Likelihood-based inference for dynamic systems, with phylodynamic applications

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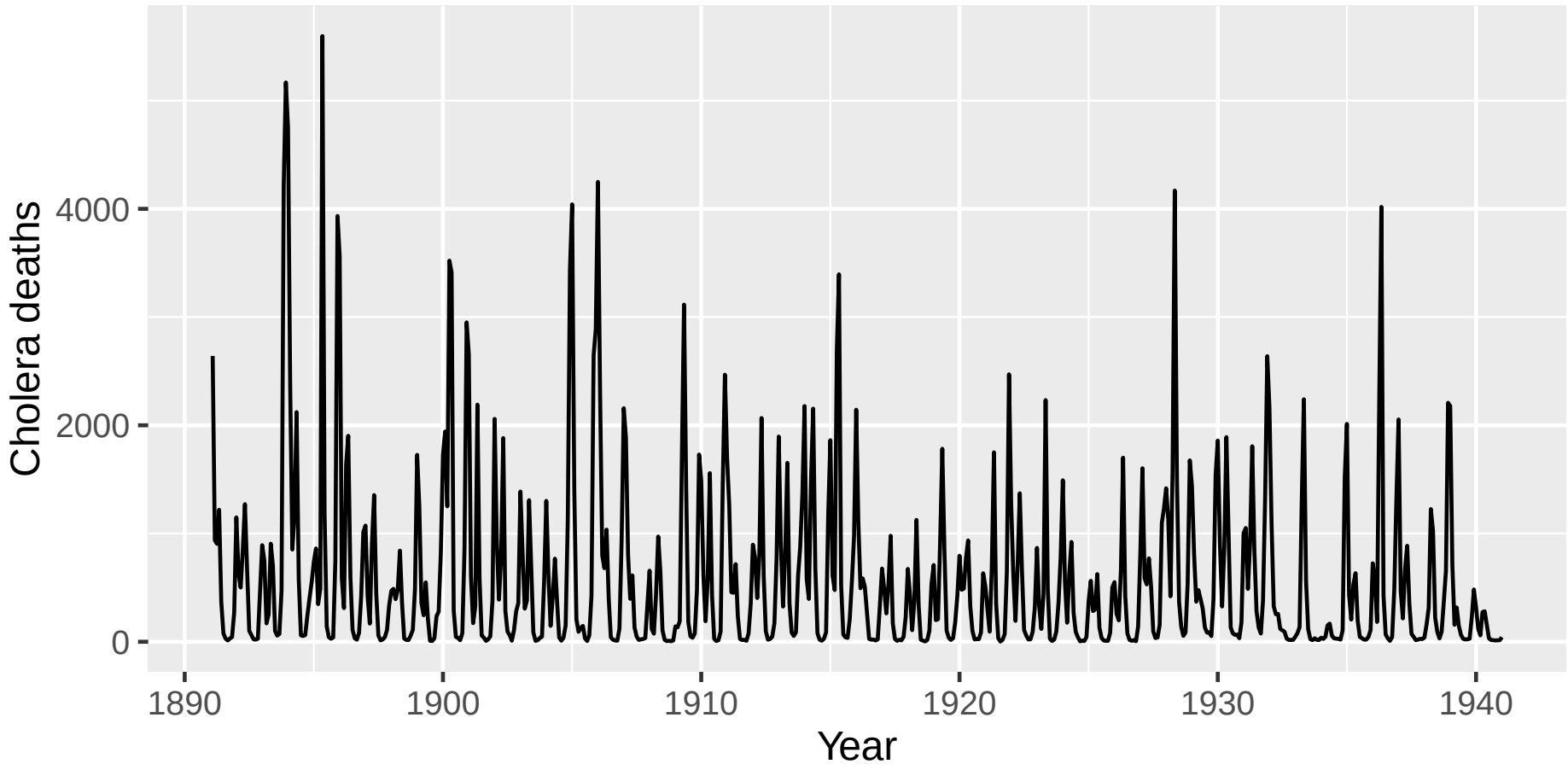
Slides are online at
`http://dept.stat.lsa.umich.edu/~ionides/talks/mfo18.pdf`

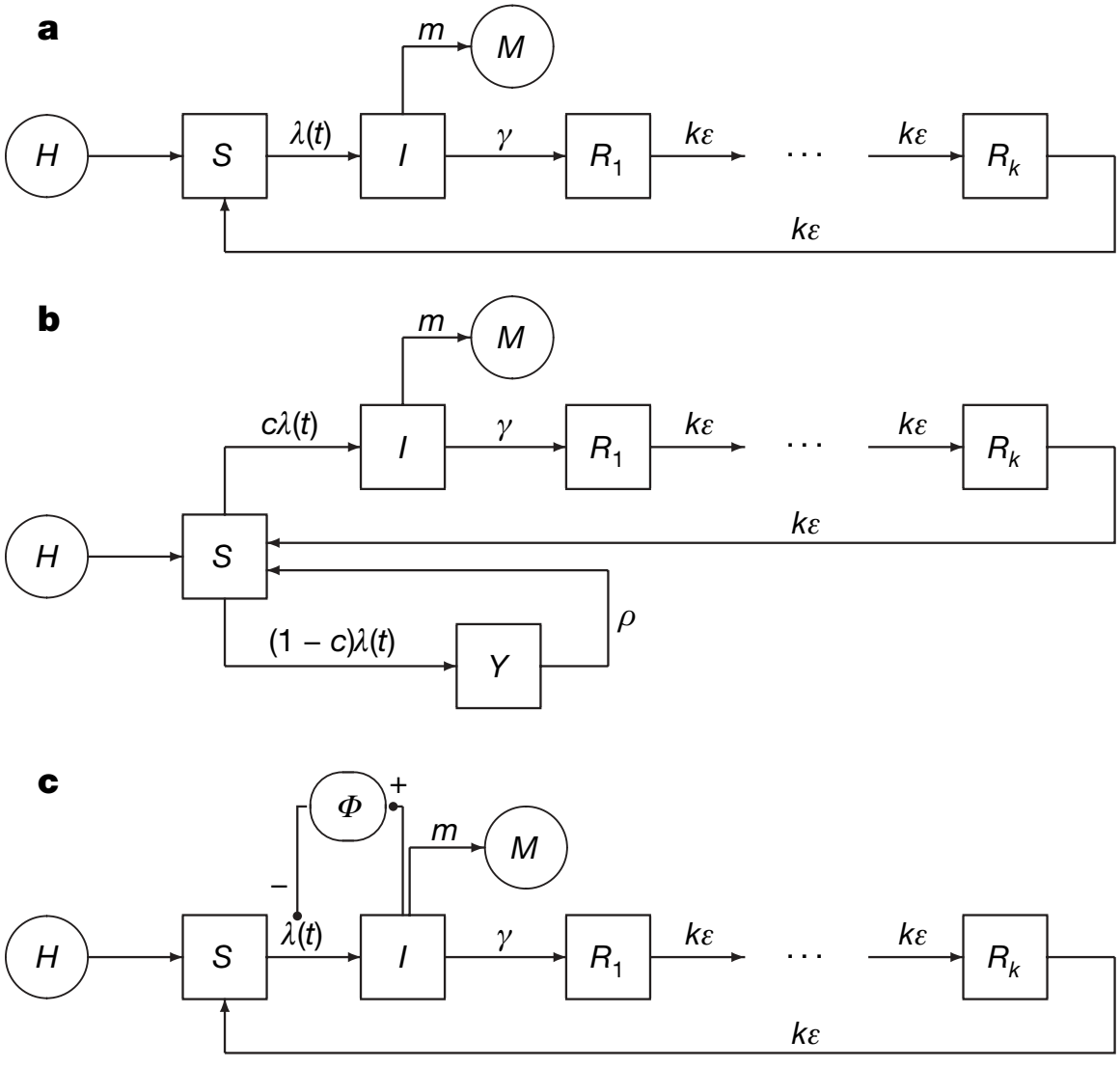
- Four years ago, I gave a talk here at MFO with a similar title.
- Back then, Alex Smith and Aaron King and I had some preliminary ideas about how to apply sequential Monte Carlo (SMC) methodology to phylodynamic problems.
- This talk reports on
  1. New approaches to the general problem of scaling SMC inference to increasingly large and complex systems.
  2. Issues specific to SMC-based phylodynamic inference.

