Dynamic models for personalized QSP

How models can help us explore big data

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Big Data

Historically, mathematical modeling has enabled us to represent the essential information from (small) data in a way that quantified relations

Then big data (data sets that are too complex for traditional data-processing) came along and promised to provide “empirically derived associations that can generate novel and useful hypotheses”.

In “pharma”, big data is usually related to genetic and HT information (and others)

But numerous issues have come up:

1) Technical inconsistencies across platforms
2) Intrinsic variability at many levels
3) Heterogeneity of complex, multifactorial diseases


BMJ

BMJ 2012;344:e2161 doi: 10.1136/bmj.e2161 (Published 3 April 2012) Page 1 of 5

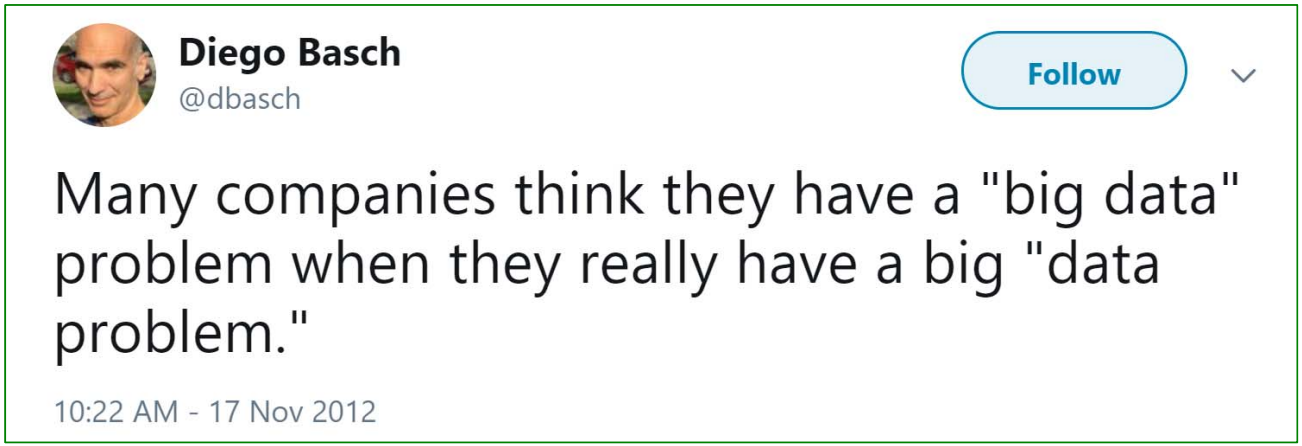
Personalised medicine: not just in our genes

Despite the identification of numerous gene-drug associations, few have been incorporated into clinical practice or guidelines. **Georgios D Kitsios** and **David M Kent** argue that if personalised medicine is to become a reality we have to look beyond our genes

Georgios D Kitsios *researcher*[1 2], David M Kent *director*[3 1]

“the notion that genetic information is uniquely important in determining the risks and benefits of treatments is clearly unwarranted and counterproductive to the broadly shared goal of tailoring care to individuals”

“Big data” problem vs. Big “data problem”



Smart Data

Smart data = {data analytics}
+ {domain knowledge}
+ {systems modeling}

Alzheimer & Dementia, 12(9):1014, 2016

Main ideas I wish to discuss:

1. {domain knowledge} + {systems modeling} may provide an actionable way for bringing big(er) data together in a meaningful way
2. Model structure and model dynamics is a better way of looking at data, as opposed to the data

The big picture

Trying to figure out

1. If there is a problem
2. What caused the problem
3. How to fix the problem

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If … by and large we are driven by the concept of "the" biomarker, i.e., [an] objective indication of [the] medical state observed from outside the patient (*Curr Opin HIV AIDS*, 5(6):463, 2010)

What … we then establish a functional relation between the biomarker and a likely deregulation of a mechanism

How … and finally, we attempt to manipulate the mechanism using a substance i.e., drug, the can induce the desired change on the mechanism.

