Inferring the dynamic mechanisms that drive ecological systems

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Outline

1. Overview of time series analysis for ecological systems.
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, cholera.
6. Outstanding challenges.

Why study inference for dynamic models in ecology?

- Long time series of fluctuating abundances provide an opportunity to test ecological theories of the relationships driving the system.

  e.g., To what extent is a herbivore population constrained by predators, food resources, or disease?

- Humans are increasingly responsible for managing ecosystems. This requires quantitative understanding of ecological relationships and the potential effect of interventions.

- Forecasting and parameter estimation are of some interest. But a primary concern is to identify the roles of population dynamics (i.e., reproduction & foodchains), evolutionary processes, and environmental covariates.

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.

Methodological problem: Inference for partially observed nonlinear stochastic dynamic systems

- A research area for 60yrs (initially inspired by rocket control theory)
- Difficulties are computational: Bayesian, likelihood and pattern-matching methods are all tricky to implement. Customized approximations and model-specific methods have been needed.
- No general-purpose software has been available.
  - ◇ WinBUGS performs poorly on these models.
  - ◇ **pomp**, an R package for partially observed Markov processes (POMPs), is being developed.

Partially Observed Markov Process (POMP) models

The unobserved Markov state 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 θ.

- 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 (Sisson et al, *PNAS*, 2007)
  3. Particle MCMC (Andrieu, 2010)

- Non-Bayesian plug-and-play:
  4. Simulation-based prediction rules (Kendall et al, *Ecology*, 1999)
  5. Iterated filtering (Ionides et al, *PNAS*, 2006)

Plug-and-play is a VERY USEFUL PROPERTY for investigating scientific models.

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 have been 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

- Bayesian inference for time-varying parameters becomes a solveable filtering problem. 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 1. (Ionides, Bretó & King, *PNAS*, 2006)

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

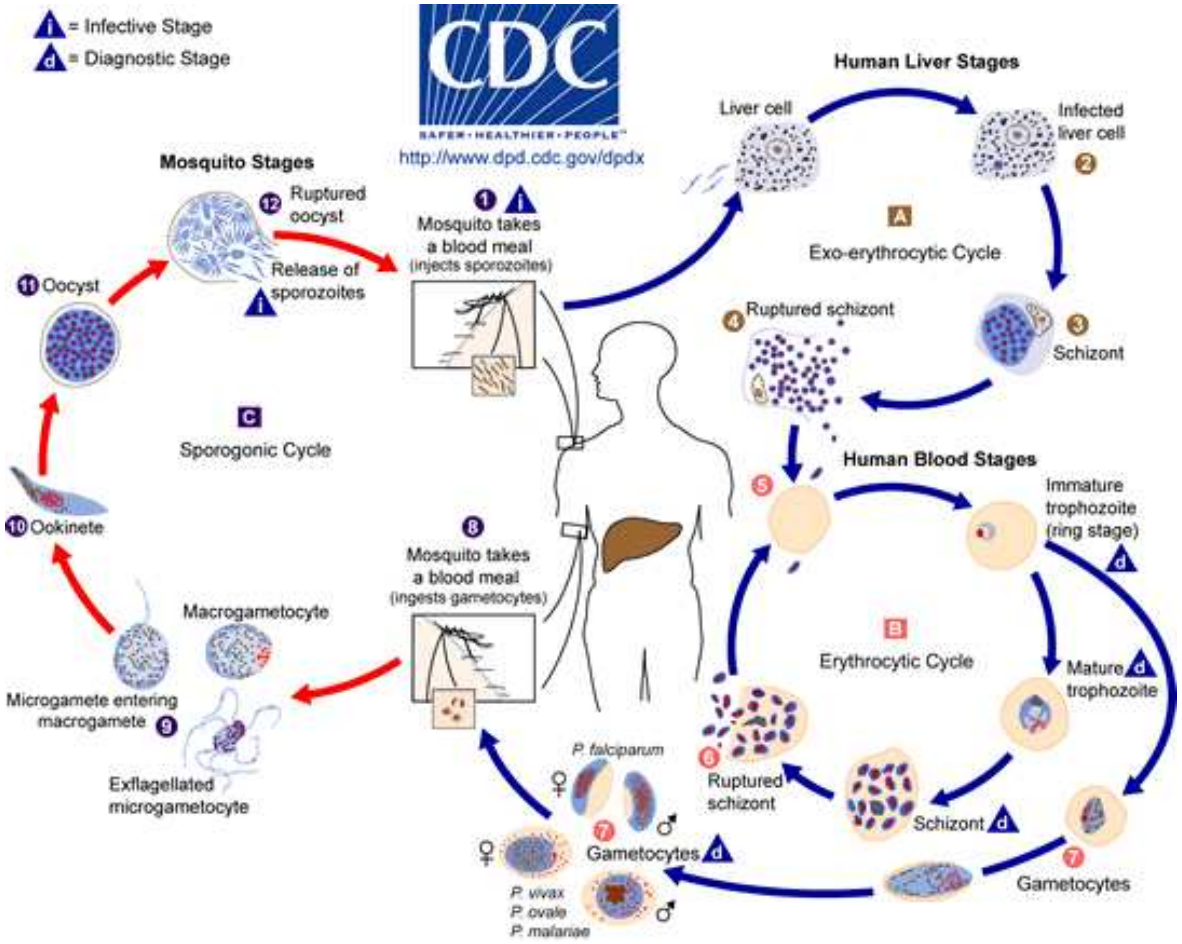
$$\begin{aligned} \hat{\theta}_t &= \hat{\theta}_t(\sigma) = E[\theta_t | y_{1:t}] \\ V_t &= V_t(\sigma) = \mathrm{Var}(\theta_t | y_{1:t-1}) \end{aligned}$$

