Cell Collective: A Collaborative Approach to Logical Models

by

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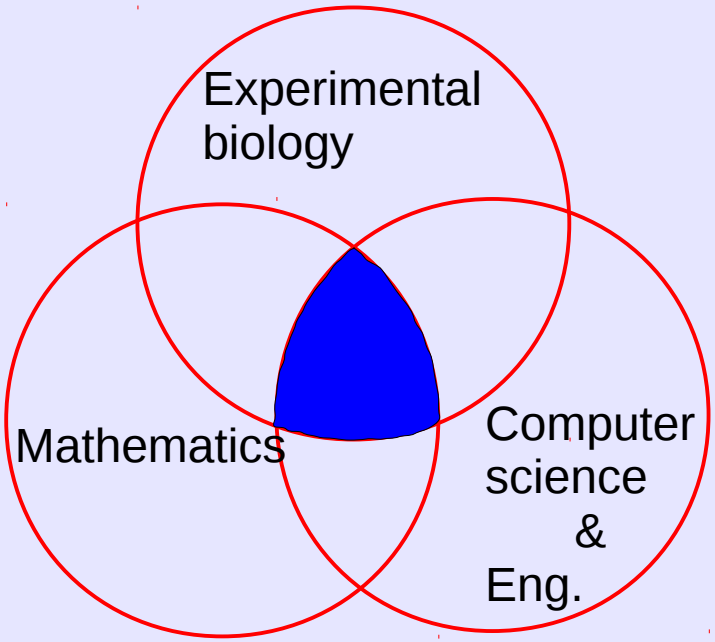
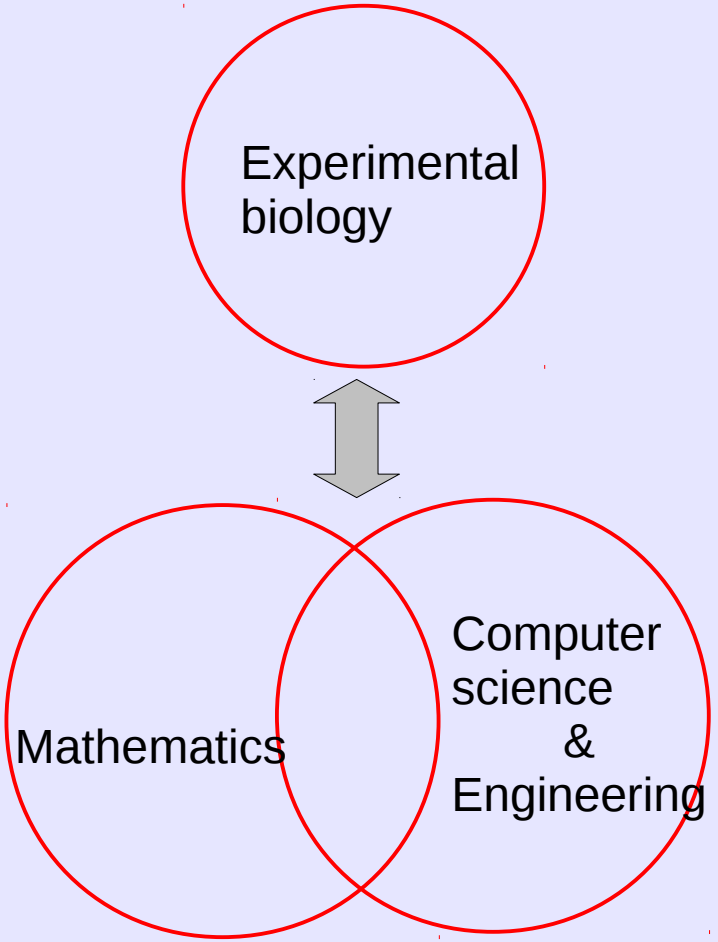
Systems Biology

The “Ideal” Systems Biology



Current state of Systems Biology



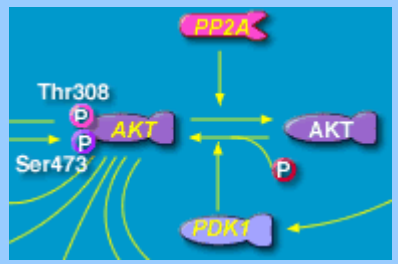
Logical models can be cumbersome to define manually

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

"Biologist friendly" collaborative software platform.

Bio-logic Builder

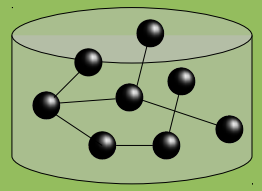
Biology



Boolean Functions

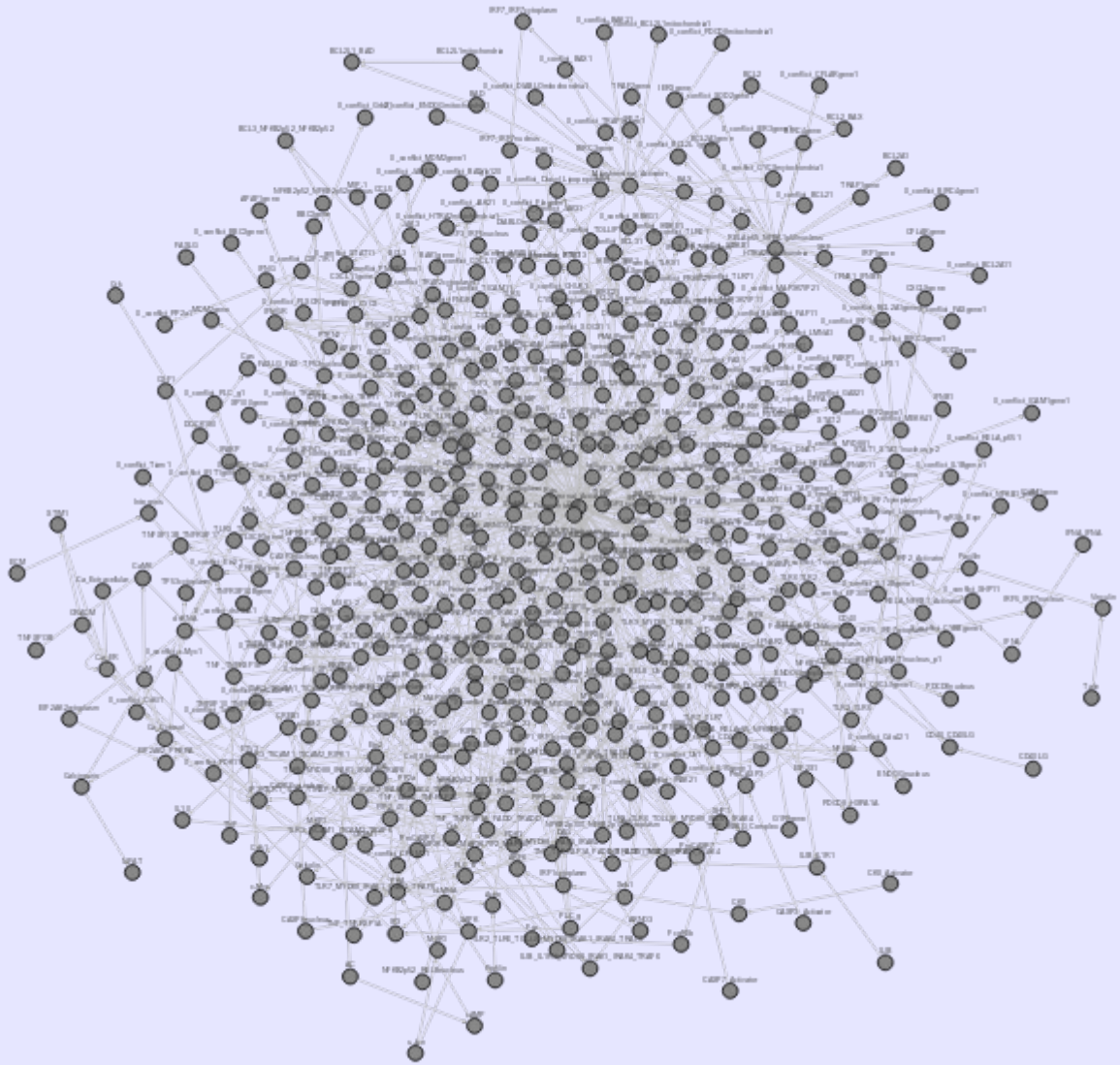
Node2 = !Node 4 + Node 1

Logical Models



(Helikar et. al. 2012.Bio-Logic Builder: A non-technical tool for building dynamical, qualitative models. *PLoS One 7(10): e46417*)

