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Modeling and Inference for Infectious Disease Dynamics: A Likelihood-Based Approach

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Abstract. Likelihood-based statistical inference has been considered in most scientific fields involving stochastic modeling. This includes infectious disease dynamics, where scientific understanding can help capture biological processes in so-called mechanistic models and their likelihood functions. However, when the likelihood of such mechanistic models lacks a closed-form expression, computational burdens are substantial. In this context, algorithmic advances have facilitated likelihood maximization, promoting the study of novel data-motivated mechanistic models over the last decade. Reviewing these models is the focus of this paper. In particular, we highlight statistical aspects of these models like overdispersion, which is key in the interface between nonlinear infectious disease modeling and data analysis. We also point out potential directions for further model exploration.

Key words and phrases: Maximum likelihood, iterated filtering, particle filter, compartment model, Lévy-driven stochastic differential equation, continuous-time Markov chain, environmental stochasticity.

1. INTRODUCTION

Stochastic models for infectious disease dynamics often fall somewhere between two extremes: the so-called phenomenological and mechanistic models, the latter having proved useful to carry out likelihood-based statistical analyses. This is a long standing dichotomy (see, e.g., Thakur, 1991) related to the so-called *algorithmic* and *data* modeling cultures in statistics (Breiman, 2001): phenomenological models are flexible and use generic strategies, including nonparametric and regression-like ideas (see, e.g., Unkel et al., 2012); mechanistic models include population models of the SIR type (see, e.g., Siettos and Russo, 2013) and use parameters and functional forms to represent as many features as data permit of biological processes thought to be at work. Unveiling such processes might be attempted using several statistical methods, weaknesses and strengths of which have been critically assessed elsewhere (King, Nguyen and Ionides, 2016, Fasiolo, Pya and Wood, 2016). Examples of such methods include nonlinear forecasting (Ellner et al., 1998), trajectory matching (Kendall et al., 1999) and synthetic likelihood (Wood, 2010). Also, Bayesian options include approximate Bayesian computation (ABC; Marjoram et al., 2003) and Particle Markov chain Monte Carlo (PMCMC; Andrieu, Doucet and Holenstein, 2010). A fundamental difference between these two methods is that ABC relies on summary statistics and PMCMC uses the full likelihood function. Another method that can be used to maximize the full likelihood function is iterated filtering (Ionides, Bretó and King, 2006, Ionides et al., 2011, 2015). Iterated filtering algorithms, unlike Markov chain Monte Carlo (MCMC) or expectation-maximization (EM) algorithms, avoid the need for analytic expressions of transition densities. These expressions become intractable as the complexity of the model increases. Iterated filtering is also statistically efficient, since it uses the full likelihood. Likelihoods are also involved in other methods but these can involve considerations beyond the model of interest, like the choice of summary statistics in ABC and synthetic likelihood, or the choice of priors (leading to heavier computational burdens) in PMCMC.

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These features make iterated filtering algorithms particularly fitted for likelihood-based analyses of mechanistic infectious disease dynamics (Dobson, 2014).

The main difficulty addressed by iterated filtering algorithms is maximization of mechanistic model likelihoods in the absence of analytic solutions. These are numerical maximization algorithms that have been implemented with success and affordable computational costs. Closed-form likelihoods can be derived for the most basic infectious disease mechanistic models (e.g., Diekmann, Heesterbeek and Britton, 2013, Chapter 5.2) and even for more sophisticated models, as long as groups of individuals involved remain small (Haber, Longini and Cotsonis, 1988, Becker, 1995). In general, and for larger populations of interest, the system will not be fully observed, leading to the use of numerical optimizers for non-Gaussian likelihoods of nonlinear, partially observed systems. Multiple algorithms to attempt such optimization have been proposed (see Kantas et al., 2015). Algorithms that have actually been applied to maximize the likelihood of time series of infectious disease data include hybrid-EM algorithms (Yang et al., 2012) and iterated filtering algorithms. Advantages of iterated filtering include lower computational burdens than comparable alternatives (Bhadra, 2010, Ionides et al., 2015), potential for more precise results for infectious disease mechanistic models (Fasiolo, Pya and Wood, 2016), and ease of implementation via the R package `pomp` (King, Nguyen and Ionides, 2016, King et al., 2017, R Core Team, 2017), which has been used to analyze a growing body of infectious disease datasets.

The range of stochastic models considered for infectious diseases has been widened, both in biological richness and in the nature of stochasticity, thanks to a great extent to the *"plug-and-play"* property of iterated filtering. Plug-and-play algorithms can by definition be applied to fit dynamic models to data as long as simulation of unobserved variables from these models is possible (Bretó et al., 2009, He, Ionides and King, 2010). This has greatly facilitated exploration of variations in existing models of interest, since it only requires adapting simulation computer code that is often easy to write to begin with. The biological aspects of such variations can be controversial but they have pointed in new directions to be studied in more detail, like high asymptomatic ratios (King et al., 2008). Variations in stochastic nature have been less prone to controversy but can be technical, like randomizing rates of continuous-time Markov chains with white noise (Bretó et al., 2009). These are two examples of exploration of infectious disease models fostered by the plug-and-play nature of iterated filtering. The plug-and-play nature of other algorithms (like PMCMC, synthetic likelihood or ABC) endows them with potential for equally valuable explorations of new infectious disease models. More details regarding the role of these other algorithms in infectious disease modeling might be found in other contributions to this special issue.

