Towards Mechanistic Pharmacodynamic Modeling for Cancer Precision Medicine

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Greenville, SC
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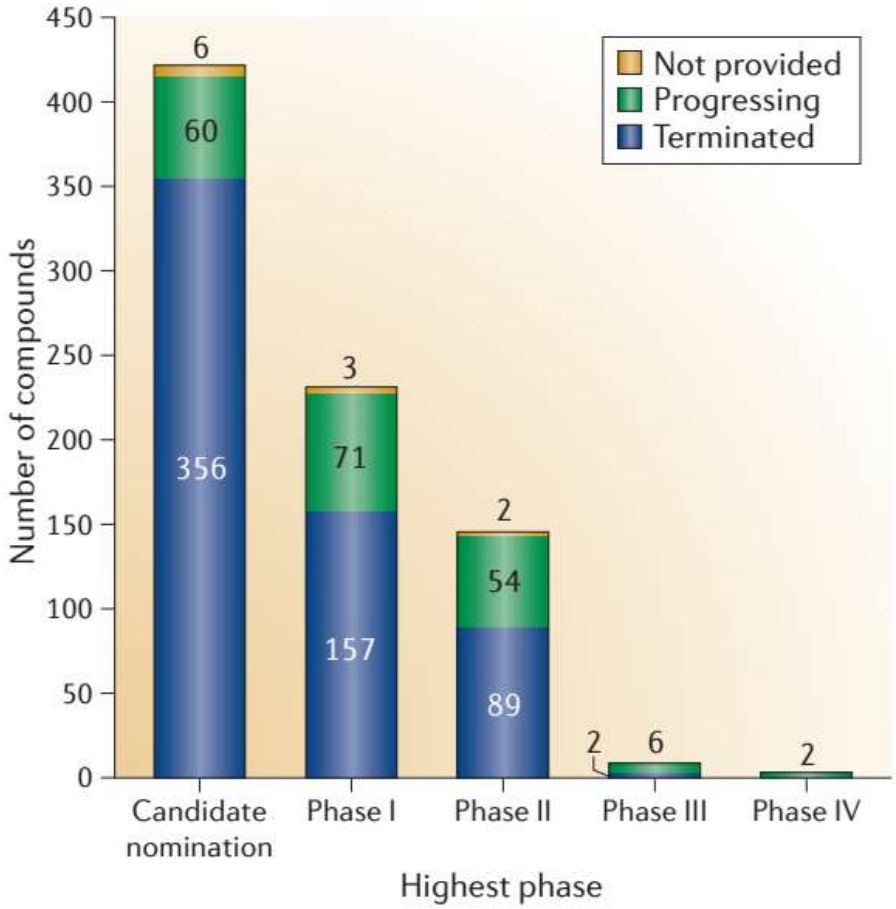
CLEMSON
CHEMICAL AND BIOMOLECULAR ENGINEERING

Snapshot of Attrition During Drug Development



808 oral small-molecule compounds at their highest recorded phase of development

Waring et al., Nat Rev Drug Discovery, 2015

Simulation is Typically an Integral Component of Design

- Example of airplane building
  - Build many airplanes, see which ones don't crash?
  - No!
  - Sufficient understanding of fluid dynamics and physics allows simulation to screen design ideas
- Human biology is far more complex and less understood—even in how to simulate it
  - Need more basic research
    - Physiological and pathophysiological mechanisms
    - Modeling and simulation methods to capture said mechanisms

Systems Pharmacology

1. Modeling

2. Simulation

3. Control

8 SEPTEMBER 2016 | VOL 537 | NATURE | S63

PRECISION MEDICINE OUTLOOK

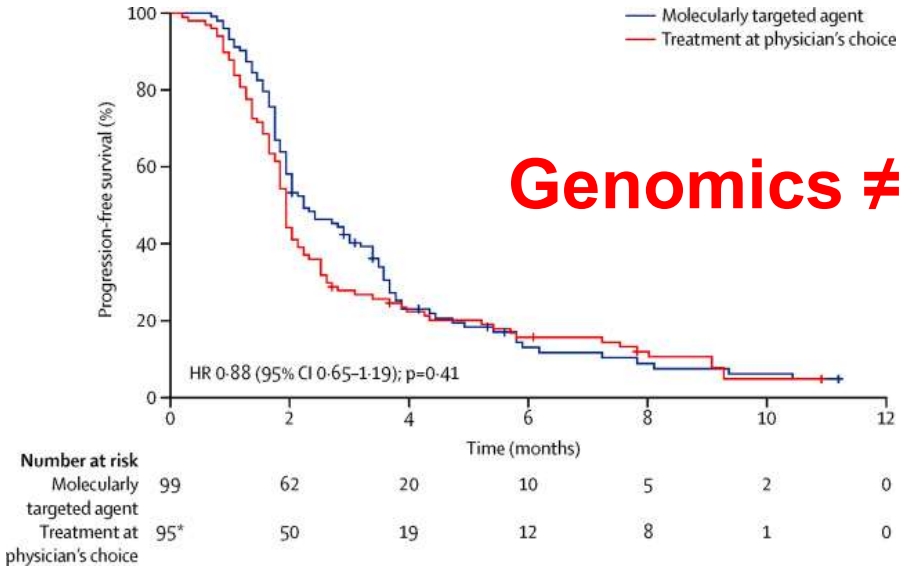
PERSPECTIVE

The precision–oncology illusion

Precision oncology has not been shown to work, and perhaps it never will, says **Vinay Prasad**.

Precision oncology promises to pair individuals with cancer with drugs that target the specific mutations in their tumour, in the hope of producing long-lasting remission and extending their

Targeted Therapy was found not to outperform Physician's Choice

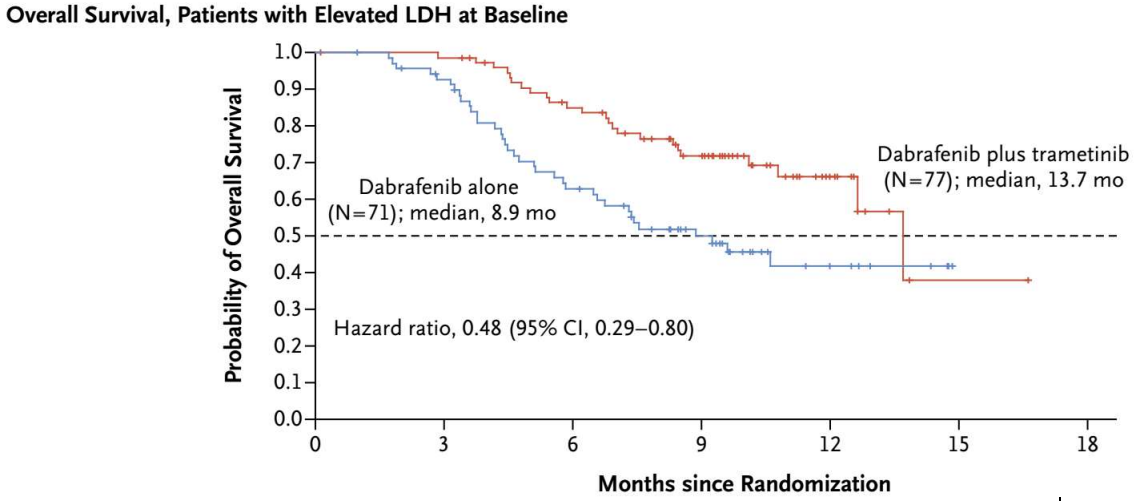


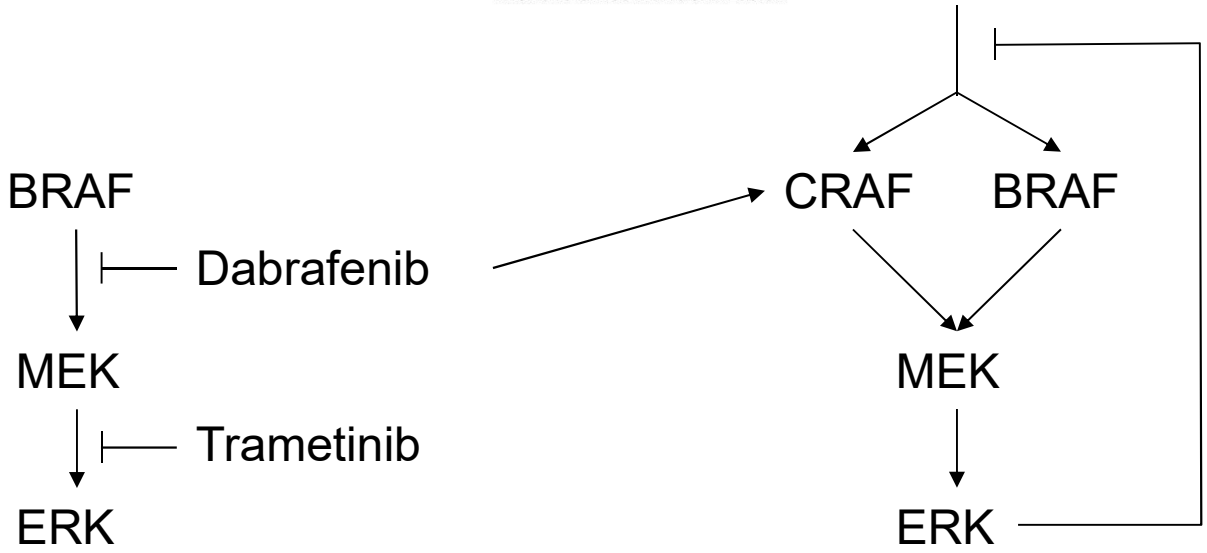
Genomics ≠ Drugs

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Combined BRAF and MEK Inhibition versus BRAF Inhibition Alone in Melanoma

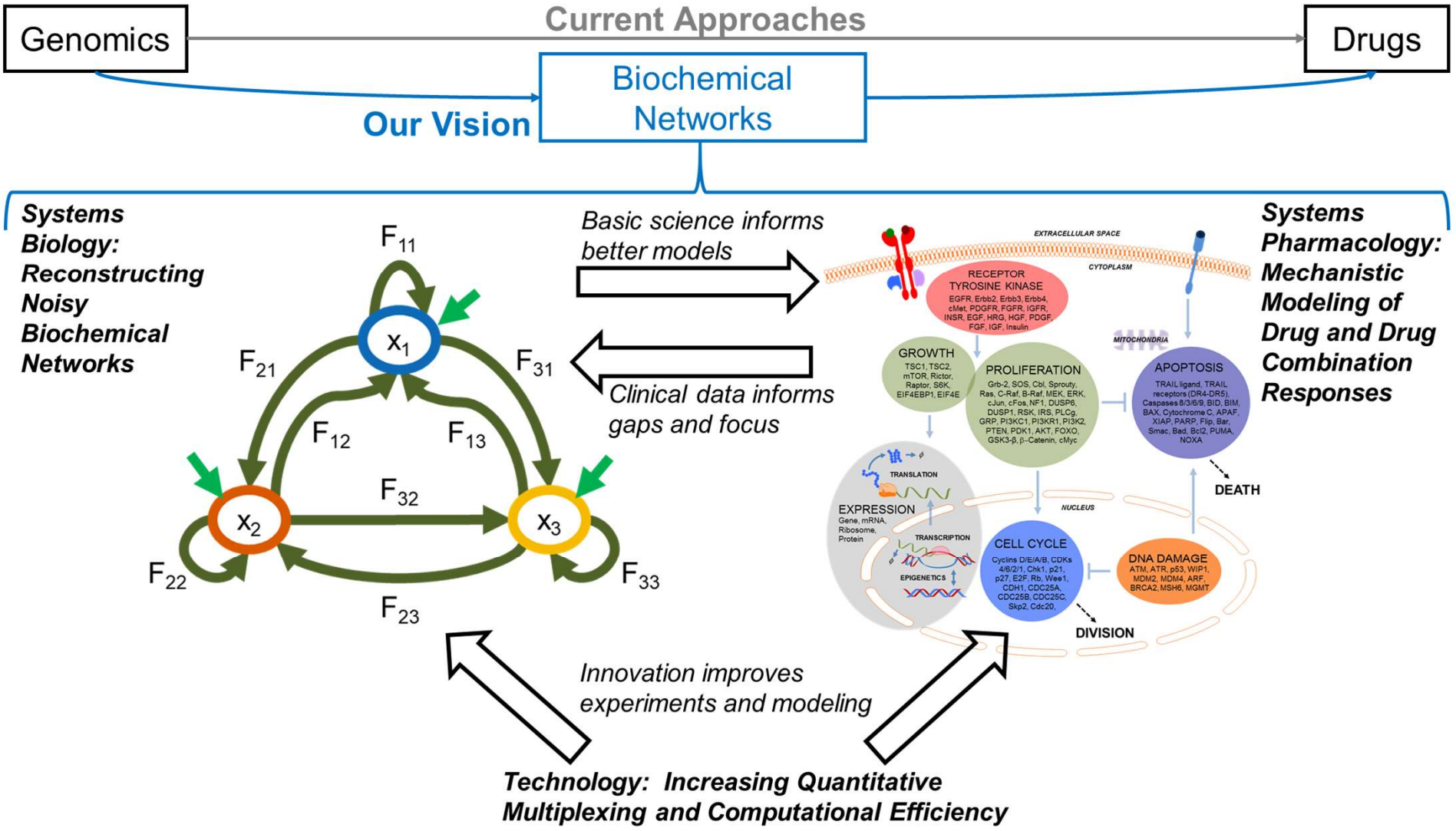




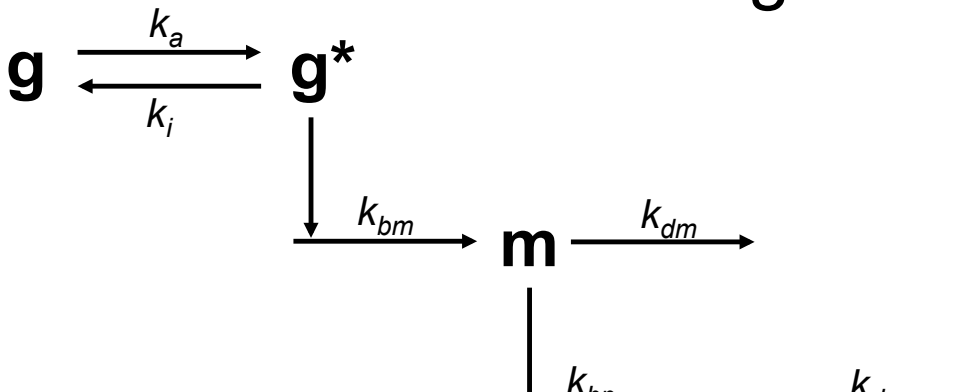
What More Does Cancer Precision Medicine Need to Consider?

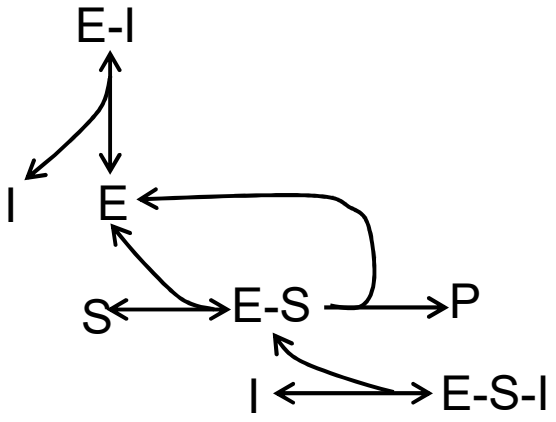
~~One Driver→One Target→One Drug~~

1. Systems
   - Driver may not be a good direct drug target
   - Drivers interact; 4-7 drivers per tumor (maybe more)
2. Polypharmacology
   - Multiple drivers→multiple targets→multiple drugs
   - Most targeted drugs are promiscuous
3. Dynamics
   - Tumors adapt and evolve on multiple time scales
4. Heterogeneity
   - Clonal cells show transient resistance
   - Cancers comprise multiple subclones with different drivers and microenvironments


Genomics
Current Approaches
Drugs
Our Vision
Biochemical Networks
Systems Biology: Reconstructing Noisy Biochemical Networks
Basic science informs better models
Clinical data informs gaps and focus
Systems Pharmacology: Mechanistic Modeling of Drug and Drug Combination Responses
F11
F21
F31
F12
F13
F32
F22
F33
F23
x1
x2
x3
EXTRACELLULAR SPACE
CYTOPLASM
RECEPTOR TYROSINE KINASE
EGFR, Erbb2, Erbb3, Erbb4, cMet, PDGFR, FGFR, IGFR, INSR, EGF, HRG, HGF, PDGF, FGF, IGF, Insulin
MITOCHONDRIA
GROWTH
TSC1, TSC2, mTOR, Rictor, Raptor, S6K, EIF4EBP1, EIF4E
PROLIFERATION
Grb-2, SOS, Cbl, Sprouty, Ras, C-Raf, B-Raf, MEK, ERK, cJun, cFos, NF1, DUSP6, DUSP1, RSK, IRS, PLCg, GRP, PI3KC1, PI3KR1, PI3K2, PTEN, PDK1, AKT, FOXO, GSK3-β, β-Catenin, cMyc
APOPTOSIS
TRAIL ligand, TRAIL receptors (DR4-DR5), Caspases 8/3/6/9, BID, BIM, BAX, Cytochrome C, APAF, XIAP, PARP, Flip, Bar, Smac, Bad, Bcl2, PUMA, NOXA
DEATH
TRANSLATION
EXPRESSION
Gene, mRNA, Ribosome, Protein
TRANSCRIPTION
EPIGENETICS
NUCLEUS
CELL CYCLE
Cyclins D/E/A/B, CDKs 4/6/2/1, Chk1, p21, p27, E2F, Rb, Wee1, CDH1, CDC25A, CDC25B, CDC25C, Skp2, Cdc20,
DNA DAMAGE
ATM, ATR, p53, WIP1, MDM2, MDM4, ARF, BRCA2, MSH6, MGMT
DIVISION
Innovation improves experiments and modeling
Technology: Increasing Quantitative Multiplexing and Computational Efficiency

Quantitative Systems Pharmacology: Mechanistic Kinetic Modeling of Biochemical Networks





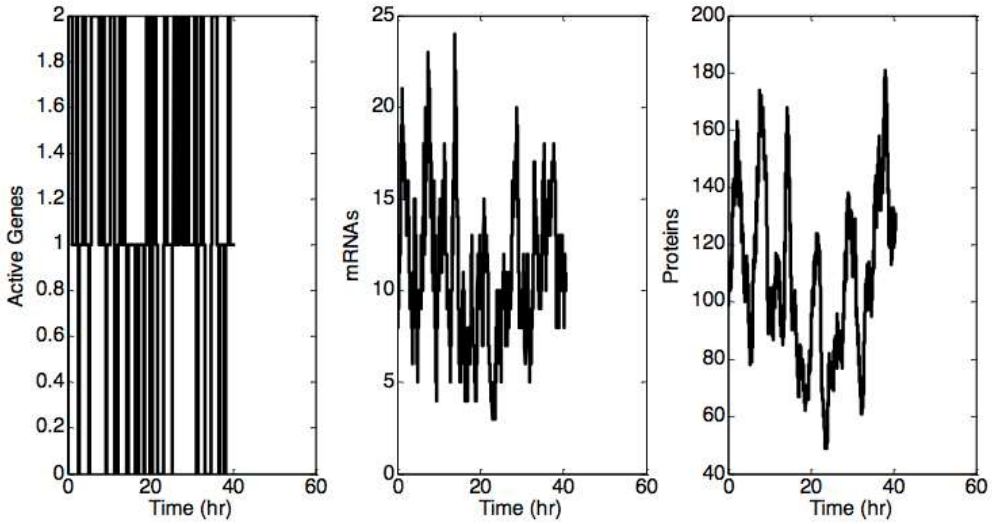
$$\frac{dp}{dt} = k_{bp}m - k_{dp}p$$

$$\frac{dm}{dt} = k_{bm}g^* - k_{dm}m$$

$$\frac{dg^*}{dt} = k_a g - k_i g^*$$

$$\frac{dg}{dt} = k_i g^* - k_a g$$

Stochastic Gene Expression



Outline

- Mechanistic Models of Cancer Cell Signaling
  - Formulation, Building, and Training
  - Stochastic Cell Cycle Entry
  - Stochastic Cell Death
- Towards Training with Big Pharmacological Data
- Reconstructing Cell Signaling Networks from Perturbation Time Course Data

