Lesson 4.
Case study:
Measles in large and small towns

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Contents

1 Introduction

Objectives

- To display a published case study using plug-and-play methods with non-trivial model complexities.

- To show how extra-demographic stochasticity can be modeled.

- To demonstrate the use of covariates in **pomp**.

- To demonstrate the use of profile likelihood in scientific inference.

- To discuss the interpretation of parameter estimates.

- To emphasize the potential need for extra sources of stochasticity in modeling.

1.1 Motivation

Challenges in inference from disease dynamics

- Understanding, forecasting, managing epidemiological systems increasingly depends on models.

- Dynamic models can be used to test causal hypotheses.

- Real epidemiological systems:

    - are nonlinear
    - are stochastic
    - are nonstationary
    - evolve in continuous time
    - have hidden variables

- can be measured only with (large) error

- Dynamics of infectious disease outbreaks illustrate this well.

- Measles is the paradigm for a nonlinear ecological system that can be well described by low-dimensional nonlinear dynamics.

- A tradition of careful modeling studies have proposed and found evidence for a number of specific mechanisms, including

  - a high value of R_0 (c. 15–20)
  - under-reporting
  - seasonality in transmission rates associated with school terms
  - response to changing birth rates
  - a birth-cohort effect
  - metapopulation dynamics
  - fadeouts and reintroductions that scale with city size
  - spatial traveling waves

- Much of this evidence has been amassed from fitting models to data, using a variety of methods.

- See Rohani and King (2010) for a review of some of the high points.

1.2 Case study

Measles in England and Wales

- We revisit a classic measles data set, weekly case reports in 954 urban centers in England and Wales during the pre-vaccine era (1950–1963).

- We examine questions regarding:

- measles extinction and recolonization

- transmission rates

- seasonality

- resupply of susceptibles

- We use a model that

  1. expresses our current understanding of measles dynamics
  2. includes a long list of mechanisms that have been proposed and demonstrated in the literature
  3. cannot be fit by existing likelihood-based methods

- We examine data from large and small towns using the same model, something no existing methods have been able to do.

- We ask: does our perspective on this disease change when we expect the models to explain the data in detail?

- What bigger lessons can we learn regarding inference for dynamical systems?

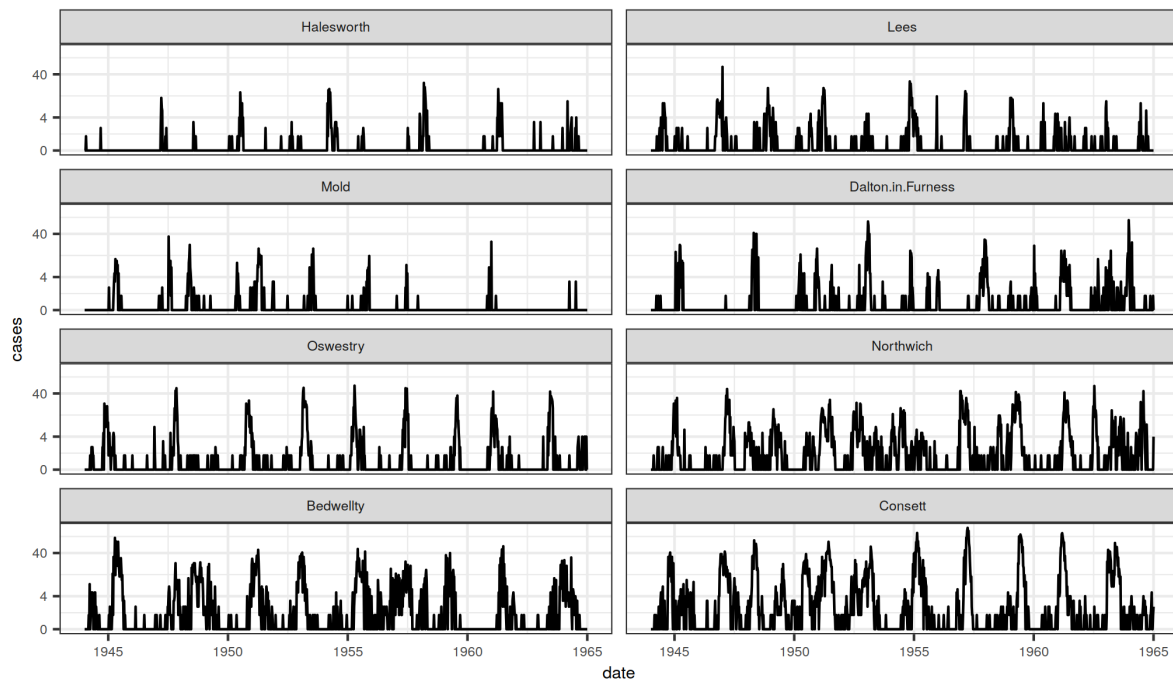**He, Ionides, & King, *J. R. Soc. Interface* (2010)**
Data sets:

- Twenty towns, including

  - 10 largest
  - 10 smaller, chosen at random

- Population sizes: 2k–3.4M

- Weekly case reports, 1950–1963

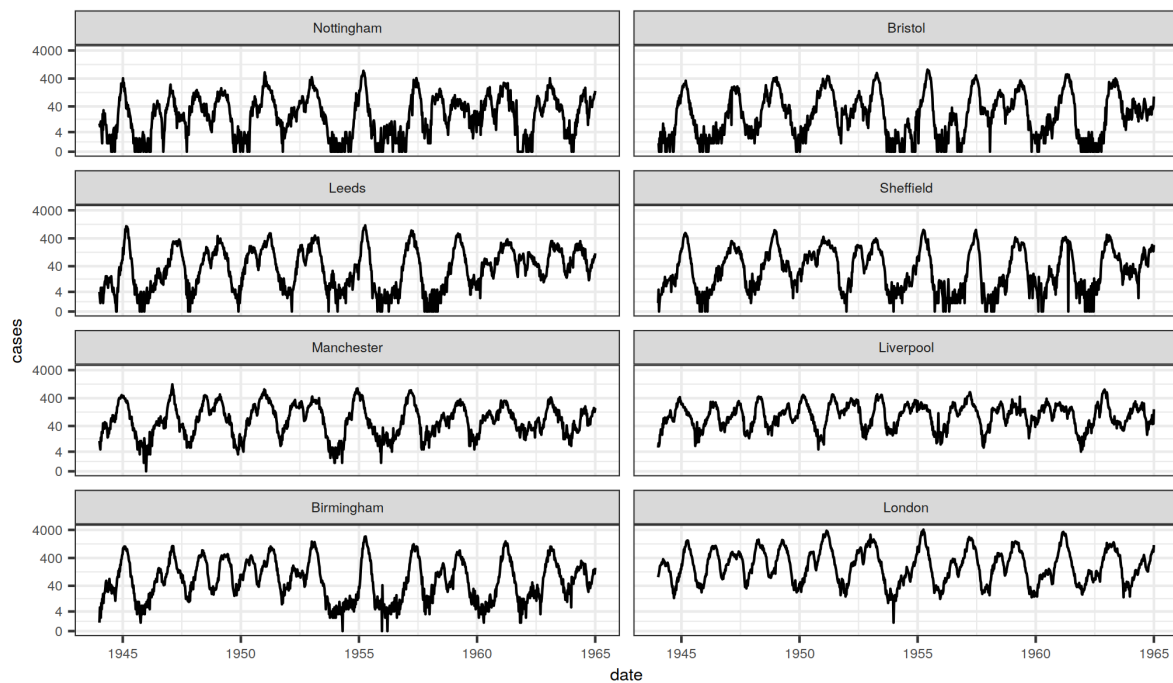- Annual birth records and population sizes, 1944–1963

Map of cities in the analysis

City case counts I: smallest 8 cities

City case counts II: largest 8 cities

Continuous-time Markov process model

Continuous-time Markov process model

- Covariates:
  - $B(t) = $ birth rate, from data
  - $N(t) = $ population size, from data
- Entry into susceptible class:

$$\mu_{BS}(t) = (1-c)\,B(t-\tau) + c\,\delta(t-\lfloor t\rfloor)\int_{t-1}^{t} B(t-\tau-s)\,ds$$

  - $c = $ cohort effect
  - $\tau = $ school-entry delay
  - $\lfloor t\rfloor = $ most recent 1 September before t
- Force of infection:
$$\mu_{SE}(t) = \tfrac{\beta(t)}{N(t)}\,(I+\iota)\,\zeta(t)$$

  - $\iota = $ imported infections
  - $\zeta(t) = $ Gamma white noise with intensity σ_{SE} [He *et al.* (2010); Bhadra *et al.* (2011)]
  - school-term transmission:

$$\beta(t) = \begin{cases} \beta_0\left(1+a(1-p)/p\right) & \text{during term} \\ \beta_0\left(1-a\right) & \text{during vacation} \end{cases}$$

    * $a = $ amplitude of seasonality
    * $p = 0.7589$ is the fraction of the year children are in school.
    * The factor $(1-p)/p$ ensures that the average transmission rate is β_0.

- Overdispersed binomial measurement model: $\text{cases}_t \mid \Delta N_{IR} = z_t \sim \text{Normal}\left(\rho\,z_t,\,\rho\,(1-\rho)\,z_t + (\psi\,\rho\,z_t)^2\right)$

Implementation in pomp

- We'll load the packages we'll need, and set the random seed, to allow reproducibility.

- Note that we'll be making heavy use of the **tidyverse** methods.

- Also, we'll be using **ggplot2** for plotting: see this brief tutorial.

- Finally, we'll use the convenient **magrittr** syntax, which is explained here.

Data and covariates

- We load the data and covariates. The data are measles reports from 20 cities in England and Wales.

- We also have information on the population sizes and birth-rates in these cities; we'll treat these variables as covariates.

- We will illustrate the pre-processing of the measles and demography data using London as an example.