Three motivating data analysis challenges

1. Time series analysis: cholera in Bangladesh.
   - The classic challenge of discovering properties of a nonlinear system from a single long time series.
   - The `pomp` R package (King et al., 2016) has made this sort of analysis accessible to Masters level statisticians (`http://ionides.github.io/531w16/final_project`).
2. Panel data analysis: dynamic variation in sexual contact rates.
   - Observations on a collection of units lead to a panel of time series.
   - Analyzed together, the panel strengthens inferences available from any one time series.
   - The `panelPomp` R package (Bretó et al., 2018).
3. Genetic sequence data: HIV transmission within and between demographic groups.
   - Genetic sequences of pathogens can inform transmission relationships between infected hosts.
   - The `genPomp` C++ program (Smith et al., 2017).

Monthly cholera deaths in Dhaka, Bangladesh, 1891-1940





Competing models

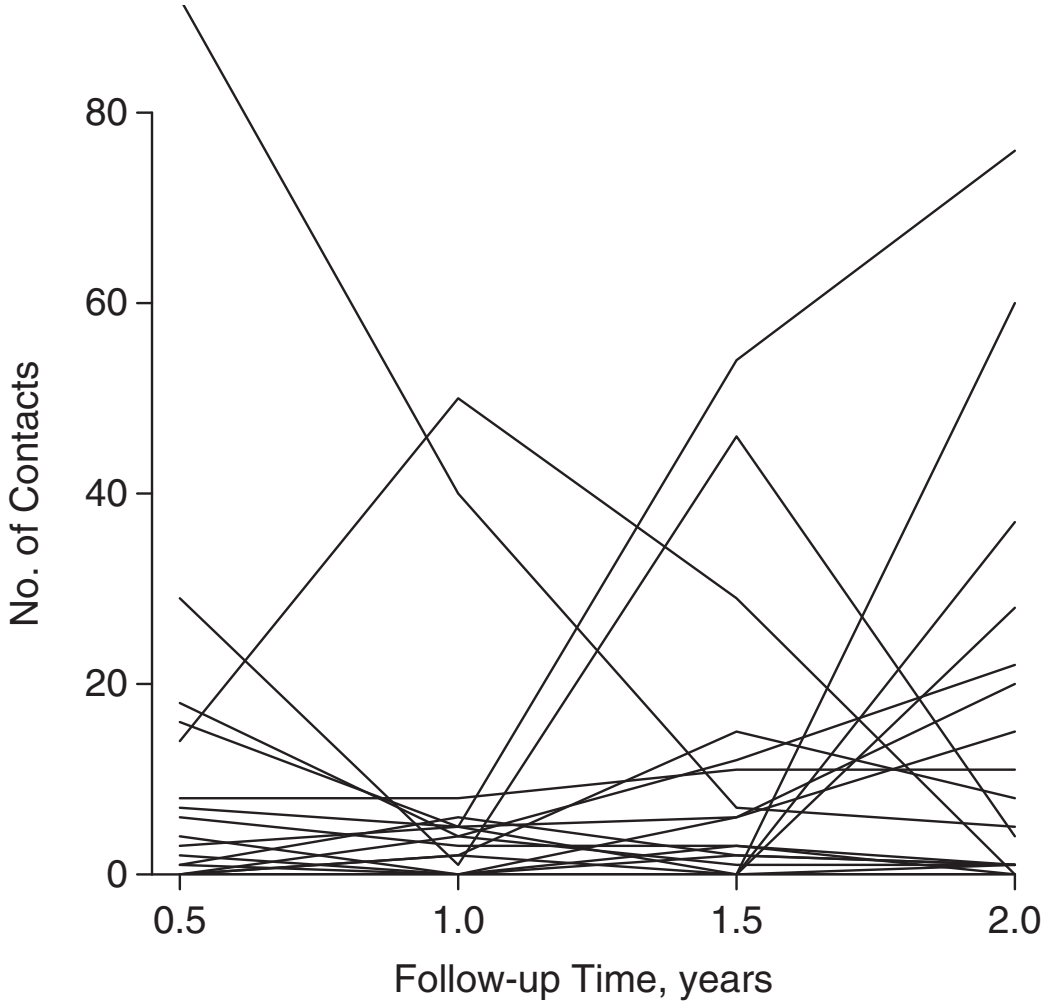
(King et al., 2008)

S	Susceptible
I	Infected
R_j	Recovered
M	Mortality
H	Population size
Y	Asymptomatics in **b**
Φ	Phage in **c**
λ	force of infection
γ	recovery rate
ϵ	loss of immunity
m	cholera mortality

2. Panel data on sexual contacts

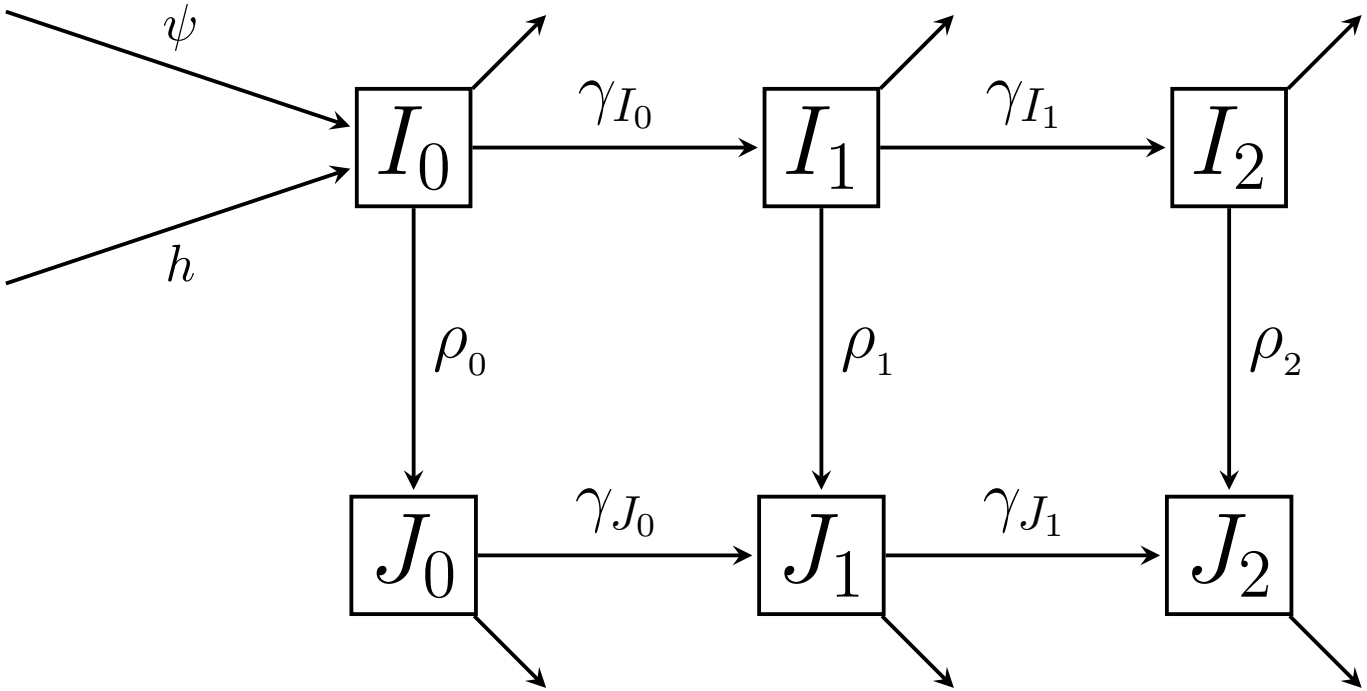
- Mathematical models of HIV transmission struggle to explain observed incidence due to the low measured probability of transmission per sexual contact.
- The anomaly can be resolved by models that include individual-level variability in sexual behavior over time.
- Romero-Severson et al. (2015) constructed behavioral models with various heterogeneities, both between individuals and within individuals over time. These models were fitted to behavioral panel data.