The goal of this paper is to review mechanistic models that have been explored via iterated filtering algorithms, which we also briefly review, while highlighting statistical aspects of these models. Both implementation and comparative performance of iterated filtering algorithms have been recently reviewed in detail from different perspectives (Fasiolo, Pya and Wood, 2016, King, Nguyen and Ionides, 2016), so we limit our description of these algorithms to Figure 2 and a supplement.[1] However, these recent reviews give just a glimpse of the collection of over twenty-five applications where iterated filtering has been used since its appearance a decade ago. The models we review represent different biological mechanisms but, more importantly, they are also different in stochastic nature. After establishing a common framework (in Section 2) that encompasses these natures, we review their differences (in Sections 3 and 4), which lead us to focusing on the statistical concept of overdispersion in infectious disease models (in Section 5). Overdispersion and the unmodeled variability it entails can lead to overly confident conclusions, for example, caused by misleadingly small standard errors (McCullagh and Nelder, 1989). This can be aggravated by severe biases, which result from nonlinearities that are commonplace in infectious disease mechanistic models (He, Ionides and King, 2010). We conclude by pointing out potential directions for further exploration of infectious disease mechanistic models (in Section 6).

2. PARTIALLY OBSERVED MARKOV PROCESS MODELS

The mathematical formulation of all the models we review is mechanistic (i.e., based on a scientific understanding of infectious disease dynamics) but varies widely in stochastic nature. To accommodate this diversity, we first introduce notation to describe these

[1]The supplement (Bretó, 2017) illustrates how iterated filtering algorithms can be used to perform likelihood-based statistical inference. It also applies recently developed methodology to account for Monte Carlo noise in confidence intervals derived from profile likelihoods (Ionides et al., 2017).

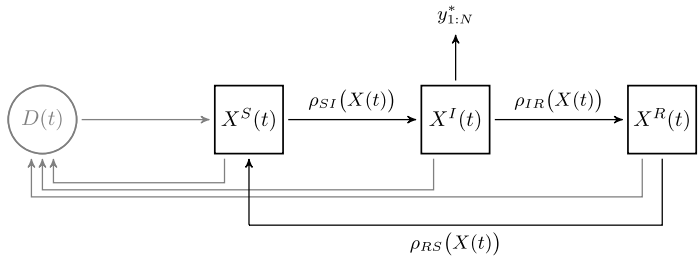

FIG. 1. *Example of diagrammatic representation of a mechanistic partially observed Markov process model of the susceptible-infectious-removed-susceptible type. Observed data and demography are also represented. The three boxes highlight a biological disease transmission mechanism where flows can occur at different rates (represented by arrow labels) between three stages (or compartments): susceptible, infectious and removed (or recovered). To deal with demography (i.e., biological births and deaths), a set of flows to and from a fictitious fourth demographic stage is also included. Due to partial observation, all data $y^*_{1:N}$ come from the infectious stage only and at times $t_1, \ldots, t_N$ only (see Section 2 for details on notation).*

models as partially observed Markov process models, an example of which appears in Figure 1.

A Partially Observed Markov Process (POMP) model (Ionides et al., 2011), also known as state-space model or hidden Markov model, consists of a stochastic process $\{X(t), t_0 \le t \in T \subseteq \mathbb{R}^+\}$ that is unobserved, except for times $t_1, \ldots, t_N$ at which observations $Y_1, \ldots, Y_N$ are available, and is parameterized by unknown parameter θ, with all of θ, Y_n, and $X(t)$ taking values in subsets of $\mathbb{R}^n$. Writing $X_n = X(t_n)$ and the collection of observations as $Y_{1:N}$ and assuming that the joint density[2] of $Y_{1:N}$ and $X_{0:N}$ exists, Markovianity of $X_{0:N}$ together with conditional independence of observations gives the joint density

$$\begin{aligned} &f_{X_{0:N},Y_{1:N}}(x_{0:N}, y_{1:N}; \theta) \\ &\quad = f_{X_0}(x_0; \theta) \prod_{n=1}^{N} f_{X_n|X_{n-1}}(x_n \mid x_{n-1}; \theta) \\ &\qquad \cdot f_{Y_n|X_n}(y_n \mid x_n; \theta). \end{aligned} \tag{2.1}$$

Writing the marginal density of $Y_{1:N}$ as $f_{Y_{1:N}}(y_{1:N}; \theta)$ and the observed data as $y^*_{1:N}$, the maximum likelihood estimate $\hat{\theta}$ maximizes the likelihood function defined as $\ell(\theta) = f_{Y_{1:N}}(y^*_{1:N}; \theta)$. Inferences based on $\ell(\theta)$, except when the system of interest is small or when linear and Gaussian approximations are appropriate, will require sophisticated statistical methods. For example, likelihood maximization may be attempted using iterated filtering algorithms, which are illustrated in Figure 2. These algorithms rely on sequential Monte Carlo algorithms (or particle filters), which are simulation-based tools that exploit the specific density decomposition of (2.1). This decomposition is also useful to identify sources of variability.