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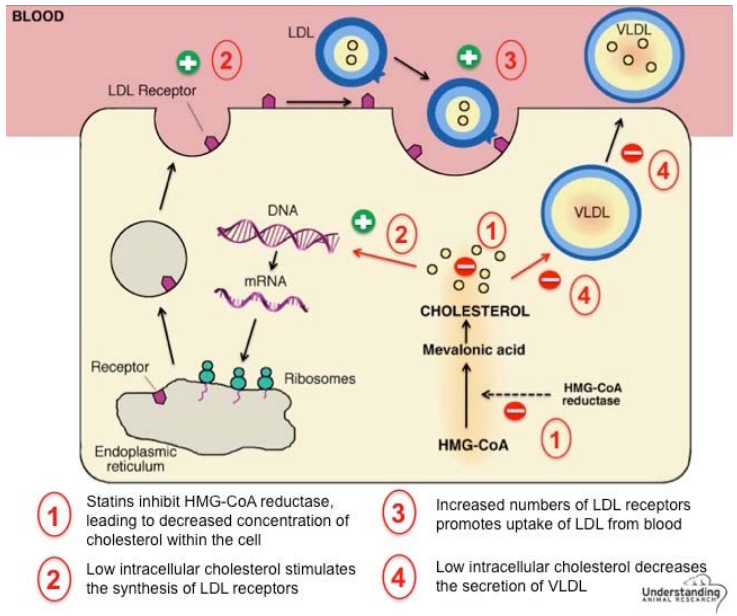

http://www.animalresearch.info/en/drug-development/drug-prescriptions/simvastatin/

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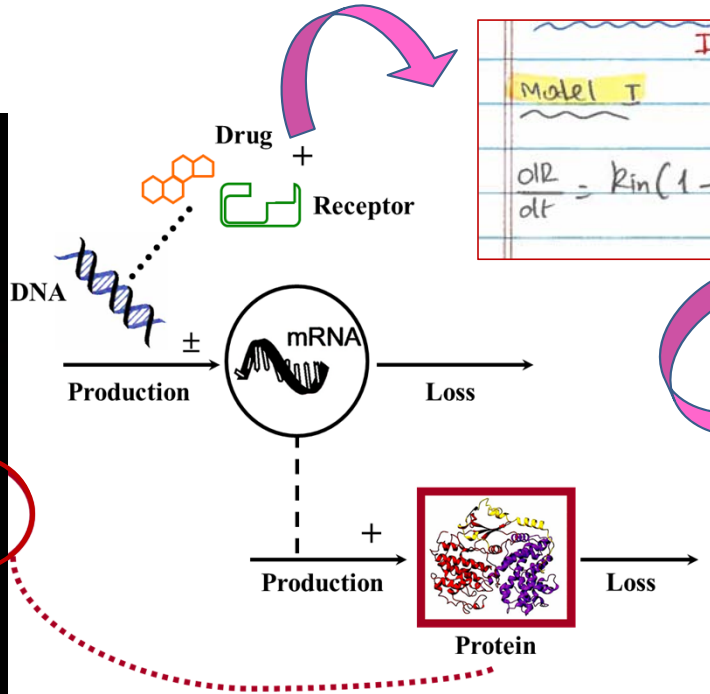
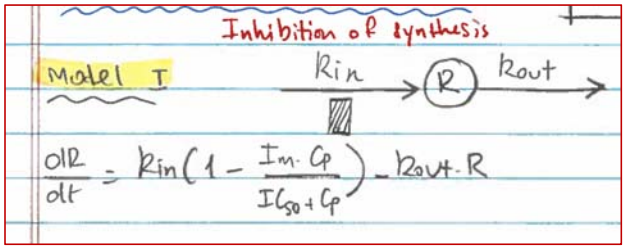
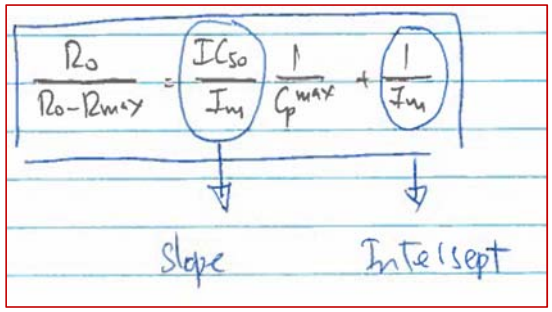
On genes, drugs and models

Models are the glue that brings together the biomarker, the mechanism and the drug

