BEEP-MBP V1.0

Bayesian Estimation of Epidemiological Parameters with Model-based Proposals

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1 Introduction

This manual is structured in the following way: The first section describes what compartmental models are and sketches out the main features of BEEPmbp (along with an easy-to-follow guide for performing a simple analysis). Section 2 sets out, from a mathematical perspective, the models and types of data that can be incorporated into analysis, and provides some details on how inference is performed. Section 3 focuses on the practicalities of how the model and data are described in an initialisation file used to set up an analysis in BEEPmbp. Section 4 looks at the various options available when running BEEPmbp, and, finally, section 5 describes the outputs that BEEPmbp generates. Some additional example applications are provided in section 6 to illustrate the versatility of this software.

1.1 Compartmental epidemiological models

Compartmental models have widely been used to model and provide understanding of the collective dynamics of interacting agents, with notable applications in epidemiology and ecology. A simple example is shown in Fig. 1. Here individuals start in the susceptible S compartment, and when infected they make the transition to an exposed E state (infected but not infectious), then they become infectious I and, finally, recover R.

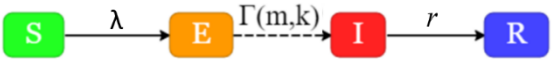


Figure 1. A compartmental model. This describes how an individual's infection status changes over time. S: susceptible, E: exposed, I: infectious, R: recovered. Individuals are infected at a rate given by the force of infection λ, undergo a non-infectious incubation period given by gamma distribution Γ (with mean time *m* and shape parameter *k*), and finally recover with mean time *r*.

Numerous levels of complexity can be added to this basic model, such as inclusion of 1) various degrees of infection severity (*e.g.* asymptomatic states, all the way up to hospitalised and dead), 2) demographic structure (*e.g.* to capture differences in susceptibility or allow for different age groups in the population to interact with each other to a greater or lesser extent), 3) spatial variation (to account for geographical variation in transmission rate), 4) temporal variation in disease transmission (*e.g.* to account for social distancing), 5) different strains of pathogen, and 6) the effect of vaccination. Incorporation of these various possibilities is discussed in sections 2 and 3.

Many disease control strategies are guided by compartmental epidemiological models. More specifically, these models can be useful to simulate infection dynamics in populations, infer epidemiological parameters from disease data, and predict future outcomes.

1.2 This software

BEEPmbp (Bayesian Estimation of Epidemiological Parameters using Model-Based Proposals) is a general-purpose software tool for performing population-based analysis on compartmental epidemiological models.

To clarify terminology, we here refer to "model parameters" as all those quantities in the model that determine how individuals behave (*e.g.* in Fig.1 this would include m, k and r as well as other parameters incorporated into λ) and "state" to represent the actual realised movement of individuals within the compartmental model over a time period under consideration (*i.e.* individuals' infection state).

BEEPmbp incorporates three different modes of operation:

Simulation – Given a set of model parameters, potential realisations of the state can be sampled from the model (note, compartmental models are inherently stochastic, so random differences in disease transmission naturally lead to differences in epidemic outcome).

Inference – This is the method by which suitable model parameters are estimated from available data (along with associated uncertainties in these estimates). BEEPmbp accepts a variety of different date types: time series measurements giving transition numbers between selected compartments (*e.g.* daily hospitalisations or weekly deaths), populations in different compartments (*e.g.* hospitalised population measured each week) and marginal data (*e.g.* age distribution for deaths).

Prediction – Based on the results of inference, predictions from the model can be made. These can either be estimates of future behaviour, or can be used to look at how things would have turned out differently had the model been altered in some specified way (otherwise known as counterfactual analysis).

Once run, BEEPmbp generates a pdf file to summarise its analysis (which may include time variation in state variables, estimates for posterior probability distributions as well as diagnostic information).

Epidemiological model features:

- Specify an arbitrary compartmental epidemiological model.
- Incorporate spatial and age-structured models.
- Capture time-variation in reproduction number R_t and external force of infection.
- Split population into arbitrary demographic classifications (*e.g.* age and/or sex).
- Incorporate susceptibility variation for different demographic groups.
- Incorporate area-based covariates to modify the force of infection, either fixed (*e.g.* population density) or time-varying (*e.g*. temperature).
- Incorporate a user specified age-mixing matrix (along with potential time modification).
- Specify a matrix for mixing between different areas (along with potential time modification).
- Perform prediction, counterfactuals as well as posterior predictive checks.

Data features:

- Accepts a variety of different data types (informing transition, populations and marginal).
- Incorporate splines to relate measured data to system properties.

Software implementation features:

- Efficient parallel implementation (written in C++ with MPI).
- Choose from 7 different inference algorithms.
- A web browser visualisation tool for viewing results on maps, graphs, histograms and tables.
- Generates pdf report for easy visualisation of outputs.

1.3 Getting started

This software is designed to work in a Linux environment and can be used both on a personal computer as well as on high performance computing (HPC). The code can be downloaded from git using the "--recursive" flag to ensure that submodules are included. For example:

```
git clone --recursive https://github.com/ScottishCovidResponse/BEEPmbp.git
```

If you have downloaded without the --recursive flag, you can update the submodules with

```
git submodule update –init
```

You need to have MPI installed to compile and run this code. This can be implemented using the command

```
module load mpi/openmpi-x86_64
```

The code uses mpicxx to compile, so this must be available. On the command line navigate to the BEEPmbp directory and type

```
make
```

to compile the software. It is now ready to use.

```
Loaded table 'scotland.csv'.

Running....

  Start:         S:5.454e+06  E:0  E:0  I:0  R:0
    t=24.25      S:5.45332e+06  E:127  E:104  I:159  R:292
    t=48.25      S:5.44568e+06  E:1419  E:1216  I:1663  R:4019
    t=72.25      S:5.3672e+06  E:14030  E:11890  I:17197  R:43681
    t=96.25      S:4.70113e+06  E:109709  E:94435  I:144739  R:403991
    t=120.25     S:2.39955e+06  E:199425  E:208513  I:422916  R:2.22359e+06
    t=144.25     S:1.24472e+06  E:36502  E:44367  I:130759  R:3.99766e+06
    t=168.25     S:1.10172e+06  E:3426  E:4402  I:14177  R:4.33027e+06
    t=192.25     S:1.08855e+06  E:327  E:362  I:1327  R:4.36343e+06
    t=216.25     S:1.08735e+06  E:42  E:41  I:123  R:4.36644e+06
    t=240.25     S:1.08719e+06  E:2  E:11  I:25  R:4.36677e+06
  End:           S:1.08718e+06  E:8  E:11  I:14  R:4.36679e+06

Simulated data in directory 'Output_EX1/Simulated_data':
  Generating data file 'EI.csv'

Generating outputs...

Output graphs are placed into 'Output_EX1/Graphs.pdf'

The source files for these graphs are referenced in 'Output_EX1/Graphs_description.txt'

Parameter values are given in 'Output_EX1/Parameter_estimates.csv'

Total time: 0.003 minutes.
```

Figure 2. Terminal output under simulation. This shows the terminal output from BEEPmbp when running the example in §1.4.1. First, the file "scotland.csv" is loaded (which provides information about the population under study, in this case a nationwide analysis of Scotland), then the simulation is performed (a summary of how compartmental populations changes at selected time points is shown). Finally, the simulated data file "EI.csv" is created in the output directory, as well as "Graphs.pdf", which gives graphical plots showing the system dynamics (see Fig. 3).

1.4 A five-minute guide

Here we provide a five-minute introduction to demonstrate how the software works in a relatively simple scenario. This consists of the following steps:

1.4.1 Simulation example

- Type the following command into the terminal

  ```
  ./beepmbp inputfile="examples/EX1.toml" mode="sim"
  ```

  This runs BEEPmbp using the example initialisation file "EX1.toml" (shown and discussed later in §3.1). This file sets up an SEIR model (see Fig. 1) and specifies the outputs that need to be displayed.
- Once run, the terminal output looks like that shown in Fig 2.
- A file "Graphs.pdf" is generated, as shown in Fig 3, which gives various plots that summarise the system dynamics.
- In the sub-directory "Simulate_data" the file "EI.csv" is created. As shown in Fig. 4, this gives simulated time-series data for the weekly number of infections.

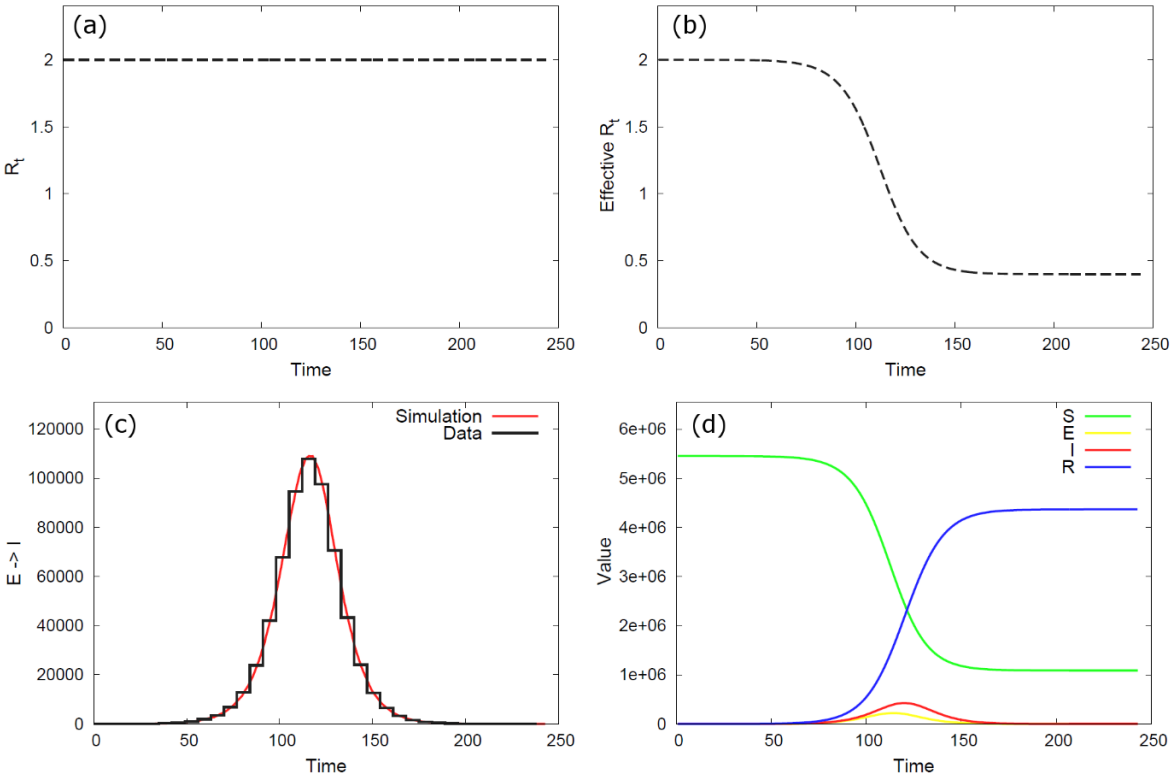


Figure 3. Simulation from model. This shows outputs from BEEPmbp (contained in the "Graphs.pdf" file in the output directory) when simulating from the SEIR in Fig. 1. (a) The reproduction number over time (which here has a constant value of 2). (b) The effective reproduction number (which starts at 2, but drops down as the epidemic progresses because of depletion of the susceptible population). (c) The red curve shows the daily number of infections (*i.e.* the rate of E to I transitions) and the black curve shows a derived simulated dataset (which in this case gives the weekly number, leading to this curve's stepped appearance). (d) The dynamic variation in each of the compartmental populations.

1	date	Data
2	2020-01-01	19
3	2020-01-08	82
4	2020-01-15	199
5	2020-01-22	388
6	2020-01-29	828
7	2020-02-05	1627
8	2020-02-12	3201
9	2020-02-19	6422
10	2020-02-26	12936
11	2020-03-04	24659
12	2020-03-11	47500
13	2020-03-18	90183
14	2020-03-25	166806
15	2020-04-01	293991
16	2020-04-08	474428
17	2020-04-15	662286
18	2020-04-22	755245
19	2020-04-29	682750
20	2020-05-06	493807
21	2020-05-13	302830
22	2020-05-20	168146
23	2020-05-27	88240
24	2020-06-03	45281
25	2020-06-10	22597
26	2020-06-17	11204
27	2020-06-24	5548
28	2020-07-01	2824
29	2020-07-08	1353
30	2020-07-15	680
31	2020-07-22	343
32	2020-07-29	180
33	2020-08-05	102
34	2020-08-12	58
35	2020-08-19	46

Figure 4. Simulated data file. This shows the data file "EI.csv" generated in §1.4.1. This example gives the weekly number of infection transitions measured from the date in the first column up until just before the date in the row below (hence there were 19 infection between the beginning of January 1st and the end of January 7th). This is the same format used when loading real data files.

1.4.2 Inference example

We now look to perform inference on the simulated data file "EI.csv" (Fig. 4) to estimate the time variation in the reproduction number.

- Type the following to run inference (note the "-n 10" refers to the number of CPU cores used and should be changed depending on your computer's architecture):

```
mpirun -n 10 ./beepmbp inputfile="examples/EX1.toml" mode="abcmbp" nparticle=200
                                ngeneration=10 nrun=4
```

  Here 'mode' indicates the type of inference algorithm used (see §4.2), with ABC-MBP being used in this particular case (run with 200 particles and over 10 generations). 'nrun' gives the number of parallel runs used (running multiple times not only improves posterior estimates, but it also allow for additional diagnostics to check for correct convergence).
- The code takes around a minute to run and the terminal output is shown in Fig. 5.
- The file "Graphs.pdf" (see Fig. 6) demonstrates that based on the transition data alone we are able to make an accurate estimate of the time variation in reproduction number.
- Looking at "Parameter_estimates.csv" in Fig. 7 we see that BEEPmbp outputs posterior estimates for the model parameters.
- Finally, the file "Graphs_diagnostic.pdf", as shown in Fig. 8, shows convergence of the algorithm on the data, provides a measure of model evidence (to compare one model against another for goodness of fit), as well as diagnostic information and probability distributions for each of the model parameters.

```
Loaded table 'scotland.csv'.
Loaded table 'EI.csv'.

Running....

Samping particles for the initial generation...
Generation 1 -     EF cut-off: 29.966 (0.481 - 85.901)   Proposals: 6
Generation 2 -     EF cut-off: 10.088 (0.267 - 28.633)   Proposals: 6
Generation 3 -     EF cut-off: 3.279 (0.146 - 9.422)   Proposals: 6
Generation 4 -     EF cut-off: 1.195 (0.075 - 3.123)   Proposals: 6
Generation 5 -     EF cut-off: 0.508 (0.048 - 1.155)   Proposals: 6
Generation 6 -     EF cut-off: 0.241 (0.034 - 0.482)   Proposals: 6
Generation 7 -     EF cut-off: 0.139 (0.026 - 0.234)   Proposals: 6
Generation 8 -     EF cut-off: 0.084 (0.019 - 0.136)   Proposals: 6
Generation 9 -     EF cut-off: 0.054 (0.017 - 0.082)   Proposals: 6
Generation 10 -     EF cut-off: 0.038 (0.012 - 0.053)   Proposals: 6

Generating outputs...

Output graphs are placed into 'Output_EX1/Graphs.pdf'
The source files for these graphs are referenced in 'Output_EX1/Graphs_description.txt'

Output diagnostic graphs are placed into 'Output_EX1/Diagnostic_Graphs.pdf'
The source files for these graphs are referenced in 'Output_EX1/Diagnostic_Graphs_description.txt'

Posterior parameter estimates are given in 'Output_EX1/Parameter_estimates.csv'

Total time: 1.080 minutes.
```

Figure 5. Terminal output under inference. This show the terminal output from BEEPmbp when running the example in §1.4.2. First the file "scotland.csv", which provides information about the population under study, and "EI.csv", which gives weekly infection data, are loaded. Inference is then performed. What is displayed next will depend on the inference algorithm selected. In this case ABC-MBP proceeds in a series of generations that transform initial prior samples to posterior samples (the reduction in EF cut-off indicates that the system state becomes closer and closer to the actual data). "Graphs.pdf" is created in the output directory, which gives graphical plots showing the system dynamics (Fig. 6), "Parameter_estimates.csv" give posterior estimates (Fig. 7), and "Diagnostic_Graphs.pdf" give addition information about inference execution (Fig. 8).

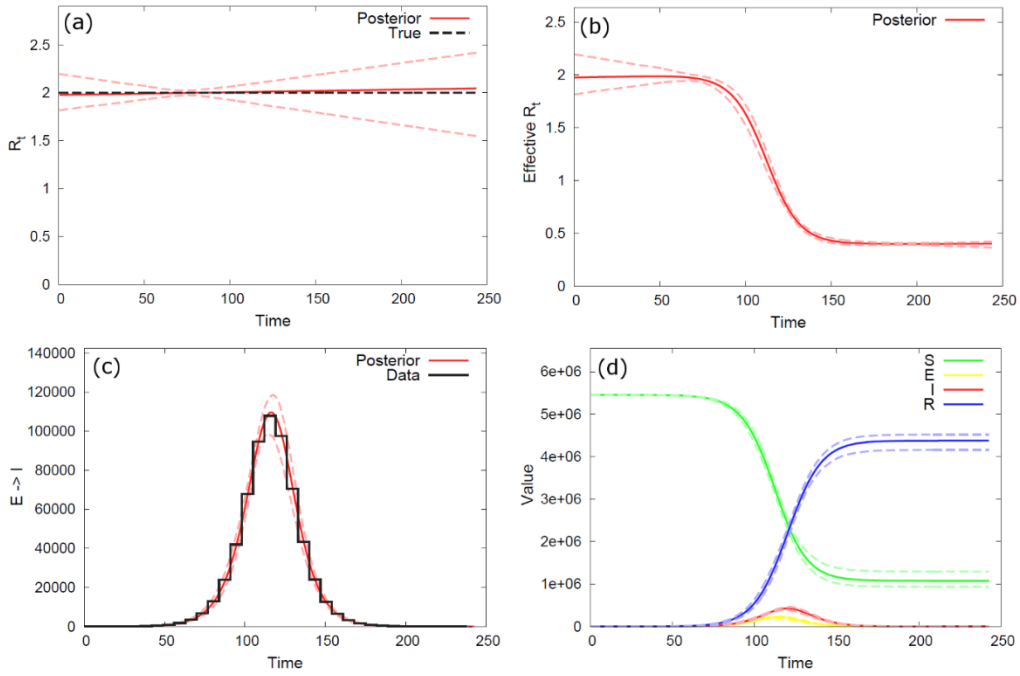


Figure 6. Inference from model. This shows some of the outputs from BEEPmbp ("Graphs.pdf") when performing inference using the data file in Fig. 4. (a) The posterior distribution for a linear fit to the reproduction number R_t, with the dashed lines representing 95% credible intervals (the black dashed line shows the true simulated value, which is close to the posterior mean indicating successful inference). (b) The effective reproduction number. (c) The red curve shows the inferred rate of infections and the black curve shows the fit with the actual data. (d) The posterior distributions for the inferred dynamic variation in each of the compartmental populations.

	A	B	C	D	E	F	G	H
1	# Posterior distributions for model parameters.							
2								
3	Name	Mean	95% CI min	95% CI max	Standard deviation	Prior	Effective sample size	Gelman-Rubin statistic
4	E mean occupancy time	4	4	4	0	Fixed(4)	---	---
5	I Infectivity	1	1	1	0	Fixed(1)	---	---
6	I mean occupancy time	4	4	4	0	Fixed(4)	---	---
7	R_spline t:0	1.98997	1.81425	2.17324	0.0949243	Uniform(0.4|4)	---	1.0119
8	R_spline t:244	2.01331	1.55577	2.40207	0.215852	Uniform(0.4|4)	---	1.01365
9	efoi_spline t:0	0.1	0.1	0.1	0	Fixed(0.1)	---	---
10	efoi_spline t:244	0.1	0.1	0.1	0	Fixed(0.1)	---	---

Figure 7. Parameter estimates. BEEPmbp generates the file "Parameter_estimates.csv" in the output directory. This file provides posterior estimates for model parameters. The different columns give: the posterior mean, 95% credible interval, standard deviation and prior (specified in the input TOML file). Effective sample size (not generated for the ABC-MBP method) and Gelman-Rubin statistics are diagnostic quantities used to ensure reliability of the results. In this particularly simple example only the spline endpoints for the reproduction number are actually estimated (and assumed to have a uniform prior between 0.4 and 4), with all other parameters set to a fixed value.

