Network-medicine algorithms

T9 - Network-medicine-based drug repurposing

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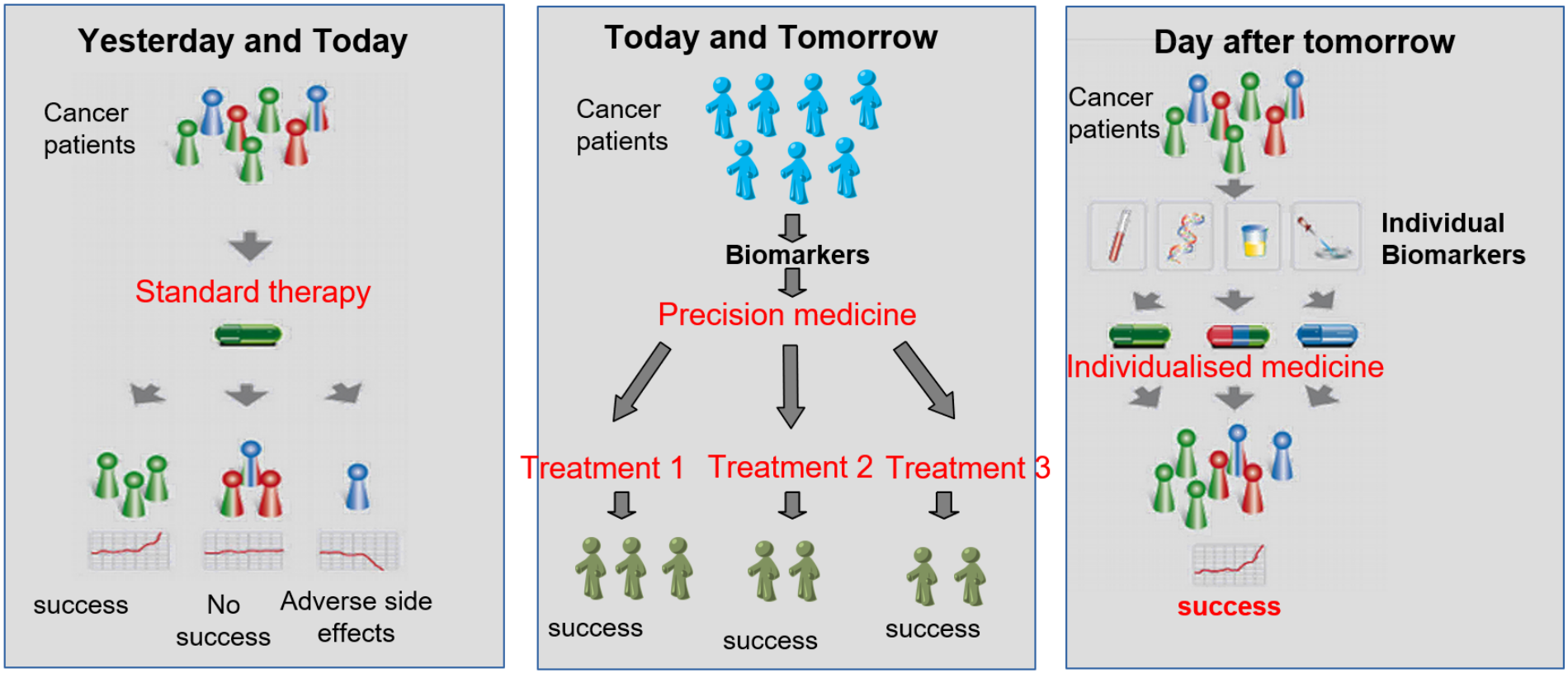
Materials adapted from Prof. Dr. David B. Blumenthal

Table of content

- Why disease module mining for precision medicine?
- Diamond and Robust
- Personalized Page Rank for drug prioritization (a.k.a. Trust Rank).

Precision medicine

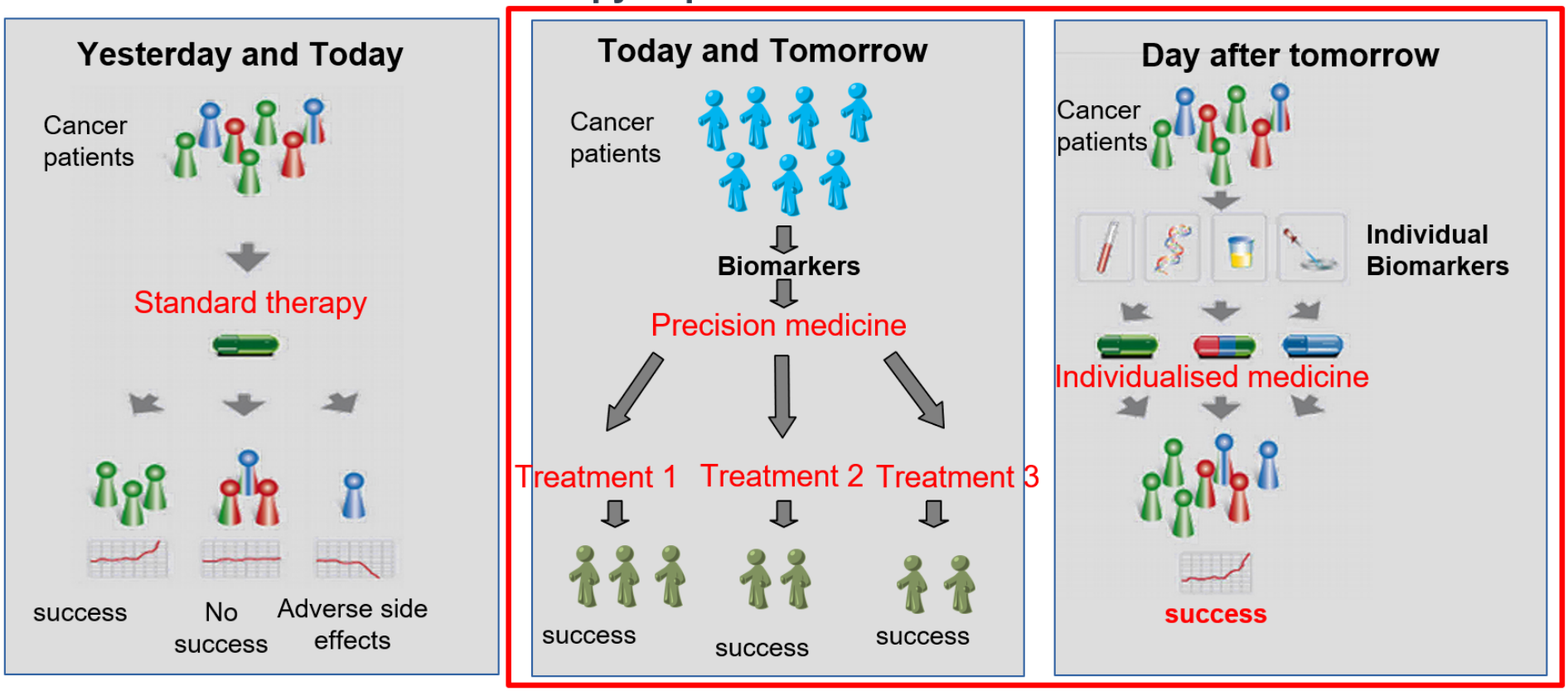
Transition from one-size-fits-all therapy to precision medicine and individualized medicine:



Courtesy Alexander König, Volker Ellenrieder UMG 2019

Precision medicine

Transition from one-size-fits-all therapy to precision medicine and individualized medicine:

