

Estimating Epidemiological Parameters of an Ebola Outbreak using BEAST2

Tutorial by [Tracy Heath](#) and [Tanja Stadler](#)

This tutorial uses the sequence data from 72 Ebola patients in Sierra Leone. The viral sequences were first presented in [Gire et al. \(Science 2014\)](#). These data were re-analyzed under complex birth-death processes to estimate key epidemiological parameters by [Stadler et al. \(PLoS Currents Outbreaks 2014\)](#).

In this exercise, we will perform a simplified analysis similar to one conducted by Stadler et al. (2014). We will use the birth-death process with serial sampling and piecewise shifts in rates (the "BD" model in the Stadler et al. 2014 study). Please refer to [Stadler et al. \(2014\)](#) and [Stadler et al. \(2013\)](#) for detailed descriptions of these models and methods.

For more information about divergence-time estimation in general and BEAST v2.2, please refer the resources and tutorials on: <http://phyloworks.org/workshops/divtime.html>. In particular see the detailed tutorial on estimating speciation times using extant and fossil data and the links and references therein: <http://treethinkers.org/tutorials/divergence-time-estimation-using-beast/>.

Important parameters for infectious disease dynamics:

- R is the **effective reproductive number**. [Stadler et al. \(2013\)](#) states that this parameter is the "number of expected secondary infections of an infected individual. The effective reproductive number is closely related to the basic reproductive number ([Anderson and May 1979](#)): the latter additionally assumes a completely susceptible population, and thus the two quantities are equal at the start of an epidemic outbreak." [called "R" in BEAST2]
- δ is the **rate of becoming non-infectious**. An individual may become non-infectious if they are cured or treated, their behavior changes, or they die. [called "becomeUninfectiousRate" in BEAST2]
- s is the **probability of sampling an individual upon becoming non-infectious**. [called "samplingProportion" in BEAST2]
- λ is the **rate of transmission (birth rate)**. [called "birth" in BEAST2]
- μ is the **viral lineage death rate**. [called "death" in BEAST2]
- ψ is the **rate each individual is sampled**. [called "sampling" in BEAST2]

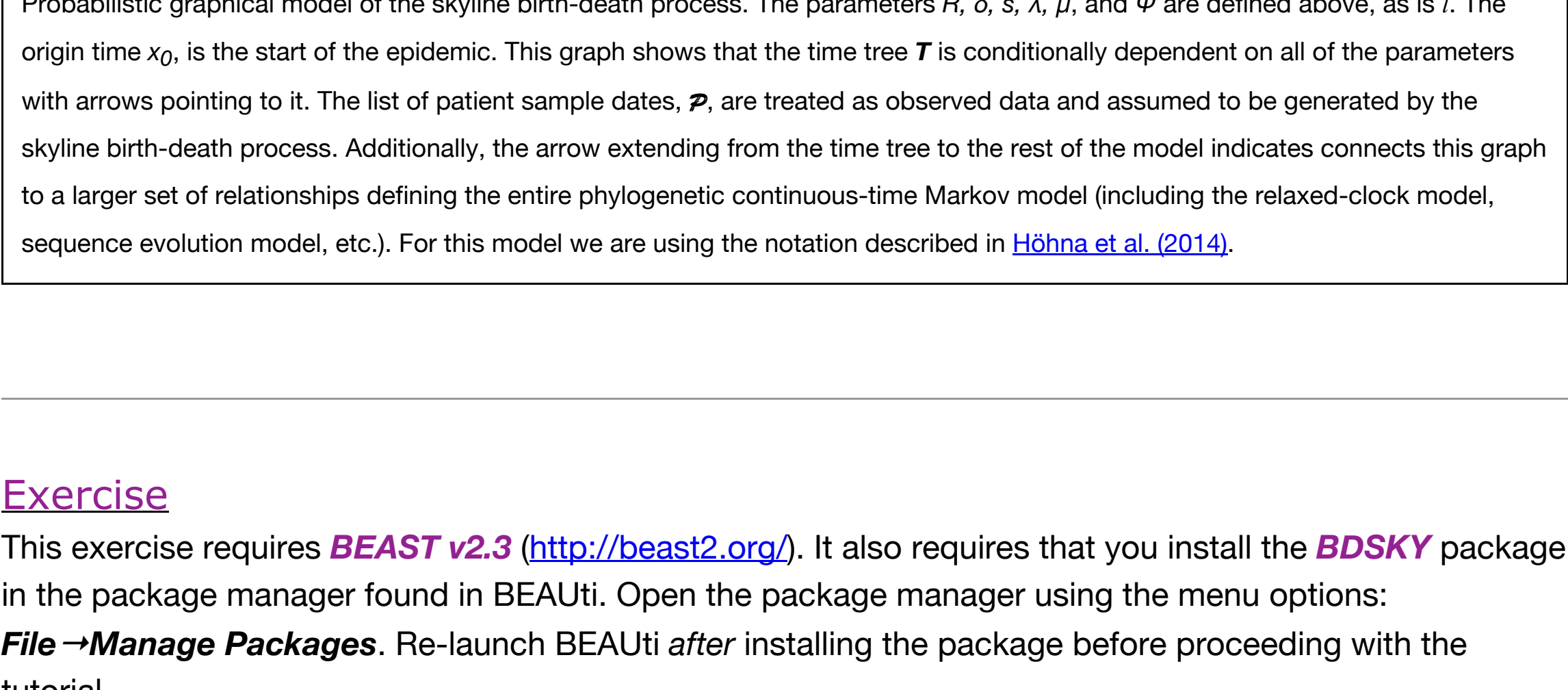
In the analyses, we will estimate R , δ , and s . The remaining parameters listed above can be calculated if we have the first three because they are defined:

