Inference for Computationally Intensive Space-time Infectious Disease Models

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Research Interests

- Statistical computing, Markov chain Monte Carlo
- Spatial models
- Applications:
  - Climate science
  - Infectious disease modeling

What This Talk is About

- Statistical inference for infectious disease models can be challenging.
- I will describe some of the challenges of fitting infectious disease models.
- I will propose a general inferential approach, borrowing from methods used in computer model emulation and calibration.
- I will focus on the gravity TSIR model used for measles dynamics but the ideas discussed are more general.

The SIR Model

- A model to explain and predict the spread of an infectious disease.
- SIR model: The population is subdivided into a set of distinct classes: individuals are either susceptible (S), infectious (I) or recovered (R).
- The SIR model describes the dynamics of the sizes of each group.

Assumptions of Basic SIR Model

- Individuals are born into the susceptible class.
- Susceptible individuals have never come into contact with the disease and are able to catch the disease, after which they move into the infectious class.
- Infectious individuals spread the disease to susceptibles, and remain in the infectious class for a given period of time (infectious period) before moving into the recovered class.
- Recovered class individuals are immune for life.

Gravity TSIR Model

- Models the number of incidences of measles in K different communities (cities).
- The model has components of a discrete time-series TSIR model for local dynamics (Bjørnstad et al., 2002; Grenfell et al. 2002).
- Similar to gravity models from transportation theory, it has an explicit formulation for the spatial transmission between different host communities.
- It allows for stochasticity inherent in the disease transmission and random immigration.
- It includes seasonality in the transmission rates.

Gravity TSIR Model: Notation

- I_{kt} : number of infected individuals in city k at time t
- S_{kt} : number of susceptible individuals in city k at time t
- L_{kt} : number of infected people moved to city k at time t
- d_{kj} : distance between cities k and j
- N_{kt}, B_{kt} : size and birth rate of city k at time t

Gravity TSIR Model

- Number of incidences of a disease at time $t+1$ for city k,

  $I_{k(t+1)} \sim \text{Poisson}(\lambda_{k(t+1)})$, where $\lambda_{k(t+1)} = \beta_t S_{kt}(I_{kt} + L_{kt})^{\alpha}$.

- $I_{k(t+1)}$ increases with I_{kt}, S_{kt}, and number of infected immigrants coming to city k at time t (L_{kt}).
- $\{\beta_t\}$ are 26 different parameters that are repeated every year to allow differences in seasonal transmission (26 = number of biweeks in a year).

(Xia, Bjørnstad and Grenfell, 2004)

Gravity TSIR Model

- Number of susceptible individuals at time $t+1$ for city k, $S_{k(t+1)} = S_{kt} + B_{kt} - I_{k(t+1)}$.
- Number of infected immigrants (latent) at time t for city k

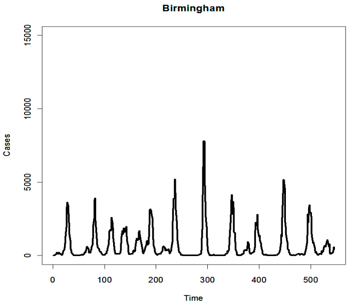
$$L_{kt} \sim \text{Gamma}(m_{kt}, 1), \text{ where } m_{kt} = \theta N_{kt}^{\tau_1} \sum_{j=1, j \neq k}^{K} \frac{(Ijt)^{\tau_2}}{d_{kj}^{\rho}}.$$

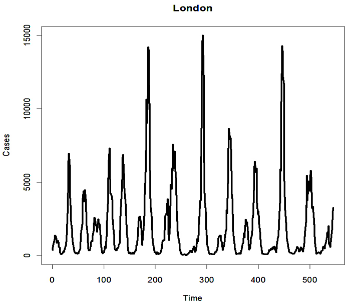
- L_{kt} increases with size of city k, number of infected people in all other cities, taking into account distances.

Inference for Measles Dynamics

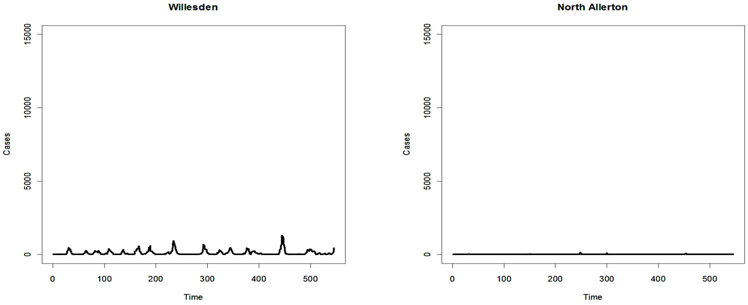
- Parameters of the model:
  - Reliable estimates of local transition parameters α and β are known (Bjørnstad et al. 2001).
  - Gravity parameters θ, τ_1, τ_2 and ρ are unknown.
- Sources of information:
  - The UK Registrar General's data for 952 cities in England and Wales for years 1944-1966 of biweekly incidences of measles.
  - Number of susceptibles from standard reconstruction algorithms (cf. Fine and Clarkson 1982a, Finkenstadt and Grenfell 2000).
- **Goal**: Infer gravity parameters $\mathbf{\Theta} = (\theta, \tau_1, \tau_2, \rho)$ from data.

