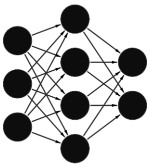
PREDICTION OF PATHOGENIC SNV

Prof. Giorgio Valentini
6 CFU

Luca Cappelletti

Lecture Notes
Year 2017/2018



IT Master Degree
Universiy of Milan
Italy
27 giugno 2018

Indice

Parte I

Dataset

1
Data points

First we begin looking at the dataset, the distributions of the given metrics and the statistical analysis of these data points.

1.1 Retrieving the dataset

The dataset can be downloaded from https://homes.di.unimi.it/valentini/ProgettoBioinformatica1718/data/.

1.2 Composition

1.2.1 Training dataset

In the training dataset there are 981389 data points, each one comprised of 26 metrics. The first 356 are pathogenic and all the others are negative.

1.2.2 Testing dataset

In the test dataset there are 190189 data points, still each one comprised of 26 metrics. The first 40 are pathogenic and the following are negative.

2 Metrics

2.1 How the graphs are realized

All the graphs are in triples: positives, negatives and mixed. All the zeros are removed as in most metrics *seemed* to indicate an unknown value.

2.1.1 Metric sample distribution

Are realized by calculating the frequencies and estimating the density distributions parameters via MLE.

2.1.2 Plot graphs

Are realized by sorting the values of the metric.

2.1.3 Normalized plot graphs

Are realized by sorting the values of the metric, with the domain and codomain normalized.

2.2 CpGobsExp

2.2.1 Metric sample distribution

The data points seem to follow a **Beta** distribution with the following parameters:

$$\alpha = 7.66897468802957955 \qquad \beta = 6778383.524935903$$
$$\text{loc} = -0.09826818916997124 \qquad \text{scale} = 306278.3184506849$$

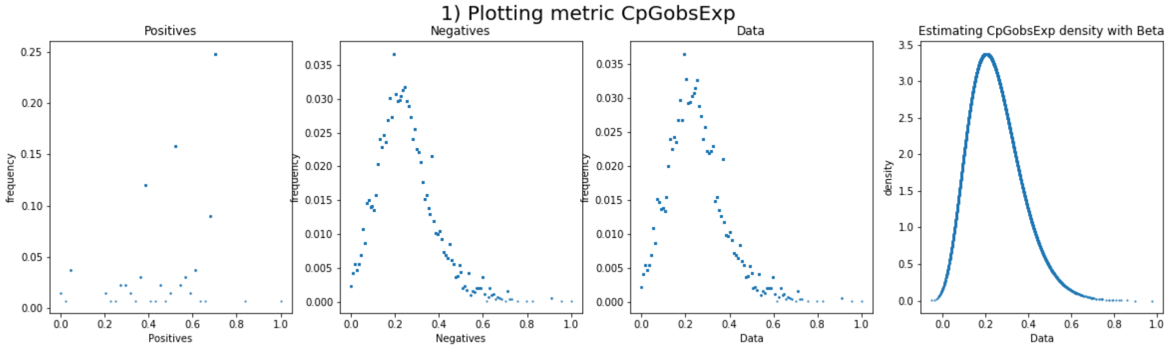


Figura 2.1: Sampling distribution of metric CpGobsExp

2.2.2 Metric values

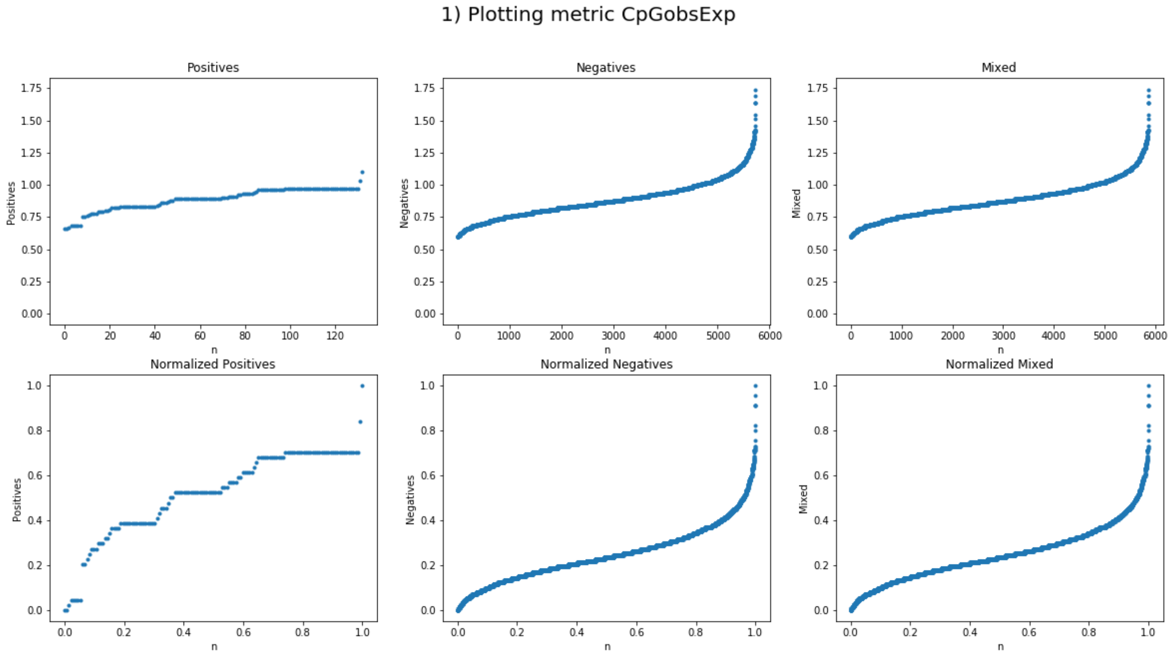


Figura 2.2: Values of metric CpGobsExp

2.3 CpGperCpG

2.3.1 Metric sample distribution

The data points seem to follow a **Beta** distribution with the following parameters:

$$\alpha = 6.402175341881067 \qquad \beta = 97129163.31117742$$
$$\text{loc} = -0.05698922703576313 \qquad \text{scale} = 4337764.42876015$$

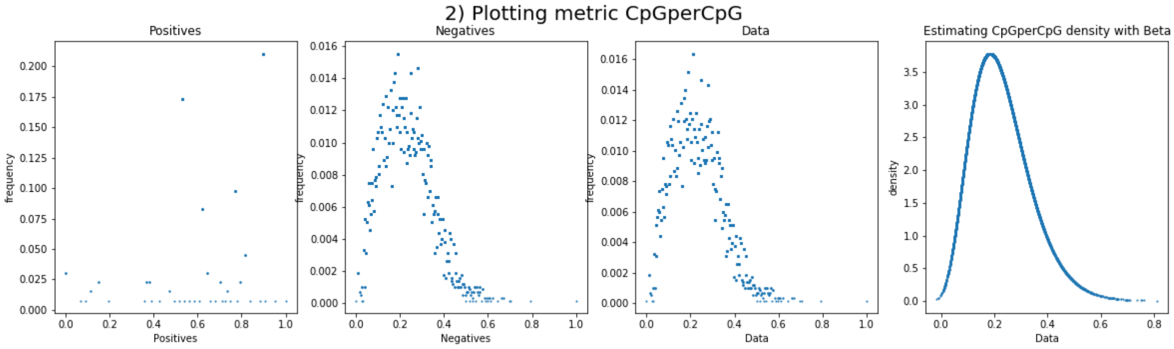


Figura 2.3: Sampling distribution of metric CpGperCpG

2.3.2 Metric values

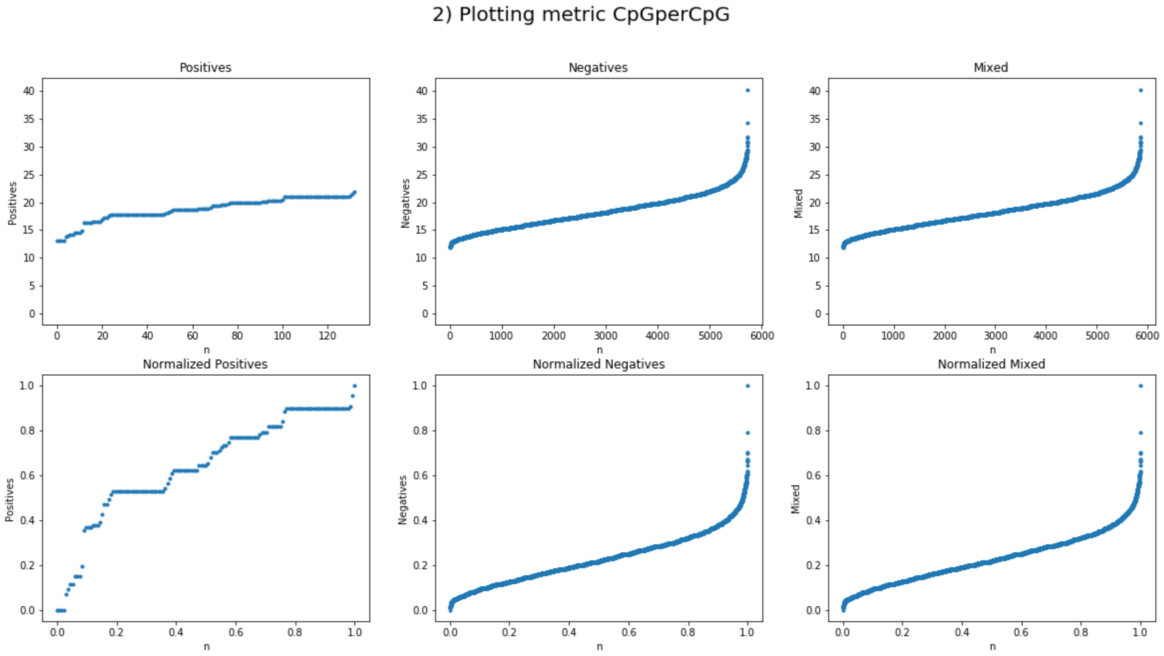


Figura 2.4: Values of metric CpGperCpG

2.4 CpGperGC

2.4.1 Metric sample distribution

The data points seem to follow a **Gaussian** distribution with the following parameters:

$$\mathbb{E}(X) = 0.4602356242601636 \qquad \mathrm{Var}(X) = 0.15949294643574352$$

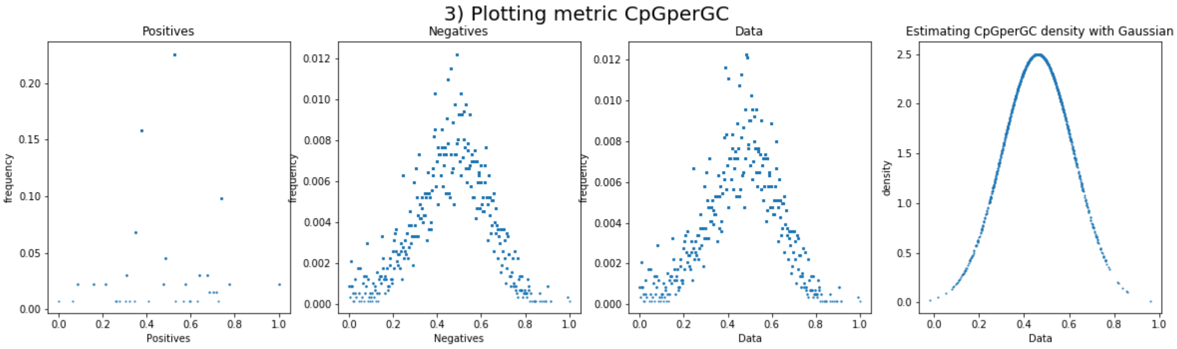


Figura 2.5: Sampling distribution of metric CpGperGC

2.4.2 Metric values

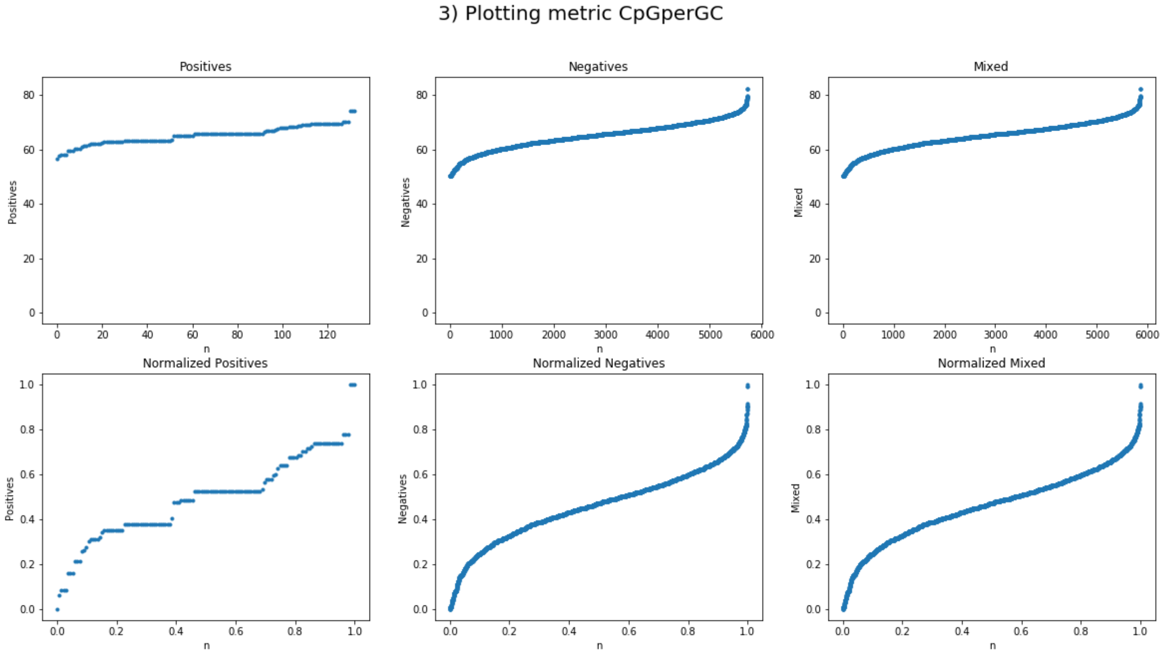


Figura 2.6: Values of metric CpGperGC

2.5 DGVCount

2.5.1 Metric sample distribution

The data points seem to follow a **Gamma** distribution with the following parameters:

$$\alpha = 0.20940038672579409 \qquad \text{loc} = -1.1962983066939984e-30 \qquad \text{scale} = 1.2347090894162929$$

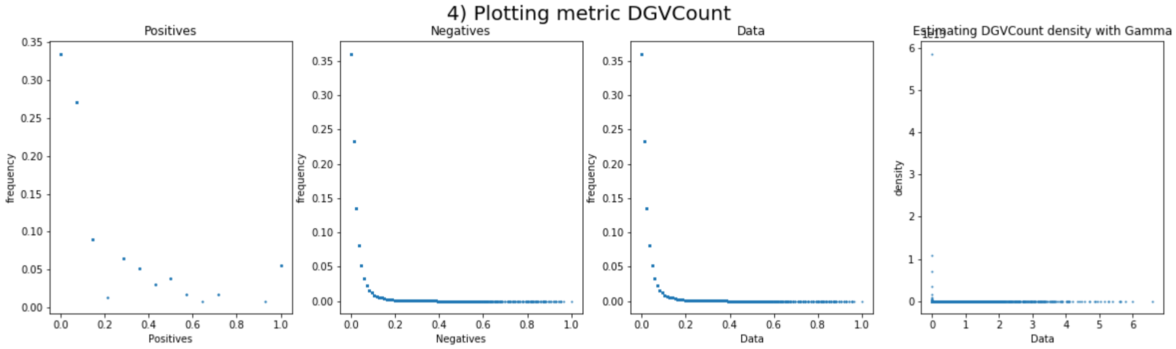


Figura 2.7: Sampling distribution of metric DGVCount

2.5.2 Metric values

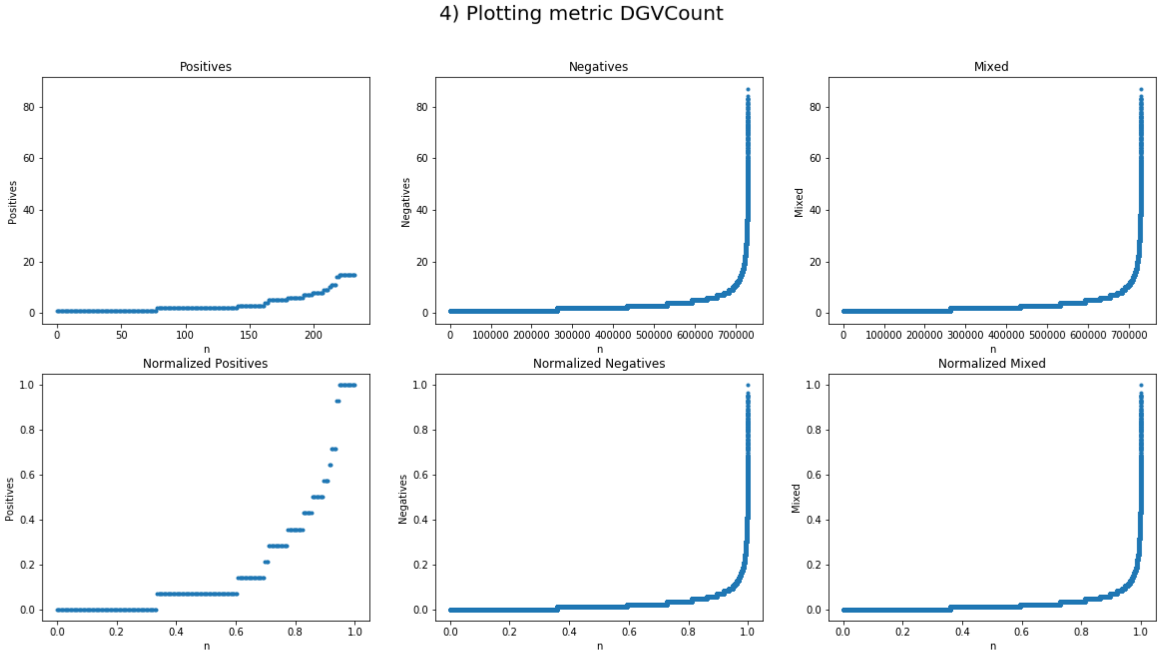


Figura 2.8: Values of metric DGVCount

2.6 DnaseClusteredHyp

2.6.1 Metric sample distribution

The data points seem to follow a **Gamma** distribution with the following parameters:

$$\alpha = 0.4176887081406805 \qquad \text{loc} = -3.362626207862299e-29 \qquad \text{scale} = 0.3676310948709975$$

