Lesson 7: Case study: ebola

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Objectives I

1. To explore the use of POMP models in the context of an out emerging infectious disease.
2. To demonstrate the use of diagnostic probes for model crit
3. To illustrate some forecasting methods based on POMP model
4. To provide an example that can be modified to apply simila to other outbreaks of emerging infectious diseases.

This lesson follows King et al. (2015), all codes for which are available on datadryad.org.

An emerging infectious disease outbreak I

Let's situate ourselves at the beginning of October 2014. The WHO situation report contained data on the number of cases in each of Guinea, Sierra Leone, and Liberia. Key questions included:

1. `How fast will the outbreak unfold?`
2. `How large will it ultimately prove?`
3. `What interventions will be most effective?`

As is to be expected in the case of a fast-moving outbreak of a novel pathogen in an underdeveloped country, the answers to these questions were sought in a context far from ideal:

- Case ascertainment is difficult and the case definition itself may be evolving.
- Surveillance effort is changing on the same timescale as the outbreak itself.

An emerging infectious disease outbreak II

- The public health and behavioral response to the outbreak is rapidly changing.

Best practices I

- The King et al. (2015) paper focused critical attention on the economical and therefore common practice of fitting deterministic transmission models to cumulative incidence data.
- Specifically, @King2015 showed how this practice easily le
- The paper recommended the use of POMP models, for several

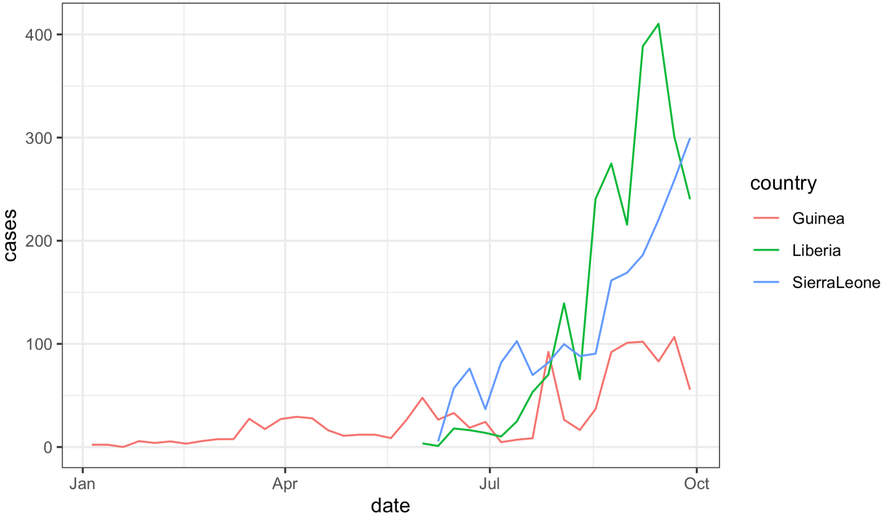
```
-

  Such models can accommodate a wide range of hypothetical for
-

  They can be readily fit to incidence data, especially during
-

  Stochastic models afford a more explicit treatment of uncert
-

  POMP models come with a number of diagnostic approaches buil
```

Situation-report data I

The data and pomp codes used to represent the transmission models are presented in a supplement.

The data we focus on here are from the WHO Situation Report of 1 October 2014. Supplementing these data are population estimates for the three countries.

Situation-report data II



SEIR model with gamma-distributed latent period I

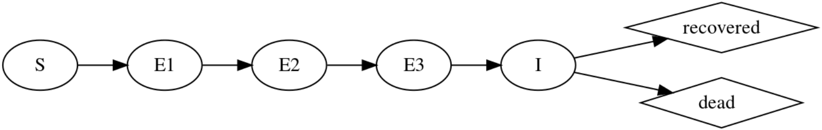
- Many of the early modeling efforts used variants on the simple SEIR model.
- Here, we'll focus on a variant that attempts a more carefu
- Specifically, this model assumes that the amount of time a

```
\begin{equation*}
  \mathrm{LP} \sim \dist{Gamma}{m,\frac{1}{m\,\alpha}},
\end{equation*}
```

where m is an integer.

