Cell Collective tutorial

Tomas Helikar

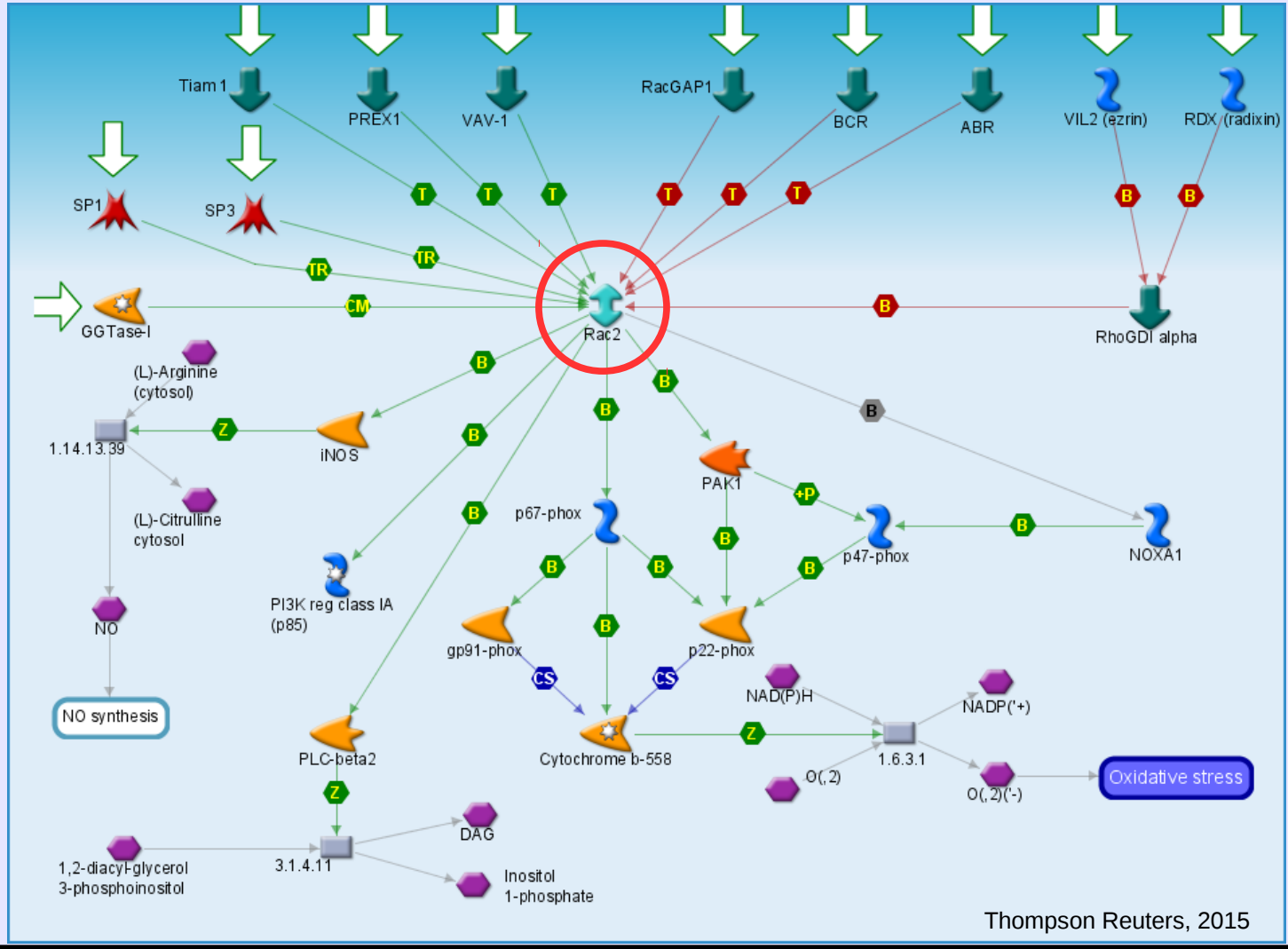
www.cellcollective.org || www.helikarlab.org || @helikarlab ||
thelikar2@unl.edu

Department of Biochemistry
University of Nebraska at Lincoln

Computational Modeling Challenges

- Combinatorial explosion of the number of states with the number of components (2^n states for *n* network components)
- Scalability of creating large-scale and accurate models
- Model transparency (can I believe the model?)
- Model (re-)usability and sharing

Challenge: Complexity



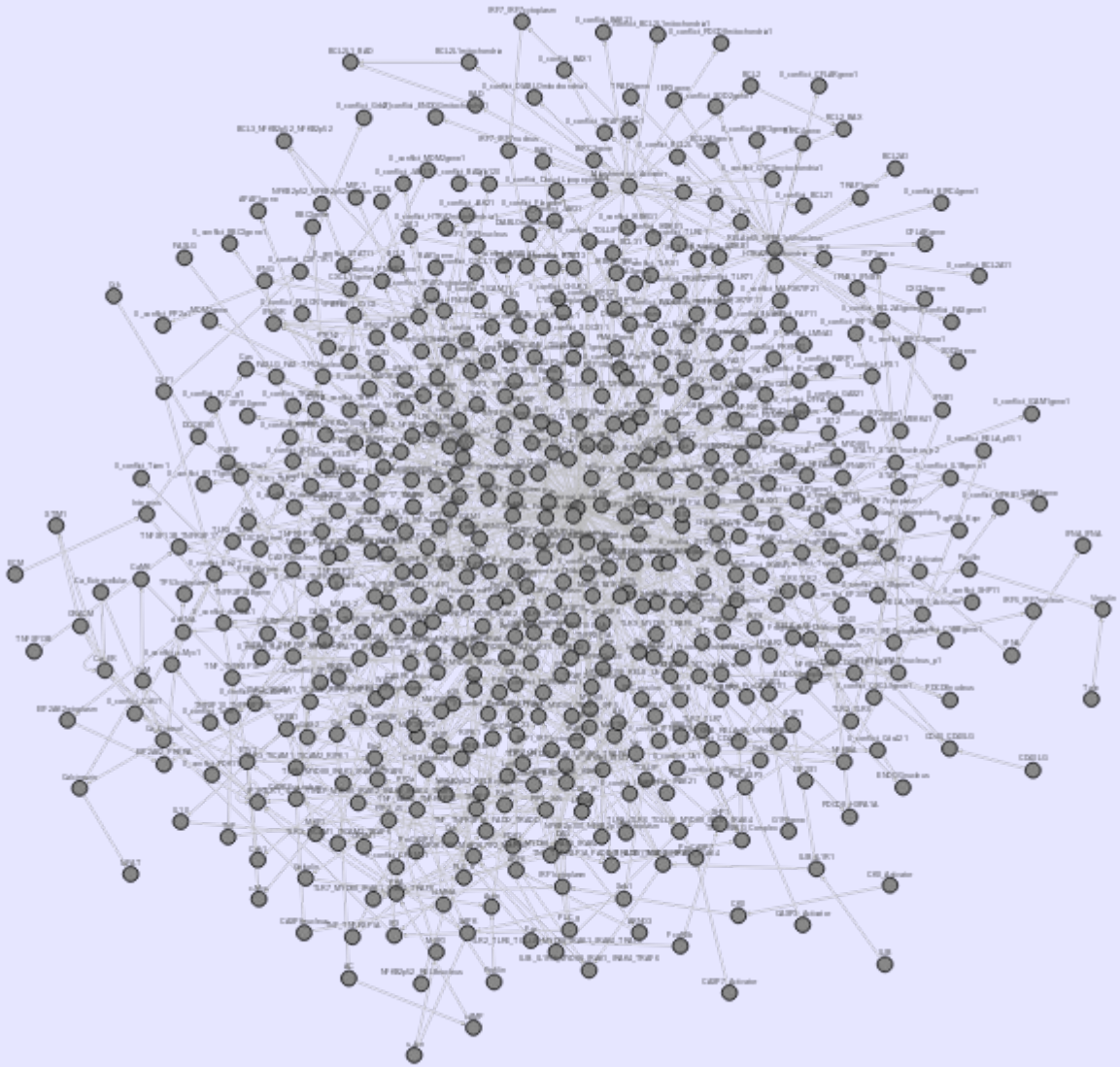
Mathematical description of the regulatory mechanism of Rac

$$
\begin{aligned}
&(RasGRF \wedge \neg(RhoGDI \wedge \neg PAK) \wedge \neg(p190RhoGAP \wedge Rac) \wedge \neg(RalBP1 \wedge Rac) \\
&\wedge ECM \wedge Integrins) \vee (Tiam \wedge \neg(RhoGDI \wedge \neg PAK) \wedge \neg(p190RhoGAP \wedge Rac) \\
&\wedge \neg(RalBP1 \wedge Rac) \wedge (ECM \wedge Integrins)) \vee (Pix_{C}ool \wedge \neg(RhoGDI \wedge \neg PAK) \\
&\wedge ((PAK \wedge G\beta\gamma \wedge ((\neg Cdc42 \wedge \neg Rac) \wedge (Integrins \wedge ECM))) \vee (\neg G\beta\gamma \wedge (Cdc42 \\
&\wedge (Integrins \wedge ECM) \wedge \neg Rac)) \vee (\neg PAK \wedge (\neg RhoGDI \wedge (\neg DOCK180 \wedge \neg(RhoGDI \wedge \neg PAK) \\
&\wedge \neg(p190RhoGAP \wedge Rac) \wedge \neg(RalBP1 \wedge Rac) \wedge \neg RasGRF \wedge \neg(RhoGDI \wedge \neg PAK) \\
&\wedge \neg(p190RhoGAP \wedge Rac) \wedge \neg(RalBP1 \wedge Rac) \wedge \neg Tiam \wedge \neg(RhoGDI \wedge \neg PAK) \\
&\wedge \neg(p190RhoGAP \wedge Rac) \wedge \neg(RalBP1 \wedge Rac)) \wedge (Integrins \wedge ECM) \wedge Cdc42 \wedge \neg Rac)))) \\
&\vee (DOCK180 \wedge \neg(RhoGDI \wedge \neg PAK) \wedge \neg(p190RhoGAP \wedge Rac) \wedge \neg(RalBP1 \wedge Rac) \\
&\wedge (ECM \wedge Integrins))
\end{aligned}
\tag{1}
$$

(Helikar et. al. 2013. *PLoS One 8(4):e61757)*

Challenge: Size

Macrophage Signaling and Gene Regulation



- 1,600+ components (proteins/protein complexes, genes, etc.)

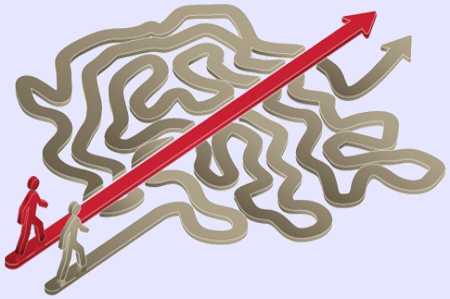
- HIV replication cycle
- CCR5 (gp120, MIP-1)
- CSF1
- Integrin
- IFNGR
- FcgR (FcgRIIb)
- Toll-like Receptor
- Interferon (alpha, beta, gamma)
- NF-kB
- Apoptosis (FAS, TNF)

Cell Collective Overview

Cell Collective: https://www.cellcollective.org

Accessibility

... to non-modelers



Collaboration

Scalability

... bigger and more accurate models

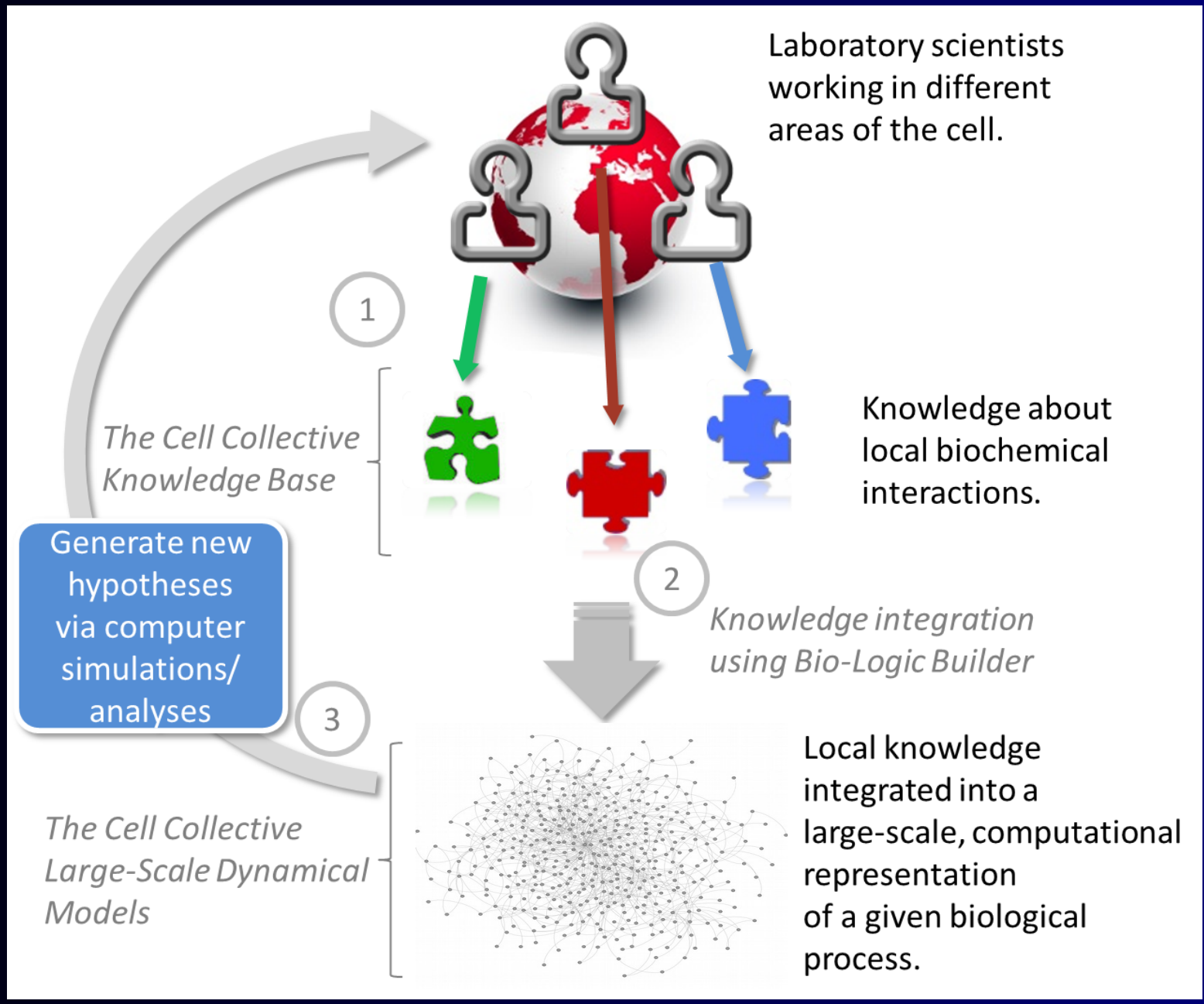
Transparency

... can I believe the models??

