Likelihood-based inference for dynamic systems

Edward Ionides
University of Michigan, Department of Statistics

Lecture 1 at Wharton Statistics Department
Tuesday 25th April, 2017

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Full-information likelihood-based inference via simulation for partially observed stochastic mechanistic models of dynamic systems

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How can a title with so many modifiers be of widespread interest?

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- Likelihood-based inference has good statistical properties (Fisher) and is consistent with deductive scientific reasoning (Neyman, Popper).
- Full-information means working with the likelihood of the entire data, not just summary statistics.

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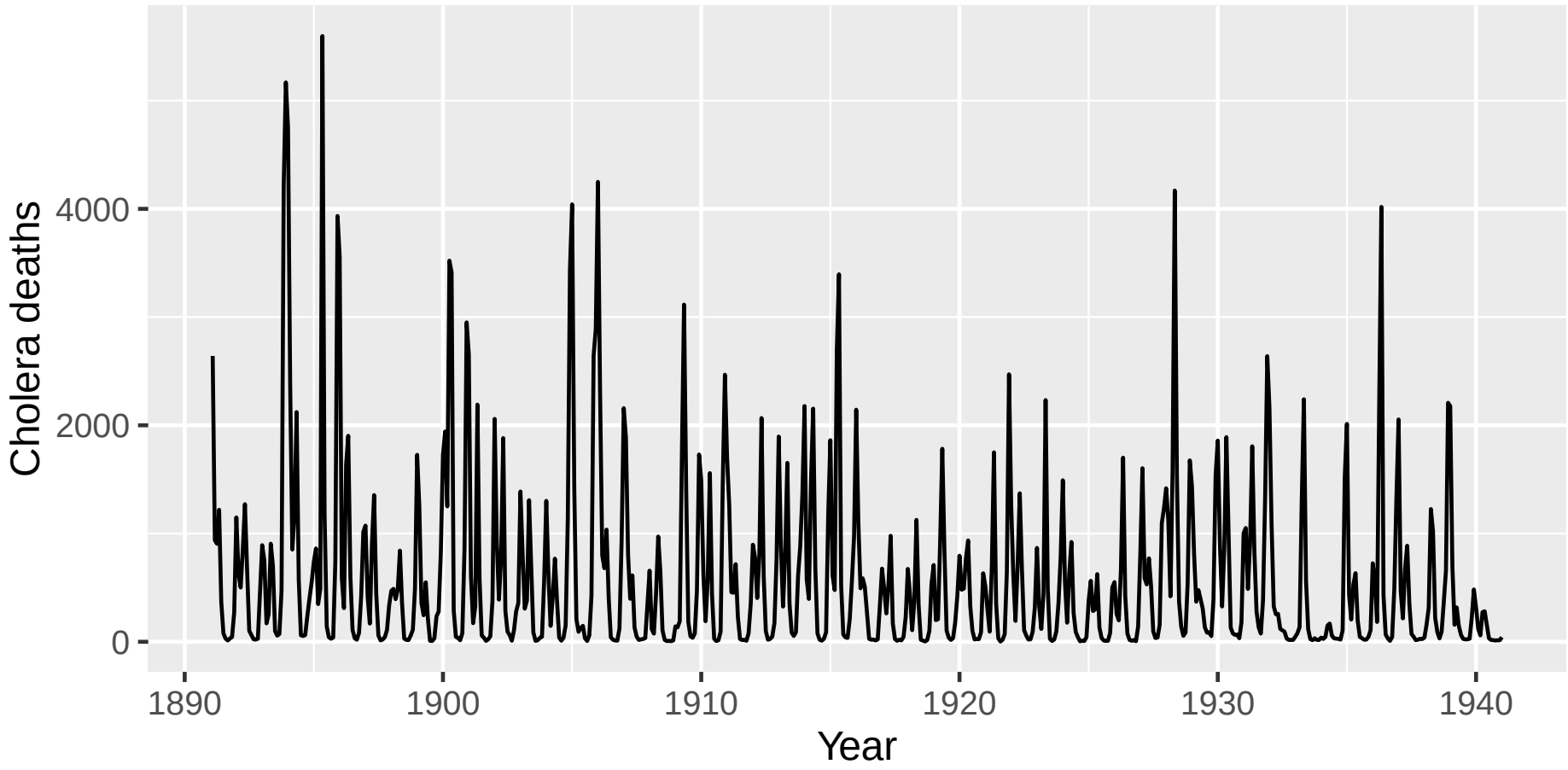
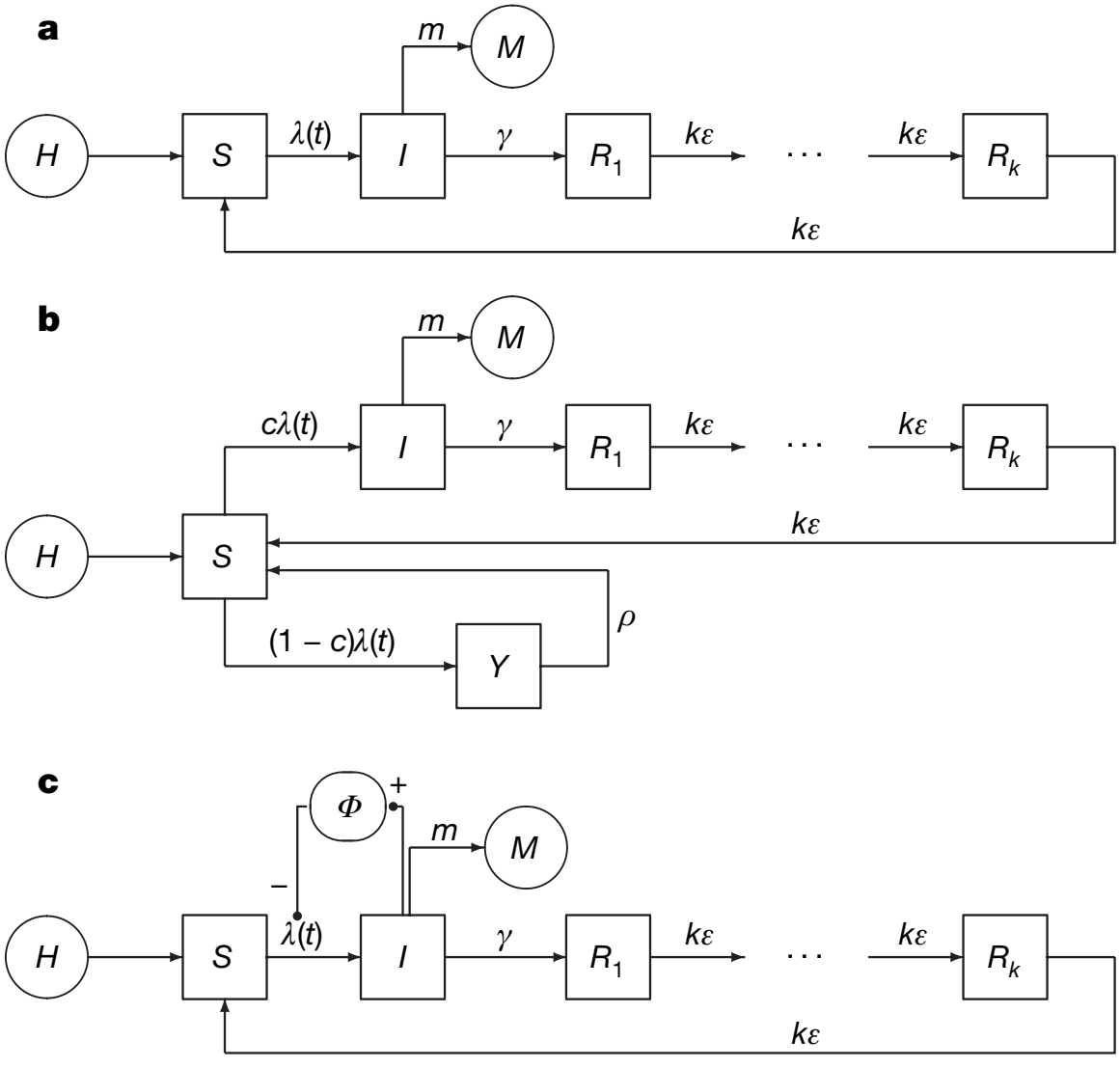
2. Panel data analysis: dynamic variation in sexual contact rates.
   - Observations on a collection of units lead to a panel of time series.
   - Analyzed together, the panel strengthens inferences available from any one time series.
3. Genetic sequence data: HIV transmission within and between demographic groups.
   - Genetic sequences of pathogens can inform transmission relationships between infected hosts. This demonstrates analysis of data having structure differing from time series.

