# Inference for partially observed stochastic dynamic systems

Mathematical Biosciences Institute workshop:

Recent advances in stastistical inference for mathematical biology

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## Edward Ionides

## The University of Michigan, Department of Statistics

## Collaborators

Anindya Bhadra (Texas A&M, Statistics)

Menno Bouma (London School of Hygiene and Tropical Medicine)

Carles Bretó (Universidad Carlos III de Madrid, Statistics)

Daihai He (McMaster University, Mathematics & Statistics)

Aaron King (Univ. of Michigan, Ecology & Evolutionary Biology)

Karina Laneri (Institut Català de Ciències del Clima, Barcelona, Spain)

Mercedes Pascual (Univ. of Michigan, Ecology & Evolutionary Biology)

## **Outline**

1. Historical overview: a decade of progress on time series analysis via mechanistic models.

2. Some practical considerations: relationship between statistical methodology and software.

3. The *plug-and-play* property.

4. Iterated filtering: theory and methodology.

5. Case studies: malaria & measles.

6. Outstanding challenges.

## Six problems of Bjørnstad and Grenfell (Science, 2001)

Obstacles for *ecological* modeling and inference via nonlinear mechanistic models:

1. Combining measurement noise and process noise.

2. Including covariates in mechanistically plausible ways.

3. Continuous time models.

4. Modeling and estimating interactions in coupled systems.

5. Dealing with unobserved variables.

6. Modeling spatial-temporal dynamics.

# From the perspective of 2001...

> ## Wanted:
>
> A framework for modeling and inference allowing consideration of arbitrary nonlinear, partially observed, vector-valued, time series models.

## Partially observed Markov process (POMP) models have been repeatedly proposed for biological systems

- A Markov (i.e., memoryless) dynamic system model enables general algorithms for inference on unobserved dynamic variables.

- Numerical methods for inferring unknown parameters and unknown model structure have been more problematic. A subtle issue: mixing properties and their consequences for numerical stability.

- General-purpose software has therefore been a challenge for stastistcal inference using non-linear non-Gaussian POMPs:

    ◇ WinBUGS performs poorly on these models.

    ◇ **pomp**, an R package for POMPs, is recently available.

## Partially Observed Markov Process (POMP) notation

The unobserved Markov dynamic process is denoted $X(t)$. For observation times $t_1, \ldots, t_N$ we write $X_n = X(t_n)$. The observable variables $Y_1, \ldots, Y_N$ are conditionally independent given $X_1, \ldots, X_N$. The model depends on an unknown parameter vector $\theta$.

- To think algorithmically, we define some function calls:

  **rprocess( )**: a draw from $f_{X_n|X_{n-1}}(x_n \,|\, x_{n-1}\,;\theta)$

  **dprocess( )**: evaluation of $f_{X_n|X_{n-1}}(x_n \,|\, x_{n-1}\,;\theta)$

  **rmeasure( )**: a draw from $f_{Y_n|X_n}(y_n \,|\, x_n\,;\theta)$

  **dmeasure( )**: evaluation of $f_{Y_n|X_n}(y_n \,|\, x_n\,;\theta)$

## Plug-and-play inference for POMP models

● An algorithm operating on a POMP is **plug-and-play** if it involves calls to

**rprocess** but not to **dprocess**. In this case, numerical solution of

sample paths is a 'black box' which is plugged into the software.

● Bayesian plug-and-play:

 1. Artificial parameter evolution (Liu and West, 2001)

 2. Approximate Bayesian Computation (Toni et al, *Interface*, 2009)

 3. Particle MCMC (Andrieu et al, *J. Roy. Statist. Soc. B*, 2010)

● Non-Bayesian plug-and-play:

 4. Simulation-based prediction rules (Kendall et al, *Ecology*, 1999)

 5. Simulated likelihood of summary statistics (Wood, *Nature*, 2010)

 6. Iterated filtering (Ionides et al, *PNAS*, 2006)

**Plug-and-play is a VERY USEFUL PROPERTY for scientific work.**

# Classification of methodologies by required operations

| | rprocess | dprocess | rmeasure | dmeasure |
|---|:---:|:---:|:---:|:---:|
| Iterated filtering | ✔ | ✗ | ✗ | ✔ |
| Liu-West SMC | ✔ | ✗ | ✗ | ✔ |
| EM via SMC | ✔ | ✔ | ✗ | ✔ |
| MCMC | ✗ | ✔ | ✗ | ✔ |
| Nonlinear forecasting | ✔ | ✗ | ✔ | ✗ |
| Particle MCMC | ✔ | ✗ | ✗ | ✔ |
| Probe matching | ✔ | ✗ | ✔ | ✗ |

- The usual workhorses of statistical computation (EM and MCMC) are not plug-and-play.