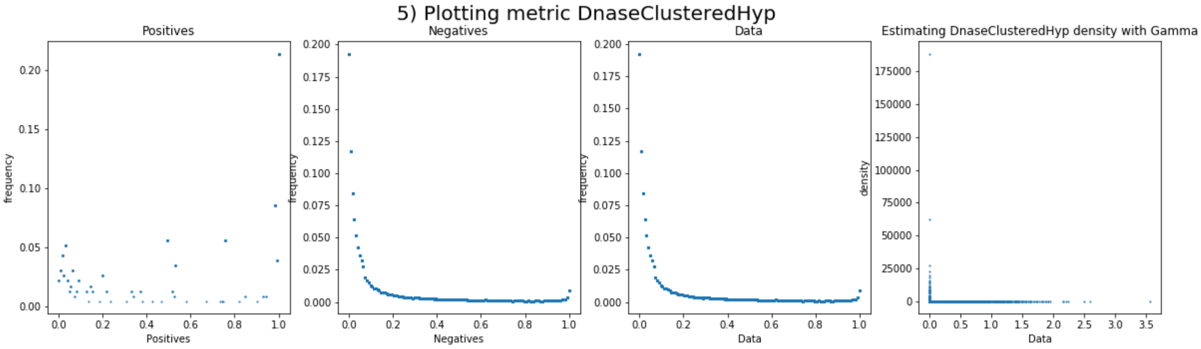


Figura 2.9: Sampling distribution of metric DnaseClusteredHyp

2.6.2 Metric values

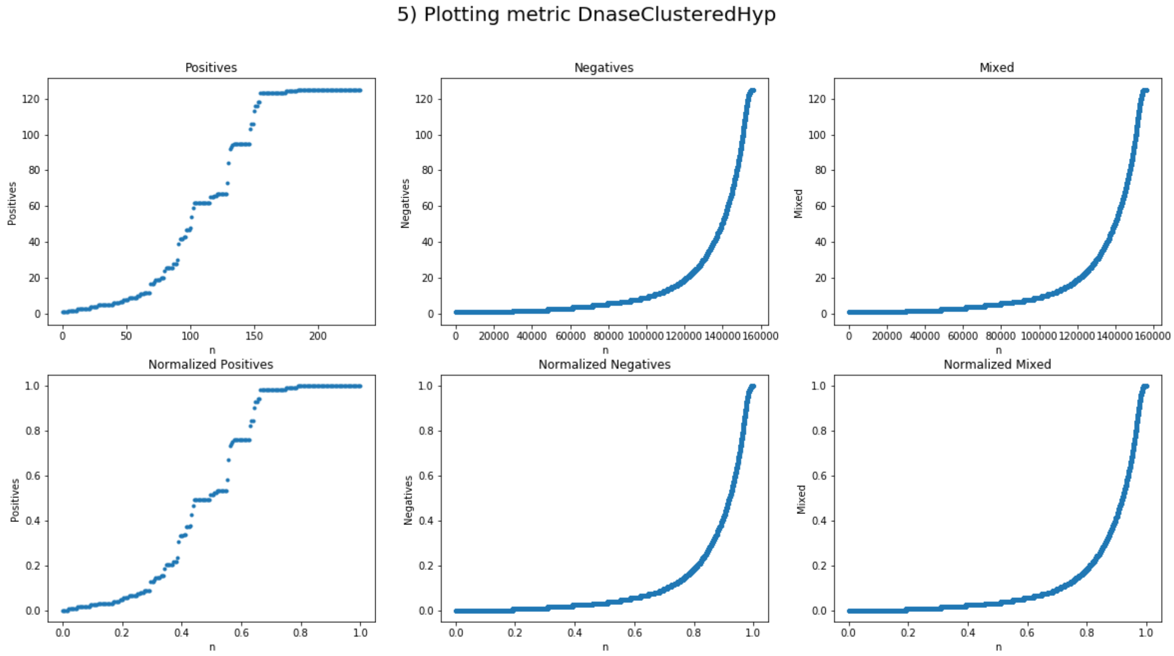


Figura 2.10: Values of metric DnaseClusteredHyp

2.7 DnaseClusteredScore

2.7.1 Metric sample distribution

The data points seem to follow **slightly** a **Beta** distribution with the following parameters:

$$\alpha = 0.2709657632937803 \qquad \beta = 0.44530002562349713$$
$$\text{loc} = -0.09309893086089688 \qquad \text{scale} = 1.0930989308608972$$

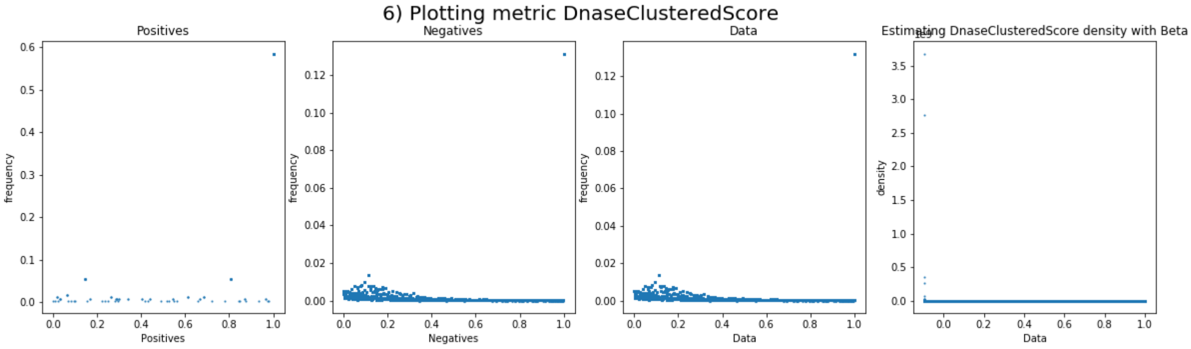


Figura 2.11: Sampling distribution of metric DnaseClusteredScore

2.7.2 Metric values

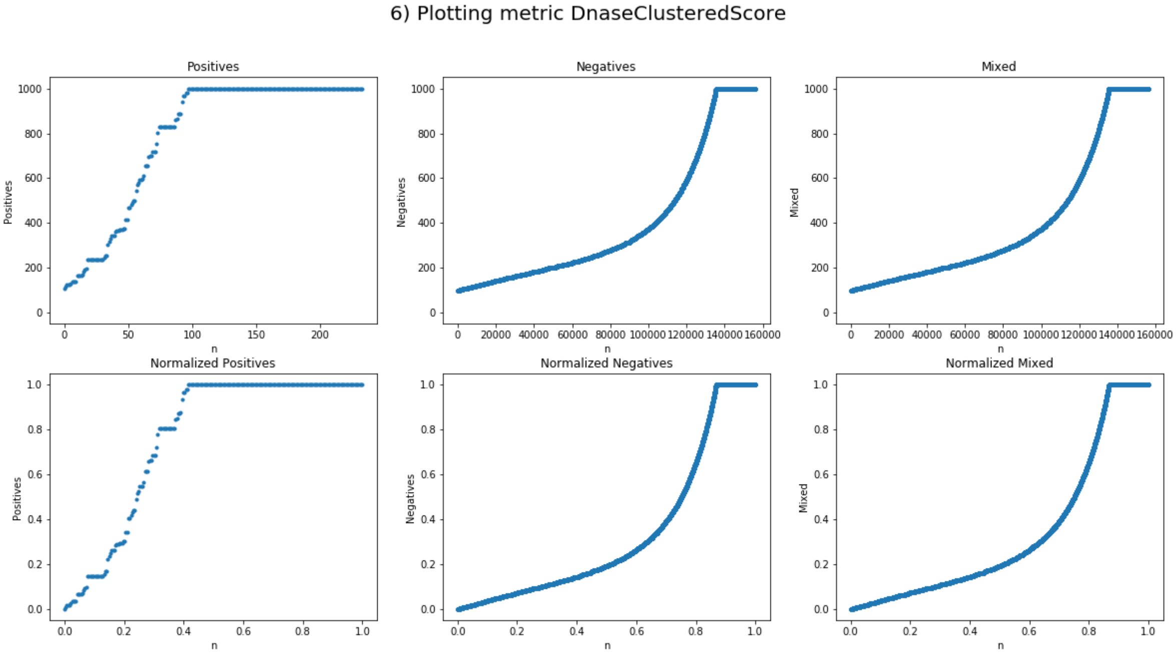


Figura 2.12: Values of metric DnaseClusteredScore

2.8 EncH3K27Ac

2.8.1 Metric sample distribution

The data points seem to follow a family of **Gamma** distributions (a speculation for this distribution could be the different groups from which the data are extracted), we will approximate them to one with a linear combination of the parameters:

$$\alpha = 0.0004042086221537893 \qquad \text{loc} = -2.859398162696207e-24 \qquad \text{scale} = 0.030769447871332\,99$$

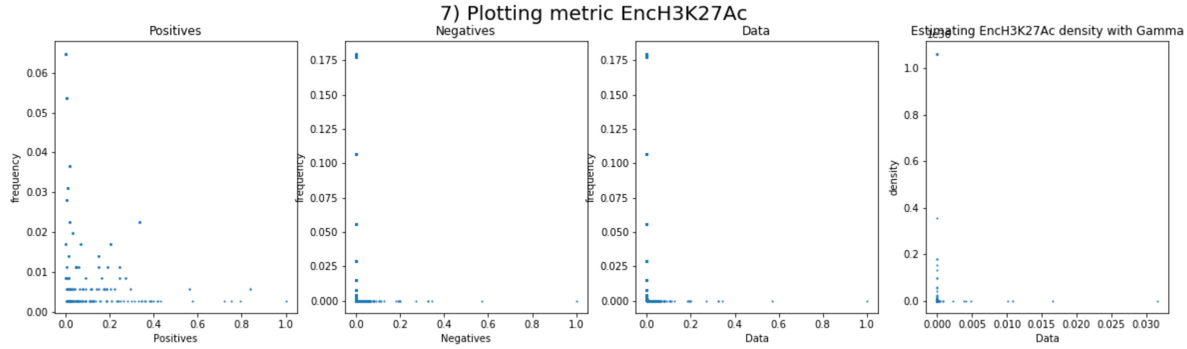


Figura 2.13: Sampling distribution of metric EncH3K27Ac

2.8.2 Metric values

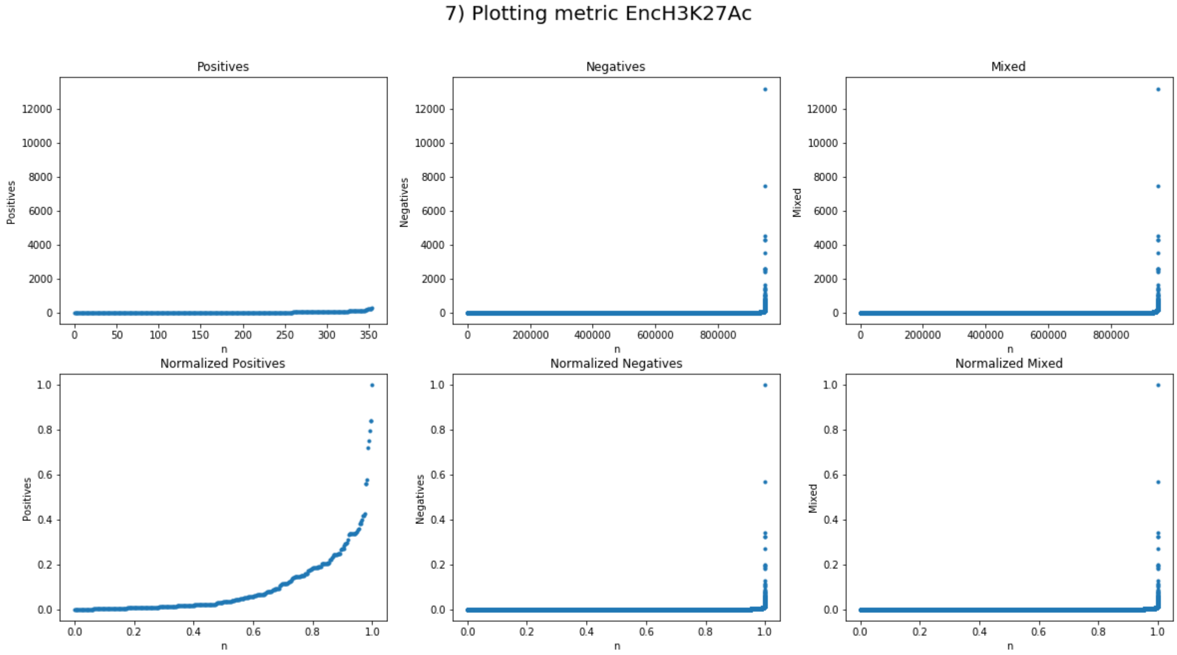


Figura 2.14: Values of metric EncH3K27Ac

2.9 EncH3K4Me1

2.9.1 Metric sample distribution

The data points seem to follow a family of **Gamma** distributions (a speculation for this distribution could be the different groups from which the data are extracted), we will approximate them to one with a linear combination of the parameters:

$$\alpha = 0.22566387737236238 \qquad \text{loc} = -6.619765504581537e-27 \qquad \text{scale} = 1.396157055181753$$

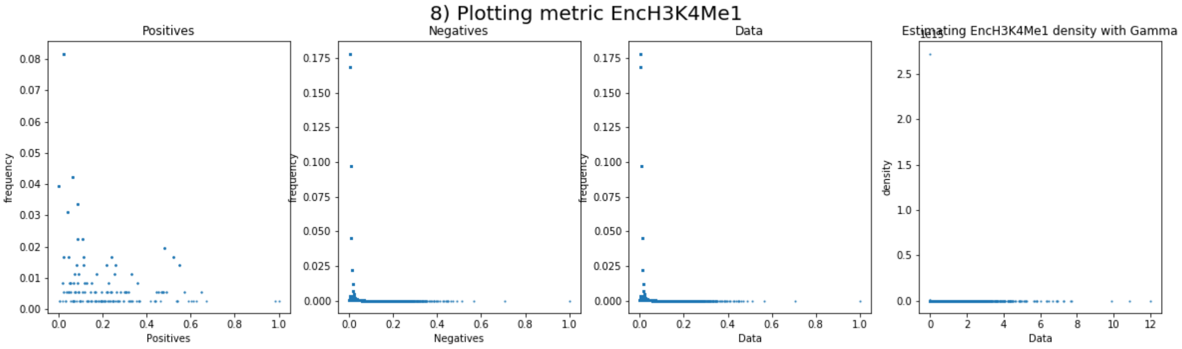


Figura 2.15: Sampling distribution of metric EncH3K4Me1

2.9.2 Metric values

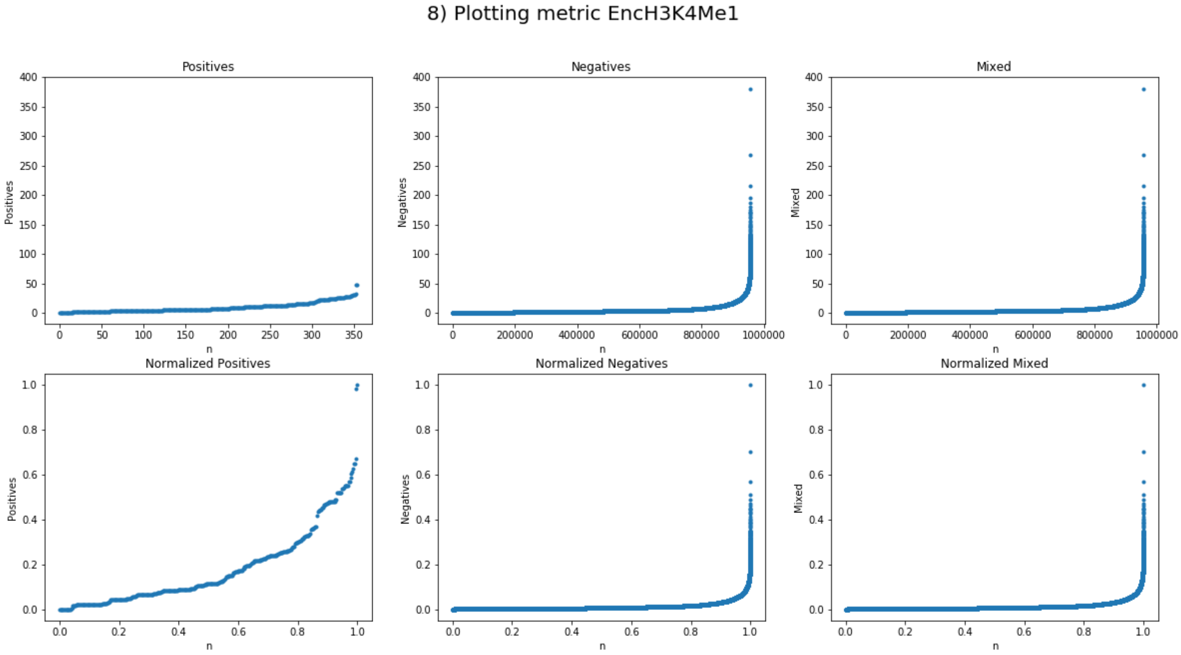


Figura 2.16: Values of metric EncH3K4Me1

2.10 EncH3K4Me3

2.10.1 Metric sample distribution

The data points seem to follow a family of **Gamma** distributions (a speculation for this distribution could be the different groups from which the data are extracted), we will approximate them to one with a linear combination of the parameters:

$$\alpha = 0.007502428717446465 \qquad \text{loc} = -3.469650119186857e-25 \qquad \text{scale} = 0.04125297431971783$$

