Evaluating the Predictive Accuracy of Reactome's Curated Biological Pathways

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Design

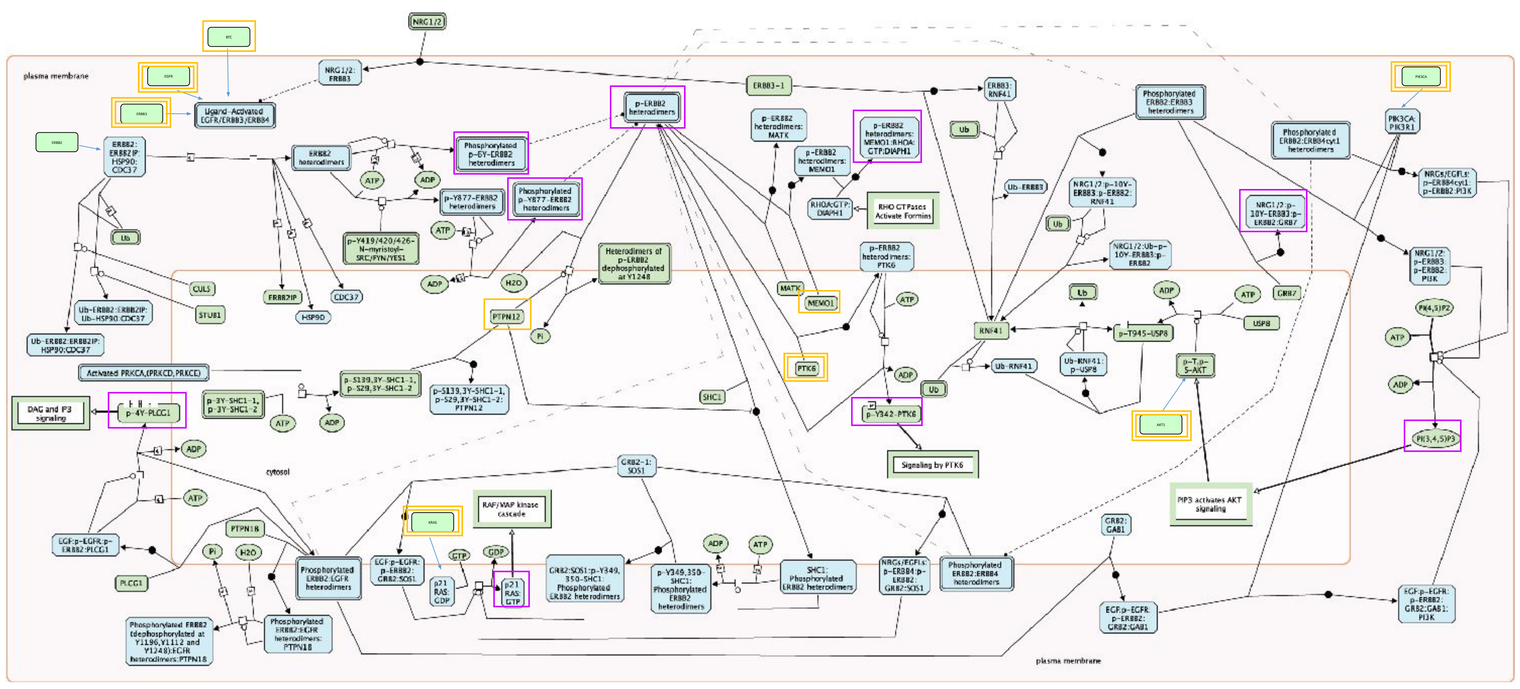
Reactome is a database of human biological pathways manually curated from the primary literature and peer-reviewed by experts. To evaluate the utility of Reactome pathways for predicting functional consequences of genetic perturbations, we compared predictions of perturbation effects based on Reactome pathways against published empirical observations. Ten cancer-relevant Reactome pathways, representing diverse biological processes such as signal transduction, cell division, DNA repair, and transcriptional regulation, were selected for testing. For each pathway, root input nodes and key pathway outputs were defined. We then used pathway-diagram-derived logic graphs to predict, either by inspection by biocurators or using a novel algorithm MP-BioPath, the effects of bidirectional perturbations (upregulation/activation or downregulation/inhibition) of single root inputs on the status of key outputs. These predictions were then compared to published empirical tests.

