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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 $\Rightarrow$ regulation ?

Objective : Pathological signature based on individual features

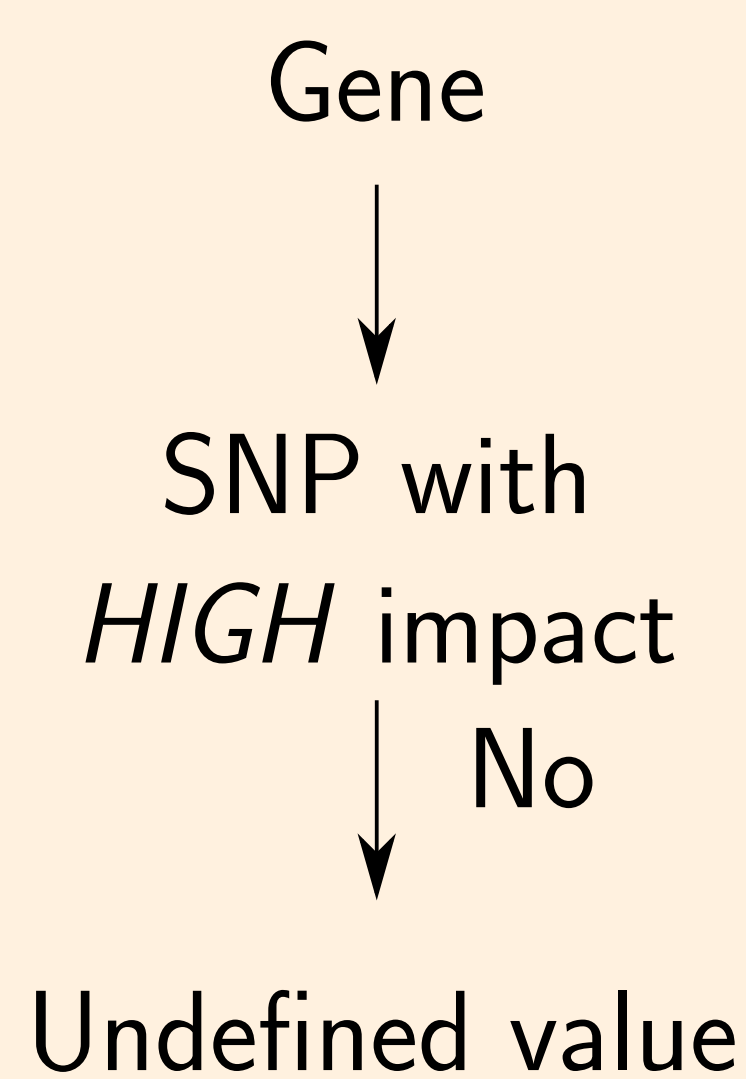
$\Rightarrow$ **Individualize** the identification of signature based on patient specific information (Polymorphism + Gene expression)

$\Rightarrow$ **Integrate multi-omics data with prior knowledge on interaction network**