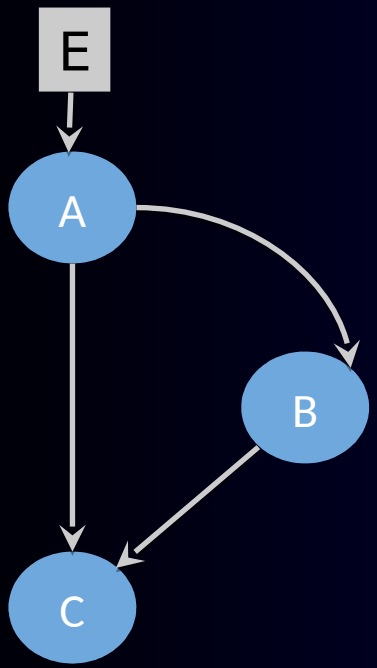
Re-usability & Reproducibility

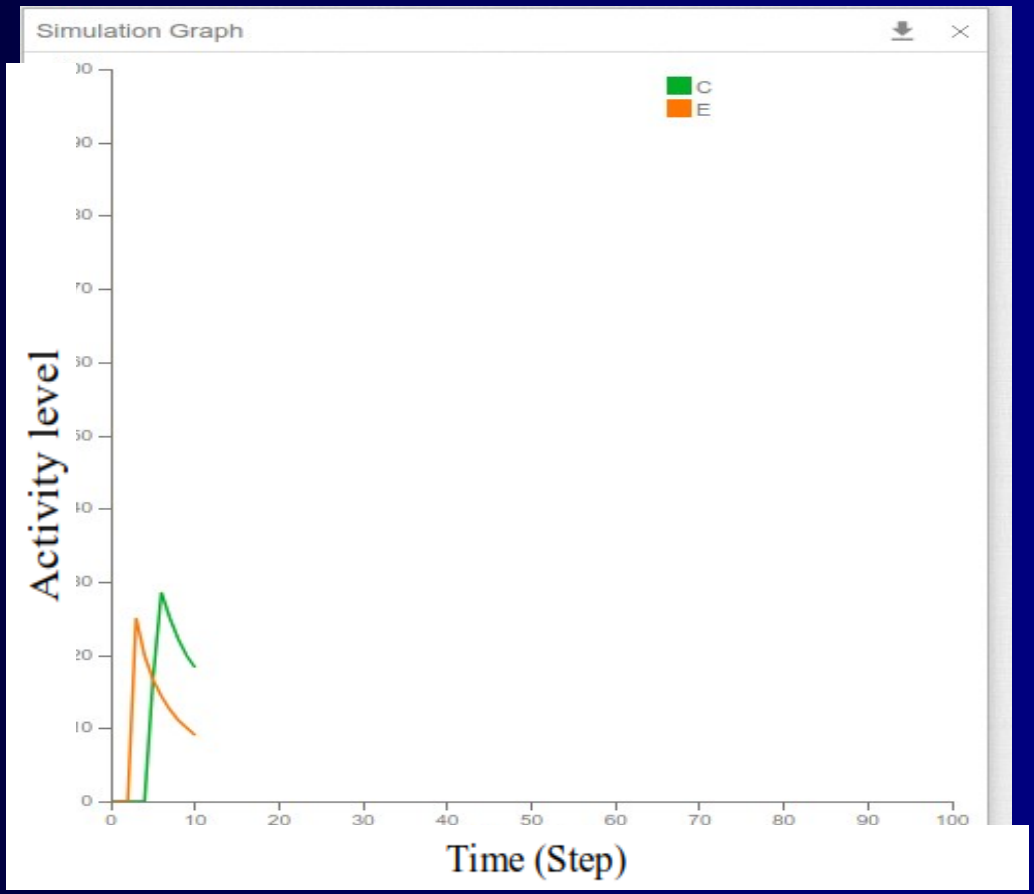
(Helikar et. al. 2012. BMC Systems Biology. 6:96; Helikar et. al. 2013. Clin Pharm & Ther.)

Cell Collective Overview



Logical Model

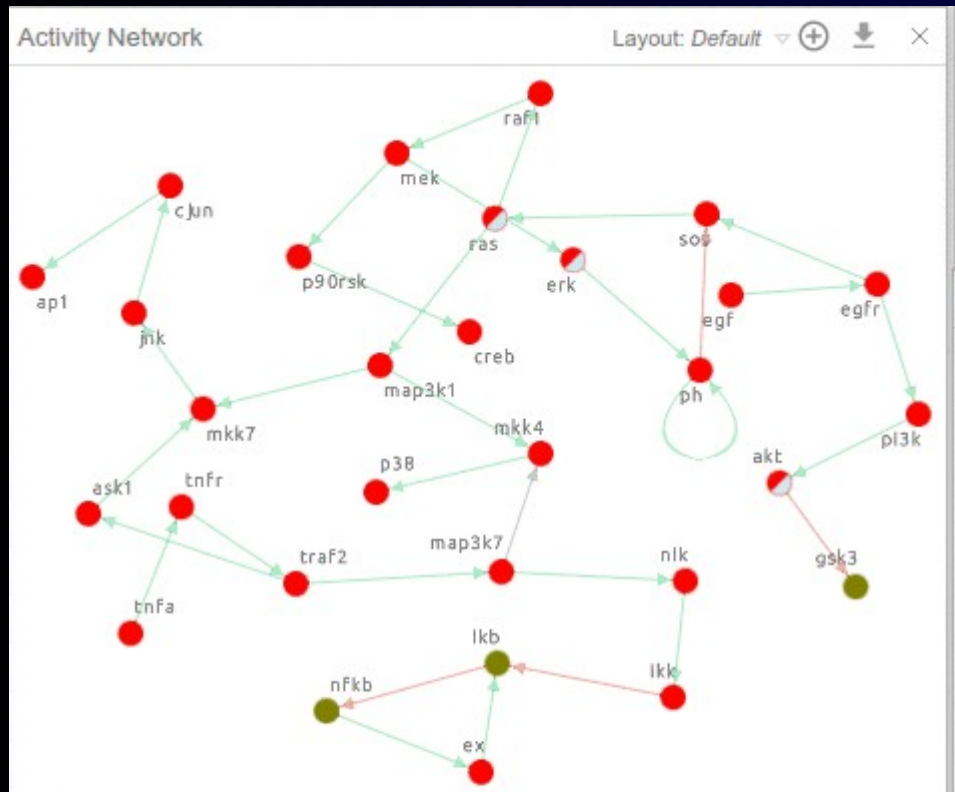


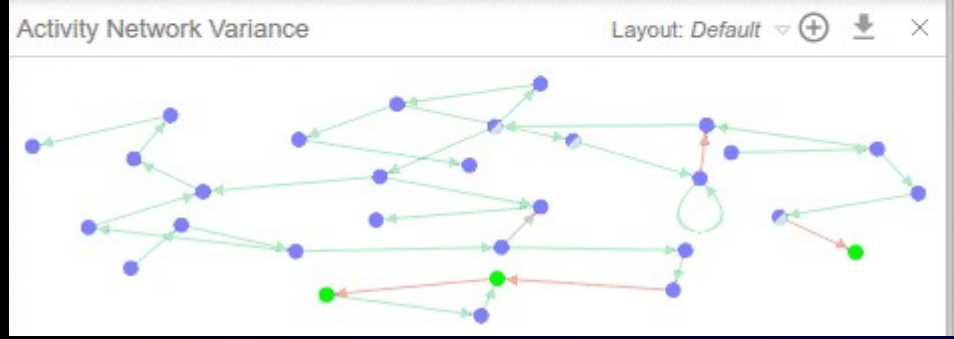


- Mechanistic
- Qualitative logic, i.e., “Proteins A or B activate protein C” (A V B → C)
- (Kinetic) parameter independent
- Efficient simulations

Helikar T., et al. PNAS (2008) Helikar T., et al. BMC Sys Bio (2012)

