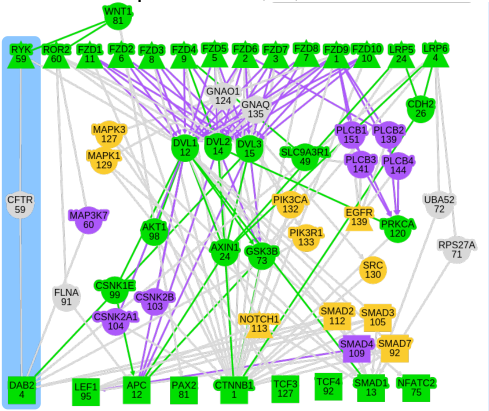
CS 3824: PathLinker

Automated Reconstruction of Human Signaling Networks

T. M. Murali

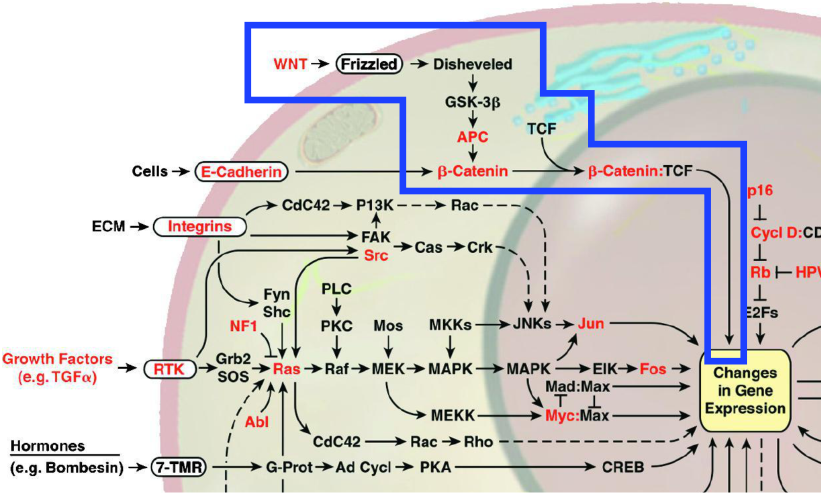
September 1, 6, 2022



Cell Signals

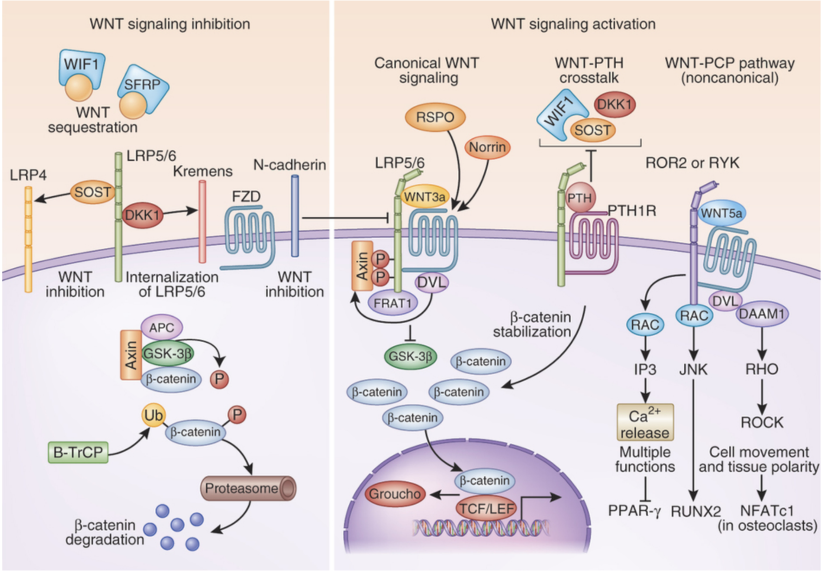
Video on Cell Signals (14 min 15 sec)

Wnt Pathway



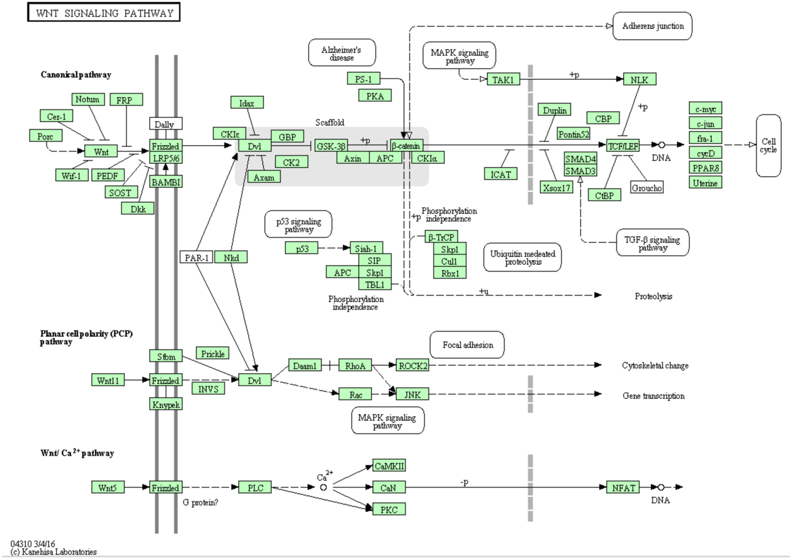
Hanahan and Wienberg. Hallmarks of cancer. Cell, 2000.

Wnt Pathway



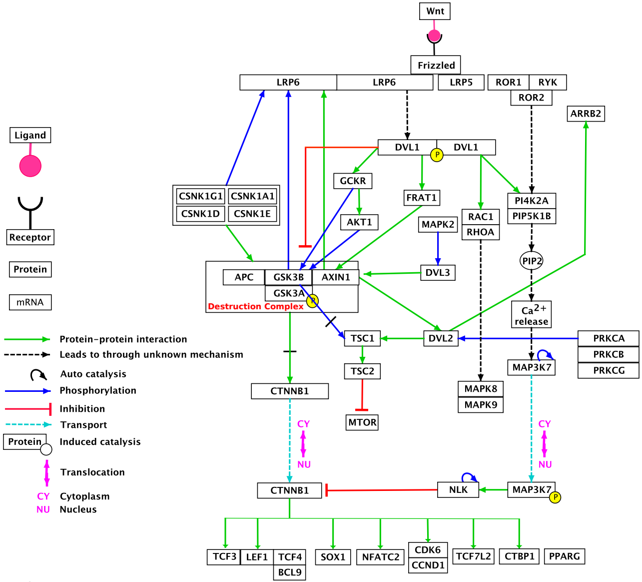
Baron and Kneissel. WNT signaling in bone homeostasis and disease: from human mutations to treatments. Nat. Med., 2013.

Wnt Signaling in a Pathway Database



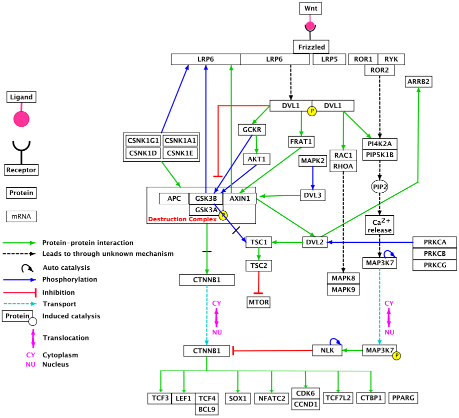
KEGG database

Wnt Signaling in a Pathway Database

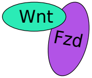


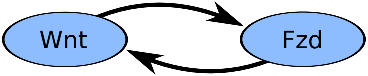
www.netpath.org/netslim

Signaling Pathways as Directed Graphs

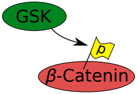


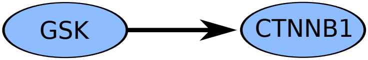
Bidirected Physical Interactions





Directed Regulatory Interactions





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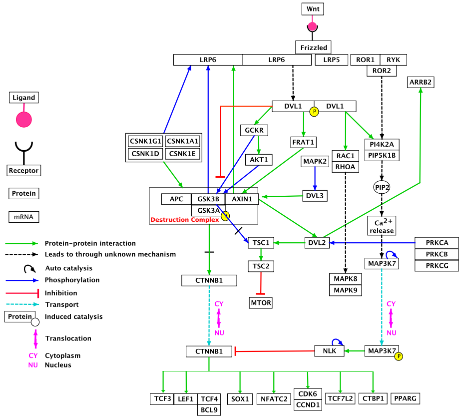

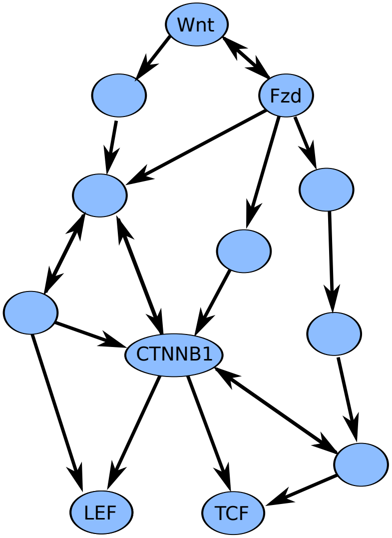

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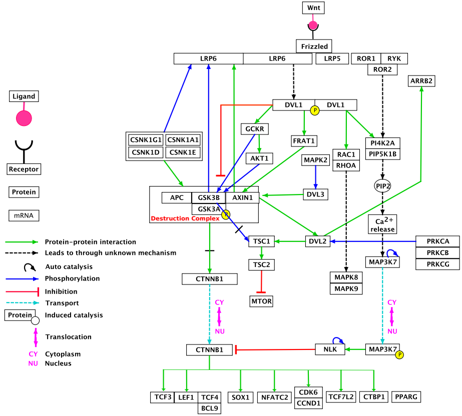
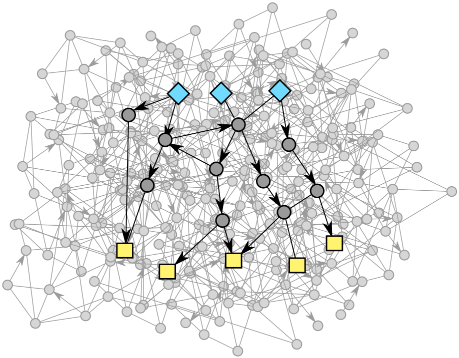
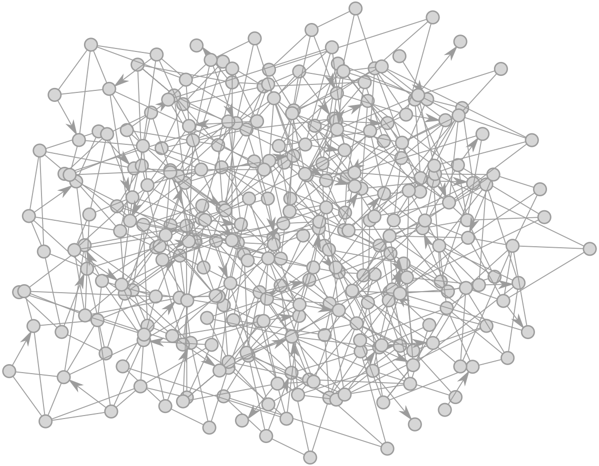