Model of Macrophage signaling & gene transcription



- ~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)

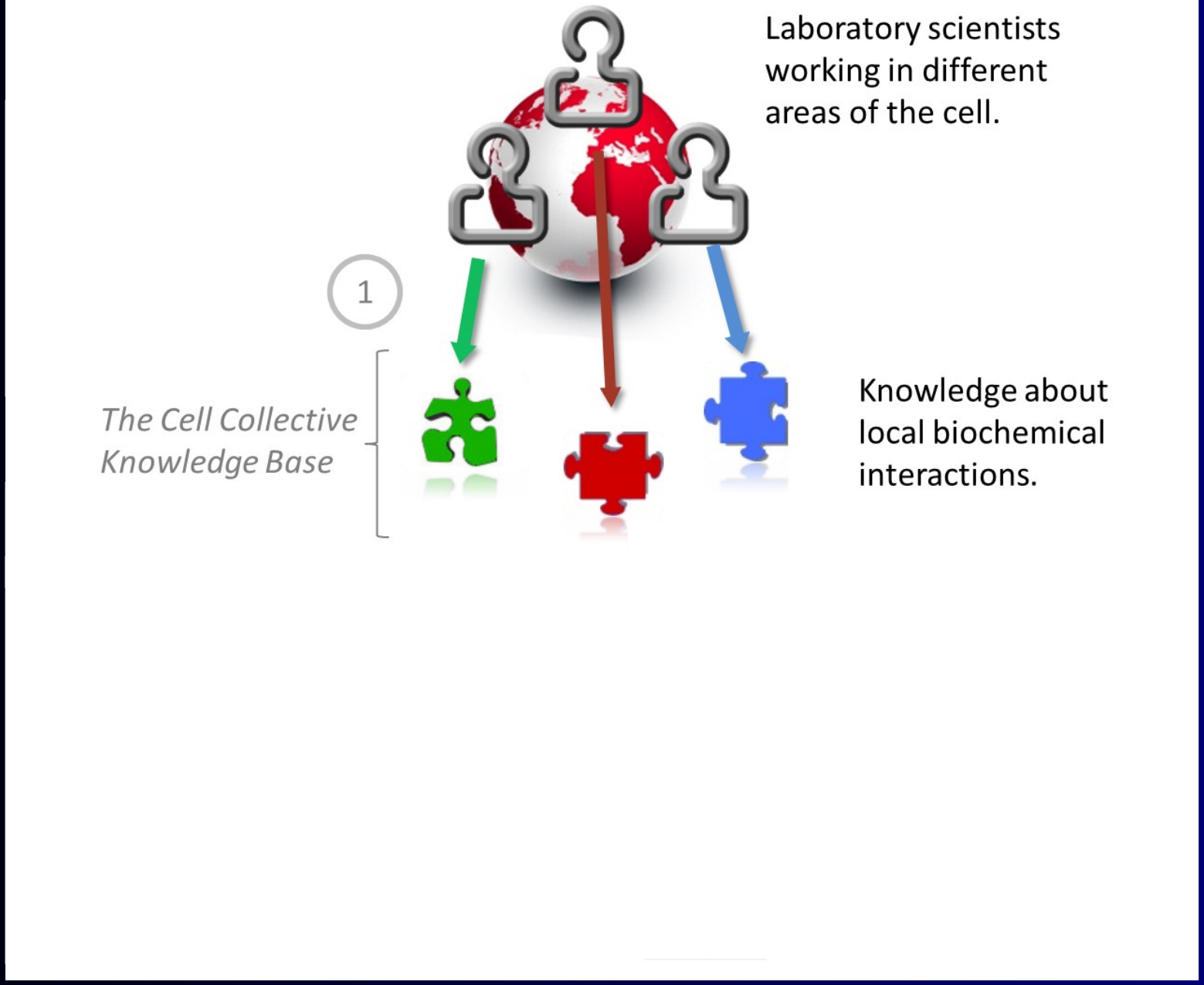
The Cell Collective

(http://www.thecellcollective.org)

"Biologist-friendly" collaborative platform for logical models.

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

Cell Collective Overview



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Erk

Regulatory Mechanism Summary [edit]

Mek activates Erk [24, 76, 36, 75, 28, 11, 12, 46, 53, 32, 42, 56, 57, 10, 30, 58, 74, 48, 50, 23, 38, 69, 35, 29, 22, 60, 44, 1, 49, 51, 67]. PP2A is a negative regulator [54, 43, 6, 48, 32, 44, 65, 73, 66, 16, 39] MKPs are negative regulators [54, 30, 64, 32, 65, 73, 38, 20, 29, 9, 59]. As far as dominance; if Erk is ON, then Mek is dominant to the negative regulators. If Erk is OFF, Mek is also dominant. If Erk is ON and everything else[pos. and negative] is OFF, Erk stays ON by itself.

Upstream Regulators

Erk [edit]

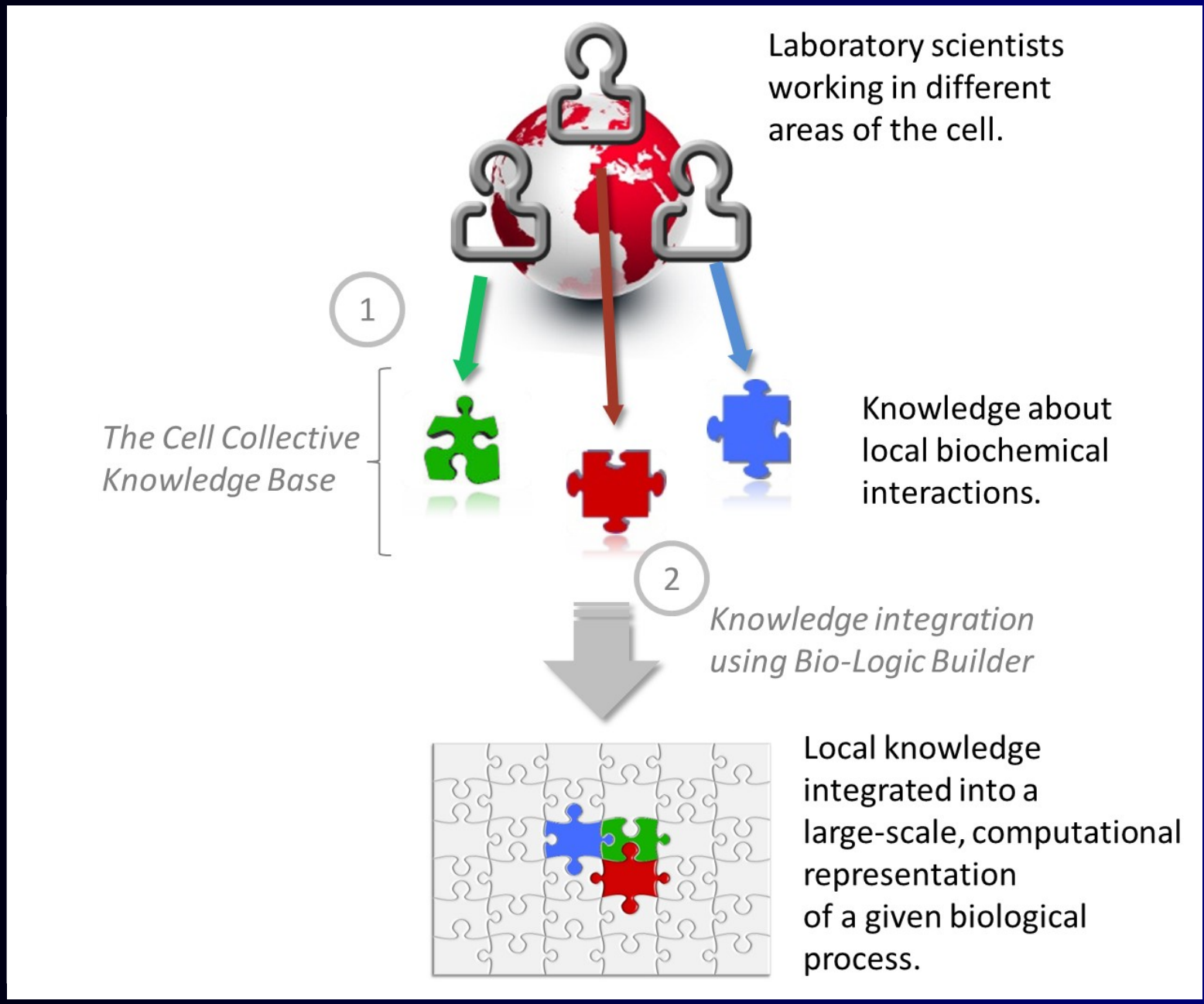
Mek [edit]

