Networks integration

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Project goals

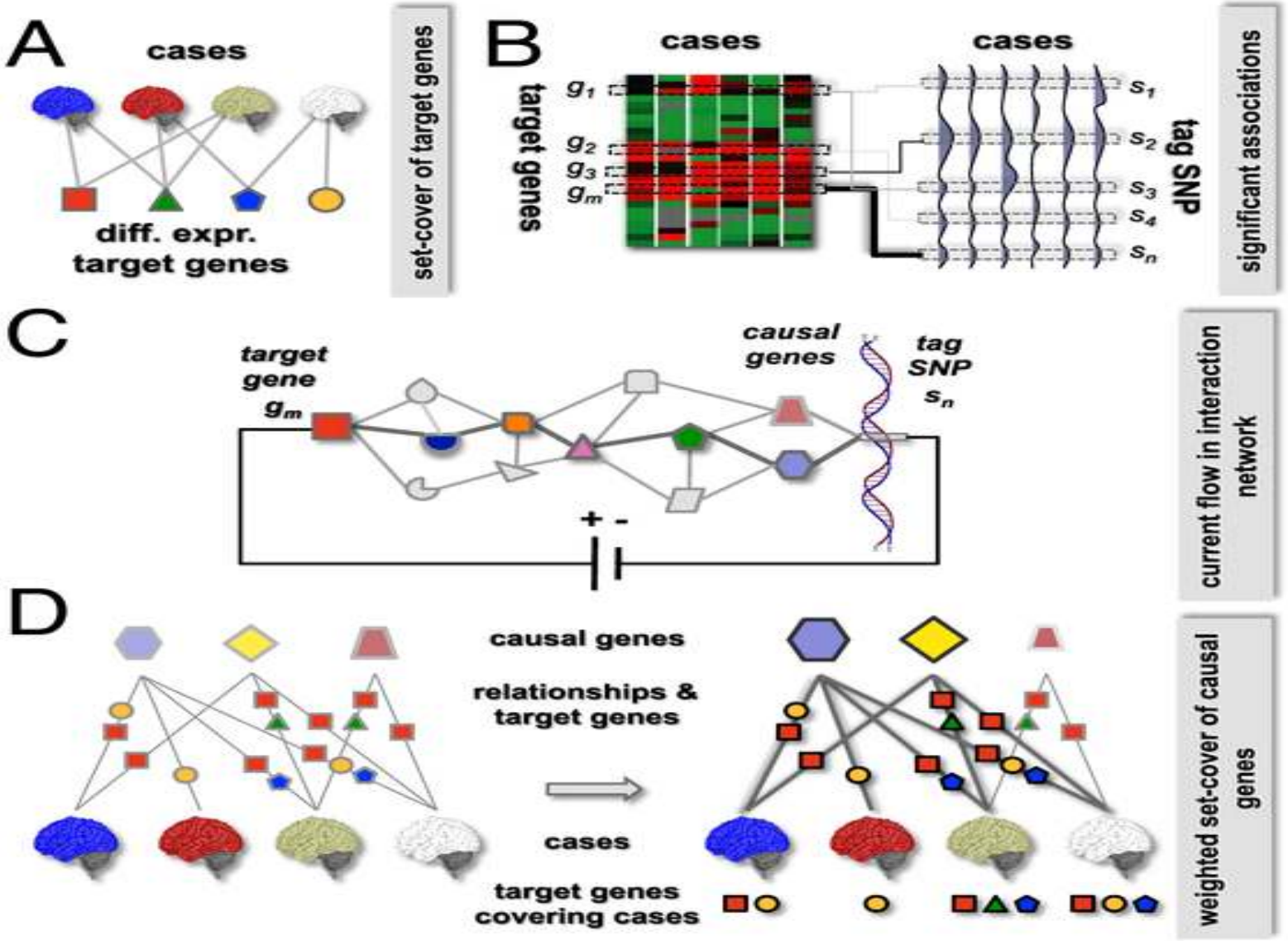
- Review an algorithm from the article: “Identifying Causal Genes and Dysregulated Pathways in Complex Diseases” (Kim et. al., 2011);
- Implement the algorithm;
- Detect and fix it bottlenecks;
- Find a way to integrate genomic data into output to reveal mechanisms of complex diseases;

ICGDP algorithm

Idea:

- take profiles of genes expression from the disease and control samples;
- take set of loci with CNV alterations from different chromosomes;
- take a network of molecular interactions containing as much as possible genes.

Result: get causal genes and dysregulated pathways.

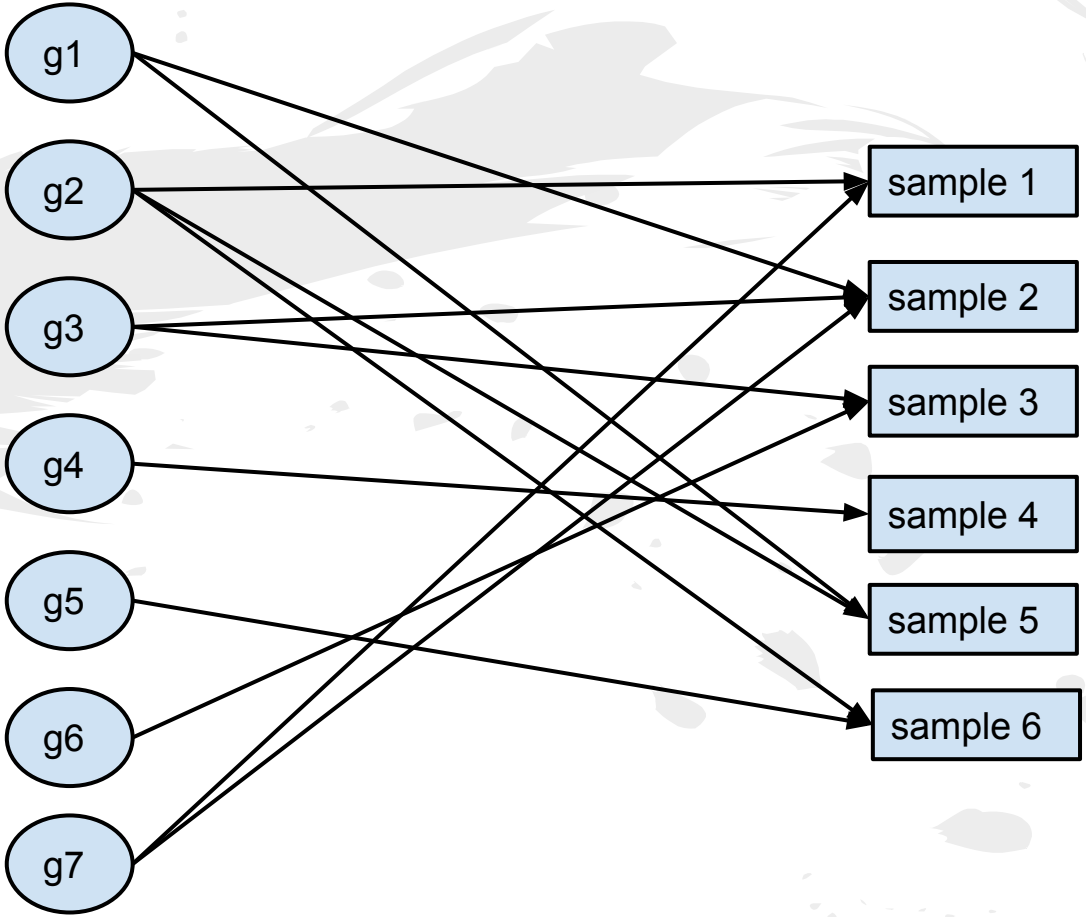

A
cases
diff. expr.
target genes
set-cover of target genes
B
cases
cases
target genes
g_1
g_2
g_3
g_m
tag SNP
s_1
s_2
s_3
s_4
s_n
significant associations
C
target
gene
g_m
causal
genes
tag
SNP
s_n
+ -
current flow in interaction network
D
causal genes
relationships &
target genes
cases
target genes
covering cases
weighted set-cover of causal genes

Overview

Selecting target genes

We stop if coverage is more or equal to A. That must be true for all samples except B.

