



**Институт
биоинформатики**



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Search for correlation of socioeconomic status and methylation profiles

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Student: Kirill Grigorev

Project premise

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EPIGENETIC EPIDEMIOLOGY

Associations with early-life socio-economic position in adult DNA methylation

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OPEN ACCESS Freely available online

PLOS ONE

Profiling of Childhood Adversity-Associated DNA Methylation Changes in Alcoholic Patients and Healthy Controls

Huiping Zhang^{1,5*}, Fan Wang^{1,5}, Henry R. Kranzler⁶, Hongyu Zhao⁴, Joel Gelernter^{1,2,3,5}

Childhood adversity and DNA methylation of genes involved in the hypothalamus–pituitary–adrenal axis and immune system: Whole-genome and candidate-gene associations

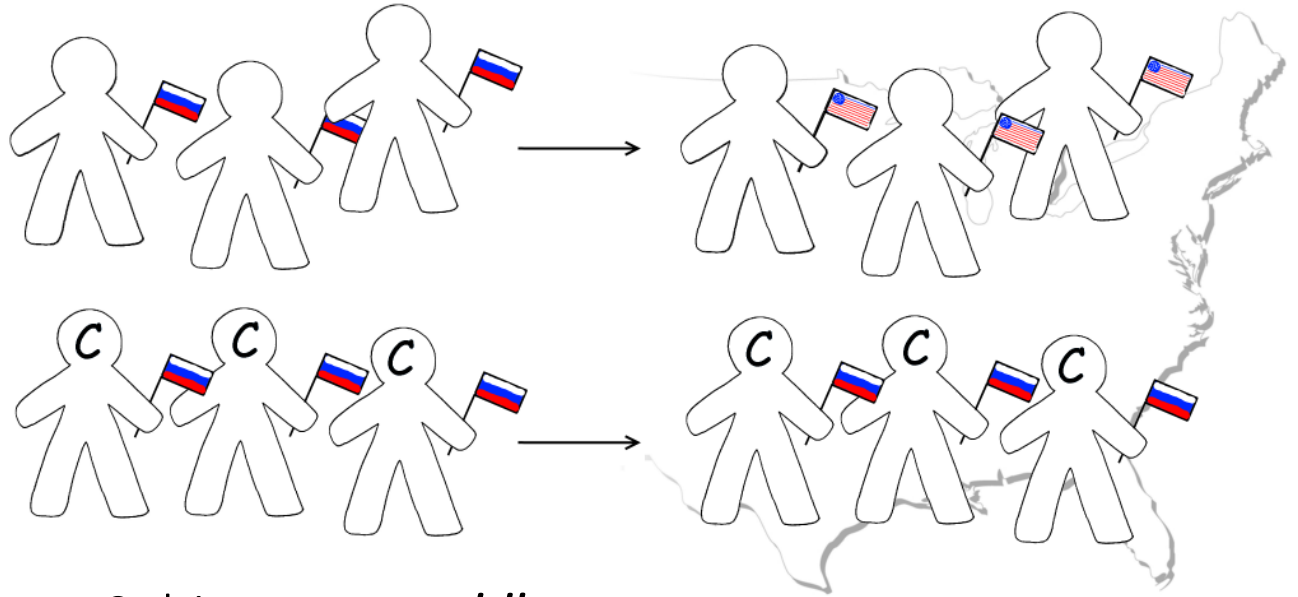
JOHANNA BICK^a, OKSANA NAUMOVA^{a,b}, SCOTT HUNTER^a, BAPTISTE BARBOT^a, MARIA LEE^a, SUNIYA S. LUTHAR^{a,c}, ADAM RAEFSKI^a, and ELENA L. GRIGORENKO^{a,c,d}

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Project goal and experiment design

Detect systematic change in methylation patterns (if any)
in orphans moving from Russia to the U.S.

Cases: Russian orphans
adopted by U.S. families

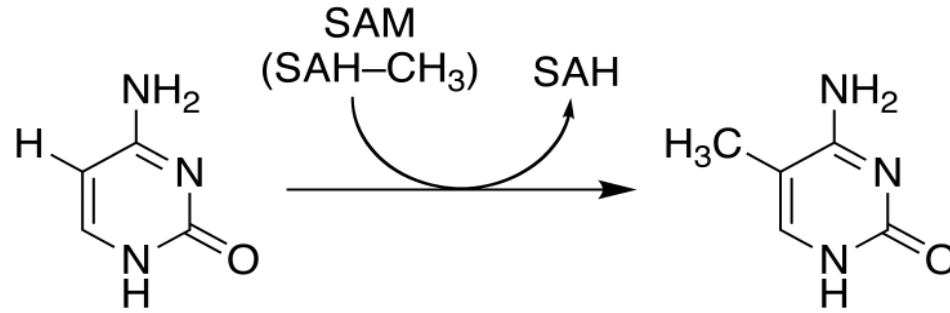


Controls: Russian children
who moved to the U.S.
with their biological
parents.