Cell Collective Real-Time Simulations

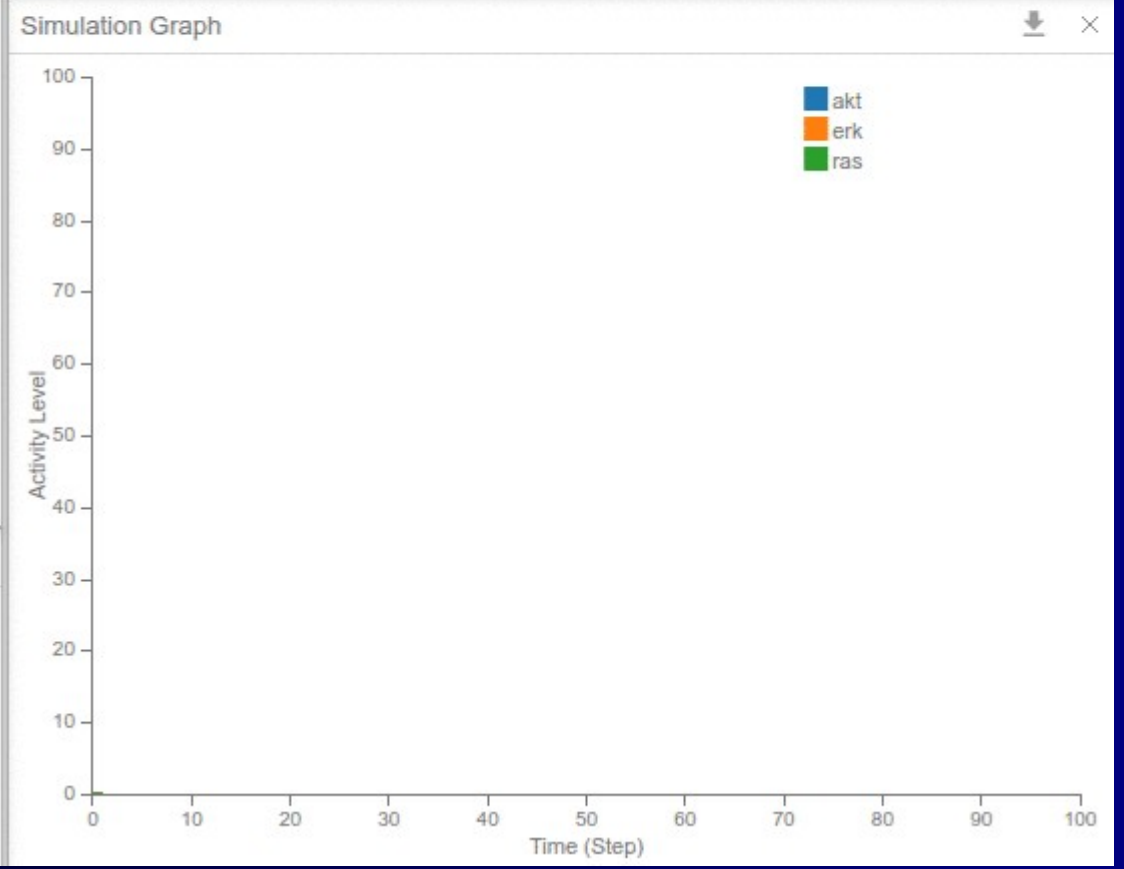




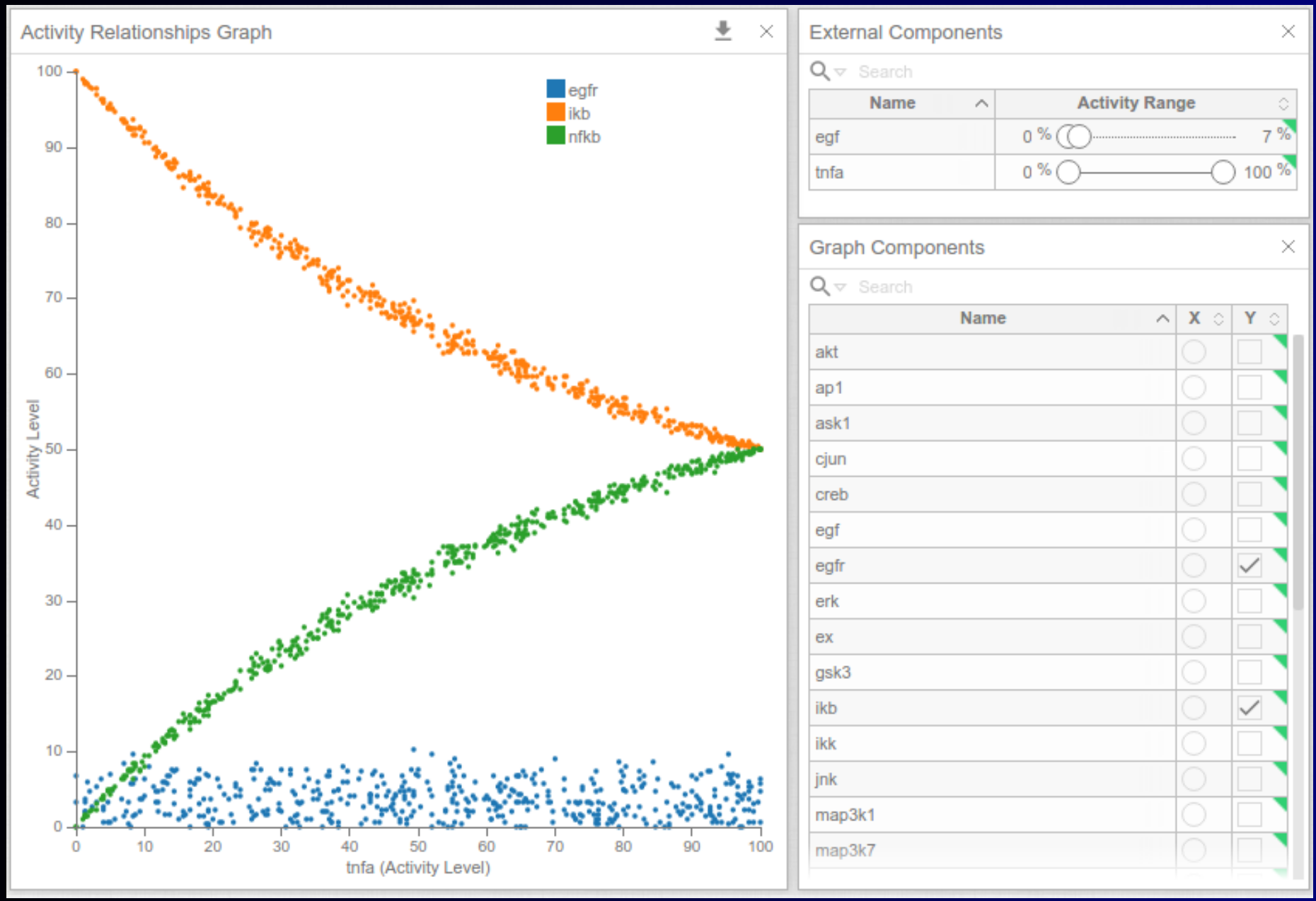
External Components

Search

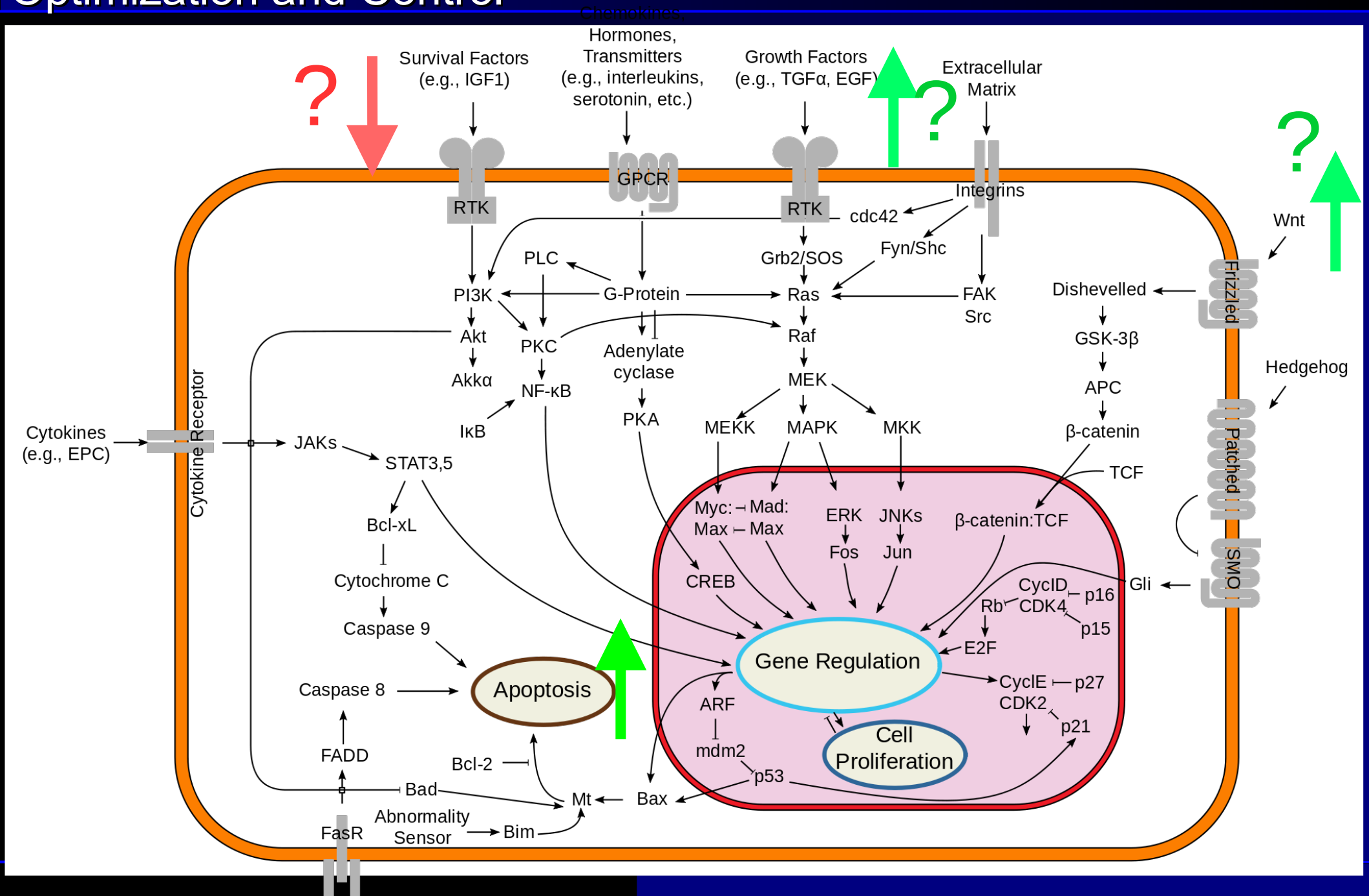
	Name	Activity
	egf	0 %
	tnfa	0 %



Input-Output Analysis (titration curves)



Optimization and Control



Cell Collective: Models annotation and transparency

cellcollective research

Tomas Helikar

IGVH mutations in chronic lymphocytic leukemia.

Knowledge Base | Simulation | Analysis | Model | Description

Components

Search

Name
ADM
AEBP1
AFF1
AICDA
AKAP12
AKT3
ALOX5
ANXA2
APLP2
APOBEC3G
APP
BLNK
BMI1
CASP3
CAV1
CCL5
CCND2
CD27
CD63
CD69
CD70

Knowledge Base *ADM*

Description

- Adrenomedullin
- Gene ID: 133
- ADM and PAMP act as hypotensive and vasodilatator agents. Both meidate the loss of plasma volume in the brain and pituitary gland and inhibit aldosterone secretion. *(Álvarez-Silva MC, 2015)*
- Gene: ADM
- UniProt ID: P35318

Regulatory Mechanism Summary

HSP90AA1 or TNF in conjunction with HSP0AA1 activates ADM. *(Hofbauer KH, 2002)* *(Masoud GN, 2015)*

Upstream Regulators

HSP90AA1

HSP90AA1 indirectly upregulates ADM expression. *(Masoud GN, 2015)*

TNF

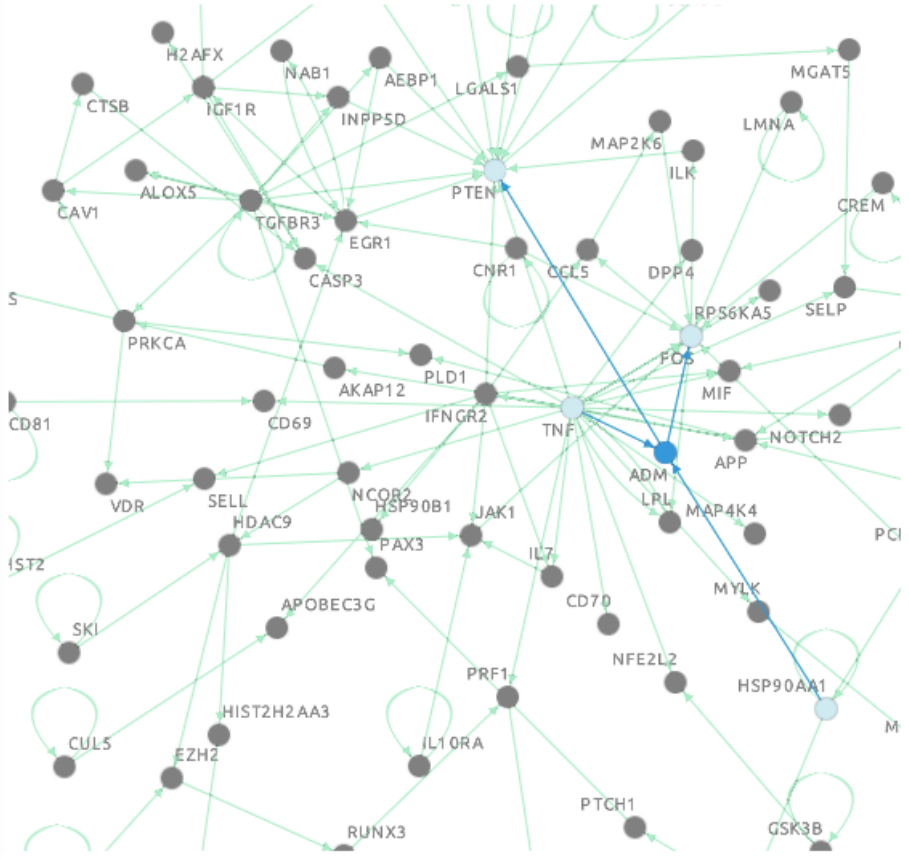
Cells treated with TNF showed upregulation of ADM mRNA. *(Hofbauer KH, 2002)*