Stochasticity in infectious disease dynamics is often considered to have either a demographic, environmental or measurement error origin (see, e.g., Lande, Engen and Saether, 2003, Nisbet and Gurney, 1982). Demographic stochasticity results from events that by chance affect some individuals in the population but not others (e.g., becoming or ceasing to be infectious), playing a major role in smaller populations. Population individuals that are infectious are connected to observed data through measurement error. Finally, environmental stochasticity affects all individuals equally (overtaking demographic stochasticity in large populations) and can result from variability in parameters θ. In (2.1), demographic variability has often been modeled via $f_{X_n|X_{n-1}}$, which aims at representing the scientific understanding and mechanisms of main interest in applications; measurement error has been modeled via $f_{Y_n|X_n}$, which, compared to $f_{X_n|X_{n-1}}$, tends to be chosen on the basis of fewer scientific considerations; and environmental variability has been modeled via both. When these choices for $f_{X_n|X_{n-1}}$ and $f_{Y_n|X_n}$ are guided by scientific understanding, we say that the likelihoods they specify via (2.1) are mechanistic.

3. MECHANISTIC LIKELIHOODS

3.1 Modeling Disease Transmission Via $f_{X_n|X_{n-1}}$

The transmission models we review aim at representing mechanisms for how individuals from a population

[2]We use the term density formally to refer to probability density functions, probability mass functions (i.e., densities with respect to the counting measure) and to mixed joint functions (i.e., involving both discrete and continuous marginal distributions).

Algorithm: Iterated filtering (IF2, Ionides et al., 2015)

input:
Simulator for $f_{X_0}(x_0;\theta)$
Simulator for $f_{X_n|X_{n-1}}(x_n \mid x_{n-1};\theta)$, n in $1:N$
Evaluator for $f_{Y_n|X_n}(y_n \mid x_n;\theta)$, n in $1:N$
Data, $y^*_{1:N}$
Number of iterations, M
Number of particles, J
Initial parameter swarm, $\{\Theta^0_j,\ j \text{ in } 1:J\}$
Perturbation density, $h_n(\theta \mid \varphi;\sigma)$, n in $0:N$
Perturbation sequence, $\sigma_{1:M}$

output:
Final parameter swarm, $\{\Theta^M_j,\ j \text{ in } 1:J\}$

Pseudocode:
For m in $1:M$
  Draw $\Theta^{F,m}_{0,j} \sim h_0(\theta \mid \Theta^{m-1}_j;\sigma_m)$ for j in $1:J$
  Draw $X^{F,m}_{0,j} \sim f_{X_0}(x_0;\Theta^{F,m}_{0,j})$ for j in $1:J$
  For n in $1:N$
    Draw $\Theta^{P,m}_{n,j} \sim h_n(\theta \mid \Theta^{F,m}_{n-1,j},\sigma_m)$ for j in $1:J$
    Draw $X^{P,m}_{n,j} \sim f_{X_n|X_{n-1}}(x_n \mid X^{F,m}_{n-1,j};\Theta^{P,m}_{n,j})$ for j in $1:J$
    Set $w^m_{n,j} = f_{Y_n|X_n}(y^*_n \mid X^{P,m}_{n,j};\Theta^{P,m}_{n,j})$ for j in $1:J$
    Draw $k_{1:J}$ with $\mathbb{P}(k_j = i) = w^m_{n,i} \cdot (\sum_{j=1}^J w^m_{n,j})^{-1}$
    Set $\Theta^{F,m}_{n,j} = \Theta^{P,m}_{n,k_j}$ and $X^{F,m}_{n,j} = X^{P,m}_{n,k_j}$ for j in $1:J$
  End For
  Set $\Theta^m_j = \Theta^{F,m}_{N,j}$ for j in $1:J$
End For

FIG. 2. *Iterated filtering algorithms rely on extending a partially observed Markov process model of interest by introducing random perturbations to the model parameters θ to then explore the original space of θ searching for values that are more likely to have produced the observed data. Convergence to a maximum likelihood estimate has been established for appropriately constructed procedures that iterate this search over the parameter space while diminishing the intensity of perturbations* (Ionides, Bretó and King, 2006, Ionides et al., 2011, 2015). *The role and timeliness of iterated filtering algorithms for infectious disease modeling have recently been pointed out* (Dobson, 2014).

progress through compartments (e.g., Jacquez, 1996) that represent the stages of a disease cycle. To accommodate the diverse stochastic natures they can have, we introduce notation to describe their compartmental aspects only and postpone details on their stochastic nature to Sections 3.1.1 through 3.1.4.

We define a compartment model (following closely Bretó and Ionides, 2011) based on a finite collection of compartments $\mathcal{C}$ and a flow set consisting of compartment pairs between which flow is possible $\mathcal{F} \subset (\mathcal{C} \times \mathcal{C})$ that excludes reflexive flow, that is, the set of pairs $\{(c,c) : c \in \mathcal{C}\}$. For each pair $(i,j) \in \mathcal{F}$, with appropriate definitions of integrals (given in Sections 3.1.1 through 3.1.4), we define cumulative flow processes $\{N_{ij}(t)\}$ by

$$N_{ij}(t) = \int_{t_0}^{t} dN_{ij}(s), \tag{3.1}$$

with $N_{ij}(t_0) = 0$, based on which we define compartment model $\{X(t)\} = \{X^c(t) : c \in \mathcal{C}\}$, representing the

size of each compartment at time t, by

$$X^c(t) = X^c(t_0) + \sum_{(i,c)\in\mathcal{F}} N_{ic}(t) - \sum_{(c,j)\in\mathcal{F}} N_{cj}(t). \tag{3.2}$$

Different models can be specified via (3.1) often involving instantaneous flow rates $\rho_{ij}(X(t))$ that represent the intensity at which flows occur. Compartment models $\{X(t)\}$ need not take all of the full unobserved process, which might include other unobserved elements of interest disconnected from the compartments (as in Sections 4.2 and 6.1).

