



www.sbvimprover.com

Network Verification Challenge (NVC)

Anita Iskandar

Philip Morris International R&D

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 with Selventa, OrangeBus and ADS. The project is funded by Philip Morris International.



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IMPROVER

SYSTEMS BIOLOGY VERIFICATION

Introduction to sbv IMPROVER

1

2
The Network
Verification
Challenge
(NVC)

3
The
“bionet”
Platform

4
Jamboree
and
Outcomes

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IMPROVER

SYSTEMS BIOLOGY VERIFICATION

Why do we need sbv IMPROVER?

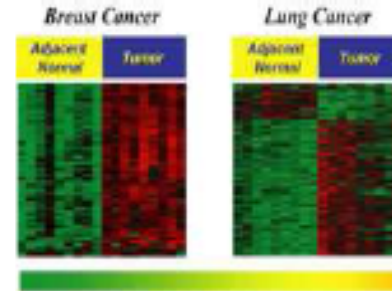
We are experiencing a data overload...



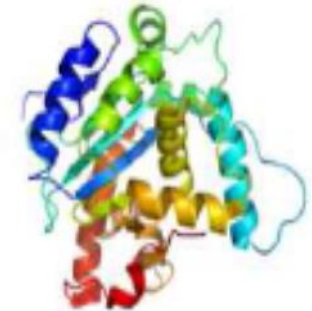
Genomic



Literature

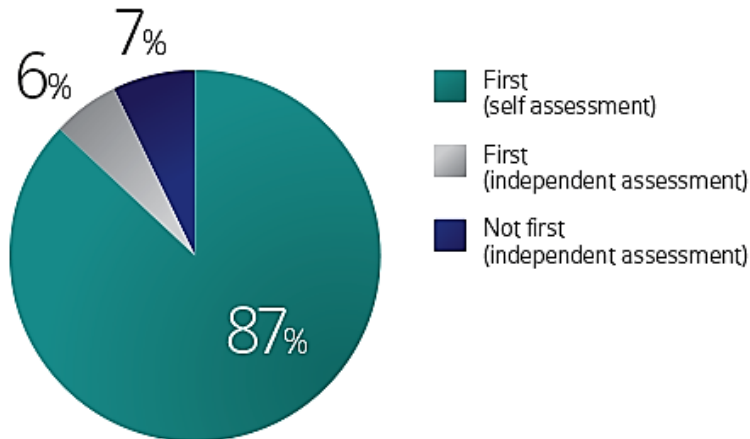


Molecular Profiles



Structures

But we lack the corresponding validation tools...



The self-assessment trap: can we all be better than average?

Mol Syst Biol. 2011 Oct 11;7:537. doi: 10.1038/msb.2011.70.

Develop a robust methodology that verifies systems biology-based approaches

Industrial Methodology for Process Verification in Research (IMProVeR): towards systems biology verification

- IMProVER has commonalities with other crowd sourcing methods
- The main concepts of IMProVER are :
 - to formalize rigorous tests that determine a go or no-go decision for a systems biology research pipeline in an industrial context
 - to inspire the development of enhanced methodologies by community participation
 - to endow the community with datasets and benchmark to provide a means for continuous improvement in subsequent generation of building blocks
- Successful implementation of IMProver will enable high credibility of a research pipeline

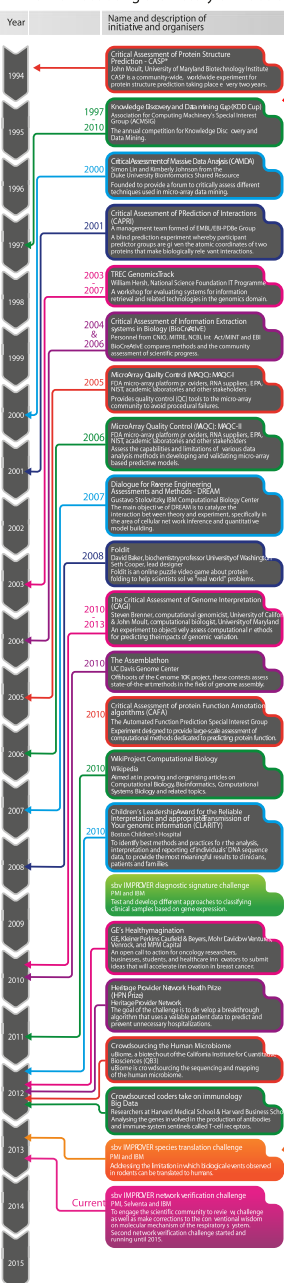
“Industrial Methodology for Process Verification in Research (IMProVeR): towards systems biology verification”

Pablo Meyer¹, Raquel Norel¹, Jörg Sprengel², Katrin Stolle³, Thomas Bonk³, Stephanie Corthesy¹, Ajay Royyuru, Julia Hoeng⁴, Manuel Peitsch⁴ and Gustavo Stolovitzky¹, J. Jeremy Rice¹

¹ IBM Computational Biology Center, Yorktown Heights, NY, USA, ² IBM Life Sciences Division, Zurich, Switzerland, ³ Phillip Morris International Research, Cologne, Germany, ⁴ Phillip Morris International Research, Neuchatel, Switzerland

Crowdsourcing in Science

Timeline illustrating the history of life sciences crowdsourcing initiatives



1994

Critical Assessment of Protein Structure Prediction - CASP*
 John Moulton, University of Maryland Biotechnology Institute
 CASP is a community-wide, worldwide experiment for protein structure prediction taking place every two years.

2005

MicroArray Quality Control (MAQC): MAQC-I
 FDA micro-array platform providers, RNA suppliers, EPA, NIST, academic laboratories and other stakeholders
 Provides quality control (QC) tools to the micro-array community to avoid procedural failures.

2012

sbv IMPROVER diagnostic signature challenge
 PMI and IBM
 Test and develop different approaches to classifying clinical samples based on gene expression.

2013

sbv IMPROVER species translation challenge
 PMI and IBM
 Addressing the limitation in which biological events observed in rodents can be translated to humans.

2013 - present

sbv IMPROVER network verification challenge
 PMI, Selventa and IBM
 To engage the scientific community to review, challenge as well as make corrections to the conventional wisdom on molecular mechanism of the respiratory system. Second network verification challenge started and running until 2015.

2004 & 2006

Critical Assessment of Information Extraction systems in Biology (BioCrAtIvE)
 Personnel from CNIO, MITRE, NCBI, Int Act/MINT and EBI
 BioCrAtIvE compares methods and the community assessment of scientific progress.

2006

MicroArray Quality Control (MAQC): MAQC-II
 FDA micro-array platform providers, RNA suppliers, EPA, NIST, academic laboratories and other stakeholders
 Assess the capabilities and limitations of various data analysis methods in developing and validating micro-array based predictive models.

