ÉCOLE POLYTECHNIQUE
FÉDÉRALE DE LAUSANNE

An algorithm for spatio-temporal clustering of genes along the chromosomes

EPFL Bachelor Project – Computer Science – Spring 2016

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Lab : Computational Systems Biology Lab (Felix Naef)

Why are we doing this research

Goals of the research

01

One:
Genes are placed in a fixed order along the chromosomes. The role of this specific positioning, if any, **is yet to be understood**

02

Two:
Are genes placed in **clusters following the same temporal pattern** along the chromosomes ?

03

Three:
If they are, would it suggest a **functional role or evolutionary advantage of the specific positioning** of genes along a chromosome

The idea

Partitioning algorithm

- How to identify the clusters and partition the genes efficiently ?
- From an O(2^{n-1}) problem to an O(N^2) using dynamic programming
- Example, if n = 1140.
  - Naïve approach : 7.46×10^{342} operations (not computable)
  - Dynamic approach : 1.3×10^{6} operations

Simple example

Partitioning algorithm

- A length **n** of a metal rod. Example for n = 4. So 2^{4-1} = 8 possible solutions
- A table of prices p_i for rods of lengths **i** = 1,. . .,n

Simple example

Partitioning algorithm

- A length n of a metal rod. Example for n = 4. So 2^3 = 8 possible solutions
- A table of prices p_i for rods of lengths i = 1,. . .,n

length i	1	2	3	4
price p_i	1	5	8	9

Simple example

Partitioning algorithm

- A length n of a metal rod. Example for n = 4. So 2^3 = 8 possible solutions
- A table of prices p_i for rods of lengths i = 1,. . .,n

length i	1	2	3	4
price p_i	1	5	8	9

- Objective : Decide how to cut the rod into pieces and maximize / minimize the price.

Simple example

Partitioning algorithm

- A length n of a metal rod. Example for n = 4. So 2^3 = 8 possible solutions
- A table of prices p_i for rods of lengths i = 1,. . .,n

length i	1	2	3	4
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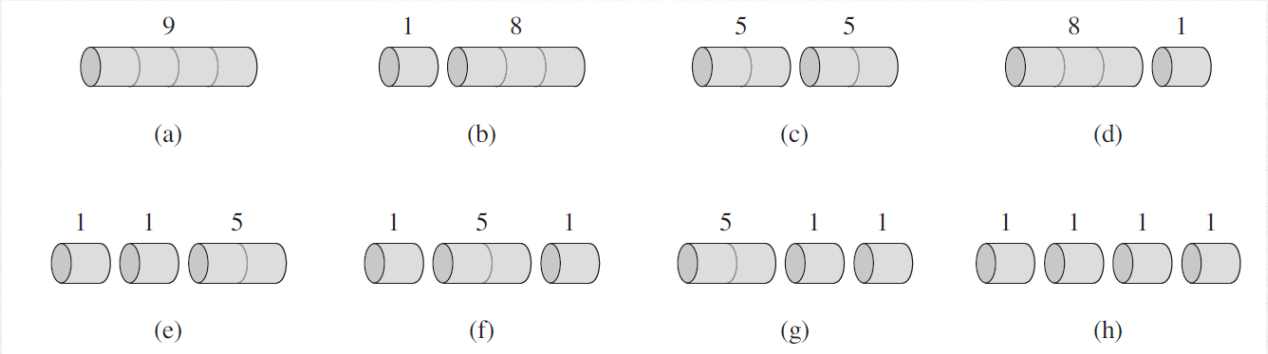

The data

RNA-Seq data

- Reveals the presence and quantity of RNA in a sample at a given moment in time
- We can identify changes in gene expression and partition the genome according to the way genes fit different models.

The data

RNA-Seq data : Sorted and filtered

- **Matrix** : Columns are genes and rows are time point measures (24 time points)

	AI838599	Gm11787	Tmem68	Tgs1	Lyn	Rps20	Plag1	Chchd7	Sdr16c5	Impad1
ZT_0_1_exon	-2.900021	-2.1866640	1.482505	1.703562	3.346512	4.028217	-2.595579	1.265885	-1.427024	3.306969
ZT_2_1_exon	-2.147666	-1.3974544	1.384402	1.742595	3.233279	3.980873	-2.763773	1.706167	-2.078519	3.251865
ZT_4_1_exon	-3.723140	-1.2730027	1.336116	1.667629	3.456569	3.989345	-3.129129	1.470803	-2.275023	3.472580
ZT_6_1_exon	-2.550986	-1.7673547	1.650827	1.780649	3.201119	4.058997	-2.771035	1.678928	-1.844185	3.514598
ZT_8_1_exon	-2.358189	-1.2414010	1.689454	1.760129	3.500712	4.044151	-3.068381	1.708180	-3.042665	3.672099
ZT_10_1_exon	-1.770339	-1.2246844	1.659832	1.981001	3.511658	4.023518	-2.739488	1.966097	-2.085763	3.673638
ZT_12_1_exon	-2.567874	-0.9173816	1.613619	1.890222	3.843681	4.233419	-2.757533	2.092891	-3.130181	3.546923
ZT_14_1_exon	-1.916705	-1.1619536	1.551675	1.805628	3.499936	4.274861	-2.667339	2.152064	-2.103284	3.307825
ZT_16_1_exon	-2.140111	-1.1703514	1.182650	2.001469	3.660696	4.125828	-2.618715	1.822264	-2.746438	3.135911
ZT_18_1_exon	-3.234543	-1.2538391	1.195542	2.058232	3.622647	4.072459	-2.653260	1.628464	-2.784652	3.213773
ZT_20_1_exon	-2.754052	-1.4439207	1.306815	1.805679	3.646546	4.243151	-2.923009	1.322040	-2.029528	3.169621
ZT_22_1_exon	-2.977634	-1.4700764	1.558112	2.019093	3.618602	4.155664	-3.234761	1.467683	-3.131982	3.492495
ZT_0_2_exon	-2.708496	-1.4014085	1.303440	1.664715	3.436299	3.989970	-2.495194	1.665081	-1.605206	3.257282
ZT_2_2_exon	-3.427011	-2.3605478	1.149422	1.506327	3.373362	4.069581	-2.603078	1.584595	-3.493889	3.348353
ZT_4_2_exon	-2.893104	-1.8023181	1.436354	1.783920	3.332191	3.917535	-2.553024	1.598997	-2.528754	3.407981
ZT_6_2_exon	-2.342655	-0.9122524	1.457620	1.688068	3.266939	4.170368	-2.976327	1.667599	-2.990295	3.560779
ZT_8_2_exon	-1.937925	-1.3376977	1.617867	1.947277	3.335588	3.929372	-2.795060	1.742269	-2.527433	3.558703
ZT_10_2_exon	-2.078174	-2.2166813	1.476735	2.012728	3.327091	3.937200	-2.689005	1.917529	-2.503246	3.540805
ZT_12_2_exon	-2.479944	-2.1153123	1.328514	1.898995	3.247362	4.045817	-2.718828	1.990023	-2.547354	3.362967
ZT_14_2_exon	-2.533102	-1.0033291	1.406451	2.006347	3.292311	4.148814	-2.533223	1.903101	-1.218718	3.278278
ZT_16_2_exon	-2.785418	-1.4341554	1.153439	1.907564	3.613436	4.171117	-2.812031	1.845097	-2.174865	3.133933
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ZT_22_2_exon	-2.886415	-1.6533395	1.314752	1.975699	3.539485	3.966283	-2.675430	1.531419	-2.124065	3.221432

>

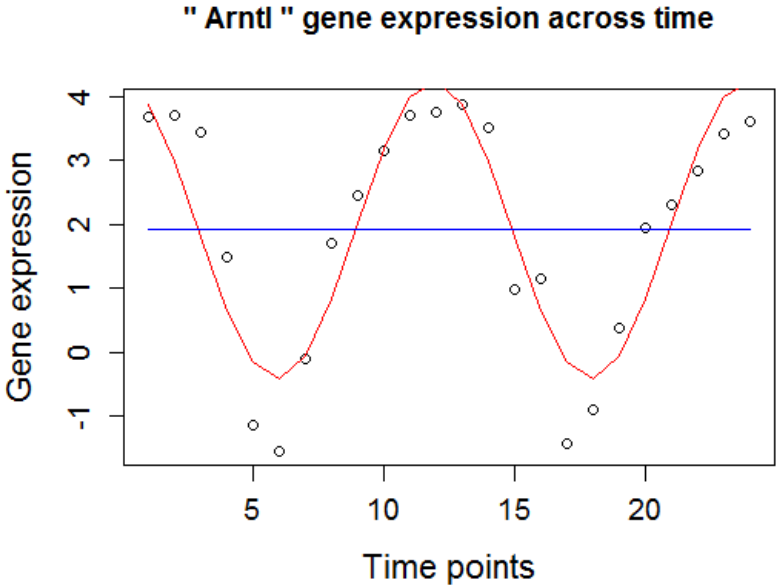
The data

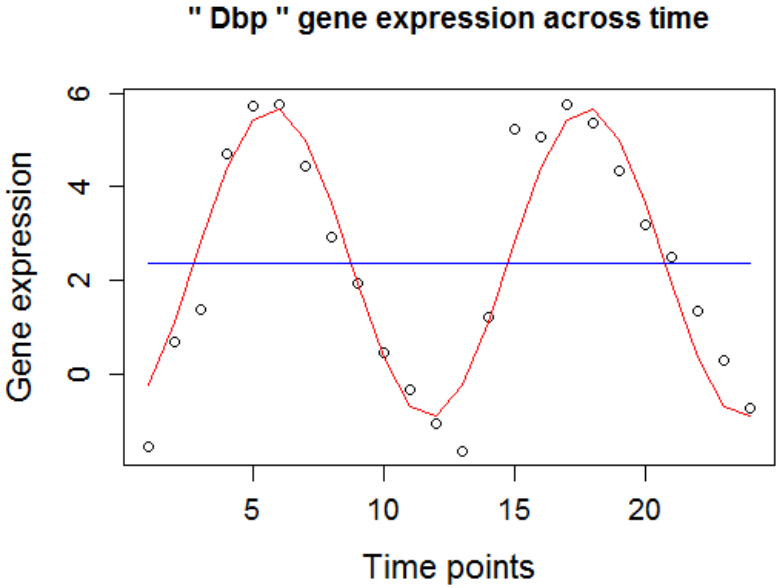
Models

- Two different models, a **flat model** and a **rhythmic (circadian) model**
- The flat model is preferred for noisy genes, the circadian model for rhythmic genes.
- Flat model : $\hat{Y} = \boldsymbol{temporal\ mean}$
- Circadian model : $\hat{Y} = \mathbf{temporal\ mean} + (\alpha \sin(2\pi f) + \beta \cos(2\pi f))$

