



Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

A comprehensive study of the phylodynamics of SARS-CoV-2 in Europe

Master Thesis

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Abstract

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Introduction

We have many sources of information, but all of them are imperfect in some aspect. Bayesian phylodynamics incorporates different beliefs and data to get a detailed picture of the epidemic. Genetic sequences as an objective source of information about virus evolution and transmission together with viral phylogenetics, transportation data and geographic data to understand the dynamics and case counts to guide the magnitude of the numbers.

We lack absolute numbers of the pandemic time resolved without reporting issues dependent. We lack understanding of the dynamics, from where to where, how often, how long.

We can use travel data as a proxy, or we can incorporate it in a model. Lemey et al. Difference we get absolute numbers, not only the rates. And we use BD model instead of coalescent, better to describe beginning of a epidemic. While due to the complex and time consuming model we down scaled to Europe and only the initial phase with the first countries to experiment relevant SARS-CoV-2 epidemics.

Material and Methods

2.1 The multitype birth death model

We have used the multitype birth-death phylodynamic model. Phylodynamics studies how phylogenetic trees are being generated and infers the population parameters behind that process. A multitype birth death process describes the evolution of an structured population. The process starts with one individual in one of the subpopulations (or demes) and it can give rise to another individual at rate β , die at death δ , migrate to other deme or be sampled at rate ϕ to become part of the phylogeny.

Since the rate of the evolution of RNA virus, in specific SARS-CoV-2 is in the same scale than the epidemic spread, we can study the transmission dynamics by looking at the virus sequences.

The parameters that we will consider are the R_0 , the becoming uninfected rate, the migration rates and the sampling proportion (proportion of no longer infectious individual that arer sampled and included in the phylogenetic tree).

Thus, the probability that we want to know is:

$$P(T, P|D)$$

This process describes the generation of the tree as part of the dynamics of the whole population, it is very rich and detailed in information. Therefore it is also possible to obtain information about the epidemic trajectory of the whole population. We can obtain the full sequence of events that describes the epidemic in each of the demes.

From the phylogenetic tree and the phylodynamics parameters we use Stochastic mapping to infer the ancestral traits and then to infer the epidemic trajectories.

$$P(Tc|T, P)$$

$$P(E|Tc, P)$$

2.2 Inferring epidemic trajectories

Stochastic mapping of ancestral traits

Read paper and tim presentation

Stochastic mapping of epidemic trajectories

From the phylogenie with ancestral locations and the set of phylodynamic parameters we can simulate epidemic trajectories using an algorithm similar to Gillespie (with tau leaping and particle filtering? the subsampling). And most improtant, we can compute the probability of that specific trajectory given those parrameters and tree.

$$P(E|Tc, P)$$

Any trajectories without the events that are respresent in the tree has probability 0, so to avoid the simualtion of this trajectories, no time effcieint, we will enforce the events that arer represented in the tree (and will include a weigth). Also to avoid low probabilities trajectories, we will importance subsample one trajectory after a certain time of simulation according to the weigths detemrined by its probabilities.

2.3 Modeling the early dynamics of SARS-CoV-2 in Europe

In our case, we have 6 demes, one for each of the countries/geographic location. A birth represents a transmission event of covid-19, a death event is an individual becoming uninfetious by overcoming the disease, being isolated or dying. From the birth rate and death rate we can estuimate the R_0 , key vallue in the epidemic understanding and control. A migration event happens when an individual travels from one country to another, we know that is an important way of covid-19 spreading and we are interested on the dynamics.

We focus our analysis in the early spread in Europe of SARS-CoV-2, therefore we constrain the analysis to the period from the origin of the epidemic to March 8, when the first European lockdown in the Lombardy region started. During this time, for the European countries we expect an unimpeded spread of the virus that could be described by a constant R_0 particular to each deme. However, the migration rates could have changed during these months due to the increase public awareness, so we will consider a different migration rate for origin to 23 jan, 23 jan to end of february and 1 to 8 of March. We assume a constant sampling proportion different for each of the demes, to account for difference in the sequencing efforts. The becoming uninfetious rate we will fixed in 36.5, assuming that one individual is infectious for a exponential time distirbuted with mean 10.

2.4 Incorporating travel data

To incorporate travel data in the model we have use a GLM model described in Lemey et al 2009. We use a generalized linear model to describe the migration matrix $K \times K$, where the predictors are the number of daily flight from one country to another from EUROSTATS, the average distance between the centroids of the country and the population sizes from origin and destinations. The predictors are log transformed, we add a pseudocount to make them all positive, and standardized as described in ..

$$m_{ij} = \text{cexp}(\sum_{i=1}^p \delta_i \beta_i x_{ij})$$

The coefficients beta describe the effect size of the predictors in the migrations rate and the delta coefficients act as a model selection variables, taking 0-1 values including or not that specific predictor in the model.

2.5 SARS-CoV 2 genome data set

GISAID. Sequences from France, Germany, Italy, Spain and other European countries. Subsampling a sequence with probability equal to the probability of having a case that day in the country, inverseley weighed by the probability of being sequenced that day.

2.6 GLM predictors data

EUROSTAT, countries considers. Distance and population datasets.

2.7 Bayesian inference of phylodynamic parameters

We use bayesian inference and Metropolis Hasting Monte Carlo algorithm to infer our phylodynamics parameters and phylogenetic tree. We use the following priors

Clock rate and substitution model. Fixed to 8×10^{-4} , HKY 4 gamma categories with priors... BDMM-Prime epi parameterization: R0 Become uninfected rate
Sampling rates Migration rates

R0

R0 constant except for China (and Italy? maybe not in the main analysis).

Prior Log Normal (0.8, 0.5) Median 2.2, 95IQR 0.8 to 5.9. (Lai A. 2020 prior log normal (0,1) median 1.0 0.1-7.10)

- Main analysis: We fix China R_0 to 2.7 (23 jan) 1.3 (10 feb) 0.8 - Use a decreasing parameter as Sarah with migration rate? But then we would need to add sequences. - Or instead of fixing it we can put a strong informative prior. - Allow Italy R_0 to change March 1.

Meta-analyses R_0 :

R_0 in China (3.14,95%CI,2.40–4.09).[?]

R_0 value 2.90 (2.32, 3.63 2.9 (95% CI: 2.1–4.5))[?]

Periods: until 23 jan R_0 2.9 23 jan - 10 feb 1.1 dashboard cevo 10 feb - 8 mar 0.43 dashboard cevo

Become uninfected rate same for all demes, fixed to 36.5. Migrations among demes, 3 epochs. Sampling proportion 0 before first sample. Upperbounded by number of cases.

Implementation BEAST 2.6.3 and BDMM-Prime package. We run 5 chains of 10^7 iterations with different seeds.

2.8 Processing of epidemic trajectories

In our case, for each set of parameters and tree we will simulate 10000 trajectories with an epsilon of 0.3 and select one of them with importance sampling. We have one trajectory for each step in the MCMC. We subsampled x .

2.9 Data availability

GISAIID data table.

2.10 Code availability and analyses reproducibility

All the code is available at ... We have implemented the full workflow with Snake-make so it's fully reproducible.

CHAPTER 3

Discussion

Bibliography

APPENDIX A

Data

APPENDIX B

Priors

Supplementary Figures