* MEK as an upstream of Erk {[24]-p(2-Fig. 1), [76]-p(3), [36]-p(5-Fig. 1), [75]-p(2-Fig. 1), [28]-p(5-Fig. 1), [11]-p(3-Fig. 1), [12]-p(1), [46]-p(1), [53]-p(3-Fig. 2), [32]-p(480, 483), [42]-p(41-Fig.6), [56]-p(2-Fig. 1), [57]-p(3)}
* Erk is phosphorylated by MEK {[10]-p(6), [30]-p(1), [58]-p(2), [74]-p(161), [48]-p(100), [50]-p(2), [23]-p(2), [38]-p(1), [69]-p(1), [35]-p(276), [29]-p(2)}
* Erk's threonine and tyrosine residues are phosphorylated by MEK {[22]-p(1)}
* MEK1/2 stimulates Erk. {[60]-p(822)}
* MEK is an immediate upstream activator of Erk {[44]-p(4), [1]-p(234)}
* Erk1/2 is phosphorylated and activated by MEK1/2 {[49]-p(1), [51]-p(2-Fig. 1), [67]-p(1), [9]-p(187-Fig. 1), [26]-p(357)}
* Mek1 and Mek2 are upstream phosphorylators and activators of Erk1 and Erk2. {[20]-p(1)}
* Erk binds to MEK-1. {[20]-p(5)}
* MEK is a dual specifcity kinase that phosphorylates (activates) Erk {[55]-p(1,2), [33]-p(322)}
* Mek phosphorylates and stimulates Erk. {[34]-p(1)}
* MEK specifically activates Erk {[68]-p(2), [29]-p(2)}
* Mek1 and inactivator MKP3 bind to same site on Erk2. {[25]-p(198)}
* Only Mek1 and Mek2 can activate Erk2. {[25]-p(200)}
* Mek1/2 phosphorylates and activates Erk. {[52]-p(2, 3)}
* Raf promotes phosphorylation of Mek, which in turn is required to activate Erk by phosphorylation. {[16]-p(1)}
* MEK phosphorylates Erk, which leads to its activation {[3]-p(1)}
* Raf propagates signals by activation the dual specifity kinase Mek1, which in turn activates Erk1/2. {[70]-p(1)}

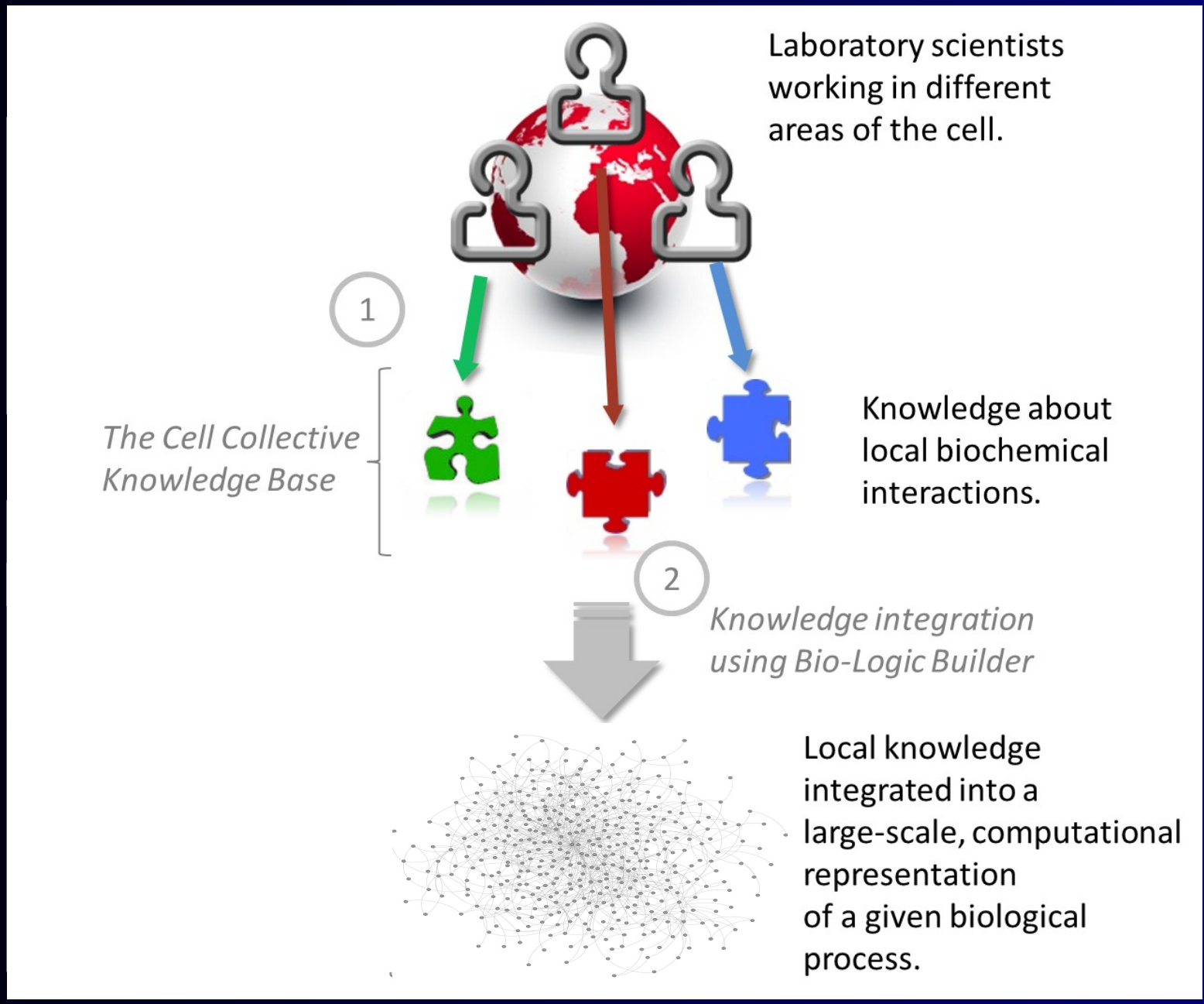
MKPs [edit]

* MKPs are upregulated upon Erk's activation and forms a negative feedback loop. {[54]-p(3, 4)} Q:Do PP2A and MKPs both have to be