- Nonlinear forecasting and probe matching are simulation-based techniques developed by scientists, likely due to the inapplicability of textbook statistical techniques

## Plug-and-play in other settings

- **Optimization**. Methods requiring only evaluation of the objective function to be optimized are sometimes called **gradient-free**. This is the same concept as plug-and-play: the code to evaluate the objective function can be *plugged into* the optimizer.

- **Complex systems**. Methods to study the behavior of large simulation models that only employ the underlying code as a "black box" to generate simulations are called **equation-free** (Kevrekidis et al., 2003, 2004).
  - ◇ This is the same concept as plug-and-play, but we prefer our label!
  - ◇ A typical goal is to determine the relationship between macroscopic phenomena (e.g. phase transitions) and microscopic properties (e.g. molecular interactions).

## The cost of plug-and-play

- Approximate Bayesian methods and simulated moment methods lead to a loss of statistical efficiency.

- In contrast, iterated filtering enables (almost) exact likelihood-based inference.

- Improvements in numerical efficiency may be possible when analytic properties are available (at the expense of plug-and-play). But many interesting dynamic models are analytically intractable—for example, it is standard to investigate systems of ordinary differential equations numerically.

## Summary of plug-and-play inference via iterated filtering

- **Filtering** is the extensively-studied problem of calculating the conditional distribution of the unobserved state vector $x_t$ given the observations up to that time, $y_1, y_2, \ldots, y_t$.

- **Iterated filtering** is a recently developed algorithm which uses a sequence of solutions to the filtering problem to maximize the likelihood function over unknown model parameters.
  (Ionides, Bretó & King. *PNAS*, 2006)

- If the filter is plug-and-play (e.g. using standard sequential Monte Carlo methods) this is inherited by iterated filtering.

## **Key idea of iterated filtering**

- The conditional distribution of time-varying parameters is a (relatively) tractable filtering problem, with favorable mixing properties.

- Set $\theta = \theta_t$ to be a random walk with

$$E[\theta_t | \theta_{t-1}] = \theta_{t-1} \qquad \mathrm{Var}(\theta_t | \theta_{t-1}) = \sigma^2$$

- The limit $\sigma \to 0$ can be used to maximize the likelihood for fixed parameters.

## Theorem. (Ionides, Bretó & King, *PNAS*, 2006)

*Suppose $\hat{\theta}_0$, $C$ and $y_{1:T}$ are fixed and define*

$$\hat{\theta}_t \;=\; \hat{\theta}_t(\sigma) = E[\theta_t|y_{1:t}]$$

$$V_t \;=\; V_t(\sigma) = \mathrm{Var}(\theta_t|y_{1:t-1})$$

*Assuming sufficient regularity conditions for a Taylor series expansion,*

$$\lim_{\sigma\to0}\sum_{t=1}^{T}V_t^{-1}(\hat{\theta}_t - \hat{\theta}_{t-1}) = (\partial/\partial\theta)\log f(y_{1:T}|\theta,\sigma{=}0)\Big|_{\theta=\hat{\theta}_0}$$

- **The limit of an appropriately weighted average of local filtered parameter estimates is the derivative of the log likelihood.**

- **Iterated filtering theory has been subsequently refined (Ionides et al, *Annals of Statistics*, 2011).**

## Infectious diseases as ecological systems

- Good spatio-temporal data are available for many human diseases.

- The 20th century saw some successes for vaccination and drug treatment. But the limitations also became evident.

  ◇ Emerging infectious diseases (SARS; HIV/AIDS; H5N1 influenza "bird flu")

  ◇ New strains and drug resistance (H1N1 "swine flu"; MRSA "the hospital super-bug"; tuberculosis; malaria)

- Controlling human/livestock/wildlife diseases involves understanding the pathogen-host ecological dynamics.