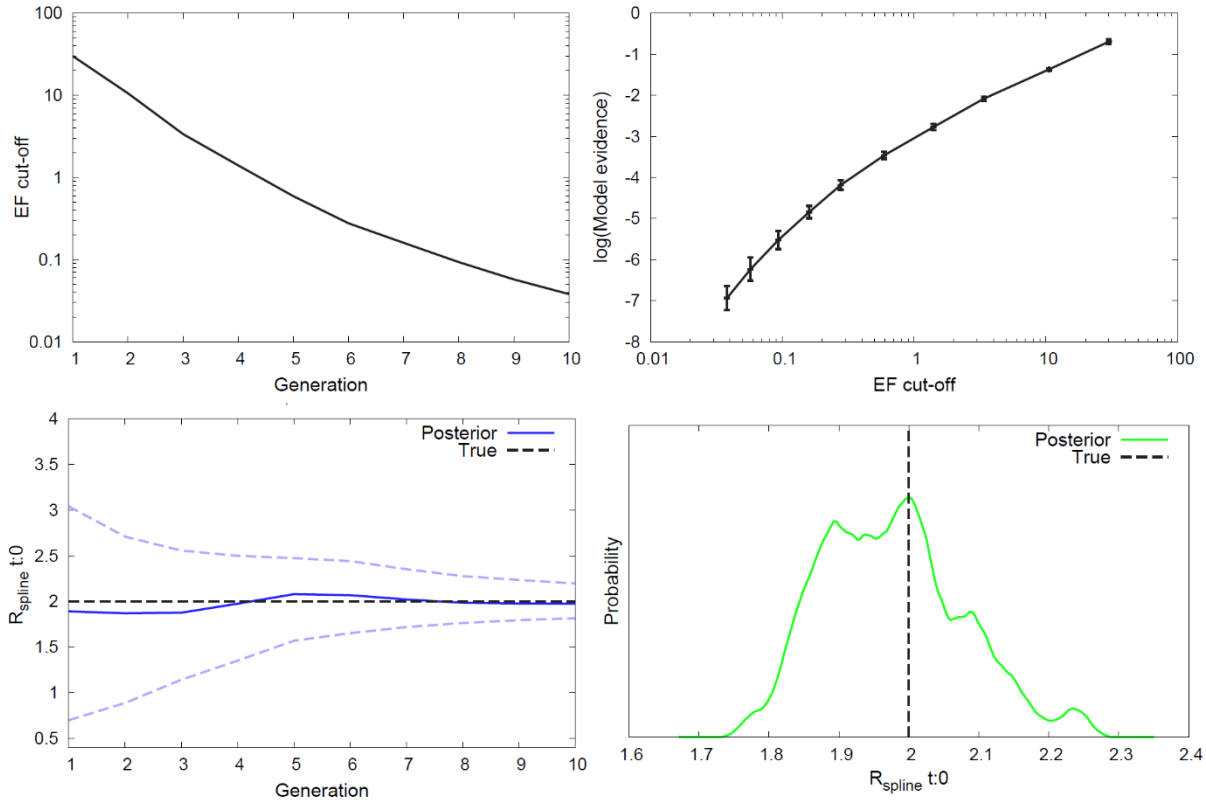


Figure 8. Additional diagnostic information. This shows the file "Diagnostic_Graphs.pdf" generated by BEEPmbp. (a) This graph shows the error function (EF) cut-off reducing as a function of generation number (this quantity, shown in Eq.(18), indicates how well the system state agrees with the data). (b) The log of the model evidence as a function of EF cut-off (higher values imply a better fit with the data). Comparing curves between models allows for effective model selection (see §2.3.5 for more details). (c) Shows how the distribution for a particular model parameter (with 95% credible intervals) moves from the prior to a good approximation of the posterior as the generations are iterated. (d) Estimate for the posterior distribution of a parameter made in the final generation. Note, the black dashed line showing the true value used to simulate the data lies well within the 95% credible interval.

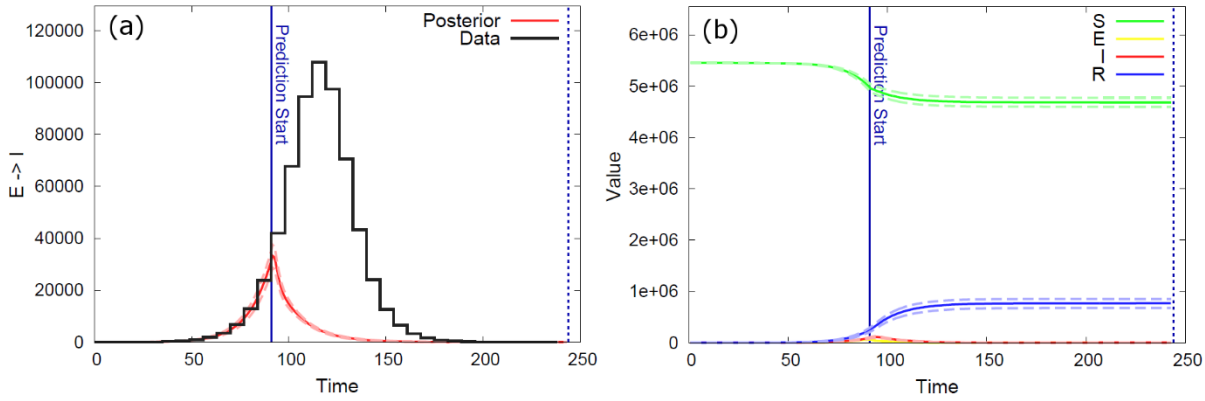


Figure 9. Prediction. These plots, shown in "Graphs.pdf", predict the effect of modifying the model such that the transmission rate is reduced by 70% after day 90 (April 1st), *e.g.* mimicking the impact of lockdown. (a) The red curves gives the modified posterior distribution for the infection rate. After the prediction start time there is a marked reduction in rate compared to the simulated dataset. (b) The modified posterior distributions for the inferred dynamic variation in each of the compartmental populations.

1.4.3 Prediction example

Whenever inference is performed posterior samples are stored in the "Posterior/samples/" directory. These samples can subsequently be used to make model predictions:

- Type the following to run prediction:

  ```
  mpirun -n 10 ./beepmbp inputfile="examples/EX1.toml" mode="prediction"
  ```

  In this case a modification to the model (as specified in "EX1.toml") is assumed that reduces the transmission rate after the 1st April (*e.g.* this could be used to represent lockdown in the case of a pandemic).
- Results from the "Graphs.pdf" file are shown in Fig. 9. This reveals a dramatic reduction in the severity of the pandemic as a result of intervention.

Clearly the example application described above relied on many simplifying assumptions which may not be valid in real world scenarios (*e.g.* infection events are not usually all known, R_t typically exhibits large temporal variation that needs to be accounted for, and the values for model parameters controlling transitions within the compartmental model are never precisely known). Nevertheless, this section has served as a useful starting point to introduce the software. Further examples are provided in §6 that explore how these additional complications can be accounted for.

2 Models, data and inference

In this section we provide a broad mathematical description of the sorts of model BEEPmbp can perform analysis with. In the next section we go on to describe, in detail, how these models are implemented in practice using a TOML initialisation file.

2.1 Epidemiological model

2.1.1 Stratification of the population

BEEPmbp assumes the population under study can potentially be stratified in three different ways:

Disease status stratification – The variable c is used to denote different compartments that specify an individual's disease status (*e.g.* in Fig. 1 c can either be S, E, I or R). BEEPmbp allows the user to specify an arbitrarily number of compartments in the model. For example, as well as susceptible, exposed, infectious and recovered compartments, others can be added to represent asymptomatic, pre-symptomatic or hospitalised individuals.

The residency time within each compartment (that is the time difference between when an individual enters and leaves a compartment) is restricted to either be exponential distributed[1] or Erlang distributed (with a shape parameter k that allows its distribution to be more highly peaked than the exponential[2]), with a model parameter setting its mean. In cases in which the compartmental model branches, further parameters are associated with the probability for individuals to pass down one branch or another.

Demographic stratification – The variable d is used to denote the demographic grouping an individual belongs to. In the simplest case this would consist of a single category such that, from an epidemiological point of view, everyone in the population behaves the same. On the other hand, the population can be split by age, sex, or any other discrete classifier. Parameters determining the mean residency time and branching probabilities from above can be made dependent on these demographic groupings (to reflect the fact that the disease affects different groups in different ways).

Geographic stratification – The variable a is used to indicate the area in which an individual resides. For a non-spatial model the system would consist of just a single area (*e.g*. a nationwide analysis), but if we are interesting in accounting for the geographic spread of disease then a could represent different areas, *e.g*. local authorities.

2.1.2 The force of infection

Whilst arbitrary compartmental model specification is allowed in BEEPmbp, only a single specified transition results from infection (in Fig. 1 this is the S→E transition). The probability per unit time of an individual becoming infected with strain s, in area a, in demographic group d at time t is given by the force of infection:

$$\lambda_{s,a,d,t} = \sigma_d \left[r_{s,t} R_t \psi_s \alpha_{a,t} \left[\sum_{a',d',c} M_{a,a',t} A_{d,d',t} i^c N^c_{a',d',t} \right] + \tfrac{1}{f} \eta_{s,a,d,t} \right]. \quad (1)$$

The various terms in this expression are explained below:

Susceptibility – σ_d gives the relative susceptibility of demographic group d. This itself is decomposed into separate susceptibilities for each demographic classification q in the model (*e.g*. q could be "Age" or "Sex") multiplied together, *i.e.*

[1] An exponentially distributed residency time is equivalent to there being a certain constant probability per unit time of leaving a compartment, consistent with a Poisson process.

[2] The Erlang is the same as the Gamma distribution with integer shape parameter. If k=1 it is the same as an exponential distribution, whereas if k is large the residency time becomes more closely distributed around its mean.

$$\sigma_d = \prod_q \sigma_{q,d_q}, \tag{2}$$

where v=d_q gives the value of classification q for demographic group d (*e.g.* if a particular d represents males in the age range 40-59 then the values for its classifications are d_{Age}="40-49" and d_{Sex}="Male") and $\hat{\sigma}_{q,v}$ is the relative susceptibility for that value. Because $\hat{\sigma}_{q,v}$ represents a *relative* susceptibility its values are constrained by

$$\sum_v \sigma_{q,v}\phi_{q,v} = 1 \quad \text{for each } q, \tag{3}$$

where $\phi_{q,v}$ is the overall proportion of individuals with value v in classification q. This ensures that for each classification the average susceptibility over the entire population is exactly one. See §3.5.3 for implementation of susceptibility variation in BEEPmbp.

Reproduction number – The quantity R_t represents the reproduction number as a function of time, which is defined to be the expected number of secondary cases directly generated by one case in a population in which nearly all individuals are susceptible (see §3.4.3 for implementation). Estimation of this quantity relies on the approach taken by Diekmann *et* al. [ref], in which R_t is calculated from the highest eigenvalue of the next generation matrix (see Appendix A for more details).

Incorporation of R_t into Eq.(1) makes sense because it would be expected that disease transmission within the population should to be proportional to the rate at which effective disease transmitting contacts occur ($r_{s,t}$ is a quantity derived from other model parameters which sets this proportionality constant[3], again see Appendix A). In reality, due to depletion of the susceptible population, the actual number of secondary cases directly generated by one case is given by the effective reproduction number R_t^{eff}. This quantity that can be derived from R_t and other model parameters (Appendix A) and is displayed as an output by BEEPmbp.

Strain effect – If more than one disease strains exists in the system, the factor ψ_s in Eq.(1) multiplies the reproduction number R_t to give its value for that particular strain s[4] (see §3.8 for implementation).

Area effects – The term $\alpha_{a,t}$ in Eq.(1) is used to incorporate geographical variation in disease transmission (see §3.6.4 for implementation). This, itself, is decomposed into various potential contributions:

$$\alpha_{a,t} = w_a \times e^{\sum_i X_{a,j} b_j} \times e^{\sum_i X'_{a,t,j} b'_j} \times h_{l_{a,t}}. \tag{4}$$

The first is a relative area effect w_a, which accounts for the fact that the overall disease transmission in one area might be different to another. This is normalised by

$$\sum_a w_a \phi_a = 1, \tag{5}$$

[3] $r_{s,t}$ essentially gives the time-varying ratio $\beta_{s,t}/(R_t\psi_s)$, where $\beta_{s,t}$ is the transmission rate.
[4] When there is one strain, ψ=1, and for more than one strain, ψ_s=1 for the reference strain.

where ϕ_a is the fraction of the population in area a, such that the average area effect is one.

The second term in Eq.(4) incorporates area fixed effects. Here $\boldsymbol{X}$ is a design matrix and $\boldsymbol{b}$ is a vector of fixed effects (note, the exponential link function ensures the rate is strictly positive). These are aimed at correlating local transmission rate with measurable factors within each area. For example, suppose column 1 in $\boldsymbol{X}$ gives the log of the local population density p_a. This would mean that Eq.(4) contains a factor given by

$$e^{\log(p_a)b_1} = p_a^{b_1}, \tag{6}$$

where b_l is a fixed effect model parameter that is set or inferred (here b_l=0 and b_l=1 correspond to frequency and density dependent transmission, respectively).

The third term in Eq.(4) allows for time-varying fixed effects.

The last term in Eq.(4) aims at estimating the effect of different levels of disease intervention l (for example one level might represent a complete lock down, whereas another might be just social distancing). The matrix $l_{a,t}$ is an input which specifies the level each area a has at any point in time t. h_l represent the relative transmission rate for level l, normalised by

$$\sum_l h_l \phi_l = 1, \tag{7}$$

where ϕ_l is the fraction of time areas spend in level l (averaged over all areas and times).

Geographical mixing of individuals – The term $M_{a,a',t}$ in Eq.(1) gives the effective contact rate of individuals between areas a and a' at time t (see §3.6.3 for implementation). Time variation is parameterised in the following way:

$$M_{a,a',t} = Z_{a,a'} m_t + D_{a,a'}(1 - m_t), \tag{8}$$

where $Z_{a,a'}$ is a constant matrix (which is an input into BEEPmbp and, for example, could be based on census commuter data[5], see Appendix C) and $D_{a,a'}$ is a diagonal matrix (with elements given by the reciprocal of the population sizes in the corresponding areas). In Eq.(8) m_t is a time-varying parameter that determines the rate of mixing between areas (m_t=0 corresponds to no mixing and m_t=1 corresponds to mixing according to $Z_{a,a'}$). If movement restriction are in place we might expect m_t to lie somewhere in between these two extremes.

Demographic mixing of individuals – This is characterised by the matrix $A_{d,d'}$ in Eq.(1) (see §3.5.1 for implementation). Currently BEEPmbp supports only age-dependent mixing factors (since age is the biggest determining factor in characterising mixing patterns in humans). In this case

$$A_{d,d',t} = B_{z,z',t}, \tag{9}$$

where z and z' are the age groups of the demographic groups d and d', respectively, and $B_{z,z',t}$ is a time dependent square matrix with size given by the number of age categories. In the first instance $B_{z,z',t}$ is taken to be a constant matrix $C_{z,z'}$ (which is itself derived from a user defined age mixing

[5] It is important to note that we only need to know the input $Z_{a,a'}$ up to a constant factor.

matrix, such as that published by POLYMOD [ref] or BBC Pandemic! [ref], see Appendix D for details) . However, time dependency can also be accounted for by defining modifications to this matrix. For example, a factor f_t (defined by a spline) could be incorporated which multiplies one of the rows and columns in $C_{z,z'}$. This allows for the mixing exhibited by one particular age group with the rest of the population to be modulated in time.

Infectivity – i^c gives the relative compartmental infectivity (see §3.4.1 for implementation). This can be used to account for the fact that some compartmental states are more infectious than others (*e.g.* asymptomatic would be expected to be less infectious than symptomatic).

Subpopulation size – $N^c_{a',d',t}$ gives the total number of individuals in compartment c, area a' and demographic group d' at time t[6].

External infections – Finally, $\eta_{s,a,d,t}$ in Eq.(1) gives the spatial and temporal variation in the external force of infection caused by infections being introduced from outside the population under study (see §3.4.4 for implementation). Note, for convenience it is divided by a factor f=10^5 such that this external rate is expressed in units of infections per 100,000 individuals[7].

2.1.3 System dynamics

BEEPmbp uses a τ-leaping algorithm (with fixed time step τ) to approximate a continuous time Gillespie algorithm[8]. We denote $p_{a,d,c,t}$ to be the population in area a, demographic group d, compartment c at time t (note, for the purposes of analysis, strain s is treated as another demographic classification in d).

Transitions within the model (*e.g*. represented by the arrows in Fig. 1) are indexed by j. They move individuals from an initial compartment i_j to a final compartment f_j. Within a time period between t and $t+\tau$ the number of transitions of type j in area a and demographic group d is taken to be Poisson distributed. For the infection transition j_{inf} this is given by

$$n_{a,d,j_{\inf},t} \sim Poisson\left(\tau p_{a,d_{-s},S,t}\lambda_{s,a,d,t}\right), \tag{10}$$

where S is the susceptible compartment[9], and the notation d_{-s} is used to represent the fact that strain is disregarded as a demographic classifier for S (an individual's strain becomes determined only after they become infected[10]).

For non-infection transitions j, the number is given by

$$n_{a,d,j,t} \sim Poisson\left(\tau p_{a,d,i_j,t} b_{d,j} / \mu_{d,i_j}\right), \tag{11}$$

[6] Note, the demographic group d specifies the strain these individuals are infected with.
[7] This factor can be modified, if necessary.
[8] τ can be specified, but by default it is set to 0.25 days.
[9] Here S is defined to be the state from which infection events occur, *e.g.* in Fig. 1 this corresponds to the "S" compartment.
[10] For simplicity, the possibility of an individual becoming infected with multiple strains is ignored.

where $b_{d,j}$ is the branching probability for individuals to move down transition j (as opposed to any other transition leaving initial compartment i_j) and μ_{d,i_j} is the residency time in i_j.

As a result of the transitions in Eq.(11), populations needs to be updated:

$$p_{a,d,c,t+\tau} = p_{a,d,c,t} + \left[\sum_{j\in\text{enter c}} n_{a,d,j,t}\right] - \left[\sum_{j\in\text{leave c}} n_{a,d,j,t}\right], \tag{12}$$

where the first sum goes over all transitions that enter compartment c (increasing its population), and the second goes all those that leave c (decreasing its population).

Erlang distributions with shape parameter k and mean residency time m are constructed by sequentially linking together k compartments, each with exponentially distributed residency time that has a mean of m/k.

The initial population sizes $p_{a,d_{-s},c,,t_{\text{start}}}$ set the initial conditions. By default all individuals are assumed to start in the susceptible compartment[11] S. Population stratification across different areas a and demographic groups d_{-s} are inputs which must be specified. For the most part these are assumed constant (so, for example, a person's place of residency remains unchanged). However, it is also possible in BEEPmbp to externally impose changes in the demographic stratification of the population. This is especially useful when accounting for vaccination. Here changes are imposed on this system (as inputs) rather than occurring as the result of an underlying stochastic process.

BEEPmbp can also be run in deterministic mode. This is an approximation to the system dynamics which becomes increasingly valid for larger epidemic sizes (and so, for example, it may be sufficiently good to run a nationwide level analysis), and allows for faster inferences to be achieved. In this case, the number of transitions is simply set to the mean of the Poisson distribution rather than being sample from it:

$$\begin{aligned} n_{a,d,j_{\text{inf}},t} &= \tau\, p_{a,d_{-s},S,t}\lambda_{s,a,d,t}, \\ n_{a,d,j,t} &= \tau\, p_{a,d,i_j,t} b_{d,j} / \mu_{d,i_j}. \end{aligned} \tag{13}$$

2.2 Data

BEEPmbp can accept data of the following types:

- **Time series transition data** – As in Fig. 4, this is represented by a list giving the number of individuals passing down a specified transition (or multiple transitions) over a series of time steps, *e.g.* every 7 days. Transitions can further be stratified by area or demographic group leading to a table of inputs (*e.g.* different columns could represent geographical areas and different rows represent different weeks). This can be used to incorporate, *e.g.*, case data, hospital admissions or death data.
- **Time series population data** – This is represented by the population in a compartment (or compartments) at a series of time points[12]. Again, this data can be stratified by age or demographic group, and can be used for, *e.g.*, hospital population data.

[11] BEEPmbp does allow for modification to this.
[12] In this case they do not need to be equally spaced in time.

- **Time series population fraction data** – The same as population data except expressed as a fraction of the entire population. This can be used for, *e.g.*, seroprevelence data[13].
- **Marginal data** – This is represented by the number of individuals going down a specified transition (or multiple transitions) over a specified time period (*e.g.* from the beginning to the end of an analysis period) stratified by area or demographic group. Such data is often publically available, *e.g.* the number of hospital admissions broken down by age group.

