

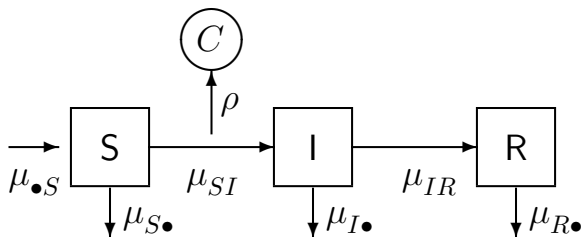
Objectives

This tutorial develops some classes of dynamic models relevant to biological systems, especially for epidemiology.

- 1 Dynamic systems can often be represented in terms of **flows** between **compartments**.
- 2 We develop the concept of a **compartmental model** for which we specify **rates** for the flows between compartments.
- 3 We show how deterministic and stochastic versions of a compartmental model are derived and related.
- 4 We introduce Euler's method to simulate from dynamic models.
- 5 We specify deterministic and stochastic compartmental models in `pomp` using Euler method simulation.

Introduction: The SIR model

- We develop deterministic and stochastic representations of a susceptible-infected-recovered (SIR) system, a fundamental class of models for disease transmission dynamics.
- We set up notation generalizing to more complex systems (Bretó et al.; 2009).



S : susceptible

R : recovered and/or removed

I : infected and infectious

C : reported cases

- We suppose that each arrow has an associated rate, so here there is a rate $\mu_{SI}(t)$ at which individuals in S transition to I , and μ_{IR} at which individuals in I transition to R .
- To account for demography (births/deaths/immigration/emmigration) we allow the possibility of a source and sink compartment, which is not usually represented on the flow diagram. We write $\mu_{\bullet S}$ for a rate of births into S , and denote mortality rates by $\mu_{S\bullet}$, $\mu_{I\bullet}$, $\mu_{R\bullet}$.
- The rates may be either constant or varying. In particular, for a simple SIR model, the recovery rate μ_{IR} is a constant but the infection rate has the time-varying form

$$\mu_{SI}(t) = \beta I(t),$$

with β being the **contact rate**. For the simplest SIR model, ignoring demography, we set

$$\mu_{\bullet S} = \mu_{S\bullet} = \mu_{I\bullet} = \mu_{R\bullet} = 0.$$

General notation for compartment models

- To develop a systematic notation, it turns out to be convenient to keep track of the flows between compartments as well as the number of individuals in each compartment. Let

$$N_{SI}(t)$$

count the number of individuals who have transitioned from S to I by time t . We say that $N_{SI}(t)$ is a **counting process**. A similarly constructed process

$$N_{IR}(t)$$

counts individuals transitioning from I to R . To include demography, we could keep track of birth and death events by the counting processes $N_{\bullet S}(t)$, $N_{S\bullet}(t)$, $N_{I\bullet}(t)$, $N_{R\bullet}(t)$.

- For discrete population compartment models, the flow counting processes are non-decreasing and integer valued.
- For continuous population compartment models, the flow counting processes are non-decreasing and real valued.

Recovering compartment processes from counting processes

- The numbers of people in each compartment can be computed via these counting processes. Ignoring demography, we have:

$$\begin{aligned}S(t) &= S(0) - N_{SI}(t) \\I(t) &= I(0) + N_{SI}(t) - N_{IR}(t) \\R(t) &= R(0) + N_{IR}(t)\end{aligned}$$

- These equations represent something like *conservation of mass*, or *what goes in must come out*.

The ordinary differential equation (ODE) interpretation of the SIR model

Together with initial conditions specifying $S(0)$, $I(0)$ and $R(0)$, we just need to write down ODEs for the flow counting processes. These are,

$$dN_{SI}/dt = \mu_{SI}(t) S(t),$$

$$dN_{IR}/dt = \mu_{IR} I(t).$$

The simple continuous-time Markov chain interpretation of the SIR model

- Continuous-time Markov chains are the basic tool for building discrete population epidemic models.
- The Markov property lets us specify a model by the transition probabilities on small intervals (together with the initial conditions). For the SIR model, we have

$$\begin{aligned}\mathbb{P}[N_{SI}(t + \delta) = N_{SI}(t) + 1] &= \mu_{SI}(t) S(t)\delta + o(\delta) \\ \mathbb{P}[N_{SI}(t + \delta) = N_{SI}(t)] &= 1 - \mu_{SI}(t) S(t)\delta + o(\delta) \\ \mathbb{P}[N_{IR}(t + \delta) = N_{IR}(t) + 1] &= \mu_{IR}(t) I(t)\delta + o(\delta) \\ \mathbb{P}[N_{IR}(t + \delta) = N_{IR}(t)] &= 1 - \mu_{IR}(t) I(t)\delta + o(\delta)\end{aligned}$$

- Here, we are using **little o notation**. We write $h(\delta) = o(\delta)$ to mean $\lim_{\delta \rightarrow 0} \frac{h(\delta)}{\delta} = 0$.