Measles Data: London and Birmingham





Measles Data: Willesden and North Allerton



Notice: 952 cities of varying sizes and levels of “infecteds.”

Complicates likelihood-based inference.

Computational Challenges

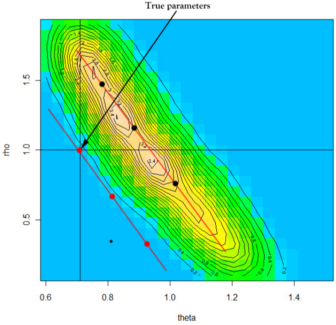
- Dimensions of the data (TK): 546*952 = 519,792.
- Number of infected immigrants $\{L_{k,t}\}$ are unobserved.
- The likelihood function is complicated:
  - Involves integrating over 519,792 latent variables.
  - Expensive calculations per iteration.

Simplifications and Gridded MCMC

- A solution:
  1. Simplify the model by fixing the number of immigrants (latent variables) at their expected values. Likelihood function is still expensive. $\approx$ 72 hours to find MLE alone.
  2. Discretize the parameter space, then pre-calculate expensive parts of the likelihood ahead of time, in parallel.
- Good news: Greatly speeds up computing, permits maximum likelihood and Bayesian inference.

Problems . . .

True Θ = ($\theta = 0.71$, $\tau_1 = 0.5$, $\tau_2 = 1$,$\rho = 1$).



Posterior surface for (θ, ρ). (τ_1, τ_2 fixed at true values)

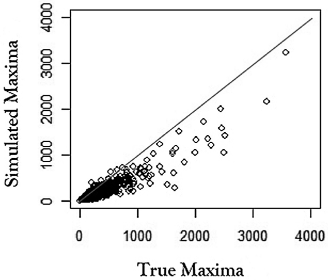
Poor inference for Θ.

Important Biological Characteristics

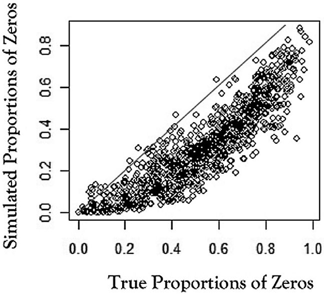
What do the biologists care about? "Signatures" of the process:

- Maximum number of incidences. $\mathbf{M} = (M_1, \cdots, M_K)$, where M_i is the maximum number of incidences for i-th city.
- Proportions of biweeks without any cases of infection. $\mathbf{P} = (P_1, \cdots, P_K)$, where P_i is the proportion of incidence free bi-weeks for i-th city.

Problems with Fitting Key Characteristics



(a)



(b)

Fitted model does not capture well important characteristics of the observations.

Back to the Drawing Board

- Likelihood-based approaches apparently do not give enough importance to features that are of scientific interest.
- A careful study confirms that these issues are not due to our simplifications or gridded MCMC.

New Approach

- Idea for alternative: instead of classical likelihood-based approach, build inferential approach that focuses on **fitting scientifically relevant features** of the data.
- Modeling/inference using summary statistics (features).
- Approximate Bayesian computing (ABC) (Pritchard et al., 1999; Beaumont et al. 2002; Marjoram et al., 2002) seems appropriate but is infeasible since simulating draws from this model is computationally expensive.

Gaussian Process-based Emulation-Calibration

- Gaussian processes are useful for emulating (approximating) complex computer models. May be useful here.

