of tissue are they have that uninfected; Bruno et al. 2010). It will be less straightforward to modify the IPM to account for detection probabilities $p < 1$.

Effects of population structure: density- and frequency-dependence

We began this review by noting that perhaps the most fundamental goal of fitting infectious disease models to time series data is to model and estimate transmission—specifically, how many uninfected individuals will contract the disease, and what factors influence that number?

Clearly, one key element of addressing these challenges concerns estimation of abundance. For open models, Dupuis and Schwarz (2007) demonstrate extension of unconditional Jolly–Seber models to multi-state situations, which allows estimation of abundance as well as the usual state-transition parameters. Challenger and Schwarz (2009) have recently extended this approach to account for classification uncertainty. One potential application of these approaches for disease models is the conditioning of state transitions on state abundance.

However, abundance is not necessarily (or even generally) the most appropriate state variable—distinctions between abundance and density (they are not the same thing; Efford 2004; Efford et al. 2009) have important implications for disease models. In most standard *SIR* models ("Appendix A"), transmission is modeled assuming 'mass action' transfer (analogous to a Type I functional response): given density S of susceptible hosts, and density I of infected hosts, then the number of new infected hosts per unit area per unit of time is βSI (see Eq. 11 in "Appendix A"). There has been some debate in the literature concerning whether or not the mass action term βSI should be scaled by total population abundance $\beta SI/N$ or not (de Jong et al. 1995, 2002; McCallum et al. 2001, 2002). The underlying issue is whether or not transmission is frequency or density dependent.

This is not merely semantics—the threshold for disease introduction is strongly influenced by whether or not the mass action term is scaled by abundance. From Eq. 11 ("Appendix A")

$$\frac{dI}{dt} = \beta SI - \gamma I$$

The pathogen will invade a population comprised entirely of susceptible hosts (i.e., $dI/dt > 0$ if $N > \gamma/\beta$. In other words, there is a threshold population density (or abundance). However, if transmission is scaled by abundance

$$\frac{dI}{dt} = (\beta SI)/N - \gamma I$$

then the pathogen will invade a population of susceptible hosts (for small I and $S = N$) if $\beta > \gamma$—a condition which does not involve abundance or density at all.

More generally, epidemiological theory suggests that a single-host pathogen is unlikely to drive its host to extinction, if disease transmission follows a density-dependent process, because disease maintenance and spread will not be possible when populations are sufficiently reduced (below a population threshold) (McCallum and Dobson 1995; de Castro and Bolker 2005). Indeed, there has been some evidence suggesting that populations would be unlikely to be driven to extinction by a density-dependent disease (Bradshaw and Brook 2005). If disease transmission is not density dependent, however, thresholds for disease maintenance will not occur and population extinction is possible (de Castro and Bolker 2005).

Clearly, the form of the transmission process is of critical importance. McCallum et al. (2001) and Caley et al.

(2009) summarize a number of the proposed forms for the transmission function—most studies have relied on using measures of abundance or density as proxies for some unseen mechanism, in much the same manner that abundance is used as a proxy for an unspecified mechansim for 'density regulation' (Lebreton 2009). Relatively few of them have been rigorously tested with empirical data. While methods for estimating abundance (and density) from spatially explicit mark–recapture are available (Link and Barker 1994; Efford 2004; Efford et al. 2009; see also Borchers' paper, this proceedings), simple estimation of 'spatial abundance' is not entirely sufficient to adequately model the contact process. Ideally, estimation of dynamic changes in abundance, density and relative 'geometry' of infected and non-infected individuals is needed. While there has been a significant interest in spatial epidemiology at the broad scale in a variety of systems (e.g., Grenfell et al. 2001; Keeling et al. 2004; Bjørnstad and Grenfell 2005; Lawson 2009; see papers by Kendall and McClintock, this issue, for application of occupancy models to spatial disease modeling), there has been relatively little empirical study of the transmission process at the local spatial scale.