References

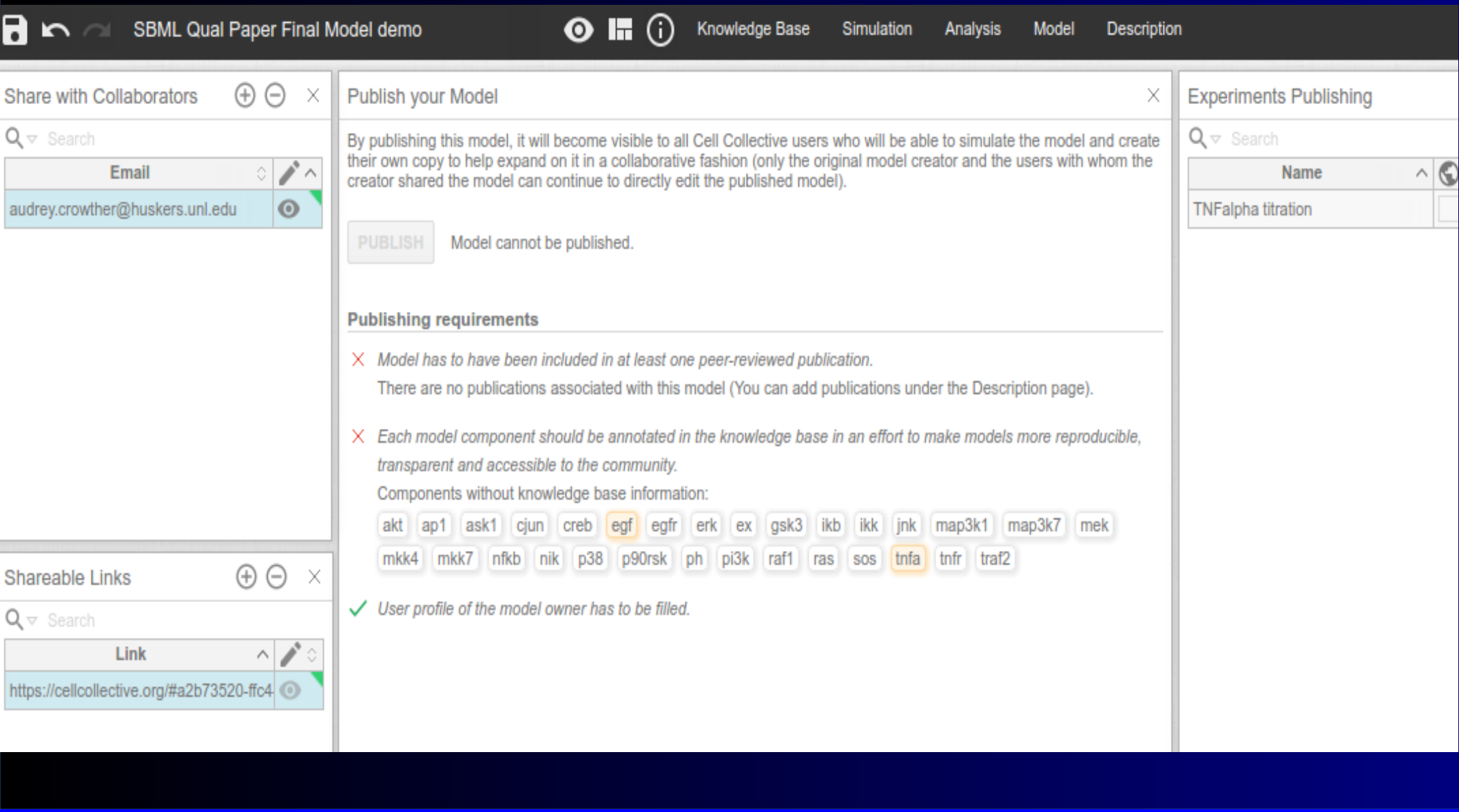
1. Hofbauer KH, Schoof E, Kurtz A, and Sandner P.*Inflammatory cytokines stimulate adrenomedullin expression through nitric oxide-dependent and -independent pathways.*Hypertension 2002 Jan39; (1) 161-7.pmid:11799096
2. Masoud GN and Li W.*HIF-1α pathway: role, regulation and intervention for cancer therapy.*Acta Pharm Sin B 2015 Sep5; (5) 378-89.pmid:26579469
3. Álvarez-Silva MC, Yepes S, Torres MM, and Barrios AF.*Proteins interaction network and modeling*

Reference Graph

Layout: *Default*



Cell Collective: Collaboration and Model Repository



Cell Collective: Collaboration and Model Repository

Published Models (76) | My Models (45) | Shared with Me (133)

RECENTLY PUBLISHED

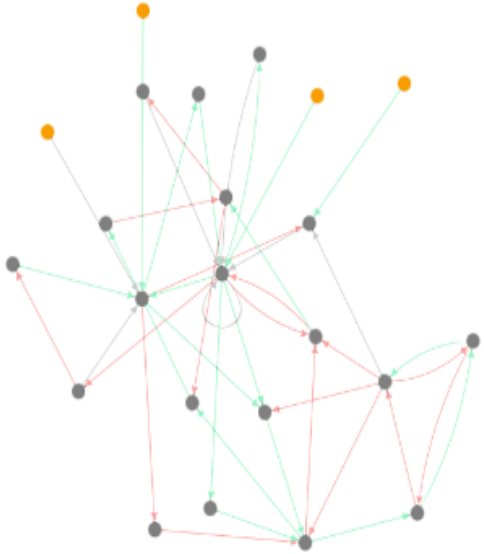
Mammalian Cell Cycle
version 1.0
Components: **20** Interactions: **51**

Author: **O Sahin et. al.**
Score: **51.1** Cited: **124**
Created: **10/19/2011** Updated: **6/7/2018**

T-LGL Survival Network 2011
version 1.0
Components: **60** Interactions: **195**

Author: **A Saddatpour et. al.**
Score: **30.0** Cited: **56**
Created: **6/2/2014** Updated: **6/5/2018**

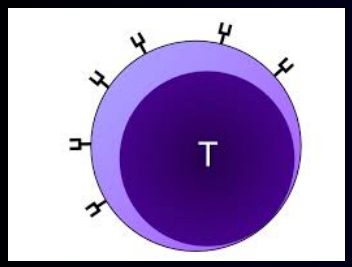
Aurora Kinase A in Neuroblastoma
version 1.0
Components: **23** Interactions: **43**

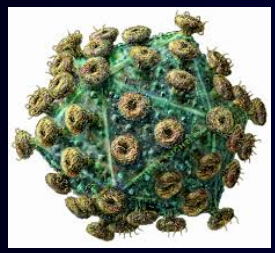


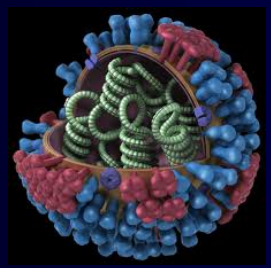
Author: **M Dahlhaus et. al.**
Score: **25.0** Cited: **0**
Created: **4/20/2017** Updated: **4/23/2018**

Yeast Apoptosis
version 1.0
Components: **73** Interactions: **114**

Author: **L Kazemzadeh et. al.**
Score: **48.0** Cited: **10**
Created: **6/4/2013** Updated: **4/18/2018**

