

Improved multi-type birth-death phylodynamic inference in BEAST 2

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Abstract

The multi-type birth-death model with sampling is a phylodynamic model which enables quantification of past population dynamics in structured populations, based on phylogenetic trees. The BEAST 2 package *bdmm* implements an algorithm for numerically computing the probability density of a phylogenetic tree given the population dynamic parameters under this model. In the initial release of *bdmm*, analyses were limited to trees consisting of up to approximately 250 genetic samples for numerical reasons. We implemented important algorithmic changes to *bdmm* which dramatically increase the number of genetic samples that can be analyzed, and improve the numerical robustness and efficiency of the calculations. Being able to use bigger datasets leads to improved precision of parameter estimates. Furthermore, we report on several model extensions to *bdmm*, inspired by properties common to empirical datasets. We apply this improved algorithm to two partly overlapping datasets of Influenza A virus HA sequences sampled around the world, one with 500 samples, the other with only 175, for comparison. We report and compare the global migration patterns and seasonal dynamics inferred from each dataset.

Availability: The latest release with our updates, *bdmm* 0.3.5, is freely available as an open access package of BEAST 2. The source code can be accessed at <https://github.com/denisekuehnert/bdmm>.

Keywords: *phylogenetics, Bayesian inference, phylodynamics, population structure*

Introduction

Genetic sequencing data taken from a measurably evolving population contain fingerprints of past population dynamics [Felsenstein, 1992]. In particular, the phylogeny spanning the sampled genetic data contains information about the mixing pattern of different populations and thus

24 contains information beyond what is encoded in classic occurrence data, see e.g. Hey and
25 Machado [2003], Stadler and Bonhoeffer [2013b]. Phylodynamic methods [Grenfell et al., 2004,
26 Kühnert et al., 2011] aim at quantifying past population dynamic parameters, such as migration
27 rates, from genetic sequencing data. Such tools have been widely used to study the spread of
28 infectious diseases in structured populations, see e.g. Dudas et al. [2017], Faria et al. [2018] as
29 examples for analyses of recent epidemic outbreaks. Both the host population and the pathogen
30 population may be structured, e.g. the host population may be geographically structured, and the
31 pathogen population may consist of a drug-sensitive and a drug-resistant subpopulation.
32 Understanding how these subpopulations interact with one another, whether they are separated by
33 geographic distance, lifestyles of the hosts, or other barriers, is a key determinant in
34 understanding how an epidemic spreads. In macroevolution, different species may also be
35 structured into different “subpopulations”, e.g. due to their geographic distribution or to trait
36 variations, see e.g. Hodges [1997]. Phylodynamic tools aim at quantifying the rates at which
37 species migrate or traits are gained or lost, and the rates of speciation and extinction within the
38 “subpopulations”, see e.g. Goldberg et al. [2010], Mayrose et al. [2011], Goldberg et al. [2011].
39 The phylodynamic analysis of structured populations can be performed using two classes of
40 models, namely coalescent-based and birth-death-based approaches. Both have their unique
41 advantages and disadvantages [Volz and Frost, 2014, Boskova et al., 2014]. Here, we report on
42 improvements to a multi-type birth-death-based approach.
43 A multi-type birth-death model is a linear birth-death model accounting for structured
44 populations. Under this model, the probability density of a phylogenetic tree can be calculated by
45 numerically integrating a system of differential equations. The use of this model within a
46 phylodynamic setting and the associated computational approach were initially proposed for
47 analyzing species phylogenies [Maddison et al., 2007] and later for analyzing pathogen
48 phylogenies [Stadler and Bonhoeffer, 2013a, Volz and Frost, 2014]. The package *bdmm* within
49 the Bayesian phylodynamic inference framework BEAST2 [Bouckaert et al., 2014] generalizes
50 the assumptions of these two initial approaches [Kühnert et al., 2016]. It further allows for
51 co-inferring phylogenetic trees together with the model parameters and thus takes phylogenetic
52 uncertainty explicitly into account. Datasets containing more than 250 genetic sequences could
53 not be analysed using the original *bdmm* package [Kühnert et al., 2016] due to numerical

