ClusDec – clustering approach to solving complete deconvolution problem

Konstantin Zaytsev

Research advisor: Maxim Artyomov

ITMO University, WashU

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Motivation

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- Gene expression analysis – widely used technique
- Samples are often mixed
- Heterogeneity confounds interpretation of data
- Deconvolution algorithms try to guess cell types and their proportion between samples

Linear assumption

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- Let S be an n × k gene expression matrix that contains k cell types and n genes.
- Let W be a k × m matrix where each column of W contains the frequencies of k cell types in a particular observation
- Let O be an n × m expression matrix that contains the observed gene expression level, where n represents the number of genes and m is the number of observed tissue samples.

The mixing process can be modeled through a linear model:

$$O = S \times W$$

Constraints

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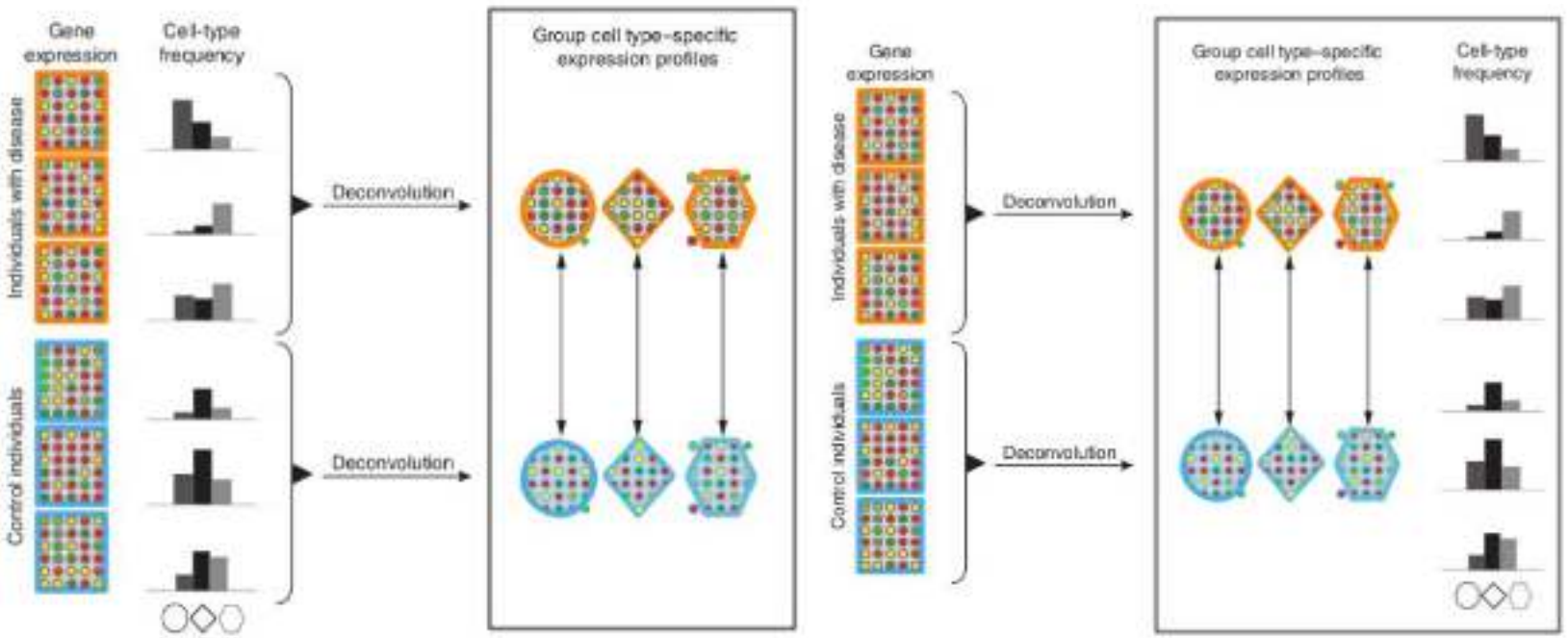
- Non-negativity: the resulting matrices S and W must be non-negative
- Sum-to-one constraint: the sum of every column of W must be equal to one

Existing approaches

Deconvolution problem can be

- Partial (additional information)
- Complete



Existing approaches

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What kind of additional information can help us make deconvolution?