Gaussian Process Model Basics

- Process at location $\mathbf{s} \in D \subset \mathbb{R}^d$ is $Z(\mathbf{s}) = \mu_{\boldsymbol{\beta}}(\mathbf{s}) + w(\mathbf{s})$. Location $\mathbf{s}$ may be physical or from "input space".
- Model dependence among spatial random variables by modeling $\{w(\mathbf{s}) : \mathbf{s} \in D\}$ as a Gaussian process.
- Infinite-dimensional process. If $\mathbf{s}_1, \ldots, \mathbf{s}_n \in D$, $\mathbf{w} = (w(\mathbf{s}_1), \ldots, w(\mathbf{s}_n))^T$ is multivariate normal.
- Parametric covariance, e.g. $\text{Cov}(Z(\mathbf{s}_i), Z(\mathbf{s}_j)) = \kappa \exp(-\|\mathbf{s}_i - \mathbf{s}_j\|/\phi)$, $\kappa > 0, \phi > 0$. Here, $\Theta = (\kappa, \phi)$.
- Let $\mathbf{Z} = (Z(\mathbf{s}_1), \ldots, Z(\mathbf{s}_n))^T$, so

$$\mathbf{Z} | \Theta, \boldsymbol{\beta} \sim N(\mu_{\boldsymbol{\beta}}, \Sigma(\Theta)).$$

GP Linear Model Prediction

- Let the predictions at the new locations $\mathbf{s}_1^*, \ldots, \mathbf{s}_m^* \in D$ be $\mathbf{Z}^* = (Z(\mathbf{s}_1^*), \ldots, Z(\mathbf{s}_m^*))^T$.
- Under the GP assumption ($\boldsymbol{\mu}_1, \boldsymbol{\mu}_2, \Sigma$ depend on $\boldsymbol{\beta}, \Theta$):

$$\begin{bmatrix} \mathbf{Z} \\ \mathbf{Z}^* \end{bmatrix} \mid \Theta, \boldsymbol{\beta} \sim N\left(\begin{bmatrix} \boldsymbol{\mu}_1 \\ \boldsymbol{\mu}_2 \end{bmatrix}, \begin{bmatrix} \Sigma_{11} & \Sigma_{12} \\ \Sigma_{21} & \Sigma_{22} \end{bmatrix} \right), \qquad (1)$$

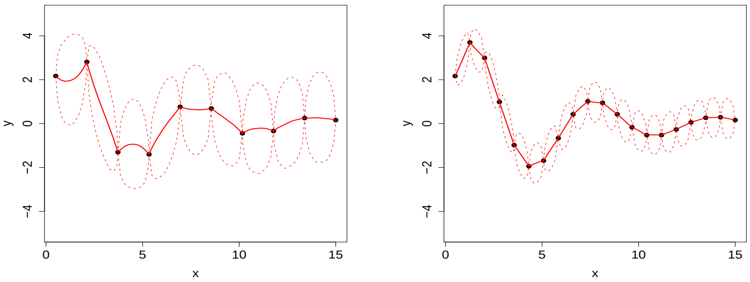
  ML: use above with ML estimates plugged-in.

  Bayes: use above, while averaging over $\Theta, \boldsymbol{\beta} \mid \mathbf{Z}$. This is the *posterior predictive distribution*.

GP Model Emulation

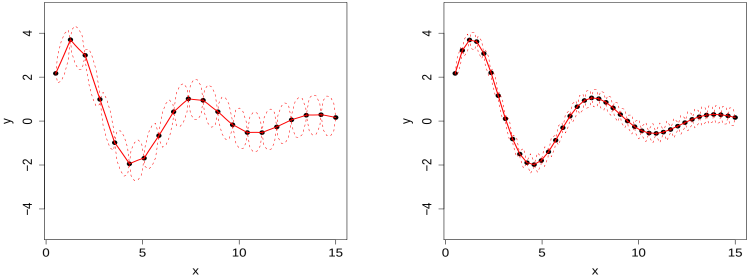
Interpolations using simple GP random effects model:

$y(x) = \mu + w(x)$, $\{w(x), x \in (0, 20)\}$ is a zero-mean GP.



Increase data from 10 to 20 points

GP Model Emulation



Increase data from 20 to 40 points

An Emulation-Based Solution

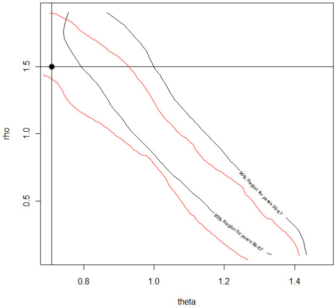
- Let vector of summary statistics from observations be $\mathbf{Z}$. Example: Maximum number of incidences for ith city.
- Simulate realizations of the gravity TSIR model at various parameter settings $\Theta_1, \Theta_2, \ldots, \Theta_p$.
- Let $\mathbf{Y}(\Theta)$ be the vector of summary statistics obtained at parameter setting Θ.
- Consider: $(\Theta_1, \mathbf{Y}(\Theta_1)), \ldots, (\Theta_p, \mathbf{Y}(\Theta_p))$.
- Stochastic emulation: Fit a Gaussian Process (GP) to above simulations.
  - Thus for any new parameter setting Θ^*, we have a predictive distribution for the process $\mathbf{Y}(\Theta^*)$.

