Verification of Causal Biological Networks Using a Web-base =d Collaborative Competition

sbv IMPROVER
SYSTEMS BIOLOGY VERIFICATION

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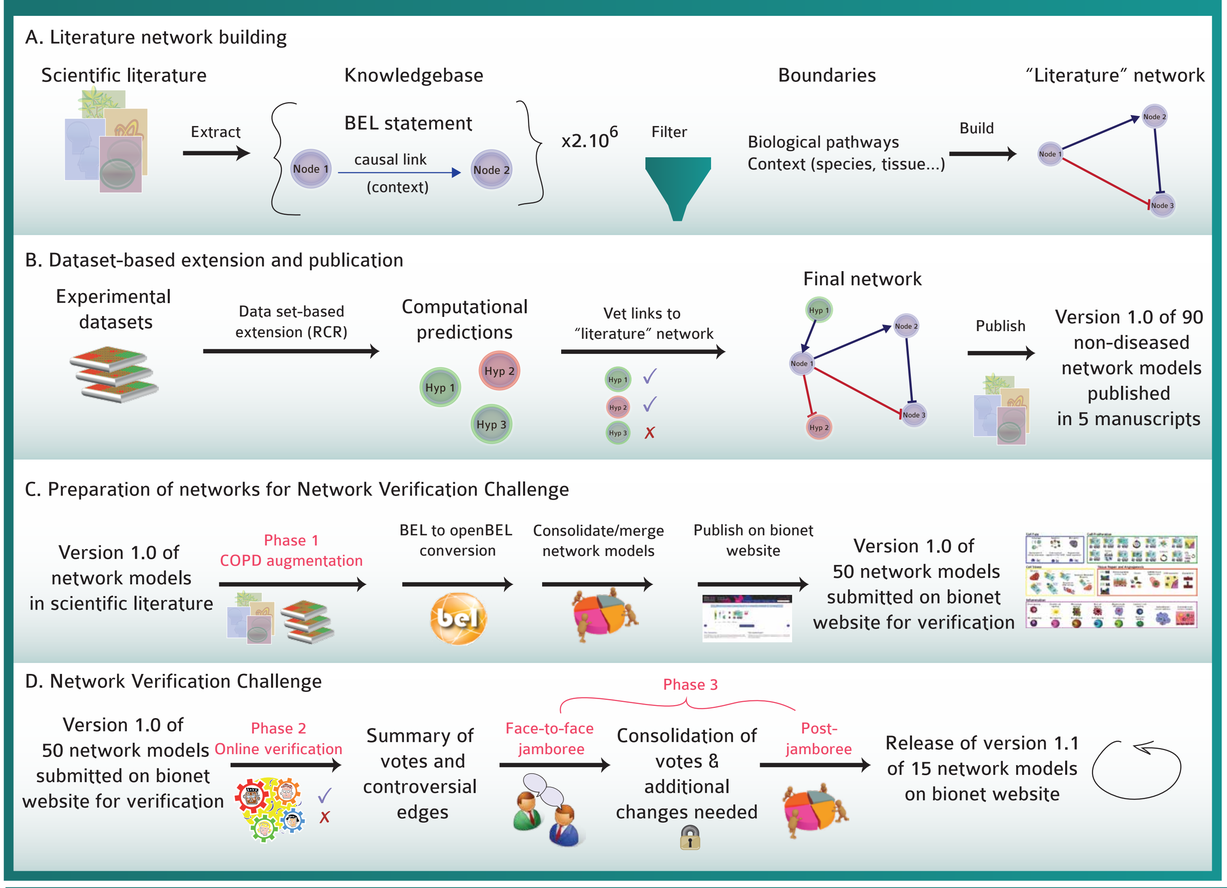
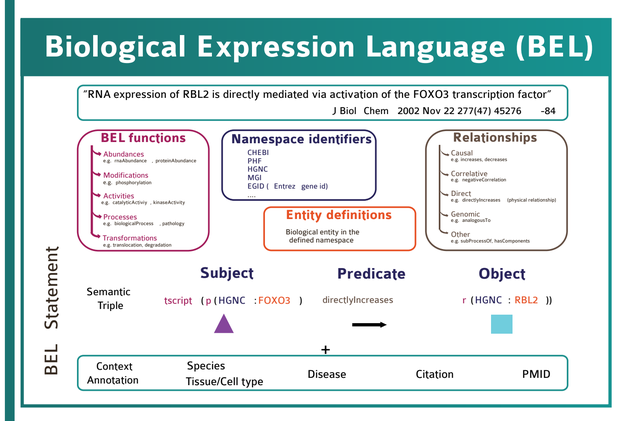
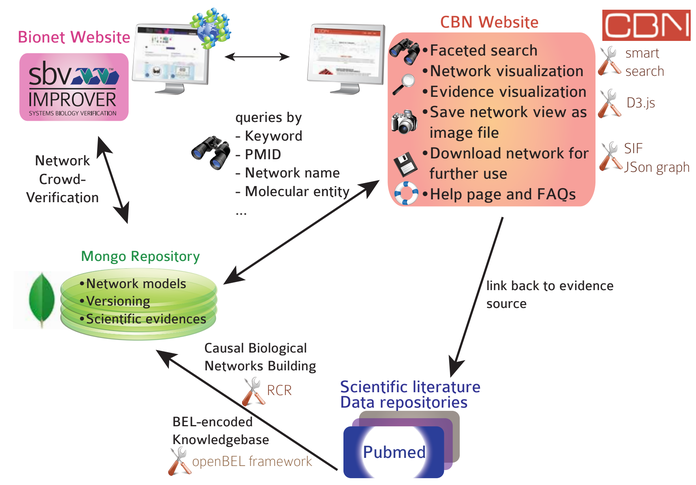
Network Verification Challenge