Total sexual contacts in 6 month intervals



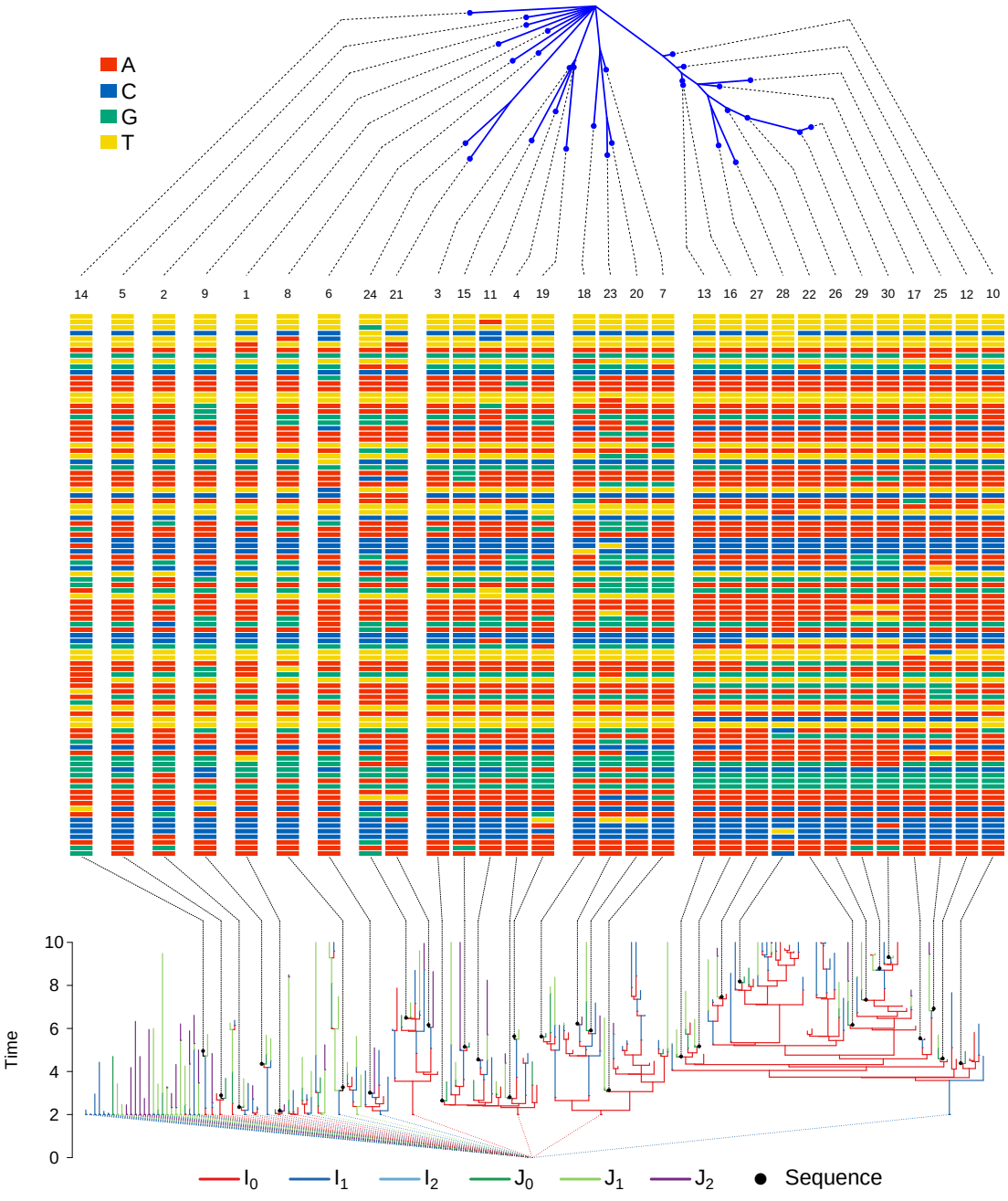
- Time series for 15 units from a panel of 882 gay men who completed a 2 year longitudinal study.
- Sexual contacts were reported in various categories: oral, anal, protected, unprotected, etc. Here, we show total reported contacts.

3. Infectious disease dynamics inferred from genetic data



A flow diagram for HIV.

- I_k classes represent undiagnosed infections.
- J_k classes represent diagnosed infections.
- $k = 0, 1, 2$ denotes early, chronic and AIDS stages.
- Infection can come from within, or outside, the study population.
- Genetic data give evidence on infectors as well as infectees.



A simulated HIV epidemic (Smith et al., 2017)

Top: phylogeny of observed sequences.

Middle: simulated sequence data from a fitted model.

Bottom: Transmission forest for the simulated epidemic.

