Marseille Medical Genetics

Mining Networks to study Rare Common Diseases

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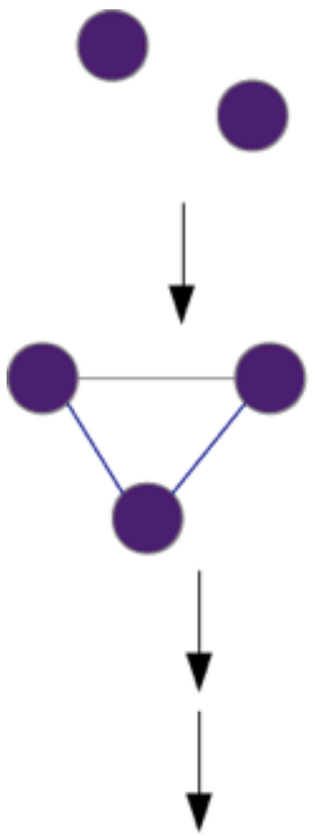
BSC, 31/01/2018

Genotype

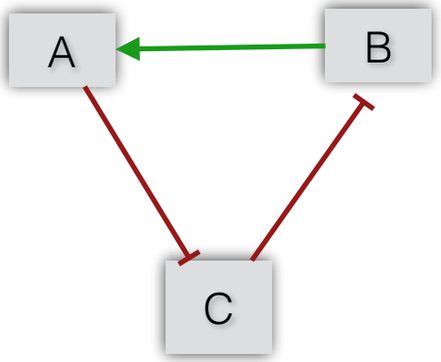


Networks !!

Phenotype

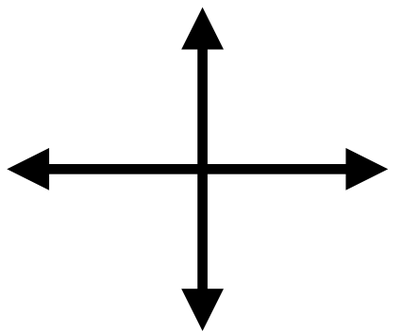
Complex Systems
Systems Biology

NSBD



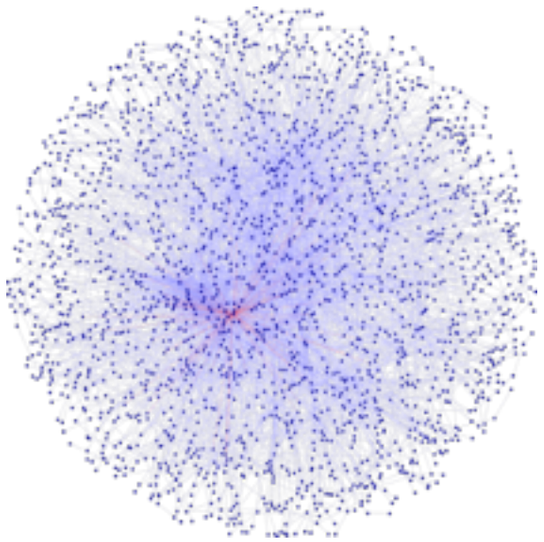
Dynamical Network Modeling

Algorithmic developments

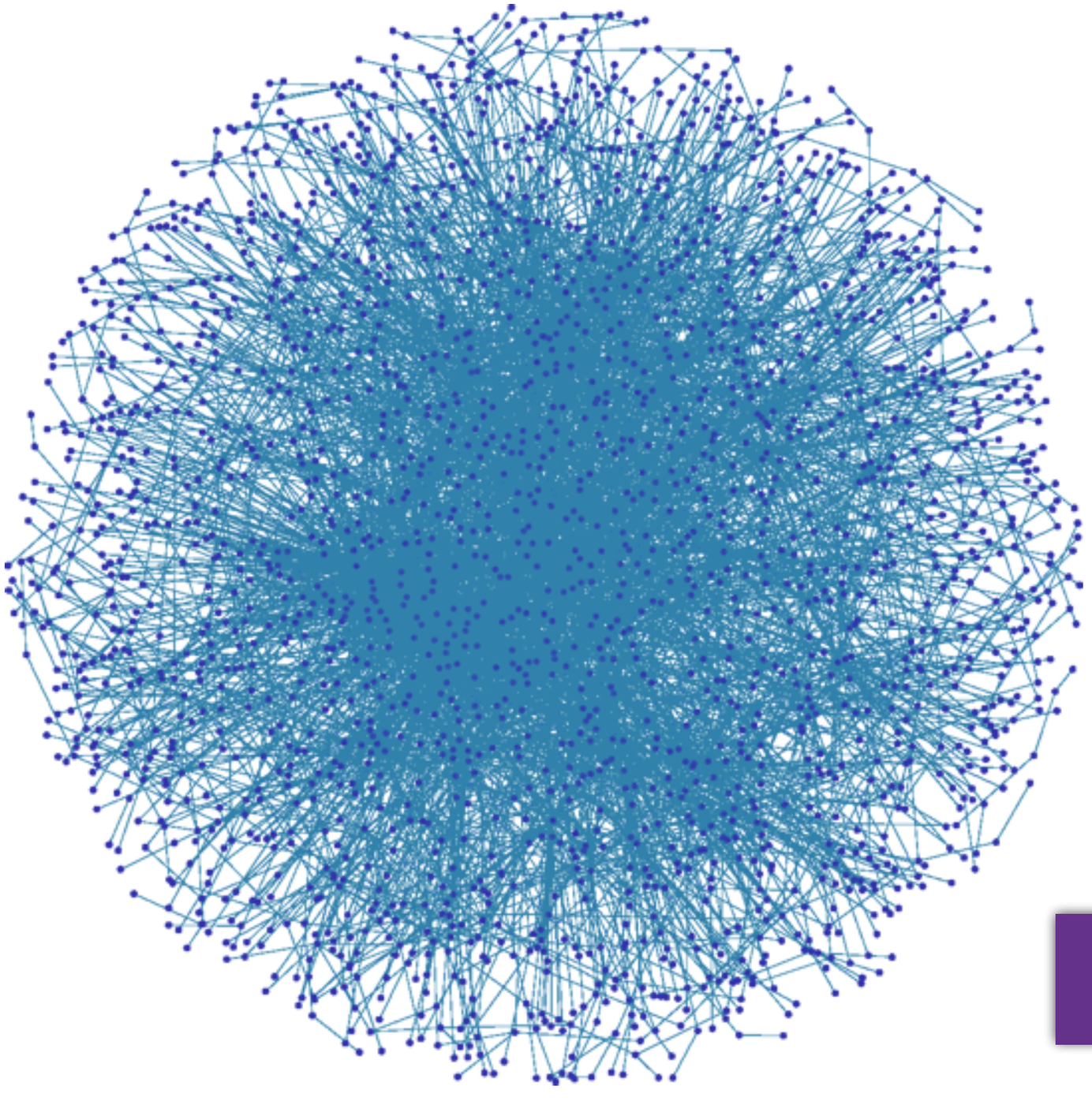


Applications to human diseases

Large-scale Network Mining

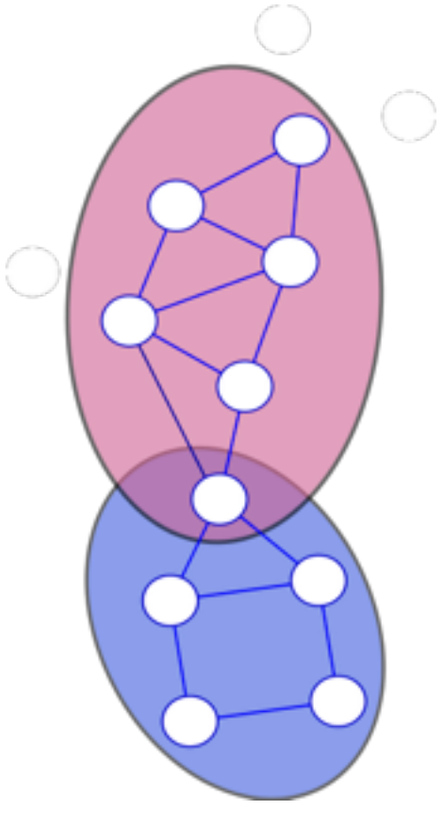


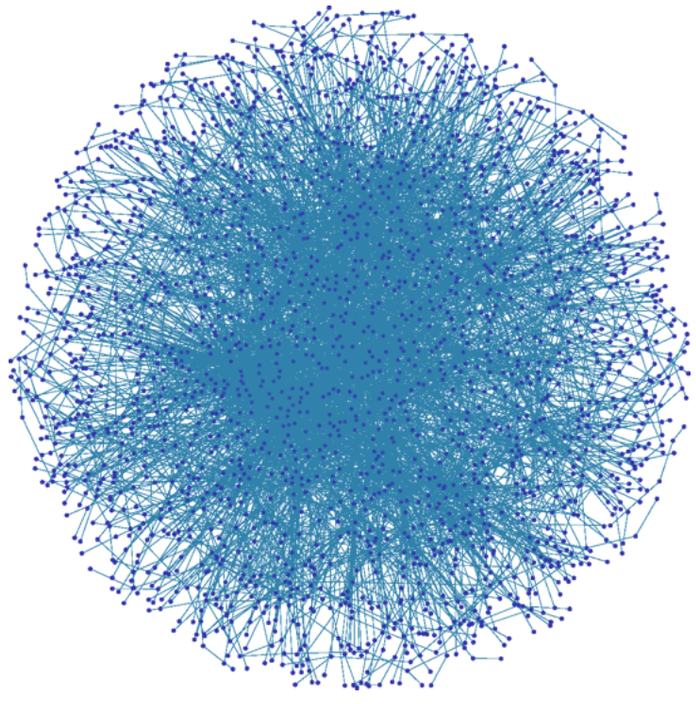
Interactome: The set of <u>known & possible</u> protein-protein interactions



~ 60 000 binary undirected interactions
~ 12 000 human proteins

How to extract relevant biological information ?



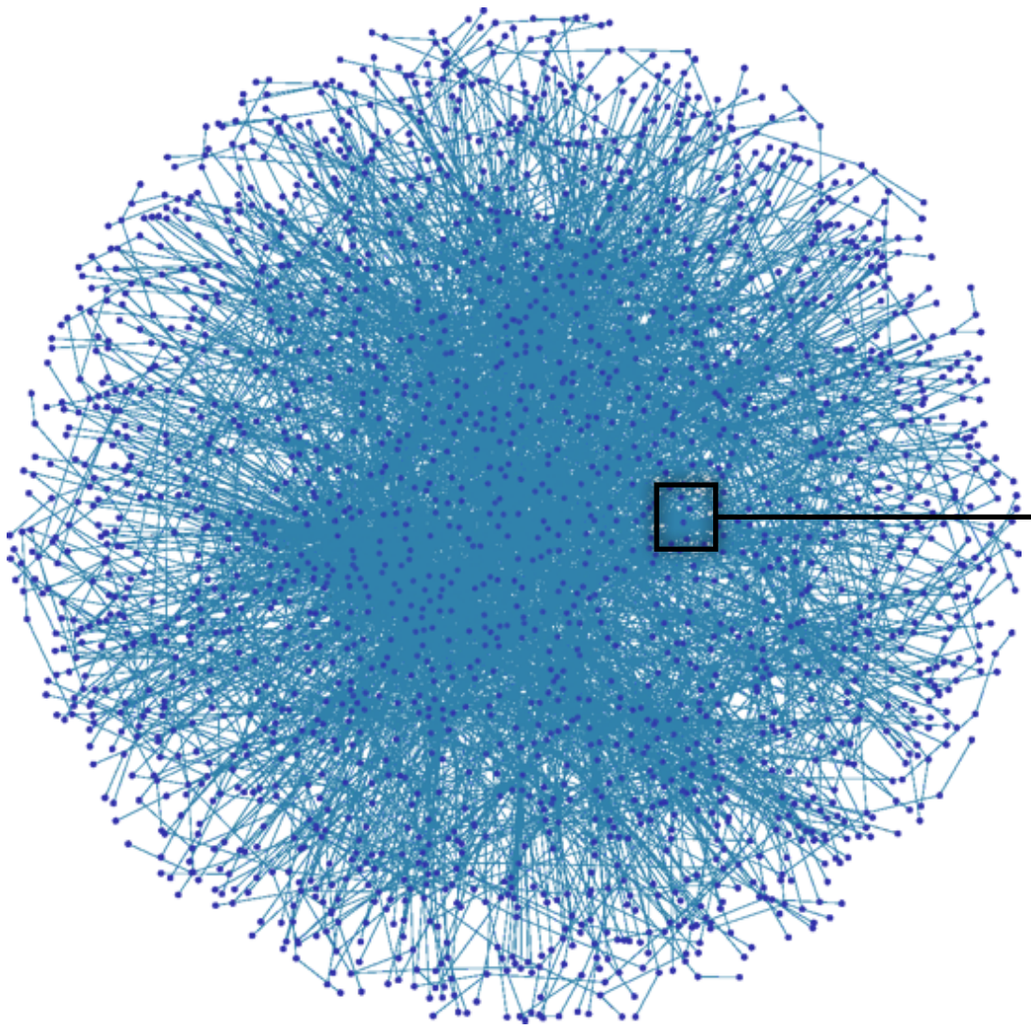


Binary interaction **Functional modules** **Interaction Networks**

Precision **Comprehensiveness**

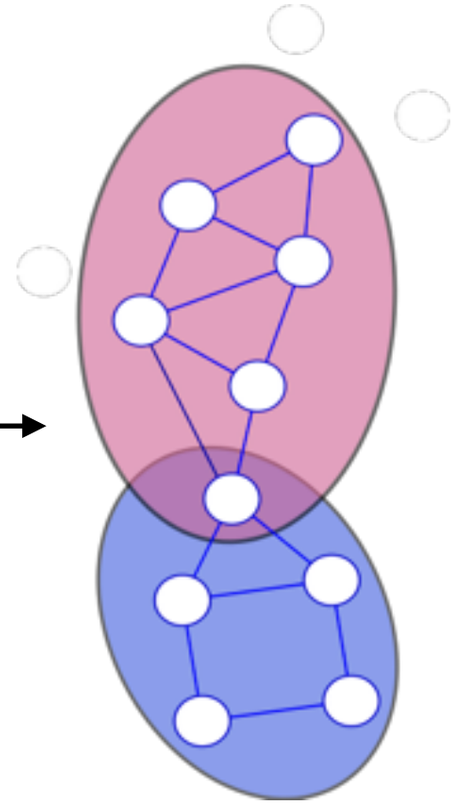
Inspired from P. Aloy, ECCB 2014

Community identification algorithms



Topology : Density,
Modularity optimization

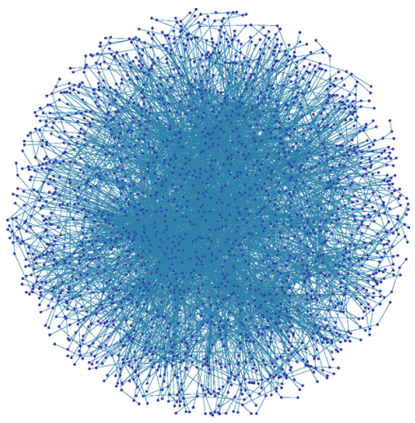
Overlapping / Disjoint



Spinelli et al. (2013)