Let's consider:
A = 2, B = 2



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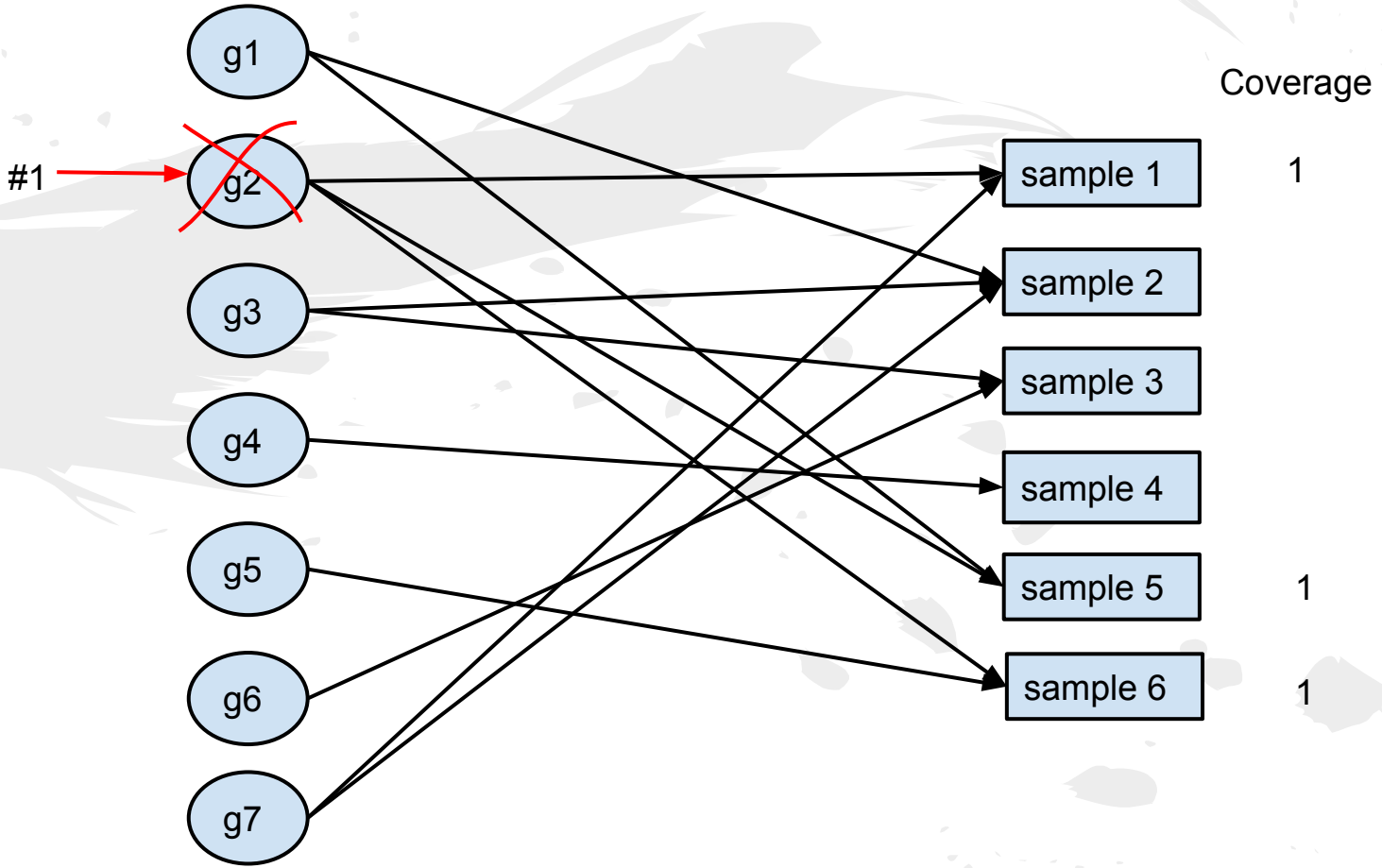

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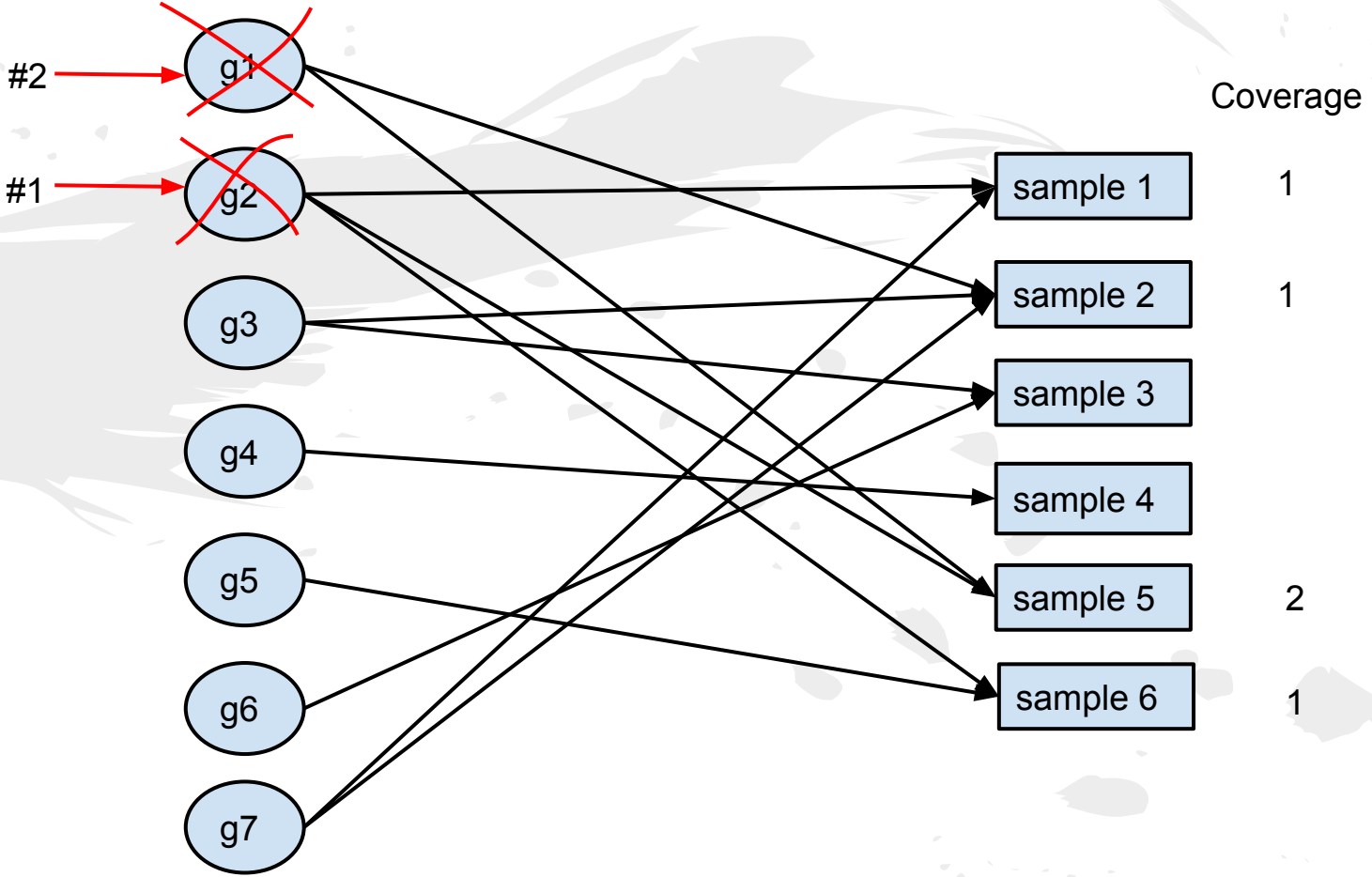

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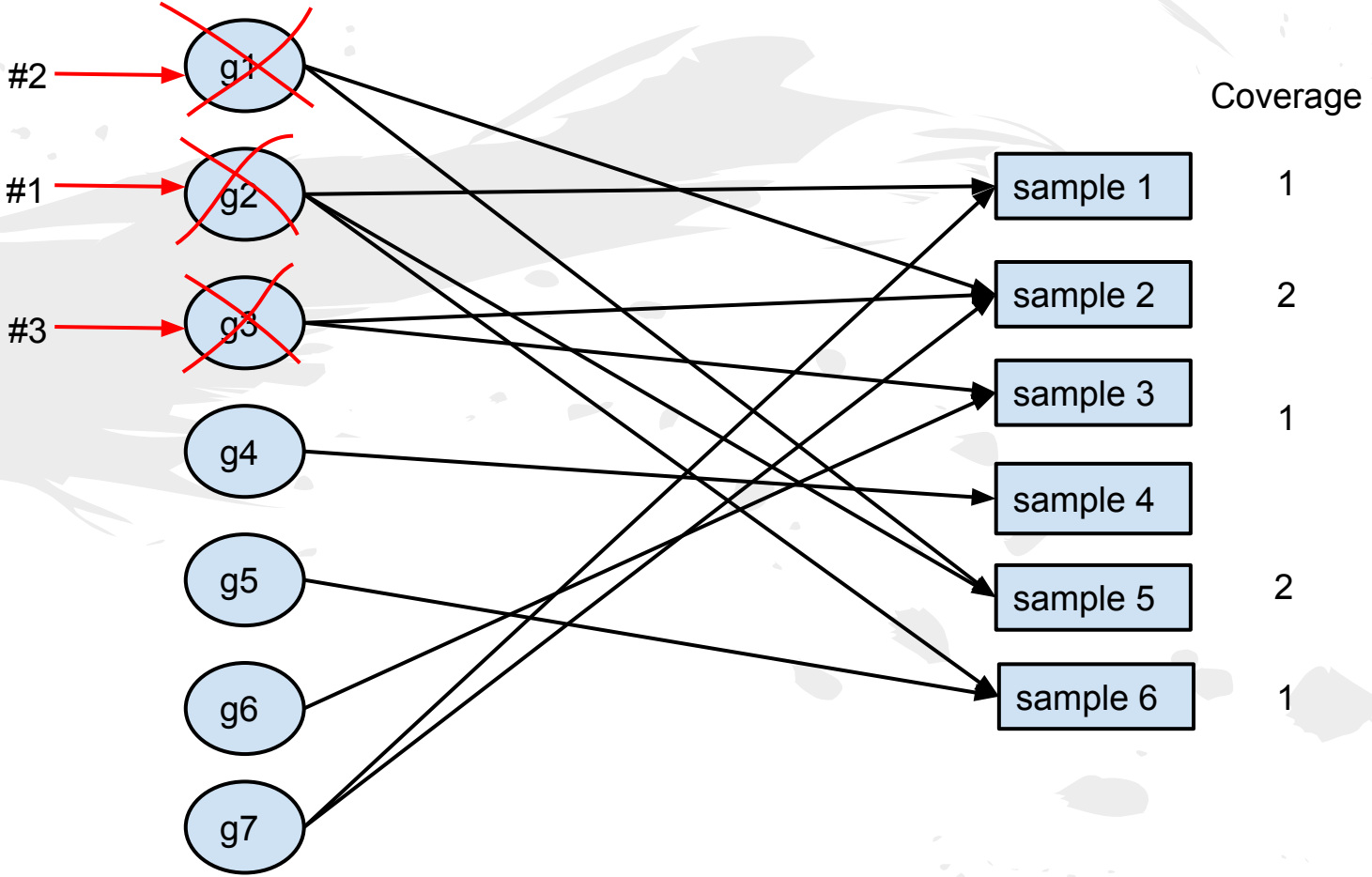