PLOS COMPUTATIONAL BIOLOGY

RESEARCH ARTICLE

A mechanistic pan-cancer pathway model informed by multi-omics data interprets stochastic cell fate responses to drugs and mitogens

Mehdi Bouhaddou[1], Anne Marie Barrette[1], Alan D. Stern[1], Rick J. Koch[1], Matthew S. DiStefano[1], Eric A. Riesel[1], Luis C. Santos[1], Annie L. Tan[1], Alex E. Mertz[1], Marc R. Birtwistle[1,2]*

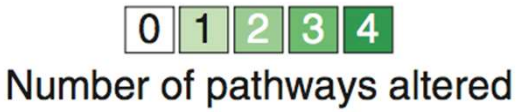
1 Department of Pharmacological Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, United States of America, **2** Department of Chemical and Biomolecular Engineering, Clemson University, Clemson, SC, United States of America

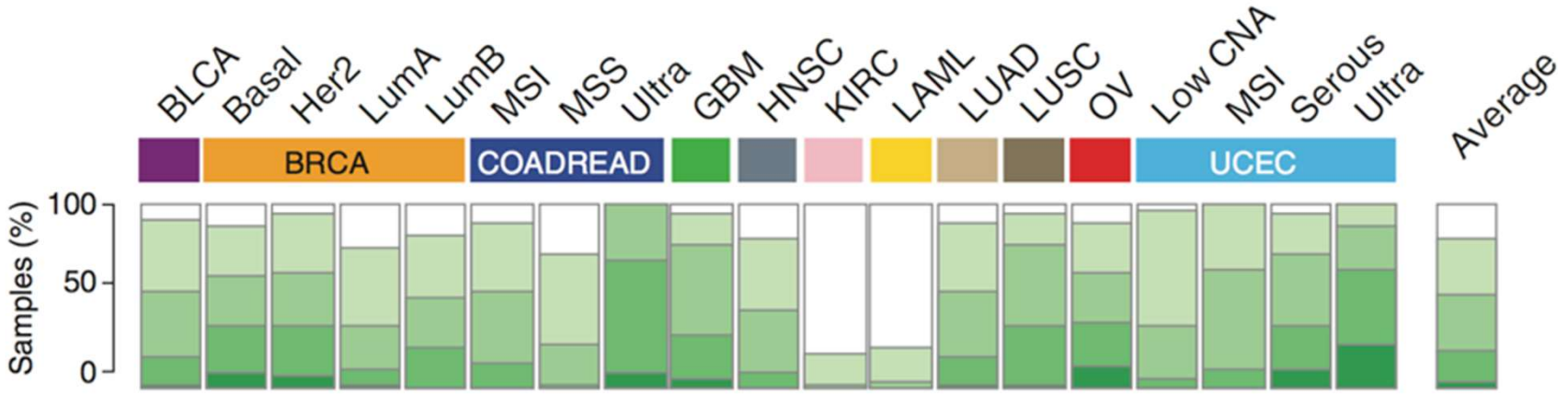
* mbirtwi@clemson.edu

Defining Model Scope

Pathways:

- RTK-RAS-RAF-MAPK
- PI3K-AKT-mTOR
- Cell Cycle
- p53-DNA Damage

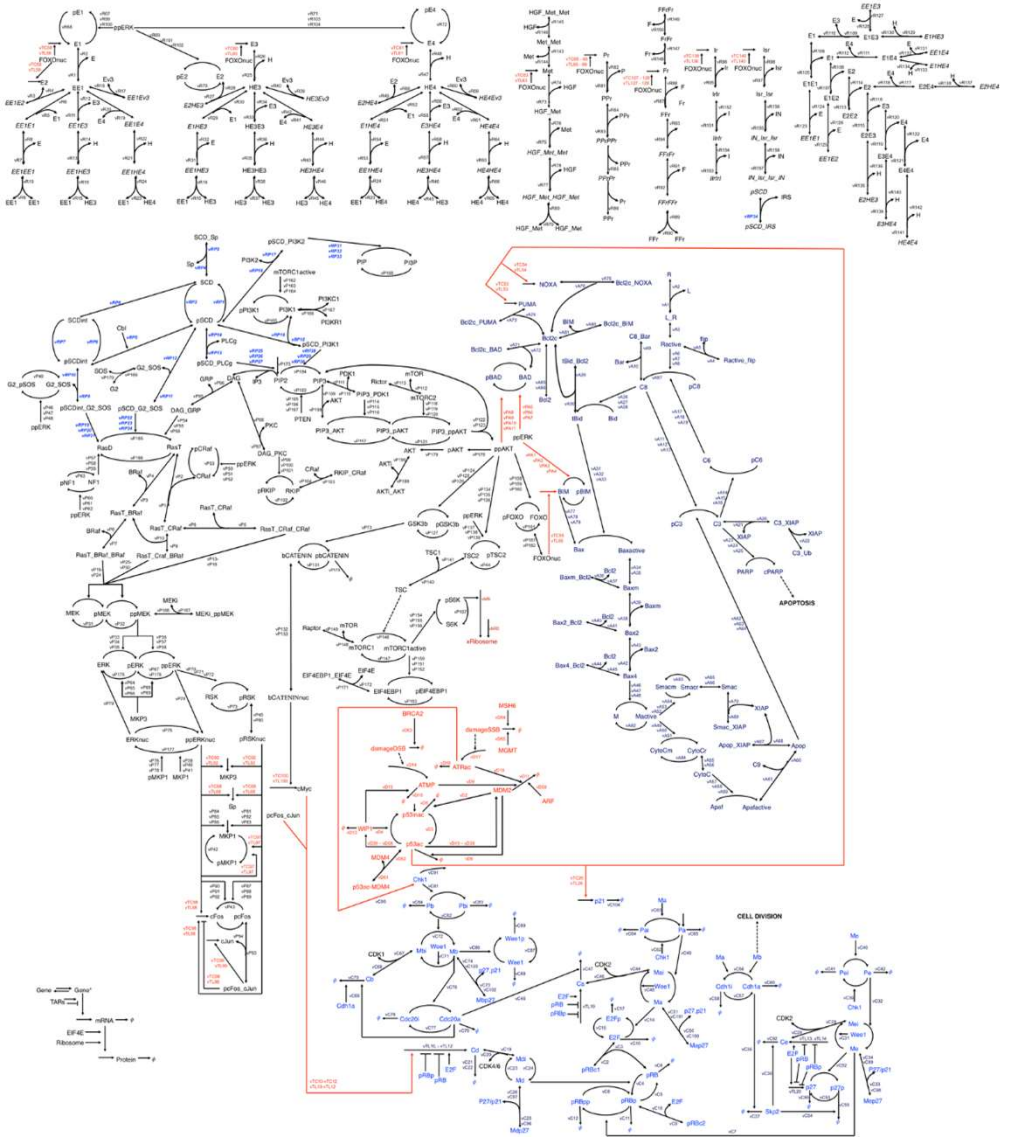




Adapted from Ciriello G et al., Nature Genetics 2013

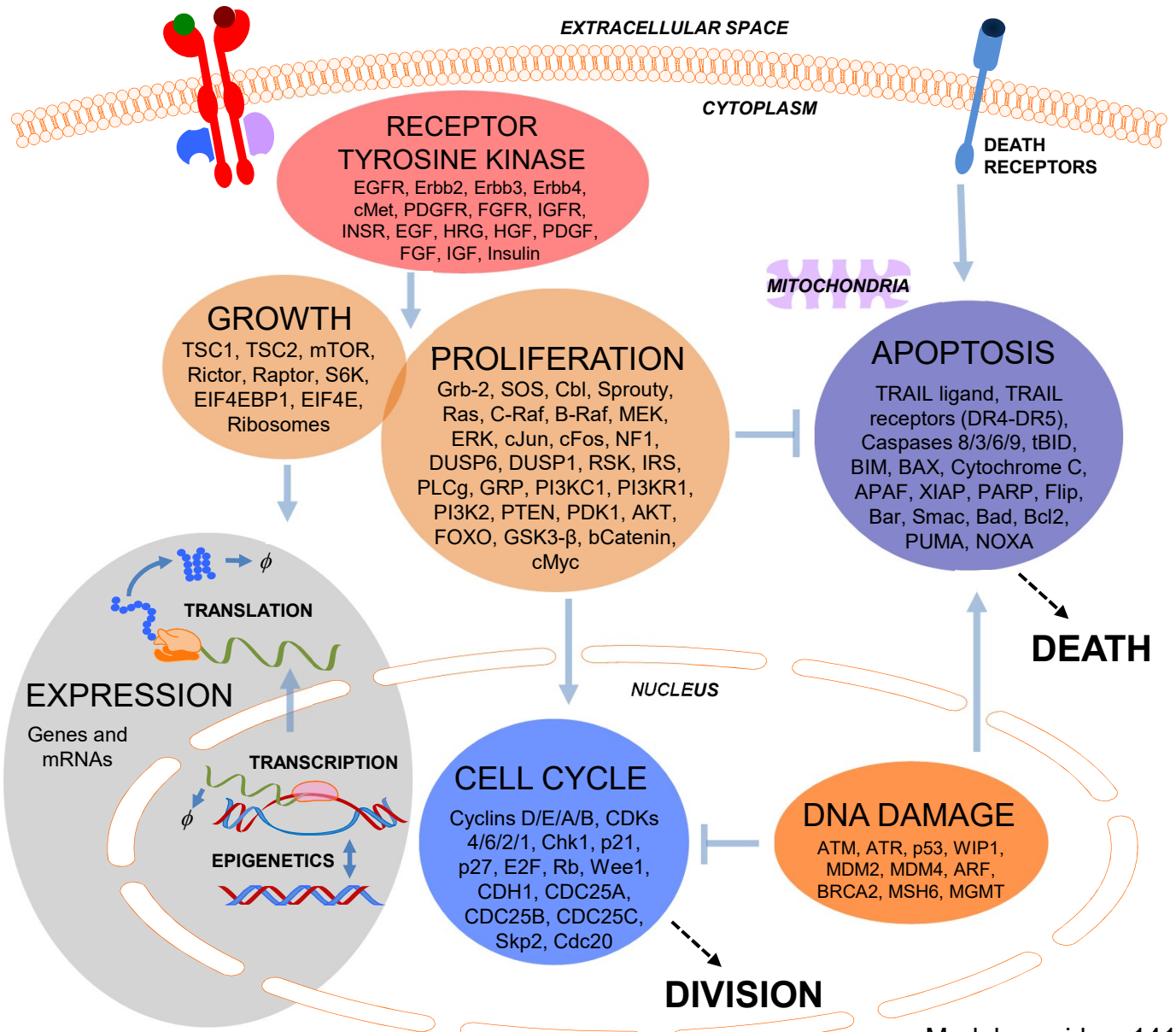
Model is Composed of Pathway-Specific Models from the Literature

Submodel	Origin
Receptor Tyrosine Kinase	• Birtwistle MR et al., MSB 2007 • Bouhaddou M & Birtwistle MR, Mol Biosys 2014 • Many others
Proliferation & Growth	• Birtwistle MR et al., MSB 2007 • Nakakuki T et al., Cell 2010 • Kriegsheim A et al., Nat Cell Bio 2009
DNA Damage	• Batchelor E et al., MSB, 2011
Cell Cycle	• Gerard C & Goldbeter A, PNAS 2009
Apoptosis	• Albeck JG et al., Plos Biology 2008
Expression	The standard model



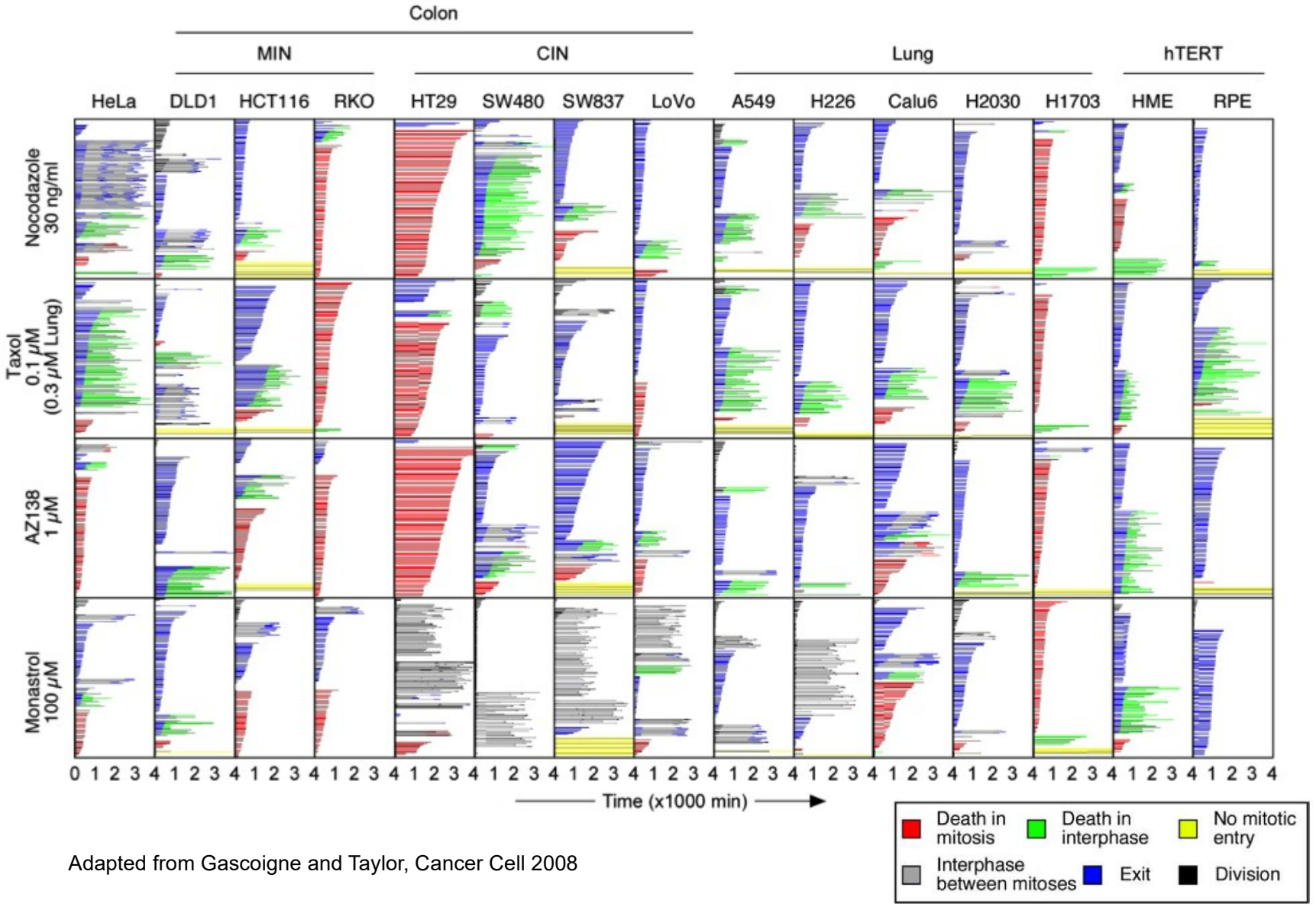
System of ordinary differential equations (ODEs)
~800 species and ~2800 reactions

A Prettier Picture



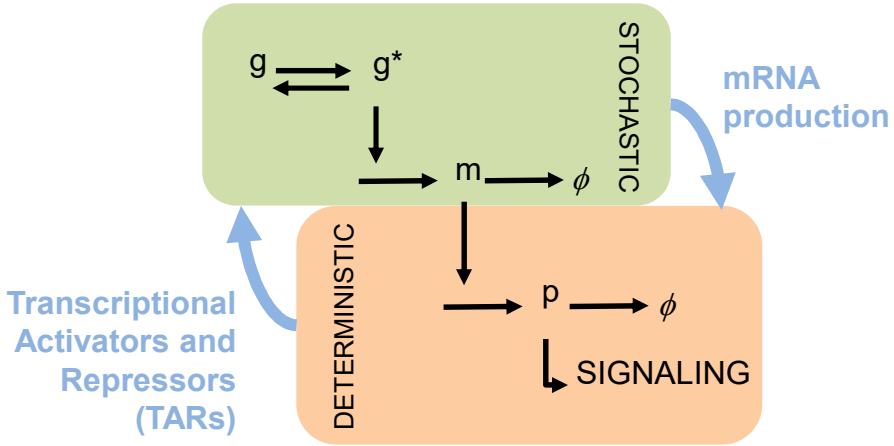
Model considers 141 genes

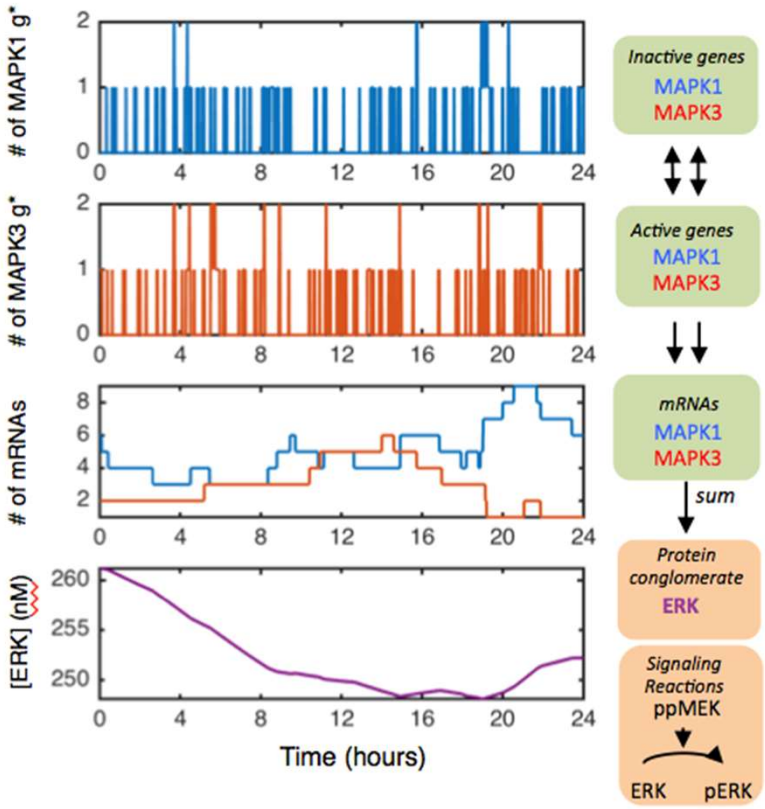
Single Cells Have Stochastic Response to Drugs



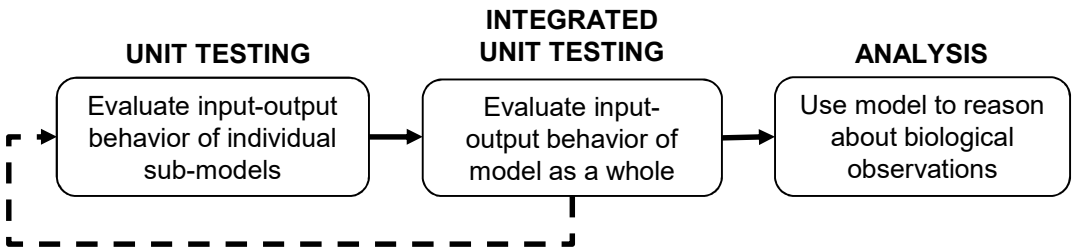
Adapted from Gascoigne and Taylor, Cancer Cell 2008

Cell-to-cell variability: Simulating Stochastic Gene Expression





Increasing Confidence in Models



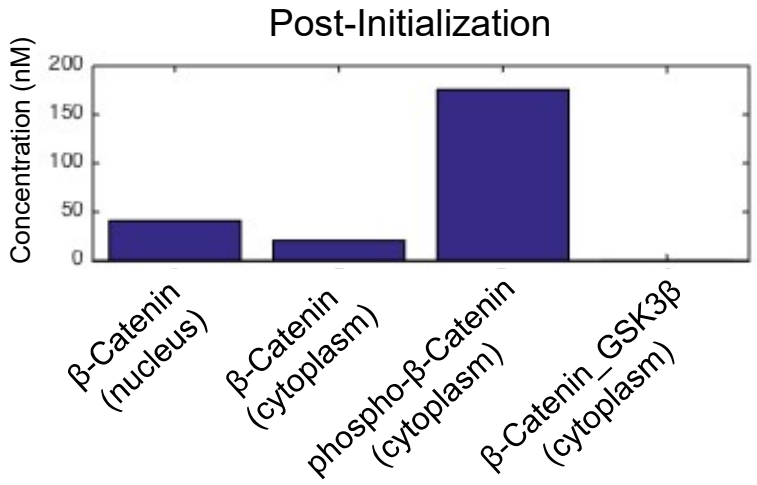
Cell context: Start with non-transformed MCF10A