Assuming sufficient regularity conditions for a Taylor series expansion,

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

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

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



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

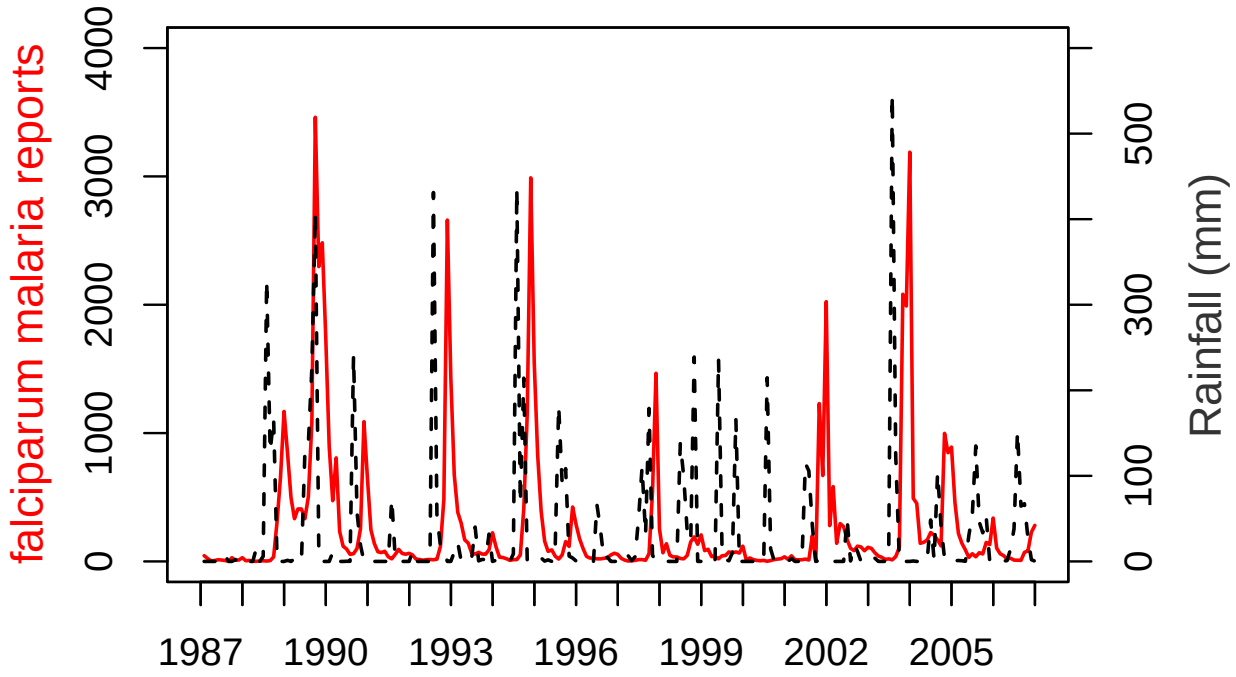
Malaria: A global challenge

- 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

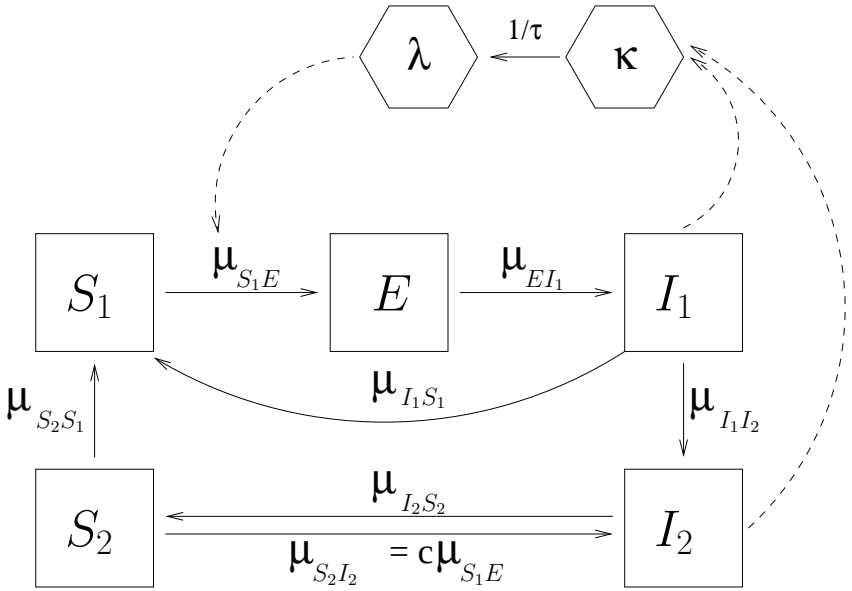
- Despite the huge literature, no dynamic model of malaria transmission has previously been fitted directly to time series data.
- Incomplete and complex immunity, dynamics in both mosquito and human stages & diagnostic difficulties (the immediate symptom is non-specific fever) have put malaria beyond the scope of previous methodology.

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, to appear in *PLoS Comp. Biol.*).



λ, force of infection; κ, 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

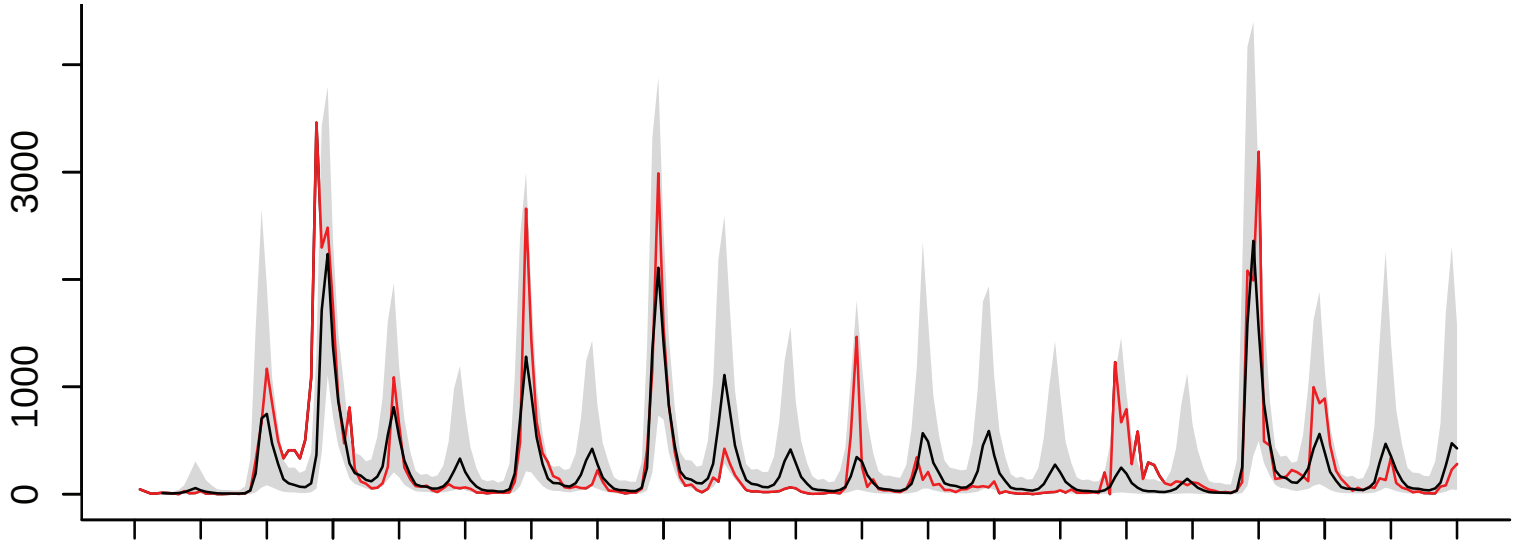
$$
\begin{aligned}
dS_1/dt &= \mu_{BS_1} P - \mu_{S_1E} S_1 + \mu_{I_1S_1} I_1 + \mu_{S_2S_1} S_2 - \mu_{S_1D} S_1 \\
dS_2/dt &= \mu_{I_2S_2} I_2 - \mu_{S_2S_1} S_2 - \mu_{S_2I_2} S_2 - \mu_{S_2D} S_2 \\
dE/dt &= \mu_{S_1E} S_1 - \mu_{EI_1} E - \mu_{ED} E \\
dI_1/dt &= \mu_{EI_1} E - \mu_{I_1S_1} I_1 - \mu_{I_1I_2} I_1 - \mu_{I_1D} I_1 \\
dI_2/dt &= \mu_{I_1I_2} I_1 + \mu_{S_2I_2} S_2 - \mu_{I_2S_2} I_2 - \mu_{I_2D} I_2 \\
d\kappa/dt &= d\lambda_0/dt \;=\; (f(t) - \kappa)\, \ell\, \tau^{-1} \\
d\lambda_i/dt &= (\lambda_{i-1} - \lambda_i)\, \ell\, \tau^{-1} \qquad \text{for } i = 1, \ldots, \ell - 1 \\
d\lambda/dt &= d\lambda_\ell/dt \;=\; (\lambda_{\ell-1} - \lambda)\, \ell\, \tau^{-1} \\
f(t) &= \frac{I_1(t) + q I_2(t)}{N(t)}\, \bar{\beta}\, \exp\Big\{ \sum_{i=1}^{n_s} \beta_i s_i(t) + Z_t \beta \Big\} \frac{d\Gamma}{dt}.
\end{aligned}
$$

