An Empirically Adjusted Reproductive Number for Stochastic Compartmental Models

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Introduction

- Compartmental models provide a simplified summary of disease progression.
- A disease process is divided into a set of discrete states.
- The change in states is modeled, either by considering changes in aggregate counts (population averaged approach), or at the individual level (agent based approach).
- These techniques are traditionally implemented using ordinary and partial differential equations, though stochastic formulations have a number of advantages.

Stochastic and Deterministic Models

- Deterministic Models
  - Computationally tractable
  - Rich literature, many generalizations
- Stochastic Models
  - Can better deal with small samples and chaotic processes
  - Full probabilistic framework, can better quantify uncertainty
  - Natural tool to incorporate multiple data sources
  - Computationally intensive, usually reliant on MCMC

Illustration

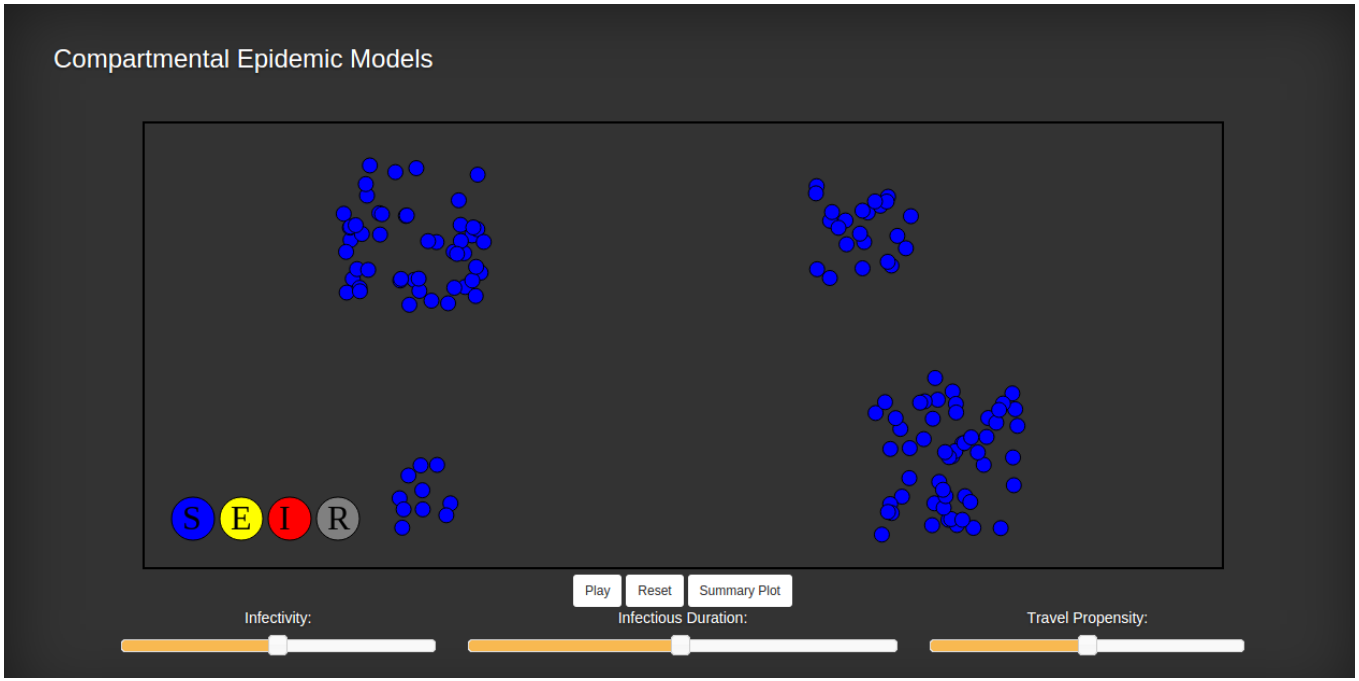


Figure : Web based SEIR simulation tool

Historical Development

- Compartmental models have been around a long time (Kermack and McKendrick (1927)), but have been radically expanded in recent years.
- Fully probabilistic SEIR: Lekone and Finkenstädt (2006)
- 'Spatial' generalizations:
  - Household Models: Cauchemez et al. (2004); van Boven et al. (2010)
  - Contact Networks: Verdasca et al. (2005); Keeling (2004)
  - Mover Stayer Framework: Sattenspiel and Dietz (1995)

Keeping track of indexes

- Discrete time points: $\{t_i : t_1, \ ..., \ t_T\}$
- Discrete spatial locations: $\{s_j : s_1, \ ..., \ s_n\}$
- Anything that varies over both: organized into a T by n matrix, so each column gives the time series for that quantity in that location.

Data Model

- We need a way to relate observed information to our underlying disease model
- Data can be of multiple types: what incidence data do we usually observe in epidemics?
  - Infection or removal times
  - Aggregated event counts
  - Event proportions in subpopulations
  - None of the above

Data Model

- The T by n data matrix is denoted $\mathbf{Y} = [\mathbf{y_1} \ ... \ \mathbf{y_n}]$
- Data may be related either to new infection counts, or to new removal counts
- The $T \times n$ matrices $\mathbf{I}^*$ and $\mathbf{R}^*$ correspond to these unobserved quantities

We then specify a data model:

$$\{y_{ij} \ | I^*_{ij}\} \overset{ind}{\sim} \ g(I^*_{ij}, \Theta)$$
$$i = 1, ..., T; \quad j = 1, ..., n$$

This can take many forms, identity, overdispersion, binomial proportion etc.