Reactome Statistics

Version 82 released on September 20, 2022

2,601	14,398	11,393	1,998	1,035	35,965
Human Pathways	Reactions	Proteins	Small Molecules	Drugs	Literature References

Inputs and Outputs for “Signaling by ERBB2”



Root inputs (double border if they are in Cancer Gene Census list). If root inputs are not directly shown in the diagram they have been redrawn and connected with the root complex/set.
Key outputs.

Tests

In total, 4968 test cases were analyzed across 10 pathways (v66), of which 847 were supported by published empirical findings.

Reactome pathway identifier	Reactome pathway name	Selected root inputs	Selected key outputs	Test cases	Test cases with available published evidence	Total number of nodes	Total number of edges
68 875	Mitotic Prophase	12	11	264	26	262	273
69242	S Phase	11	9	198	25	409	437
69620	Cell Cycle Checkpoints	7	14	196	55	511	552
195721	Signaling by WNT	7	37	518	49	817	953
453279	Mitotic G1 phase and G1/S transition	17	26	884	89	431	556
1227986	Signaling by ERBB2	10	9	180	49	212	246
1257604	PIP3 activates AKT signaling	16	14	448	200	781	1066
3700989	Transcriptional Regulation by TP53	18	51	1836	257	1106	1276
5673001	RAF MAP kinase cascade	7	6	84	49	641	834
5693567	HDR through Homologous Recombination (HRR) or Single Strand Annealing (SSA)	18	10	360	48	279	310

Results

Out of the 847 test cases, curators' predictions agreed with the experimental evidence in 670 and disagreed in 177 cases, resulting in ~81% overall accuracy.

MP-BioPath predictions agreed with experimental evidence for 625 and disagreed for 222 test cases, resulting in ~75% overall accuracy. The expected accuracy of random guessing was 33%.

Per-pathway accuracy did not correlate with the number of pathway edges nor the number of pathway nodes but varied across pathways, ranging from 56% (curator)/44% (MP-BioPath) for 'Mitotic G1 phase and G1/S transition' to 100% (curator)/94% (MP-BioPath) for 'RAF/MAP kinase cascade'.

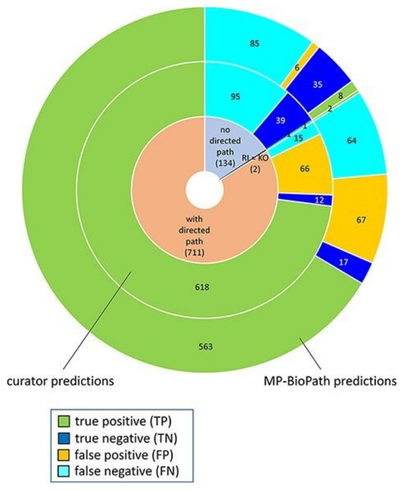
This study highlights the potential of pathway databases such as Reactome in modeling genetic perturbations, promoting standardization of experimental pathway activity readout, and supporting hypothesis-driven research by revealing relationships between pathway inputs and outputs that have not yet been directly experimentally tested.

The single biggest attribute of the pathways which affected the accuracy of both curator and MP-BioPath (computational) predictions is the existence of a path between each input and corresponding output.

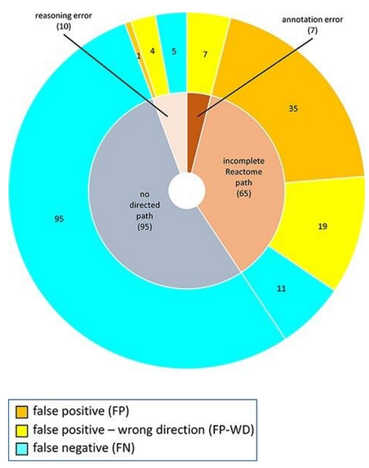
Of those that were incorrectly predicted by curators a very small number were due to reasoning errors or from annotation errors.

Computationally the major reason for false predictions involved the predicted change not being large enough to reach the cutoff for either up- or downregulation.