red: undiagnosed early infection

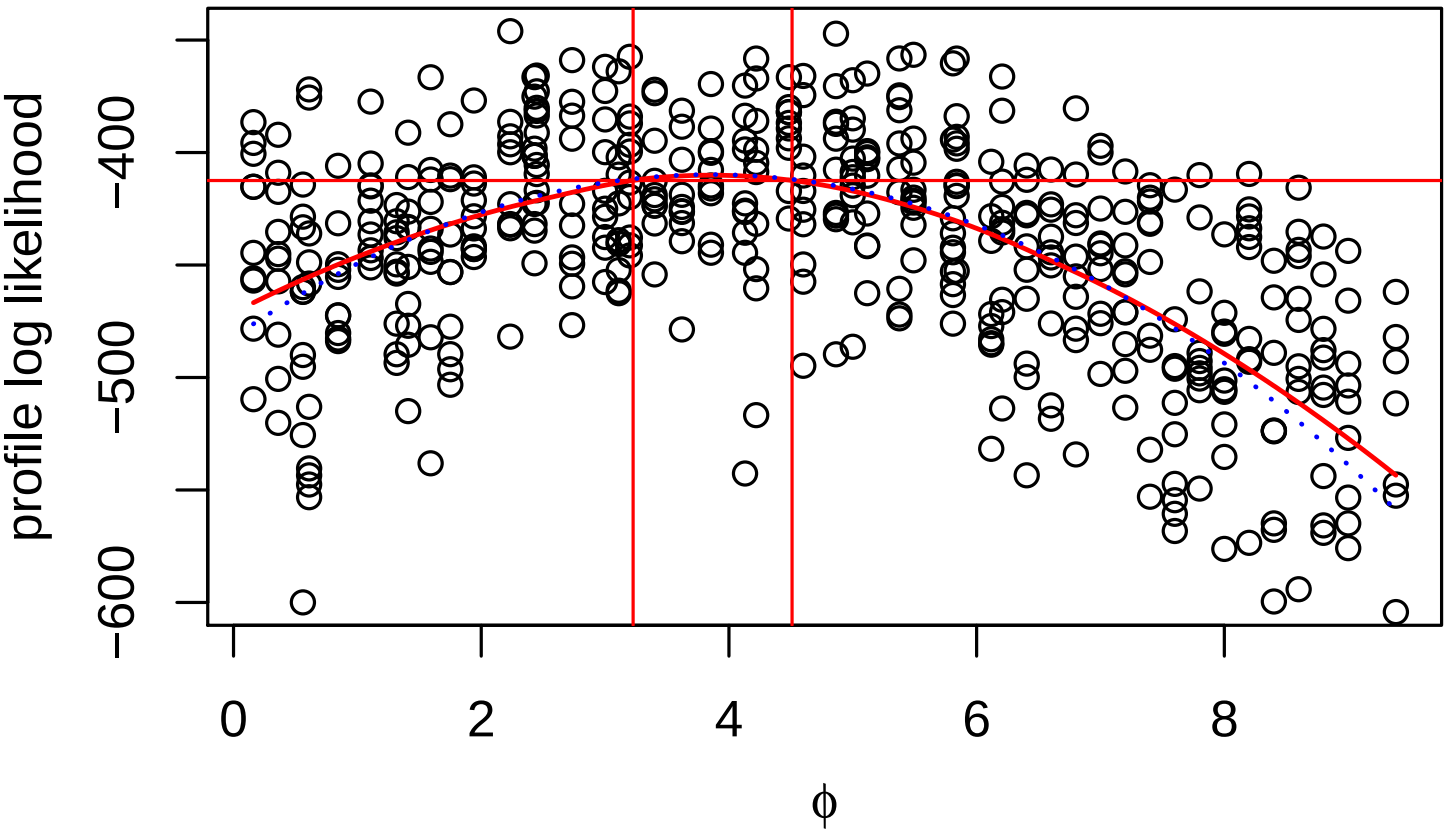
blue: undiagnosed chronic infection

green: diagnosed

Innovations for general POMP models

- New Monte Carlo optimization algorithms facilitate likelihood maximization for large partially observed Markov process (POMP) models: **iterated filtering**.
  - Iterated filtering algorithms optimize the likelihood using a sequence of random parameter perturbations, with decreasing magnitude. Sequential Monte Carlo (SMC) provides a tool for numerical solution to this nonlinear filtering problem.
  - Existing variations on expectation-maximization (EM) and Markov chain Monte Carlo (MCMC) do not scale well for these problems.
  - We are doing parametric inference. The main problem using likelihood or Bayesian methods is computational. If existing methods worked computationally, there would be no problem!
- A new perspective on likelihood-based inference via **Monte Carlo profile likelihood**.

Monte Carlo profile for genetic data on HIV dynamics



- ϕ models HIV transmitted by recently infected, diagnosed individuals.
- The profile confidence interval is constructed by a cutoff that is adjusted for the Monte Carlo variability (Ionides et al., 2017).
  - A proper 95% cutoff is 2.35. Without Monte Carlo error, it is 1.92.
  - Each point took approximately 10 core days to compute.
  - Alternative approaches struggle with Monte Carlo likelihood error of order 100 log units.

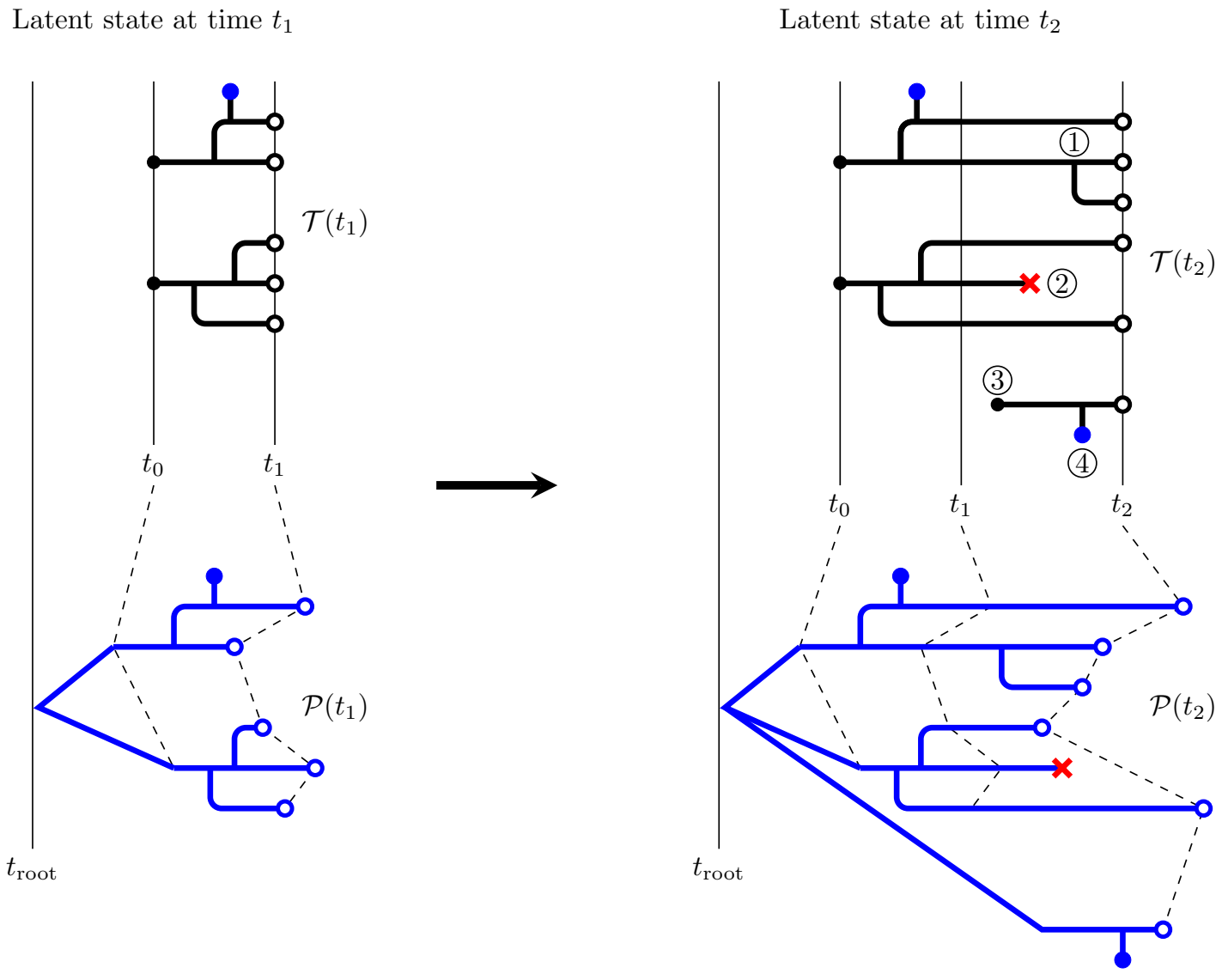
Previous uses of SMC for phylodynamic inference