1. Time series analysis: cholera in Bangladesh

- Cholera is severe diarrhea caused by a bacterium, *Vibrio cholerae*. Death from dehydration can result rapidly without medical treatment.
- A cholera epidemic in Haiti, from 2010, has led to over 9,000 deaths (Luquero et al., 2016), comparable to the total Ebola deaths in the 2014–2015 African epidemic.
- Management of all infectious diseases is assisted by quantitative models of transmission dynamics:
  - Zika, drug-resistant bacterial infections in hospitals, malaria, the current global effort to eradicate polio, etc.
  - Diseases of agricultural crops, farm animals and wildlife.
- Models should be confronted with data — statistical analysis!
- An endless source of challenges for interested statisticians.
- Our cholera example will demonstrate that fitting a dynamic model to data can lead to qualitative scientific insights as well as quantitative understanding.

Monthly cholera deaths in Dhaka, Bangladesh, 1891-1940





Competing models

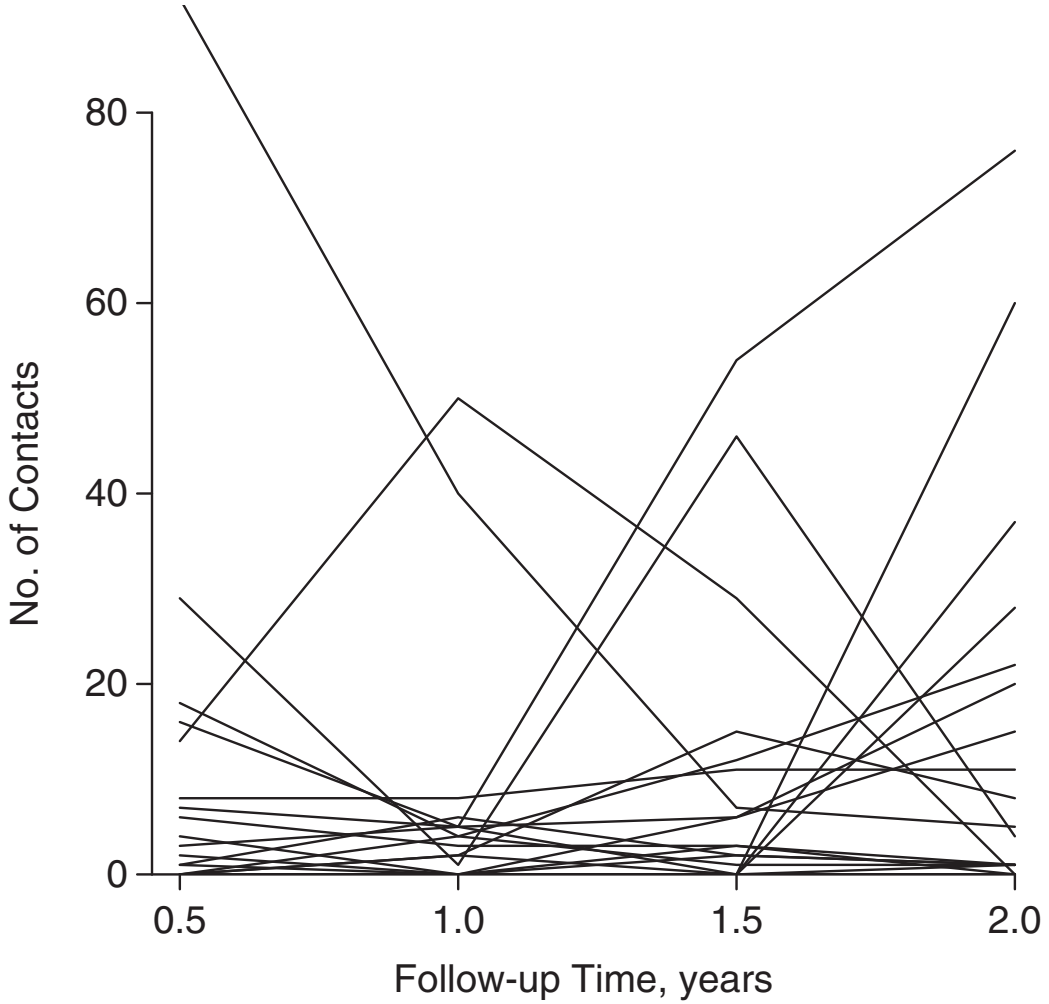
(King et al., 2008)

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.
- This raises the question of whether dynamic variation in individual sexual behavior is a real phenomenon that can be observed and measured.
- We are motivated to construct behavioral models with various heterogeneities, both between individuals and within individuals over time, and see which models best explain available behavioral 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 (Romero-Severson et al., 2015).
- Sexual contacts were reported in various categories: oral, anal, protected, unprotected, etc. Here, we show total reported contacts.