- S (gene expression in expected cell types)
- W (cell type proportions)
- Signature genes !

Signature genes

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What is signature gene? We assume signature gene to be highly expressed in only one cell type.

$$S = \begin{vmatrix} g_{1,1} & 0 & 0 & .. & 0 & 0 \\ g_{2,1} & g_{2,2} & g_{2,3} & .. & g_{2,k-1} & g_{2,k} \\ 0 & g_{3,2} & 0 & .. & 0 & 0 \\ g_{4,1} & g_{4,2} & g_{4,3} & .. & g_{4,k-1} & g_{4,k} \\ .. & .. & .. & .. & .. & .. \\ 0 & 0 & 0 & .. & g_{n-3,k-1} & 0 \\ 0 & 0 & 0 & .. & g_{n-2,k-1} & 0 \\ g_{n-1,1} & g_{n-1,2} & g_{n-1,3} & .. & g_{n-1,k-1} & g_{n-1,k} \\ 0 & 0 & 0 & .. & 0 & g_{n,k} \end{vmatrix}$$

In this example genes 1, 3, n-3, n-2, n are signatures

Existing approaches

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All known approaches to deconvolution solve partial deconvolution problem:

- DSA (Zhong et al. BMC Bioinformatics 2013)
- CIBERSORT (Newman AM, Liu CL et al. Nat Methods 2015)
- NMF approaches (Gaujoux 2012)
- and more

There's **no complete** deconvolution algorithm

The idea: find signatures

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The main idea:

- Somehow find signature genes in dataset
- Perform signature gene-based partial deconvolution algorithm

The idea: clustering

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How do we get signature genes from dataset?
”Clus” is for clustering ! Usual practice in gene expression analysis is to use correlation as a distance

- Kmeans
- WGCNA clustering

Signature genes will definitely fall into the same cluster

The idea: clustering

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But just correlation is not enough

- Lets assume we know the proportions of one particular cell type c (c-th row in matrix W)
- How does signature to this cell type gene expression have to look like? Since we assume that signature gene i is only expressed in one cell type c:

$$O_i = W_c * O_{i,c}$$

- Thus any pair of signature to one cell type gene expression profiles must be linearly dependent
- But if we use correlation we will also put into the same cluster pair of genes which are just collinear:

$$O_i = A + B * O_j$$

The idea: correlation-like distance

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What can we use as a distance so? Lets just remove means from correlation

$$d_{x,y} = \frac{\sum_{i=1}^{n}(x_i)(y_i)}{\sqrt{\sum_{i=1}^{n}(x_i)^2}\sqrt{\sum_{i=1}^{n}(y_i)^2}} = \frac{\langle x, y\rangle}{||x|| * ||y||}$$

The idea: further steps

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Lets assume we found the clusters. What's next?

- Take some of these clusters (ones that have enough genes and correlation inside the cluster is good enough)
- Use genes in these clusters as signatures in partial deconvolution algorithm for every combination of k clusters from good clusters
- For every combination measure the accuracy of deconvolution
- Choose the best describing combination of cluster

The idea: DSA-like deconvolution

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- Takes list of signature genes as input
- Every signature expression profile is then divided by its maximum as normalization
- For every cluster we take mean of gene profiles thus we will have k vectors corresponding to ”raw” proportions of these cell types
- Fit sum-to-one constraint: find vector C such that

$$\widetilde{W}_{m\times k} \times C_{k\times 1} = 1_{m\times 1}$$

- And the resulting W is

$$W_{k\times m} = \left(\widetilde{W}_{m\times k} \times \begin{vmatrix} C_1 & .. & 0 \\ .. & .. & .. \\ 0 & .. & C_k \end{vmatrix}\right)^T$$

The idea: deconvolution

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When we found W, we run DSA with given W to find S matrix. These W and S (and signature genes as well) are deconvolution results

How to measure accuracy

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This question is next to ”how to interpret deconvolution results?”