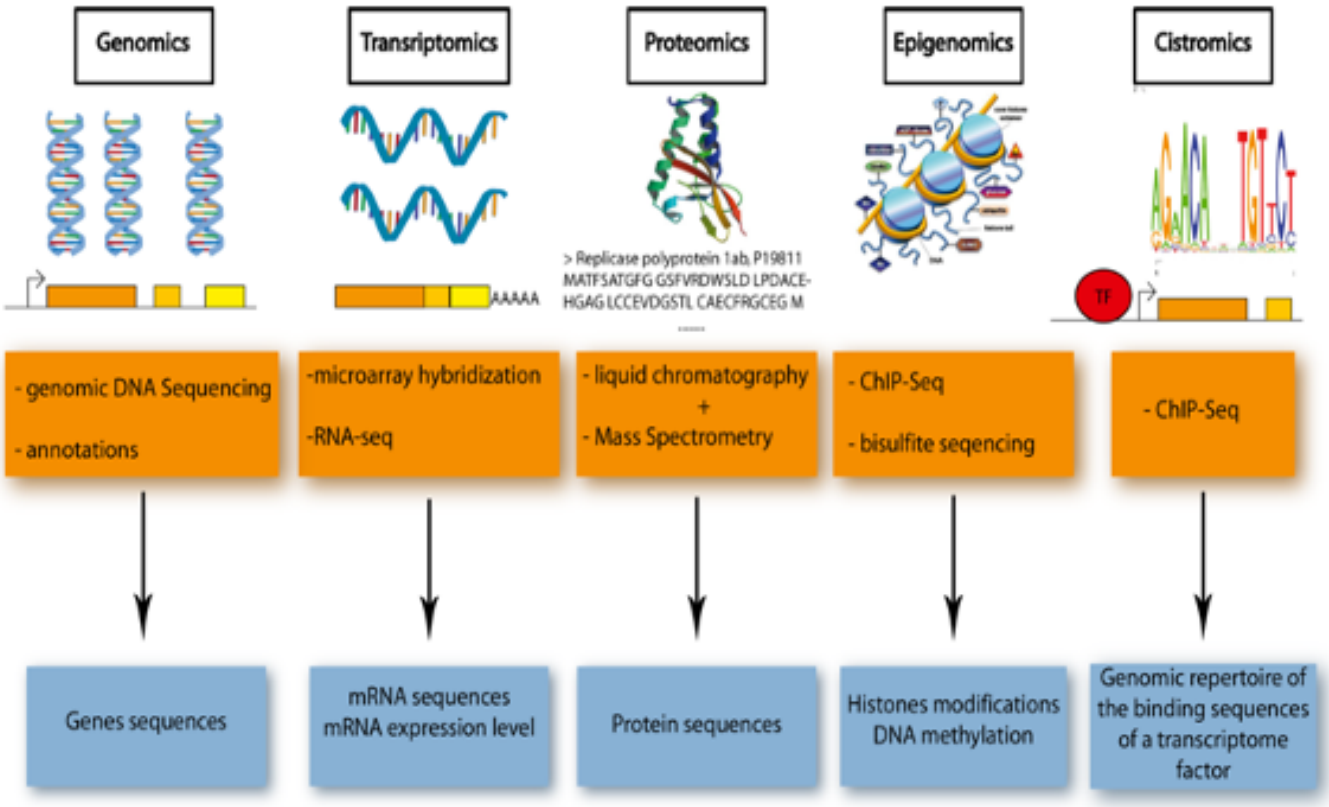


Courtesy Alexander König, Volker Ellenrieder UMG 2019

The Holy Grail of Precision Medicine

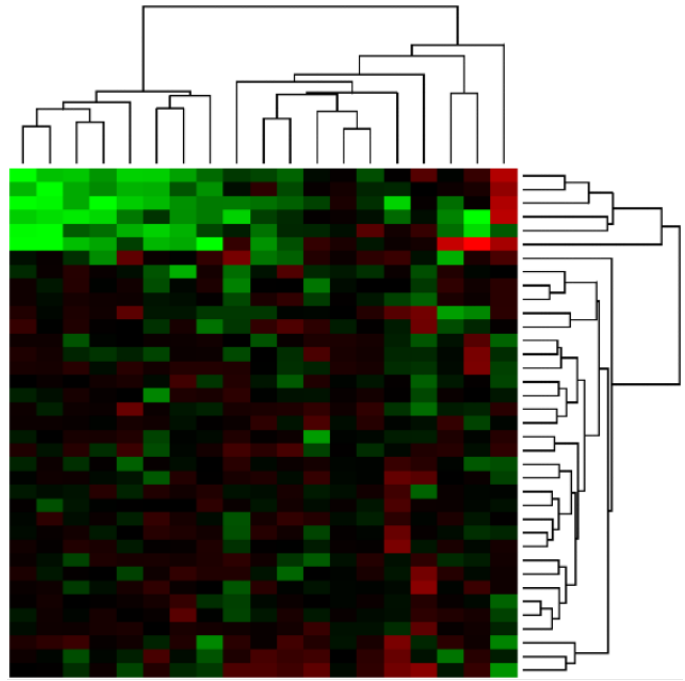
- **Goal:** Understand molecular mechanisms driving complex disease.
  - ⇝ Might pave the way for novel, causally effective treatment strategies.
- **How to:**
  - Mine omics data for candidate disease mechanisms.
  - Validate the predicted mechanisms in silico to assess initial plausibility.
  - Validate the most promising candidate mechanisms in pre-clinical studies.

Reminder: Different Types of Omics Data



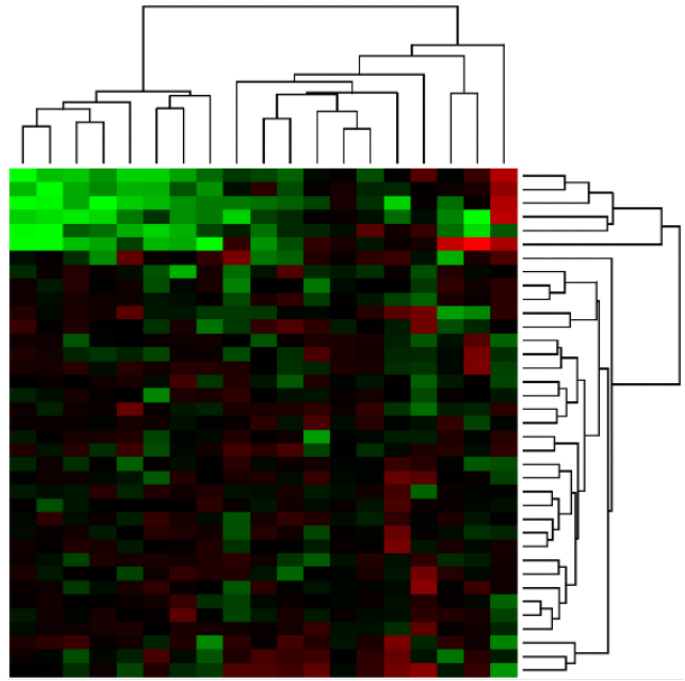
Classical Statistical Data Mining on Omics Data?

- Large number of variables (e.g. genes).
- Small number of samples.
  - $\rightsquigarrow$ Very bad sample-to-feature ratio.
    - Noise.
    - **Solution: gather billion of data points?**

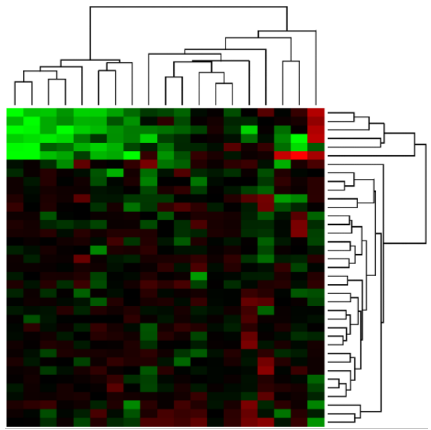


Classical Statistical Data Mining on Omics Data?

- Large number of variables (e.g. genes).
- Small number of samples.
  - ⇝ Very bad sample-to-feature ratio.
    - Noise.
    - **Solution: gather billion of data points?**
- **Standard analyses ignore effects of interactions.**



Integrating Omics and Network Information



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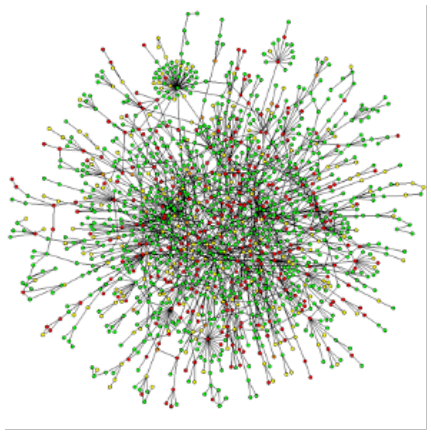


- Mitigates shortcomings of purely statistical analyses.
- Find novel potential mechanisms, biomarkers, and drug targets.

⇝ Paves the way for personalized medicine.

Disease Module Mining

Generic Problem Formulation

Given omics data for a disease of interest and a biological network, design a method to compute one or several subnetworks (disease modules) within the biological network that constitute promising candidate disease mechanisms.