**Example: malaria (mosquito-transmitted *Plasmodium* infection)**
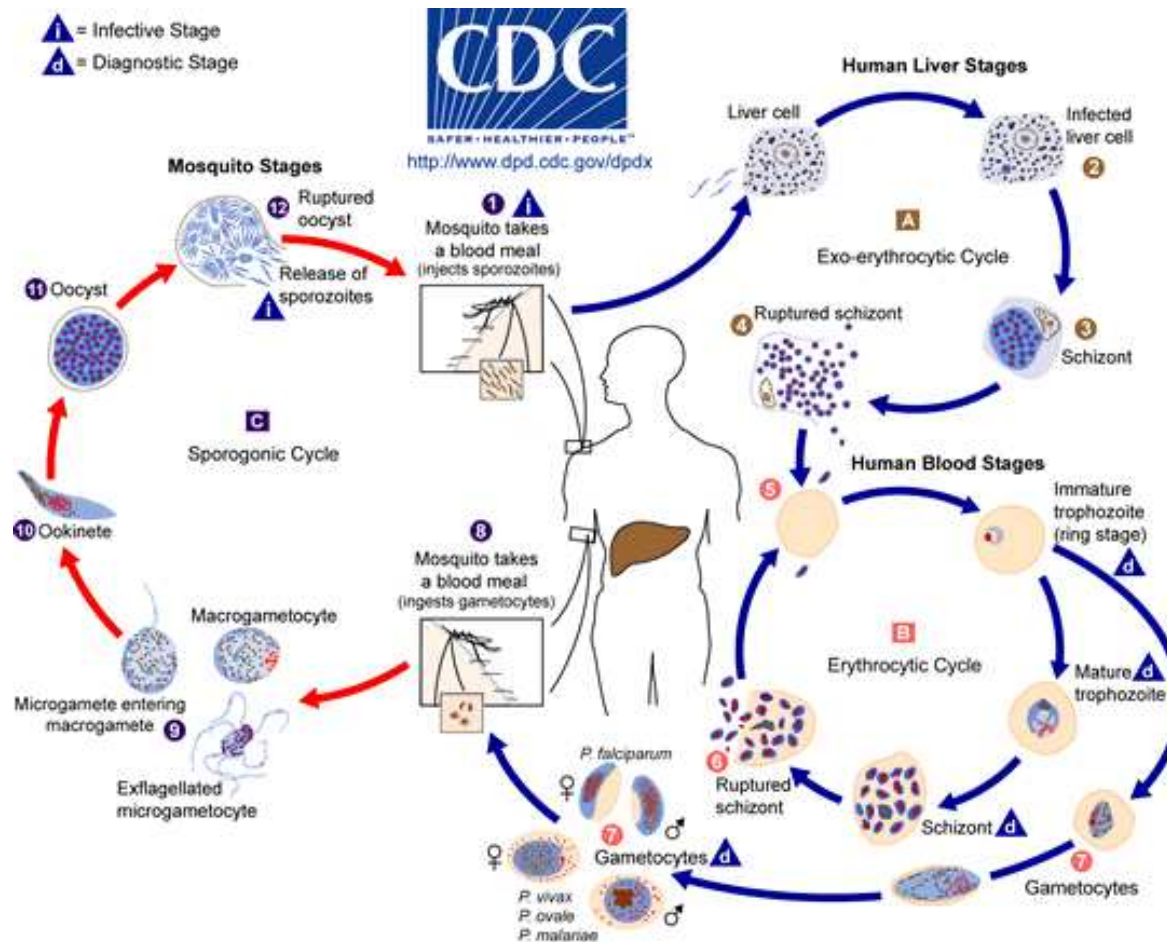


Despite extensive study of the disease system (mosquito, *Plasmodium* & human immunology) ecological dynamics of malaria remain hotly debated.

## Malaria: A global challenge

- Bill Gates would like to eradicate it, but others have tried before...

- There has been extensive debate on whether/how global climate change will affect malaria burden—a model validated by data is required.

## From the perspective of statistical methodology

- Despite the huge literature, no dynamic model of malaria transmission has previously been fitted directly to time series data.

- Difficulties include: Incomplete and complex immunity; dynamics in both mosquito and human stages; diagnostic difficulties (the immediate symptom is non-specific fever).

- Malaria is beyond the scope of methods developed for simpler diseases.