- SMC techniques have previously been used for inferring phylogenies (Bouchard-Côté et al., 2012), and for phylodynamic inference conditional on a phylogeny (Rasmussen et al., 2011).
- These approaches avoid the high-dimensional, computationally challenging problem of joint inference.
- Several innovations were necessary to realize computationally feasible SMC on models and datasets of scientific interest.
  - Dimension reduction: constructing the POMP model with genetic sequences only in the measurement model to reduce the dimension of the latent variables.
  - Algorithm parallelization.
  - Hierarchical sampling.
  - Just-in-time construction of state variables.
  - Restriction to a class of physical molecular clocks.
  - Maximization of the likelihood using iterated filtering.

The latent process for a GenPOMP

- The **latent Markov process**, $\{X(t),\ t \in \mathbb{T}\}$, with $\mathbb{T} = [t_0,\ t_{\text{end}}]$, models the population dynamics and also includes any other processes needed to describe the evolution of the pathogen.
- Suppose we can write $X(t) = \big(\mathcal{T}(t),\ \mathcal{P}(t),\ \mathcal{U}(t)\big)$, where
  - $\mathcal{T}(t)$ is the **transmission forest**,
  - $\mathcal{P}(t)$ is the **pathogen phylogeny** equipped with a relaxed molecular clock,
  - $\mathcal{U}(t)$ represents the **state of the pathogen and host populations**.
- For example, $\mathcal{U}(t)$ may categorize each individual in the host population into classes representing different stages of infection.
- We suppose that $\{\mathcal{U}(t), t \in \mathbb{T}\}$ is itself a Markov process.
- The **plug-and-play property** (Bretó et al., 2009; He et al., 2010) makes our methods applicable to any latent process for which a simulator exists.

Simulating a GenPOMP from t_1 to t_2

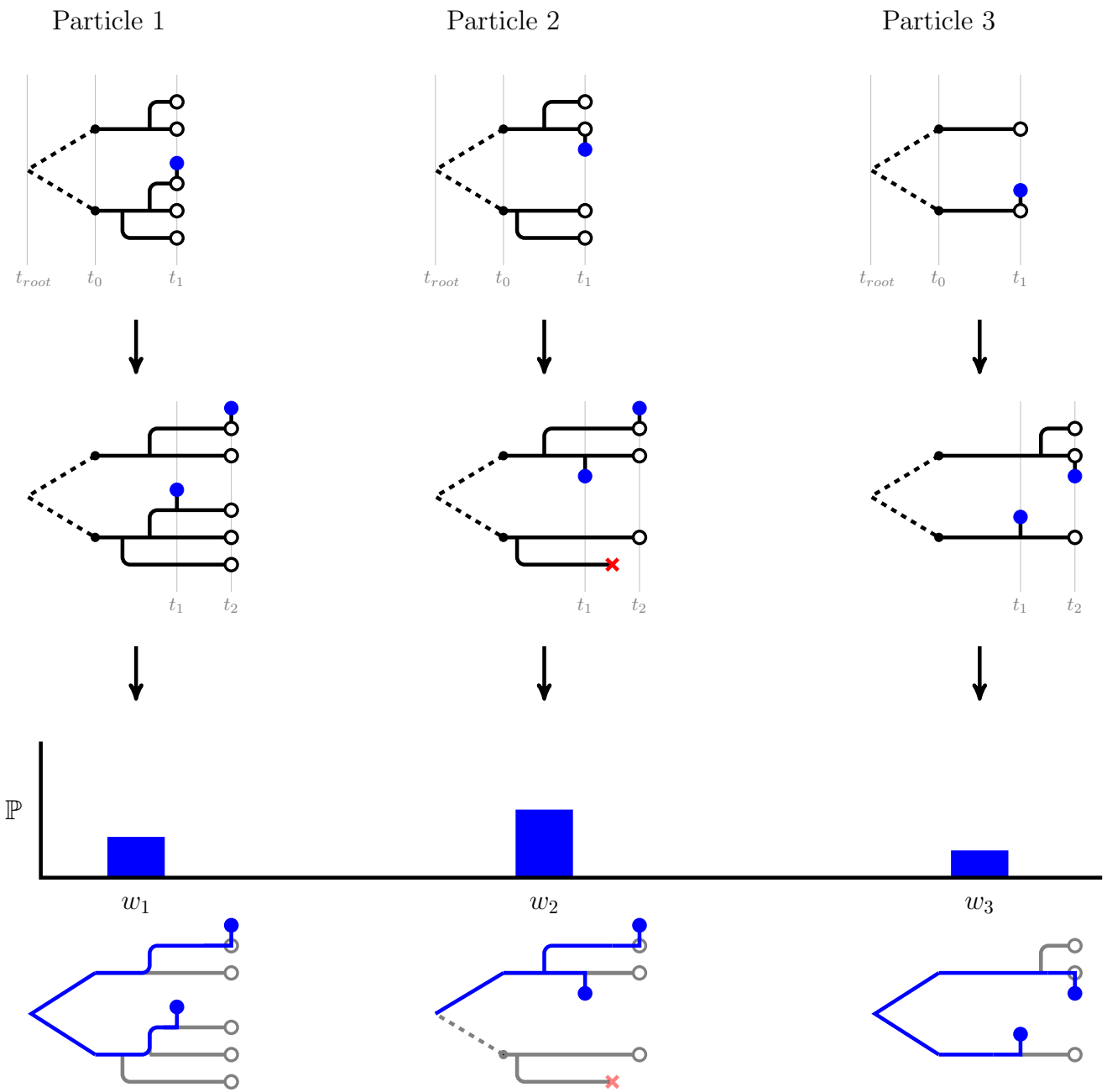


- Black: transmission forest, $\mathcal{T}(t)$. Blue: pathogen phylogeny, $\mathcal{P}(t)$.

Annotations for the GenPOMP schematic diagram

- The branching pattern of the pathogen phylogeny mirrors that of $\mathcal{T}(t)$ over the interval $[t_0, t_1]$, so pathogen lineages are assumed to branch exactly at transmission events. This simplifying assumption can be changed.
- Randomness in the rate of evolution—a relaxed molecular clock—results in random edge lengths in $\mathcal{P}(t)$.
- At ①, an active node splits in two when a transmission event occurs.
- At ②, an active node becomes a dead node ($\times$) when an infected host emigrates, recovers, or dies.
- At ③, an immigration event gives rise to a new active node with its own root.
- At ④, a sequence node ($\bullet$) is spawned when a sample is taken.

GenSMC: Sequential Monte Carlo for a GenPOMP



1. **Proposal**. Simulate particles forward from time t_1 to time t_2. Then select an individual to be sequenced.

2. **Weighting**. Based on the structure of the proposed transmission forest, construct the subtree of the phylogeny that connects the observed sequences. Use this subtree to compute weight of the particle: the conditional probability of the new sequence.