Verification and Sharing Platforms



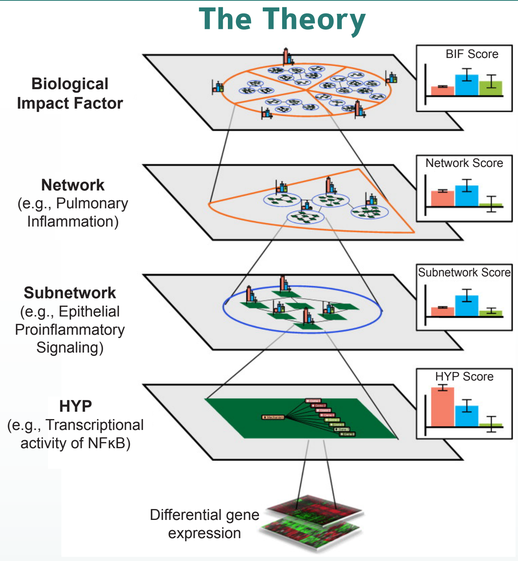


A web-based crowdsourcing platform provides an easy way to share the network models allowing frequent updates by the scientific community. The platform is meant to facilitate the collaborative review of networks and is part of the sbvIMPROVER Network Verification Challenge (NVC) (https://sbvimprover.com/).

The CBN Database Web site (http://causalbionet.com/) offers an interface that accesses different versions of the network models, ranging from the 98 original non-diseased models (version1.0, 98) to the consolidated COPD-relevant models (version 1.1), and to the crowd-verified network models (version 1.2)