Question 2.1. What is the link between little o notation and the derivative?

Explain why

$$f(x + \delta) = f(x) + \delta g(x) + o(\delta)$$

is the same statement as

$$\frac{df}{dx} = g(x).$$

What considerations might help you choose which of these notations to use?

Simple counting processes

- A **simple counting process** is one which cannot count more than one event at a time.
- Technically, the SIR Markov chain model we have written is simple. One may want to model the extra randomness resulting from multiple simultaneous events: someone sneezing in a bus; large gatherings at football matches; etc. This extra randomness may even be critical to match the variability in data.
- Later in the course, we may see situations where this extra randomness plays an important role. Setting up the model using counting processes, as we have done here, turns out to be useful for this.

Euler's method for ordinary differential equations (ODEs)

- Euler (1707-1783) wanted a numeric solution of an ODE $dx/dt = h(x)$ with an initial condition $x(0)$.
- He supposed this ODE has some true solution $x(t)$ which could not be worked out analytically. He therefore wished to approximate $x(t)$ numerically.

- He initialized the numerical solution at the known starting value,

$$\tilde{x}(0) = x(0).$$

- For $k = 1, 2, \dots$, he supposed that the gradient dx/dt is approximately constant over the small time interval $k\delta \leq t \leq (k+1)\delta$.
- Therefore, he defined

$$\tilde{x}((k+1)\delta) = \tilde{x}(k\delta) + \delta h(\tilde{x}(k\delta)).$$

This only defines $\tilde{x}(t)$ when t is a multiple of δ , but suppose $\tilde{x}(t)$ is constant between these discrete times.

- We now have a numerical scheme, stepping forwards in time increments of size δ , that can be readily evaluated by computer (or by hand, if you are Euler).

Euler's method versus other numerical methods

- Mathematical analysis of Euler's method says that, as long as the function $h(x)$ is not too exotic, then $x(t)$ is well approximated by $\tilde{x}(t)$ when the discretization time-step, δ , is sufficiently small.
- Euler's method is not the only numerical scheme to solve ODEs. More advanced schemes have better convergence properties, meaning that the numerical approximation is closer to $x(t)$. However, there are 3 reasons we choose to lean heavily on Euler's method:
 - ① Euler's method is the simplest (following the KISS principle).
 - ② Euler's method extends naturally to stochastic models, both continuous-time Markov chains models and stochastic differential equation (SDE) models.
 - ③ Close approximation of the numerical solutions to a continuous-time model is less important than it may at first appear, a topic to be discussed.

Some comments on using continuous-time models and discretized approximations

- In some physical and engineering situations, a system follows an ODE model closely. For example, Newton's laws provide a very good approximation to the motions of celestial bodies.
- In many biological situations, ODE models only become close mathematical approximations to reality at reasonably large scale. On small temporal scales, models cannot usually capture the full scope of biological variation and biological complexity.
- If we are going to expect substantial error in using $x(t)$ to model a biological system, maybe the numerical solution $\tilde{x}(t)$ represents the system being modeled as well as $x(t)$ does.
- If our model fitting, model investigation, and final conclusions are all based on our numerical solution $\tilde{x}(t)$ (i.e., we are sticking entirely to simulation-based methods) then we are most immediately concerned with how well $\tilde{x}(t)$ describes the system of interest. $\tilde{x}(t)$ becomes more important than the original model, $x(t)$.

Using numerical solutions as scientific models

- It is important that a scientist fully describe the numerical model $\tilde{x}(t)$. Arguably, the main purpose of the original model $x(t)$ is to give a succinct description of how $\tilde{x}(t)$ was constructed.
- All numerical methods are, ultimately, discretizations. Epidemiologically, setting δ to be a day, or an hour, can be quite different from setting δ to be two weeks or a month. For continuous-time modeling, we still require that δ is small compared to the timescale of the process being modeled, so the choice of δ should not play an explicit role in the interpretation of the model.
- Putting more emphasis on the scientific role of the numerical solution itself reminds you that the numerical solution has to do more than approximate a target model in some asymptotic sense: the numerical solution should be a sensible model in its own right.