The data

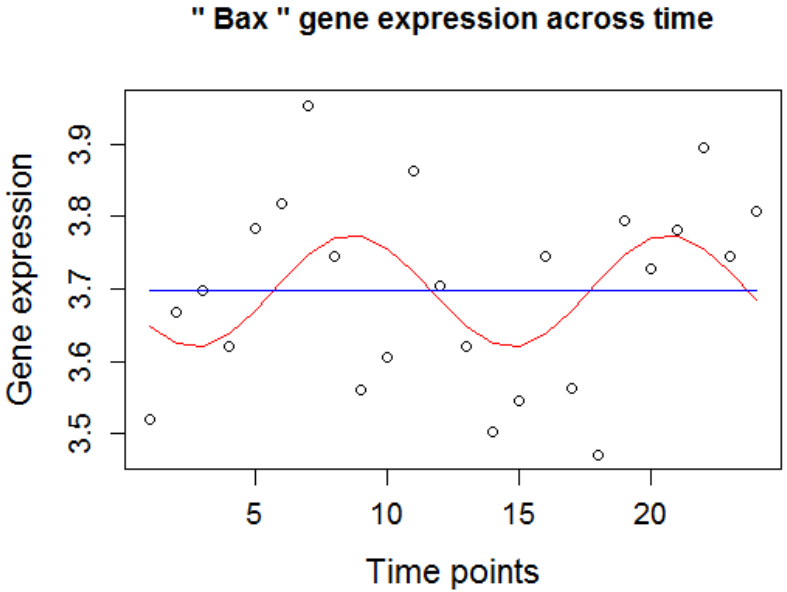
Gene expression and model fitting

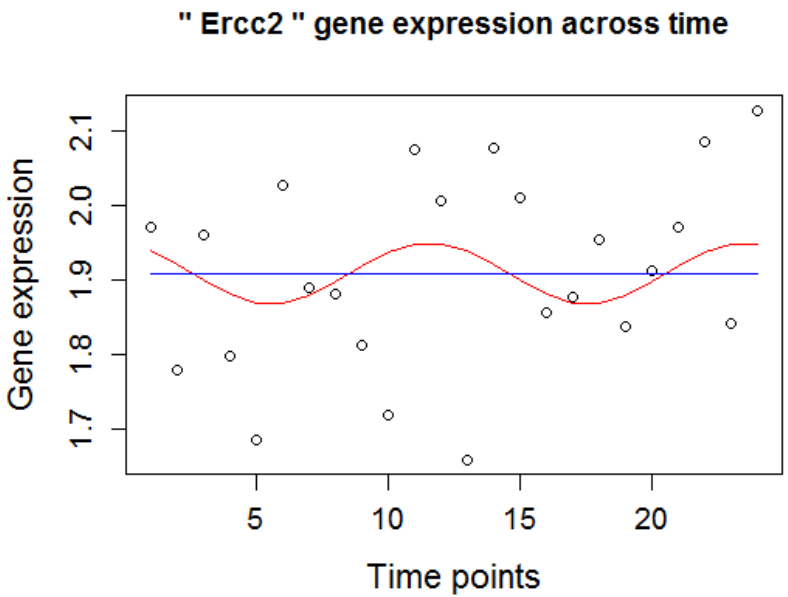




The data

Gene expression and model fitting





Real partitioning

Partitioning algorithm

We are actually doing quite the same than the rod cutting with our RNA-Seq data

- Where **n** is the number of genes of a chromosome we want to partition
- We try to minimize the score instead of maximizing it

What is the equivalent to the **prices** of the rod cutting algorithm ?

Real partitioning

Model selection

- The «price» is computed for each block of genes by :
- $\mathbf{min}\{score\ of\ flat\ model,\ score\ of\ circadian\ model\}$

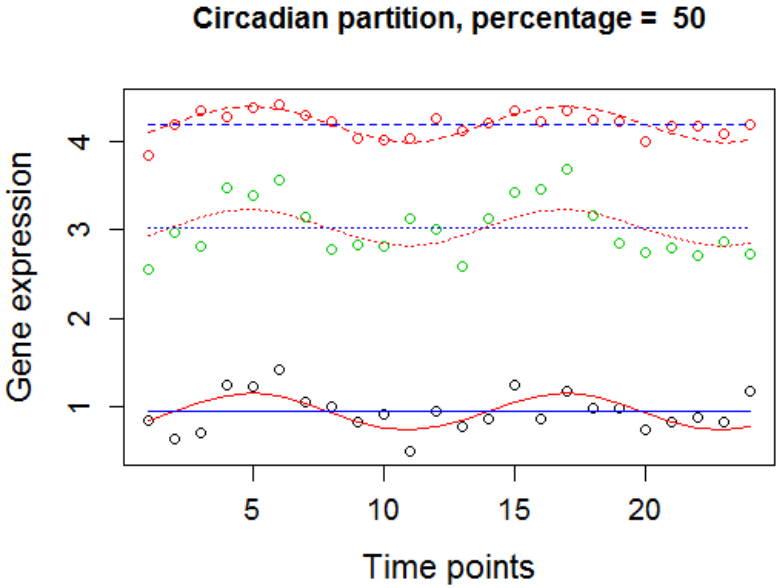
- Where the score is : the residue (square of the errors) + a penalty.

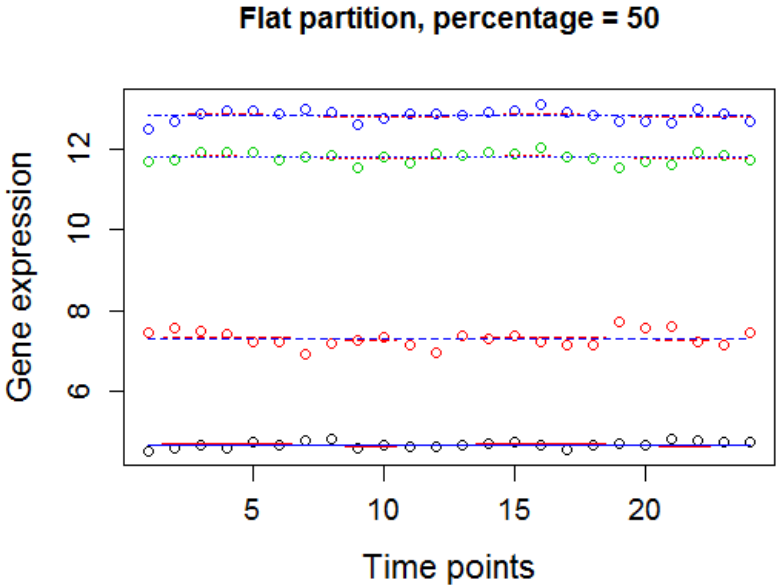
- Model 1 is the flat model and model 2 is a circadian (rhythmic model) :

- **Residue** of a block : $\sum_{i=1}^{n}(M_i - \hat{Y}_{ji})^2$,
  for j = 1, 2 (for model 1 and 2), M is the RNA-Seq matrix and $\hat{Y}_j$ is the predictor matrix

The data

Gene expression and model fitting for blocks of genes

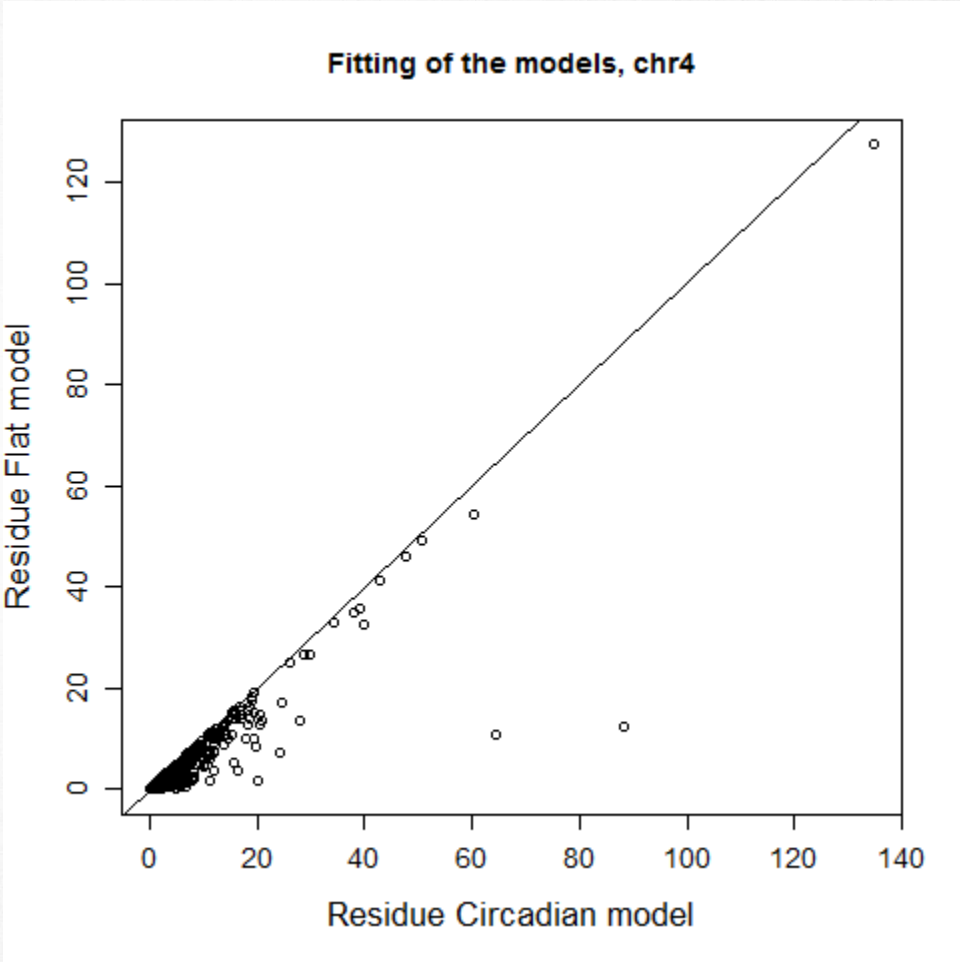




Real partitioning

Model selection

Circadian model (residues) fits the data at least as good as the flat model !



Real partitioning

Model selection

- Have to introduce a penalty : Score = residue + penalty
- First attempt : Bayesian information criterion
- $BIC = residue + \sigma^2 \times k \log(n)$,
  where **k** is the number of parameters and **n** is the number of data points inside the considered block and σ a customizable value.
- Problem : Not additive. The algorithm takes advantage of the principle of optimality : For each j, $1 \leq j \leq n$, the fitness function is the fitness of the optimal subpartition prior to j + the fitness of the last block itself.
- We need to conserve this additivity for the penalty as well.

Real partitioning

Model selection

- Have to introduce a penalty : Score = residue + penalty
- Second attempt
- Penalty = $residue + \sigma^2 \times (k+1) \times \log(N)$,
  Where k is the number of parameters, N the total number of data points and σ a customizable value.
- Problem : Solves additive issue of BIC
- Full penalty : $(\sum(k_b + 1)) \times \log(N)$

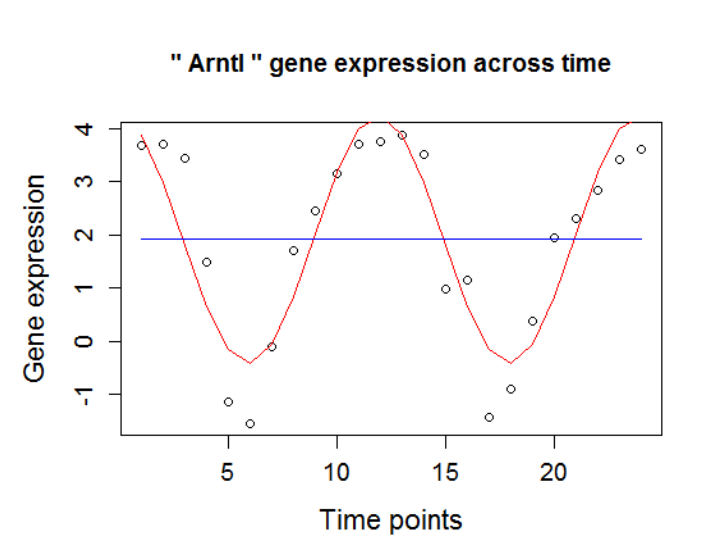
Real partitioning

Model selection

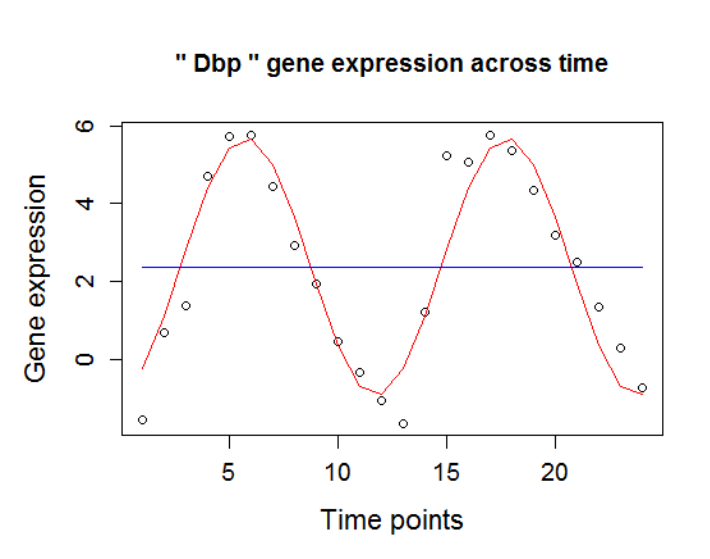
- Have to introduce a penalty : Score = residue + penalty
- Second attempt
- Penalty = $residue + \sigma^2 \times (k+1) \times \log(N)$,
  Where **k** is the number of parameters, **N** the total number of data points and σ a customizable value.
- **Why + 1 ?** We add a value in order to differentiate a same block of genes containing X genes with different blocks containing the same X genes.
- To avoid having both blocks having the same penalty.
- We chose to add 1, but it could have been any other positive value.