2007

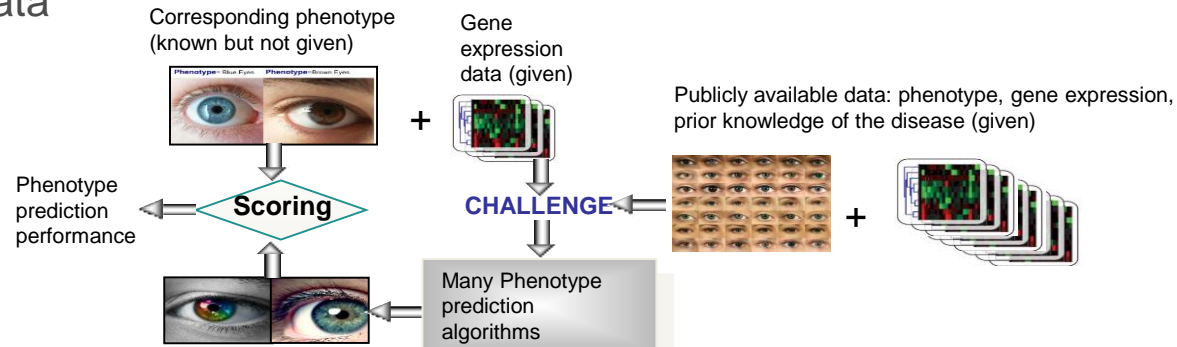
Dialogue for Reverse Engineering Assessments and Methods - DREAM
 Gustavo Stolovitzky, IBM Computational Biology Center
 The main objective of DREAM is to catalyze the interaction between theory and experiment, specifically in the area of cellular network inference and quantitative model building.

2013 - present

sbv IMPROVER network verification challenge
 PMI, Selventa and IBM
 To engage the scientific community to review, challenge as well as make corrections to the conventional wisdom on molecular mechanism of the respiratory system. Second network verification challenge started and running until 2015.

2012	2013	2014				2015			
		Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4

Diagnostic Signature: Best analytical approaches to predicting phenotype from gene expression data

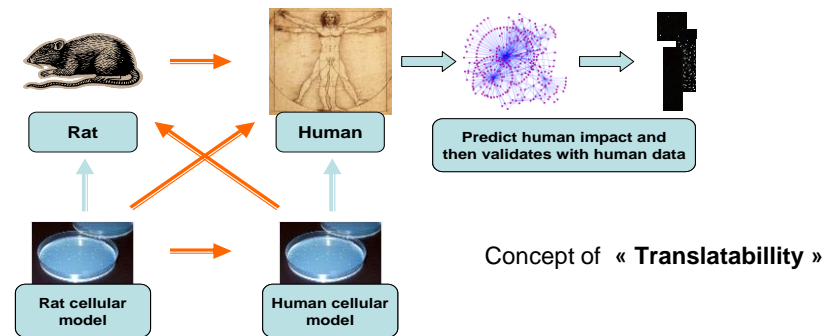


Open

Benchmarking

Species translation: Accuracy and limitations of rodent models for human diseases

Open



Network verification: Verify and enhance pulmonary biological network models

NVC1

NVC 2

Future Challenges: Being planned



The Network
Verification
Challenge
(NVC)

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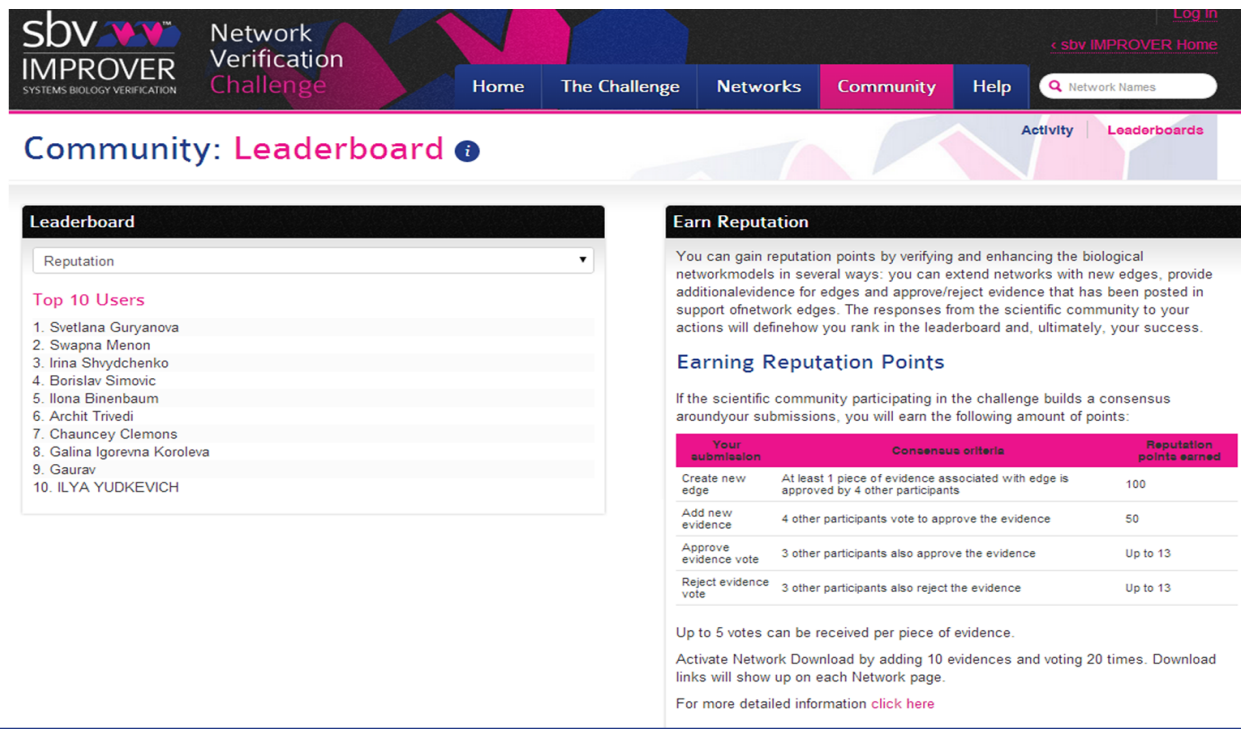
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Challenge 3 – Biological Networks Verification

The third sbv IMPROVER Challenge: Biological Network Verification

The purpose of this challenge was to engage the scientific community in the review of biological network models that are suitable for drug discovery, toxicological and mechanistic research in respiratory disease.

It used innovative concepts of reputation-based engines and state of the art web application for online network verification.



The screenshot shows the sbv IMPROVER Network Verification Challenge website. The top navigation bar includes links for Home, The Challenge, Networks, Community, and Help. A search bar for Network Names is also present. The main content area is titled "Community: Leaderboard" and features two sections: "Leaderboard" and "Earn Reputation".

Leaderboard

Reputation

Top 10 Users

1. Svetlana Guryanova
2. Swapna Menon
3. Irina Shvydchenko
4. Borislav Simovic
5. Ilona Binenbaum
6. Archit Trivedi
7. Chauncey Clemons
8. Galina Igorevna Koroleva
9. Gaurav
10. ILYA YUDKEVICH

Earn Reputation

You can gain reputation points by verifying and enhancing the biological network models in several ways: you can extend networks with new edges, provide additional evidence for edges and approve/reject evidence that has been posted in support of network edges. The responses from the scientific community to your actions will define how you rank in the leaderboard and, ultimately, your success.