- This means that the latent period has expectation $1/\alph
- We implement Gamma distributions using the so-called *line

SEIR model with gamma-distributed latent period II



The observations are modeled as a negative binomial process conditional on the number of infections. That is, if C_t are the reported cases at week t and H_t is the true incidence, then we postulate that $C_t|H_t$ is negative binomial with

$$\mathbb{E}\left[C_t|H_t\right] = \rho\, H_t$$

and

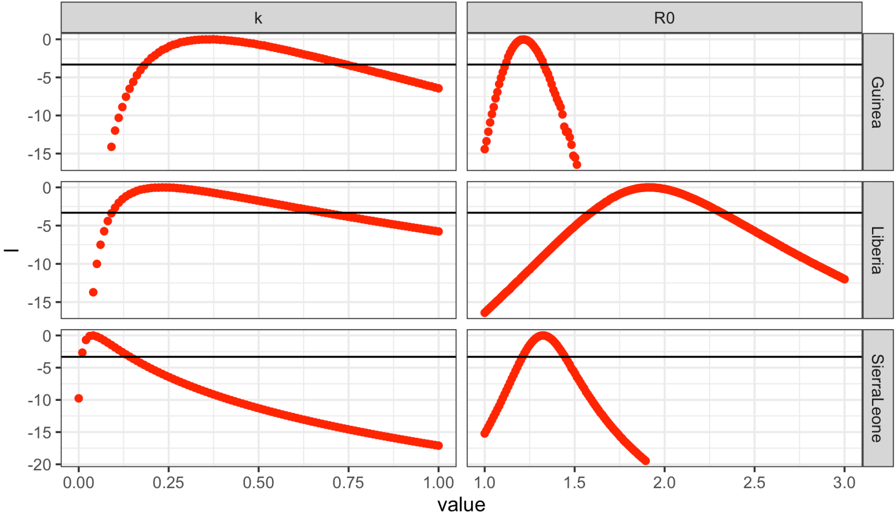
$$\mathrm{Var}\left[C_t|H_t\right] = \rho\, H_t\, (1 + k\, \rho\, H_t).$$

The negative binomial process allows for overdispersion in the counts. This overdispersion is controlled by parameter k.

Parameter estimates I

- King et al. (2015) estimated parameters for this model for each country.
- A Latin hypercube design was used to initiate a large numb
- Profile likelihoods were computed for each country against
- Full details are given [on the datadryad.org site](https:/
- Codes for this document are [available here](./codes.R).
  The results of these calculations are loaded and displayed
- The following are plots of the profile likelihoods.
  The horizontal line represents the critical value of the l

Parameter estimates II



Diagnostics *or* Model Criticism I

- Parameter estimation is the process of finding the parameters that are "best", in some sense, for a given model, from among the set of those that make sense for that model.
- Model selection, likewise, aims at identifying the "best" model, in some sense, from among a set of candidates.
- One can do both of these things more or less well, but no matter how carefully they are done, the best of a bad set of models is still bad.
- Let's investigate the model here, at its maximum-likelihood parameters, to see if we can identify problems.
- The guiding principle in this is that, if the model is "good", then the data are a plausible realization of that model.
- Therefore, we can compare the data directly against model simulations.

Diagnostics *or* Model Criticism II

- Moreover, we can quantify the agreement between simulations and data in any way we like.
- Any statistic, or set of statistics, that can be applied to the data can also be applied to simulations.
- Shortcomings of the model should manifest themselves as discrepancies between the model-predicted distribution of such statistics and their value on the data.
- pomp provides tools to facilitate this process.
- Specifically, the `probe` function applies a set of user-specified summary statistics or *probes*, to the model and the data, and quantifies the degree of disagreement in several ways.
- `Let's see how this is done using the model for the Guinean`

Model simulations I

From our profile-likelihood calculations, we extract the MLE:

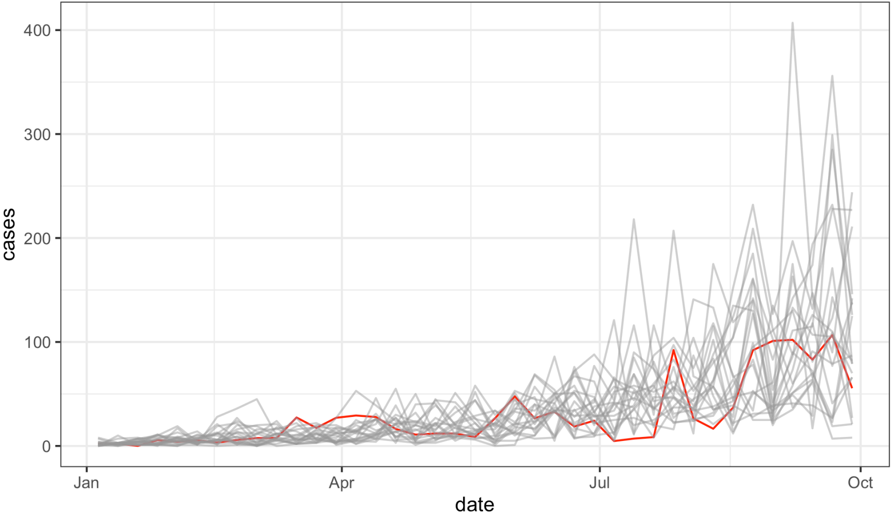
```
profs |>
  filter(country=="Guinea") |>
  filter(loglik==max(loglik)) |>
  select(-loglik,-loglik.se,-country,-profile) -> coef(gin)
```

Here, `profs` contains the profile-likelihood calculations displayed previously and `gin` is a pomp object containing the model and data for Guinea.
The following generates and plots some simulations on the same axes as the data.

Model simulations II

```
gin |>
  simulate(nsim=20,format="data.frame",include.data=TRUE) |>
  mutate(
    date=min(dat$date)+7*(week-1),
    is.data=ifelse(.id=="data","yes","no")
  ) |>
  ggplot(aes(x=date,y=cases,group=.id,color=is.data,alpha=is.
  geom_line()+
  guides(color="none",alpha="none")+
  scale_color_manual(values=c(no=gray(0.6),yes="red"))+
  scale_alpha_manual(values=c(no=0.5,yes=1))
```

Model simulations III



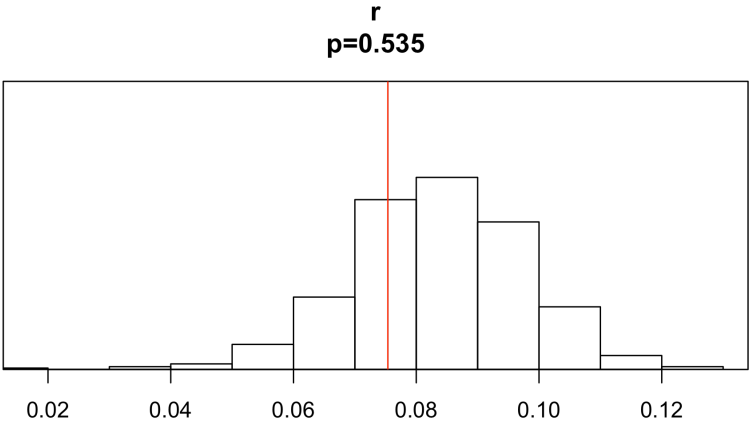
Diagnostic probes I

- Does the data look like it could have come from the model?
  - The simulations appear to be growing a bit more quickly than the data.
- Let's try to quantify this.
  - First, we'll write a function that estimates the exponential growth rate by linear regression.
  - Then, we'll apply it to the data and to 500 simulations.
- In the following, `gin` is a pomp object containing the model and the data from the Guinea outbreak.