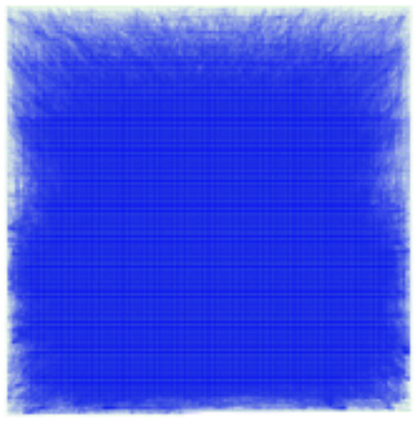
Many Biological Networks

PPI



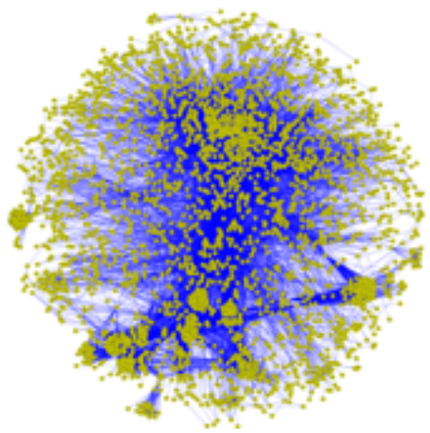
~60 000 edges

Co-expr



~1 400 000 edges

Pathways



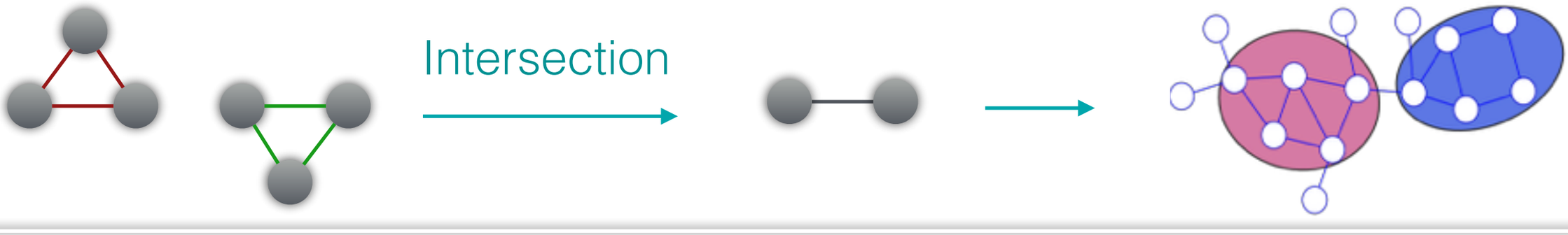
~250 000 edges

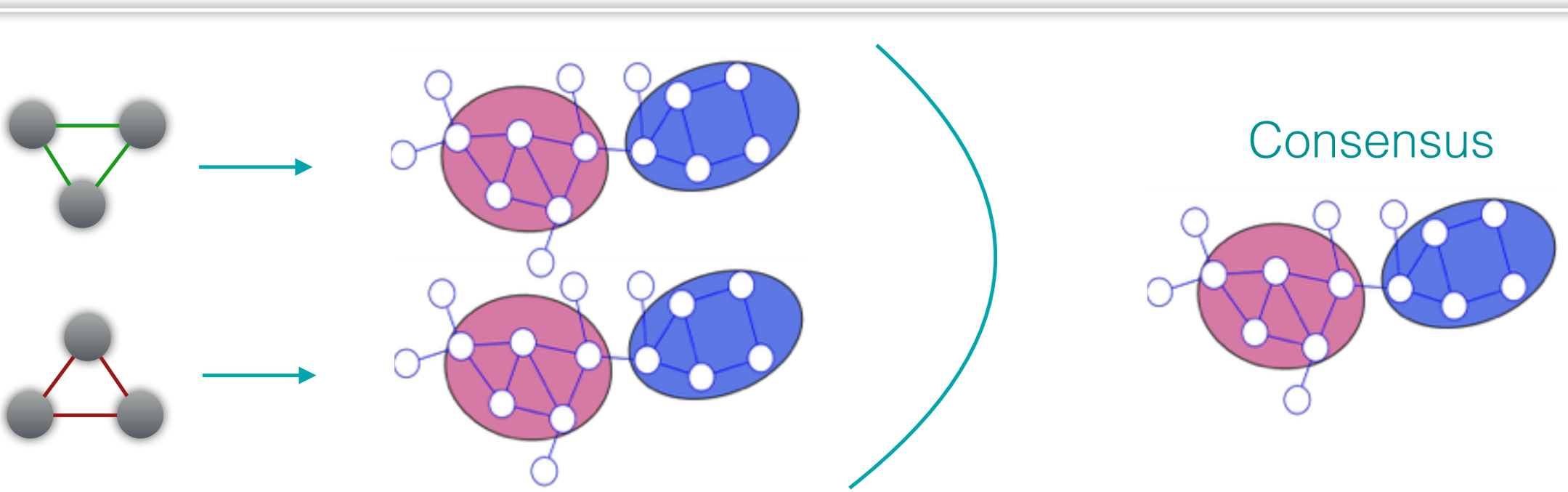
Complexes

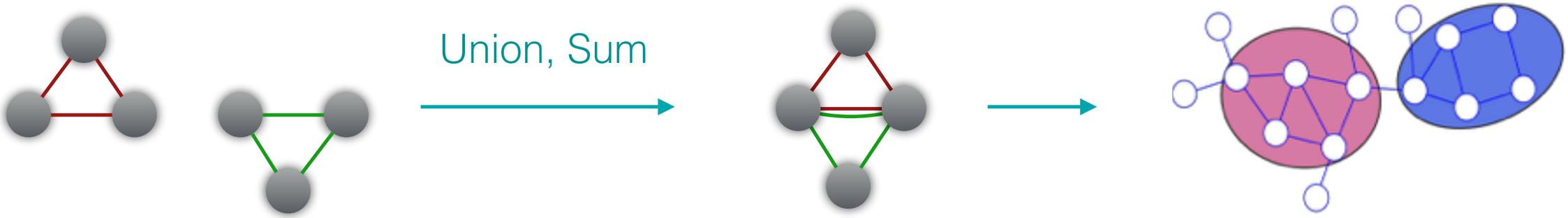
~40 000 edges

How do we combine many network/ interaction sources?