Temporal Process Model

- Initial n-vectors: $\mathbf{S_0}$, $\mathbf{E_0}$, $\mathbf{I_0}, \mathbf{R_0}$
- Transitions:

$$\mathbf{S}_{i+1} = \mathbf{S}_i - \mathbf{E}_i^*$$
$$\mathbf{E}_{i+1} = \mathbf{E}_i - \mathbf{I}_i^* + \mathbf{E}_i^*$$
$$\mathbf{I}_{i+1} = \mathbf{I}_i - \mathbf{R}_i^* + \mathbf{I}_i^*$$
$$\mathbf{R}_{i+1} = \mathbf{R}_i + \mathbf{R}_i^*$$

$$\{E_{ij}^* | \pi_{ij}^{(SE)}, S_{ij}\} \overset{ind}{\sim} binom(S_{ij}, {\pi_{ij}}^{(SE)})$$
$$\{I_{ij}^* | \pi^{(EI)}, E_{ij}\} \overset{ind}{\sim} binom(E_{ij}, \pi^{(EI)})$$
$$\{R_{ij}^* | \pi^{(IR)}, I_{ij}\} \overset{ind}{\sim} binom(I_{ij}, \pi^{(IR)})$$

Spatial Process Model

- Spatial heterogeneity is naturally incorporated into the exposure probability: $\pi_{ij}^{(SE)}$
- Motivating definitions/assumptions:
  - Number of 'contacts' K per person within a spatial unit s_j at time t_i follows a Poisson distribution, $K \sim Pois(\lambda_{ij})$.
  - When individuals travel to other spatial locations, their contact behavior is well modeled by the contact behavior of that spatial unit.
  - Contact between spatial locations is proportional to a weighted sum of known pairwise 'distance' measures. These distance metrics are expressed as $n \times n$ matrices: $\{\mathbf{D}_z;\ z = 1, ..., Z\}$, with associated spatial autocorrelation parameters $\{\rho_z\}$ subject to $\sum_{z=1}^{Z} \rho_z \leq 1$ and $\{0 \leq \rho_z < 1 : z = 1, ..., z\}$.

Spatial Process Model

Resulting parametric form:

$$\pi_{ij}^{(SE)} = 1 - exp\left(\left\{-\eta_{i.} - \sum_{z=1}^{Z} \rho_z(\mathbf{D}_z \eta_{i.})\right\}_j\right)$$

- $\eta_{i.} = \{\frac{I_{i1}}{N_{i1}} e^{\theta_{i1}}, \ ..., \ \frac{I_{in}}{N_{in}} e^{\theta_{in}}\}.$,
- $\theta_{ij} = \lambda_{ij} p$, confounded, where p is the infection probability conditional on a contact event.

Parameter Model

- Organize intensity parameters, $\{\theta_{ij}\}$, into a $T \times n$ matrix
- let the $T \times 1$ column vector $\boldsymbol{\theta}_j = \mathbf{X_j}\boldsymbol{\beta}$, $\boldsymbol{\beta}_{P\times 1}$
- $\pi_i^{(EI)} = 1 - exp(-\gamma_{(EI)})$
- $\pi_i^{(IR)} = 1 - exp(-\gamma_{(IR)})$
- $\gamma_{(EI)} \sim gamma(\alpha_{(EI)}, \beta_{(EI)})$
- $\gamma_{(IR)} \sim gamma(\alpha_{(IR)}, \beta_{(IR)})$

libSpatialSEIR

- 'spatialSEIR' R package wraps underlying C++ library
- Object oriented structure allows on the fly sampling reconfiguration
- Optional OpenCL interface allows computation involving graphics cards or multi-core CPU's
- Aims to allow (relatively) simple implementation of any spatial SEIR(S) model as parameterized here

MCMC Sampling Techniques

General strategy:

1. Initial sampler adjustment period to learn effective Metropolis tuning parameters by evaluate sampler acceptance rate every 10-100 iterations
2. Set compartment samplers to use alternating proposal distributions: proportional update binomial draws based on probability terms, and discretized, whole compartment update using centered normal distributions.
3. Enable periodic 'IterationTasks':
   - Decorrelation steps (Graves et al. (2011)) for linear model parameters
   - Forced joint sampling: $\gamma^{(EI)}, \boldsymbol{\beta}$
4. Run the samplers to convergence

Reproductive Numbers

The expected number of secondary infections caused by a single infectious individual in a large, entirely susceptible, population.

- This concept has a long history, and has been calculated in many ways.
- It is particularly useful for its 'thresholding' behavior - if $\mathcal{R}_0$ is greater than 1, we expect the pathogen to invade a population. If it is less than 1, we expect the disease to die out.
- How does a quantity like this generalize to time varying intensity processes?

Reproductive Numbers: a Simple Stochastic SEIR Example

Consider the simplest special case of the spatial SEIR model we've discussed: a single location analysis with a single intensity parameter.

1. Compartments, transition matrices, intensity process, etc. are all $T \times 1$ column vectors.
2. The intensity design matrix $\mathbf{X}$ is a $T \times 1$ vector of ones.
3. β is a scalar parameter

$\mathcal{R}_0$ in this case has been shown to be equal to $\frac{e^{\beta}}{\gamma_{(IR)}}$. This is intuitive, as e^{β} is the estimated infection rate and $\frac{1}{\gamma_{(IR)}}$ is the mean of the exponentially distributed infectious time.

Reproductive Numbers: Existing Generalizations

- $\mathcal{R}_0(t)$
  - Generalization to more nuanced intensity processes
  - Originally conceived in the single location case: $\mathcal{R}_0(t_i) = \frac{e^{(\mathbf{X}\beta)_i}}{\gamma_{(IR)}}$
  - Easy to further generalize this idea to spatial case, or over any other features incorporated into intensity process linear model
  - There may not be a single scalar interpretable $\mathcal{R}_0$, depending on the chosen intensity process
- Effective $\mathcal{R}_0$
  - Applies a scaling factor to $\mathcal{R}_0$ or $\mathcal{R}_0(t)$: the susceptible fraction, $\frac{S}{N}$.
  - Intended to capture the decrease in transmission due to an exhausted supply of susceptibles, though often $\frac{S}{N} \approx 1$
  - Closely related to 'replacement number' in deterministic models

Reproductive Numbers: Existing Generalizations

There are a number of problems with these approaches.

- Conceptual framework is quite abstract (large susceptible population, single infectious individual)
- These approaches are entirely dependent on, and extremely sensitive to, the parametric form of the intensity process (examples to follow)
- Stochastic SEIR models estimate compartment sizes and transitions, but this information is not incorporated (with the partial exception of effective $\mathcal{R}_0$)

We propose a new reproductive measure which is grounded in the population under study, but is not necessarily less generalizable.

Empirically Adjusted Reproductive Number: $\mathcal{R}^{(EA)}$

We modify the traditional conceptual $\mathcal{R}_0$ framework, by considering:

> *the expected number of secondary infections caused by an infectious individual in a particular population.*

This may not sound like much of a difference, but it has a very natural expression in the notation we've established.