Euler's method for a discrete SIR model

- Recall the simple continuous-time Markov chain interpretation of the SIR model without demography:

$$\begin{aligned}\mathbb{P}[N_{SI}(t + \delta) = N_{SI}(t) + 1] &= \mu_{SI}(t) S(t)\delta + o(\delta), \\ \mathbb{P}[N_{IR}(t + \delta) = N_{IR}(t) + 1] &= \mu_{IR} I(t)\delta + o(\delta).\end{aligned}$$

- We look for a numerical solution with state variables $\tilde{S}(k\delta)$, $\tilde{I}(k\delta)$, $\tilde{R}(k\delta)$.
- The counting processes for the flows between compartments are $\tilde{N}_{SI}(t)$ and $\tilde{N}_{IR}(t)$. The counting processes are related to the numbers of individuals in the compartments by the same flow equations we had before:

$$\begin{aligned}\tilde{S}(k\delta) &= S(0) - \tilde{N}_{SI}(k\delta) \\ \tilde{I}(k\delta) &= I(0) + \tilde{N}_{SI}(k\delta) - \tilde{N}_{IR}(k\delta) \\ \tilde{R}(k\delta) &= R(0) + \tilde{N}_{IR}(k\delta)\end{aligned}$$

- We focus on a numerical solution to $N_{SI}(t)$, since the same methods can also be applied to $N_{IR}(t)$.

Three different stochastic Euler solutions at times $t = k\delta$

- 1 A Poisson approximation.

$$\tilde{N}_{SI}(t + \delta) = \tilde{N}_{SI}(t) + \text{Poisson}[\mu_{SI}(\tilde{I}(t)) \tilde{S}(t) \delta],$$

where $\text{Poisson}(\mu)$ is a Poisson random variable with mean μ and

$$\mu_{SI}(\tilde{I}(t)) = \beta \tilde{I}(t).$$

- 2 A binomial approximation with transition probabilities approximated by rate times time.

$$\tilde{N}_{SI}(t + \delta) = \tilde{N}_{SI}(t) + \text{Binomial}[\tilde{S}(t), \mu_{SI}(\tilde{I}(t)) \delta],$$

where $\text{Binomial}(n, p)$ is a binomial random variable with mean np and variance $np(1 - p)$.

- 3 A binomial approximation with exponential transition probabilities.

$$\tilde{N}_{SI}(t + \delta) = \tilde{N}_{SI}(t) + \text{Binomial}[\tilde{S}(t), 1 - \exp\{-\mu_{SI}(\tilde{I}(t))\delta\}].$$

- Conceptually, it is simplest to think of (1) or (2). Numerically, it is usually preferable to implement (3).

Compartment models as stochastic differential equations

- The Euler method extends naturally to stochastic differential equations (SDEs).
- A natural way to add stochastic variation to an ODE $dx/dt = h(x)$ is

$$dX/dt = h(X) + \sigma dB/dt$$

where $\{B(t)\}$ is Brownian motion and so dB/dt is Brownian noise.

- An Euler approximation $\tilde{X}(t)$ is

$$\tilde{X}((k+1)\delta) = \tilde{X}(k\delta) + \delta h(\tilde{X}(k\delta)) + \sigma\sqrt{\delta} Z_k$$

where Z_1, Z_2, \dots is a sequence of independent standard normal random variables, i.e., $Z_k \sim N[0, 1]$.

- Although SDEs are often considered an advanced topic in probability, the Euler approximation doesn't demand much more than familiarity with the normal distribution.

Euler's method vs Gillespie's algorithm

Question 2.2. A widely used, exact simulation method for continuous time Markov chains is Gillespie's algorithm. We do not put much emphasis on Gillespie's algorithm here. Why? When would you prefer an implementation of Gillespie's algorithm to an Euler solution?