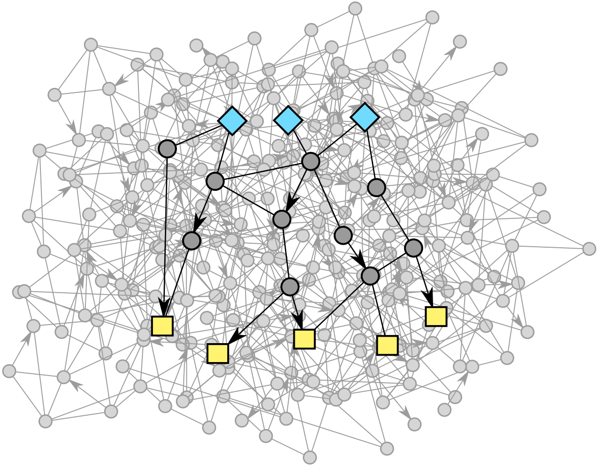


Reconstructing Signaling Pathways



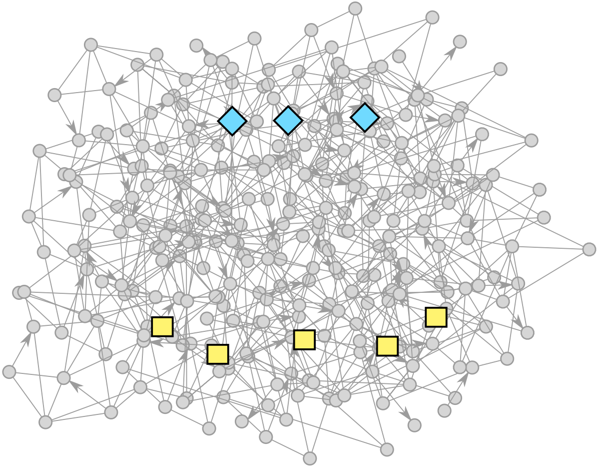
Human protein-protein interaction network
All known interactions among human proteins

Reconstructing Signaling Pathways



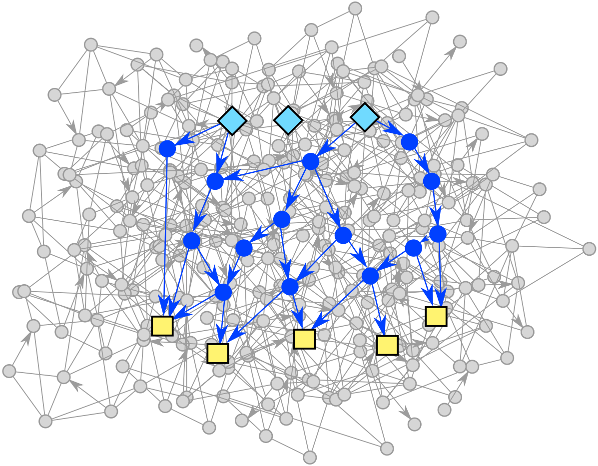
A pathway is a subgraph of the interaction network

Reconstructing Signaling Pathways



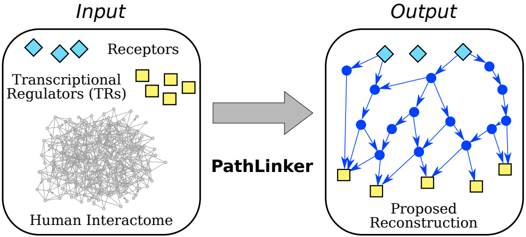
Question: Can we reconstruct the pathway given only receptors and transcriptional factors?

Reconstructing Signaling Pathways



Proposed pathway reconstruction

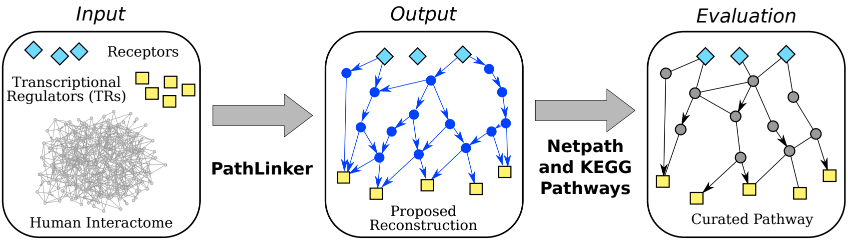
Automated Reconstruction of Signaling Pathways



- Developed **PathLinker** to reconstruct *proteins and interactions*
- **Systematically evaluated** PathLinker and other algorithms on human signaling pathways from the NetPath and KEGG databases

"Pathways on Demand: Automatic Reconstruction of Human Signaling Pathways," Ritz et al., Systems Biology and Applications, a Nature partner journal, 2, 16002, 2016.

Automated Reconstruction of Signaling Pathways



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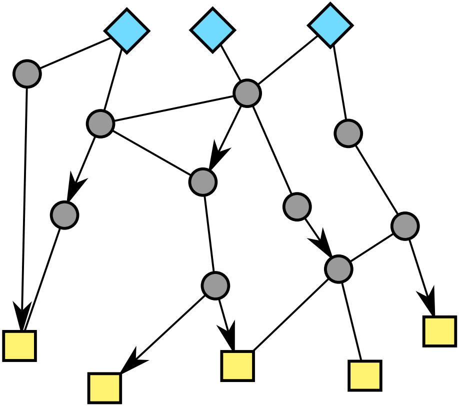
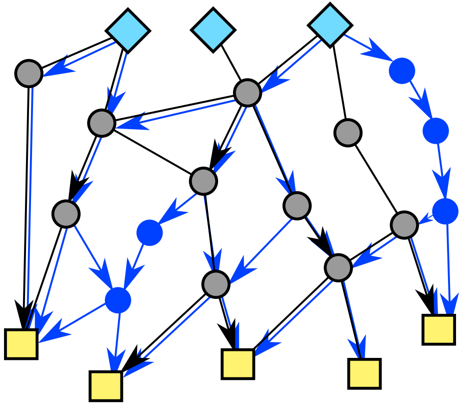
Evaluation of Reconstructed Pathways



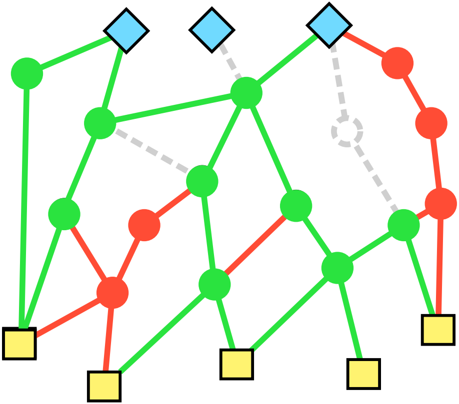
Curated Pathway

Evaluation of Reconstructed Pathways



Curated Pathway and Proposed Reconstruction

Evaluation of Reconstructed Pathways



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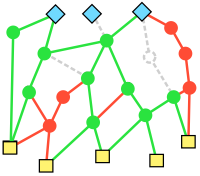

Recall:

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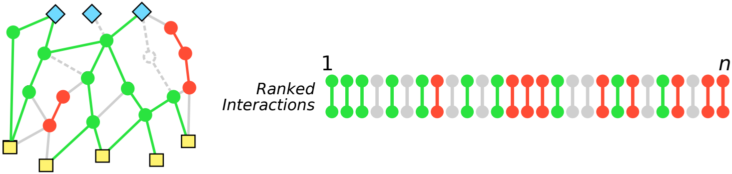

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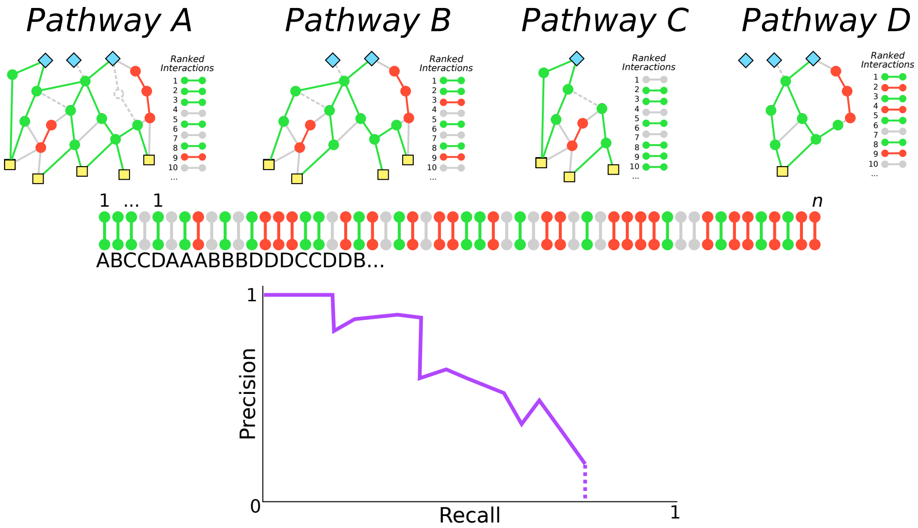
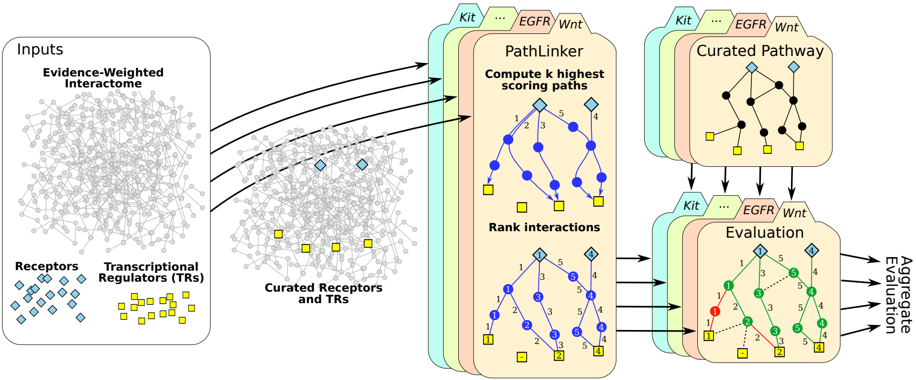
Evaluating Multiple Reconstructions

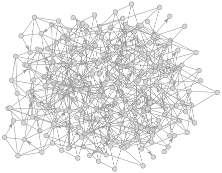


Complete Pipeline



Inputs for Pathway Reconstruction

Protein-Protein Interactome



- 12K nodes and 152K directed edges
- 61K physical interactions[1−4]
  BIND, DIP, InnateDB, IntAct, MINT, MatrixDB, Reactome, NetPath, KEGG, SPIKE
- 30K signaling interactions[2−4]
  NetPath, KEGG, SPIKE

[1] *Aranda et al., PSICQUIC and PSISSCORE: assessing and scoring molecular interactions. Nature Methods, 2011.*
[2] *Kandasmy et al., NetPath: a public resource of curated signaling transduction pathways. Genome Biology, 2010.*
[3] *Kanehisa et al., KEGG for integration and interpretation of large-scale molecular data sets. Nucleic Acids Research, 2012.*
[4] *Paz et al., SPIKE: a database of highly curated human signaling pathways. Nucleic Acids Research, 2009.*

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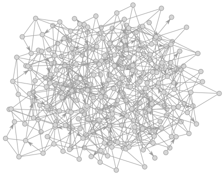
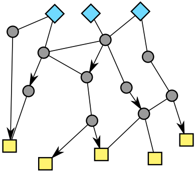
Signaling Pathways from NetPath[2]

- 15 immune and cancer pathways
  List of NetPath Pathways

2,124 Receptors[5]

2,286 Transcriptional Regulators[6,7]





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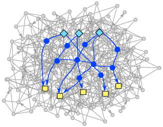
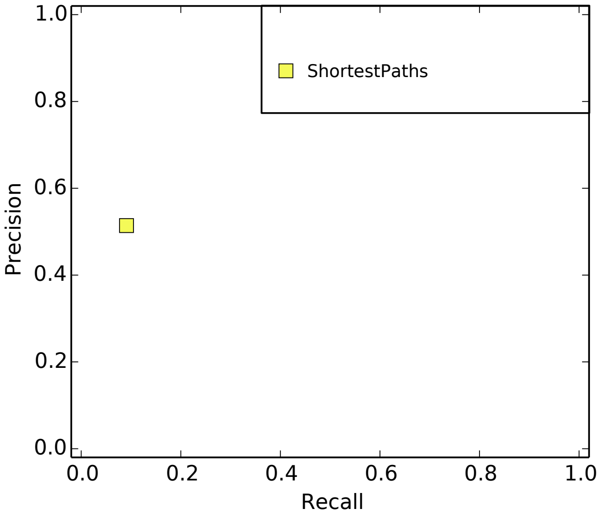
[4] *Paz et al., SPIKE: a database of highly curated human signaling pathways. Nucleic Acids Research, 2009.*
[5] *Almen et al., Mapping the human membrane proteome: a majority of the human membrane proteins can be classified according to function and evolutionary origin. BMC Biology, 2009.*
[6] *Ravasi et al., An atlas of combinatorial transcriptional regulation in mouse and man. Cell, 2010.*
[7] *Vaquerizas et al., A census of human transcription factors; function, expression and evolution. Nature Review Genetics, 2009.*