54 instability. This limitation was a strong impediment to obtaining reliable results, particularly for
55 analysis of structured populations, as quantifying parameters which characterize each
56 subpopulation requires a significant amount of samples from each of them. The instability was
57 due to numerical underflow in the probability density calculations, meaning that probability
58 values extremely close to zero could not be accurately calculated and stored. We have solved the
59 numerical instability issue of *bdtmm*, thereby lifting the hard limit on the number of samples that
60 can be analysed. In addition, the practical usefulness of the *bdtmm* package was previously
61 restricted by the amount of computation time required to carry out analyses. We report here on
62 significant improvements in computation efficiency. As a result, *bdtmm* can now handle datasets
63 containing several hundred genetic samples. Finally, we made the multi-type birth-death model
64 more general in several ways: homochronous sampling events can now occur at multiple times
65 (not only the present), individuals are no longer necessarily removed upon sampling, and the
66 migration rate specification has been made more flexible by allowing for piecewise-constant
67 changes through time.

68 Overall, these model generalizations and implementation improvements enable more reliable and
69 ambitious empirical data analyses. Below, we use the new release of *bdtmm* to quantify Influenza
70 A virus spread around the globe as an example application, and compare the results obtained with
71 those from the reduced dataset analysed in [Kühnert et al., 2016].

72 **Methods**

73 **Description of the extended multi-type birth-death model**

74 First, we formally define the multi-type birth-death model on d types [Kühnert et al., 2016]
75 including the generalizations introduced in this work. The process starts at time 0 with one
76 individual, this is also called the origin of the process and the origin of the resulting tree. This
77 individual is of type $i \in \{1 \dots d\}$, with probability h_i (where $\sum_{i=1}^d h_i = 1$). The process ends
78 after T time units (at present). The time interval $(0, T)$ is partitioned into n intervals through
79 $0 < t_1 < \dots < t_{n-1} < T$, and we define $t_0 := 0$ and $t_n := T$. Each individual at time t ,
80 $t_{k-1} \leq t < t_k$, $k \in \{1 \dots n\}$ of type $i \in \{1 \dots d\}$, gives rise to an additional individual of type