New Inferential Approach

1. Predictive distribution provides a probability model (the Gaussian process emulator) that connects the parameters to the *observed* summary statistics $\mathbf{Z}$. This gives us a likelihood function. ("emulator likelihood")
2. ML or Bayesian inference to obtain estimates of $\boldsymbol{\Theta}$.

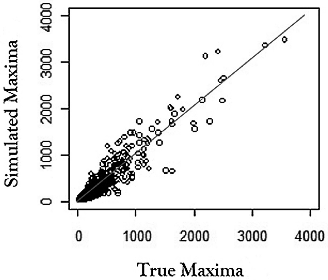
Skipping lots of important details: dimension reduction, computational issues, worrying about discrepancy between model and data etc. ...

Improved Inference for Θ



95% C.I.'s for (θ, ρ): Solid black line: the likelihood-based method; Solid red line: the Gaussian process emulator.

Fitting Biological Characteristics using GP-approach



(a)

(b)

Fitted model better captures important characteristics of the data.

Summary

- Our Gaussian process-based inferential approach focuses on biologically important characteristics. Very useful and interesting to scientists in many disciplines.
- Our approach simultaneously improves parameter inference, model fit, and addresses computational challenges.
- Not discussed here: We are able to apply our approach to the England-Wales data set and obtain useful scientific conclusions.
- This approach is useful in a number of other settings (ongoing research).

Collaborators

- Roman Jandarov, Ph.D. Student, Dept of Statistics, Penn State University.
- Ottar Bjørnstad, Center for Infectious Disease Dynamics, Penn State University.
- Bryan Grenfell, Ecology and Evolutionary Biology, Princeton University.

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Modeling with Gaussian Processes

- Gaussian processes (GPs) are useful models for dependent processes, e.g. time series, spatial data.
- GPs are also very useful for modeling complicated functions.

  Key idea: dependence (spatial random effects) adjusts for non-linear relationships between input and output.

Summary of Inferential Problem

Let parameter of interest be θ (here θ=K_v).

Statistical problem:

- Model output is a bivariate spatial process at each θ: $\mathbf{Y} = ((\mathbf{Y}_1(\psi_1), \mathbf{Y}_2(\psi_1)), (\mathbf{Y}_1(\psi_2), \mathbf{Y}_2(\psi_2)), \dots, (\mathbf{Y}_1(\psi_K), \mathbf{Y}_2(\psi_K)),$ where $\{\psi_1, \psi_2, \dots, \psi_K\}$ is a set of plausible θ values.
- Observations: $\mathbf{Z} = (\mathbf{Z}_1, \mathbf{Z}_2)$.
- What can we learn about θ given $\mathbf{Z}, \mathbf{Y}$?

Bayesian Approach

A Bayesian framework is useful for computer model calibration:

- There is usually real prior information about $\boldsymbol{\theta}$.
- The likelihood surface for $\boldsymbol{\theta}$ may often be highly multimodal and there may be identifiability issues; useful to have easy access to the full posterior distribution.
- If $\boldsymbol{\theta}$ is multivariate, important to look at bivariate and marginal distributions: easier w/ sample-based approach.
- Amenable to hierarchical specification: we will exploit this for multivariate spatial process model.

Kennedy and O'Hagan (2001); Bayarri, Berger et al. (2007, 2008).

Latter provides wavelets-based approach for functional output.

Two-stage Approach to Inference

1. Find probability model for $\mathbf{Z}$ (data) using $\mathbf{Y}$ (simulations.)
   - Model relationship between $\mathbf{Z} = (\mathbf{Z}_1, \mathbf{Z}_2)$ and $\boldsymbol{\theta}$ via flexible emulator for model output $\mathbf{Y} = (\mathbf{Y}_1, \mathbf{Y}_2)$.
   - Add model discrepancy and measurement error:

   $$\mathbf{Z} = \boldsymbol{\eta}(\mathbf{Y}, \boldsymbol{\theta}) + \boldsymbol{\delta}(\mathbf{Y}) + \boldsymbol{\epsilon}$$

   where $\boldsymbol{\delta}(\mathbf{Y}) = (\boldsymbol{\delta}_1,\ \boldsymbol{\delta}_2)^T$ is the model discrepancy, also modeled as a GP. $\boldsymbol{\epsilon} = (\boldsymbol{\epsilon}_1,\ \boldsymbol{\epsilon}_2)^T$ is the observation error.
2. Posterior distribution $\pi(\boldsymbol{\theta} \mid \mathbf{Y}, \mathbf{Z})$ derived from prior on $\boldsymbol{\theta}$ and likelihood based on above model.