Subject age: **toddlers**

Time interval between sequencing: **6 months**

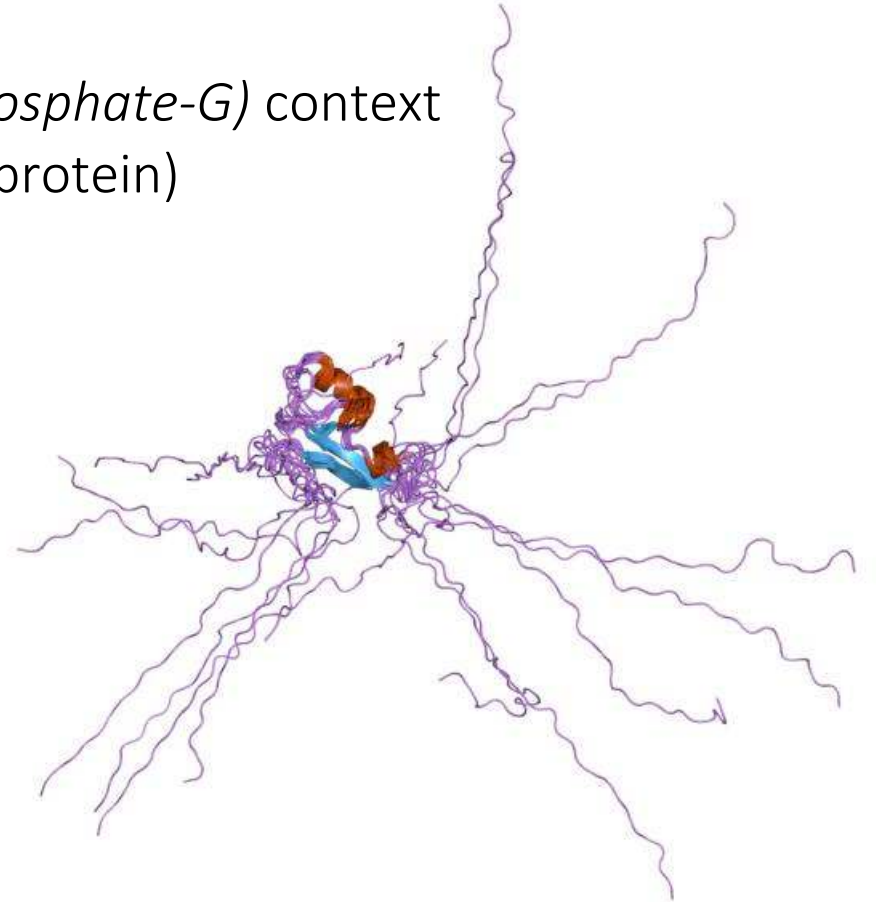
Cytosine methylation



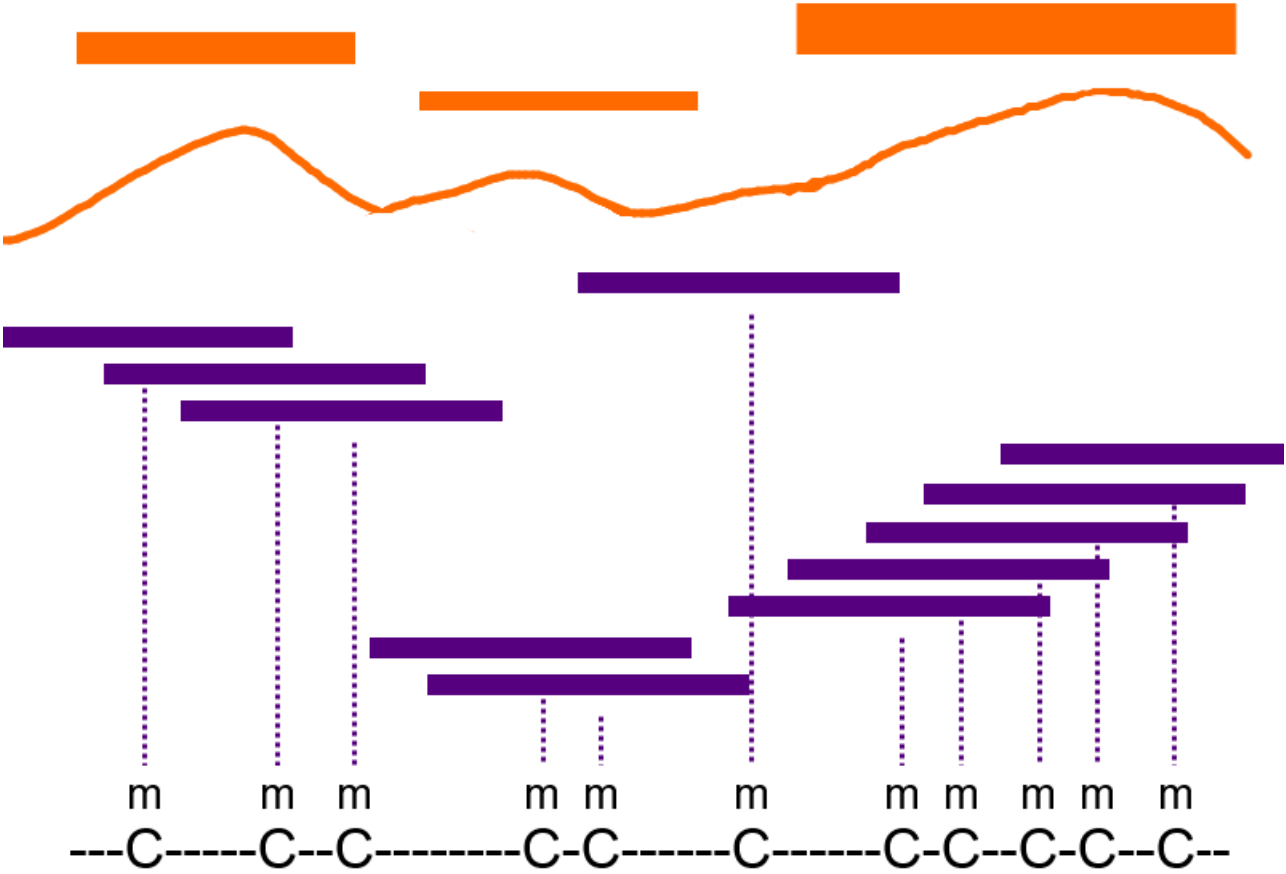
- Typically occurs in CpG (*C-phosphate-G*) context
- Is involved in regulation of gene transcription

Cytosine methylation: MBD-Seq

1. Methylation typically occurs in CpG (*C-phosphate-G*) context
2. **MBD** = Methyl-CpG Binding Domain (in a protein)
3. Can use MBD in ChIP-seq
4. **Peak calling etc. (MACS, SICER, custom)**
5. Methylated region detection