Design Decisions to be Made

- Which exact input should our method accept?
- Which algorithmic model should our method employ?

Which Molecular Networks?

PPI Networks

- Can pinpoint to interacting proteins driving a disease.
- \+ Easy to obtain from public databases.
- \+ Experimentally confirmed interactions.
- – Subject to study bias.
- – Often unspecific.

GRNs

- Can pinpoint to gene regulatory cascades that break down in a disease.
- – Only very incomplete GRNs are experimentally confirmed.
- – Typically inferred from gene expression data.
- – Very noisy.
- \+ De novo inferred and therefore not subject to study bias.
- – More targeted, tissue-specific information.

Projecting the Omics Data onto the Networks: Seed Genes Obtained from Gene Expression Data or Genome-Wide Association Studies

- Compute gene-level *P*-values from gene expression or GWAS data.
- Set significance cutoff and keep significant genes as seeds (binary input).
- For many diseases, similarly computed lists of seed genes can be obtained from public databases.

\+ Very simply and user-friendly input format.

– Possible information loss due to binarization.

– Arbitrariness in selecting the cutoff.

Input Used by Existing Tools

Gene Expression Matrix

- COSINE
- GXNA
- GrandForest

Indicator Matrix

- KeyPathwayMiner

Gene Scores

- HotNet2
- Hierarchical HotNet
- NetCore

Seed Genes

- ClustEx2
- **DIAMOnD**
- MuST
- DOMINO
- **ROBUST**

DIAMOnD

- One of the most widely used DMMM (based on number of citations).
- Expects undirected networks (e. g., PPI networks) and seed genes as input.

RESEARCH ARTICLE

A DIseAse MOdule Detection (DIAMOnD) Algorithm Derived from a Systematic Analysis of Connectivity Patterns of Disease Proteins in the Human Interactome

Susan Dina Ghiassian[1,2☯], Jörg Menche[1,2,3☯], Albert-László Barabási[1,2,3,4*]

DIAMOnD

Task

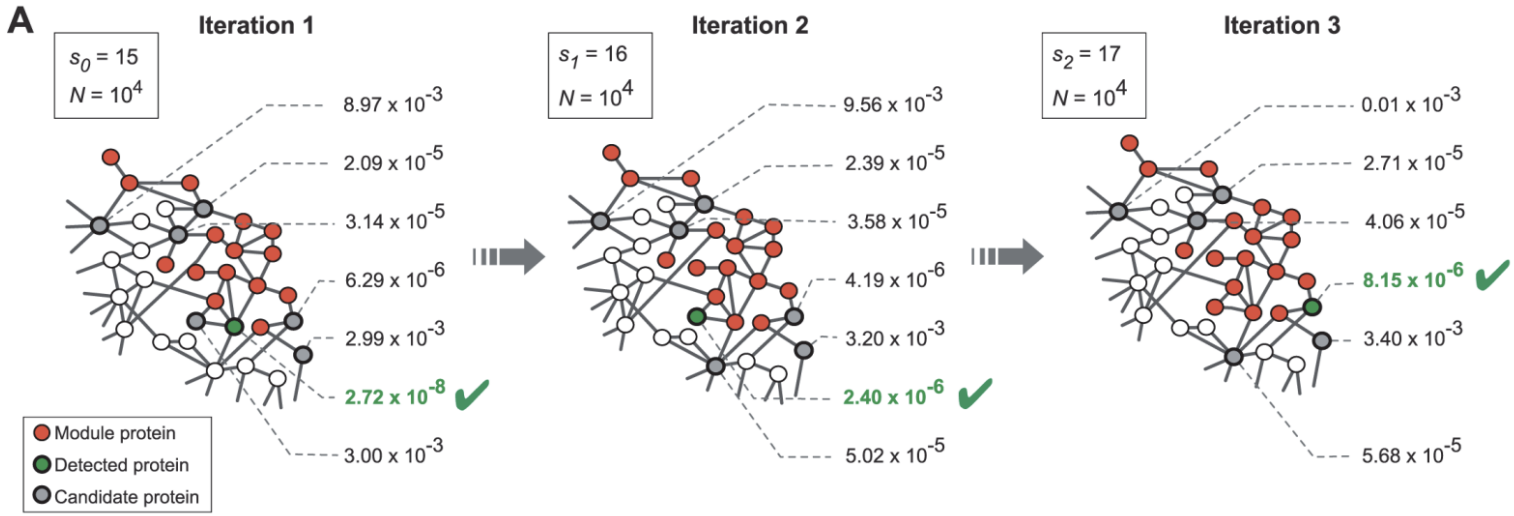
Given biological network $G = (V, E)$ and set of disease-associated seed genes $S \subset V$, find module $G[M]$ constituting a promising candidate disease mechanism, where $M \subset V$ is a node set with $M \supset S$.

Approach

1. **Assumption:** Treat seed sets S as proxies for modules M that should be predicted.
2. **Data integration:** Collect seed sets for many complex diseases.
3. **Data analysis:** Find network property characterizing these seed sets.
4. **Algorithm design:** Use this property to extend the seed sets to disease modules containing them.

The DIAMOnD Algorithm

1. Initialize module M with seed set.
2. Compute connectivity significance for all genes adjacent to a node in M but not contained in it.
3. Put node with smallest P-value into M.
4. Iterate until desired module size has been reached.



Connectivity Significance

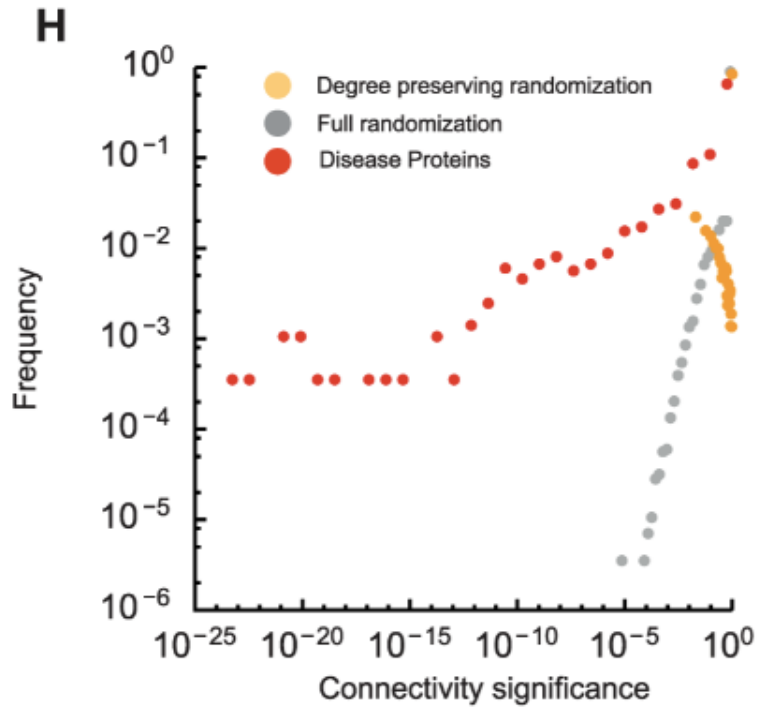
- Consider network with N genes (nodes) and $s_0 < N$ disease-associated seed genes.
- Assume that seed genes are randomly scattered across the network.
- It checks: "Is this protein more connected to the known disease genes than we'd expect just by chance, given its degree?"

Connectivity Significance of Disease-Associated Genes (I)

Comparison Against Random Genes and Randomized Networks

- Compute connectivity significance *P*-values for disease genes.
- Compare against randomly sampled genes.
- Compare agains disease genes in networks randomized with configuration model (degree-preserving).

⇝ Connectivity *P*-values are much smaller for disease genes than for random genes or randomized networks.