Results

ShortestPaths



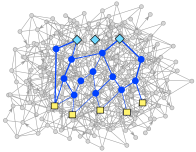


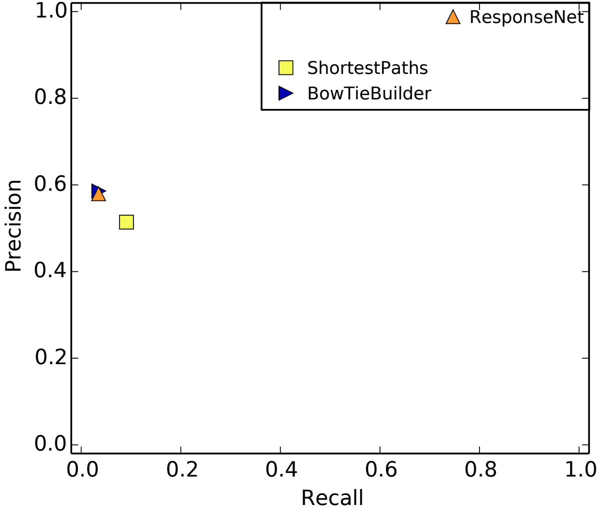
Steffen et al., Automated modelling of signal transduction networks. BMC Bioinformatics, 2002.

Results

Network Flow:

ResponseNet

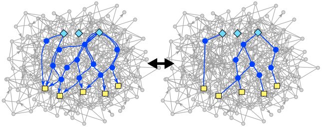




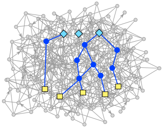
Yeger-Lotem et al., Bridging high-throughput genetic and transcriptional data reveals cellular responses to alpha-synuclein toxicity. Nature Genetics, 2009.

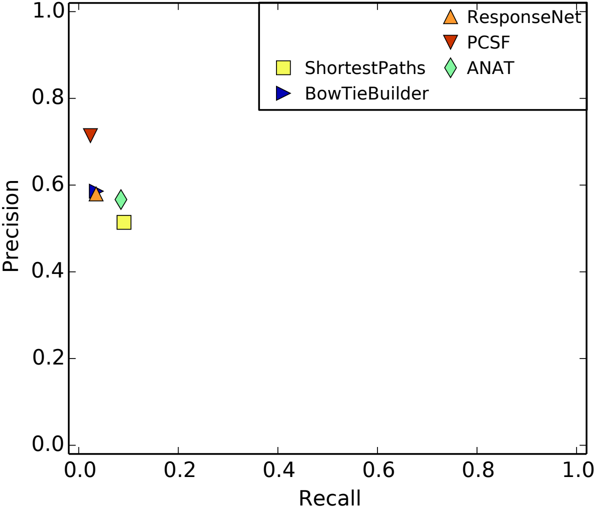
Results

Between ShortestPaths and Steiner Tree: ANAT



Prize Collecting Steiner Forest (PCSF)

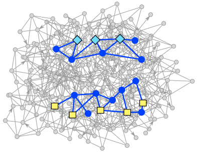


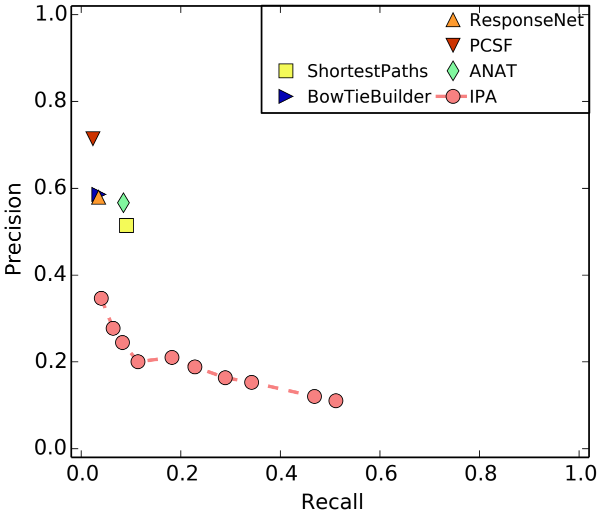


Yosef et al., ANAT: A tool for constructing and analyzing functional protein networks. Science Signaling, 2011.
Tuncbag et al., Simultaneous reconstruction of multiple signaling pathways via the prize-collecting Steiner forest problem. Journal of Computational Biology, 2013.

Results

Ingenuity Pathway Analyzer (IPA)

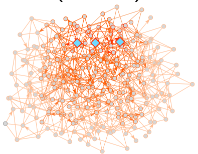


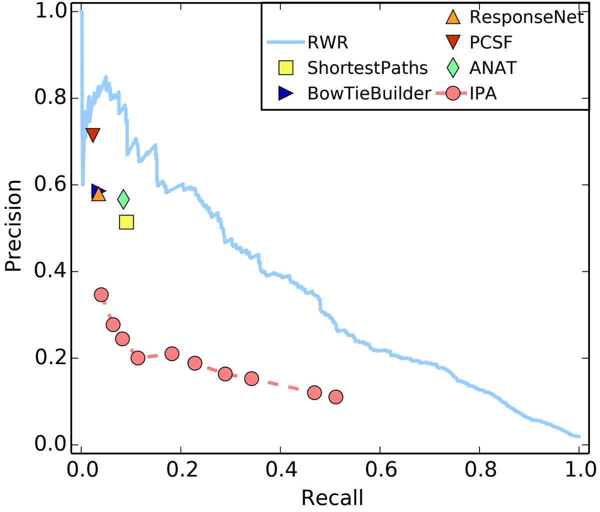


Ingenuity Pathway Analysis. IPA Network Generation Algorithm. White Paper, 2005.

Results

Random Walk with Restarts (RWR)





Page et al., The PageRank citation ranking: Bringing order to the web. Technical Report, 1999.

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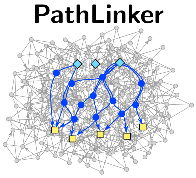
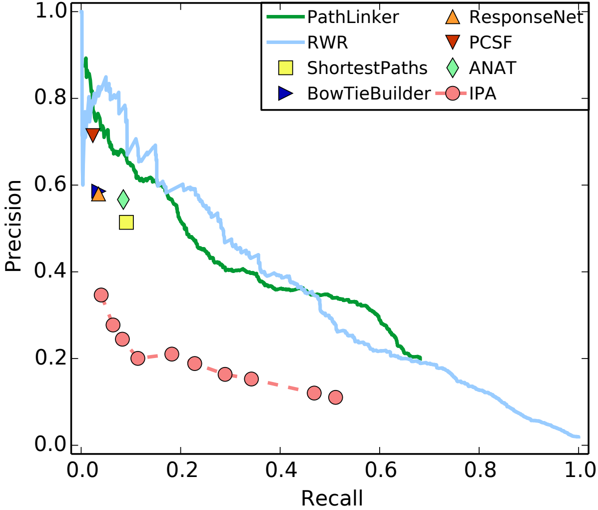
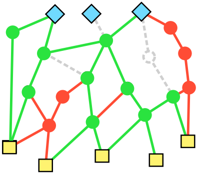




Yen. Finding the k shortest loopless paths in a network. Management Science, 1971.
This paper.

Evaluation of Reconstructed Pathways



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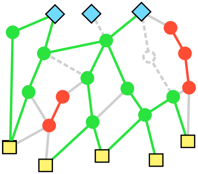

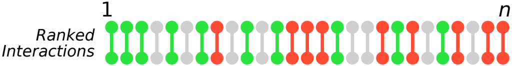

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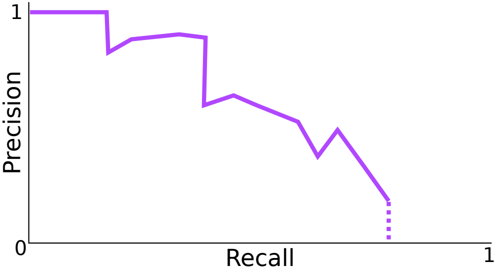
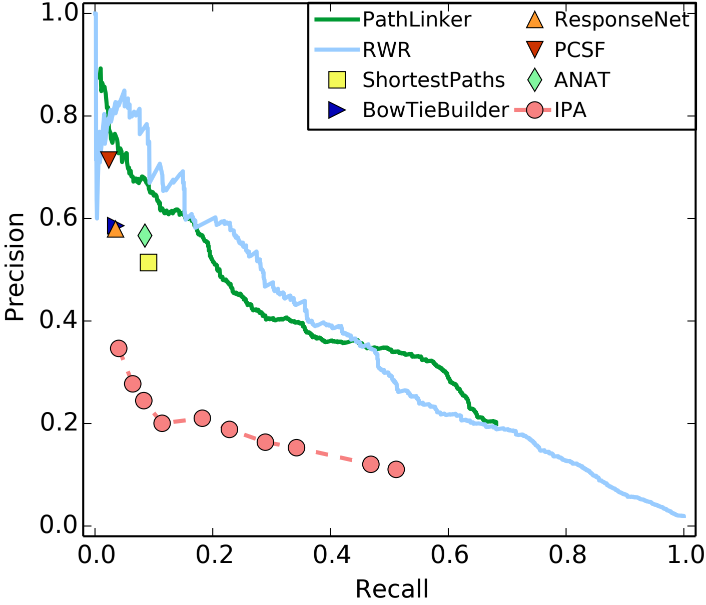


Ignore Pathway-Adjacent Negatives



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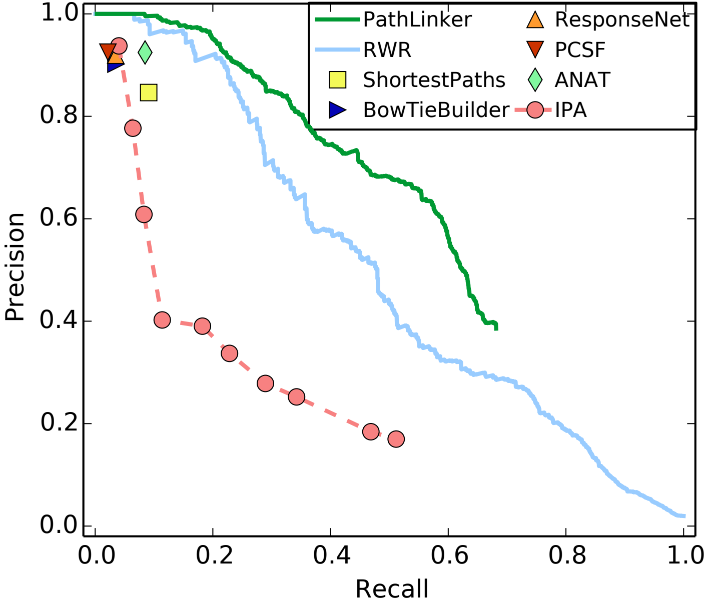
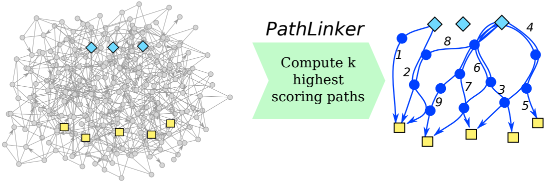


Why does PathLinker improve over other methods?