Modeling dynamic variation in sexual contact rates

- Individual i is modeled via a dynamic latent contact rate process,

$$\{X_i(t),\, 0 \le t \le 2\},$$

  giving rise to a measurement process,

$$\{Y_{ij},\, j \in 1{:}4\}.$$

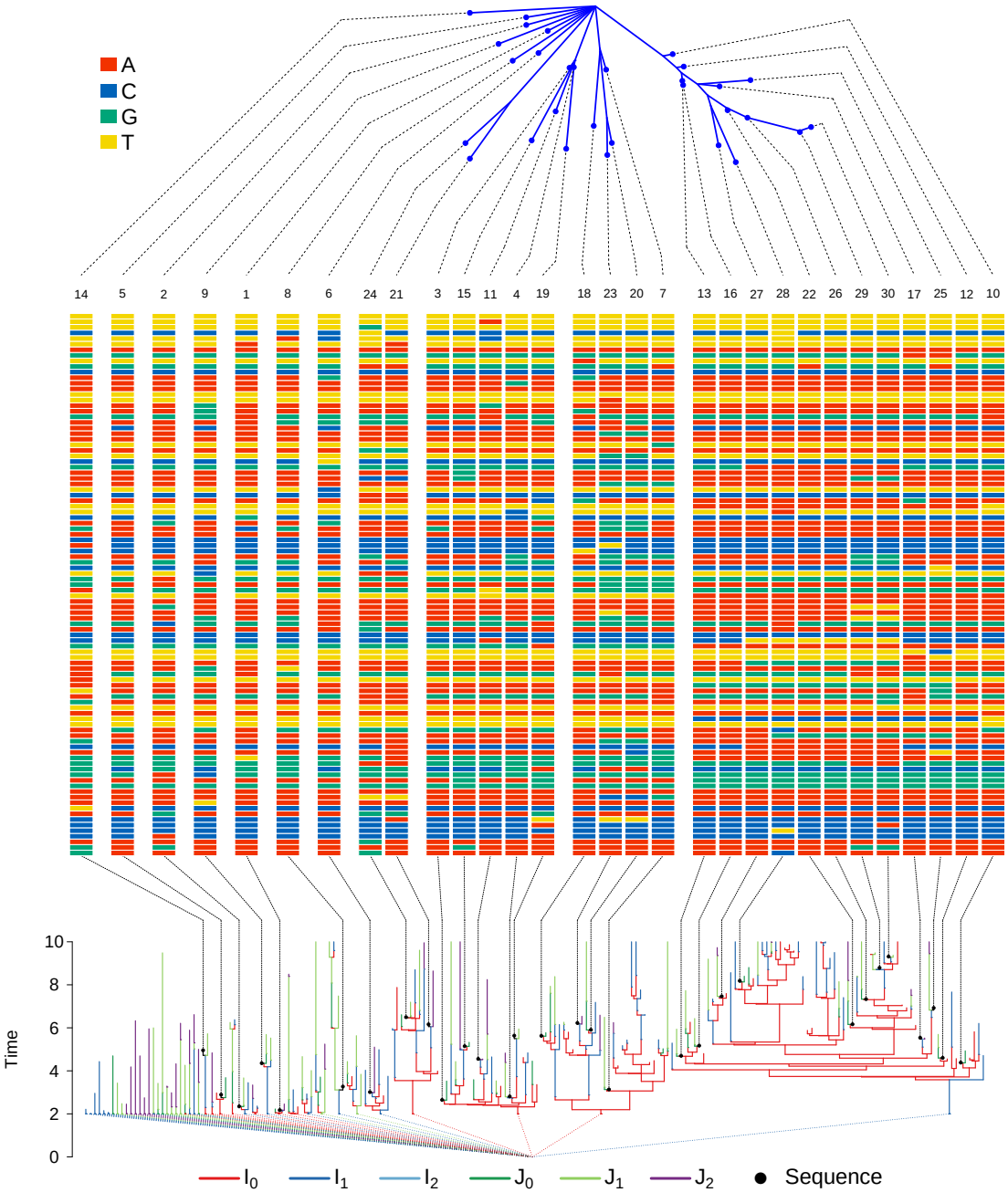
- We will construct models that can explain data,

$$\{y^*_{ij},\, i \in 1{:}882,\, j \in 1{:}4\},$$

  in terms of dynamic variation and/or between-individual heterogeneity and/or overdispersion.
- Which, if any, of these effects are statistically identifiable from available data is an empirical question.
- We look for statistical methodology that can fit flexible classes of scientifically interpretable models.