Earning Reputation Points

If the scientific community participating in the challenge builds a consensus around your submissions, you will earn the following amount of points:

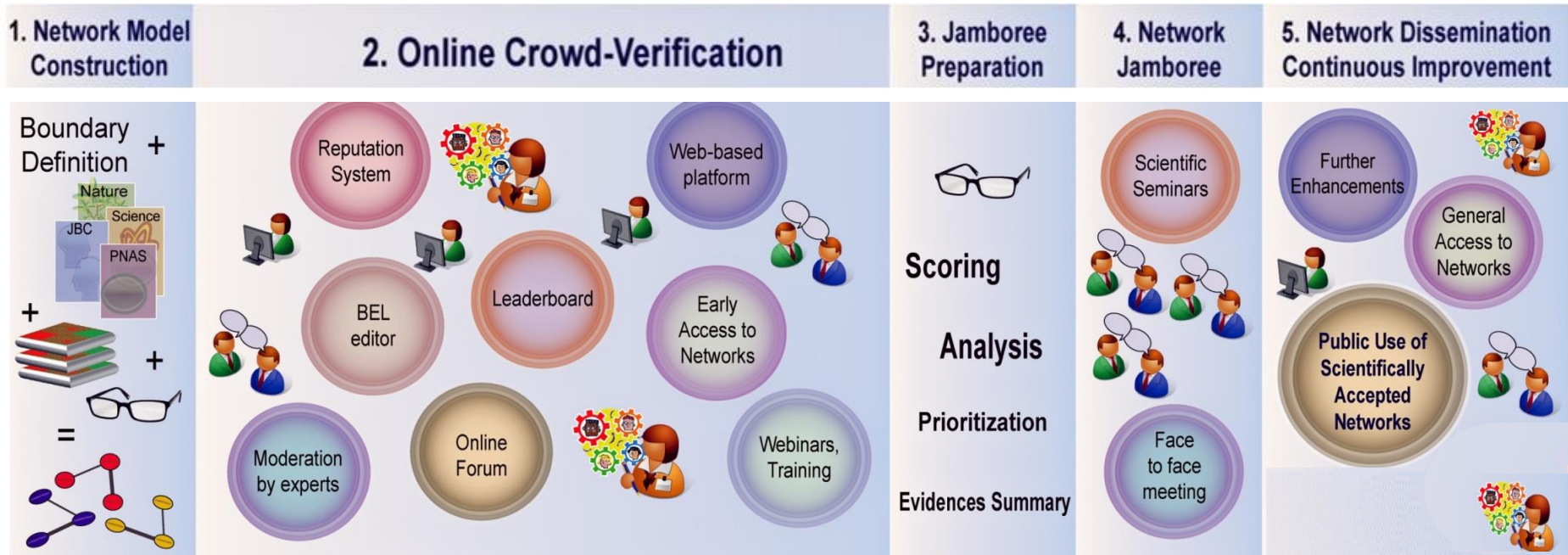
Your submission	Consensus criteria	Reputation points earned
Create new edge	At least 1 piece of evidence associated with edge is approved by 4 other participants	100
Add new evidence	4 other participants vote to approve the evidence	50
Approve evidence vote	3 other participants also approve the evidence	Up to 13
Reject evidence vote	3 other participants also reject the evidence	Up to 13

Up to 5 votes can be received per piece of evidence.

Activate Network Download by adding 10 evidences and voting 20 times. Download links will show up on each Network page.

For more detailed information [click here](#)

Steps in the sbv IMPROVER Network Verification Challenge (NVC)



The sbv IMPROVER project team (2013). On Crowd-verification of Biological Networks. *Bioinformatics and Biology Insights* 2013:7 307-325.

Steps in the sbv IMPROVER Network Verification Challenge (NVC)

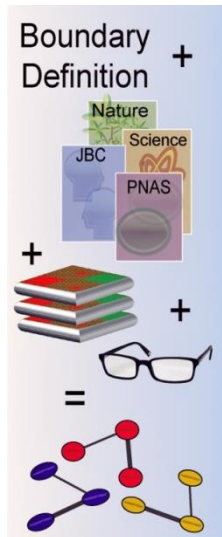
1. Network Model Construction

2. Online Crowd-Verification

3. Jamboree Preparation

4. Network Jamboree

5. Network Dissemination Continuous Improvement



The sbv IMPROVER project team (2013). On Crowd-verification of Biological Networks. **Bioinformatics and Biology Insights 2013:7 307-325.**

Model Types and Boundaries

1. Network Model Construction

2. Online Crowd-Verification

3. Jamboree Preparation

4. Network Jamboree

5. Network Dissemination Continuous Improvement



Species: Human (primarily), although mouse and rat evidence was included when supporting literature from human context was not available.

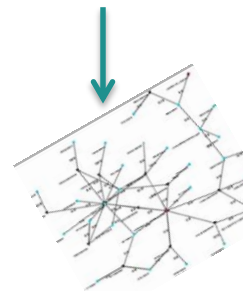
Tissue: Respiratory tissue (primarily).

Disease: Non-diseased tissue (augmented with chronic obstructive pulmonary disease biology only (e.g. lung cancer context was excluded)).



Cell-specific Signaling

Example: Macrophage Signaling Network



Physiologic Signaling

Example: Oxidative Stress



Canonical Signaling

Example: MAPK Network



Networks Were Built Using Literature and Human Transcriptomic Data

1. Network Model Construction

2. Online Crowd-Verification

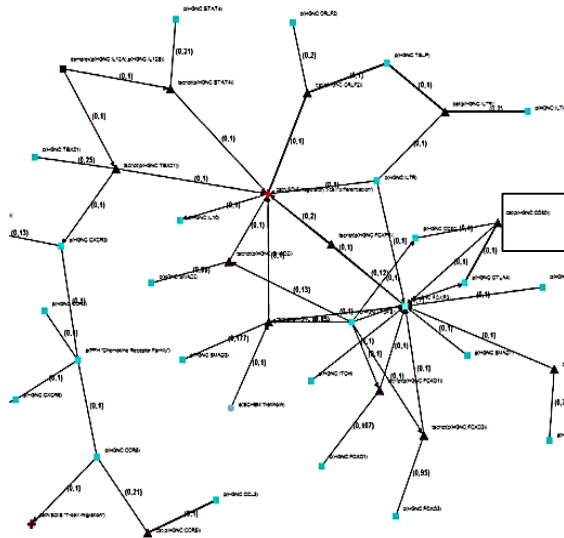
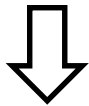
3. Jamboree Preparation

4. Network Jamboree

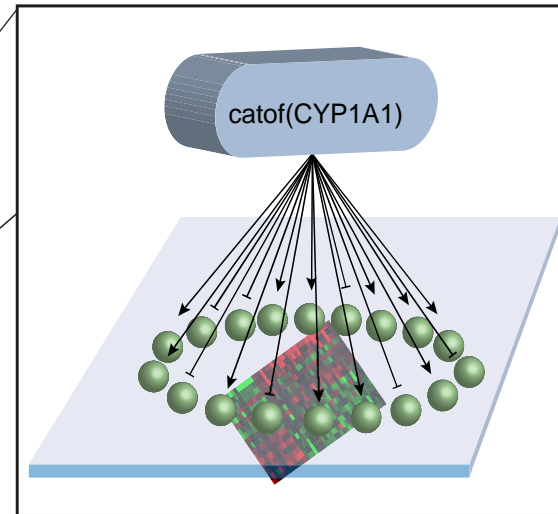
5. Network Dissemination Continuous Improvement



PubMed



Backward Reasoning is used to infer active mechanisms from transcriptomic data to enhance the literature model
 Catlett NL, et al. (2013). BMC Bioinformatics, 14, 340.