## Malaria and rainfall in Kutch (an arid region of NW India)
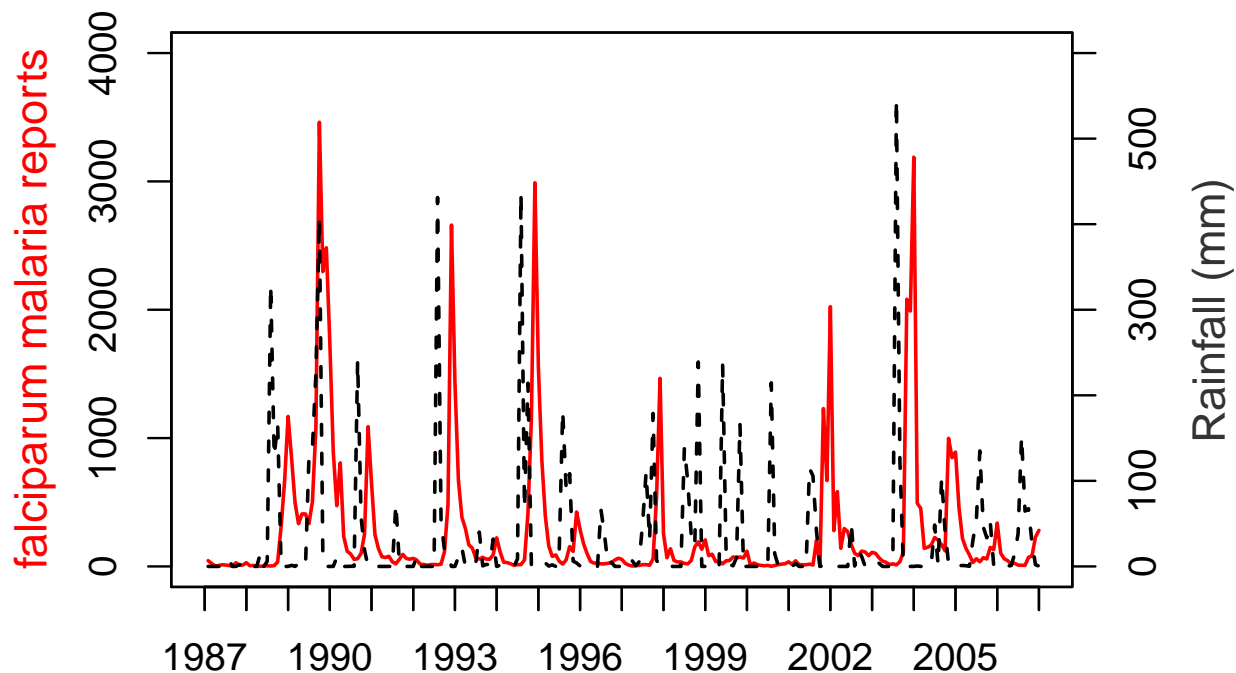


- To what extent are cycles driven by immunity rising and falling? To what extent are they driven by rainfall?

## A dynamic model (Laneri et al, *PLoS Comp. Biol.*, 2010).
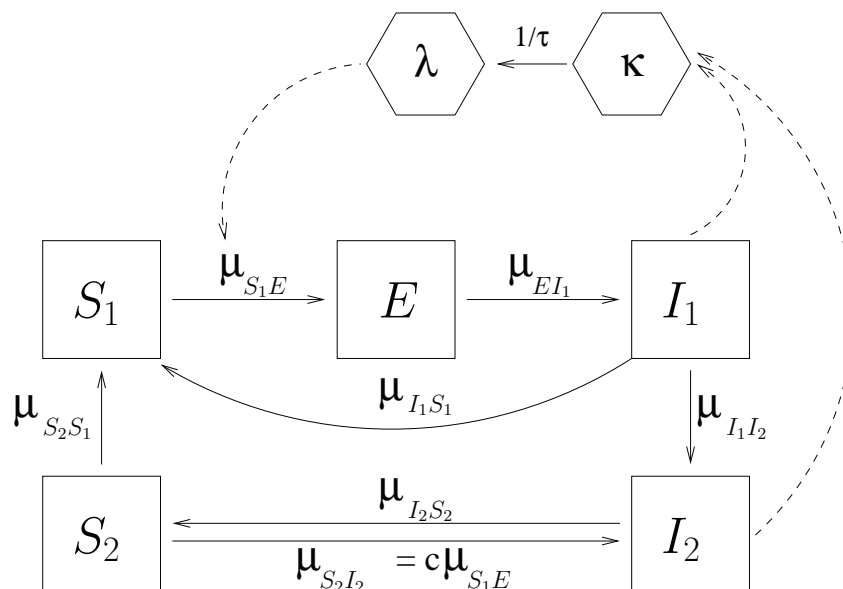


$\lambda$, force of infection; $\kappa$, latent force of infection; $S_1$, fully susceptible humans; $S_2$ clinically protected (partially immune); $I_1$, clinically infected; $I_2$, asymptomatically infected.

**Minimal complexity acceptable to scientists**

$\approx$ **Maximal complexity acceptable to available data**

## Model representation: coupled SDEs driven by Lévy noise

$$dS_1/dt \;=\; \mu_{BS_1}P - \mu_{S_1E}S_1 + \mu_{I_1S_1}I_1 + \mu_{S_2S_1}S_2 - \mu_{S_1D}S_1$$

$$dS_2/dt \;=\; \mu_{I_2S_2}I_2 - \mu_{S_2S_1}S_2 - \mu_{S_2I_2}S_2 - \mu_{S_2D}S_2$$

$$dE/dt \;=\; \mu_{S_1E}S_1 - \mu_{EI_1}E - \mu_{ED}E$$

$$dI_1/dt \;=\; \mu_{EI_1}E - \mu_{I_1S_1}I_1 - \mu_{I_1I_2}I_1 - \mu_{I_1D}I_1$$