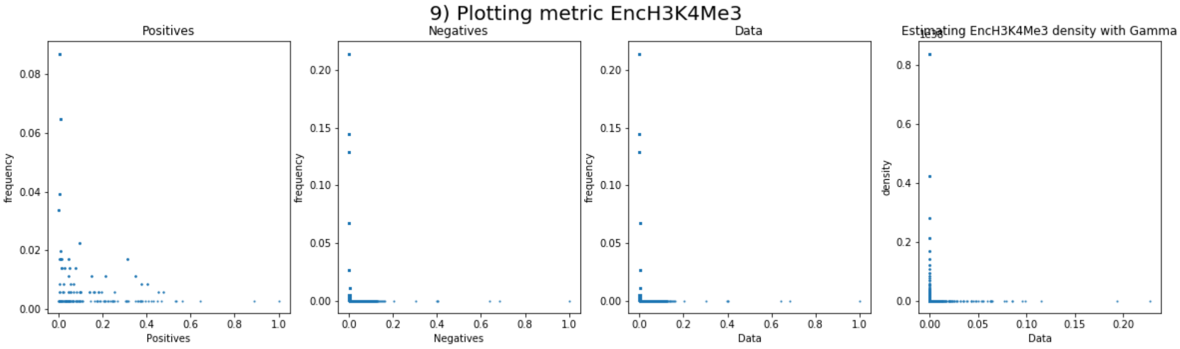


Figura 2.17: Sampling distribution of metric EncH3K4Me3

2.10.2 Metric values

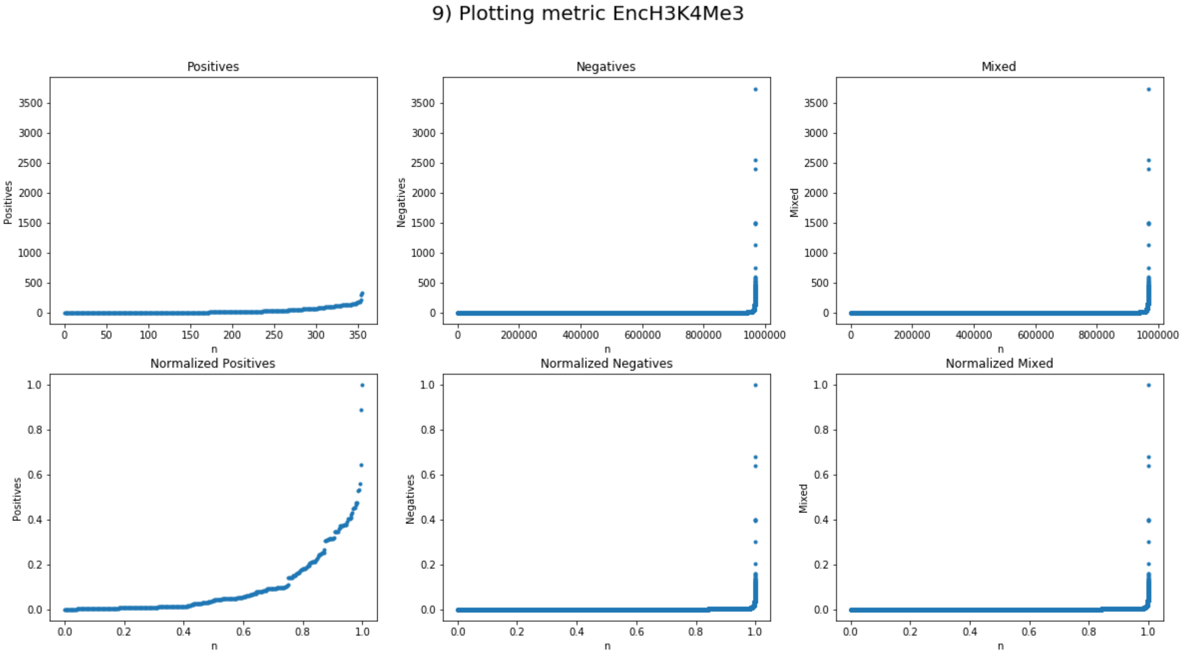


Figura 2.18: Values of metric EncH3K4Me3

2.11 GCContent

2.11.1 Metric sample distribution

The data points seem to be a combination of two **Gaussian** distributions. This will be approximated to one with the following parameters:

$$\mathbb{E}(X) = 0.4482813176478024 \qquad \mathrm{Var}(X) = 0.1097424869360011$$

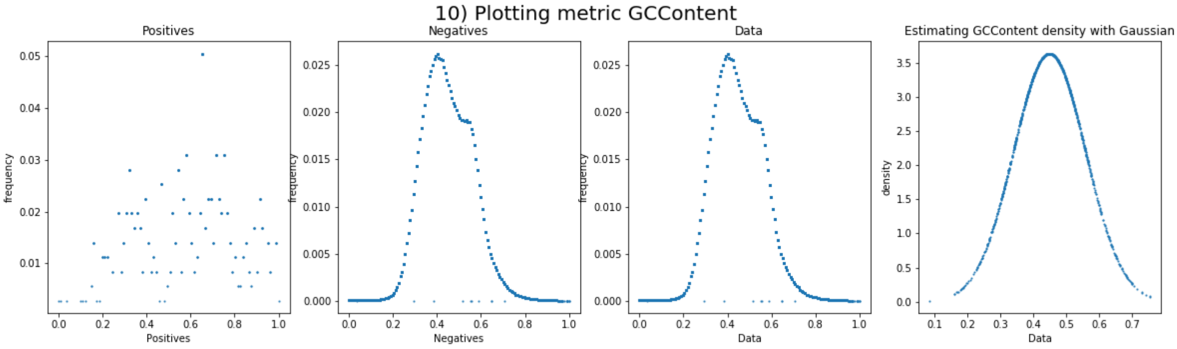


Figura 2.19: Sampling distribution of metric GCContent

2.11.2 Metric values

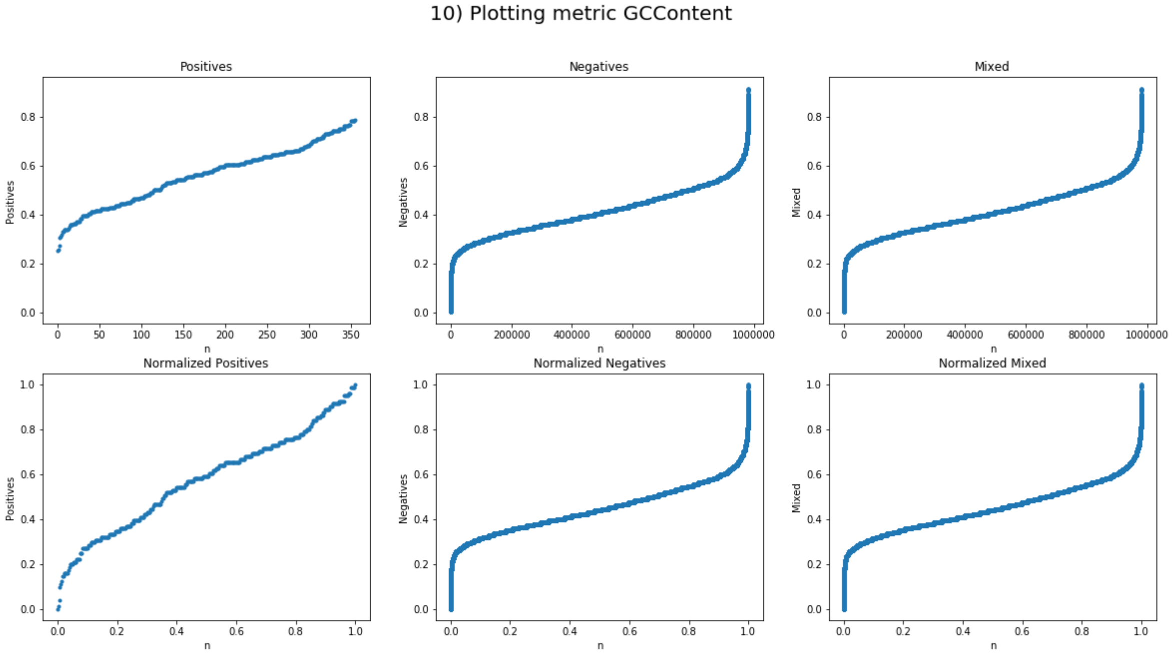


Figura 2.20: Values of metric GCContent

2.12 GerpRS

2.12.1 Metric sample distribution

The data points seem to follow a family of **Gamma** distributions (a speculation for this distribution could be the different groups from which the data are extracted), we will approximate them to one with a linear combination of the parameters:

$$\alpha = 0.8688332877203315 \qquad \text{loc} = -1.7081810436826354e-28 \qquad \text{scale} = 0.11512094125204281$$

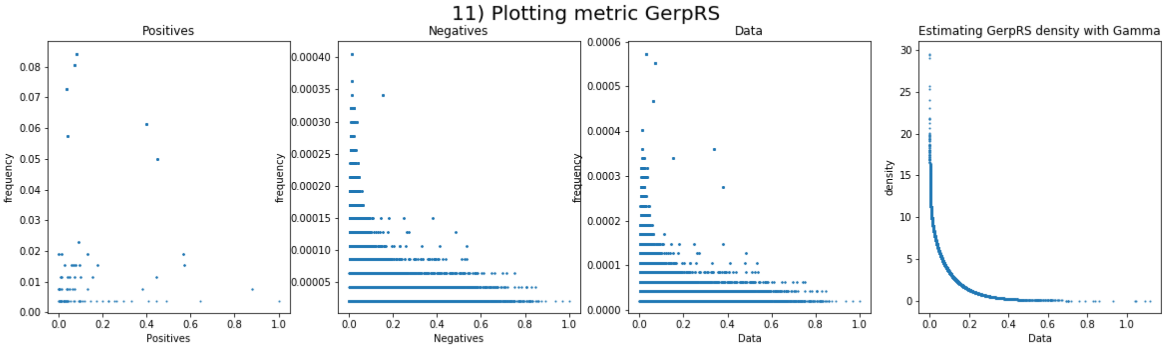


Figura 2.21: Sampling distribution of metric GerpRS

2.12.2 Metric values

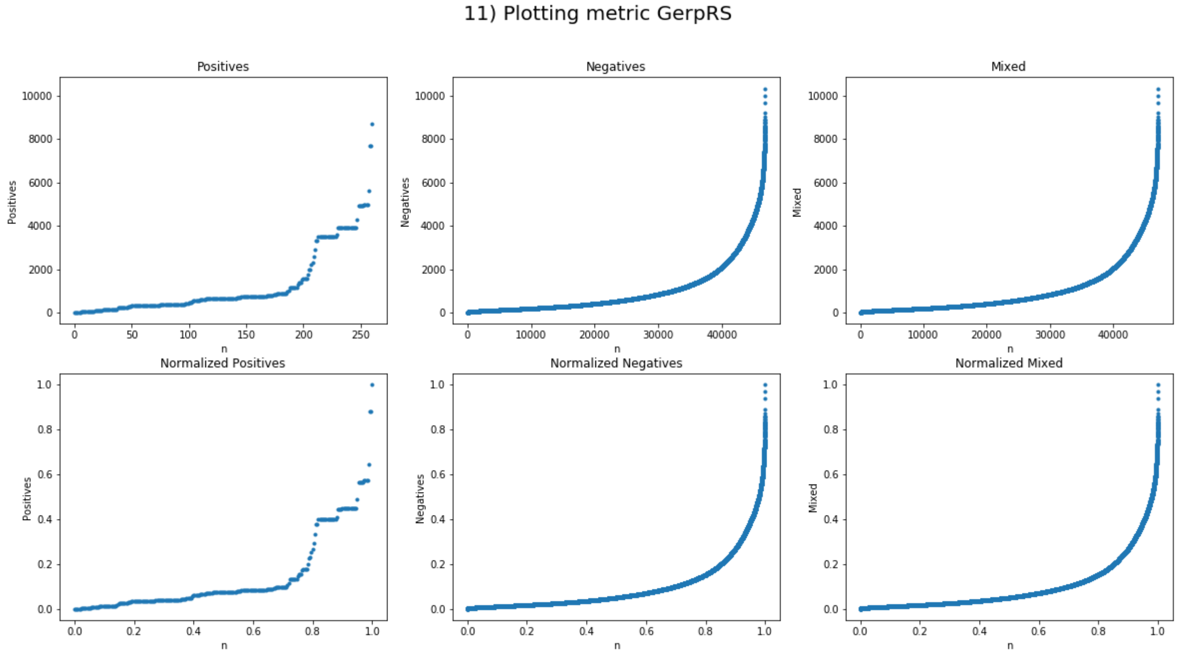


Figura 2.22: Values of metric GerpRS

2.13 GerpRSpv

2.13.1 Metric sample distribution

The data points seem to follow a family of **Gamma** distributions (a speculation for this distribution could be the different groups from which the data are extracted), we will approximate them to one with a linear combination of the parameters:

$$\alpha = 0.5165290213220888 \qquad \text{loc} = -6.952792177974854e-30 \qquad \text{scale} = 0.2530358950266992$$

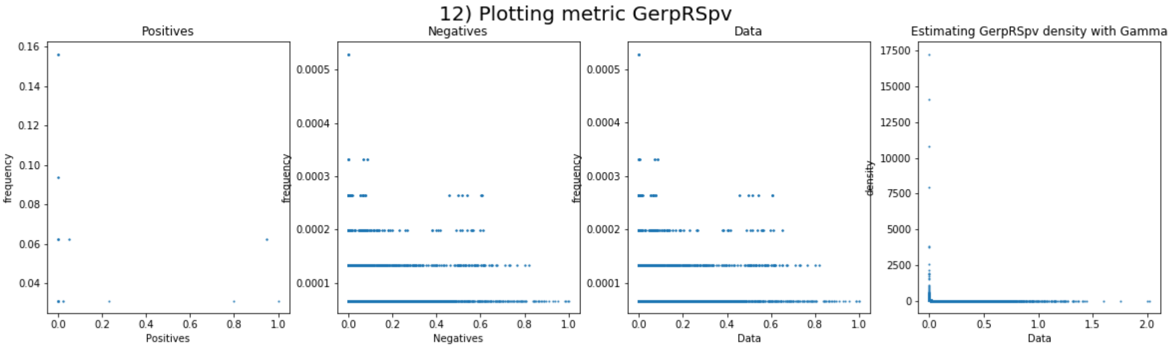


Figura 2.23: Sampling distribution of metric GerpRSpv

2.13.2 Metric values

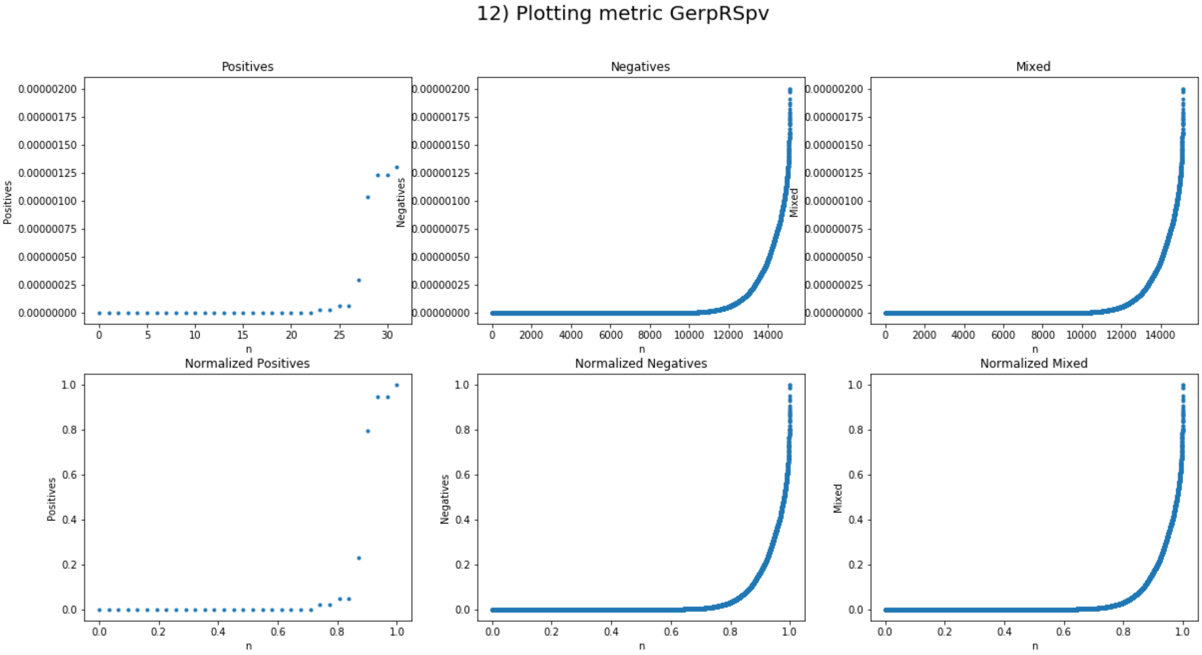


Figura 2.24: Values of metric GerpRSpv

2.14 ISCApath

2.14.1 Metric sample distribution

The data points seem to follow a **Gamma** distribution with the following parameters:

$$\alpha = 0.08318618903703257 \qquad \text{loc} = -1.9358902729364646e-30 \qquad \text{scale} = 1.2606790181148981$$