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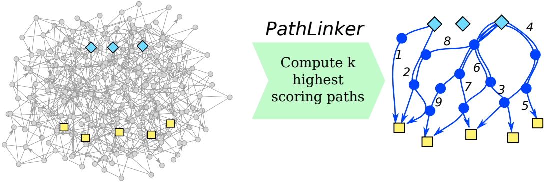

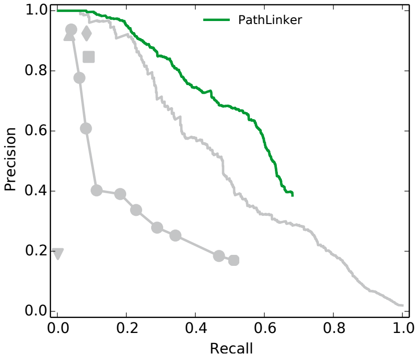

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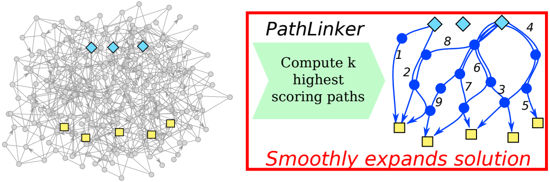

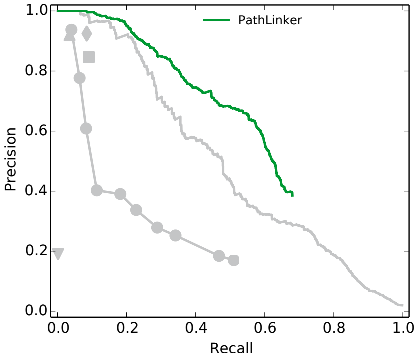

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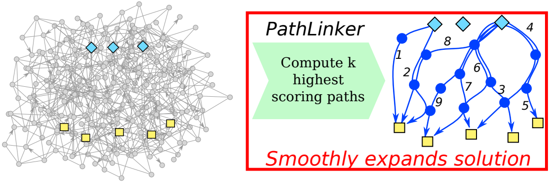

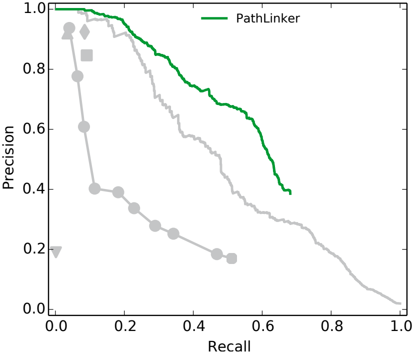

Parameter sweep

Algorithms Compared

Abbreviation	**Algorithm Type**
ShortestPaths	Shortest paths from every receptor to every TR
PathLinker	*k* shortest paths from any receptor to any TR
RWR	Random walk with restarts (aka PageRank)
ResponseNet	Network flow
ANAT	Tradeoff between shortest paths and Steiner trees
PCSF	Prize-Collecting Steiner Forest
IPA	Ingenuity Pathway Analyzer: grow subnetworks greedily
BowTieBuilder	Approximation to the Steiner tree connecting receptors and TRs

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Drunkard's Walk

- A drunk person leaves a bar.
- They move in steps, either by one unit to the right or by one unit to the left.
- When will they reach their home at the end of the street?
- If they return to the bar, they can only step out.

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- If they return to the bar, they can only step out.
- How do we think about this problem?
- Street is the x-axis, bar is at $x = 0$, house is at $x = n$.
- Where could the drunk be after 1 step? After 2 steps? After 3 steps? After k steps?
- What is the probability that the drunk reaches home after k steps?
- What is the probability that the drunk reaches home at all?

Random Walk on a Grid

- A random walker leaves a starting location (conveniently at $(0, 0)$).
- They move in steps, either by one unit to the right, left, top, or bottom.
- When will they reach their destination, which is at (n, n)?

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- A random walker leaves a starting location (conveniently at $(0, 0)$).
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- When will they reach their destination, which is at (n, n)?
- Where could the walker be after 1 step? After 2 steps? After 3 steps? After k steps?
- What is the probability that the walker reaches their destination after k steps?

Random Walk on a Grid

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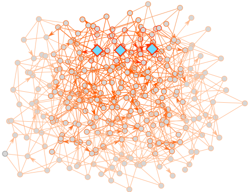
- They move in steps, either by one unit to the right, left, top, or bottom.
- When will they reach their destination, which is at (n,n)?
- Where could the walker be after 1 step? After 2 steps? After 3 steps? After k steps?
- What is the probability that the walker reaches their destination after k steps?
- Convenient to think of the grid as a graph. Can generalise the problem to a graph.

RWR Algorithm

Given weighted, directed graph $G = (V, E, W)$, receptors $S \subset V$ and TRs $T \subset V$, and a parameter $0 \leq q < 1$.

- Walker at u transitions as follows:

Walk: With prob. $1 - q$, walk to neighbor x with prob. w_{ux}/d_u (outdegree)



Page et al., The PageRank citation ranking: Bringing order to the web. Technical Report, 1999.

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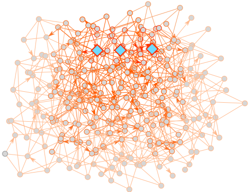

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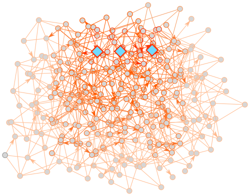

- Compute the probability $p(v)$ each node is visited as steps $\rightarrow \infty$.

$$p(v) = \frac{q}{|S|}[v \in S] + (1 - q) \sum_{u \in N_v^{\text{in}}} \frac{w_{uv}}{d_u} p(u).$$

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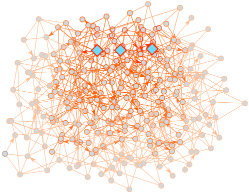

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$$p(v) = \frac{q}{|S|}[v \in S] + (1 - q) \sum_{u \in N_v^{\text{in}}} \frac{w_{uv}}{d_u} p(u).$$

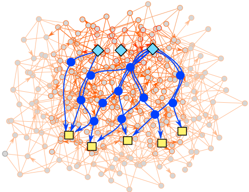
- Output edges in decreasing order of edge fluxes: $f_{uv} = p_u w_{uv}$

Page et al., The PageRank citation ranking: Bringing order to the web. Technical Report, 1999.

PathLinker Algorithm

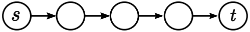
Given weighted, directed graph $G = (V, E, W)$, receptors $S \subset V$ and TRs $T \subset V$.

- Find the k "highest-scoring" paths from any $s \in S$ to any $t \in T$.
- Replace Dijkstra's algorithm with the A* algorithm for significant practical speedup.



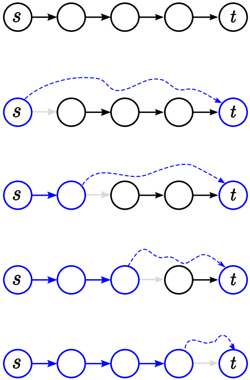
Yen. Finding the k shortest loopless paths in a network. Management Science, 1971.

Shortest Loopless Paths – Basic Idea



- Naïve Approaches (time-consuming):
  - Enumerate all paths from s to t and sort.
  - Obtain $k-1$ shortest paths, hide an edge from each path and find a shortest path in the modified network. Test all combinations.

Shortest Loopless Paths – Basic Idea



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  - Enumerate all paths from s to t and sort.
  - Obtain $k-1$ shortest paths, hide an edge from each path and find a shortest path in the modified network. Test all combinations.
- Basic idea of Yen's algorithm:
  - Compute the shortest path from s to t
  - The k^{th} shortest path will be a deviation from the previously-discovered shortest path.

Shortest Loopless Paths

- $\{s, v_2, v_3, \ldots, t\}$ denotes a simple path from s to t
- $P^k = \{s, P^k_2, P^k_3, \ldots, P^k_{|P^k|-1}, t\}$ is the k^{th} shortest path from s to t

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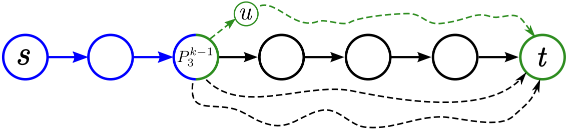
- D^k_i is the "deviation from P^{k-1} at node P^{k-1}_i"
  More specifically, the shortest $s \rightsquigarrow t$ path that:
  1. coincides with P^{k-1} from s to P^{k-1}_i
  2. deviates to a node u where u is not used as this deviation in any of the $k-1$ shortest paths
  3. reaches t by a shortest path from u without using any node in the first part of the path



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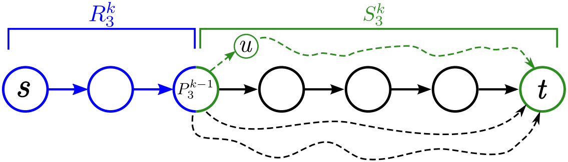
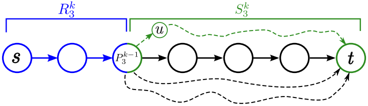


- $R^k_i = \{s, P^k_2, P^k_3, \ldots, P^k_i\}$ is the root of D^k_i
- $S^k_i = \{P^k_i, \ldots, t\}$ is the spur of D^k_i

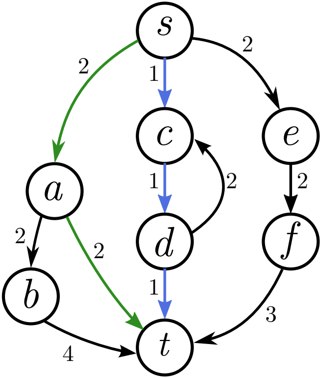
Shortest Loopless Paths

- Find the shortest path P^1
- For $k = 2, 3, \ldots$, find P^k as follows:

Let $B^k = B^{k-1}$, the set of candidate paths from iteration $k - 1$
for $1 \leq i < |P^{k-1}|$ **do**
    Let $x = P_i^{k-1}$
    Hide incoming edges to x for the remainder of iteration k
    for each j such that the first i nodes in in P^j match P^{k-1} **do**
        Hide edge (x, P_{i+1}^j) for the remainder of iteration k
    end for
    R_i^k is the first i nodes of P^{k-1}
    S_i^k is the shortest path from x to t
    Join R_i^k and S_i^k to form D_i^k
    Add candidate path D_i^k to B^k
end for
Remove the shortest path from B^k and return it



Example – Find P^3

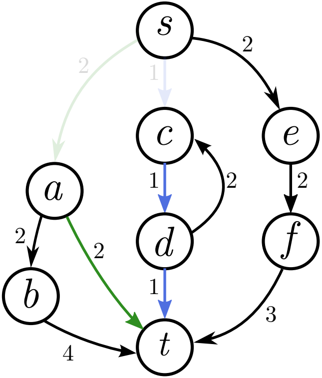


$P^1 = \{s, c, d, t\}$

$P^2 = \{s, a, t\}$

$P^3 =$?

Example – Hide Edges for Root $\{s\}$

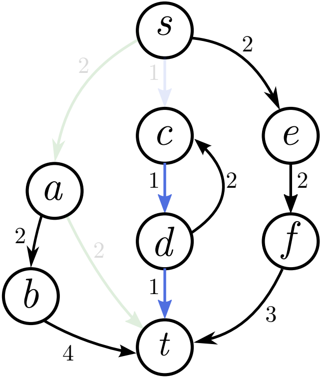


$P^1 = \{s, c, d, t\}$

$P^2 = \{s, a, t\}$

$P^3 =$?

Example – Hide Edges for Root $\{s, a\}$

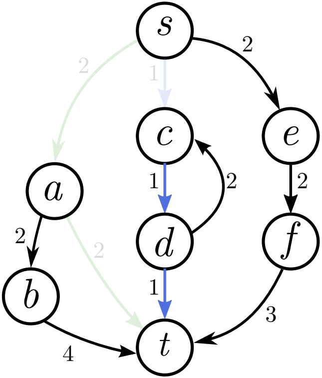


$P^1 = \{s, c, d, t\}$

$P^2 = \{s, a, t\}$

$P^3 =$?