$$dI_2/dt \;=\; \mu_{I_1I_2}I_1 + \mu_{S_2I_2}S_2 - \mu_{I_2S_2}I_2 - \mu_{I_2D}I_2$$

$$d\kappa/dt \;=\; d\lambda_0/dt \;=\; (f(t) - \kappa)\,\ell\,\tau^{-1}$$

$$d\lambda_i/dt \;=\; (\lambda_{i-1} - \lambda_i)\,\ell\,\tau^{-1} \qquad \text{for } i = 1, \dots, \ell-1$$

$$d\lambda/dt \;=\; d\lambda_\ell/dt \;=\; (\lambda_{\ell-1} - \lambda)\,\ell\,\tau^{-1}$$
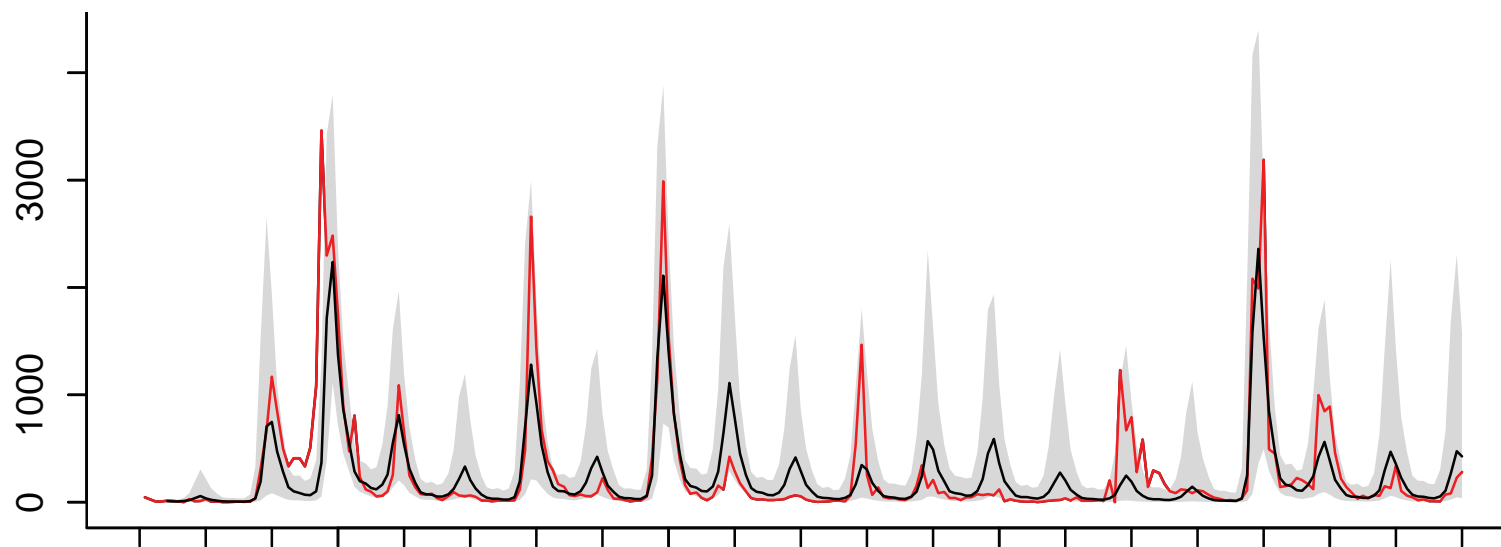
$$f(t) \;=\; \frac{I_1(t) + qI_2(t)}{N(t)}\,\bar\beta\,\exp\left\{ \sum_{i=1}^{n_s} \beta_i s_i(t) + Z_t\beta \right\}\frac{d\Gamma}{dt}.$$

$Z_t$ is a vector of climate covariates (here, rainfall).

$\sum_{i=1}^{n_s} \beta_i s_i(t)$ is a spline representation of seasonality.

## Conclusions from malaria data analysis

● Rainfall (with an appropriate delay and threshold) a critical role in
determining interannual cycles.