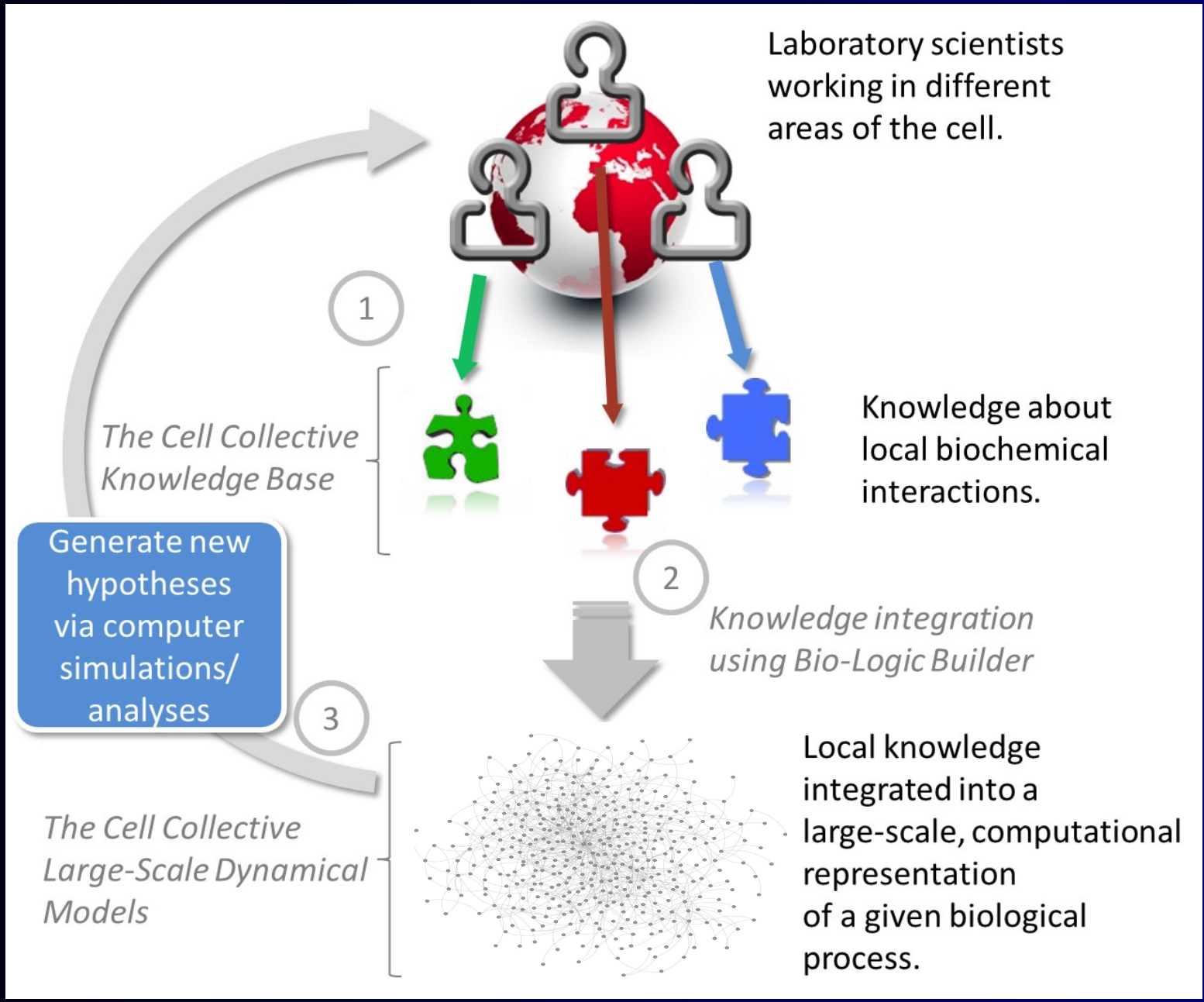
Cell Collective Overview



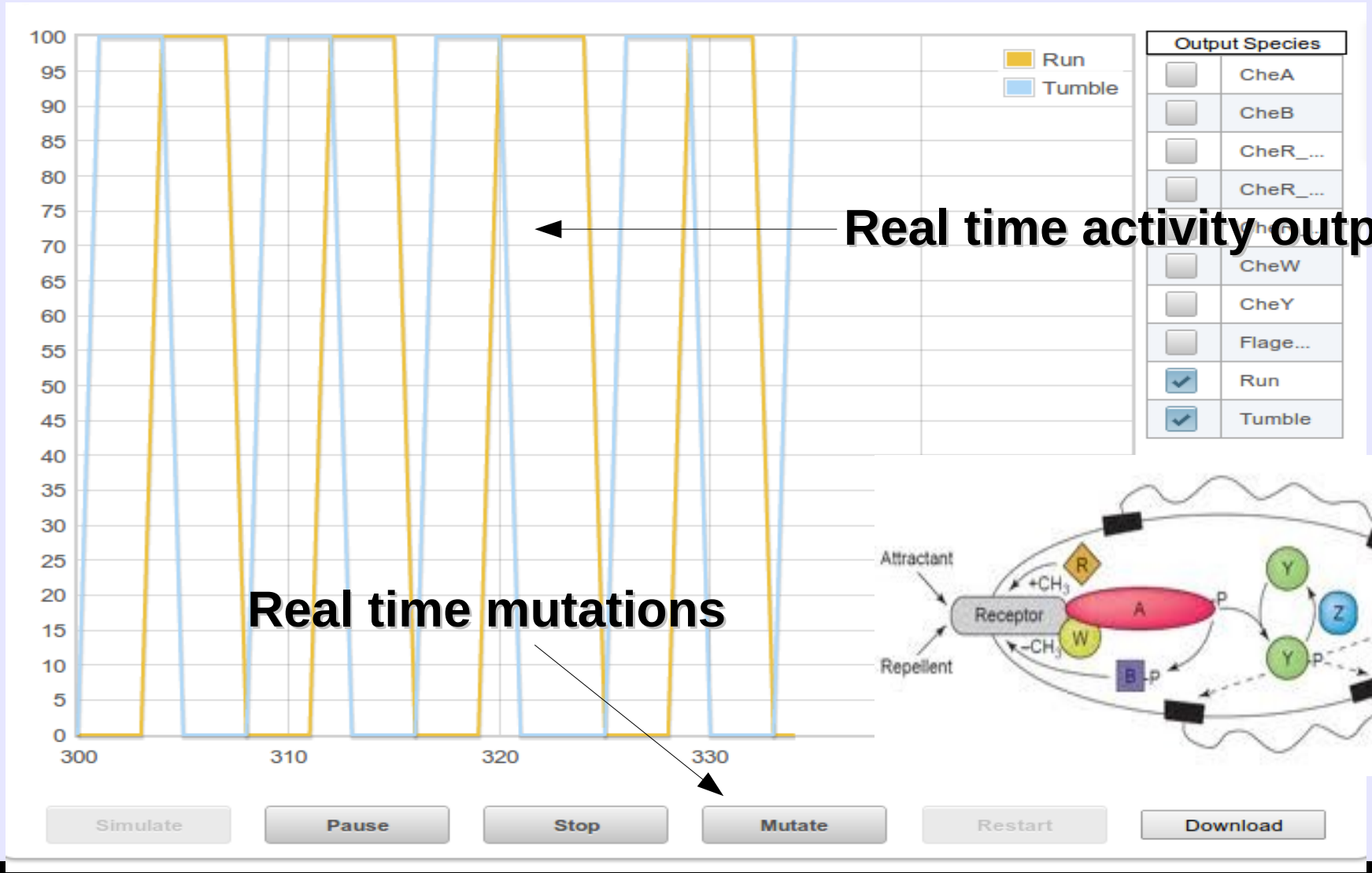
Cell Collective Overview



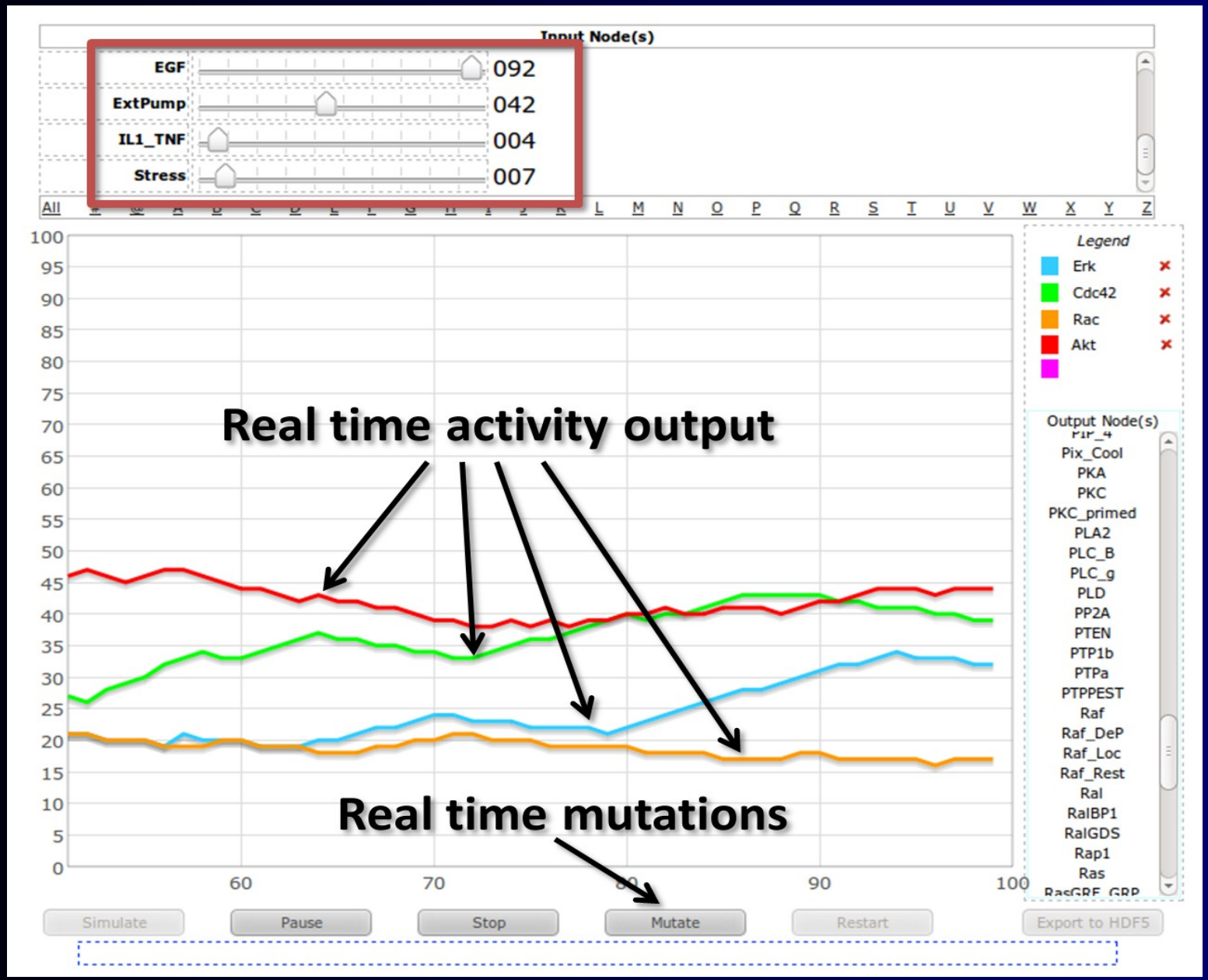
Cell Collective Overview



Cell Collective Real-Time Simulations