Data Set	Tissue	Stimulus
GSE 18341	Whole lung	LPS
GSE 2322	Lung neutrophil	Endotoxin

Network Models are Constructed with Nodes and Referenced Edges using BEL (*Biological Expression Language*)

1. Network Model Construction

2. Online Crowd-Verification

3. Jamboree Preparation

4. Network Jamboree

5. Network Dissemination Continuous Improvement

Literature Reference:

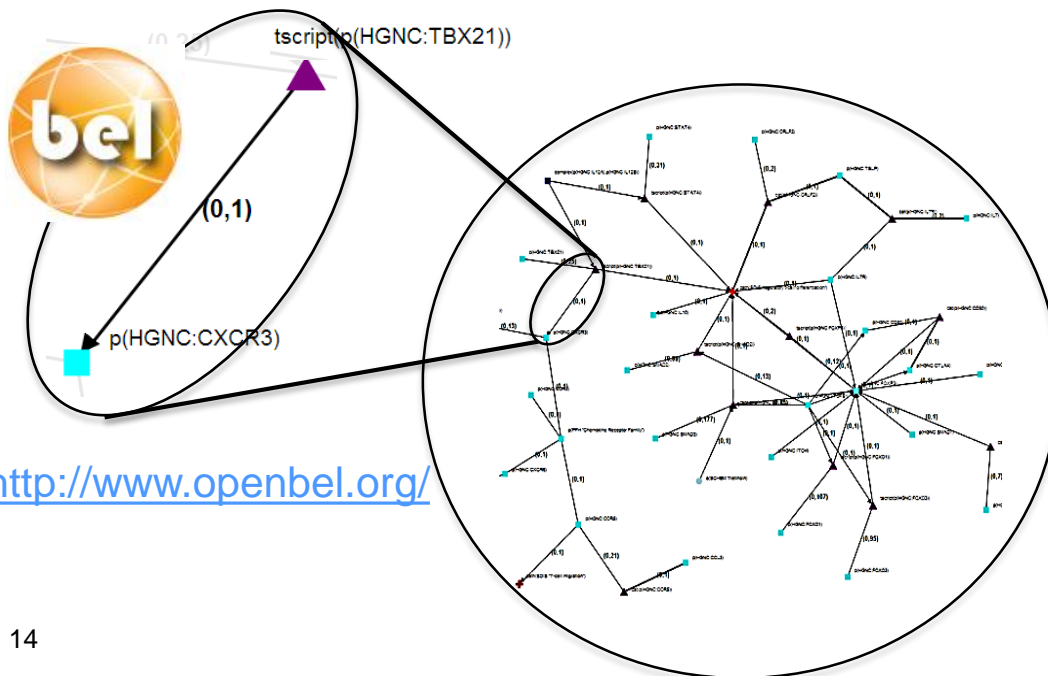
J Allergy Clin Immunol, 2004 May;113(5):987-94.

Sustained T-bet expression confers polarized human TH2 cells with TH1-like cytokine production and migratory capacities.

Quotation: "T-bet (TBX21) transfection also induced...CXCR3 expression on human TH2 cells"

Context: Human TH2 cell

Edge: TBX21 transcriptional activity increases CXCR3 protein abundance



The networks are supported by thousands of peer-reviewed scientific findings

To learn more, watch the videos/webinars:
<https://sbvimprover.com/challenge-3/tutorials>

Steps in the sbv IMPROVER Network Verification Challenge (NVC)

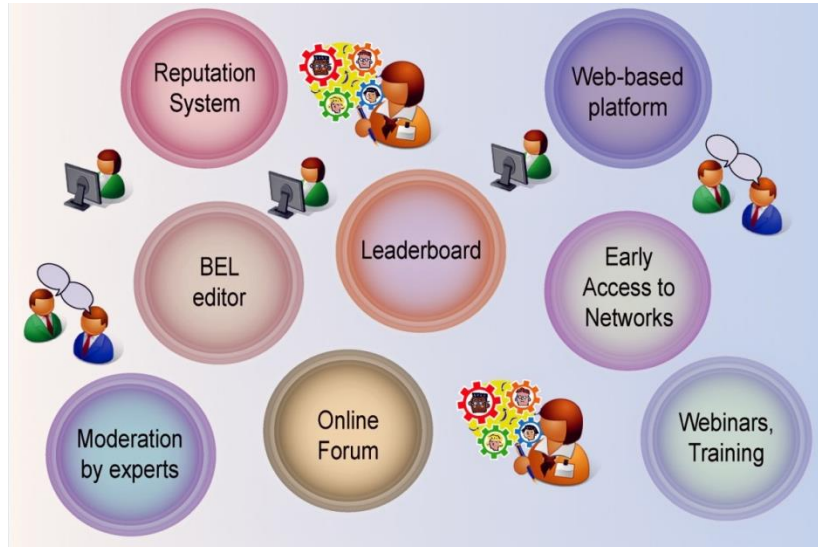
1. Network Model Construction

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The sbv IMPROVER project team (2013). On Crowd-verification of Biological Networks. **Bioinformatics and Biology Insights 2013:7 307-325.**

50 Network Models in the NVC:

1. Network Model Construction

2. Online Crowd-Verification

3. Jamboree Preparation

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5. Network Dissemination Continuous Improvement

Cell Fate

<p>Autophagy</p> <p>Mechanisms of Cellular senescence</p>	<p>Apoptosis</p> <p>Transcriptional Regulation of the SASP</p>	<p>Necroptosis</p> <p>Regulation by Tumor suppressors</p>
---	--	---

Cell Proliferation

<p>MAPK</p>	<p>Growth Factors</p>	<p>mTOR</p>	<p>Clock</p>	<p>Notch</p>	<p>Epigenetics</p>	<p>PGE2</p>	<p>Cell Interaction</p>
<p>Wnt</p>	<p>Calcium</p>	<p>Hedgehog</p>	<p>Nuclear Receptors</p>	<p>Hox</p>	<p>Cell cycle</p>	<p>Jak-Stat</p>	<p>CDKN2A</p>

Cell Stress

<p>ER Stress</p>	<p>Oxidative Stress</p>	<p>Xenobiotic Metabolism Response</p>
<p>Osmotic Stress</p>	<p>Hypoxic Stress</p>	<p>Response to DNA Damage</p>

Tissue Repair and Angiogenesis

<p>Tissue Damage</p>	<p>Immune Regulation of Tissue Repair</p>	<p>Fibrosis</p>	<p>Epithelial Mucus Hypersecretion</p>	<p>ECM Degradation</p>	<p>Angiogenesis</p>
<p>Wound Healing</p>					

Inflammation

<p>B-cell signaling</p>	<p>Dendritic Cell Signaling</p>	<p>Macrophage Signaling</p>	<p>Mast Cell Signaling</p>	<p>Megakaryocytes Differentiation</p>	<p>Cytotoxic T-cell Signaling</p>	<p>Epithelial Innate Immune Activation</p>	<p>Endothelial Innate Immune Activation</p>
<p>NK cell signaling</p>	<p>Th1 Signaling</p>	<p>Th2 Signaling</p>	<p>Th17 Signaling</p>	<p>Treg Signaling</p>	<p>Neutrophil Signaling</p>		