The structure of the model rationalizes data and infers system properties







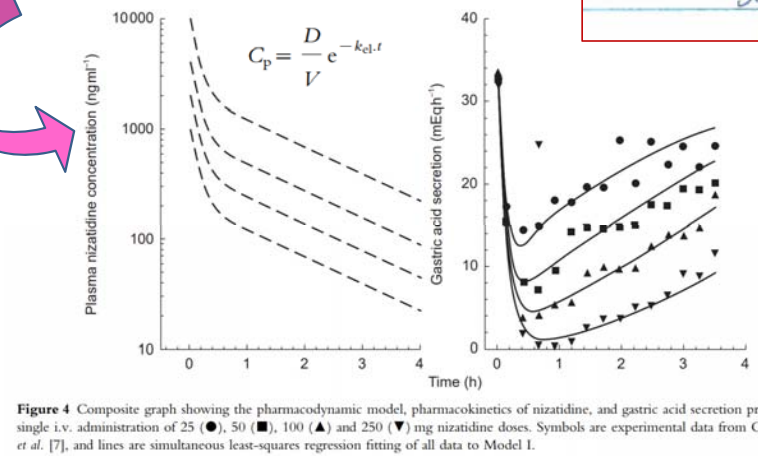


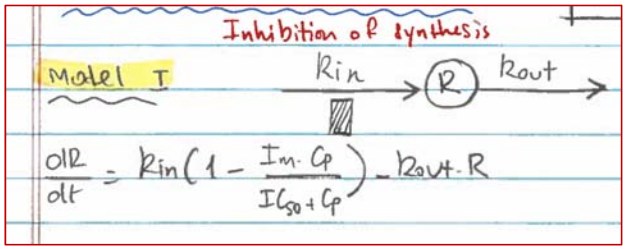
Figure 4 Composite graph showing the pharmacodynamic model, pharmacokinetics of nizatidine, and gastric acid secretion profiles after single i.v. administration of 25 (●), 50 (■), 100 (▲) and 250 (▼) mg nizatidine doses. Symbols are experimental data from Callaghan *et al.* [7], and lines are simultaneous least-squares regression fitting of all data to Model I.

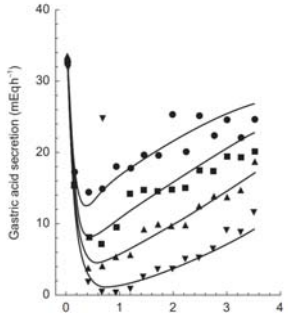
Adapted from W.J. Jusko

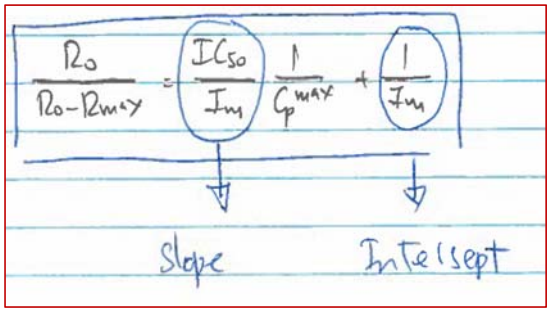
Br J Clin Pharmacol, 45(3):229, 1998

Model ⇔ Data … is a two-way street

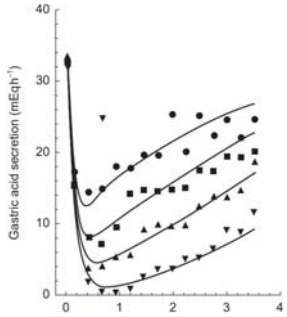
If a mechanism can be hypothesized, we use the data to infer the model parameters

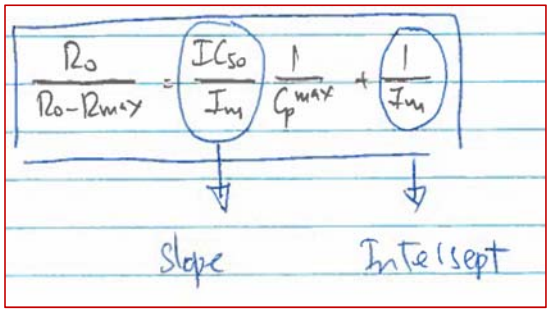


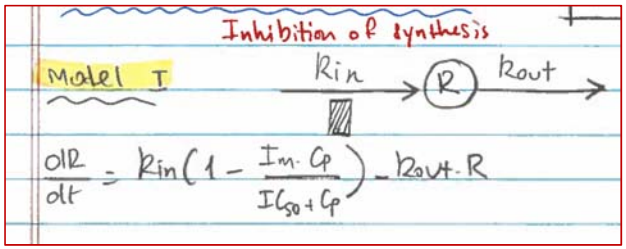




Otherwise, we use the data to infer model structures suggestive of a mechanism







The latter is very important or else data remain data and observations lead, at best, to correlations

Promise of big data

Big data is not (much) more of the same: types; dimensions within a scale; scales; conditions; subjects; everything