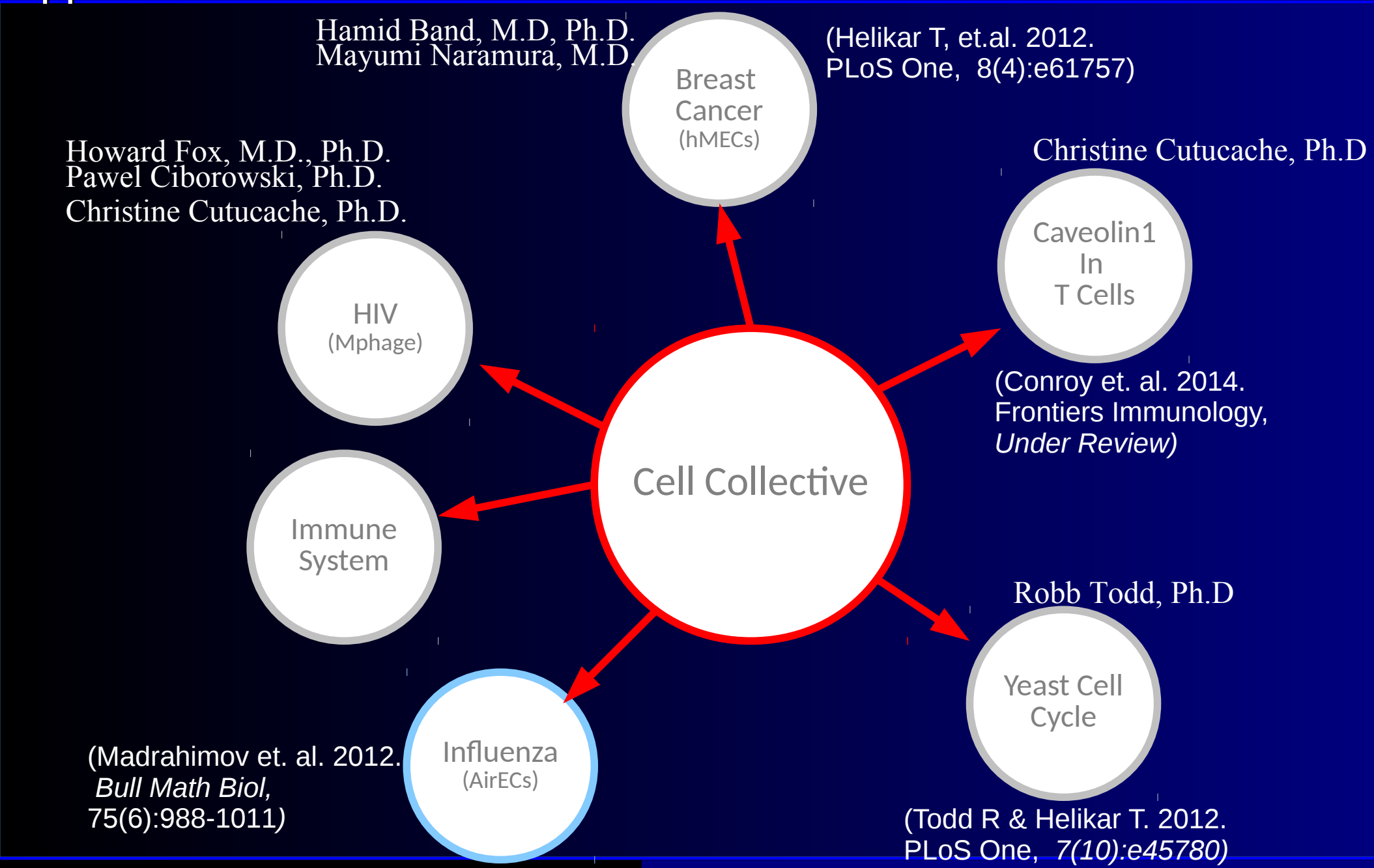




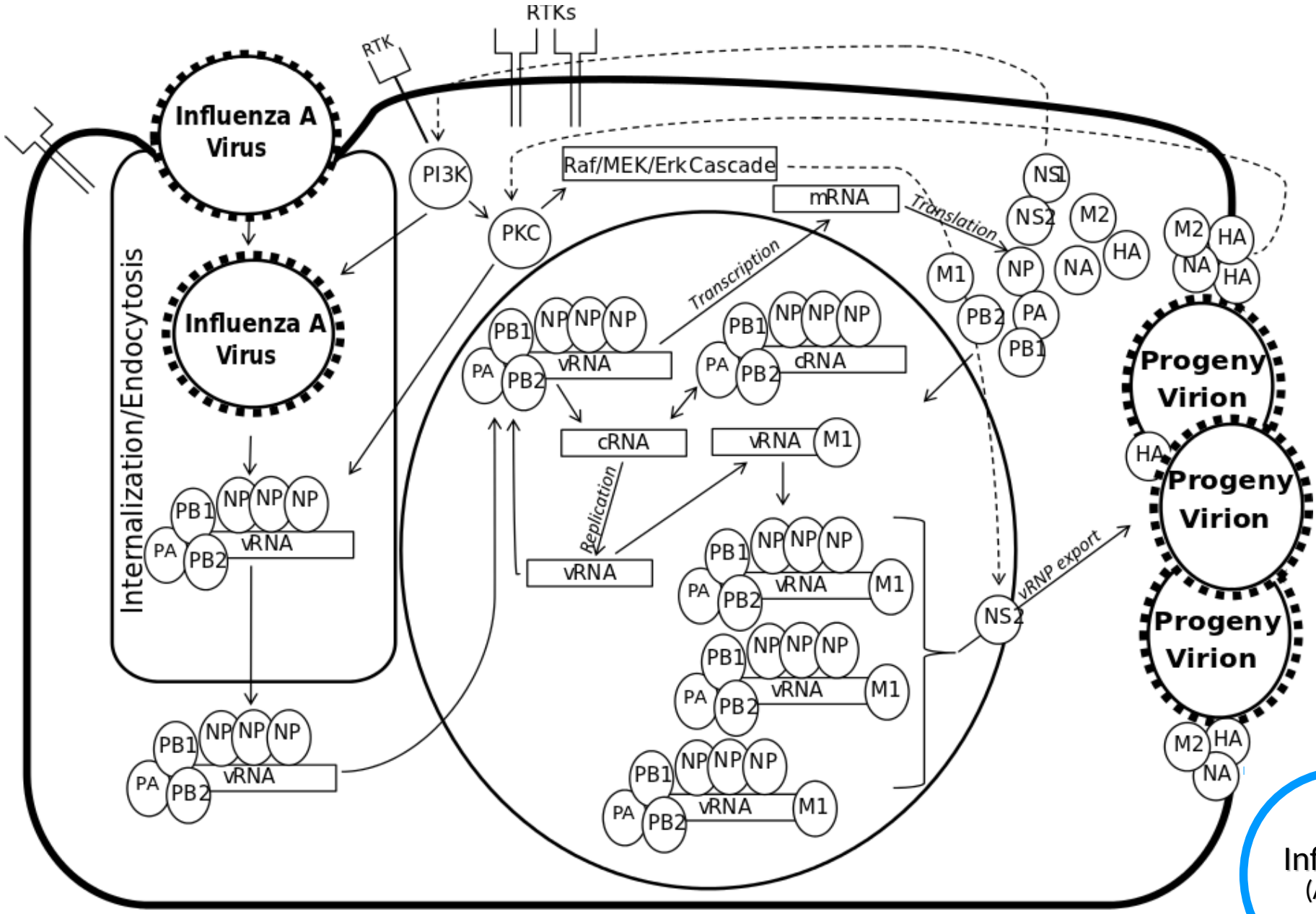


Example Case Studies

Applications and Case Studies

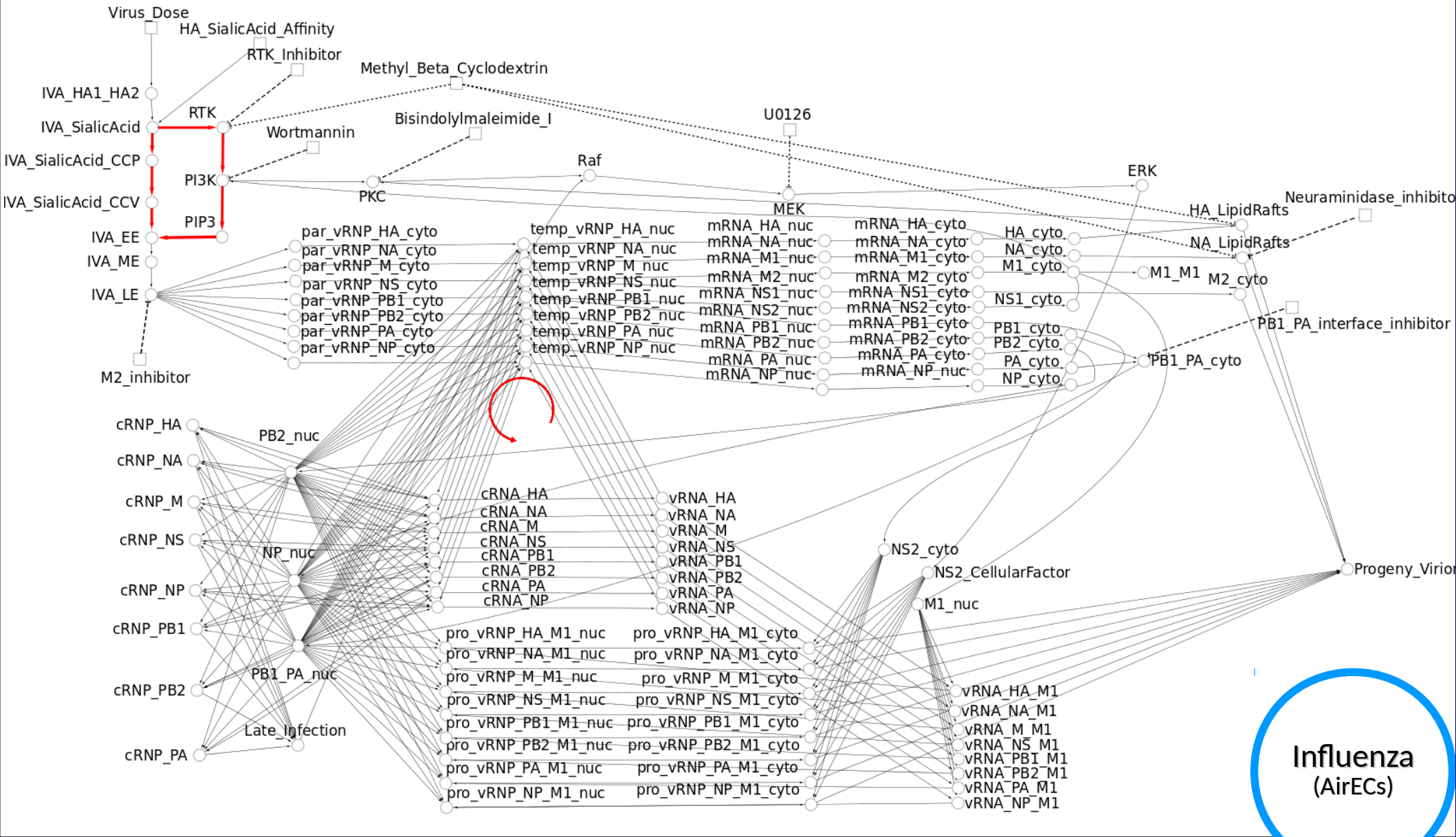


Influenza Infection Dynamics



(Madrahimov A et. al. 2013. *Bulletin of Mathematical Biology,* 2012. 75(6):988-1011)

Influenza Infection Dynamics



Influenza
(AirECs)

(Madrahimov A et. al. 2013. *Bulletin of Mathematical Biology,* 2012. 75(6):988-1011)

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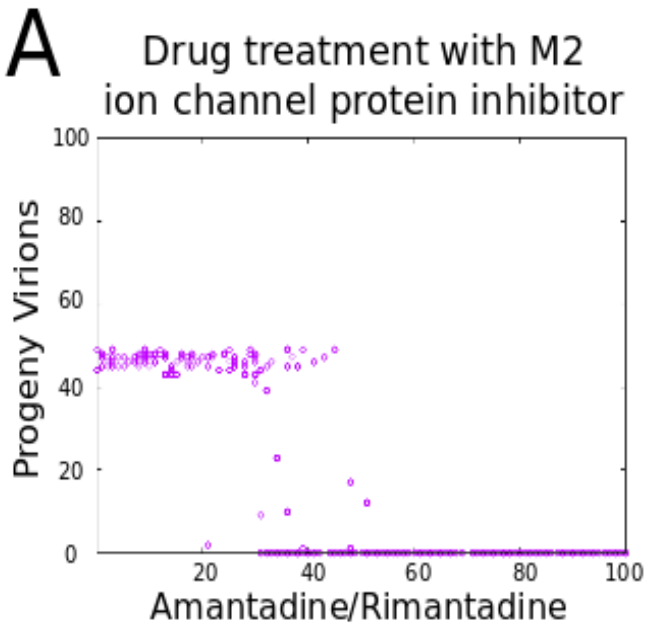
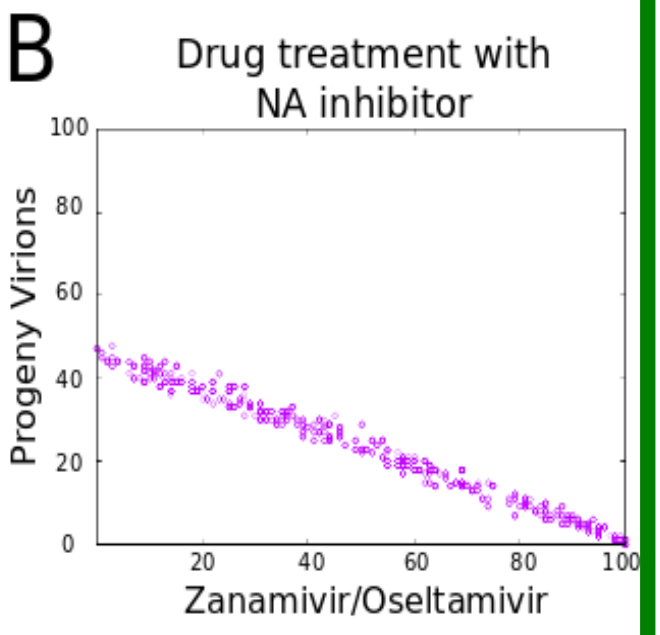
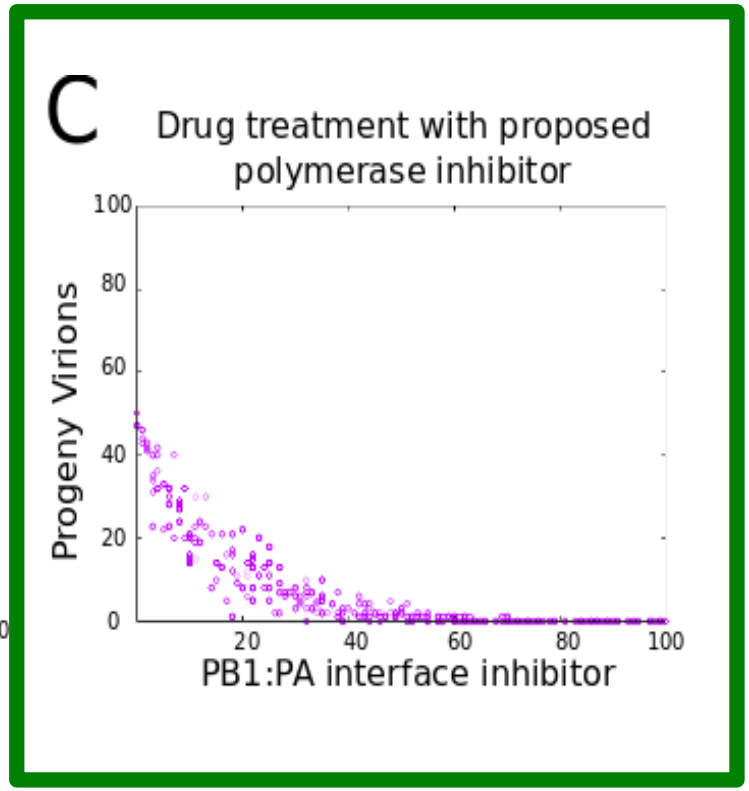