3.1.1 *Ordinary differential equation models*. Compartment models may be specified in (3.1) as sets of coupled (or systems) of ordinary differential equations by defining

$$\frac{dN_{ij}(t)}{dt} = \rho_{ij}\big(X(t)\big)X^i(t)$$

with solution $\{X(t)\}$. This kind of deterministic specification of disease transmission has a long history (Kermack and McKendrick, 1927). More recently, this specification of $f_{X_n|X_{n-1}}$ has been used with iterated filtering in combination with environmental models (resulting in the diffusion and stochastic differential equation models described next).

3.1.2 *Diffusion process models*. Compartment models may be specified in (3.1) as diffusion processes by defining

$$dN_{ij}(t) = \rho_{ij}\big(X(t)\big)X^i(t)\,dt + \sigma_{ij}\big(X(t)\big)\,dB_{ij}(t)$$

with solution $\{X(t)\}$. Choices for the infinitesimal standard deviation function σ_{ij} range from setting it to zero (to recover ordinary differential equations) to being proportional to $\sqrt{X^i(t)}$ or $X^i(t)$ (as in Ionides, Bretó and King, 2006, King et al., 2008), a choice that we revisit in Section 4.1.1.

3.1.3 *Stochastic differential equation models driven by Lévy processes*. Compartment models may be specified in (3.1) as stochastic differential equations driven by Lévy processes $\{L_{ij}(t)\}$ by defining

$$dN_{ij}(t) = \rho_{ij}\big(X(t)\big)X^i(t)\,dL_{ij}(t)$$

with solution $\{X(t)\}$. Analogously to setting $\sigma_{ij}(X(t)) = 0$ in diffusions, allowing some processes to be degenerate, that is, $L_{ij}(t) = t$, specifies deterministic components (as in Laneri et al., 2010, 2015, Bhadra et al., 2011, Roy et al., 2013, 2015, Martinez et al., 2016). We revisit these models in the context of parameter randomization in Section 4.1.

3.1.4 *Continuous-time Markov chain models*. Compartment models may be specified in (3.1) as continuous-time Markov chain mechanisms $\{X(t)\}$ implied by the system $\{N(t)\}$ of coupled, interacting Markov counting processes $\{N_{ij}(t)\}$ with transition rates $\rho_{ij}(x)x^i$ (Brémaud, 1999). These in turn imply transition probabilities

$$\begin{aligned} &P\big(N_{ij}(t+h) = n_{ij}|N(t) = n\big) \\ &\quad = 1 - \rho_{ij}(x)x^i h + o(h), \\ &P\big(N_{ij}(t+h) = n_{ij}+1|N(t) = n\big) \\ &\quad = \rho_{ij}(x)x^i h + o(h), \\ &P\big(N_{ij}(t+h) > n_{ij}+1|N(t) = n\big) = o(h), \end{aligned} \tag{3.3}$$

where the values of x follow from n using (3.2). This kind of stochastic specification of transmission models also has a long history (Bartlett, 1960). More recently, this specification of $f_{X_n|X_{n-1}}$ has been used with iterated filtering in combination with measurement models (Camacho et al., 2011, He et al., 2011, 2013, Earn et al., 2012, Blackwood et al., 2013b, King et al., 2015) and with both measurement and environmental models (Bretó et al., 2009, He, Ionides and King, 2010, Shrestha, King and Rohani, 2011, Shrestha et al., 2013, 2015, Magpantay et al., 2016, King, Nguyen and Ionides, 2016).

3.1.5 *Discrete time models*. Compartment models may be specified in (3.1) as discrete time systems resembling the continuous-time Markov chain of the previous section by specifying difference equations or by letting $N_{ij}(t_{n+1}) - N_{ij}(t_n)$ in (3.2) be random variables with conditional mean $\rho_{ij}(X(t_n))X^i(t_n)$. Variations on discrete-time specifications include different integer-valued distributions (e.g., Poisson, binomial and negative binomial) and different additional steps [e.g., susceptible reconstruction in the case of TSIR models (Grenfell, Bjørnstad and Finkenstadt, 2002)]. This specification of $f_{X_n|X_{n-1}}$ has been used with iterated filtering in combination with measurement models (Blackwood et al., 2013a, Blake et al., 2014) and both measurement and environmental models (Lavine et al., 2013, Martinez-Bakker, King and Rohani, 2015, Bakker et al., 2016).

3.2 Modeling Disease Measurement Via $f_{Y_n|X_n}$

The measurement models we review are variations on a binomial sampling mechanism. We describe them

in a common framework by defining discrete-time process $\{C_n\}$ that cumulates new infections between observation times, that is,

$$C_{n+1} = \sum_{(j,I)\in\mathcal{F}} N_{jI}(t_{n+1}) - N_{jI}(t_n). \tag{3.4}$$

3.2.1 *Binomial model*. In a binomial sampling mechanism, the C_n individuals are sampled independently with equal probability π, that is, $f_{Y_n|X_n}$ is assumed to be a binomial density [conditional on C_n, as in Blackwood et al. (2013b) and in Blake et al. (2014)]. This mechanism ties the (conditional) mean and variance of observations.