$$R = \frac{\lambda}{\mu + \psi}, \quad \delta = \mu + \psi, \quad s = \frac{\psi}{\mu + \psi}$$

Thus we can compute λ , μ , and ψ given:

$$\lambda = R\delta, \quad \mu = \delta - s\delta, \quad \psi = s\delta$$

In this exercise, we also assume that there are l intervals, evenly spaced, over the tree. These intervals are delineated by shifts in the value of R and because λ is determined by R , λ also changes over time. Below is the probabilistic graphical model depicting the conditional dependence structure of all of the parameters in our skyline birth-death model. It is also possible to consider a model the other parameters (δ , s , μ , ψ) also change over time as in [Stadler et al. \(2013\)](#), however, we will not consider that more complex model in this exercise.



Probabilistic graphical model of the skyline birth-death process. The parameters R , δ , s , λ , μ , and ψ are defined above, as is l . The origin time x_0 , is the start of the epidemic. This graph shows that the time tree T is conditionally dependent on all of the parameters with arrows pointing to it. The list of patient sample dates, P , are treated as observed data and assumed to be generated by the skyline birth-death process. Additionally, the arrow extending from the time tree to the rest of the model indicates connects this graph to a larger set of relationships defining the entire phylogenetic continuous-time Markov model (including the relaxed-clock model, sequence evolution model, etc.). For this model we are using the notation described in [Höhna et al. \(2014\)](#).

Exercise

This exercise requires **BEAST v2.3** (<http://beast2.org/>). It also requires that you install the **BDSKY** package in the package manager found in BEAUti. Open the package manager using the menu options:

File → Manage Packages. Re-launch BEAUti *after* installing the package before proceeding with the tutorial.

Download the sequence data from: <http://bit.ly/1JjoSaP>. This file is called "ebola_simple.nex".

Open BEAUti and import the sequence from ebola_simple.nex. To do this go to the menu:

File → Import Alignment.

Note that the sequences are all given explicit names indicating the patient, location, and date of the sample: 'EBOV_KM034560_G3682_SierraLeone_G_2014/05/28'. These serially sampled sequences need to be given dates. The dates and tip ages can be extracted from their names.

Go to the **Tip Dates** window in BEAUti and check the **Use tip dates** box.

☒ Use tip dates

Dates specified as:

year

Since some time in the past

Guess

Clear

Name	Date	Height
EBOV_KM034560_G3682_SierraLeone_G_2014/05/28	2014.4327625570777	0.05753424657518735
EBOV_KM034558_G3679_SierraLeone_G_2014/05/28	2014.4327625570777	0.05753424657518735
EBOV_KM034559_G3679_SierraLeone_G_2014/05/28	2014.4327625570777	0.05753424657518735
EBOV_KM034561_G3682_SierraLeone_G_2014/05/28	2014.4327625570777	0.05753424657518735
EBOV_KM034562_G3682_SierraLeone_G_2014/05/28	2014.4327625570777	0.05753424657518735
EBOV_KM034563_G3682_SierraLeone_G_2014/05/28	2014.4327625570777	0.05753424657518735
EBOV_KM034564_G3682_SierraLeone_G_2014/05/28	2014.4327625570777	0.05753424657518735
EBOV_KM034565_G3682_SierraLeone_G_2014/05/28	2014.4327625570777	0.05753424657518735
EBOV_KM034566_G3682_SierraLeone_G_2014/05/28	2014.4327625570777	0.05753424657518735
EBOV_KM034567_G3682_SierraLeone_G_2014/05/28	2014.4327625570777	0.05753424657518735
EBOV_KM034568_G3682_SierraLeone_G_2014/05/28	2014.4327625570777	0.05753424657518735
EBOV_KM034569_G3682_SierraLeone_G_2014/05/28	2014.4327625570777	0.05753424657518735
EBOV_KM034570_G3682_SierraLeone_G_2014/05/28	2014.4327625570777	0.05753424657518735
EBOV_KM034571_G3682_SierraLeone_G_2014/05/28	2014.4327625570777	0.05753424657518735
EBOV_KM034572_G3682_SierraLeone_G_2014/05/28	2014.4327625570777	0.05753424657518735
EBOV_KM034573_G3682_SierraLeone_G_2014/05/28	2014.4327625570777	0.05753424657518735
EBOV_KM034574_G3682_SierraLeone_G_2014/05/28	2014.4327625570777	0.05753424657518735
EBOV_KM034575_G3682_SierraLeone_G_2014/05/28	2014.4327625570777	0.05753424657518735
EBOV_KM034576_G3682_SierraLeone_G_2014/05/28	2014.4327625570777	0.05753424657518735
EBOV_KM034577_G3682_SierraLeone_G_2014/05/28	2014.4327625570777	0.05753424657518735
EBOV_KM034578_G3682_SierraLeone_G_2014/05/28	2014.4327625570777	0.05753424657518735
EBOV_KM034579_G3682_SierraLeone_G_2014/05/28	2014.4327625570777	0.05753424657518735
EBOV_KM034580_G3682_SierraLeone_G_2014/05/28	2014.4327625570777	0.05753424657518735
EBOV_KM034581_G3682_SierraLeone_G_2014/05/28	2014.4327625570777	0.05753424657518735
EBOV_KM034582_G3682_SierraLeone_G_2014/05/28	2014.4327625570777	0.05753424657518735
EBOV_KM034583_G3682_SierraLeone_G_2014/05/28	2014.4327625570777	0.05753424657518735
EBOV_KM034584_G3682_SierraLeone_G_2014/05/28	2014.4327625570777	0.05753424657518735
EBOV_KM034585_G3682_SierraLeone_G_2014/05/28	2014.4327625570777	0.05753424657518735
EBOV_KM034586_G3682_SierraLeone_G_2014/05/28	2014.4327625570777	0.05753424657518735
EBOV_KM034587_G3682_SierraLeone_G_2014/05/28	2014.4327625570777	0.05753424657518735
EBOV_KM034588_G3682_SierraLeone_G_2014/05/28	2014.4327625570777	0.05753424657518735
EBOV_KM034589_G3682_SierraLeone_G_2014/05/28	2014.4327625570777	0.05753424657518735
EBOV_KM034590_G3682_SierraLeone_G_2014/05/28	2014.4327625570777	0.05753424657518735
EBOV_KM034591_G3682_SierraLeone_G_2014/05/28	2014.4327625570777	0.05753424657518735
EBOV_KM034592_G3682_SierraLeone_G_2014/05/28	2014.4327625570777	0.05753424657518735
EBOV_KM034593_G3682_SierraLeone_G_2014/05/28	2014.4327625570777	0.05753424657518735
EBOV_KM034594_G3682_SierraLeone_G_2014/05/28	2014.4327625570777	0.05753424657518735
EBOV_KM034595_G3682_SierraLeone_G_2014/05/28	2014.4327625570777	0.05753424657518735
EBOV_KM034596_G3682_SierraLeone_G_2014/05/28	2014.4327625570777	0.05753424657518735
EBOV_KM034597_G3682_SierraLeone_G_2014/05/28	2014.4327625570777	0.05753424657518735
EBOV_KM034598_G3682_SierraLeone_G_2014/05/28	2014.4327625570777	0.05753424657518735
EBOV_KM034599_G3682_SierraLeone_G_2014/05/28	2014.4327625570777	0.05753424657518735
EBOV_KM034600_G3682_SierraLeone_G_2014/05/28	2014.4327625570777	0.05753424657518735

With the dates specified as **year** and **Since some time in the past**, click on the button called **Guess**.

BEAUti will extract the dates from the sequence names, given that they are provided using a specific text pattern. Here, the dates all follow the last "_" character. Indicate that you want to **use everything** after this character and click **OK**.