81 $j \in \{1 \dots d\}$, with birth rate $\lambda_{ij,k}$, migrates to type j with rate $m_{ij,k}$ (with $m_{ii,k} = 0$), dies with
82 rate $\mu_{i,k}$, and is sampled with rate $\psi_{i,k}$. At time t_k , each individual of type i is sampled with
83 probability $\rho_{i,k}$. Upon sampling (either with rate $\psi_{i,k}$ or probability $\rho_{i,k}$), the individual is
84 removed from the infectious pool with probability $r_{i,k}$. We summarize all birth-rates $\lambda_{ij,k}$ in $\boldsymbol{\lambda}$,
85 migration rates $m_{ij,k}$ in \boldsymbol{m} , death rates $\mu_{i,k}$ in $\boldsymbol{\mu}$, sampling rates $\psi_{i,k}$ in $\boldsymbol{\psi}$, sampling probabilities
86 $\rho_{i,k}$ in $\boldsymbol{\rho}$ and removal probabilities $r_{i,k}$ in \boldsymbol{r} , $i, j \in \{1, \dots, d\}, k \in \{1, \dots, n\}$. The model
87 described in Kühnert et al. [2016] is a special case of the above, assuming that migration rates are
88 constant through time (i.e. do not depend on k), removal probabilities are constant through time
89 and across types (i.e. do not depend on k and i), and that $\rho_{i,k} = 0$ for $k < n$ and $i \in \{1 \dots d\}$.
90 This process gives rise to complete trees on sampled and non-sampled individuals with types
91 being assigned to all branches at all times (Figure 1, left). Following each branching event, one
92 offspring is assigned to be the “left” offspring, and one the “right” offspring, each assignment has
93 probability $\frac{1}{2}$. In the figure, we draw the branch with assignment “left” on the left and the branch
94 with assignment “right” on the right. Such trees are called oriented trees, and considering
95 oriented trees will facilitate calculations of probability densities of trees. Pruning all lineages
96 without sampled descendants leads to the *sampled phylogeny* (Figure 1, middle and right). The
97 orientation of a branch in the sampled phylogeny is the orientation of the corresponding branch
98 descending the common branching event in the complete tree. When the sampled phylogeny is
99 annotated with the types along each branch, we refer to it as a *branch-typed tree* (Figure 1,
100 middle). On the other hand, if we discard these annotations but keep the types of the sampled
101 individuals, we call the resulting object a *sample-typed (or tip-typed) tree* (Figure 1, right).
102 Below, we state the probability density of the sampled tree (i.e. the sample-typed or branch-typed
103 tree) given the multi-type birth–death parameters $\boldsymbol{\lambda}, \boldsymbol{m}, \boldsymbol{\mu}, \boldsymbol{\psi}, \boldsymbol{\rho}, \boldsymbol{r}, T$. This probability density is
104 obtained by integrating probability densities g from the leaf nodes (or “tips”), backwards along
105 all edges (or “branches”), to the origin of the tree. Our notation here is based on previous work
106 [Kühnert et al., 2016, Stadler et al., 2013], and the probabilities $p_{i,k}(t)$ and $g_{i,k}^e(t)$ relate to E and
107 D in Maddison et al. [2007], Stadler and Bonhoeffer [2013a], respectively.
108 Every branching event in the sampled tree gives rise to a node with degree 3 (i.e. 3 branches are
109 attached). Every sampling event gives rise to a node of degree 2 (called “sampled ancestor”) or 1
110 (called “tip”, as defined above). A sampling event at time $t = t_k, k \in \{1, \dots, n\}$, is referred to as

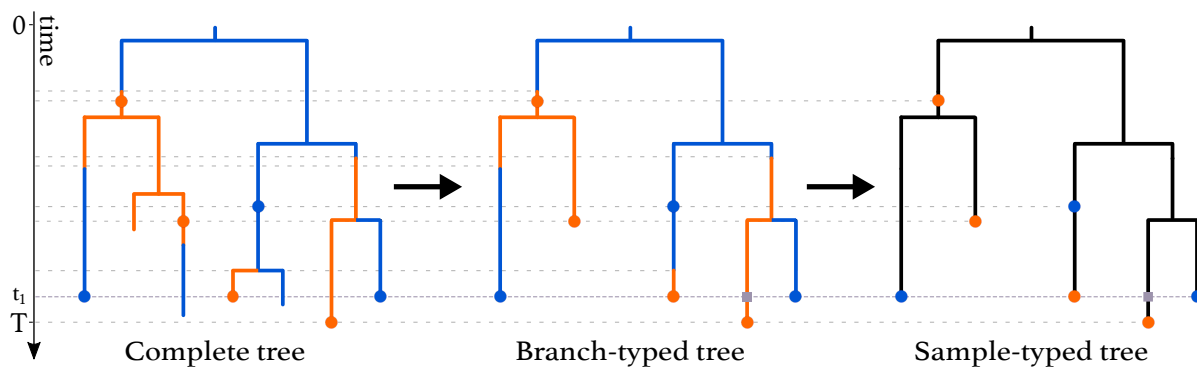


Figure 1: Complete tree (left) and sampled trees (middle and right) obtained from a multi-type birth-death process with two types. The orange and blue dots on the trees represent sampled individuals and are coloured according to the type these individuals belong to. A ρ -sampling event happens at time t_1 . The grey squares represent degree-2 nodes added to branches crossing this event. ρ -sampling also happens at present (time T). As seen in the complete tree, the first three individuals who were sampled were not removed from the population upon sampling, while the four individuals giving rise to the later samples were removed upon sampling.