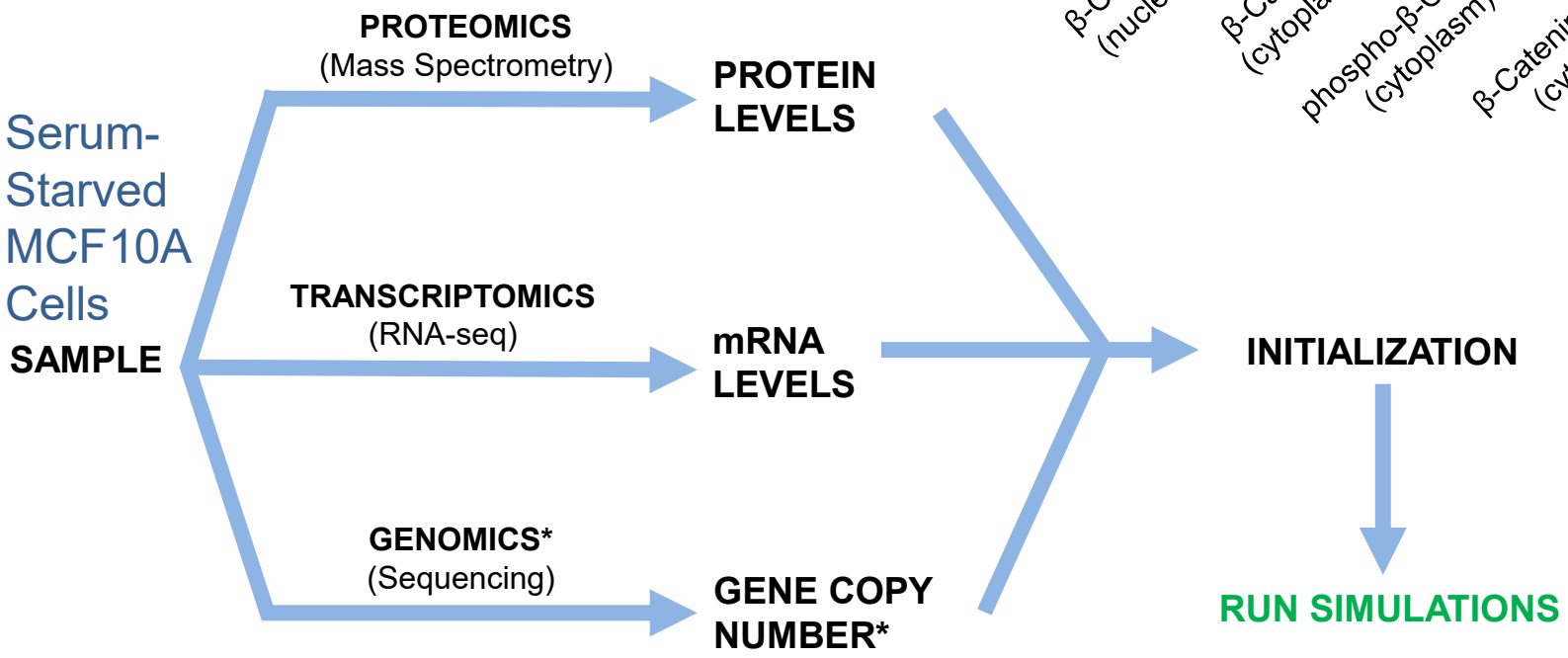
- Predictable phenotypic behaviors
- Few alterations
- Extensive literature data and widely studied

Unit Testing—Expression: Tailoring Model to Quantitative Expression Context

Define "expression context":

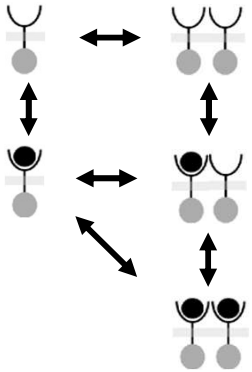
1. **GENOME**: Gene copy number
2. **TRANSCRIPTOME**: mRNA levels
3. **PROTEOME**: Protein levels



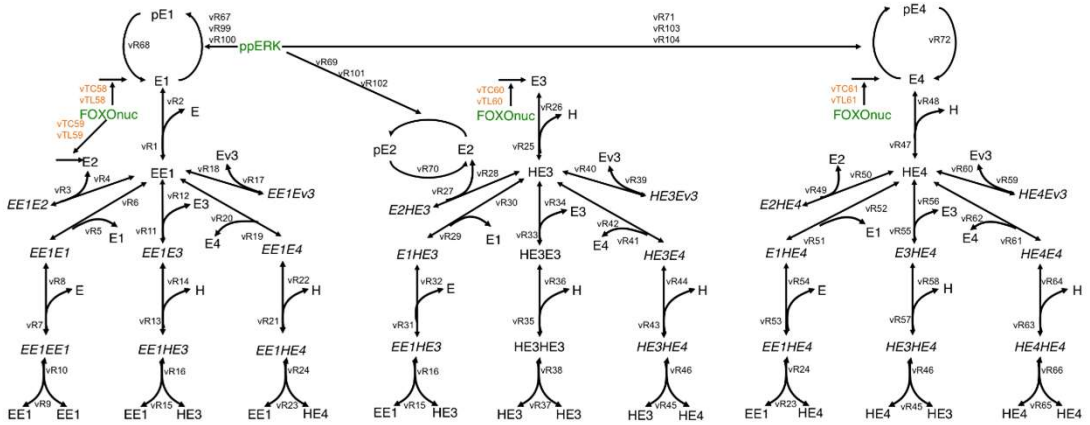


* Bessette et al., Plos One 2015

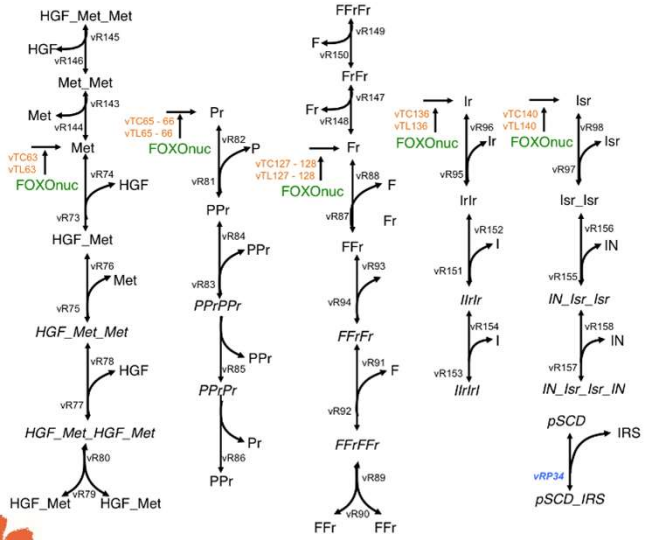
Unit Testing – Receptor Tyrosine Kinase (RTK)



EGFR ErbB2 ErbB3 ErbB4



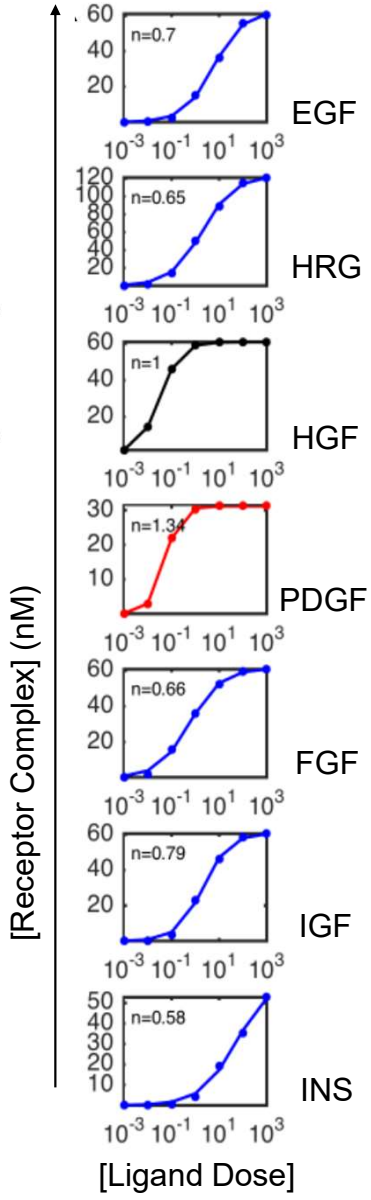
cMET PDGFR FGFR IGFR INSR



LITERATURE DICTATES

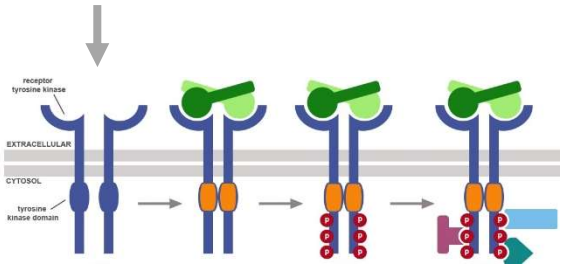
- Negative cooperativity (n<1)
- No cooperativity (n=1)
- Positive cooperativity (n>1)

Ligand-Receptor Cooperativity Behavior



Unit Testing – Proliferation & Growth

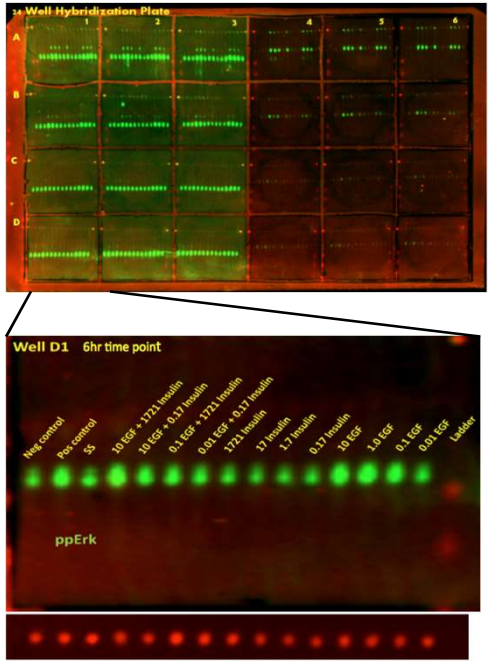
EGF and Insulin



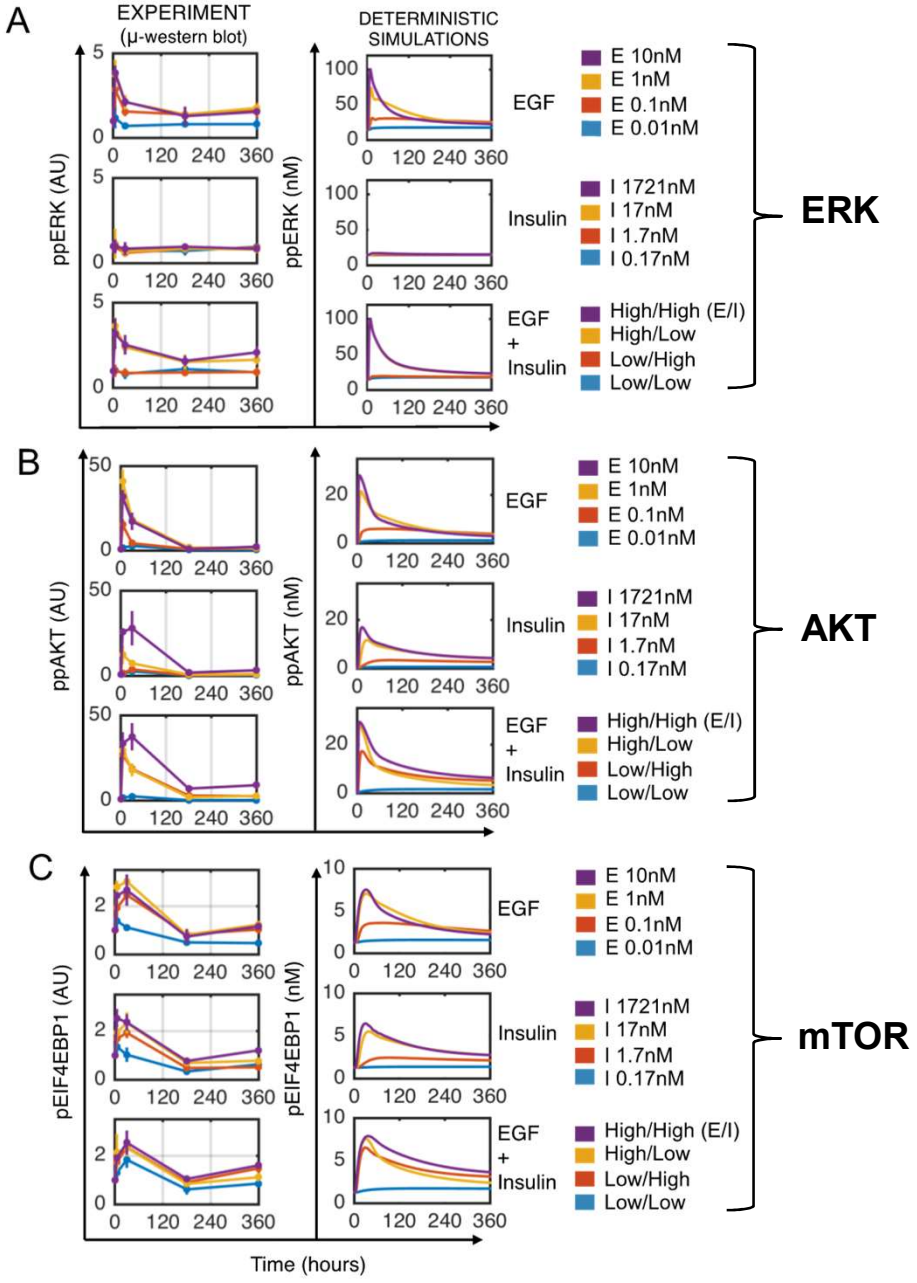
ERK **AKT**

mTOR

Micro-Western Blot



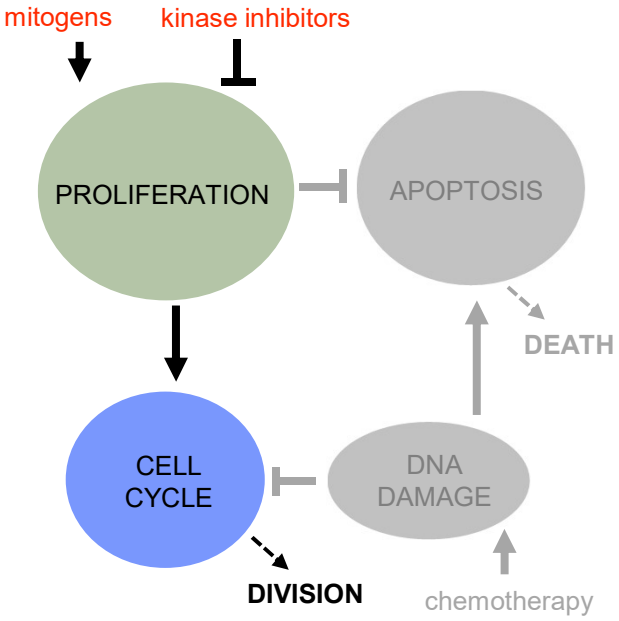
Experiments by Rick Koch and Anne Marie Barrette

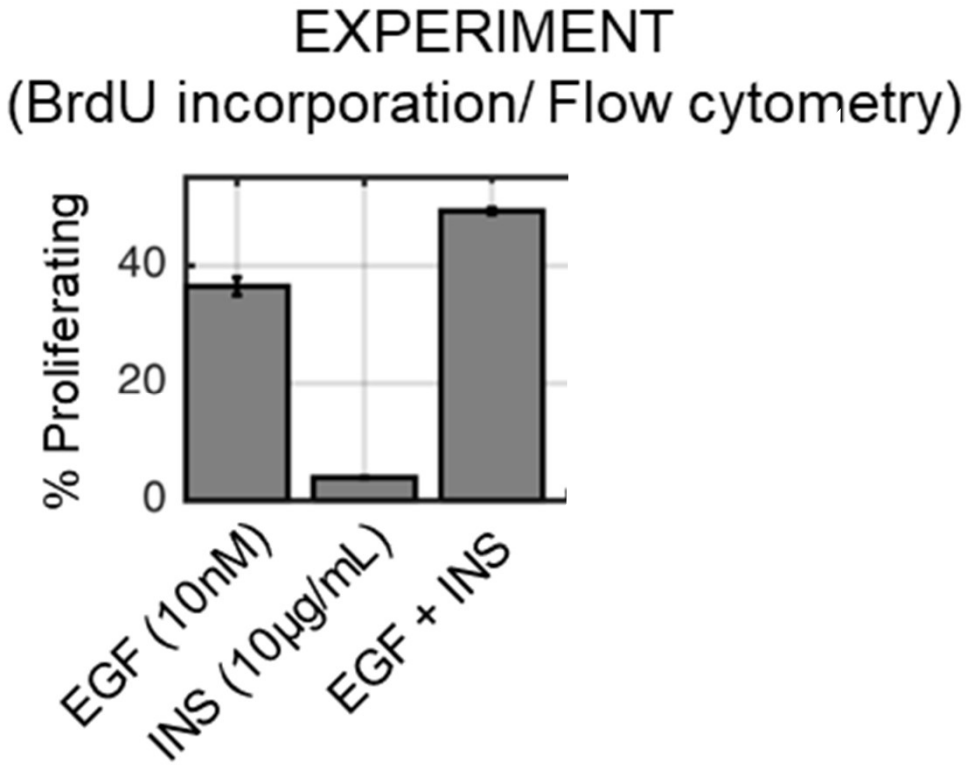


Unit Testing

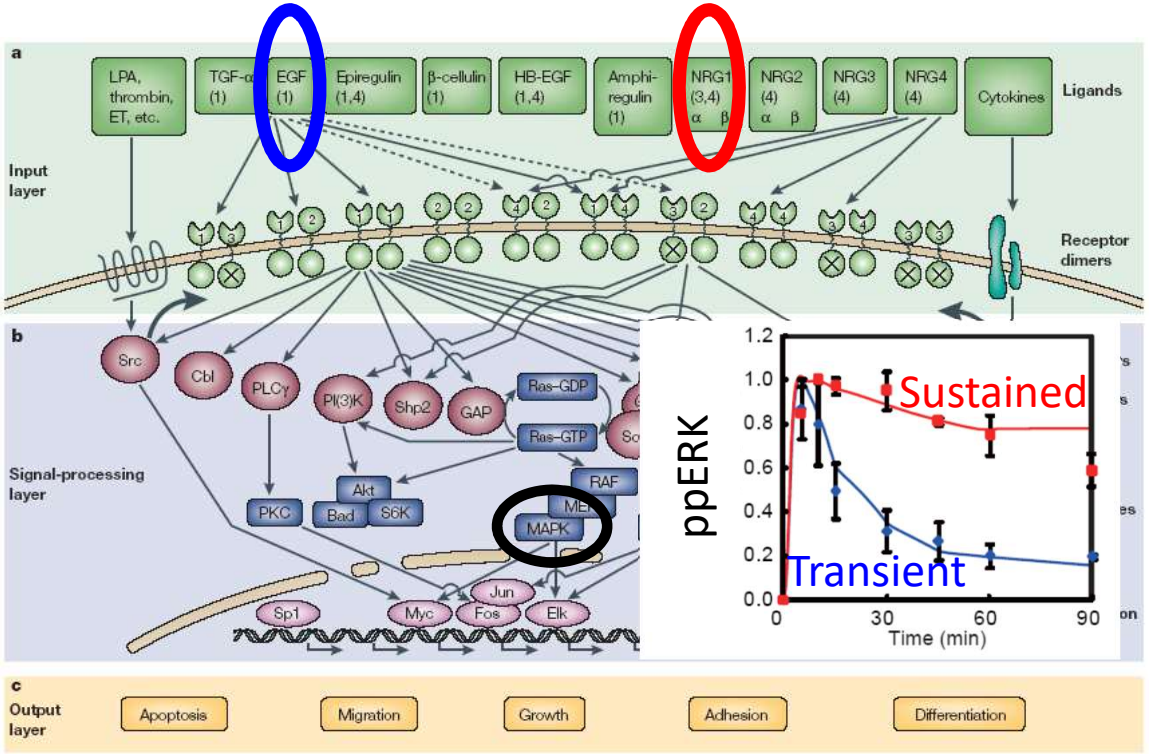
Submodel	Required Properties for Each Submodel
Receptor Tyrosine Kinase	• Ligand-receptor cooperativity matches experimental observations. • Receptor trafficking kinetics reflects experimental observations.
Proliferation & Growth	• Receptor pathway preferences match experimental observations. • Basal activity fluxes through ERK and AKT pathways exist, tailored to the serum-starved state. • Dynamic dose responses of ERK, AKT, and mTOR signaling matches experimental western blot data.
Cell Cycle	• Cell cycle entry is driven by induction of cyclin D mRNA. • Order and timing of cyclin/cdk complexes matches established observations. • Cell cycle duration matches that in MCF10A cells. • Upregulation of p21 arrests the cell cycle.
Apoptosis	• Robustness against small death signals. • Model exhibits all-or-nothing death response when apoptosis signaling surpasses threshold. • Dose and dynamics of TRAIL-induced extrinsic apoptosis matches experimental observations. • Intrinsic apoptosis signaling responds to interrupted survival signaling and DNA damage induced upregulation of pro-apoptotic proteins.
DNA Damage	• Convert original delayed differential equations into ordinary differential equations. • p53 dynamics corresponding to single- and double-stranded DNA breaks matches experimental observations. • Rate of DNA damage repair is dependent on levels of repair enzymes. • p53 activation dynamics exhibit “digital” and not “analog” behavior, whereby the number of p53 pulses, but not pulse height or width, scales to magnitude of DNA damage. • Etoposide-induced DNA damage is dependent on the cell cycle stage (S-phase).
Expression	• Model is tailored to genomic, transcriptomic, and proteomic context of MCF10A cells. • Stochastic gene expression is simulated with a computationally efficient algorithm. • Cell-to-cell variability in mRNA and protein levels matches experimental observations. • EIF4E levels possess extrinsic control over the translation rate. • Ribosomes double during the course of one cell cycle.