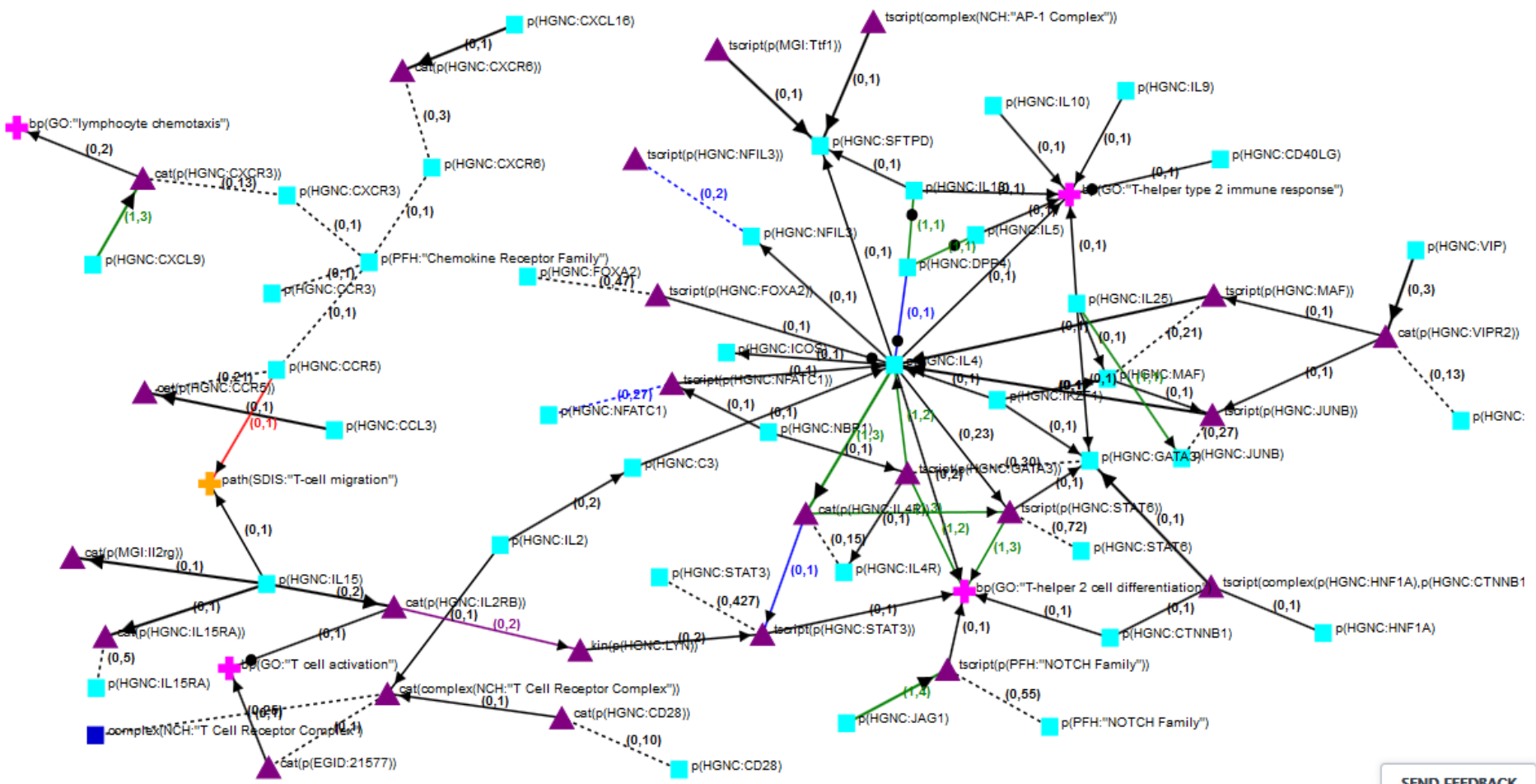


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The Networks Page



The Network Page

1. Network Model Construction

2. Online Crowd-Verification

3. Jamboree Preparation

4. Network Jamboree

5. Network Dissemination Continuous Improvement

 complex(p(HGNC:ECT2),p(HGNC:KLHL20)) increases gtp(p(HGNC:RHOA))

The complex(protein abundance of ECT2 and protein abundance of KLHL20) increases the GTP-bound activity of the protein abundance of RHOA.

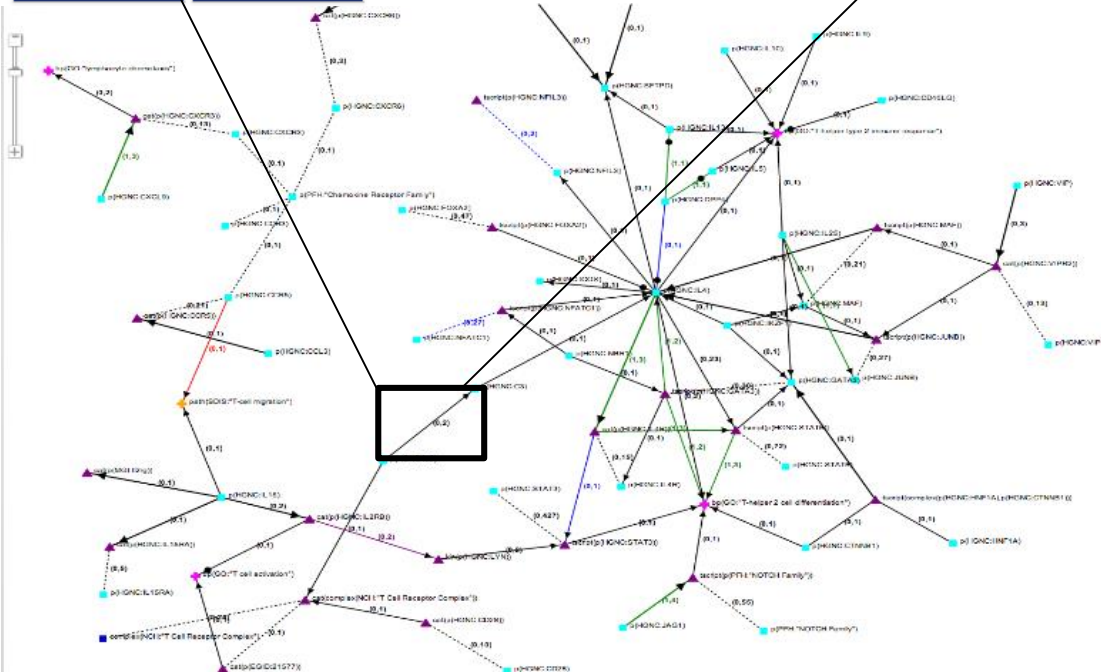
Quotation: KLEIP directly binds to the RhoGEF ECT2, which promotes the exchange from GDP with GTP on RhoA

Reference: 17395875 Circ Res 2007 Apr 27 100(8) 1155-63

Species Human
Cell Endothelial Cells

Locked Reset Display Network Details Network Activity Legend Comments Nodes Edges

Clone Evidence New Evidence



Approve

Reject

Vote Type: APPROVE

- The Evidence is relevant to the network and meets the boundary conditions, and has been accurately extracted from the Reference paper cited.
- The Evidence is relevant to the network and meets the boundary conditions, but has not been accurately extracted from the Reference paper cited.

Is the context information (Including Species, Cell, Disease, and Tissue) correctly and completely extracted from the Reference paper?

Yes No

Does the BEL statement correctly capture what is described in the Reference paper (e.g., correct node name or relationship edge)?

Yes No

- The Evidence should not be in the network (e.g., it does not meet the boundary conditions or is not relevant to the biological process described in the network).