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

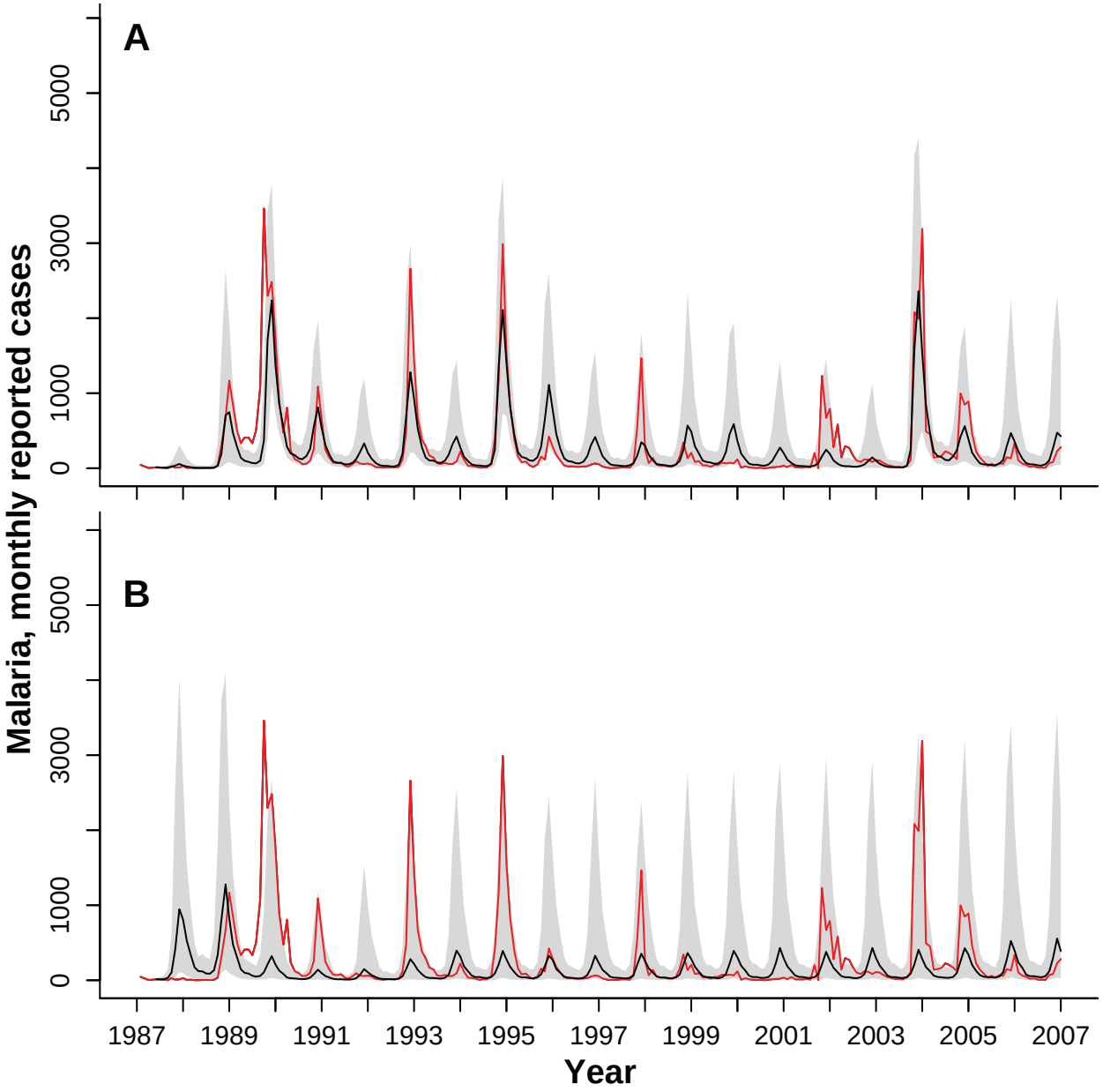
$\sum_{i=1}^{n_s} \beta_i s_i(t)$ is a spline representation of seasonality.

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.

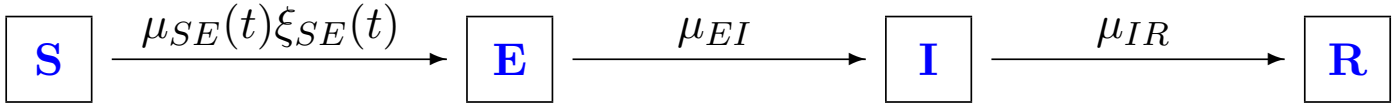
- **We do this by defining our model as a limit of discrete-time models. We call such models *implicit*.** This is backwards to the usual approach of checking that a numerical scheme (i.e. a discretization) converges to the desired model.

- 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*) and He et al (2010, *J. Roy. Soc. Interface).*

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.