Example Applications of Network Models

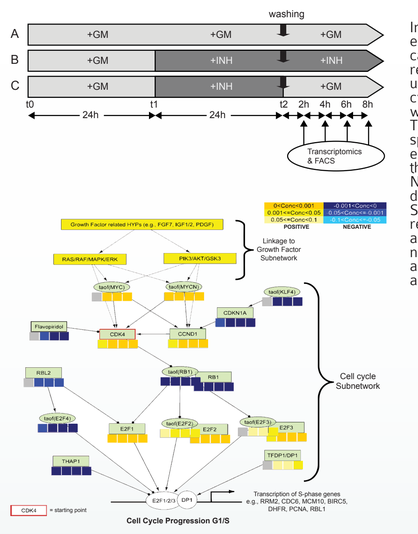
The Theory



Network and scoring hierarchy. The network hierarchy is composed of HYP, subnetwork, and network, while the scoring hierarchy also includes the BIF level (an aggregation across a collection of networks). HYPs form the basis of the scoring hierarchy and their scores are computed from differential expression of their downstream gene nodes. Subnetworks are composed of nodes, many of which are HYPs, connected by causal relationships (edges). Subnetwork scores are computed from the scores of their constituent HYPs. Networks are a structured group of subnetworks that together define distinct cellular functions. Network scores are computed from their subnetwork scores. The Biological Impact Factor (BIF) is the highest level of aggregation, and represents the overall biological impact as mechanistically assessed by the networks' score.

From Thomson, T. M., Sewer, A., Martin, F., Belcastro, V., Frushour, B. P., Gebel, S., Park, J., Schlage, W. K., Talikka, M., Vasilyev, D. M., Westra, J. W., Hoeng, J. & Peitsch, M. C. 2013. Quantitative assessment of biological impact using transcriptomic data and mechanistic network models.
Toxicol Appl Pharmacol, 272(3), pp 863-78.