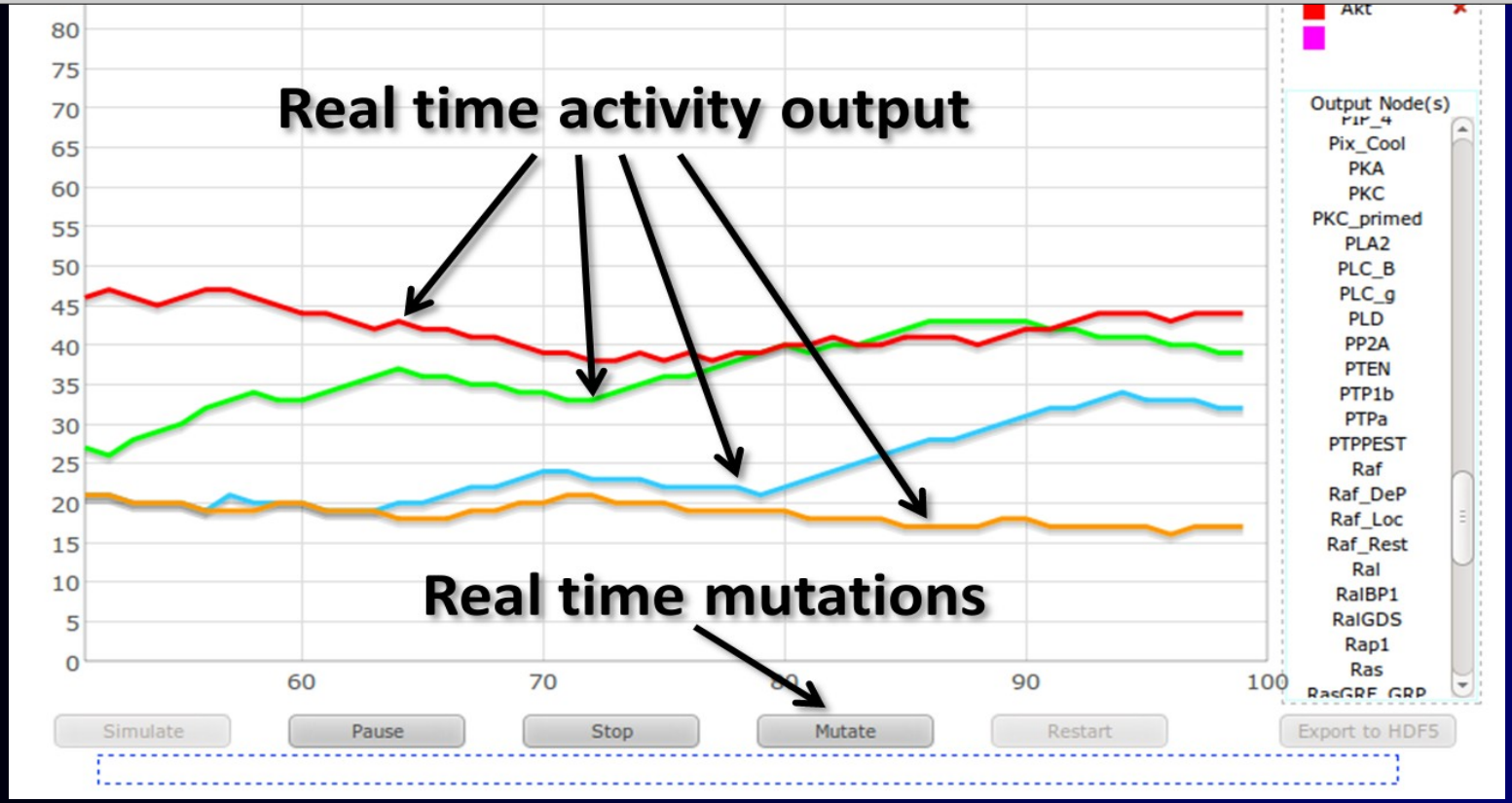
Cell Collective Real-Time Simulations



Cell Collective Real-Time Simulations

0	1	1	0	0	1	0	1	1	0	1	0	0	1	0	1	1	0	1	0
-	**50**	**100**	**50**	0	50	50	50	100	50	50	50	0	50	50	50	100	50	50	50