Integrated Unit Testing – Cell Cycle
How are synergistic EGF and Insulin signals integrated by the cell?

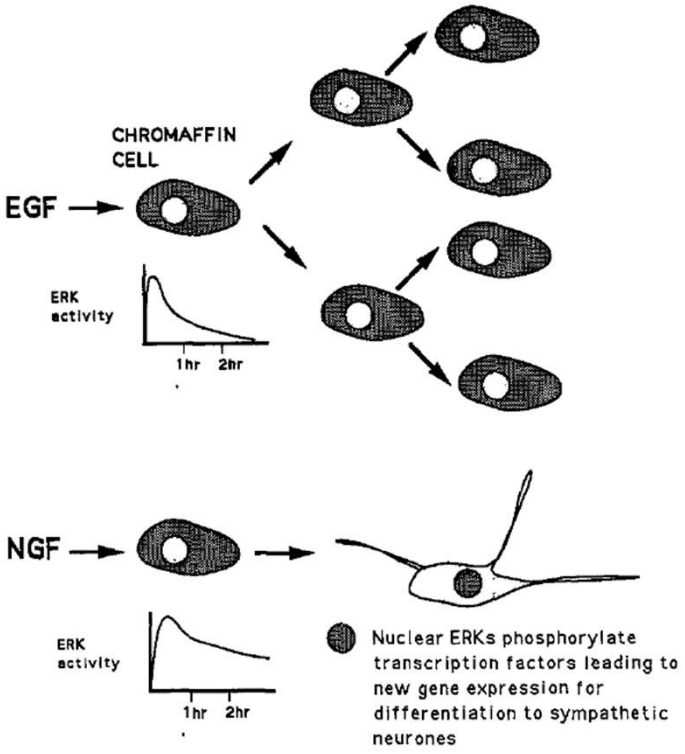




Spatiotemporal Dynamics of Signaling?



PC-12 Cells



Adapted from Marshall, *Cell*, 1995

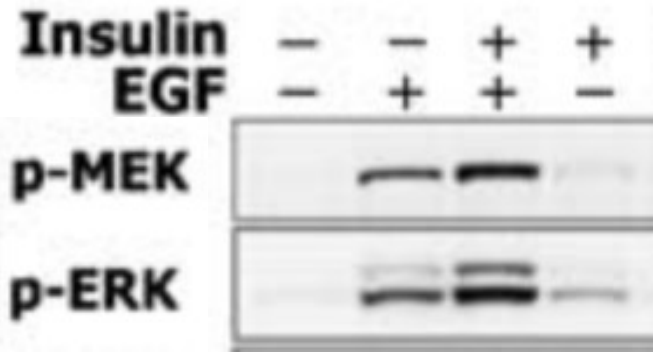
Molecular Systems Biology 5; Article number 256; doi:10.1038/msb.2009.19
Citation: *Molecular Systems Biology* 5:256

www.molecularsystemsbiology.com

molecular systems biology

Systems-level interactions between insulin–EGF networks amplify mitogenic signaling

Nikolay Borisov[1,6], Edita Aksamitiene[1,6], Anatoly Kiyatkin[1,6], Stefan Legewie[2], Jan Berkhout[1], Thomas Maiwald[1,3], Nikolai P Kaimachnikov[1,4], Jens Timmer[3], Jan B Hoek[1] and Boris N Kholodenko[1,5,*]

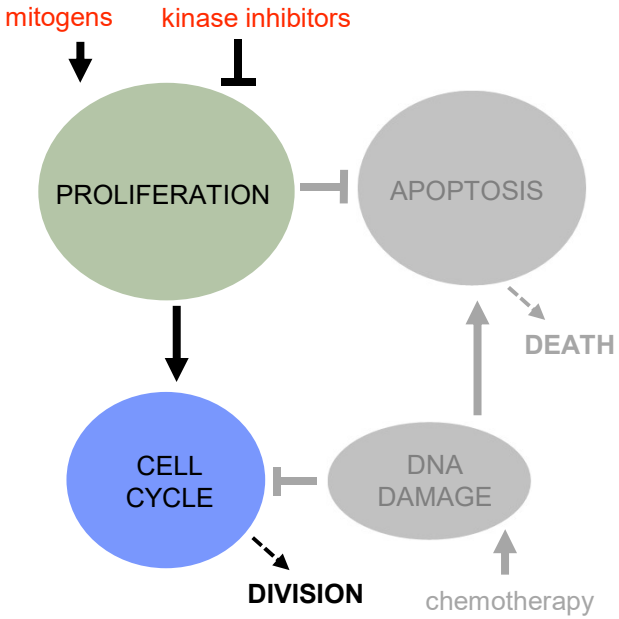


HEK293 cells

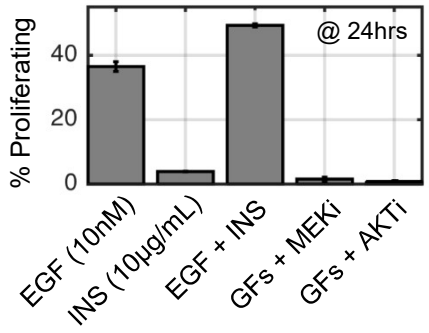
Short times (under 15 min)

Integrated Unit Testing – Cell Cycle

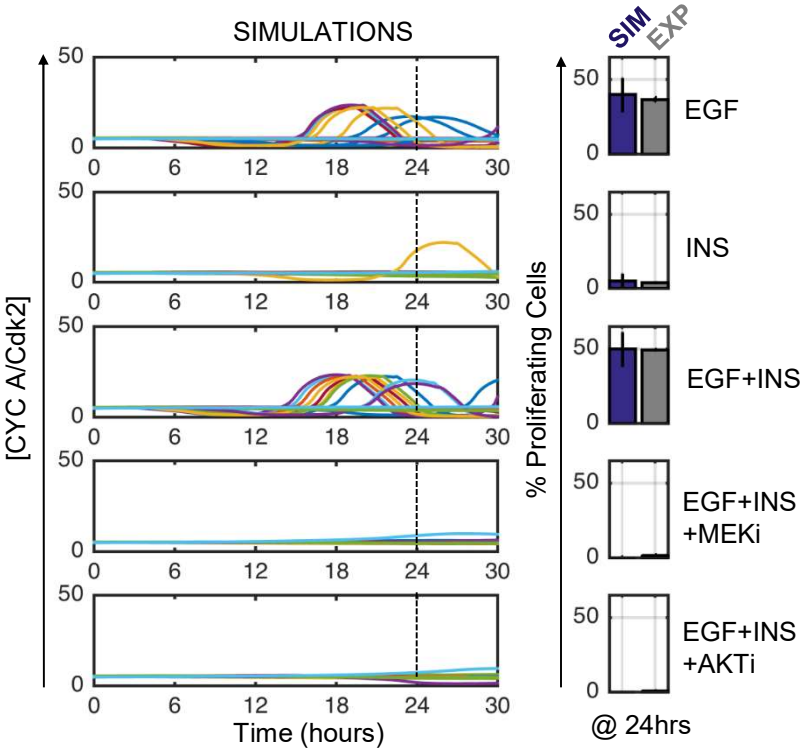
How are synergistic EGF and Insulin signals integrated by the cell?



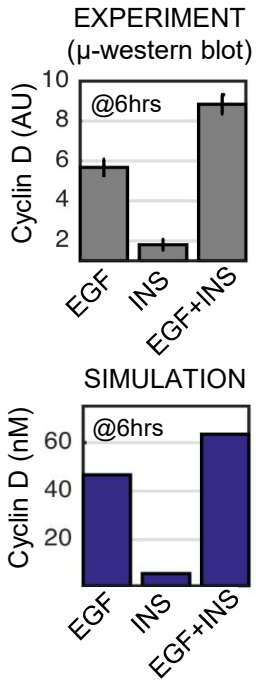
EXPERIMENT
(BrdU incorporation/ Flow cytometry)



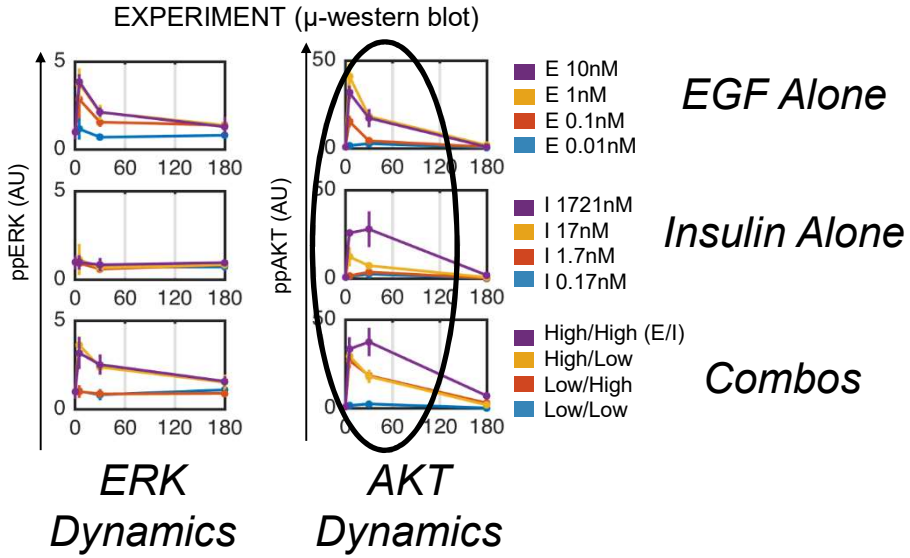
Cell Fate

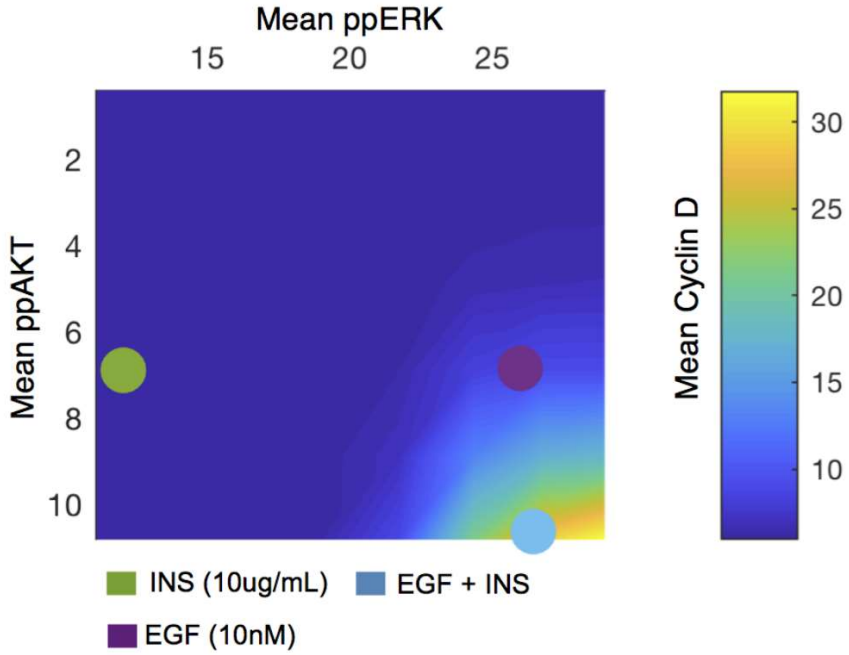


Biochemistry

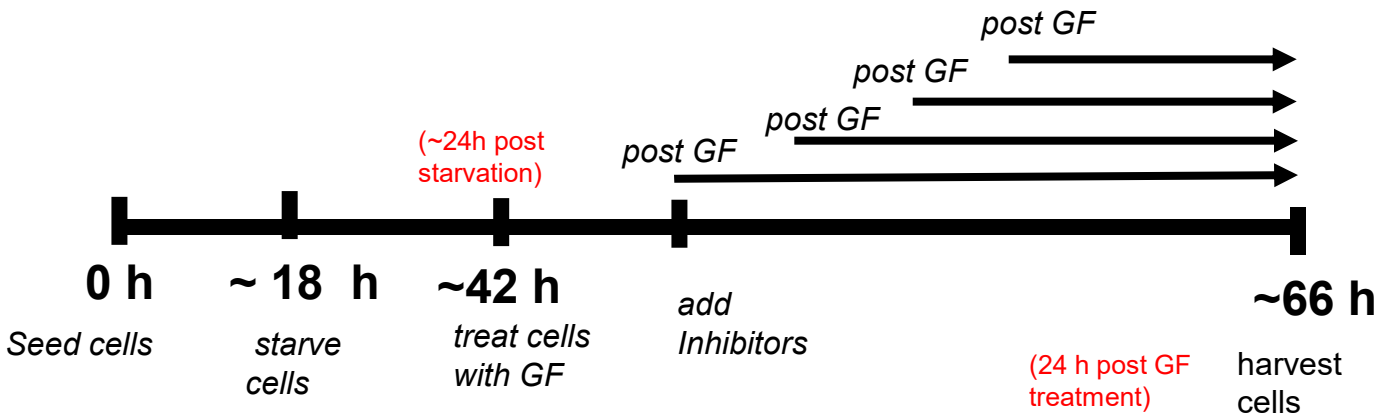


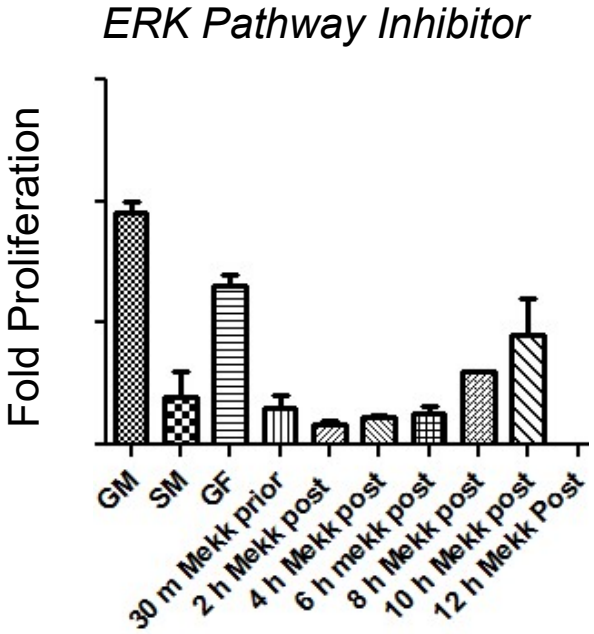
Analysis: Prolonged AKT Activation Explains EGF and Insulin S-Phase Synergy



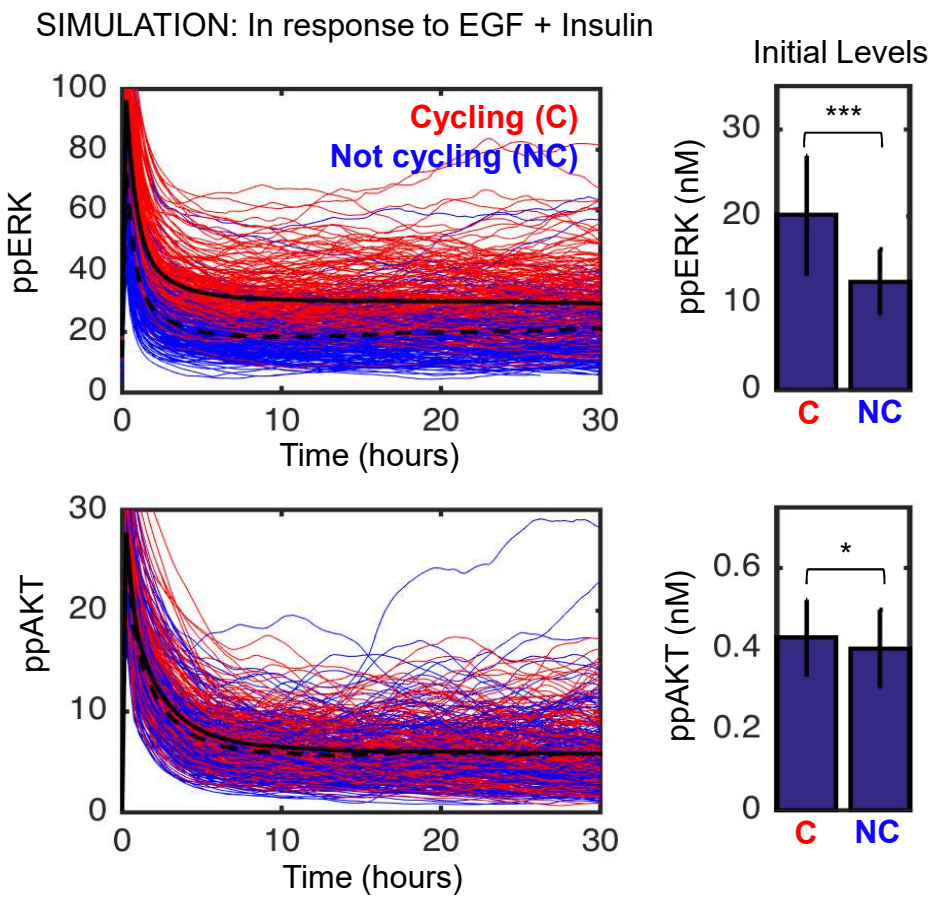


Inhibitor Time Course Experiments





Analysis – Cell Cycle:
Phospho-ERK levels dictate stochastic cell cycle entry



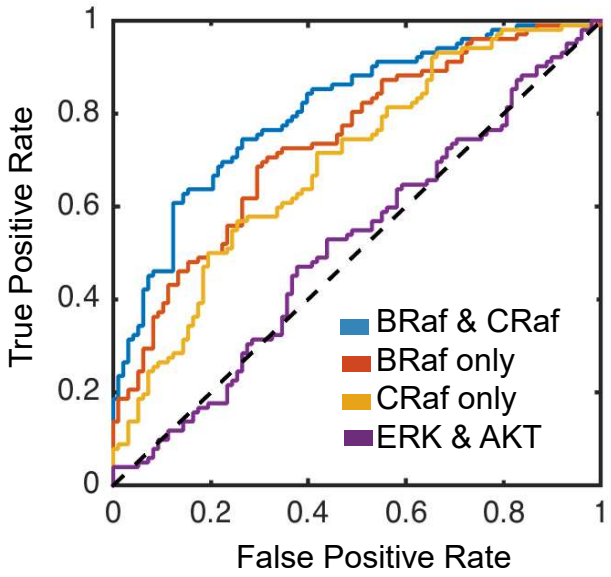
Analysis – Cell Cycle: Can Stochastic Cell Cycle Response Be Predicted?

