Identification of causal signature using omics data integration and network reasoning-based analysis

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Introduction

Identifying a **pathological signature** for a complex disease remains a challenge.

The actual definition of a signature in the context of a disease is :

- a set of features able to separate **two populations**
- based on **statistical test**

Features can be further used as candidate **therapeutic targets**.

Limits of current approaches

1. Limited to one omic layer
2. Require a clear stratification of population
3. Identified features = mix causes, consequences and noise
4. Limited to the most striking effects ⇒ regulation ?

Objective : Pathological signature based on individual features

⇒ **Individualize** the identification of signature based on patient specific information (Polymorphism + Gene expression)

⇒ **Integrate multi-omics data with prior knowledge on interaction network**

Method

Part 1 : Discretization of omics data

By patient

Genotyping

Gene → SNP with *HIGH* impact → Yes → Filter and discretization over gene expression → Value in { 1 ; -1 }

SNP with *HIGH* impact → No → Undefined value

eQTL → Filter and discretization over gene expression

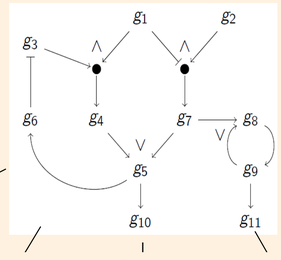
Gene expression

Analysis of each gene expression → ? ? ? → < [Interval of expression for each gene in control population] < → Value in : { -1 , 0 , 1 }

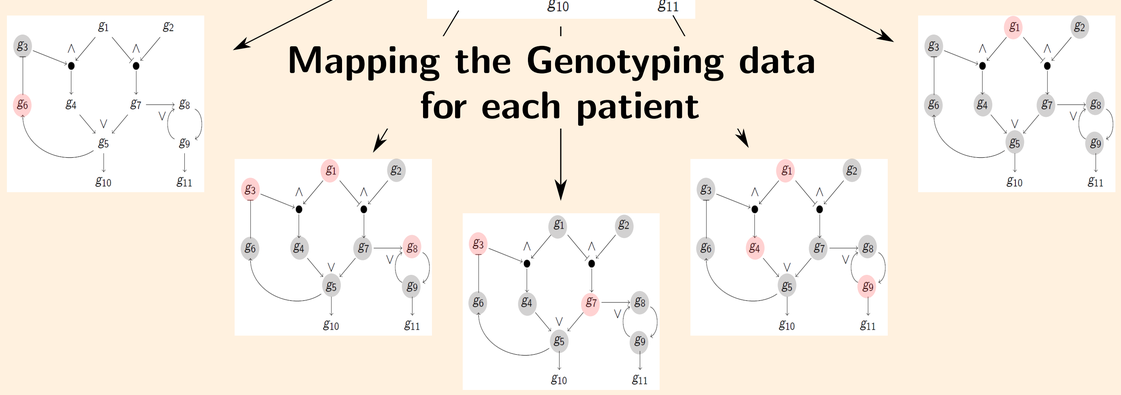
Part 2 : One-by-one patient approach

One biological network

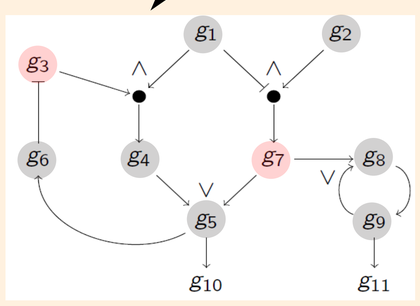
KRF [1] (Pathway Commons)



Mapping the Genotyping data for each patient



Part 3 : Identifying Minimal Intervention Set (MIS)



Dynamic of the system ?
Regulatory dependancies ?

Need to clamp other variables (= MIS [2])
in order to
explain the phenotype based on the genotype ?
Caspo [3]

Stable state of the system
=
Gene Expression
=
Phenotype

[1] Blavy, P. et al (2014) BMC Systems Biology

[2] Samaga, R. et al (2010) Journal of Computational Biology

[3] Videla, S. et al.. (2017). Bioinformatics

Conclusion & Perspectives

Diagnosis signature from literature is insufficiant for complex disease

Identify a signature by taking into account the dependencies of regulation

Causal signature ⇒ Minimal set of MIS between patients

⇒ New stratification of patients

⇒ Enrich signature with clinical criteria

⇒ Propose candidate therapeutic targets