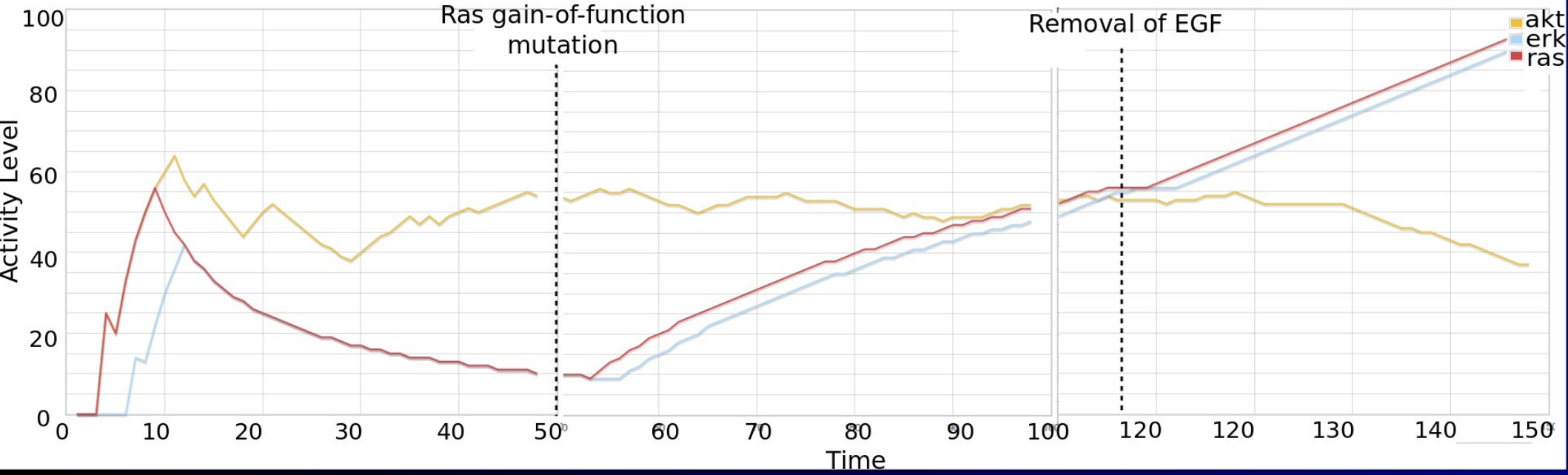
0	1	1	0	0	1	0	1	1	0	1	0	0	1	0	1	1	0	1	0
-	-	-	-	**40**	**60**	40	40	60	60	60	60	40	40	40	40	60	60	60	60