The data

Gene expression and model fitting



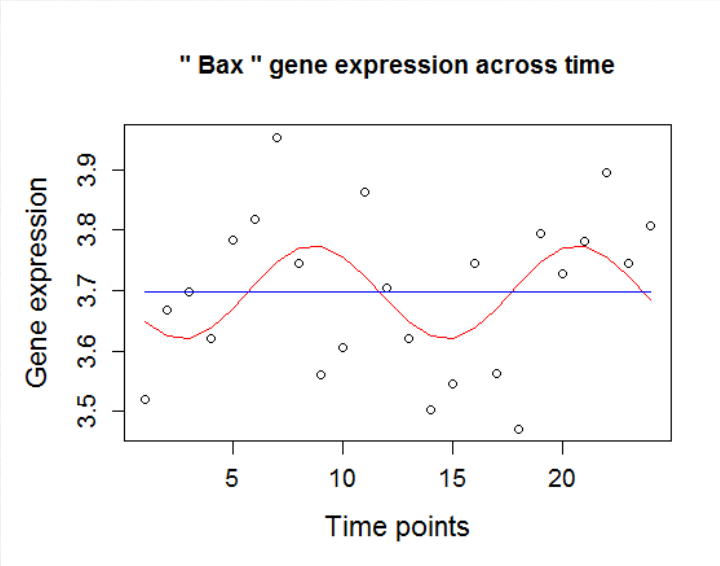
Flat score = 79 / Circadian score = 14.81



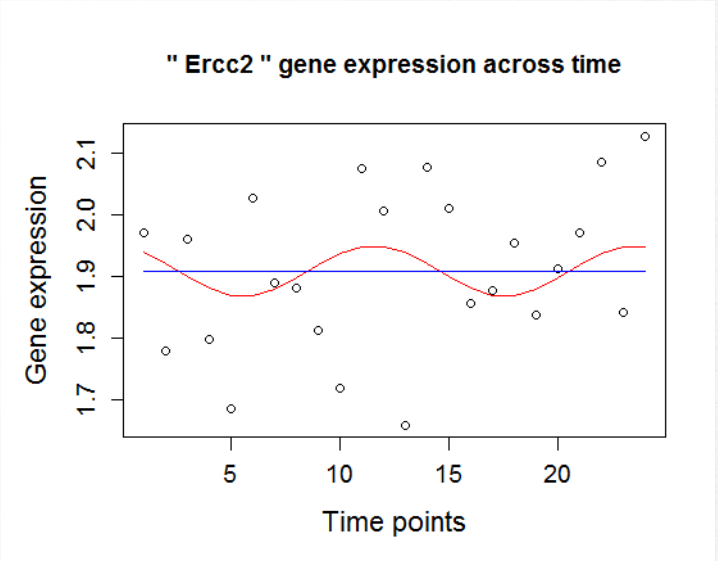
Flat score = 149.1 / Circadian score = 18.63

The data

Gene expression and model fitting



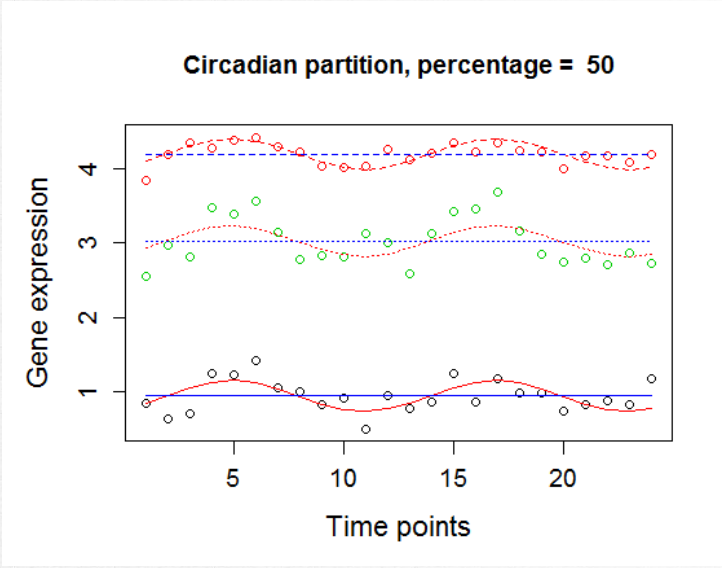
Flat score = 1.39/ Circadian score = 2.31



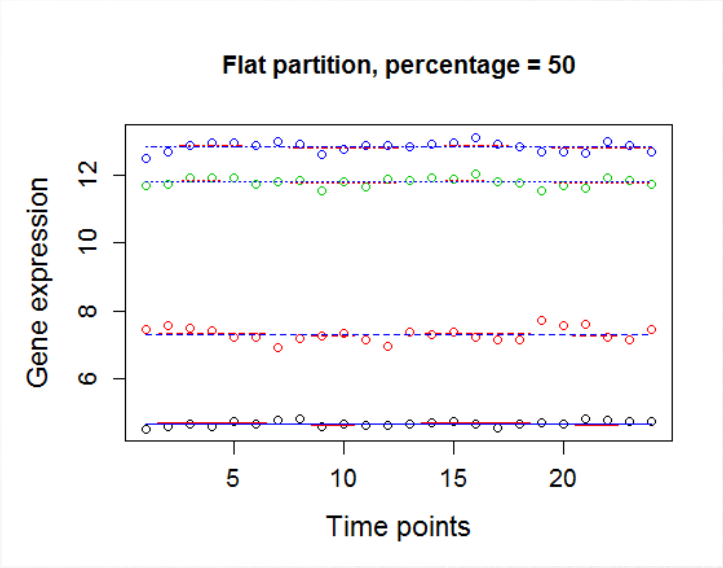
Flat score = 1.38 / Circadian score = 2.35

The data

Gene expression and model fitting for blocks of genes



Flat score = 6.01 / Circadian score = 5.47



Flat score = 4.37 / Circadian score = 5.3

Real partitioning

Model selection

- Instead of using an abstract sigma value, we transformed the definition of sigma to the **a priori percentage of the rythmic genes**

Real partitioning

Model selection

- Instead of using an abstract sigma value, we transformed the definition of sigma to the **a priori percentage of the rythmic genes**

- In order for the circadian model to be chosen over the flat model we need :
- $res.2 + \sigma^2(m + 2 + 1)\log(N) < res.1 + \sigma^2(m + 1)\log(N)$

Real partitioning

Model selection

- Instead of using an abstract sigma value, we transformed the definition of sigma to the **a priori percentage of the rythmic genes**

- In order for the circadian model to be chosen over the flat model we need :
- $res.2 + \sigma^2(m+2+1)\log(N) < res.1 + \sigma^2(m+1)\log(N)$, where m is the number of genes in the considered block

- Through simple calculations, we obtain :
- $res.1 - res.2 > 2\sigma^2\log(N)$

Real partitioning

Model selection

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- $res.2 + \sigma^2(m + 2 + 1)\log(N) < res.1 + \sigma^2(m + 1)\log(N)$

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- $cuttof > 2\sigma^2 \log(N)$

Real partitioning

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- In order for the circadian model to be chosen over the flat model we need :
- $res.2 + \sigma^2(m+2+1)\log(N) < res.1 + \sigma^2(m+1)\log(N)$

- Through simple calculations, we obtain :
- $cuttof > 2\sigma^2\log(N)$

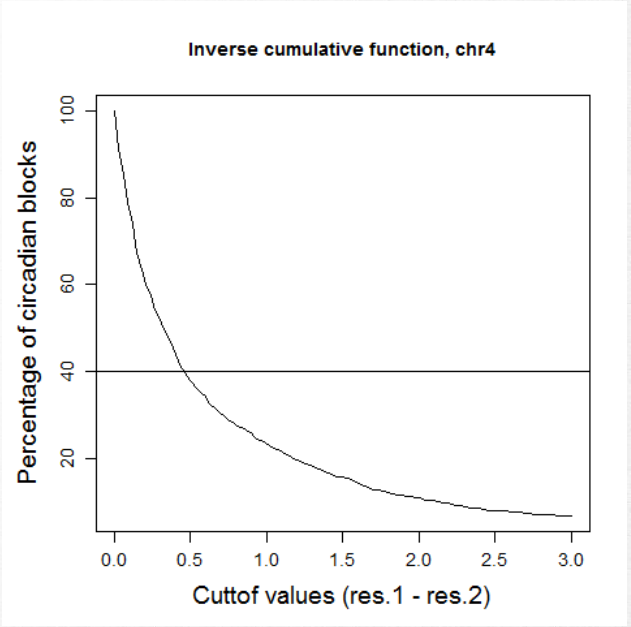
- So we find the value of sigma squared as : $\sigma^2 = \frac{cuttof}{2\log(N)}$

Real partitioning

Model selection

- Instead of using an abstract sigma value, we compute a value of sigma given **the percentage of expected circadian genes**

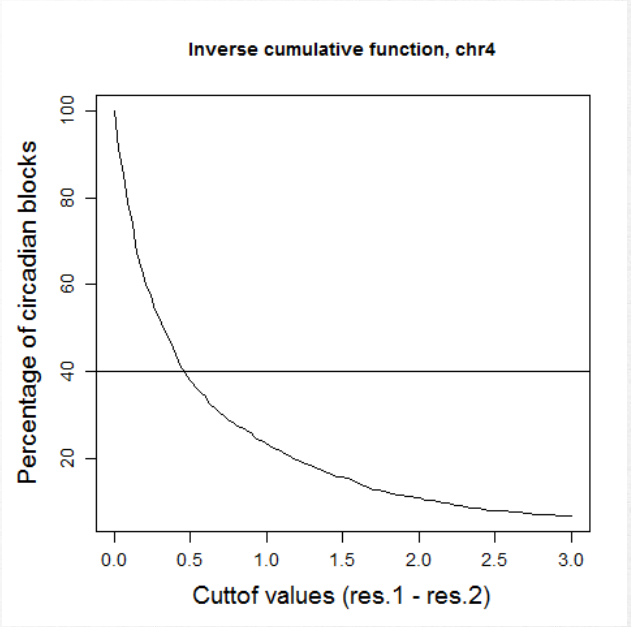
- We use the inverse cumulative function to find it :