2.3 Bayesian inference

Collectively the model parameters are referred to as θ. The initial populations $p_{a,d_{-s},c,,t_{\text{start}}}$ and transitions between states $n_{a,d,j,t}$ define the system dynamics. These are collectively referred to as ξ. In reality, ξ is not known, and from a Bayesian point of view is considered as a set of latent model variables.

Application of Bayes' theorem implies that the posterior probability distribution is given by

$$\pi(\theta,\xi \mid y) \propto \pi\left(y \mid \xi\right) L(\xi \mid \theta)\pi(\theta), \tag{14}$$

where $\pi(y|\xi)$ is the "observation model", which gives the probability of the data given a system state, $L(\xi|\theta)$ is the "latent process likelihood", which gives the probability of the state given a set of model parameters, and, finally, $\pi(\theta)$ is the prior, which captures the state of knowledge regarding parameter values before data y is considered.

BEEPmbp incorporates 7 different inference algorithms which aim to generate samples from the posterior distribution in Eq.(14). These methods can be split into two contrasting approaches:

2.3.1 Power posterior

Whilst Eq.(14) represent an ideal, often it is found that generating true posterior samples takes an infeasibly long CPU time, especially when y contains a lot of data[14]. One way around this to consider a modified distribution called the power posterior:

$$\pi_{PP}(\theta,\xi \mid y,\phi_{post}) \propto \left[\pi\left(y \mid \xi\right)\right]^{\phi_{\text{post}}} L(\xi \mid \theta)\pi(\theta), \tag{15}$$

where ϕ_{post} is a parameter called the inverse temperature. When ϕ_{post}=1 the true posterior is recovered and when ϕ_{post}=0 the system maps of the prior (with disregard for the data). Setting ϕ_{post} less than one can substantial speed up inference, but only marginally affect posterior estimates (essentially justifying this approach).

Four different inference algorithms aim to draw samples from the power posterior in Eq.(15):

Markov chain Monte Carlo with model-based proposals (MCMC-MBP) – This approach runs an MCMC chain at a specified ϕ_{post} using so-called model-based proposals (MBPs). MBPs allow for joint

[13] Seroprevalence studies gather random samples of individuals from the population to estimate the current infection rate.

[14] When the data is very restrictive on the states the system can accept, this can lead to long mixing times and/or the system becoming stuck in metastable states.

proposals in θ and ξ to explore the power posterior more efficiently than changes made in conventional data augmentation schemes[15].

Metropolis coupled MCMC (MC^3) – Here K separate MCMC chains, indexed by k, are run in parallel (again, making use of MBPs). The inverse temperatures of these chains are selected to span from the posterior (k=1) to the prior (k=K) [16]:

$$\phi_k = \left(\frac{K-k}{K-1}\right)^4 \phi_{post}. \tag{16}$$

This approach has the advantage of improved mixing[17] (states can be swapped between chains), is less prone to getting stuck in metastable states (the higher temperature chains effective smooth out the posterior landscape allowing for a greater degree of exploration) and can be used to estimate the model evidence (see §2.3.5 later). However, this method does come with the addition computational burden of running multiple chains.

Particle annealed importance sampling using MBPs (PAIS-MBP) - PAIS-MBP starts with a number of randomly sampled "particles" from the prior. The algorithm proceeds through a series of generations and within each generation: a) the inverse temperature is increased such that, on average, half of the particles are copied and half are culled, and b) a series of MBPs allow particles to explore parameter and state space (to avoid degeneracy).

Particle-MCMC (PMCMC) – This runs a single MCMC chain at a specified inverse temperature ϕ_{post}, but here the state ξ is constructed separately for each Metropolis-Hastings proposal. This construction requires a sequential Monte Carlo filtering step that uses multiple parallel simulations from the model, otherwise known as particles, along with filtering of these particles at predetermined time intervals. When large amounts of data are analysed, this method requires a large number of particles to efficiently run, which can lead to very computationally slow proposals. However, PMCMC tends to mix faster than other approaches, helping to mitigate this effect.

2.3.2 Approximate Bayesian computation

Rather than use the full observation model in Eq.(14), approximate Bayesian computation (ABC) relies on introducing a measure the fit between the data y and the state ξ called the error function (EF). We define a model "sample" to be generated by first sampling the model parameters θ from the prior $\pi(\theta)$ and then simulating the state ξ from the model. Under ABC the posterior distribution is approximated by sampled states θ and ξ for which EF is below a given cut-off value EF_{cutoff}. This can be represented by

$$\pi_{ABC}(\theta, \xi \mid y, EF_{\text{cutoff}}) \propto H\left(EF(y \mid \xi) - EF_{\text{cutoff}}\right) L(\xi \mid \theta)\pi(\theta), \tag{17}$$

where H is the Heaviside step function.

---

[15] These would typically make small changes to each of the quantities in $n_{a,d,j,t}$ and accept or reject these changes based on a Metropolis-Hastings probability.

[16] Note, the power 4 is found to empirically work well under most scenarios. This factor, however, can be specified in the software using the 'invT_power' command.

[17] Good mixing implies that consecutive samples along the MCMC chain are less correlated.

For convenience we assume that the error function is functionally related to the observation model through[18]

$$EF(y \mid \xi) = -2\log\left(\pi\left(y \mid \xi\right)\right). \tag{18}$$

BEEPmbp incorporates three algorithms for generating samples from Eq.(17):

Approximate Bayesian Computation (ABC) – This generates posterior samples by means of a simple ABC rejection sampling scheme. This sample from the model (as described above) and accepts only those samples with error function below the cut-off.

Approximate Bayesian Computation using sequential Monte Carlo (ABC-SMC) – This runs over a number of generations, with the previous generation being used as an importance sampler for the next. Under some circumstances this approach is significantly more computationally efficient than the standard ABC algorithm.

Approximate Bayesian Computation with model-based proposals (ABC-MBP) – This starts with a number of randomly sampled "particles" from the prior (a particle comprises of a parameter set and a system state). The algorithm proceeds through a series of generations and within each generation: a) the EF cut-off is reduced such that half the particles are copied and half are culled, and b) a series of MBPs allow particles to explore parameter and state space (to avoid degeneracy).

2.3.3 Observation models

Here we list different possible observation models that BEEPmbp can use to relate the observed data to the equivalent quantity derived from the state ξ (note through the relationship in Eq.(18) this also defines potential error functions that can be used).

For simplicity BEEPmbp assumes that observations are independent[19], and so

$$\pi\left(y \mid \xi\right) = \prod_i \pi\left(y_i \mid Y_i(\xi)\right), \tag{19}$$

where i indexes measurements, y_i is the value of the ith measurement (*e.g.* this could come from one of the table entries in Fig. 4) and Y_i is the equivalent value derived from the state ξ. The possible choices are:

- **Normal** – The data is normally distributed around the state value with variance set to the mean:

$$\pi\left(y_i \mid Y_i(\xi)\right) = N(y_i \mid Y_i(\xi), {}_i\, Y_i(\xi) + \varepsilon), \tag{20}$$

  where $N(x|\mu,\sigma^2)$ is normal probability for x given a mean μ and variance σ^2 (note, ε=0.5 is a small constant introduced to ensure validity even when y_i is zero).
- **Poisson** – The data is Poisson distributed around the state value:

[18] This definition implies that a normally distributed observation model transforms to a sum of residuals error function.

[19] This assumption is valid for transition data, but less so for population data (*e.g.* the hospital population on one day will clearly be strongly correlated to that from the previous day).

$$\pi\left(y_i \mid Y_i(\xi)\right) = P(y_i \mid Y_i(\xi)), \tag{21}$$

where $P(x|\mu)$ is the Poisson probability distribution for x given a mean μ.

- **Negative binomial** – The data has a negative binomial distribution around the state value:

$$\pi\left(y_i \mid Y_i(\xi)\right) = NB(y_i \mid Y_i(\xi), k), \tag{22}$$

where $NB(x|\mu,r)$ is the negative binomial probability distribution for x given a mean μ and shape parameter r. This parameterisation implies a variance of $\mu + \mu^2/r$, and so the negative binomial is over-disperse when compared to a Poisson distribution (which has a variance of just μ).

- **Scaled** – This uses the square of the log of the relative size of y_i or Y_i (measured as a fraction) as the basis of an error function:

$$EF(y_i \mid Y_i(\xi)) = \left[\log\left(\frac{y_i+\varepsilon}{Y_i+\varepsilon}\right)\right]^2, \tag{23}$$

where ε=0.5 is a small constant introduced to ensure validity even when y_i or Y_i are zero. Converted this into an observation model using Eq.(18) gives

$$\pi\left(y_i \mid Y_i(\xi)\right) = e^{-\frac{1}{2}\left[\log\left(\frac{y_i+\varepsilon}{Y_i+\varepsilon}\right)\right]^2}. \tag{24}$$

The options above can be selected separately for each of the data files loaded into BEEPmbp. Incorporate of thresholds into the model is discussed in Appendix E. For most problems, the scaled approach seems to work best, and so this is used by default.

2.3.4 Incomplete observations

For some measureable quantities we can be confident that the values from data are directly comparable into the data types in §2.2, *e.g.* statistics on hospitalisations and deaths. However for other measureable quantities things become less clear. Consider the daily number of disease cases. Here it is tempting to directly relate these to the daily number of infection transitions that occur in the model. This, however, might represent a huge underestimate, because observed cases heavily depend on rate at which individuals are tested (also tests are imperfect and do not pick up all infections)[20] . This is further complicated by the fact that testing effort may have changed over time.

To help mitigate this, BEEPmbp allows for $Y_i(\xi)$ to be modified in such a way that it can be used to directly compare to the data y_i. In particular a time-dependent scaling can be added:

$$Y_i' = s_t Y_i, \tag{25}$$

where s_t is a time-varying spline (which can either be specified or inferred). This modified value is then used in the observation model in §2.3.3.

[20] The test sensitivity *Se* characterises the probability that a truly infected individual generates a positive test result.

Considering the daily case data discussed above, this would first need be shifted in time[21] (to account for the difference in time between becoming infected and becoming a case), and then it could be directly compared to the modified $Y_i(\xi)$ (using Eq.(25) which accounts for time variation in testing availability) through the observation model.

2.3.5 Model evidence

The model evidence (ME) $\pi(y)$ is a measure for comparing how well the data y agrees with the model[22]. One way to define this is as the expected value of the observation model over random samples from the model ξ [23]:

$$\pi(y) = \left\langle \pi\left(y \mid \xi\right) \right\rangle_{\xi} \tag{26}$$

Models that generate samples in good agreement with the data have a higher ME (because their observation model probability is higher) and *vice versa*.

As discussed above, for most practical applications it is not possible to sample from the true posterior. Following sections 2.3.1, the ME for the power posterior is given by

$$\pi(y \mid \phi_{post}) = \left\langle \left[\pi\left(y \mid \xi\right) \right]^{\phi_{post}} \right\rangle_{\xi}, \tag{27}$$

and for ABC approaches in §2.3.2

$$\pi(y \mid EF_{\text{cutoff}}) = \left\langle H\left(EF(y \mid \xi) - EF_{\text{cutoff}}\right) \right\rangle_{\xi}. \tag{28}$$

It is important to note that the ME is not just a single value, but depends on either the inverse temperature of the prior ϕ_{post} or error function cut-off EF_{cutoff}. When performing model comparison, therefore, care must be taken to ensure it is done so at a consistent value of ϕ_{post} (or EF_{cutoff}). The ratio in ME gives the Bayes factors between models. A Bayes factor above 3.2 is considered substantial support for one model over another, and over 10 provides strong evidence (Kass and Raftery (1995)).

Appendix F describes how the ME is calculated for the algorithms which can estimate this quantity[24].

[21] When time series data is loaded into BEEPmbp it can be shifted in time by setting the 'shift' property.
[22] Other model selection techniques such as DIC have proven to be notoriously unreliable for the sorts of epidemiological model considered here.
[23] These are generated by first sampling model parameters θ from the prior $\pi(\theta)$ and then simulating the state ξ from the model.
[24] PMCMC and MCMC-MBP are not able to estimate model evidence because they only explore parameter space around the posterior.

3 The input TOML file

The input TOML file contains the information BEEPmbp requires in order to define the model (from §2), reference data files, and perform simulation, inference or prediction. An index of all TOML commands is given in a glossary at the end of the manual. BEEPmbp also contains numerous examples, as discussed in §6, which help to illustrate practical uses for this software.

3.1 A simple example

We first go through the following very simple example (taken from the file "examples/EX1.toml" and first introduced in §1.4):

```
time_format = "year-month-day"
start = "2020-01-01"
end = "2020-09-01"
datadir = "examples/Data_EX1"
outputdir = "Output_EX1"
comps = [{name="S"},
         {name="E", dist="Erlang", k="2", mean_value="4"},
         {name="I", dist="Exp", mean_value="4", inf_value="1"},
         {name="R"}]
trans = [{from="S", to="E", infection="yes"},
         {from="E", to="I"},
         {from="I", to="R"}]
R_spline = [{value="2.0", prior="Uniform(0.4,4)"}]
efoi_spline = [{value="0.1"}]
areas = "scotland.csv"
data_tables = [{type="transition", observation="E->I", timestep="7", file="EI.csv"}]
state_outputs = [
      {plot_name="Dynamics", type="population", observation="S", line_colour="green"},
      {plot_name="Dynamics", type="population", observation="E", line_colour="yellow"},
      {plot_name="Dynamics", type="population", observation="I", line_colour="red"},
      {plot_name="Dynamics", type="population", observation="R", line_colour="blue"}
       ]
modification = [{start="2020-04-01", type="beta_fac", factor="0.3"}]
```

'time_format' determines how time is represented (in both the TOML file and also any data files). This can take the values "*year-month-day*", "day/month/year", "day.month.year" or "number", and is set depending on the type of data available.

'start' and 'end' give the start and end dates/times for analysis.

'datadir' defines the location of the data directory.

'outputdir' indicates where outputs from BEEPmbp are placed.

'comps' defines the compartments in the model, which in this case are specified to be: susceptible S, exposed E, infectious I and recovered R (see Fig. 1). 'dist' specifies the distribution given to the

residency time, where "Exp" denotes the exponential distribution and "Erlang" denotes the Erlang distribution (with corresponding shape parameter k). Under simulation the means of these distributions are specified by 'mean_value'. If no distribution is set, it is assumed that no transitions leave the compartment[25]. The relative infectiousness is set by 'inf_value', and if omitted is assumed zero[26].

'trans' defines the transitions in the model (corresponding to the arrows in Fig 1). Setting 'infection' to "yes" indicates the infection transition (only one such transition can be defined in this way). The rate of this particular transition is determined by the force of infection in Eq.(1).

'R_spline' defines a spline that describes how the reproduction number R_t in Eq.(1) changes over time (see §3.3 for how splines are defined). In this particularly simple case, its value is set to be constant. The prior is set to a uniform distribution between 0.4 and 4, which means under inference the spline that specifies R_t is bounded between these two values.

'efoi_spline' defines a spline giving the external force of infection $\eta_{s,a,d,t}$ Eq.(1). This is used to generate infections in the system that initiate epidemics in the first place. By default, its value is expressed as the probability of infection per unit time per 100,000 individuals[27].

'areas' specifies a file giving information about the population under study. This file must reside in the 'datadir' directory and can either be in ".csv" format (in which case columns are separated by commas) or ".txt" format (columns are tab separated). Here the file "scotland.csv" is:

```
area,population
Scotland,5454000
```

One column in this file must have the heading "area", and this to refers the geographical area under consideration. This particular example gives a non-spatial analysis (focusing on a nationwide analysis of Scotland), but a list of different areas could be provided (see §3.6 for further details on spatial model). Another column must have the heading "population" (or alternatively several columns stratifying the population into different demographic groups, see §3.5).

'data_tables' incorporates data files (which can again be in ".csv" or ".txt" formats). In the example above, 'data_tables' reads in the number of transitions between compartments E and I per day from the file "EI.csv" (note, when run in inference mode these files should be placed in the data directory, whereas in simulation mode these data files are actually generated in the "Simulate_data" sub-directory in the output). Figure 4 shows this data file.

'state_outputs' can be used to generate additional graphical plots (*e.g.* see Fig.3(d) and 6(d)).

'modification' is used to specify a changes to the model when performing prediction, as discussed in §1.4.3.

[25] With the exception of the infection transition, for which the force of infection determines the transition rate.
[26] If the model contains multiple infectious states, setting different values can be used to set their relative infectivity.
[27] This factor can be changed using the 'efoi_factor' command.

Having introduced this simple example, we now systematically go through different aspects of model and data specification to show how more complex scenarios can be dealt with.

3.2 Priors

In the TOML file above all parameters were assumed known except for R_t, which was taken to have a uniform prior. In fact any specified parameter can have a prior distribution associated with it and this is used when inference is performed.

For most parameters priors can take any of the following possibilities: “Fixed(.)” to fix the parameter value, “Uniform(.,.)” for a uniform distribution within a range, “Exp(.)” for an exponential distribution with specified mean and “Gamma(.,.)” for a gamma distribution with specified mean and standard deviation.

For some parameters it is necessary to apply Dirichlet priors. These are used in circumstances in which a series of parameters (or quantities derived from parameters) are required to add to one. A clear example is branching probabilities, but Dirichlet priors are also used for parameters giving relative susceptibilities, area effects, and level effects[28]. Two types of Dirichlet prior specification can be made: 1) “Dir(*)” is used to apply an uninformative flat prior and 2) “Dir(mean,sd)” applies an informative prior with a specified mean and standard deviation[29].

Additionally, priors can be set that enforce the ordering of certain parameter. In this example

```
R_spline = [{param="R0 | R1 | R2 | R2”, value="2.0 | 1.9 | 1.5 | 0.6", prior="Uniform(0.4,4)"}]
prior_order="R0 > R1 | R1 > R2 | R2 > R3"
```

the command ‘prior_order’ ensures that under inference the reproduction number R_t must strictly reduce over time. This may be consistent with the prior belief that implementing intervention strategies must inevitably reduce disease transmission.

It is important to note that data often provides little information about some model parameters[30]. If priors are uninformative and diffuse, this can result in a much longer computational time to perform inference than otherwise. Therefore, wherever possible it is advisable to place as restrictive priors on model parameters

3.3 Splines

Piecewise linear splines are used in BEEPmbp to capture time variation in model parameters (see Fig. 10). We now provide a description of how these splines are defined (note, the examples below use R_t, but the same basic definitions apply to all splines).

3.3.1 Simulation

First we look at defining a spline for use in simulation. Here is an example (shown in Fig. 10(a)):

```
R_spline = [{bp="start | 2020-03-01 | 2020-07-15 | end", param="R0 | R1 | R2 | R3”,
```

[28] This ensures the normalisation conditions in Eq.(3), (5) and (7) are strictly satisfied.
[29] For N Dirichlet parameters, N-1 means are specified and a single value for ‘sd’ (all other values are set to ‘*’). This restriction arises because the Dirichlet prior support only N free parameters.
[30] In which case the posterior distribution maps out almost the same distribution as the prior.

```
                value="2.0 | 1.5 | 0.5 | 1.0"}]
```

'bp' defines the breakpoints in time along the spline. Each breakpoint is separated by a '|' character (spaces either side of this are ignored). The special keywords 'start' and 'end' refer to the start and end times specified in the analysis. If 'bp' is not set, its default value is taken to be "start|end", *i.e.* representing a simple line across the analysis time period. In the case above, intermediate breakpoints are set on March 1st and July 15th 2020.

'param' defines the names of parameters associated with each of the breakpoints. If 'param' is not specified, BEEPmbp automatically generates informative names for the parameters, *e.g.* "R(t) t:0" would be the name given to the first parameter along this spline.

'value' sets the values those parameters take under simulation.

.

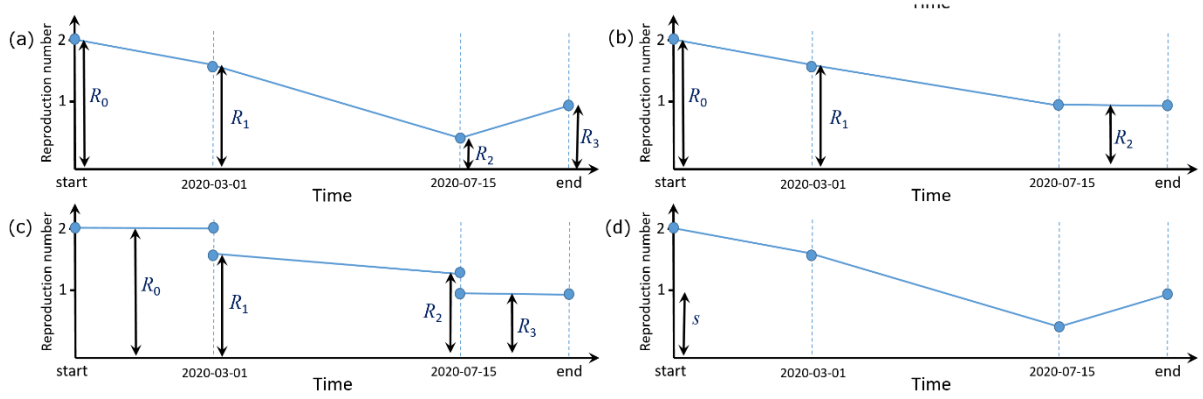


Figure 10: Types of spline – This shows different ways in which splines can be defined (see §3.3 for details). (a) A piecewise linear spline defined by four breakpoints with four parameters R_0-R_3 specify the heights at each breakpoint. (b) The last two breakpoints share the same parameter (hence the spline is flat during this region). (c) This spline has discontinuities. (d) This spline uses a time-varying factor to specify it (a single parameter multiplies the entire profile).