Dimension reduction: A measurement model integrating the sequence evolution model

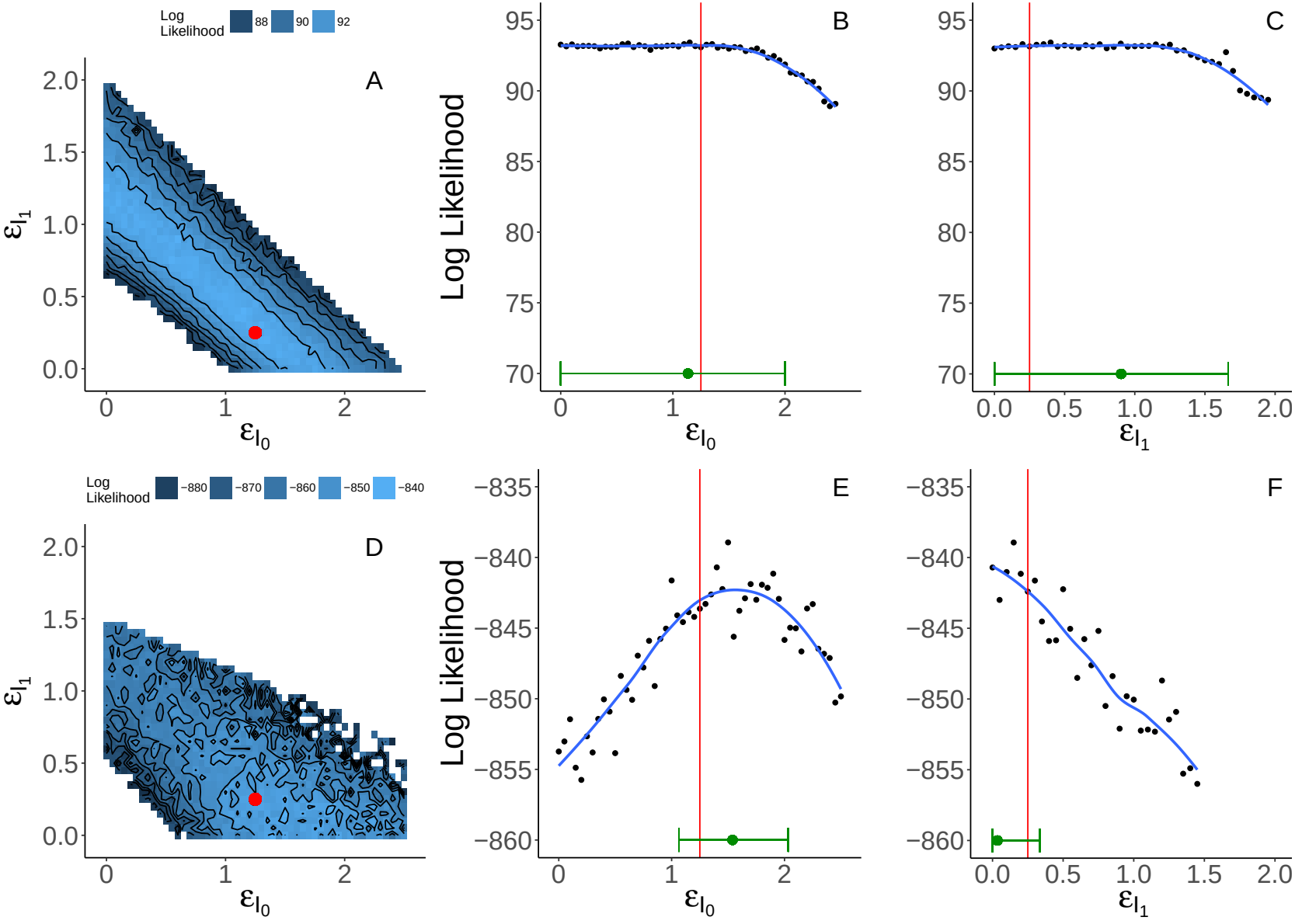
- We put the evolutionary process for the genetic sequences into the measurement model.
- Formally, let a measurement consist of an assignment of a new sequence to an individual in the transmission tree.
- The measurement density involves finding the likelihood of the new sequence given the old sequences and the tree. This likelihood can be computed efficiently by the *peeling* algorithm.
- Particles representing the latent process do not have to include the high-dimensional pathogen genome.

Restriction to a class of physical molecular clocks

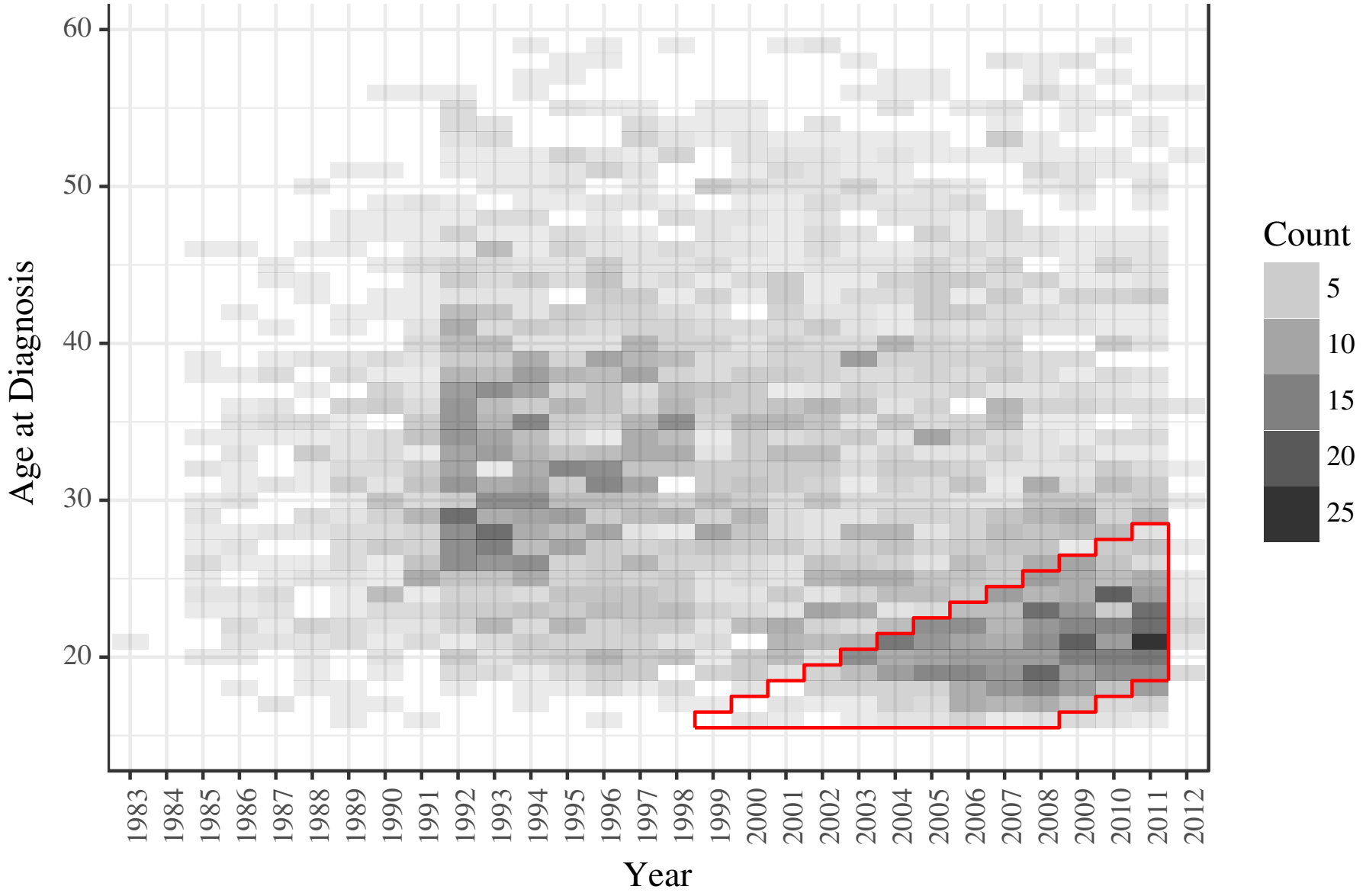
- A strict molecular clock models the rate of evolution as constant through time and across lineages, assuming (i) sequence evolution is Markovian; (ii) no simultaneous mutations.
- These assumptions imply a Poisson-like mean-variance relationship (Bretó and Ionides, 2011).
- Overdispersion (known as a relaxed clock) has been shown to improve the fit of phylogenetic models to observed genetic sequences in many cases (Drummond et al., 2006).
- In our approach, this corresponds to constructing each edge length of $\mathcal{P}(t)$ as a stochastic process on the corresponding edge of $\mathcal{T}(t)$.
- Various forms of such processes have been assumed in the literature, but not all are self-consistent under Markovian assumptions.
- For example, log normal clock perturbations lack an additivity property: adding a node to split a branch must change the evolutionary process along that branch.
- We suppose the relaxed clock is a non-decreasing continuous-valued Lévy process. In practice, we use a Gamma process clock.