Real partitioning

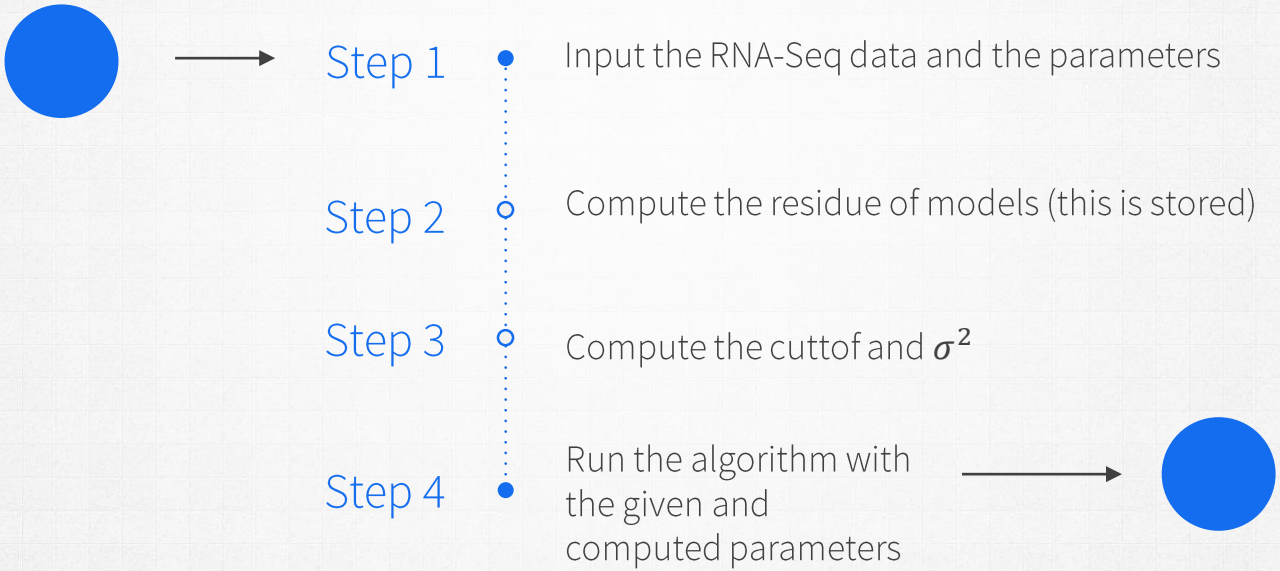
Model selection

- Instead of using an abstract sigma value, we compute a value of sigma given **the percentage of expected circadian genes**
- We use the inverse cumulative function to find it :
- **Cuttof for a percentage of 40%** = 0.4621029
- $\sigma^2 = {}^{cuttof}/_{2\ \log(N)}$ = 0.02289724



Complete algorithm

Pipeline of computation



Complete algorithm

Pipeline of computation

Github repository

Results

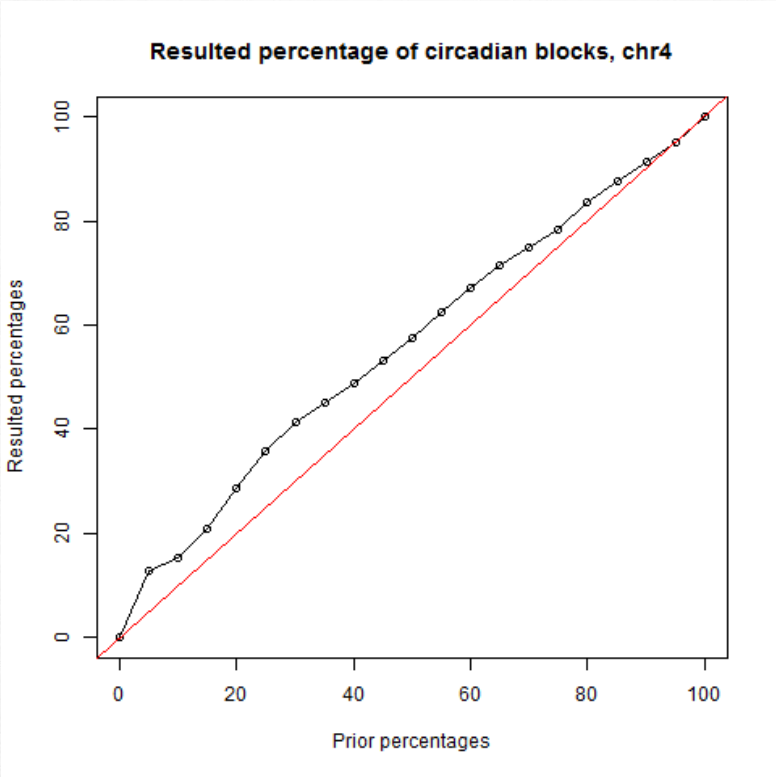
Do clusters of genes actually exist ?

- We ran the algorithm for chromosomes with randomly permuted genes
- 50 times each

- Comparison of sizes of circadian partitions

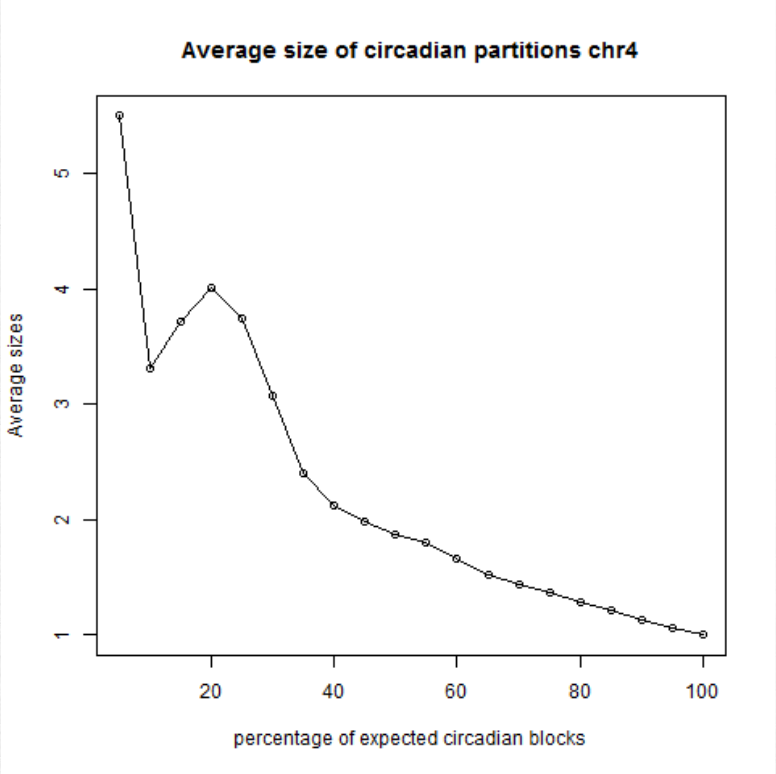
Results

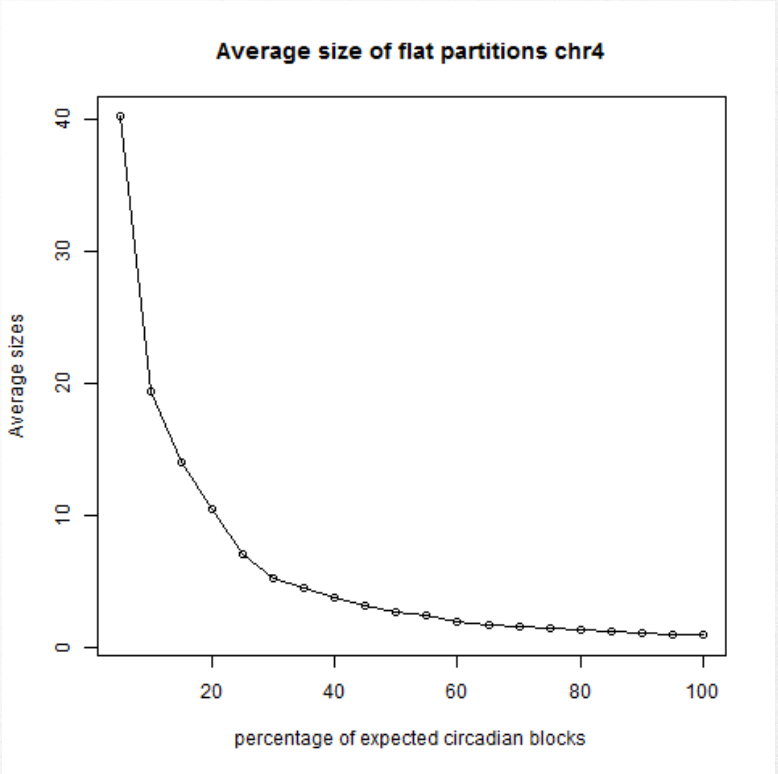
Resulted percentages of circadian blocks