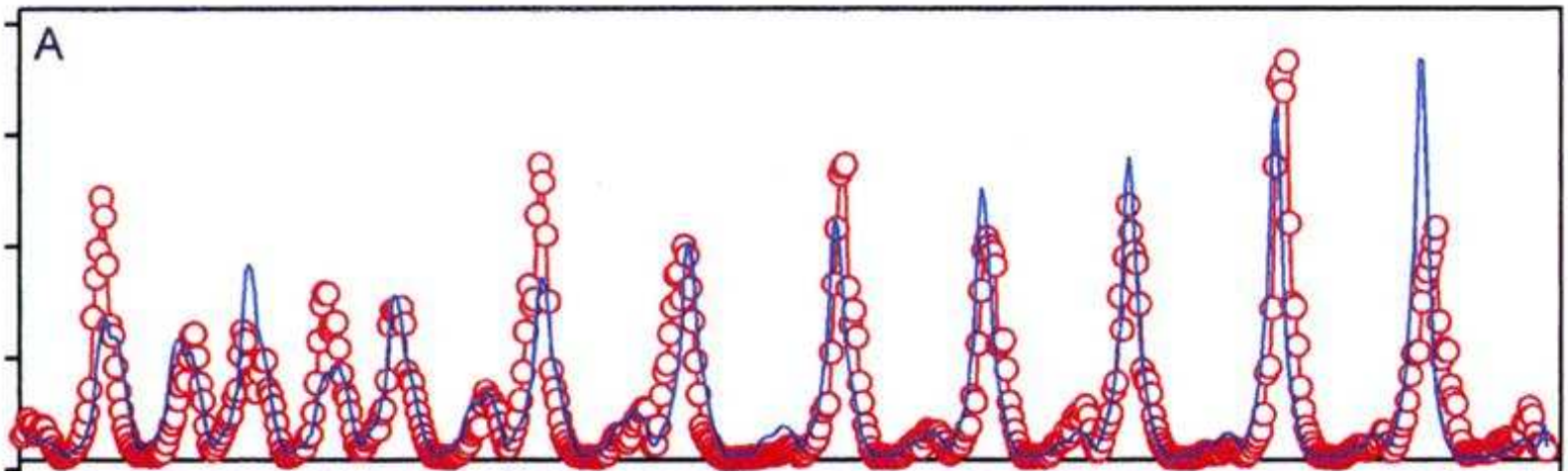


Susceptible $\longrightarrow$ Exposed (latent) $\longrightarrow$ Infected $\longrightarrow$ Recovered,

with noise intensity σ_{SE} on the force of infection.

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

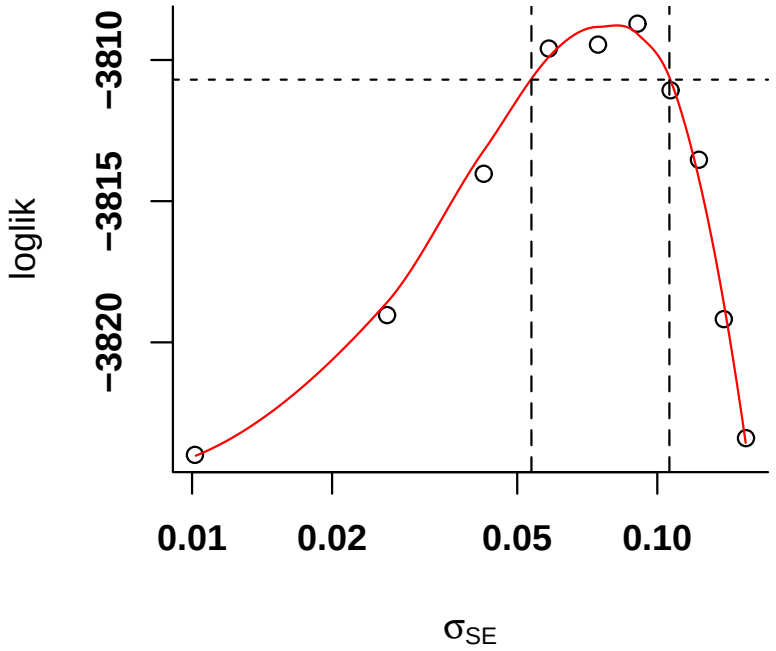
- Comprehensive doctor reports in western Europe and America before vaccination (≈ 1968) are textbook data.

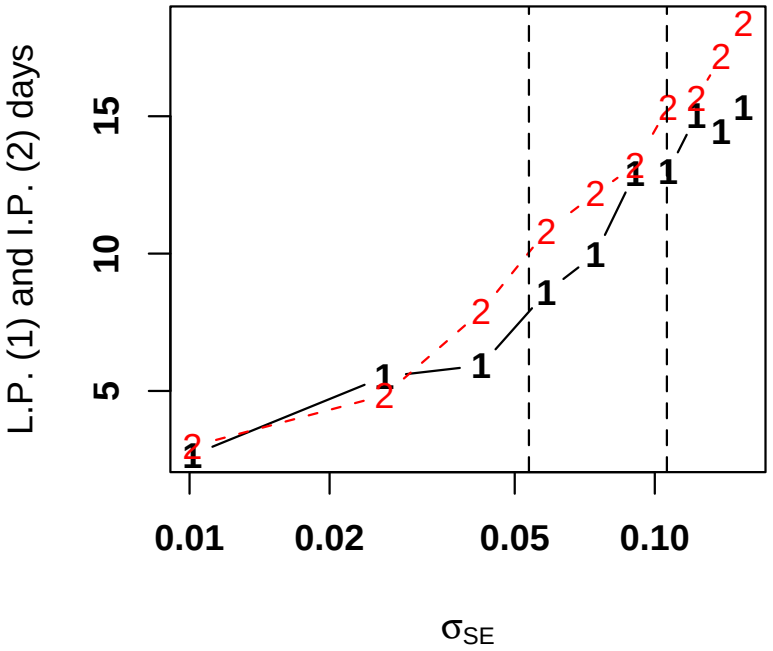


- Measles cases in London 1944–1965 (circles and red lines) and a deterministic SEIR fit (blue line) (from Grenfell *et al*, 2002).
- A deterministic fit, specified by the initial values in January 1944, captures remarkably many features.

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

- Profile likelihood for σ_{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 force of infection substantially improves the fit, and has consequences for parameter estimates.





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 other model mis-specification? 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.

- **It is increasingly possible to carry out data analysis via nonlinear mechanistic stochastic dynamic models**. This can build links between the mathematical modeling community (within which models are typically conceptual and qualitative) and quantitative applications (testing hypotheses about mechanisms, forecasting, evaluating the consequences of interventions). Increasingly many long time series are available. **Much work remains to be done!**

- Many models of interest are beyond current algorithms & computational resources. New data types (e.g., genetic markers for some or all reported individuals) both enable and require the fitting of more complex models.