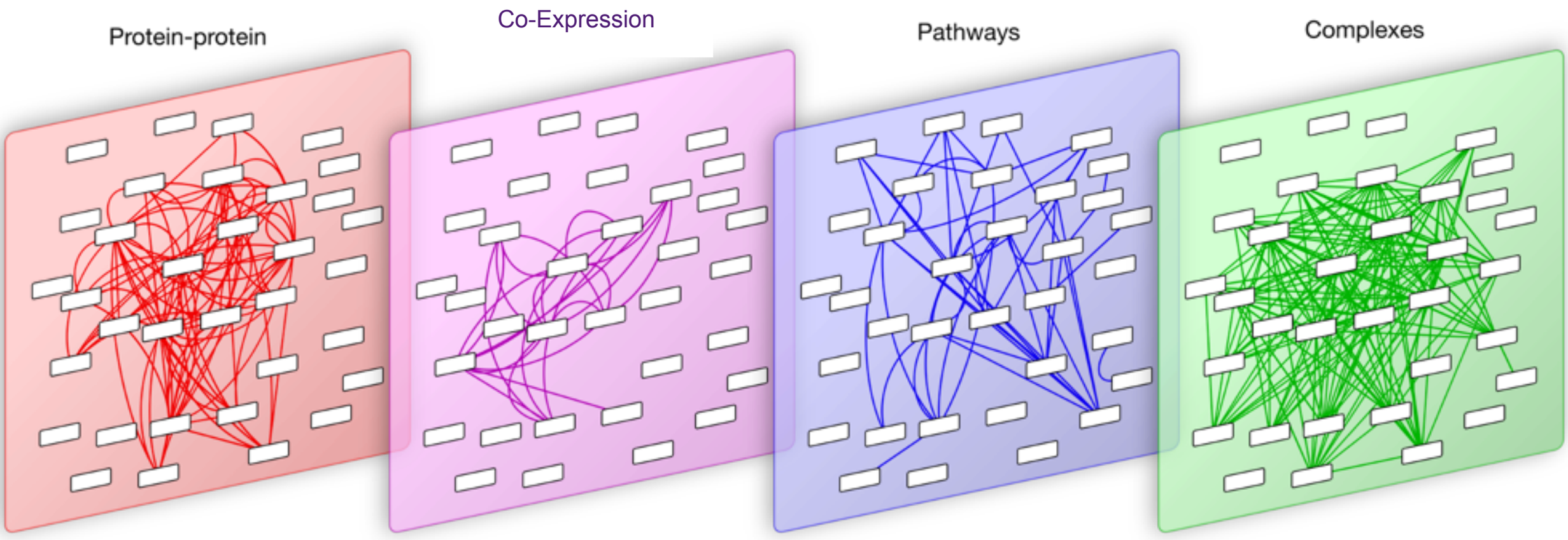
Communities from many Networks





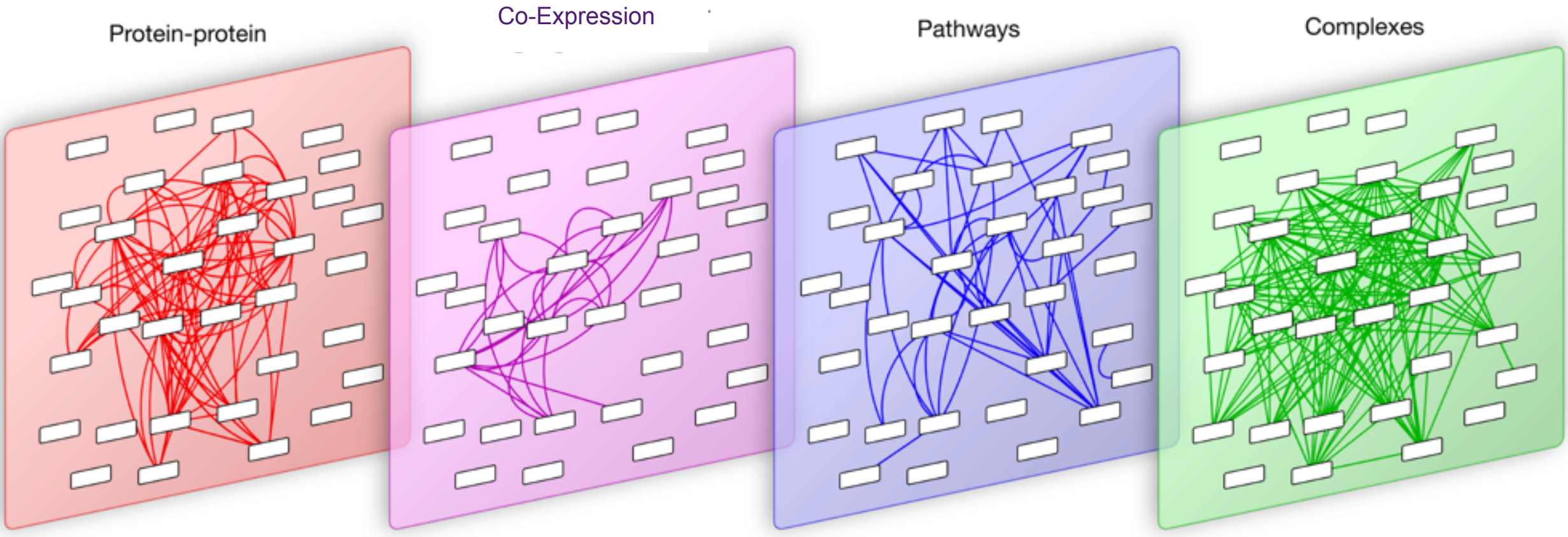


Multiplex framework

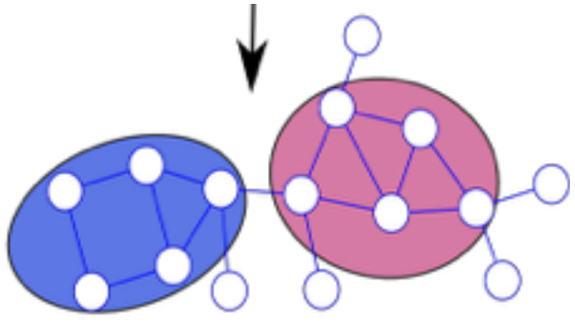


Multiplex, Multi-layer, Multi-slice

Multiplex framework

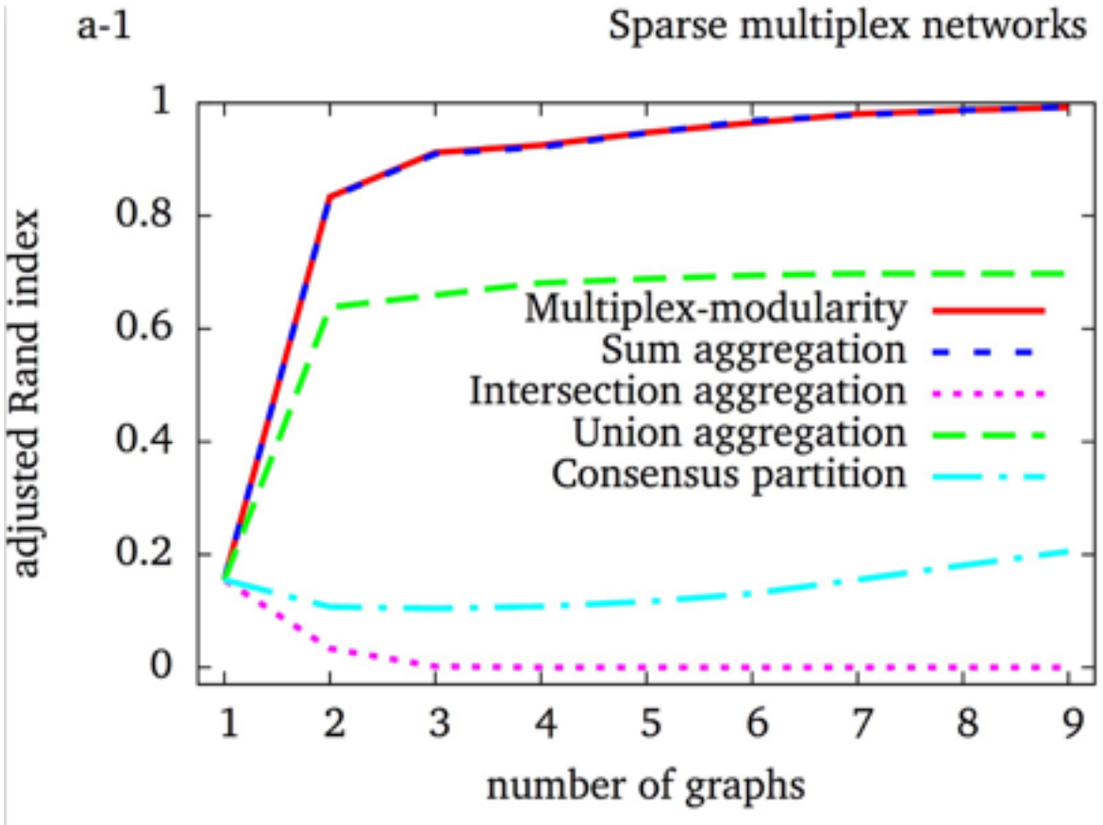


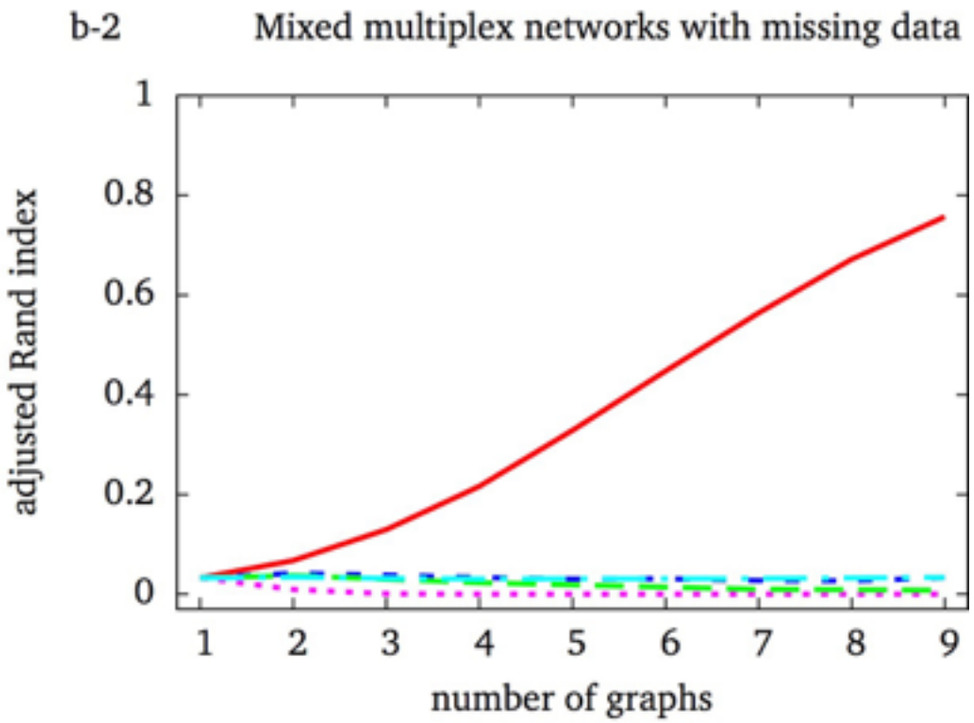
Multiplex-modularity



$$Q^M((X^{(g)})_g, \mathbf{c}) = \sum_a \left[\sum_g \frac{\sum_{\{i,j\}} X_{i,j}^{(g)}}{2m^g} - \sum_g \frac{\sum_{\{i,j\}} k_i^g k_j^g}{(2m^g)^2} \right]$$

Simulated networks

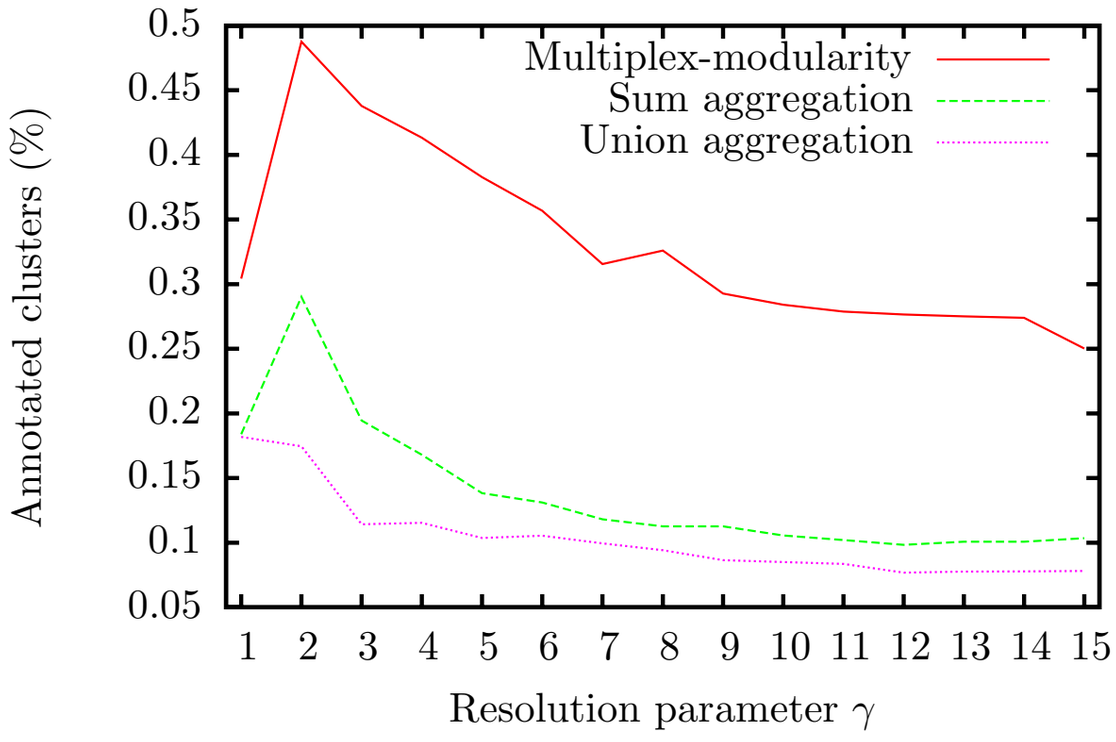




=> Considering many networks improves the detection of communities
=> Multiplex framework more efficient with mixed and incomplete networks

https://github.com/gilles-didier/**MoITi**

Real biological networks



=> More annotated

Didier et al. (2015) https://github.com/gilles-didier/**MolTi**

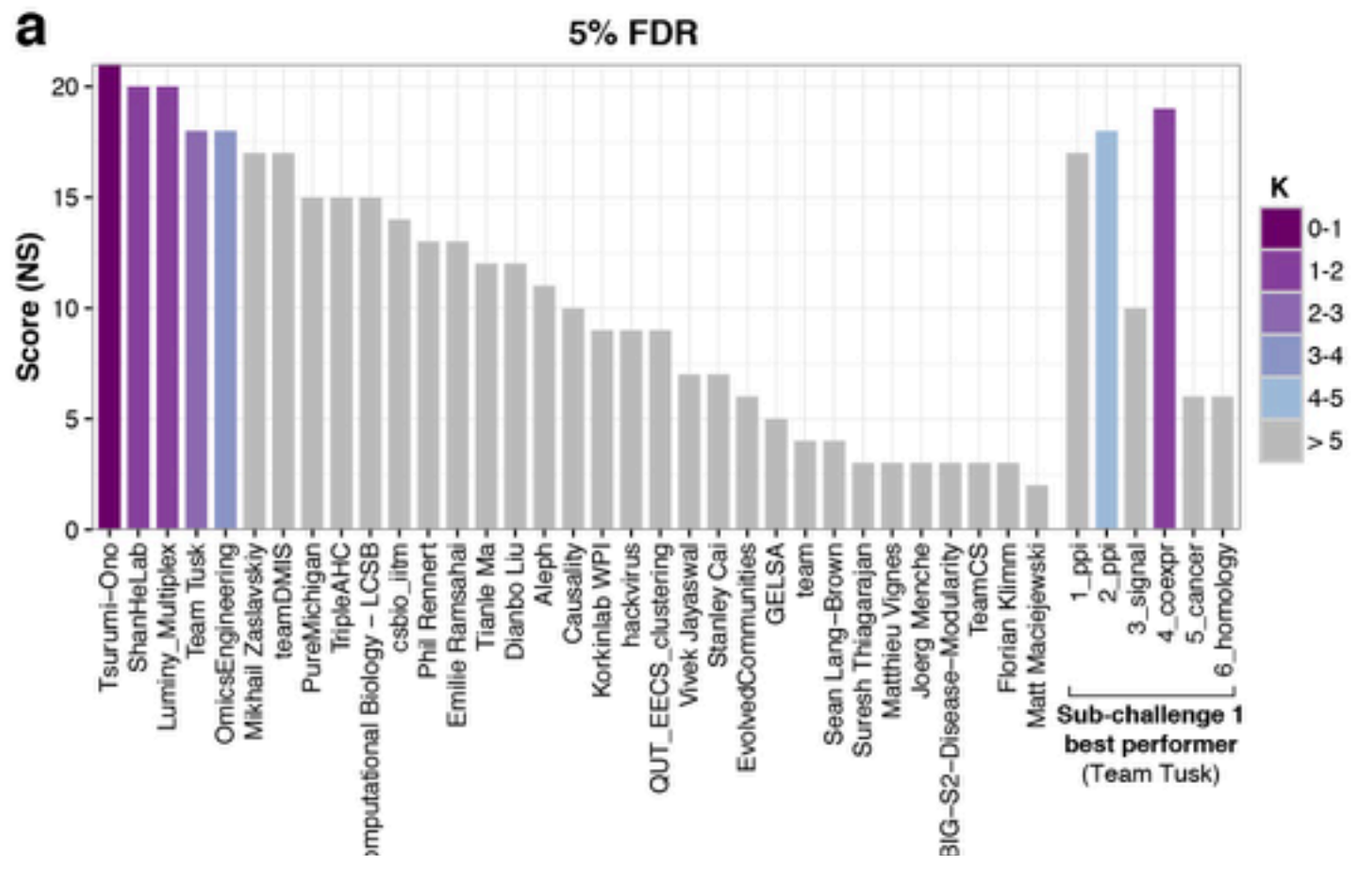
Disease Module Identification DREAM Challenge

Discover disease pathways in genomic networks

DREAM CHALLENGES powered by Sage Bionetworks

UNIL | Université de Lausanne · SIB Swiss Institute of Bioinformatics · Joint Research Center for Computational Biomedicine · RWTH AACHEN UNIVERSITY · IBM · Sage BIONETWORKS · Cell

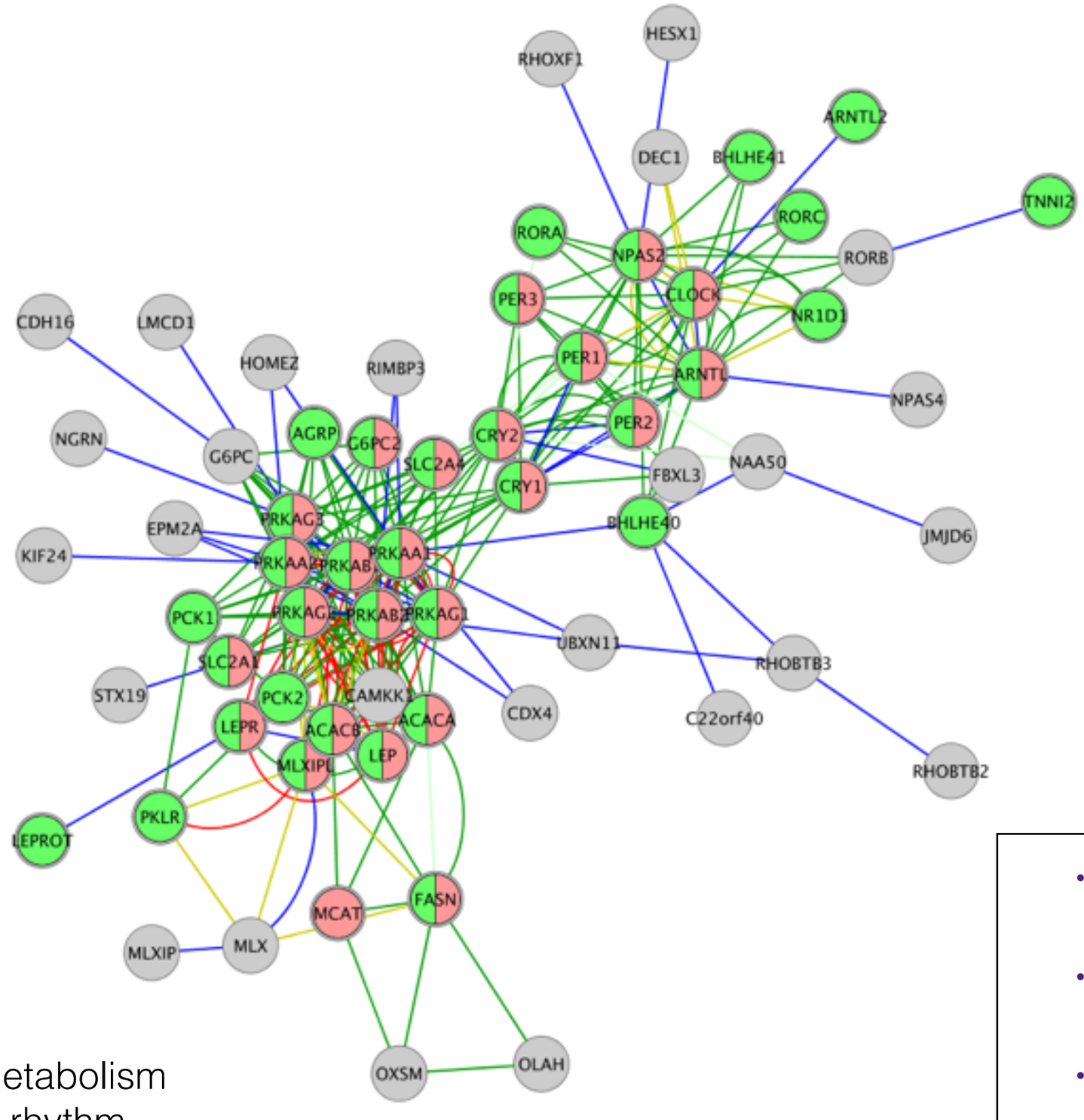
- **6 anonymous networks**
- **2 sub-challenges:**
  monoplex and multiplex
- **Modules enriched in**
  GWAS-significant genes



Molti 2.0 => randomization, recursion

Consortium paper in prep.