Cell Collective Real-Time Simulations

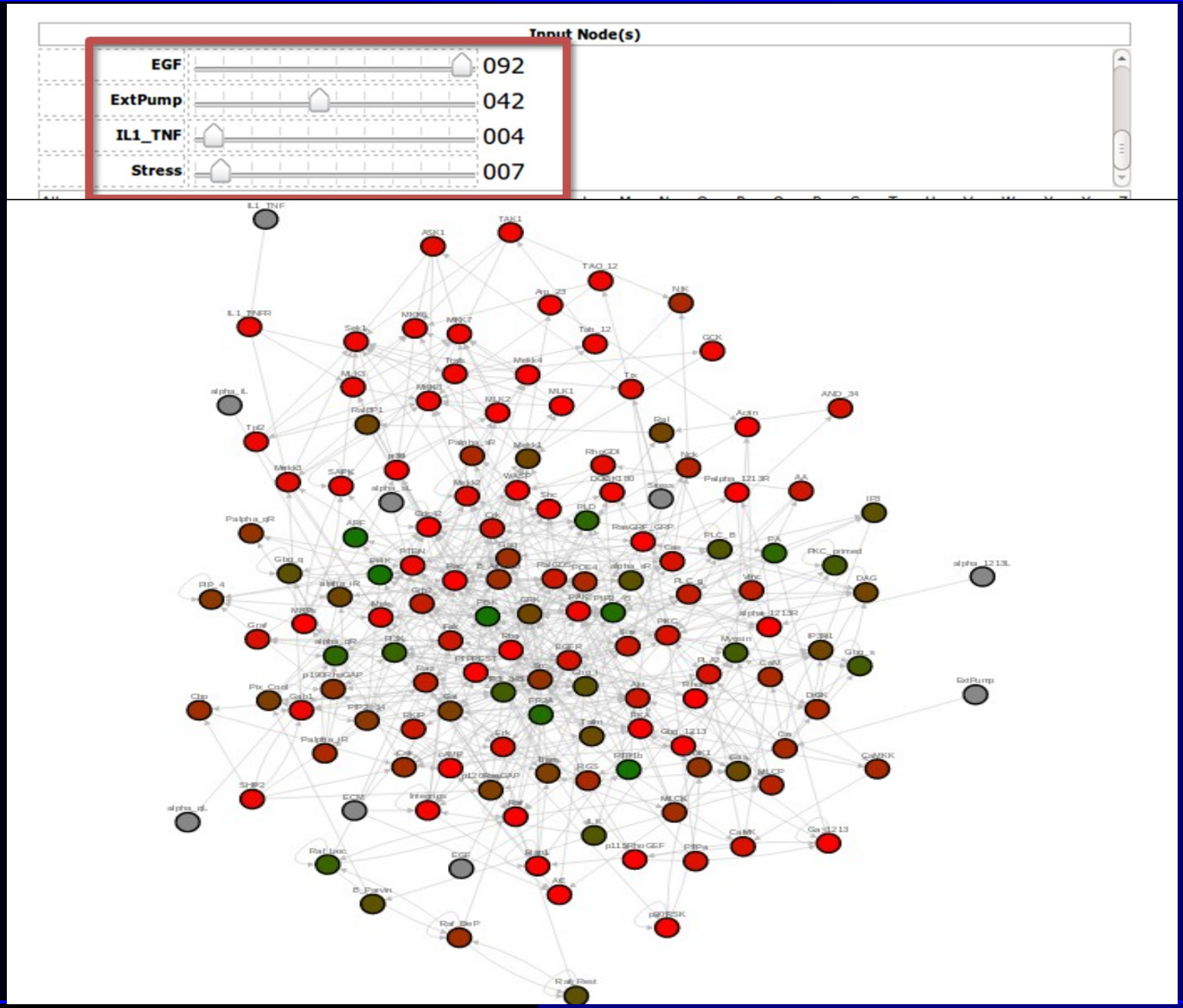
egf		50
tnfa		0

egf		0
tnfa		0

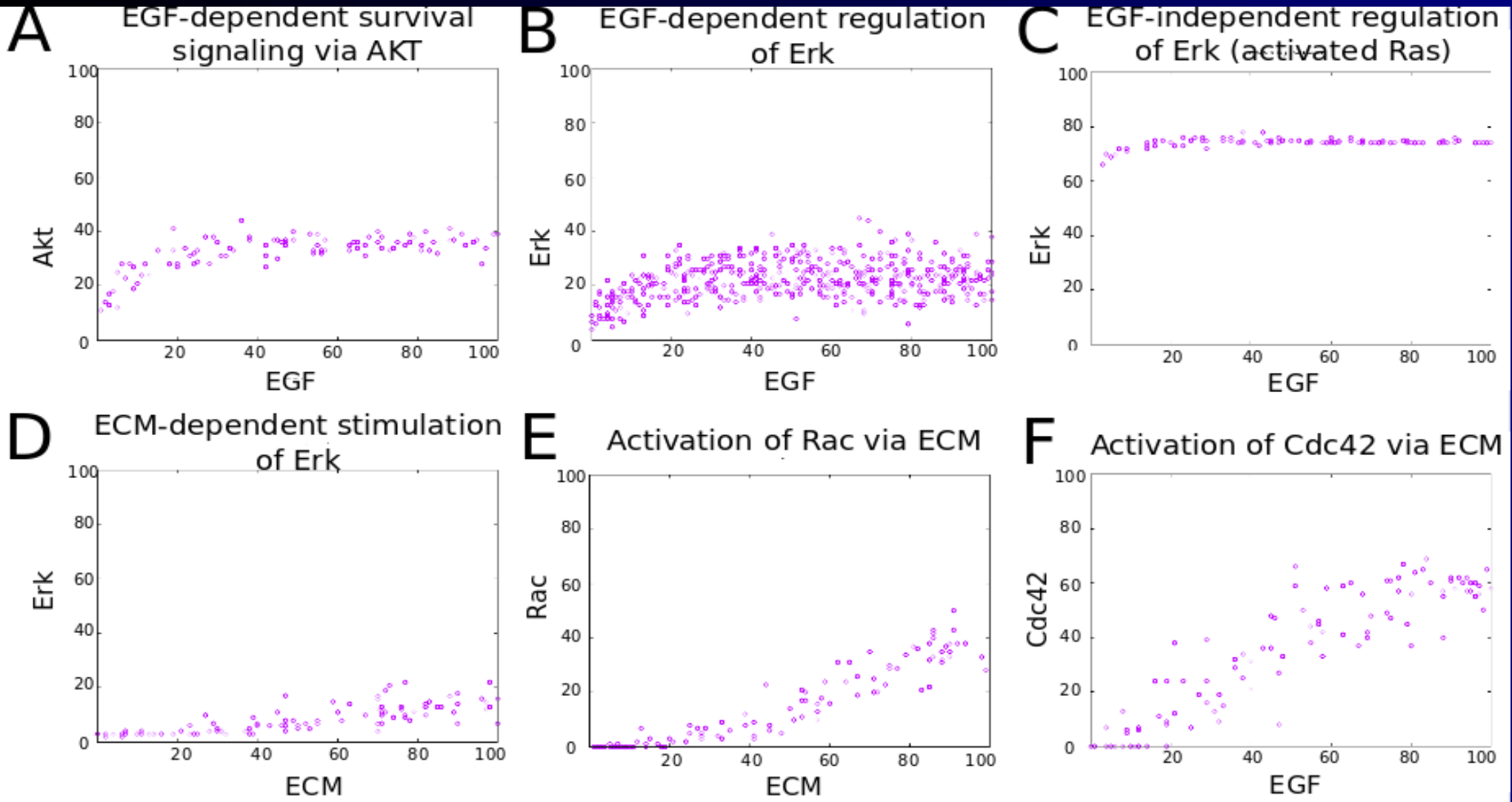


EGFR/TGFaR model: Julio Saez-Rodriguez group

Cell Collective Real-Time Simulations



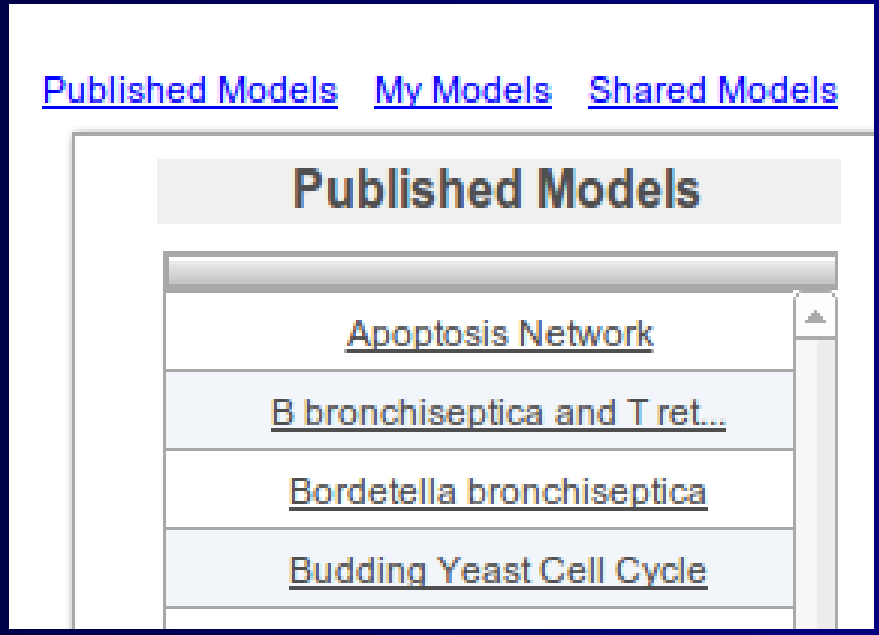
Input-Output Analysis



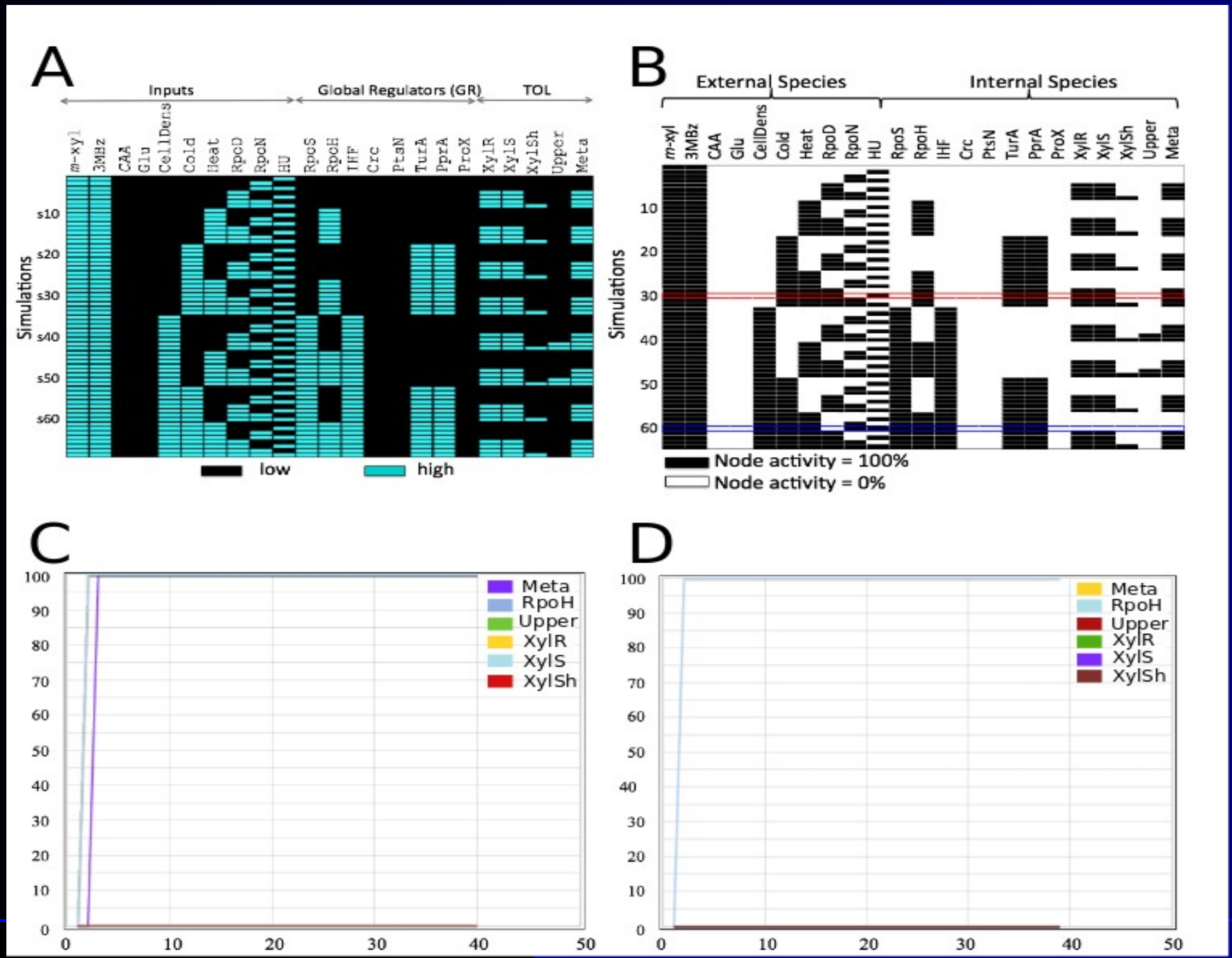
(Helikar T, et.al. 2012. PLoS One, 8(4):e61757)