Failing to properly specify the functional form of the transmission process can strongly impact the modeling and management of disease (e.g., Choisy and Rohani 2006). Fully specifying the functional form will require not only assessment of the temporal and spatial interactions of susceptible and infected hosts, but would also need to account for significant sources of heterogeneity among individuals, in terms of patterns of interaction within ('mixing', Chowell et al. 2006; 'group size',Hochachka and Dhondt 2006; 'dominance structures', Hawley et al. 2007; Zucchini et al. 2008) and among species (e.g., Craft et al. 2008).

Fitting frequency-dependent or density-dependent transmission models to animal encounter data may be especially problematic, as writing a complete data likelihood in this case requires that one keep track of the abundance (or density) of animals in each infection state at each point in time. Such models have been fit to abundance time series (with uncertainty in the partitioning of several disease states) by updating possible event sequences at each iteration of an MCMC sampler (Gibson and Renshaw 1998). However, in the case of imperfect detection, the problem of unknown dimension becomes more of an issue, although data augmentation (sensu Royle and Dorazio 2008) may provide a partial solution. An alternative approach might be to estimate covariance between density or frequency and state-specific transition probabilities in a multi-state robust design (sensu Kendall et al. 2004), by fitting a hyperdistribution to the population and transition parameters in a random effects framework. Such models could be fit in MARK or WinBUGS, although we are unaware of any examples where this has been done. Although theory and computation in either case both require further work, we are excited about these approaches because they would potentially lend themselves to relaxation of a number of key assumptions.

History matters: memory models, sojourn time, and related issues

Another common challenge in estimating disease parameters concerns the simplifying assumption that the underlying process being modeled is first-order Markov. However, for many disease systems, the probability of transition from one state to another will depend at least partially on higher-order history, in either one of two ways: (1) transition from state i to j at time t will depend on previous state at time $t-1$ (for simple second order Markov models; so-called 'memory models'), or (2) transition will not only depend on current state but also on the entry time into the state (in which case, the process is semi-Markov)—entry time is generally not observed in wild populations although it can, in some cases, be estimated from encounter data from marked individuals; e.g., Pledger et al. (2009). Failing to account for sojourn time can significantly bias estimates of key parameters (e.g., Joe and Pollock 2002; Fletcher and Efford 2009). Higher-order Markov models have been previously described for multi-state mark–recapture (Hestbeck et al. 1991), but are seldom used in studies of wild populations, primarily because of the increased data needs to achieve satisfactory parameter estimates for higher-order transitions. Adding one or more hidden states to a higher-order Markov process compounds this problem—in an Rth order HMM with N states, there are N^R transition probabilities. Recent work by Engelbrecht and du Preez (2009) (following on from du Preez 1998; du Preez and Weber 1999) has shown that any order HMM can be represented by an equivalent first-order model. The implication of this result is that all existing algorithms used for analysis of first-order HMM can be directly applied to higher-order HMM (HOHMM). Such first-order equivalence also simplifies the interpretation of HOHMMs. Analysis of HOHMM is relatively common in bioinformatics (e.g., Koski 2002; Ching et al. 2003; Gollery 2008) and signal and image processing (e.g., Benyoussef et al. 2008). Of course, there is still the challenge of estimating order. Morvai and Weiss (2005) have discussed methods which appear robust provided the observation time series is ergodic and stationary.

Finally, if there is significant heterogeneity among individuals in the norm of reaction relating time in state and probability of a state transition, such transitions will (in practice) be stochastic and 'noisy'; while Bretó et al. (2008) have recently described approaches for accounting

for such heterogeneity based on interacting Poisson processes, they noted that care is required in modeling Gaussian noise. They suggested that using an individual frailty model (discussed in Cam 2009) might improve fit to data. Of course, modeling individual heterogeneity can be carried to an extreme (Cauchemez et al. (2008) inferred transmission parameters for a partially observed Markov process with a state vector of size ca. 105, modeling every individual in a small town). We suspect this is not a likely prospect for most studies of wild populations.[6]

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Appendices

Appendix A. Classical disease models: a (very) short review

"*It is utterly implausible that a mathematical formula should make the future known to us, and those who think it can would once have believed in witchcraft…*"—B. de Jouvenel

The literature on the mathematical modeling of disease dynamics is enormous—here, we provide only a brief introduction (very brief) to provide some of the necessary terminology and classical model structures. The reader is referred to Daley and Gani (2001) for a general introduction; see Diekmann and Heesterbeek (2000) and Keeling and Rohani (2007) for more mathematically advanced treatments.