Example – Find Shortest Spur for Each Root



$P^1 = \{s, c, d, t\}$

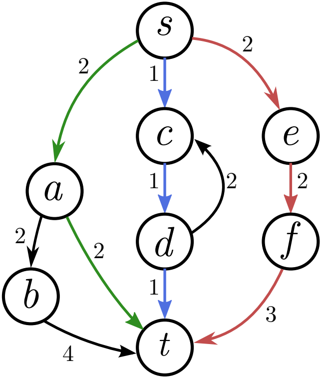
$P^2 = \{s, a, t\}$

$P^3 = \quad ?$

$S_1^3 = \{s, e, f, t\}$

$S_2^3 = \{a, b, t\}$

Example – Identify Shortest Deviation



$P^1 = \{s, c, d, t\}$

$P^2 = \{s, a, t\}$

$P^3 =$?

$S_1^3 = \{s, e, f, t\}$

$S_2^3 = \{a, b, t\}$

$D_1^3 = \{s, e, f, t\}$

$D_2^3 = \{s, a, b, t\}$

How do we find S_i^k efficiently?

- For $k = 2, 3, \ldots$, find P^k as follows:

  Let $B^k = B^{k-1}$, the set of candidate paths from iteration $k - 1$
  for $1 \leq i < |P^{k-1}|$ **do**
      Let $x = P_i^{k-1}$
      Hide incoming edges to x for the remainder of iteration k
      for each j such that the first i nodes in in P^j match P^{k-1} **do**
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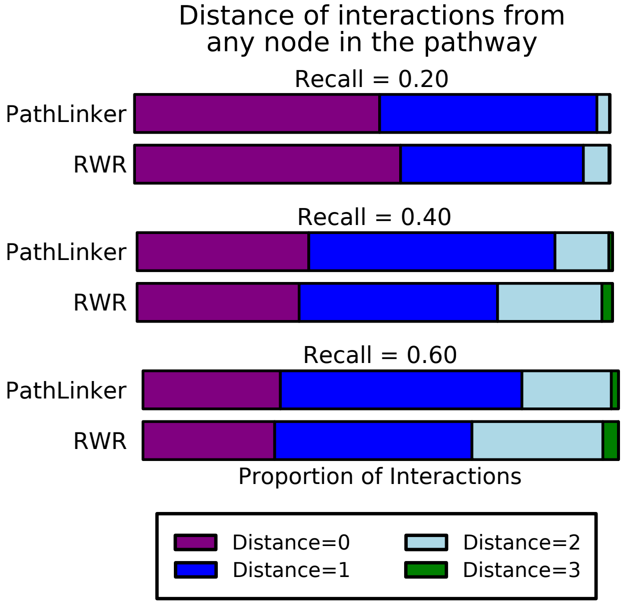
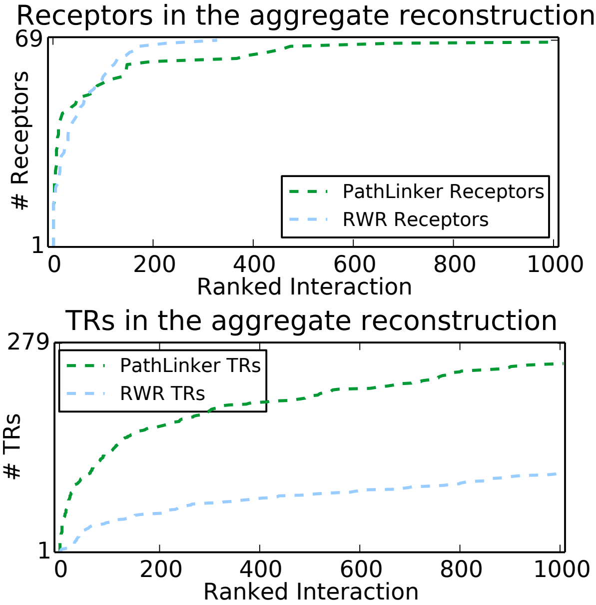
      end for
      R_i^k is the first i nodes of P^{k-1}
      S_i^k is the shortest path from x to t
      Join R_i^k and S_i^k to form D_i^k
      Add candidate path D_i^k to B^k
  end for
  Remove the shortest path from B^k and return it

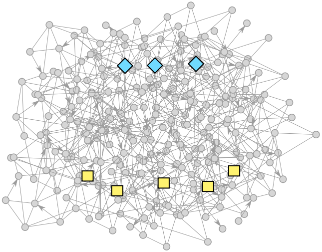
Compare Distances to Curated Pathway

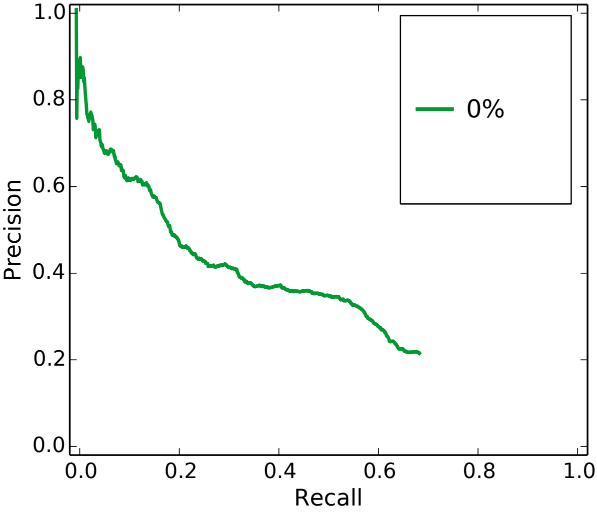


Compare Rate of Recovery of Receptors/TRs



Add Noise to Inputs





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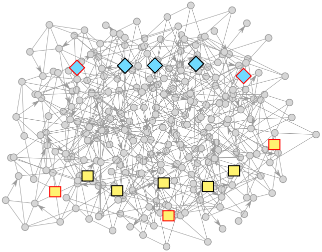

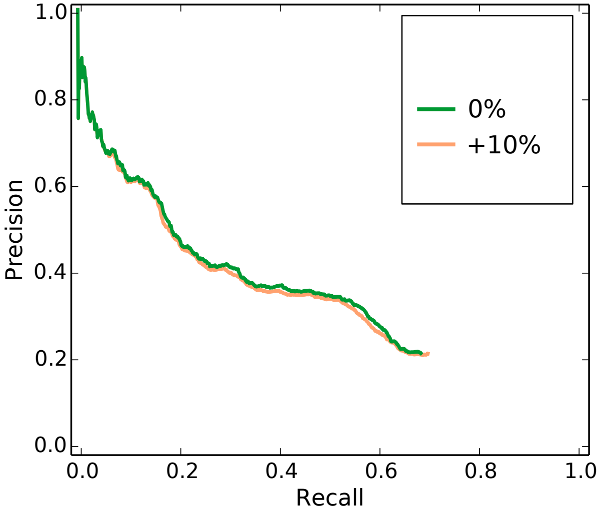

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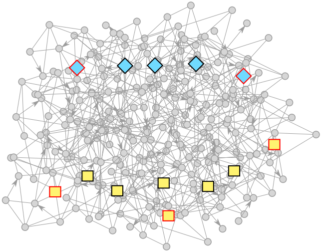

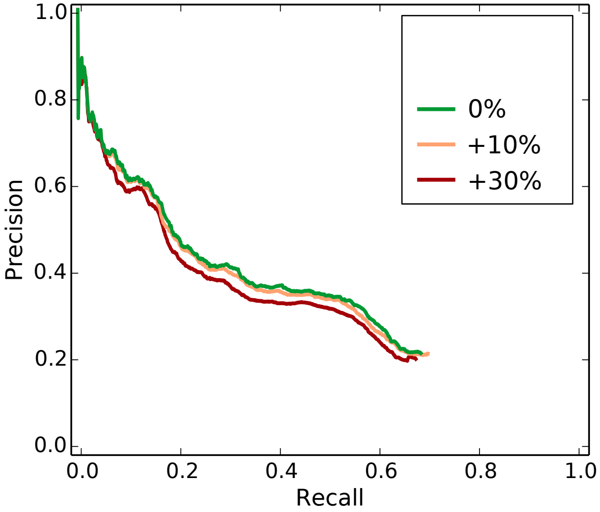

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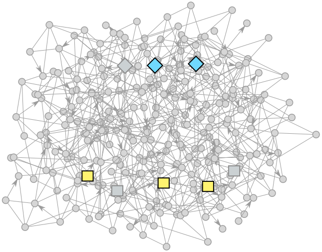

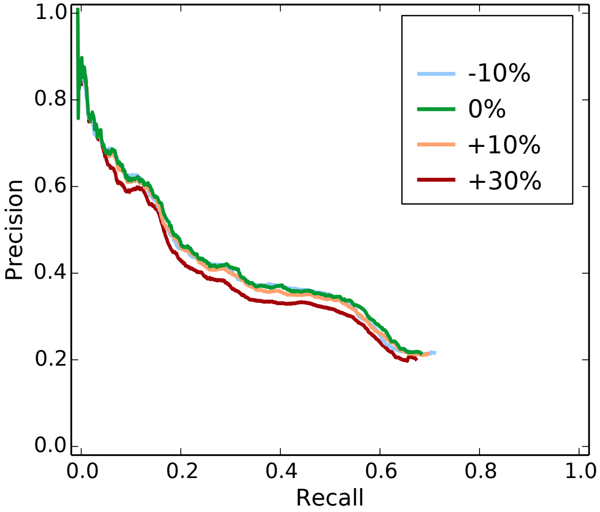

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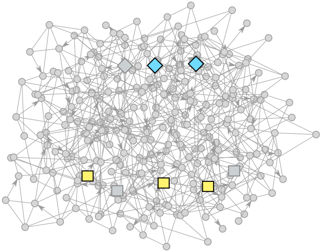
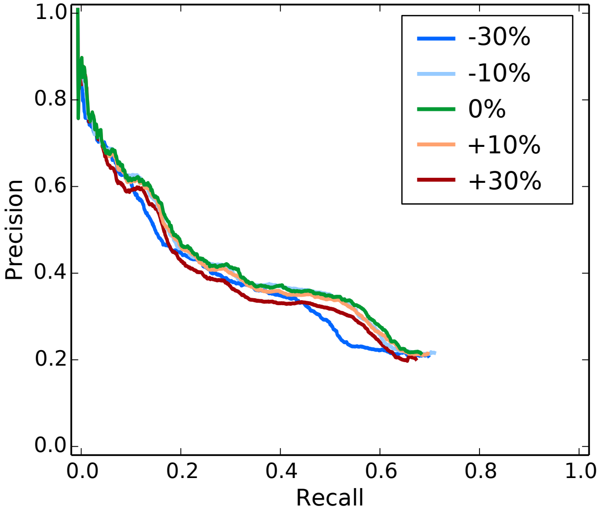
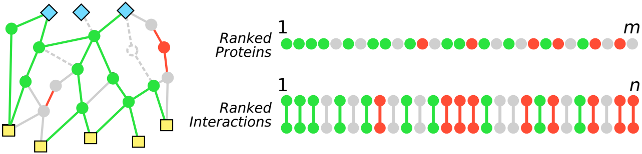
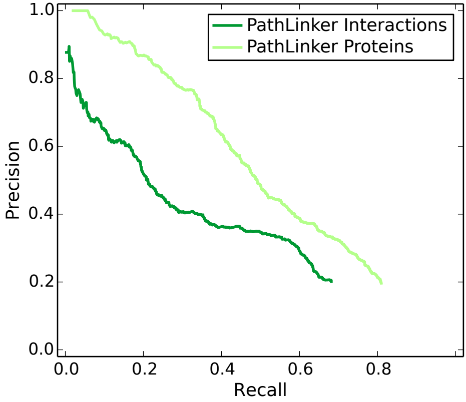