Disease-Community data integration



Prostate Cancer

Diabetes Mellitus

Fatty acid metabolism

Circadian rhythm

- **Processes deregulated / impacted in diseases**
- **Predict new disease-associated genes**
- **Study disease-disease relationships**

Mendelian

Polygenic

Common

Monogenic

Complex

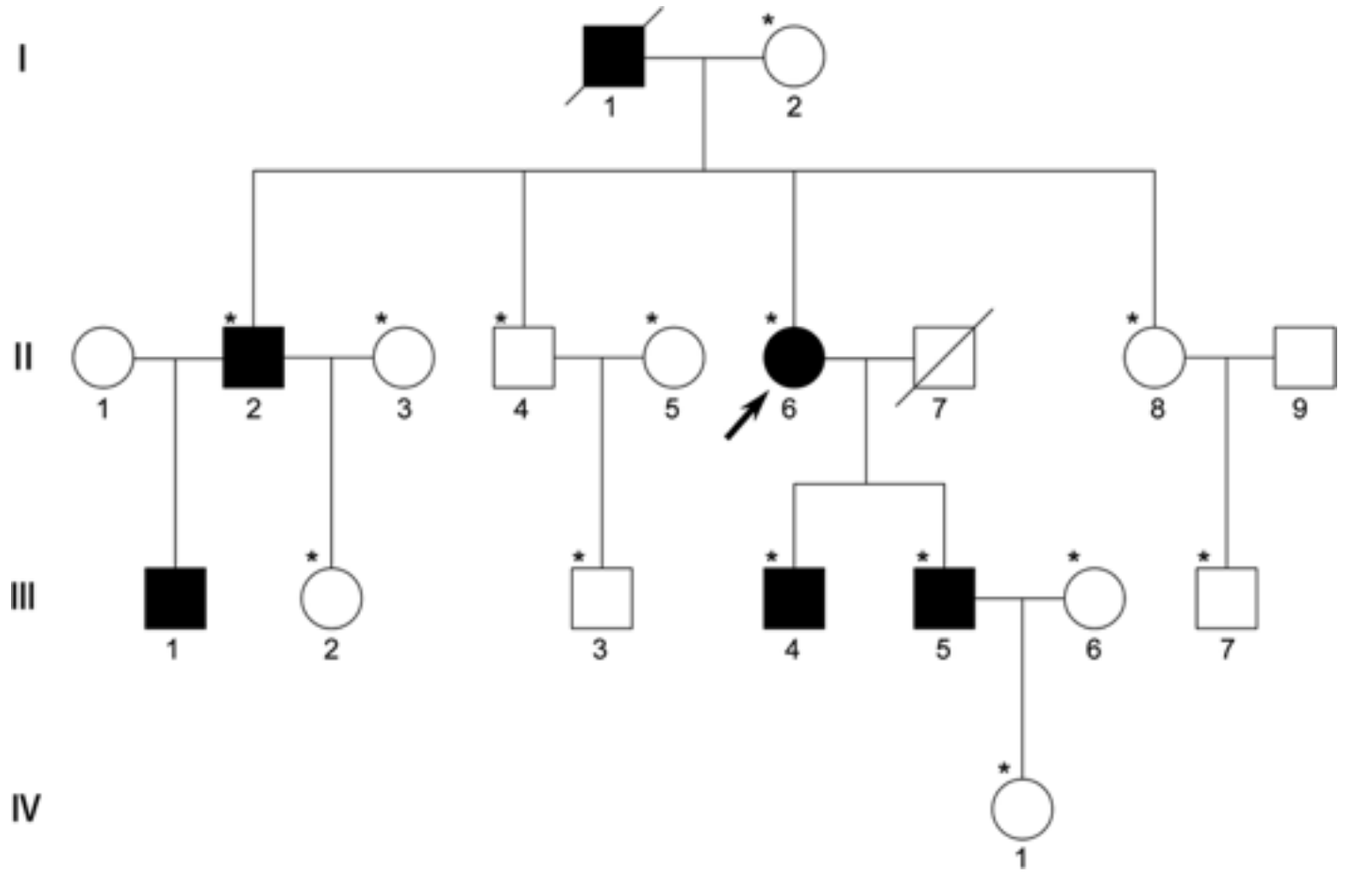
Orphan

Rare

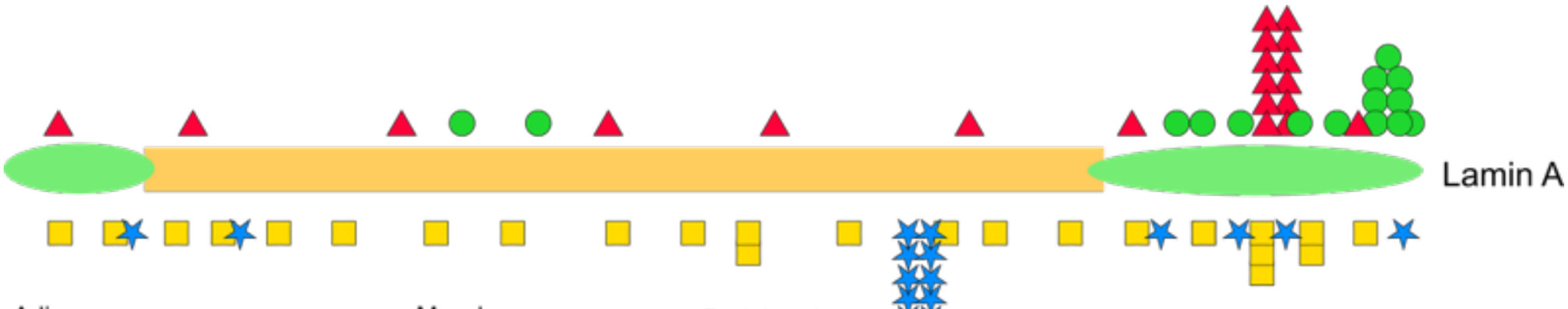
Multigenic

Rare genetic diseases

- Mono/Oligo-genics
- Mendelian inheritance / de novo
- Also very complex …



Clinical heterogeneity
Ex: Laminopathies



Adipose

▲ Familial partial Lipodystrophie, Dunnigan type

Muscle

■ Emery-Dreifuss muscular dystrophy, type 2

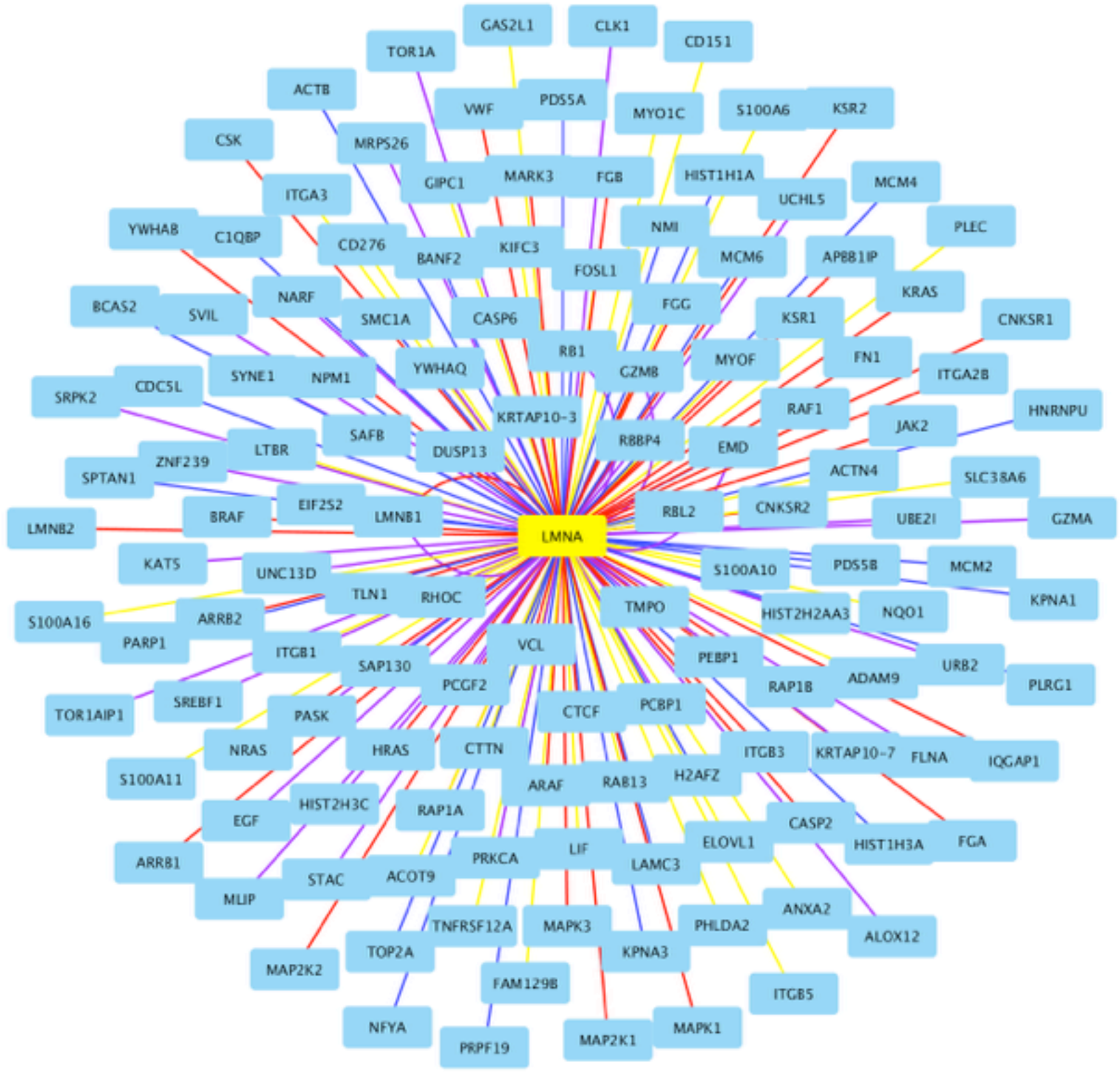
Peripheral nerve

★Charcot-Marie-Tooth, CMT2B1

Multiple

● Hutchinson-Gilford Progeria

LMNA interactome



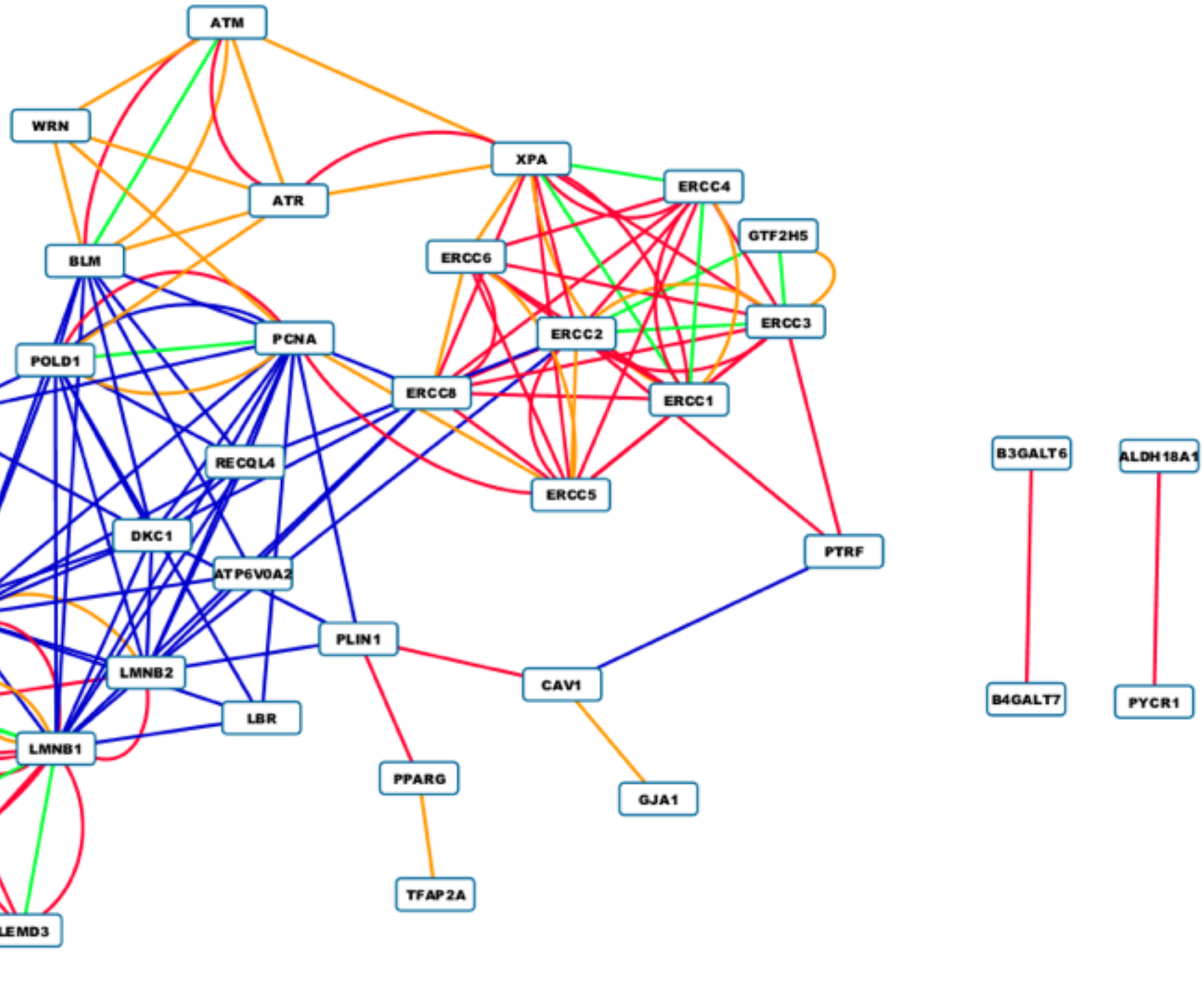
Locus heterogeneity
Ex: Premature Aging Syndromes