● Immunity plays a role at faster timescales (controlling annual peaks)



**Simulations forward from 1987 to 2007, from the MLE, with
prescribed rainfall**. Showing monthly case reports (red), simulation
median (black) and 10th to 90th percentiles (grey). Without rainfall, the
model cannot come close to this.
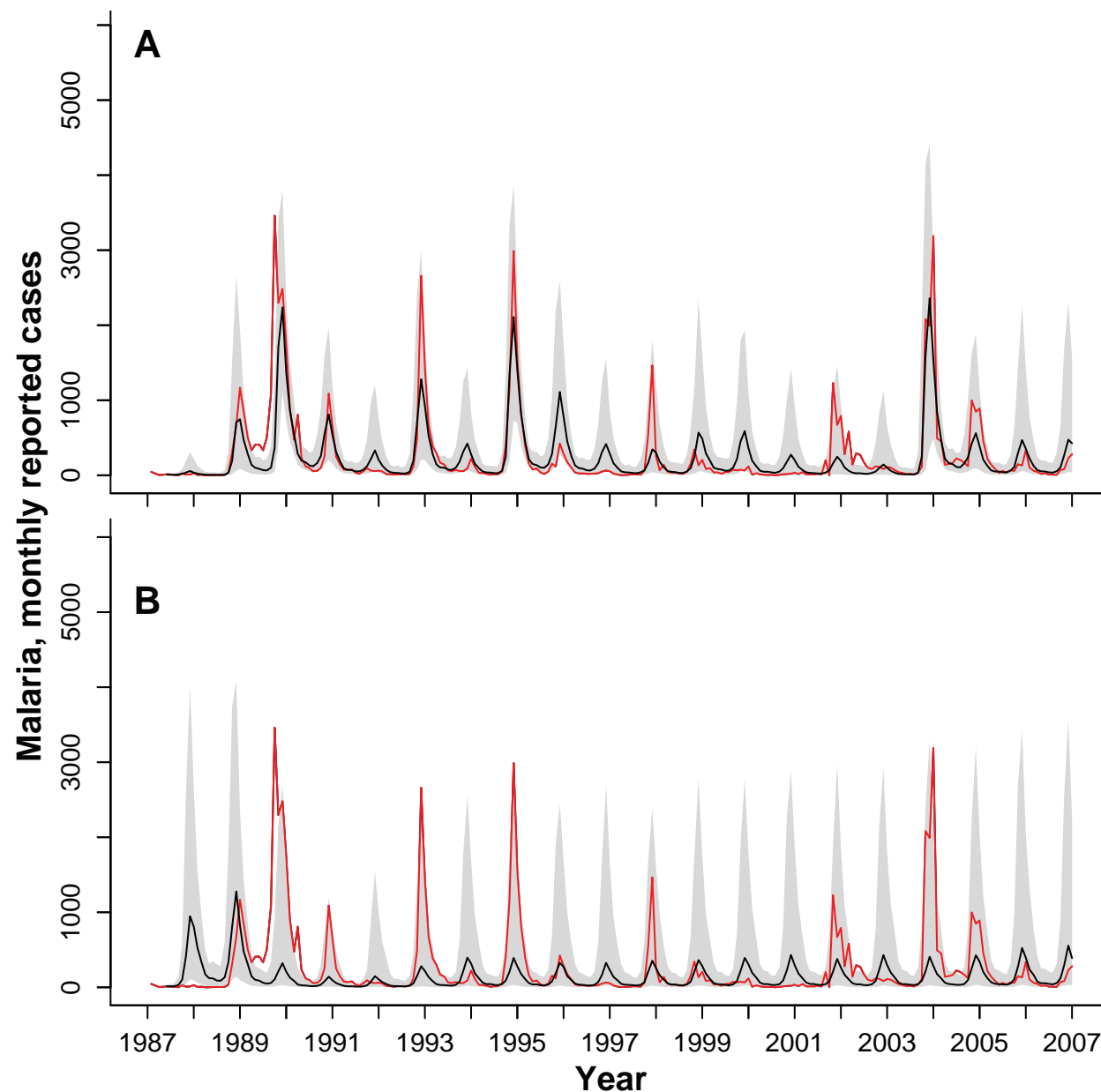
**Simulations forward from 1987 to 2007 from fitted models (A) with rainfall; (B) without rainfall.** Showing monthly case reports (red), simulation median (black) and 10th to 90th percentiles (grey).

# Stochastic differential equations (SDEs) vs. Markov chains

- SDEs are a simple way to add stochasticity to widely used ordinary differential equation models for population dynamics.

- When some species have low abundance (e.g. fade-outs and re-introductions of diseases within a population) discreteness can become important.

- This motivates the consideration of discrete population, continuous time POMP models (Markov chains).

## Over-dispersion in Markov chain models of populations

- **Remarkably, in the vast literatures on continuous-time individual-based Markov chains for population dynamics (e.g. applied to ecology and chemical reactions) no-one has previously proposed models capable of over-dispersion.**

- It turns out that the usual assumption that no events occur simultaneously creates fundamental limitations in the statistical properties of the resulting class of models.

- Over-dispersion is the rule, not the exception, in data.