Progeny virion exit

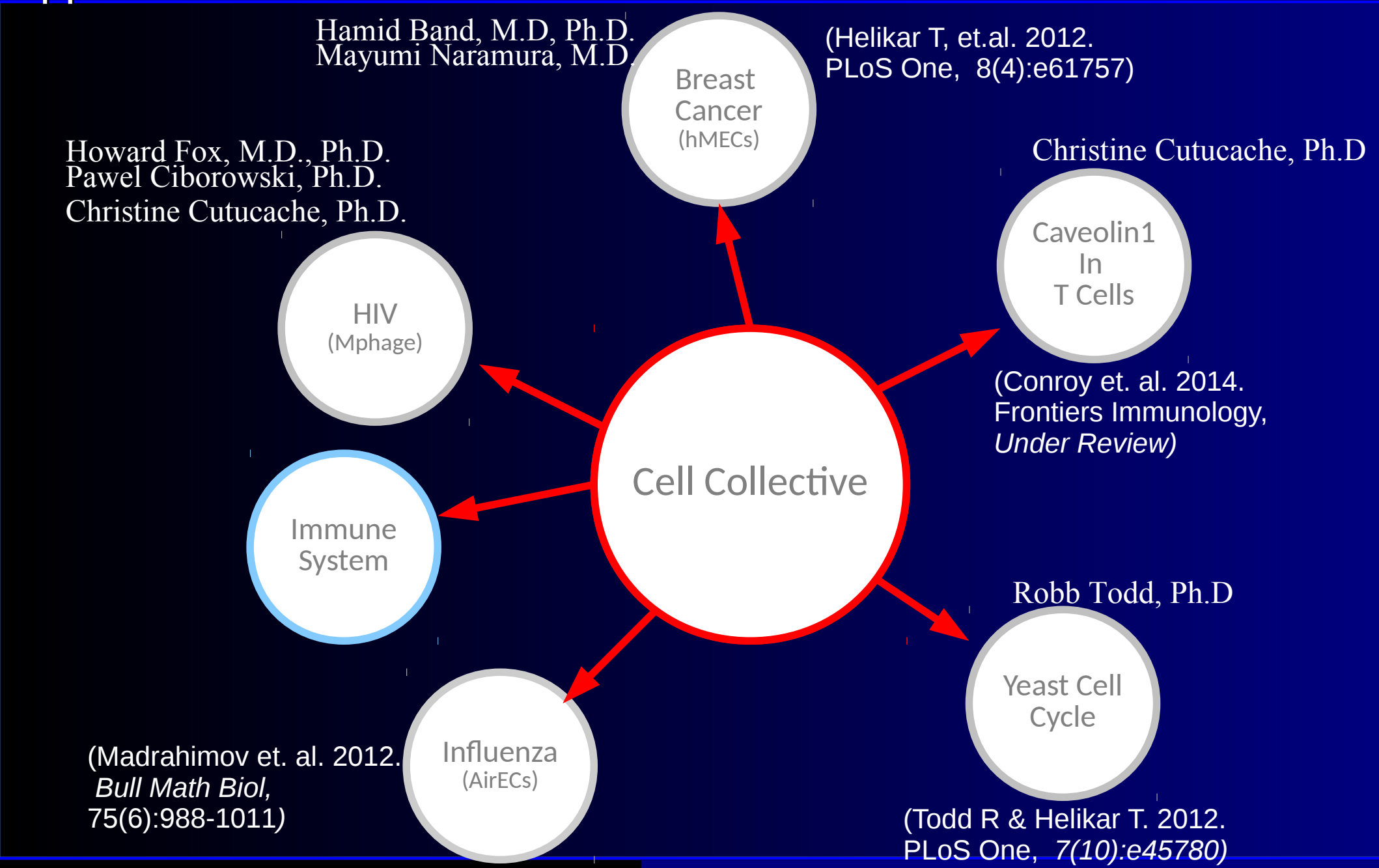
Virus entry

Viral replication

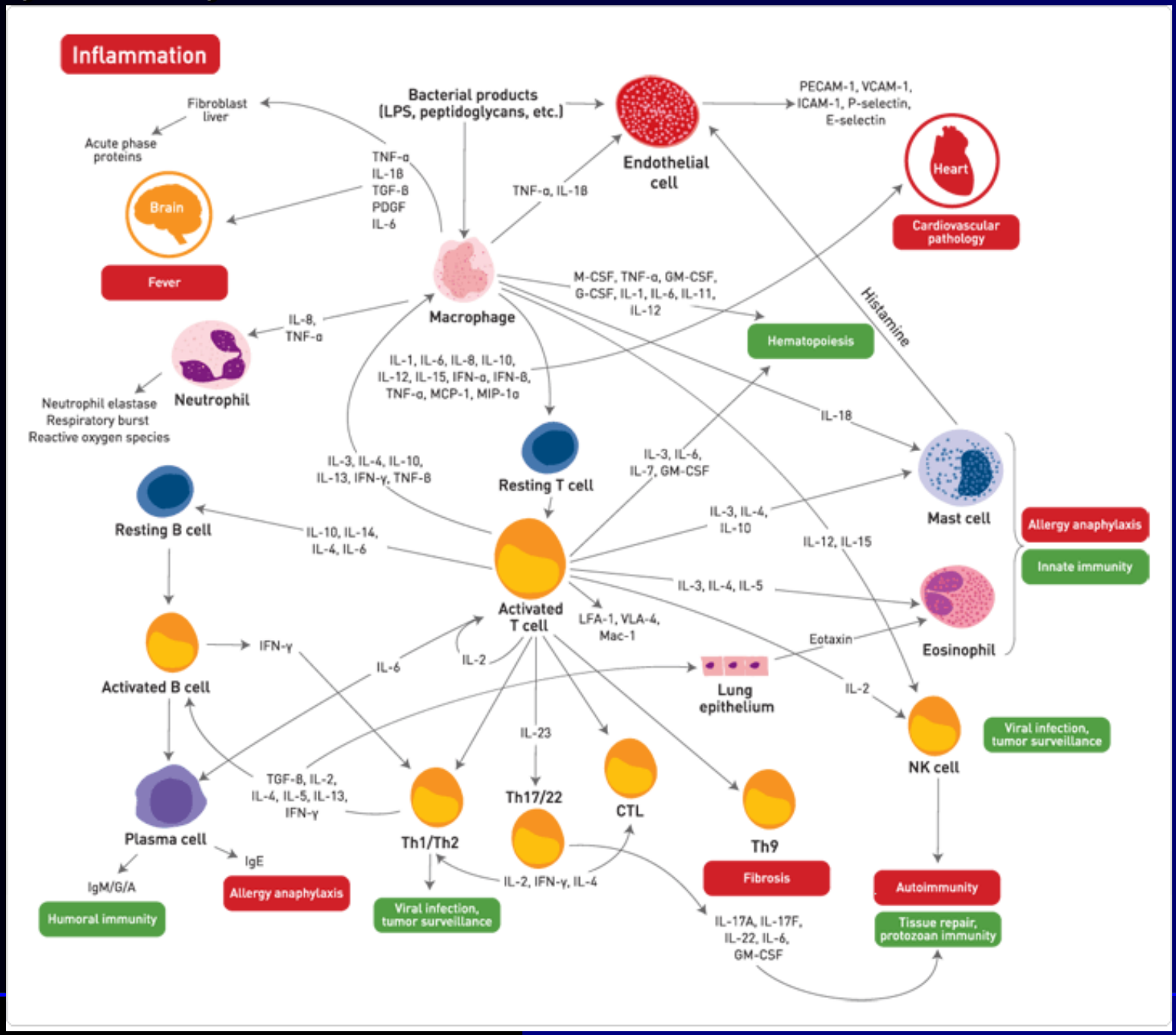
Influenza
(AirECs)

(Madrahimov A et. al. 2013. *Bulletin of Mathematical Biology,* 2012. 75(6):988-1011)

Applications and Case Studies



Immune system dynamics



Comprehensive Computational Model of the Immune System

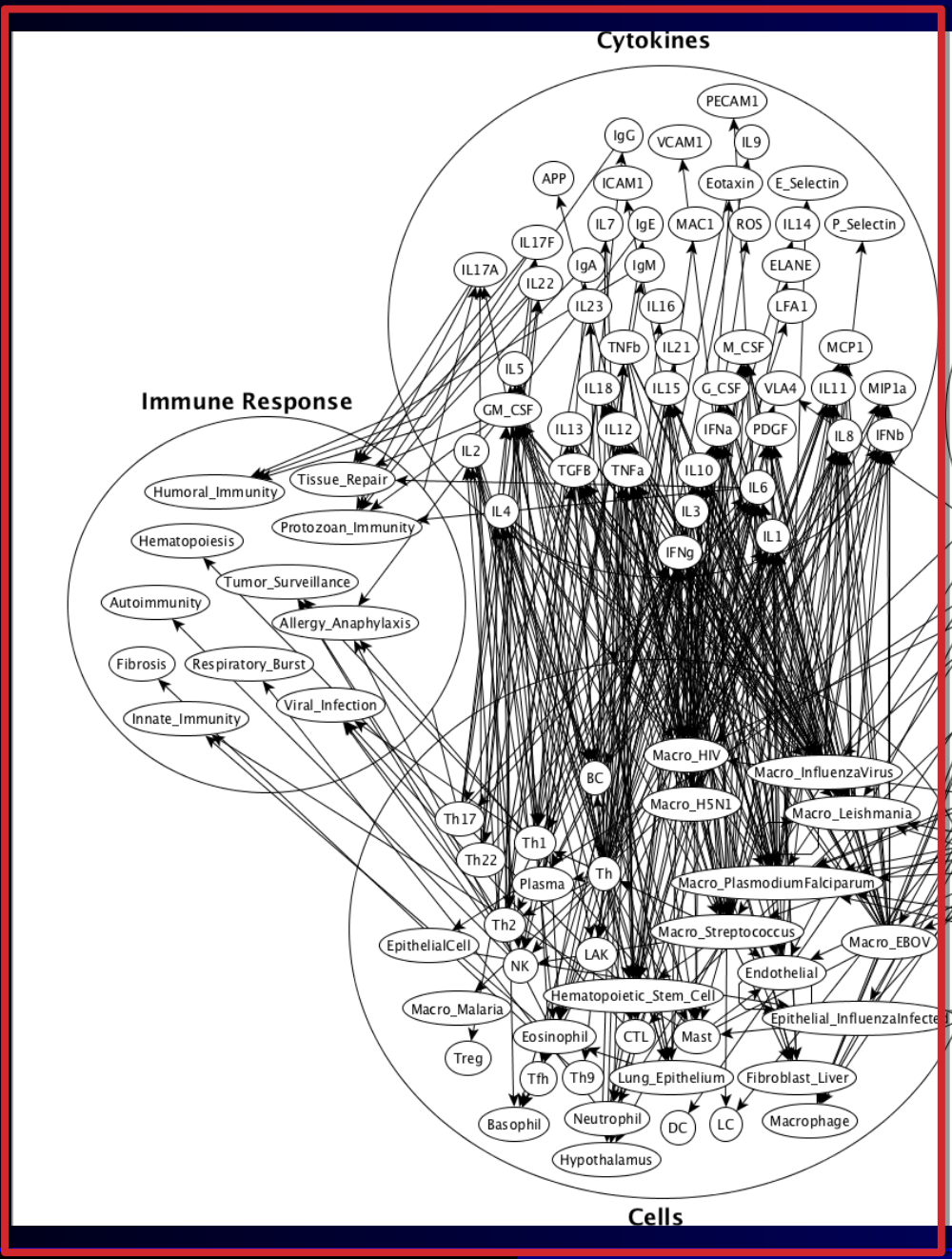
* 164 Components
* 9 Pathogens:

Mtb
Helminth
Influenza
Ebola
HIV
HPV
Leishmania
Candida Albicans
Plasmodium Falc

* 35 Cytokines
* 26 Cell types

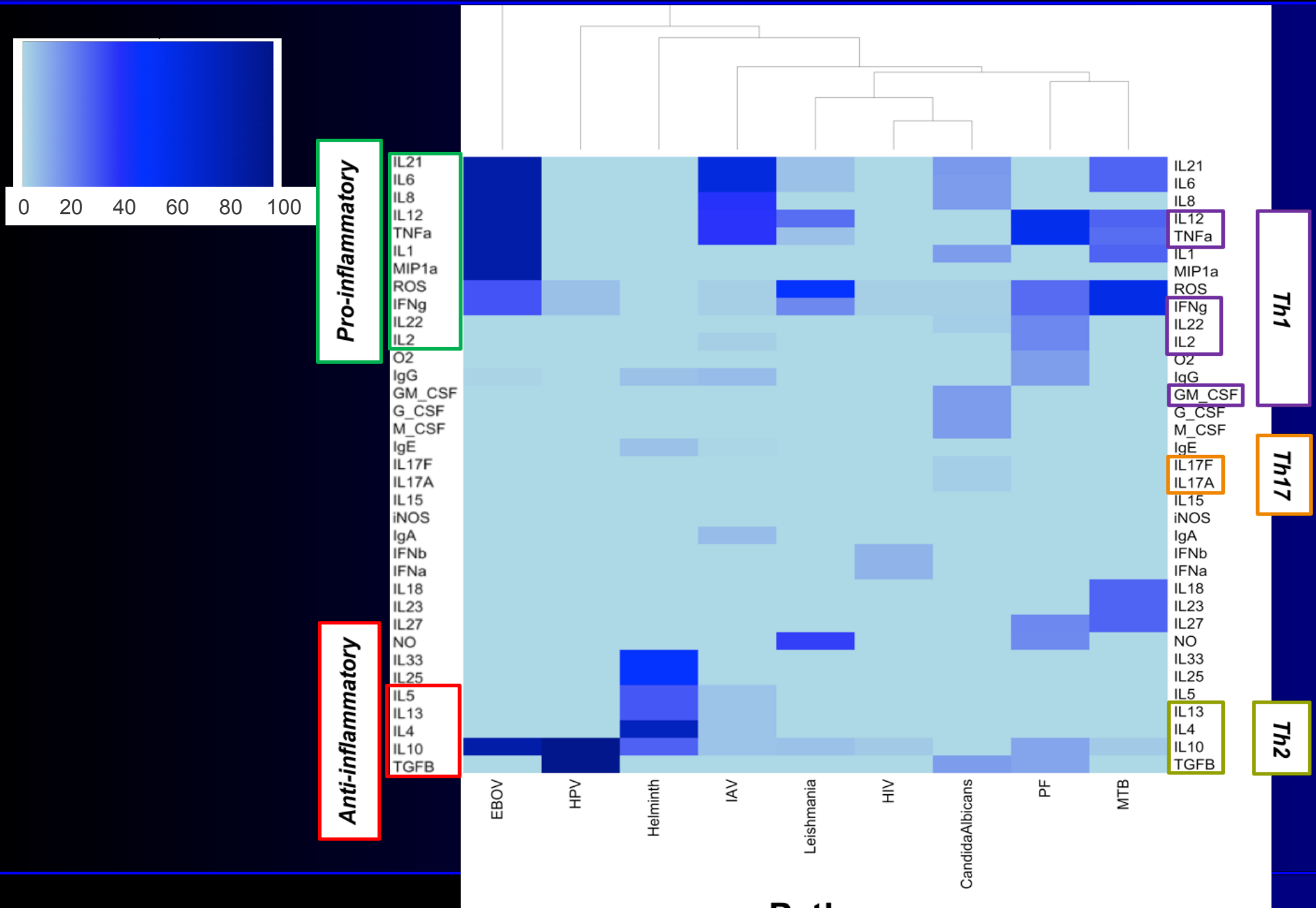
* 506 interactions

* 224 papers



Mohammed., et al. In Preparation

Model Simulations



Comprehensive Computational Model of the Immune System - validation

Infectious Agent	Cell Target	Immune Response	Reference
HIV	DCs, Macrophages, CD4 T	Th1, Th2, CD8+	*Banks et al. 2008*
HPV	Keratinocytes	Th1, CD8+	*Scott et al. 2001*
Ebola	Dendritic Cells, Macrophages, Monocytes	Th1, Th2, CD8+, IgG	*Le Roy et al. 2001*
Influenza A virus	Epithelial, Dendritic	Th1, Th2, CD8+, IgA, IgG, IgM	*Ada et al. 1986*
Mycobacterium tuberculosis	Macrophages, Neutrophils	Th1, CD8+	*O'Garra et al. 2013*
Helminth	Endothelial, Epithelial, Macrophages, NKT	Th2, IgE, IgG	*Gause et al. 2003*
Plasmodium	Erythrocytes	Th1, IgE, IgG	*Malaguarnera et al. 2002*
Leishmania	DCs, Mac, Monocytes, Neutrophil, NK	Th1, IgE	*Awasthi et al. 2004*

Mohammed., et al. In Preparation

Applications and Case Studies

Hamid Band, M.D, Ph.D.
Mayumi Naramura, M.D.

Breast Cancer (hMECs)

(Helikar T, et.al. 2012. PLoS One, 8(4):e61757)

Howard Fox, M.D., Ph.D.
Pawel Ciborowski, Ph.D.
Christine Cutucache, Ph.D.

HIV (Mphage)

Christine Cutucache, Ph.D

Caveolin1 In T Cells

(Conroy et. al. 2014. Frontiers Immunology,

Front Physiol. 2018; 9: 878.
Published online 2018 Aug 2. doi: 10.3389/fphys.2018.00878
PMCID: PMC6083813
PMID: 30116195

A Mechanistic Computational Model Reveals That Plasticity of $CD4^+$ T Cell Differentiation Is a Function of Cytokine Composition and Dosage

Bhanwar Lal Puniya,[1] Robert G. Todd,[2,*] Akram Mohammed,[1] Deborah M. Brown,[3,4] Matteo Barberis,[5,6,*] and Tomáš Helikar[1,*]

(Madrahimov et. al. 2012. *Bull Math Biol,* 75(6):988-1011)

Influenza (AirECs)

(Todd R & Helikar T. 2012. PLoS One, *7(10):e45780)*

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Christine Cutucache, Ph.D

Caveolin1 In T Cells

HIV

ORIGINAL RESEARCH ARTICLE

Front. Bioeng. Biotechnol., 11 February 2016 | http://dx.doi.org/10.3389/fbioe.2016.00010

CrossMark

Systems Perturbation Analysis of a Large-Scale Signal Transduction Model Reveals Potentially Influential Candidates for Cancer Therapeutics

Influenza (AirECs)

(Madrahimov et. al. 2012. *Bull Math Biol,* 75(6):988-1011)

Cycle

(Todd R & Helikar T. 2012. PLoS One, *7(10):e45780)*

Applications and Case Studies

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Christine Cutucache, Ph.D.