Results

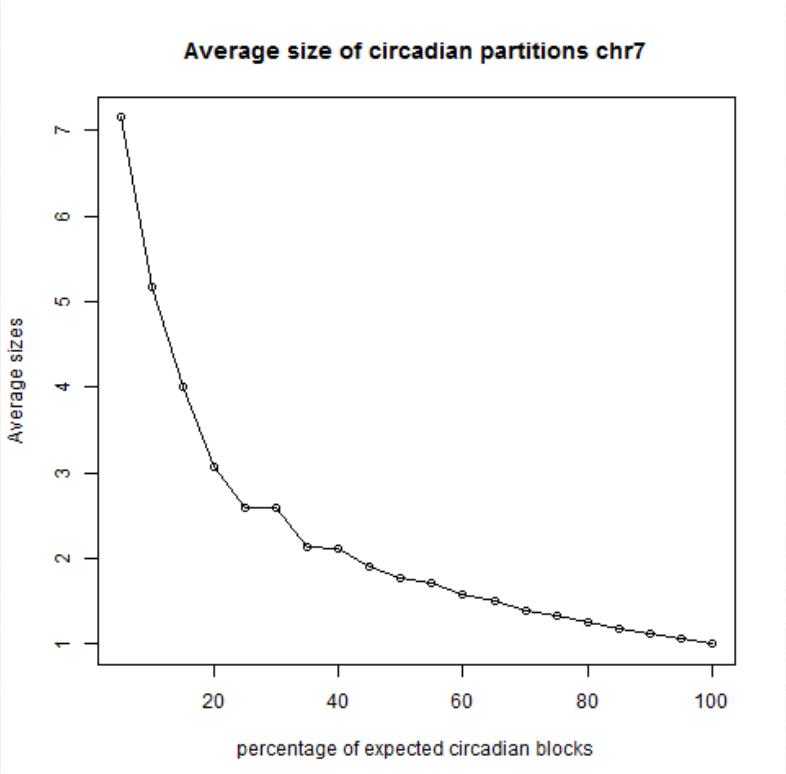
Average size of partitions

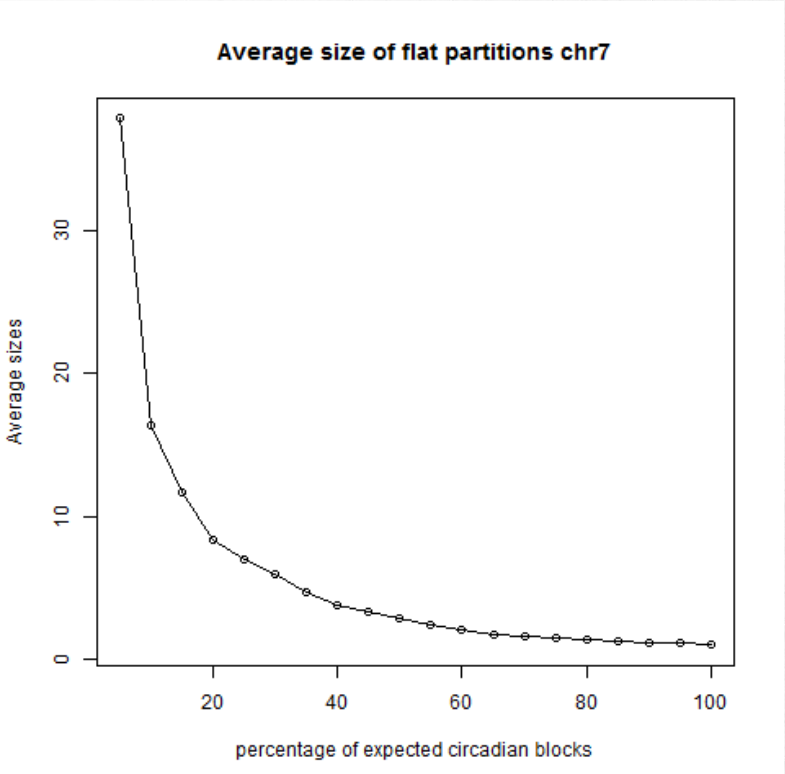




Results

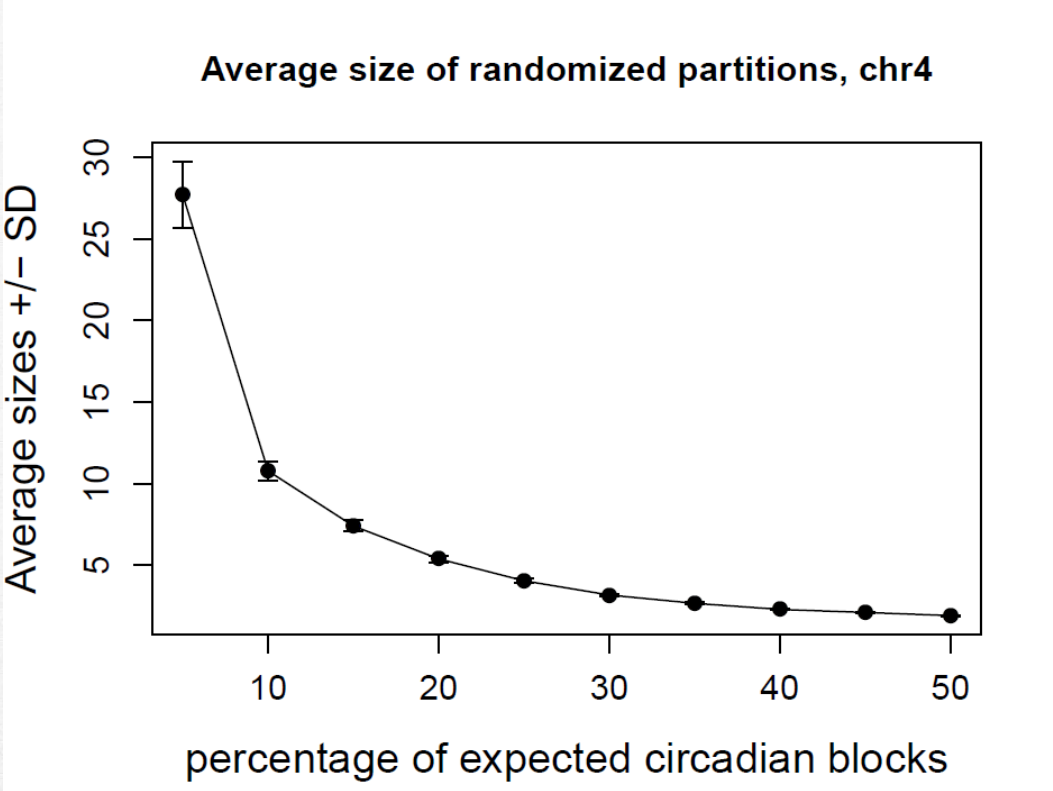
Average size of partitions





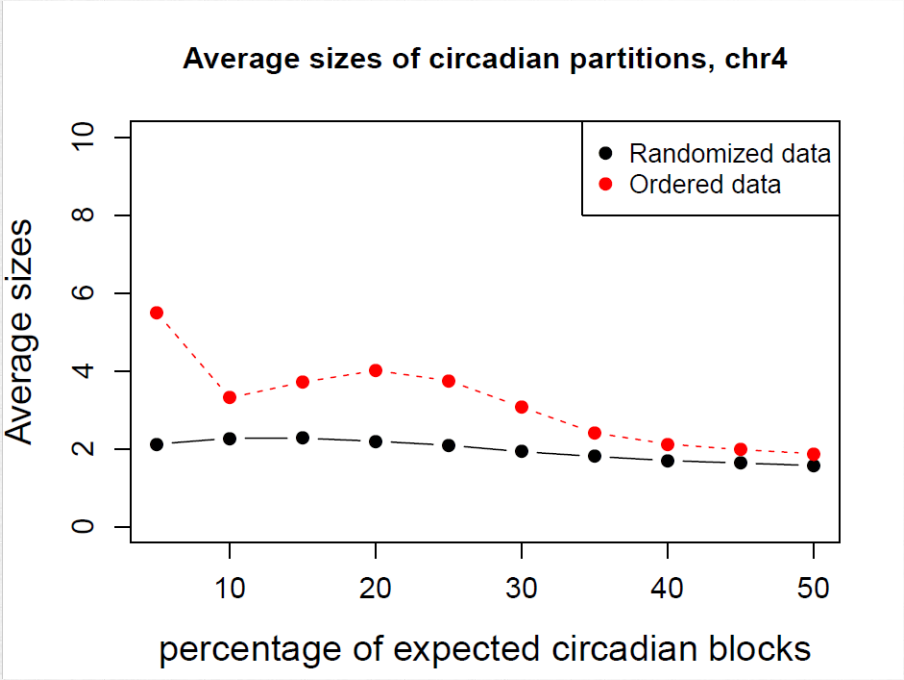
Results

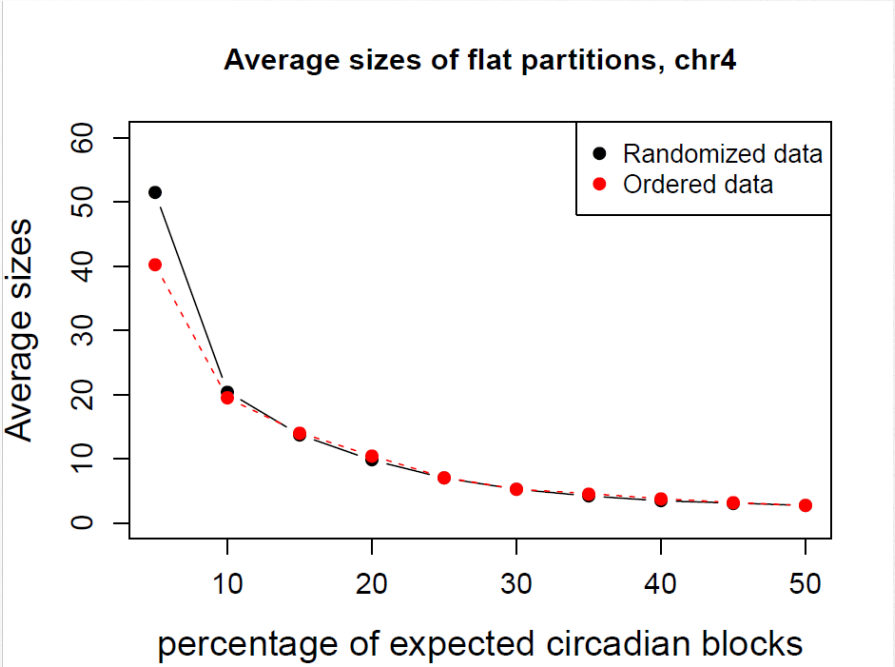
Average size of randomized partitions with error bars