Thank you!

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

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

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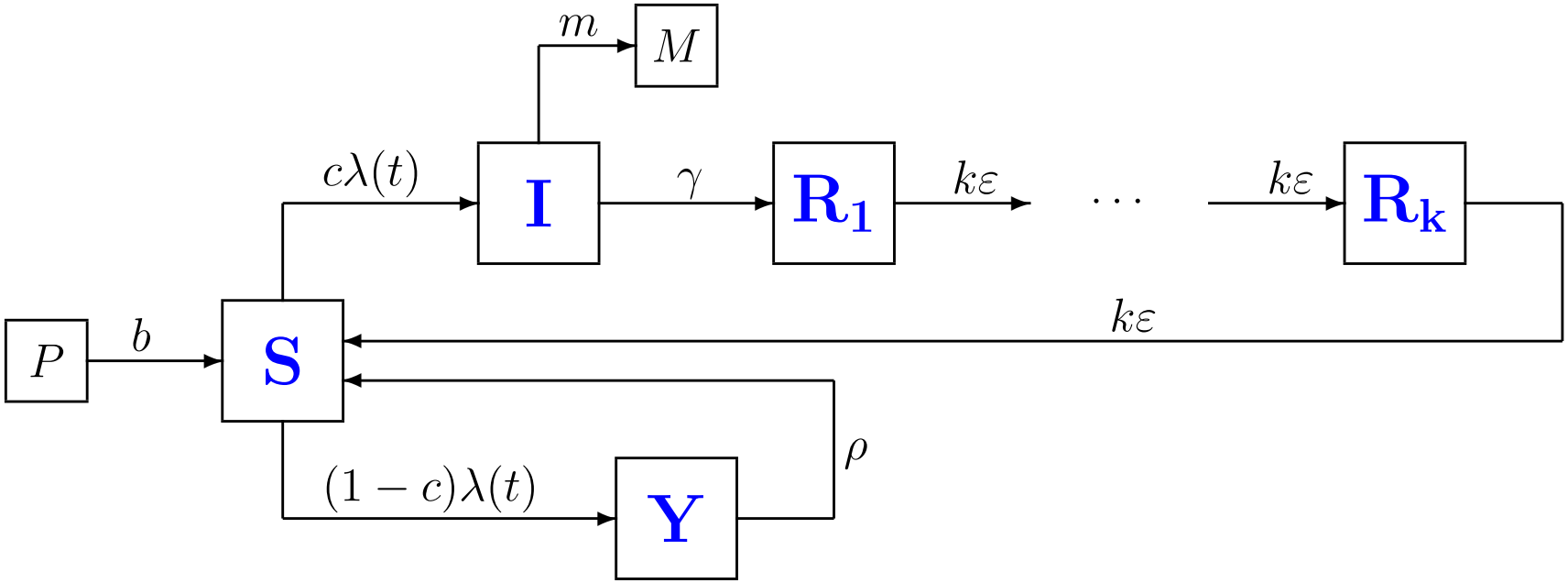
Example: cholera (bacterial diarrhea caused by *Vibrio cholerae*)


m
M
cλ(t)
I
γ
R1
kε
...
kε
Rk
kε
P
b
S
ρ
(1 − c)λ(t)
Y

parameter	symbol
force of infection	$\lambda(t)$
probability of severe infection	c
recovery rate	γ
disease death rate	m
mean long-term immune period	$1/\varepsilon$
CV of long-term immune period	$1/\sqrt{k}$
mean short-term immune period	$1/\rho$

Cholera model: nonlinear SDE driven by Gaussian noise $\xi(t)$

$$\frac{d}{dt}S(t) = k\epsilon\, R_k + \rho\, Y + \frac{d}{dt}P(t) + \delta\, P(t) - (\lambda(t) + \delta)\, S$$

$$\frac{d}{dt}I(t) = c\,\lambda(t)\, S - (m + \gamma + \delta)\, I(t)$$

$$\frac{d}{dt}Y(t) = (1-c)\,\lambda(t)\, S - (\rho + \delta)\, Y$$

$$\frac{d}{dt}R_1(t) = \gamma\, I - (k\,\epsilon + \delta)\, R_1$$

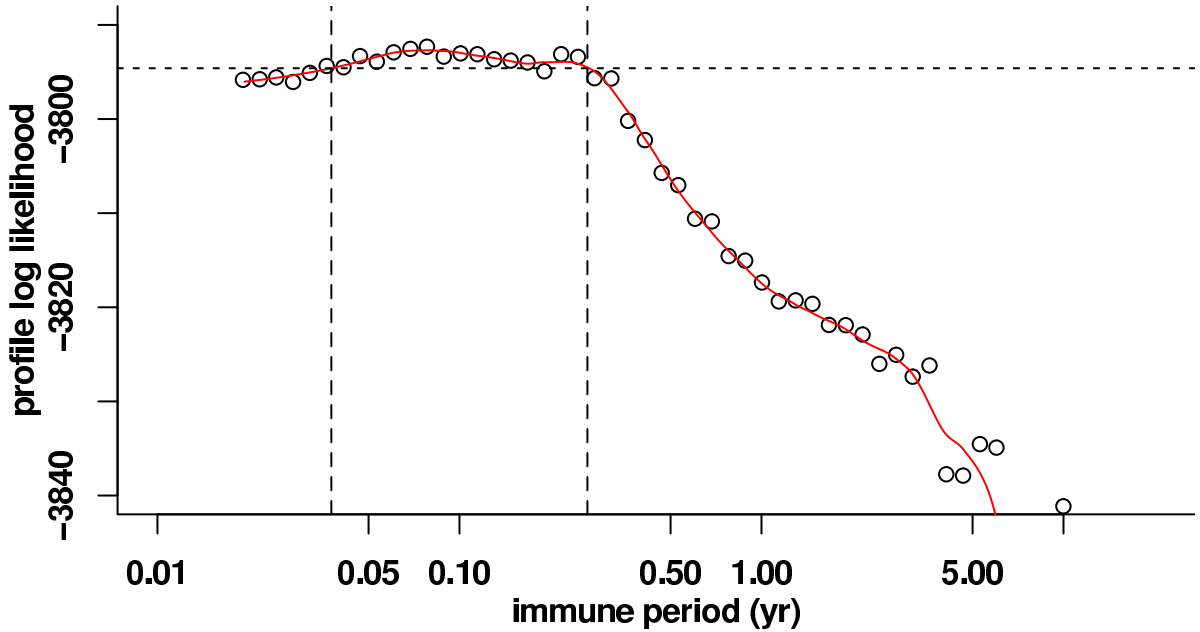
$$\vdots$$

$$\frac{d}{dt}R_k(t) = k\,\epsilon\, R_{k-1} - (k\,\epsilon + \delta)\, R_k$$

Stochastic force of infection, with periodic cubic spline $\beta_{seas}(t)$:

$$\lambda(t) = \left(e^{\beta_{trend}\, t}\, \beta_{seas}(t) + \xi(t)\right)\, \frac{I(t)}{P(t)} + \omega$$