Comment

Submit

Th2 Signaling

Locked

Reset Display

Network Details

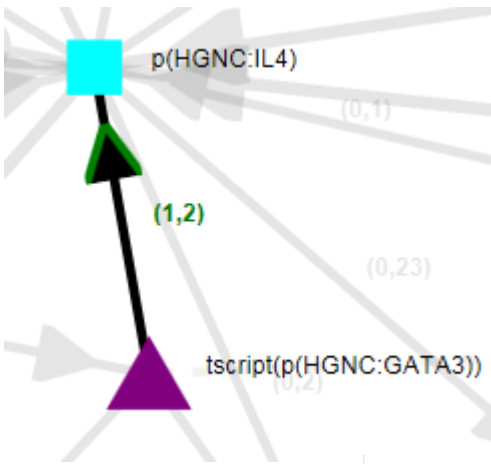
Network Activity ▾

Legend

Comments

Nodes

Edges



Selected Edge

tscript(p(HGNC:GATA3)) increases p(HGNC:IL4)

Comment

New Evidence

Evidence (2)

- 4 0 Mouse ::
- 4 0 Mouse :: t-cell ::

Votes

Created By	Voted	Reason	Comment
svgur	Accepted	The Evidence is relevant to the network and meets the boundary conditions, and has been accurately extracted from the Reference paper cited.	
koroev	Accepted	The Evidence is relevant to the network and meets the boundary conditions, and has been accurately extracted from the Reference paper cited.	
ishv	Accepted	The Evidence is relevant to the network and meets the boundary conditions, and has been accurately extracted from the Reference paper cited.	
eschrier	Accepted	The Evidence is relevant to the network and meets the boundary conditions, and has been accurately extracted from the Reference paper cited.	

Node List (70)

-- Show All --

- p(HGNC:CXCR6)
- p(HGNC:IL4R)
- p(HGNC:IL10)
- oat(p(EGID:21577))
- bp(GO:"lymphocyte chemotaxis")
- p(HGNC:IKZF1)
- oat(p(HGNC:CD28))
- bp(GO:"T-helper 2 cell differentiation")
- p(HGNC:CD40LG)
- p(HGNC:IL5)
- tscript(p(HGNC:MAF))
- oat(p(HGNC:IL15RA))

Network Verification Challenge

Jean Binder | 00 pts | 3 badges | [Logout](#)

[sbv IMPROVER Home](#)

Home

The Challenge

Networks

Community

Help

Activity

Leaderboards

Community: Activity

These are the networks that have received the most attention from the participants in the Verification Challenge to date. Filter the list below to view what edges have been created, and what has been voted on.

Under the link 'Leaderboard' you can view how well you are performing in comparison to measured by reputation points. The rankings on the Leaderboard are tentative and subject to the [Challenge Rules](#)

-- All Networks -- My Actions

Vote on Evidence Views(0)

Status: ACTIVE

Edge: $\text{deg}(p(\text{MGI:Rbpj})) \text{ directlyDecreases } p(\text{HGNC:RBPJ})$

Context: Mouse ::

Quotation: We therefore propose that BAZF supports angiogenic sprouting regulate Notch signaling

a day ago | Network: **Angiogenesis**

Edge Created

Status: OPEN

$p(\text{HGNC:TGB1}) \text{ Increases } bp(\text{GO:} \text{"canonical wnt signalling pathw})$

Community: Leaderboard i

Leaderboard

Reputation

Top 10 Users

1. Svetlana Guryanova
2. Swapna Menon
3. Irina Shvydchenko
4. Borislav Simovic
5. Ilona Binenbaum
6. Archit Trivedi
7. Chauncey Clemons
8. Galina Igorevna Koroleva
9. Gaurav
10. ILYA YUDKEVICH

Personal Ranking

1. Tambovtseva Anna 0
2. Xi Cheng 0
3. Chiu Man 0
4. Diego A. Morales 0
5. Elena Kozhemyakina 0

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Jean Binder | 00 pts | 3 badges | Logout

sbv IMPROVER Home

Home | The Challenge | Networks | Community | Help

Network Names

Full Name

Jean Binder

[Administer Actions](#)
[Moderator Actions](#)

Rank: 177
Points: 0
Created Evidences: 0
Created Edges: 0
Total times voted: 0

Team name: Internal Support Team

[How to earn more points](#)

Activity

No Recent Activity

Badges

Badges Earned



Earn More Badges

Comments



Evidence



Edge



Votes



Open Phase of the NVC1

1. Network Model Construction

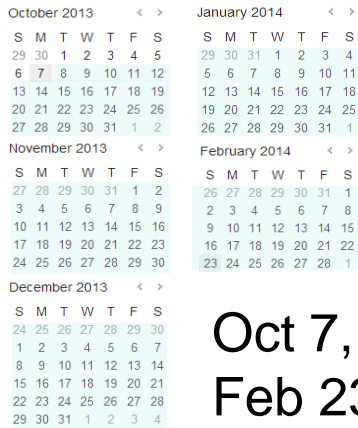
2. Online Crowd-Verification

3. Jamboree Preparation

4. Network Jamboree

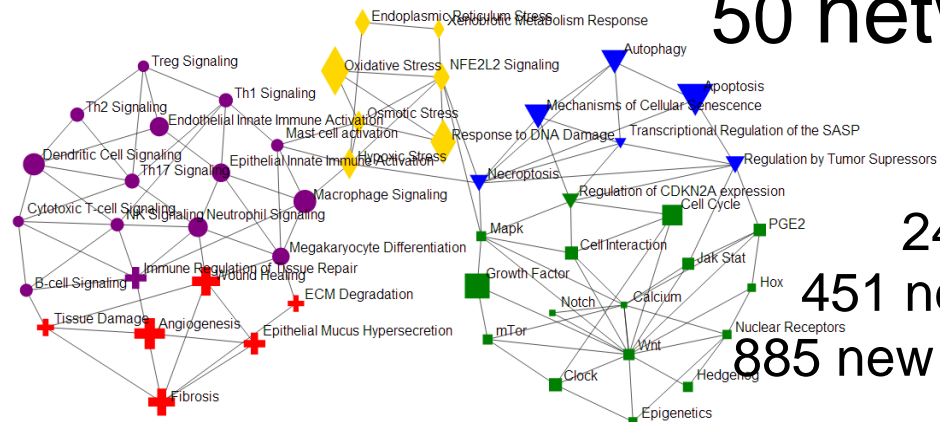
5. Network Dissemination Continuous Improvement