3. Infectious disease dynamics inferred from genetic data

- Genetic sequences from pathogens can provide information about infectious disease dynamics that may supplement or replace information from other epidemiological observations.
- Traditional incidence data tells who gets infected, but not who transmitted it.
- Genetic sequence data for pathogens is increasingly available.
- Statistically rigorous reconciliation of genetic sequence data with nonlinear, structured population dynamics has been an open problem.
- Formally, the disease dynamics and molecular evolution processes can be jointly modeled. How do we do inference for this complex system?



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

Top: phylogeny of observed sequences.

Middle: simulated sequence data. Actual data are confidential.

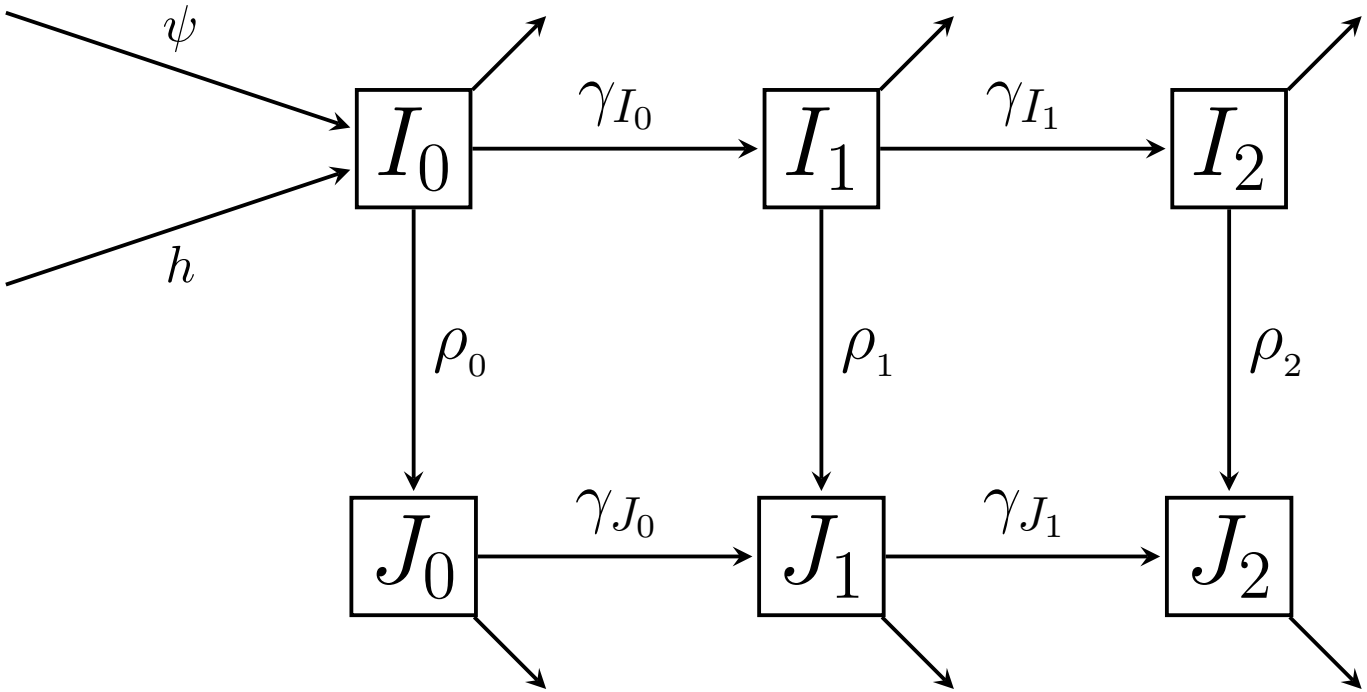
Bottom: Transmission forest for the full epidemic.

red: undiagnosed early infection

blue: undiagnosed chronic infection

green: diagnosed

Model for infection and disease progression



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.