BIONETS

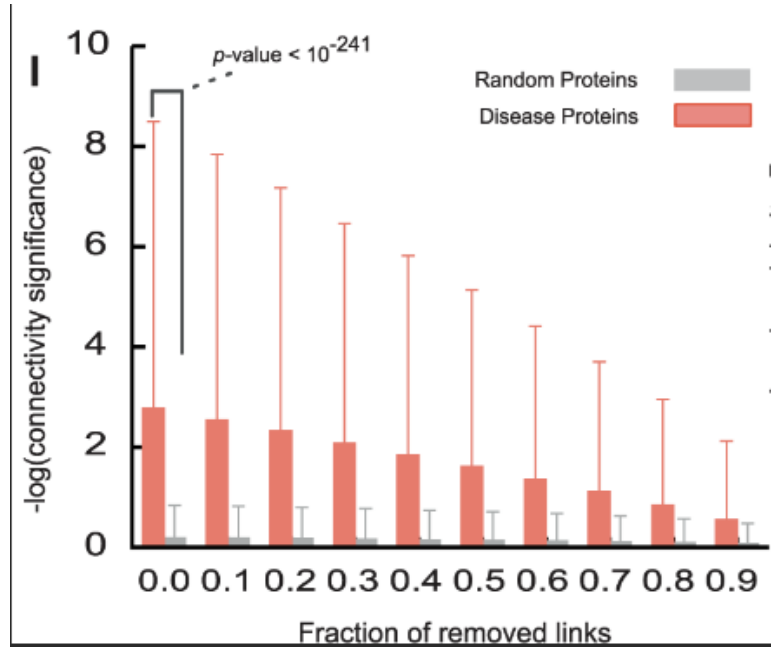
FAU

Connectivity Significance of Disease-Associated Genes (II)

Comparison Against Random Gene Sets with Random Removal of Edges

- Connectivity significance of disease genes drops with increasing number of removed edges.
- Connectivity significance of random genes remains largely unchanged.

⇝ Connectivity significance seams to be the right measure to characterize disease module.



Properties of the DIAMOnD Algorithm

- Genes contained in predicted modules have high connectivity significance by design.
- Implicitly assumes that known seeds constitute the core of the module (modules grow in a BFS-like way).
- All initial seeds always end up in the predicted module.
- Desired module size is a parameter that has to be provided by the user.

ROBUST

- DMMM from our lab.
- Also expects undirected networks (e. g., PPI networks) and seed genes as input.
- Designed to overcome robustness deficit of previous DMMMs.

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Article Contents

Abstract

Author notes

Supplementary data

ACCEPTED MANUSCRIPT

Robust disease module mining via enumeration of diverse prize-collecting Steiner trees

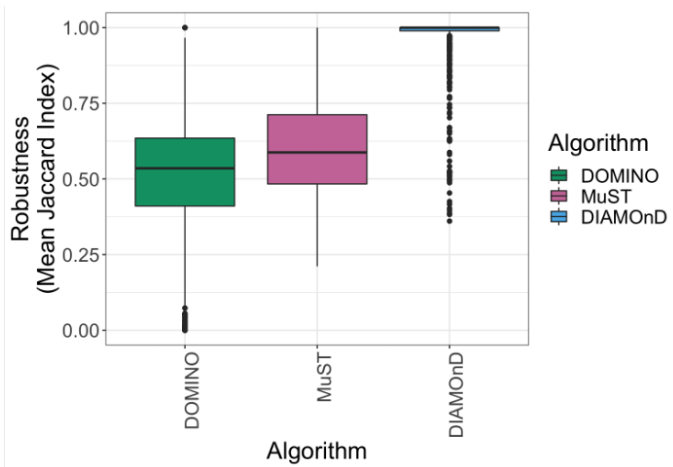
Judith Bernett, Dominik Krupke, Sepideh Sadegh, Jan Baumbach, Sándor P Fekete, Tim Kacprowski, Markus List, David B Blumenthal ✉ Author Notes

Bioinformatics, btab876, https://doi.org/10.1093/bioinformatics/btab876

Published: 04 January 2022 **Article history** ▾

Why Another Method?

- **Robustness of DMMMs:** Mean Jaccard index ($|M \cap M'|/|M \cup M'|$) of modules computed by DMMM when run multiple times on equivalent input (e. g., permuted storage order of network).
- DMMMs lack robustness and are subject to random bias.
- Robustness is important for trustworthiness of DMMMs.
- Biomedical scientists often hesitant to invest time and money in wet-lab validation of non-robust disease modules.
- **Question:** How can the robustness of DMMMs be improved?



Naïve Approach

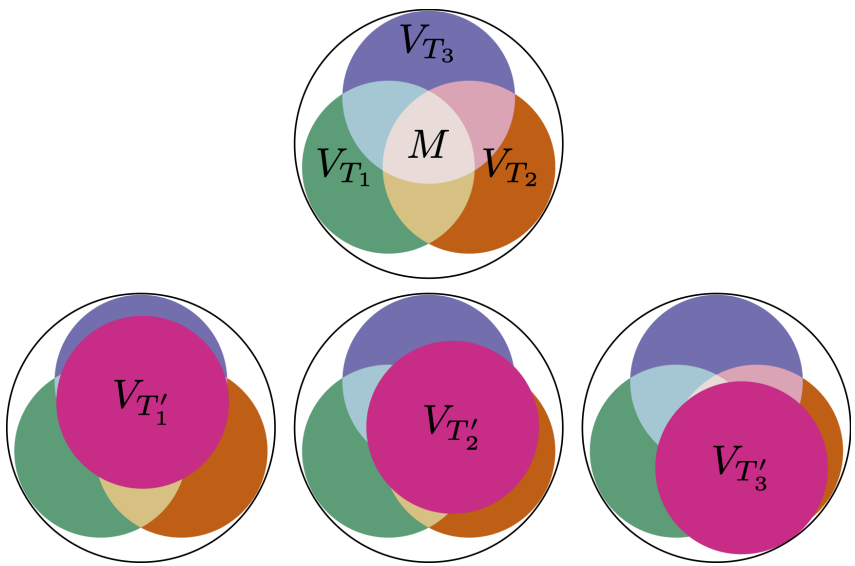
1. Repeat n times:
   - Shuffle input.
   - Run preferred DMMM to obtain disease module M_i.
2. Return subgraph $G[M]$ induced by nodes contained in at least a fraction $\tau \in (0, 1]$ of computed modules ($M := \{v \in V \mid |\{i \mid v \in M_i\}| \geq \tau \cdot n\}$).

Problems

- Increases runtime by a factor of n.
- The modules M_i might not be sufficiently diverse to ensure robustness.

Abstract Approach

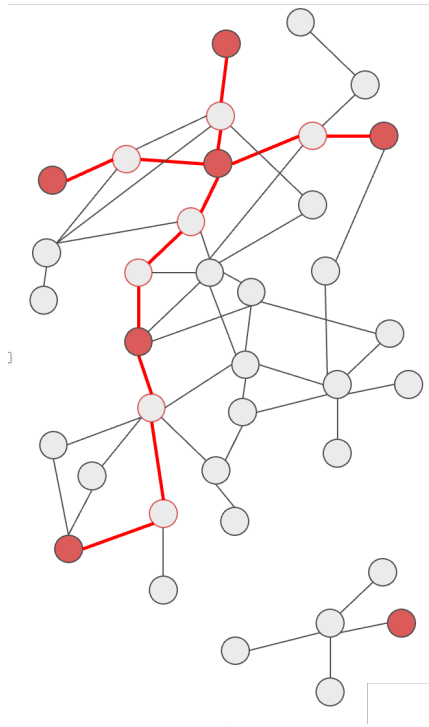
1. Model disease module mining problem as suitable mathematical optimization problem.
2. Design an algorithm to enumerate a diverse set of near-optimal solutions.
3. Return subgraph induced by nodes contained in many of the diverse solutions (as in naïve approach).



The Model Employed by ROBUST

Minimum-Weight Steiner Trees (MWSTs)

- Given (edge-weighted) graph $G = (V, E, w)$ and seeds $S \subseteq V$, compute tree $T = (V_T, E_T)$ with $S \subseteq V_T$ minimizing $\sum_{e \in E_T} w(e)$.
- *NP*-hard but efficient approximation algorithms exist.
- Unit edge weights in our case: $w \equiv 1$.



Prize-Collecting Steiner Trees

- Given graph $G = (V, E, w, p)$ with non-negative edge weights and node prizes, compute tree $T = (V_T, E_T)$ minimizing the following objective:

$$\min \underbrace{\sum_{e \in E_T} w(e)}_{\text{minimize}} + \underbrace{\sum_{v \in V \setminus V_T} p(v)}_{\underbrace{\sum_{v \in V} p(v)}_{\text{constant}} - \underbrace{\sum_{v \in V_T} p(v)}_{\text{maximize}}}$$

- Again *NP*-hard, but (very) efficient approximation algorithms exist.
- **Prizes for seeds:** High but not infinite to encourage inclusion of seeds.
- **Prizes for non-seeds:** Low but not zero, used to ensure diversity.

