k-PathA: *k-shortest* Path A*lgorithm*

(pronounce as "Qué Pasa")

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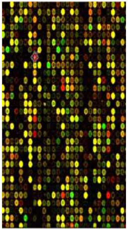
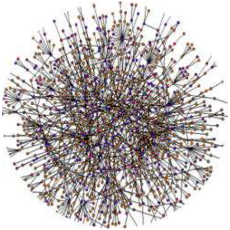
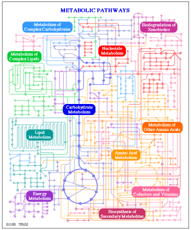
The Situation

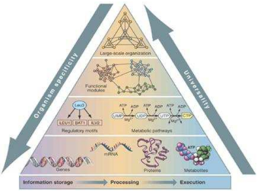


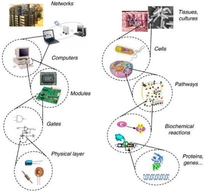




- Situation: Tons of available data on different levels
- Challenge: Derive useful information of structure and behavior of the biological systems

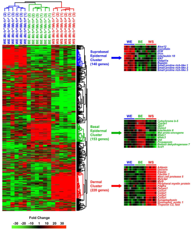
The Systems-Biology Approach





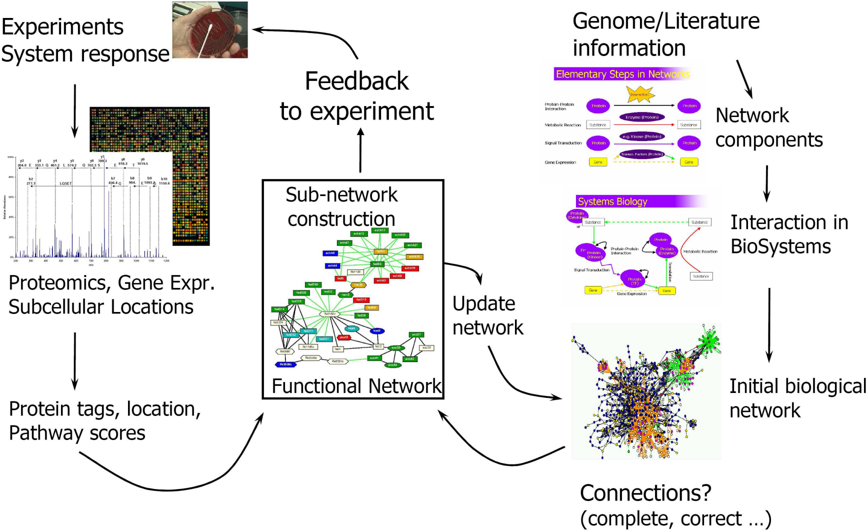
- Before SB: extensive research on single components
- SB says: interactions between components are more important
- SB looks beyond single genes, proteins, etc..
- SB looks at networks because they can give more insights
- SB combines data from different levels, components, conditions

Gene Expression



- Cell response to external conditions
- Expression Change = Control vs Experiment
- Biomarkers = Genes with high Expression Change
- Correlated genes are likely to share function
- Gene expression profiling, Gene clustering show some success
- But ...

Response Networks



Experiments
System response

Proteomics, Gene Expr.
Subcellular Locations

Protein tags, location,
Pathway scores

Feedback
to experiment

Sub-network
construction

Functional Network

Update
network

Genome/Literature
information

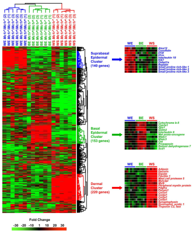
Network
components

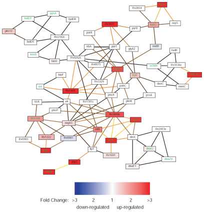
Interaction in
BioSystems

Initial biological
network

Connections?
(complete, correct ...)

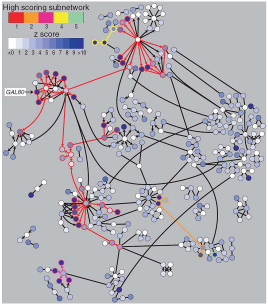
Gene Clusters vs Response Networks





- Genes in Response networks do not have to be active under all conditions
- Response networks underlie the constraints of the molecular interaction network
- Also non-correlated Genes can be included if they connect correlated genes
- Response networks of different conditions can be combined (response networks of new drugs can be compared to those of known drugs)