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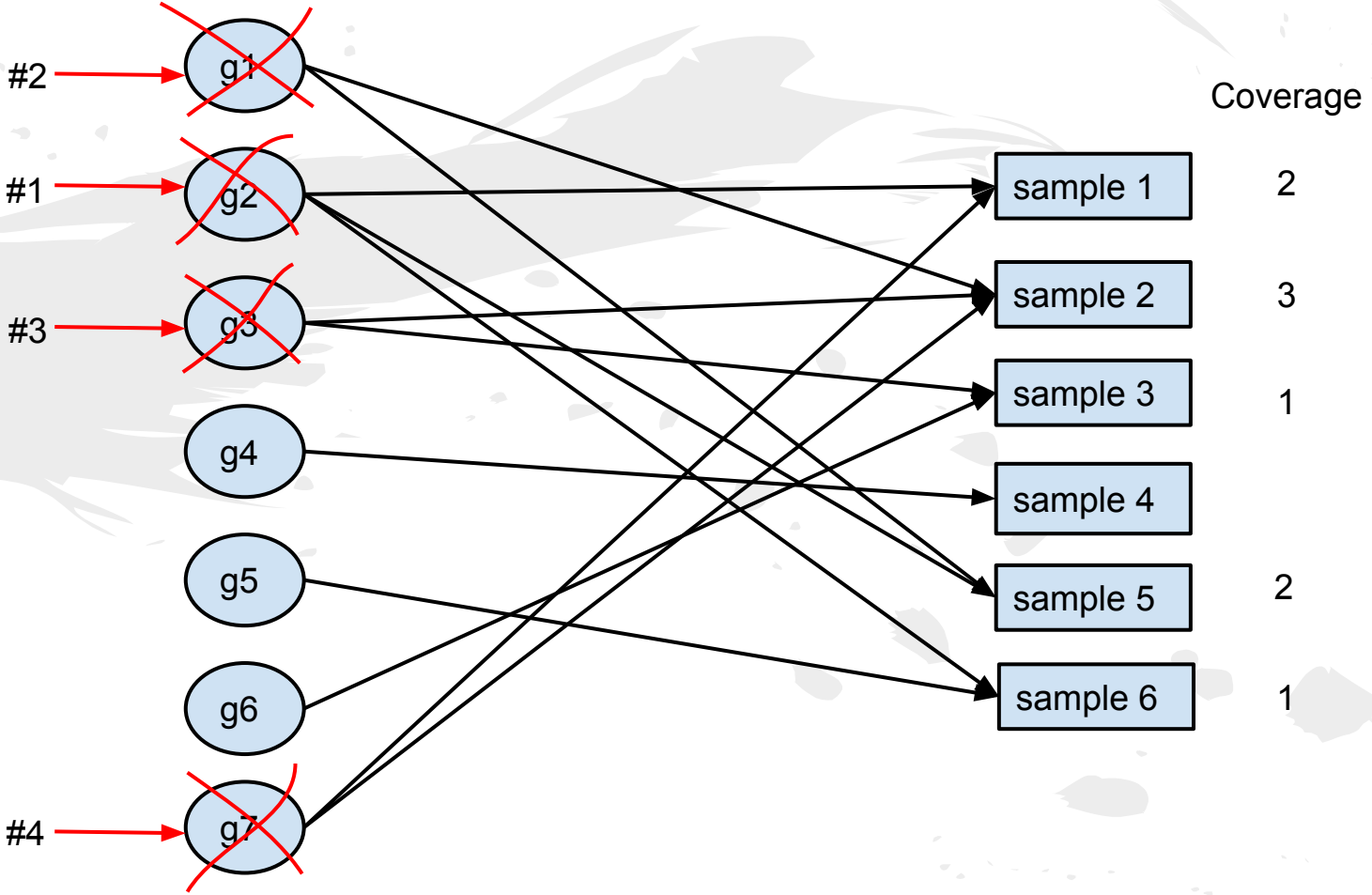

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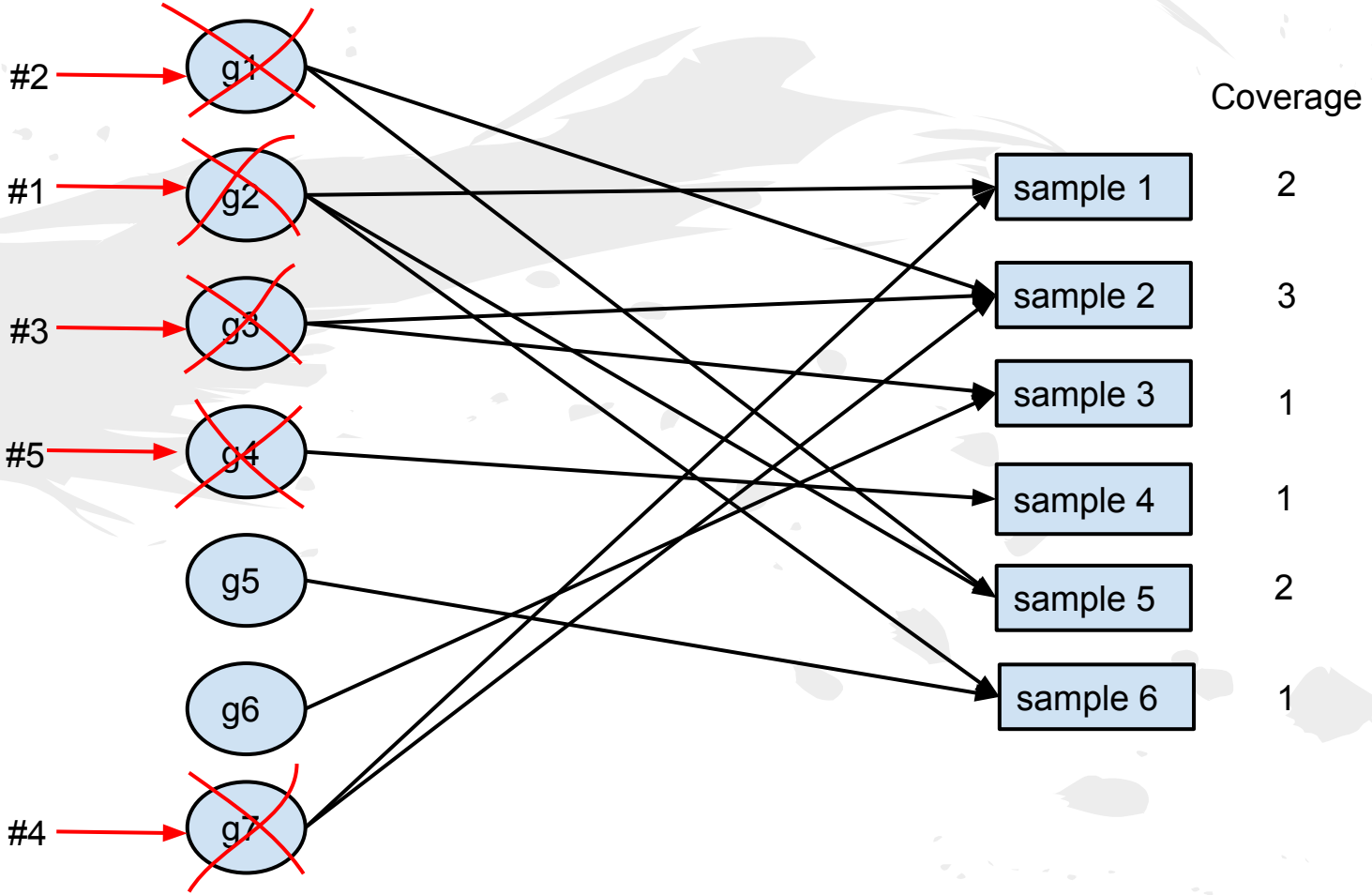