Data and covariate plots
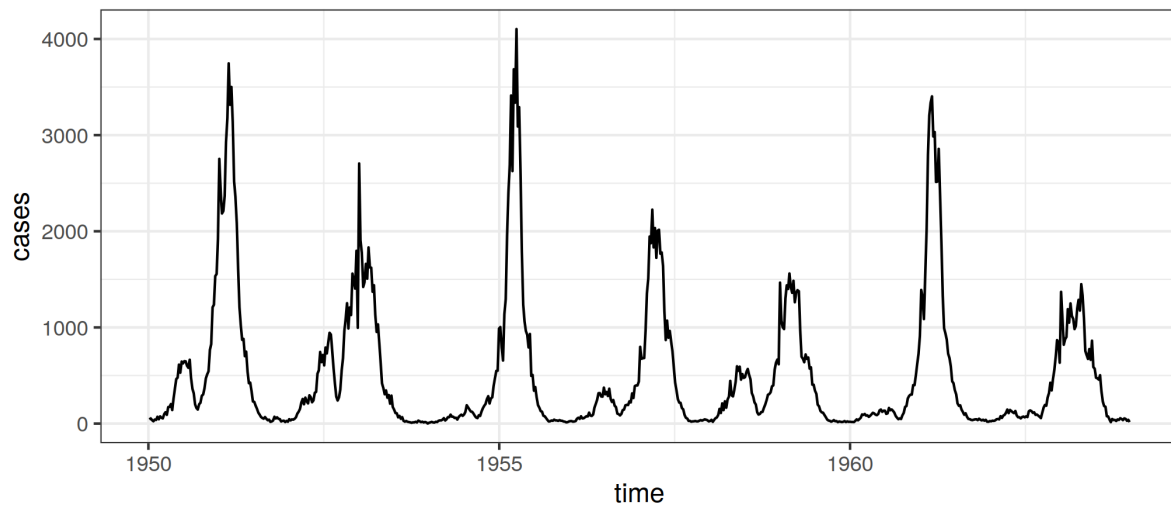
Now, we smooth the covariates. Note that we delay the entry of newborns into the susceptible pool.
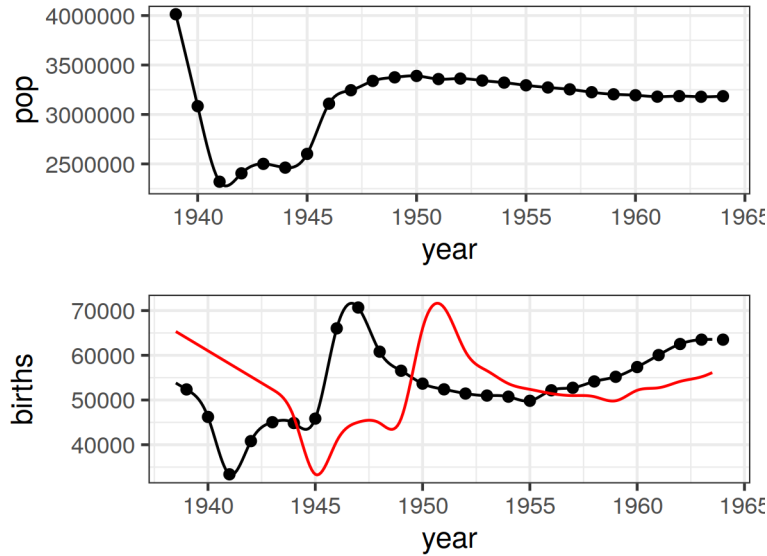
The partially observed Markov process model

We require a simulator for our model. Notable complexities include:

1. Incorporation of the known birthrate.

2. The birth-cohort effect: a specified fraction (`cohort`) of the cohort enter the susceptible pool all at once.

3. Seasonality in the transmission rate: during school terms, the transmission rate is higher than it is during holidays.

4. Extra-demographic stochasticity in the form of a Gamma white-noise term acting multiplicatively on the force of infection.

5. Demographic stochasticity implmented using Euler-multinomial distributions.

Implementation of the process model

```
double beta, br, seas, foi, dw, births;
double rate[6], trans[6];

// cohort effect
if (fabs(t-floor(t)-251.0/365.0) < 0.5*dt)
  br = cohort*birthrate/dt + (1-cohort)*birthrate;
else
      br = (1.0-cohort)*birthrate;

// term-time seasonality
t = (t-floor(t))*365.25;
if ((t>=7&&t<=100) ||
    (t>=115&&t<=199) ||
    (t>=252&&t<=300) || (t>=308&&t<=356))
    seas = 1.0+amplitude*0.2411/0.7589;
else
    seas = 1.0-amplitude;
```

```
// transmission rate
beta = R0*(gamma+mu)*seas;
// expected force of infection
foi = beta*pow(I+iota,alpha)/pop;
// white noise (extrademographic stochasticity)
dw = rgammawn(sigmaSE,dt);
rate[0] = foi*dw/dt;  // stochastic force of infection
rate[1] = mu;                     // natural S death
rate[2] = sigma;              // rate of ending of latent stage
rate[3] = mu;                     // natural E death
rate[4] = gamma;             // recovery
rate[5] = mu;                     // natural I death


// Poisson births
births = rpois(br*dt);
```

```
// transitions between classes
reulermultinom(2,S,&rate[0],dt,&trans[0]);
reulermultinom(2,E,&rate[2],dt,&trans[2]);
reulermultinom(2,I,&rate[4],dt,&trans[4]);

S += births   - trans[0] - trans[1];
E += trans[0] - trans[2] - trans[3];
I += trans[2] - trans[4] - trans[5];
R = pop - S - E - I;
W += (dw - dt)/sigmaSE;  // standardized i.i.d. white noise
C += trans[4];           // true incidence
```

- In the above, C represents the true incidence, i.e., the number of new infections occurring over an interval.

- Since recognized measles infections are quarantined, we argue that most infection occurs before case recognition so that true incidence is a measure of the number of individuals progressing from the I to the R compartment in a given interval.

State initializations
We complete the process model definition by specifying the distribution of initial unobserved states. The following codes assume that the fraction of the population in each of the four compartments is known.

```
rinit <- Csnippet("
double m = pop/(S_0+E_0+I_0+R_0);
S = nearbyint(m*S_0);
E = nearbyint(m*E_0);
I = nearbyint(m*I_0);
R = nearbyint(m*R_0);
W = 0;
C = 0;
")
```

The measurement model I

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- We'll model both under-reporting and measurement error.

- We want $\mathbb{E}[\text{cases}|C] = \rho\,C$, where C is the true incidence and $0 < \rho < 1$ is the reporting efficiency.

- We'll also assume that $\mathrm{Var}[\text{cases}|C] = \rho\,(1-\rho)\,C + (\psi\,\rho\,C)^2$, where ψ quantifies overdispersion.

- Note that when $\psi = 0$, the variance-mean relation is that of the binomial distribution. To be specific, we'll choose cases—$C \sim f(\cdot|\rho,\psi,C)$, where

$$f(c|\rho,\psi,C)$$
$$=\Phi(c+\tfrac{1}{2},\rho\,C,\rho\,(1-\rho)\,C + (\psi\,\rho\,C)^2)-$$
$$\Phi(c-\tfrac{1}{2},\rho\,C,\rho\,(1-\rho)\,C + (\psi\,\rho\,C)^2)$$

where $\Phi(x,\mu,\sigma^2)$ is the c.d.f. of the normal distribution with mean μ and variance σ^2.