Christine Cutucache, Ph.D

Caveolin1 In T Cells

ORIGINAL RESEARCH ARTICLE

Front. Immunol., 05 December 2014 | http://dx.doi.org/10.3389/fimmu.2014.00599

Design, assessment, and *in vivo* evaluation of a computational model illustrating the role of CAV1 in CD4$^+$ T-lymphocytes

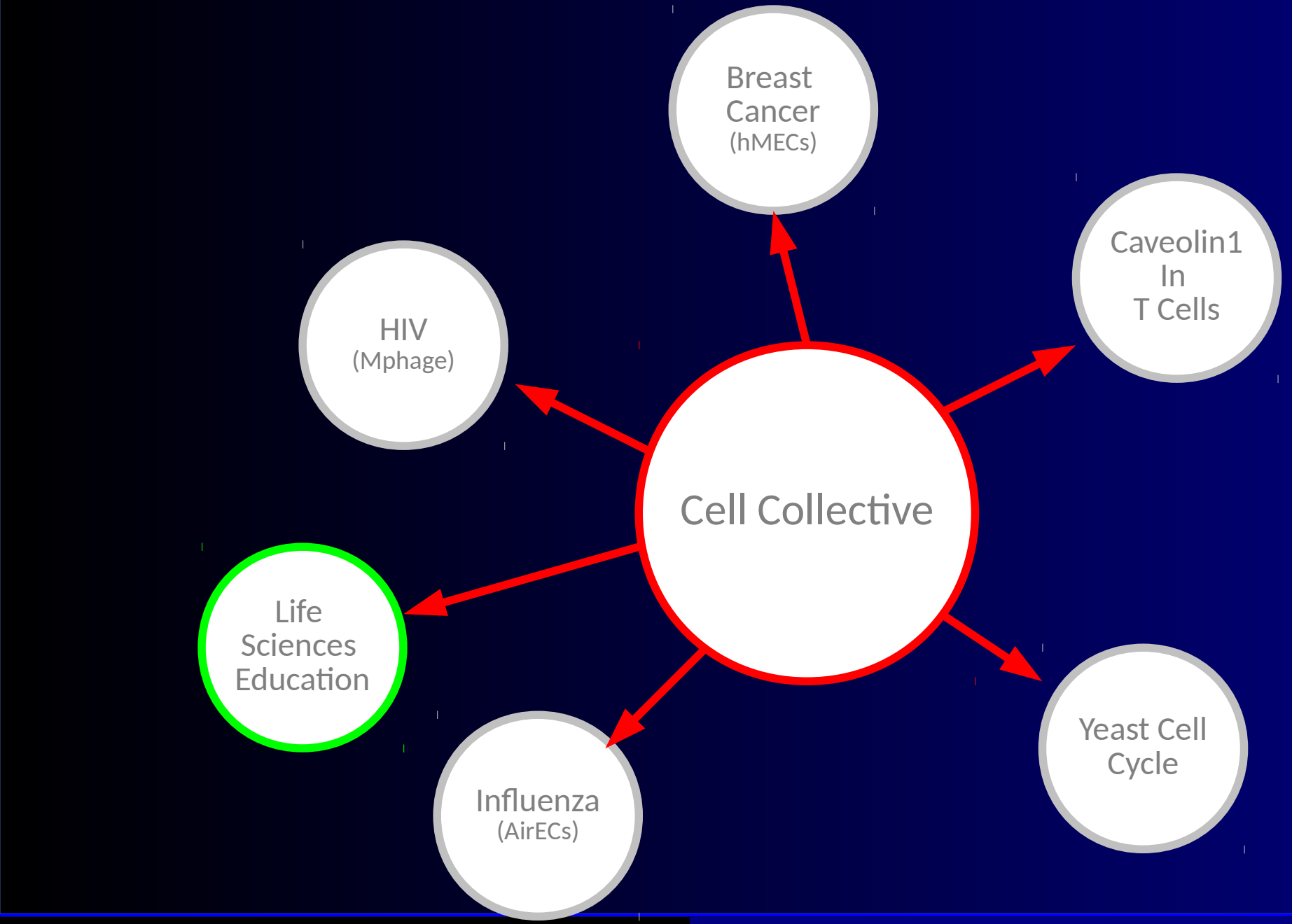
Brittany D. Conroy[1†], Tyler A. Herek[1†], Timothy D. Shew[1†], Matthew Latner[1], Joshua J. Larson[1], Laura Allen[1], Paul H. Davis[1], Tomáš Helikar[2] and Christine E. Cutucache[1*]

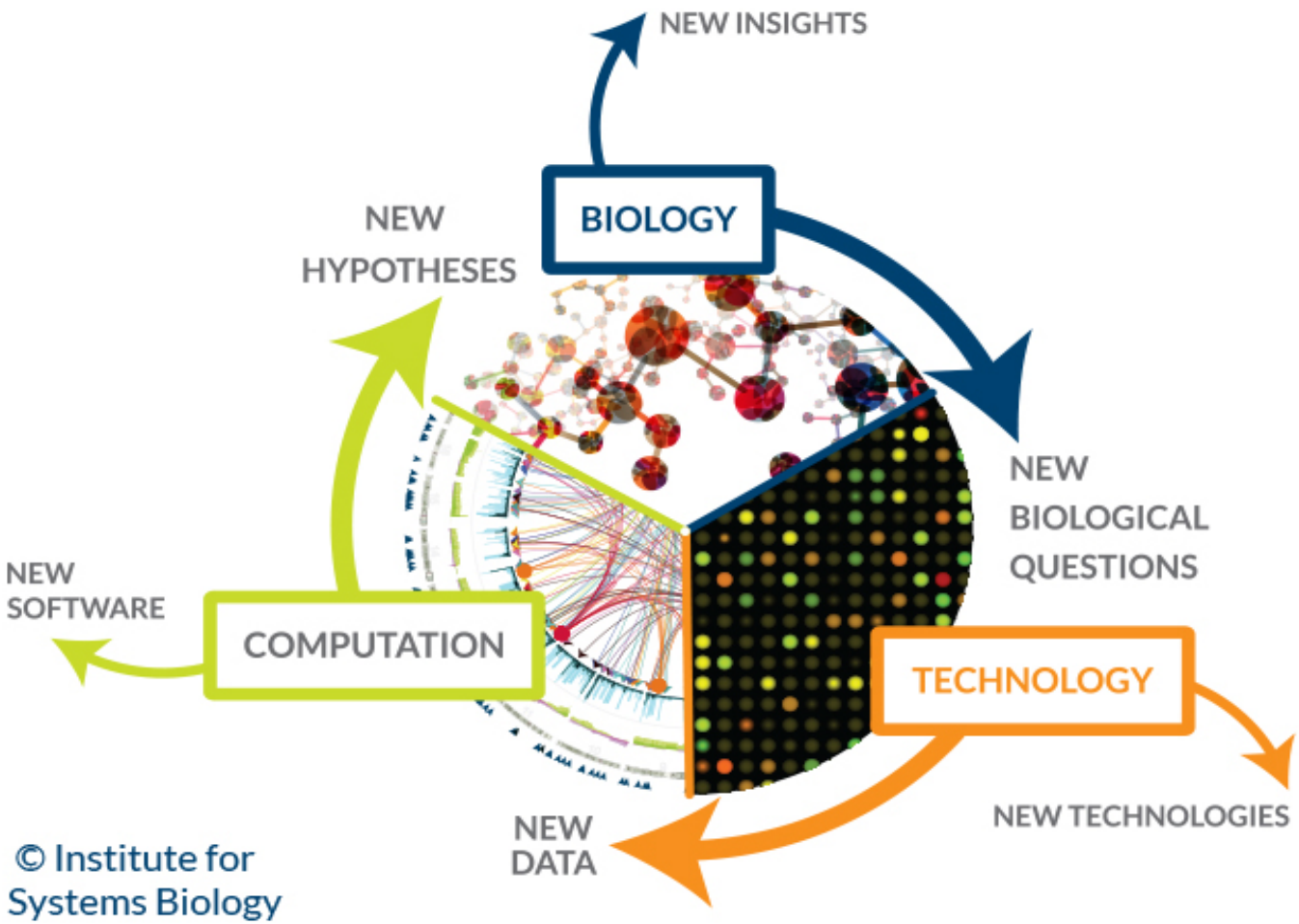
(Madrahimov et. al. 2012. *Bull Math Biol,* 75(6):988-1011)

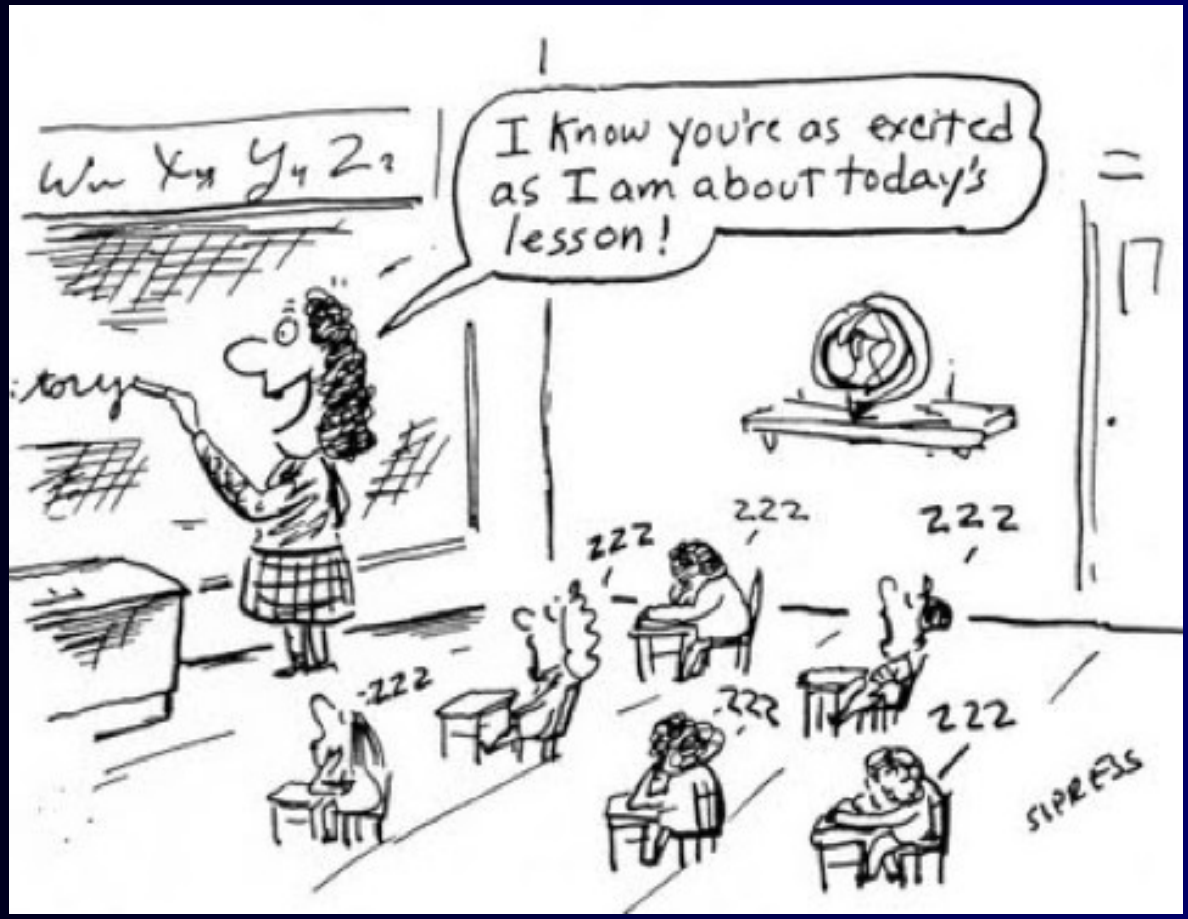
Influenza (AirECs)

(Todd R & Helikar T. 2012. PLoS One, *7(10):e45780)*

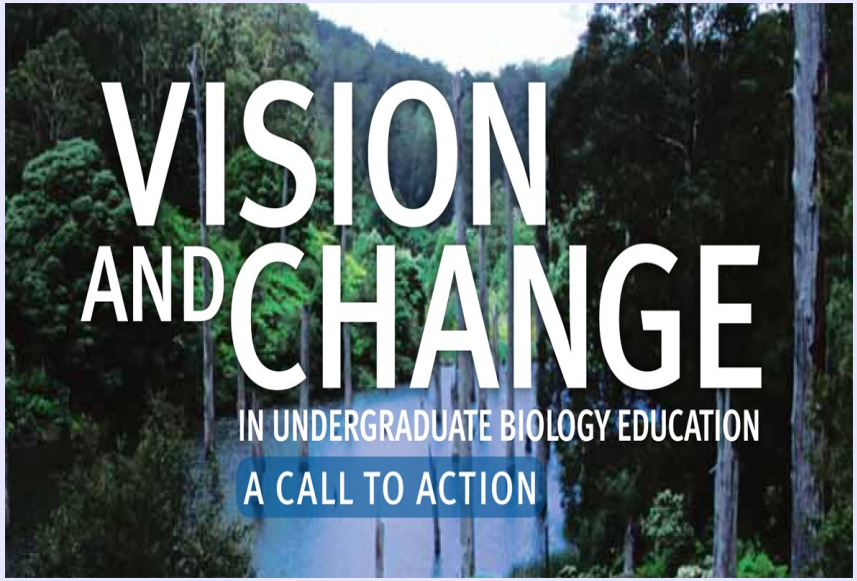
Computational biology in complex networks