- Perhaps this discrepancy went un-noticed before statistical techniques became available to fit these models to data.

# Implicit models for plug-and-play inference

- Adding "white noise" to the transition rates of existing Markov chain population models would be a way to introduce an infinitesimal variance parameter, by analogy with the theory of SDEs.

- **We do this by defining our model as a limit of discrete-time models. We call such models *implicit*.** This is backwards to the usual approach of checking that a numerical scheme (i.e. a discretization) converges to the desired model.

- Implicit models are convenient for numerical solution, by definition, and therefore fit in well with plug-and-play methodology.

- Details in Bretó et al (2009, *AoAS*); Bretó & Ionides (2011, *Stoc. Proc. Appl.*).

## Measles: an exhaustively studied system

- Measles is simple: direct infection of susceptibles by infecteds; characteristic symptoms leading to accurate clinical diagnosis; life-long immunity following infection.

$$\boxed{S} \xrightarrow{\mu_{SE}(t)\xi_{SE}(t)} \boxed{E} \xrightarrow{\mu_{EI}} \boxed{I} \xrightarrow{\mu_{IR}} \boxed{R}$$
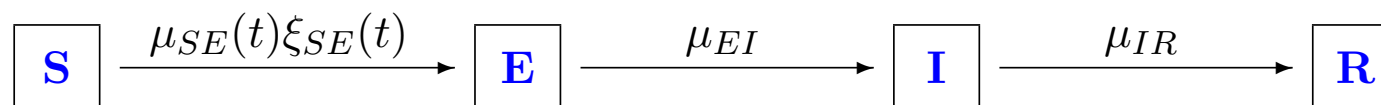
Susceptible $\rightarrow$ Exposed (latent) $\rightarrow$ Infected $\rightarrow$ Recovered, with noise intensity $\sigma_{SE}$ on the force of infection.

- Measles is still a substantial health issue in sub-Saharan Africa.

- A global eradication program is under debate.

- Comprehensive doctor reports in western Europe and America before vaccination ($\approx 1968$) are textbook data.
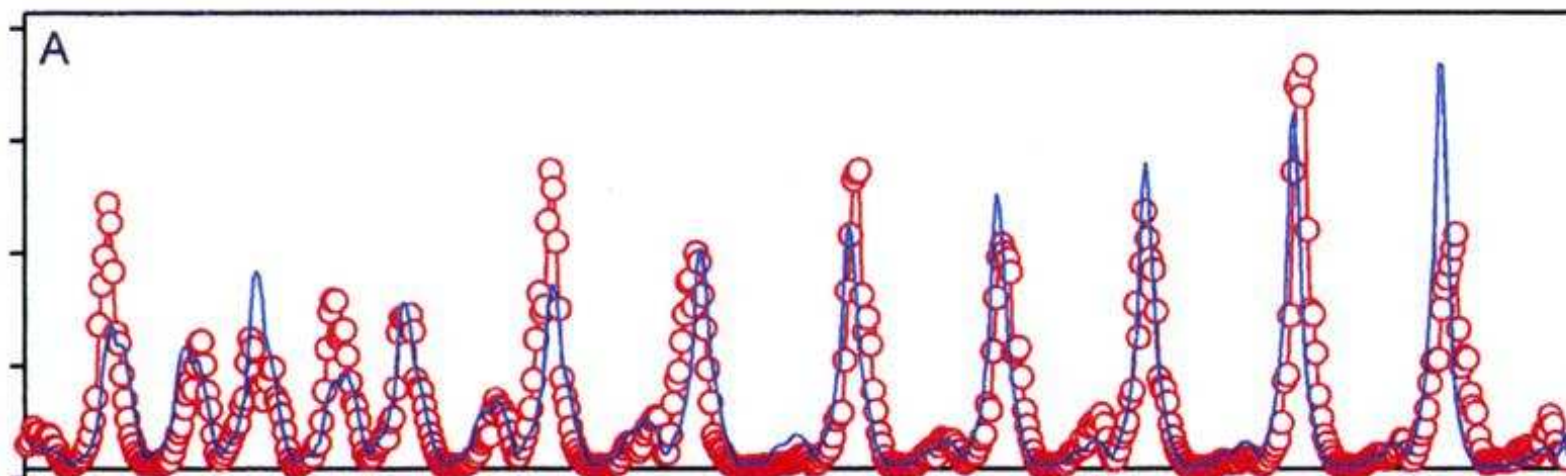
- Measles cases in London 1944–1965 (circles and red lines) and a deterministic SEIR fit (blue line) (from Grenfell *et al*, 2002).

- A deterministic fit, specified by the initial values in January 1944, captures remarkably many features.