Diagnostic probes II

```r
growth.rate <- function (y) {
  cases <- y["cases",]
  fit <- lm(log1p(cases)~seq_along(cases))
  unname(coef(fit)[2])
}

gin |>
  probe(probes=list(r=growth.rate),nsim=500) |>
  plot()
```

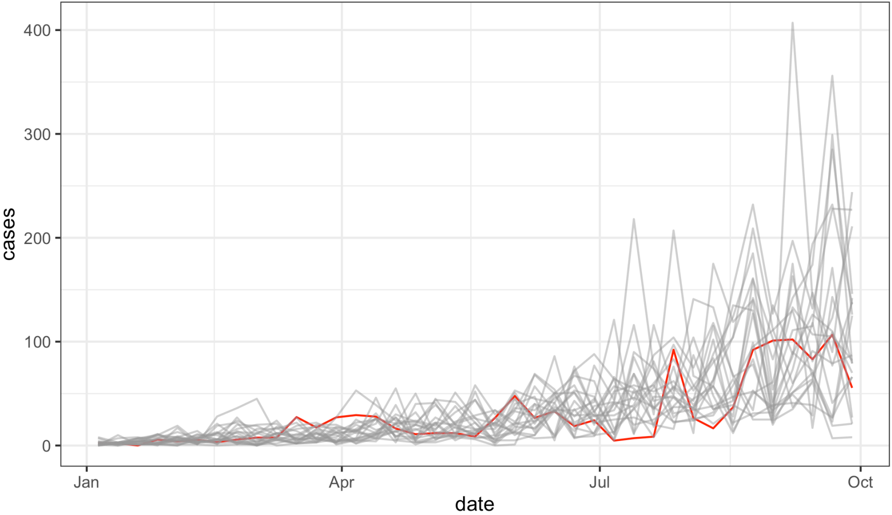
Diagnostic probes III



Diagnostic probes IV

- Do these results bear out our suspicion that the model and data differ in terms of growth rate?

Diagnostic probes V

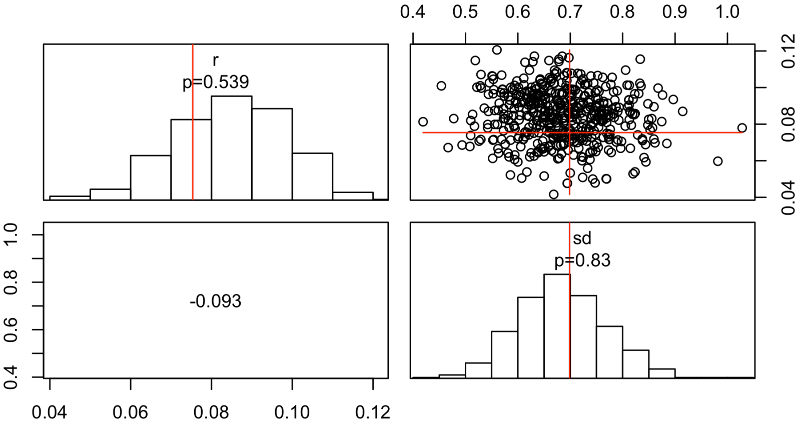


Diagnostic probes VI

- The simulations also appear to be more highly variable around the trend than do the data.

```
growth.rate.plus <- function (y) {
  cases <- y["cases",]
  fit <- lm(log1p(cases)~seq_along(cases))
  c(r=unname(coef(fit)[2]),sd=sd(residuals(fit)))
}

gin |>
  probe(probes=list(growth.rate.plus),nsim=500) |>
  plot()
```

Diagnostic probes VII



Diagnostic probes VIII

- Do we see evidence for lack of fit of model to data?
- Let's also look more carefully at the distribution of values about the trend using the 1st and 3rd quartiles.
- Also, it looks like the data are less jagged than the simulations. We can quantify this using the autocorrelation function (ACF).

Diagnostic probes IX

```
log1p.detrend <- function (y) {
  cases <- y["cases",]
  fit <- lm(log1p(cases)~seq_along(cases))
  y["cases",] <- as.numeric(residuals(fit))
  y
}

gin |>
  probe(nsim=500,
    probes=list(
      growth.rate.plus,
      probe_quantile(var="cases",prob=c(0.25,0.75)),
      probe_acf(var="cases",lags=c(1,2),type="correlation",
        transform=log1p.detrend)) |>
  plot()
```

The Sierra Leone outbreak

Apply probes to investigate the extent to which the SEIR model above is an adequate description of the data from the Sierra Leone outbreak. Have a look at the probes provided with pomp: `?basic.probes`. Try also to come up with some informative probes of your own. Discuss the implications of your findings.