111 a ρ -sampled node. All other nodes corresponding to samples are referred to as ψ -sampled nodes.
 112 Further, degree-2 nodes are put at time t_k on all lineages crossing time t_k , $k = 1, \dots, n - 1$ as
 113 shown at time t_1 in Figure 1. In a branch-typed tree, a node of degree 2 also occurs on a lineage at
 114 a time point when a type-change occurs. Such type changes may be the result of either migrations
 115 or birth events in which one of the descendant subtrees is unsampled (Figure 1, middle).
 116 We highlight that in *bdmm*, we assume that the most recent sampling event happens at time T .
 117 This is equivalent to assuming that the sampling effort was terminated directly after the last
 118 sample was collected, and overcomes the necessity for users to specify the time between the last
 119 sample and the termination of the sampling effort at time T .
 120 The derivation of the probability density of a sampled tree under the extended multi-type
 121 birth-death model is developed in Supplementary Information (SI) (section S1).

122 Implementation improvements

123 The computation of probability densities of sampled trees under the multi-type birth-death model
 124 require numerically solving Ordinary Differential Equations (ODEs) along each tree branch. We
 125 significantly improved the robustness of the original *bdmm* implementation, which suffered from
 126 instabilities caused by underflow of these numerical calculations. Compared to the original
 127 implementation, we prevent underflow by implementing an extended precision floating point

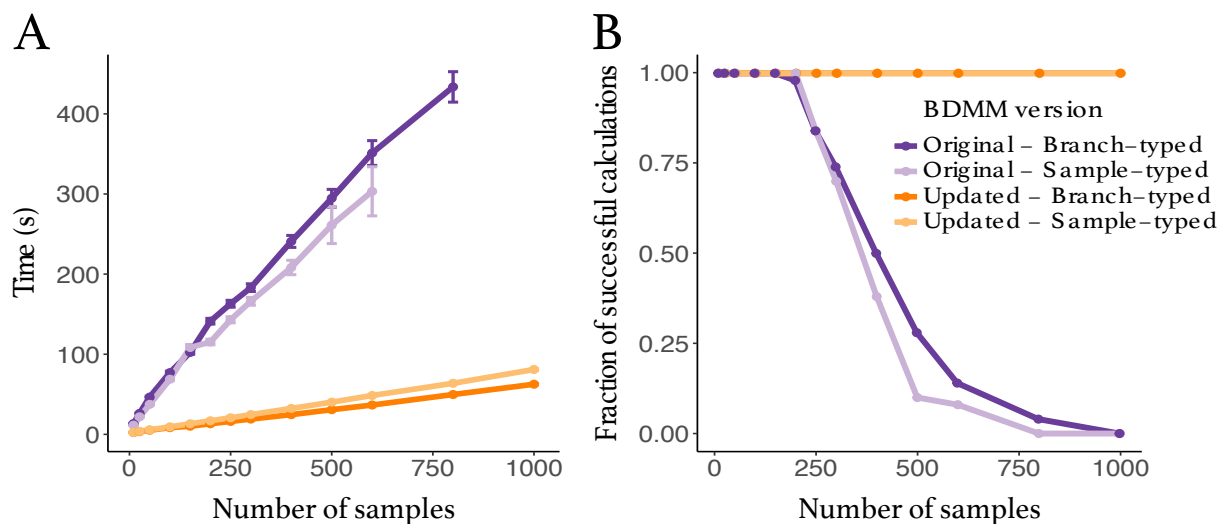


Figure 2: Comparison between the original and updated implementation of the multi-type birth-death model. **A**: Speed comparison. Only successful calculations were taken into account i.e. calculations where the log-probability density was different from $-\infty$. **B**: Success in calculating probability density values plotted against tree size. The values presented in this panel correspond to the same set of calculations as the one in panel A.

128 representation (EPFP) for storing intermediary calculation results. Additional to this
129 improvement in stability, we improved the efficiency of the probability density calculations, by 1)
130 using an adaptive-step-size integrator for numerical integration, 2) performing preliminary
131 calculations and storing the results for use during the main calculation step and 3) distributing
132 calculations among threads running in parallel. Details can be found in SI section S2.