NEW INSIGHTS
BIOLOGY
NEW HYPOTHESES
NEW BIOLOGICAL QUESTIONS
NEW SOFTWARE
COMPUTATION
TECHNOLOGY
NEW TECHNOLOGIES
NEW DATA
© Institute for Systems Biology



Stains et. al. Science. 2018



NEXT GENERATION SCIENCE STANDARDS

Core Concepts

- **Systems**
- Structure and function
- Information flow, exchange, storage
- Evolution
- Pathways and transformation of energy and matter

Core Competencies

- **Modeling, simulations, computational, and systems-level approaches to discovery and analysis**
- Process of science
- Quantitative reasoning
- Interdisciplinary communication and collaboration
- Science and Society

AAAS, 2011

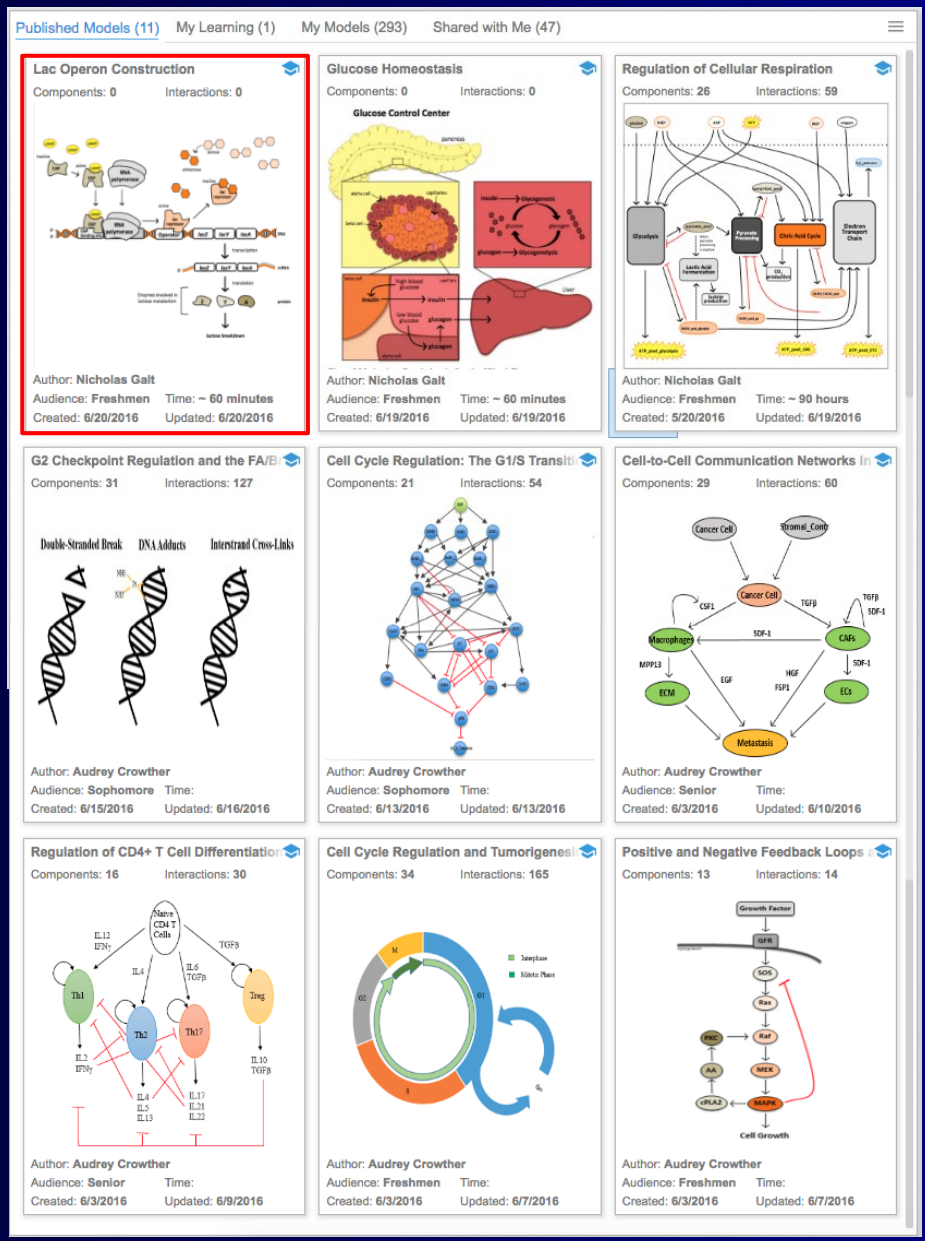
Broad application

Activity Types

- Concept Maps
- Simulation and investigation of pre-constructed models
- Model Construction and Simulation

Key Design Features

- Self-contained
- Simple, turn-key implementation
- Predict/observe/explain scenarios
- Assessible
- Modular implementation
  - Laboratory activity
  - Homework
  - In-class activity



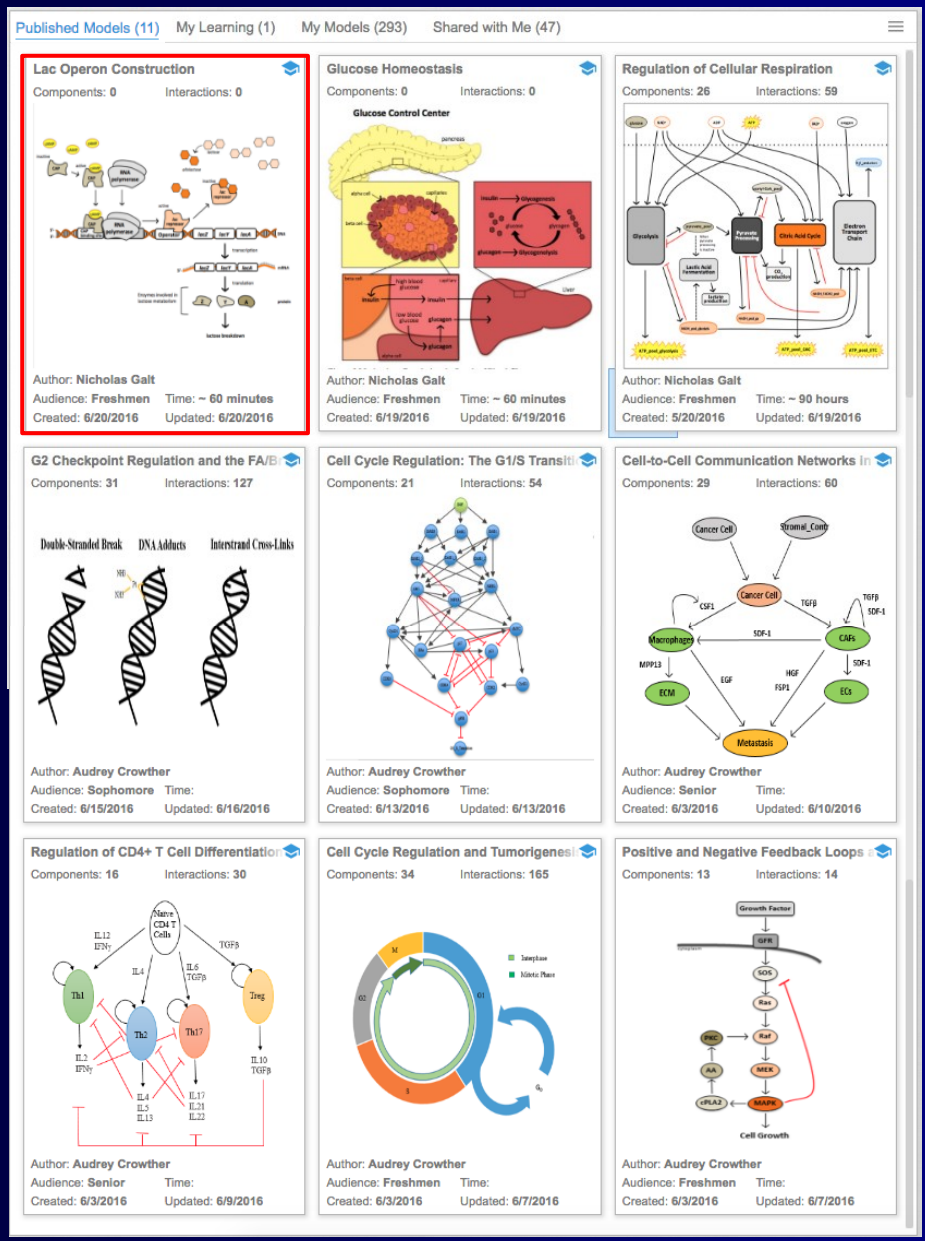
Broad application

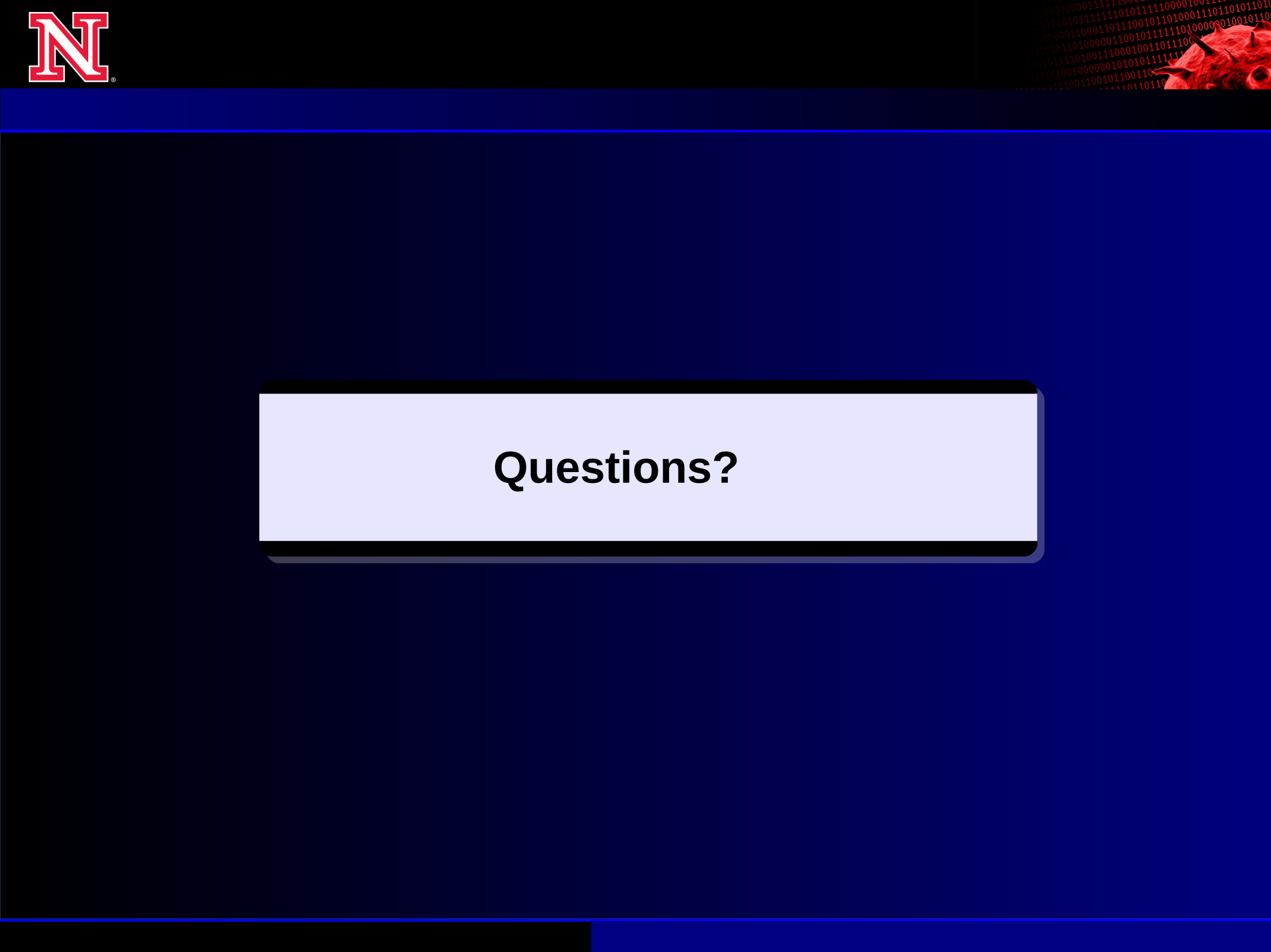
Topics

- Cell respiration
- Glucose homeostasis
- Cell cycle
- Photosynthesis
- Gene regulation
- Food web dynamics

Courses

- Biochemistry
- Intro biology courses
- Immunology
- Cancer Biology
- Many others




Questions?

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