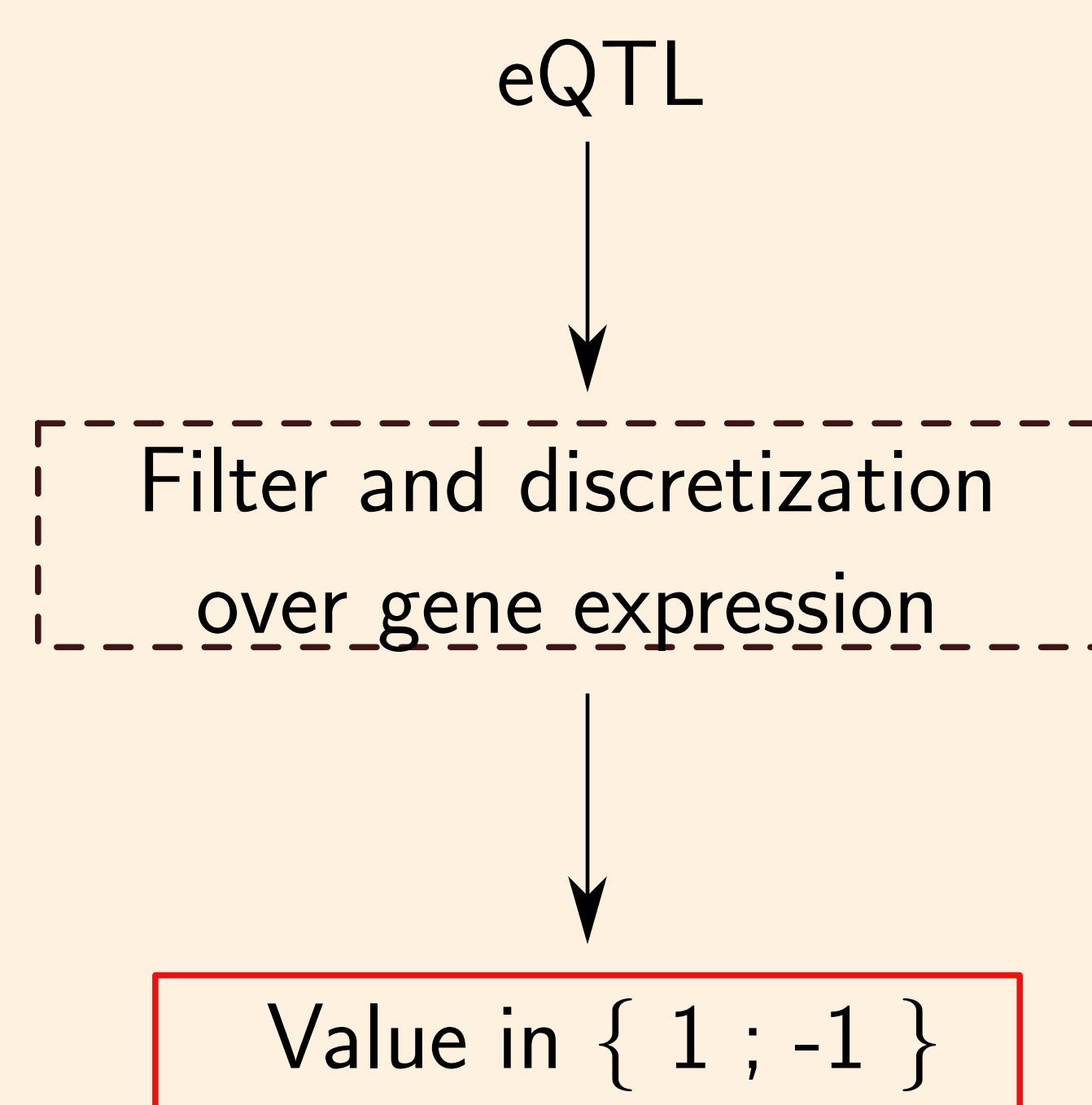
Method

Part 1 : Discretization of omics data

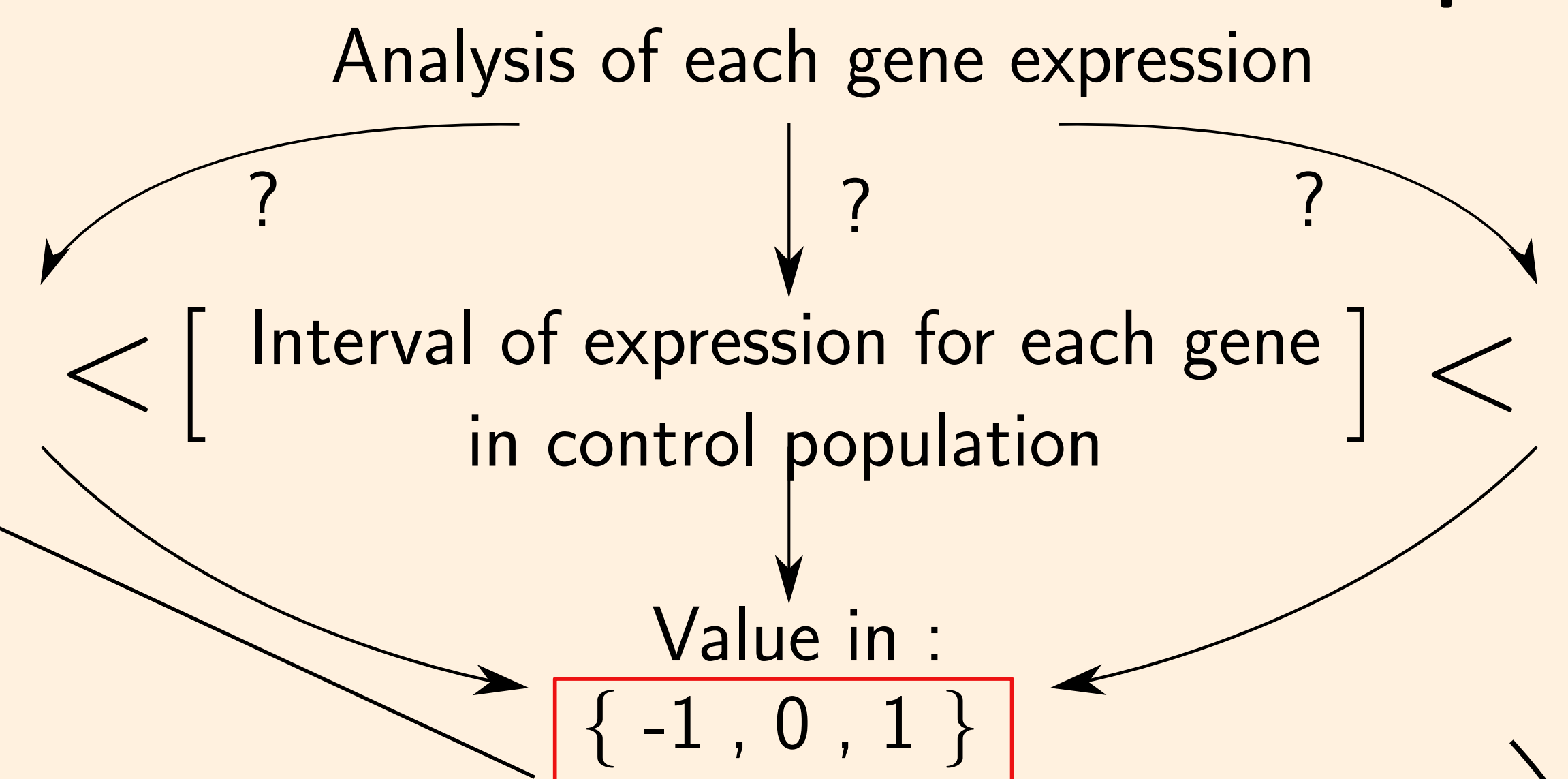
Genotyping



By patient

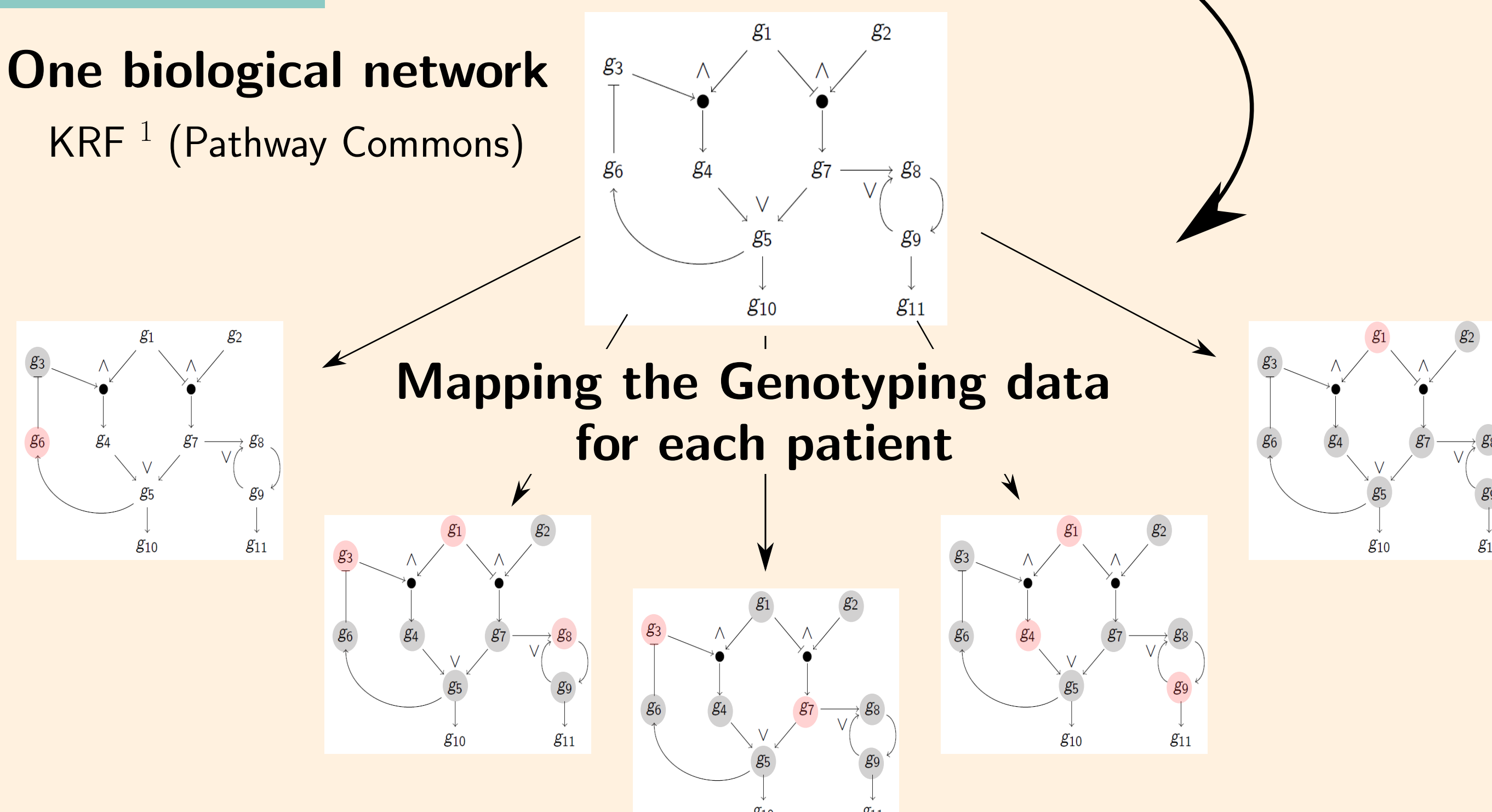


Gene expression

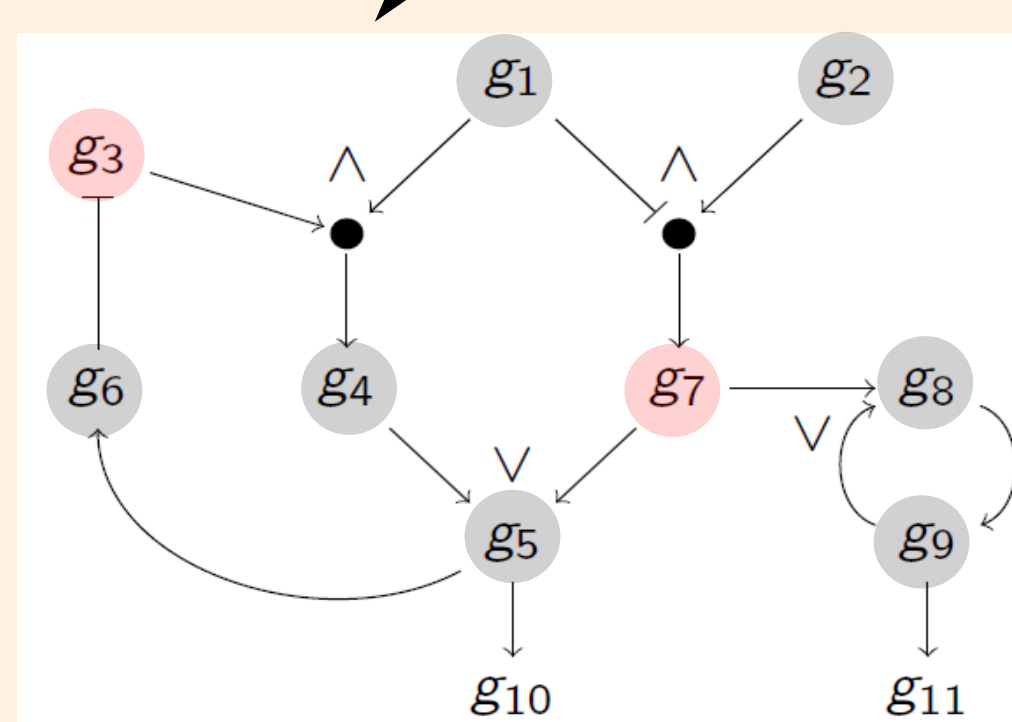


Part 2 : One-by-one patient approach

One biological network KRF¹ (Pathway Commons)



Part 3 : Identifying Minimal Intervention Set (MIS)



Dynamic of the system ?
Regulatory dependancies ?

Need to clamp other variables (= MIS²)
in order to
explain the phenotype based on the genotype ?
Caspo³

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 insufficient for complex disease
Identify a signature by taking into account the dependencies of regulation

Causal signature $\Rightarrow$ Minimal set of MIS between patients

- $\Rightarrow$ New stratification of patients
- $\Rightarrow$ Enrich signature with clinical criteria
- $\Rightarrow$ Propose candidate therapeutic targets