5 months



Oct 7, 2013 –
 Feb 23, 2014

50 networks

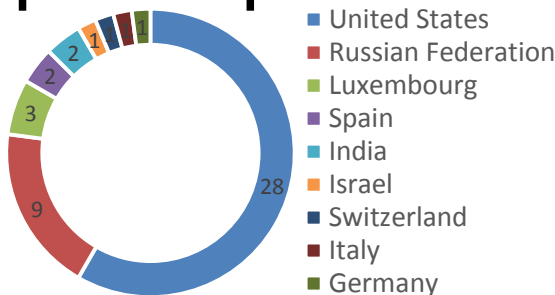


2456 votes

451 new edges

885 new evidence

150 participants



from 18 countries



Overview of Actions in the Network Verification Challenge

1. Network Model Construction

2. Online Crowd-Verification

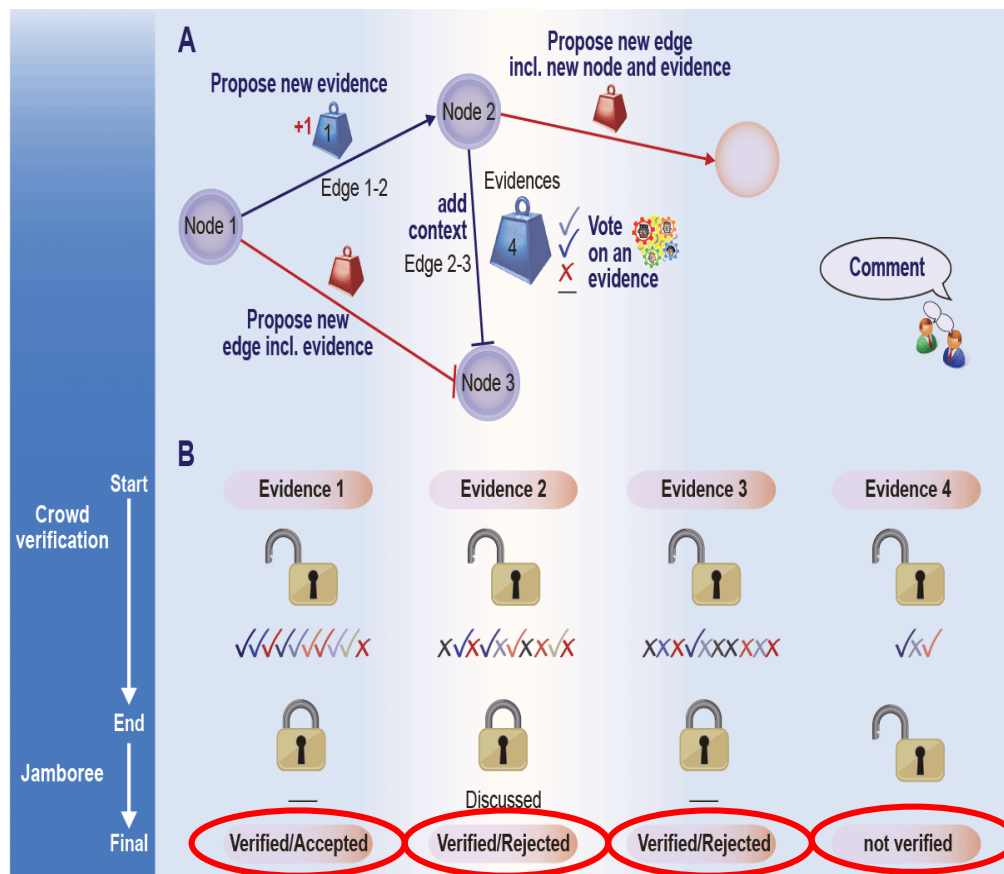
3. Jamboree Preparation

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5. Network Dissemination Continuous Improvement

The outcome of the online verification process is the result of the combination of submissions by different participants

- Each edge can have four possible states at the end of the challenge:
- **Verified:** There is at least one verified piece of evidence associated with the edge.
- **Ambiguous:** Participants are divided on whether a piece of evidence supports the edge
- **Rejected:** All evidence that has been suggested in favor of an edge has been rejected by the overwhelming majority of participants
- **Not verified:** The evidence for an edge did not receive sufficient submissions from participants to be considered verified.



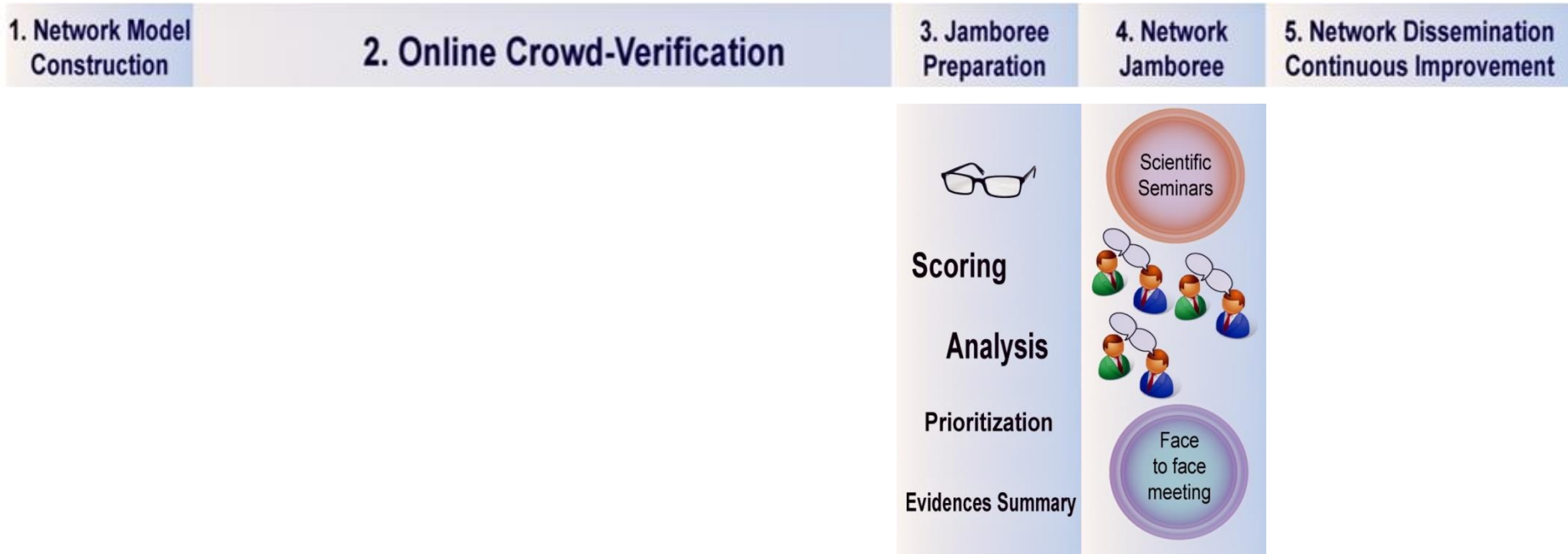


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Steps in the sbv IMPROVER Network Verification Challenge



The sbv IMPROVER project team (2013). On Crowd-verification of Biological Networks. **Bioinformatics and Biology Insights 2013:7 307-325.**

50 Network Models in the NVC: 15 Discussed during NVC1 Jamboree

1. Network Model Construction

2. Online Crowd-Verification

3. Jamboree Preparation

4. Network Jamboree

5. Network Dissemination Continuous Improvement

Cell Fate

Autophagy

Apoptosis

Necroptosis

Mechanisms of Cellular senescence

Transcriptional Regulation of the SASP

Regulation by Tumor suppressors

Cell Proliferation

MAPK

Growth Factors

mTOR

Clock

Notch

Epigenetics

PGE2

Cell Interaction

Wnt

Calcium

Hedgehog

Nuclear Receptors

Hox

Cell cycle

Jak-Stat

CDKN2A

Cell Stress

ER Stress

Oxidative Stress

Xenobiotic Metabolism Response

Osmotic Stress

Hypoxic Stress

Response to DNA Damage

AHR

CYP450

Tissue Repair and Angiogenesis

Tissue Damage

Immune Regulation of Tissue Repair

Fibrosis

Epithelial Mucus Hypersecretion

ECM Degradation

Angiogenesis

Wound Healing

Inflammation

B-cell signaling

Dendritic Cell Signaling

Macrophage Signaling

Mast Cell Signaling

Megakaryocytes Differentiation

Cytotoxic T-cell Signaling

Epithelial Innate Immune Activation

Endothelial Innate Immune Activation

NK cell signaling

Th1 Signaling

Th2 Signaling

Th17 Signaling

Treg Signaling

Neutrophil Signaling

1. Network Model
Construction

2. Online Crowd-Verification

3. Jamboree
Preparation

4. Network
Jamboree

5. Network Dissemination
Continuous Improvement

Congratulations to the Best Performers from the sbv IMPROVER Biological Network Verification Challenge

In March 2014, the results of the third sbv IMPROVER challenge were shared with the scientific community at the sbv IMPROVER Jamboree in Montreux, Switzerland.