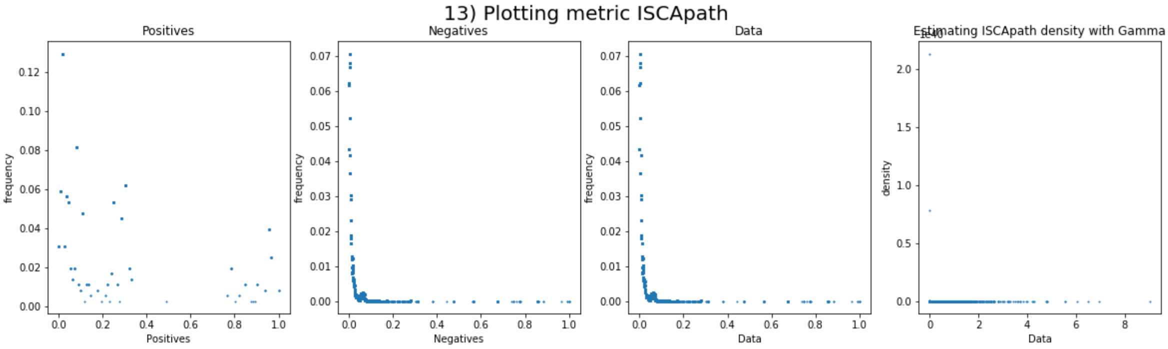


Figura 2.25: Sampling distribution of metric ISCApath

2.14.2 Metric values

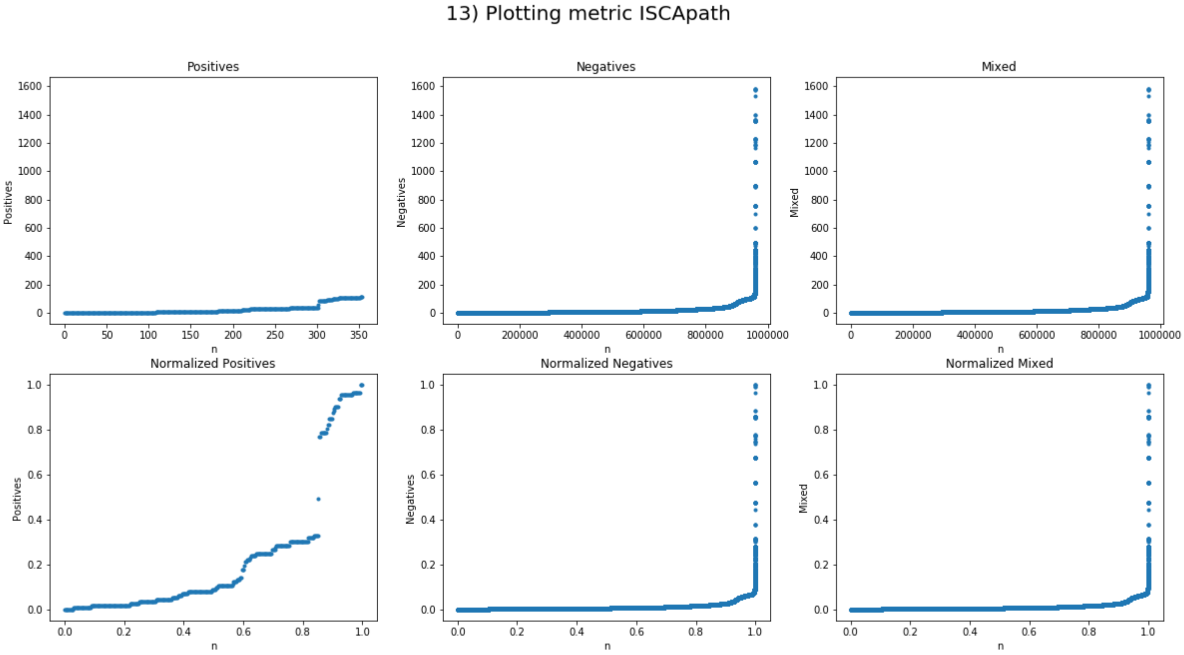


Figura 2.26: Values of metric ISCApath

2.15 commonVar

2.15.1 Metric sample distribution

The data points seem to follow an **Exponential Weibull** distribution with the following parameters:

$$\alpha = 5.038707296051438 \qquad \beta = 1.0160276119461702$$
$$\text{loc} = -0.012528678364149837 \qquad \text{scale} = 0.025052745155722922$$

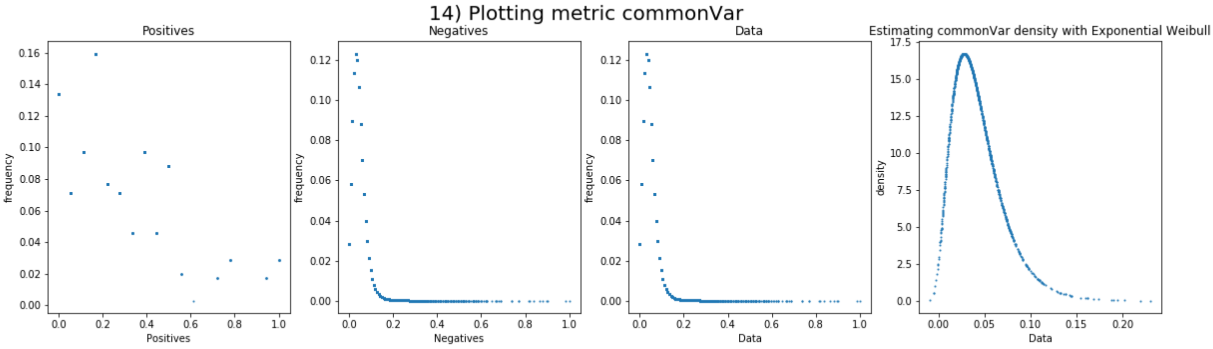


Figura 2.27: Sampling distribution of metric commonVar

2.15.2 Metric values

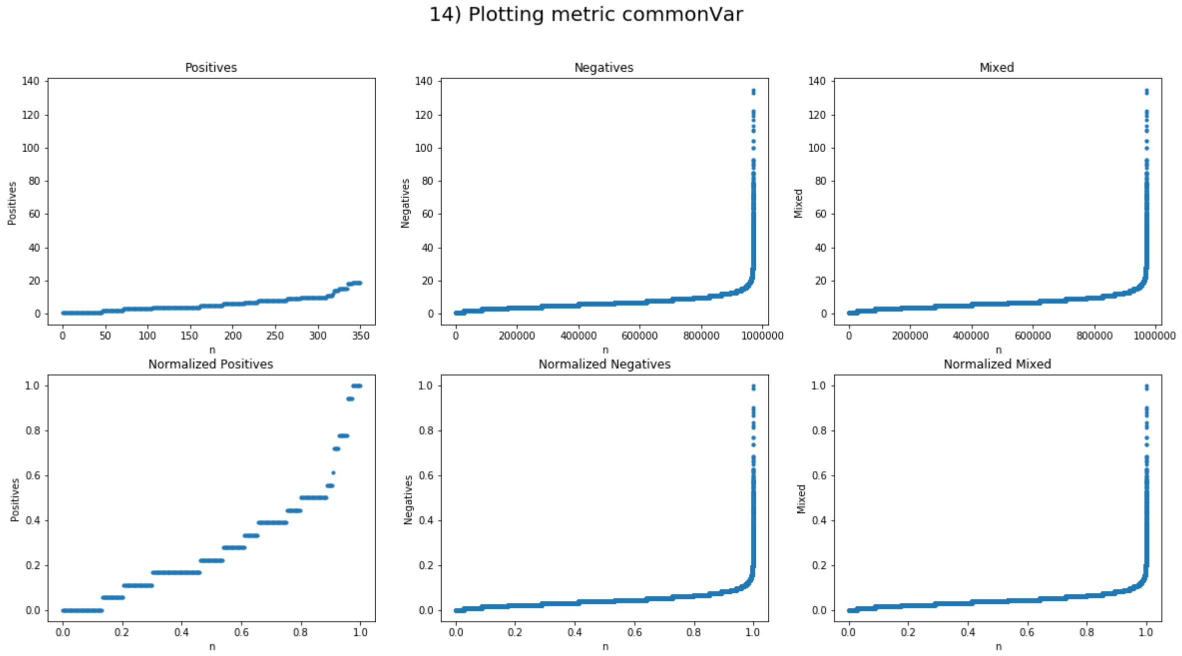


Figura 2.28: Values of metric commonVar

2.16 dbVARCount

2.16.1 Metric sample distribution

The data points seem to follow a **Gamma** distribution with the following parameters:

$$\alpha = 0.20940038672579409 \qquad \text{loc} = -1.1962983066939984e-30 \qquad \text{scale} = 1.2347090894162929$$

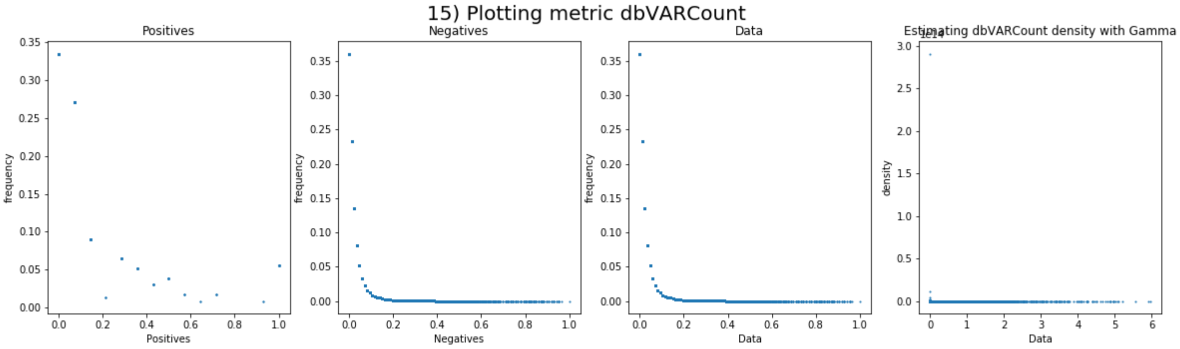


Figura 2.29: Sampling distribution of metric dbVARCount

2.16.2 Metric values

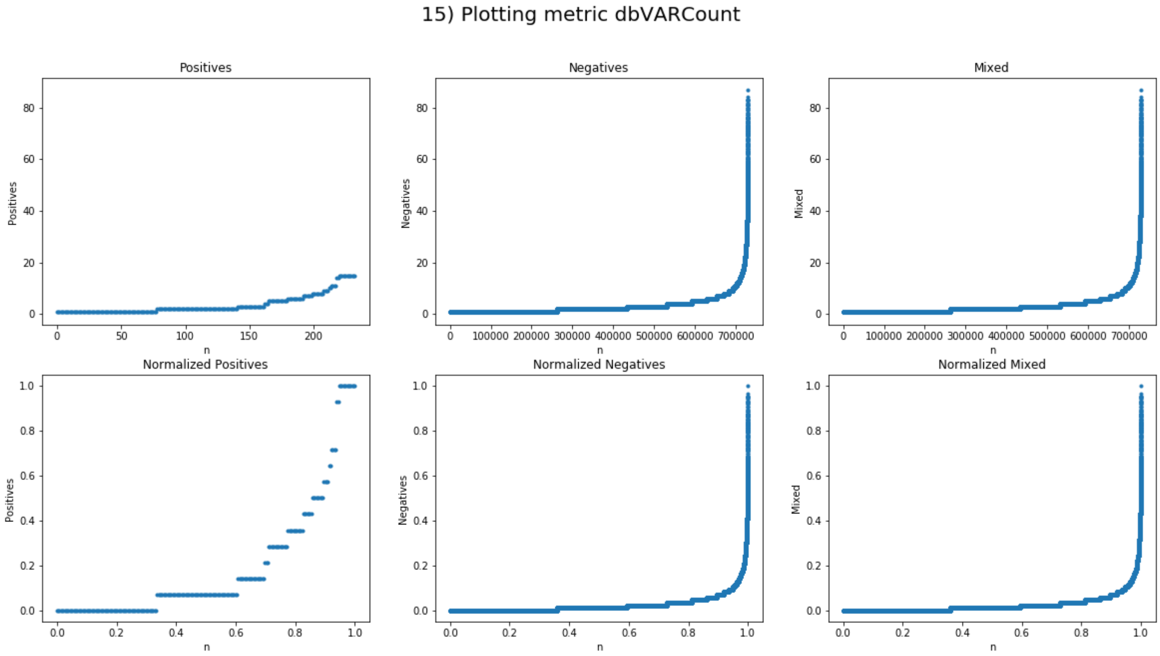


Figura 2.30: Values of metric dbVARCount

2.17 fantom5Perm

2.17.1 Metric sample distribution

The data points seem to follow a **Gamma** distribution with the following parameters:

$$\alpha = 0.06895533706017208 \qquad \text{loc} = -3.220296247423778e-30 \qquad \text{scale} = 1.2605014923175824$$

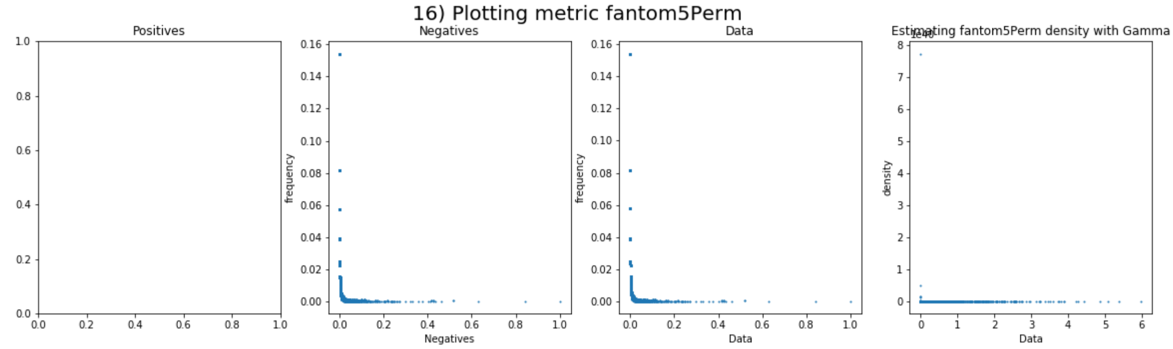


Figura 2.31: Sampling distribution of metric fantom5Perm

2.17.2 Metric values

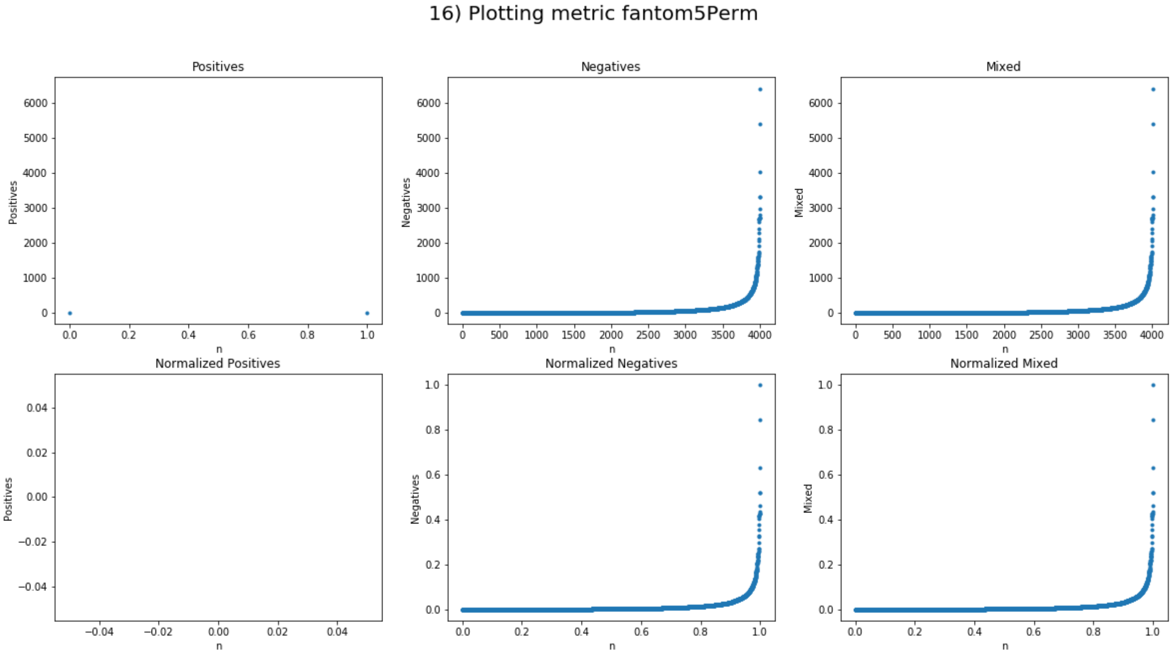


Figura 2.32: Values of metric fantom5Perm

2.18 fantom5Robust

2.18.1 Metric sample distribution

The data points seem to follow a **Gamma** distribution with the following parameters:

$$\alpha = 0.08983952110680529 \qquad \text{loc} = -3.220296247423778e-30 \qquad \text{scale} = 1.2605014923175824$$

