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

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Introduction

Identifying a \textit{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 \textit{two populations}
- based on \textit{statistical test}

Features can be further used as candidate \textit{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

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

$\Rightarrow$ \textbf{Integrate} multi-omics data with prior knowledge on interaction network

Method

\textbf{Part 1: Discretization of omics data}

\textbf{Genotyping}

\text{Gene $\rightarrow$ SNP with HIGH impact $\rightarrow$ Yes $\rightarrow$ Filter and discretization over gene expression $\rightarrow$ Value in \{1 ; -1\}}

\text{Undefined value $\rightarrow$ No $\rightarrow$ Gene expression $\rightarrow$ Analysis of each gene expression $\rightarrow$ Value in \{-1 , 0 , 1\}}

\text{Interval of expression for each gene in control population $\Rightarrow$ Mapping the Genotyping data for each patient $\Rightarrow$ Dynamic of the system ? $\Rightarrow$ Regulatory dependancies ?}

\text{Stable state of the system $\Rightarrow$ Gene Expression $\Rightarrow$ Phenotype $\Rightarrow$ Need to clamp other variables (= MIS $^2$) in order to explain the phenotype based on the genotype ?}

\textsuperscript{1} Blavy, P. et al (2014) BMC Systems Biology
\textsuperscript{3} Videla, S. et al. (2017). Bioinformatics

\textbf{Part 2: One-by-one patient approach}

\text{One biological network KRF $^1$ (Pathway Commons) $\Rightarrow$ Mapping the Genotyping data for each patient $\Rightarrow$ Dynamic of the system ? $\Rightarrow$ Regulatory dependancies ?}

\text{Stable state of the system $\Rightarrow$ Gene Expression $\Rightarrow$ Phenotype $\Rightarrow$ Need to clamp other variables (= MIS $^2$) in order to explain the phenotype based on the genotype ?}

\textbf{Part 3: Identifying Minimal Intervention Set (MIS)}

Conclusion & Perspectives

Diagnosis signature from literature is insufficient for complex disease
Identify a signature by taking into account the dependencies of regulation

\textbf{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