3.2.2 *Poisson model*. Specifying a Poisson density with parameter πC_n [as in Camacho et al. (2011) and in Shrestha, King and Rohani (2011)] also ties the observation mean and variance. However, unlike binomial models, Poisson models have unbounded support. Extending the support of the measurement model can provide mechanisms to capture false positive diagnoses, an idea developed in more detail in Section 6.1. Unbounded supports are ultimately a modeling decision—albeit one that may result in simulated measurements exceeding the total population size—that can be accommodated by different statistical methods. The Poisson model approximates a binomial mechanism for large C_n and small π and has also been considered as part of a mixture distribution to produce a negative binomial model.

3.2.3 *Negative binomial model*. Specifying a negative binomial density with mean πC_n and variance $\pi C_n + \tau^2\pi^2 C_n^2$ is more common in applications than the binomial or Poisson models (Bretó et al., 2009, Laneri et al., 2010, 2015, Bhadra et al., 2011, He et al., 2011, 2013, Earn et al., 2012, Roy et al., 2013, 2015, King et al., 2015, King, Nguyen and Ionides, 2016, Magpantay et al., 2016, Martinez et al., 2016). Unlike the binomial and Poisson models, the negative binomial model relaxes the constraint on the observation mean and variance, as we discuss further in the context of parameter randomization in Section 4.2.

3.2.4 *Gaussian model*. Specifying a Gaussian density matching the mean and approximating the variance of the binomial mechanism above is also common in applications. Such Gaussian approximations have been used both directly or discretizing them by accumulating the density on the nonnegative integers (allowing for zero inflated counts, as in He, Ionides and King, 2010, Martinez-Bakker, King and Rohani, 2015). The models we review depart from a genuine binomial variance $\pi C_n(1-\pi)$ in different ways. Some address the constraint on the mean and variance by using one or even two additional parameters, that is, letting the Gaussian variance be $\pi C_n\tau$ (Shrestha et al., 2013, 2015) or $\pi C_n\tau_1 + \tau_2$ (Blackwood et al., 2013a); some include a quadratic term, that is, $\pi C_n(1-\pi) + \tau C_n^2$ (Lavine et al., 2013, He, Ionides and King, 2010); and some include only such quadratic term (Ionides, Bretó and King, 2006, King et al., 2008, Martinez-Bakker, King and Rohani, 2015, Bakker et al., 2016). We revisit these choices in the context of parameter randomization in Section 4.2.

4. ENVIRONMENTAL MODELS

The environmental models we review aim at representing changes that affect the entire population. Such changes can be modeled by randomizing parameters of the transmission and measurement models, an approach that can be linked to overdispersion, which we address in more detail in Sections 5 and 6. While we distinguish between measurement and transmission environments, only the latter seem to have been considered in the literature tackling theoretical aspects of environmental stochasticity (e.g., Bretó and Ionides, 2011, Braumann, 2010, Bretó et al., 2009, Varughese and Fatti, 2008, Marion, Renshaw and Gibson, 2000, Engen, Bakke and Islam, 1998).

4.1 Models for Noisy Parameters in Transmission Models

The models for noisy parameters in transmission models that we review aim at capturing white noise, that is, changes in parameters that are independent over disjoint intervals of time.

4.1.1 *Differential equation models*. Additive Gaussian white noise can be introduced in rates of the ordinary differential equations of Section 3.1.1 by combining those ordinary differential equations

$$\frac{dN_{ij}(t)}{dt} = \rho_{ij}\big(X(t)\big)X^i(t)$$

with diffusions of the form

$$d\rho_{ij}(t) = \bar{\rho}_{ij}\big(X(t)\big)\,dt + \sigma_{ij}\big(X(t)\big)\,dW(t)$$

to define a new diffusion

$$dN_{ij}(t) = \bar{\rho}_{ij}\big(X(t)\big)X^i(t)\,dt + \sigma_{ij}\big(X(t)\big)X^i(t)\,dW(t).$$

This approach results in an infinitesimal variance proportional to the square of the initial population size

$X^i(t)$ [while proportionality to $X^i(t)$ would represent demographic stochasticity, as defined in Engen, Bakke and Islam, 1998]. In fact, this is the approach that led to formulating the diffusion models cited in Section 3.1.2, as well as the models cited in Section 3.1.3 (where multiplicative gamma white noise is introduced instead). Environmental noise can be introduced analogously in stochastic differential equation models.

4.1.2 *Continuous-time Markov chain models*. Multiplicative Lévy white noise can be introduced in rates $\rho_{ij}(x)x^i$ of the continuous-time Markov chains of Section 3.1.4 by combining those rates, which lead to transition probabilities

$$P\big(N_{ij}(t+h) = n_{ij} + 1 | N(t) = n\big) = \rho_{ij}(x)x^i h + o(h),$$

with gamma white noise

$$\xi(t) = d\Gamma(t)/dt$$

to define a new continuous-time Markov chain based on new randomized rates $\rho_{ij}(x)x^i\xi(t)$ (as in Bretó et al., 2009, Bretó and Ionides, 2011). That this approach results in an infinitesimal variance proportional to the square of the initial population size is not as immediate as with the differential equations of the previous section, so we postpone arguing so in more detail to Section 5. These models were introduced in Bretó et al. (2009) and subsequently used with iterated filtering in He, Ionides and King (2010), Shrestha, King and Rohani (2011), Shrestha et al. (2013, 2015), and Magpantay et al. (2016).