Forecasting and forecasting uncertainty I

- To this point in the course, we've focused on using POMP models to answer scientific questions, i.e., to compare alternative hypothetical explanations for the data in hand.
- Of course, we can also use them to make forecasts.
- A set of key issues surrounds quantifying the forecast unc
- This arises from four sources:

1. measurement error
2. process noise
3. parametric uncertainty
4. structural uncertainty

Forecasting and forecasting uncertainty II

- Here, we'll explore how we can account for the first three of these in making forecasts for the Sierra Leone outbreak.

Parameter uncertainty I

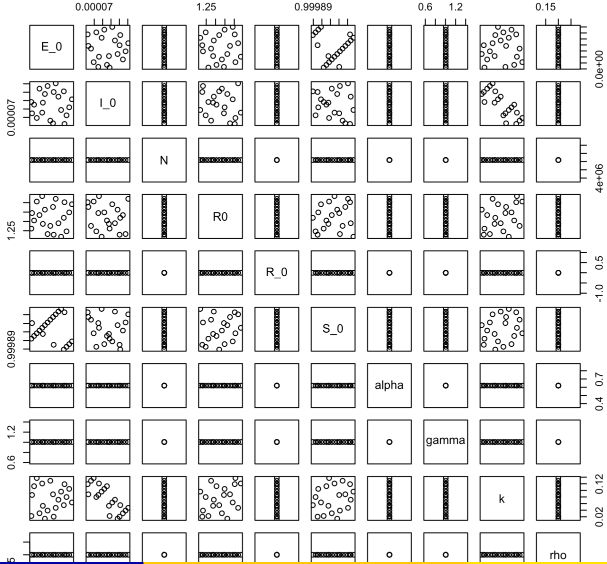
We take an *empirical Bayes* approach.
First, we set up a collection of parameter vectors in a neighborhood of the maximum likelihood estimate containing the region of high likelihood.

```
profs |>
  filter(country=="SierraLeone") |>
  select(-country,-profile,-loglik.se) |>
  filter(loglik>max(loglik)-0.5*qchisq(df=1,p=0.99)) |>
  gather(parameter,value) |>
  group_by(parameter) |>
  summarize(min=min(value),max=max(value)) |>
  ungroup() |>
  filter(parameter!="loglik") |>
  column_to_rownames("parameter") |>
  as.matrix() -> ranges
```

Parameter uncertainty II

```
sobol_design(
  lower=ranges[,"min"],
  upper=ranges[,"max"],
  nseq=20
) -> params
plot(params)
```

Parameter uncertainty III



Process noise and measurement error I

Next, we carry out a particle filter at each parameter vector, which gives us estimates of both the likelihood and the filter distribution at that parameter value.

```r
M1 <- ebolaModel("SierraLeone")

M1 |> pfilter(params=p,Np=2000,save.states=TRUE) -> pf
```

We extract the state variables at the end of the data for use as initial conditions for the forecasts.

Process noise and measurement error II

```
pf |>
  saved_states() |> ## latent state for each particle
  tail(1) |>        ## last timepoint only
  melt() |>         ## reshape and rename the state variab
  pivot_wider() |>
  group_by(.id) |>
  summarize(S_0=S, E_0=E1+E2+E3, I_0=I, R_0=R) |>
  pivot_longer(-.id) |>
  spread(.id,value) |>
  column_to_rownames("name") |>
  as.matrix() -> x
```

Process noise and measurement error III

The final states are now stored in x.
We simulate forward from the initial condition, up to the desired forecast horizon, to give a forecast corresponding to the selected parameter vector.
To do this, we first set up a matrix of parameters:

```
    pp <- parmat(unlist(p),ncol(x))
```

Then, we generate simulations over the "calibration period" (i.e., the time interval over which we have data). We record the likelihood of the data given the parameter vector:

Process noise and measurement error IV

```
M1 |>
  simulate(params=pp,format="data.frame") |>
  select(.id,week,cases) |>
  mutate(
    period="calibration",
    loglik=logLik(pf)
  ) -> calib
```

Now, we create a new pomp object for the forecasting.

```
M2 <- M1
time(M2) <- max(time(M1))+seq_len(horizon)
timezero(M2) <- max(time(M1))
```

Process noise and measurement error V

We set the initial conditions to the ones determined above and perform forecast simulations.

```
pp[rownames(x),] <- x

M2 |>
  simulate(params=pp,format="data.frame") |>
  select(.id,week,cases) |>
  mutate(
    period="projection",
    loglik=logLik(pf)
  ) -> proj
```

We combine the calibration and projection simulations into a single data frame.