liste_genes_vieillissement prematuré.txt

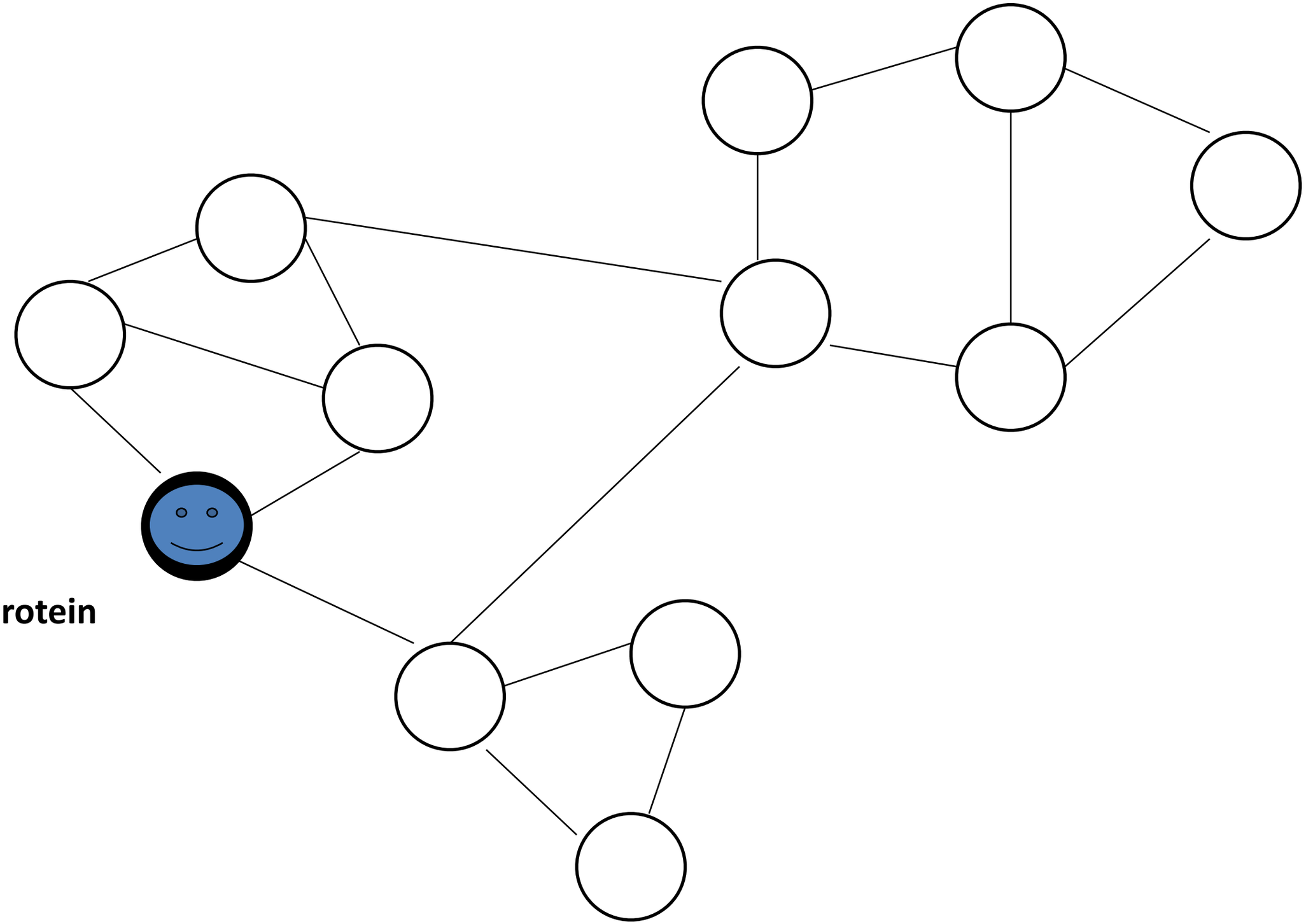
BANF1	NM_003860
BLM	NM_000057
ERCC1	NM_001983
ERCC2	NM_000400
ERCC3	NM_000122
ERCC6	NM_000124
ERCC8	NM_000082
GTF2H5	NM_207118
LMNA	NM_170707
RECQL4	NM_004260
MPLKIP	NM_138701
WRN	NM_000553
XPA	NM_000380
ERCC5	NM_000123
ZMPSTE24	NM_005857
PIK3R1	NM_181523
B4GALT7	NM_007255
B3GALT6	NM_080605
ALDH18A1	NM_002860
ATP6V0A2	NM_012463
ATM	NM_000051
ATR	NM_001184
GJA1	NM_000165
PTDSS1	NM_014754
ERCC4	NM_005236
POLD1	NM_002691
FBN1	NM_000138
TFAP2A	NM_003220
PCNA	NM_002592
TERC	NR_001566
DKC1	NM_001363
PYCR1	NM_006907

Assistance Publique
Hôpitaux de Marseille

Premature aging interactome



Random Walk with Restart



Seed Protein

Adapted from http://slideplayer.com/slide/5223771/

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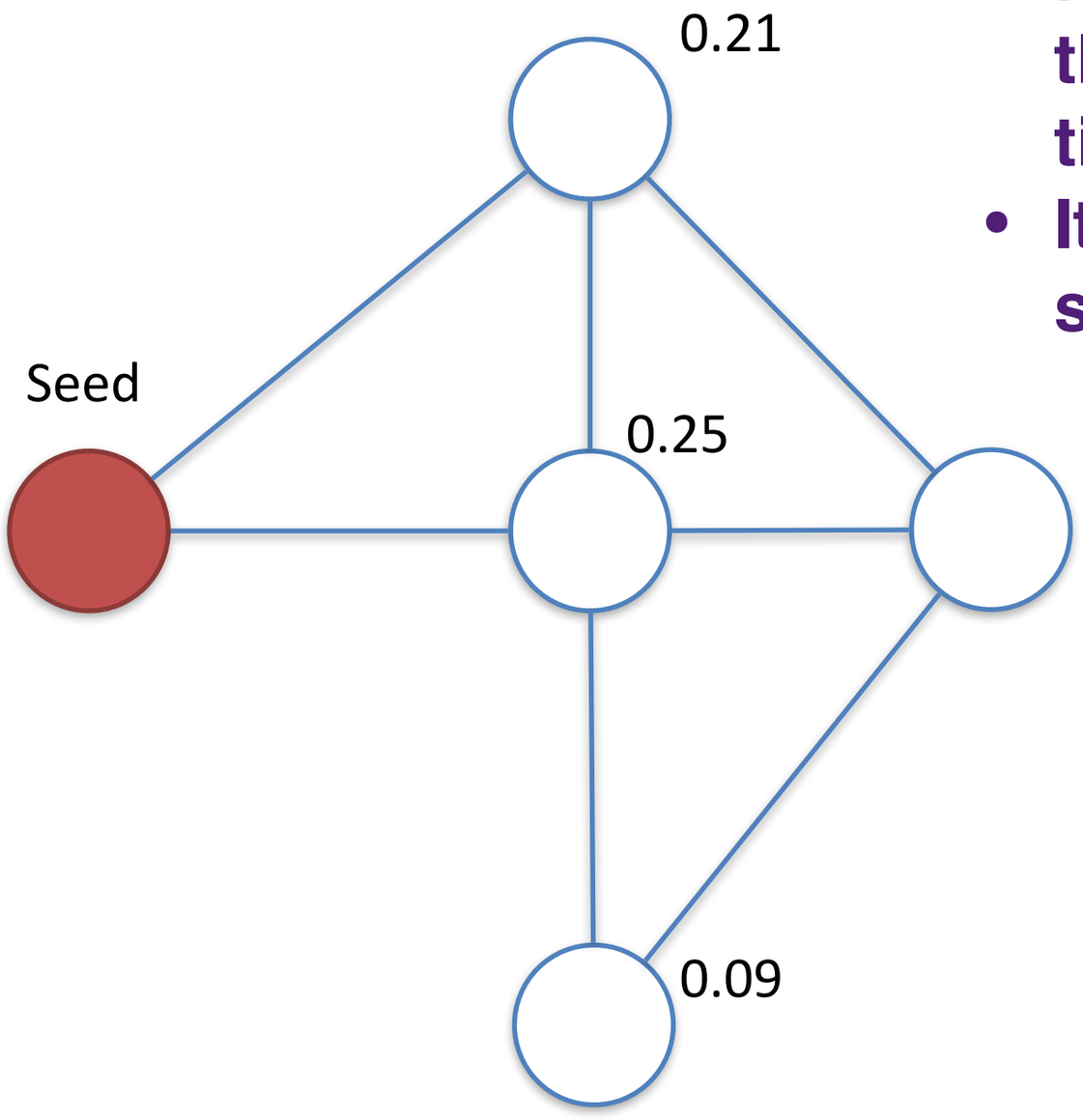
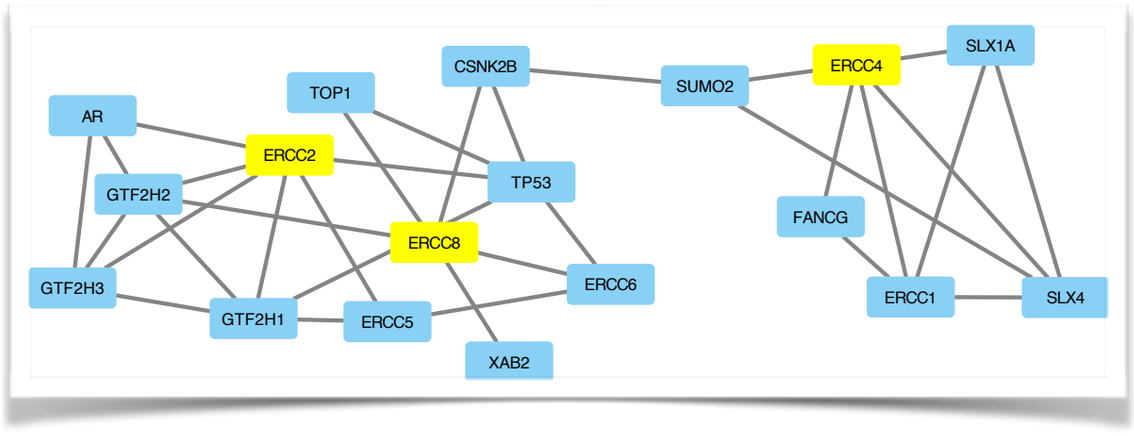
Random Walk with Restart

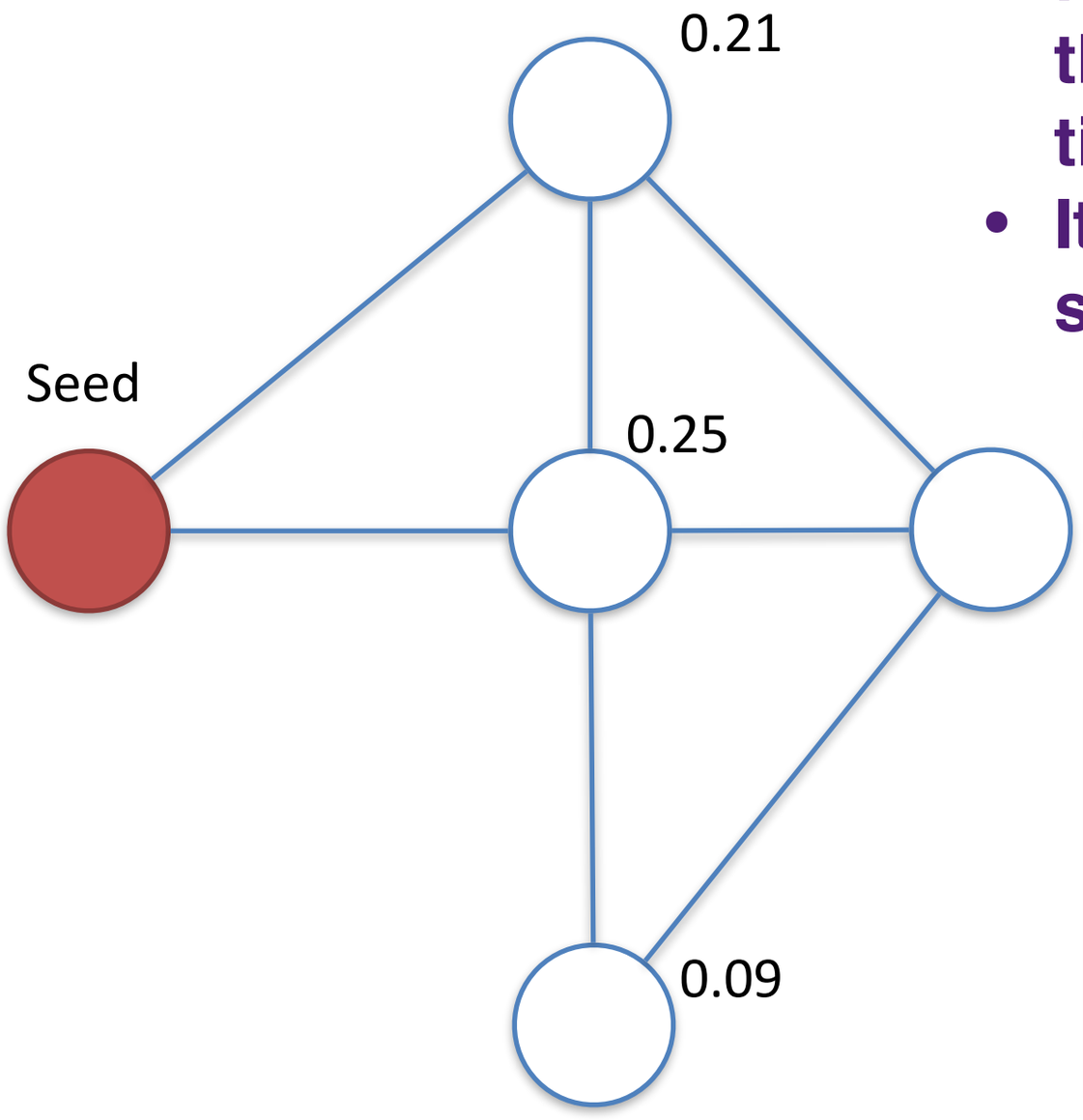


- **RWR estimates the probability that the particle visits each node when time tends to infinity**
- **It is a measure of proximity to the seeds**