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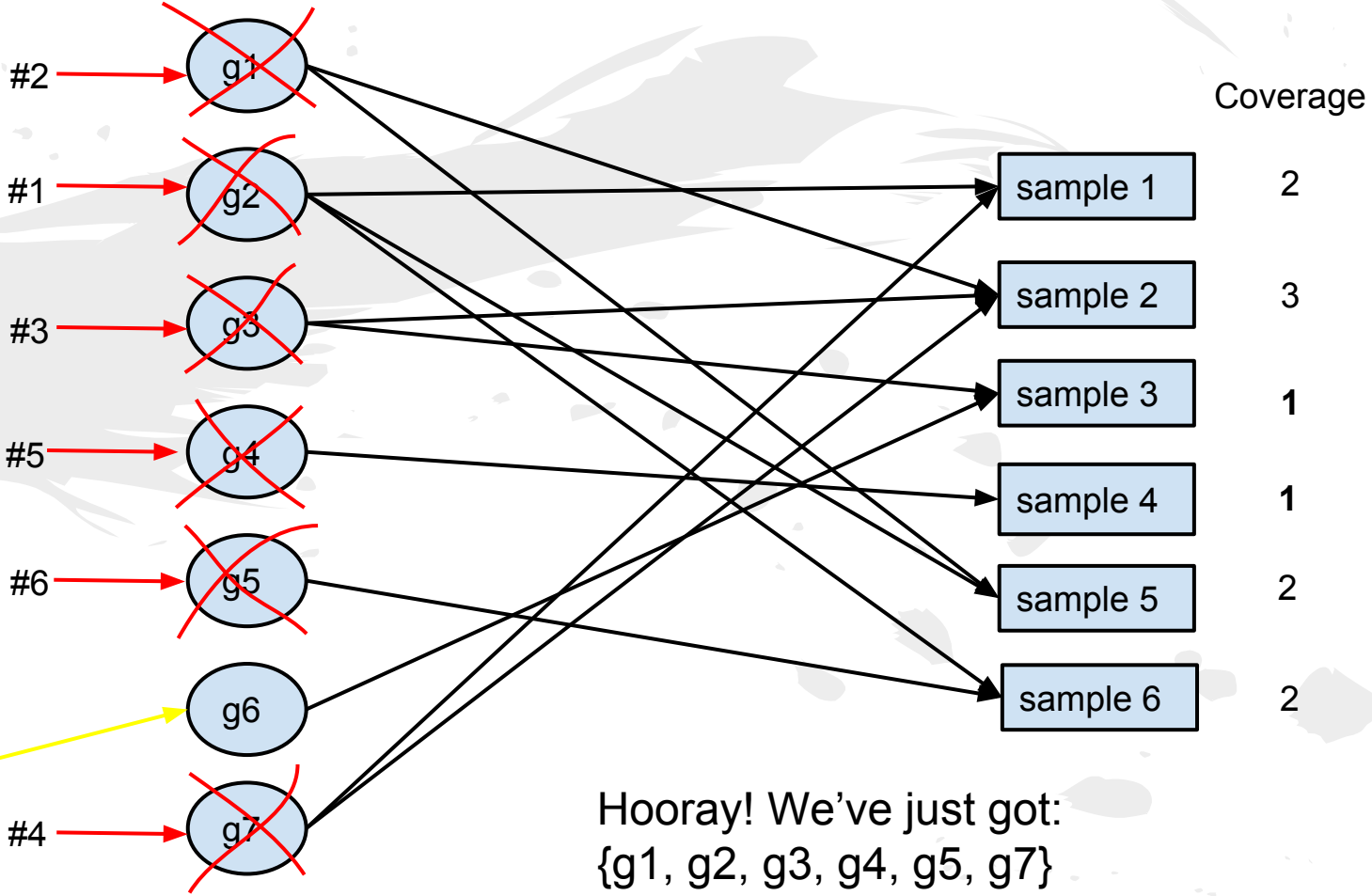
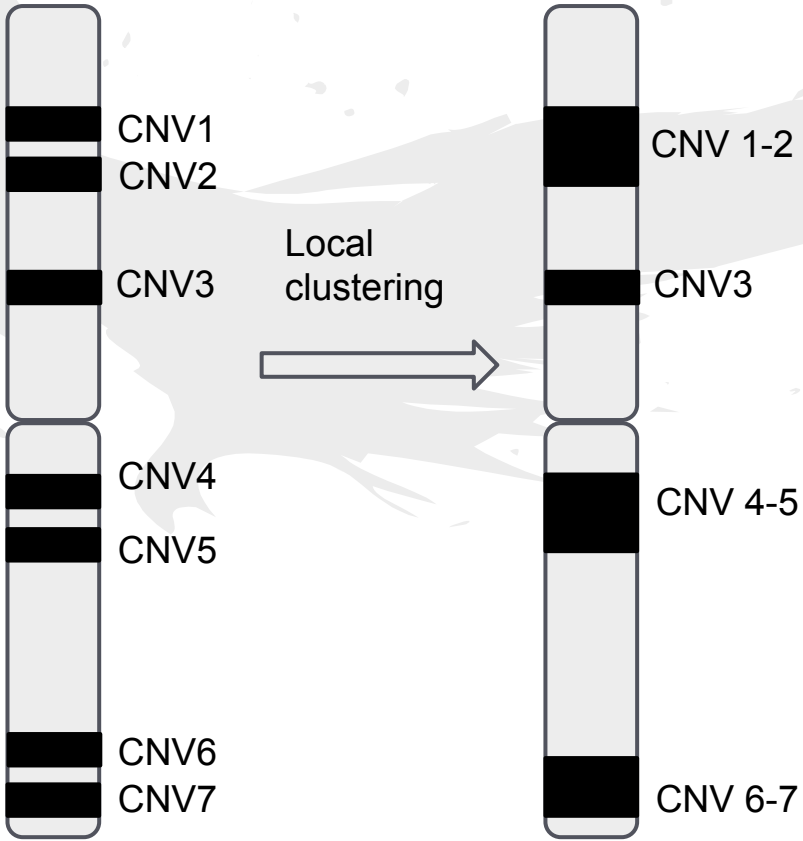


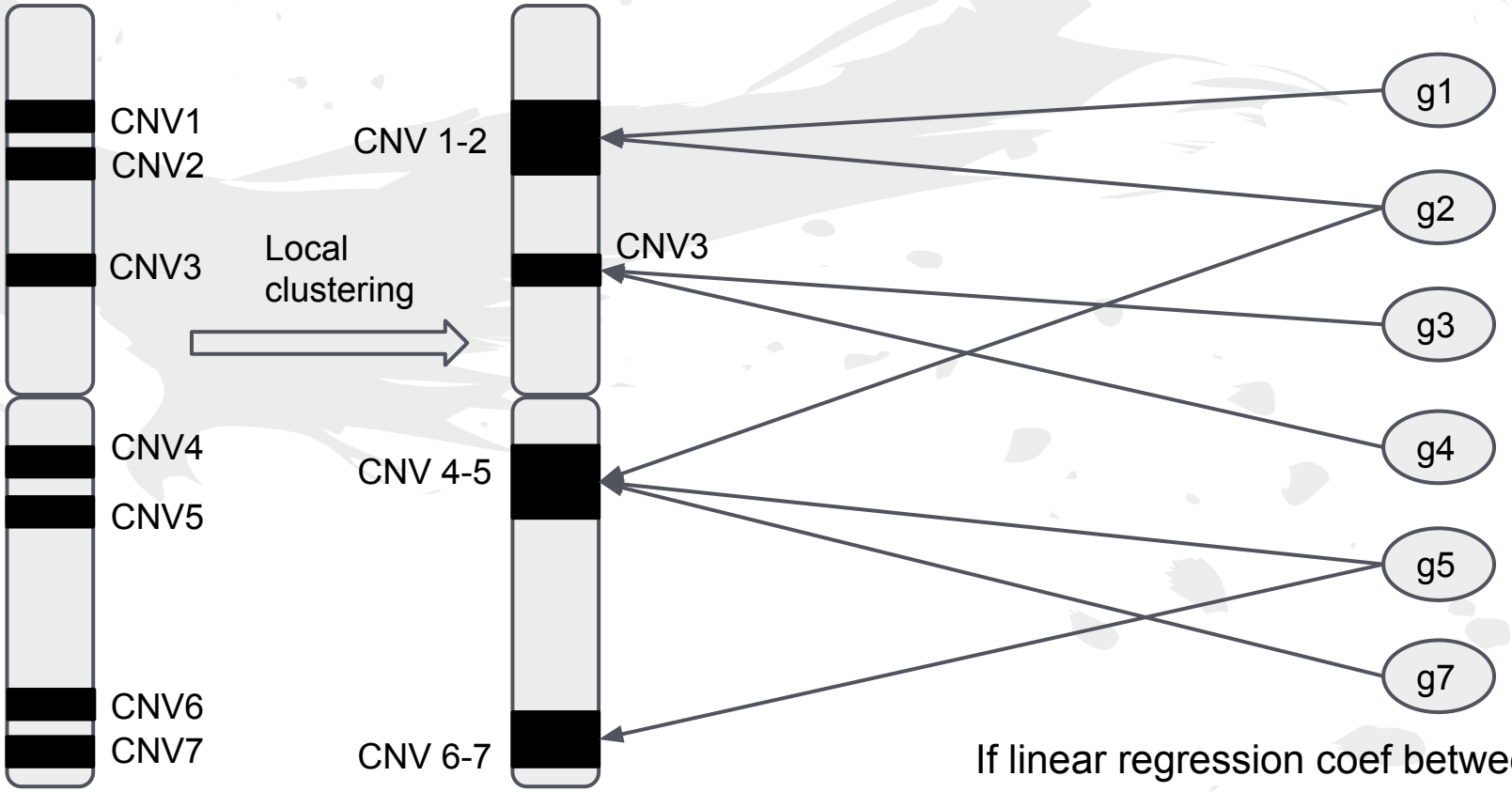
Hooray! We've just got:
{g1, g2, g3, g4, g5, g7}