3.3.2 Inference

When performing inference the expression above could still be used, but this would fix the spline to a specified set of parameters. In most cases we actually wish to estimate these parameters from the data. To do this we must add in a specification for the prior:

```
R_spline = [{bp="start | 2020-03-01 | 2020-07-15 | end", param="R0 | R1 | R2 | R3",
                value="2.0 | 1.5 | 0.5 | 1.0", prior="Uniform(0.4,4)"}]
```

By default, the same prior specification gets applied to all spline parameters, although individual specification is also possible. For example

```
prior="Uniform(0.4,4) | Exp(1.1) | Uniform(0.2,2) | Uniform(1.0,3)"
```

sets a different priors for each parameter.

As well as a prior on each of the model parameters, a smoothing prior can also be placed on the splines itself. This is used to suppress unphysical fluctuations. For example during a real pandemic we would not expect the reproduction number to go drastically up or down week on week. Rather we would expect it to vary in a smooth way. This is incorporated into the model by the addition of:

```
smooth_type="smooth", smooth = "0.5"
```

'smooth_type' specifies the type of smoothing and 'smooth' sets its strength s[31]. Three different types of smoothing can be selected from:

- "no_smooth" – Implies no smoothing (used as default).
- "smooth" – Implies a smoothing prior given by

$$\pi(\theta^{spline}) = \prod_{b=1}^{B-1} N(\theta_{b+1}^{spline} \mid \theta_b^{spline}, s^2), \tag{29}$$

  where N is the normal probability distribution, b indexes the B breakpoints and θ_b^{spline} represents the parameters along on the breakpoints.
- "log_smooth" – Implies a smoothing prior given by

$$\pi(\theta^{spline}) = \prod_{b=1}^{B-1} LN(\theta_{b+1}^{spline} \mid \theta_b^{spline}, s^2), \tag{30}$$

  where LN is the log-normal probability distribution in this case. This type of smoothing is appropriate when the spline represents a strictly positive quantity.

3.3.3 Different types of spline

Figure 10 shows some different ways in which splines can be defined:

Parameter repeated – Figure 10(b) shows an example in which a single parameter is used on more than one breakpoint[32]:

```
R_spline = [{bp="start | 2020-03-01 | 2020-07-15 | end", param="R0 | R1 | R2 | R2",
              value="2.0 | 1.5 | 1.0 | 1.0"}]
```

Discontinuity – Figure 10(c) shows how discontinuities can be added by repeating the same breakpoint times:

```
R_spline = [{bp="start | 2020-03-01 | 2020-03-01 | 2020-07-15 | 2020-07-15  | end",
              param="R0 | R0 | R1 | R2 | R3 | R3", value="2.0 | 2.0 | 1.6 | 1.4 | 1.0 | 1.0"}]
```

Note, these discontinuities are not acted on by smoothing priors in Eqs.(29) and (30).

Time-varying factor – Figure 10(d) shows an example in which a time-varying factor is used. Here the shape of the curve is fixed, but just a single parameter s multiplies the entire curve (hence during inference only a single parameter needs to be estimated):

```
R_spline = [{bp="start | 2020-03-01 | 2020-07-15 | end", param="s",
```

[31] This strength can be set individually for each breakpoint by separating values using the '|' character.
[32] In this case, the numbers set in 'values' must be the same each time the same parameter is used.

```
                value= "1.0", factor="2.0 | 1.5 | 0.5 | 1.0"}]
```

Whilst not usually appropriate for reproduction number, such an approach can be applicable to the external force of infection (for which movement data between the population under study and elsewhere can potentially be estimated, *e.g.* by air traffic movement).

3.3.4 Using a file to define a spline

If the spline contains numerous breakpoints, definition of them in the TOML file itself can be somewhat cumbersome. Instead, BEEPmbp allows for the possibility of loading information about the spline from a file. For example, the spline used in Fig. 10(c) could equally be represented by

```
R_spline = [{bp="[Breakpoint:R.csv]", param="[Parameter:R.csv]", value="[Value:R.csv]"}]
```

where the file 'R.csv' is shown in Fig. 11 (this uses the format "[Column name:File name]".

	A	B	C
1	Breakpoint	Parameter	Value
2	start	R0	2
3	01/03/2020	R0	2
4	01/03/2020	R1	1.6
5	15/07/2020	R2	1.4
6	15/07/2020	R3	1
7	end	R3	1

Figure 11. Spline file. Shows an example file "R.csv" used to define a spline.

3.3.5 Other spline properties

'geo_filt' – As applied to 'R_spline' and 'efoi_spline', this specifies the area on which the spline acts (optional, set to all areas by default).

'name' – Specifies the name of the spline. This is used when the spline is referred to elsewhere in the TOML code.

3.4 Setting up the compartmental model

In the notation below we take 'X' to represent either 'param' to specify a parameter name (optional), 'value' to specify its numerical value (for simulation or also inference, if that value is fixed) or 'prior' to specify the prior distribution for that parameter (inference only).

3.4.1 Compartments and transitions

Compartments are set up using the 'comp' command. The following example sets up an SEIRD model (in this model individuals can either recover or die after becoming infected):

```
comps = [{name="S"},
         {name="E", dist="Erlang", k="2", mean_value="3", mean_prior="Uniform(2,4)"},
         {name="I", dist="Exp", mean_value="4", mean_prior="Uniform(3,5)", inf_value="1"},
         {name="R"},
         {name="D"}]
```

'name' gives the name for the compartment.

'dist' gives the distribution type (with shape parameter k specified for Erlang distributions).

'mean_X' defines the mean residency time (appropriate if transitions leave the compartment). This can be set separately for different demographic groups (see §3.4.2). In this example, a uniform prior has been placed on of potential residency times within compartments E and I.

'inf_X' defines the relative infectivity (assumed zero if unspecified).

Transitions in the model are setup using the command ‘trans’, for example

```
trans = [{from="S", to="E", infection="yes"},
         {from="E", to="I"},
         {from="I", to="R", prob_value="0.9", prob_prior="Dir(*)"},
         {from="I", to="D", prob_value="*", prob_prior="Dir(*)"}]
```

‘from’ and ‘to’ specify the initial and final compartments of the transition.

‘infection’ specifies the infection transition (only one may be set).

‘prob_X’ specifies the probability of moving down a given branch (note, this only needs to be specified when the ‘from’ compartment has more than one transition leaving it). Because the sum of branching probabilities for all transitions leaving a compartment must be one, so one of these probabilities does not need to be specified (because it can be calculated from the others). This is indicated by using the ‘*’ symbol. Here ‘prob_prior’ defines a flat Dirichlet prior (see §3.2).

3.4.2 Demographic dependency

It might be expected that the mean residency times and branching probabilities, introduced in the previous section, depend on the demographic grouping to which an individual belongs (see §3.5 for how these grouping are defined).

For example, suppose a model contains three age groups: “child”, “adult” and “elderly”. Within ‘comp’, an age-based dependency on the recovery time could be added in the following way:

```
{from="I", to="R", mean_param="IR_Y | IR_A | IR_E", mean_value="age: 2.6 | 3.4 | 5"}
```

Within either ‘mean_param’ or ‘mean_value’ the specification of demographic classification followed by a colon sets the demographic dependency. Note, the order of the values in ‘mean_value’ must follow the order in which the demographic categories are defined within the classification (see §3.5).

If there is a further dependency on another demographic classification, this can also be set. For example

```
{from="I", to="R", mean_param="tE_YM | tE_AM | tE_EM | tE_YF | tE_AF | tE_EF",
                   mean_value="age,Sex : 3.4 | 4 | 2.3 | 3.6 | 4.2 | 5.5"
```

would be used to specify age and sex dependency.

Similarly, demographic dependencies can be added to branching probabilities in ‘trans’.

3.4.3 Specifying the reproduction number R_t

The command ‘R_spline’ is used to specify R_t, a spline giving time variation in the reproduction number in Eq.(1) . For example,

```
R_spline = [{bp="start | 2020-03-01 | 2020-07-15 | end", param="R0 | R1 | R2 | R3",
             value="2.0 | 1.5 | 0.5 | 1.0", prior="Uniform(0.4,4)"}]
```

sets up the spline shown Fig. 10(a), with a prior restricting its value to the range 0.4 to 4 under inference (see §3.3 for further details on spline specification).

In spatial models the same spline R_t is typically used for all the areas in the system. BEEPmbp does, however, allow for different splines to be fit to different areas (or aggregations of areas) separately using 'geo_filt'[33]. In this example, a different spline is fit to England and Scotland[34]:

```
R_spline = [{bp="start | 2020-03-01 | 2020-07-15 | end", param="EngR0|EngR1|EngR2|EngR3",
              value="2.0 | 1.5 | 0.5 | 1.0", prior="Uniform(0.4,4)", geo_filt="Nation:England"},
            {bp="start | 2020-03-01 | 2020-07-15 | end", param="ScoR0|ScoR1|ScoR2|ScoR3",
              value="2.3 | 1.2 | 1.3 | 0.9", prior="Uniform(0.4,4)", geo_filt="Nation:Scotland"}]
```

3.4.4 Specifying the external force of infection

The command 'efoi_spline' is used to define a spline setting the external force of infection $\eta_{s,a,d,t}$ in Eq.(1). This term generates infections in the system initiated elsewhere. By default, its value is expressed as the probability of infection per unit time per 100,000 individuals (although this can be changed using the 'efoi_factor' command).

Unlike R_t, it is usually not possible to infer the shape of the profile of external infection[35]. However one way in which it can be incorporate is the following:

```
efoi_spline = [{param="phi", value="1", bp="[bp:phi_spline.txt]", factor="[fac:phi_spline.txt]"}]
```

Here the 'factor' property is used to specify the daily expected external force of infection (which can be derived from, *e.g.*, movement in and out of the area and rates of disease in the interacting population).

Other optional properties can be set: 1) As with R_t above, 'geo_filt' can be set to specify different geographical regions separately, 2) 'strain' can be used to specify a force of infection for a specific strain (see §3.8), and 3) 'age_dist' can set the fraction of externally infected individuals in different age groups.

3.5 Defining demographic groups

It may be that, from an epidemiological point of view, different demographic groups in the population behave differently. This section described how these groupings are specified.

3.5.1 Age stratification

Age stratification in the population can be incorporated by defining 'ages', for example

```
ages = {cats="age0-19 | age20-69 | age70+"}
```

specifies three age groups (young, adult and elderly).

[33] In essence R_t is replaced by $R_{a,t}$ in Eq.(1).

[34] Note, from section 3.6, it is assumed that the 'areas' file contains a column with heading "Nation" and either "England" or "Scotland" is specified on each of the rows.

[35] This is because once local transmission gets going the external contribution to the overall infection rate is typically very low.

'cats' specifies the categories (separated by '|'). How the population is divided into age groups is discussed in §3.6.2.

If 'ages' has N age categories, 'age_mixing_matrix' must be set to a file giving an NxN matrix that captures interactions between individuals in the same and different age groups (this is used to derive the matrix $C_{z,z'}$ just below Eq.(9), as explained in Appendix D).

On top of this BEEPmbp allow for modification of $C_{z,z'}$ through the 'age_mixing_modify' command. For example

```
age_mixing_modify = [{type="row_column", agecat="age70+", bp="[bp:amm.csv]",
      value="[value:amm.csv]", prior="Uniform(0,5)", smooth_type="log_smooth", smooth="0.3"}]
```

sets up a smoothed spline which multiplies the row and column of $C_{z,z'}$ corresponding to the age category "age70+". For example, this could be used to study the effect of varying levels of shielding for the elderly.

3.5.2 Other demographic classifications

Other stratifications can be specified by setting 'democats', for example

```
democats = [{name="Sex", cats="Male | Female"},
            {name="Ethnicity", cats="White | Black | Asian"}]
```

'name' describes the classification and 'cats' provides the different categories that classification can take (separated by '|'). Note, the CPU time of the algorithm scales multiplicatively with the classification sizes (hence this model would run approximately 2×3=6 times slower than a non-stratified model).

3.5.3 Variation in susceptibility

Optionally, differences in susceptibility for different age and/or demographic groups can be set or inferred (these corresponds to the values of $\hat{\sigma}_{q,v}$ in Eq.(2)). For example

```
ages = { cats="age0-19 | age20-69 | age70+", sus_value="0.7 | 1.0 | *", sus_prior="Dir(*)"}
```

'sus_X' defines the relative susceptibility for different age groups (optional, set to 1 by default). Note, because of the normalisation condition in Eq.(3), not all values need to specified, which is why one value is set to the '*' symbol. 'sus_prior' must take a Dirichlet distribution.

3.5.4 Incorporating changes in demographic groups

The command 'democat_change' allows for the proportions within a specified demographic classification in the susceptible population to vary over time (*e.g.* this can be used to study the effect of vaccination), for example

```
democats = [{name="Vac Status", cats="Vac | Not Vac"}]
democat_change = [{name="Vac Status", file="vac.csv"}]
```

'name' references the name for the demographic classification that is changing.

'file' gives the name of the data file (see Fig. 12 as an example). This must have a 'Date' column and columns for all but one of the demographic categories. The numbers can either be populations, percentages or fractions. At times between the specified dates the demographic make-up is linearly interpolated.

	A	B
1	Date	Vac
2	2021-01-01	0
3	2021-02-01	75400
4	2021-03-01	143455
5	2021-04-01	284530
6	2021-05-01	545356
7	2021-06-01	843564

Figure 12. Vaccination data. Shows example file "vac.csv".

Two further specifications can be made:

'democats_filt' specifies a filter to include only a specified demographic groups (*e.g.* 'democats_filt ="Sex:Male"' would mean that the specified demographic changes are made on males only).

'geo_filt' specifies a geography over which the observation are made (*e.g.* 'geo_filt ="Nation:Scotland"' would mean that specified demographic changes are made in Scotland only.

	A	B	C	D	E	F	G	H	I	J
1	area	name	nhs region	density	age0-19	age20-69	age70+	Male	Female	area effect
2	S12000005	Clackmannanshire	S08000019	3.23327	11269	33087	7044	25225	26175	1.3
3	S12000006	Dumfries and Galloway	S08000017	0.231554	29158	92583	27049	72321	76469	0.7
4	S12000008	East Ayrshire	S08000015	0.965354	26223	78457	17160	59105	62735	1.2
5	S12000010	East Lothian	S08000024	1.557614	23750	66839	15201	50719	55071	0.6
6	S12000011	East Renfrewshire	S08000031	5.461709	23834	57594	13742	45473	49697	1.5
7	S12000013	Na h-Eileanan Siar	S08000028	0.0878	5305	16648	4877	13247	13583	2.3
8	S12000014	Falkirk	S08000019	5.392018	35007	104352	20981	78497	81843	0.6
9	S12000017	Highland	S08000022	0.091814	49231	149837	36472	115391	120149	0.9
10	S12000018	Inverclyde	S08000031	4.871019	15906	50622	11622	37401	40749	1.3
	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮

Figure 13: Area specification. This gives an example of a file specifying different local authorities in Scotland (taken from "example/Data_EX2/Scotland_LA.csv"). The columns are as follows: 'area' specifies a unique area code, 'name' gives the name of the local authority (not used in analysis), 'nhs region' specifies which NHS region the local authority belongs to, 'density' gives the population density, 'age#' gives populations in different age groups, 'Male' and 'Female' give populations broken into sexes, and, finally, 'area effect' is a fictional relative area effect data used for simulation purposes.

3.6 Spatial models

3.6.1 Loading area information

The 'areas' command is used to specify a file in the data directory giving information about the population under study and the geographical region in which that population resides, for example

```
areas= "Scotland_LA.csv"
```

Figure 13 shows an extract of a file giving information about local authorities in Scotland.

Generally speaking, the 'areas' file must contains the following columns: "area" (which gives a code or name that uniquely identifies each area), other coarser geographical scales if they are used (*e.g.*

'nhs region' amalgamates local authorities into NHS regions), columns for covariates in the model (*e.g.* population density)[36] and, potentially, the initial population make-up (see below).

3.6.2 The initial population

This section discusses how information about the initial population ($p_{a,d_s,c,,t_{\text{start}}}$ in §2.1.3) is loaded into BEEPmbp. In fact, it can be incorporated in one of two ways:

Within the 'areas' file – If the model is not age-stratified (*i.e.* the command 'ages' is unspecified), a column with the heading "population" in the file 'areas' gives the total population size within each area. For age-stratified models, in the first instance BEEPmbp looks for column headings in the 'areas' file corresponding to the specified age categories (*e.g.* "age0-19", see Fig. 13). Failing that, it takes the text preceding the number range (which is "age" is this particular case), and then looks to add up columns with headings given by this text plus a number in the range specified[37]. For other demographic classifications the 'areas' file must contain column headings corresponding to each category, with values given as either populations, percentages, or fractions. Here we assume that probabilities of being in different categorisations are independent, *e.g.* the population of males in the age range 0-19 would be equal to the population in 0-19 multiplied the fraction of males. This assumption is usually reasonably valid in most cases, although it can break down (*e.g.* individuals in older age groups are predominantly female). To overcome this limitation the following option can be used.

	A	B	C	D	E
1	area	age	Sex	compartment	population
2	S12000005	age0-19	Male	S	5530
3	S12000005	age20-69	Male	S	16238
4	S12000005	age70+	Male	S	3457
5	S12000005	age0-19	Female	S	5739
6	S12000005	age20-69	Female	S	16849
7	S12000005	age70+	Female	S	3587
8	S12000006	age0-19	Male	S	14173
9	S12000006	age20-69	Male	S	45001
10	S12000006	age70+	Male	S	13147
	⋮		⋮		⋮

Figure 14. Population initialisation file. This shows an example of a file that could be used with 'init_pop' to specify the initial population. Note, the ordering of row/columns is unimportant.

Using initialisation file 'init_pop' – Alternatively the initial populations can be specified within a file specified using the 'init_pop' command. This file must contain the headings "area" (giving the area name, as specified in the 'areas' file), "age" (if the model is age stratified), the names for any demographic categories, "strain" (if different strains are specified), "compartment" (specifying the name of the compartment) and, finally, "population". The file then consists of series of rows that list every possible combination of options followed by the corresponding population within that grouping (*e.g.* see Fig. 14).

[36] The columns do not have to have any particular order, provided they have the correct headings. Other columns may also exist which are not used by the analysis.

[37] Suppose 'areas' contained columns for yearly age intervals: "age0", "age1",….,"age99". An age category set to "age0-19" would correctly add up all columns from "age0" and "age19" and use this for analysis. Additionally, ending with a + sign, *e.g.* "age70+", adds up all columns at and above that value.

3.6.3 Geographical mixing

When more than one area is specified it becomes necessary to load a matrix that captures the interactions between areas. This is achieved by the following command

```
geo_mixing_matrix = "census_flow_data.csv"
```

If the model contains A areas, the specified file must contain an $A \times A$ table (with no headings) that sets $Z_{a,a'}$ in Eq.(8). A description on how to derive such a matrix from census flow data is provided in Appendix C.

In addition, the spline m_t in Eq.(8), which allows for time0variation in mixing, is specified by the command 'geo_mixing_modify'. For example

```
geo_mixing_modify = [{bp="[bp:gmm.csv]", value="[value:gmm.csv]", prior="Uniform(0,1)"}]
```

sets a spline which is defined using the file 'gmm.csv' and under inference is bounded between 0 and 1 (see §3.3 for more details on spline). If not specified, m_t=1 is assumed.

3.6.4 Area effects

The following four commands refer to the four contributions to area effects in Eq.(4).

Firstly, relative area effects w_a are incorporated by

```
area_effect = {value="[area effect:Scotland_LA.csv]", prior="Dir(*)"}
```

Note, in Fig. 13 the column 'area effect' contains values used when simulating from the model, and a flat Dirichlet prior is used when performing inference (this ensures the average area effect is 1).