Most disease models are constructed by subdividing the population into discrete divisions ('compartments') reflecting the underlying disease 'state' of the individual. Frequently, these states include individuals that may be susceptible to infection (S), those that are infected (I), and those who are 'removed' (R), either by virtue of having died, or potentially recovered with some degree of immunity. The dynamics of such an *SIR*-type system are governed by the rate of transition between states (Fig. 4).

The classical Ross–Kermack–McKendrick *SIR* model represented in Fig. 5 is a sequential model with a single absorbing state (implying permanent removal from the susceptible class, typically by death, or permanent immunity). Although there are a very large number of elaborations of this simple model (e.g., the *SIRS* model, where removal from the susceptible class is not permanent, as might be expected if immunity to the pathogen is temporary), we focus here on the classical deterministic *SIR* model since it is very general.

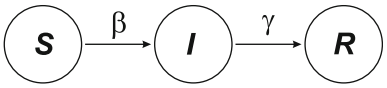

Fig. 4 Classical *SIR* compartmental model. Nodes refer to susceptible (S), infected (or infectious) (I), and 'removed' or recovered (R) disease states. Transition parameters β and γ reflect rate of movement between successive disease states over some time scale

Classical SIR models: deterministic, continuous time

The *SIR* model (Fig. 4) in continuous time is traditionally represented by a set of coupled ordinary differential equations:

$$\begin{aligned}\frac{dS}{dt} &= -\beta IS \\ \frac{dI}{dt} &= \beta IS - \gamma I \\ \frac{dR}{dt} &= \gamma I\end{aligned} \tag{11}$$

Analysis of such models generally focuses on two things: the conditions under which the system described by these equations is at equilibrium, and the sensitivity of this equilibrium (or any other point in plausible state space) to perturbation of one or more parameters. Classical sensitivity analysis uses partial derivatives of model output with respect to parameters in the model—the most common approach is based on finalization analysis, where equations for the partial derivatives of the solution of a particular model with respect to parameters are found by differentiating the model

$$\frac{\partial}{\partial t}\left(\frac{\partial x}{\partial \theta}\right) = D_x f(x(t);\theta)\frac{\partial x}{\partial \theta} + D_\theta f(x(t);\theta)$$

where $\partial x/\partial\theta$ is the gradient of x with respect to parameter θ, and $D_x f$ and $D_\theta f$ are the Jacobians of f (model functions) with respect to x and θ, respectively. The stability and local transient dynamics of equilibria (and other fixed points) defined by the system of equations is determined by the eigenspectrum of the Jacobian matrix. See Keeling and Gilligan (2000) and Buzby et al. (2008) for a general discussion, with application to analysis of a vector-transmitted disease system.

Analysis of the equilibrium condition(s) often provide qualitative insights to the conditions necessary for an

[6] Despite the apparent efforts of Emmanuelle Cam and her colleagues to do nearly that with Kittiwakes (*Rissa tridactyla*) breeding on the Brittany coast.

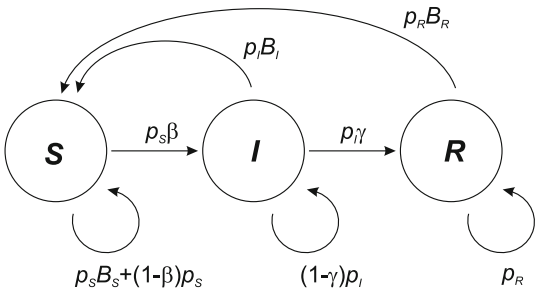

Fig. 5 Life cycle graph for a *SIR*-type disease (modified following Oli et al. 2006), assuming a post-breeding census. Nodes represent susceptible (*S*), infective (*I*) and removed (*R*) disease states. Model parameters are p_k = survival probability of individuals in disease state k ($k = S$, I or R), β is the probability that a susceptible individual becomes infective between time (t) and ($t + 1$), γ = the probability that an infective individual recovers between time (t) and ($t + 1$), B_k is the fertility rate of individuals in disease state k