Getting associated loci



CNV = copy number variations for all disease samples

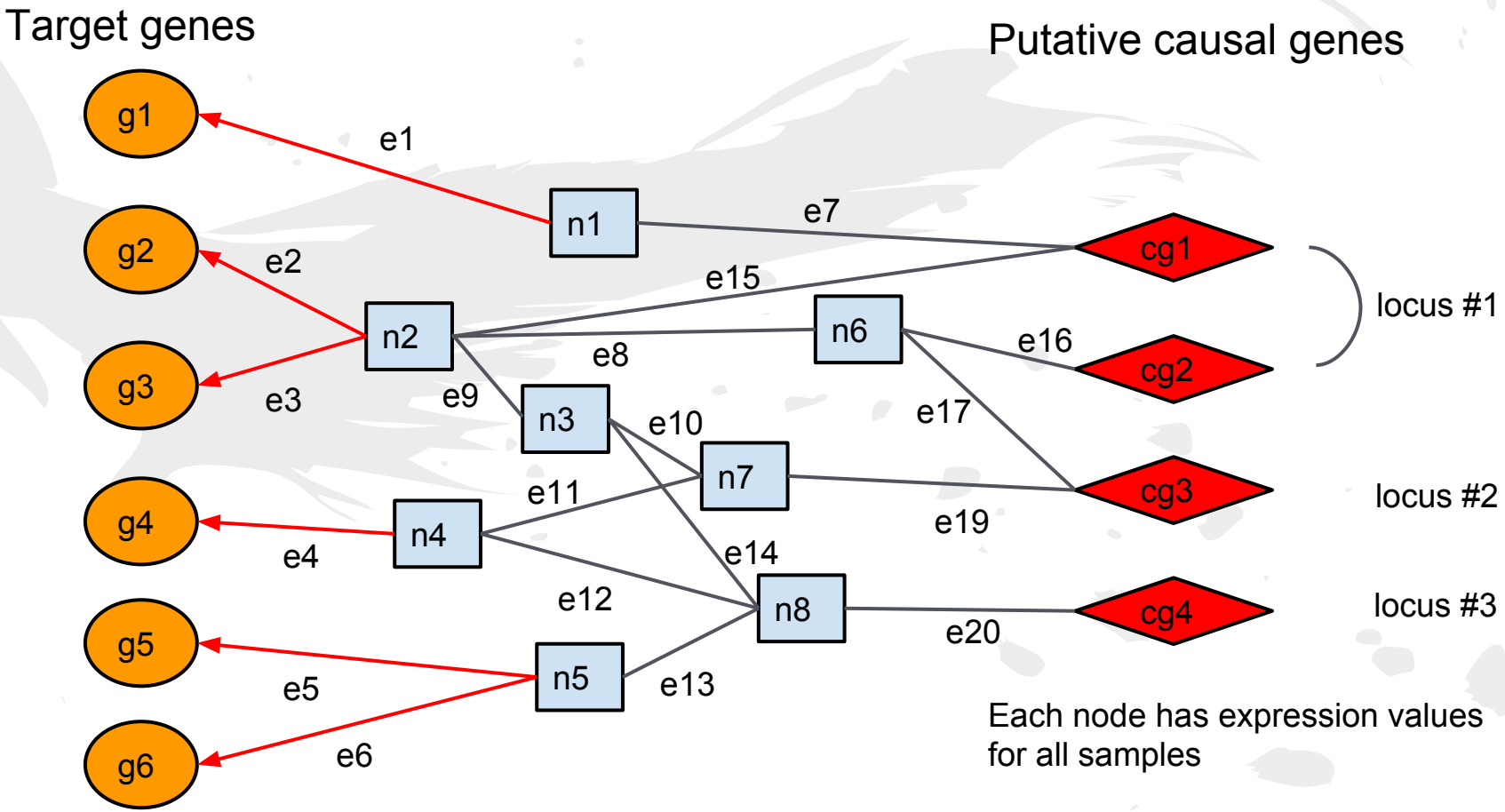
Getting associated loci



CNV = copy number variations for all disease samples

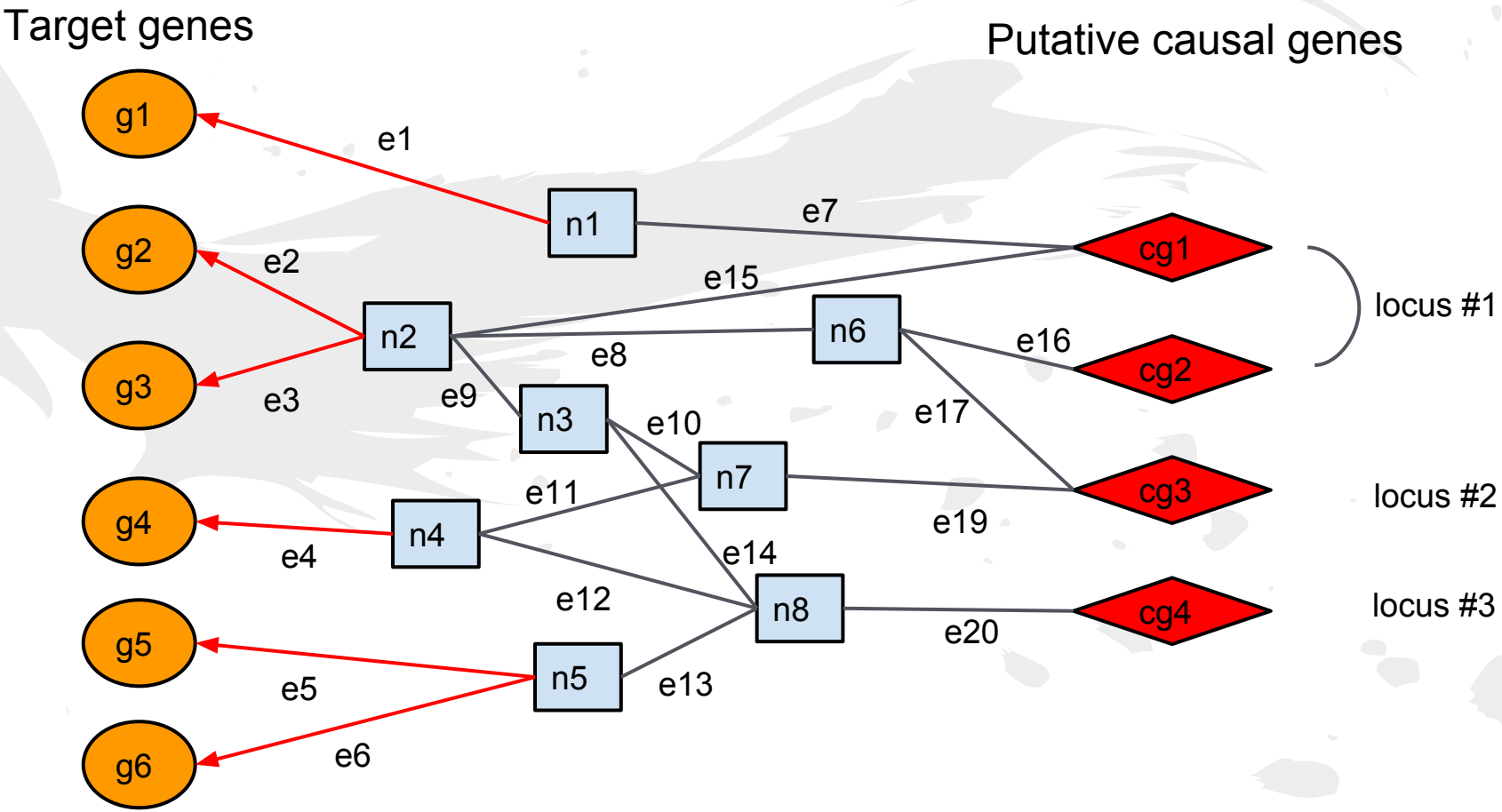
If linear regression coef between gene expression and CNV values > THRESHOLD then we take such locus