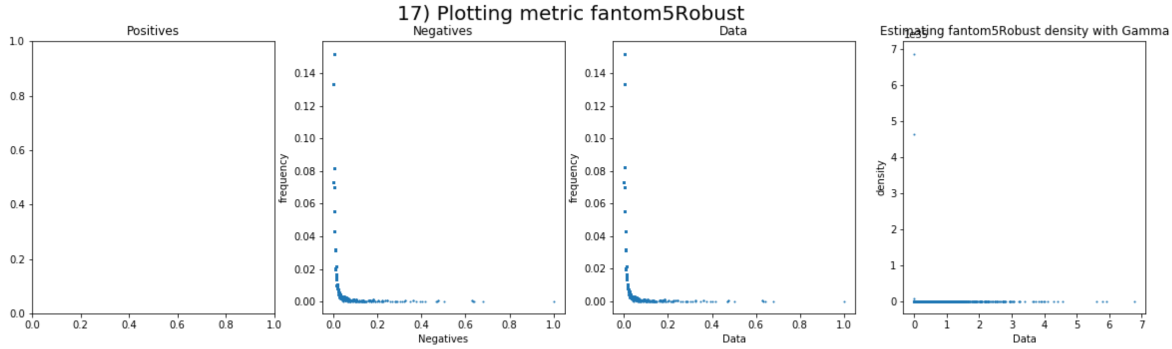


Figura 2.33: Sampling distribution of metric fantom5Robust

2.18.2 Metric values

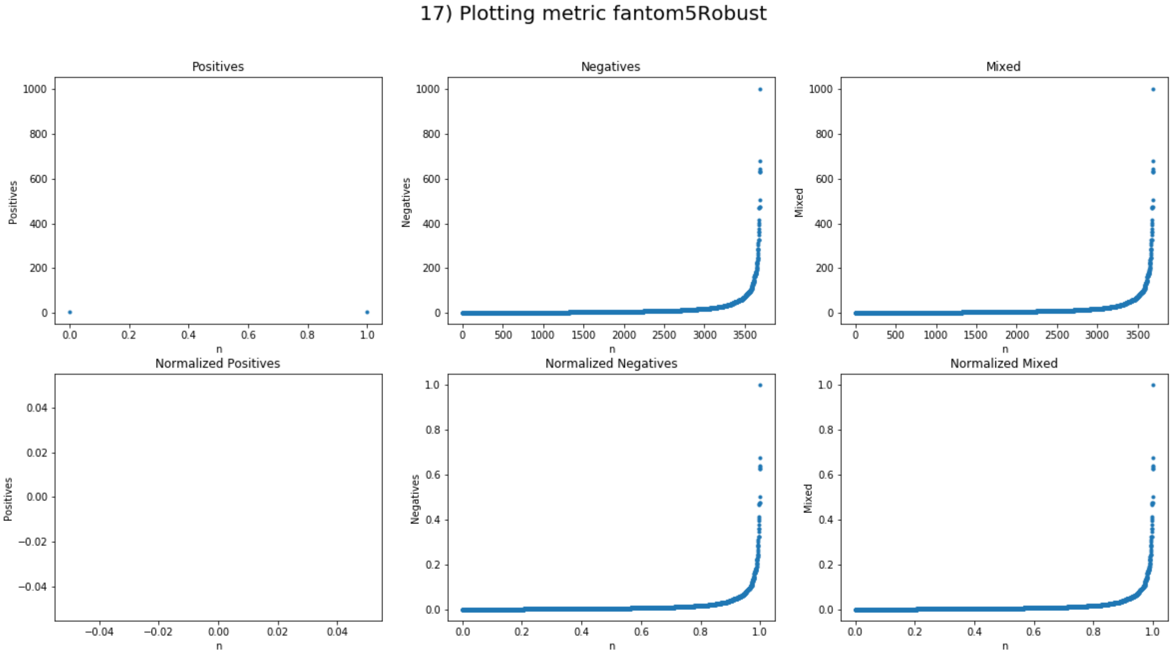


Figura 2.34: Values of metric fantom5Robust

2.19 fracRareCommon

2.19.1 Metric sample distribution

The data points seem to follow an **Beta** distribution with the following parameters:

$$\alpha = 2772.739504773501 \qquad \beta = 14.986077009876375$$
$$\text{loc} = -69.93503912437342 \qquad \text{scale} = 71.09741090721741$$

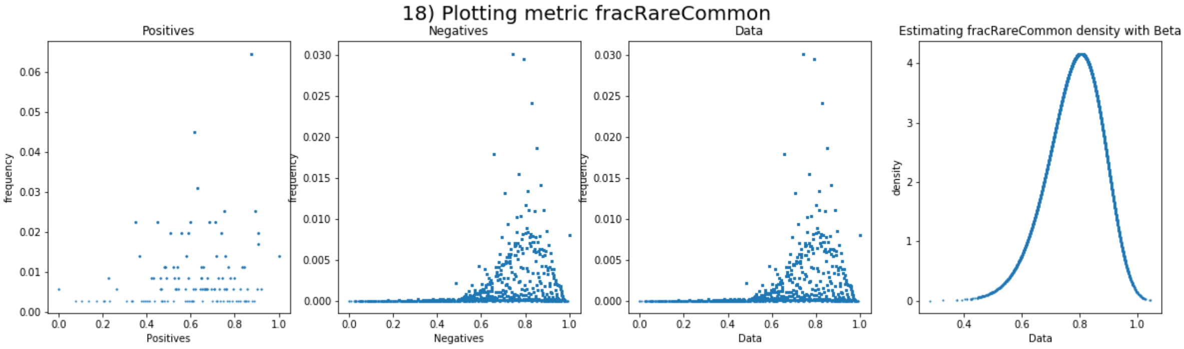


Figura 2.35: Sampling distribution of metric fracRareCommon

2.19.2 Metric values

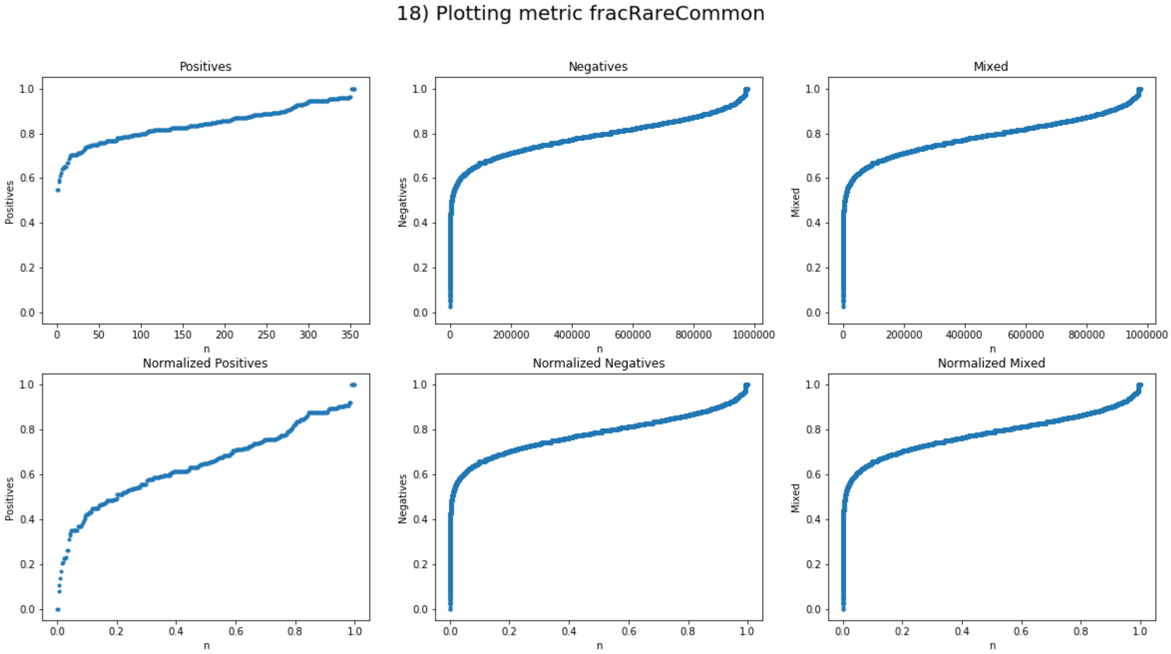


Figura 2.36: Values of metric fracRareCommon

2.20 mamPhastCons46way

2.20.1 Metric sample distribution

The data points seem to follow a **Gamma** distribution with the following parameters:

$$\alpha = 0.3215099801387991 \qquad \text{loc} = -6.260887365023215e-31 \qquad \text{scale} = 0.45230902834164866$$

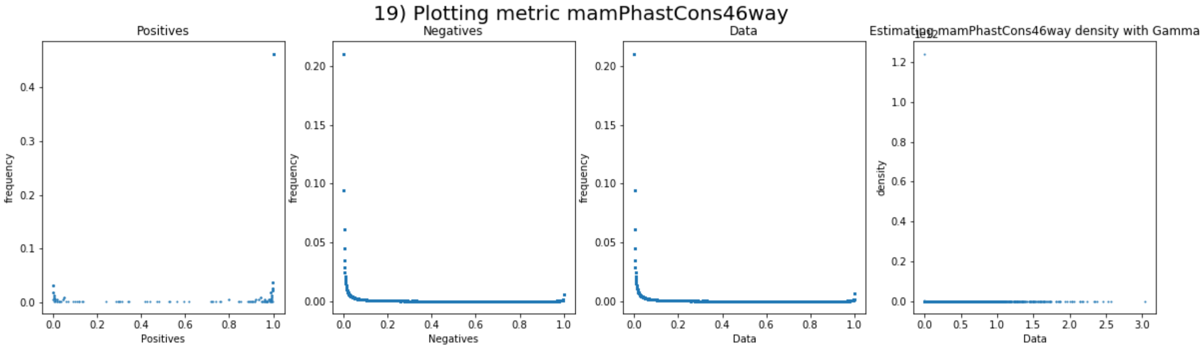


Figura 2.37: Sampling distribution of metric mamPhastCons46way

2.20.2 Metric values

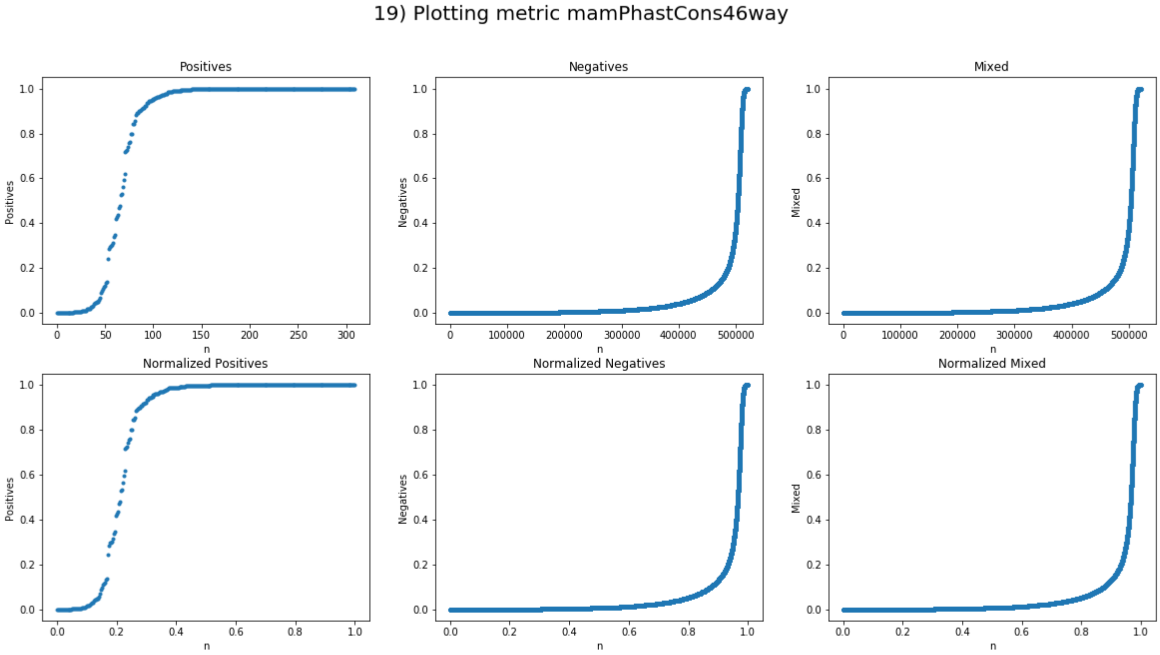


Figura 2.38: Values of metric mamPhastCons46way

2.21 mamPhyloP46way

2.21.1 Metric sample distribution

The data points seem to follow a **Gaussian** distribution with the following parameters:

$$\mathbb{E}(X) = 0.7032457913828309 \qquad \mathrm{Var}(X) = 0.07627203289198752$$

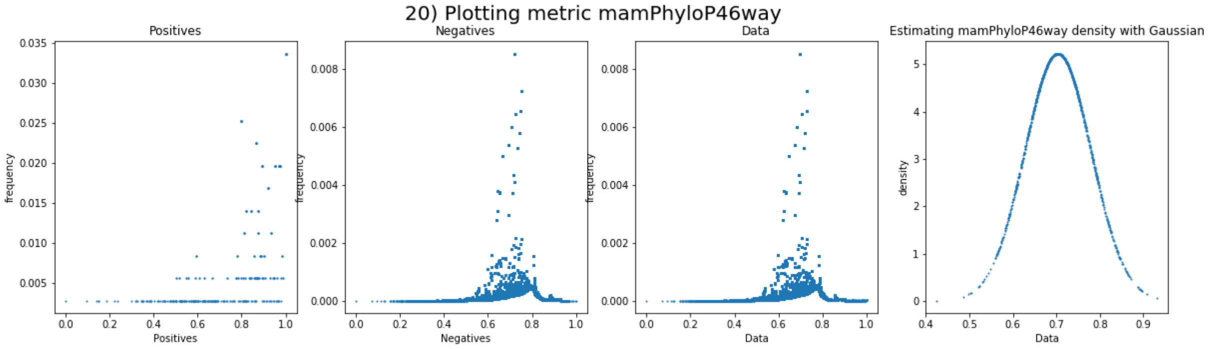


Figura 2.39: Sampling distribution of metric mamPhyloP46way

2.21.2 Metric values

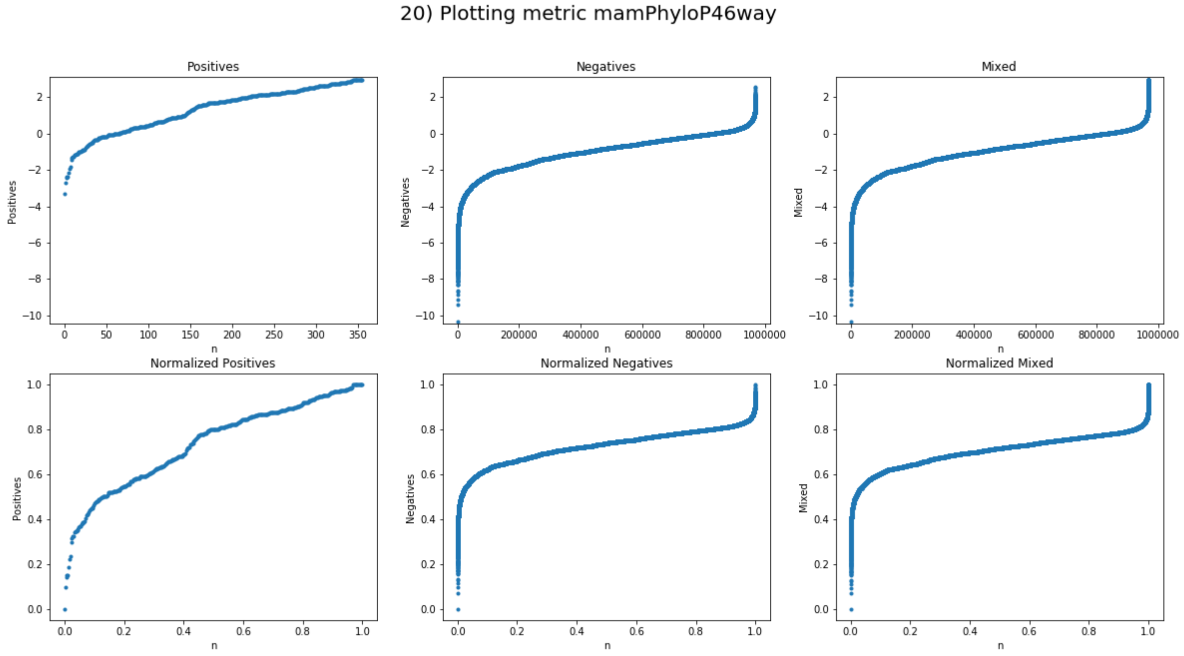


Figura 2.40: Values of metric mamPhyloP46way

2.22 numTFBSConserved

2.22.1 Metric sample distribution

The data points seem to follow a **exponential** distribution with the following parameters:

$$\mathbb{E}(X) = -4.600037873301623e - 12 \qquad \mathrm{Var}(X) = 0.033419421646804975$$