Secondly, fixed effects. Columns of the design matrix $\boldsymbol{X}$ are added using

```
area_covars= [{name="density", param="b1", value="0.1", prior="Uniform(0,1)", func="log"}]
```

'name' must correspond to one of the columns in the 'areas' file (see Fig. 13).

'func' gives an optional functional transformation given to the raw data (this can be "linear" to leave it unchanged, or "log" to log transform).

This example shows one fixed effect but more columns to $\boldsymbol{X}$ can be added within the square brackets.

Thirdly, time-varying fixed effects. These are factors which might, in principle, affect disease transition, *e.g.* temperature or rainfall. For example

```
area_tv_covars = [{file="areatvcovars.csv", param="b2", value="0.1", prior="Uniform(0,1)",
                   func="linear"}]
```

where the file 'tvcovars_spatial.csv' contains information about the matrix $X'_{a,t}$ for a single fixed effect. 'tvcovars_spatial.csv' must contain time-varying columns for each of the areas (see Fig. 15 for an example).

In cases in which $X'_{a,t}$ is independent of area a, the following command can be used:

```
tv_covars = [{name="covar", file="tvcovars.csv", param="b2", value="0.1",
              prior="Uniform(0,1)", func="linear"}]
```

where the file 'tvcovars.csv' would contain a column specified in 'name' that would inform X'_t.

Lastly, level effects allow for different levels of disease intervention to be estimated. The level effects matrix $l_{a,t}$ is loaded using

```
level_effect = {file="level.csv", param="level1 | level2", value="0.5 | 2", prior="Dir(*)"}
```

The file 'level.csv' contains a table with dates going down rows and areas along columns, as shown in Fig 16.

Figure 15: For time-varying fixed effects. This shows an extract from 'examples/Data_EX2/areatvcovars.csv', which is a fictional dataset giving average air temperature. Different columns represent areas (see Fig. 13 for area specification) and different rows give dates.

	A	B	C	D	E	F	G	H	I	J	K
1	Date	S12000005	S12000006	S12000008	S12000010	S12000011	S12000013	S12000014	S12000017	S12000018	S12000019
2	2020-01-01	level1	level1	level2	level1	level1	level2	level2	level2	level2	level2
3	2020-01-02	level1	level1	level2	level1	level1	level2	level2	level2	level2	level2
4	2020-01-03	level2	level1	level2	level1	level1	level2	level2	level2	level2	level2
5	2020-01-04	level2	level1	level2	level1	level1	level2	level2	level2	level2	level2
6	2020-01-05	level2	level1	level2	level1	level1	level2	level2	level2	level2	level2
7	2020-01-06	level2	level1	level2	level1	level1	level2	level2	level2	level2	level2
8	2020-01-07	level1	level1	level2	level1	level1	level2	level2	level2	level2	level2
9	2020-01-08	level1	level1	level2	level1	level2	level2	level2	level2	level2	level2
10	2020-01-09	level1	level1	level2	level1	level2	level2	level2	level2	level2	level2

Figure 16: Level effects. This shows an extract from the file 'examples/Data_EX2/level.csv'. This fictional dataset assigns each area to one of two disease intervention levels as a function of time. Different columns represent areas (see Fig. 13 for area specification) and different rows give dates.

3.7 Data tables

This section describes how the command 'data_tables' is used to load the different types of data discussed in §2.2. For example

```
data_tables = [{type="transition", observation="E->I", timestep="7", file="EI.csv",
                obsmodel ="scale", shift="2"}]
```

'type' indicates the type of data, which can take four different values:

- "transition" – This gives time series information about the number of individuals moving down a specified transition(s).

- "population" – This gives time series population numbers within a specified compartment)s_.
- "population_fraction" – This gives time series population fractions within a specified compartment(s).
- "marginal" - This gives the total number of transitions over a given time period, typically stratified by a demographic classification.

‘observation’ describes what is observed. When the type is "transition" or "marginal" this is given by the initial compartment followed by “->” and then the final compartment (additionally, multiple transitions can be specified, *e.g.* “I->D,I->R”, and the sum of them is used). For "population" or "population_fraction" this is simply the compartment under measurement (or several compartments that are comma separated).

‘timestep’ sets an integer which gives the number of time units between observations (for ‘transition’ type only).

‘file’ specifies the name of the file. This must be either a tab-separated ‘.txt’ text file or a ‘.csv’ file.

‘obsmodel’ sets the observation model, which relates the observations to the underlying system state. Four possibilities exist: "normal", "poisson", "negbin" and "scale" (optional and set to "scale" by default). See §2.3.3 for details.

Three further optional specifications can be made regarding timings:

‘shift’ allows for the date/time of the data to be shifted by a specified number (*e.g.* case data can be used as a proxy for infection times, but it first needs to be shifted to account for the difference in time between an individual becoming infected and when they become a case).

‘start’ and ‘end’ gives the first and last date/time for the data. In the case of time-series data these are usually just automatically taken from the data tables provided. For marginal data they are assumed, unless specified, to coincide with the analysis period.

3.7.1 Geographical and demographic filtering

Considering transition data, the ‘observation’ property allows us to specify which transition is observed. However, suppose we actually separately have measurements for each of the areas in the system. This is an example of adding a geographic dependency. Alternatively the data might only provide information about males. This is an example of demographic filtering. The following specifications can be made within ‘data_tables’ to add geographical or demographic dependencies as well as filters:

‘geo_dep’ allows for multiple columns in the data file to each refer to a different geographic group, *e.g.* ‘geo_dep="area"’ would give columns for each of the geographical areas, but other geographies could be used (if we set ‘geo_dep="nhs_region"’ then the data would apply to the different NHS regions in Fig. 13).

‘geo_filt’ filters the geography over which the observation are made, *e.g.* ‘geo_filt="nhs_region: S08000019"’ would mean that the data would apply to only that specific NHS region. If more than one option is filtered then they can be comma separated.

‘democats_dep’ allows for multiple columns in the data file to each refer to a different demographic group, *e.g.* ‘democats_dep="Sex"’ would imply that the data has two columns, one for ‘Male’ and one for ‘Female’).

‘democats_filt’ filters the demographic group observed (*e.g.* ‘democats_dep="Sex:Male"’ would mean that observations are made on males only).

3.7.2 Missing and thresholded data

In cases in which the data contains missing values the ‘nodata_str’ TOML command can be set which specifies the character or string that denotes missing value, *e.g.* ‘nodata_str = "NA"’ (by default this is set to ".").

For non-identifiability reasons, in some cases data is “thresholded”. This means a particular character or string is used to represent the fact that the data is at or below a specified threshold. This string is specified by the ‘threshold_str’ command (*e.g.* ‘threshold_str="<=5") and the numerical threshold itself is set in ‘data_tables’ by the ‘threshold’ property.

3.7.3 Partial observation

BEEPmbp provides two ways to incorporate the fact that raw data may need be transformed before it can be incorporated into the model (as discussed in §2.3.4):

‘factor’ sets a factor which multiplies the value given in ‘observation’ to get to the data, *e.g*. this can be used to incorporate a known test sensitivity (optional, by default set to 1).

‘factor_spline’ references the name of a spline that sets the factor between the value given in ‘observation’ and the observed data (*i.e.* s_t in Eq.(25)). The spline itself is specified by the ‘obs_spline’ command. For example

```
data_tables = [{type="transition", observation="E->I", file="IH.csv", factor_spline="obs1"}]
obs_spline = [{name="obs1", value="0.1|0.3|0.5", prior="Uniform(0,1)", bp="start|20.03.20|end"}]
```

implies that the fraction of actual E->I transitions observed varies, starting at 10% and ending at 50%. As well as being able to set the spline s_t, it can also be inferred from the data.

3.8 Different disease strains

Different strains of a disease can have different properties, *e.g.* variation in transmission rate and recovery time. They can be incorporated into the model using the ‘strains’ command, for example

```
strains = {cats="s1 | s2", sus_value="0.7 | 1.0 | *", sus_prior="Dir(*)",
           Rfactor_value="1.0 | 2.0", Rfactor_prior="Fixed(1) | Uniform(0.5,2)"}
```

‘cats’ provides names for the different strains.

‘sus_X’ can optionally be used to vary the susceptibility of individuals to different strains.

‘Rfactor_X’ sets the factor by which R_t is increased to account for a difference in transmission rate (typically one strain is set to 1 to become the reference for the others). This sets the parameter ψ_s in Eq.(1).

In terms of filtering and dependencies in §3.7.1, strains are treated like a demographic classification, *e.g.* 'democats_dep="strain:s1"' would be used to add data about strain 's1'.

3.9 System dynamics

As discussed in §2.1.3, continuous time Gillespie algorithm system dynamics are approximated using a finite time step τ-leaping algorithm. The value τ is set by $1/Q$, where integer Q is the number of discrete time steps per unit time. Q can be set by

```
steps_per_unit_time = 2
```

and by default it has a value 4 (*i.e.* τ is a quarter of a day). Reducing Q can reduce the computational time to run inference, although this can also lead to substantial discretisation error. Crucially, τ should be substantially less than the compartmental residency times specified in the model.

The underlying system dynamics can be set using the command

```
dynamics = "deterministic"
```

or alternatively set to "stochastic" (which is assumed by default)[38].

3.10 Model modification

Modifications to the model (as used when making predictions in §4.3) are specified using the 'modification' command. For example

```
modification = [{type="trans_rate_fac", start="2020-4-01", trans="S->E", factor="0.5"}]
```

specifies that from April 1st the number of infections in the model reduced by a factor of a half (in essence something causes disease transmission to become reduced).

Here we list different possible modifications that can be applied to the model:

'type' denotes the type of change. This can be one of the following:

- "trans_rate_fac" – This changes the rate of a specified transition by a factor ('trans' and 'factor' must be set).
- "beta_fac" – Changes the transmission rate by a factor ('factor' must be set).
- "efoi_fac" – Changes the external force of infection by a factor ('factor' must be set).
- "spline_fac" – Multiplies a spline by a factor ('name' must correspond to 'name' set in a spline and 'factor' must be set).
- "spline_set" – Sets the value of a spline ('name' must correspond to 'name' set in a spline and 'factor' must be set).

'start' and 'end' gives the duration for the change.

'strain' is specifies if only a particular strain is referred to (optional).

[38] When the system dynamics are deterministic, the ABC-MBP, PAIS-MBP, MCMC-MBP and MC^3 inference algorithms cannot be used as MBPs rely on stochastic dynamics to operate.

‘geo_filt’ sets the modification to apply to a particular geography (optional).

‘democats_filt’ sets the modification to apply to a particular demographic category (optional).

3.11 Tailoring Outputs

3.11.1 Generating state outputs

In the output ‘Graphs.pdf’ file (see §5), it is possible to add other informative plots, if needed. The command ‘state_outputs’ works in much the same way as ‘data_tables’, but rather than reading input files (or generating simulated data) corresponding to a particular observation, here just graphs are generated. In this example

```
state_outputs = [
        {plot_name="Dynamics", type="population", observation="S", line_colour="green"},
        {plot_name="Dynamics", type="population", observation="E", line_colour="yellow"},
        {plot_name="Dynamics", type="population", observation="I", line_colour="red"},
        {plot_name="Dynamics", type="population", observation="R", line_colour="blue"}]
```

‘plot_name’ sets the name of the final plot. Using this more than once allows for multiple lines to be placed on the same plot.

‘line_colour’ sets the colour of the line in the final plot. This can take the values ‘black’, ‘red’, ‘blue’, ‘green’, ‘yellow’, ‘cyan’, ‘magenta’ (and by default an automatic colour scheme is selected).

See Glossary for other specifications.

3.11.2 Probability of reaching a specified compartment

Under certain circumstance it is of interest to find out the overall probability that individuals reach a particular compartment in the model, *e.g.* if set to the dead D compartment this can be used to calculate the infection fatality rate. This can be specified using the ‘prob_reach’ command, *e.g.*

```
prob_reach = [{name="ifr", comp="D"}]
```

‘name’ is used in the output file.

‘comp’ specifies the compartment which is reached.

3.11.3 Probability distribution plots

BEEPmbp allows some flexibility in the way in which probability distributions are plotted, as specified in ‘output_prop’. For example

```
output_prop = {probdist="kde", h="5"}
```

‘probdist’ sets how probability distributions are displayed: "kde" for kernel density estimation or "bin" for binning.

‘nbin’ determines the number of bins used when binning (optional, 200 by default).

‘h’ sets a smoothness parameter when using kernel density estimation (optional, 10 by default).

3.11.4 Setting time labels

When setting up the model and generating outputs, it is sometimes useful to represent specific times of interest in the analysis with labels. These can be specified in the following way:

```
time_labels = [{name="Lockdown", time="2020-03-23"}]
```

Further labels can be added by comma separating them inside the square brackets. These labels can subsequent be used instead of dates in the TOML file (*e.g.* when specifying the breakpoints in a spline), and are also placed as vertical reference lines in the final time-based output graphs.

4 Running BEEPmbp

Once the input TOML file is specified and BEEPmbp is compiled (using the "make" command) it can be run by executing "./beepmbp" on the command line followed by a specification of the input file name. Following that, additional commands can be specified[39] that can be used to quickly change analysis without having to edit the input file each time.

4.1 Simulation-based approaches

Two different simulation-based modes of operation can be selected from:

4.1.1 Single Simulation

This simulates the state of the system given a set of model parameters.

```
./beepmbp inputfile="file.toml" mode="sim" seed=10
```

Since simulations are stochastic, the outcome will depend on how the pseudorandom number generator is initialised. In BEEPmbp this is set by specifying a 'seed'[40] (optional).

4.1.2 Multiple simulation

This simulates from the model multiple times and outputs the distributions in states generated (see "Graphs.pdf" in the output directory). This make it possible to visualise the level of inherent stochastic variation in the model.

```
./beepmbp inputfile="file.toml" mode="multisim" nsimulation=100
```

This has the following option:

- *nsimulation* – specifies the number of simulations to be performed.

4.2 Inference

BEEPmbp incorporates seven inference algorithms (briefly discussed in §2.3) that all aim to perform essentially the same task: to generate posterior samples for model parameters and the system state. Which of these algorithms to choose, however, may depend on the scenario under consideration, with some methods performing computationally better or worst depending on the situation. They are split into two broad classes: those which aim to reduces an error function (ABC-MBP, ABC, ABC-SMC) and those which aim to incorporate a specified observation model (PAIS-MBP, PMCMC,

[39] Note, these will override any existing specifications in the TOML file itself.
[40] The 'seed' command can also be set in other modes to test for the influence of this on the outcome.

MCMC-MBP, MC^3). In most cases ABC-MBP seems to work best for the former and PAIS-MBP for the latter.

As well as the options below, each algorithm can set the 'nrun' option, which replicates analysis over multiple runs. This is normally recommended, as it checks that all runs converge on the same posterior (through Gelman-Rubin diagnostic statistics).

4.2.1 Approximate Bayesian Computation with model-based proposals (ABC-MBP)

The following command implements the ABC-MBP algorithm:

```
./beepmbp inputfile="file.toml"  mode="abcmbp"  nparticle=200  ngeneration=40
```

with the following options:

- *nparticle* – Sets the number of particles (200 is typical as this yields approximately 200 random samples from the posterior).
- *ngeneration* – Gives the number of generations (a suitable value is problem dependent, but typically this lies in the range 10-100, depending on model complexity).
- *cutoff_final* – As an alternative to setting '*ngeneration'*, this iterates generations until a specified EF_{cutoff} is reached.
- *nupdate* – Sets the number of MCMC 'updates' used per particle per generation (by default set to 1, but larger values can improving mixing and avoid degeneracy). Each update consists of a variety of MBPs on each of the model parameters as well as on combinations of them.
- *GR_max* – as an alternative to '*nupdate'* this iterates updates on each generation until the Gelman-Rubin statistic for all parameter is below this specified threshold.

4.2.2 Particle annealed importance sampling with model-based proposals (PAIS-MBP)

Whereas ABC-MBP aims to generate the posterior by reducing the error function below a cut-off value, here we assume a full observation model and aim to generate the posterior from that.

```
./beepmbp inputfile="file.toml"  mode="pais"  nparticle=200  ngeneration=40
```

This has the same command options as ABC-MBP, except:

- *invT_final* – As an alternative to setting '*ngeneration'* this iterates generations until a specified inverse temperature ϕ_{post} is reached (instead of 'cutoff_final' in ABC-MBP).
- *quench_factor* - Sets the rate of quenching (optional, set to 0.5 by default such that on average half the particle each generation are discarded).

4.2.3 Approximate Bayesian computation (ABC)

This generates posterior samples by means of a simple ABC rejection-sampling scheme.

```
./beepmbp inputfile="file.toml"  mode="abc"  nsample=200  cutoff_frac=0.01
```

with the following options:

- *nsample* – This specifies the number of posterior sample we wish to obtain.
- *GR_max* – as an alternative to '*nsample'* this iterates the algorithm until the Gelman-Rubin statistic for all parameters is below this specified threshold.

- *cutoff* – Sets the EF_{cutoff} such that only simulated states with EF below this threshold are accepted.
- *cutoff_frac* – An alternative to '*cutoff*', this first generates random samples and then automatically adjusts the EF_{cutoff} such that a specified fraction of them are accepted. This has the advantage that EF_{cutoff} does not need to be chosen (which is difficult in practice), but has the disadvantage of using much more memory (because it is necessary to store all generated states).

4.2.4 Approximate Bayesian computation with sequential Monte Carlo (ABC-SMC)

This runs over a number of generations, with the previous generation used as an importance sampler for the next. Under some circumstances this approach is significantly more computationally efficient than the standard ABC algorithm.

```
./beepmbp inputfile="file.toml"  mode="abcsmc"  nsample=200  ngeneration=5  cutoff_frac=0.5
```

with the following options:

- *nsample* – This specifies the number of samples in each generation.
- *GR_max* – as an alternative to '*nsample*', this iterates the algorithm until the Gelman-Rubin statistic for all parameters is below a specified threshold.
- *ngeneration* – Gives the number of generations.
- *cutoff_final* – As an alternative to setting '*ngeneration*', this iterates generations until a specified EF_{cutoff} is reached.
- *cutoff_frac* – Specifies how the cut-off in EF is chosen such that a certain fraction of particles are accepted for the next generation (optional, by default set to 0.5).
- prop_size – Sets the proposal size (optional, set to 1 by default). This factor scales the MVN estimate of the posterior distribution in the previous generation to set the parameter proposal kernel.

4.2.5 Particle Markov chain Monte Carlo (PMCMC)

This runs an MCMC chain in parameter space with a particle filter used to generate an unbiased estimate for the agreement between the model and the data.

```
 ./beepmbp inputfile="file.toml"  mode="pmcmc"  nsample=5000  nparticle=200
```

with the following options:

- nsample – This gives the number of samples on the MCMC chain (note, this is typically much higher than for other methods because successive samples are highly correlated).
- *GR_max* – as an alternative to '*nsample*' this iterates the algorithm until the Gelman-Rubin statistic for all parameters is below a specified threshold.
- *nparticle* – This gives the number of particles used in the filter (a higher number allows for a better agreement with the data but is computationally slower).
- *invT* – Sets the inverse temperature of the posterior ϕ_{post}.
- *nburnin* – Sets the number of MCMC iteration for burn-in (optional, by default set to a quarter of '*nsample*').

- *nthin* – This thins stored posterior samples by a factor to save memory (optional, by default set to 1).

4.2.6 Markov chain Monte Carlo (MCMC-MBP)

This runs a single MCMC chains and makes use of MBPs for fast mixing.

```
./beepmbp inputfile="file.toml"  mode="mcmcmbp"  nsample=1000  invT=1
```

with the following options:

- *nsample* – This gives the number of samples on the MCMC chain (note this is typically much higher than other methods because successive samples are highly correlated).
- *GR_max* – as an alternative to '*nsample'*, this iterates the algorithm until the Gelman-Rubin statistic for all parameters is below a specified threshold.
- *invT* – Sets the inverse temperature of the posterior ϕ_{post}.
- *nburnin* – Sets the number of MCMC iteration for burn-in (optional, by default set to a quarter of '*nsample*').
- *nthin* – This thins stored posterior samples by a factor to save memory (optional, by default set to 1).