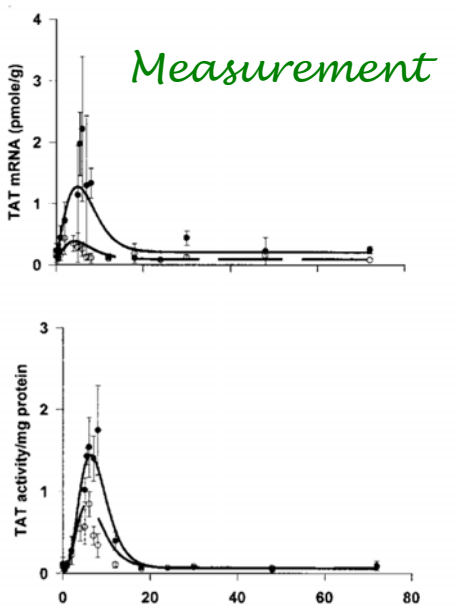
Big data makes the problem (much more) multidimensional, in more ways than one

But … big data are “too complex” to analyze, so the question is how to “upgrade the information content of big data”

Hypothesis: can [computational] models act as the integrators and interpreters of the information captured by big data?

One gene – one protein

Tyrosine aminotransferase (TAT) enzyme is one of the most well-studied and well-characterized enzymes which reflects a prototype response in terms of gene-mediated steroid induction



JPKPD, 29(1):1, 2002

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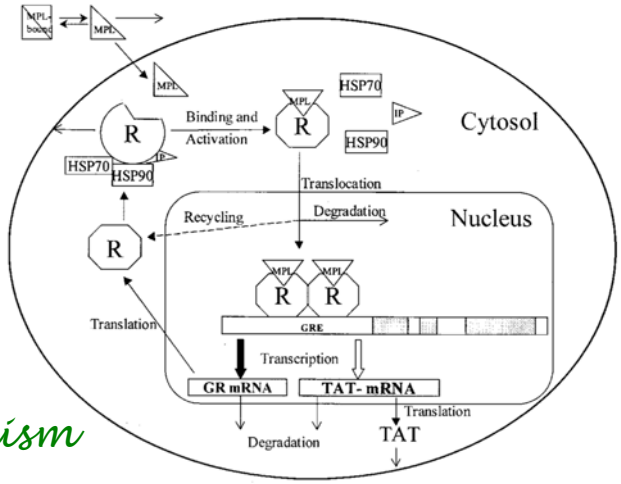
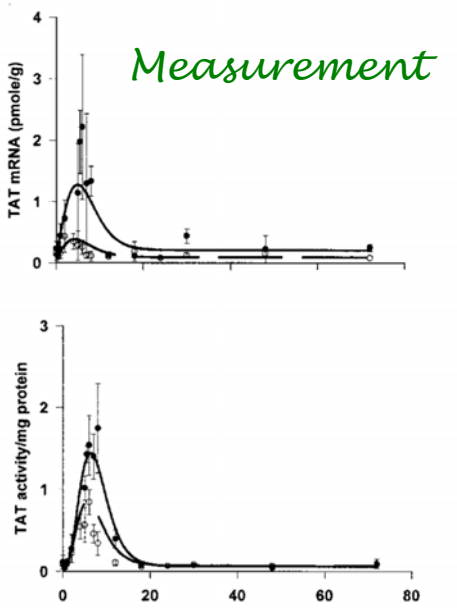


Measurement



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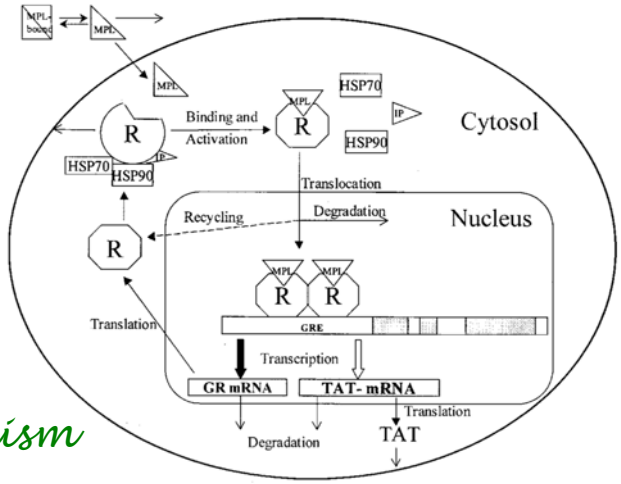