4.1.3 *Discrete time models*. Multiplicative gamma white noise can be introduced in parameters of the discrete time models of Section 3.1.5 as stochastic difference equations or as a mixture of the original random variables with a sequence of independent gamma random variables to define new discrete-time models with conditional variances of increments appropriately scaling as desired with either the initial population size or with its square (as done with iterated filtering in Lavine et al., 2013, Martinez-Bakker, King and Rohani, 2015, Bakker et al., 2016).

4.2 Models for Noisy Parameters in Measurement Models

For measurement models, introducing noise by randomizing parameters needs to be reconciled with our assumption of conditional independence of observations from Section 2. Such independence can be easily accommodated when introducing noise that is white, that is, changes in parameters that are independent between observation times. However, this white noise nature of the noisy parameters of measurement models has rarely been explicitly pointed out. Since establishing a white noise nature is a useful starting point to consider nonwhite noises, we introduce some notation. This notation introduces an additional hierarchical layer—and additional complexity that can distract from the goals we seek by introducing it. Nevertheless, we consider this notation focusing on the two things it facilitates: on one hand, establishing that the models we review are indeed introducing white noise; and, on the other, our discussion of alternative noises in Section 6. Noise in the parameters of the measurement model can be introduced by including it in the unobserved process. Consider splitting the unobserved process $\{X(t)\} = \{(X^{(1)}(t), X^{(2)}(t))\}$ so that $\{X^{(1)}(t)\}$ models the unobserved process in the absence of noise in parameters of the measurement model and that $\{X^{(2)}(t)\}$ models such noise. Note that including additional noise in the unobserved process in this way increases the sequential Monte Carlo variability and should be avoided if possible, for example, when introducing white noise. Assuming that $\{X_n^{(2)}\}$ is a strict white noise sequence (i.e., all pairs $X_k^{(2)}$ and $X_m^{(2)}$ are independent) and that $\{X_n^{(2)}\}$ and $\{X_n^{(1)}\}$ are independent, we can write the likelihood as

$$\begin{aligned} f_{Y_{1:N}} &= \int\int f_{X_{0:N},Y_{1:N}}\, dx_{0:N}^{(2)}\, dx_{0:N}^{(1)} \\ &= \int f_{X_{0:N}^{(1)},Y_{1:N}}\, dx_{0:N}^{(1)}, \end{aligned}$$

where

$$f_{X_{0:N}^{(1)},Y_{1:N}} = f_{X_0^{(1)}} \prod_{n=1}^{N} f_{X_n^{(1)}|X_{n-1}^{(1)}} f_{Y_n|X_n^{(1)}}, \tag{4.1}$$

$$f_{X_0^{(1)}} = \int f_{X_0}\, dx_0^{(2)},$$

$$f_{Y_n|X_n^{(1)}} = \int \frac{f_{Y_n,X_n}}{f_{X_n^{(1)}}}\, dx_n^{(2)}$$

$$= \int \frac{f_{Y_n|X_n} f_{X_n^{(1)}|X_n^{(2)}} f_{X_n^{(2)}}}{f_{X_n^{(1)}}}\, dx_n^{(2)} \tag{4.2}$$

$$= \int f_{Y_n|X_n} f_{X_n^{(2)}}\, dx_n^{(2)}.$$

If the stated independence assumptions hold, joint density (4.1) is an alternative to the original joint density (2.1). This alternative density gives the same likelihood function while avoiding introducing noise for measurement parameters in the unobserved process.

This, in turn, enables more efficient implementations of sequential Monte Carlo tools. However, this gain in efficiency comes at the cost of a closed-form expression for measurement density (4.2). A celebrated example of such gain through closed-form measurement densities is the gamma Poisson hierarchy, that is, specifying $f_{Y_n|X_n}$ as a conditional Poisson density with rate ΠC_n and $f_{X_n^{(2)}}$ as a gamma density for Π. This hierarchy gives for (4.2) the celebrated negative binomial density of Section 3.2.3. As done in most references of that section, the negative binomial model can be specified directly instead of as a gamma Poisson hierarchy. Here, in order to help make our point that this negative binomial model corresponds to environmental measurement noise that is white, we have emphasized the hierarchical representation.

Hierarchies where parameters of the measurement models of Section 3.2 are randomized can be specified to relax moment constraints. A two-layer binomial hierarchy for $f_{Y_n|X_n^{(1)}}$ can be specified as the binomial mechanism of (3.4) in the top layer and a bottom layer with a white noise sequence of success probabilities $\Pi_n = X_n^{(2)}$ following some distribution with support the interval $(0, 1)$ and $E[\Pi_n] = \pi$. Observations Y_n have variances (conditional on C_n)