The measurement model II
The following computes $\mathbb{P}[\text{cases}|C]$.

```
dmeas <- Csnippet("
double m = rho*C;
double v = m*(1.0-rho+psi*psi*m);
double tol = 1.0e-18;
if (cases > 0.0) {
  lik = pnorm(cases+0.5,m,sqrt(v)+tol,1,0)-pnorm(cases-0.5,m,sqrt(v)+tol,1,0)+tol;
} else {
  lik = pnorm(cases+0.5,m,sqrt(v)+tol,1,0)+tol;
}
")
```

Case simulations
The following codes simulate cases$|C$.

```
rmeas <- Csnippet("
double m = rho*C;
double v = m*(1.0-rho+psi*psi*m);
double tol = 1.0e-18;
cases = rnorm(m,sqrt(v)+tol);
if (cases > 0.0) {
  cases = nearbyint(cases);
} else {
  cases = 0.0;
}
")
```

Constructing the 'pomp' object

```
dat %>%
  pomp(t0=with(dat,2*time[1]-time[2]),
       time="time",
       rprocess=euler(Csnippet(rproc),delta.t=1/365.25),
       rinit=rinit,
       dmeasure=dmeas,
       rmeasure=rmeas,
```

```
    covar=covariate_table(covar,times="time"),
    accumvars=c("C","W"),
    statenames=c("S","E","I","R","C","W"),
    paramnames=c("R0","mu","sigma","gamma","alpha","iota",
                 "rho","sigmaSE","psi","cohort","amplitude",
                 "S_0","E_0","I_0","R_0")
    ) -> m1
```

Estimates from He *et al.* (2010)

He *et al.* (2010) estimated the parameters of this model. The full set is included in the R code accompanying this document, where they are read into a data frame called `mles`.

We verify that we get the same likelihood as He *et al.* (2010). Change eval to T

```
library(foreach)
library(doParallel)
library(doRNG)

registerDoParallel()
registerDoRNG(998468235L)

foreach(i=1:4) %dopar% {
  library(pomp)
  pfilter(m1,Np=10000,params=theta)
} -> pfs
logmeanexp(sapply(pfs,logLik),se=TRUE)
```
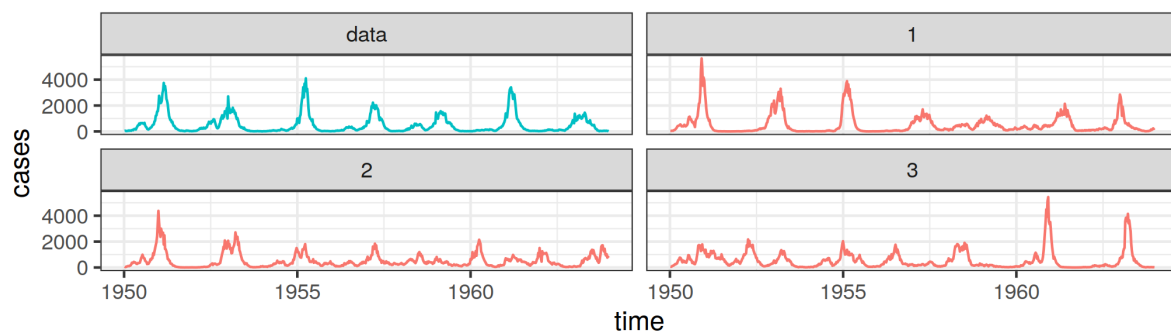
Simulations at the MLE

```
m1 %>%
  simulate(params=theta,nsim=3,format="d",include.data=TRUE) %>%
  ggplot(aes(x=time,y=cases,group=.id,color=(.id=="data")))+
  guides(color=FALSE)+
  geom_line()+facet_wrap(~.id,ncol=2)
```


Parameter transformations

- The parameters are constrained to be positive, and some of them are constrained to lie between 0 and 1.

- We can turn the likelihood maximization problem into an unconstrained maximization problem by transforming the parameters.

- Specifically, to enforce positivity, we log transform, to constrain parameters to $(0, 1)$, we logit transform, and to confine parameters to the unit simplex, we use the log-barycentric transformation.

```
pt <- parameter_trans(
  log=c("sigma","gamma","sigmaSE","psi","R0"),
  logit=c("cohort","amplitude"),
  barycentric=c("S_0","E_0","I_0","R_0")
)
m1 %>%
  pomp(partrans=pt,
       statenames=c("S","E","I","R","C","W"),
       paramnames=c("R0","mu","sigma","gamma","alpha","iota",
                    "rho","sigmaSE","psi","cohort","amplitude",
                    "S_0","E_0","I_0","R_0")) -> m1
```

Results from He *et al.* (2010)
The linked document shows how a likelihood profile can be constructed using IF2 The fitting procedure used is as follows:
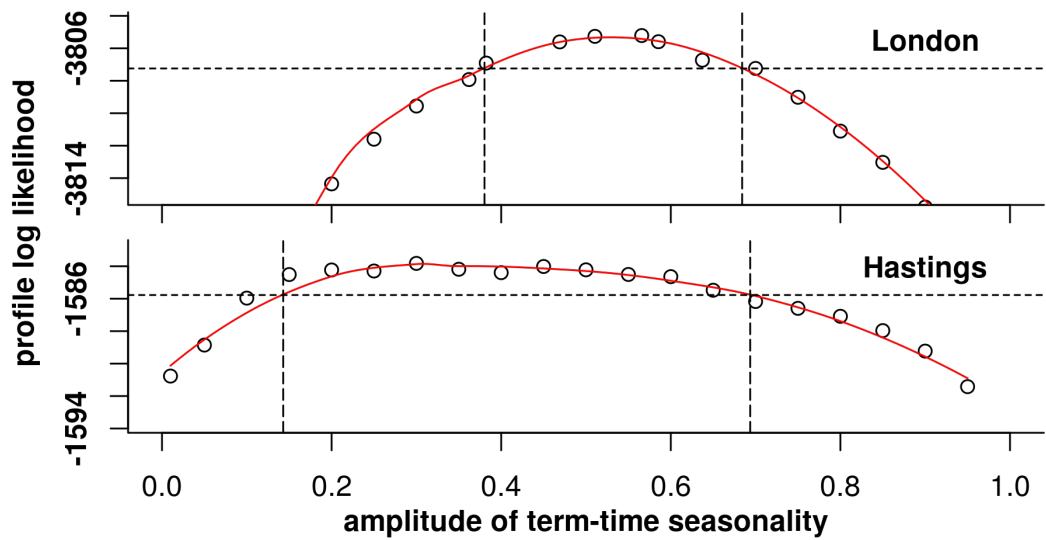
- A large number of searches were started at points across the parameter space.