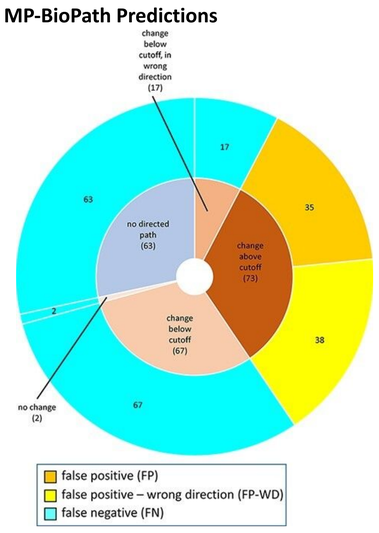
Predictions Overview



Curator Predictions



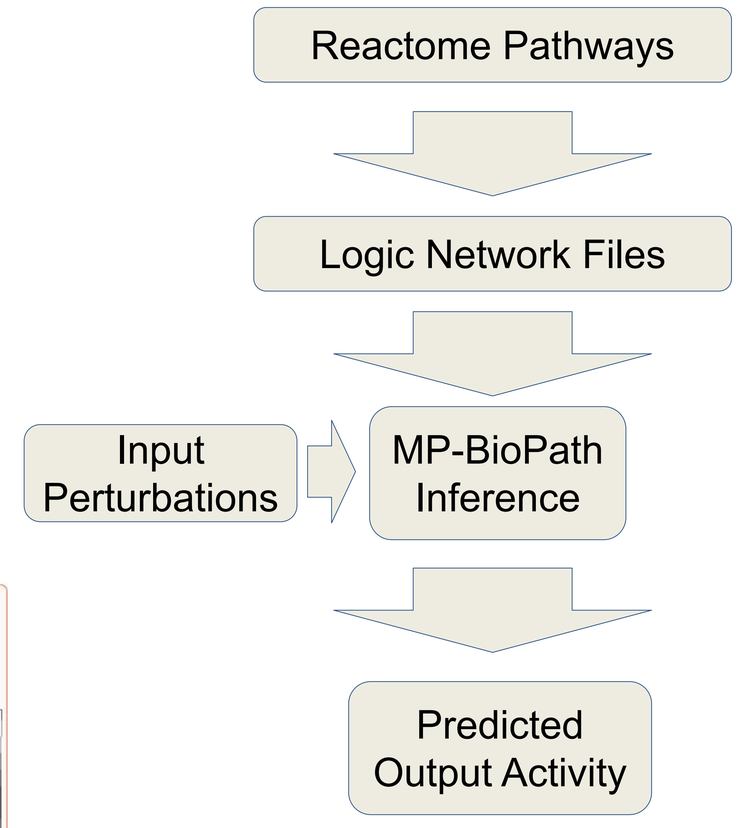
MP-BioPath Predictions



Current Developments

We are automating the generation of logical networks from the Reactome pathways. Tests from the 82 pathways are applied to the generated pathways to show sufficient accuracy. We intend to provide all the Reactome pathways for each release and a user interface allowing users to predict pathway level activity from experimental datasets.

Analysis Pipeline:



Goals

- Deconvolute entity sets into individual entities and reactions in logic networks.
- Provide predicted accuracy of pathways, without tests, based on pathway topography.
- Create UI for running inference and visualizing results.
- Generate Pathway level Functional Impact score based on inferred output activity.
- Predict the impact of multiple genetic perturbations and/or drugs effects.
- Cluster experimental/patient samples based on predicted pathway functional impact scores.
- Release a web based user interface for running MP-BioPath.

Summary and conclusions

Using empirical evidence we have been able to accurately predict the impact of single gene perturbations on the outputs of Reactome pathways both manually and computationally.

Computational (MP-BioPath) prediction accuracy did not differ significantly from curator derived predictions at ~80%.

We are working on fully automating the generation of the pathway-derived logical networks, have plans for continuous maintenance and improvement of MP-BioPath, including a web based user interface.

Publication

https://doi.org/10.1093/database/baac009

Poster

http://doi.org/10.3180/poster/20221109wright

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