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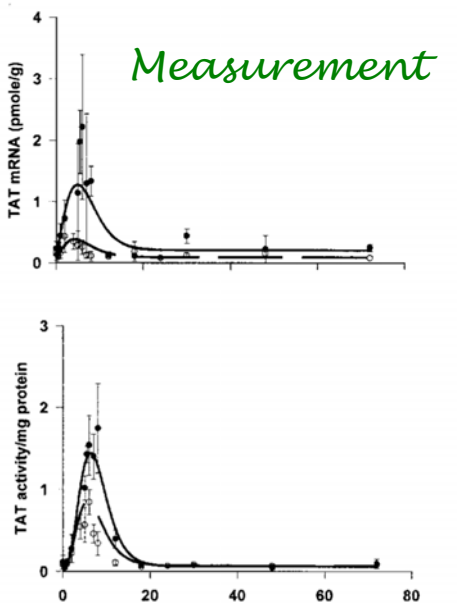
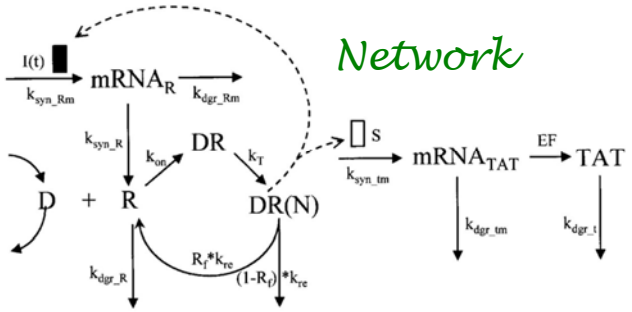


Network



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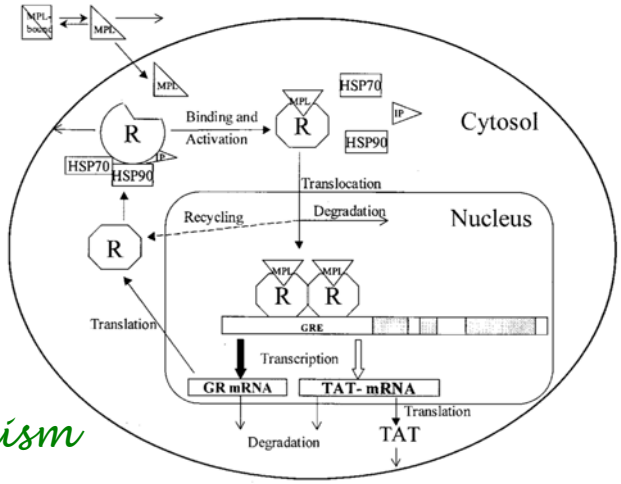

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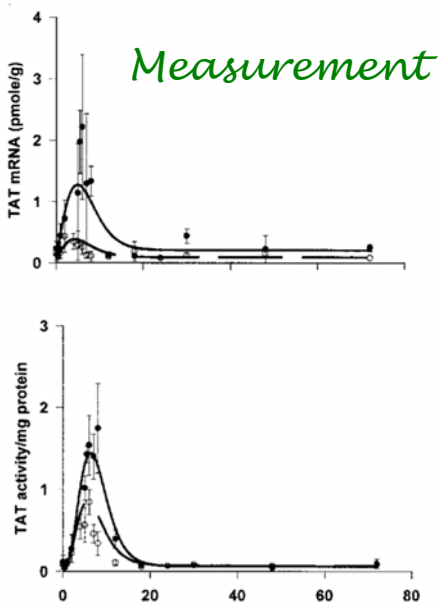


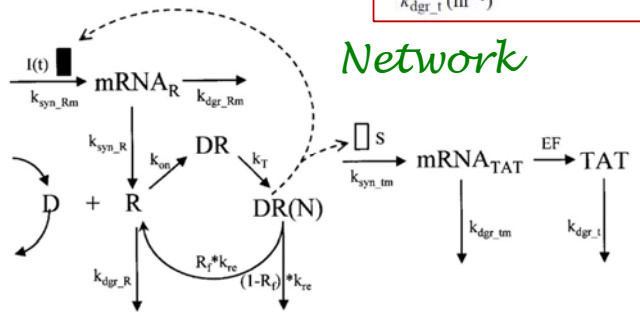
Model

$$\frac{dTAT_m}{dt} = k_{syn\_tm} \cdot (1 + S \cdot DR(N)) - k_{dgr\_tm} \cdot TAT_m \quad (13)$$

$$\frac{dTAT}{dt} = EF \cdot (TAT_m)^{\gamma} - k_{dgr\_t} \cdot TAT \quad (14)$$

TAT Dynamics (estimated)	Value
S (L/nmole/mg protein)	0.0287
k_{dgr_tm} (hr^{-1})	0.383
γ	1.804
k_{dgr_t} (hr^{-1})	0.6904