- Iterated filtering was used to maximize the likelihood.

- We obtained point estimates of all parameters for 20 cities.

- We constructed profile likelihoods to quantify uncertainty in London and Hastings.
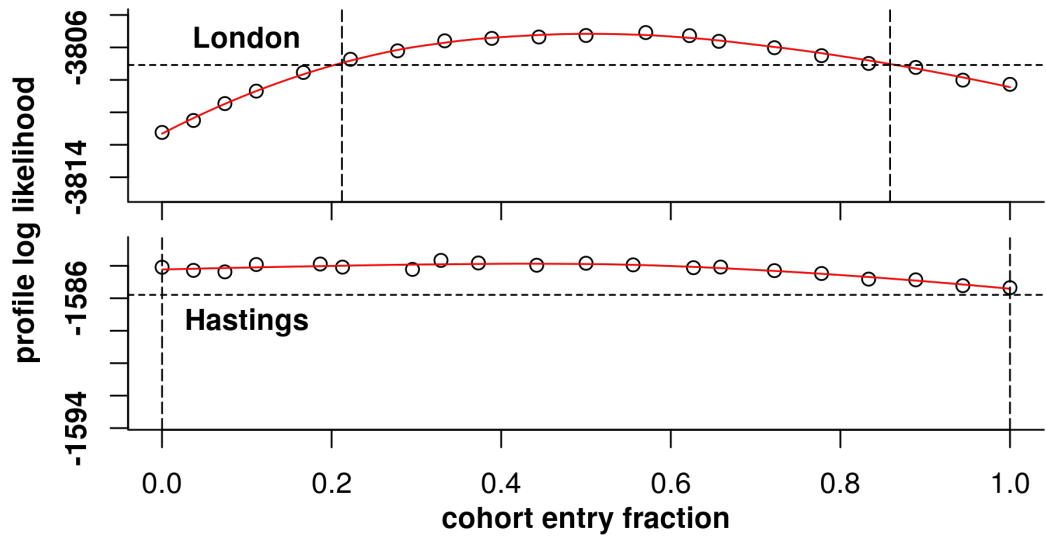
Imported infections

$$\text{force of infection} = \mu_{SE} = \frac{\beta(t)}{N(t)} \left(I + \iota \right) \zeta(t)$$
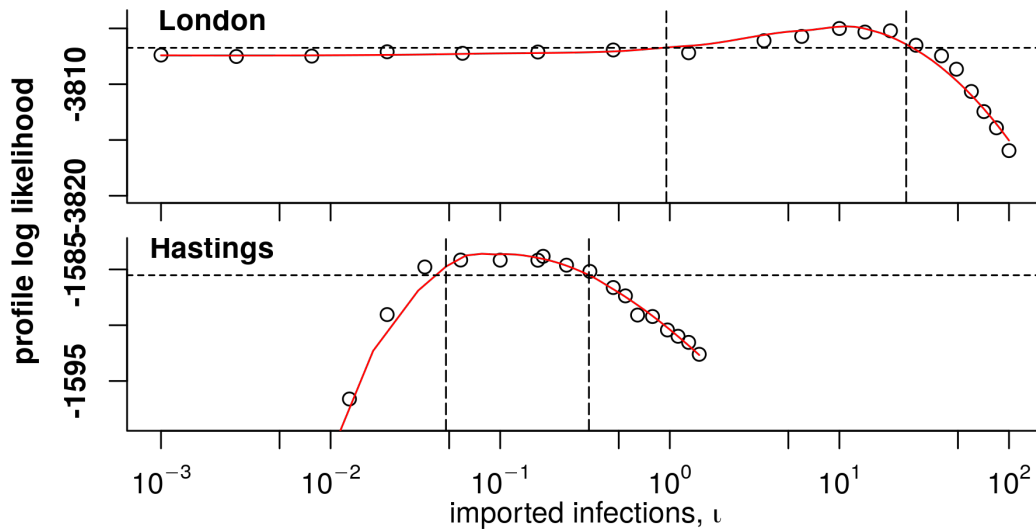
Seasonality