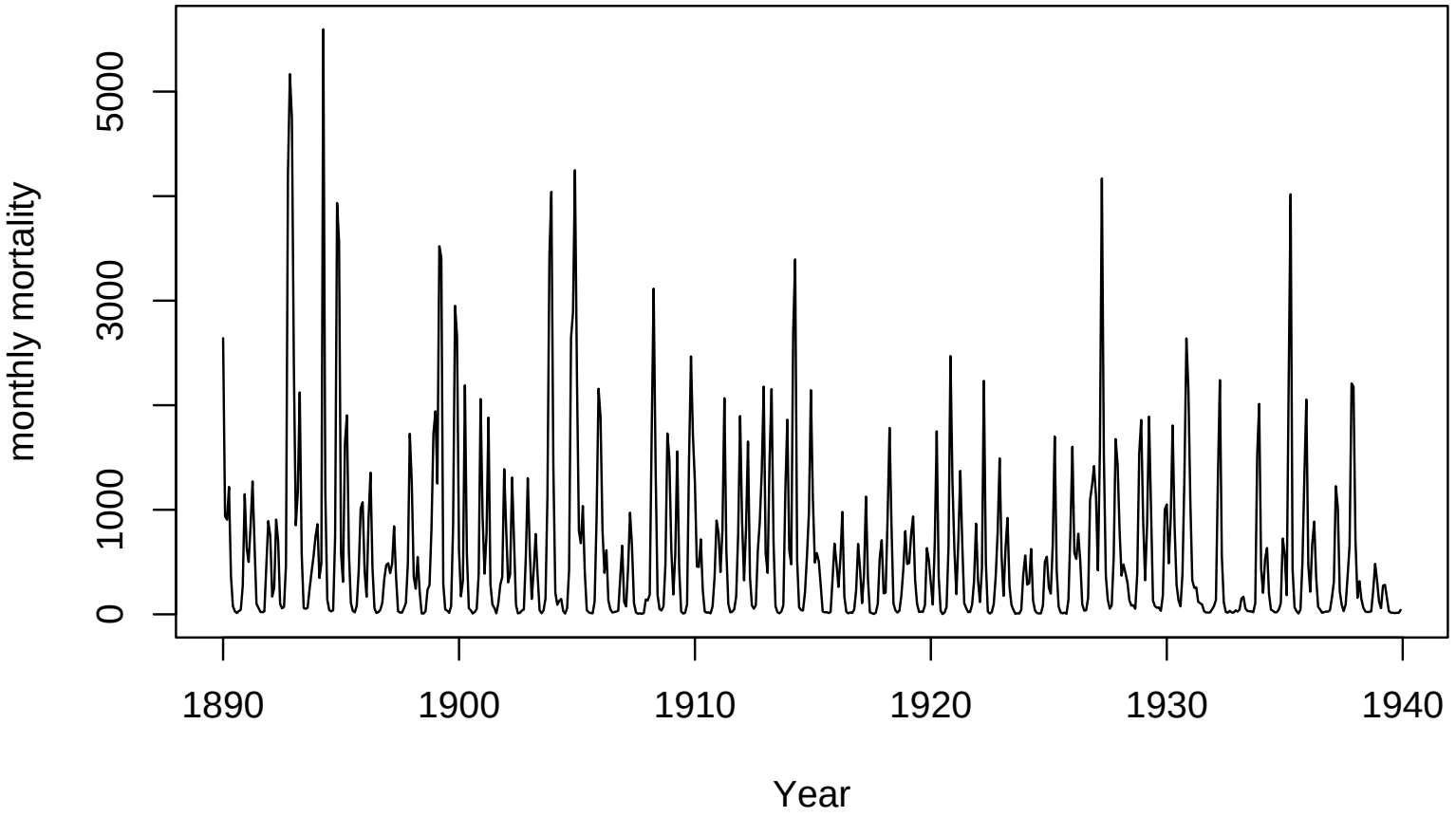
Duration of immunity



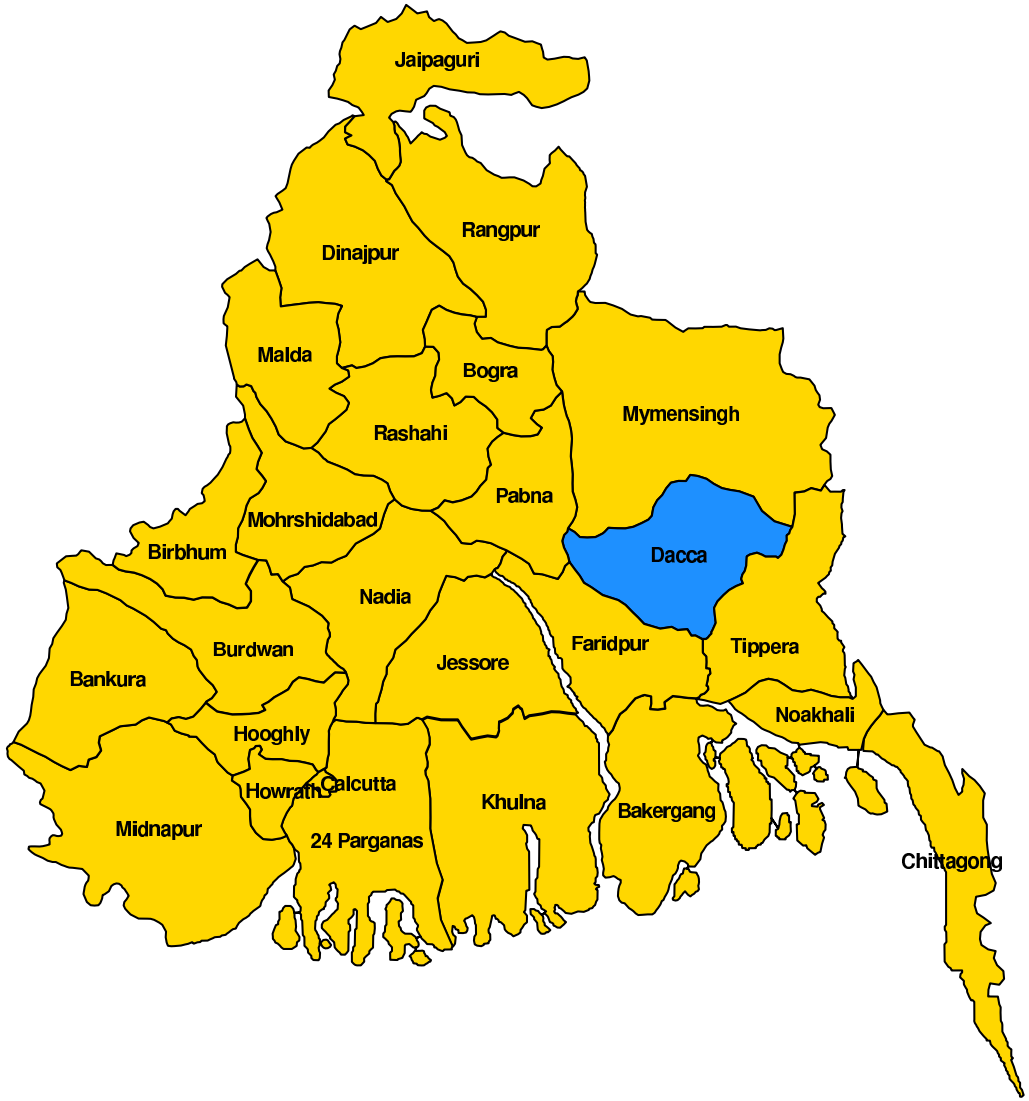
- Profile likelihood of immune period for historical time series data in Dacca, Bangladesh. Other districts give similar results.
- **Conclusion: asymptomatic infections have short-term immunity with epidemiological consequences**