4.2.7 Metropolis-coupled Markov chain Monte Carlo (MC^3)

This runs multiple MCMC chains in parallel, with the "hottest" chain mapping out the prior and the "coldest" chain mapping out an approximation to the posterior with a specified inverse temperature.

```
./beepmbp inputfile="file.toml"  mode="mc3"  nsample=1000  nchain=80  invT_final=300
```

with the following options:

- *nchain* – gives the number of MCMC chains used (this needs to be sufficiently large to allow for adjacent chains to "overlap").
- *nsample* – This gives the number of samples on the MCMC chain (note this is typically much higher than other methods because successive samples are highly correlated).
- *GR_max* – as an alternative to '*nsample'*, this iterates the algorithm until the Gelman-Rubin statistic for all parameters is below a specified threshold.
- *invT_final* – Sets the inverse temperature of the posterior chain ϕ_{post}.
- *invT_start* – Sets the inverse temperature for the highest temperature chain (optional, by default set to zero, corresponding to the prior).
- *nburnin* – Sets the number of MCMC iteration for burn-in (optional, by default set to a quarter of '*nsample*').
- *nquench* – Sets the rate at which temperature is quenched during the burn-in period (optional, by default set to half of '*nburnin*').
- *nthin* – This thins stored posterior samples by a factor to save memory (optional, by default set to 1).

4.3 Prediction

When inference is performed a series of posterior samples for model parameters θ and system state ξ are generated and saved into the “Posterior/samples” directory. When run in "prediction" mode, BEEPmbp loads these samples and uses them to generate predictions, for example

```
./beepmbp inputfile="file.toml"  mode="prediction"  prediction_end="2022-4-01"
```

with the following options:

- *prediction_start* – Sets the start time (optional, by default set to either when modification is made to the model or the inference ending time, whichever is earlier).
- *prediction_end* – Sets the end time (optional, by default set to inference ending time).
- *modification* – Allows for specification of any modifications to the model (optional, see §3.10 for details).
- *nsim_per_sample* – Sets the number of simulations per posterior sample (optional, by default set to 4).

Four types of analysis can be performed using "prediction" mode:

Future prediction – Here the aim is take all available data and predict which is likely to happen in the future (assuming transmission rates and other splines remain constant after the end of the period used during inference). This is achieved by setting some future value for ‘prediction_end’ and viewing “Graphs.pdf” in the output directory to see how the system evolves. Alternatively, different future scenarios could be looked at by adding changes to the model through ‘modification’.

Counterfactual analysis – Here the aim is to investigate how things would have turned out differently had different measures been taken (*e.g.* alternative disease intervention strategies). This would typically use the same time period as for inference, but make changes to the model through ‘modification’.

Posterior predictive checks – These are used to check the model is performing in accordance with the data. Typically a time ‘prediction_start’ would be selected and then subsequently states generate from simulation would be checked against the observed data. A poor fit implies the model is not good.

4.4 Parallelisation

To increase computational speed BEEPmbp can be run on multiple CPU cores. In this case execution on the command line is preceded by “mpirun –n” followed by the number of cores. For example the ABC-MBP method can be run using:

```
mpirun –n 10 ./beepmbp inputfile="file.toml"  mode="abcmbp"  nparticle=200  ngeneration=40
```

This will complete almost 10 times faster because it is run on 10 CPU cores in parallel (which communicate with one other using MPI). Note, when run in parallel the number of particles must be a multiple of the number of CPU cores (so they can be distributed evenly across cores).

5 Outputs from BEEPmbp

5.1 Files generated

We give a brief description below of the various files and folders generated in the output directory once analysis is complete:

- **Parameter_estimates.csv** – If inference is performed, this file gives the posterior means and 95% credible intervals for each of the model parameters. Furthermore, estimates for some derived quantities are also included, *e.g.* the generation time (see Appendix A), and quantities specified in 'prob_reach' (see §3.11.2).
  To check inference has been performed correctly, the estimates for effective samples size[41] for each of the model parameters should exceed around 200 and the Gelman-Rubin statistics should be less than around 1.05.
- **Graphs.pdf** – This visualises outputs from BEEPmbp ("Graphs_description.txt" provides information about the source data).
- **Diagnostic_Graphs.pdf** – This visualises additional outputs associated with diagnostics ("Diagnostic_Graphs_description.txt" provides information about the source data).
- **Model_specification.txt –** This gives a summary of the model used to perform the analysis.
- **Posterior** – This folder contains files giving posterior probability distributions for the model parameters. These are arranged in a number of different ways:
  - *parameter* - Contains files for the model parameters.
  - *state* - Contains files which compare the system state with that observed in the actual data files.
  - *spline* - Contains files giving time variation in splines used within the model.
  - *susceptibility* - Contains files giving the variation in susceptibility for different demographic classifications within the model.
  - *sample* - Contains files giving raw posterior samples.
  - *Rmap.csv* - For spatial models this gives the variation in reproduction number R across different areas.
- **Simulated_data** – This gives simulated data files corresponding to the specifications provided in the input TOML file.
- **Diagnostics** – This provides diagnostic information to inform how well the algorithm is performing:
  - *Generation.csv* - Shows how model parameters move from the prior distribution to an approximation of the posterior distribution as a function of the generation number.
  - *MCMC_proposals.csv* - This shows the performance of MCMC proposals (if used).

5.2 Graphical interface

To aid easy visualisation of results BEEPmbp includes a simple graphical interface which will work in any web browser. This can be viewed by clicking on "visBEEPmbp.html" in the analysis output directory.

[41] Note, not all algorithms generate an estimate for effective sample size.

5.2.1 Maps

When plotting maps the command 'area_plot' can be used to specify a file giving the boundaries of the areas in the system, *e.g.*

```
area_plot = { boundary="Scotland_areas.geojson", projection="equirectangular"}
```

Here '*projection*' is a used to specify how the coordinates are projected onto the map ("equirectangular" is appropriate when longitude/latitude are being used, otherwise "uniform" is used by default). 'area_plot' supports the '.geojson' and '.kml' file formats, and allows for both longitude/latitude measurements as well as grids coordinates. Alternatively 'area_plot' can be used to specify columns giving the average positions of the areas, in which case BEEPmbp will automatically construct a Voronoi tessellation to derive areas from these.

6 Examples

This section goes through a series of examples that help to illustrate the power of BEEPmbp. The files for these can be found in the "examples" directory.

EX 1: Simple SEIR model

This example assumes time series data for the I→R transition. The code is shown in §3.1 with outputs given in Figs. 2-9.

EX 2: Spatial SEIRD model

This uses a spatial model made up of local authorities in Scotland. Area fixed effects, level effects and covariates are estimates from infection and death data.

EX 3: Age and sex stratified SEIRD model

EX 4: Age stratified SEIRD model with vaccination

EX 5: Applying to disease transmission experiments

License and warranty

Citing BEEPmbp

We kindly request that those who do use BEEPmbp analysis in their publications to cite this tool:

Pooley CM, Doeschl-Wilson AB, Marion G., *BEEPmbp – A flexible tool for simulation, inference and prediction using compartmental models*. To be submitted (2021).

Acknowledgments

We would like to acknowledge the contribution of two libraries used within the software: toml11 (github.com/ToruNiina/toml11), which is a C++ TOML parser that BEEPmbp uses to read in the input TOML file, and nlohmann/json (github.com/nlohmann/json), which is a JSON parser for converting geographic areas into visual outputs.

References

Appendix A: The reproduction number R_t

The model in Eq.(1) is parameterised in terms of a time-varying quantity R_t referred to as the "reproduction number". This appendix explains what this quantity is and how it is related to other model parameters. For clarity we ignore the effect of strain (although this could easily be incorporated below by simply changing every instance of R_t with $R_t\psi_s$[42]).

Definitions

We begin with a clarification of terminology:

Generation – An epidemic starts with a single infected individual. We refer to this as "generation 1". That individual then goes on to infect other secondary infections which make up generation 2. Those individuals subsequently infect generation 3, and so on and so forth.

Basic reproduction number R_0 – This is often defined to be the expected number of cases directly caused by the individual in generation 1 (*i.e.* in contact with an otherwise completely susceptible population). However, for models that include different demographic classifications, *e.g.* age and/or sex, or complex compartmental structures, careful consideration needs to be given to precisely how R_0 is calculated. In particular, just averaging over the demographic possibilities for the initially infected individual is not enough. One must also consider what happens in subsequent generations in the early phase of an epidemic to get a meaningful estimate for R_0 (because it typically takes several generations for the distribution in demographic groups that cause the bulk of disease transmission to manifest). See below for how R_0 is actually calculated.

Time-varying reproduction number R_t – This sets the value R_0 would have taken if the initial rate of mixing between individuals in the population is taken to be the same as that at time t. As such, R_t should be interpreted as a quantity proportional to the rate at which individuals come into contact with each other (with each contact allowing for the possibility of disease transmission). So, for example, when R_t goes down it indicates that either individuals are meeting less frequently, or disease control are blocking transmission somehow, such as mask wearing. Note, disease transmission only actually occurs when contacts occur between infected and susceptible individuals. It is important to remember, therefore, that R_t *does not* account for the reduction in the susceptible fraction of the population as the epidemic progresses.

Time-varying effective reproduction number R_t^{eff} – The effective reproduction number is the expected number of cases directly caused by an infected individual as a function of time t. Note, this *does* take into account the fact that as the epidemic progresses the fraction of susceptible individuals reduces (causing effective transmission upon contact of individuals to become less and less common). $R_t^{\mathrm{eff}}$is always less than R_t and if it reduces below 1 then herd immunity in reached (*i.e.* the disease will naturally die out over time). R_t^{eff} is an output from BEEPmbp.

Relationship between reproduction number and transmission rate

Perhaps a more standard way to write the force of infection in Eq.(1) is in terms of a transmission rate parameter:

[42] ψ_s is the factor increase in reproduction number for a given strain s.

$$\lambda_{a,d,t} = \beta_t \sigma_d \alpha_{a,t} \sum_{a',d',c} M_{a,a',t} A_{d,d',t} i^c N^c_{a',d',t}, \quad \text{(A1)}$$

where here we ignore the external force of infection (as it doesn't play a role in the calculation of reproduction number). β_t is called the "transmission rate", and it is a proportionality constant that relates quantities measuring the general mixing of individuals in the population to the actual probability per unit time of an individual becoming infected (so β_t incorporates effects such as mask wearing, social distancing etc…). Comparing Eqs.(1) and (A1) we see that

$$\beta_t = r_t R_t. \quad \text{(A2)}$$

This equation simply states that the transmission rate is proportional to the reproduction number through a factor r_t. BEEPmbp works by first parameterising a spline that represent R_t and then calculating r_t to obtain the force of infection in Eq.(1) (see below for how this is done in practice).

Calculating R_t

We outline here the approach taken by Diekmann *et* al. to calculate the reproduction number R_t (remembering the definition from above, that R_t is the value that R_0 would have taken assuming a disease transmission rate at time t).

First, a set of compartmental states Ω for which individuals are infected (but not necessarily infectious) is identified. For the purposes of explanation, we refer to the example SEIR compartmental model in Fig. 1[43]. Here $\Omega=\{\mathrm{E}_d,\mathrm{I}_d\}$, where d goes over all demographic possibilities. We consider the case of two demographic groups (denoted M and F for male and female), but the results below can easily be extended for arbitrary d.

A vector $\mathbf{v}=(\mathrm{E_M},\mathrm{E_F},\mathrm{I_M},\mathrm{I_F})^{\mathrm{T}}$ is defined[44] to be the number of individuals in each of the infected compartments in Ω. In the deterministic case the time evolution in $\mathbf{v}$ is given by

$$\frac{d\mathbf{v}}{dt} = (\mathbf{F}_t - \mathbf{\Sigma})\mathbf{v}, \quad \text{(A3)}$$

where $\mathbf{F}_t$ is a matrix accounting for the rate of individuals *entering* compartments contained in Ω, and $\mathbf{\Sigma}$ is a matrix accounting for transitions *between* and *leaving* compartments within Ω.

From Fig. 1 we see that individuals enter Ω through the exposed $\mathrm{E_M}$ and $\mathrm{E_F}$ states, caused by infectious individuals in the I state (this is derived from the force of infection in Eq.(A1)):

$$\mathbf{F}_t = \beta_t \left\langle \alpha_{a,t} \right\rangle_a \begin{bmatrix} 0 & 0 & \phi_M \sigma_M A_{M,M,t} i^I & \phi_M \sigma_M A_{M,F,t} i^I \\ 0 & 0 & \phi_F \sigma_F A_{F,M,t} i^I & \phi_F \sigma_F A_{F,F,t} i^I \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}, \quad \text{(A4)}$$

[43] For simplicity we take the case when the Erlang distribution is a simply exponential by setting k=1.
[44] The superscript "T" strands from transpose, and this converts a row vector into a column vector.

where $\langle \ldots \rangle_a$ denotes an average of the area effects[45], ϕ_d gives the fraction of the population in demographic group d, σ_d gives the relative susceptibility, $\mathbf{A}$ is a (potentially time-varying) matrix giving the contact rate between demographic groups and, finally, i^c is the infectivity of compartment c.

The matrix $\mathbf{\Sigma}$, representing transitions between and leaving the infected states Ω, is given by:

$$\mathbf{\Sigma} = \begin{bmatrix} \frac{1}{m_M} & 0 & 0 & 0 \\ 0 & \frac{1}{m_F} & 0 & 0 \\ -\frac{1}{m_M} & 0 & \frac{1}{r_M} & 0 \\ 0 & -\frac{1}{m_F} & 0 & \frac{1}{r_F} \end{bmatrix}, \tag{A5}$$

where m_d and r_d are the mean residency times in the E and I states. This was constructed by considering each transition in the model in turn. Denoting the initial and final infected compartments to be i and j, matrix element Σ_{ii} gets a positive contribution given by the individual rate (because individuals are leaving state i) and Σ_{ji} gets a corresponding negative contribution (because those individuals are entering state j). Note, if j is not one of the infected states in Ω, this second contribution is ignored.

The inverse of the matrix in Eq.(A5) is given by

$$\mathbf{\Sigma}^{-1} = \begin{bmatrix} m_M & 0 & 0 & 0 \\ 0 & m_F & 0 & 0 \\ r_M & 0 & r_M & 0 \\ 0 & r_F & 0 & r_F \end{bmatrix}. \tag{A6}$$

This has a simple interpretation: If an individual enters state i, Σ_{ji}^{-1}gives the time, on average, that individual is expected to (eventually) spend in state j. For example, inspecting the first column in Eq.(A6) we see that if an individual enters state $\mathrm{E_M}$ (at the top) it will stay in $\mathrm{E_M}$ for time m_M, spend no time in $\mathrm{E_F}$ (individuals do not change their demographic state), time r_M in state $\mathrm{I_M}$, and no time in state $\mathrm{I_F}$.

We now construct the next generation matrix $\mathbf{K}_t$. We denote $\mathbf{w}_g$ to be a vector giving the number of individuals entering the different states in Ω in generation g. The equivalent vector for the next generation is given by[46]

$$\mathbf{w}_{g+1} = \mathbf{K}_t \mathbf{w}_g \quad \text{where} \quad \mathbf{K}_t = \mathbf{F}_t \mathbf{\Sigma}^{-1}. \tag{A7}$$

The reasoning behind this expression is as follows: Suppose we consider an individual in generation g that enters state i. As described above, during its infected lifetime this individual spends on

[45] This average is weighed by the populations in each of the areas a.

[46] In fact because individuals usually only enter Ω through a limited number of states ($\mathrm{E_M}$ and $\mathrm{E_F}$ in our example), then, without loss of generality, $\mathbf{w}$ and $\mathbf{K}$ can be defined for just these states. This is a commonly used technique to increase computational efficiency.

average Σ_{ji}^{-1} in each state j. But in doing so Eq.(A4) tells us that through its own infectiousness it will generate F_{kj} new infected individuals in each of the states k. This means that $w_{g+1,k}$ gains a contribution $F_{kj}\Sigma_{ji}^{-1}$ for each of the $w_{g,i}$ individuals in generation g that enter state i. Summing over all the possible values for i and j gives the relationship in Eq.(A7).

Next we ask the question what happens when we iterate Eq.(A7) over many generations? It turns out that this equation can be solved[47], as shown in Appendix B. In summary, as the generations increase, so $\mathbf{w}_g$ becomes proportional to the normalised eigenvector $\mathbf{e}$ of the matrix $\mathbf{K}_t$ which has the largest eigenvalue. The value of this eigenvalue provides an estimate for R_t (by definition this is the average number of infections an individual in one generation causes in the next).

The eigenvector $\mathbf{e}$ itself has an intuitive explanation. Supposing that the mixing matrix $\mathbf{A}$ implies that certain demographic groups come into contact more often, *e.g.* younger age groups. Irrespective of the age of the person who initiates an epidemic, eventually those driving disease progression will be the young and so $\mathbf{e}$ will have proportionately larger values associated with entering the exposed state for young individuals.

The careful reader may wonder why the spatial elements in Eq.(A4) have been simply averaged over. An alternative would be to consider the system as a whole with each of the compartments in each of the spatial locations having its own states in Ω. This is indeed possible to do, however the stumbling block comes when one considers Eq.(A7). The reason lies in the fact that the number of generations for $\mathbf{w}$ to actually converge on the eigenvector $\mathbf{e}$ with largest eigenvalue becomes infeasibly large. It would be of the order of time taken for a single person to infect the rest of the country, and this cannot be reconciled with the fact that R_t should represent early epidemic behaviour. Consequently such an approach would seem ill-advised, yielding unrealistically high values[48] for R_t.

Calculating $r_{s,t}$

The previous section showed that given a transmission rate β_t an estimate for R_t could be made. BEEPmbp, however, works the opposite way around. Parameters are used to inform a spline for R_t, and this in turn is used to calculate β_t. We now provide an description of how this is done.

First, we define the quantity

$$\mathbf{F}'_t = \frac{\mathbf{F}_t}{\beta_t}. \tag{A8}$$

From Eq.(A4) we see that $\mathbf{F'}_t$ is independent of β_t and so can be calculated using known model parameters. Next, we define a modified next generation matrix:

$$\mathbf{K}'_t = \mathbf{F}'_t\boldsymbol{\Sigma}^{-1}. \tag{A9}$$

[47] We assume the timescale of the initial phase of the epidemic is slow compared to time variation in other model parameters, *e.g.* β_t.

[48] In essence it would imply that R_t for the whole country would be almost the same as the area a with the highest R_t.

The largest eigenvalue of this matrix gives R_t divided by β_t. From Eq.(A2) we see that taking the reciprocal of this quantity gives r_t. For systems with multiple strains, we calculate r_t separately for each strain s, and this defines $r_{s,t}$ in Eq.(1).

The reason BEEPmbp parameterises R_t (rather than β_t) is twofold: Firstly it allows for realistic priors to easily be placed on the model (previous studies may have established that R_t is within some realistic range, *e.g.* 2-4), which is not true of β, and secondly it was found to be an effective way to improve MCMC mixing[49].

Calculating R_t^{eff}

As mentioned above, the effective reproduction number is the expected number of cases directly caused by an infected individual as a function of time t. This has to account for the fact that some susceptible individuals have already been infected, recovered and acquired immunity.

Equation (A4) is modified to now give

$$\mathbf{F}'_{sus,t} = \frac{\mathbf{F}_{sus,t}}{\beta_t} = \left\langle \alpha_{a,t} \right\rangle_a \begin{bmatrix} 0 & 0 & \phi^{sus}_{M,t}\sigma_M A_{M,M,t} i^I & \phi^{sus}_{M,t}\sigma_M A_{M,F,t} i^I \\ 0 & 0 & \phi^{sus}_{F,t}\sigma_F A_{F,M,t} i^I & \phi^{sus}_{F,t}\sigma_F A_{F,F,t} i^I \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}, \tag{A10}$$

where ϕ_d^{sus} is the fraction of the population in demographic group d that are *susceptible*. This can be used to calculate a new modified NGM:

$$\mathbf{K}'_{sus,t} = \mathbf{F}'_{sus,t}\boldsymbol{\Sigma}^{-1}. \tag{A11}$$

If we define the largest eigenvalue of $\mathbf{K}'_t$ in Eq.(A9) to be λ_t, and for $\mathbf{K}'_{sus,t}$ in Eq.(A11) to be $\lambda_{sus,t}$, the effective reproduction number can be related to R_t through

$$R_t^{eff} = \frac{\lambda_{sus,t}}{\lambda_t} R_t. \tag{A12}$$

A graph showing R_t^{eff} is automatically generated by BEEPmbp, as displayed in the 'Graphs.pdf' file.

Calculating the generation time

Another derived output from BEEPmbp is the generation time. This is defined to be the time interval between when an individual becomes infected and the average time that person transmits their infection to others. This quantity is important because it specifies how fast infections are spreading within the community with the passing of each generation.