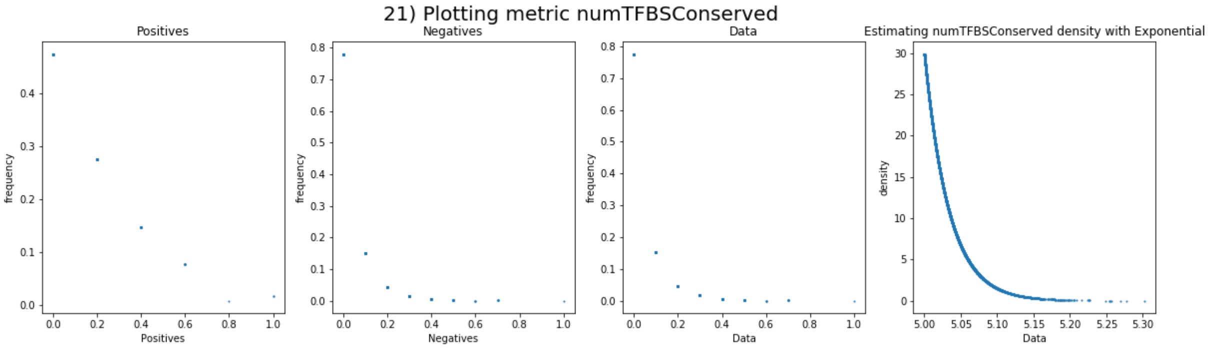


Figura 2.41: Sampling distribution of metric numTFBSConserved

2.22.2 Metric values

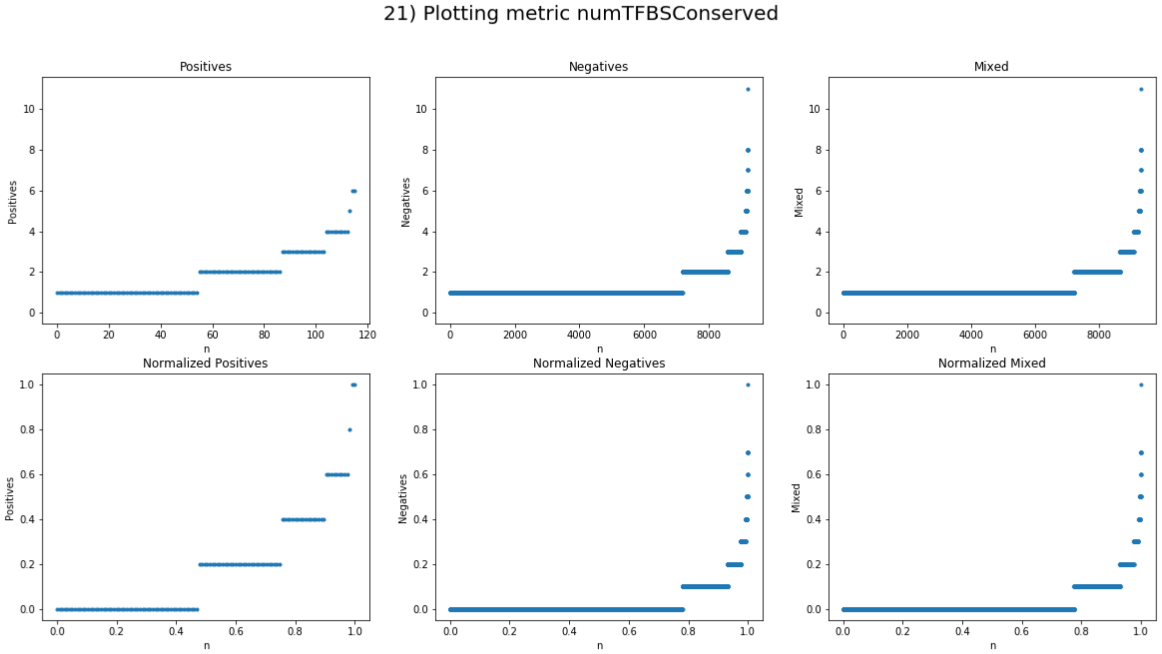


Figura 2.42: Values of metric numTFBSConserved

2.23 priPhastCons46way

2.23.1 Metric sample distribution

The data points seem to follow a **Gamma** distribution with the following parameters:

$$\alpha = 0.2836383862597563 \qquad \text{loc} = -1.8643137904859329e-31 \qquad \text{scale} = 0.37399746075497264$$

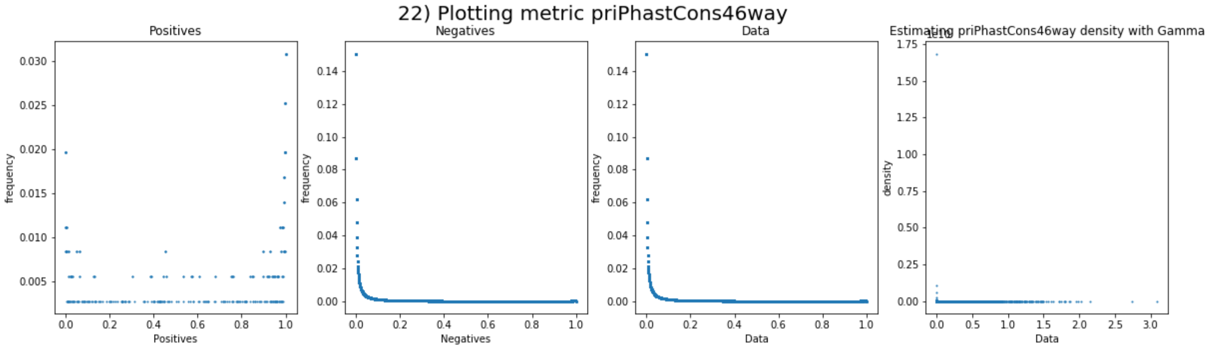


Figura 2.43: Sampling distribution of metric priPhastCons46way

2.23.2 Metric values

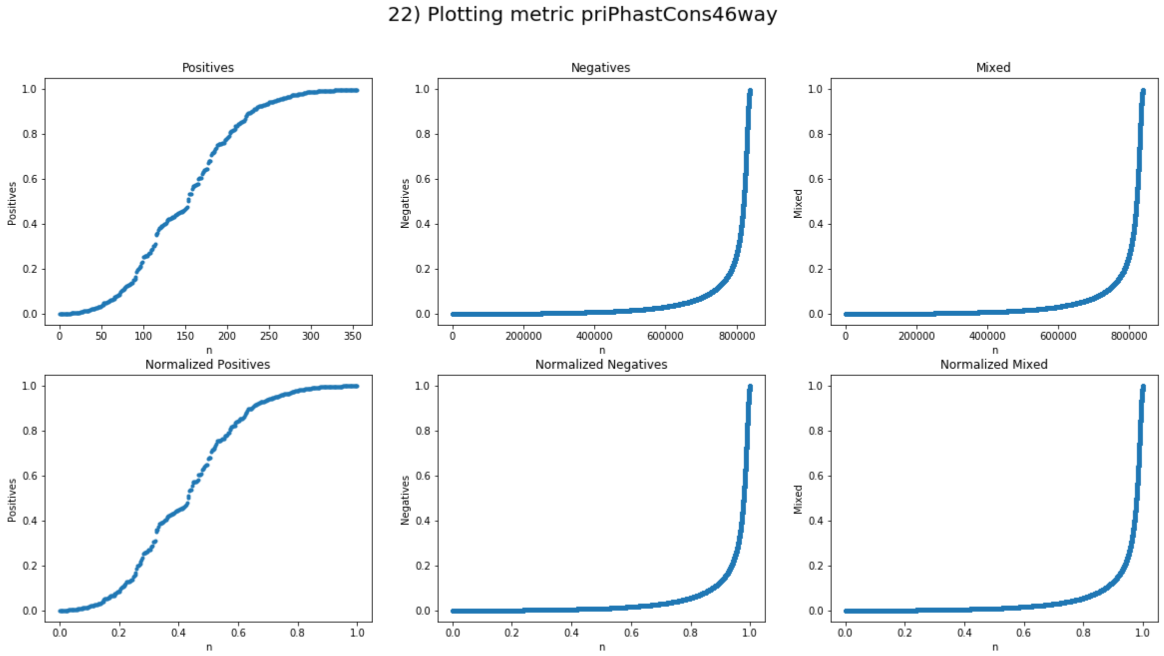


Figura 2.44: Values of metric priPhastCons46way

2.24 priPhyloP46way

2.24.1 Metric sample distribution

The data points seem to follow an **Beta** distribution with the following parameters:

$$\alpha = 2095270.7440875275 \qquad \beta = 4.199025269606416$$
$$\text{loc} = -103376.03746996864 \qquad \text{scale} = 103377.03863437689$$

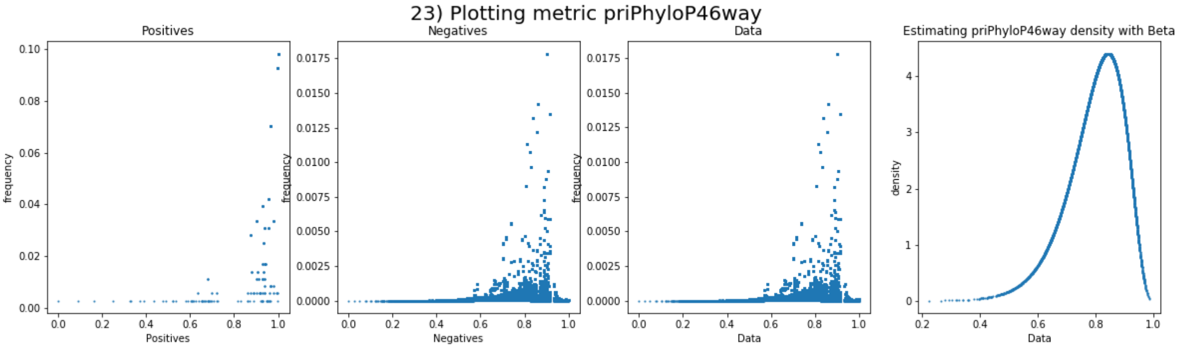


Figura 2.45: Sampling distribution of metric priPhyloP46way

2.24.2 Metric values

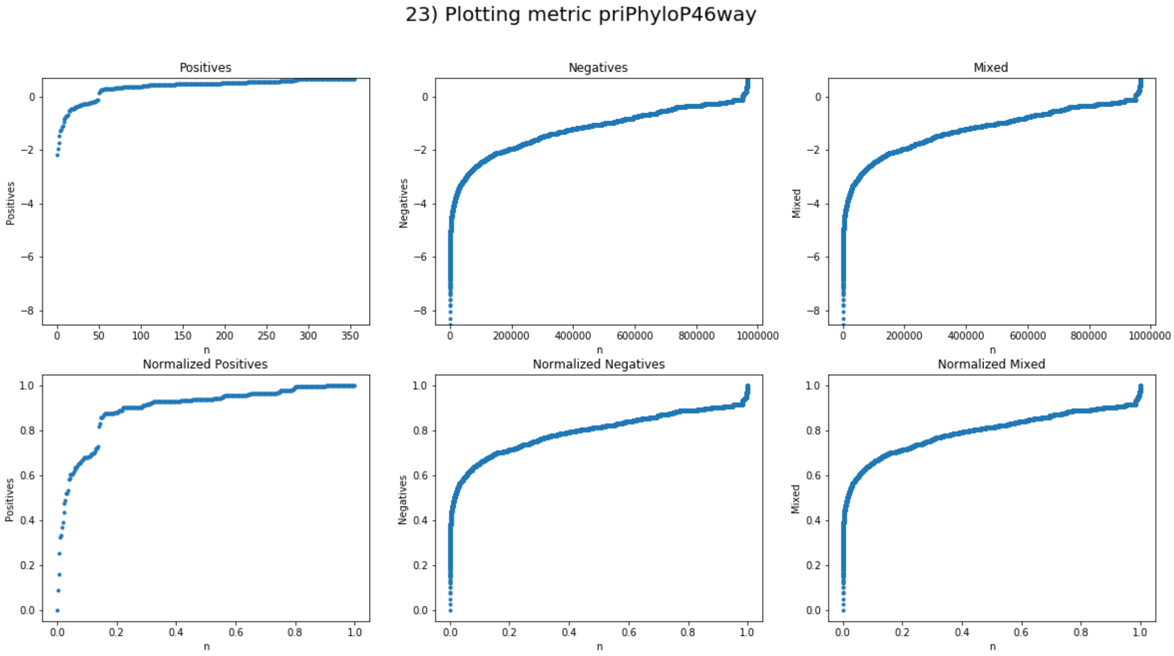


Figura 2.46: Values of metric priPhyloP46way

2.25 rareVar

2.25.1 Metric sample distribution

The data points seem to follow an **Beta** distribution with the following parameters:

$$\alpha = 14.148202647100376 \qquad \beta = 7669045.025220526$$
$$\text{loc} = -0.008523116473417407 \qquad \text{scale} = 28973.953544984728$$

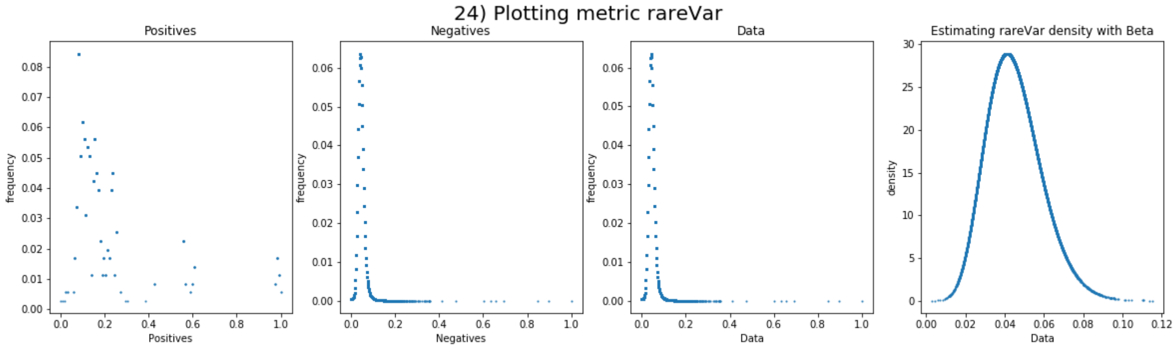


Figura 2.47: Sampling distribution of metric rareVar

2.25.2 Metric values

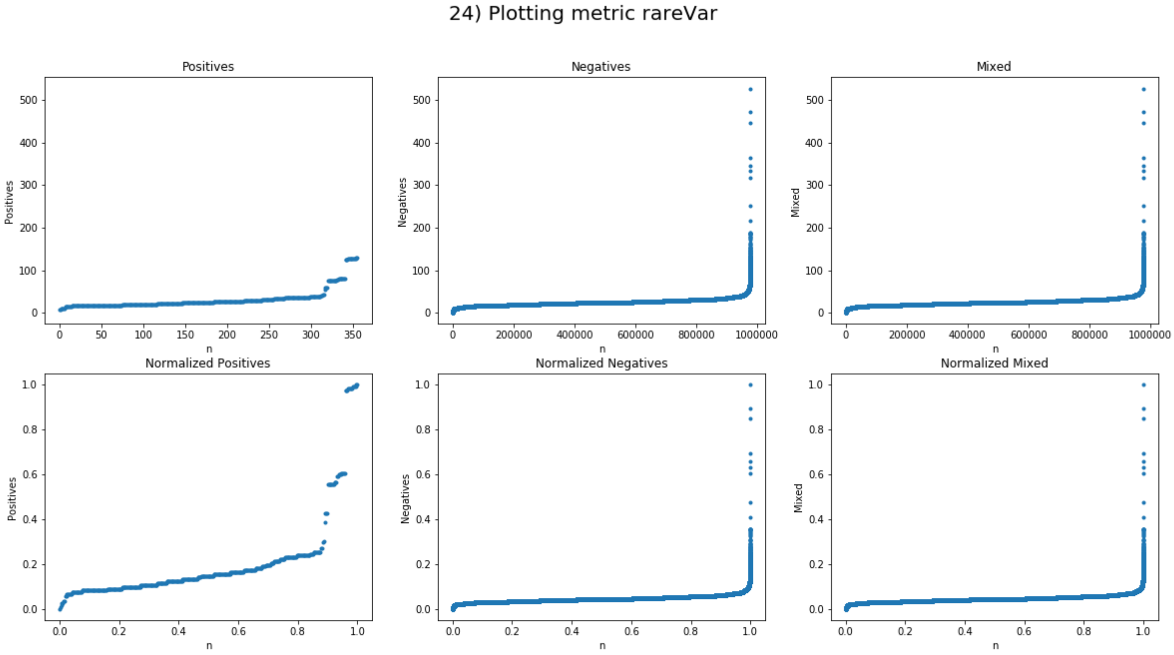


Figura 2.48: Values of metric rareVar

2.26 verPhastCons46way

2.26.1 Metric sample distribution

The data points seem to follow a **Gamma** distribution with the following parameters:

$$\alpha = 0.4378982063415524 \qquad \text{loc} = -2.5307968883256733e-31 \qquad \text{scale} = 0.43138079305533483$$