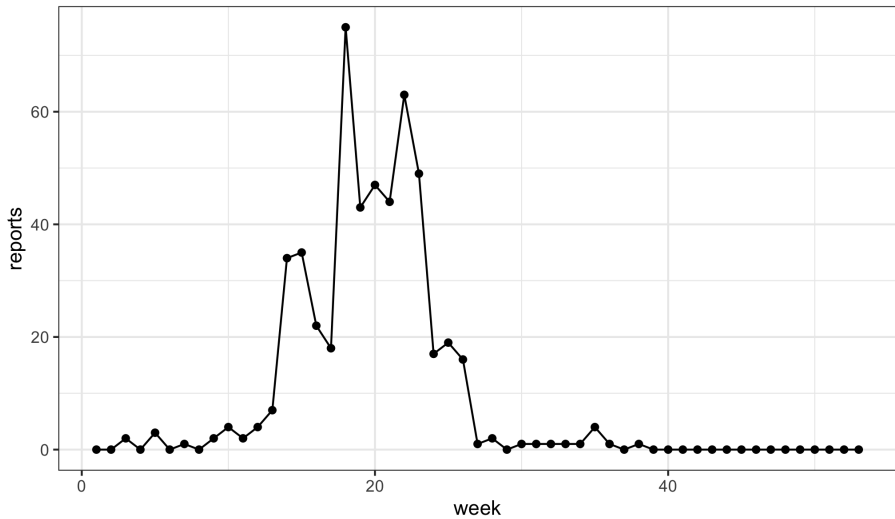
Numerically, Gillespie's algorithm is often approximated using so-called tau-leaping methods. These are closely related to Euler's approach. In this context, the Euler method has sometimes been called a tau-leaping.

Compartmental models in pomp: The Consett measles outbreak

- As an example that we can probe in some depth, let's look at outbreak of measles that occurred in the small town of Consett in England in 1948.
- We download the data. Examine them:

```
read_csv("https://kingaa.github.io/sbied/stochsim/Measles_Consett_1948.csv") %>%  
  select(week, reports=cases) -> meas  
head(as.data.frame(meas), 5)
```

##	week	reports
## 1	1	0
## 2	2	0
## 3	3	2
## 4	4	0
## 5	5	3



A simple POMP model for measles

- These are incidence data: The `reports` variable counts the number of reports of new measles cases each week.
- Let us model the outbreak using the simple SIR model.
- Our tasks will be, first, to estimate the parameters of the SIR and, second, to decide whether or not the SIR model is an adequate description of these data.
- The rate at which individuals move from S to I is the **force of infection**, $\mu_{SI} = \beta I/N$, while that at which individuals move into the R class is μ_{IR} .

Framing the SIR as a POMP model

- The unobserved state variables, in this case, are the numbers of individuals, $S(t)$, $I(t)$, $R(t)$ in the S, I, and R compartments, respectively.
- It's reasonable in this case to view the population size $N = S(t) + I(t) + R(t)$, as fixed at the known population size of 38,000.
- The numbers that actually move from one compartment to another over any particular time interval are modeled as stochastic processes.
- In this case, we'll assume that the stochasticity is purely demographic, i.e., that each individual in a compartment at any given time faces the same risk of exiting the compartment.
- **Demographic stochasticity** is the unavoidable randomness that arises from chance events occurring in a discrete and finite population.

Implementing the model

- To implement the model in `pomp`, the first thing we need is a stochastic simulator for the unobserved state process.
- We've seen that there are several ways of approximating a stochastic compartment model for numerical purposes. We follow method 3 above, modeling the number, ΔN_{SI} , moving from S to I over interval Δt as

$$\Delta N_{SI} \sim \text{Binomial} \left(S, 1 - e^{-\beta I/N \Delta t} \right),$$

and the number moving from I to R as

$$\Delta N_{IR} \sim \text{Binomial} \left(I, 1 - e^{-\mu_{IR} \Delta t} \right).$$

```
sir_step <- function (S, I, R, N, Beta, mu_IR, delta.t, ...) {  
  dN_SI <- rbinom(n=1, size=S, prob=1-exp(-Beta*I/N*delta.t))  
  dN_IR <- rbinom(n=1, size=I, prob=1-exp(-mu_IR*delta.t))  
  S <- S - dN_SI  
  I <- I + dN_SI - dN_IR  
  R <- R + dN_IR  
  c(S = S, I = I, R = R)  
}
```

- At day zero, we'll assume that $I = 1$ but we don't know how many people are susceptible, so we'll treat this fraction, η , as a parameter to be estimated.

```
sir_init <- function(N, eta, ...) {  
  c(S = round(N*eta), I = 1, R = round(N*(1-eta)))  
}
```

- We fold these basic model components, with the data, into a pomp object thus:

```
meas %>%  
  pomp(times="week", t0=0,  
        rprocess=euler(sir_step, delta.t=1/7),  
        rinit=sir_init  
  ) -> measSIR
```