  (King, Ionides, Pascual & Bouma, *Nature*, 2008).

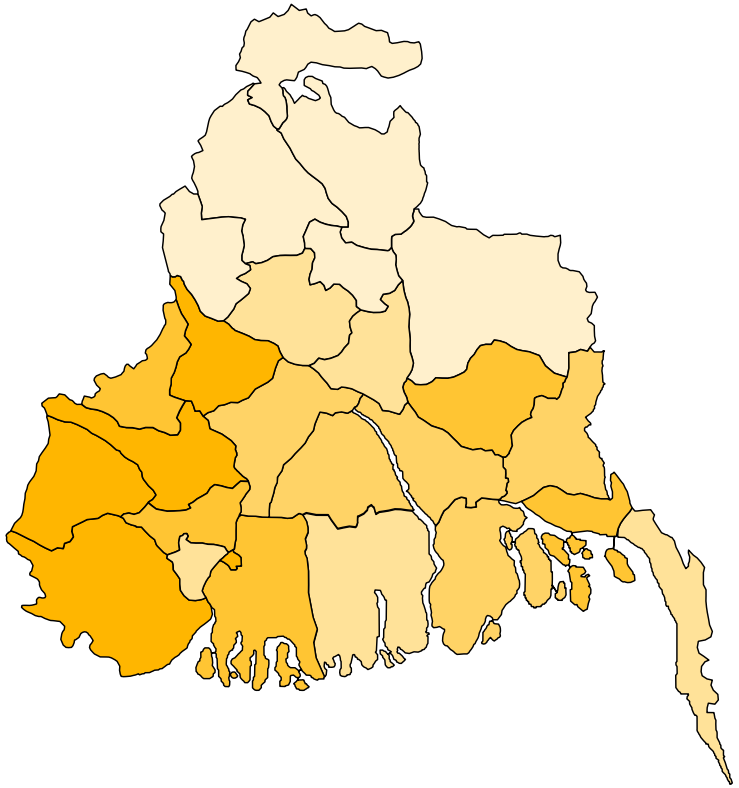
Monthly reported cholera mortality for Dacca, 1890–1940



Historic Bengal (now Bangladesh and the Indian state of West Bengal)



Parameter estimates vary smoothly across space



Example: estimated effect of environmental cholera (larger environmental reservoirs are shown as darker orange).

An iterated filtering algorithm

Select $\hat{\theta}^{(1)}$, σ_1, c, α and N.

For n in $1, \ldots, N$

(i) set $\sigma = \sigma_1 \alpha^{n-1}$ and initialize $E[\theta_0^{(n)}] = \hat{\theta}^{(n)}$, $\mathrm{Var}(\theta_0^{(n)}) = c\sigma^2$.

(ii) For $t = 1, \ldots, T$, evaluate **filtering means** $\hat{\theta}_t^{(n)} = E[\theta_t^{(n)} | y_{1:t}]$ and **prediction variances** $V_{t,n} = \mathrm{Var}(\theta_t^{(n)} | y_{1:t-1})$.

(iii) $\hat{\theta}^{(n+1)} = \hat{\theta}^{(n)} + V_{1,n} \sum_{t=1}^{T} V_{t,n}^{-1} (\hat{\theta}_t^{(n)} - \hat{\theta}_{t-1}^{(n)})$

- **Each iteration updates $\hat{\theta}_n$ using an average of the filtering means with weights determined by the prediction variances.**
- **$\hat{\theta}^{(N+1)}$ converges to a (local) maximum of the likelihood as $N \to \infty$, under regularity conditions.**

Iterated filtering via sequential Monte Carlo: A brief tutorial

- Let $\{X^F_{t,j}, j = 1, \ldots, J\}$ solve the filtering problem at time t by having (approximately) marginal density $f(x_t|y_{1:t})$.

- **Move particles according to the state process dynamics:**
  Make $X^P_{t+1,j}$ a draw from $f(x_{t+1}|x_t{=}X^F_{t,j})$. Then $\{X^P_{t+1,j}\}$ is a draw from $f(x_{t+1}|y_{1:t})$, solving the prediction problem at time $t+1$.

- **Prune particles according likelihood given data:**
  Make $X^F_{t+1,j}$ a drawn from $\{X^P_{t+1,j}\}$ with probability proportional to $w_j = f(y_t|x_t{=}X^P_{t,j})$. Then $\{X^F_{t+1,j}\}$ solves the filtering problem at $t+1$.

- $E[x_t|y_{1:t}]$ and $\mathrm{Var}(x_t|y_{1:t-1})$ are calculated as the sample mean and variance of $X^F_{t,k}$ and $X^P_{t,k}$ respectively.

Two analogies

- Like the **EM algorithm**, iterated filtering is an optimization trick that takes advantage of a special model structure (partially observed Markov processes).
- Like **simulated annealing**, iterated filtering introduces stochasticity, resulting in “thermal fluctuations” which “cool” toward a “freezing point” at a likelihood maximum.