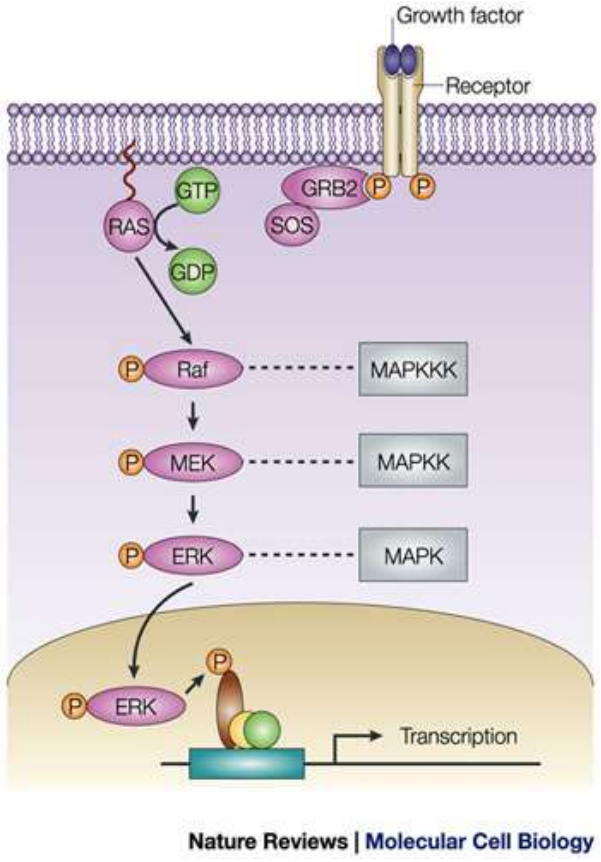
1. Lasso regression
   Predictors: Total initial protein levels
   Responses: Cycling or non-cycling
   → BRaf and CRaf were top hits

2. Train SVM classifier with top hits

3. Test performance of classifier

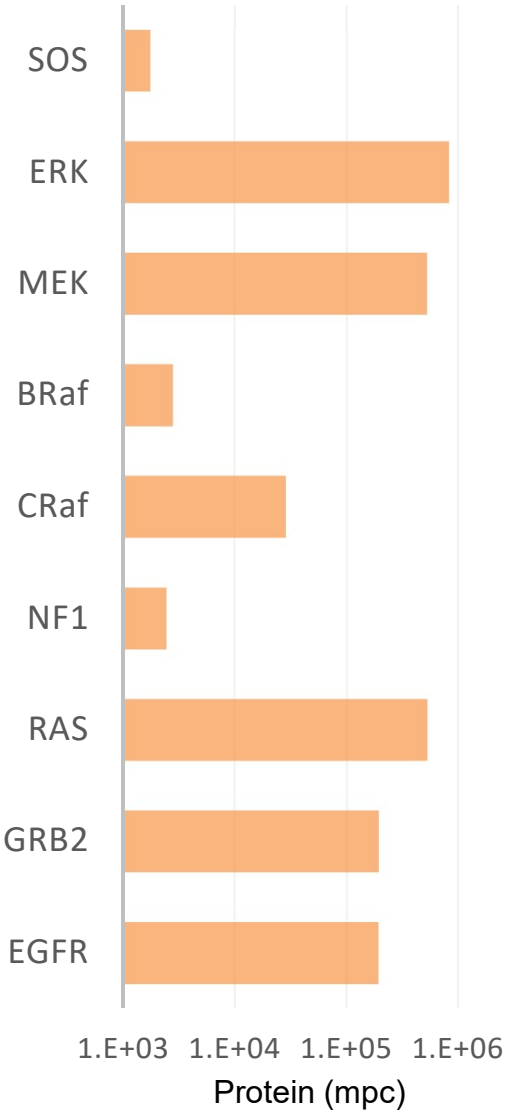
Based on total initial protein levels



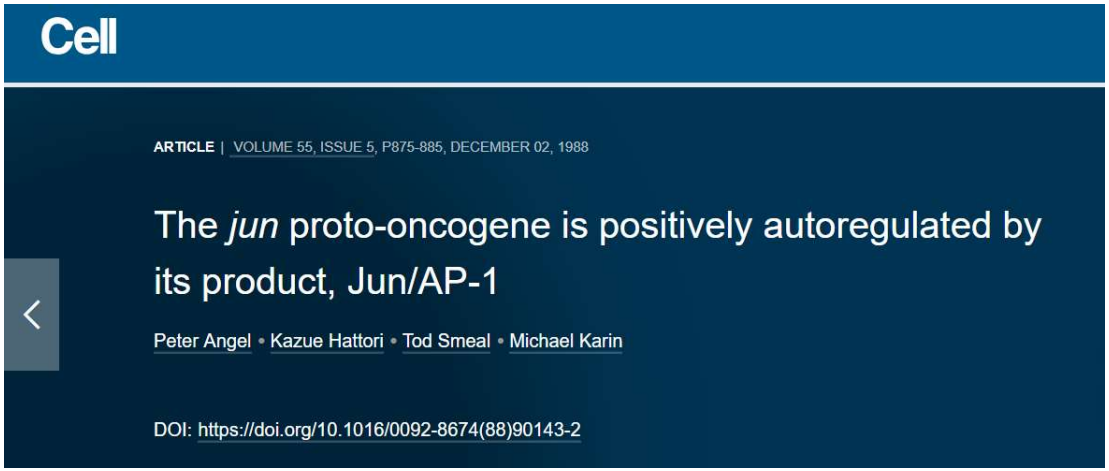


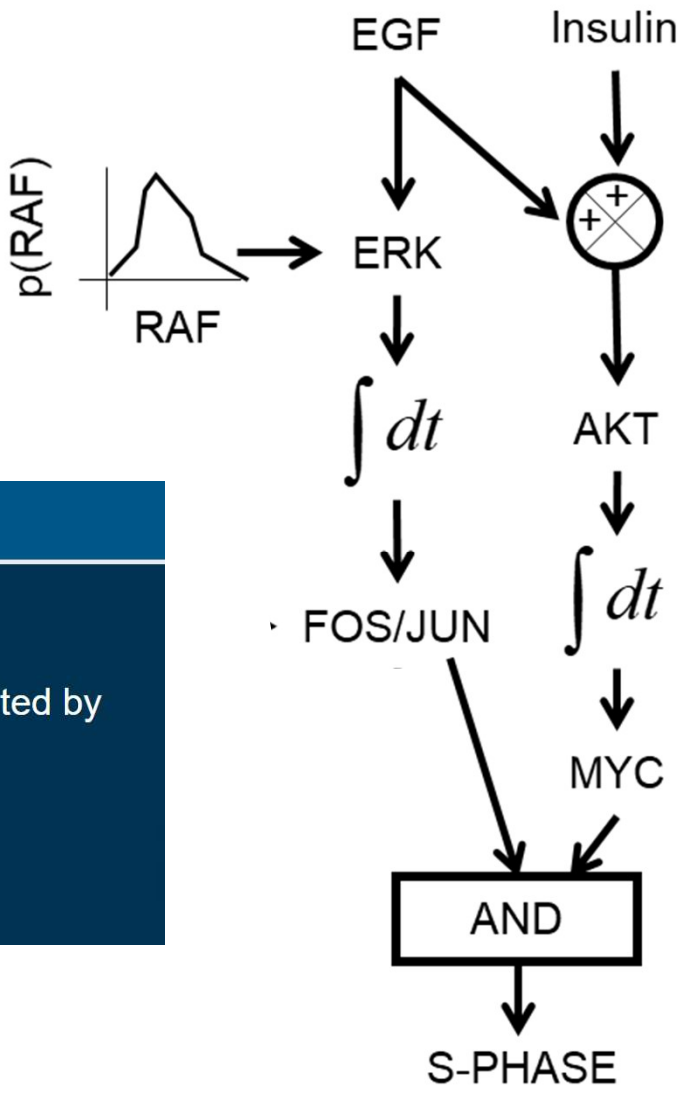
Kim and Bar-Sagi, Nat Rev Mol Cell Bio 2004

In MCF10A cells:

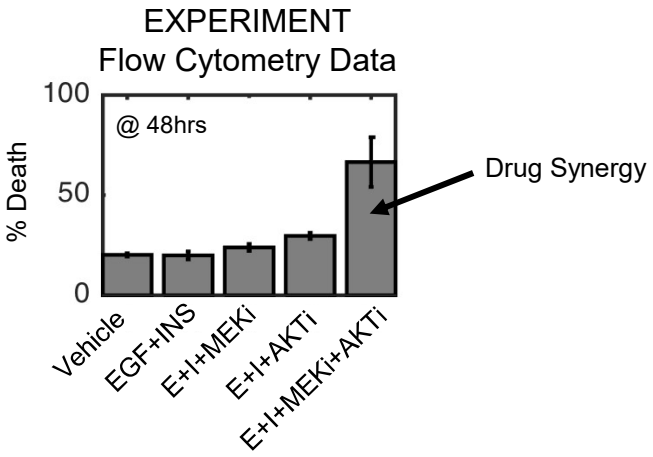


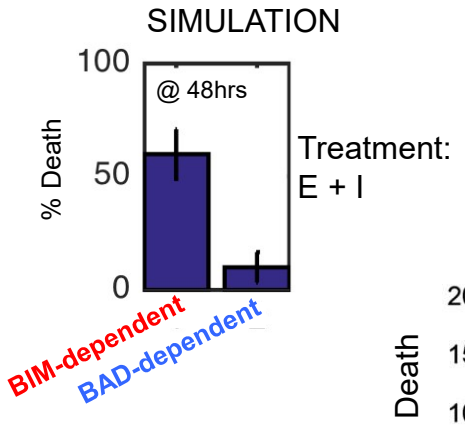
Emerging logic of integrative S-phase entry control

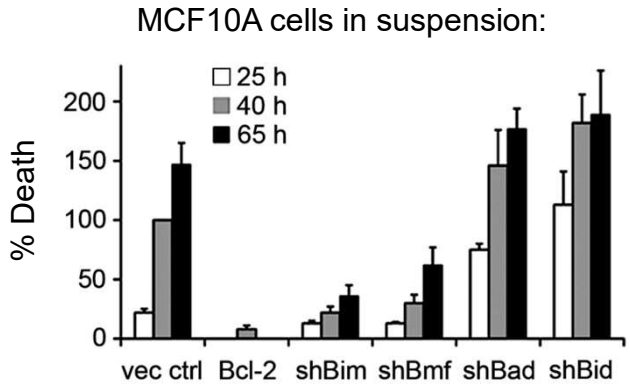




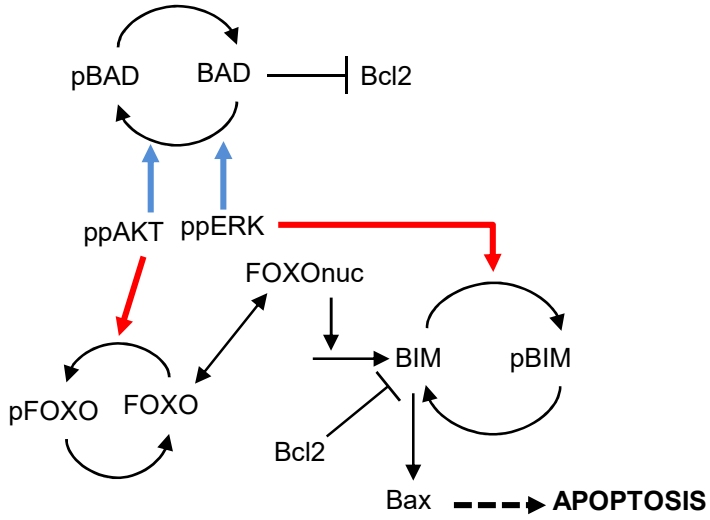
Analysis – Apoptosis: Mechanistic Insight into Drug Synergy





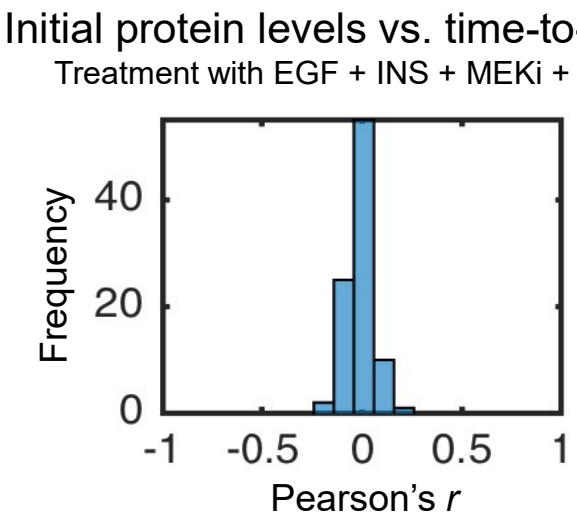


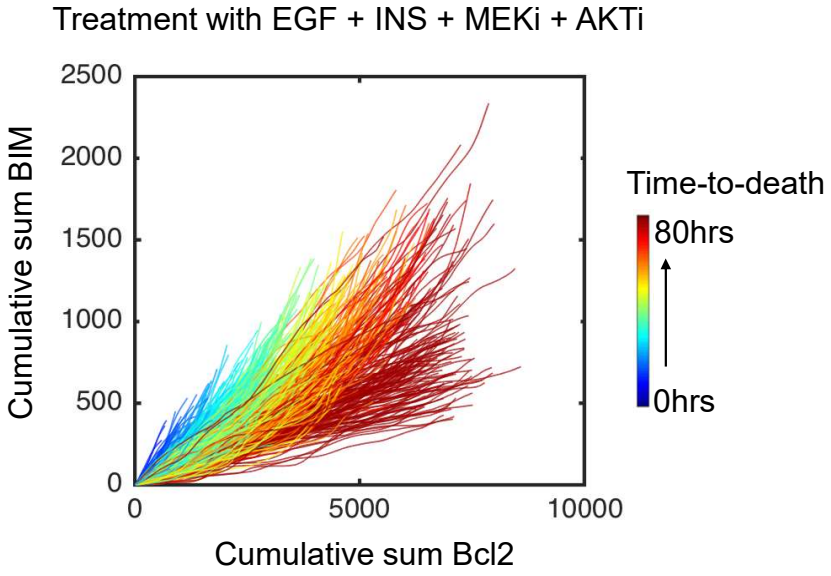
Schmelzle et al., PNAS, 2006

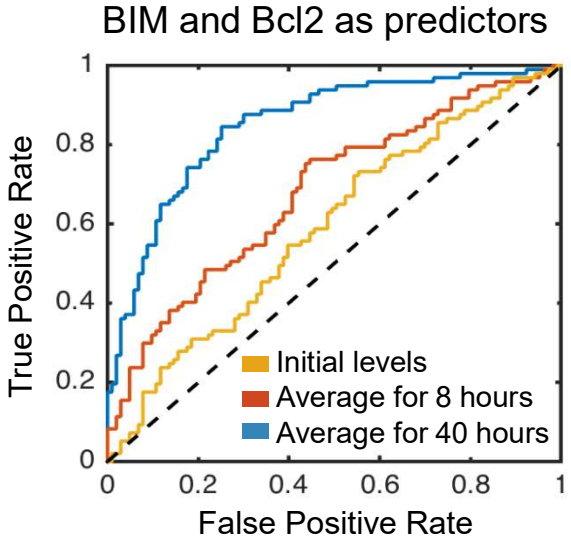


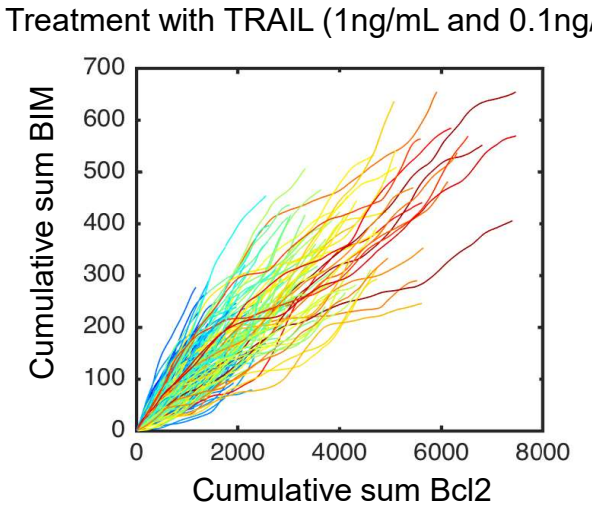
	ppERK	ppAKT	Total BIM Levels	Phos-BIM	Active BIM
MEKi	OFF	ON	Normal	Low	Low
AKTi	ON	OFF	High	High	Low
MEKi + AKTi	OFF	OFF	High	Low	High

Balance between BIM and Bcl2 levels over time predict the induction of intrinsic apoptosis



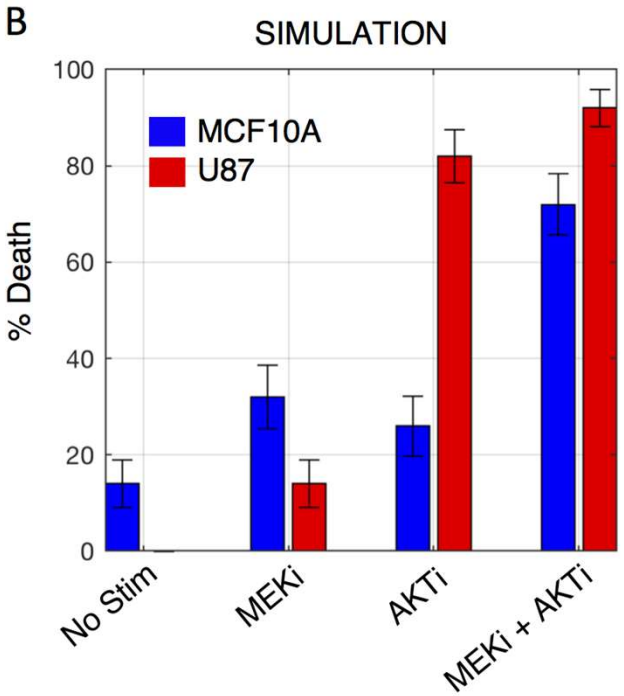


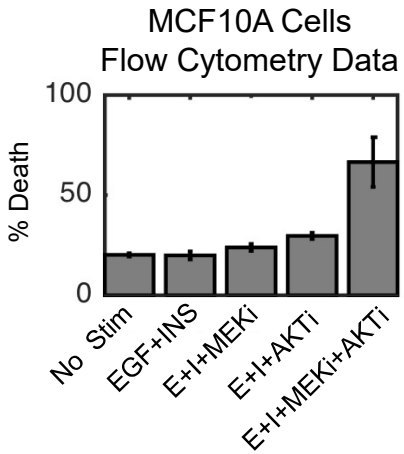




Is the Model Predictive in Different Contexts?

Tailoring: Model initialized with mRNAseq data (us) and mutations (literature) from U87 cells.