Notable findings

Cohort effect

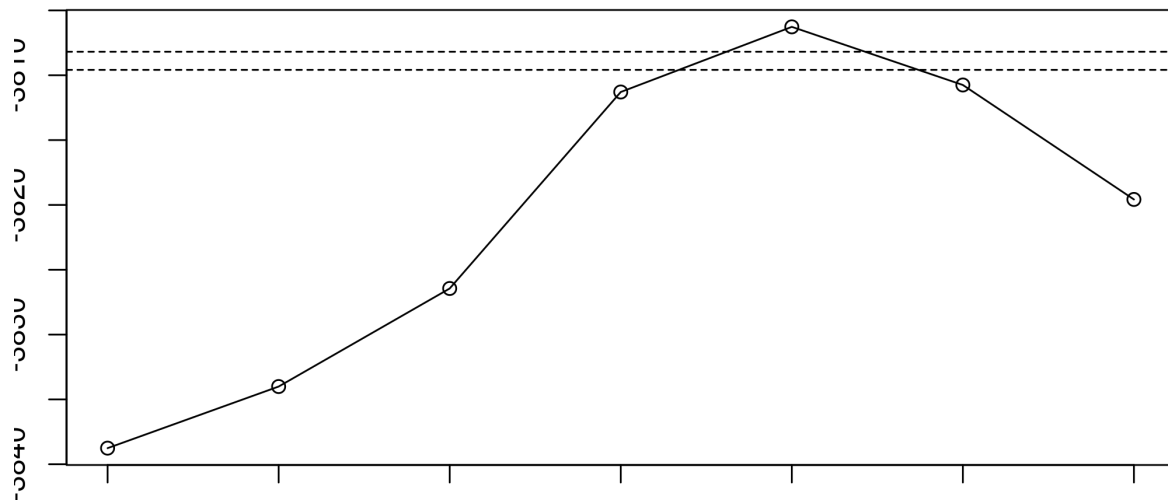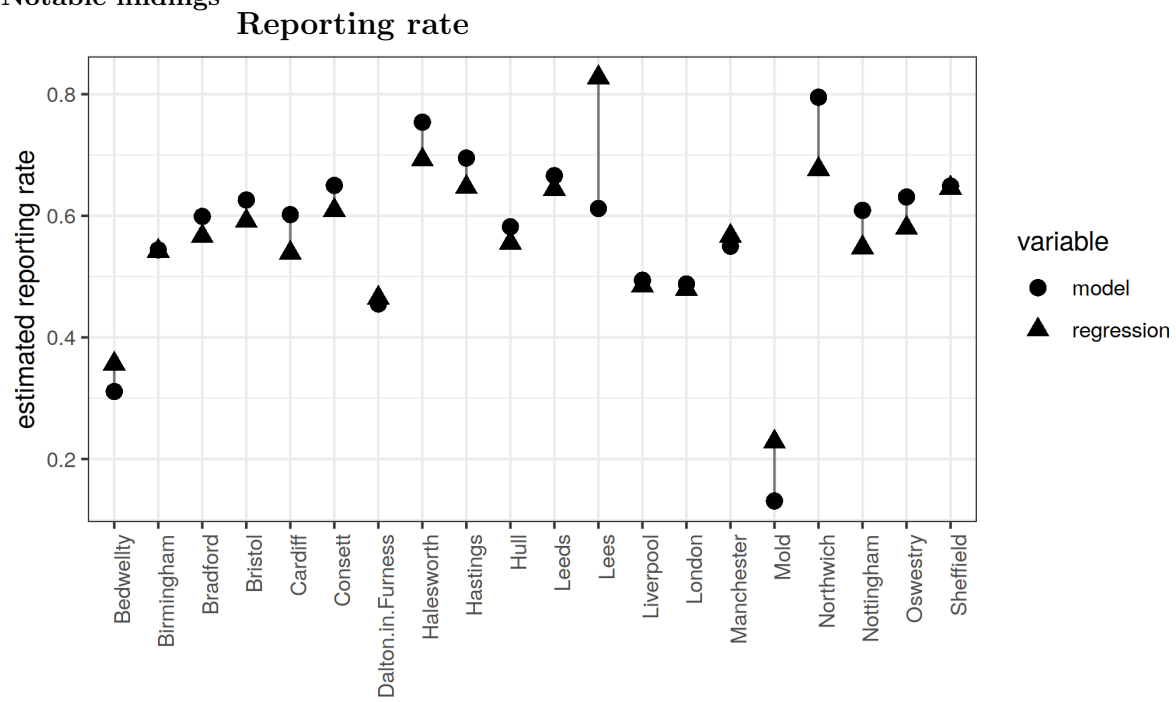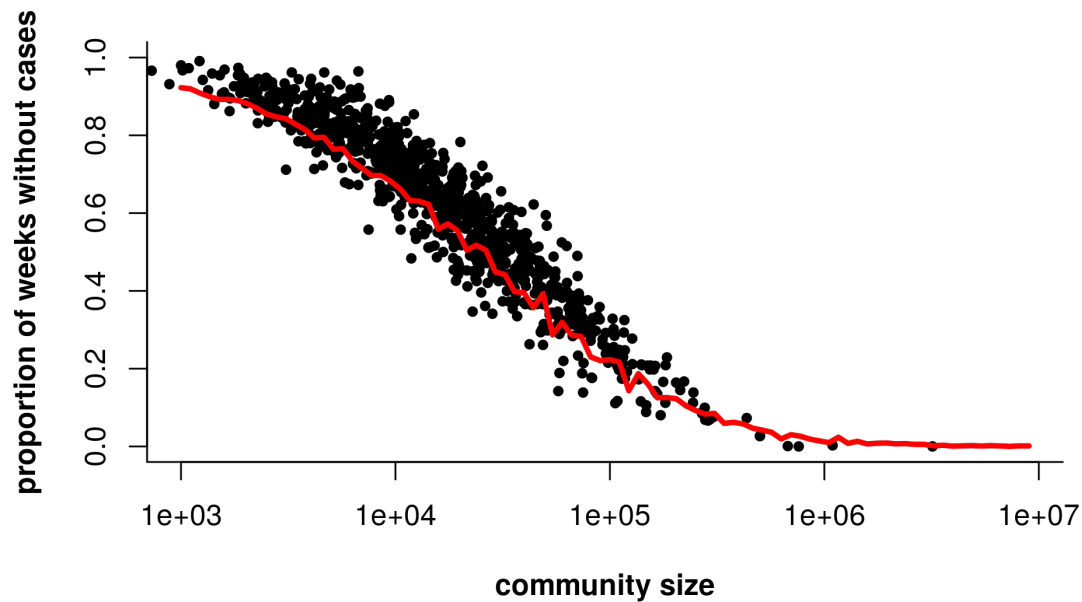**Notable findings**