Network Model Verification

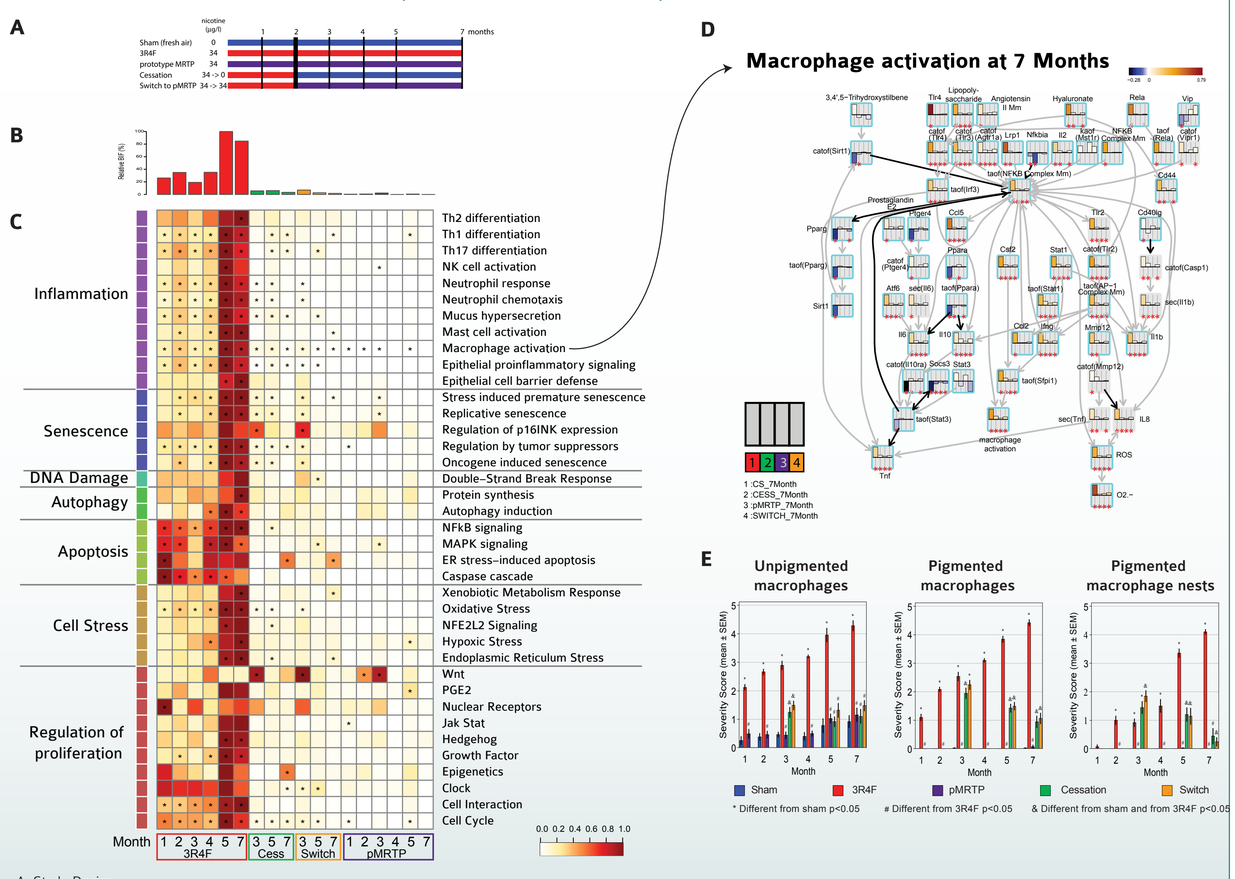


In this study a gene expression dataset, capturing systems responses in NHBE cells under proliferation and cell cycle inhibitory conditions, was generated. The experiment was specifically designed to evaluate the correctness of the Cell Proliferation Network model previously described in (Westra, Schlage et al. 2011), representing a manually assembled biological network model followed by an automatic network augmentation.

RCR results overlaid on a part of the Cell Cycle sub-network model. Nodes of the Cell Cycle sub-network model are organized in a network structure, and RCR results are shown as heat maps (concordance levels) beneath the name of each hypothesis. Upstream part of the network represents the link to the Growth Factor sub-network. The middle part shows hypotheses of the Cell Cycle sub-network model directly responsible for the S-phase genes transcriptional response (bottom part of the network).

From: Belcastro, V., Poussin, C., Gebel, S., Mathis, C., Schlage, W. K., Lichtner, R. B., Quadt-Humme, S., Wagner, S., Hoeng, J. & Peitsch, M. C. 2013. Systematic verification of upstream regulators of a computable cellular proliferation network model on non-diseased lung cells using a dedicated dataset.
Bioinform Biol Insights, 7: 217-30.

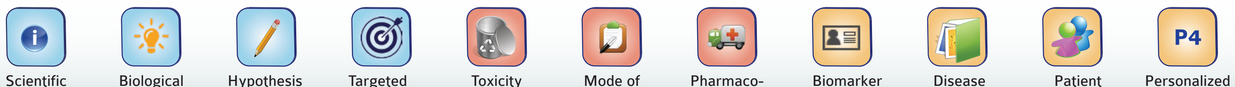
Systems Toxicology Application



A. Study Design.
B. Biological Impact Factor in lung
C. NPA heatmap of all subnetworks tested with significant score in at least one contrast.
D. Backbone score for the macrophage activation network at the 7-month time point.
E. Histological score for macrophages counts in lung tissue of mice in the same experiment.

From: Phillips, B., Veljkovic, E., Peck, M. J., Buettner, A., Elamin, A., Guedj, E., Vuillaume, G., Ivanov, N. V., Martin, F., Boue, S., Schlage, W. K., Schneider, T., Titz, B., Talikka, M., Vanscheeuwijck, P., Hoeng, J. & Peitsch, M. C. 2015. A 7-month cigarette smoke inhalation study in C57BL/6 mice demonstrates reduced lung inflammation and emphysema following smoking cessation or aerosol exposure from a prototypic modified risk tobacco product.
Food and Chemical Toxicology, In Press

Foreseen Network Model Applications



Jamboree 2015 - Barcelona

Scientific experts and best challenge contributors will meet to discuss, conclude, and verify the actions on the networks, and to listen to keynote lectures:

- "OpenBEL - A platform for capture, share, and use of biological knowledge"
  Dr. Natalie Catlett (Selventa, USA)
- "Information extraction and text mining in the context of systems biology projects"
  Dr. Michael Liebman (PQ Analytics, LLC, USA)
- "Garuda platform and scientific challenges"
  Dr. Samik Ghosh (the Systems Biology Institute, Japan)
- "Systems Biology Meets Clinical Medicine: Bridging the Gap"
  Dr. Alfonso Valencia (the Spanish National Bioinformatics Institute, Spain)
- "Current challenges and opportunities for the text mining of interactions"
  Dr. Raul Rodiguez (Roche Pharmaceuticals, Switzerland)
- "The Text Analytics Challenge BioCreative V - Extraction of causal network information in BEL"
  Dr. Fabio Rinaldi (the Institute of Comp. Linguistics in the Uni Zurich, Switzerland)
- "Adverse Outcome Pathways; A Framework for Organizing Mechanistic Information to Improve Chemical Assessment"
  Dr. Kristie Sullivan (Physicians Committee for Responsible Medicine, USA)
- "Adverse outcome pathways as tools to asses drug-induced toxicity"
  Dr. Mathieu Vinken (the Free University of Brussels, Belgium)

Key References

- On crowd-verification and biological networks. Bioinformatics and Biology Insights, 2013.
- Reputation-based collaborative network biology. Pacific Symposium for Bioinformatics Online Proceedings, 2015.
- Enhancement of COPD biological networks using a web-based collaboration interface. F1000 Research, 2015.
- Causal Biological Network (CBN) database: a comprehensive platform of causal biological network models focused on the pulmonary and vascular systems. Database, in press.
- Systematic verification of upstream regulators of a computable cellular proliferation network model on non-diseased lung cells using a dedicated dataset. Bioinform Biol Insights, 2013.
- Quantitative assessment of biological impact using transcriptomic data and mechanistic network models. Toxicol Appl Pharmacol, 2013.
- Construction of a computable network model for DNA damage, autophagy, cell death, and senescence. Bioinformatics and biology insights 2013
- A network-based approach to quantifying the impact of biologically active substances. Drug Discov Today, 2012
- Case study: the role of mechanistic network models in systems toxicology. Drug Discov Today, 2014
- A 28-day rat inhalation study with an integrated molecular toxicology endpoint demonstrates reduced exposure effects for a prototypic modified risk tobacco product compared with conventional cigarettes. Food Chem Toxicol, 2014
- Quantification of biological network perturbations for mechanistic insight and diagnostics using two-layer causal models. BMC Bioinformatics, 2014
- Assessment of network perturbation amplitudes by applying high-throughput data to causal biological networks. BMC Syst Biol, 2012
- Construction of a Computable Network Model of Tissue Repair and Angiogenesis in the Lung. Clinical Toxicology, 2013
- A 7-month cigarette smoke inhalation study in C57BL/6 mice demonstrates reduced lung inflammation and emphysema following smoking cessation or aerosol exposure from a prototypic modified risk tobacco product. Food and Chemical Toxicology, In Press
- A computable cellular stress network model for non-diseased pulmonary and cardiovascular tissue. BMC Syst Biol, 2011
- Construction of a computable cell proliferation network focused on non-diseased lung cells. BMC Syst Biol, 2011
- A modular cell-type focused inflammatory process network model for non-diseased pulmonary tissue. Bioinform Biol Insights, 2013

The sbv IMPROVER project, the website and the symposia are part of a collaborative project designed to enable scientists to learn about and contribute to the development of a new crowd sourcing method for verification of scientific data and results. The current challenges, website and biological network models were developed and are maintained as part of a collaboration among Philip Morris International, Selventa, OrangeBus, and ADS. The project is led and funded by Philip Morris International. For more information on the focus of Philip Morris International's research, please visit www.pmi.com.

www.sbvimprover.com