A genPomp simulation study

Top: diagnosis data only. Bottom: including sequence data



Detroit data: a young black MSM epidemic



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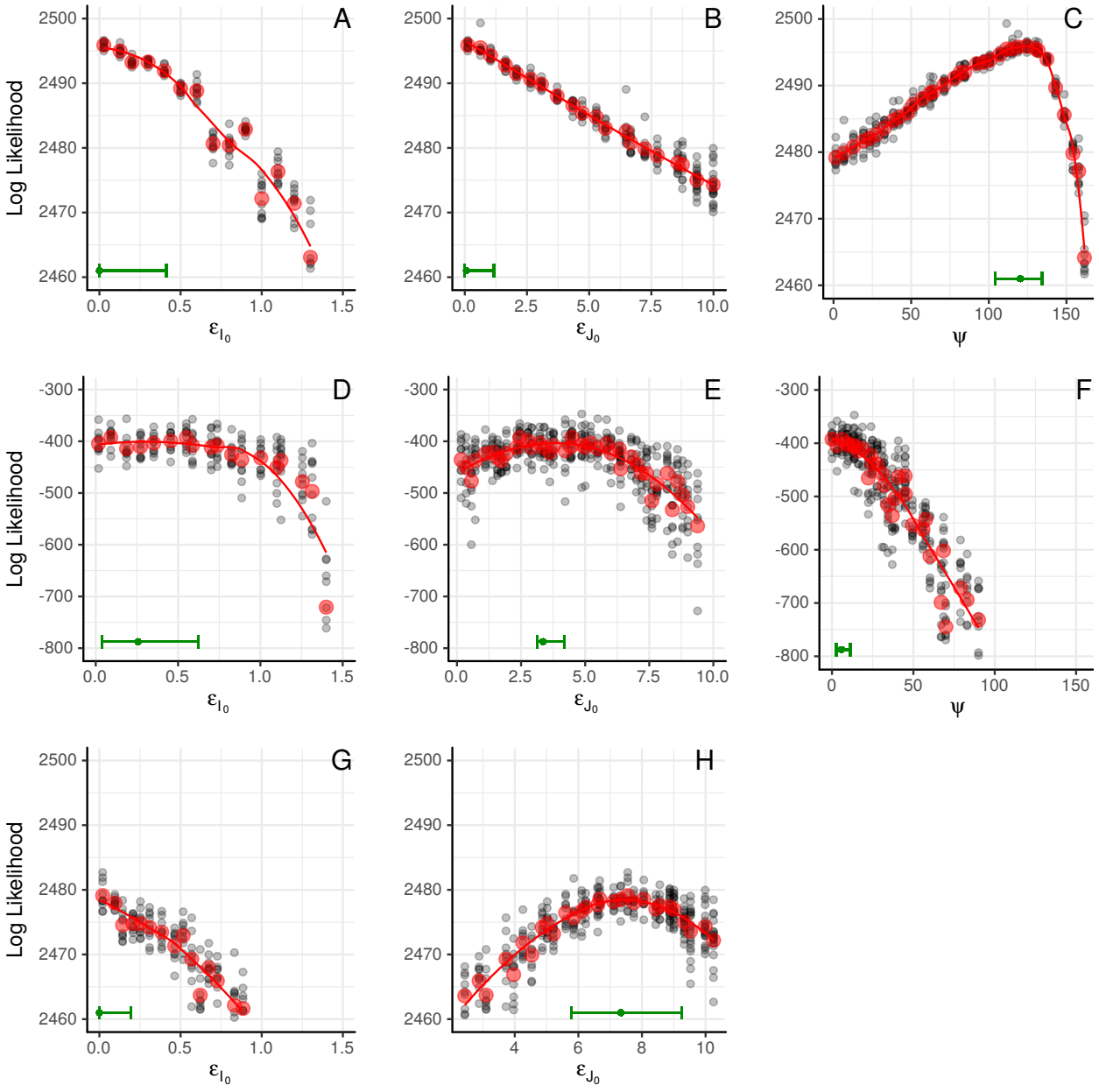


A-C. Diagnosis only.

D-F. Including sequence data.

G-H. Diagnosis only, fixing $\psi = 0$.

Moving forward from Smith et al (2017, MBE)

- `genPomp` was demonstrated on simulation-based phylodynamic likelihood inference for general dynamic models with order 100 sequences and order 1000 infected individuals.
- Further work is needed to scale to larger systems.
- We are working other applications within the current scale constraints, including nosocomial disease transmission.
- Having access to the full phylodynamic likelihood facilitates investigations of what (if anything) is lost by 2-step methods and summary statistic methods such as ABC.
- **Preliminary results**: The Volz/Rasmussen likelihood approximation works well if the true phylogeny is known. Phylogenetic uncertainty, especially when the phylogeny is constructed under assumptions different from the latent dynamic system, can lead to substantial bias in estimates and confidence regions.