Enrichment: regions the MACS2 way

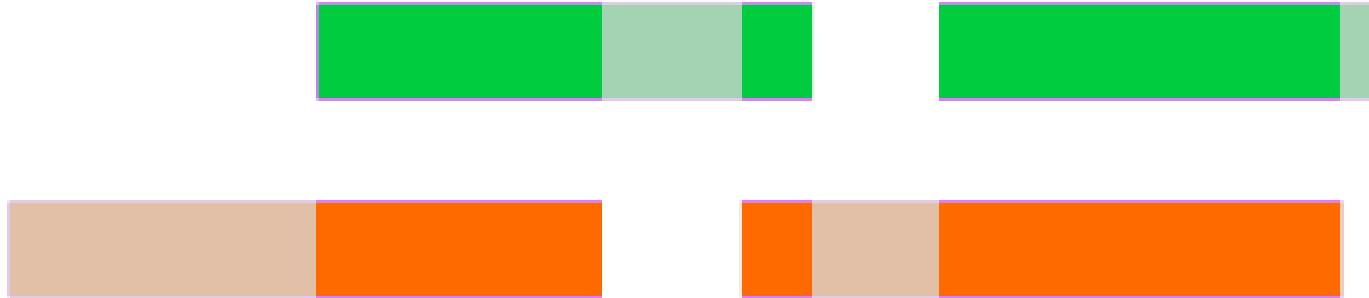


Enrichment: interpretation

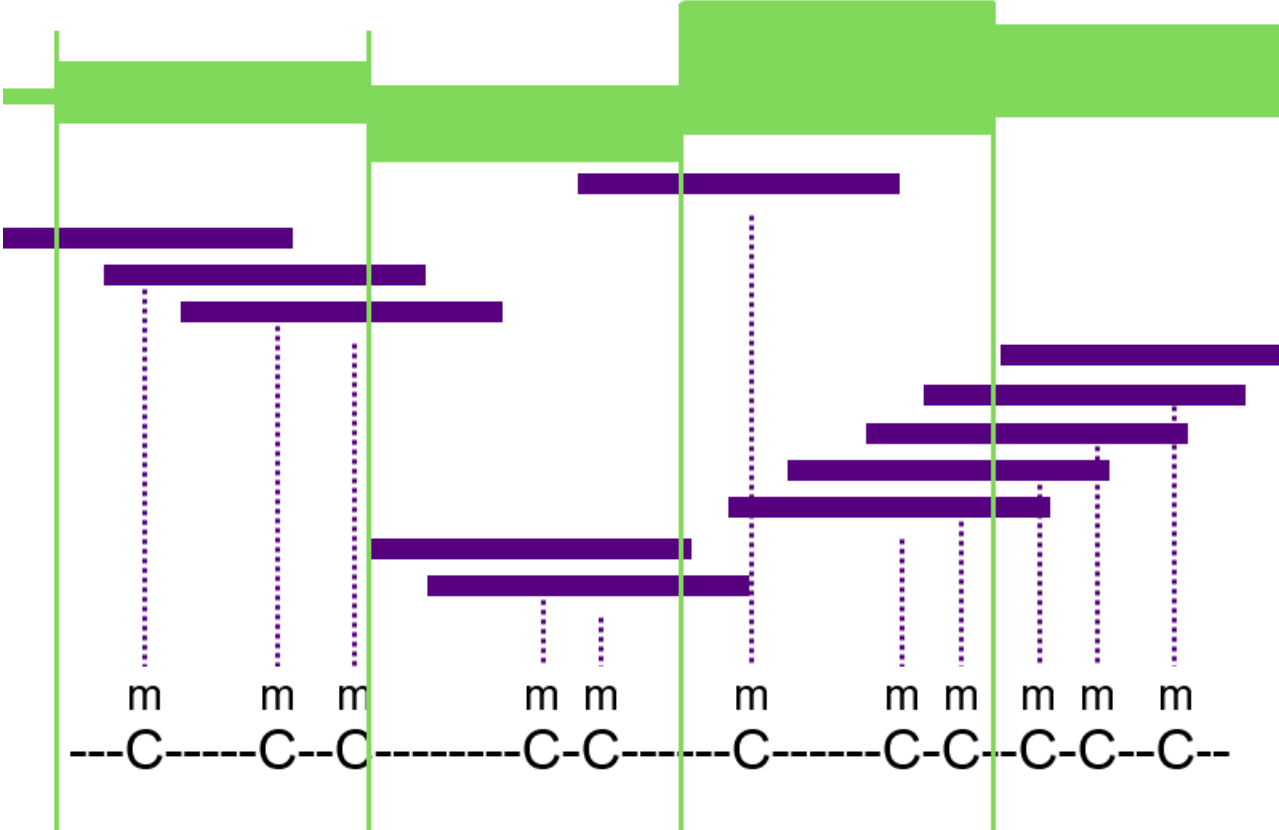
General idea

Find regions where enrichment changes:

- in the *same* direction for all *cases*
- in the *different* direction for all *controls*



Enrichment: regions our way ©



Enrichment: interpretation

General idea

Find regions where enrichment changes:

- in the *same* direction for all *cases*
- in the *different* direction for all *controls*