Outline

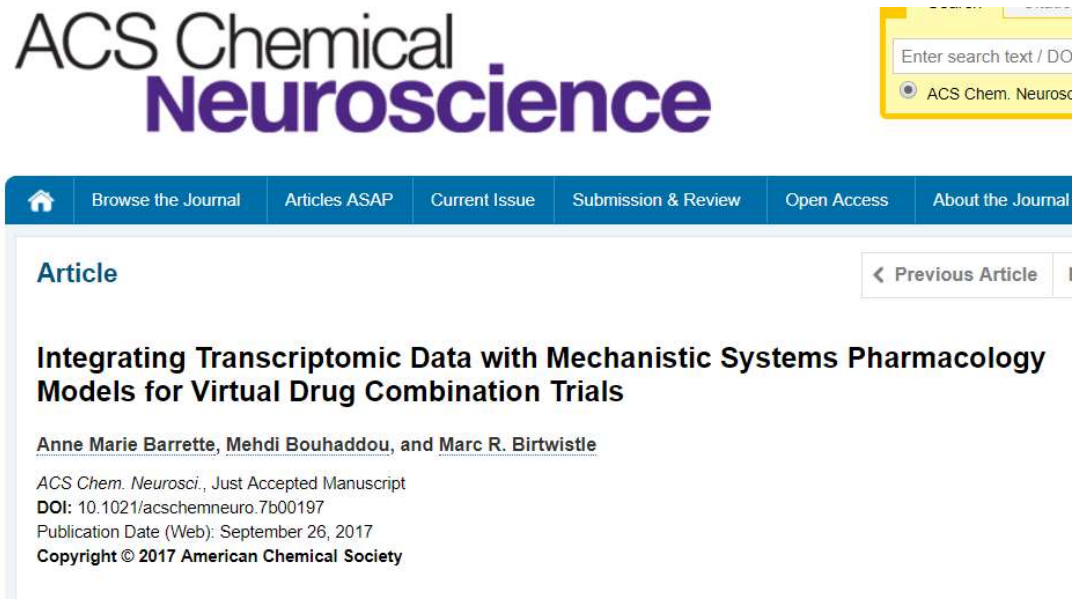
- Mechanistic Models of Cancer Cell Signaling
  - Formulation, Building, and Training
  - Stochastic Cell Cycle Entry
  - Stochastic Cell Death

- Towards Training with Big Pharmacological Data

- Reconstructing Cell Signaling Networks from Perturbation Time Course Data

Vision for Such Models

- Given a patient, what drug(s) to use?
  - Precision medicine
  - Dose and scheduling optimization
- Given a drug, what patient(s) will respond?
  - Inclusion in or exclusion from clinical trials
  - What drugs to combine



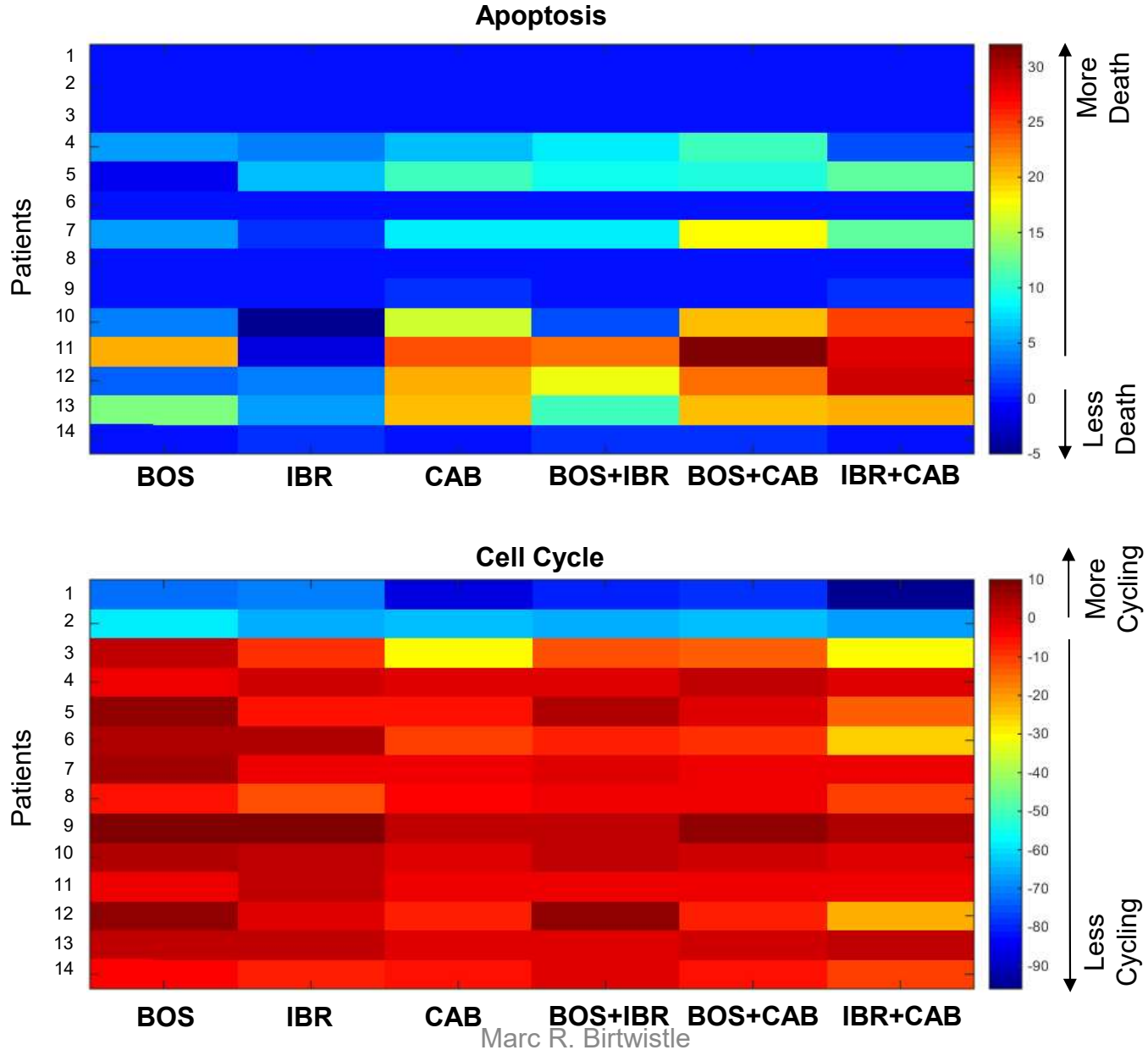
Tailoring the Model to 14 Glioblastoma (GBM) Patients from The Cancer Genome Atlas (TCGA)

Three Promiscuous Kinase Inhibitors or Their Combinations for a Heterogeneous Tumor

Modeling Three Promiscuous, Brain-Penetrant Kinase Inhibitors

Drug	Gene Targets	Model Targets	k_on (1/s/nM)	k_off (1/s)
Bosutinib	MAP2K1/MAP2K2	MEK	1	288
	RPS6KA1/RPS6KA3	RSK	1	1115
	PRKCA/PRKCG	PKC	1	1567
	CHEK1	Chk1	1	1168
	FGFR1	Fr	1	2206
	IGF1R	Ir	1	2285
	INSR	Isr	1	669
	PDGFRA	Pr	1	3081
Ibrutinib	BRAF	Braf	1	1128
	EGFR	E1	1	18
	ERBB3	E3	1	1
	FGFR1/FGFR2	Fr	1	707
	GSK3B	GSK3b	1	2571
	IGF1R	Ir	1	4882
	INSR	Isr	1	1326
	MTOR	mTOR	1	8091
	PDPK1	PDK1	1	2448
	PIK3CA/PIK3CB/PIK3CD/PIK3CG	PI3KC1	1	2039
	RAF1	Craf	1	2333
	RPS6KA1/RPS6KA3/RPS6KA2	RSK	1	6447
Cabozantinib	BRAF	Braf	1	2961
	EGFR	E1	1	864
	FGFR1/FGFR2	Fr	1	2153
	IGF1R	Ir	1	8236
	INSR	Isr	1	1880
	MAP2K1	MEK	1	214
	MET	MET	1	1
	PDGFRA	Pr	1	1
	PIK3CA	PI3KC1	1	1084
	PIK3R1	PI3KR1	1	1084
	RAF1	Craf	1	1078

Results Across Drugs and Patients

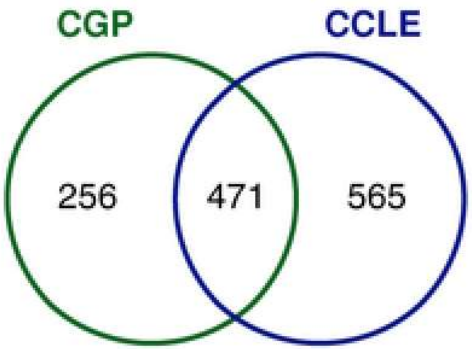


The Cancer Cell Line Encyclopedia (CCLE) and the Cancer Genome Project (CGP) Contain Pharmacogenomic Profiles of Cancer Cell Lines

CGP

CCLE

Cancer Cell Lines

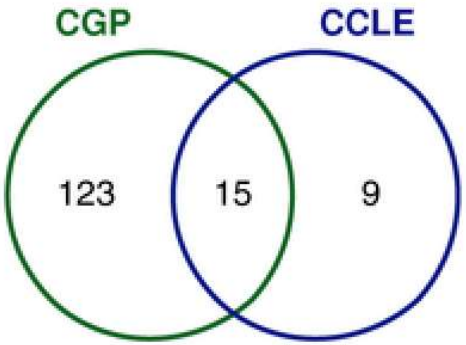


mRNA Sequencing
Microarray, RNAseq

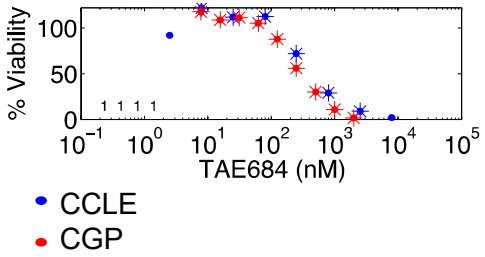
Gene Mutation Analysis
e.g. BRAF V600E

Copy Number Variation
e.g. EGFR amplification

Drugs



Drug Perturbation Studies



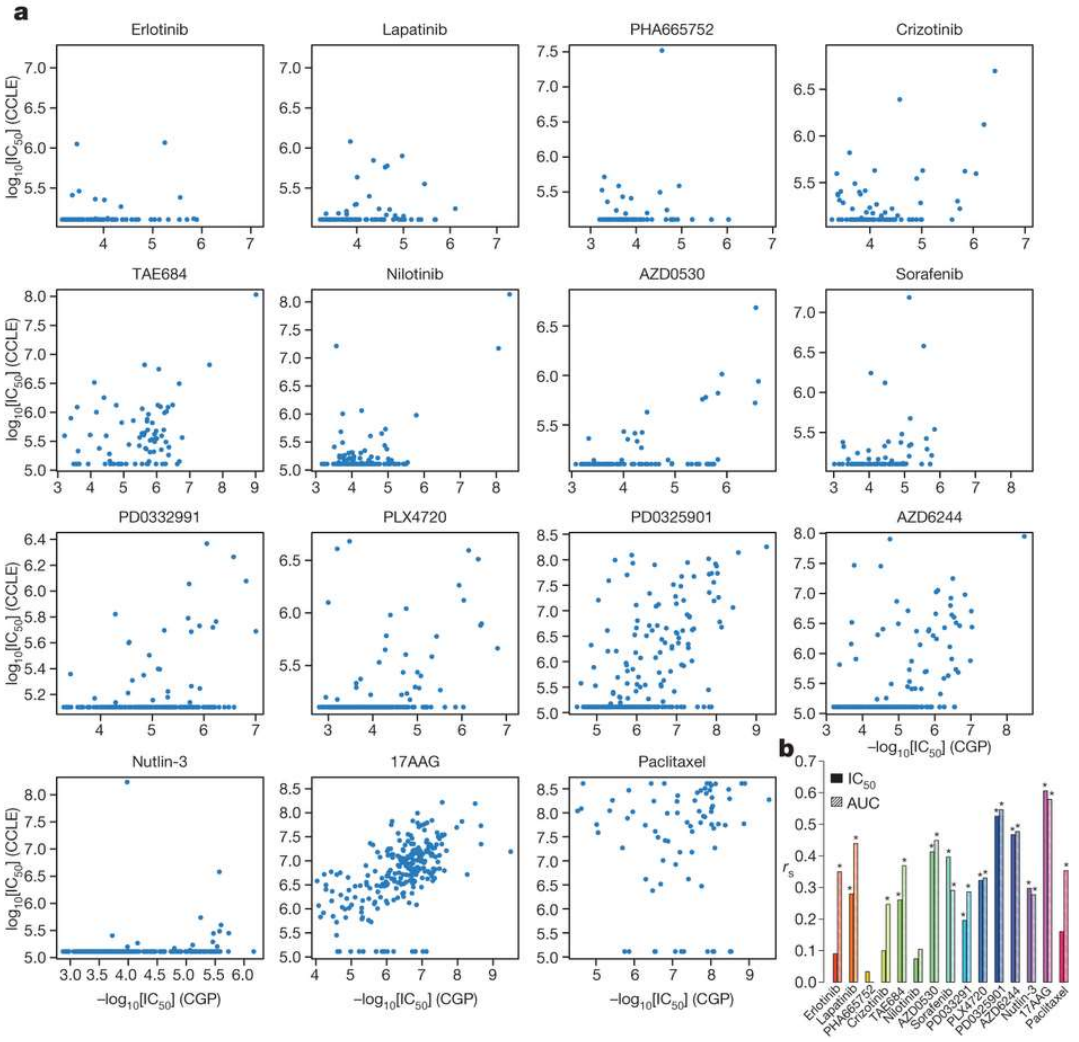
Compound	Target(s)	Class
Erlotinib	EGFR	Kinase inhibitor
Lapatinib	EGFR,HER2	Kinase inhibitor
PHA-665752	c-MET	Kinase inhibitor
Crizotinib	c-MET,ALK	Kinase inhibitor
TAE684	ALK	Kinase inhibitor
Nilotinib	Abl/Bcr-Abl	Kinase inhibitor
AZD0530	Src,Abl/Bcr-Abl,EGFR	Kinase inhibitor
Sorafenib	Flt3, C-KIT, PDGFRbeta, RET, Raf kinase B, Raf kinase C, VEGFR-1, KDR, FLT4	Kinase inhibitor
PD-0332991	CDK4/6	Kinase inhibitor
PLX4720	RAF	Kinase inhibitor
PD-0325901	MEK	Kinase inhibitor
AZD6244	MEK	Kinase inhibitor
Nutlin-3	MDM2	Other
17-AAG	HSP90	Other
Paclitaxel	beta-tubulin	Cytotoxic

ANALYSIS

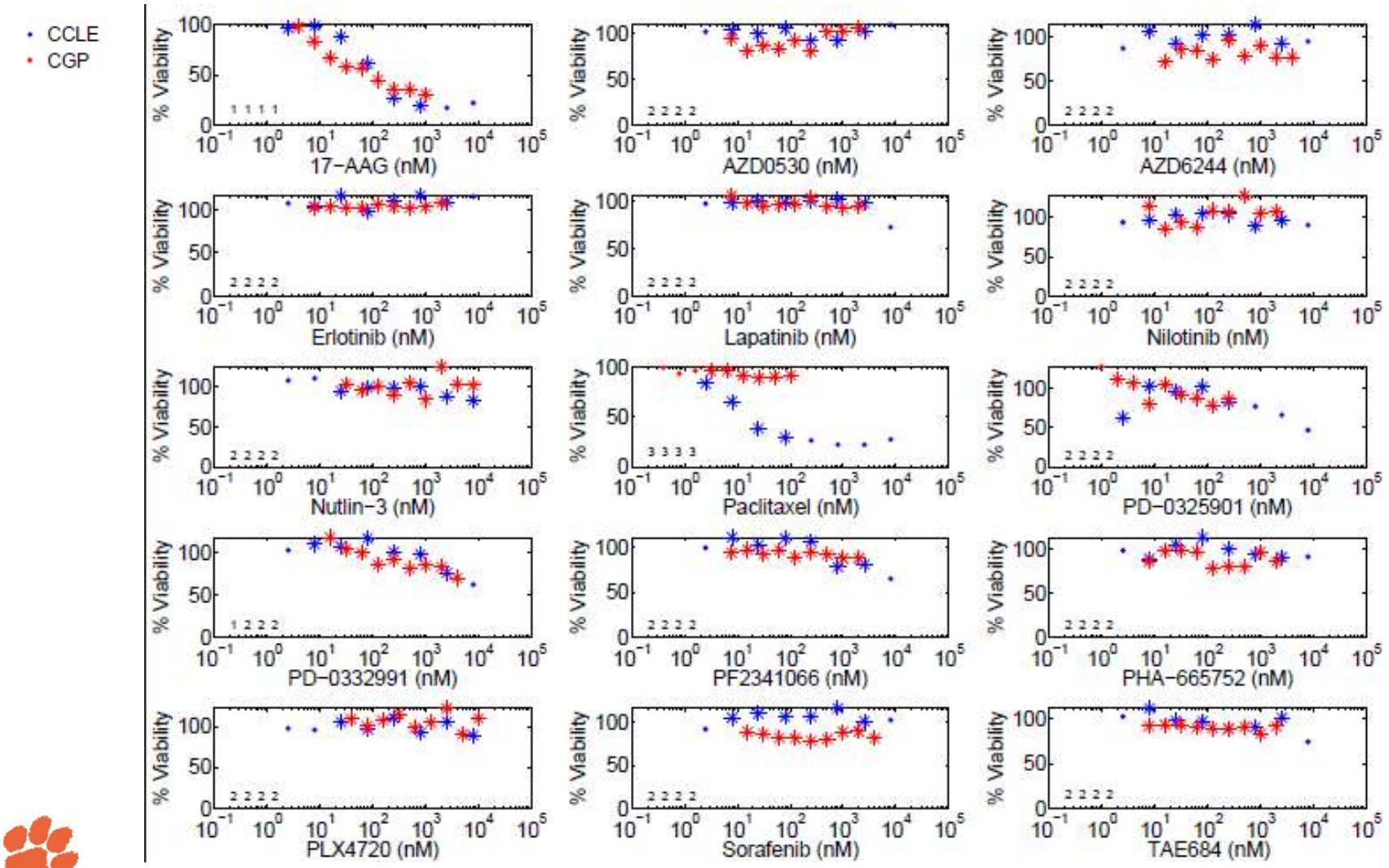
doi:10.1038/nature12831

Inconsistency in large pharmacogenomic studies

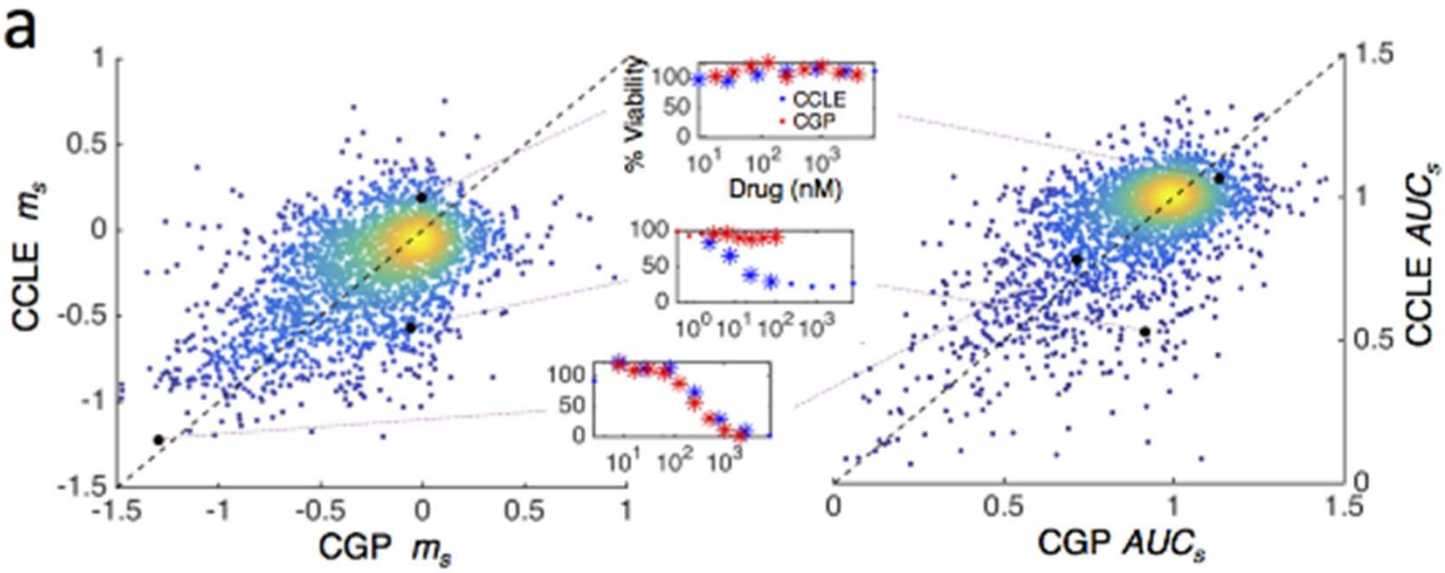
Benjamin Haibe-Kains[1,2], Nehme El-Hachem[1], Nicolai Juul Birkbak[3], Andrew C. Jin[4], Andrew H. Beck[4]*, Hugo J. W. L. Aerts[5,6,7]* & John Quackenbush[5,8]*