$$C_n\pi(1-\pi) + \big(C_n^2 - C_n\big)V[\Pi_n], \tag{4.3}$$

where the first term is the $V[Y_n|C_n]$ when $V[\Pi_n] = 0$ and the second term is nonnegative (and equal to zero if and only if C_n takes values zero or one). Expression (4.3) can both help interpret parameter estimates from the multiple flavors of Gaussian approximations described in Section 3.2.4 and help assess evidence from data regarding the appropriateness of randomized binomial mechanisms, for which $V[\Pi]$ in (4.3) should be estimated to fall inside the interval $(0, 1)$. Corresponding conditional variances can be useful for the same purposes if other hierarchies are used. A Poisson hierarchy can be specified with a Poisson density with parameter $\Pi_n C_n$ and a white noise sequence of Π_n with nonnegative support and $E[\Pi_n] = \pi$. Observations Y_n then have conditional variances

$$\pi C_n + C_n^2\pi^2\big(E\big[\Pi_n^2\big]/\pi^2 - 1\big),$$

where again the first term is the $V[Y_n|C_n]$ when $V[\Pi_n] = 0$ and the second term is nonnegative (and equal to zero if and only if C_n takes values zero or one). We say that these binomial and Poisson hierarchies are overdispersed, meaning that they allow for more dispersion that the constrained original models.

5. OVERDISPERSION IN TRANSMISSION MODELS

Overdispersion and the potential biases and distortions on confidence levels it entails can be addressed more effectively in the context of a theoretical framework. Such theoretical considerations on overdispersion in transmission models become more complex than the hierarchies or mixtures of distributions involved in the measurement models of the previous section. This complexity results in part from accounting for continuous time, which leads to stochastic calculus and related ideas, including simultaneous transitions and change of time.

Dispersion constraints of the Markov chain transmission models from Section 3.1.4 $\{X(t)\}$ are inherited from the counting processes involved $\{N(t)\}$, which have equal infinitesimal means and variances. These constraints necessarily follow from the combination of not allowing for simultaneous transitions and having exponential inter-event times (Bretó et al., 2009, Bretó and Ionides, 2011). These two conditions still hold for mixed processes (Snyder and Miller, 1991, Daley and Vere-Jones, 2003) where parameters are held constant over time at some random initial value. Such mixing produces differences between trajectories but not within them (see, e.g., Hougaard, Lee and Whitmore, 1997) and hence does not produce overdispersion (Bretó and Ionides, 2011). The assumption of exponential inter-event times has been questioned (Lloyd, 2001) and an alternative approach consisting in chaining artificial sequences of compartments has been explored (Wearing, Rohani and Keeling, 2005, Keeling and Rohani, 2008). Alternatively, one might explore the possibility of some transitions occurring at the same time (possibly as an approximation to models with clustered transitions relative to exponential inter-event times).

Simultaneous transitions can occur under some conditions (see, e.g., Bretó, 2012b, Kozubowski and Podgórski, 2009, Lee and Whitmore, 1993) when time is changed by a stochastic process or clock (see, e.g., Bochner, 1949, Barndorff-Nielsen and Shiryaev, 2010). In particular, simultaneous transitions arise naturally when individual transitions are accumulated and released at once at discontinuity points of paths of the new time, as happens when time is changed by a Poisson clock (Bretó, 2014b) or by the gamma clock of Section 4.1. Although such simultaneous transitions are necessary for overdispersion of continuous-time Markov chains (Bretó and Ionides, 2011), overdispersion can be described in different terms, for example,

in terms of randomized transition rates, as in the following example.

Consider a continuous-time Markov chain defined by (3.3) with a single compartment (of initial size x) and a single possible transition (out of the compartment). The corresponding univariate counting process $\{N(t)\}$ counts individuals who, at rate $\lambda(n) = (x-n)\rho$, have left the compartment by time t. $\{N(t)\}$ has increments that follow a binomial distribution (Renshaw, 1991) and satisfies Kolmogorov's Backward Differential System (KBDS; Brémaud, 1999). Since $\{N(t)\}$ is simple (i.e., it increases by no more than one count at a time; Daley and Vere-Jones, 2003), this KBDS is uniquely specified by $\lambda(n)$. Now define a new process $\{N^\star(t)\}$ for which the same KBDS holds but with $\lambda(n)$ replaced by a new, noisy rate $\lambda(n)\xi(t)$, that is, the original rate is multiplied by gamma continuous-time white noise $\xi(t) = d\Gamma(t)/dt$. This multiplication defines a stochastic version of the original KBDS that, after appropriately defining stochastic integration against gamma processes, is also satisfied by time-changed process $\{N(\Gamma(t))\}$. Writing $H = \Gamma(t+h) - \Gamma(t)$, the increment $N^\star(t+h) - N^\star(t)$ has variance conditional on $N^\star(t) = n^\star$ given by

$$(x-n^\star)^2 V\big[e^{-\rho H}\big] + (x-n^\star)E\big[e^{-\rho H}\big(1-e^{-\rho H}\big)\big],$$

and a Taylor series expansion of the moment generating function of the gamma distributed H confirms that neither of these two terms vanishes infinitesimally. Note that these terms might vanish if the time change had continuous paths or if rates were randomized by the derivative of paths of such time change (e.g., randomized by stationary Ornstein–Uhlenbeck processes, as in Nisbet and Gurney, 1982, Marion, Renshaw and Gibson, 2000, Varughese and Fatti, 2008). This property of this univariate binomial death process can be extended to the multivariate compartment models used in applications, for which transition probabilities are no longer binomially distributed. To do this, instead of changing time of the now multivariate Markov chain, multivariate models can be defined directly as systems of interacting univariate time-changed counting processes (as in Bretó, 2012a).