# Is demographic stochasticity ($\sigma_{SE} = 0$) plausible?

- Profile likelihood for $\sigma_{SE}$ and effect on estimated latent period (L.P.) and infectious period (I.P.) for London, 1950–1964.

- Variability of $\approx 5\%$ per year on the infection rate substantially improves the fit, and affects scientific conclusions (He et al, *JRSI*, 2010).
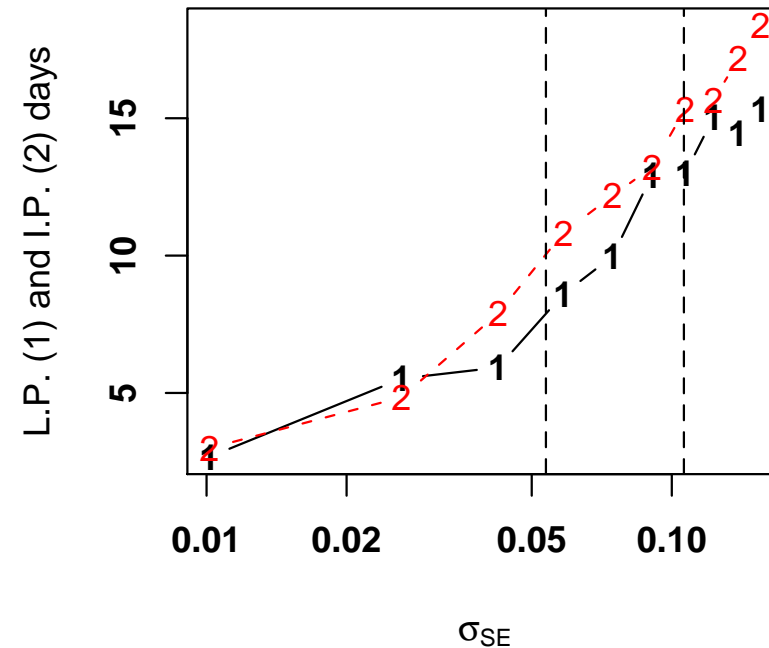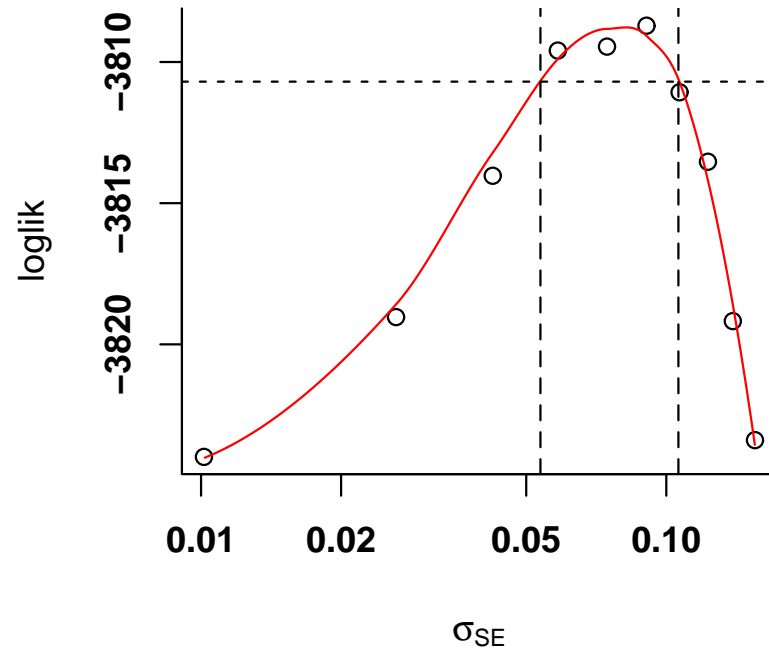
## Interpretation of over-dispersion

- Social and environmental events (e.g., football matches, weather) lead to stochastic variation in rates: **environmental stochasticity**.

- A catch-all for **model misspecification**? It is common practice in linear regression to bear in mind that the "error" terms contain un-modeled processes as well as truly stochastic effects. This reasoning can be applied to dynamic models as well.

## **Conclusions and outstanding challenges**

- Plug-and-play statistical methodology permits likelihood-based analysis of flexible classes of stochastic dynamic models.

- Many models of interest are beyond current algorithms & computational resources. Much work remains to be done!

- New data types (e.g., genetic sequence data on pathogens for some or all infected hosts) both enable and require the fitting of more complex models.

- Spatio-temporal models and individual-level models in large populations are typically beyond the scope of current plug-and-play methods, unless some special model structure can be exploited.

# Thank you!

These slides (including references for the citations) are available at

`www.stat.lsa.umich.edu/~ionides`

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