133 Results

134 Evaluation of numerical improvements

135 We compared the robustness and efficiency of the improved *bdmm* package against its original
136 version. We considered varying tree sizes, between 10 and 1000 samples. For each tree size, we
137 simulated 50 branch-typed and 50 sample-typed trees under the multi-type birth-death model
138 using randomly-drawn parameter values from the distributions shown in SI Table S1. For each
139 simulated tree, we measured the time taken to perform the calculation of the probability density
140 given the parameter values under which the tree was simulated, using the updated and the
141 original *bdmm* implementation. We report the wall-clock time taken to perform this calculation
142 5000 times (Fig. 2). All computations are performed on a MacBook Pro with a dual-core 2.3

143 GHz Intel Core i5 processor. The new implementation of *bdmm* is on average 9 times faster than
144 the original (Fig. 2A). The robustness of the updated implementation is demonstrated by
145 reporting how often the implementations return $-\infty$ for the probability density in log space. We
146 call these calculations “failures”, the most likely cause of error being underflow. Our new
147 implementation shows no calculation failure for trees with up to 1000 samples, while in the
148 original implementation calculations often fail for trees with more than 250 samples (Fig. 2B).

149 **Influenza A virus (H3N2) analysis**

150 As an example of a biological question which can be investigated with *bdmm*, we analysed 500
151 H3N2 influenza virus HA sequences sampled around the globe from 2000 to 2006 and aim to
152 recover the seasonal dynamics of the global epidemics. The dataset is a subset of the data
153 analysed by Vaughan et al. [2014], taken from three different regions around the globe: New
154 York (North, $n = 167$), New Zealand (South, $n = 215$) and Hong Kong (Tropics, $n = 118$). As a
155 comparison, we performed an identical analysis with the H3N2 influenza dataset of 175
156 sequences sampled between 2003 and 2006 used in [Kühnert et al., 2016]. This dataset of 175
157 sequences was also a subset of the data by Vaughan et al. [2014], and it also groups samples from
158 3 locations denoted as North (for northern hemisphere), South (for southern hemisphere) and
159 Tropic (for tropical regions). Note that the latter dataset comes from more geographically-spread
160 samples and thus we do not expect results from both analysis to be perfectly comparable. As we
161 deal with pathogen sequence data, we adopt the epidemiological parametrization of the
162 multi-type birth-death model as detailed in Kühnert et al. [2016]. The epidemiological
163 parametrization substitutes birth, death and sampling rates with effective reproduction numbers
164 within types, rate at which hosts become noninfectious and sampling proportions. To study the
165 seasonal dynamics of the global epidemic, we allow the effective reproduction number R_e to vary
166 through time. To do so, we subdivide time into six-month intervals (starting April 1st and
167 October 1st) and we constrain effective reproduction number values corresponding to the same
168 season across different years to be equal for each particular location. Further details on the data
169 analysis configuration can be found in Supplementary section S3.

170 The analysis of the larger dataset (500 samples) allows for the reconstruction of the evolutionary
171 tree encompassing a longer time period, and therefore gives a more long-term and detailed view