(Brown, Oleson, Porter 2015)

(Porter and Brown, 2015)

Empirically Adjusted Reproductive Number: $\mathcal{R}^{(EA)}$

- The average number of infections caused by a single individual at a particular place/time is the total number of such infections divided by the infectious count.
- Let the indicator $I_k(t_i, s_j, s_l)$ mark the event that a person k from spatial location s_j is infected at time t_i by contact from within spatial location s_l, and note that $P(I_k(t_i, s_j, s_l)) = 0$ unless person k is a member of the susceptible class $\mathcal{S}$.

$$E\Big[\sum_{k=0}^{N_{i,j}}(I_k(t_i, s_j, s_l))\Big] = S_{i,j} \cdot P(I_k(t_i, s_j, s_l)|k \in \mathcal{S}) \rightarrow \frac{S_{i,j}P(I_k(t_i, s_j, s_l)|k \in \mathcal{S})}{I_{ij}}$$

Empirically Adjusted Reproductive Number: $\mathcal{R}^{(EA)}$

These highly specific infection events have an explicit parametric form in this framework.

$$P(I_k(t_i, s_j, s_l)|k \in \mathcal{S}) = 1 - exp\left(-\sum_{z=1}^{Z} \rho_z \{\mathbf{D}_z\}_{jl} \cdot \eta_{il}\right), \; j \neq l$$

$$1 - exp\left(-\eta_{il}\right), \; j = l$$

$$\eta_{il} = \frac{I_{il}}{N_l} e^{\theta_{il}}$$

These expectations can be arranged into a time specific $n \times n$ 'next generation matrix', $\mathbf{G}(t_i)$ if we express them as an average, dividing by the relevant number of infectious individuals. The resulting quantity is defined to be zero if I_{ij} is equal to zero.

Empirically Adjusted Reproductive Number: $\mathcal{R}^{(EA)}$

In the usual next generation matrix approach to $\mathcal{R}_0$ estimation, we would consider the spectral radius (dominant eigenvalue) of the resulting matrix. Here, we note instead that the row sums give the average number of infections caused at the chosen time point by each infectious individual in the spatial location with the same (row) index.

Finally, instead of multiplying by the average infectious period, we take the expected value over the distribution of infectious times:

$$\boldsymbol{\mathcal{R}}^{(EA)}(t) = \left(\sum_{t=t_i}^{t_\infty} \mathbf{G}(t) \cdot \left[\prod_{k=t_{j+1}}^{t} (1 - \pi_k^{(IR)}) \right] \right) [1]_{n \times 1}.$$

$\mathcal{R}^{(EA)}$- additional connections to $\mathcal{R}_0$

Consider a single spatial unit with a fixed size population of susceptibles at the time t_i when a single infectious individual is introduced. Note that, in this case, $S_t \approx N \; \forall \; t$, and again assume a single intensity parameter.

$$\mathcal{R}^{(EA)}(t_i) = \sum_{t=t_i}^{t_\infty} \left(\frac{N}{I_t}\right)(1 - exp\{-\frac{I_t}{N}e^{\theta}\})(1-\pi^{(IR)})^{(t-t_i)}.$$

If assume I_t remains equal to one long enough that the remaining terms in this infinite summation are negligible, we have the approximate equality

$$\mathcal{R}^{(EA)}(t_i) \approx \left[\frac{(1 - exp\{-\frac{1}{N}e^{\theta}\})}{\left(\frac{1}{N}\right)}\right]\left[\sum_{t=t_i}^{t_\infty}(1-\pi^{(IR)})^{(t-t_i)}\right].$$

which is only reasonable if $1-\pi^{(IR)}$ is very small.

$\mathcal{R}^{(EA)}$- additional connections to $\mathcal{R}_0$

$$\lim_{N\to\infty}\left(\left[\frac{(1-exp\{-\frac{1}{N}e^{\theta}\})}{(\frac{1}{N})}\right]\left[\sum_{t=t_i}^{t_\infty}(1-\pi^{(IR)})^{(t-t_i)}\right]\right)=\frac{e^{\theta}}{\pi^{(IR)}}$$

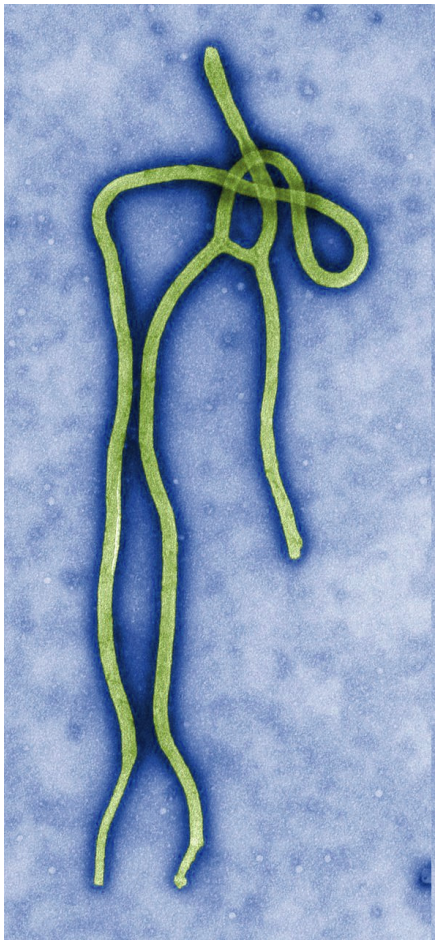
Recall that the traditional expression for $\mathcal{R}_0$ is $\frac{e^{\theta}}{\gamma_{(IR)}}$. This derivation emphasizes that $\mathcal{R}_0(t)$ ignores the nonlinear effect on the contact rate of the number of infectious individuals.

Reproductive Number Comparison

Consider the various reproductive numbers, applied to the single location, single intensity parameter case, at time t_i.

- $\mathcal{R}_0$: $\frac{e^{\theta}}{\gamma_{(IR)}}$
- Artificially constrained $\mathcal{R}^{(EA)}$: $\frac{e^{\theta}}{\pi^{(IR)}}$
- Effective $\mathcal{R}_0$: $\left(\frac{S_i}{N}\right)\left(\frac{e^{\theta}}{\gamma_{(IR)}}\right)$
- $\mathcal{R}^{(EA)}$: $\sum_{t=t_i}^{t_\infty}\left(\frac{S_i}{I_i}\left[1-exp\left(-\frac{I_i}{N}e^{\theta_i}\right)\right]\left[\prod_{k=t_{j+1}}^{t}(1-\pi_k^{(IR)})\right]\right)$