We now show how to calculate the generation time using the example from above. Based on the analysis in Appendix B, the fraction of individuals entering state i is given by the corresponding element in the eigenvector e_i. Equation (A6) shows a matrix Σ_{ji}^{-1} giving the average time those

[49] Effectively it is a re-parameterisation of the model for which variables are not so highly correlated in the posterior.

individuals then go on to spend in state j. Whilst in state j they initiate new infections in each of the compartments k at a rate given by F_{kj} (see Eq.(A4)). The average timing of those new infections is given by the elements of the following vector:

$$\boldsymbol{\tau} = (\tfrac{1}{2}m_M, \tfrac{1}{2}m_F, m_M + \tfrac{1}{2}r_M, m_F + \tfrac{1}{2}r_A)^T. \quad \text{(A13)}$$

Combining these contributions yields the final result

$$T_{gen} = \frac{\sum_{k,j,i} F_{kj}\tau_j \Sigma^{-1}_{ji} e_i}{\sum_{k,j,i} F_{kj}\Sigma^{-1}_{ji} e_i}. \quad \text{(A14)}$$

Appendix B: Solving iterative matrix equations

This appendix outlines the solution to the matrix equation in Eq.(A7). Note, we drop the index t because we assume that the initial spread of the disease is fast compared to the timescale over which model parameter changes (such as the transmission rate β_t).

We refer to $\mathbf{e}$ as an "eigenvector" and λ as an "eigenvalue" of a matrix $\mathbf{K}$ if it solves the equation

$$\boldsymbol{Ke} = \lambda \boldsymbol{e}. \quad \text{(B1)}$$

In general a square matrix of size N will actually have N eigenvectors $\mathbf{e}_j$ and eigenvalues λ_j, ordered such that λ_1 is the highest and λ_N is the lowest. These can collectively be written as

$$\mathbf{KU} = \mathbf{U}\begin{bmatrix} \lambda_1 & 0 & 0 & \cdots \\ 0 & \lambda_2 & 0 & \cdots \\ 0 & 0 & \lambda_3 & \cdots \\ \vdots & \vdots & \vdots & \ddots \end{bmatrix} \quad \text{(B2)}$$

where $\mathbf{U}=[\mathbf{e}_1, \mathbf{e}_2, \mathbf{e}_3,\ldots]$ is a matrix made up of the eigenvectors. Multiplying both sides of Eq.(B2) by the inverse matrix $\mathbf{U}^{-1}$ and substituting this expression for $\mathbf{K}$ into Eq.(A7) gives

$$\begin{aligned} \mathbf{w}_g &= \mathbf{K}^{g-1}\mathbf{w}_1 \\ &= \left(\mathbf{U}\begin{bmatrix} \lambda_1 & 0 & 0 & \cdots \\ 0 & \lambda_2 & 0 & \cdots \\ 0 & 0 & \lambda_3 & \cdots \\ \vdots & \vdots & \vdots & \ddots \end{bmatrix} \right)^{-1} \mathbf{w}_1 \\ &= \mathbf{U}\begin{bmatrix} \lambda_1^{g-1} & 0 & 0 & \cdots \\ 0 & \lambda_2^{g-1} & 0 & \cdots \\ 0 & 0 & \lambda_3^{g-1} & \cdots \\ \vdots & \vdots & \vdots & \ddots \end{bmatrix} . \end{aligned} \quad \text{(B3)}$$

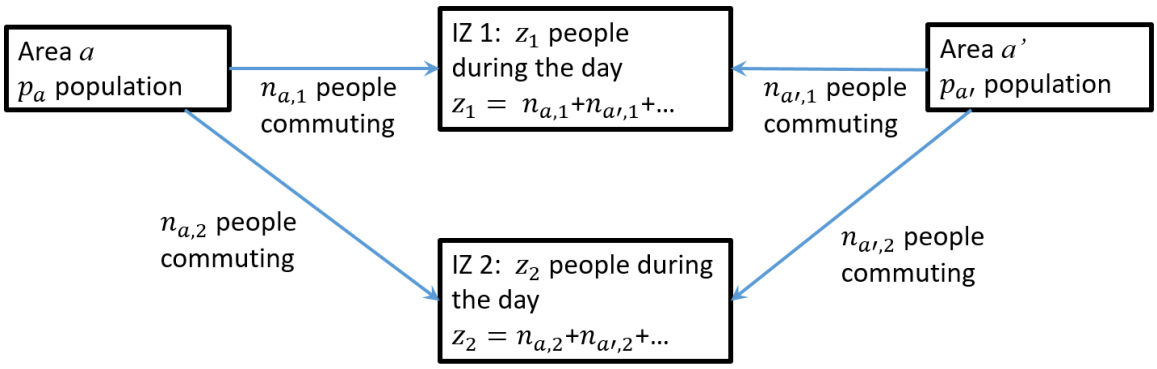
A key feature of this relationship is that as the generation number g increases, so the diagonal element that corresponds to the largest eigenvalue λ_1 dominates over all the others (which also

means that $\mathbf{w}_g$ become proportional to the eigenvector $\mathbf{e}_1$). Because the overall number of individuals in $\mathbf{w}_g$ goes up by a proportion λ_1 each generation, so λ_1 provides an approximation to R_t.

Appendix C: Derivation of the geographical mixing matrix Z

This appendix explains how the geographical mixing matrix $Z_{a,a'}$ in Eq.(8), and incorporated into the model using the 'geo_mixing_matrix' TOML command (see §3.6.3), can be derived from data giving the movement of individuals within and between areas.

As an example we consider the census data from 2011. This splits up the geography of the UK into middle layer super output areas[50] (MSOAs) in England and Wales and intermediate zones[51] (IZs) in Scotland. To avoid confusion we collectively refer to these as IZs. The census flow data itself provides a matrix giving the number of individuals commuting from any given IZ to any other IZ. Analysis using BEEPmbp, however, is usually performed on a coarser geographical scale (*e.g.* on a local authority level), so this must be accounted for.



The diagram above illustrates the basic procedure. We consider two (potentially) different areas a and a' (*e.g.* local authorities) and consider the rate at which individuals come into contact. Each area a has a population p_a that can be estimated from census data. During the day people move to work in a way defined by the census flow data, where $n_{a,k}$ gives the number of individuals moving from area a to IZ k. Note, those people who don't commute are assumed to remain in their own IZ (by adding an appropriate contribution to $n_{a,k}$).

Suppose someone in area a is infectious. The probability of them travelling to IZ k is given by $n_{a,k}/p_a$. Assuming random mixing of individuals in IZ k, the probability of them passing on their infection to someone in area a' is proportional to $n_{a',k}/z_k$ (where z_k is the total number of people commuting to IZ k, see diagram). Consequently the force of infection from area a to a' via k is proportional to $(n_{a,k}/p_a)(n_{a',k}/z_k)/\,p_{a'}$. Summing this over all intermediate IZs k gives the final result:

[50] These are 7,201 areas covering England and Wales.
[51] These are 1,279 areas covering Scotland.

$$Z_{a,a'} \propto \frac{1}{p_a p_{a'}} \sum_k \frac{n_{a,k} n_{a',k}}{z_k}. \quad \text{(C1)}$$

The matrix $\boldsymbol{Z}$ is normalised such that each infected individual is expected to infect the same number of secondary cases on average (geographical variation in force of infection explicitly enters the model through the area effects in Eq.(1)).

Note, the matrix in Eq.(C1) is symmetric, as would be expected since the overall number of contacts between individuals in different areas must be the same.

Appendix D: Derivation of age contact matrix

The matrix $C_{z,z'}$ used in Eq.(9) gives the rate of contacts between different age groups z in the population. Previous reports (*e.g.* Prem *et al.* [ref], POLYMOD [ref] and BBC Pandemic [ref]) have published estimates for a different matrix $K_{z,z'}$, which gives the average number of contacts in age category z made by an individual in age category z' (note, following convention z denotes the row of the matrix and z' is the column). $\boldsymbol{K}$ is a matrix read into BEEPmbp using the 'age_mixing_matrix' TOML command (see §3.5.1). We explain here how $\boldsymbol{C}$ is calculate from $\boldsymbol{K}$.

Suppose the number of people in each age category is given by N_z. Because $\boldsymbol{K}$ acts to generate a force of infection, so the raw numbers in $K_{z,z'}$ must be divided by N_z to ensure that infections are generated in proportion to the number of contacts:

$$C_{z,z'} = \frac{K_{z,z'}}{N_z}. \quad \text{(D1)}$$

Note, the total number of contacts between individuals in categories z and z' must be the same, *i.e.*

$$K_{z,z'} N_{z'} = K_{z',z} N_i. \quad \text{(D2)}$$

This means that whilst $K_{z,z'}$ is asymmetric, the matrix $\boldsymbol{C}$ is symmetric. This can be seen as follows:

$$C_{z,z'} = \frac{K_{z,z'}}{N_z} = \frac{C_{z',z} N_z}{N_z N_{z'}} = \frac{K_{z',z}}{N_{z'}} = C_{z',z} \quad \text{(D3)}$$

In reality, the matrix $\boldsymbol{C}$ generated above becomes asymmetric due to stochastic noise introduced by sampling used to generate the raw data in the first place. To reduce this noise we here enforce symmetry be updating $\boldsymbol{C}$ according to

$$C^{\text{new}}_{z,z'} = \tfrac{1}{2}(C_{z,z'} + C_{z',z}). \quad \text{(D4)}$$

Appendix E: Accounting for thresholds in the observation model

This appendix shows expressions for the observation model (see §2.3.3) when the data y_i is set to be thresholded, *i.e.* its precise value is unknown, but it is at or below some specified threshold value V (note, the value for V is set using the 'threshold' property within 'data_tables', as described in §3.7).

- **Normal** – If Y_i is less than or equal to the threshold value V the observation model has a constant maximal value (which makes sense because the observation and data are entirely consistent), whereas if Y_i is larger than V the observation model probability correspondingly goes down:

$$\left.\begin{array}{rl} \pi\left(\text{Thresholded} \mid Y_i(\xi)\right) = N(V \mid V, V+\varepsilon) & \\ \pi\left(\text{Thresholded} \mid Y_i(\xi)\right) = N(V \mid Y_i(\xi), Y_i(\xi)+\varepsilon) & \end{array}\right\} \begin{array}{l} \text{If } Y_i(\xi) \le V \\ \text{If } Y_i(\xi) > V \end{array} \quad \text{(E1)}$$

  where $N(x|\mu,\sigma^2)$ is normal probability for x given a mean μ and variance σ^2 and ε=0.5.
- **Poisson** – In this case the observation model is calculated by simply adding up the probabilities for each possible value v up to V:

$$\pi\left(\text{Thresholded} \mid Y_i(\xi)\right) = \sum_{v=0}^{V} P(v \mid Y_i(\xi)), \quad \text{(E2)}$$

  where $P(x|\mu)$ is the Poisson probability distribution for x given a mean μ.
- **Negative binomial** – Similarly:

$$\pi\left(\text{Thresholded} \mid Y_i(\xi)\right) = \sum_{v=0}^{V} NB(v \mid Y_i(\xi), k), \quad \text{(E3)}$$

  where $NB(x|\mu,r)$ is the negative binomial probability distribution for x given a mean μ and shape parameter r.
- **Scaled** – If Y_i is less than or equal to the threshold value V the observation model has a constant maximal value of 1 (which makes sense because the observation and data are entirely consistent), whereas if Y_i is larger than V the observation model probability correspondingly goes down:

$$\left.\begin{array}{rl} \pi\left(\text{Thresholded} \mid Y_i(\xi)\right) = 1 & \\ \pi\left(\text{Thresholded} \mid Y_i(\xi)\right) = e^{-\frac{1}{2}\left[\log\left(\frac{V+\varepsilon}{Y_i+\varepsilon}\right)\right]^2} & \end{array}\right\} \begin{array}{l} \text{If } Y_i(\xi) \le V \\ \text{If } Y_i(\xi) > V \end{array} \quad \text{(E4)}$$

  Here, ε=0.5 is a small constant introduced to ensure validity even when y_i or Y_i are zero.

Appendix F: Calculation of the model evidence

This appendix explains how the model evidence from §2.3.5 is estimated for the different inference algorithms:

Metropolis coupled MCMC (MC^3)

This algorithm runs K separate MCMC chains, indexed by k (where k=1 represents the posterior and k=K represents the prior). The inverse temperature for each of these chains is given by

$$\phi_k = \left(\frac{K-k}{K-1}\right)^4 \phi_{post}. \quad \text{(F1)}$$

The model evidence is calculated using

$$\pi(y \mid \phi_1) = \prod_{k=2}^{K} \left(\frac{1}{N} \sum_{i=1}^{N} \pi(y \mid \xi_i^k)^{\phi_{k-1}-\phi_k} \right), \quad \text{(F2)}$$

where ξ_i^k are a series of N state samples (indexed by i) generated on chain k.

Particle annealed importance sampling using MBPs (PAIS-MBP)

This algorithm proceed in a series of generations indexed by g (where g=1 represent the prior and g=G represents the posterior estimate). The model evidence is given by

$$\pi(y \mid \phi_G) = \prod_{g=1}^{G-1} \left(\frac{1}{N} \sum_{i=1}^{N} \pi(y \mid \xi_i^g)^{\phi_{g+1}-\phi_g} \right), \quad \text{(F3)}$$

where ξ_i^g are N state samples (indexed by i) generated in generation g (which has inverse temperature ϕ_g).

Approximate Bayesian Computation (ABC)

For a given error function cutoff EF_{cutoff}, the model evidence is simply given by the fraction of samples accepted.

Approximate Bayesian Computation sequential Monte Carlo (ABC-SMC)

This algorithm works in the following way. Suppose generation g contains N parameter samples θ_i^g indexed by i with weights w_i^g. A new parameter sample θ_{new} is generated from this by first selecting i in proportion to w_i^g and then sampling from a multivariate normal kernel distribution centred at θ_i^g with a covariance matrix approximation to the posterior Σ:

$$\theta_{new} \sim MVN(\theta_i^g, \Sigma). \quad \text{(F4)}$$

Considering this an application of importance sampling, then for θ_{new} to be considered a random sample from the prior $\pi(\theta)$ it must be weighted according to

$$w_{new} = \frac{\pi(\theta_{new})}{\sum_{i=1}^{N} w_i^g \, p_{MVN}(\theta_{new} \mid \theta_i^g, \Sigma)}, \quad \text{(F5)}$$

where p_{MNV} is the multivariate normal probability density function for the kernel.

A new state ξ_{new} is simulated from the model using θ_{new}. If the error function for ξ_{new} is less than EF_{cutoff}, θ_{new} becomes a new sample to be used in the next generation.

An estimate for the model evidence[52] is given by:

[52] This expression is, in fact, applicable to any generation, but is usually most accurate for the last.

$$\pi(y \mid EF_{cutoff}) = \frac{\sum_{\text{new accepted}} w_{new}}{\sum_{\text{new}} w_{new}}, \tag{F6}$$

where the top sum goes over the weights of only accepted parameter samples, and the bottom sums over all samples.

Approximate Bayesian Computation with model-based proposals (ABC-MBP)

This algorithm proceed in a series of generations indexed by g (where g=1 represent the prior and g=G represents the posterior estimate). Because phase space is divided in two each time a new generation is added, the model evidence for a given generation g is approximately given by 2^g. However, a slightly more accurate expression, which uses all samples from all generations, can be calculated in the following way

$$\pi(y \mid EF^{G}_{\text{cutoff}}) = \prod_{g=1}^{G-1} \left[\frac{\sum_{g'=1}^{g} \sum_{i=1}^{N} H\left(EF^{g'+1}_{\text{cutoff}} - EF(\xi_i^{g'})\right)}{\sum_{g'=1}^{g} \sum_{i=1}^{N} H\left(EF^{g'}_{\text{cutoff}} - EF(\xi_i^{g'})\right)} \right], \tag{F7}$$

where ξ_i^g are N state samples (indexed by i) generated in generation g and H is the Heaviside step function (this gives a contribution of one if the error function on the sample is smaller than the cut-off).

Glossary: An index of all TOML commands

This provides an alphabetical list of all the commands that can be used in the input TOML file:

Command	Description
age_mixing_ matrix **§3.5.1**	Sets the name of a file containing an age-stratified contact matrix $\boldsymbol{K}$ (see Appendix I for further details). This square matrix must have the same dimensions as the number of age categories specified in 'ages' (if ages has only one category, 'age_mixing_matrix' does not need to be specified). Specifically, matrix element $K_{z,z'}$ gives the number of contacts in age category z made by an individual in age category z' (note, following convention z denotes the row of the matrix and z' is the column). *E.g.* age_mixing_matrix = "BBC-Pandemic.csv"
age_mixing_ modify **§3.5.1**	This is used to modify the basic mixing matrix as a function of time (here the file "amm.csv" informs a spline, see §3.3). *E.g.* age_mixing_modify = [{type="row_column", agecat="age70+", bp="[bp:amm.csv]", value="[value:amm.csv]", prior="Uniform(0,5)", smooth_type="log_smooth", smooth="0.3"}] *type* – Determines the type of modification. Currently only one is supported:

	• "row_column" – This multiplies a row and column for a specified age category in the contact matrix $C_{z,z'}$ (see Appendix I) by a factor specified in a subsequently defined spline. *agecat* – Specifies the age category to which the modification is applied.
ages **§3.5.1**	Specifies the age categories used in the analysis. *E.g.* ages = {cats="age0-19 | age20-69 | age70+", sus_value="0.7 | 1.0 | *", sus_prior="Dir(*)"} *cats* – Sets the age categories (separated by '|'). *sus_X* – Defines the relative susceptibility for different age categories.
area_plot **§5.2**	Defines how areas are plotted using BEEPmbp's visual tool. *E.g.* area_plot = { boundary="Scotland_areas.geojson", projection="equirectangular"} *boundary* – Provide the name a file which gives information about the boundaries of areas (currently '.geojson' and '.kml' geographical file formats are supported). *x_column / y_column* – Defines the columns in the 'areas' file which give the mean x and y position of the areas, *e.g.* mean longnitude and latitude (note this is an alternative to 'boundary' in cases in which in which this data is unavailable). *projection* – Sets the functional transformation of coordinates when plotting. Either "uniform" (by default) or "equirectangular" (suitable when displaying longitude/latitude data).
area_covars **§3.6.4**	Defines covariates for areas. These are used for estimating the contribution coming from fixed quantities within areas potentially related to disease transmission. *E.g.* area_covars= [{name="density", param="b1", value="0.1", prior="Uniform(0,1)", func="log"}] *name* – The name of the covariate (note this column heading must appear in the 'areas' file). *X* – Defines the parameter to be estimated. *func* - Sets the functional transformation to the raw data ("linear" or "log").

area_tv_covars **§3.6.4**	Defines time-varying covariates for areas. These are used for estimating the contribution coming from time-varying quantities within areas potentially related to disease transmission. *E.g.* area_tv_covars = [{file="tvcovars.csv", param="b2", value="0.1", prior="Uniform(0,1)", func="linear"}] *file* – Defines a file giving geographical covariate information as a function of time. *X* – Defines the parameter to be estimated. *func* - Sets the functional transformation to the raw data ("linear" or "log").
area_effect **§3.6.4**	These represent factors that modify the relative rate of transmission in different areas. *E.g.* area_effect = {value="[area effect:Scotland_LA.csv]", prior="Dir(*)"} *X* – Defines the parameters to be estimated. A Dirichlet prior is used to ensure the average area effect is 1 (see §3.2).
areas **§3.6.1**	Sets the filename of a table giving information about geographical areas (this can either be in tab-separated '.txt' text format or '.csv' format). *E.g.* areas= "areadata.csv" The table contains the following column: "area" (which gives a code or name that uniquely identifies each area), other coarser geographical scales if they are used (*e.g.* 'nhs region' amalgamates local authorities into NHS regions), columns for covariates in the model (*e.g.* population density)[53] and, potentially, the initial population make-up (see §3.6.2).
comps **§3.4.1**	Defines compartments in the model. *E.g.* comps = [{name="S"}, {name="E", dist="Erlang", k="2", mean_value="4"}, {name="I", dist="Exp", mean_value="4", inf_value="1"}, {name="R"}] *name* – Sets the name of a compartment. *mean_X* – Defines the model parameter(s) used for the mean waiting time (this can depend on demographic category, see §3.4.2).