Selecting causal genes



Network of interactions consists of ppi, pdi and pho events

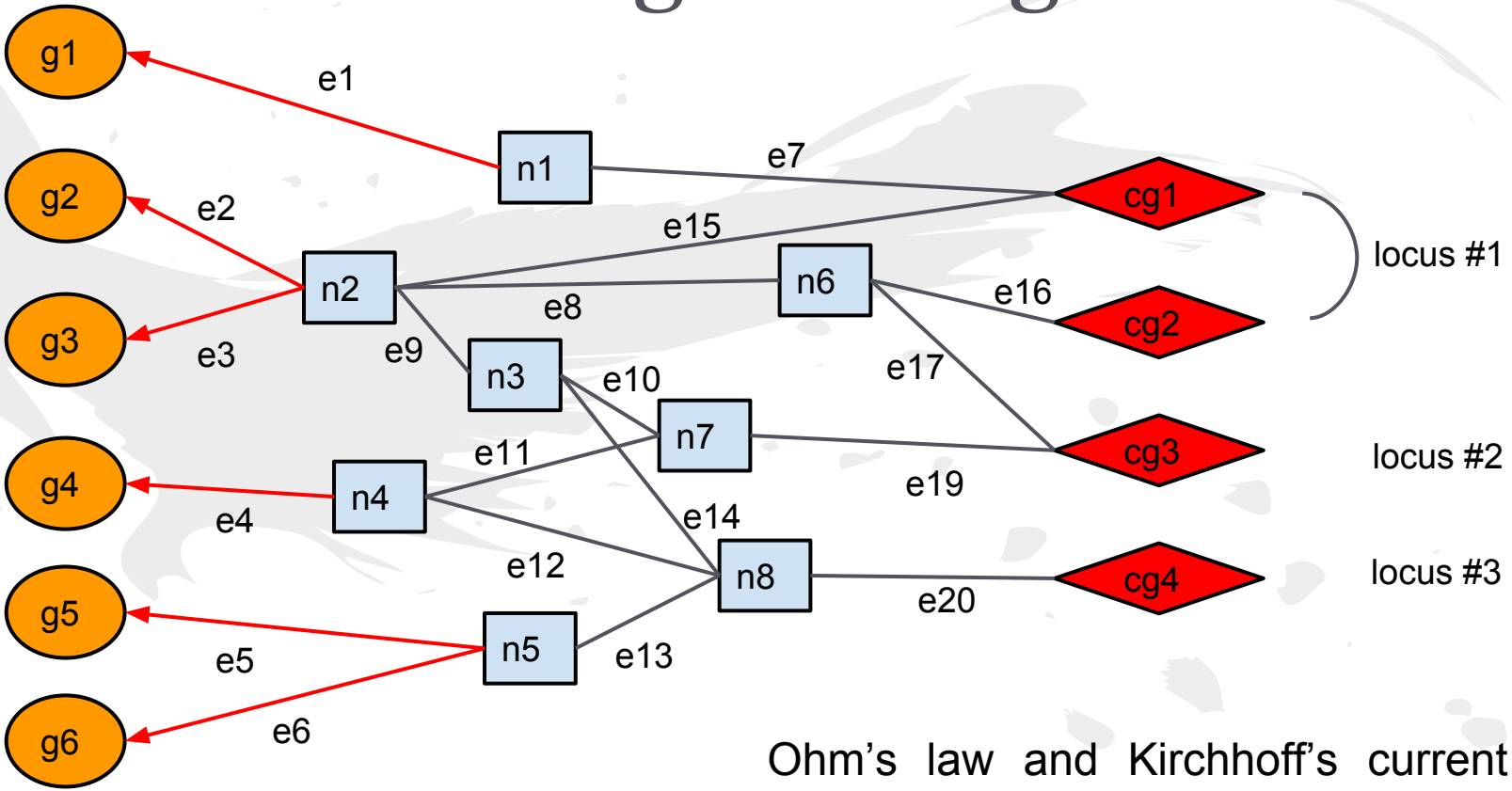
Selecting causal genes



Selecting causal genes

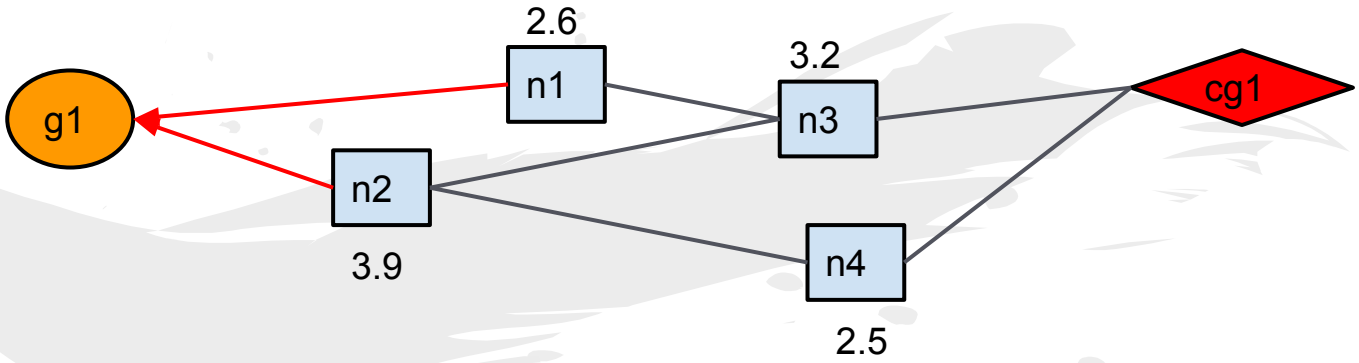
- Modelling flow of information requires set of rules for both nodes and edges;
- Need to set values for each node using correlation between this node and target gene node and each edge as mean of its nodes;
- Flow passes easily those nodes that are most correlated with target node;
- Physics saves the day;

Selecting causal genes

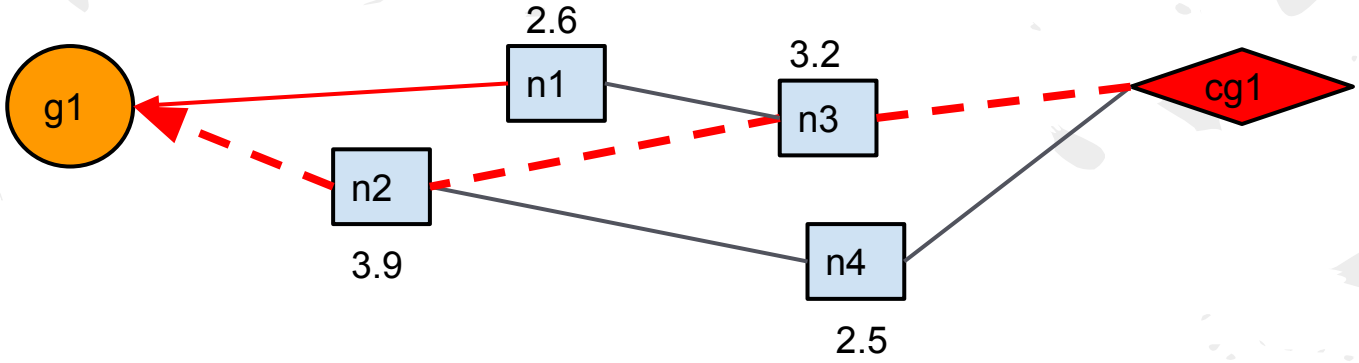


Ohm's law and Kirchhoff's current law allow to compute current to each causal gene (and also for each node).

Identifying dysregulated pathways



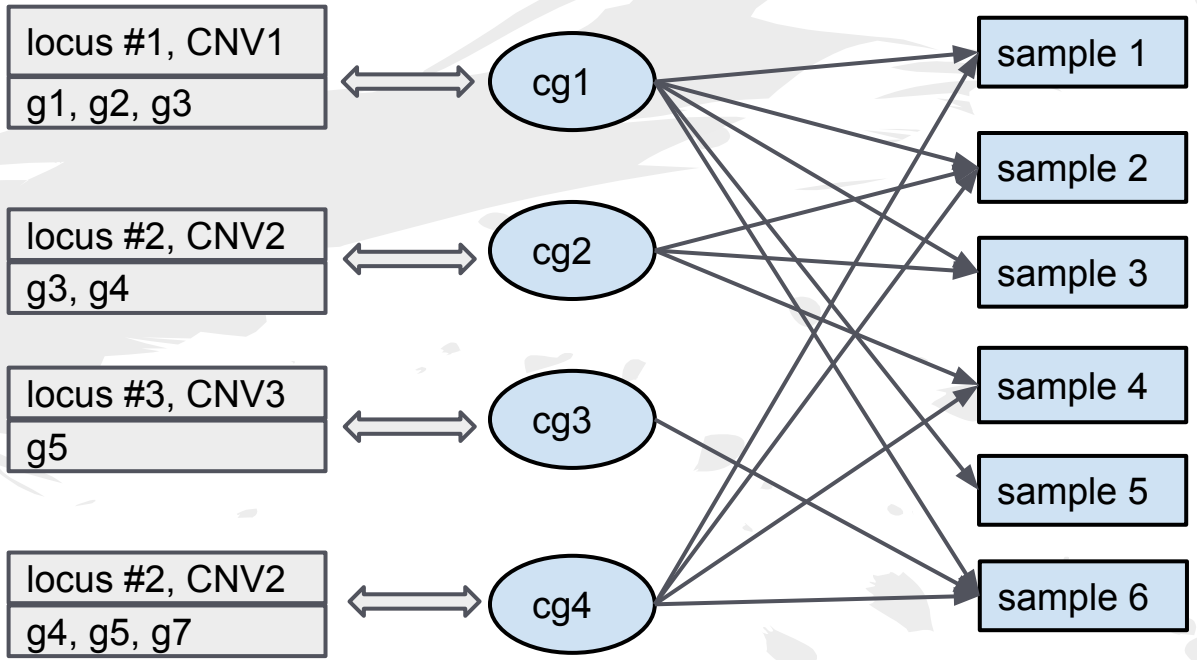
Choose a path to get max value of current for all its genes:



Selecting final causal genes

We stop if coverage weight is more or equal to W. That must be true for all samples except B.

Let's consider:
W = 2, B = 2



We want to select minimum number of relevant genes connected with samples

Selecting final causal genes

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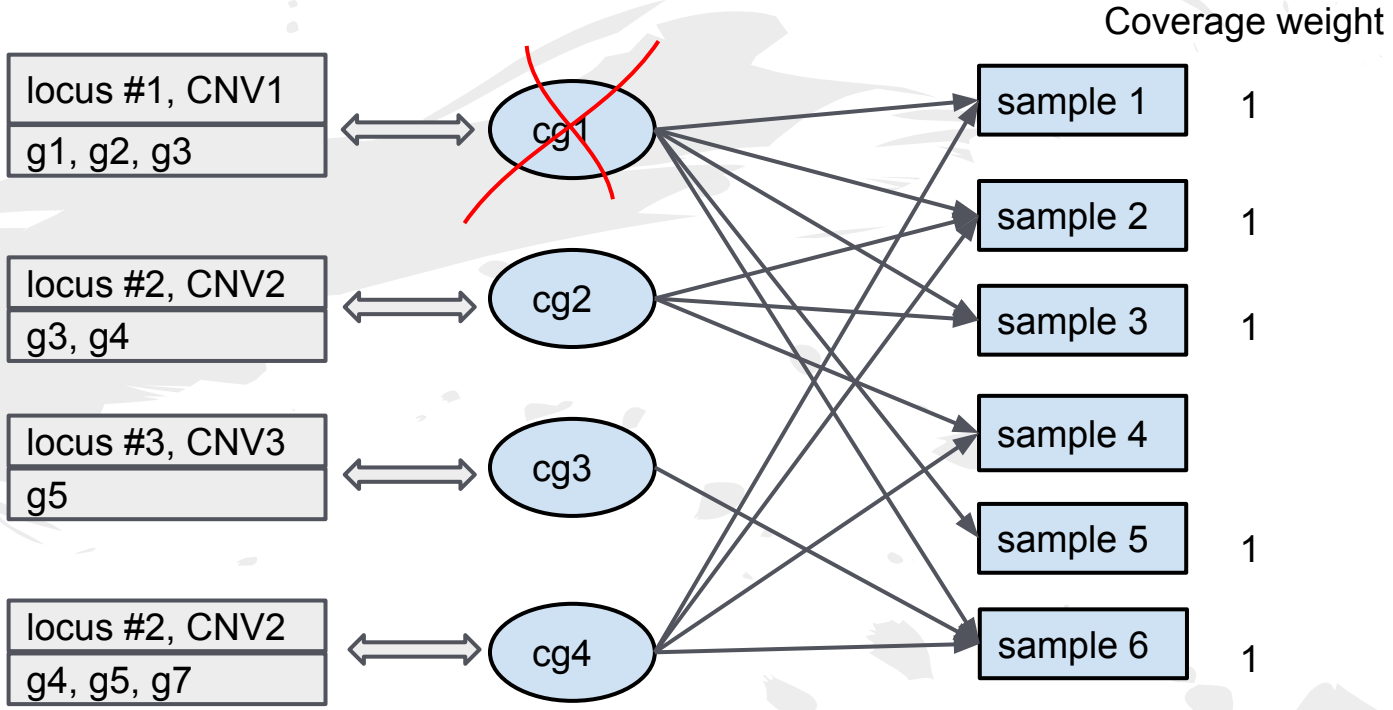

Take cg1 because it has total weight 5 (edges count)