Enumerating Diverse Prize-Collecting Steiner Trees

- **Line 1:** Initialize prizes for seeds based on diameter (longest shortest path) of graph (and maximum weight).
- **Line 2:** Initialize prizes for non-seeds based on hyper-parameter $\alpha \in (0, 1]$ (and minimum weight).
- **Line 4:** Enumerate up to n prize-collecting Steiner tree.
- **Lines 5 – 7:** Compute next Steiner tree. Break if already seen before.
- **Line 8:** Decrease prizes for non-seeds used in previous Steiner tree by factor $\beta \in [0, 1)$ to ensure diversity.

Algorithm 1: ROBUST

Input: Graph $G = (V, E)$, seeds $S \subseteq V$, parameters $n \in \mathbb{N}$, $\alpha \in (0, 1]$, $\beta \in [0, 1)$, $\tau \in (0, 1]$.
Output: Robust disease module for seeds S.

1 $\mathcal{T} \leftarrow$ `enumerate_diverse`(G, S, n, α, β);
2 $M \leftarrow \{v \in V \mid |\{V_T \in \mathcal{T} \mid v \in V_T\}| \geq \tau \cdot |\mathcal{T}|\}$;
3 **return** $G[M]$;

Algorithm 2: `enumerate_diverse`

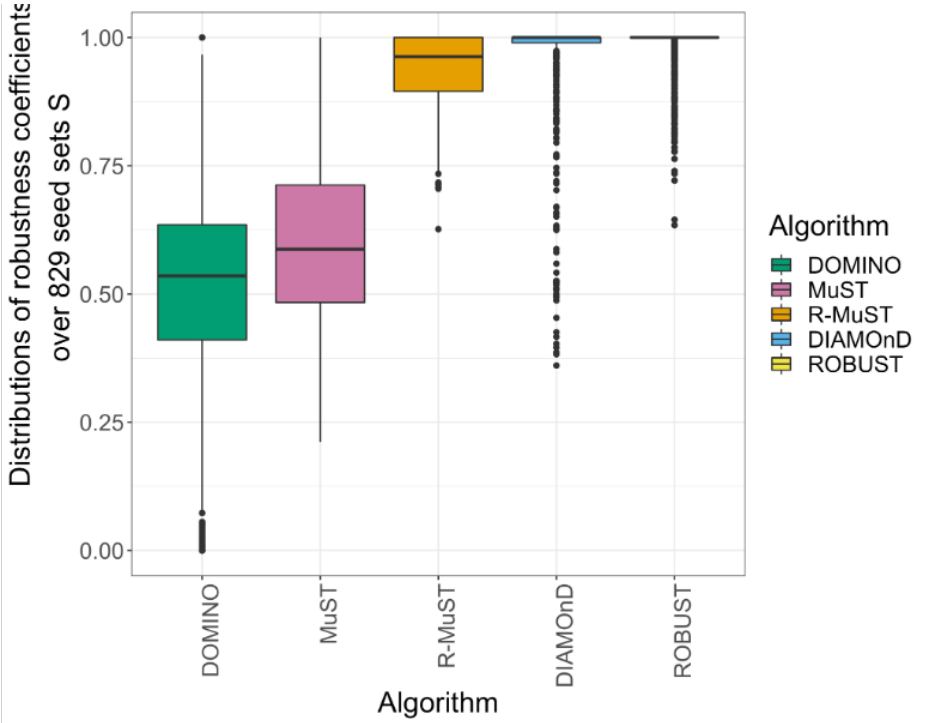
Input: Graph $G = (V, E)$, seeds $S \subseteq V$, edge weights $w : E \to \mathbb{R}_{\geq 0}$, parameters $n \in \mathbb{N}$, $\alpha \in (0, 1]$, $\beta \in [0, 1)$.
Output: Set $\mathcal{T}$ of diverse PCST node sets.

1 **for** $v \in S$ **do** $p(v) \leftarrow 2 \cdot \mathrm{diam}(G) \cdot \max_{e \in E} w(e)$;
2 **for** $v \in V \setminus S$ **do** $p(v) \leftarrow \alpha \cdot \min_{e \in E} w(e)$;
3 $\mathcal{T} \leftarrow \emptyset$;
4 **while** $|\mathcal{T}| < n$ **do**
5 $\quad (V_T, E_T) \leftarrow$ `pcst_apx`(G, w, p);
6 $\quad$ **if** $V_T \in \mathcal{T}$ **then break** ;
7 $\quad \mathcal{T} \leftarrow \mathcal{T} \cup \{V_T\}$;
8 $\quad$ **for** $v \in V_T \setminus S$ **do** $p(v) \leftarrow \beta \cdot p(v)$;
9 **return** $\mathcal{T}$

Effect of the Hyper-Parameters

- $n \in \mathbb{N}$: Coverage vs. runtime. Increasing n increases the runtime but also the fraction of the space of all near-optimal generalized Steiner trees covered by ROBUST. Should be set to high value if affordable.
- $\tau \in (0, 1]$: Explorativeness vs. robustness. Increasing τ increases the robustness but decreases the explorativeness. Should be set to smallest possible value such that robustness is still acceptable.
- $\alpha \in (0, 1]$: Increasing α increases the allowed diversion from cheapest Steiner tree. Should be set to smallest possible value such that robustness is still acceptable.
- $\beta \in [0, 1)$: Controls the decrease of prizes for non-seeds and thereby affects diversity. Must be chosen via hyper-parameter tuning.

Robustness in Comparison to Competitors



Mann-Whitney *U* Test

Alternative hypothesis: DMMM 1 yields larger robustness coefficients than DMMM 2.

DMMM 1	DMMM 2	*P*-Value
ROBUST	DOMINO	1.668×10^{-278}
ROBUST	MuST	3.847×10^{-226}
ROBUST	R-MuST	4.460×10^{-68}
ROBUST	DIAMOnD	6.796×10^{-6}

Drug Prioritization via Personalized PageRank (PPR)

Augment G with drugs to enable drug scoring via PPR.

- **Proteins (PPI):** $G = (V, E)$, undirected, possibly weighted. Adjacency $A \in \mathbb{R}^{|V|\times|V|}$ with $A_{ij} = A_{ji} \geq 0$.
- **Drugs:** set D. Each drug $d \in D$ targets a subset $T(d) \subseteq V$ (drug–target relations).
- **Edges involving drugs:**

$$E_{DT} = \{(d, t) : d \in D,\ t \in T(d)\},$$

- **Augmented undirected graph:**

$$G^+ = (V^+, E^+), \quad V^+ = V \cup D, \quad E^+ = E \cup E_{DT} \cup E_{DD}.$$

Let $A^+ \in \mathbb{R}^{|V^+|\times|V^+|}$ be the symmetric adjacency of G^+ (weights allowed).

- **Walk matrix (column-stochastic):**

$$d_j^+ = \sum_i A_{ij}^+, \quad P_{ij}^+ = \frac{A_{ij}^+}{d_j^+} \quad \text{(so each column of } P^+ \text{ sums to 1).}$$

Drug Prioritization via Personalized PageRank (PPR)

- **Personalization on disease seeds (genes only):**

$$p_i = \begin{cases} \frac{1}{|S|}, & i \in S \\ 0, & i \notin S \end{cases} \qquad \left(p \in \mathbb{R}^{|V^+|},\ \sum_i p_i = 1\right).$$

Personalized PageRank (PPR) on G^+:

$$\boxed{r \;=\; \alpha P^+ r \;+\; (1-\alpha)\, p} \qquad \Longleftrightarrow \qquad r \;=\; (1-\alpha)\,(I-\alpha P^+)^{-1} p,$$

with damping $\alpha \in (0,1)$, $r \in \mathbb{R}^{|V^+|}$, $r_i \geq 0$, $\sum_i r_i = 1$.

Interpretation (undirected G^+): r is a *proximity/affinity* from the seed set S to all nodes in $V^+ = V \cup D$ via many short random-walk paths (longer paths exponentially down-weighted by α).

PPR on the Augmented Graph & Drug Scoring

Drug prioritization: read out scores on drug nodes.

$$\boxed{score(d) \;:=\; r(d), \qquad d \in D}$$

Higher $score(d)$ means drug d lies closer to the disease seeds S through protein targets and network connectivity.