The preceding theoretical considerations regarding overdispersion in transmission models were largely motivated by the data analysis in Bretó et al. (2009). This illustrates how data-based evidence obtained from infectious disease mechanistic modeling and plug-and-play methodology can guide and point in directions in which to pursue theoretical contributions.

6. DISCUSSION

Overdispersion has been studied from multiple perspectives, including applications involving count data, applied probability involving stochastic processes of counts, and statistical modeling involving both. The study of overdispersion in the context of infectious disease dynamics has been and can be further facilitated by the synergy between mechanistic models and iterated filtering algorithms.

The interaction between plug-and-play algorithms and mechanistic modeling is similar to a mutualistic symbiosis: mechanistic modeling often involves describing mechanisms as sequences of actions or events that result in change. Such descriptions naturally translate into simulation algorithms that in turn are the basis of plug-and-play methods. In return, plug-and-play methods extract evidence from data that might suggest changes to the initially hypothesized mechanisms and, accordingly, to the simulation algorithms. For the transmission models described in Section 3.1, exact (or at least accurate) simulation is often possible using appropriate numerical algorithms, like Runge–Kutta methods for ordinary differential equations, Euler-type algorithms for diffusions and Lévy-driven differential equations, and exact (Gillespie, 1977) or approximate algorithms (Gillespie, 2001) for continuous-time Markov chains. Such synergy exists between mechanistic modeling and iterated filtering but it does not address issues that in general affect likelihood maximization or sequential Monte Carlo, including rough surfaces (Fasiolo, Pya and Wood, 2016), small measurement variances, system dimensionality and parameter identifiability. This synergy can be exploited to further explore overdispersion in measurement models.

6.1 Overdispersion in Measurement Models

Approaching overdispersion in measurement models by randomizing parameters as in Section 4.2 can be complemented by other model variations that exploit plug-and-play methodology. Accounting for overdispersion in measurement models can facilitate separating measurement variability from the rest of variability sources. It has been pointed out that failing to separate these sources entails dangers, both in the context of population dynamics in general (Nadeem et al., 2016) and of infectious disease dynamics in particular (see, e.g., Fujiwara, 2009, Gibbons et al., 2014). Moreover, measurement models have been receiving more attention motivated by the access to massive datasets related to infectious diseases in recent times (Huang, 2016).

Here, we focus on two variations on the models of Section 3.2 for noisy parameters in measurement models that seem to have been so far unexplored: dependent environmental noise and diagnosis error.

Temporal dependence in the environment affecting measurements can be easily implemented in the POMP and plug-and-play frameworks, for example, as in Section 4.2 but replacing the white noise model for $\{X_n^{(2)}\}$ by some other models. Environmental dependence has received attention in the population dynamics literature but only regarding transmission models (Fujiwara, 2009, Lande, Engen and Saether, 2003), for example, in the form of random-walk rates (Renshaw, 1991). Random-walk dependence in measurement models has been considered in other fields as well (see, e.g., Bretó, 2014a, Müller and Petalas, 2010). Random walks are a form of strong dependence. As another example for extreme environmental dependence, consider a randomized binomial measurement model with Π_0 following some distribution and $\Pi_n = \Pi_0$ for all n. Other forms of dependence have also been considered in other fields, for example, integer ARMA (or INARMA) processes (McKenzie, 1985, Scotto, Weiß and Gouveia, 2015), which illustrate that there is a range of dependence levels compatible with binomial (or Poisson) observation marginal distributions.

Diagnosis error can be incorporated into the binomial sampling mechanism of Section 3.2. This results in a mechanism that, like negative binomial models and unlike alternative binomial mixtures (like the beta binomial), assigns a nonzero likelihood to observing more cases than new infectious individuals between observation times (as does, e.g., the additive constant in the measurement variance of Blackwood et al., 2013a). To account for false negative diagnoses, let π be the probability of an infectious individual being sampled and correctly diagnosed (as opposed to that of simply being sampled). False positive diagnoses might be accounted for by letting observations Y_n be the sum of (conditionally independent) false (F_n) and true (T_n) positive diagnoses. If $F_n|C_n, T_n \sim \text{Poisson}(\lambda)$ and $T_n|C_n, F_n \sim \text{Binomial}(C_n, \pi)$, this approach leads to convenient closed-form expressions

$$P(Y_n = y|C_n = c) = \sum_{t=0}^{y} \mathbb{I}\{t \le c\} \binom{c}{t} \pi^t (1-\pi)^{c-t} \frac{e^{-\lambda} \lambda^{(y-t)}}{(y-t)!}$$

which are nonzero for $c < y$. This mechanism is an analogy at the measurement level of immigration of infectious from outside the population at the transmission level, albeit it lacking dynamic effects. This example illustrates the potential for further exploration based on scientific understanding of measurement models and overdispersion.

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SUPPLEMENTARY MATERIAL

Supplement to "Modeling and Inference for Infectious Disease Dynamics: A Likelihood-Based Approach" (DOI: 10.1214/17-STS636SUPPA; .pdf). An illustration of how to apply IF2 for an infectious disease model.

Supplement to "Modeling and Inference for Infectious Disease Dynamics: A Likelihood-Based Approach" (DOI: 10.1214/17-STS636SUPPB; .zip). Source code of supplement.

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