$$\mathbf{p}_{t+1} = (1-r)M\mathbf{p}_t + r\mathbf{p}_0$$



Random Walk with Restart



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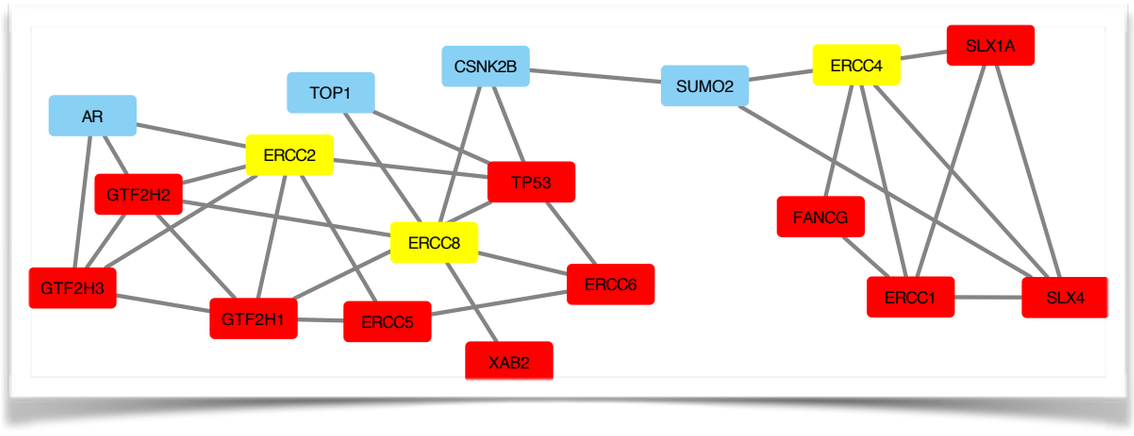
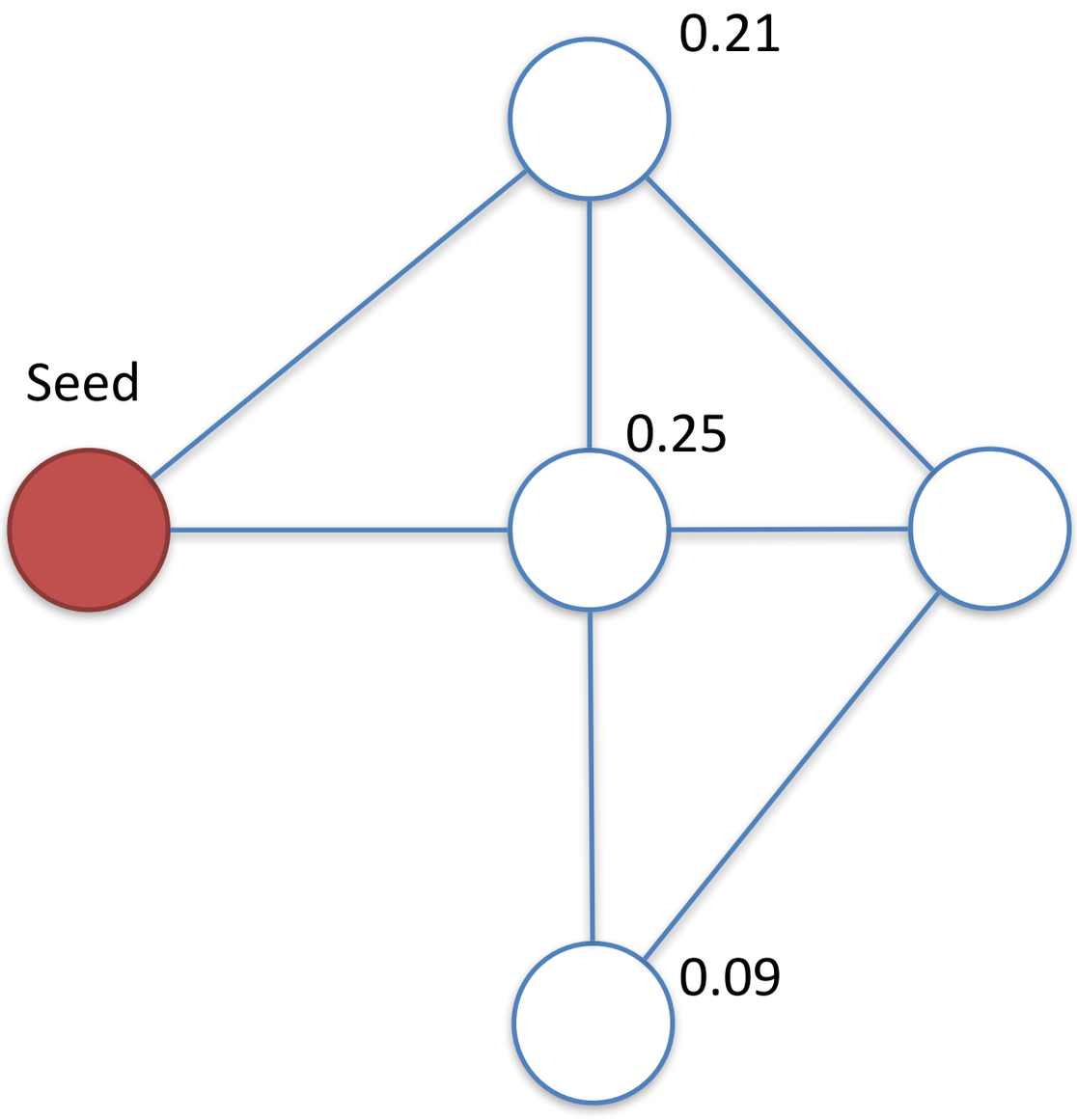
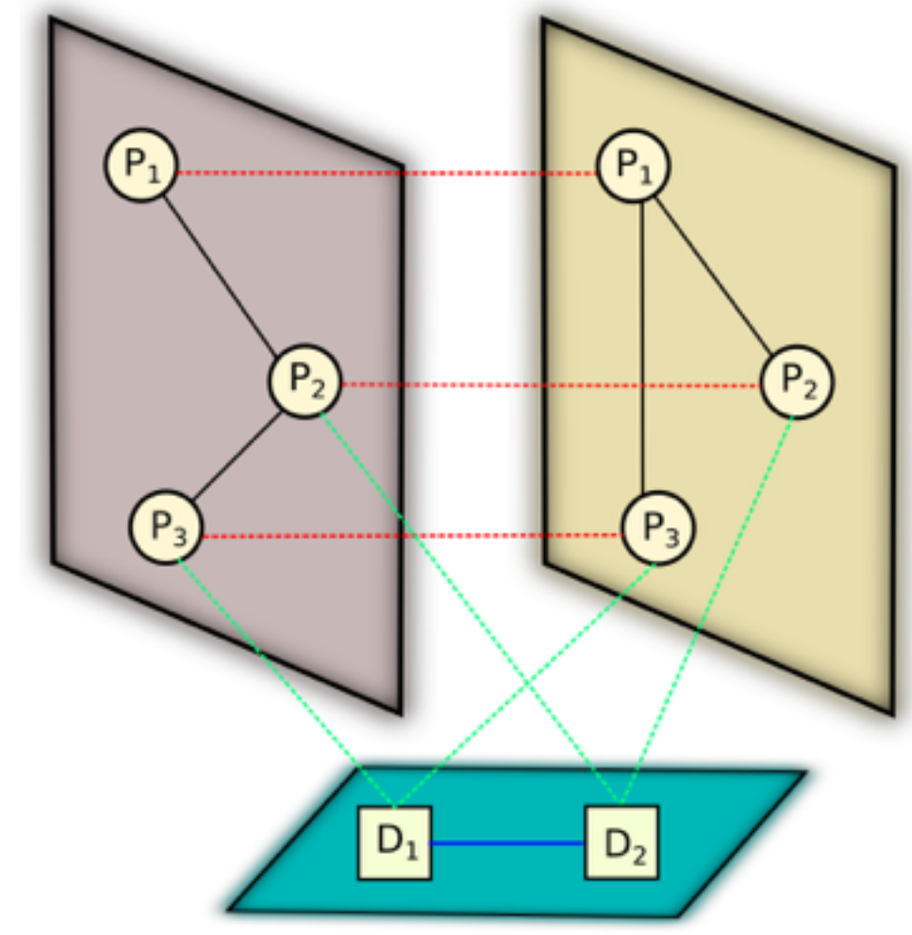


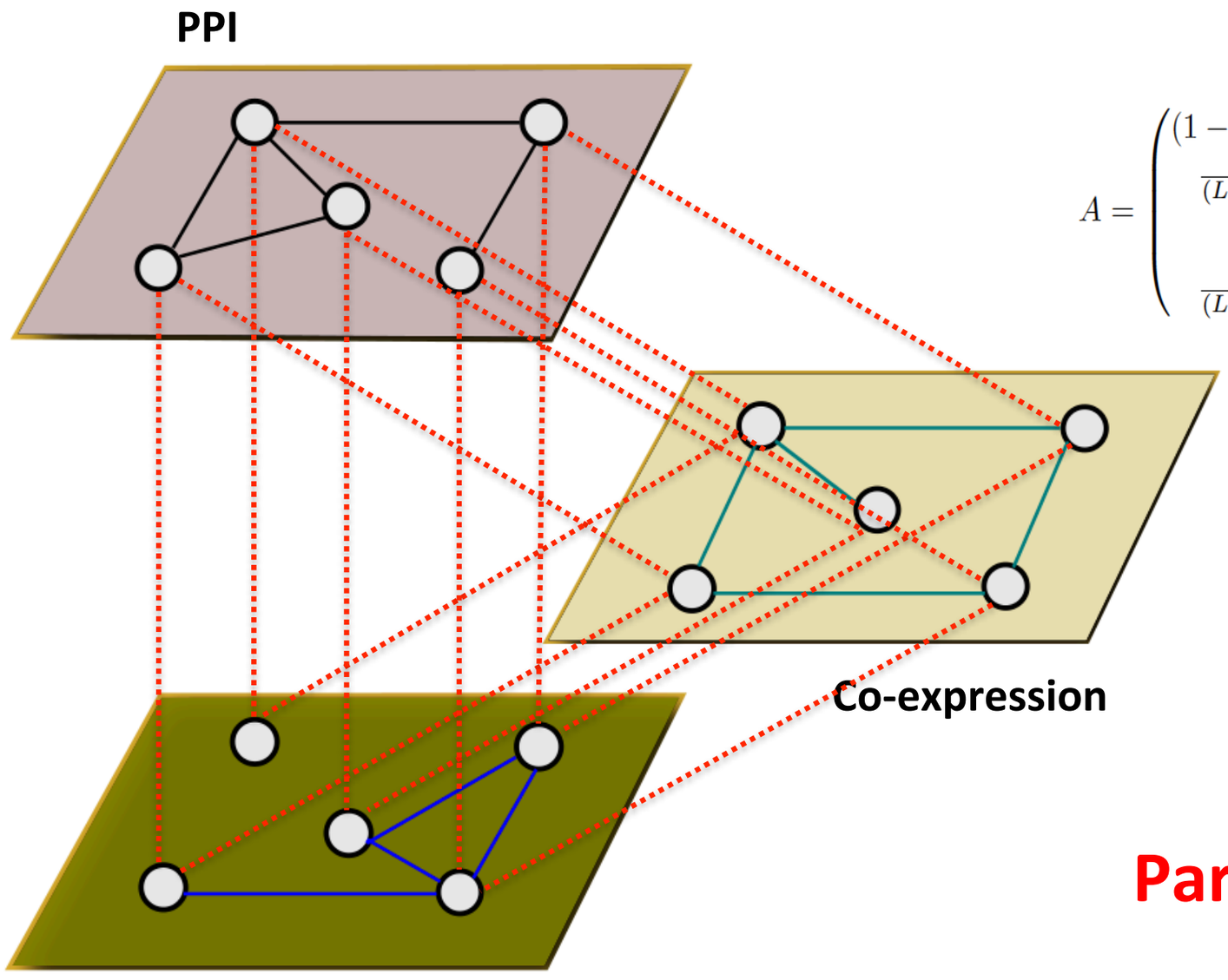
Random Walk with Restart in Multiplex and Heterogeneous Networks





Alberto Valdeolivas

Extension of RWR to Multiplex Networks (RWR-M)

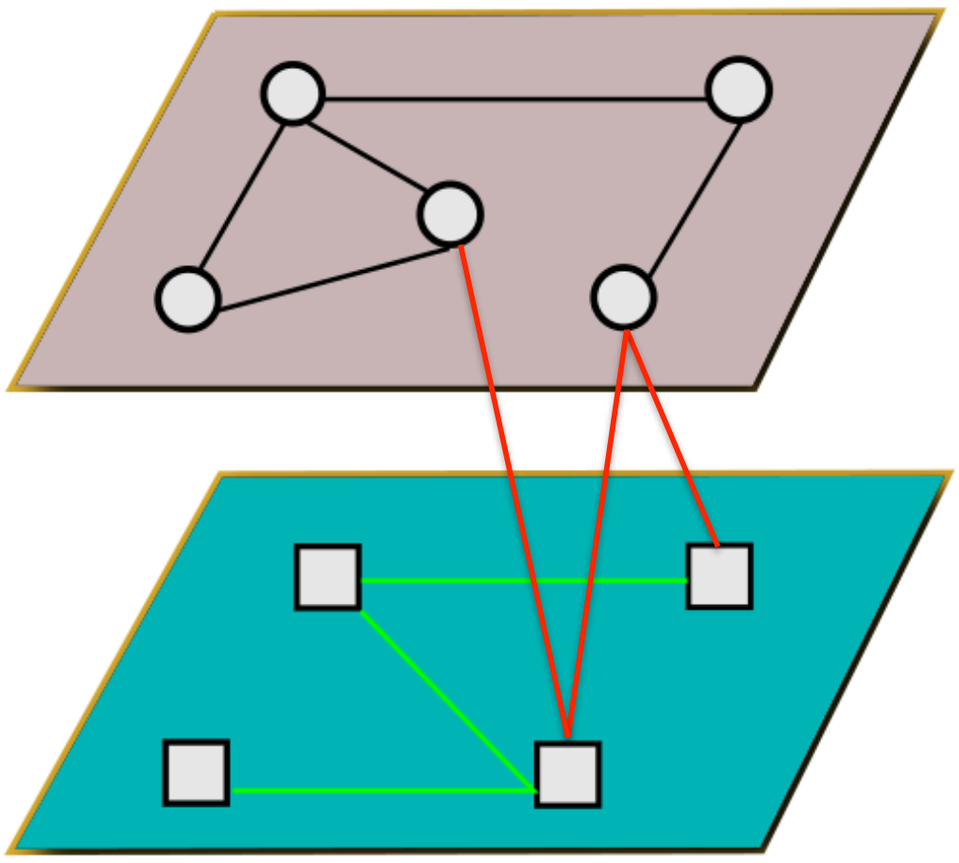


$$A = \begin{pmatrix} (1-\delta)A^{[1]} & \frac{\delta}{(L-1)}\mathbf{I} & \cdots & \frac{\delta}{(L-1)}\mathbf{I} \\ \frac{\delta}{(L-1)}\mathbf{I} & (1-\delta)A^{[2]} & \cdots & \frac{\delta}{(L-1)}\mathbf{I} \\ \vdots & \vdots & \ddots & \vdots \\ \frac{\delta}{(L-1)}\mathbf{I} & \frac{\delta}{(L-1)}\mathbf{I} & \cdots & (1-\delta)A^{[L]} \end{pmatrix}$$