We proudly announce the Best Performers of the Biological Network Verification Challenge:



From left to right:

- » Qingxian Lu » Jennifer Park (Selventa, Organizer) » Aravind Tallam
- » Julia Hoeng (Philip Morris International, Organizer and Host)
- » Larisa Fedorova » Svetlana Guryanova » Edward Sanders
- » Galina Igorevna Koroleva » Gema Villa Fombuena
- » Rahul Kumar » Norberto Díaz-Díaz » Swapna Menon
- » Ilona Binenbaum » Mariya Zelikman » Ilya Yudkevich
- » Manuel Peitsch (Philip Morris International, Organizer and Host)

- Not in the picture:**
- » Vladimir Bondarenko » Oleg V. Bulgakov
 - » Vera Cherkasova » Julia Guzova » Elena Kozhemyakina
 - » Noa Lavid » Yael Ouliel » Samantha C. Peterson
 - » Alexander Prokhorov » Sarah Schrier » Golan Schwaitzer Neta
 - » Irina Shvydchenko » John Wu

The sbv IMPROVER project is part of a collaborative project organized and funded by Philip Morris International Research and Development. It is 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.

Join the ongoing sbv IMPROVER Biological Network Verification Challenge **Please visit: www.sbvimprover.com**



Steps in the sbv IMPROVER Network Verification Challenge

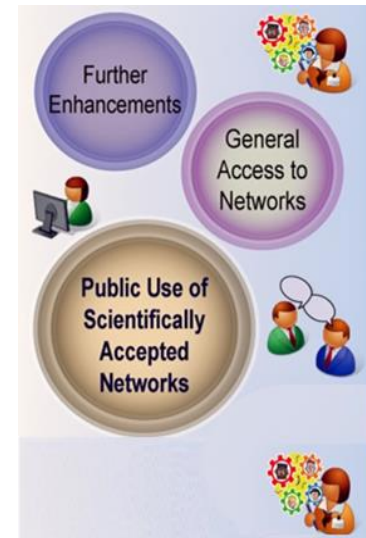
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The sbv IMPROVER project team (2013). On Crowd-verification of Biological Networks. **Bioinformatics and Biology Insights 2013:7 307-325.**

NVC2: Continue to Refine Networks Using the Crowd

1. Network Model Construction

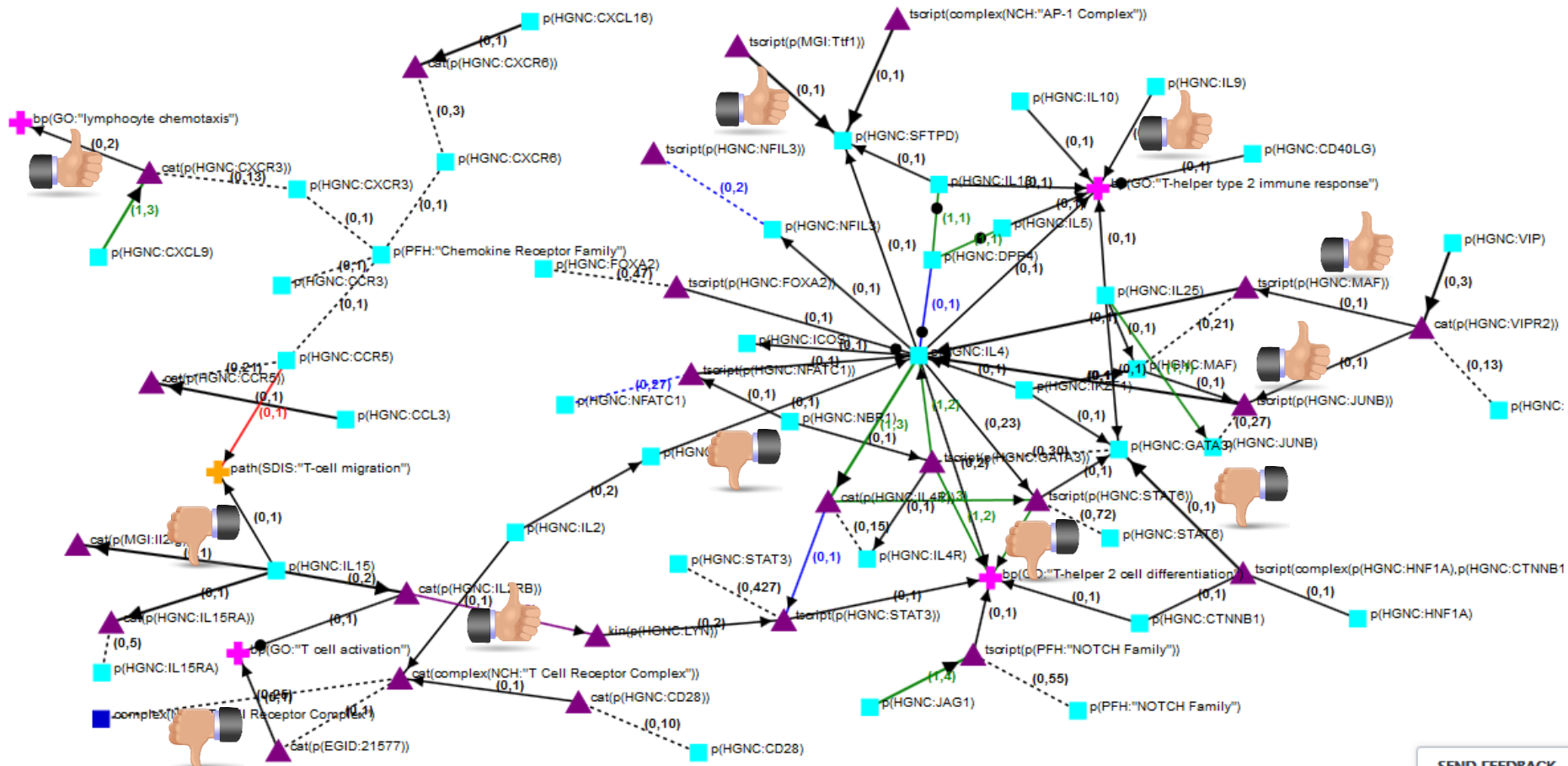
2. Online Crowd-Verification

3. Jamboree Preparation

4. Network Jamboree

5. Network Dissemination Continuous Improvement

Vote on evidence, create new edges, add missing nodes



SEND FEEDBACK

Why should you participate?

- Gain access to high quality and novel data
- Enhance your visibility and gain recognition
- Engage with peers to advance the field
- Being invited to the Jamboree

NVC2:

Network Verification Challenge 2

Engage in an online verification process to review, challenge and enhance biological network models.

[Go to the challenge website](#)

NVC2 Important Dates

1. Network Model Construction

2. Online Crowd-Verification

3. Jamboree Preparation

4. Network Jamboree

5. Network Dissemination Continuous Improvement

Open Phase

Jamboree Activities

Feb 2014

Jul 2014

Sept 2014

Dec 2014

Apr 2015

Mid-2015

NVC2 Started

↑
Today:

ECCB workshop

NVC2 Open Phase Ends

Best Performer Invitation and Jamboree Preparation

Network Dissemination

2nd International Summit on

Integrative Biology

August 04-05, 2014 Chicago, USA

- Attend the **European Conference on Computational Biology (ECCB) workshop Sunday Sept 7** in Strasbourg, France to learn about and discuss crowd engagement methods to advance research (W13 - sbv IMPROVER Workshop)



www.sbvimprover.com

Acknowledgements to the Global Team



Institutes and Companies Represented

Advantage Integral

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Nestlé Institute of Health Sciences

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SBI

Selventa

SIB Swiss Institute of Bioinformatics

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University of Toledo

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