Selecting final causal genes

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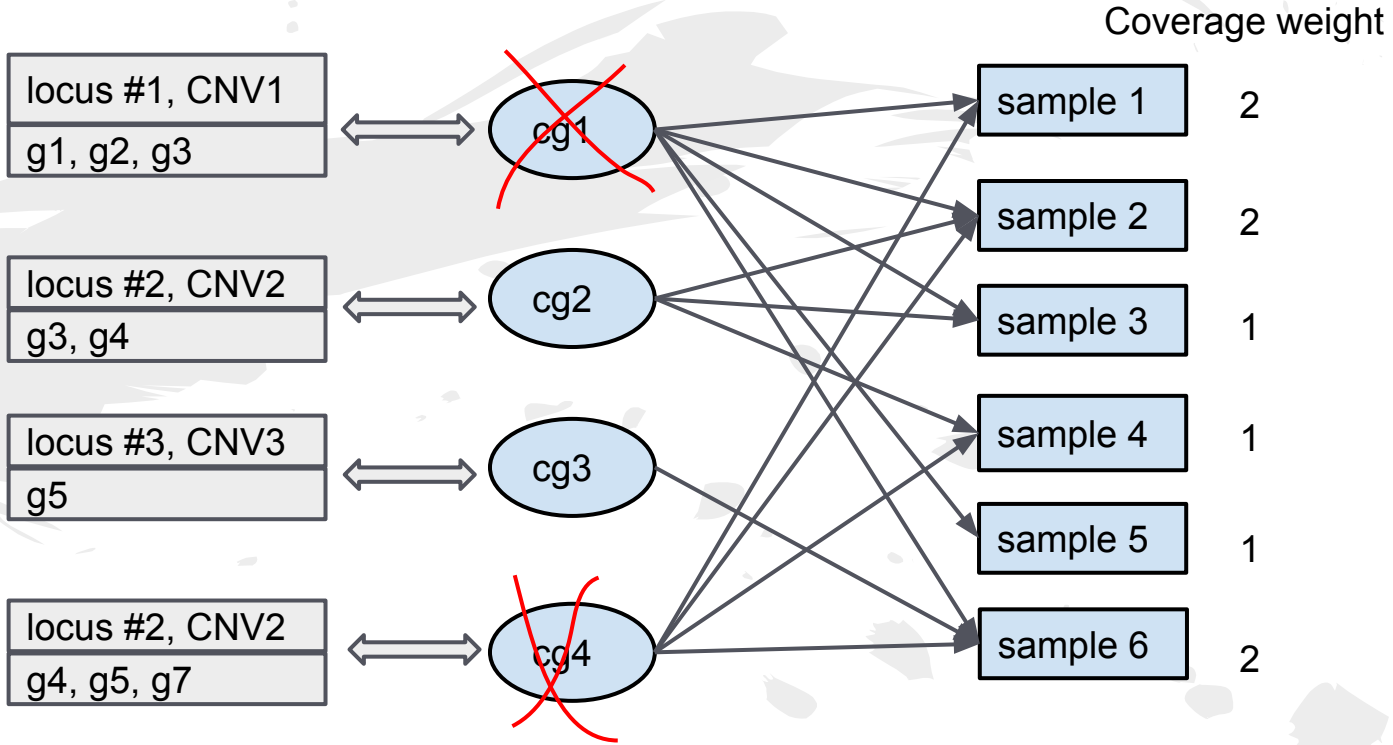

Take cg4 because it has total weight 4 (edges count)

Selecting final causal genes

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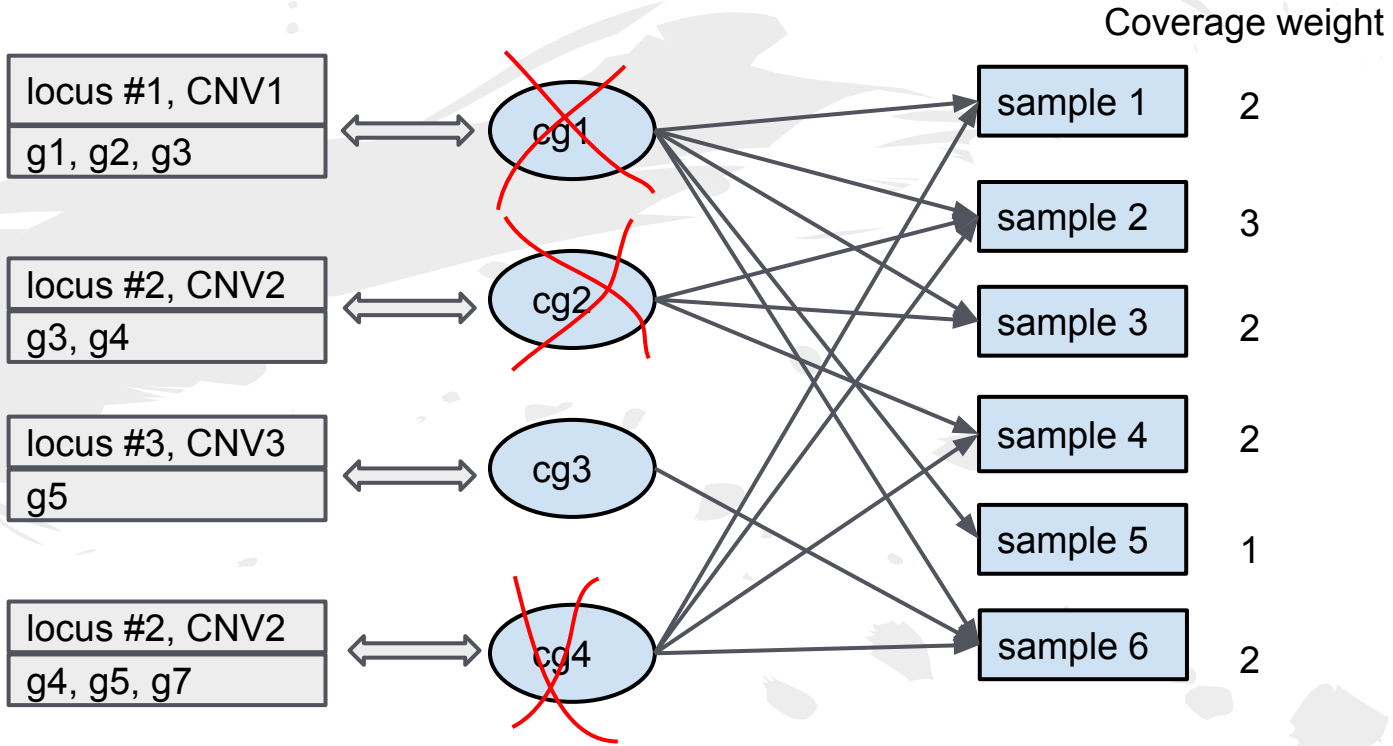

Take cg2 because it has total weight 3 (edges count).
Hooray! We've just got: {cg1, cg2, cg4}

Implementation details

A lot of parsing data

Work with statistics

Python + numpy + networkx?

Work with graph-like structures

Avoiding one bottleneck

We stop if coverage is more or equal to A. That must be true for all samples except B.

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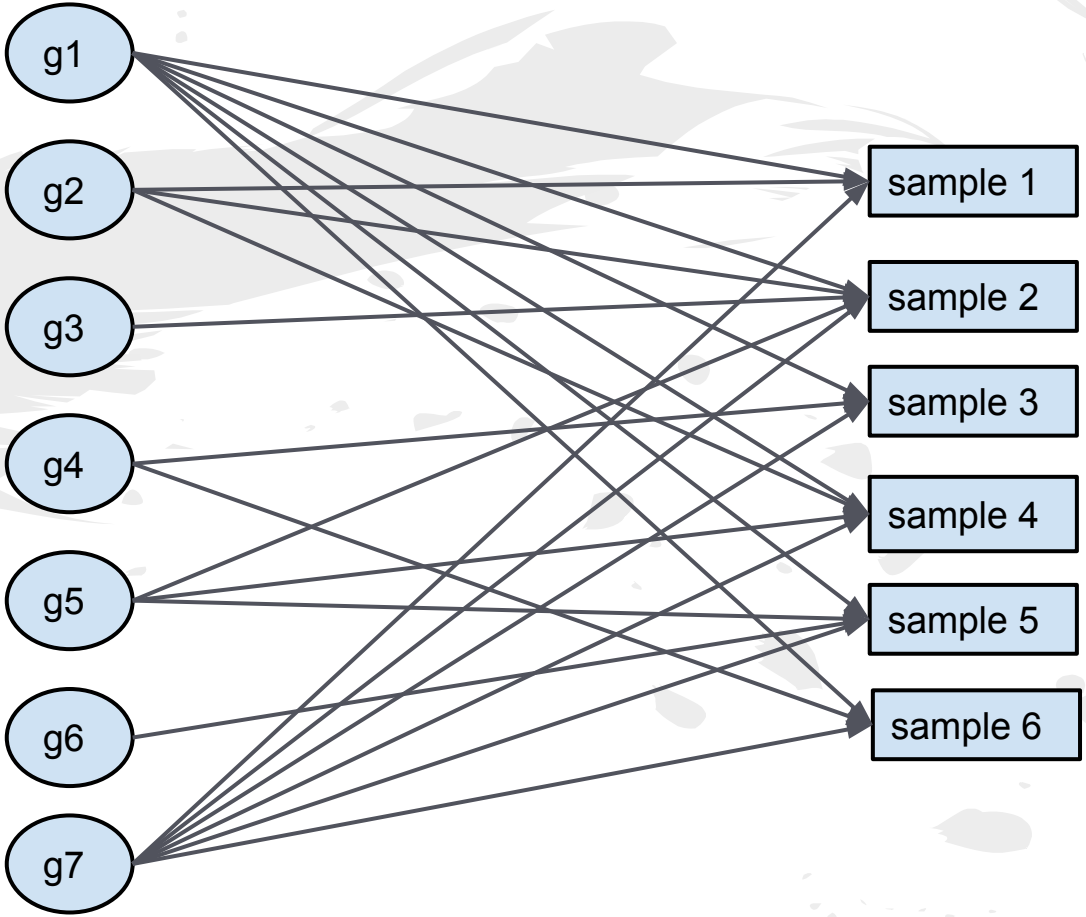