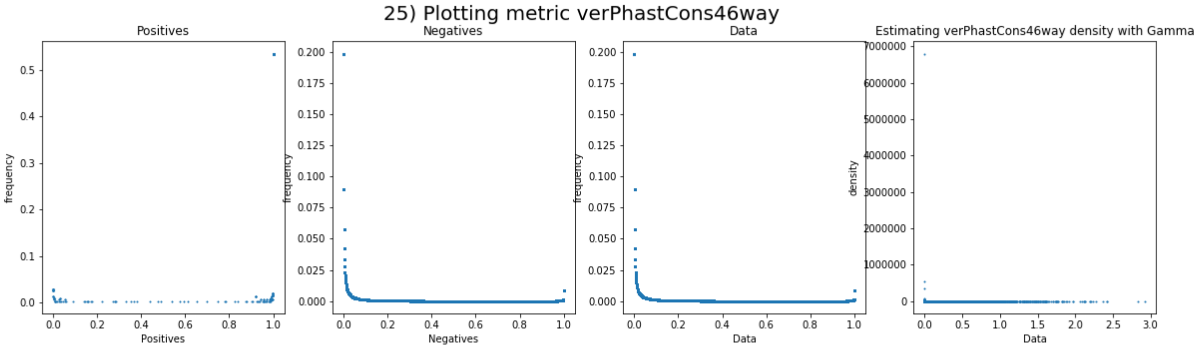


Figura 2.49: Sampling distribution of metric verPhastCons46way

2.26.2 Metric values

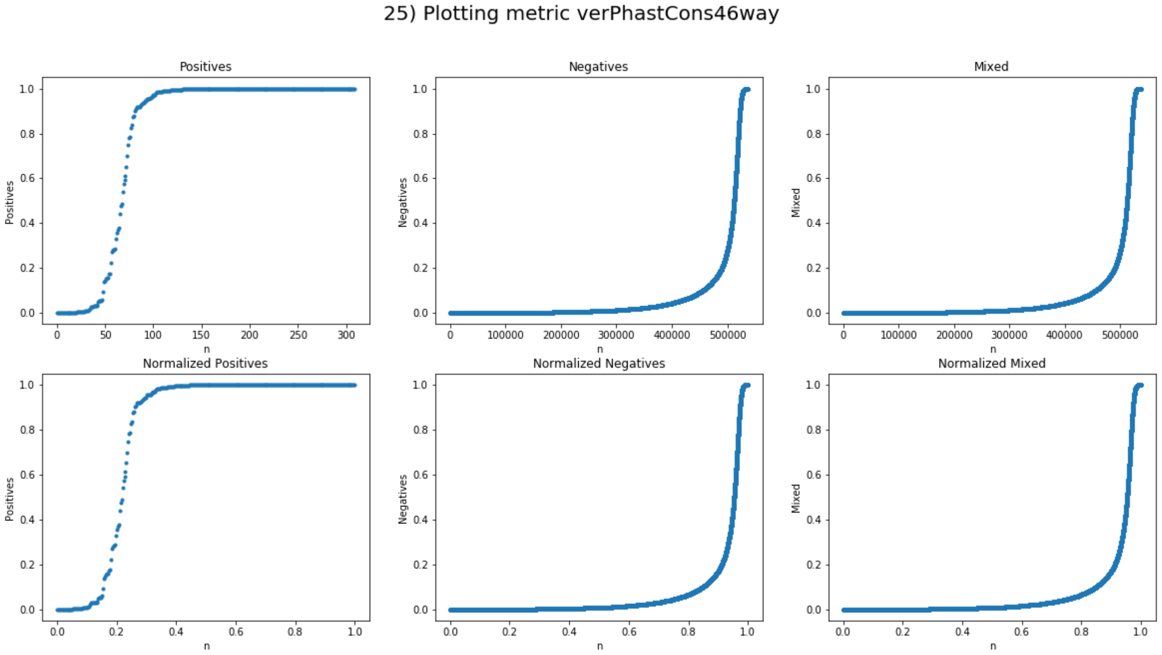


Figura 2.50: Values of metric verPhastCons46way

2.27 verPhyloP46way

2.27.1 Metric sample distribution

The data points seem to follow a **Gaussian** distribution with the following parameters:

$$\mathbb{E}(X) = 0.5723779382558164 \qquad \mathrm{Var}(X) = 0.0662715947139185$$

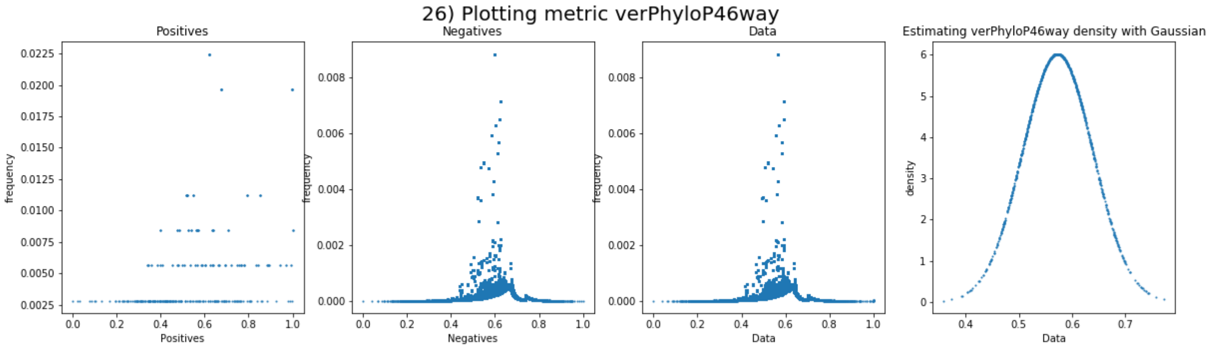


Figura 2.51: Sampling distribution of metric verPhyloP46way

2.27.2 Metric values

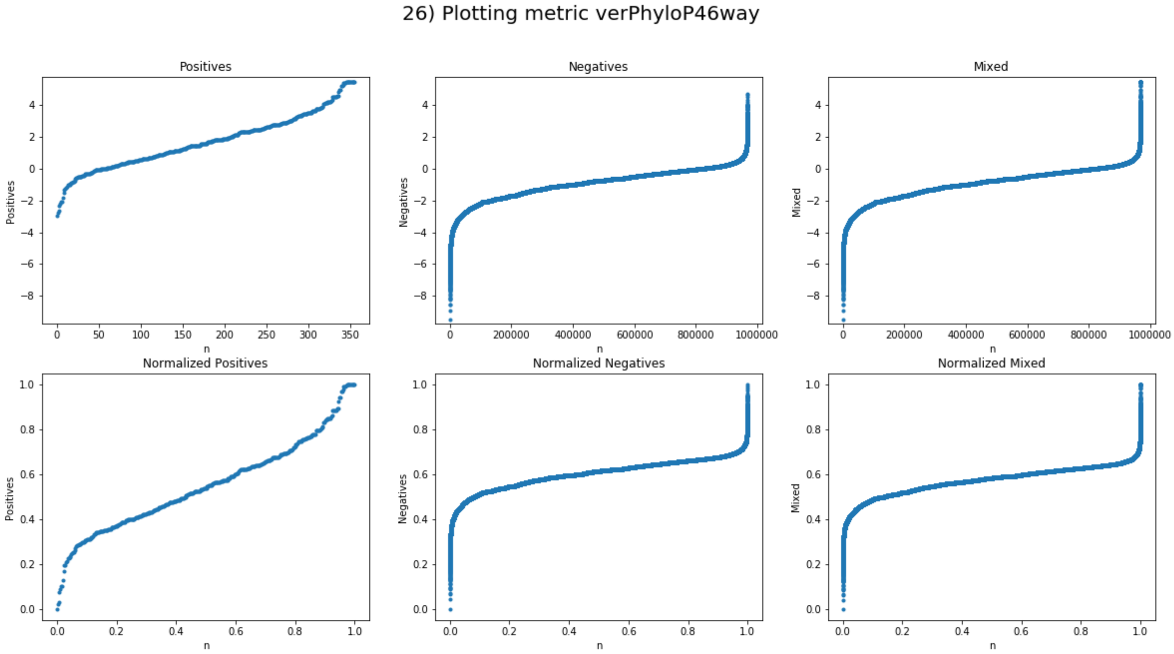


Figura 2.52: Values of metric verPhyloP46way

3
Metric distribution summary

The metrics seem to follow these sample distributions:

Metric	**Distribution**
CpGobsExp	Beta
CpGperCpG	Beta
CpGperGC	Gaussian
DGVCount	Gamma
DnaseClusteredHyp	Gamma
EncH3K27Ac	Gamma
GCContent	Gaussian
EncH3K4Me3	Gamma
ISCApath	Gamma
DnaseClusteredScore	Beta
EncH3K4Me1	Gamma
GerpRS	Gamma
GerpRSpv	Gamma
commonVar	Exponential Weibull
dbVARCount	Gamma
fantom5Perm	Gamma
fantom5Robust	Gamma
mamPhastCons46way	Gamma
priPhastCons46way	Gamma
rareVar	Beta
verPhastCons46way	Gamma
numTFBSConserved	Exponential
fracRareCommon	Beta
priPhyloP46way	Beta
verPhyloP46way	Gaussian
mamPhyloP46way	Gaussian

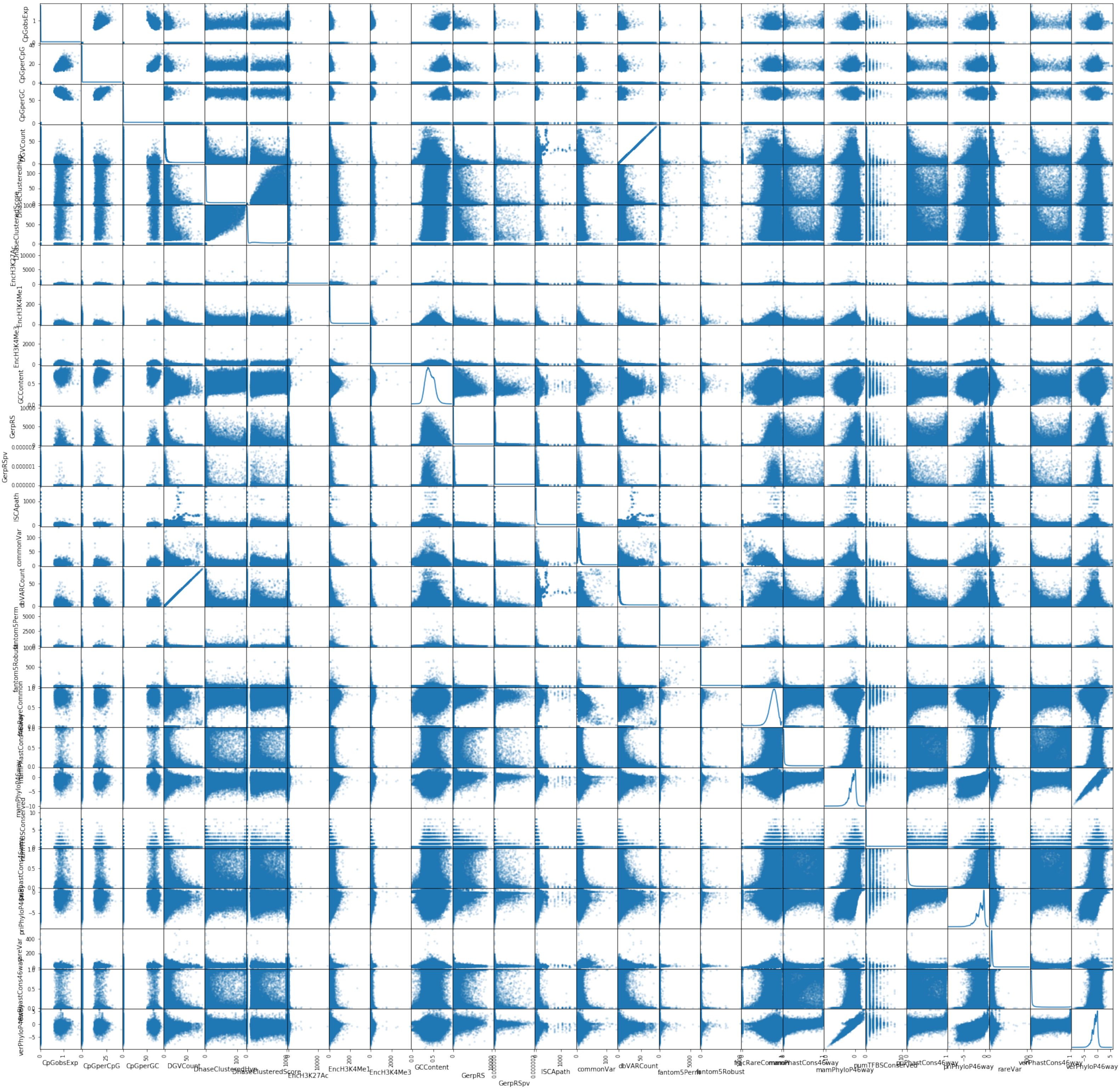
Tabella 3.1: Metrics and their distribution

4
Scatter plot

We now proceed to draw a scatter plot trying to identify eventual data correlations.

4.1 Scatter plot

A scatter plot with higher resolution is available in the project repository.



4.2 Identified data correlations

Data correlations seem to exist between:

4.2.1 dbVARCount and DGVCount

There is a strong correlation between this two metrics: let's look again at the data plots to see if they follow a similar trend:

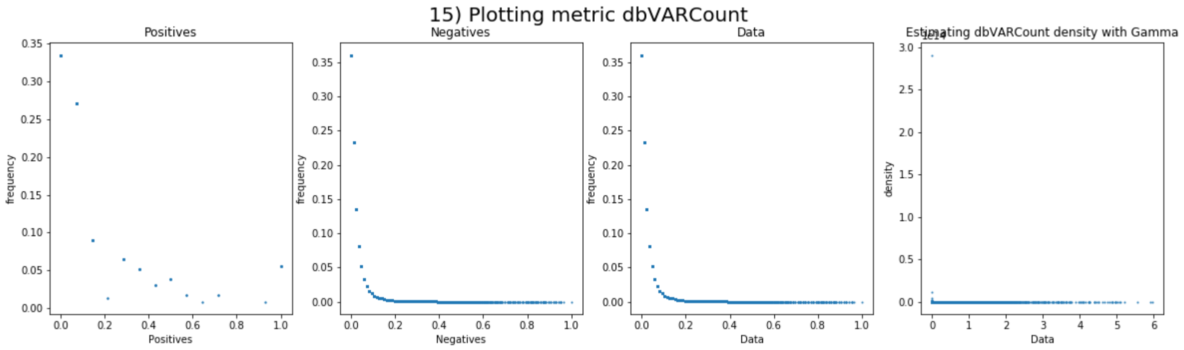


Figura 4.1: Sampling distribution of metric dbVARCount

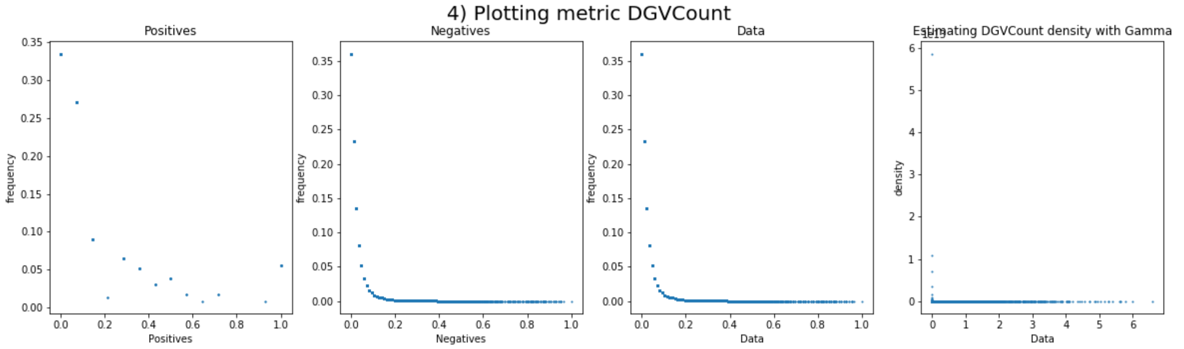


Figura 4.2: Sampling distribution of metric DGVCount

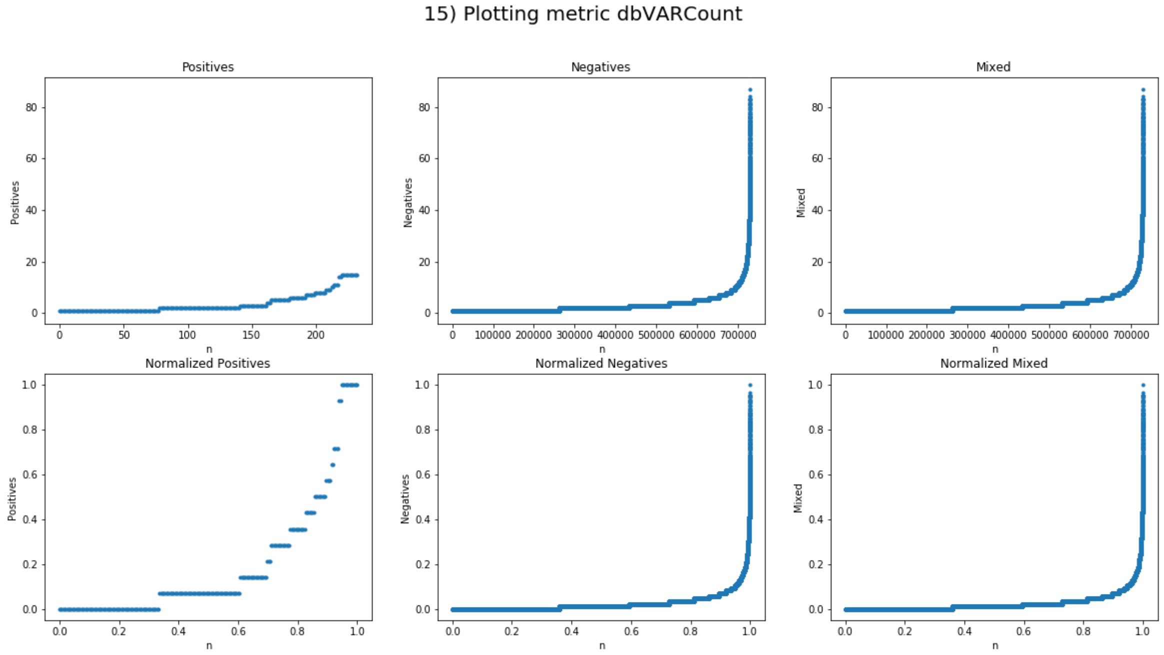


Figura 4.3: Values of metric dbVARCount

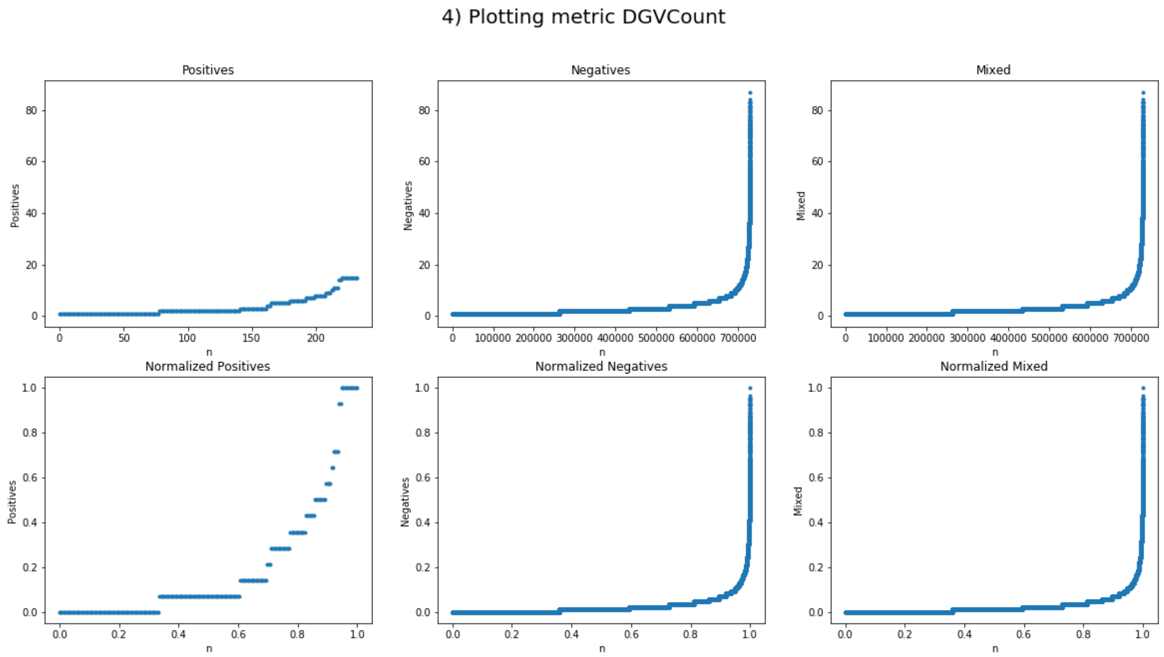


Figura 4.4: Values of metric DGVCount

The two metrics seem **highly** correlated, if not the **same metric**. This means that one of the two could be removed from the dataset, as it does not add any useful information.