A general mechanistic model

- A compartment model groups a population into c compartments.
- $X(t) = (X_1(t), \ldots, X_c(t))$ can be written in terms of the flows $N_{ij}(t)$ from i to j, via a **conservation of mass** identity:

$$X_i(t) = X_i(0) + \sum_{j \neq i} N_{ji}(t) - \sum_{j \neq i} N_{ij}(t).$$

- Each **flow** N_{ij} is associated with a **rate** function $\mu_{ij} = \mu_{ij}(t, X(t))$.
- Here, $X_i(t)$ is non-negative integer valued. $X(t)$ models a population divided into c groups; μ_{ij} is the rate at which each individual in compartment i moves to j.
- This makes the compartment model closed. Immigration, birth and death can be included via source and sink compartments.

Noise for rates of Markov chain compartment models

- For each rate μ_{ij} between pairs of compartments (i, j) we specify an **integrated noise process** $\Gamma_{ij}(t)$ giving rise to a **noise process** $\xi_{ij}(t) = \frac{d}{dt}\Gamma_{ij}(t)$.

Properties of the integrated noise processes $\Gamma_{ij}(t)$

P1 Independent increments.

P2 Stationary increments.

P3 Non-negative increments. Therefore, $\xi_{ij}(t) = \frac{d}{dt}\Gamma_{ij}(t)$ is **non-negative white noise**.

P4 Unbiased multiplicative noise: $E[\Gamma_{ij}(t)] = t$.

P5 Partial independence: Γ_{ij} independent of Γ_{ik} for $j \neq k$.

P6 Full independence: all noise processes independent.

P7 **Gamma noise**: marginally, $\Gamma_{ij}(t)$ is a gamma process.

A general over-dispersed compartment model

This is an implicit model: we use an Euler approximation to define the process:

1. Divide the interval $[0, T]$ into N intervals of width $\delta = T/N$
2. Set initial value $X(0)$
3. FOR $n = 0$ to $N - 1$
4. Generate noise increments $\{\Delta\Gamma_{ij} = \Gamma_{ij}(n\delta + \delta) - \Gamma_{ij}(n\delta)\}$
5. Generate process increments $(\Delta N_{i1}, \ldots, \Delta N_{i,i-1}, \Delta N_{i,i+1}, \Delta N_{ic}, R_i)$
   $\sim$ Multinomial$(X_i(n\delta), p_{i1}, \ldots, p_{i,i-1}, p_{i,i+1}, \ldots, p_{ic}, 1-\sum_{k\neq i} p_{ik})$
   where $p_{ij} = p_{ij}(\{\mu_{ij}(n\delta, X(n\delta))\}, \{\Delta\Gamma_{ij}\})$ is given in (1) below
6. Set $X_i(n\delta + \delta) = R_i + \sum_{j\neq i} \Delta N_{ji}$
7. END FOR

The limiting Markov chain is specified follows:

$$P[\Delta N_{ij} = n_{ij}, \text{ for all } 1 \le i \le c, 1 \le j \le c, i \ne j \mid X(t) = (x_1, \ldots, x_c)]$$

$$= E\left[\prod_{i=1}^{c}\left\{\binom{x_i}{n_{i1} \ \ldots \ n_{ii-1} \ n_{ii+1} \ \ldots \ n_{ic} \ \ r_i}(1-\textstyle\sum_{k\ne i} p_{ik})^{r_i}\displaystyle\prod_{j\ne i} p_{ij}^{n_{ij}}\right\}\right] + o(\delta)$$

where $r_i = x_i - \sum_{k\ne i} n_{ik}$, $\binom{n}{n_1 \ \ldots \ n_c}$ is a multinomial coefficient and

$$\begin{aligned} p_{ij} &= p_{ij}(\{\mu_{ij}(t,x)\}, \{\Delta\Gamma_{ij}(t)\}) \\ &= (1-\exp\{-\sum_k \mu_{ik}\Delta\Gamma_{ik}\})\mu_{ij}\Delta\Gamma_{ij}/\sum_k \mu_{ik}\Delta\Gamma_{ik}, \end{aligned} \quad (1)$$

with $\mu_{ij} = \mu_{ij}(t,x)$.

Theorem 1 (Breto, He, Ionides & King, 2009). Supposing assumptions (P1–P5) about the noise process, this limit does indeed specify a Markov chain.

Proof. An explicit construction involving exponential transition clocks for each individual, based on the method of Sellke (1983). Such methods are standard for networks of interacting Poisson processes (i.e., our compartment model with no noise). Care is required here due to the introduction of noise.

Theorem 1, formal statement. Suppose (P1–P5) and that $\mu_{ij}(t,x)$ is uniformly continuous as a function of t. Let $C(\zeta,0)$ be the compartment containing individual ζ at time $t=0$. Set $\tau_{\zeta,0}=0$, and generate independent $\mathrm{Exponential}(1)$ random variables $M_{\zeta,0,j}$ for each ζ and $j \neq C(\zeta,0)$. For $m \geq 1$, recursively set

$$\tau_{\zeta,m,j} = \inf\left\{t : \int_{\tau_{\zeta,m-1}}^{t} \mu_{C(\zeta,m-1),j}(s,X(s))\, d\Gamma_{C(\zeta,m-1),j}(s) > M_{\zeta,m-1,j}\right\}.$$

At time $\tau_{\zeta,m} = \min_j \tau_{\zeta,m,j}$, set $C(\zeta,m) = \arg\min_j \tau_{\zeta,m,j}$ and for each $j \neq C(\zeta,m)$ generate an independent $\mathrm{Exponential}(1)$ random variable $M_{\zeta,m,j}$. The increments

$dN_{ij}(t) = \sum_{\zeta,m} \mathbb{I}\{C(\zeta,m-1)=i, C(\zeta,m)=j, \tau_{\zeta,m}=t\}$

specify a Markov chain $X(t)$ whose infinitesimal transition probabilities are given by the limit of the numerical algorithm as $\delta \to 0$.

Theorem 2 (Breto, He, Ionides & King, 2009). For the case of independent gamma noise, an analytic formula is available for the infinitesimal probabilities and infinitesimal moments of this chain.

Theorem 2, formal statement. Supposing (P1–P7), the infinitesimal transition probabilities are

$$P[\Delta N_{ij} = n_{ij}, \text{ for all } i \neq j \mid X(t) = (x_1, \ldots, x_c)]$$
$$= \prod_i \prod_{j \neq i} \pi(n_{ij}, x_i, \mu_{ij}, \sigma_{ij}) + o(\delta)$$

where

$$\pi(n, x, \mu, \sigma) = 1_{\{n=0\}} + \delta \binom{x}{n} \sum_{k=0}^{n} \binom{n}{k} (-1)^{n-k+1} \sigma^{-2} \ln\left(1 + \sigma^2 \mu (x-k)\right)$$