Results

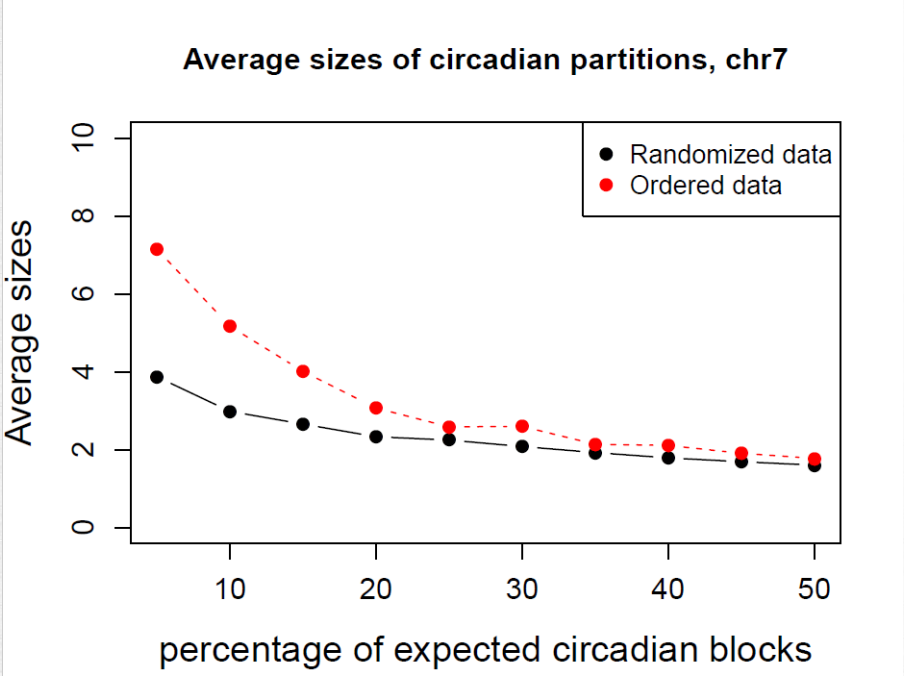
Average size of randomized partitions

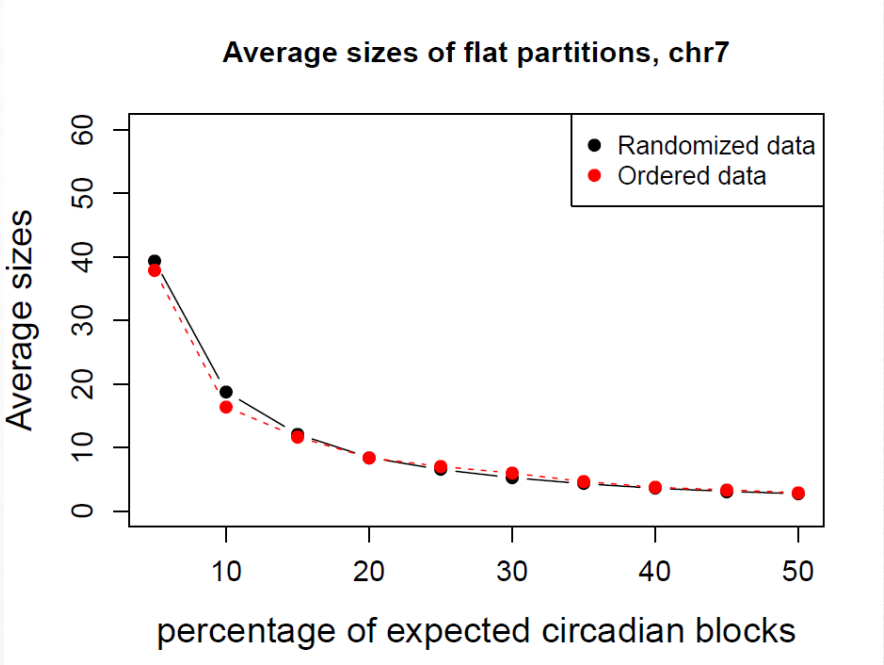




Results

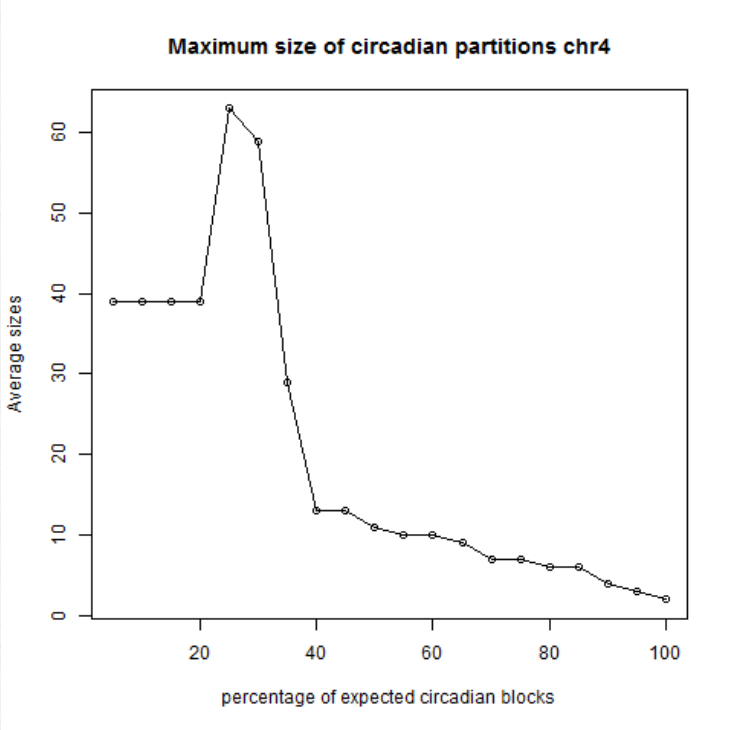
Average size of randomized partitions

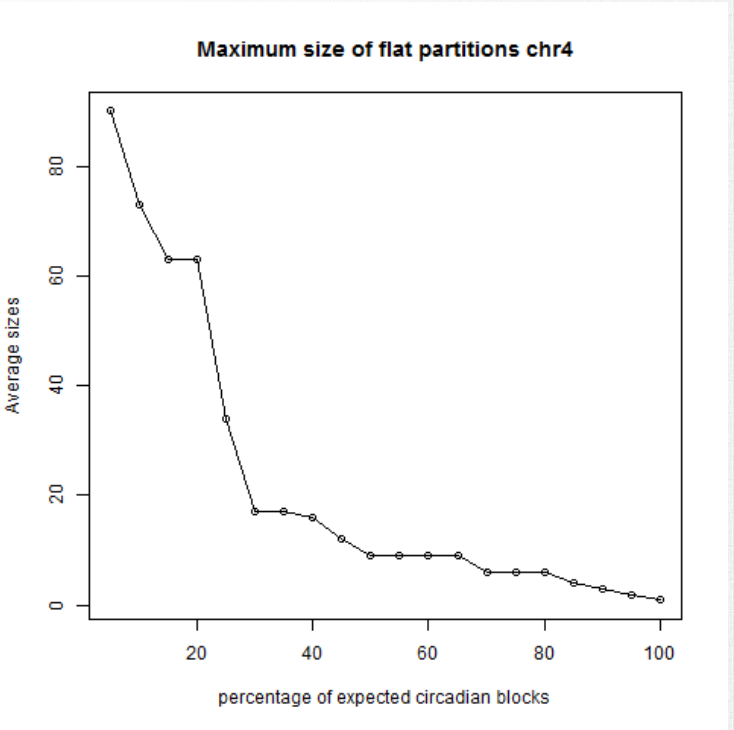




Results

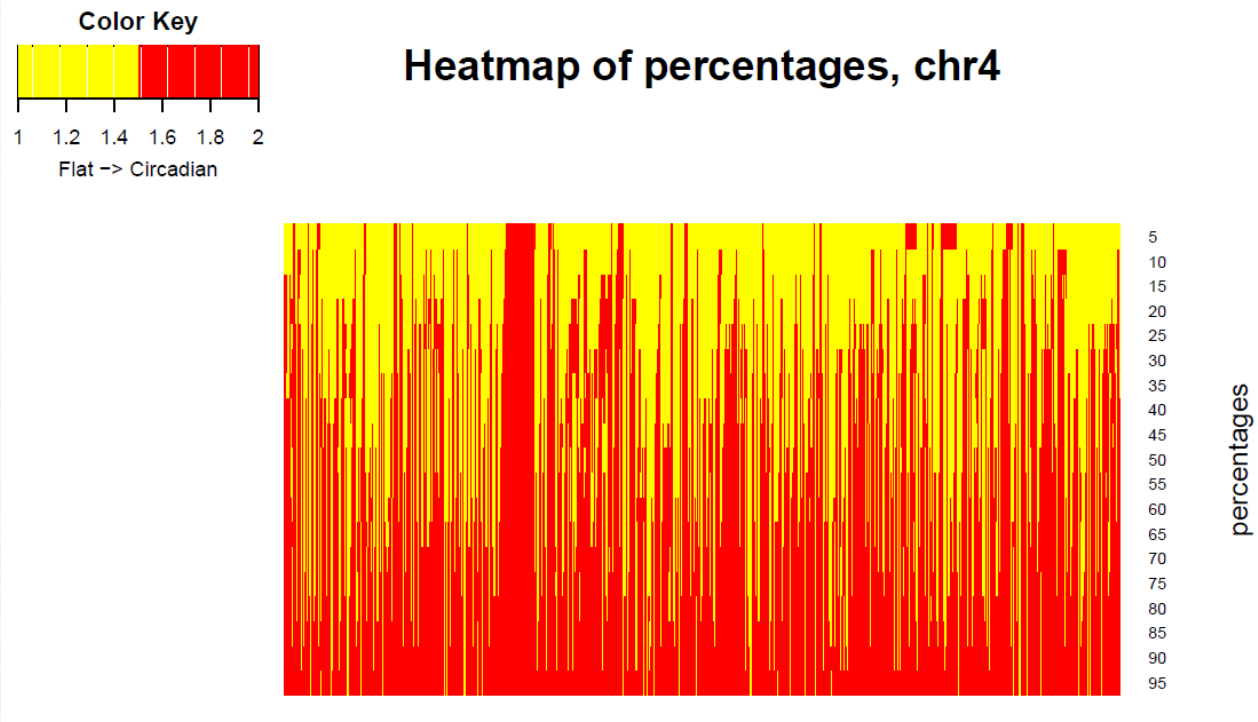
Maximum sizes of partitions





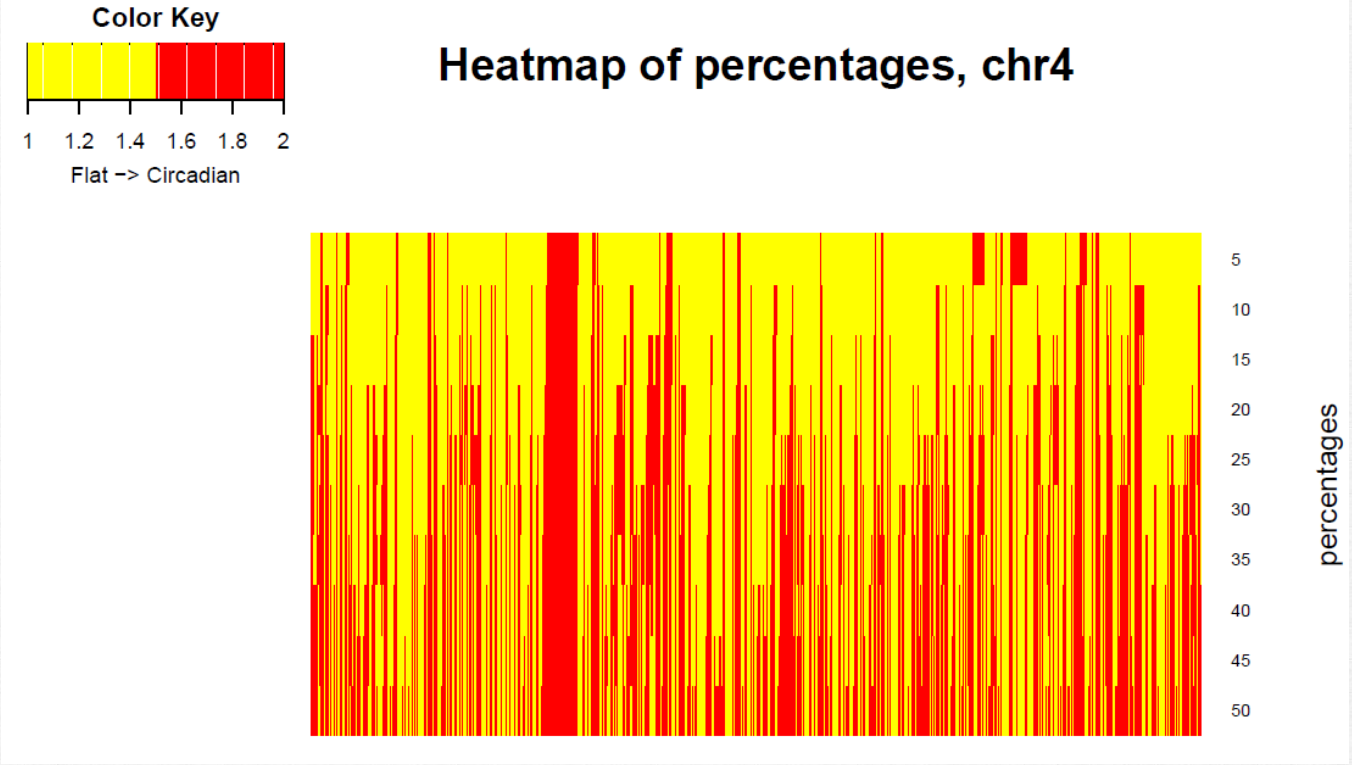
Results