Birth delay

Figure 1: Profile likelihood for birth-cohort delay, showing 95% and 99% critical values of the log likelihood.
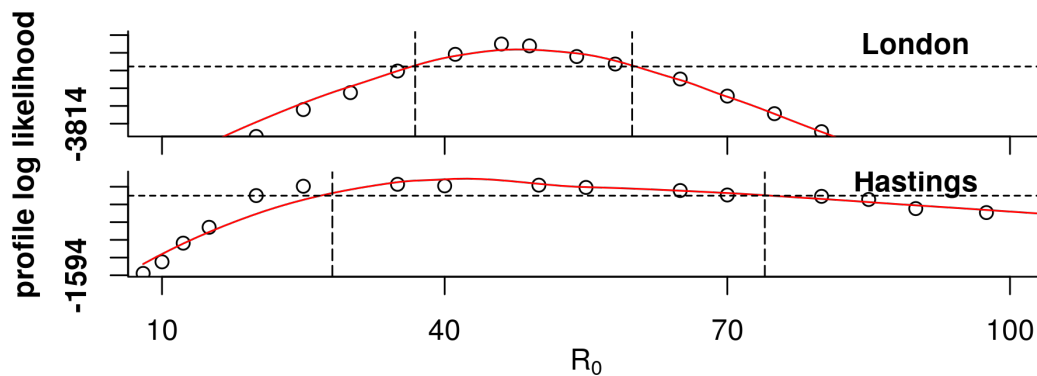
Notable findings

Notable findings

Predicted vs observed critical community size

Problematic results

R_0 estimates inconsistent with literature

- Recall that R_0 : a measure of how communicable an infection is.

- Existing estimates of R_0 (c. 15–20) come from two sources: serology surveys, and models fit to data using feature-based methods.

Problematic results

Parameter estimates

	pop	R0	amplitude	LP	IP
Halesworth	2170	33.100	0.381	7.870	2.290

```
Lees                 4250 29.700     0.153  8.510   2.050
Mold                 6410 21.400     0.271  5.930   1.780
Dalton.in.Furness   10600 28.300     0.203  5.480   1.980
Oswestry            11000 52.900     0.339 10.300   2.710
Northwich           18300 30.100     0.423  8.510   3.020
Bedwellty           28900 24.700     0.160  6.820   3.030
Consett             39100 35.900     0.200  9.080   2.660
Hastings            65700 34.200     0.299  7.000   5.440
Cardiff            245000 34.400     0.223  9.870   3.090
Bradford           294000 32.100     0.236  8.510   3.360
Hull               302000 38.900     0.221  9.180   5.460
Nottingham         307000 22.600     0.157  5.720   3.700
Bristol            443000 26.800     0.203  6.190   4.940
Leeds              510000 47.800     0.267  9.480  10.900
Sheffield          515000 33.100     0.313  7.230   6.380
Manchester         704000 32.900     0.290 11.100   6.940
Liverpool          802000 48.100     0.305  7.900   9.800
Birmingham        1120000 43.400     0.428  8.510  11.600
London            3390000 56.800     0.554 13.100  12.500
r                       NA  0.455    0.301  0.322   0.946
                  alpha   iota    rho    psi sigmaSE
Halesworth        0.948 0.00912  0.754  0.641  0.0748
Lees              0.968 0.03110  0.612  0.681  0.0802
Mold              1.040 0.01450  0.131  2.870  0.0544
Dalton.in.Furness 0.989 0.03860  0.455  0.818  0.0779
Oswestry          1.040 0.02980  0.631  0.476  0.0699
Northwich         0.948 0.06020  0.795  0.402  0.0857
Bedwellty         0.937 0.03960  0.311  0.951  0.0611
Consett           1.010 0.07310  0.650  0.406  0.0712
Hastings          1.000 0.18600  0.695  0.396  0.0955
Cardiff           0.996 0.14100  0.602  0.270  0.0539
Bradford          0.991 0.24400  0.599  0.190  0.0451
Hull              0.968 0.14200  0.582  0.256  0.0636
Nottingham        0.982 0.17000  0.609  0.258  0.0380
Bristol           1.010 0.44100  0.626  0.201  0.0392
Leeds             1.000 1.25000  0.666  0.167  0.0778
Sheffield         1.020 0.85300  0.649  0.175  0.0428
Manchester        0.965 0.59000  0.550  0.161  0.0551
Liverpool         0.978 0.26300  0.494  0.136  0.0533
Birmingham        1.010 0.34300  0.544  0.178  0.0611
London            0.976 2.90000  0.488  0.116  0.0878
r                 0.106 0.93200 -0.203 -0.931 -0.3260
```
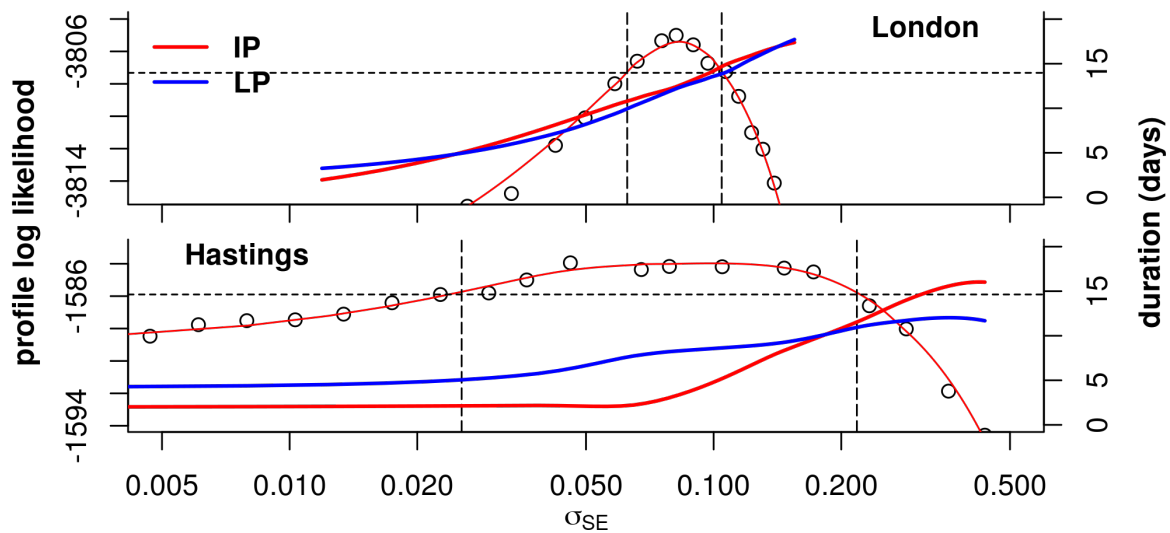
$r = \mathrm{cor}(\log \hat{\theta}, \log N_{1950})$