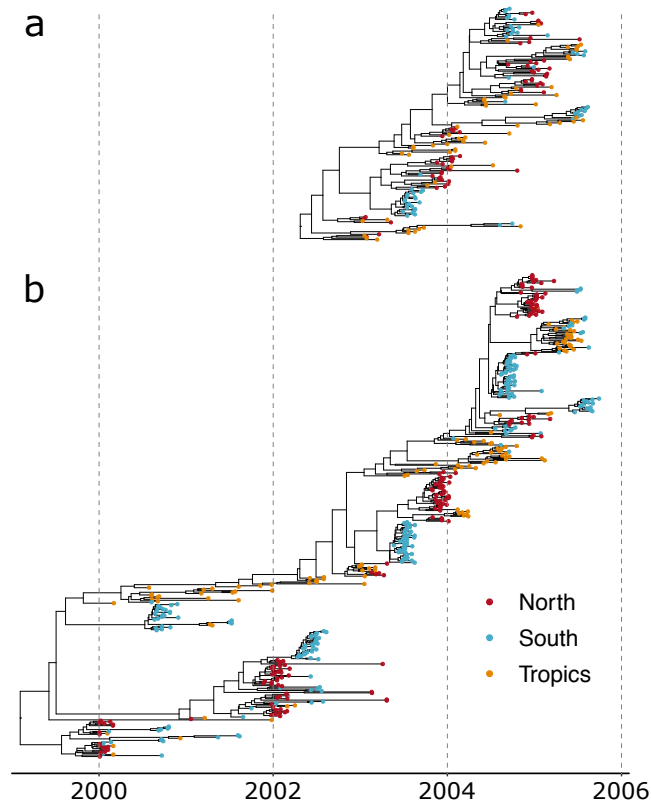


Figure 3: Maximum-Clade Credibility (MCC) trees for analyses with 175 samples (a) and 500 samples (b).

172 of the evolution of the global epidemic (see Fig 3 for the Maximum-Clade Credibility trees).
173 As can be expected for the tropical location, in both analyses, effective reproduction numbers for
174 H3N2 influenza A are inferred to be close to one year-round (Fig 4A). Conversely, strong
175 seasonal variations can be observed in Northern and Southern hemisphere locations. There, the
176 effective reproduction number is close to one in winter, while it is much lower in summer.
177 Inferences from the small and large datasets are mostly in agreement. A subtle difference
178 appears: in the larger dataset, the effective reproduction number in winter seasons and in the
179 tropical location are closer to one, with less variation across estimates. This seems to indicate
180 that the variations between estimates observed with the smaller dataset including samples from
181 2003 to 2006 (for instance R_e in winter in the North compared to R_e in winter in the South) are
182 due to stochastic fluctuations which are averaged out when considering a longer period of
183 transmission dynamics in the larger dataset covering the years 2000 to 2006.
184 Precise inference of migration rates is more difficult, as is reflected by the significant uncertainty
185 we obtain on the estimates (Fig 4B). Still, we observe in general that the uncertainty is reduced
186 for the inference performed with the larger dataset, as expected. A significant difference between