Acknowledgements

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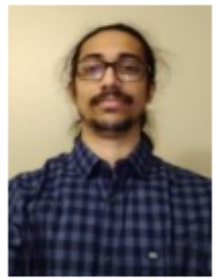

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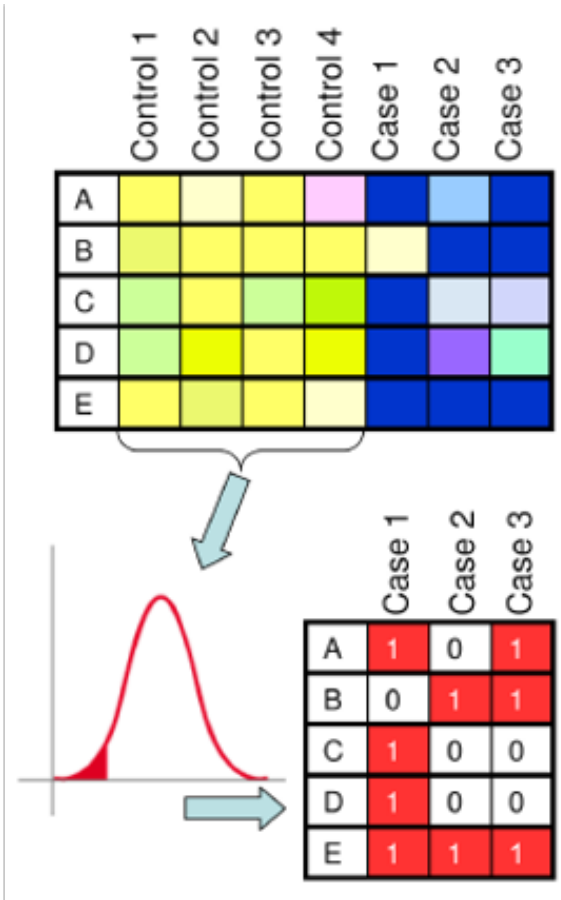
Projecting the Omics Data onto the Networks (I): Directly Using the Gene Expression Matrix

- Let $\mathcal{G}$ be set of genes and $\mathcal{P}$ be set of patients.
- Gene expression matrix is of form $\mathsf{X} \in \mathbb{R}^{\mathcal{G} \times \mathcal{P}}$.
- In our molecular networks, nodes correspond (or can be mapped) to genes.

$\rightsquigarrow$ Can use row $\mathsf{X}_{g,\bullet}$ as $|\mathcal{P}|$-dimensional node attribute of node (gene) $g \in \mathcal{G}$.

- If phenotype case/control information is available, we additionally store a global indicator vector $\mathsf{b} \in \{0,1\}^{\mathcal{P}}$, where $b_p = 1$ if and only if $p \in \mathcal{P}$ is a case patient.

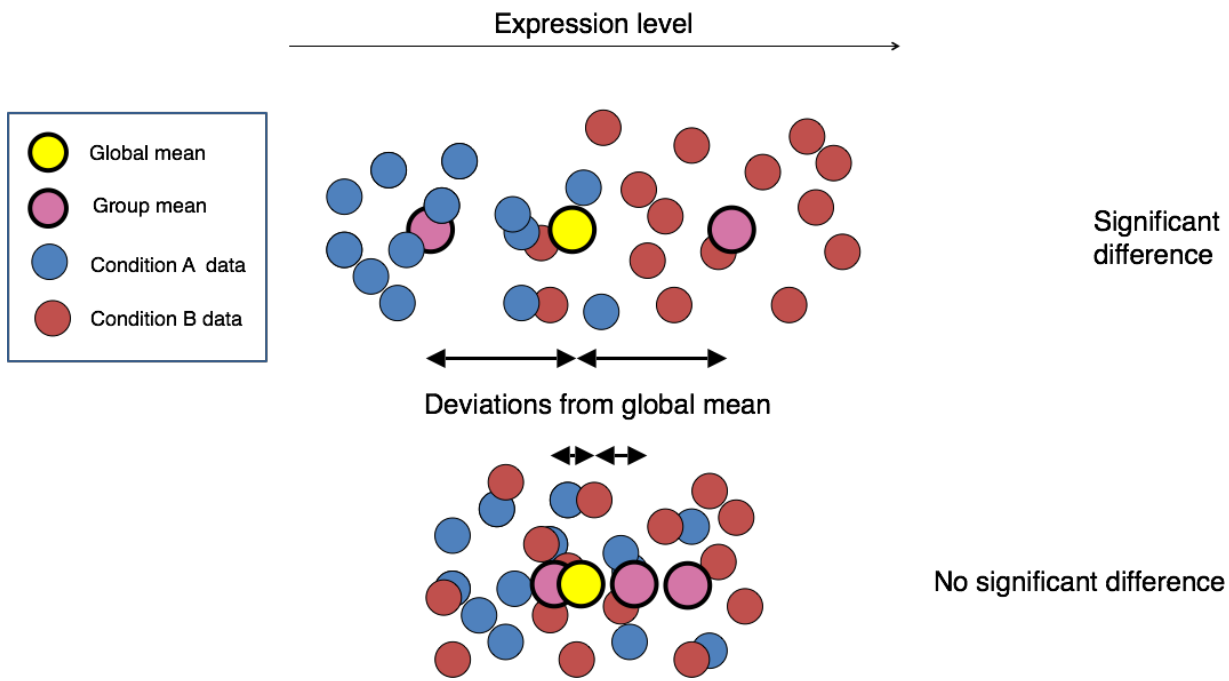
Projecting the Omics Data onto the Networks (II): Using an Indicator Matrix Derived from the Gene Expression Matrix



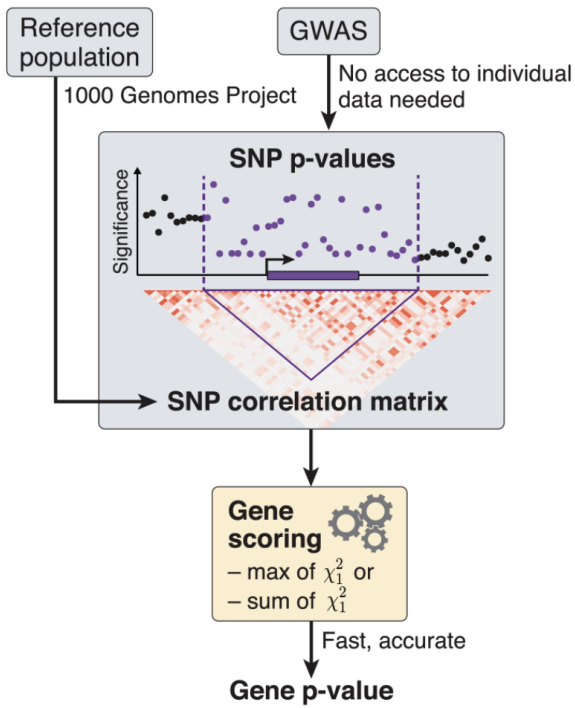
- For each gene, fit background gene expression distribution based on the control samples only.
- For each gene and each case patient, compute *P*-value for diversion from background.
- Select threshold for significance cutoff.

Projecting the Omics Data onto the Networks (III): Gene Scores Obtained from Gene Expression Data

- For each gene, compute P-value of differential expression in case samples.
- Use $-\log P$-value as gene score.



Projecting the Omics Data onto the Networks (IV): Gene Scores Obtained from Genome-Wide Association Studies (GWAS, Genomics Data)



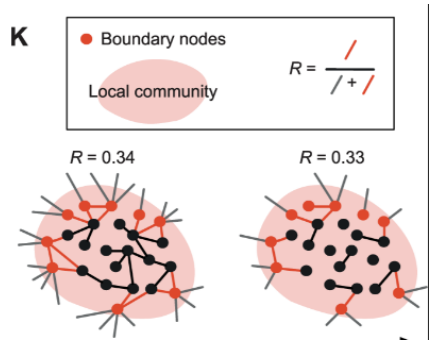
- GWAS yield *P*-values for individual genetic variants.
- Aggregate *P*-values for variants associated to gene to obtain gene-level *P*-values.
- Use $-\log P$-value as gene score.