Heatmap percentages 5 to 95



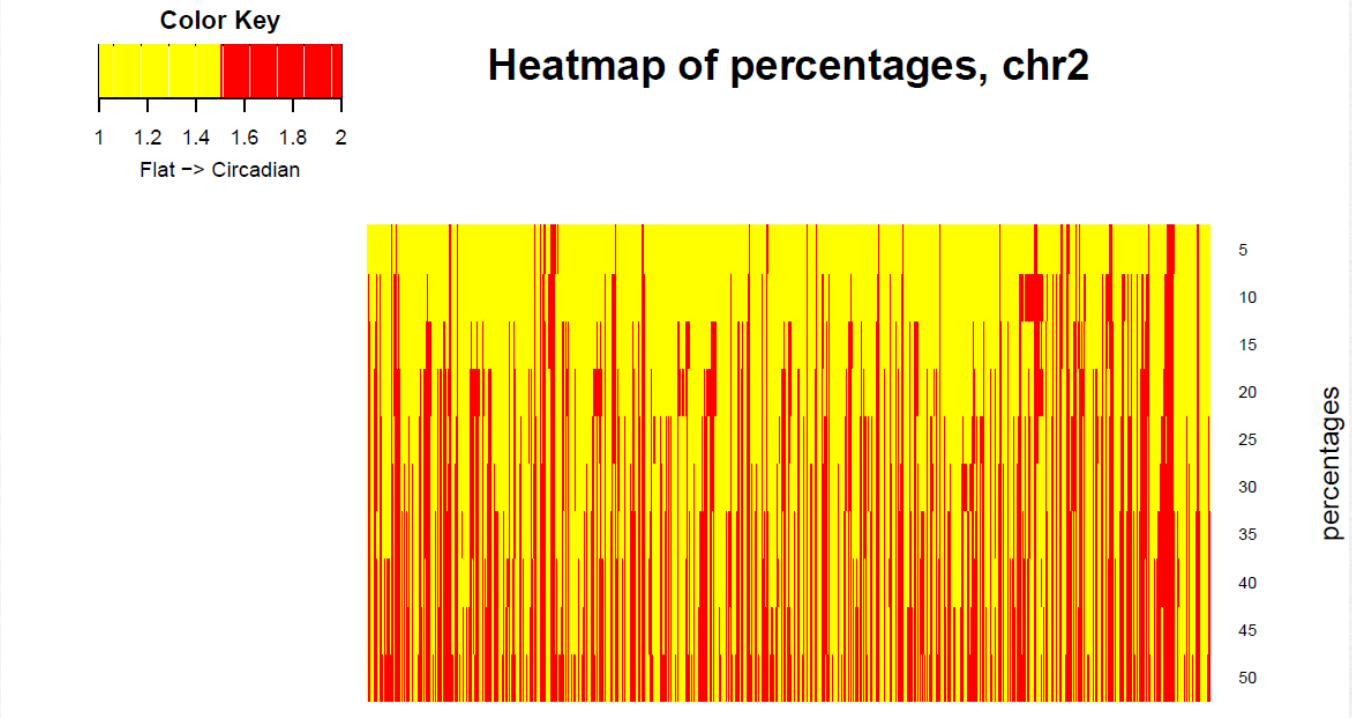
Results

Heatmap percentages 5 to 50



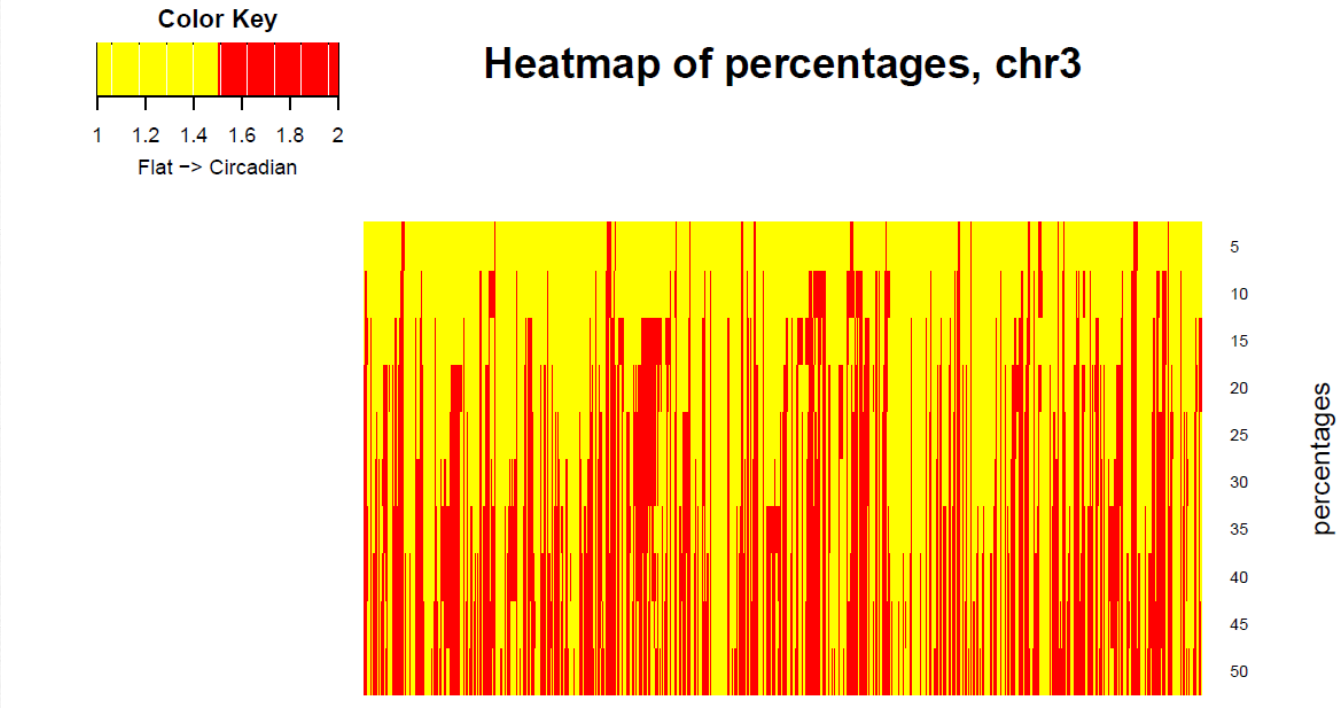
Results

Heatmap percentages 5 to 50



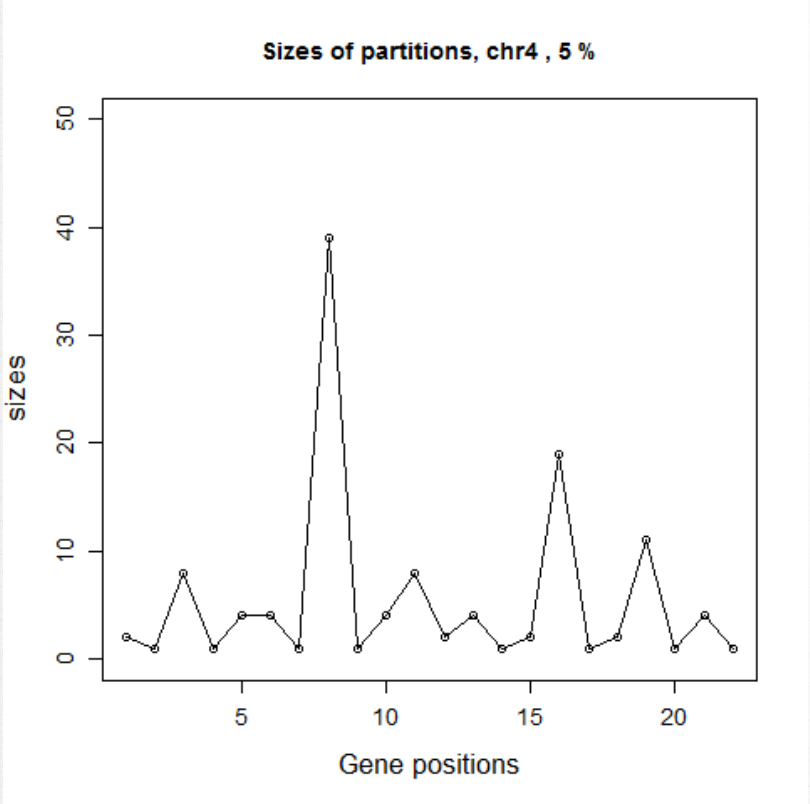
Results

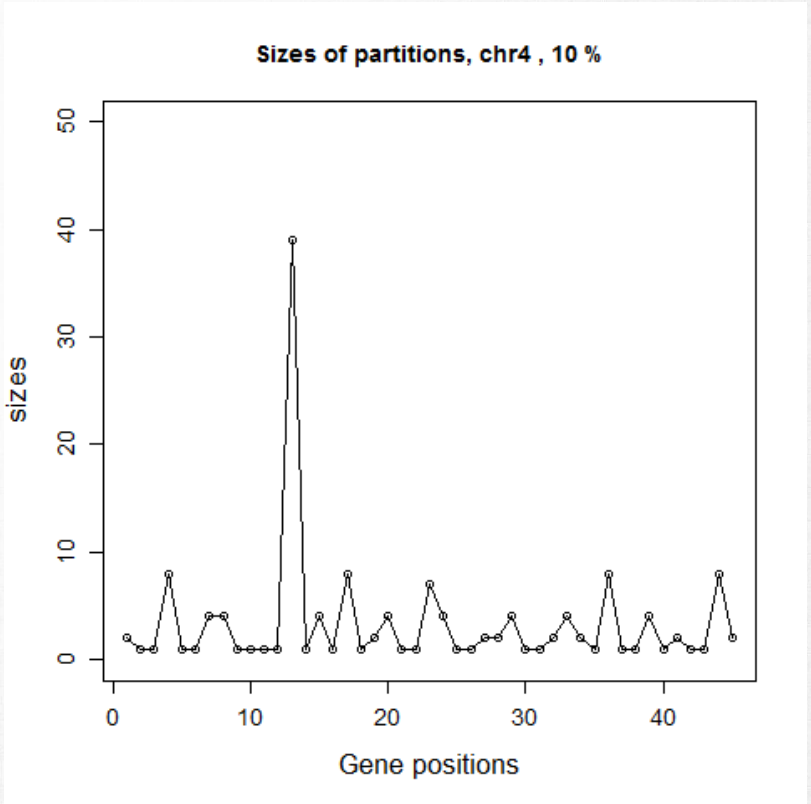
Heatmap percentages 5 to 50



Results

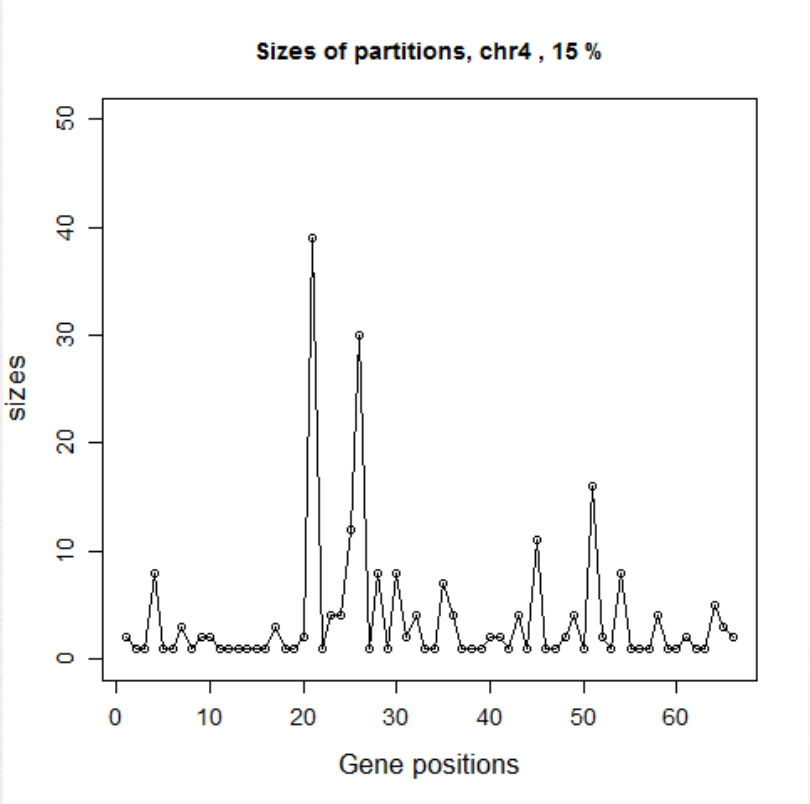
Do clusters of genes actually exist ?