Network



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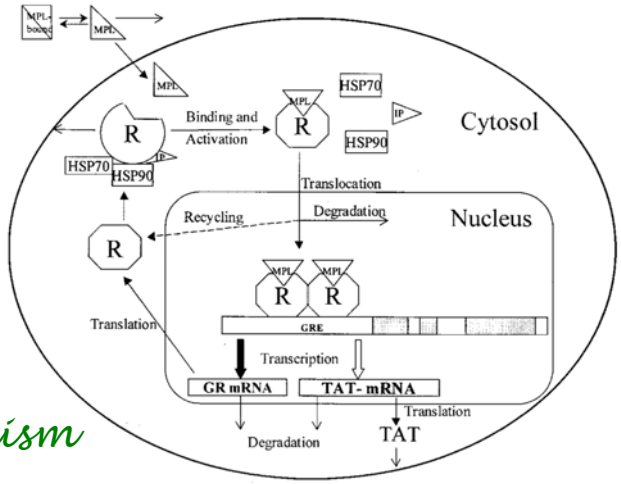

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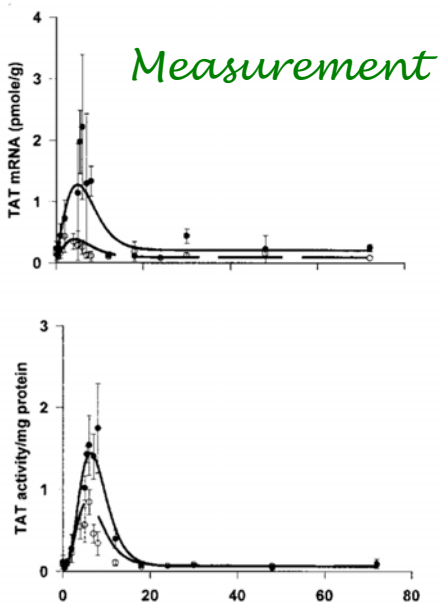

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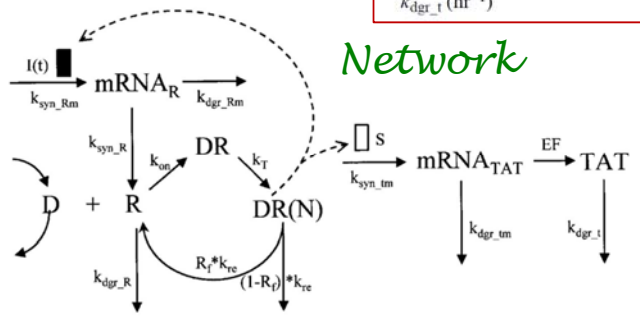
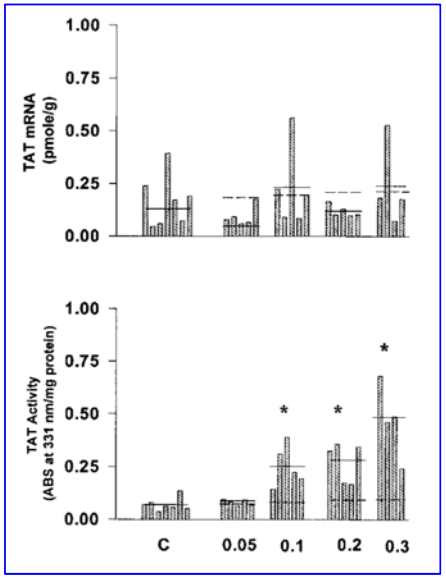
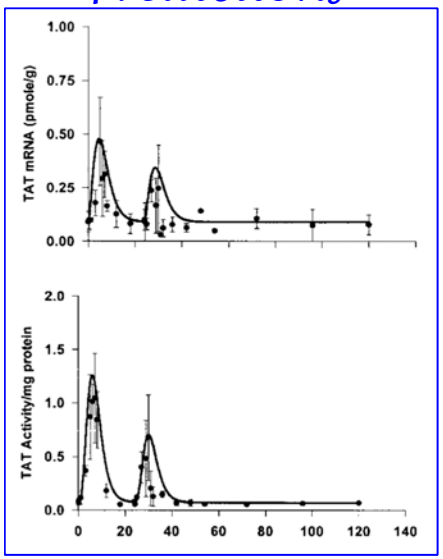