Strengths and limitations of the GenPOMP framework

Strengths:

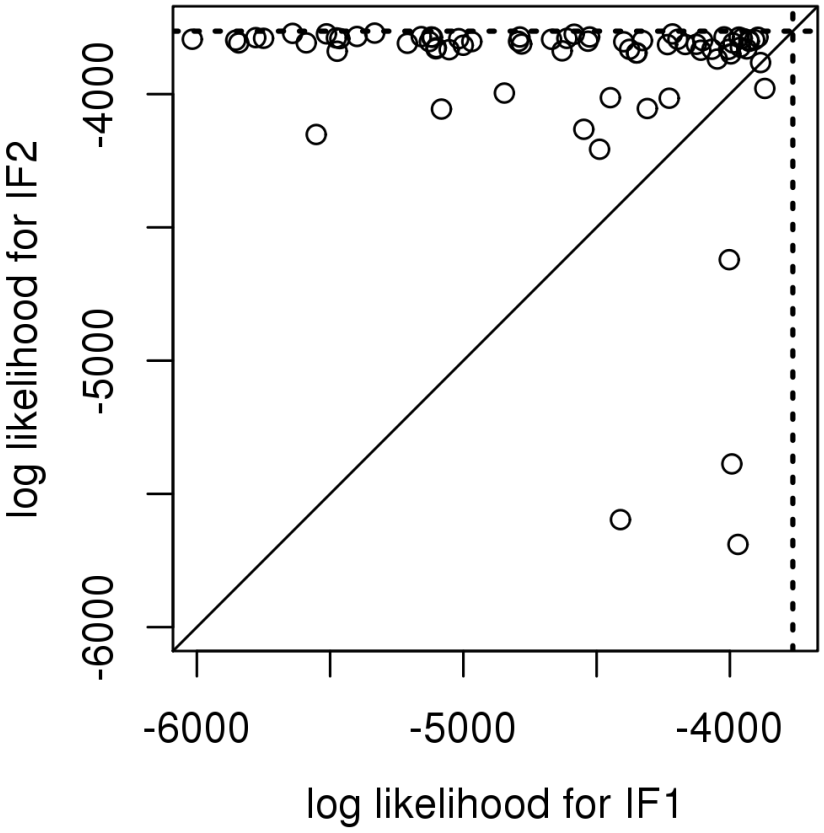
- A large and general model class for population dynamics.
- Statistically efficient inference.
- Can be used to assess loss of information and biases in methods that scale better.

Limitations:

- Computational requirement.
- Some detailed individual-based models may not fit easily into the GenPOMP framework.

A brief introduction to iterated filtering

- Successful SMC allows likelihood evaluation.
- This likelihood evaluation is both costly and noisy for non-small problems, so requires specialized algorithms to enable effective inference.
- The IF1 iterated filtering algorithm of (Ionides et al., 2006) averaged filtered parameters in a perturbed model, repeating with successively smaller perturbations.
- The IF2 algorithm of (Ionides et al., 2015) simply feeds perturbed particles at the end of one filtering iteration back as starting values for the next iteration, with decreasing perturbations.
- IF1 made possible some previously inaccessible inferences, but IF2 is much better!



Comparison of IF1 and IF2 on the cholera model.

Algorithmic tuning parameters for both IF1 and IF2 were set at the values chosen by King et al (2008) for IF1.

- Log likelihoods of the parameter vector output by IF1 and IF2, both started at a uniform draw from a large 23-dimensional hyper-rectangle.
- Dotted lines show the maximum log likelihood.

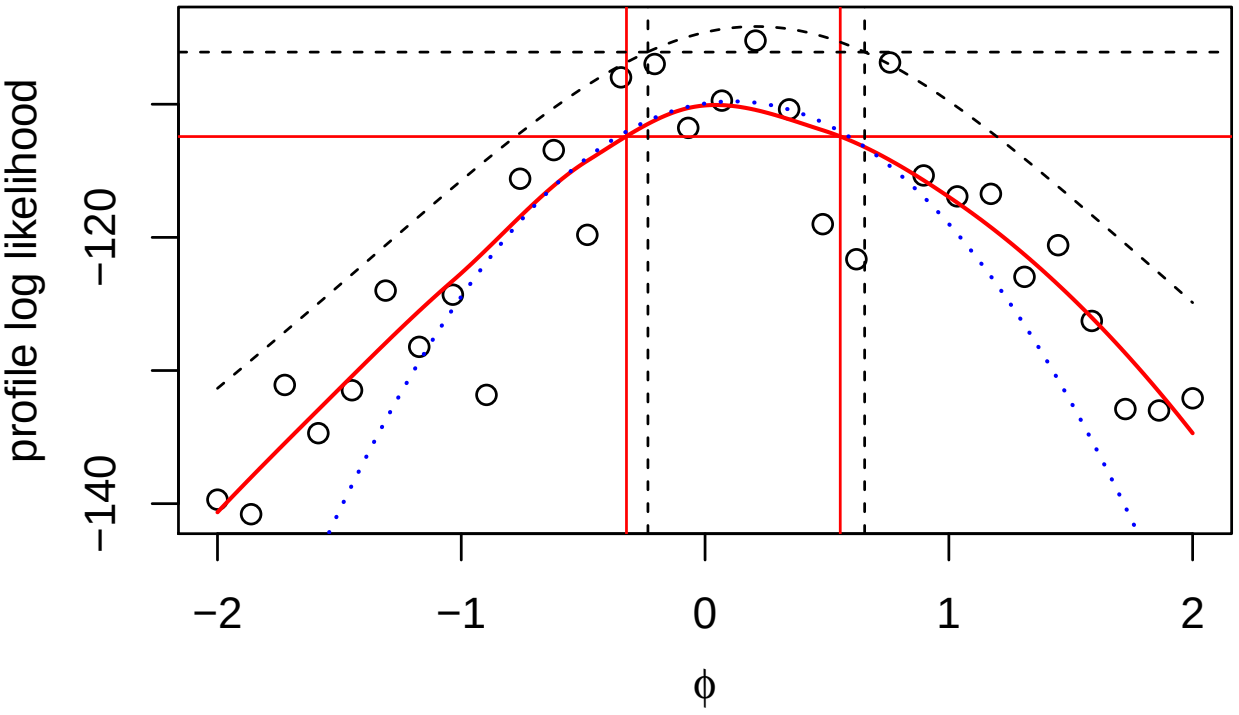
Monte Carlo adjusted profile (MCAP) confidence intervals

- The usual cutoff $\delta = 1.92$ for a 95% profile confidence interval is based on an asymptotic quadratic log likelihood (Wilks' χ^2 theorem).
- Profile intervals are robust to reparameterization.
- A Wilks limit also applies to give a cutoff for a smoothed Monte Carlo profile based on a quadratic approximation (Ionides et al., 2017),

$$\delta_{MCAP} = z_\alpha^2 \left(a \times \mathrm{SE}_{\mathrm{mc}}^2 + \frac{1}{2} \right),$$

  where z_α is the $1 - \alpha/2$ normal quantile, a is the quadratic coefficient of a quadratic regression near the profile maximum, $\mathrm{SE}_{\mathrm{mc}}$ is the Monte Carlo error of the maximum of this quadratic.
- if $\mathrm{SE}_{\mathrm{mc}} = 0$, the cutoff for $\alpha = 0.05$ reduces to $\delta_{MCAP} = 1.96^2/2 = 1.92$.
- We apply this cutoff after estimating the profile via a locally weighted quadratic smoother.
- We call this procedure a **Monte Carlo adjusted profile (MCAP)**.

A toy: MCAP for a log normal model



Points show Monte Carlo profile evaluations. Black dashed lines: exact profile and 95% confidence interval. Solid red lines: MCAP confidence interval. Dotted blue line: quadratic approximation.

	Exact profile	MCAP profile	Bootstrap	Quadratic
Coverage %	94.3	93.4	93.3	93.3
Mean width	0.78	0.88	0.94	0.92

Collaborators

Contributors to the methodologies developed:

- Aaron King
- Alex Smith
- Carles Breto
- Joonha Park
- Dao Nguyen

Collaborators influencing our phylodynamic work:

- Jim Koopman
- Erik Volz
- Ethan Romero-Severson

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