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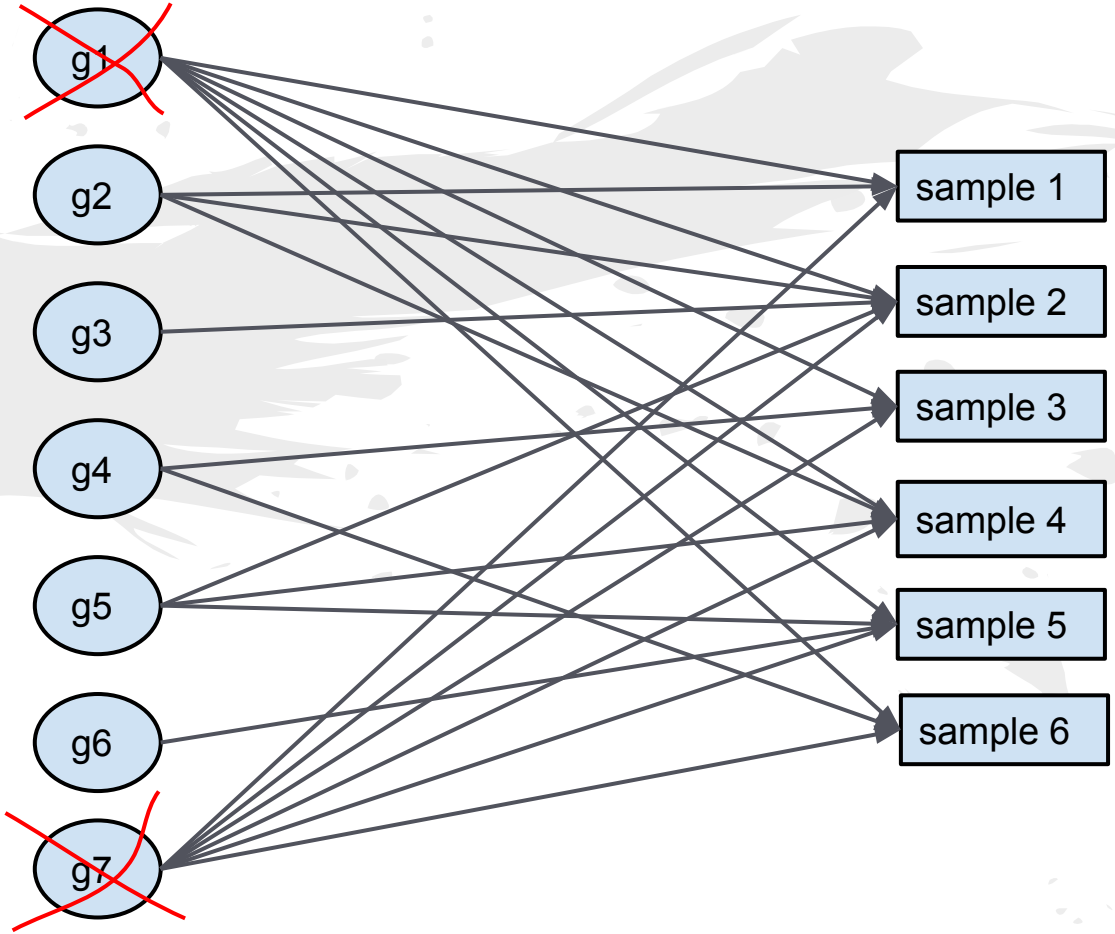


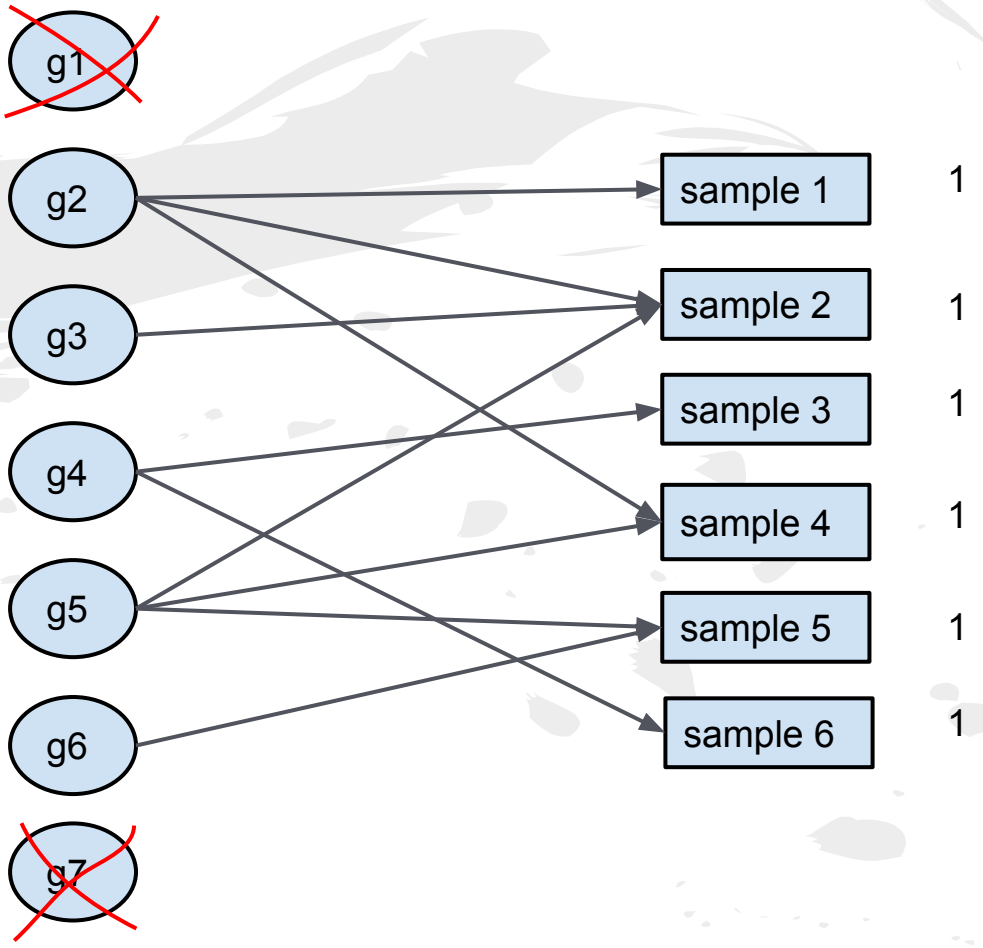
OK. We've just got {g1, g7}.

Hey!
What is about g2 and g4???

Avoiding one bottleneck

Possible solution:

- take those genes that have twice more connections that all other genes;
- consider significant genes as exactly one gene;
- run usual algorithm without these significant genes;



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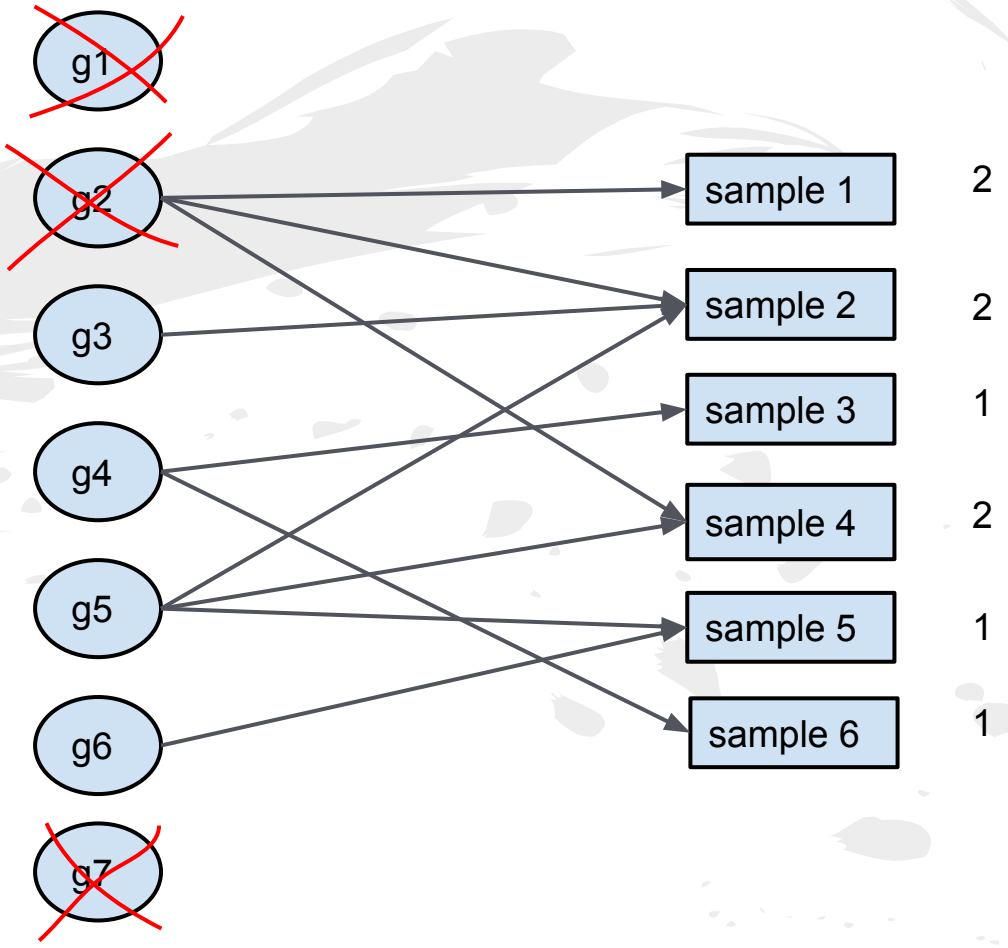

Avoiding one bottleneck

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Let's consider:
A = 2, B = 2

We've just got {g1, g7, g2, g5}.

Improvements to the existing tool

- Target genes selection algorithm enhancement;
- Refactoring of source code;
- User-friendliness;
- Source code lines reduction;
- Github repo:

  https://github.com/RaiaN/netQTL

Questions?