Illustrative Examples: Ebola

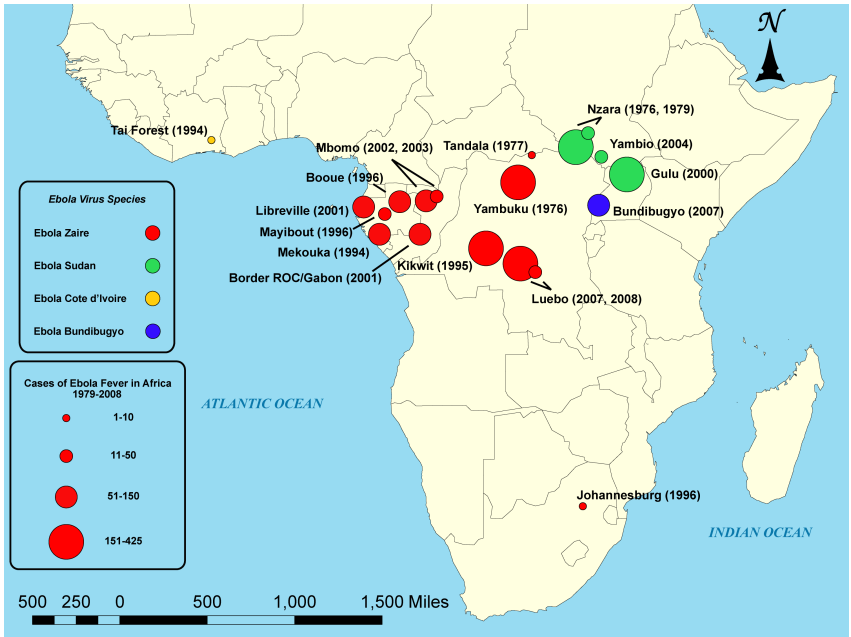


Here we consider two very different outbreaks of Ebola Virus Disease (EVD)

1. The 1995 Ebola outbreak in DRC
   - Single location
   - Simple, coordinated response
2. The ongoing epidemic in West Africa
   - Geographically diverse
   - Multinational/multi-organizational response
   - Considerable uncertainty in disease surveillance data

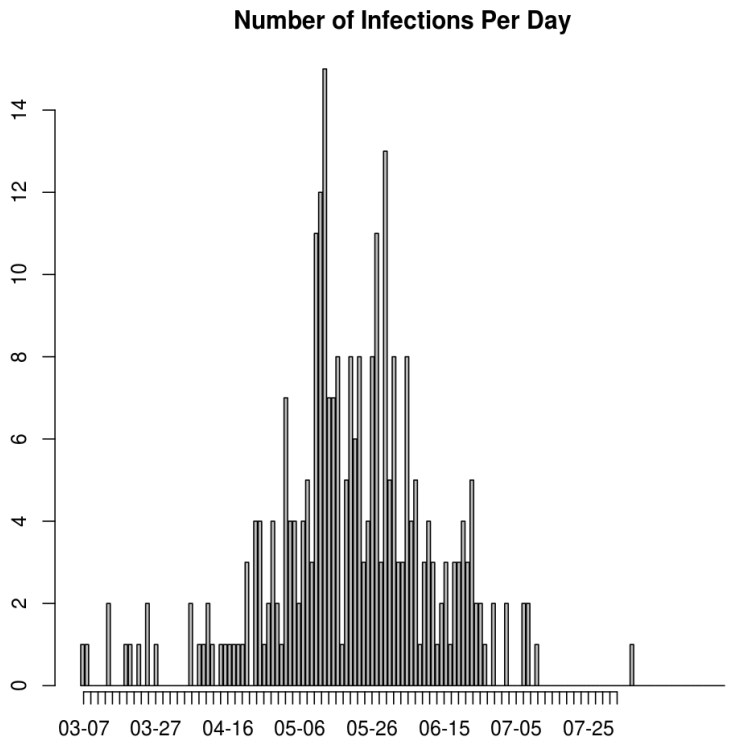
The 1995 Ebola Outbreak in Kikwit, Congo

- Kikwit is a large city in the Bandundu region of DRC
- There were a total of 316 documented cases of Ebola
- The epidemic began in March and lasted until July
- Control efforts began in mid-May, and continued until the epidemic was contained
- This epidemic has been well studied