Comparing CCLE and CGP—Manual Look at U87 Responses



Slope and Area Under Curve Within Shared Dose Range Demonstrate Reasonable Quantitative Agreement

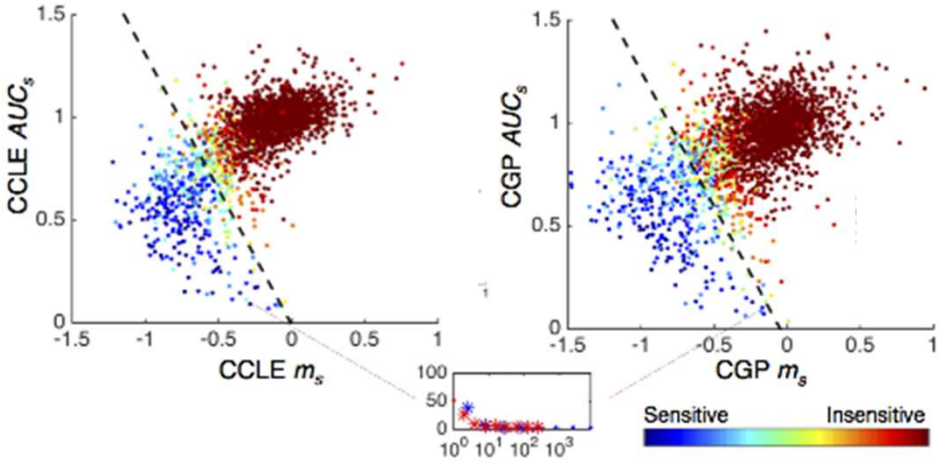


Many cell lines are insensitive to most drugs—IC50 is undefined and not expected to be consistent

Bouhaddou et al., Nature, 2016

Manual Curation of Binary Sensitivity Suggests Consistency

8 independent people manually determined binary sensitivity for all 2520 shared cell line/drug pairs



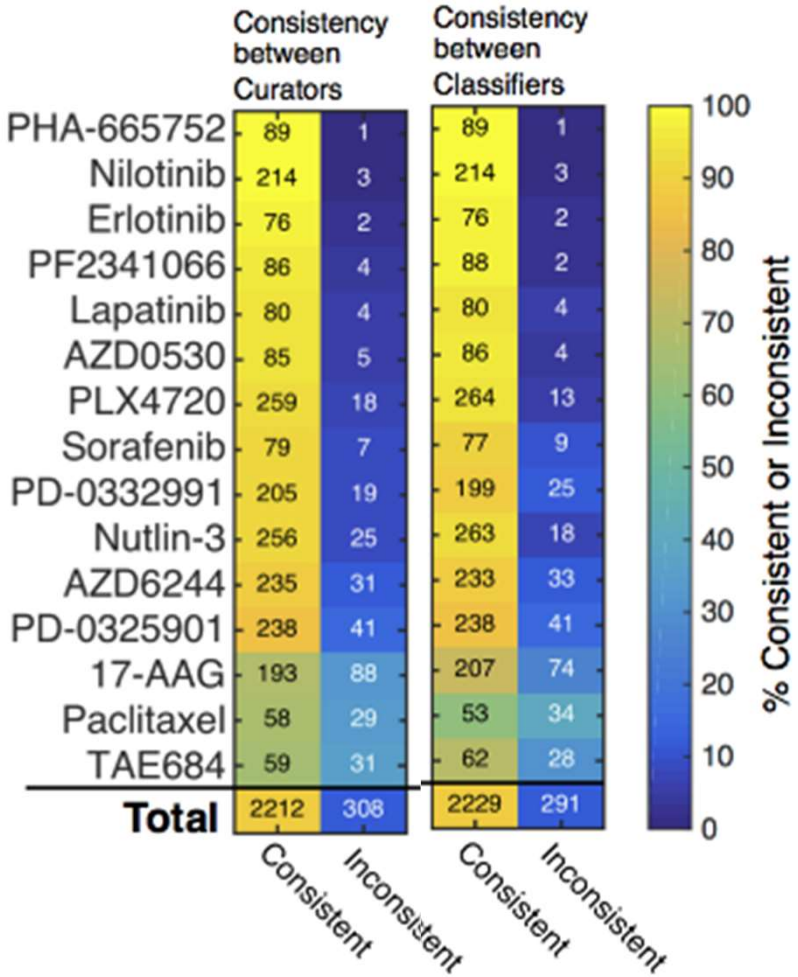
NATURE | BRIEF COMMUNICATION ARISING

Drug response consistency in CCLE and CGP

Mehdi Bouhaddou, Matthew S. DiStefano, Eric A. Riesel, Emilce Carrasco, Hadassa Y. Holzapfel, DeAnalisa C. Jones, Gregory R. Smith, Alan D. Stern, Sulaiman S. Somani, T. Victoria Thompson & Marc R. Birtwistle

Affiliations | Corresponding author

Nature **540**, E9–E10 (01 December 2016) | doi:10.1038/nature20580
Received 15 November 2014 | Accepted 13 October 2016 | Published online 30 November 2016 | Corrected online **19 July 2017**



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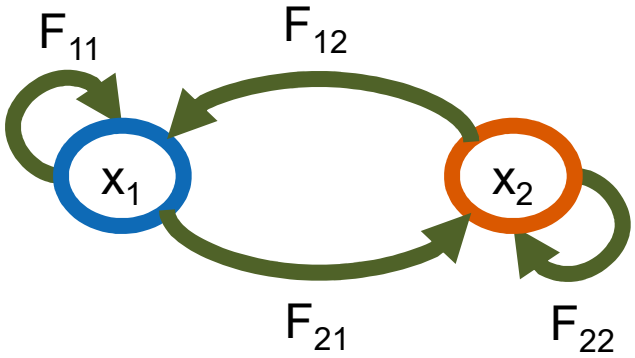
New Results

Network Reconstruction from Perturbation Time Course Data

Gregory R Smith, Mehdi Bouhaddou, Alan D Stern, Caitlin M Anglin, Orrod M Zadeh, Jake Erskin, Marc Birtwistle

doi: https://doi.org/10.1101/341008

Identifying Uncertain or Context-Specific Structural Aspects of Signaling Networks



Chicken and egg problem→causality when loops are present?

What experimental designs are sufficient to uniquely identify all such edges, their directionality, and some information about their magnitude?

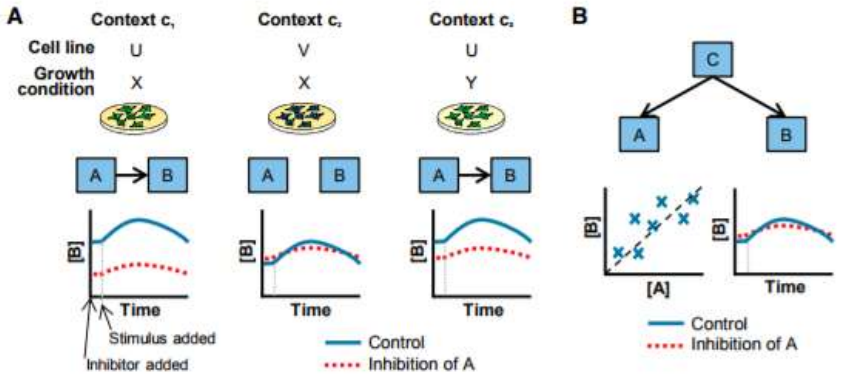
Perturbation Time Courses Can Help

Cell Systems
Article

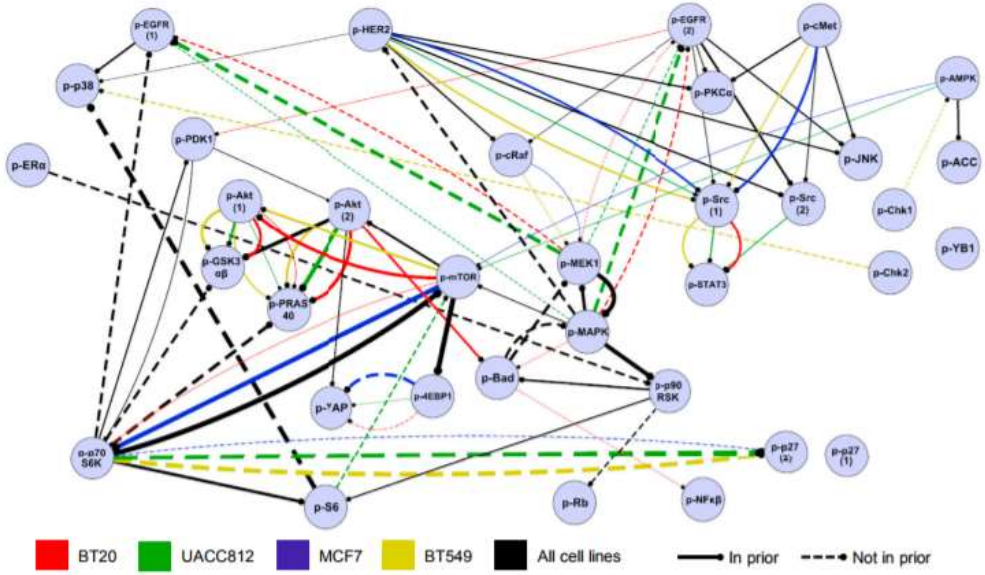
Context Specificity in Causal Signaling Networks Revealed by Phosphoprotein Profiling

Steven M. Hill,[1,12] Nicole K. Nesser,[2,12] Katie Johnson-Camacho,[2] Mara Jeffress,[3] Aimee Johnson,[4] Chris Boniface,[2] Simon E.F. Spencer,[5] Yiling Lu,[6] Laura M. Heiser,[7] Yancey Lawrence,[2,13] Nupur T. Pande,[8,9] James E. Korkola,[7] Joe W. Gray,[7,9,10] Gordon B. Mills,[6] Sach Mukherjee,[1,11,14,*] and Paul T. Spellman[2,15,*]

Direct vs. Indirect Effects



Context-Specific Edges



What perturbation time courses are sufficient to uniquely identify all such edges, their directionality, and (perhaps) some information about their magnitude?

Can we infer loops, including self-regulation?

Dynamic Modular Response Analysis

BIOINFORMATICS

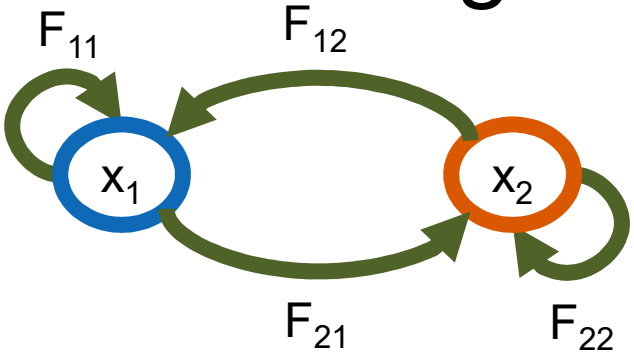
Vol. 20 no. 12 2004, pages 1877–1886
doi:10.1093/bioinformatics/bth173

Inferring dynamic architecture of cellular networks using time series of gene expression, protein and metabolite data

Eduardo Sontag[1], Anatoly Kiyatkin[2] and Boris N. Kholodenko[2,]*

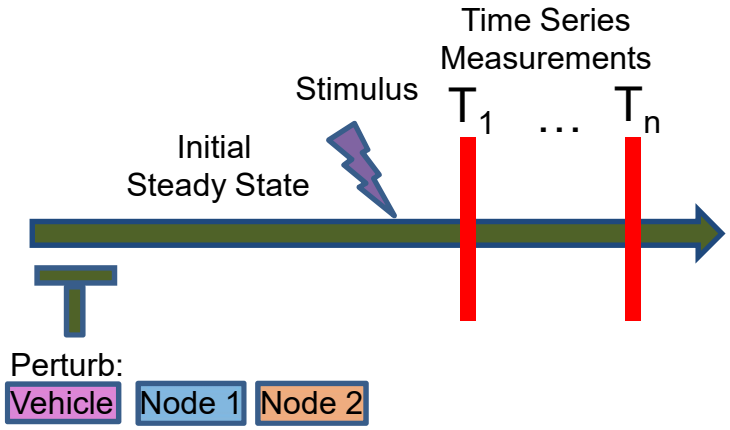
- Requires two perturbations per node (e.g. production and consumption)
- Requires estimates of 1st and 2nd time derivatives

A Sensible Perturbation Time Course Design Could Be Sufficient



$$\left.\frac{dx_1}{dt}\right|_{t=t_{k+1}} = f_1(x_1(k+1),x_2(k+1)) \approx f_1(x_1(k),x_2(k)) + \underbrace{\frac{\partial}{\partial x_1}\left(f_1(x_1(k),x_2(k))\right)}_{F_{11}}\left(x_1(k+1)-x_1(k)\right) + \underbrace{\frac{\partial}{\partial x_2}\left(f_1(x_1(k),x_2(k))\right)}_{F_{12}}\left(x_2(k+1)-x_2(k)\right)$$

$$\left.\frac{dx_2}{dt}\right|_{t=t_{k+1}} = f_2(x_1(k+1),x_2(k+1)) \approx f_2(x_1(k),x_2(k)) + \underbrace{\frac{\partial}{\partial x_1}\left(f_2(x_1(k),x_2(k))\right)}_{F_{21}}\left(x_1(k+1)-x_1(k)\right) + \underbrace{\frac{\partial}{\partial x_2}\left(f_2(x_1(k),x_2(k))\right)}_{F_{22}}\left(x_2(k+1)-x_2(k)\right)$$



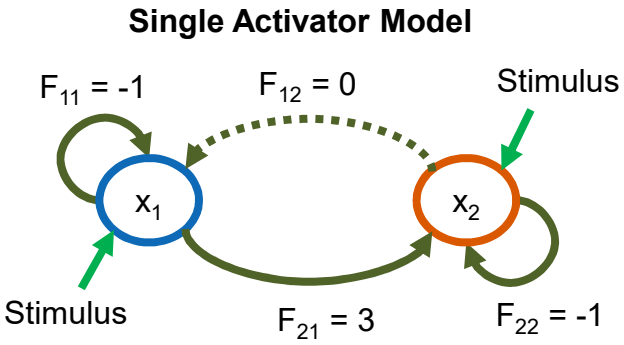
$$\begin{bmatrix} y_1(k) \\ y_1^{(2)}(k) \end{bmatrix} = \begin{bmatrix} x_1(k+1)-x_1(k) & x_2(k+1)-x_2(k) \\ x_1^{(2)}(k)-x_1(k) & x_2^{(2)}(k)-x_2(k) \end{bmatrix} \begin{bmatrix} F_{11}(k) \\ F_{12}(k) \end{bmatrix}$$

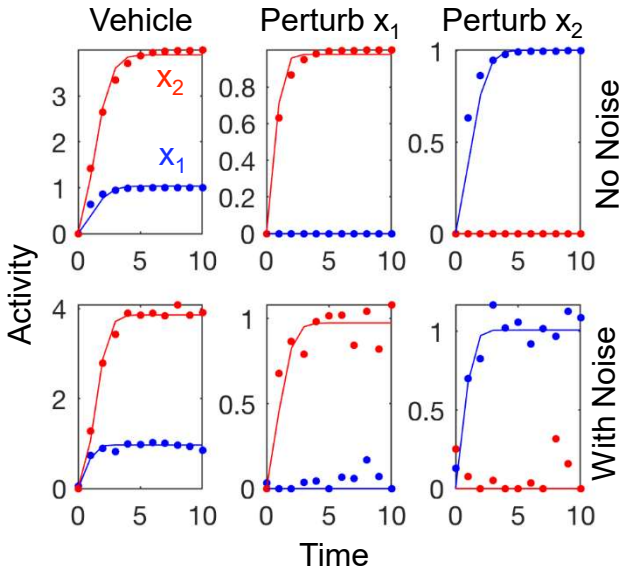
$$\begin{bmatrix} y_2(k) \\ y_2^{(1)}(k) \end{bmatrix} = \begin{bmatrix} x_1(k+1)-x_1(k) & x_2(k+1)-x_2(k) \\ x_1^{(1)}(k)-x_1(k) & x_2^{(1)}(k)-x_2(k) \end{bmatrix} \begin{bmatrix} F_{21}(k) \\ F_{22}(k) \end{bmatrix}$$