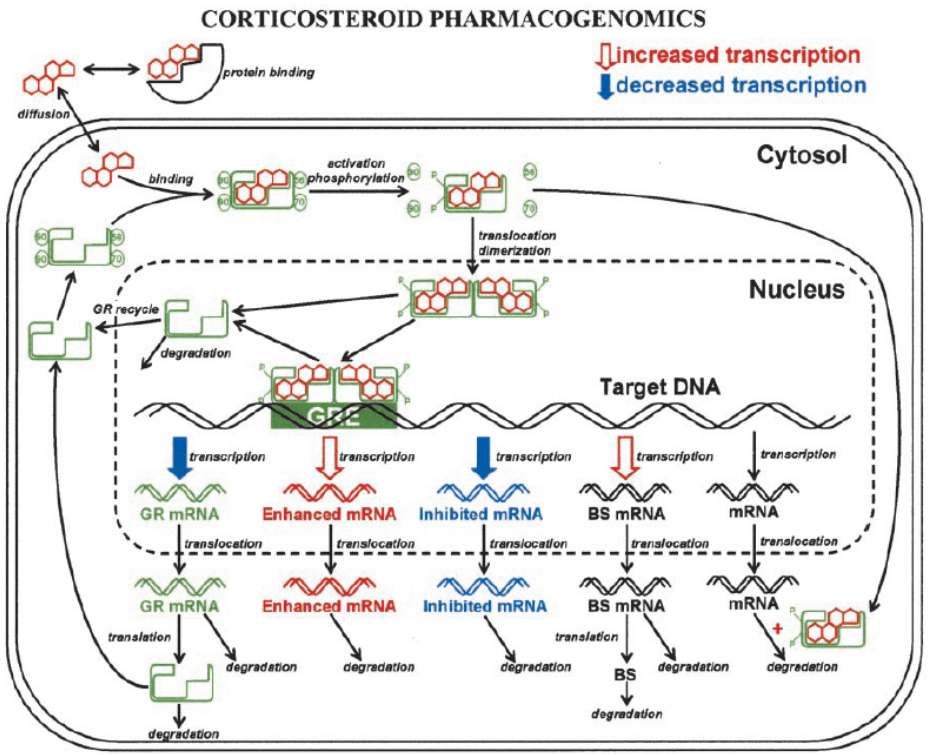
JPKPD, 29(1):1, 2002

Predictions



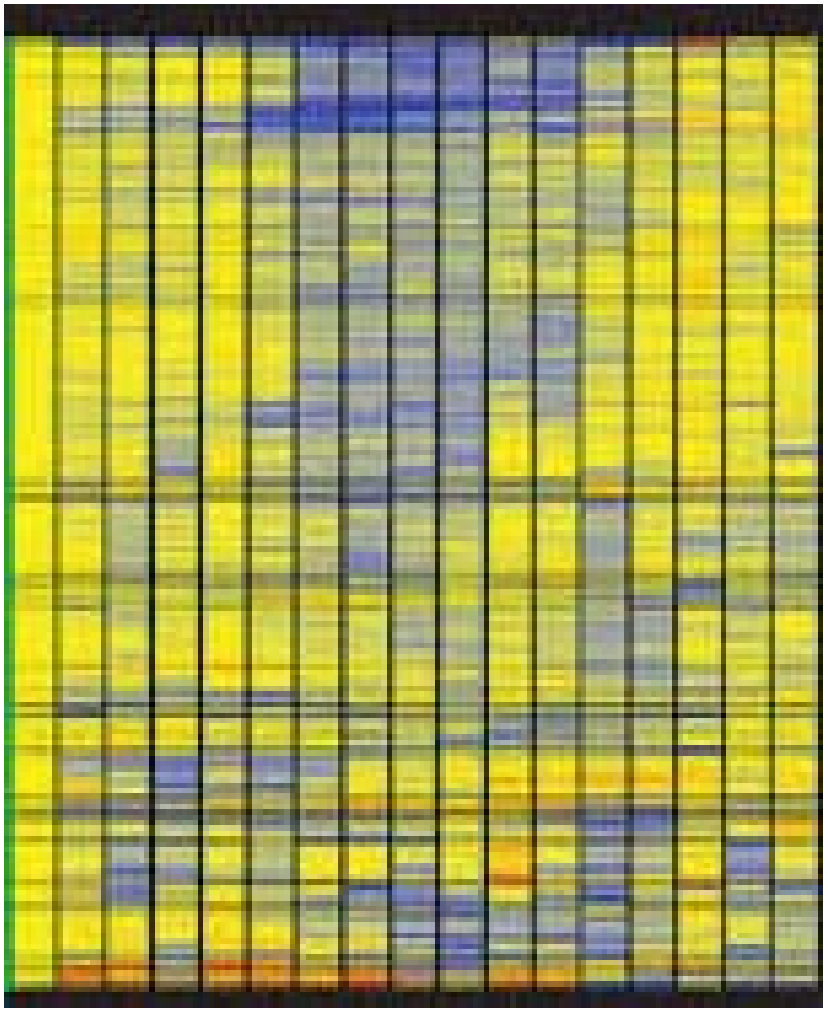


Hight throughout transcriptomics

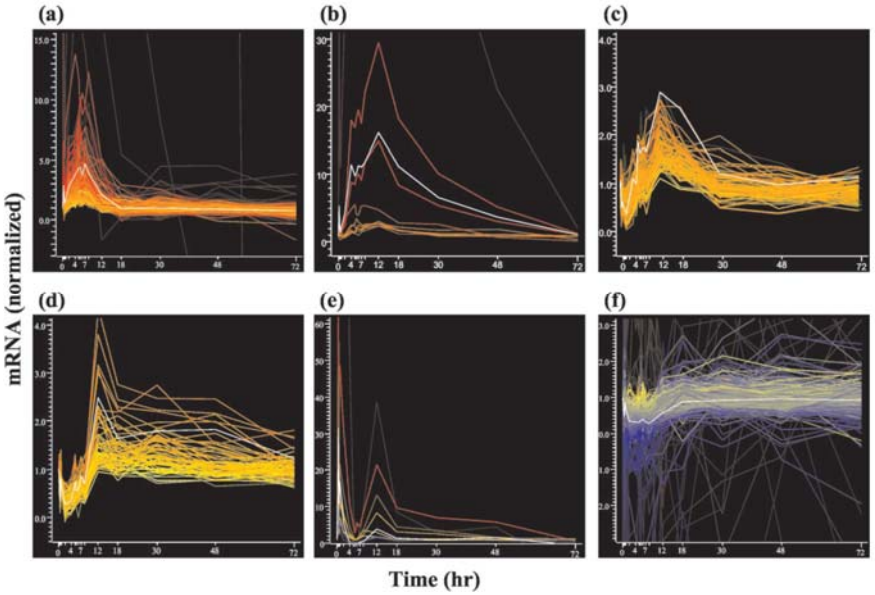


JPET, 307(1):93, 2003

This may not be technically "big", but it is definitely getting "bigger"