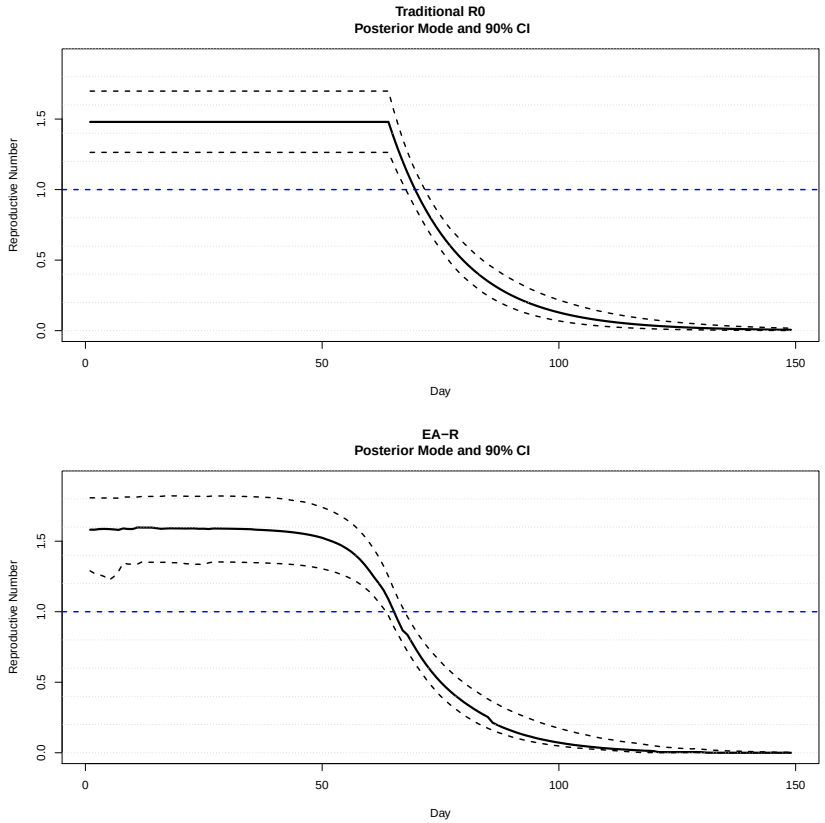


The 1995 Ebola Outbreak in Kikwit, Congo

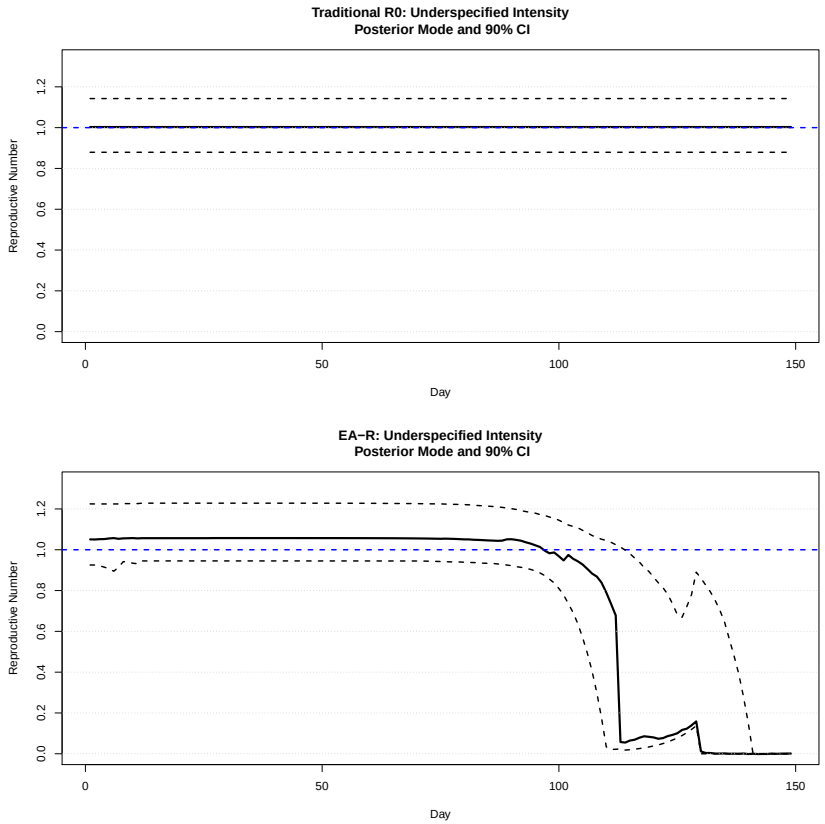
- The effect of the intervention is immediately obvious from the figure of raw case counts
- Lekone and Finkenstädt (2006) employ a two part intensity process:
  1. Intercept, providing a baseline intensity for the epidemic
  2. A linear time term (on the linear predictor scale) starting on the date control efforts began



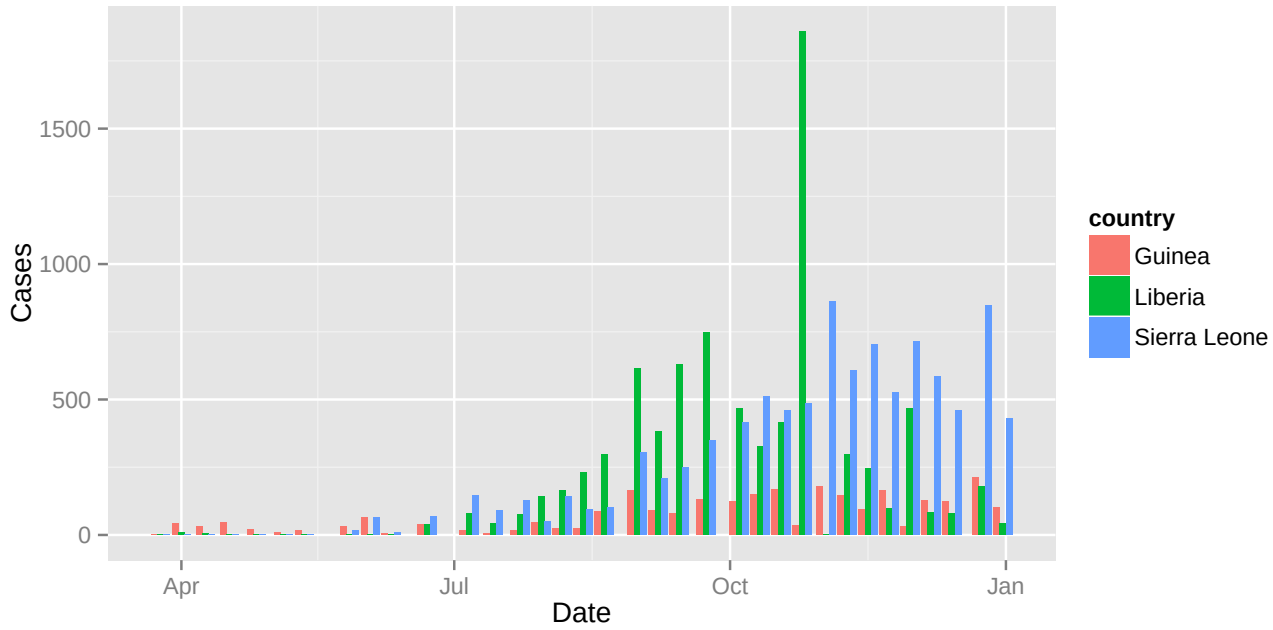
The 1995 Ebola Outbreak in Kikwit, Congo: Canonical Model