- Proportions of cell types and signature genes are the results of deconvolution
- No one can guarantee that we will find biology in these genes
-

How to measure:

- How good we fit sum-to-one constraint
- Correlation between samples in O and S $\times$ W

How to test

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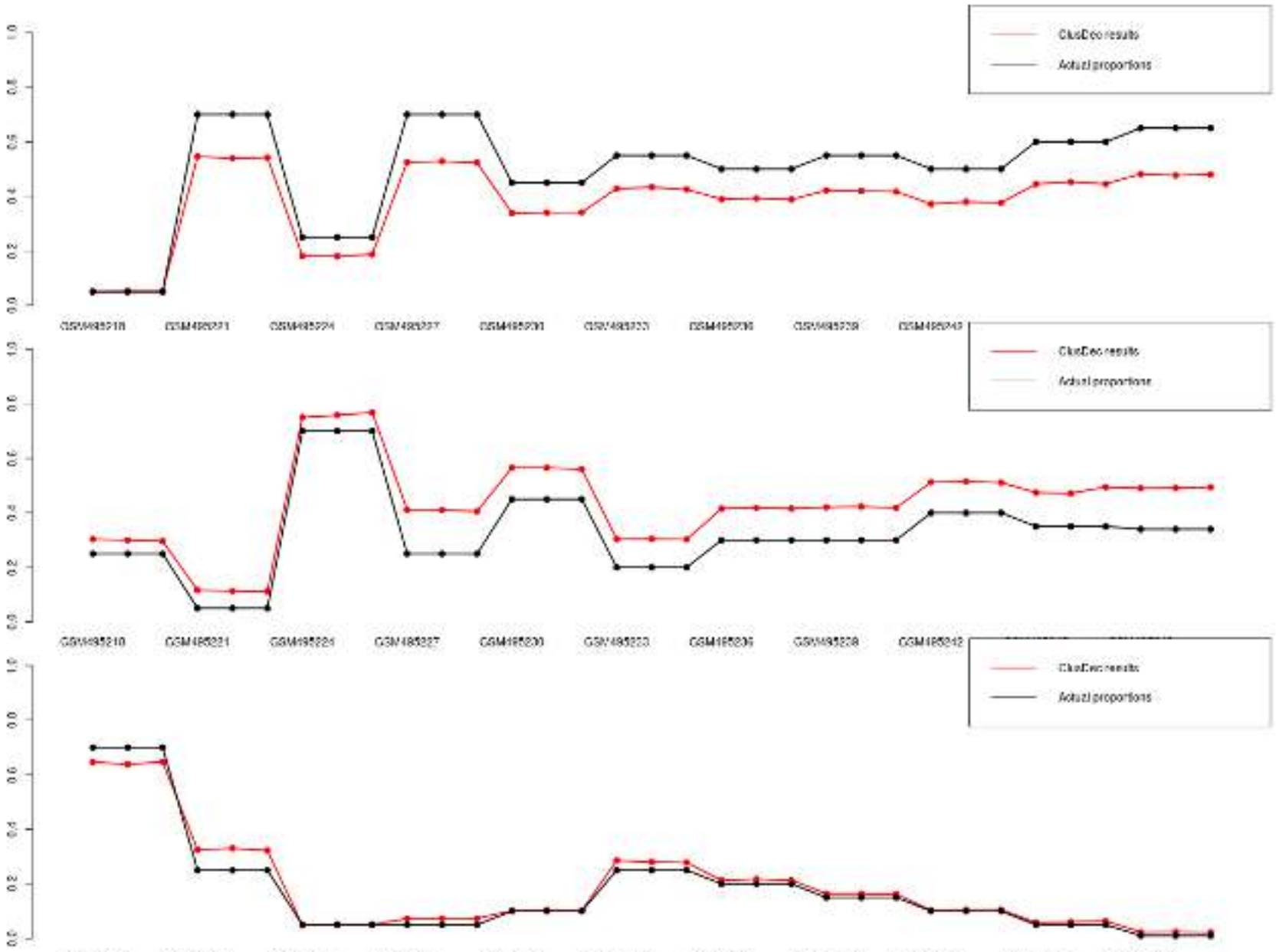