- Now assume the case reports result from a process by which new infections are diagnosed and reported with probability ρ , which we can think of as the probability that a child's parents take the child to the doctor, who recognizes measles and reports it to the authorities.
- Measles symptoms tend to be quite recognizable, and children with measles tend to be confined to bed. Therefore diagnosed cases have, presumably, a much lower transmission rate. Accordingly, let's treat each week's reports as being related to the number of individuals who have moved from I to R over the course of that week.
- We need a variable to track these daily counts. We modify our rprocess function above, adding a variable H to tally the true incidence.


```

sir_step <- function (S, I, R, H, N, Beta, mu_IR, delta.t, ...) {
  dN_SI <- rbinom(n=1,size=S,prob=1-exp(-Beta*I/N*delta.t))
  dN_IR <- rbinom(n=1,size=I,prob=1-exp(-mu_IR*delta.t))
  S <- S - dN_SI
  I <- I + dN_SI - dN_IR
  R <- R + dN_IR
  H <- H + dN_IR;
  c(S = S, I = I, R = R, H = H)
}

sir_init <- function (N, eta, ...) {
  c(S = round(N*eta), I = 1, R = round(N*(1-eta)), H = 0)
}

```

- In pomp terminology, H is an **accumulator variable**. Since we want H to tally only the incidence over the week, we'll need to reset it to zero at the beginning of each week. We accomplish this using the `accumvars` argument to `pomp`:

```
measSIR %>%  
  pomp(  
    rprocess=euler(sir_step,delta.t=1/7),  
    rinit=sir_init,accumvars="H"  
  ) -> measSIR
```

- Now, we'll model the data as a binomial process,

$$\text{reports}_t \sim \text{Binomial}(H(t) - H(t - 1), \rho).$$

- Now, to include the observations in the model, we must write either a `dmeasure` or an `rmeasure` component, or both:

```
dmeas <- function (reports, H, rho, log, ...) {  
  dbinom(x=reports, size=H, prob=rho, log=log)  
}  
  
rmeas <- function (H, rho, ...) {  
  c(reports=rbinom(n=1, size=H, prob=rho))  
}
```

- We then put these into our `pomp` object:

```
measSIR %>% pomp(rmeasure=rmeas, dmeasure=dmeas) -> measSIR
```

Specifying model components using C snippets

- Although we can always specify basic model components using R functions, as above, we'll typically want the computational speed up that we can obtain only by using compiled native code.
- `pomp` provides a facility for doing so with ease, using **C snippets**.
- A C snippet is a small piece of C code used to specify a basic model component.
- For example, a C snippets encoding the `rprocess` for an `sir` model is as follows.

```
sir_step <- Csnippet("  
  double dN_SI = rbinom(S,1-exp(-Beta*I/N*dt));  
  double dN_IR = rbinom(I,1-exp(-mu_IR*dt));  
  S -= dN_SI;  
  I += dN_SI - dN_IR;  
  R += dN_IR;  
  H += dN_IR;  
")
```

- C snippets for the initializer and measurement model are:

```
sir_init <- Csnippet("  
  S = nearbyint(eta*N);  
  I = 1;  
  R = nearbyint((1-eta)*N);  
  H = 0;  
")  
  
dmeas <- Csnippet("  
  lik = dbinom(reports,H,rho,give_log);  
")  
  
rmeas <- Csnippet("  
  reports = rbinom(H,rho);  
")
```

- A call to `pomp` replaces the basic model components with these, much faster, implementations:

```
measSIR %>%  
  pomp(rprocess=euler(sir_step,delta.t=1/7),  
    rinit=sir_init,  
    rmeasure=rmeas,  
    dmeasure=dmeas,  
    accumvars="H",  
    statenames=c("S","I","R","H"),  
    paramnames=c("Beta","mu_IR","N","eta","rho")  
  ) -> measSIR
```

- Note that, when using C snippets, one has to tell `pomp` which of the variables referenced in the C snippets are state variables and which are parameters. This is accomplished using the `statenames` and `paramnames` arguments.