[53] The columns do not have to have any particular order, provided they have the correct headings. Other columns may also exist which are not used by the analysis.

	inf_X – Sets a model parameter that specifies the relative infectivity for that compartment (if not set it is assumed to be zero).
cutoff **§4.2.3**	Specifies the cut-off in the error function ('abc' mode). *E.g.* cutoff = 1
cutoff_final **§4.2.1, §4.2.4**	Sets the final error function cut-off for the 'abc-mbp' mode (optional and by default set to zero corresponding to the prior). *E.g.* cutoff_final = 0.1
cutoff_frac **§4.2.3**	Specifies the fraction of accepted samples in the 'abc' mode. *E.g.* cutoff_frac = 0.01
datadir **§3.1**	Sets the directory where the data files are stored. *E.g.* datadir = "examples/Data_EX1"
data_tables **§3.7**	Provides information about the files that contain epidemiological data (multiple files are comma separated inside the square brackets). *E.g.* data_tables = [{file="EI.csv", type="transition", observation="E->I", timestep="7"}] *file* – The name of the file. This must be either a tab-separated '.txt' text file or a '.csv' file. *type* – Indicates the type of data: • "transition" – Time series information about the number of individuals moving down a transition (or transitions). • "population" – Time series population numbers within a specified compartment (or compartments). • "population_fraction" – Time series measurements for the population fraction within a specified compartment (or compartments). • "marginal" – The total number of transitions over a time period, typically stratified by a demographic classification. *observation* – Describes what is observed. When the type is "transition" or "marginal" this is given by the initial compartment followed by "->" and then the final compartment (additionally, multiple transitions can be specified, *e.g.* "I->D,I->R", would give the sum down both transitions). For "population" or

	"population_fraction" types, this is simply the name of the compartment under measurement (or several compartments that are comma separated). *obsmodel* – This sets the observation model which relates the observed data to the system state (optional and set to "scale" by default). Four possibilities exist: "normal", "poisson", "negbin" and "scale" (see §2.3.3 for details). *geo_filt* – This give the geography over which the observation are made (optional). The name for this corresponds to a specified column in the 'areas' file. *geo_dep* – This optional specification allows for multiple columns of data each referring to a given geographic group (*e.g.* 'geo_dep="area"' would give columns for each of the geographical areas). *democats_filt* – Filters to include only specified demographic groups (*e.g.* 'democats_dep="Sex:Male"' would mean that observations are made on only males). *democats_dep* – This optional specification allows for multiple columns of data each referring to a given demographic group (*e.g.* 'democats_dep="Sex"' would imply that the data has two columns, one for 'Male' and one for 'Female'). *start* – Sets the first measurement date for the data (optional and by default taken from the data table). *end* – Sets the last measurement date for the data (optional and by default taken from the data table). *shift* – Allows for the raw data's date/time to be shifted by a specified number. *timestep* – An integer which sets the time step (for "transition" type only). *threshold* – Sets the threshold value (see 'threshold_str'). *factor* – Sets a factor which multiplies the value given in 'observation' to get to the data, *e.g*. this can be used to incorporate a test sensitivity (optional, by default set to 1). *factor_spline* – Uses a spline to provide the factor between the value given in 'observation' and the observed data. *weight* – This can give preferential weight when fitting the data (optional, by default 1). A higher value implies that this particular data will be fit more stringently than others.

	line_colour – Sets the colour of the line in the final plot. This can take the values "black", "red", "blue", "green", "yellow", "cyan", "magenta" (optional, by default set to red).
democats **§3.5.2**	Sets one or more demographic classifications. *E.g.* democats = [{name="Sex", cats="Male | Female"}, {name="Ethnicity", cats="White | Black | Asian"}] *name* – Sets the name for the demographic classification. *cats* – Sets the different categories within the classification. *sus_X* – Defines a parameter giving the relative susceptibility.
democat_change **§3.5.4**	This allows for the proportions within a specified demographic classification in the susceptible population to vary over time (for example, this could be used to study the effect of vaccination). *E.g.* democats = [{name="Vac Status", cats="Vac | Not Vac"}] democat_change = [{name="Vac Status", file="vac.csv"}] *name* – References the name for the demographic classification (set in 'democats'). *file* – The name of the file providing information about the change. This must be either a tab-separated '.txt' text file or a '.csv' file. *democats_filt* – Filters to include only specified demographic groups (*e.g.* setting this to "Sex:Male" would mean that the specified changes are made only on males). *geo_filt* – This give the geography over which the observation are made (*e.g.* setting this to "area:S12000005" would mean that the specified changes are made only on individuals in this particular area).
dynamics **§3.9**	Used to determine the underlying system dynamics and can take the values "stochastic" or "deterministic" (optional, by default set to "stochastic"). *E.g.* dynamics = "deterministic" When run in deterministic mode, model inference methods that rely on MBPs cannot be used.
efoi_factor **§3.4.4**	This sets the denominator for the external force of infection (optional, by default set to infections per unit time per 100,000 individuals).

	E.g. efoi_factor = 100000
efoi_spline **§3.4.4**	Defines linear splines used to represent the external force of infection. *E.g.* efoi_spline = [{param="phi", value="1", bp="[bp:phi_spline.txt]", factor="[fac:phi_spline.txt]"}] See §3.3 for generally how splines are defined. Also: *geo_filt* – Specifies the area on which the spline acts (optional, set to all areas by default). *age_dist* – Specifies the fraction of individuals in different ages groups becoming infected as a result of the external force of infection (optional, by default they are set proportional to the population sizes in each demographic group). *strain* – If more than one strains exists in the model this specifies which one is being referred to (optional, set to all strains by default).
end **§3.1**	The ending time for the simulation or inference (in days or as a date). *E.g.* end = "2020-12-31"
geo_mixing_ matrix **§3.6.3**	This sets a files used to define the geographic mixing matrix between different regions. *E.g.* geo_mixing_matrix = "census_flow_data.csv"
geo_mixing_ modify **§3.6.3**	Defines a spline that informs the relative rate of mixing of individuals between regions. Specifically, this parameter multiplies the diagonal elements specified in the 'geo_mixing_matrix'. *E.g.* geo_mixing_modify = [{bp="[bp:gmm.csv]", value="[value:gmm.csv]", prior="Uniform(0,1)"}] See §3.3 for how splines are defined.
GR_max **§4.2**	This sets the maximum value for the Gelman-Rubin statistics when terminating the algorithm using this measure (note, this requires 'nrun' to be set to larger than 1). *E.g.* GR_max = 1.1
init_pop **§3.6.2**	Specifies a file giving information about the make-up of the initial population. *E.g.* init_pop = "initpop.csv",
invT	Sets the inverse temperature for the posterior in the 'pmcmc' and 'mcmcmbp' modes.

§4.2.5, §4.2.6	*E.g.* invT = 1.0
invT_final **§4.2.2, §4.2.7**	Sets the final inverse temperature (a) in the 'pais' mode or (b) for the highest temperature chain in the 'mc3' mode (optional and by default set to zero corresponding to the prior). *E.g.* invT_final = 0.1
invT_start **§4.2.7**	Sets the inverse temperature for the highest temperature chain in the 'mc3' mode (optional and by default set to zero corresponding to the prior). *E.g.* invT_start = 0.01
invT_power **§2.3.1**	Sets the power used to determine inverse temperatures in Eq.(16) (optional, by default set to 4). *E.g.* invT_power = 6
inputfile **§1.4**	Sets the input TOML file. *E.g.* inputfile="examples/EX1.toml"
level_effect **§3.6.3**	Allows different areas to have different levels of disease transmission (this can be used to incorporate levels of disease intervention, for example lockdown vs social distancing vs nothing). *E.g.* level_effect = {file="level.csv", param="level1 | level2", value="0.5 | 2", prior="Dir(*)"} *file* – The name of a file providing information about the levels (this must be a table with rows giving different dates, columns giving different areas and the table elements themselves set to one of the values in 'param'). *X* – Sets parameters that represent the relative disease transmission rate for different levels.
mcmc_update	Sets which proposals are used for the MCMC updates *E.g.* mcmc_update = { full_mvn = "off", mvn = "on", single="on", demo_spec="on", mean_time="on", neighbour="on", joint="on", mvn_multiple="off", multiple_factor=1.0} Used only in tuning and testing the algorithm,
mode **§4.1**	This selects the mode of operation when BEEPmbp is run. *E.g.* mode = "sim" The following possibilities exist:

	"sim" – Simulates from the model. "multisim" – Simulated multiple times to generate an ensemble of outputs. "prediction" – Performs model prediction (based on posterior samples). "abcmbp" – Performs inference using the ABC-MBP algorithm. "pais" – Performs inference using the PAIS-MBP algorithm. "abc" – Performs inference using the ABC algorithm. "abcsmc" – Performs inference using the ABC-SMC algorithm. "pmcmc" – Performs inference using the PMCMC algorithm. "mcmcmbp" – Performs inference using the MCMC-MBP algorithm. "mc3" – Performs inference using the MC^3 algorithm.
modification **§3.10**	In 'prediction' mode this specifies the change or changes made to the model. *E.g.* modification = [{start="2020-4-01", type="trans_rate_fac", trans="S->E", factor="0.5"}] *start* – Sets the start time for the change (optional, by default set to 'start' used in the analysis). *end* – Sets the end time for the change (optional, by default set to 'end' used in the analysis). *type* – Denotes the type of change. This can be one of the following types: • "trans_rate_fac" – This changes the rate of a specified transition by a factor ('trans' and 'factor' must be set). • "beta_fac" – Changes the transmission rate by a factor ('factor' must be set). • "efoi_fac" – Changes the external force of infection by a factor ('factor' must be set). • "spline_fac" – Multiplies a spline by a factor ('name' must correspond to 'name' set in a spline and 'factor' must be set). • "spline_set" – Sets the value of a spline ('name' must correspond to 'name' set in a spline and 'factor' must be set). *factor* – Specifies the factor for the modification (if needed). *value* – Specifies the value for the modification (if needed). *name* – Specifies the name of the spline affected (if needed).

	trans – Specifies the transition on which the change applies. *strain* – Specified if only a particular strain is referred to (optional). *geo_filt* – Specified to only applies to a particular geographical area (optional). *democats_filt* – Specified to only apply to a particular demographic category or set of categories (optional).
nburnin **§4.2.5-7**	Sets the number of 'burn-in' steps when performing MCMC (used in the 'pmcmc', 'mcmcmbp' and 'mc3' modes). *E.g.* nburnin = 100 By default burn-in is set to a quarter of the number of samples 'nsample'
nchain **§4.2.7**	Sets the number of chains used when performing MC^3 in the mode 'mc3' *E.g.* nchain = 20
ngeneration **§4.2.1, §4.2.2, §4.2.4**	Sets the number of generations (required in the 'abcmbp', 'abcsmc' and 'pais' modes). *E.g.* ngeneration = 40
nodata_str **§3.7.2**	Defines the string used in files to represent the fact that no data is available (optional, by default set to ".") *E.g.* nodata_str = "NA"
nparticle **§4.2.1, §4.2.2, §4.2.5**	The number of particles (required in the 'abcmbp', 'pais' and 'pmcmc' modes) *E.g.* nparticle = 100
nquench **§4.2.7**	The number of iterations used in quenching the system when using the 'mcmcmbp' or 'mc3' modes (optional, set to a half of 'nburnin' by default). *E.g.* nquench = 100
nrun **§4**	Sets the number of runs which are performed in parallel (optional, used for inference and set to one by default). *E.g.* nrun = 4
nsample **§4.2.3-7**	Sets the number of samples to be generated (used in the 'abc', 'abcsmc', 'pmcmc', 'mcmcmbp' and 'mc3' modes). *E.g.* nsample = 200

nsimulation **§4.1.2**	Sets the number of simulations in 'multisim' mode. *E.g.* nsimulation = 100
nsim_per_sample **§4.3**	Sets the number of simulations per posterior sample in 'prediction' mode (optional, by default set to 4). *E.g.* nsim_per_sample = 10
nthin **§4.2.5-7**	Sets the thinning of samples in the 'pmcmc', 'mcmcmbp' and 'mc3' modes. This is used to save computational memory such that not every system sample is stored (which is typically not necessary because samples are highly correlated in these approaches). *E.g.* nthin = 10
nupdate **§4.2.1, §4.2.2**	Sets the number of MCMC 'updates' used per generation in the 'abcmbp' and pais' modes (by default set to 1). Here an update performs MBPs on each of the model parameters as well as combinations of them. *E.g.* nupdate = 2
obs_spline **§3.7.3**	Defines linear splines that are used as factors to relate the 'observation' quantity in 'data_tables' with the actual data observed. *E.g.* data_tables = [{type="transition", observation="E->I", file="IH.csv", factor_spline="obs1"}] obs_spline = [{name="obs1", value="0.1|0.3|0.5", prior="Uniform(0,1)", bp="start|20.03.20|end"}] This implies that the fraction of actual E->I transitions observed varies, starting at 10% and ending at 50%. As well as being able to set this spline, it can also be inferred from the data. See §3.3 for how splines are defined.
outputdir **§3.1**	Sets the name of the output directory (optional, set to "Output" by default). *E.g.* outputdir = "Output_EX1"
output_prop **§3.11.3**	Sets properties of the output. *E.g.* output_prop = {probdist="kde", h="5"} *probdist* – Sets how probability distributions are displayed. Either "kde" for kernel density estimation or "bin" for binning. *nbin* – Determines the number of bins used when binning (optional, set to 200 by default).

	h – Sets a smoothness parameter when using kernel density estimation (optional, set to 10 by default).
quench_factor **§4.2.2**	Sets the rate of quenching in the 'pais' mode (optional, set to 0.5 by default such that on average half of all particles each generation are discarded). *E.g.* quench_factor = 0.1
prediction_end **§4.3**	Sets the end time (optional, by default set to inference end time). *E.g.* prediction_end = "2022-02-01"
prediction_start **§4.3**	In 'prediction' mode this sets the start time (optional, by default set to either when the first modification is made to the model or the inference end time, whichever is earlier). *E.g.* prediction_start = "2021-05-01"
prior_order **§3.2**	This command is used to specify any ordering of the parameters. *E.g.* R_spline = [{param="R0 | R1 | R2 | R2", value="2.0 | 1.9 | 1.5 | 0.6", prior="Uniform(0.4,4)"}] prior_order = "R0 > R1 | R1 > R2 | R2 > R3" In this example, the ordering ensures that the reproduction number is constrained to go down, consistent with the prior belief that implementing intervention strategies reduces disease transitions.
prop_size **§4.2.4**	Sets the proposal size in the 'abcsmc' mode (optional, set to 1 by default). This factor scales the MVN estimate of the posterior distribution in the previous generation to set the parameter proposal kernel. *E.g.* prop_size = 1.5
prob_reach **§3.11.2**	The probability of reaching a given compartment if infected. For example if set to the dead "D" compartment this can be used to calculate the infection fatality rate. *E.g.* prob_reach = [{name="ifr", comp="D"}] *name* – The name as generated in the output file. *comp* – The compartment reached.
region_effect	Set if there is a regional effect incorporated at a particular geographical scale. *E.g.* region_effect = {geography="area", sigma_value="0.3"}

	geography – The geography over which the regional effect acts (optional, set to all areas by default). *sigma_X* – The standard deviation in the regional effect.
R_spline **§3.4.3**	Defines the linear spline used to represent time variation in the reproduction number R_t. *E.g.* R_spline = [{bp="start | 2020-03-01 | 2020-07-15 | end", param="R0 | R1 | R2 | R3", value="2.0 | 1.5 | 0.5 | 1.0", prior="Uniform(0.4,4)", smooth_type="log_smooth", smooth = "0.5" }] *name* – Specifies the name of the spline (optional, by default set to "R_t"). *bp* – The times at which the breakpoints occur (note these must begin and end with the 'start' and 'end' times set for analysis. *X* – Sets parameters used for each spline point. *smooth_type* – Sets the type of smoothing used. The possible values are "no_smooth", "smooth" and "log_smooth" (optional, set to "no_smooth" by default). *smooth* – The strength of smoothing. *factor* – A multiplicative factor which multiplies the value of the parameter on each spline point (optional). *geo_filt* – Specifies the area(s) on which the spline acts (optional, set to all areas by default). See §3.3 for further details on defining splines.
seed **§4.1.1**	This is a positive integer used to set the initial value of the pseudorandom number generator. Note, because the model is stochastic in nature, changing this seed will lead to a different simulated results. Varying it can also be used to change the initial conditions for the inference algorithms (useful when checking for consistent convergence on the true posterior). *E.g.* seed = 10
start **§3.1**	Sets the start time for the simulation or inference (in days or as a date, as specified in 'time_format'). *E.g.* start = "2020-01-01"
state_outputs **§3.11.1**	This allows for posterior graphs of the state to be plotted. *E.g.* state_outputs = [

	{plot_name="Dynamics", type="population", observation="S"}, {plot_name="Dynamics", type="population", observation="E"}, {plot_name="Dynamics", type="population", observation="I"}, {plot_name="Dynamics", type="population", observation="R"}] This generates a single plot with title “Dynamics” that contains four curves representing the different compartmental populations in an SEIR model. *type* – Indicates the type of observation: • "transition" – Time series information about the number of individuals moving down a transition (or transitions). • "population" – Time series population numbers within a specified compartment (or compartments). • "population_fraction" – Time series measurements for the population fraction within a specified compartment (or compartments). • "marginal" – The total number of transitions over a time period, typically stratified by a demographic classification. *observation* – Describes what is observed. When the type is "transition" or "marginal" this is given by the initial compartment followed by "->" and then the final compartment (additionally, multiple transitions can be specified, *e.g*. "I->D,I->R", would give the sum down both transitions). For "population" or "population_fraction" types, this is simply the name of the compartment under measurement (or several compartments that are comma separated). *geo_filt* – This give the geography over which the observation are made (optional). The name for this corresponds to a specified column in the ‘areas’ file. *democats_filt* – Filters to include only specified demographic groups (*e.g.* ‘democats_dep="Sex:Male"’ would mean that observations are made on only males). *line_colour* – Sets the colour of the line in the final plot. This can take the values "black", "red", "blue", "green", "yellow", "cyan", "magenta" (optional, automatically generated by default). *plot_name* – Sets the name of the final plot (optional). Note, multiple lines can be put on the same plot by giving them the same ‘*plot_name*’.
steps_per_unit_time **§3.9**	Sets the number of discrete time steps performed per unit time (optional, set to 4 by default). Larger values mean the tau leaping algorithm better approximates the continuous time Gillespie algorithm, but take computationally longer to run.

	E.g. steps_per_unit_time = 4
strains **§3.8**	Used to specify different strains of virus. *E.g.* strains = {cats="s1 | s2", sus_value="0.7 | 1.0 | *", sus_prior="Dir(*)", Rfactor_value="1.0 | 2.0", Rfactor_prior="Fixed(1) | Uniform(0.5,2)"} *cats* – Sets the names of the names of the strains. *sus_X* – Used to vary the susceptibility of individuals to different strains (optional). *Rfactor_X* – This gives the factor by which R_t increases for the different strains (usually one would be fixed to a value 1 to represent the reference strain).
threshold_str **§3.7.2**	When data contains thresholded values, this sets the string used in the data to represent this fact (optional, by default set to "*"). *E.g.* threshold = "<=5" If now in 'data_tables' we set 'threshold="5"' then values of "<=5" in the data file are interpreted as at or below 5.
time_format **§3.1**	This determines the format in which times are represented in the input TOML file and any data files. *E.g.* time_format = "year-month-day" The following possibilities exist: • "*year-month-day*" – This uses the format "2020-03-01" to represent 1st March. • "day/month/year" – This uses the format "01/03/2020" to represent 1st March. • *number* – An integer is used to represent the time (*e.g.* the number of days since some reference time point in the past).
time_labels **§3.11.4**	Sets time labels used to represent specific times of interest in the analysis. Not only can these be used subsequent instead of dates (*e.g.* when specifying the breakpoints in splines), but they are also placed as vertical reference lines on the final time-based output graphs. *E.g.* time_labels = [{name="Lockdown", time="2020-03-23"}]
trans **§3.4.1**	Defines transitions between compartments. *E.g.* trans = [{from="S", to="E", infection="yes"}, {from="E", to="I"}, {from="I", to="R", prob_value="0.9", prob_prior="Dir(*)"},

	{from="I", to="D", prob_value="*", prob_prior="Dir(*)"}] *from* – Sets the initial compartment. *to* – Sets the final compartment. *infection* – Specifies the infection transition (only one may be set). *prob_X* – Specifies the probability of moving down a given branch (note, this only needs to be specified when the 'from' compartment has more than one transition leaving it). Because the sum of branching probabilities for all transitions leaving a compartment must be one, so one of these probabilities does not need to be specified (because it can be calculated from the others). This is indicated by using the '*' symbol. Values can be set separately for different demographic groups (see §3.4.2). If not fixed, a Dirichlet prior is used during inference (see §3.2).
trans_combine	When using transition data, this combines data values until they are above this specified value. This can help inference when data is highly stochastic and transition rates are low. *E.g.* trans_combine =50
tv_covars **§3.6.4**	Defines time-varying covariates. These are used for estimating the contribution coming from time-varying quantities potentially related to disease transmission. *E.g.* tv_covars = [{name="covar", file="tvcovars.csv", param="b2", value="0.1", prior="Uniform(0,1)", func="linear"}] *name* – The name of the covariate (this heading must appear in the specified 'file'). *file* – Defines a file giving geographical covariate information as a function of time. *X* – Defines the parameter to be estimated. *func* - Sets the functional transformation to the raw data ("linear" or "log").