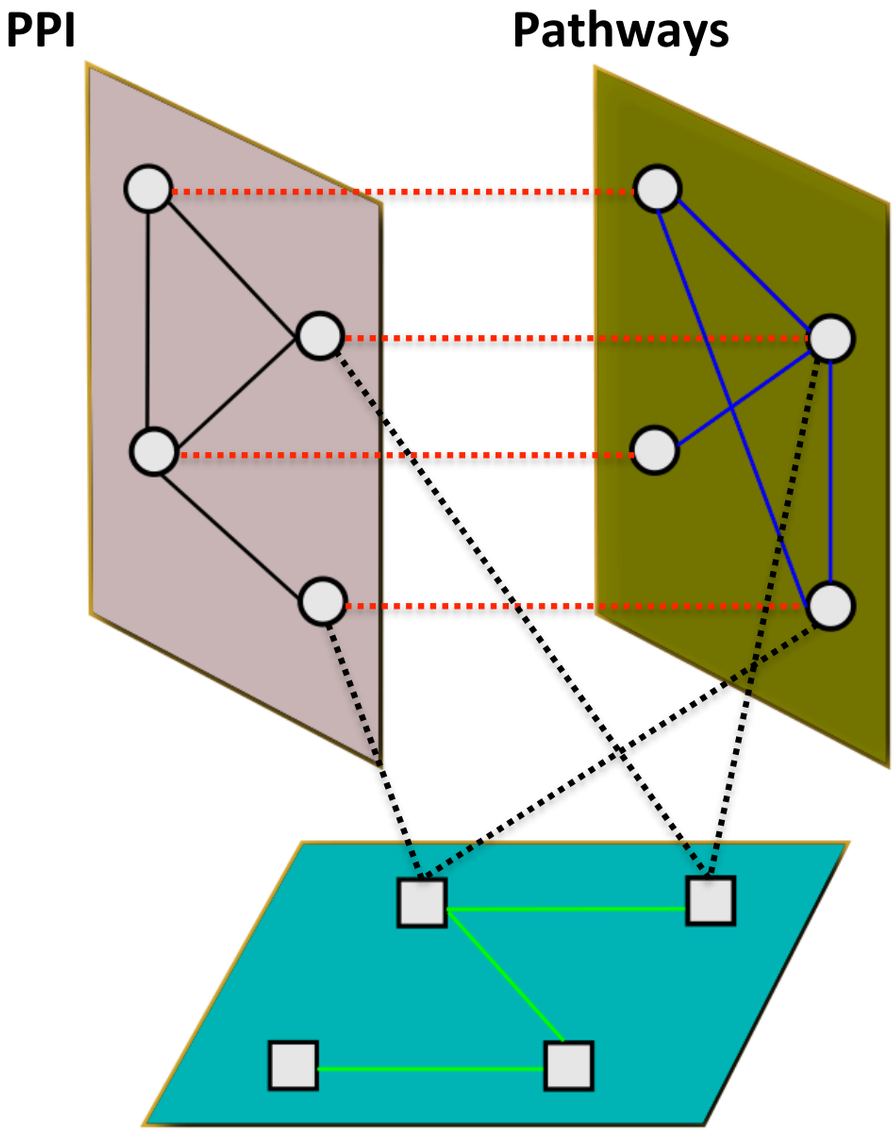
$$\overline{\mathbf{p}}_{t+1} = (1-r)M\overline{\mathbf{p}}_t + r\overline{\mathbf{p}}_{RS}$$

Parameters to tune:
δ and τ

Heterogeneous Networks



Extension of RWR to Multiplex and Heterogeneous Networks (RWR-MH)



$$\widetilde{\mathbf{p}}_{t+1} = (1-r)H\widetilde{\mathbf{p}}_t + r\widetilde{\mathbf{p}}_{RS}$$

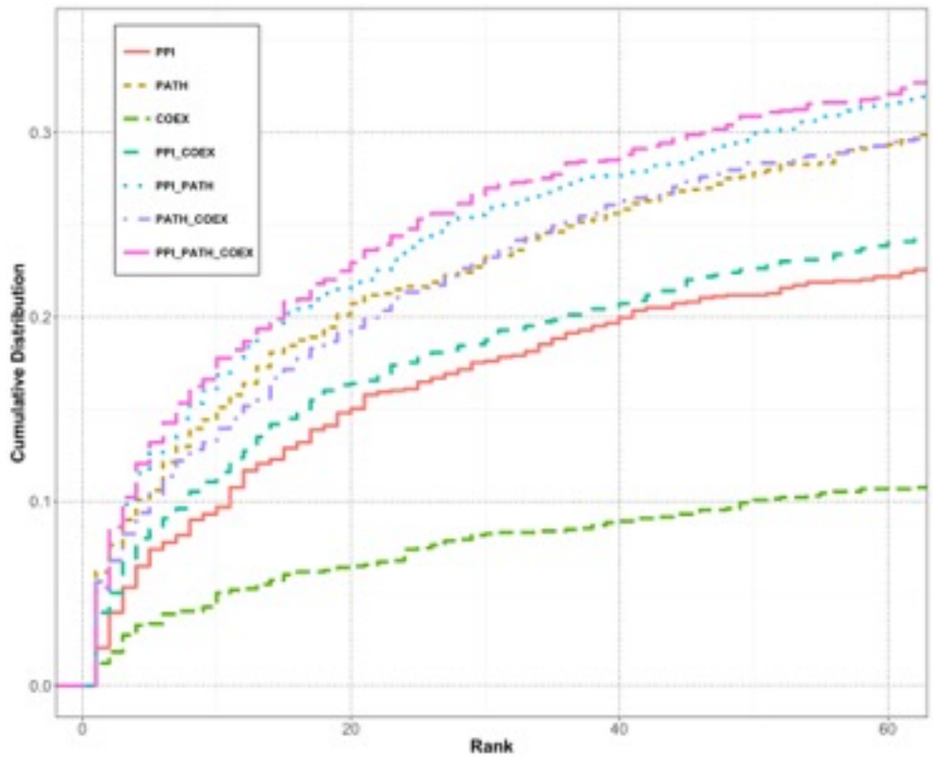
$$H = \begin{bmatrix} H_{PP} & H_{PD} \\ H_{DP} & H_{DD} \end{bmatrix}$$

$$H_{DP}(a,j) = \begin{cases} \lambda B(j,a)/\sum_{k=1}^{n} B(k,a), & \text{if } \sum_{k=1}^{n} B(k,a) \neq 0 \\ 0, & \text{otherwise} \end{cases}$$

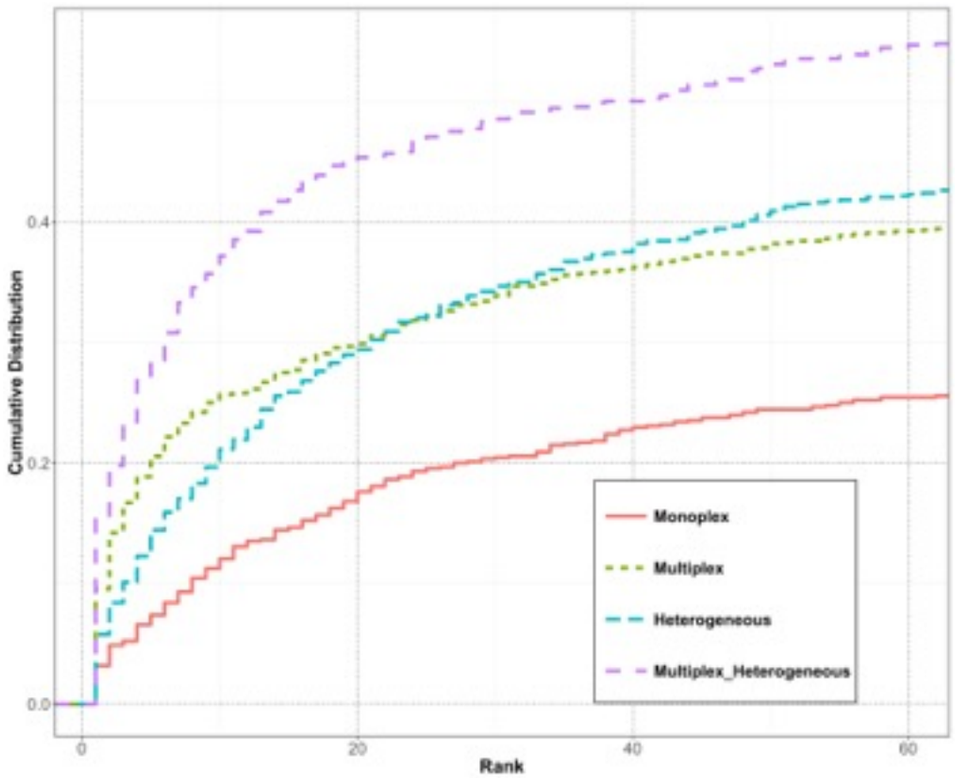
$$H_{DD}(a,b) = \begin{cases} A_D(a,b)/\sum_{k=1}^{m} A_D(a,k), & \text{if } \sum_{k=1}^{n} B(k,b) = 0 \\ (1-\lambda)A_D(a,b)/\sum_{k=1}^{m} A_D(a,k), & \text{otherwise} \end{cases}$$

Parameters to tune:
λ and η

Leave-One-Out Cross Validation



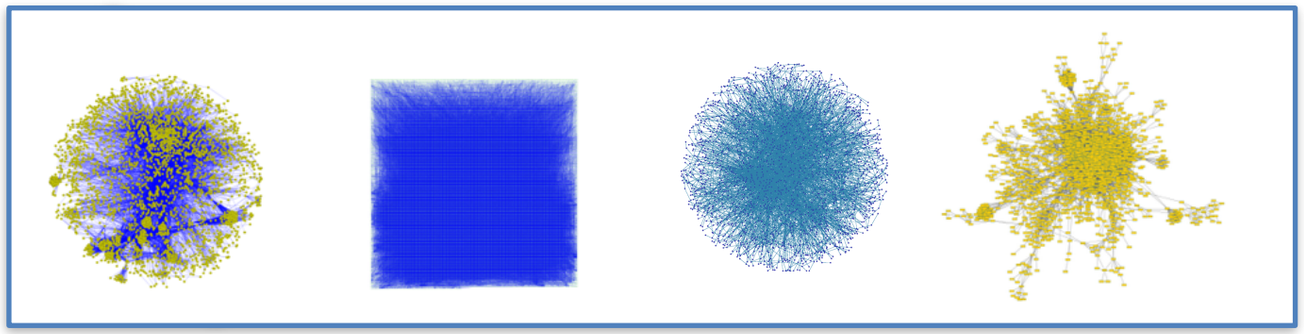
Multiplex versus monoplex



Multiplex-heterogeneous

Valdeolivas et al. bioRxiv 2017.

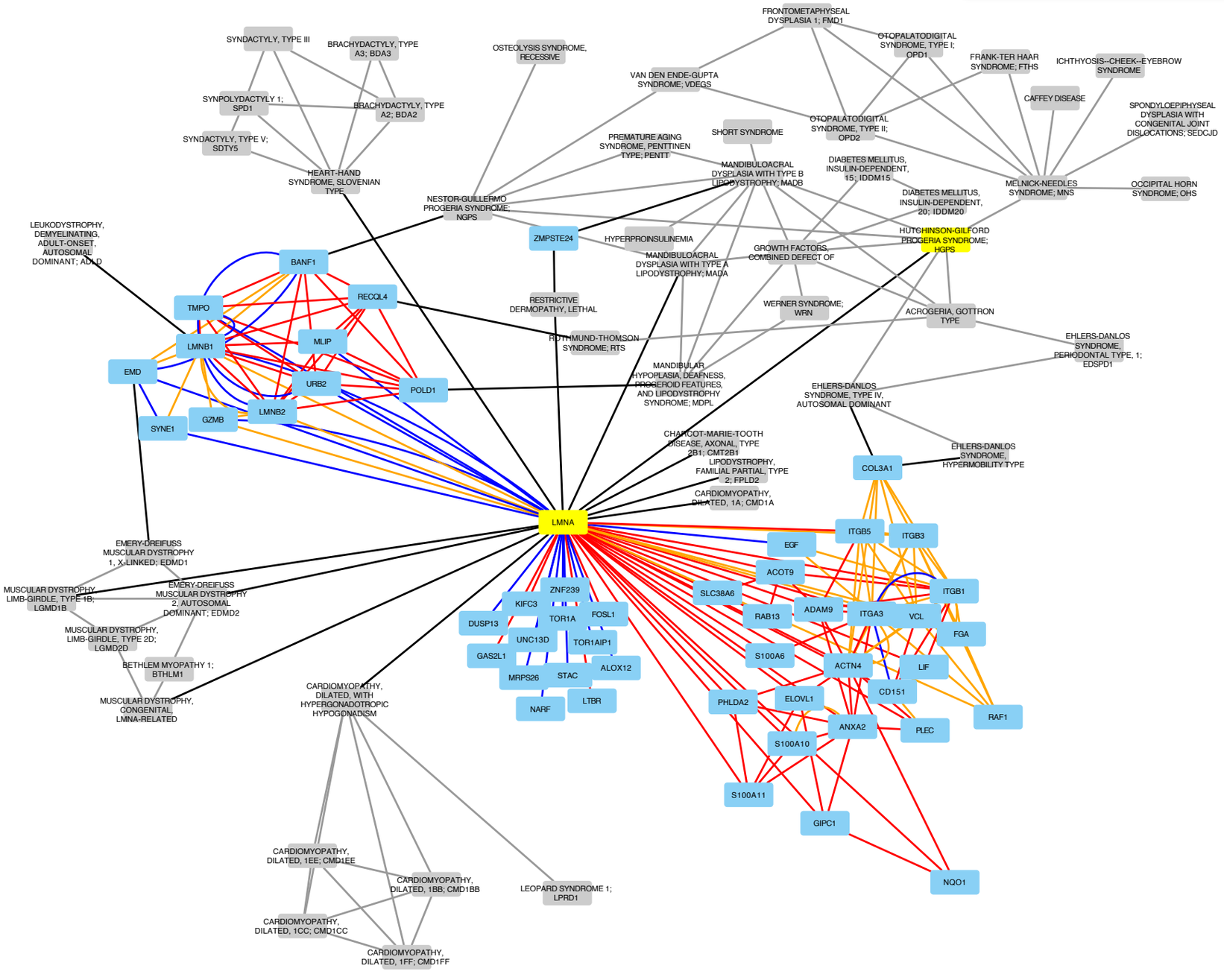
Application: Explore Network vicinity of disease and disease gene