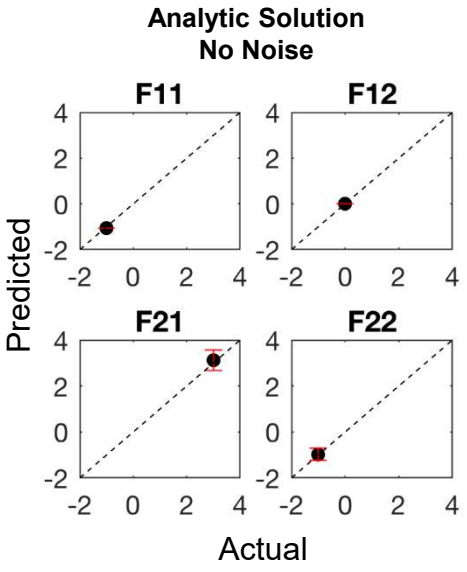
Calculated from Data

To Learn

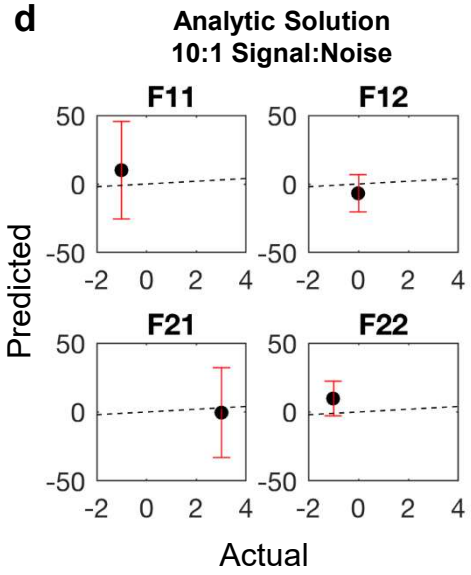
Practical Implementation



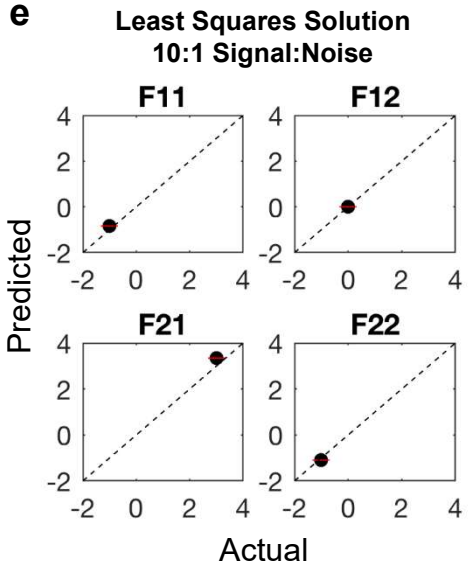




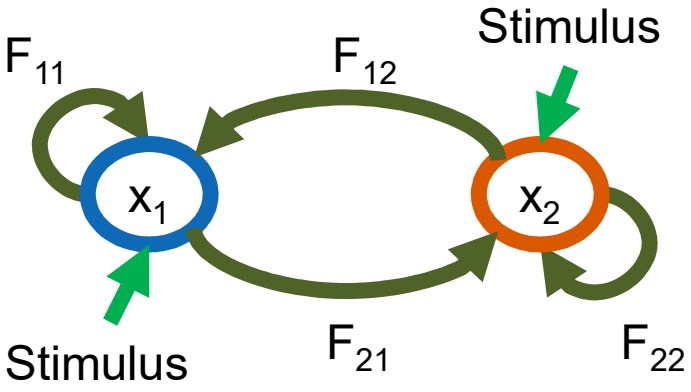
d



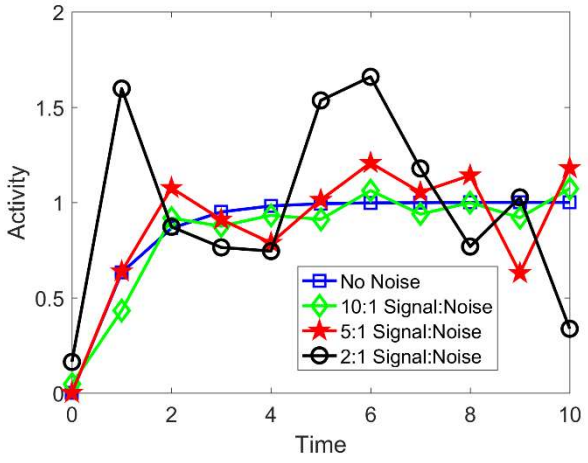
e



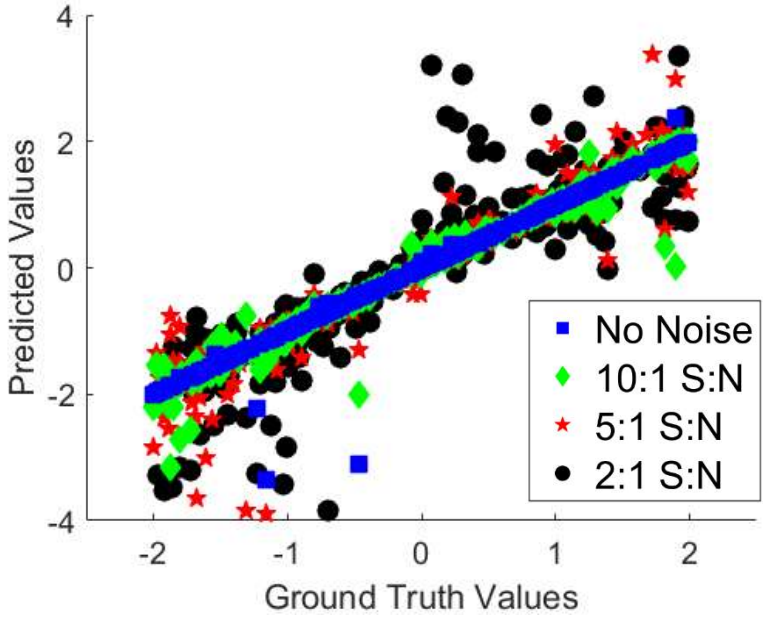
Random Two Node Systems

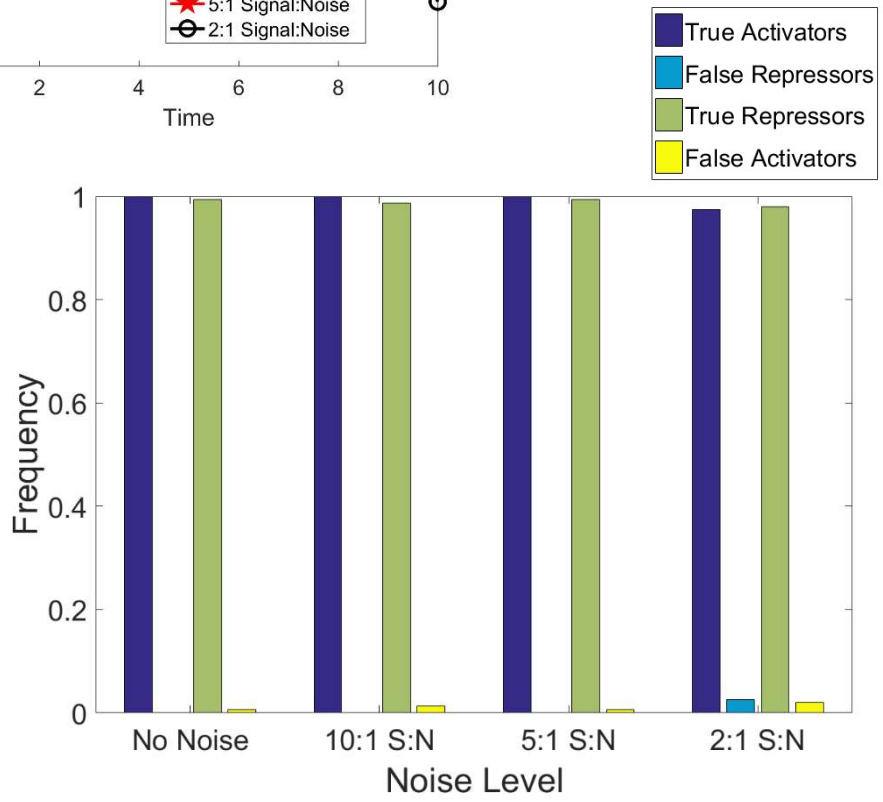


Sample Across Values

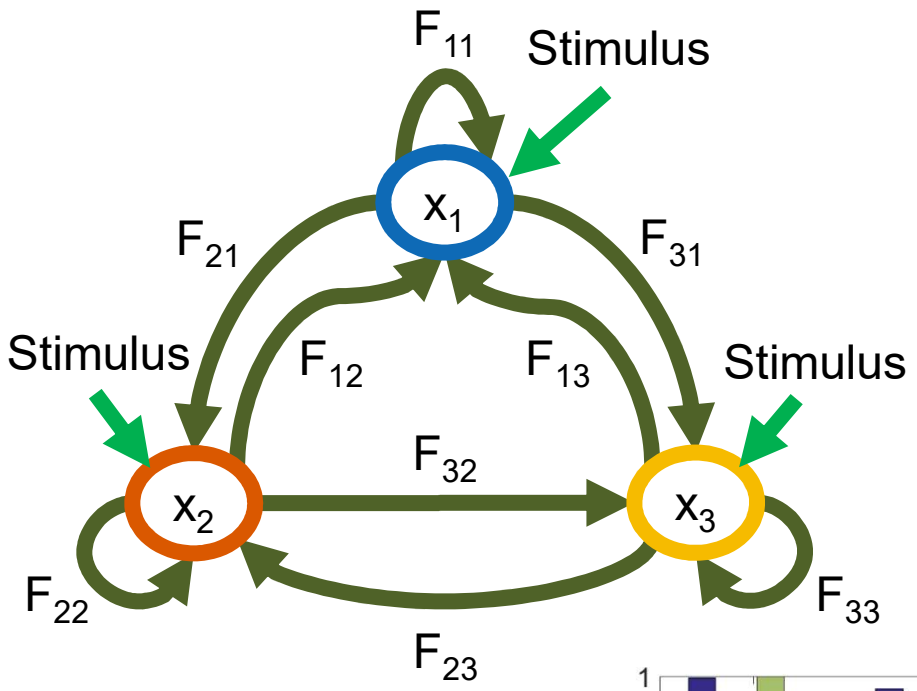


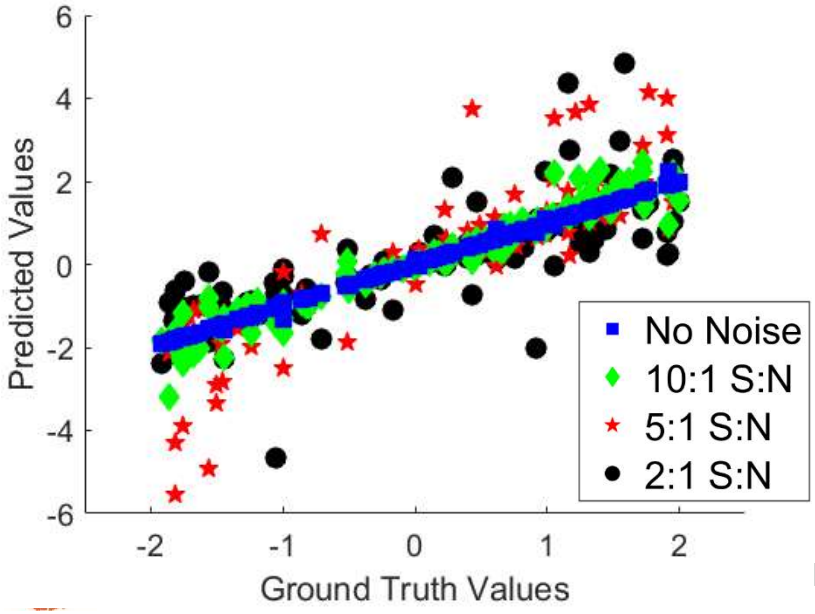
Example Simulated Time Courses

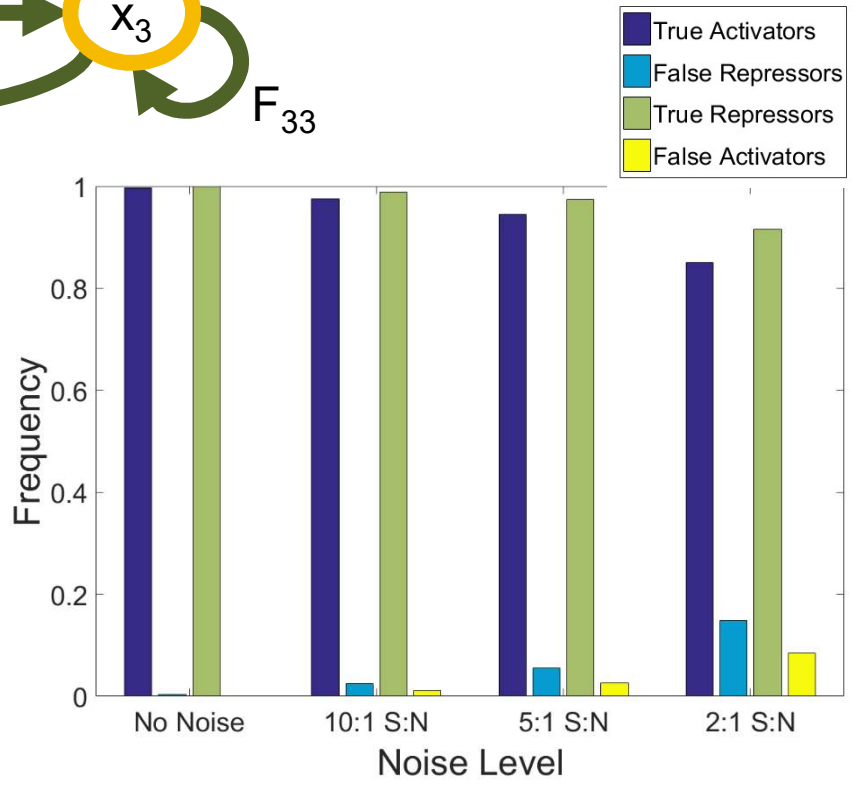




Random Three Node Systems







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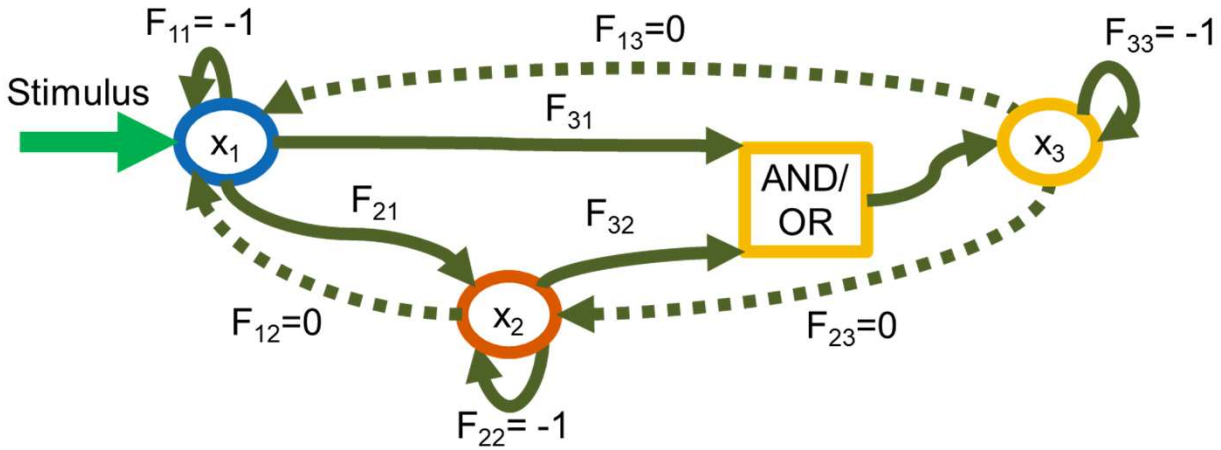
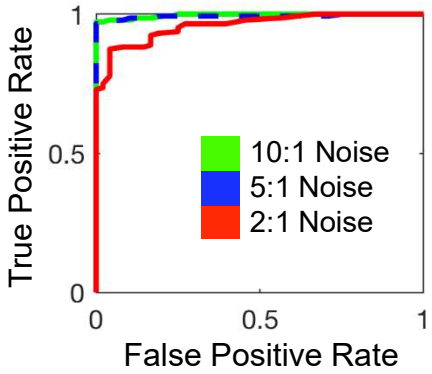
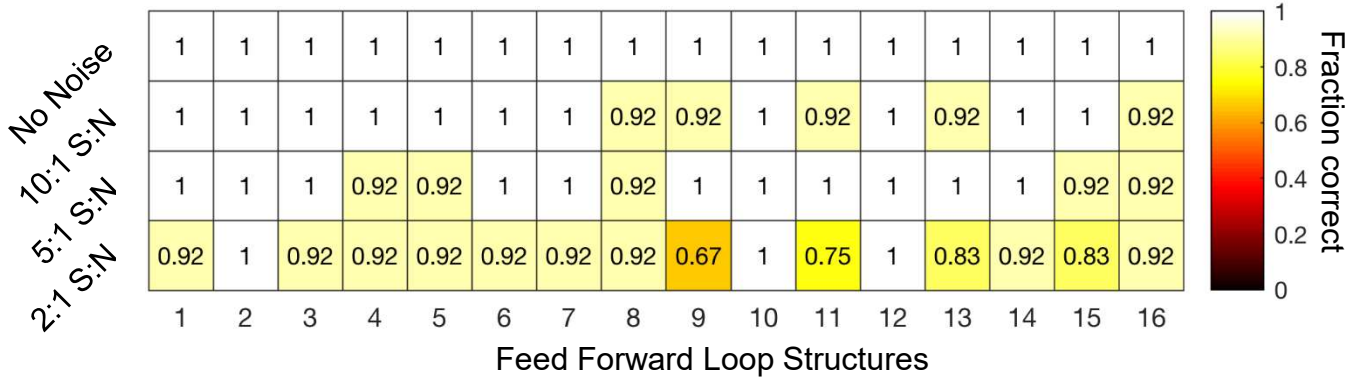
Sixteen Different Feedforward Loop Models







Remaining Questions

- How does performance scale to larger networks?
- How can we effectively incorporate prior knowledge?
- What about “dirty” perturbations?

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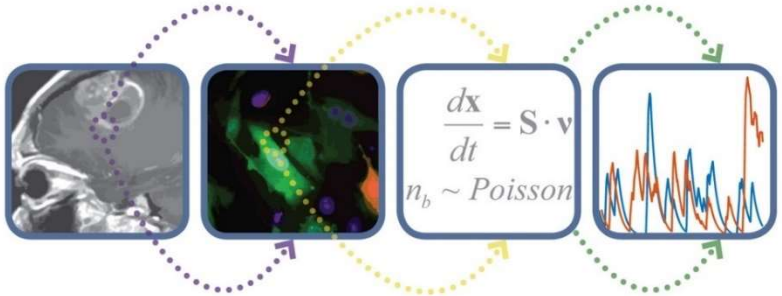
CHEMICAL AND BIOMOLECULAR ENGINEERING



SINGLE-CELL CANCER SYSTEMS BIOLOGY AND PHARMACOLOGY

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–Roche

DToxS

IMAT Innovative Molecular Analysis Technologies

gsk

Roche

Mehdi Bouhaddou

Anne Marie Barrette

Greg Smith

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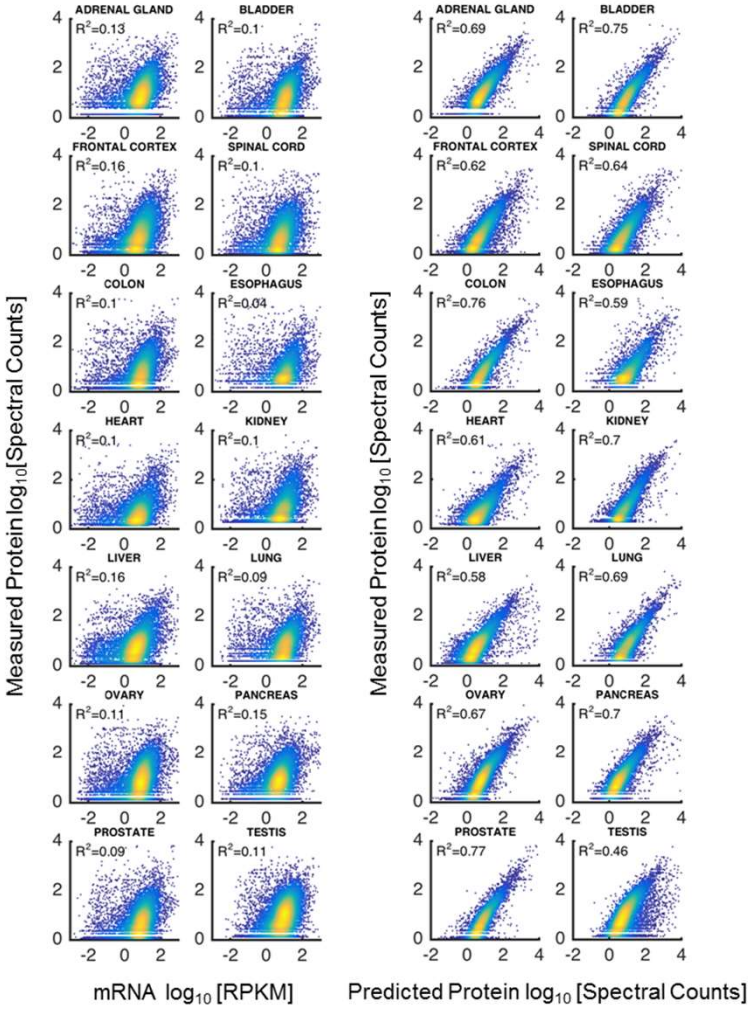
Predicting Protein Levels from mRNA Levels

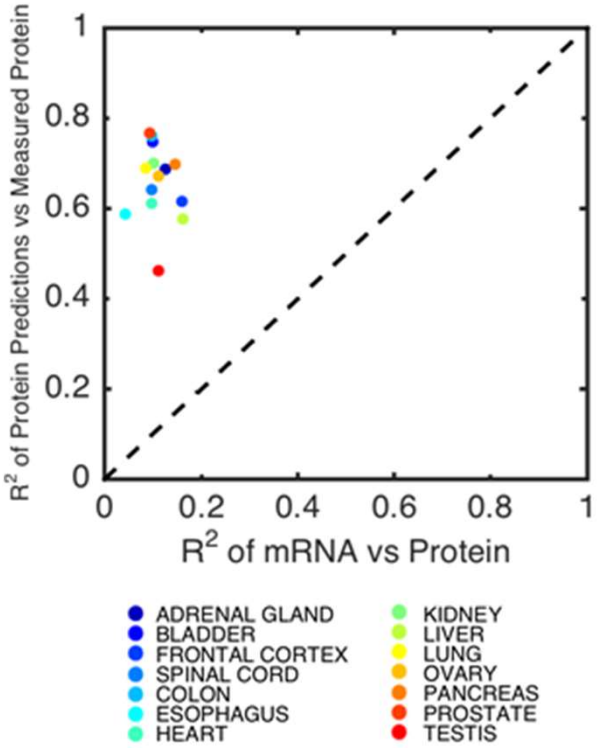
$$p_i = \frac{m_i \cdot k_{bp}}{k_{dp}}$$

Assume Single Ratio for All Genes

Estimate Single Ratio per Gene, But Same Across Tissues

$$p_i = \frac{m_i \cdot k_{bpi}}{k_{dpi}}$$





Data from GTEx and Human Proteome Map for 14 Tissue Types

Alief Moulana, Mehdi Bouhaddou and DeAnalisa Jones, Under Revision