One Possible Property: Local Modularity

- For some module M, let $B \subset M$ be boundary of M, i. e., the set of nodes u with at least one neighbor $v \notin M$.
- Let $T := \{uv \in E \mid u \in B \vee v \in B\}$ be set of all edges incident with a boundary node.
- Let $I := \{uv \in E \mid u \in B \vee v \in B \wedge u, v \in M\}$ be set of all edges incident with a boundary node and both endpoints in module M.
- Note that $I \subsetneq T$.
- Then the local modularity R is defined follows:

$$R := \frac{|I|}{|T|}$$

- Note that $0 \leq R < 1$.

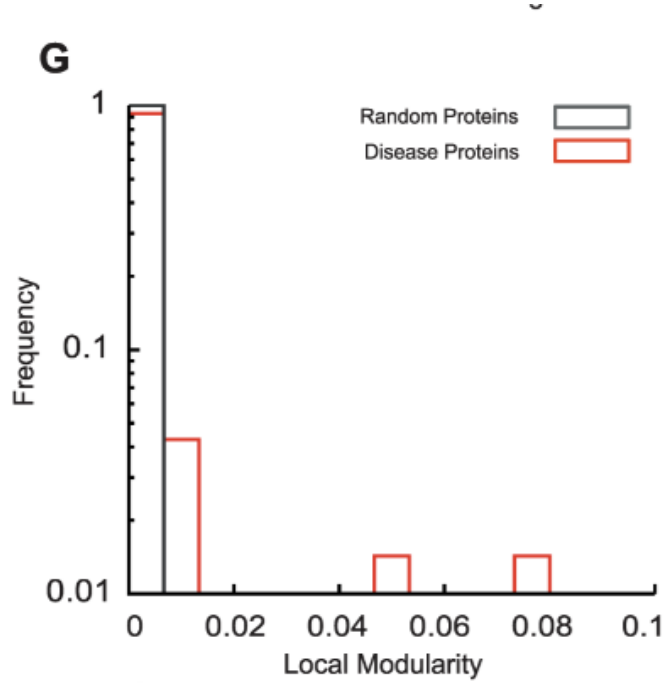


Local Modularity of Sets of Disease-Associated Genes (I)

Comparison Against Random Gene Sets

- Compute local modularity R for sets of disease genes.
- Compare against random gene sets.

$\rightsquigarrow$ R is significantly larger for disease genes but still pretty close to 0.

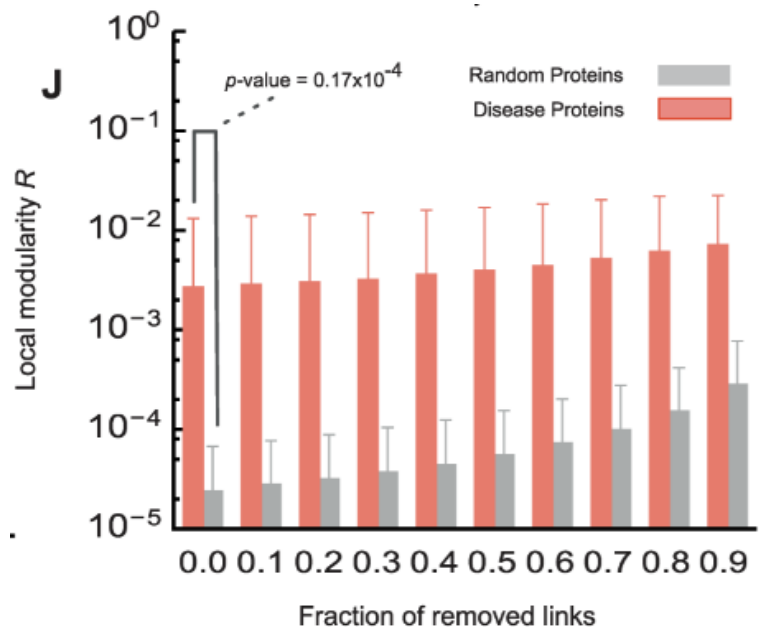


Local Modularity of Sets of Disease-Associated Genes (II)

Comparison Against Random Gene Sets with Random Removal of Edges

- Randomly remove edges from the network.
- If R was a good measure to characterize disease modules, it should drop with increasing number of removed edges.
- This is not the case.

$\rightsquigarrow$ R might not be the best measure to characterize disease module.



Connectivity Significance

- Consider network with N genes (nodes) and $s_0 < N$ disease-associated seed genes.
- Assume that seed genes are randomly scattered across the network.
- What is the probability $P_{N,s_0}(k, k_s)$ that a gene with with k neighbors has exactly $k_i \leq k$ neighbors among the s_0 seed genes?
- Given by hypergeometric distribution:

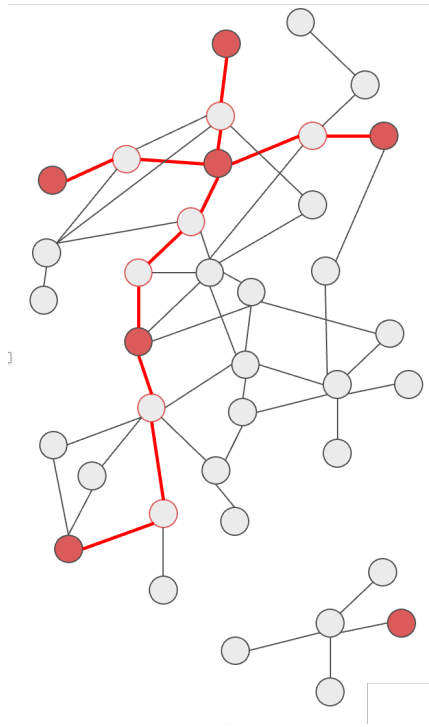
$$P_{N,s_0}(k, k_i) = \frac{\binom{s_0}{k_i}\binom{N-s_0}{k-k_i}}{\binom{N}{k}}$$

$\rightsquigarrow$ **Connectivity P-value:** Probability under null-model that node with k neighbors has at least k_s neighbors among the seeds:

$$P_{N,s_0}(k, k_i \geq k_s) = \sum_{k_i=k_s}^{k} P_{N,s_0}(k, k_i)$$

From Generalized MWSTs to Prize-Collecting Steiner Trees

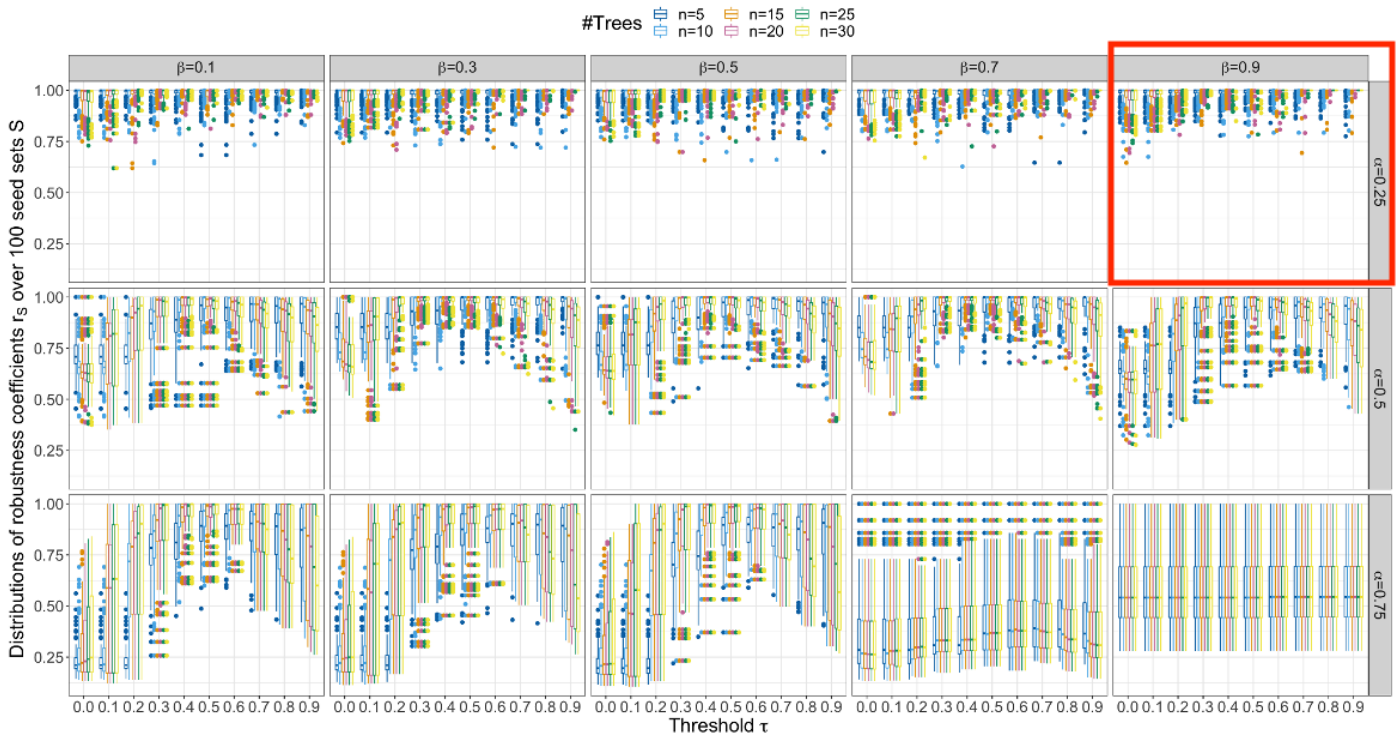
- Our seeds are potentially noisy (e. g., false positives in GWAS).
- We do not enforce $S \subseteq V_T$ but only encourage the inclusion of seed.
- Seeds that are very far away from the other seeds will not be connected in the module.
- To achieve this, we use **prize-collecting** Steiner trees instead of MWSTs.