Guessing plausible parameter values

- To check our codes are working as intended, we simulate. To do this, we'll need some parameters. A little thought will get us some ballpark estimates.
- Recall that \mathfrak{R}_0 is the expected number of secondary infections resulting from one primary infection introduced into a fully susceptible population. For an SIR infection, one has that $\mathfrak{R}_0 \approx \frac{L}{A}$, where L is the lifespan of a host and A is the mean age of infection. Analysis of age-stratified serology data establish that the mean age of infection for measles during this period was around 4–5yr (?). Assuming a lifespan of 60–70yr, we have a rough estimate of $\mathfrak{R}_0 \approx 15$.
- From the basic theory of SIR epidemics, we have the final-size equation

$$\mathfrak{R}_0 = -\frac{\log(1-f)}{f},$$

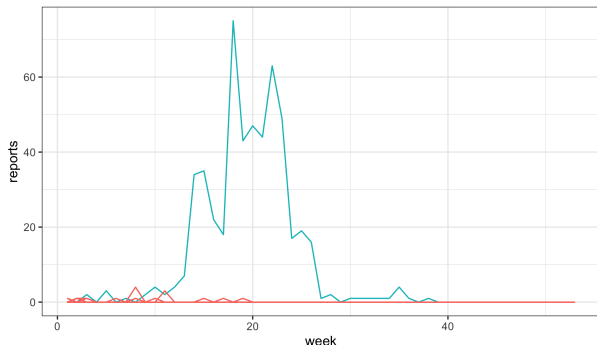
where f is the final size of the epidemic—the fraction of those susceptible at the beginning of the outbreak who ultimately become infected. For $\mathfrak{R}_0 > 5$, this equation predicts that $f > 0.99$.

- In the data, it looks like there were a total of 521 infections.
Assuming $50\eta = \frac{S_0}{N} \approx 0.027$.
- If the infectious period is roughly 2wk, then $1/\mu_{IR} \approx 2 \text{ wk}$ and $\beta = \mu_{IR} \mathfrak{R}_0 \approx 7.5 \text{ wk}^{-1}$.

- Let's simulate the model at these parameters.

```
measSIR %>% simulate(params=c(Beta=7.5,mu_IR=0.5,rho=0.5,eta=0.03,N=1000,nsim=20,format="data.frame",include.data=TRUE) -> sims
```

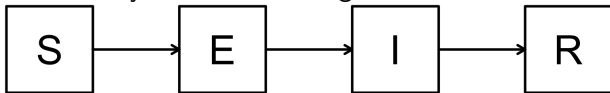
```
sims %>%  
  ggplot(aes(x=week,y=reports,group=.id,color=.id=="data"))+  
  geom_line()+ guides(color=FALSE)
```



This leaves something to be desired. In the exercises, you'll see if this model can do better.

Question 2.3. Explore the SIR model. Fiddle with the parameters to see if you can't find a model for which the data are a more plausible realization.
Worked solution to the Exercise

Question 2.4. The SEIR model. Below is a diagram of the so-called SEIR model. This differs from the SIR model in that infected individuals must pass a period of latency before becoming infectious.



Modify the codes above to construct a `pomp` object containing the flu data and an SEIR model. Perform simulations as above and adjust parameters to get a sense of whether improvement is possible by including a latent period.

Worked solution to the Exercise

Acknowledgments and License

- This tutorial is prepared for the Simulation-based Inference for Epidemiological Dynamics module at the 12th Annual Summer Institute in Statistics and Modeling in Infectious Diseases, SISIMID 2020. Previous versions were presented at SISIMID by ELI and AAK in 2015–2019. Carles Breto assisted in 2018.
- Produced with R version 4.0.0 and pomp version 3.0.1.1.
- These notes are an updated version of previous Simulation-Based Inference for Epidemiological Dynamics courses taught by A. A. King and E. L. Ionides from 2015-2019.
- Licensed under the Creative Commons attribution-noncommercial license. Please share and remix noncommercially, mentioning its origin.



References I

- Bhadra, A., Ionides, E. L., Laneri, K., Pascual, M., Bouma, M. and 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.
- Bretó, C., He, D., Ionides, E. L. and King, A. A. (2009). Time series analysis via mechanistic models, *Annals of Applied Statistics* **3**(1): 319–348.
- Gillespie, D. T. (1977). Exact stochastic simulation of coupled chemical reactions, *Journal of Physical Chemistry* **81**: 2340–2361.
- Gillespie, D. T. (2001). Approximate accelerated stochastic simulation of chemically reacting systems, *Journal of Chemical Physics* **115**(4): 1716–1733.
- He, D., Ionides, E. L. and King, A. A. (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.

Laneri, K., Bhadra, A., Ionides, E. L., Bouma, M., Yadav, R., Dhiman, R. and Pascual, M. (2010). Forcing versus feedback: Epidemic malaria and monsoon rains in NW India, *PLoS Computational Biology* **6**: e1000898.