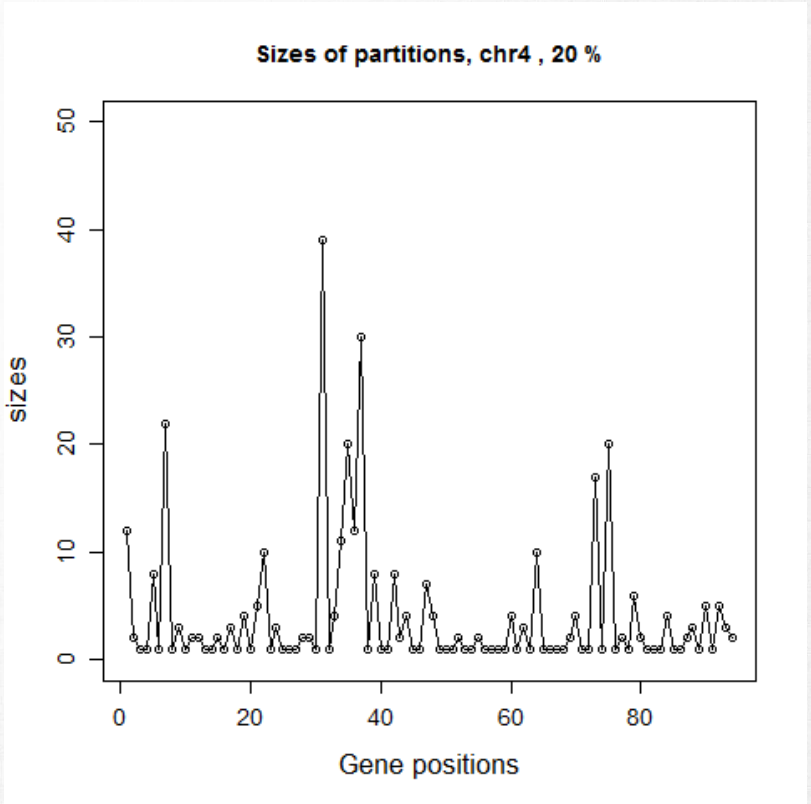




Results

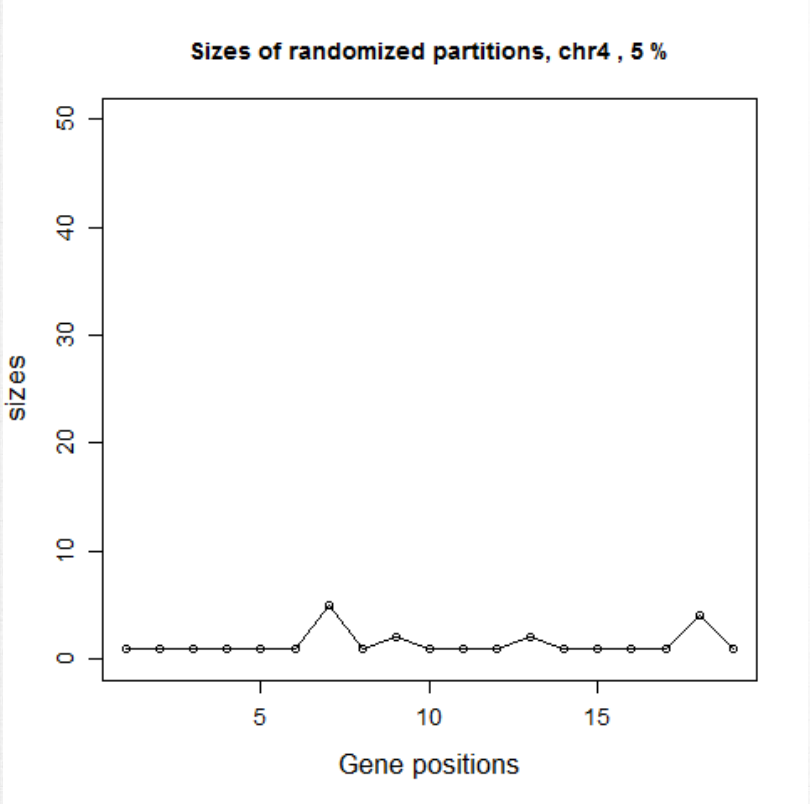
Do clusters of genes actually exist ?

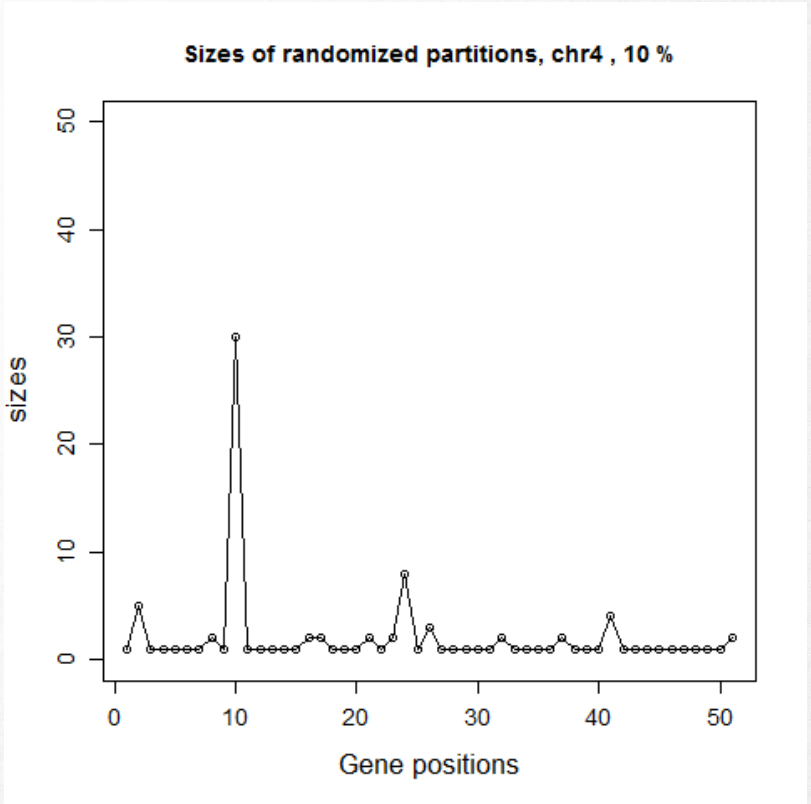




Results

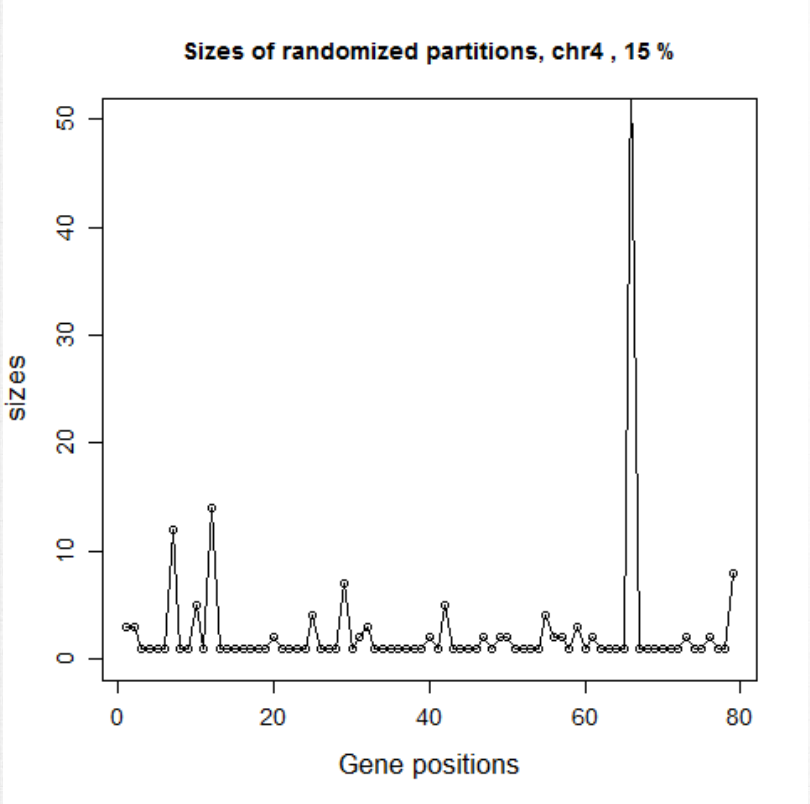
Do clusters of genes actually exist ?

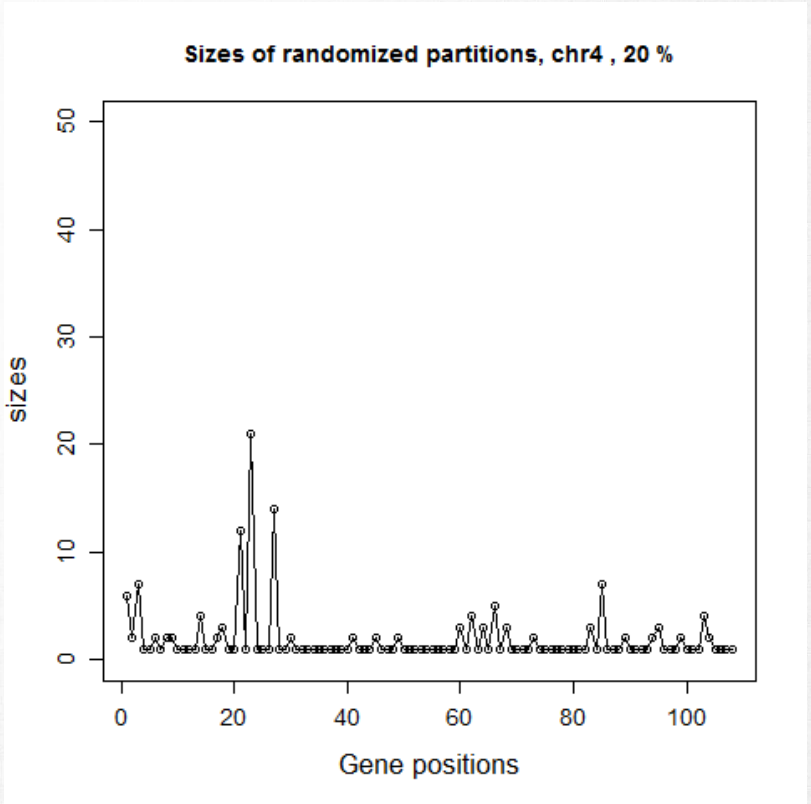




Results

Do clusters of genes actually exist ?





A final review

CONCLUSIONS

- We adopted an algorithm for partitioning genes along the chromosomes that show the same temporal pattern of expression
- For this specific task, we proposed a new score that solves the issue with the standard BIC approach.
- We identified blocks of genes along the chromosome with a similar temporal pattern.
- We transformed the definition of sigma to the a priori percentage of the rhythmic genes.
- By randomization we can see that the specific positioning of genes are relevant to the expression pattern.

A final review

FUTURE DIRECTIONS

- Test other models for describing more diverse dynamical patterns of expression
- Using other data set within the same framework and see whether the partitioning is reproducible across data types and conditions.
- Overlay the identified partitions with the chromosome conformation capture (3C) data to introgate the potential interaction between genes placed in the same block type.
- Showing that the genes within the same topological association domain (TAD) are tend to be similar in terms of expression profile.

THANK YOU

Feel free ton clone the github repository

https://github.com/darioAnongba/bachelorProject