Hyper-Parameter Tuning for Robustness (I)

- Increasing α decreased robustness, increasing β increased it.

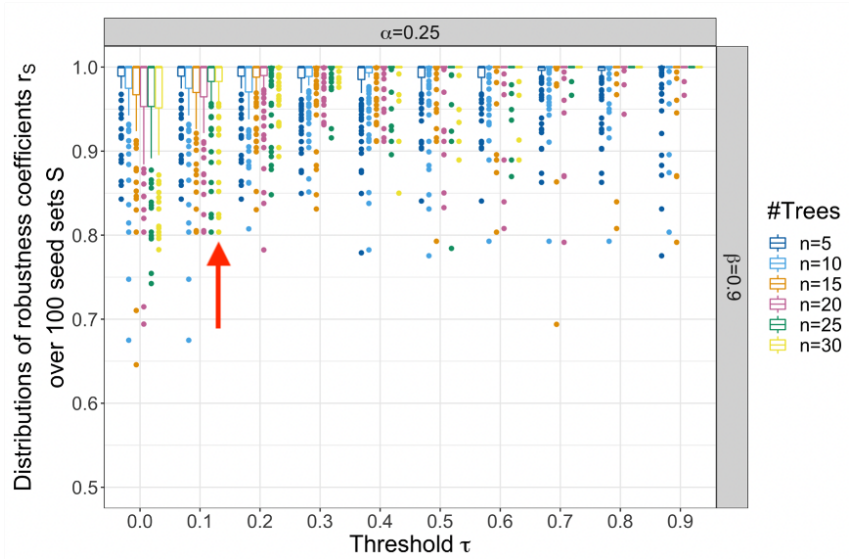
$\rightsquigarrow$ Focus on $\alpha = 0.25$ and $\beta = 0.9$.



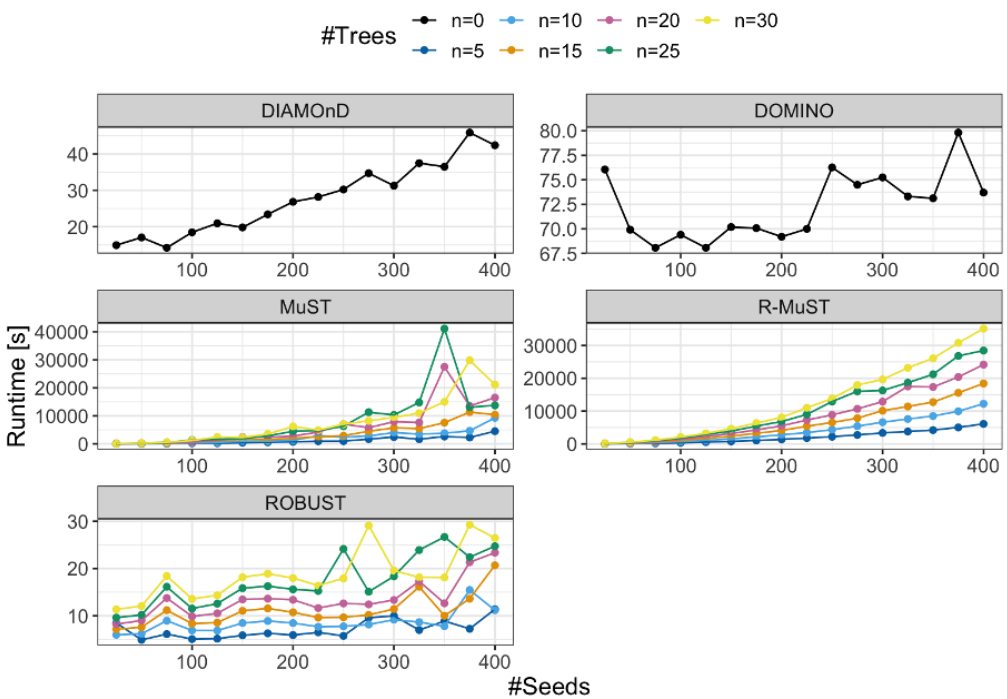
Hyper-Parameter Tuning for Robustness (II)

- Very good robustness already for $\tau = 0.1$ and $n = 30$.
- Runtime still acceptable for $n = 30$ trees.

$\rightsquigarrow$ Use hyper-parameter setup $(\alpha, \beta, n, \tau) = (0.25, 0.9, 30, 0.1)$ for comparison against competitors.

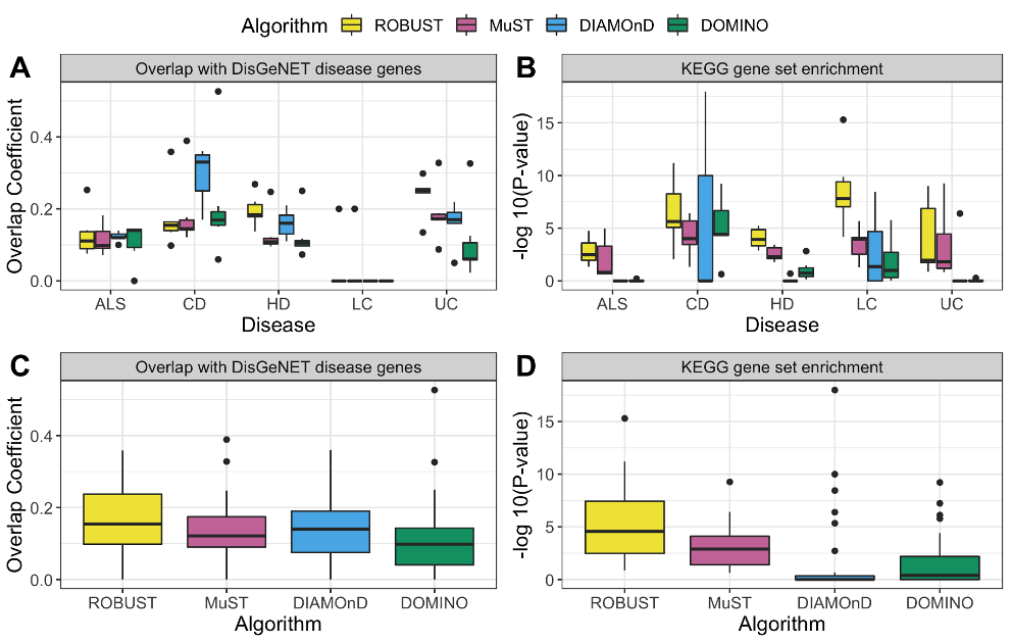


Runtime in Comparison to Competitors



- MuST and R-MuST around 2 orders of magnitude slower.
- Runtime increases sub-linearly for ROBUST and DOMINO, linearly for DIAMOnD.
- Number of trees affect ROBUST's runtime very moderately.

Functional Relevance in Comparison to Competitors



- Seeds derived from gene expression data for five complex diseases.
- Tests run on five different PPI networks (from databases).
- Functional relevance measure via overlap w. r. t. disease genes from databases (KEGG, DisGeNET).