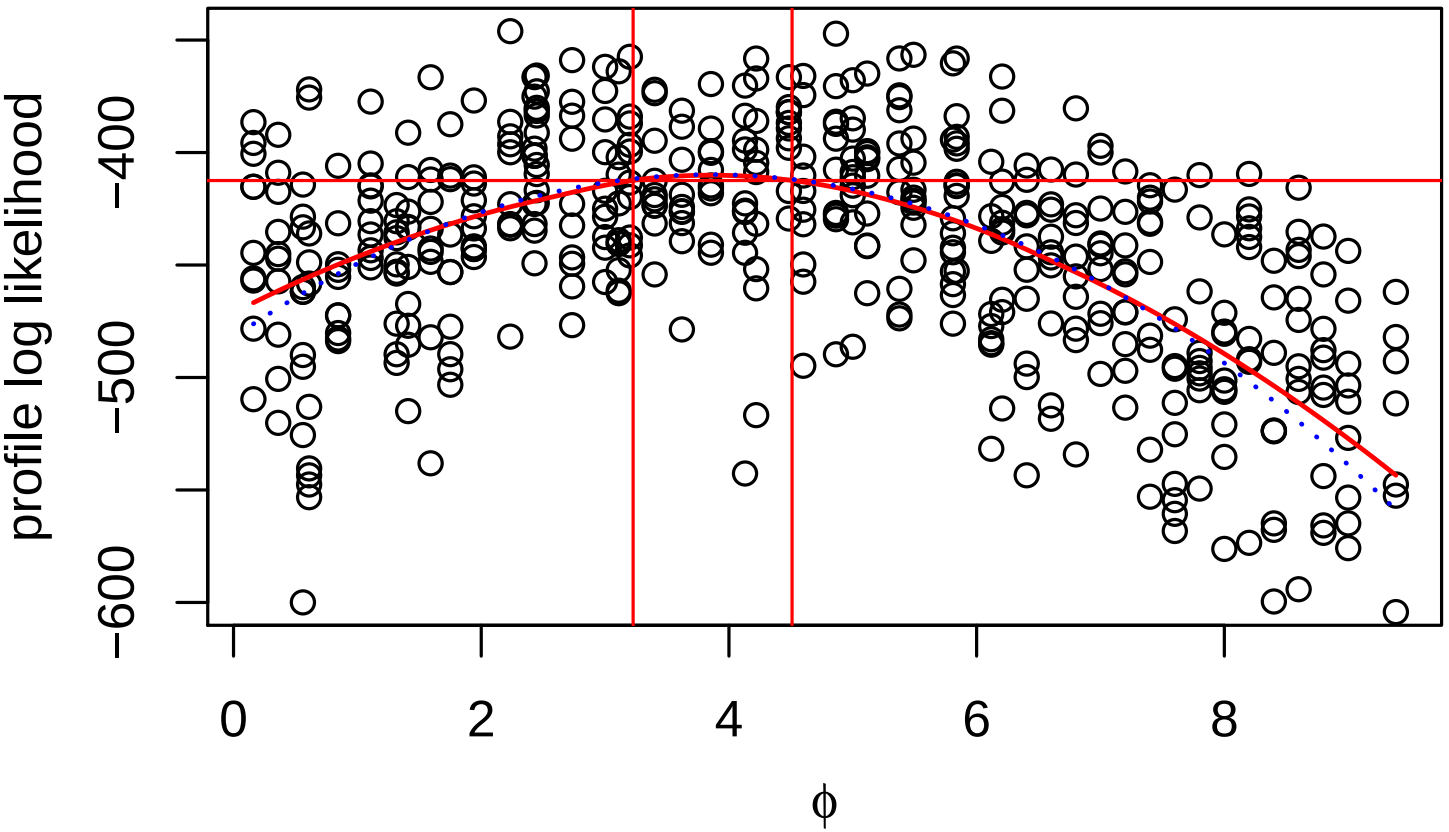
4. Inference for nonlinear mechanistic **spatiotemporal** models

- Many processes of interest happen in both space and time.
  - Movements of all species (animals, pathogens, plant seeds, etc) are basic ecological processes.
  - Business logistics place supply and demand in space and time.
- Spatiotemporal analysis is a generalization of panel data, where units in the panel correspond to spatial locations.
  - For panel analysis, units are modeled as independent.
  - For spatiotemporal analysis, units can have dynamic dependence.
- Spatiotemporal inference is a frontier that is beyond the scope of this seminar series.
- The ideas we develop here can be extended to spatiotemporal analysis (manuscript in preparation).

Key innovations

- 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., 2016).
  - 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.

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