The 1995 Ebola Outbreak in Kikwit, Congo: Intercept Only Model

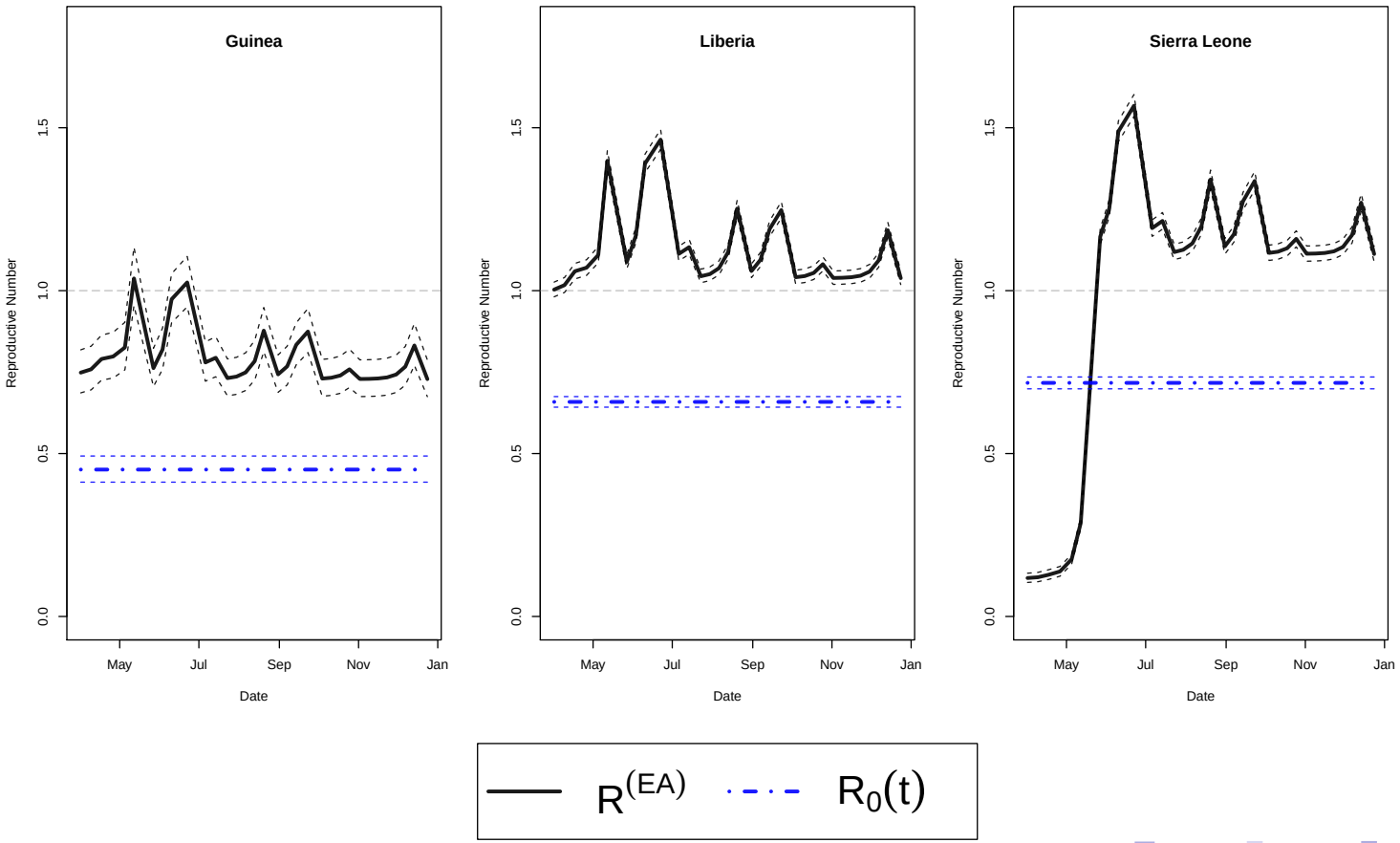


The Ongoing Ebola Epidemic in West Africa

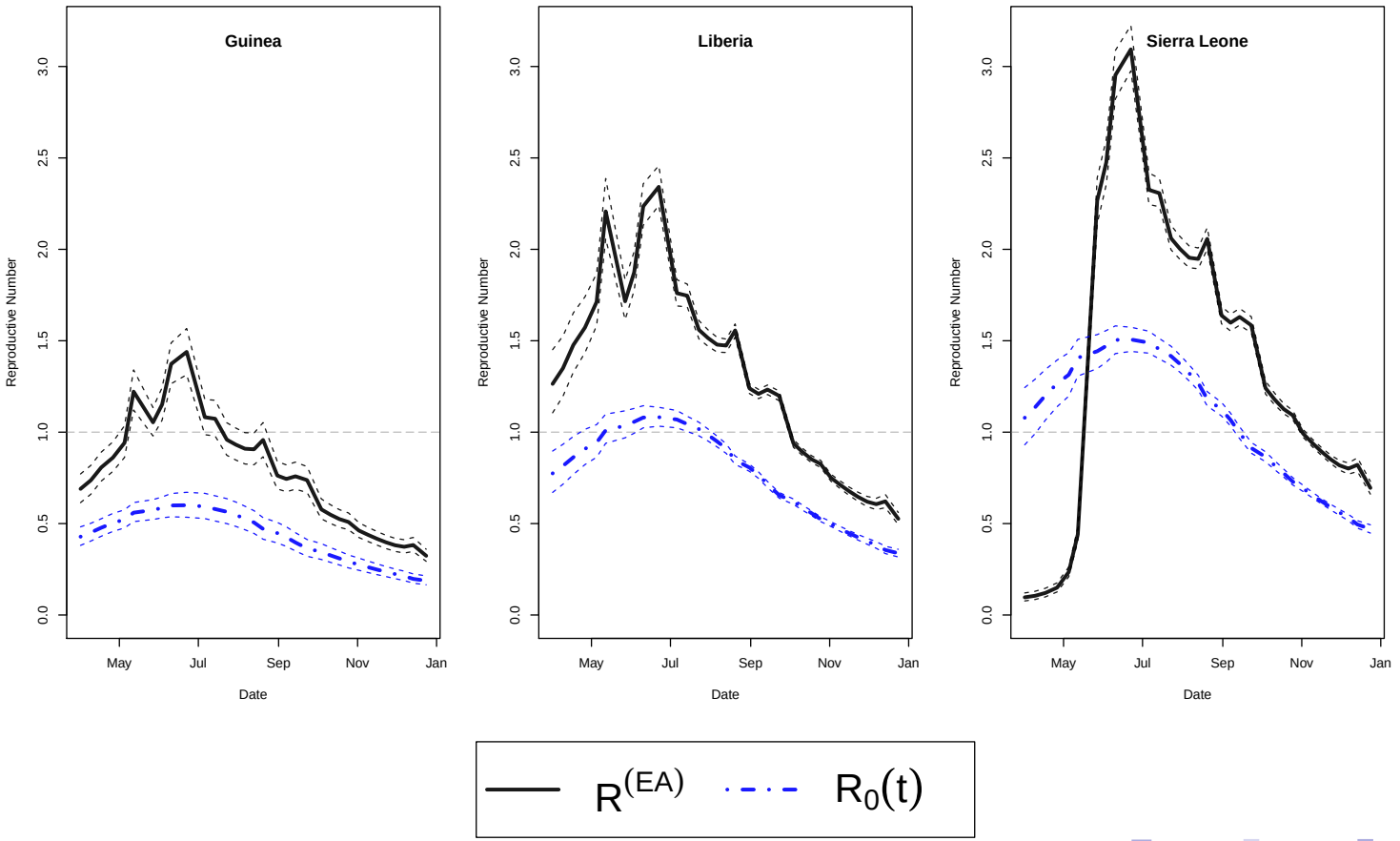


Unlike the previous case, this epidemic is ongoing, and does not have the benefit of a simple intervention summary. We instead use our observations about reproductive numbers to help choose an adequate model.