Process noise and measurement error VI

```
    bind_rows(calib,proj) -> sims
```

We repeat this procedure for each parameter vector, binding the results into a single data frame. See this lesson's R script for details.
We give these prediction distributions weights proportional to the estimated likelihoods of the parameter vectors.

```
sims |>
  mutate(weight=exp(loglik-mean(loglik))) |>
  arrange(week,.id) -> sims
```

We verify that our effective sample size is large.

Process noise and measurement error VII

```
sims |>
  filter(week==max(week)) |>
  summarize(ess=sum(weight)^2/sum(weight^2))
```

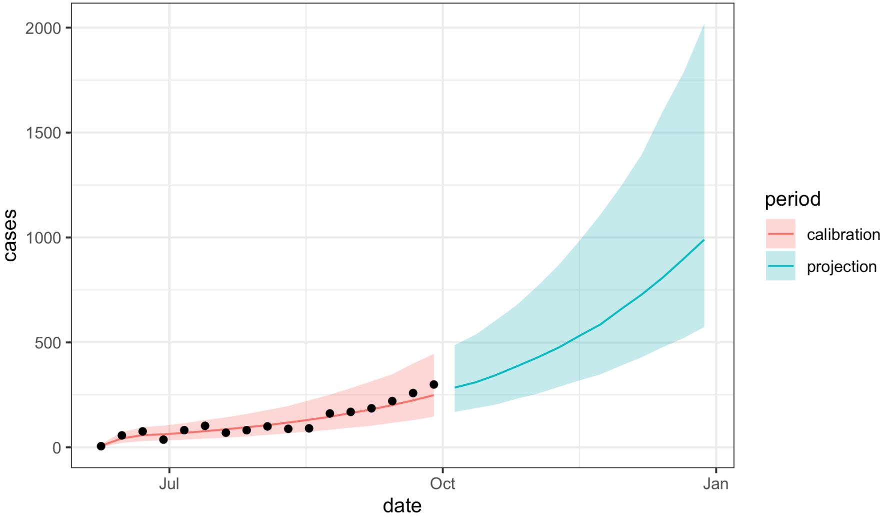
```
      ess
 10485.34
```

Finally, we compute quantiles of the forecast incidence.

Process noise and measurement error VIII

```
sims |>
  group_by(week,period) |>
  reframe(
    p=c(0.025,0.5,0.975),
    value=wquant(cases,weights=weight,probs=p),
    name=c("lower","median","upper")
  ) |>
  select(-p) |>
  pivot_wider() |>
  ungroup() |>
  mutate(date=min(dat$date)+7*(week-1)) -> simq
```

Process noise and measurement error IX



Decomposing the uncertainty

As we have discussed, the uncertainty shown in the forecasts above has three sources: parameter uncertainty, process noise, and measurement error. Show how you can break the total uncertainty into these three components. Produce plots similar to that above showing each of the components.

References I

King, Aaron A., Matthieu Domenech de Cellès, Felicia M. G. Magpantay, and Pejman Rohani. 2015. "Avoidable Errors in the Modelling of Outbreaks of Emerging Pathogens, with Special Reference to Ebola." *Proc R Soc Lond B* 282 (1806): 20150347. https://doi.org/10.1098/rspb.2015.0347.

License, acknowledgments, and links I

- This lesson is prepared for the Simulation-based Inference for Epidemiological Dynamics module at the Summer Institute in Statistics and Modeling in Infectious Diseases, SISMID.
- The materials build on previous versions of this course and related courses.
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- Produced with R version 4.4.0 and pomp version 5.9.
- Compiled on 2024-06-17.

Back to Lesson
Model construction supplement
R codes for this lesson