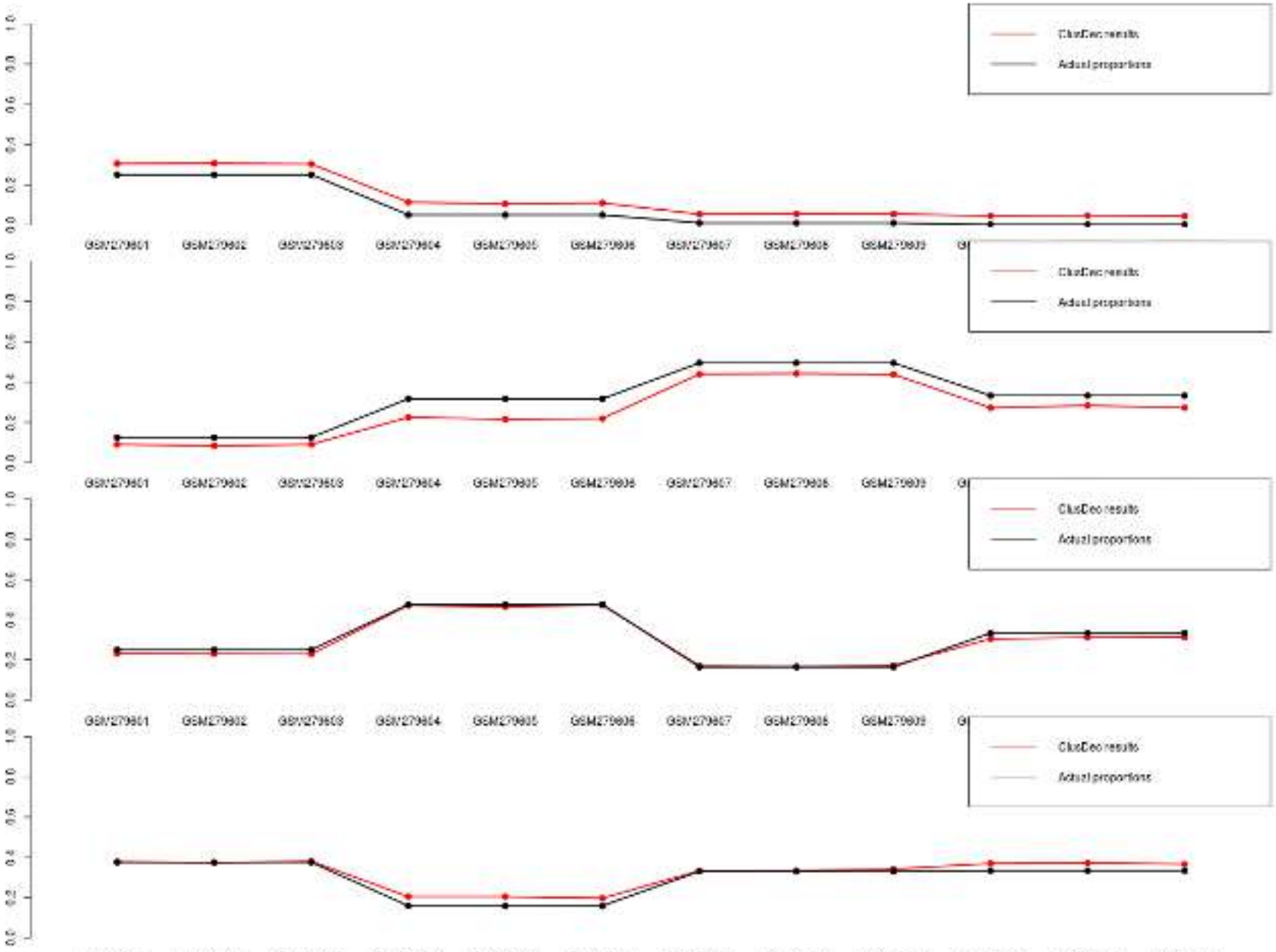
- Benchmark datasets: GSE19830 (the mixture of brain, lung and liver tissues), GSE11058 (the mixture of immune cell lines Jurkat, IM-9, Raji, THP-1). We know the actual proportions of cell types in these datasets
- GSE52245: human PBMC after vaccination
- GSE27563: mice PBCs with tumors
- GSE35710: adipose tissues