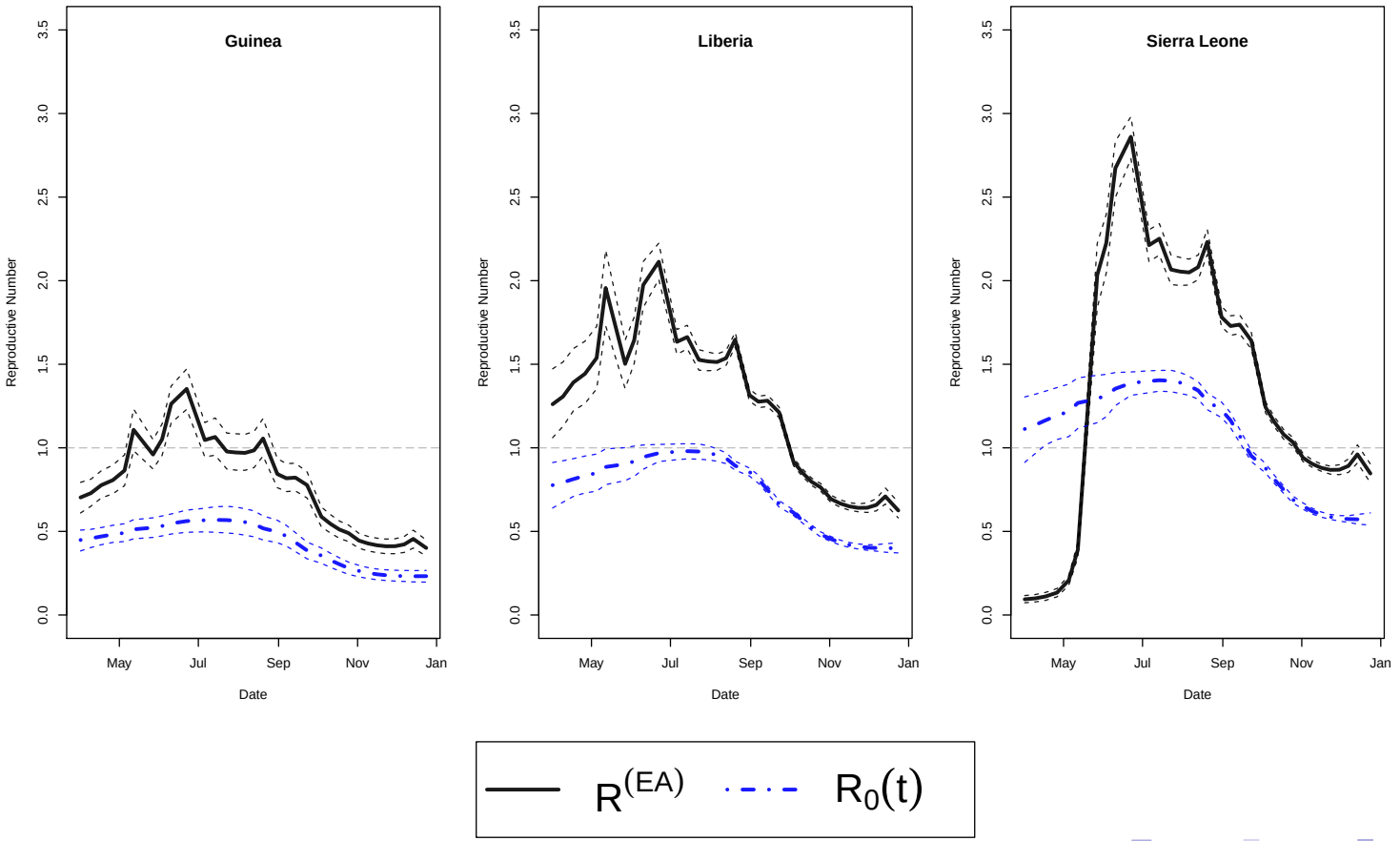
West Africa: Intercepts Only Model



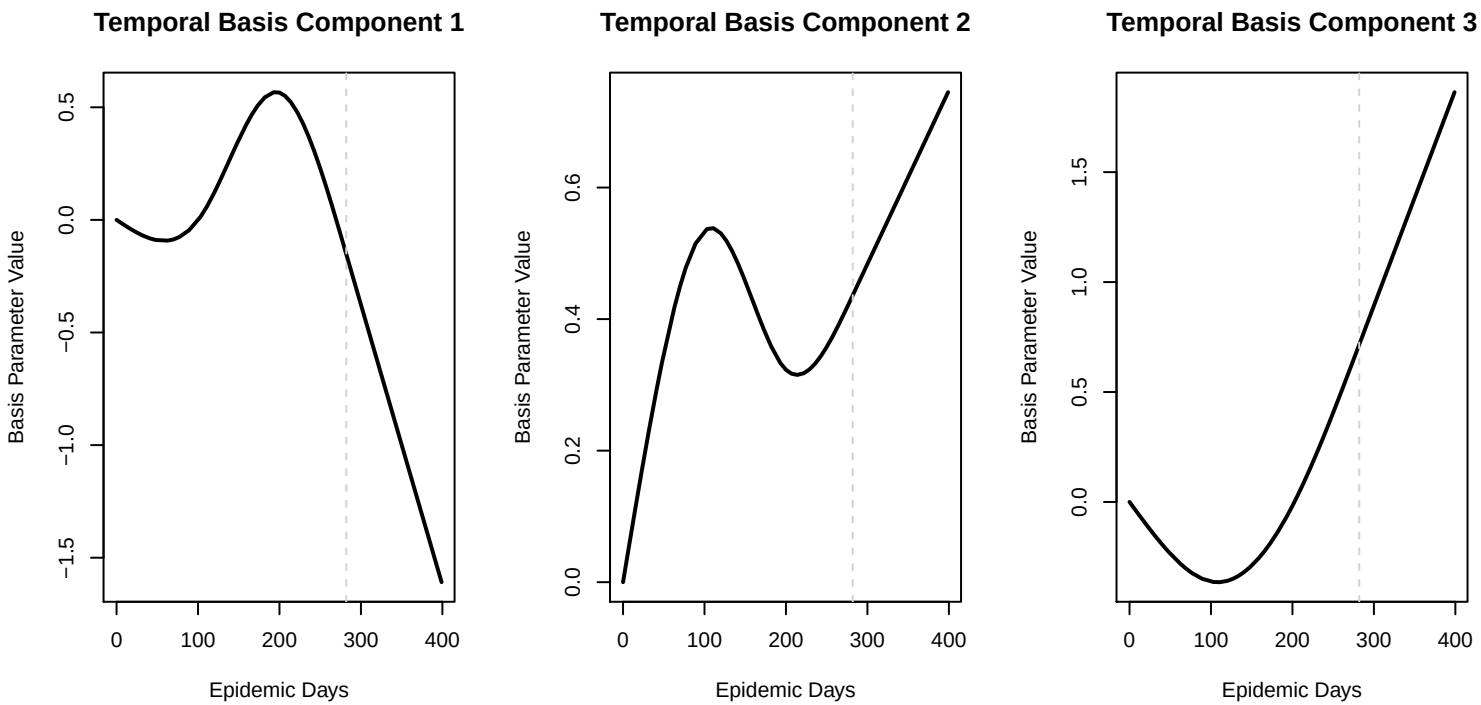
West Africa: Intercepts + 3 DF Spline Basis Model