Cell Collective statistics

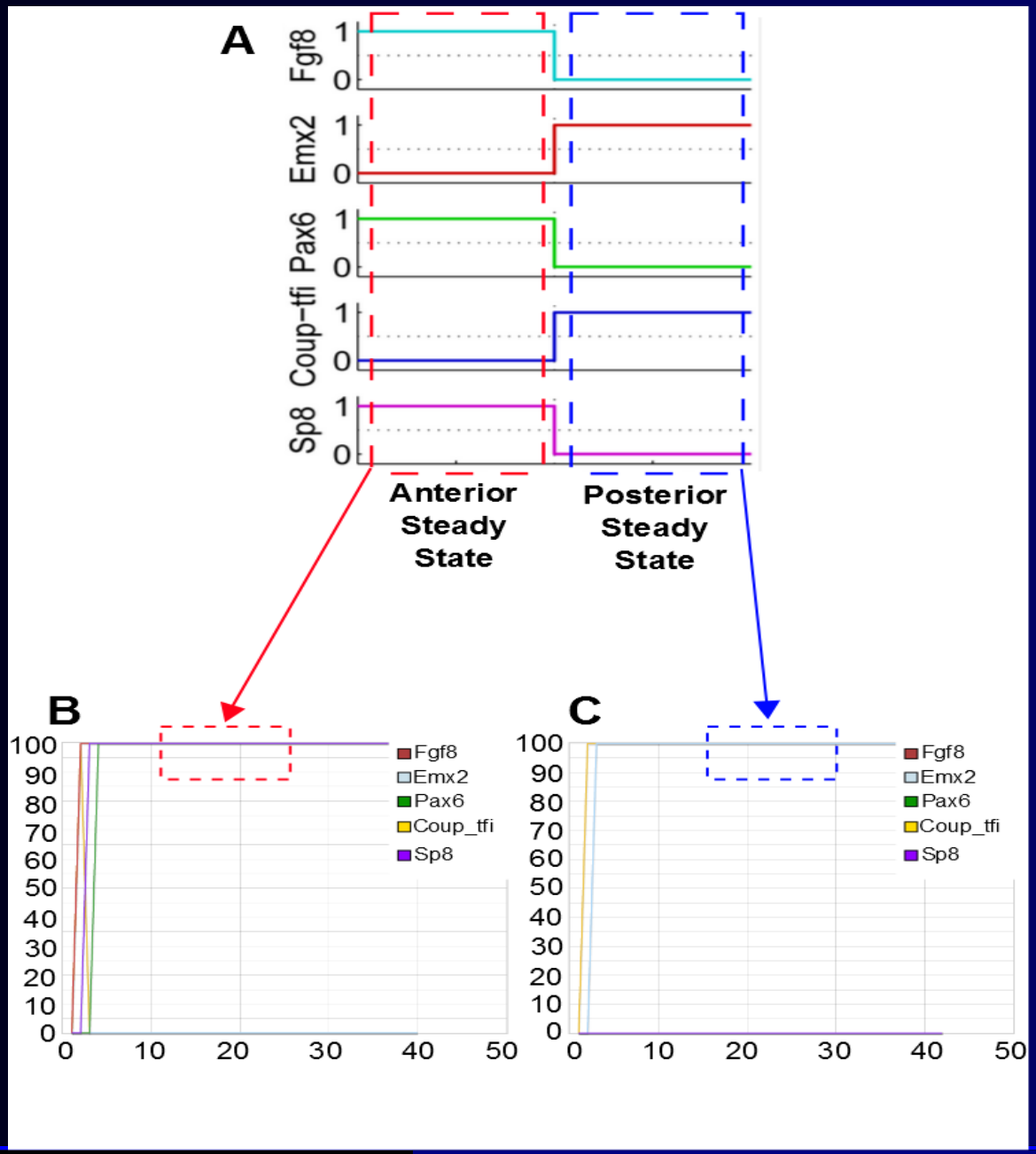
- 700+ models (seed models for various organisms – **bacteria, virus, flies, human**, etc., as well as biological process: **signal transduction, gene regulation, metabolism**, etc.)
- ~ 47k model components (nodes)
- ~ 200,000 citations



Seed Model: TOL model (Silva-Rocha and de Lorenzo, 2013b)



Seed Model: Mammalian cortical development (Giacomantonio and Goodhill, 2010)



Seed Models

- 31 models (public)
- ~ 2000 components
- ~ 4600 interactions
- SBML qual export

Model	# of Components	# of Interactions	Avg. Connectivity	Reference
Apoptosis Network	41	72	1.76	(Mai and Liu, 2009)
B bronchiseptica and T retortaeformis coinfection	53	135	2.55	(Thakar *et al.*, 2012)
Bordetella bronchiseptica	33	73	2.39	(Thakar *et al.*, 2012)
Budding Yeast Cell Cycle	20	43	2.15	(Irons, 2009)
Cardiac development	15	38	2.53	(Herrmann *et al.*, 2012b)
Cholesterol Regulatory Pathway	34	43	1.27	(Kervizic and Corcos, 2008)
Cortical Area Development	6	15	2.50	(Giacomantonio and Goodhill, 2010b)
Death Receptor Signaling	28	45	1.61	(Calzone *et al.*, 2010b)
Differentiation of T lymphocytes	50	97	1.94	(Martínez-Sosa and Mendoza, 2013)
EGFR_ErbB Signaling_1	104	227	2.18	(Samaga *et al.*, 2009a)
Epithelial Cell	247	1,100	4.45	(Tomáš Helikar *et al.*, 2013b)
FA BRCA pathway	28	123	4.39	(Rodriguez *et al.*, 2012)
Fibroblast	139	557	4.01	(Helikar *et al.*, 2008b)
Glucose Repression Signaling Pathway	37	53	1.43	(Christensen *et al.*, 2009)
Guard Cell Abscisic Acid Signaling	44	79	1.80	(Li *et al.*, 2006b)
IL-1 Signaling	117	217	1.86	(Ryll *et al.*, 2011)
IL-6 Signalling	86	147	1.71	(Ryll *et al.*, 2011)
Influenza A Virus	131	302	2.31	(Madrahimov *et al.*, 2012)
Keratinocyte	68	102	1.50	(Singh *et al.*, 2012)
Macrophage	321	533	1.66	(Raza *et al.*, 2008)
Mammalian Cell Cycle	20	51	2.55	(Sahin *et al.*, 2009b)
Mammalian Cell Cycle 2006	10	35	3.50	(Fauré *et al.*, 2006b)
Oxidative Stress Pathway	19	31	1.63	(Sridharan *et al.*, 2012b)
T Cell Receptor Signaling 2007				(Saez-Rodriguez *et al.*, 2007)
T-LGL Survival Network 2008	61	193	3.16	(Zhang *et al.*, 2008)
Th cell differentiation	19	30	1.58	(Mendoza, 2006)
TOL Regulatory Network	24	48	2.00	(Silva-Rocha and de Lorenzo, 2013b)
Trichostrongylus retortaeformis	26	58	2.23	(Thakar *et al.*, 2012)
Yeast Apoptosis	73	114	1.56	(Kazemzadeh *et al.*, 2012b)
Yeast Cell Cycle 2004	18	36	2.00	(F Li *et al.*, 2004)

Current & Future Efforts

- API – suggestions from the CoLoMoTo community to prioritize the information that could be accessed in the Cell Collective?
- Web GUI for LogicalModels library
- Support for threshold models
- Support for multi-valued networks (conversion to Boolean networks?)
- Model versioning

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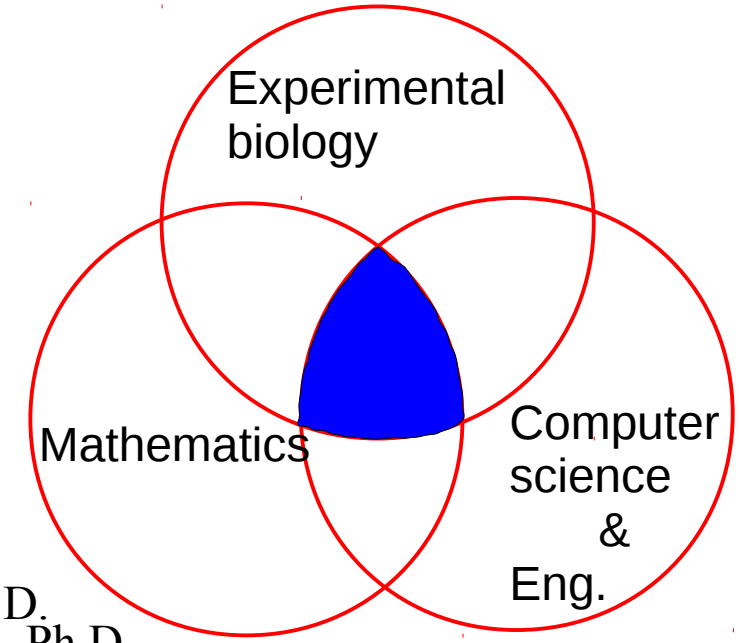

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