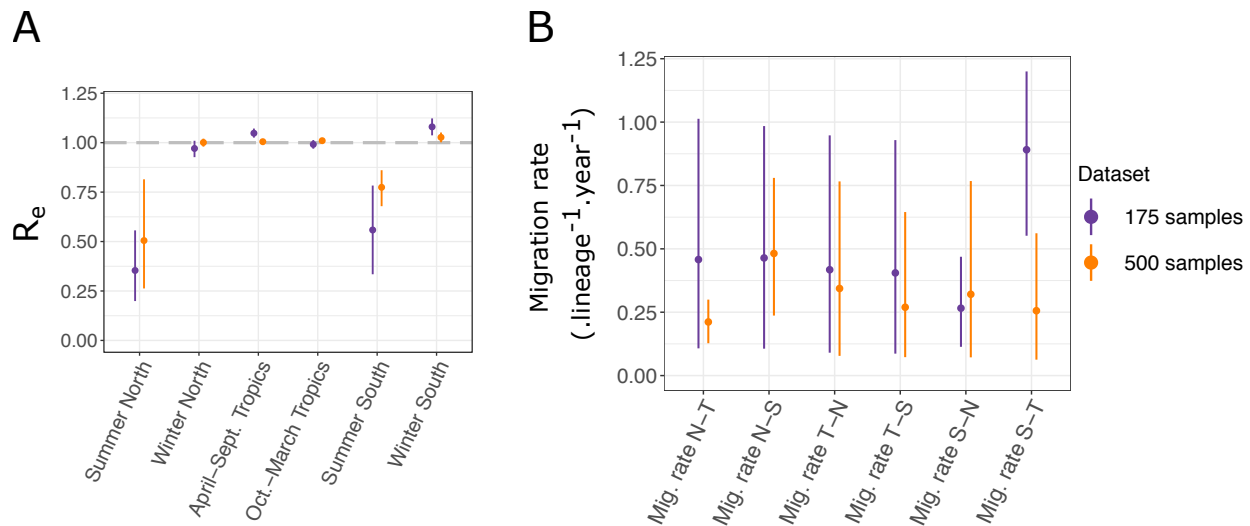


Figure 4: **A:** Seasonal effective reproduction numbers for each sample location, for both datasets. **B:** Migration rates inferred for each dataset. N, T and S refer respectively to North, South and Tropics. For instance, “*Mig. rate N-T*” represents the migration rate from the Northern location to the Tropical one.

187 the migration rates inferred from the Southern to Tropical locations arises between the two
 188 analysis. With the larger dataset, the estimated rate is much lower than with the smaller one, and
 189 more in range with the other migration rate estimates. Detailed results of all the parameter
 190 estimates for both analyses are available in Table S3. Most notably, estimates of root locations
 191 for both datasets are very similar. In both cases, the tropical location is the most likely location
 192 for the root; however, neither of the two other locations can be entirely excluded.

193 Discussion

194 The multi-type birth-death model with its updated implementation in the *bdmm* package for
 195 BEAST 2 provides a flexible method for taking into account the effect of population structure
 196 when performing phylodynamic genetic sequence analysis. Compared to the original
 197 implementation, we now prevent underflow of numerical calculations and speed up calculations
 198 by almost an order of magnitude. The size limit of around 250 samples for datasets which could
 199 be handled by *bdmm* is thus lifted and significantly larger datasets can now be analysed. We
 200 demonstrate this improvement by analysing two datasets of Influenza A virus H3N2 genetic data
 201 from around the globe. One dataset has 500 samples and could not have been analyzed with the
 202 original version of *bdmm*, the other one contains 175 samples and is the original example dataset

203 analyzed in [Kühnert et al., 2016]. Overall, we observe, as could be expected, that analysing a
204 dataset with more samples gives a more long-term picture of the global transmission patterns and
205 reduces the general uncertainty on parameter estimates.

206 With the addition of so-called ρ -sampling events in the past, intense sampling efforts limited to
207 short periods of time (leading to many samples being taken nearly simultaneously) can be easily
208 modelled as instantaneous sampling events across the entire population (or sub-population),
209 rather than as non-instantaneous sampling over small sampling intervals. This simplifies the
210 modelling of intense pathogen sequencing efforts in very short time windows. When using a
211 multi-type birth-death model in the macroevolutionary framework, ρ -sampling can be used to
212 model fossil samples originating from the same rock layer. By allowing the removal probability r
213 (the probability for an individual to be removed from the infectious population upon sampling) to
214 be type-dependent and to vary across time intervals, as well as allowing migration rates between
215 types to vary across time intervals, we further increase the generality and flexibility of the
216 multi-type birth-death model.

217 We focused on an epidemiological application of *bdmm*, where we co-infer the phylogenetic trees
218 to take into account the phylogenetic uncertainty. However, the *bdmm* modelling assumptions are
219 equally applicable to the analysis of macroevolutionary data, in which context *bdmm* allows for
220 the joint inference of trees with fossil samples under structured models. In the context of the
221 exploration of trait-dependent speciation, structured birth-death models such as the binary-state
222 speciation and extinction model (BiSSE) [Maddison, 2006, FitzJohn, 2012] have been shown to
223 possibly produce spurious associations between character state and speciation rate when applied
224 to empirical phylogenies [Rabosky and Goldberg, 2015]. When used in this fashion, users of
225 *bdmm* should assess the propensity for Type I errors with their dataset through neutral trait
226 simulations, as suggested by Rabosky and Goldberg [2015].

227 In summary, we expect the new release of *bdmm* to become a standard tool for phylodynamic
228 analysis of sequencing data and phylogenetic trees from structured populations.

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