4.2.2 mamPhyloP46way and verPhyloP46way

There is a some correlation between this two metrics: let's look again at the data plots to see if they follow a similar trend:

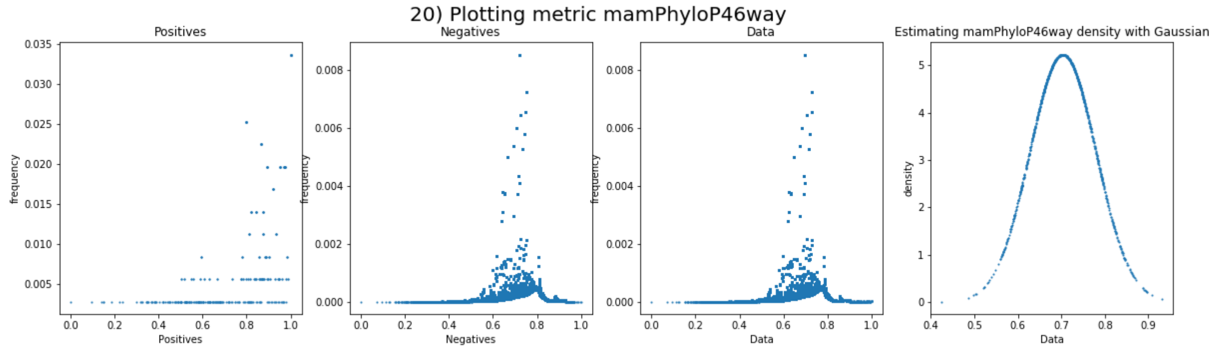


Figura 4.5: Sampling distribution of metric mamPhyloP46way

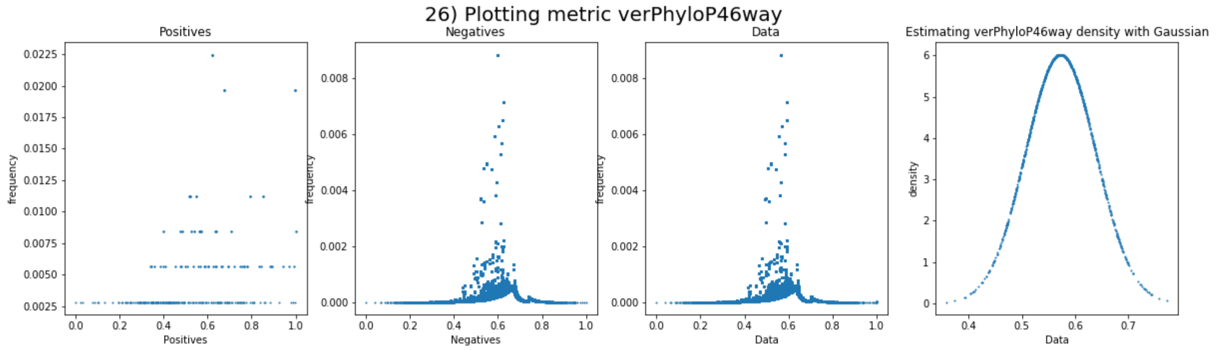


Figura 4.6: Sampling distribution of metric verPhyloP46way

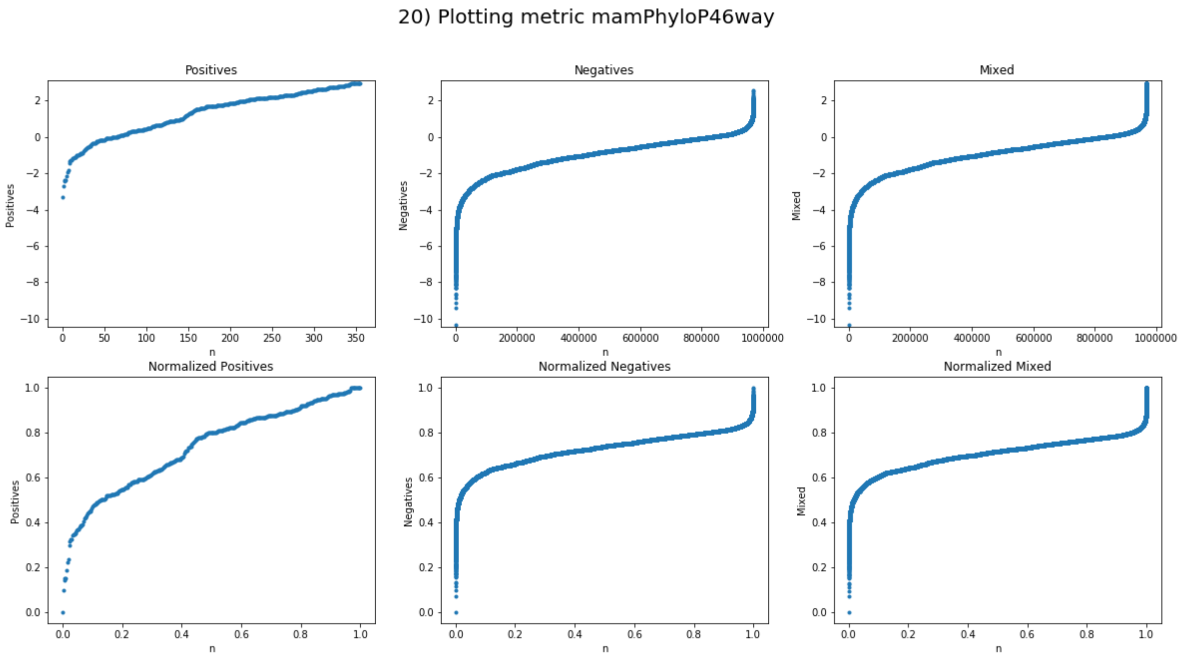


Figura 4.7: Values of metric mamPhyloP46way

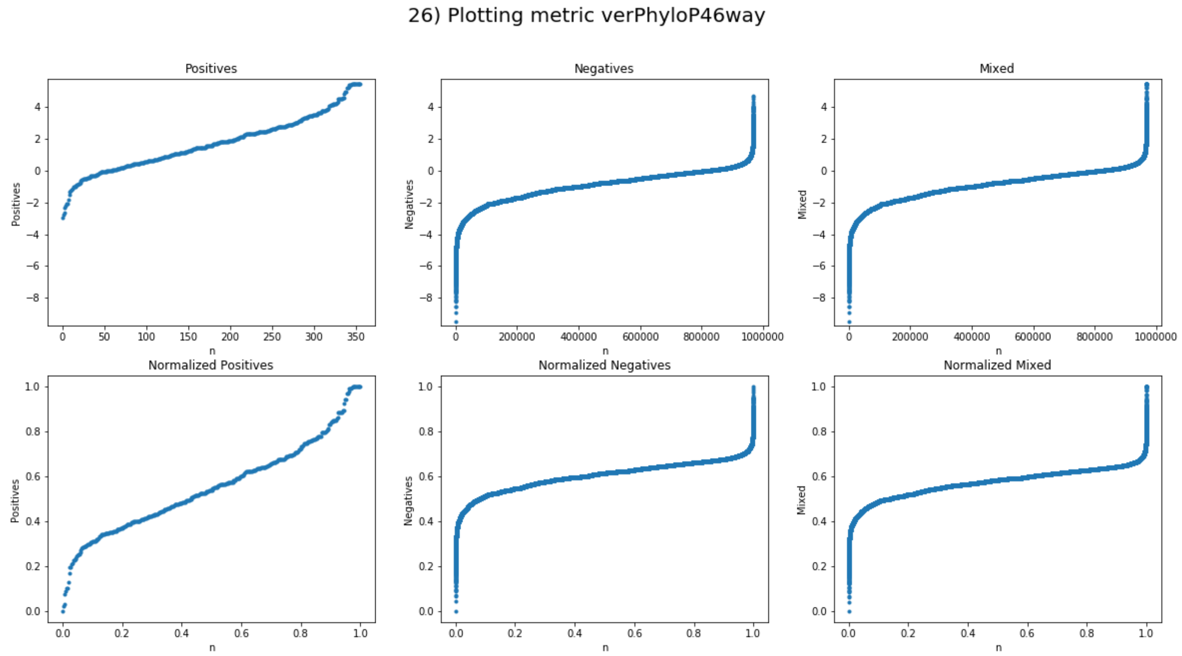


Figura 4.8: Values of metric verPhyloP46way

The two metrics seem **slightly** correlated, but not enough to consider removing one of the two.

Parte II

Theory

5
Input modelling

5.1 Input values

The values used for each metric are the 3 following:

5.1.1 Normalized metric

Clearly one of the important metrics is the metric itself, that will be normalized to allow for input in $[0,1]$ range:

$$\text{metric}' = \frac{\text{metric} - \min\{\text{metric values}\}}{\max\{\text{metric values}\} - \min\{\text{metric values}\}}$$

Figura 5.1: Input normalization to $[0,1]$ range

5.1.2 Rarity

Another value we will be using in the input layer of the network is the rarity of the metric value, modelled as the surprise value of the estimated sampling distribution of the metric:

If M is the estimated metric distribution cumulative distribution function (CDF), m is the value assumed by the metric in the given data point and ϵ is a range, we can model **rarity** as follows:

$$\mathbb{P}(m-\epsilon \leqslant X \leqslant m+\epsilon) = M(m+\epsilon) - M(m-\epsilon) \qquad \text{rarity}(m) = 1 - \mathbb{P}(m-\epsilon \leqslant X \leqslant m+\epsilon)$$

Figura 5.2: Rarity

5.1.3 Entropy

The third and final value used will be **entropy**, obtained using the estimated metric probability:

$$H(x) = -\mathbb{P}(m-\epsilon \leqslant X \leqslant m+\epsilon)\log\mathbb{P}(m-\epsilon \leqslant X \leqslant m+\epsilon)$$

Figura 5.3: Entropy

5.2 Feet

The input layer is comprised of 25 (number of metrics, excluded the one recognized to be in strong correlation to another) *feet*, meaning tiny networks that are used to limit the initial linear combination of the metric input values to themselves.

Each feet is modelled as a locally connected dense layer, with a window of 3 neurons.

5.3 Oversampling of positives

Since the positive values are just the 0.036% of the dataset we'll oversample these to weight more these values. Since the variance of positive data points is too high to extrapolate a distribution to generate significant new fuzzy data points, simple duplication will be used.

5.4 Undersampling of negatives

Since the negative values are more than the 99.96% of the dataset we'll undersample these to weight less these values.

5.5 Oversampling and undersampling targets

Oversampling and undersampling target will be to have a training dataset with 1% of positives and 99% of negatives.

5.6 Absence of information

Absence of information about a given metric will be modelled as **zeros**, meaning all values relative to the given absent metric for that data point will be treated as zero.

6

Output modelling

The output layer of the neural network is modelled by **two** neurons, one representing the positive class and one the negative class, with a **sigmoid** as activation function.

7

Weight initialization

7.1 Weight distribution based on input distribution

Since input values are not from any particular distribution or hold properties such as $\mathbb{E}(X) = 0$ or $\mathrm{Var}(X) = 1$ (in some metrics mean and variance are far from these values) they do not suggest to use any specific distribution.

7.2 Weight distribution based on activation functions and regularization layers

The codomain values from the activation functions, being SELU for most of the network, tend to hold the properties of $\mathbb{E}(X) = 0$ and $\mathrm{Var}(X) = 1$ (http://arxiv.org/abs/1706.02515). These values are then regularized to penalize extreme weights that may appear when variance starts with a value significantly away from 1.

For these properties weight will be initialized by extracting them from a Gaussian with $\mathbb{E}(X) = 0$ and $\mathrm{Var}(X) = 1$.

8

Locally connected dense layers

The first two layers will be locally connected dense layers, to exploit the positional information of the input values.

Other than the group of triples, input will be sorted by distribution kind so that the initial interpolations happen mostly with data from the same distribution family.

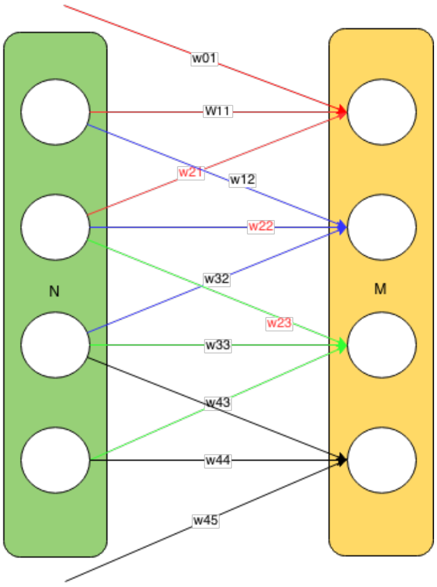


Figura 8.1: Locally connected layer

8.1 Activation function

We'll be using a **leaky relu** for the locally connected dense layers with $\alpha = 0.3$.

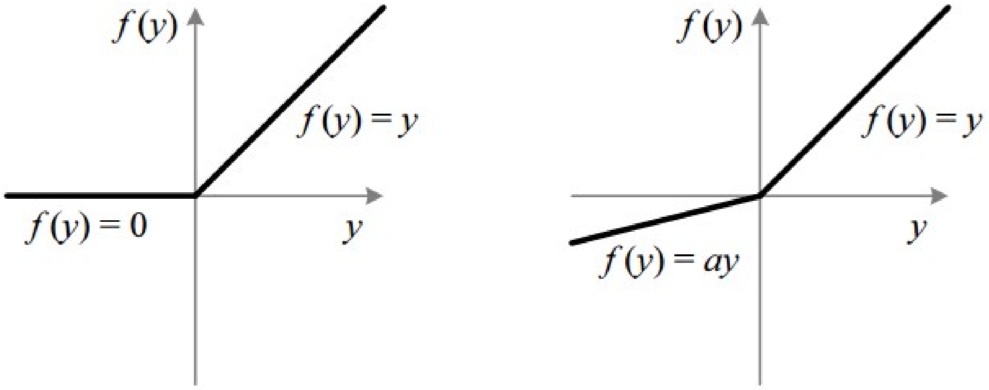


Figura 8.2: RELU and Leaky RELU

9 Dense layers

For the following hidden layers we will be using dense connected layers, with a piramidal structure (reducing the number of the neurons from 26 to 2).

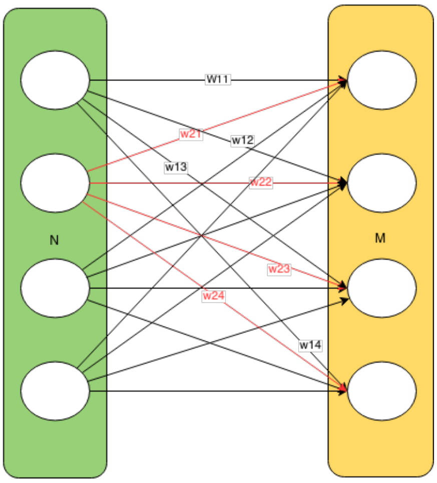


Figura 9.1: Dense connected layer

9.1 Activation function

We'll be using again **leaky relu** and experimenting with **SELU** for the dense layers:

$$\operatorname{selu}(x) = \lambda \begin{cases} x & x > 0 \\ \alpha e^{x} - \alpha & x \leqslant 0 \end{cases}$$

Figura 9.2: SELU

9.2 Regularization

Regularization layers will be alternated to the dense layers to penalize weight extreme growth.

9.3 Drop out

In addition to regularization, also **drop out** of 10% of neurons per hidden layer will be applied.

10 References

LatexTools does not compile references at this time.