emerging pathogen to increase in a population of susceptible hosts. For example, if we apply the constraint that $N = S + I + R$ is a constant (which implies that $dS/dt + dI/dt + dR/dt = 0$), we can look at the dynamics of the system simply by focusing on two of the three variables. If we consider S and I, we see that the invasion of a population that initially consists entirely of susceptible individuals requires that $dI/dt > 0$, which is clearly possible only if ($\beta S - \gamma > 0$); unless the rate of increase in the number of infective individuals is greater than the rate at which they are removed, then dI/dt cannot be greater than 0.

We can re-arrange this condition as

$$R_o = \frac{\beta S}{\gamma} > 1 \qquad (12)$$

Traditionally, R_o is known as the *reproductive number* for the disease (occasionally also referred to as the basic reproduction ratio). We see that βS is the *rate* at which an infective causes new infections. Since $1/\gamma$ is the mean time an individual is infective, then R_o is the mean number of new infections caused by a single infective individual. The incidence of the disease will increase if $R_o > 1$, and decline if $R_o < 1$.

The reproductive number R_o is fundamental for analysis of disease dynamics. For example, if $S_{max} = N$ (which is the null initial condition where all individuals in the population are susceptible), then $dI/dt > 0$ if and only if $N > \gamma/\beta$ (which is equivalent to $R_o > 1$), indicating there is a minimum population size necessary for the pathogen to invade (i.e., for $dI/dt > 0$).

In the classical *SIR* model, the function $F = \beta I$ models the transition from the susceptible compartment to the infectious compartment. Generally, this function $F = \beta I$ is referred to as the *force of infection*.

Classical SIR models: deterministic, discrete time

Compared to continuous time models, discrete time forms of classic epidemiological models have received little attention (see van Boven and Weissing 2004; Oli et al. 2006; Korobeinikov et al. 2008 as notable exceptions). One possible discrete parameterization of the *SIR* equation, based on a post-breeding census is shown in Fig. 5

Here, we allow for state-specific survival and fertility (production of neonates). This model can be reduced to the equivalent constant N model discussed above, by fixing survival at 1 and fertility to 0.

Following Oli et al. (2006), we can decompose the projection matrix **A** corresponding to life cycle graph as the sum of a transition matrix **T**, where the elements (t_{ij}) represent the probability than an individual in state j at time (t) will be in state i at time ($t + 1$), and a fecundity matrix **F**, where the elements f_{ij} are the expected number of type i offspring produced at ($t + 1$) by an individual in state j at time (t); $\mathbf{A} = \mathbf{T}+\mathbf{F}$ (Cochran and Ellner 1992; Caswell 2001). The fundamental matrix **N** is defined as $\mathbf{I} + \mathbf{T} + \mathbf{T}^2 + = (\mathbf{I} - \mathbf{T})^{-1} \equiv \mathbf{N}$ where **I** is an identity matrix with dimension equal to the number of disease states. The fundamental matrix **N** gives the expected number of time steps in each state. Since the fertility matrix **F** gives the expected number of offspring produced by each stage per time step, then the matrix $\mathbf{R} = \mathbf{FN}$ has elements r_{ij} which quantify the expected lifetime production of offspring of type i by an individual in state j. The dominant eigenvalue of **R** is the net reproduction ratio R_o. Further, evaluation of the sensitivity of key population parameters (e.g., λ,R_0) is straightforward in the projection matrix framework.

However, while discrete-time analogues of many disease model parameters are available (see Oli et al. 2006 for a general review, and discussion of important differences in calculating and interpreting several key disease paramors), we note that the discretization of both disease state and time have important implications for the modeling of disease dynamics, and the estimation of model parameters. Most interactions in disease systems are truly continuous (at least temporally)—discrete-time models generally represent approximations to continuous systems, necessitated in many instances by the discrete timing of sampling (or, equivalently, the aggregation of disease data into discrete time frames). The statistical challenge in the estimation of disease parameters concerns the need for methods to accommodate discretized systems, which are typically only partially observable, non-stationary and (generally) nonlinear.