☒ use everything

after last

_

You can see now that each sequence is given a date that is a value relative to year 0. Thus, the sequence sampled on 28 May 2014 is 2014.4327625570777. The tip heights are computed relative to the most recent sample, which has a height of 0.0. The units are in years, thus one day is a difference in tip height of $1/365 = 0.002739726$.

Go to the Site Model window and change the sequence model to HKY+G.

Substitution Rate: 1.0

estimate

Gamma Category Count: 4

estimate

Shape: 1.0

estimate

Proportion Invariant: 0.0

estimate

HKY

estimate

Kappa: 2.0

estimate

Frequencies: Estimated

estimate

For this analysis, in the **Clock Model** window we will leave the default **Strict Clock** and estimate the clock rate.

Go to the **Priors** window.

Change the tree prior to **Birth Death Skyline Serial**

Tree: tebola_simple Birth Death Skyline Serial

Origin: 100.0

estimate

R0: 2.0

estimate

Become Uninfectious Rate: 1.0

estimate

Sampling Proportion: 0.01

estimate

Set the prior on the effective reproductive rate (R) to a lognormal with a log-mean of 0.0 and standard deviation of 1.25.

R0.s.tebola_simple Log Normal initial = [2.0] [0.0,Infinity] prior on R0.s.tebola_simple