Some results: GSE19830



Some results: GSE11058



Some results: GSE52245

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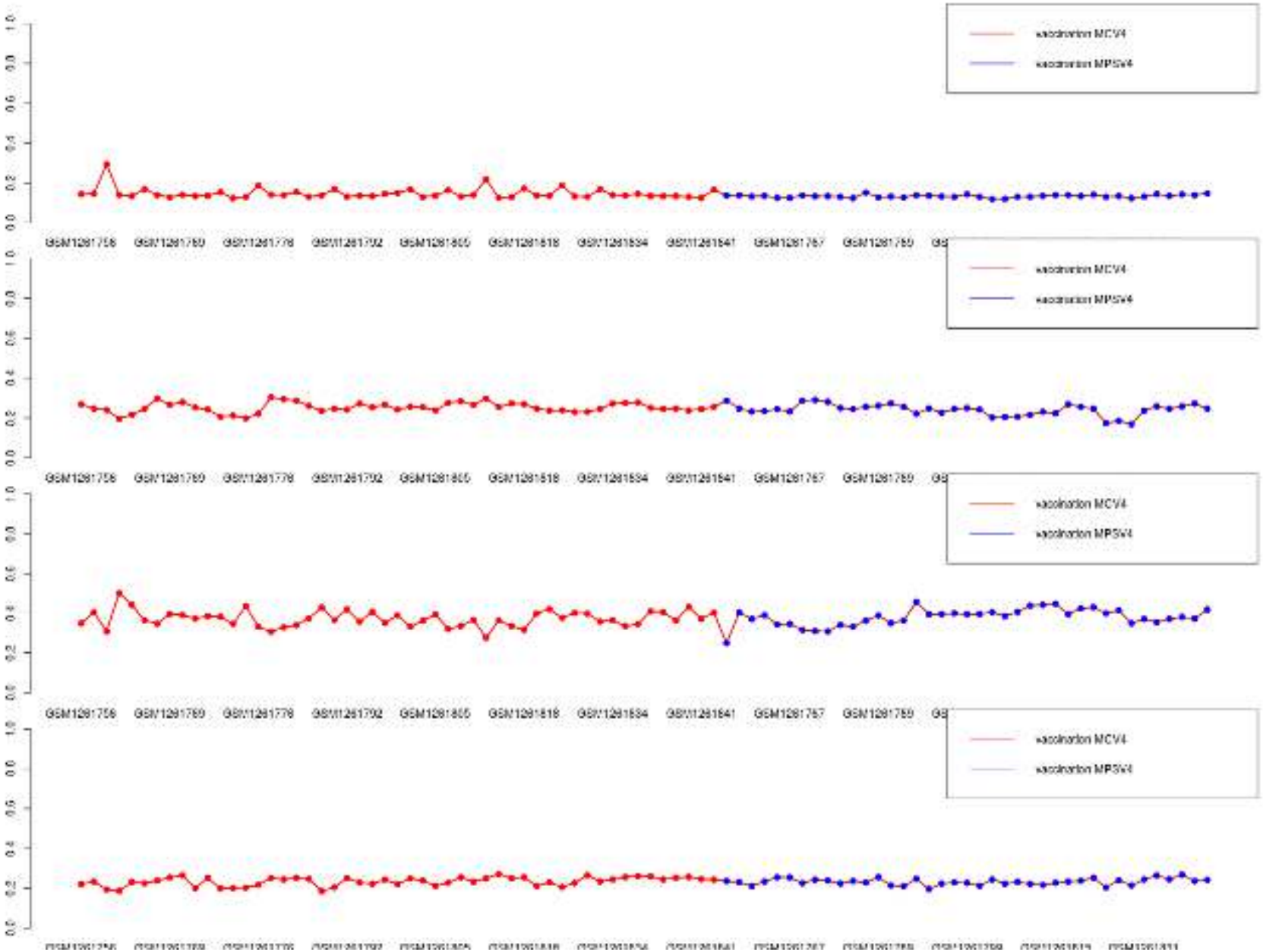

Results summary

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- ClusDec works pretty well on benchmark dataset
- ClusDec can find some biology
- Interpretation of results is not easy at all

Further work

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- Understanding what cluster is good is still vague
- How to check accuracy of deconvolution is still an open question
- Current cluster size on practice is about 20-60 genes. Can we enlarge it to make result easier to interpret

Thank you

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Any questions?