Appendix B. HMM models: a (very) short introduction

A system can be modeled by a HMM if the sequence of hidden states is Markov, and if the sequence of observations are either independent, or Markov, given the hidden state.

A HMM is specified by:

Q, the set of possible states $\{q_1, q_2, \ldots, q_n\}$

O, the output 'alphabet' (often referred to as 'emission' distributions'); the set of observed 'event' states (sensu Pradel 2005); $\{o_1, o_2, \ldots, o_m\}$

π_i, the probability of being in state q_i at time $t = 0$ (i.e., the initial states)

Φ, the matrix of transition probabilities ϕ_{ij}, where $\phi_{ij} = \Pr(\text{entering state } q_j \text{ at time } t+1 \mid \text{being in state } q_i \text{ at time } t)$. Assuming the system is Markov, then the state transitions do not depend on the previous states at earlier times.

B, the matrix of output probabilities $\{b_j(k)\}$ (i.e., the 'observed event' array), where $b_j(k) = \Pr(\text{producing 'event' } v_k \text{ at time } t \mid \text{being in state } q_j \text{ at time } t)$

Formally, we define a HMM model M as

$$M = (\Phi, \mathbf{B}, \pi)$$

The key point is that the data consist of observations of the events **V**, which are mapped to the underlying Markovian transitions between unobserved states **Q** by the transition matrices **Φ** and **B**. A Markov chain has a strict one-to-one mapping between observations and underlying states. This is not a requirement for HMM, where an observation can typically be generated by several different states, and the probabilities of generating an observation given a state differ.

From above, we define Q to be an unobserved fixed state sequence (path through possible states **Q**) of length T (i.e., T sampling events), and corresponding observations O made at discrete time intervals:

$$Q = q_1, q_2, \ldots, q_T$$
$$O = o_1, o_2, \ldots, o_T$$

Given O, there are 3 primary questions of interest:

1. What is the probability of the observed 'event history' O, given the model M? In other words, we wish to calculate $Pr(O|M)$. This is usually referred to as *evaluation*.
2. At each time step, what state is most likely? In other words, what is the hidden state sequence Q that was most likely to have produced a given observation sequence O? It is important to note that the sequence of states computed by this criterion might be impossible. Thus more often we are interested in what single sequence of states has the largest probability of occurrence. That is, find the state sequence $q_1, q_2, \ldots, q_T$ such that $Pr(o_1, o_2, \ldots, o_T|M)$ is maximized. This is usually referred to as *decoding*.
3. Given some data, how do we "learn" a good hidden Markov model to describe the data? That is, given the structure of a HMM, and observed event data, how do we parameterize the model which maximizes $Pr(O|M)$? This is referred to as *learning*.

Due to the large number of possible sample paths, even for low dimension HMM with small time horizon T, the need for an efficient algorithm to satisfy the objectives (noted above) should be apparent. Consider, for example, the *evaluation* problem—trying to find the probability of observations $O = \{o_1, o_2, \ldots, o_T\}$ by means of considering all possible hidden state sequences is clearly impractical (for even simple problems, the number of possible state sequences R is astronomically large). Generally, dynamic programming approaches are used to minimize the computational burden. Forward–backward and Viterbi algorithms are frequently applied to the evaluation and decoding problems, respectively. For the learning problem (estimation of parameters for the HMM), the Baum–Welch algorithm is frequently used (the Baum–Welch algorithm is a generalized expectation–maximization routine, and can compute maximum likelihood estimates and posterior mode estimates for the parameters—both transition and event probabilities—of a HMM, when given only 'events' as training data), but analysis with complete data (sensu Schofield and Barker 2008) is certainly also possible. The Baum–Welch and related estimation approaches do not estimate the number of states—that must be specified and fixed. For a more comprehensive introduction to general inference from HMM, see Cappé et al. (2005).

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