M: 0.0

estimate

S: 1.25

estimate

☐ Mean In Real Space

Offset: 0.0

0.70000.60000.50000.40000.30000.20000.10000.0.00000.0.00250.0.00500.0.00750.0.01000.0.01250.0.01500.0.01750.0.02000.0.02250.0.02500.0.02750.0.03000.0.03250.0.03500.0.03750.0.04000.0.04250.0.04500.0.04750.0.05000.0.05250.0.05500.0.05750.0.06000.0.06250.0.06500.0.06750.0.07000.0.07250.0.07500.0.07750.0.08000.0.08250.0.08500.0.08750.0.09000.0.09250.0.09500.0.09750.1.0.10250.1.00250.1.00500.1.00750.1.01000.1.01250.1.01500.1.01750.1.02000.1.02250.1.02500.1.02750.1.03000.1.03250.1.03500.1.03750.1.04000.1.04250.1.04500.1.04750.1.05000.1.05250.1.05500.1.05750.1.06000.1.06250.1.06500.1.06750.1.07000.1.07250.1.07500.1.07750.1.08000.1.08250.1.08500.1.08750.1.09000.1.09250.1.09500.1.09750.2.0.20250.2.00250.2.00500.2.00750.2.01000.2.01250.2.01500.2.01750.2.02000.2.02250.2.02500.2.02750.2.03000.2.03250.2.03500.2.03750.2.04000.2.04250.2.04500.2.04750.2.05000.2.05250.2.05500.2.05750.2.06000.2.06250.2.06500.2.06750.2.07000.2.07250.2.07500.2.07750.2.08000.2.08250.2.08500.2.08750.2.09000.2.09250.2.09500.2.09750.3.0.30250.3.00250.3.00500.3.00750.3.01000.3.01250.3.01500.3.01750.3.02000.3.02250.3.02500.3.02750.3.03000.3.03250.3.03500.3.03750.3.04000.3.04250.3.04500.3.04750.3.05000.3.05250.3.05500.3.05750.3.06000.3.06250.3.06500.3.06750.3.07000.3.07250.3.07500.3.07750.3.08000.3.08250.3.08500.3.08750.3.09000.3.09250.3.09500.3.09750.4.0.40250.4.00250.4.00500.4.00750.4.01000.4.01250.4.01500.4.01750.4.02000.4.02250.4.02500.4.02750.4.03000.4.03250.4.03500.4.03750.4.04000.4.04250.4.04500.4.04750.4.05000.4.05250.4.05500.4.05750.4.06000.4.06250.4.06500.4.06750.4.07000.4.07250.4.07500.4.07750.4.08000.4.08250.4.08500.4.08750.4.09000.4.09250.4.09500.4.09750.5.0.50250.5.00250.5.00500.5.00750.5.01000.5.01250.5.01500.5.01750.5.02000.5.02250.5.02500.5.02750.5.03000.5.03250.5.03500.5.03750.5.04000.5.04250.5.04500.5.04750.5.05000.5.05250.5.05500.5.05750.5.06000.5.06250.5.06500.5.06750.5.07000.5.07250.5.07500.5.07750.5.08000.5.08250.5.08500.5.08750.5.09000.5.09250.5.09500.5.09750.6.0.60250.6.00250.6.00500.6.00750.6.01000.6.01250.6.01500.6.01750.6.02000.6.02250.6.02500.6.02750.6.03000.6.03250.6.03500.6.03750.6.04000.6.04250.6.04500.6.04750.6.05000.6.05250.6.05500.6.05750.6.06000.6.06250.6.06500.6.06750.6.07000.6.07250.6.07500.6.07750.6.08000.6.08250.6.08500.6.08750.6.09000.6.09250.6.09500.6.09750.7.0.70250.7.00250.7.00500.7.00750.7.01000.7.01250.7.01500.7.01750.7.02000.7.02250.7.02500.7.02750.7.03000.7.03250.7.03500.7.03750.7.04000.7.04250.7.04500.7.04750.7.05000.7.05250.7.05500.7.05750.7.06000.7.06250.7.06500.7.06750.7.07000.7.07250.7.07500.7.07750.7.08000.7.08250.7.08500.7.08750.7.09000.7.09250.7.09500.7.09750.8.0.80250.8.00250.8.00500.8.00750.8.01000.8.01250.8.01500.8.01750.8.02000.8.02250.8.02500.8.02750.8.03000.8.03250.8.03500.8.03750.8.04000.8.04250.8.04500.8.04750.8.05000.8.05250.8.05500.8.05750.8.06000.8.06250.8.06500.8.06750.8.07000.8.07250.8.07500.8.07750.8.08000.8.08250.8.08500.8.08750.8.09000.8.09250.8.09500.8.09750.9.0.90250.9.00250.9.00500.9.00750.9.01000.9.01250.9.01500.9.01750.9.02000.9.02250.9.02500.9.02750.9.03000.9.03250.9.03500.9.03750.9.04000.9.04250.9.04500.9.04750.9.05000.9.05250.9.05500.9.05750.9.06000.9.06250.9.06500.9.06750.9.07000.9.07250.9.07500.9.07750.9.08000.9.08250.9.08500.9.08750.9.09000.9.09250.9.09500.9.09750.1.0.100250.1.000250.1.000500.1.000750.1.001000.1.001250.1.001500.1.001750.1.002000.1.002250.1.002500.1.002750.1.003000.1.003250.1.003500.1.003750.1.004000.1.004250.1.004500.1.004750.1.005000.1.005250.1.005500.1.005750.1.006000.1.006250.1.006500.1.006750.1.007000.1.007250.1.007500.1.007750.1.008000.1.008250.1.008500.1.008750.1.009000.1.009250.1.009500.1.009750.1.010000.1.010250.1.010500.1.010750.1.011000.1.011250.1.011500.1.011750.1.012000.1.012250.1.012500.1.012750.1.013000.1.013250.1.013500.1.013750.1.014000.1.014250.1.014500.1.014750.1.015000.1.015250.1.015500.1.015750.1.016000.1.016250.1.016500.1.016750.1.017000.1.017250.1.017500.1.017750.1.018000.1.018250.1.018500.1.018750.1.019000.1.019250.1.019500.1.019750.2.0.200250.2.000250.2.000500.2.000750.2.001000.2.001250.2.001500.2.001750.2.002000.2.002250.2.002500.2.002750.2.003000.2.003250.2.003500.2.003750.2.004000.2.004250.2.004500.2.004750.2.005000.2.005250.2.005500.2.005750.2.006000.2.006250.2.006500.2.006750.2.007000.2.007250.2.007500.2.007750.2.008000.2.008250.2.008500.2.008750.2.009000.2.009250.2.009500.2.009750.3.0.300250.3.000250.3.000500.3.000750.3.001000.3.001250.3.001500.3.001750.3.002000.3.002250.3.002500.3.002750.3.003000.3.003250.3.003500.3.003750.3.004000.3.004250.3.004500.3.004750.3.005000.3.005250.3.005500.3.005750.3.006000.3.006250.3.006500.3.006750.3.007000.3.007250.3.007500.3.007750.3.008000.3.008250.3.008500.3.008750.3.009000.3.009250.3.009500.3.009750.4.0.400250.4.000250.4.000500.4.000750.4.001000.4.001250.4.001500.4.001750.4.002000.4.002250.4.002500.4.002750.4.003000.4.003250.4.003500.4.003750.4.004000.4.004250.4.004500.4.004750.4.005000.4.005250.4.005500.4.005750.4.006000.4.006250.4.006500.4.006750.4.007000.4.007250.4.007500.4.007750.4.008000.4.008250.4.008500.4.008750.4.009000.4.009250.4.009500.4.009750.5.0.500250.5.000250.5.000500.5.000750.5.001000.5.001250.5.001500.5.001750.5.0