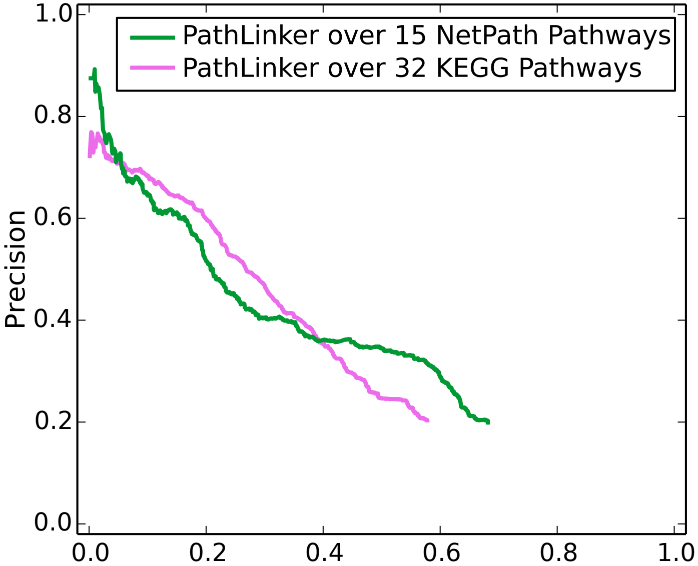
Compare to Reconstructing Proteins



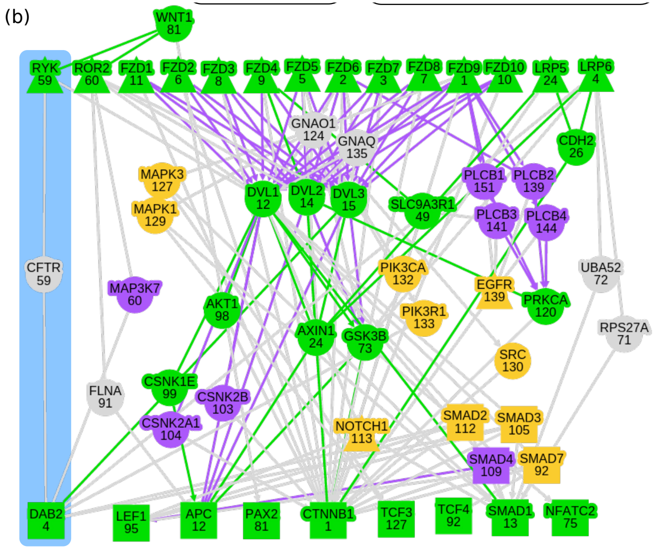


Reconstruct KEGG Pathways

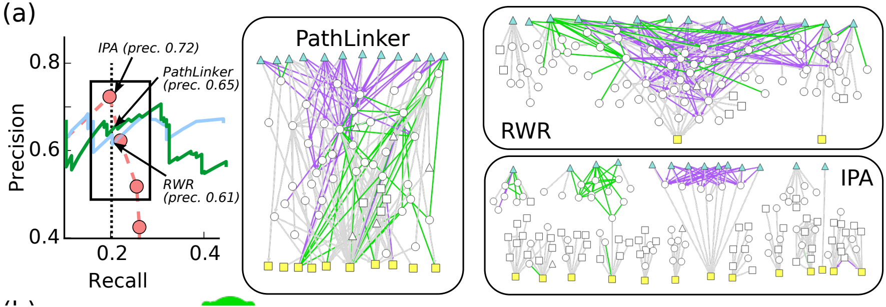
List of KEGG Pathways

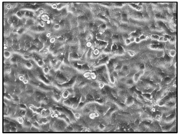


Wnt Signaling Pathway: Top 200 PathLinker Paths



Comparing Wnt Reconstructions





HEK293 Cells

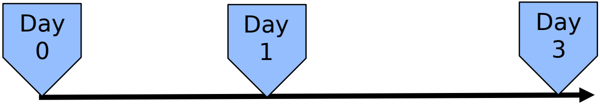
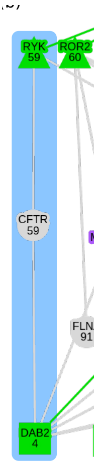
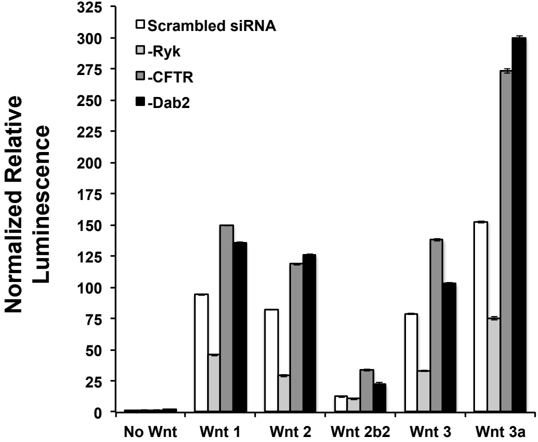


Plate cells and siRNA silence gene of interest

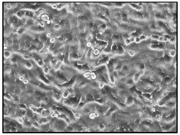
Transfect secreted Wnt3a (sWnt3a) stimulus **and Luciferase reporter**

Measure **luminescence**

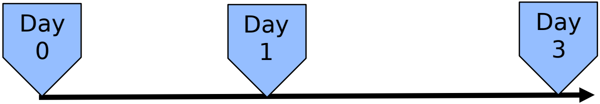


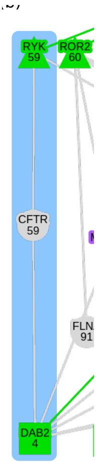


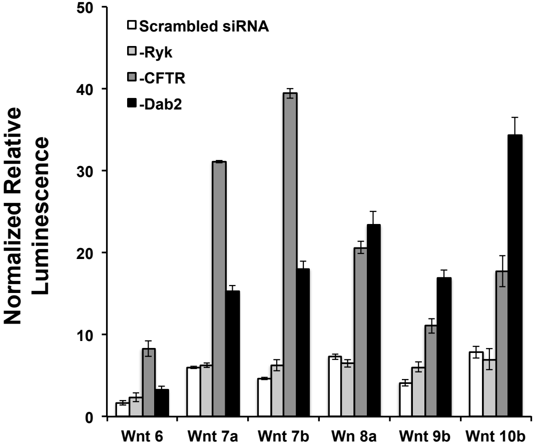
Luciferase Reporter Efficacy *siRNA Silencing Efficacy* *CoIP*



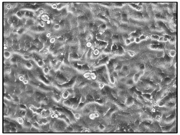
HEK293 Cells







Luciferase Reporter Efficacy | siRNA Silencing Efficacy | CoIP



HEK293 Cells

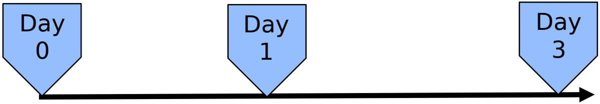
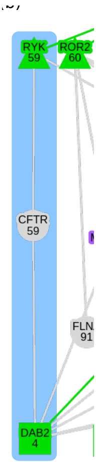
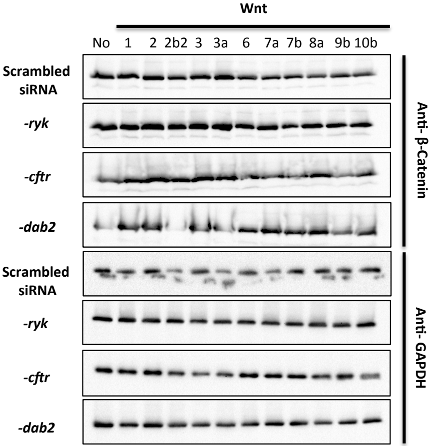


Plate cells and siRNA silence gene of interest

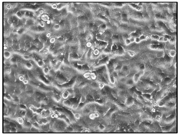
Transfect secreted Wnt3a (sWnt3a) stimulus

Measure **cellular B-catenin levels**

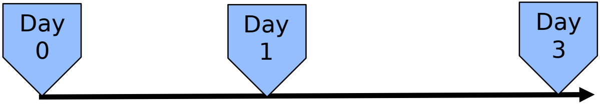


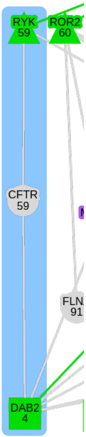


Luciferase Reporter Efficacy | siRNA Silencing Efficacy | CoIP



HEK293 Cells

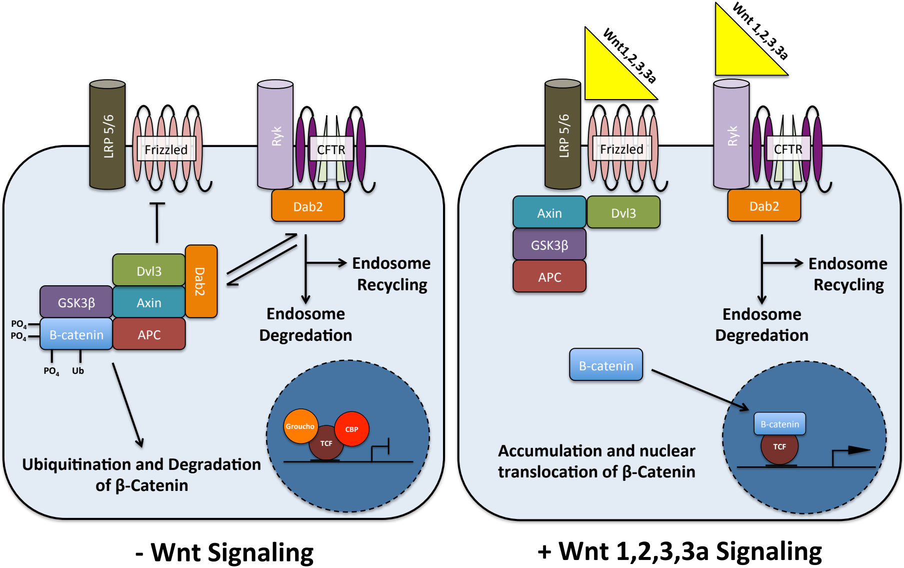




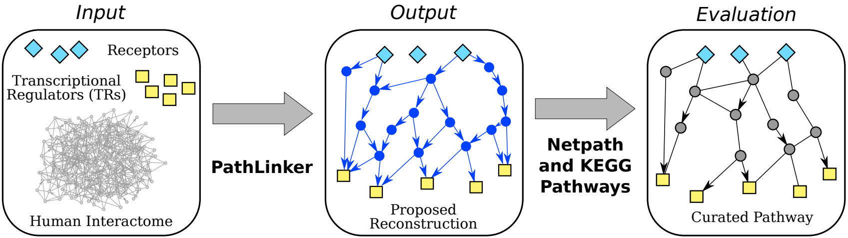
	Control		-Ryk		-CFTR		-Dab2	
Wnt	**NRL**	**QNβ**	**NRL**	**QNβ**	**NRL**	**QNβ**	**NRL**	**QNβ**
No Wnt	--	--	--	--	--	--	--	--
Wnt 1	VS	++	S	-	VS	+	VS	++
Wnt 2	VS	+	S	++	VS	++	VS	++
Wnt 2b2	W	-	W	+	S	++	W	-
Wnt 3	VS	++	S	++	VS	++	VS	++
Wnt 3a	VS	++	VS	++	VS	++	VS	++
Wnt 6	W	++	W	+	W	+	W	++
Wnt 7a	W	-	W	+	S	-	W	++
Wnt 7b	W	++	W	-	S	-	W	++
Wn 8a	W	-	W	-	W	++	W	++
Wnt 9b	W	-	W	-	W	-	W	++
Wnt 10b	W	-	W	-	W	++	S	++