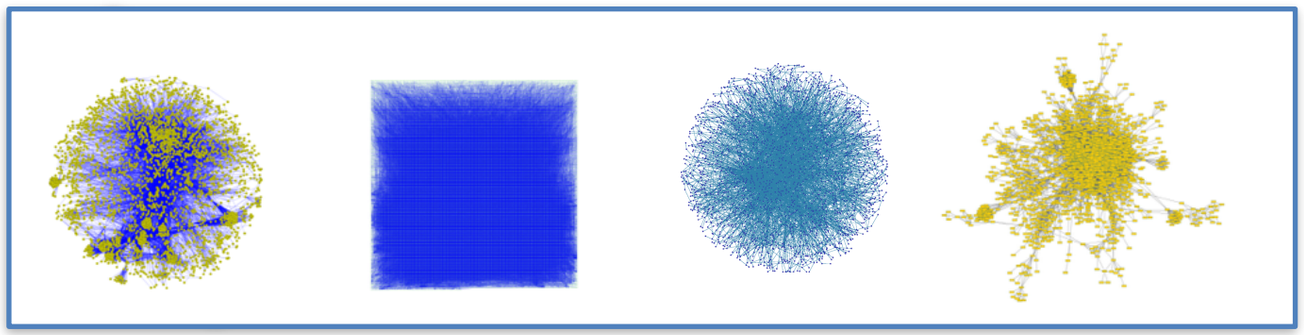


Disease-disease network

Random Walk with Restart

Top 50

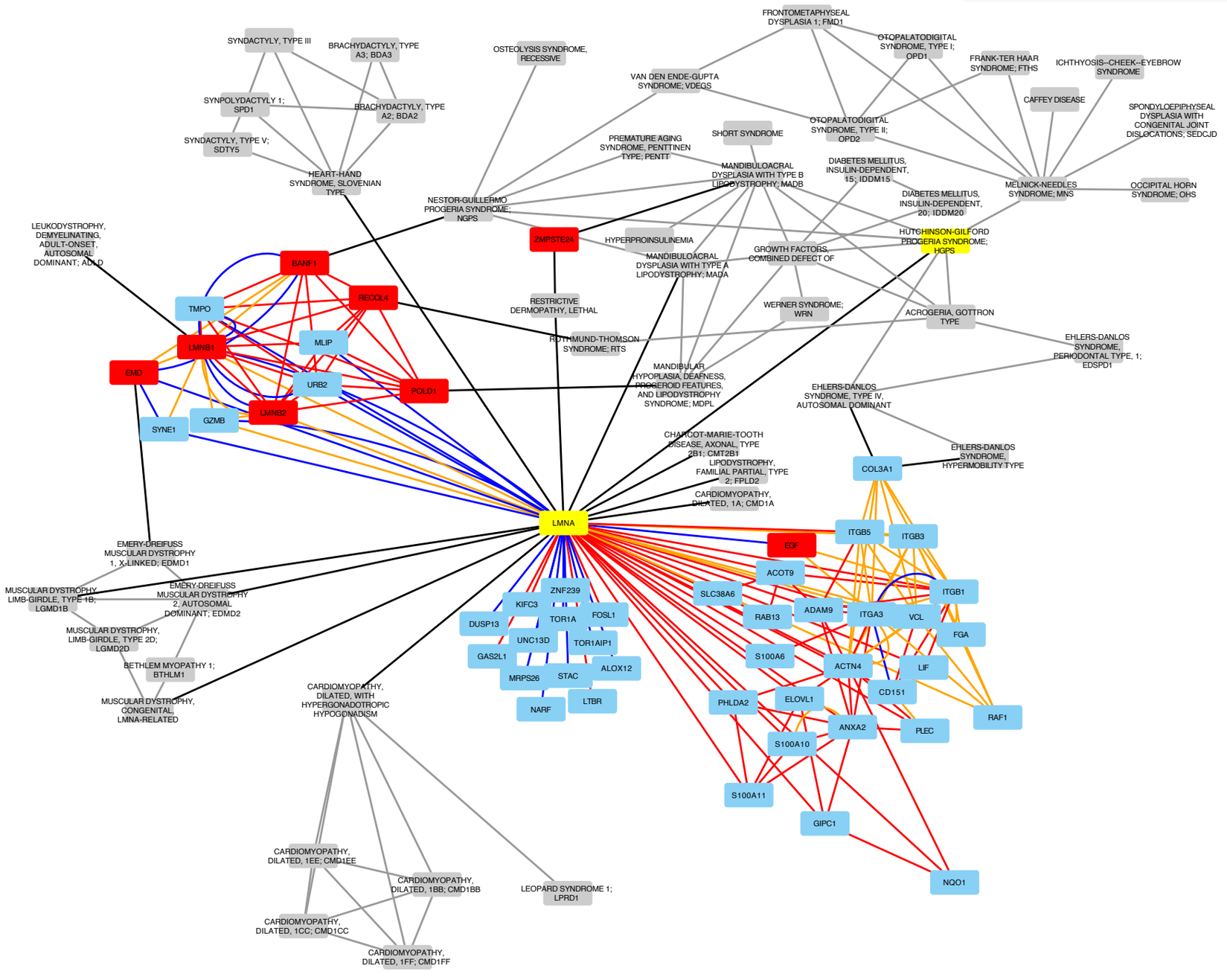




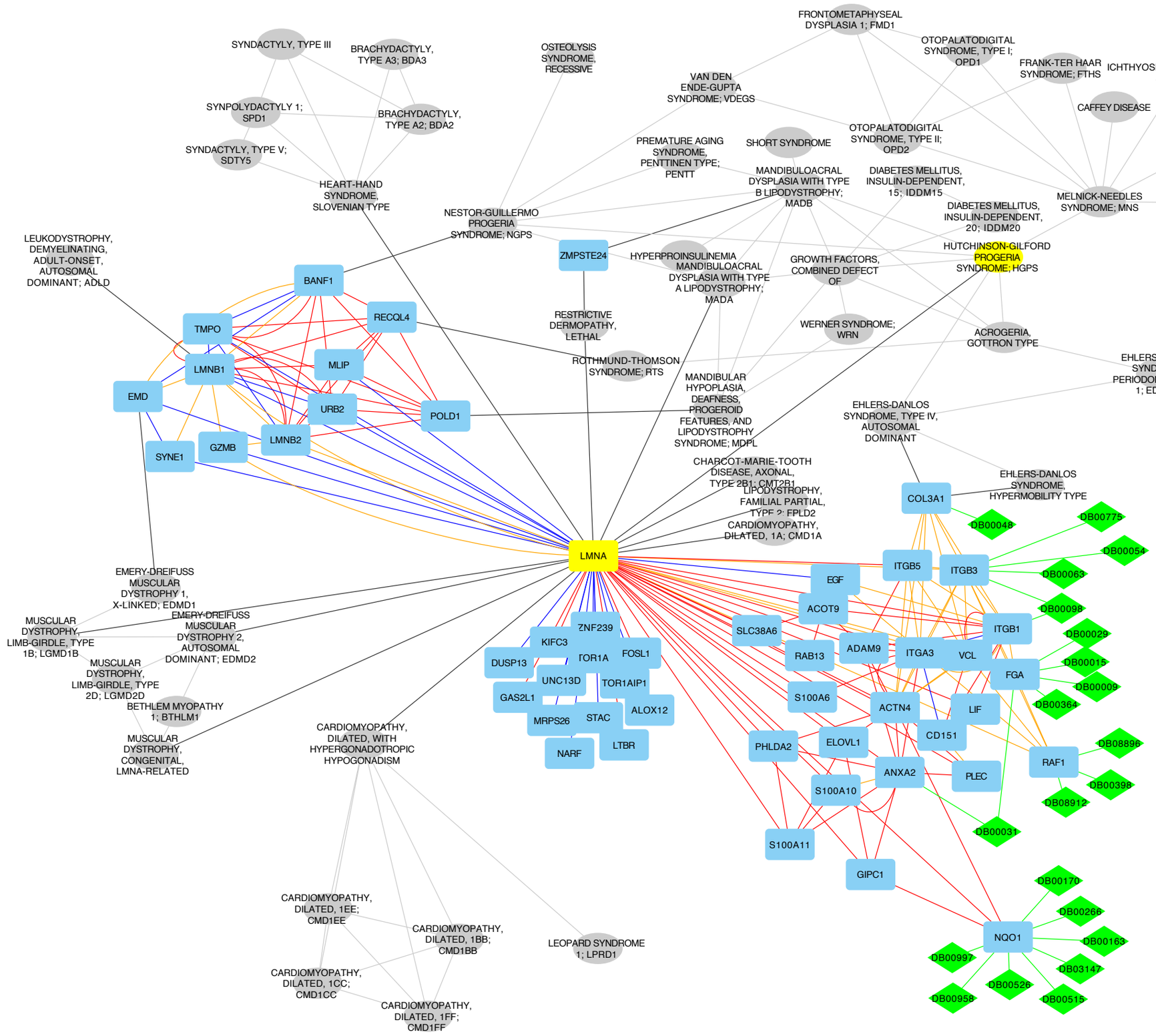
Application: Explore Network vicinity of disease and disease gene

Disease-disease network

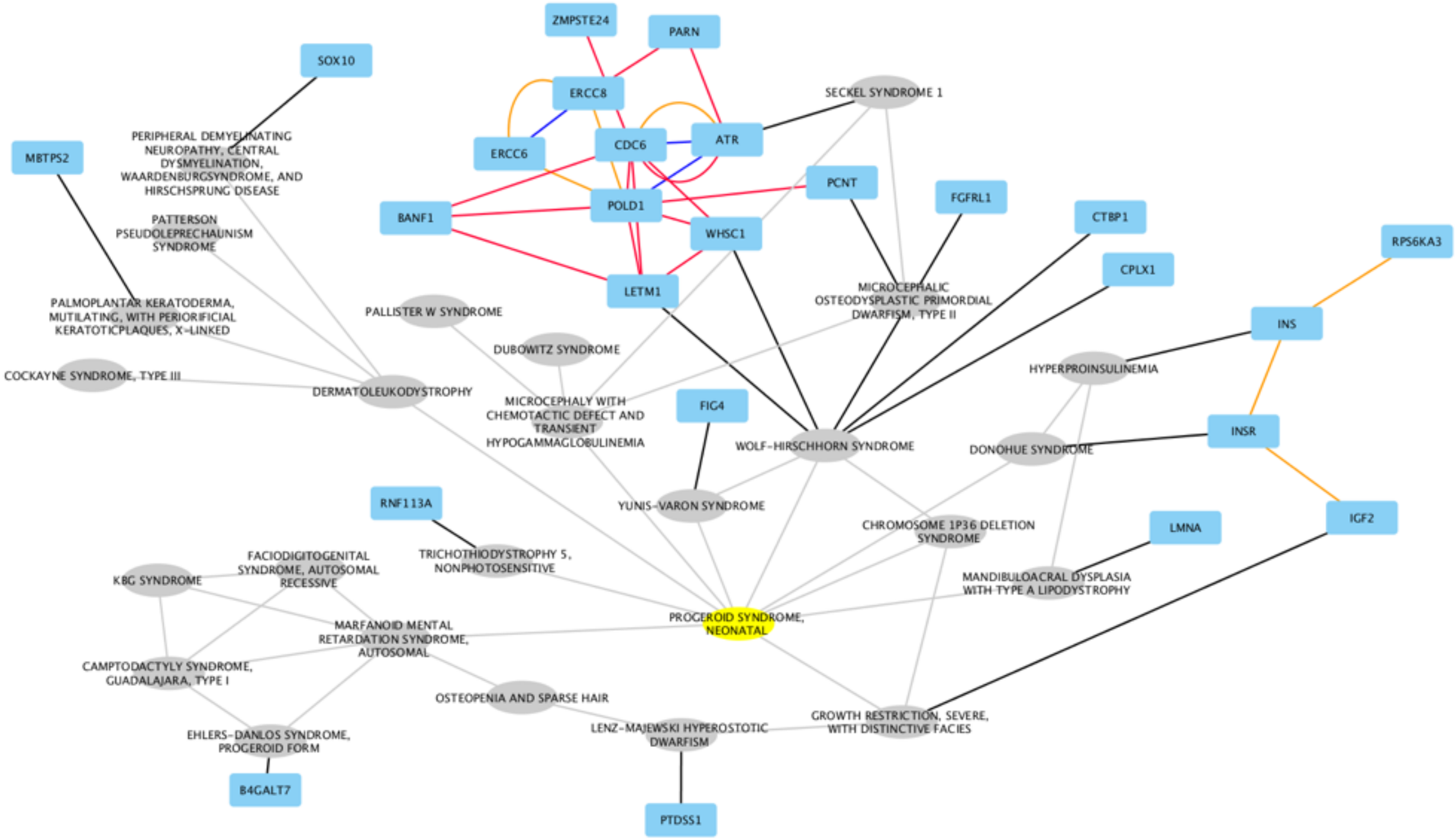
Physiological aging



Application: drug repurposing

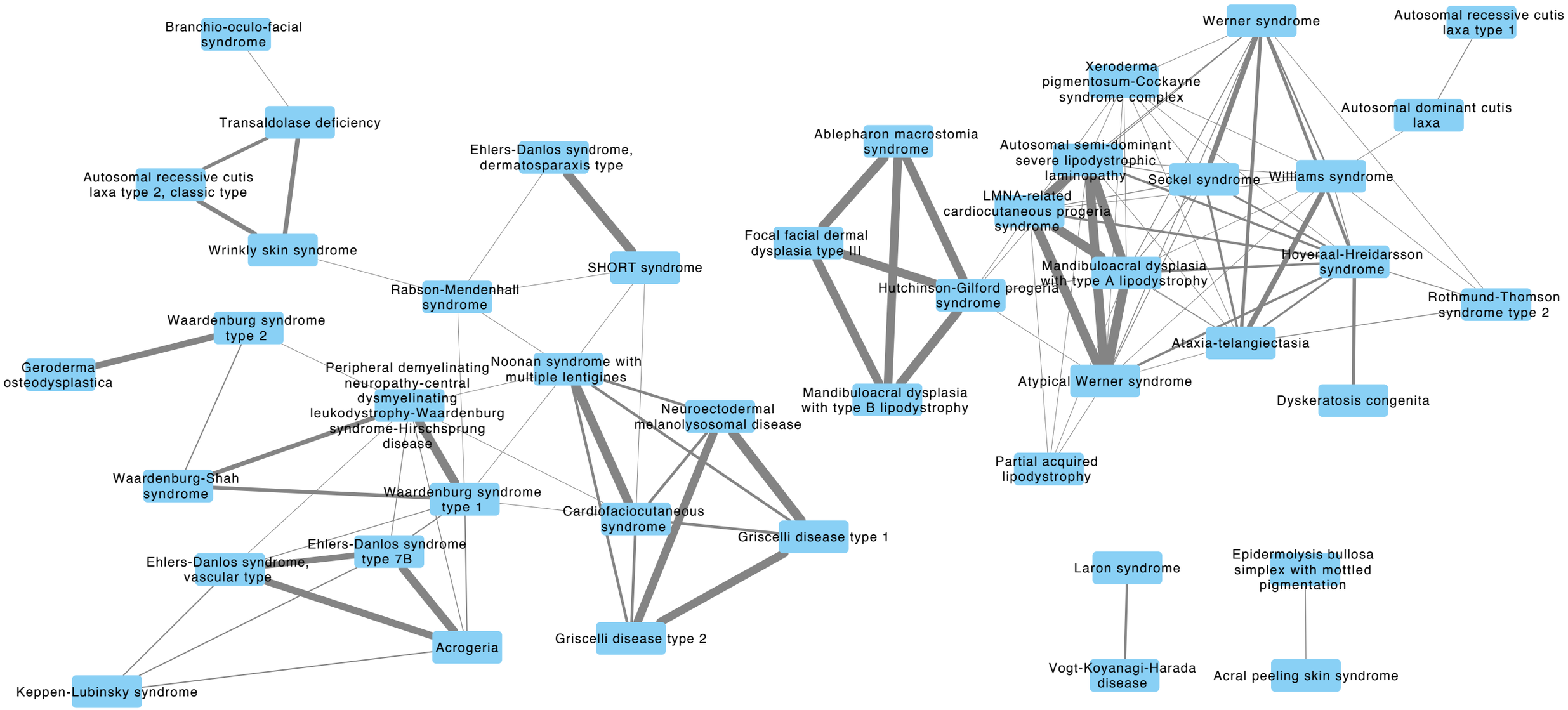


Application: diagnosis NGS



Application: disease classification and comorbidities

- All ~50 diseases with “premature aging” phenotype in HPO => associated genes
- For each disease => Top 25 genes - subnetworks with RWR-M



Plan cancer

PEPS Bio-Maths-Info

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