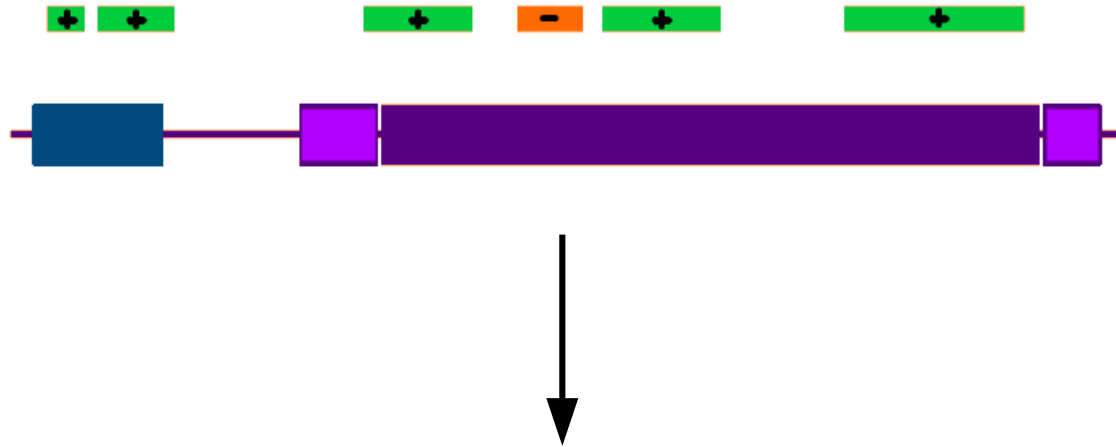
Notes on filtering:

- differences lower than a certain threshold are considered zero
- zero is a direction different from growth or decline



Finding affected genes

Intersect regions and genes



genes with biggest cumulative change
(all regions must change *in uniform direction!*)

Finding affected genes

Examples:

# gene id	region count	significance
ENSG00000153707	8 / 8	0.513472427213
ENSG00000179242	7 / 7	0.713335805813
ENSG00000196338	2 / 2	1.7097332516
ENSG00000267369	2 / 2	0.950590042702
ENSG00000259009	2 / 2	2.08073993732
ENSG00000155093	15 / 9	1.35778573742

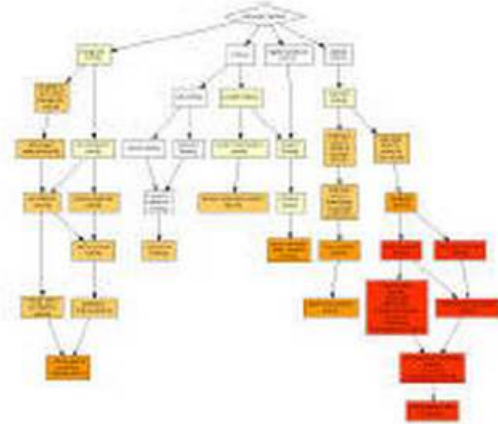
Affected gene clusters by function

Enter **Gene Ontology**

... and...



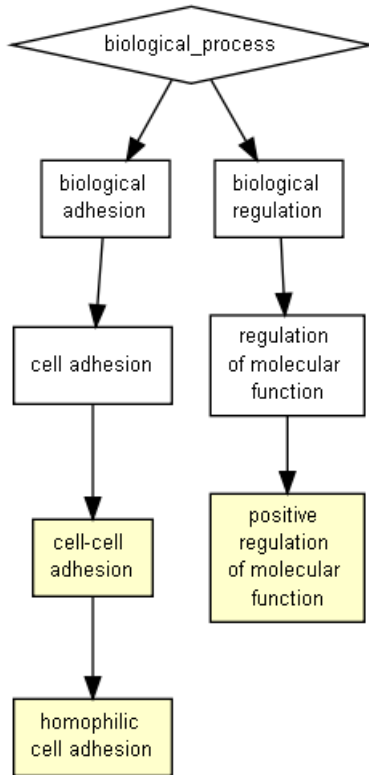
GORILLA



Gene Ontology enRiChment anaLysis and visuaLizAtion tool

GORilla is nice. It reports GO terms for genes and clusters them by function.

Affected gene clusters by function



Example of found cluster:

GO:0044093 “Positive regulation of molecular function”
(p-value 8.84e-4)

Includes genes:

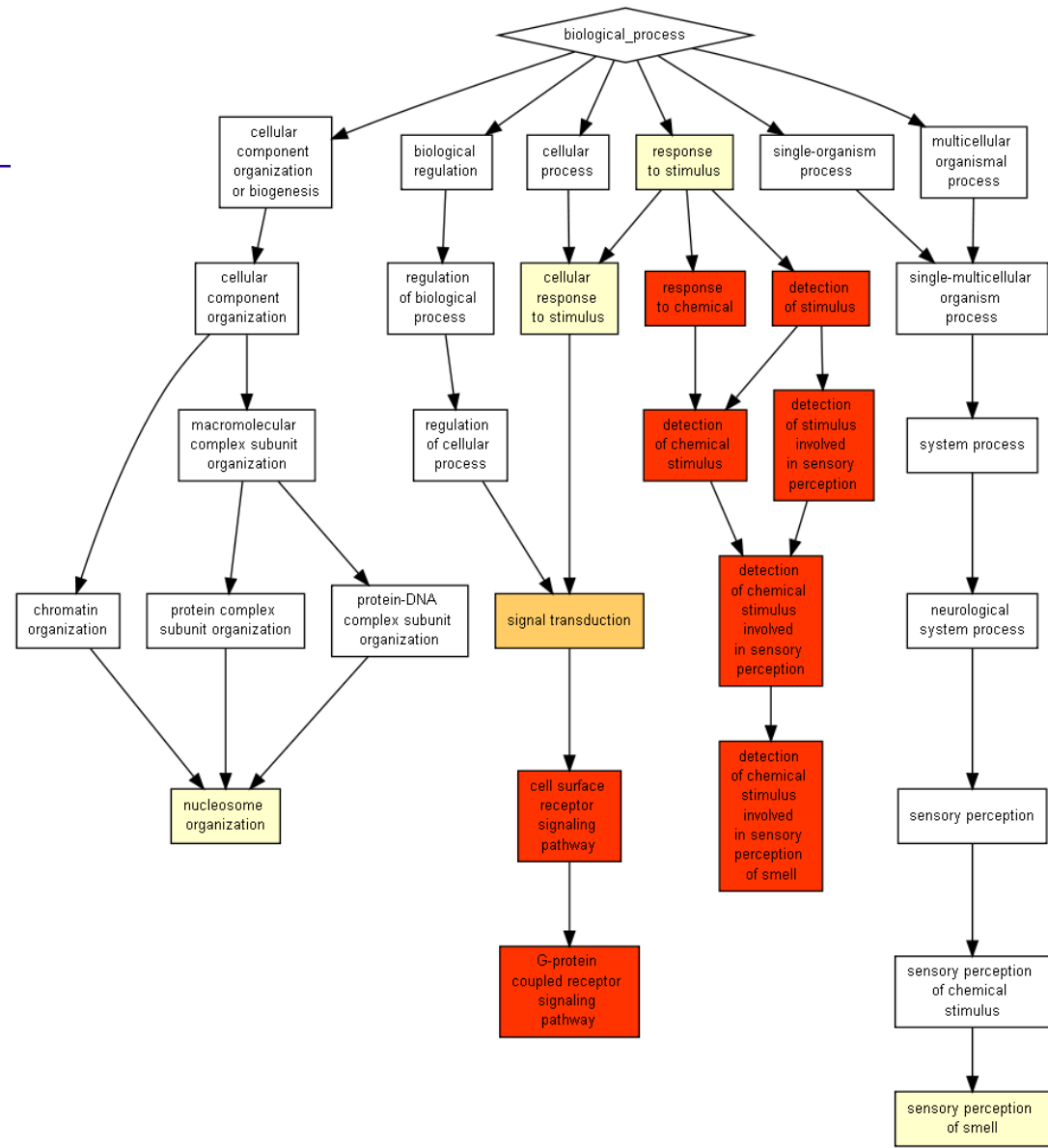
- **HDAC4** (histone deacetylase 4)
critical role in transcription regulation
- **RPTOR** (regulatory associated protein of mtor, complex 1)
cell growth regulation
- **NLGN3** (neuroligin 3)
formation of synapses, synaptic signal transmission

Pairwise assessment

As a parallel route of research, it was decided to look at methylation dynamics for each individual over time. The dynamics were overwhelmingly similar (which the previous method filtered out as expected).

Genes with olfactory functions are being methylated.

This is in good concordance with existing literature on early life development.



Conclusion

Results:

- A pipeline was created for detection of methylation profile changes;
- A successful proof-of-concept run was executed on a sample dataset;
- Using the alternative (pairwise) approach, some early life developmental patterns were corroborated.



github.com/LankyCyril/Loki

Conclusion

Future plans:

- Improve and expand the pipeline; (better mathematical models, new approaches)
- Apply the pipeline to a bigger dataset; assess biological significance of obtained results.



github.com/LankyCyril/Loki

Orphans' methylomes



bioinformaticsinstitute.ru
dobzhanskycenter.ru