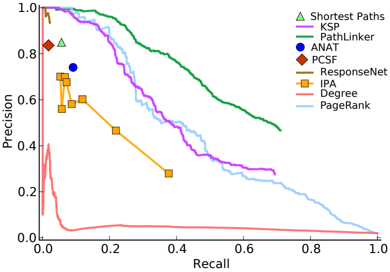
Luciferase Reporter Efficacy *siRNA Silencing Efficacy* *CoIP*

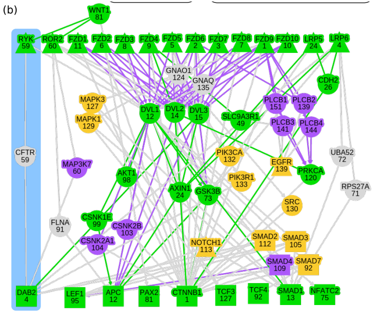
New Model: Dvl is an Ampliflier of Wnt Signaling



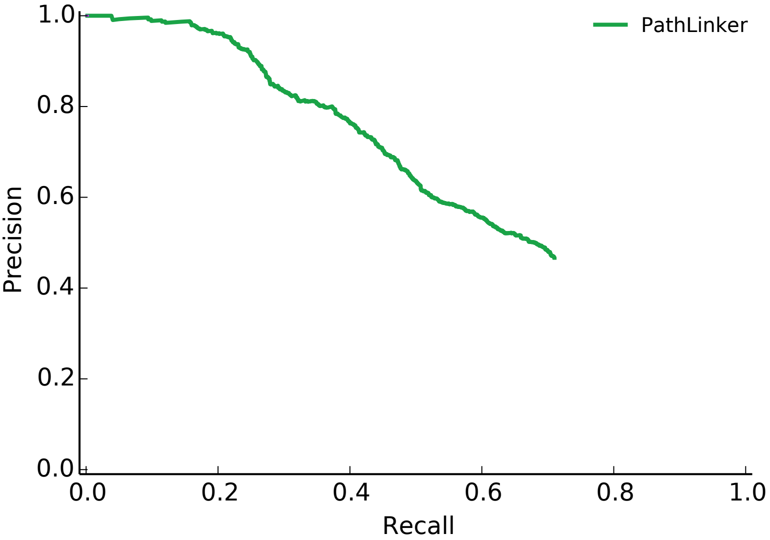
PathLinker Summary







How Many Paths Does PathLinker Need to Compute?



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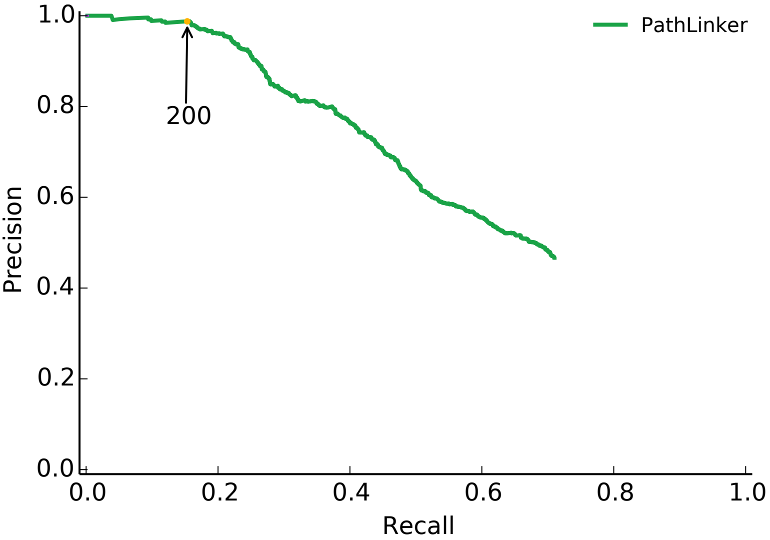

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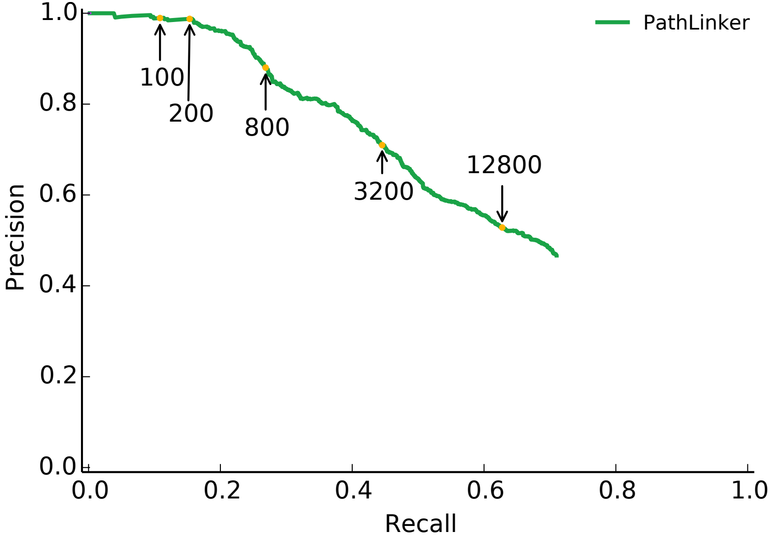
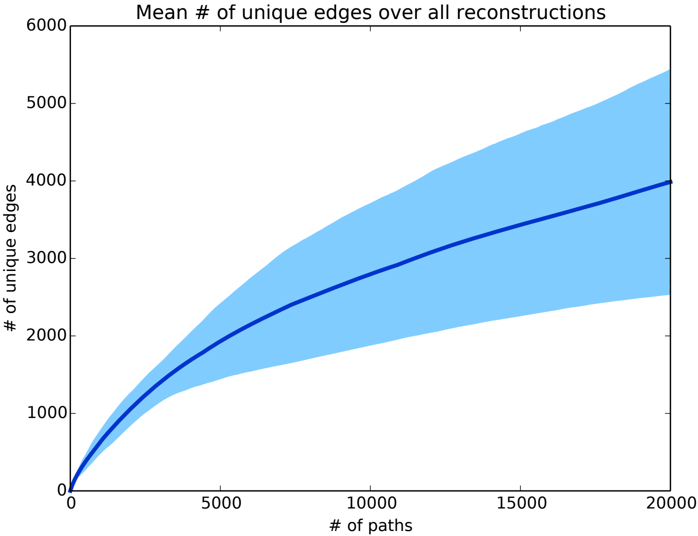


We compute 20,000 paths to achieve a recall of 0.7.

▸ Performance

How Many Paths Does PathLinker Need to Compute?



We compute 20,000 paths to achieve a recall of 0.7.

Performance

NetPath Pathways

1. The pathway contains at least one receptor.
2. The pathway contains at least one TR, and
3. The minimum cut between the receptors and TRs was at least three in the NetPath pathway.

Pathway	#Nodes	#Edges	Min Cut	# Receptors	# TRs
BDNF	72	139	4	5	4
EGFR1	231	1456	30	6	33
IL1	43	178	7	3	5
IL2	67	242	16	3	12
IL3	70	176	5	2	9
IL6	53	162	6	4	14
IL7	18	52	5	2	3
Kit Receptor	76	207	5	6	8
Leptin	55	135	8	3	15
Prolactin	68	199	10	4	9
RANKL	57	142	4	2	12
TCR	154	504	8	4	21
TGFβ Receptor	209	863	32	5	78
TNFα	239	913	15	4	44
Wnt	106	428	7	14	14

◂ Inputs for Pathway Reconstruction

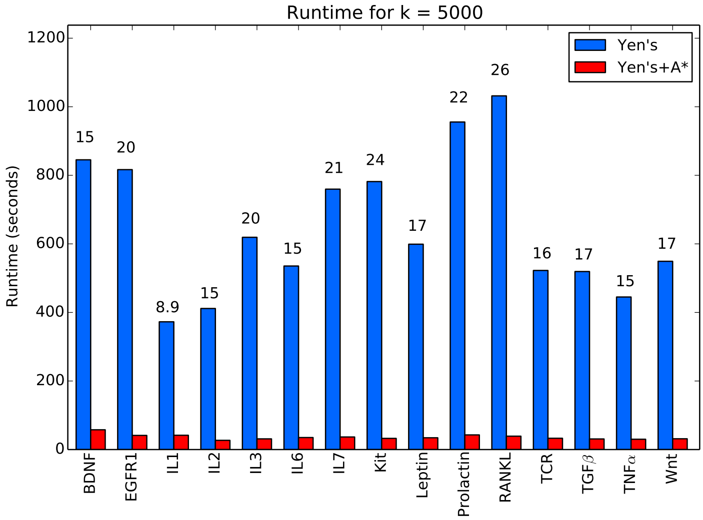
KEGG Pathways

◂ KEGG Results

1. The Pathway is related to signaling.
2. The pathway contains at least one receptor.
3. The pathway contains at least one TR, and
4. The minimum cut between the receptors and TRs was ≥ 3 in the KEGG pathway.

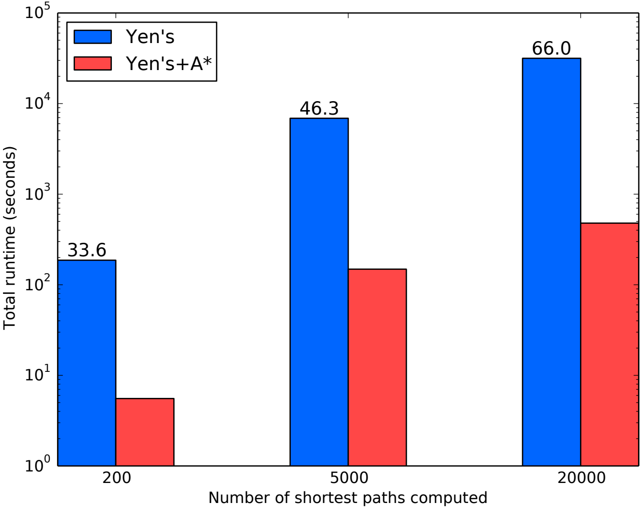
Name	KEGG ID	Name	KEGG ID
Adherens junction	hsa04520	Adipocytokine signaling pathway	hsa04920
Apoptosis	hsa04210	Axon guidance	hsa04360
Chemokine signaling pathway	hsa04062	Circadian entrainment	hsa04713
Dopaminergic synapse	hsa04728	Endocytosis	hsa04144
ErbB signaling pathway	hsa04012	Focal adhesion	hsa04510
FoxO signaling pathway	hsa04068	GnRH signaling pathway	hsa04912
HIF-1 signaling pathway	hsa04066	Hippo signaling pathway	hsa04390
Insulin signaling pathway	hsa04910	Jak-STAT signaling pathway	hsa04630
Prolactin signaling pathway	hsa04917	MAPK signaling pathway	hsa04010
Melanogenesis	hsa04916	Natural killer cell mediated cytotoxicity	hsa04650
Neurotrophin signaling pathway	hsa04722	NF-kappa B signaling pathway	hsa04064
Notch signaling pathway	hsa04330	Osteoclast differentiation	hsa04380
TGF-beta signaling pathway	hsa04350	Thyroid hormone signaling pathway	hsa04919
Tight junction	hsa04530	Toll-like receptor signaling pathway	hsa04620
VEGF signaling pathway	hsa04370	Wnt signaling pathway	hsa04310
Leukocyte transendothelial migration	hsa04670	Signaling pathways regulating pluripotency of stem cells	hsa04550

PathLinker Performance



▸ How Many Paths?