**Problematic results**

Extrademographic stochasticity

$$\mu_{SE} = \frac{\beta(t)}{N(t)} \left(I + \iota \right) \zeta(t)$$
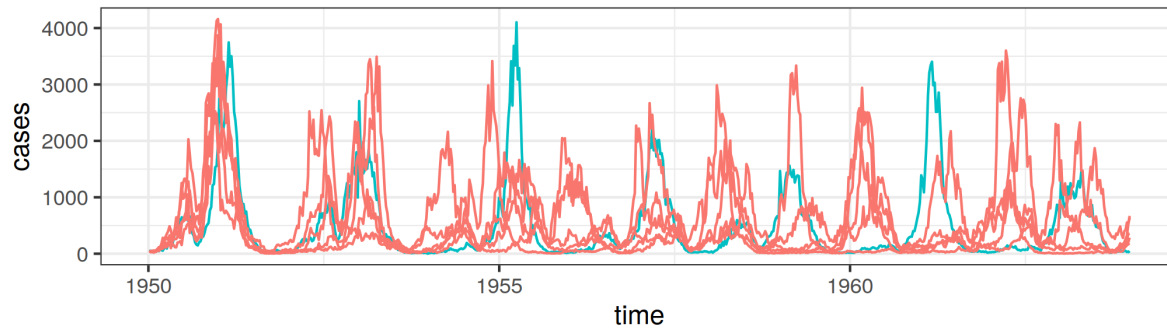
Questions

- What does it mean that parameter estimates from the fitting disagree with estimates from other data?

- How can one interpret the correlation between infectious period and city size in the parameter estimates?

- How do we interpret the need for extrademographic stochasticity in this model?

Simulations at the MLE
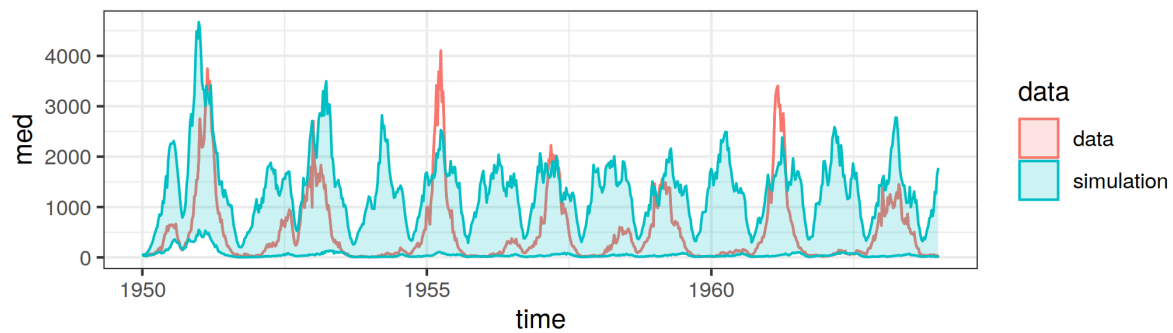
Exercise 4.1. Reformulate the model

- Modify the He *et al.* (2010) model to remove the cohort effect. Run simulations and compute likelihoods to convince yourself that the resulting codes agree with the original ones for 'cohort = 0'.

- Now modify the transmission seasonality to use a sinusoidal form. How many parameters must you use? Fixing the other parameters at their MLE values, compute and visualize a profile likelihood over these parameters.

Exercise 4.2. Extrademographic stochasticity

Set the extrademographic stochasticity parameter $\sigma_{SE} = 0$, set $\alpha = 1$, and fix ρ and ι at their MLE values, then maximize the likelihood over the remaining parameters.

- How do your results compare with those at the MLE? Compare likelihoods but also use simulations to diagnose differences between the models.

References

Bhadra A, Ionides EL, Laneri K, Pascual M, Bouma M, Dhiman R (2011). "Malaria in Northwest India: Data analysis via partially observed stochastic differential equation models driven by Lévy noise." *Journal of the American Statistical Association*, **106**, 440–451. doi: 10.1198/jasa.2011.ap10323.

He D, Ionides EL, King AA (2010). "Plug-and-play inference for disease dynamics: measles in large and small populations as a case study." *Journal of the Royal Society, Interface*, **7**, 271–283. doi: 10.1098/rsif.2009.0151.

Rohani P, King AA (2010). "Never mind the length, feel the quality: the impact of long-term epidemiological data sets on theory, application and policy." *Trends in Ecology & Evolution*, **25**(10), 611–618. doi: 10.1016/j.tree.2010.07.010.

License, acknowledgments, and links

- Produced with R version 4.0.2 and **pomp** version 3.0.2.1.