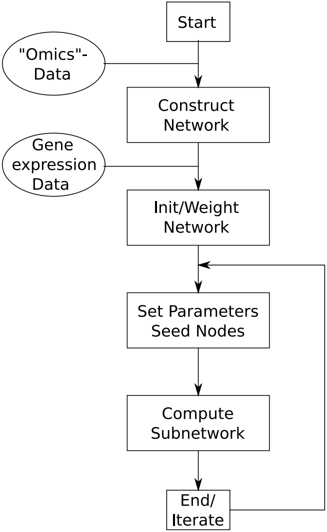
Response Networks - Computation



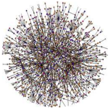
- Generated Sub-Networks have to be scored and compared against random Sub-Networks
- Computationally costly - Heuristics
- Still costly for large Networks - parallel Heuristics

k-PathA Approach - Overview

- Construction of Network
- Choice of Seednodes
- Generation of Sub-Network by spanning k-shortest Paths
- Scoring Sub-Networks
- Optimizing - Iterating

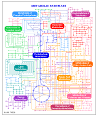


Network Construction



Nodes and Edges

+



Edges

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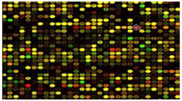
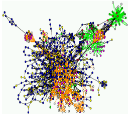


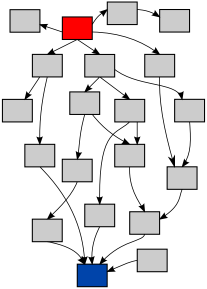
Node- and Edge-Weights

=



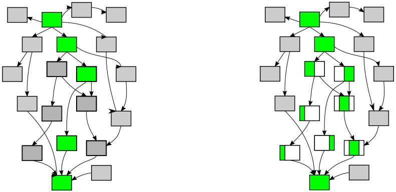
Network

Subnetworks - Preperation



- Choice of the Sub-Network borders = Seed Nodes
- Option 1: User Input
- Option 2: Randomly
- Option 3: Set of Nodes with highest weights
- In the Optimization step the set is changed

Sub-Networks - Generation

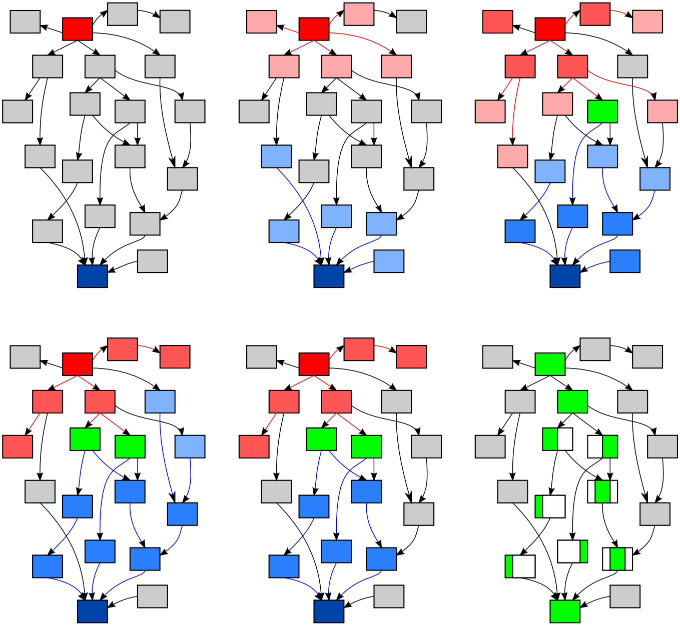


Definition

The k-th shortest simple path problem consists of the determination of a set of simple (loopless) paths between two nodes $P^k = \{p_1, p_2, \dots, p_k\} \subseteq P$, such that $\forall p \in P - P^k \wedge p^k \in P^k : cost(p^k) \leq cost(p)$.

- Spanning k-shortest simple (loopless) Paths
- Forward-, Backward Chaining Approach = Search from both Seeds
- Combination of Paths from both sides

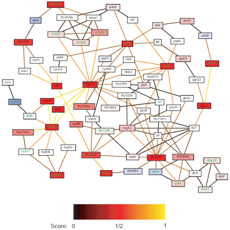
Sub-Networks - Generation

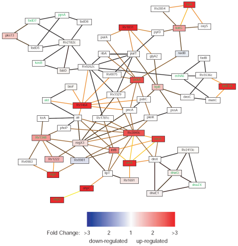


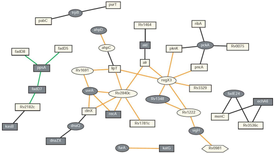
Sub-Networks - Scoring

- Expression values are normalized
- Nodeweights are ≥ 0
- < 1 down-regulated
- > 1 up-regulated
- $LinkCost(l_{x,y}) = \log(|x + y|)$
- $PathwayCost(p) = \frac{\sum_{l \in L_p} LinkCost(l)}{|L|^k}$