West Africa: Intercepts + 5 DF Spline Basis Model

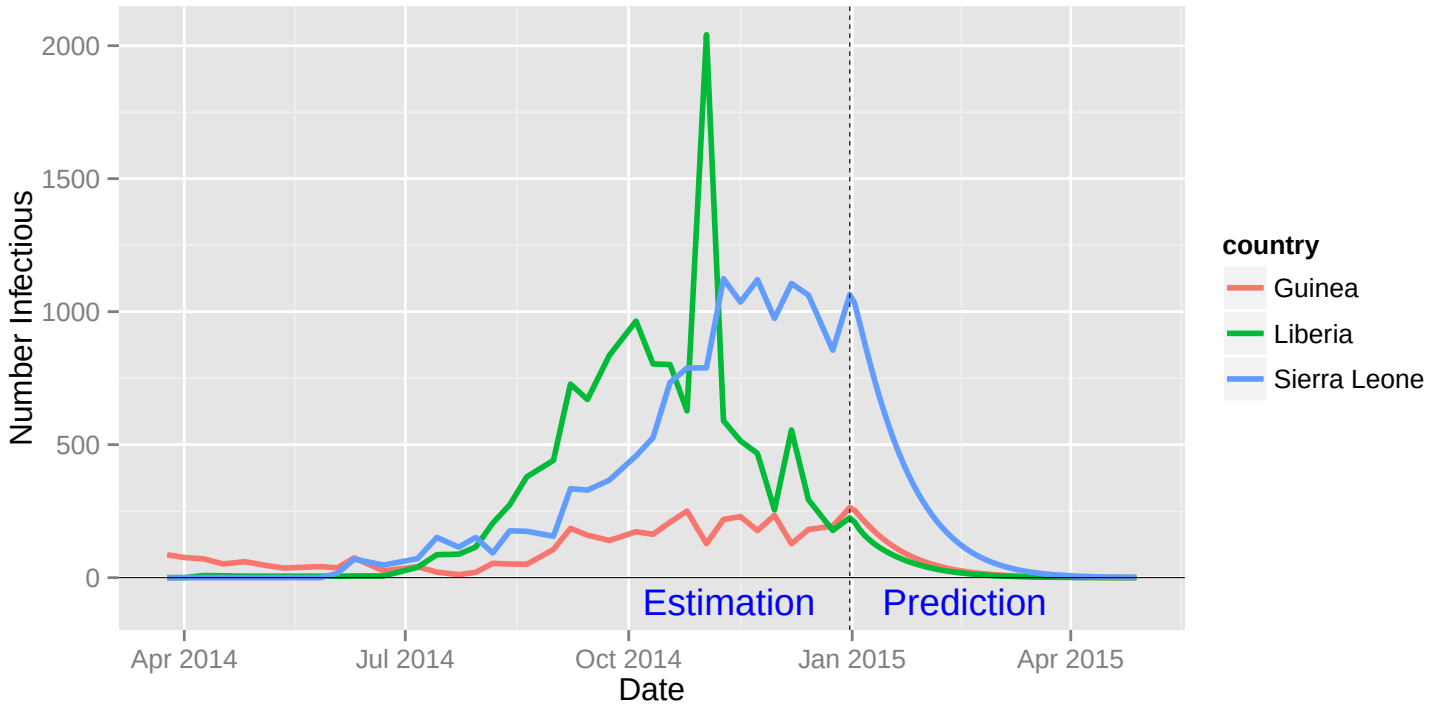


Final Model: Spline Basis Illustration



Final Model: Resulting Predictions

Figure : Number of Currently Infectious Individuals - Estimated and Predicted



Conclusions: Ebola

- Must be very cautious
  - No true prior belief in form of spline basis, so extrapolation is questionable
  - Degree, type, and changes in underreporting are unclear
  - The potential for a widespread outbreak in a fourth country is not addressed
- Nevertheless, we consider the results weak evidence that, large changes in population behavior or international intervention notwithstanding, the epidemic should begin continue to decline in the near future.
- Best prediction for epidemic containment is April/May, but reliable estimates of the probability of this event are not available.

Conclusions: $\mathcal{R}^{(EA)}$

- While traditional reproductive numbers are invaluable, they can perform poorly in certain circumstances.
- It seems wise to compare these values with $\mathcal{R}^{(EA)}$, especially given its ease of computation.
- Empirically adjusted measures can help with model selection, and give more specific lack of fit feedback than aggregate measures like BIC/DIC. This is particularly important given the computational challenges involved.
- Clearly, a reliance on graphical comparison is not ideal - more work remains to be done quantifying this model selection role.

Future Work in Compartmental Models

- Further exploration of context specific empirically adjusted reproductive numbers ($\mathcal{R}_0^{(EA)}$)
- Improve sampling algorithms, explore alternate posterior approximation techniques
  - Currently, computations are fast, but inefficient.
  - Placing the work in a context which could benefit more directly from parallelization seems promising.
- Add optional enhancements for sparse distance matrices (using Eigen)
- Create more general compartmental modeling software.
  - libSpatialSEIR is already modular, but only within the SEIR(S) framework
  - The building blocks of compartmental models are relatively simple:
    - Input compartment(s)
    - Output compartment(s)
    - Transition probability structure(s)

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