PathLinker Performance



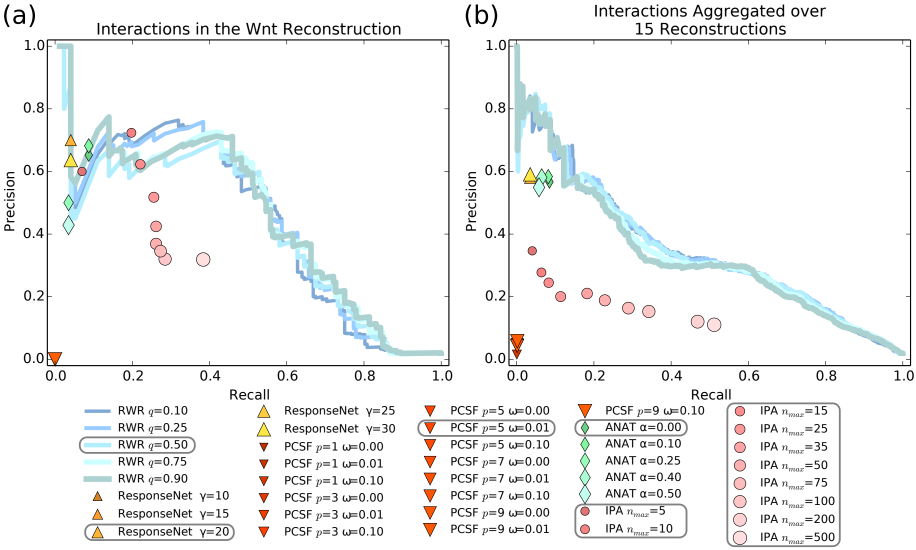
▸ How Many Paths?

Algorithm Internal Parameters

Algorithm	Parameter	Meaning
PathLinker	k	Number of shortest paths
RWR	q	Teleportation probability
ANAT	α	Tradeoff between global (Steiner tree) and local (shortest path) solution
PCSF	ω	Penalty for adding a new tree
	p	Prize for each node
ResponseNet	γ	Number of interactions that carry flow
IPA	n_{max}	Maximum sub-network size

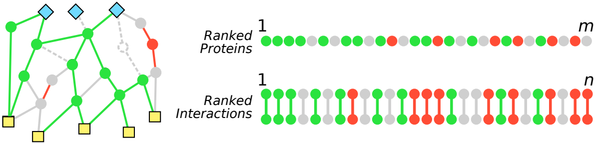
PathLinker Summary

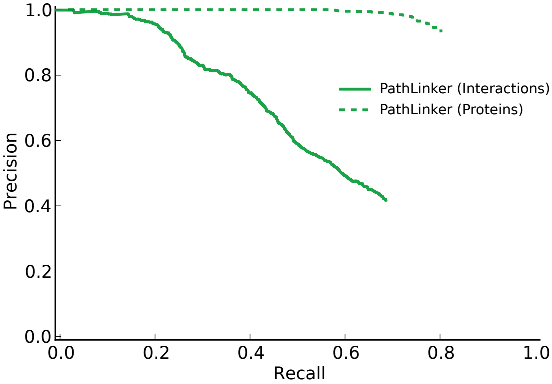
Algorithm Internal Parameters



◂ PathLinker Summary

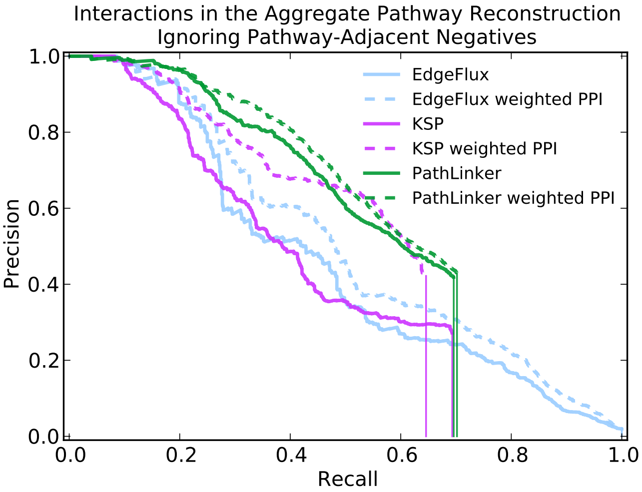
Recovering Proteins in a Pathway





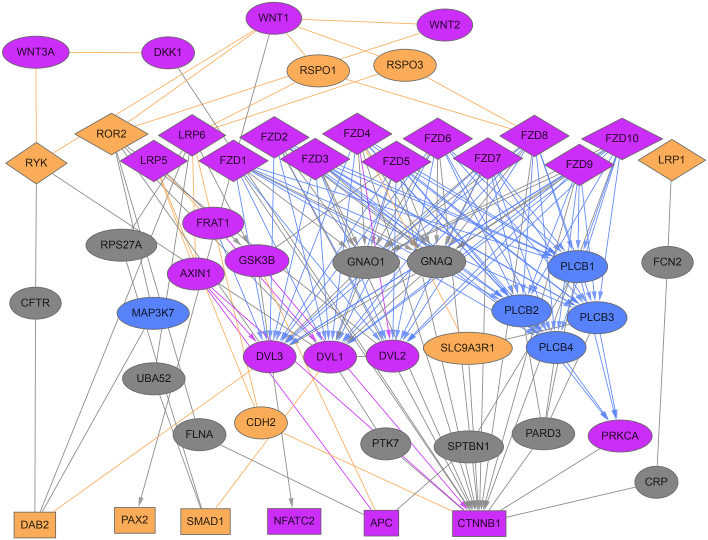
PathLinker Summary

PathLinker on a Weighted PPI

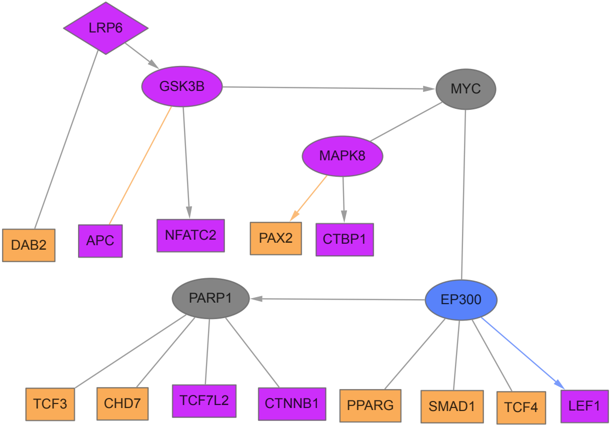


▸ PathLinker Summary

PathLinker Network

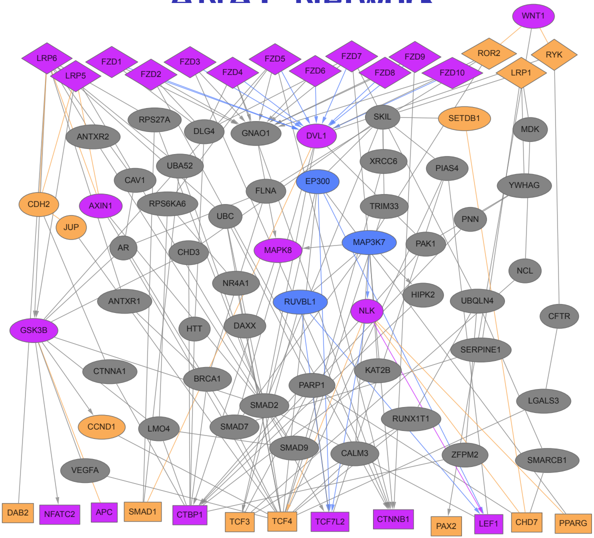


PCSF Network



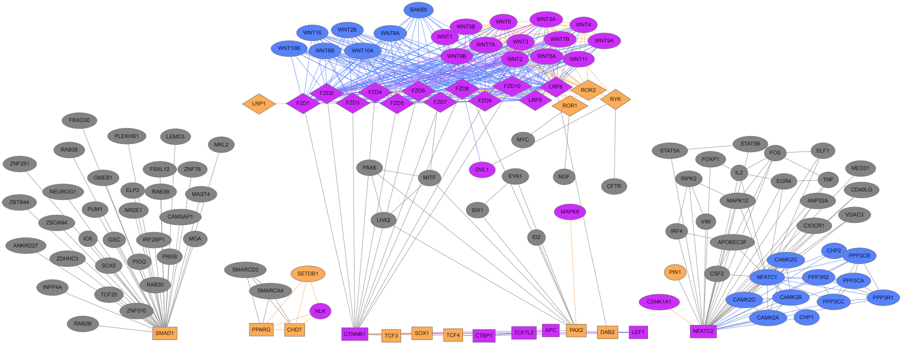
▸ PathLinker Network

ANAT Network



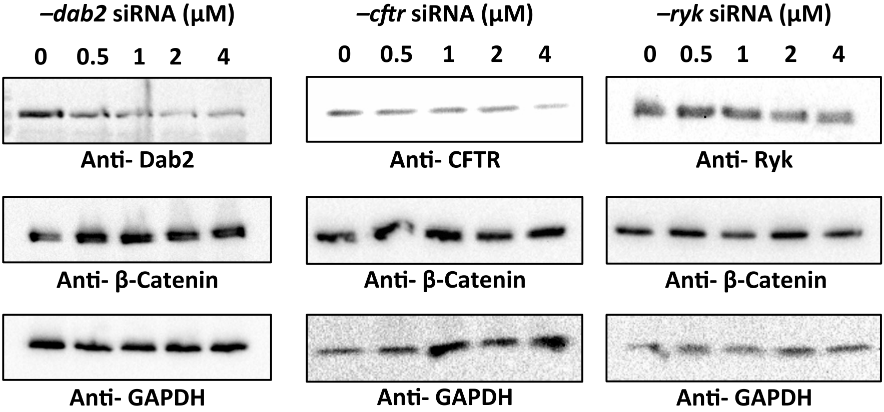
▸ PathLinker Network

IPA Network



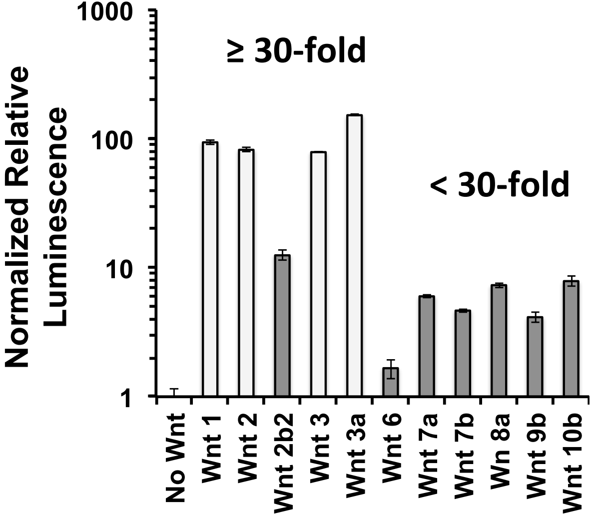
PathLinker Network

Luciferase Reporter Efficacy



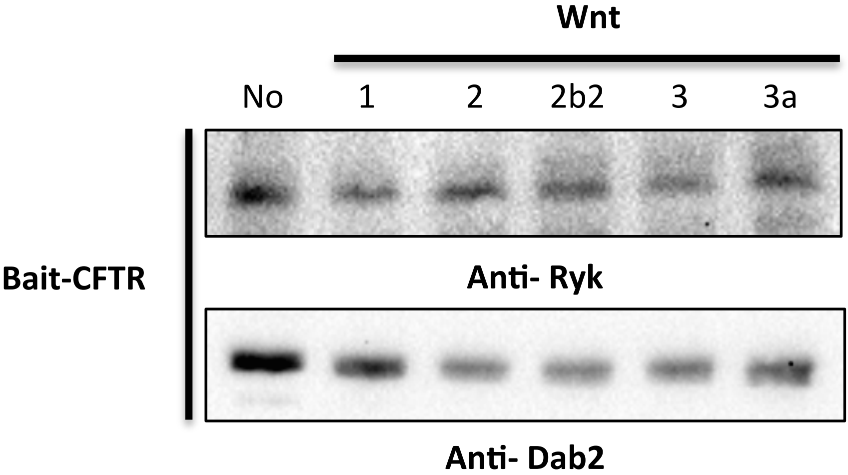
siRNA Experiments

siRNA Silencing Efficacy



▸ sWnt3a Experiments

Co-Immunoprecipitation Experiments



▸ sWnt3a Experiments