Sub-Networks - Combination

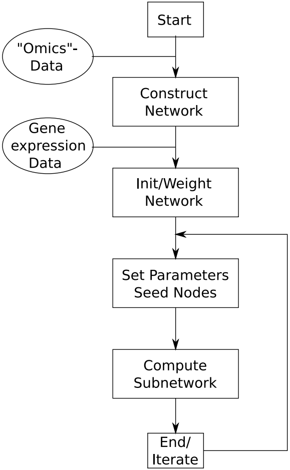






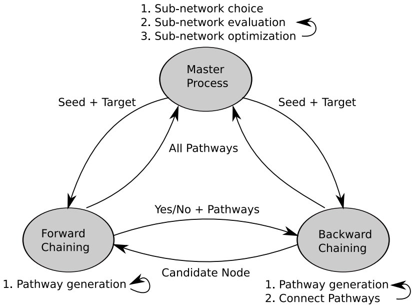
- Combine Sub-Networks for different Conditions
- Can show Similarities of Drug Responses
- $PC(X,Y) = \frac{(E(XY) - E(X)E(Y))}{\sqrt{Var(X)Var(Y)}}$
- $FPC(X,Y) = PC(X^{(2,n)}Y^{(1,n-1)})$
- $BPC(X,Y) = PC(Y^{(2,n)}X^{(1,n-1)})$

Sub-Networks - Optimization



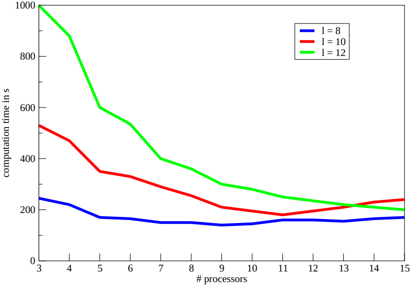
- Change of Seed nodes in every iteration
- Genetic algorithm: e.g. hill climbing

Parallel Implementation



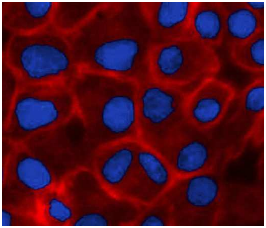
- Communication through message passing
- No shared Memory necessary
- 3 types of Nodes
- Master - Sub-Network Handling
- Forward - Path search and Common Node Checking
- Backward - Path search and Combination of Paths

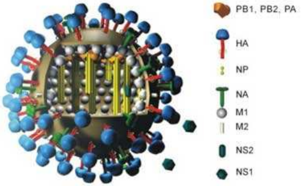
Parallel Implementation Behavior



- For larger Networks or high k and l: it scales linear
- For small Networks: communication is big part

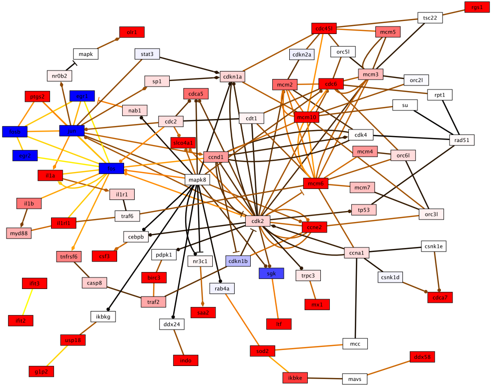
Application





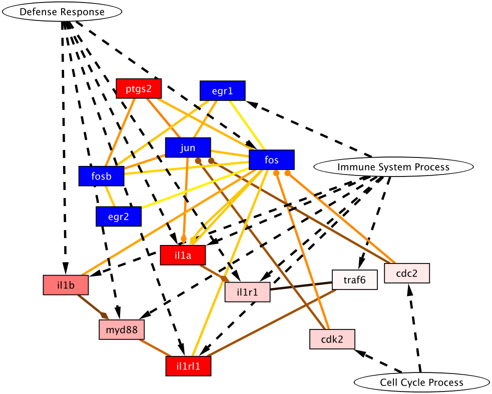
- Human-hybrid Network: 45,041 nodes + 438,567 edges
- Human bronchial cells
- Influenza (H5N1) infection (24h)
- Control: Mock infection (24h)
- $k = 3$, $l = 13$

Application



- Two well known processes affected by viral infections are present in the response network
- Cell-Cycle Genes (cdk2 and cdc's) are up-regulated
- Transcription factors known as early responders (fos and jun) are down-regulated

Application



- Comparison with other viral infection (LMCV, Djavani et al)
- Cell Cycle Process is modulated to induce apoptosis in the same way
- Immune Response is targeted similarly
- Moderate differences in the Host Response

Conclusions

- Computationally feasible through Parallel Implementation
- No shared Memory needed
- Flexible because new kinds of interactions can be introduced
- Flexible because of different scoring functions
- Response Networks for different conditions
- Comparison with other drug or viral responses possible

Acknowledgements

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For your Attention