HT transcriptomics can be looked at in many different ways



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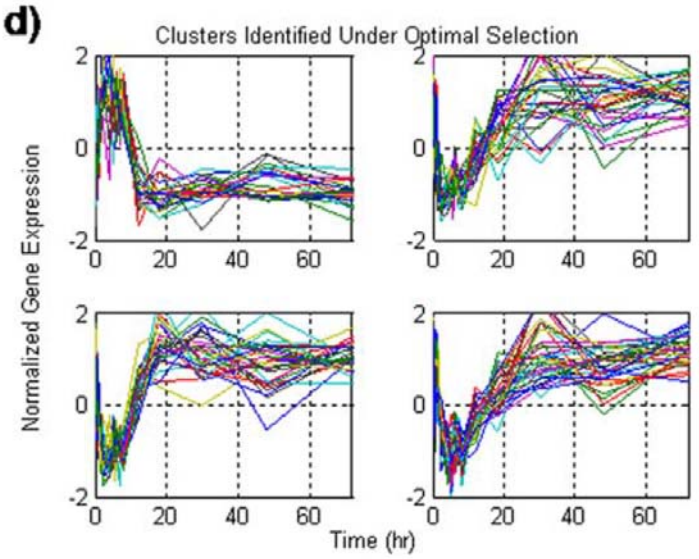
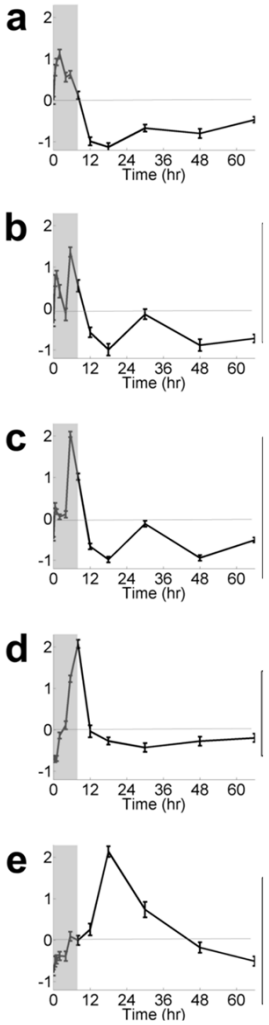
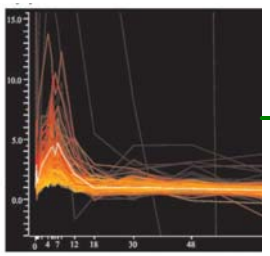


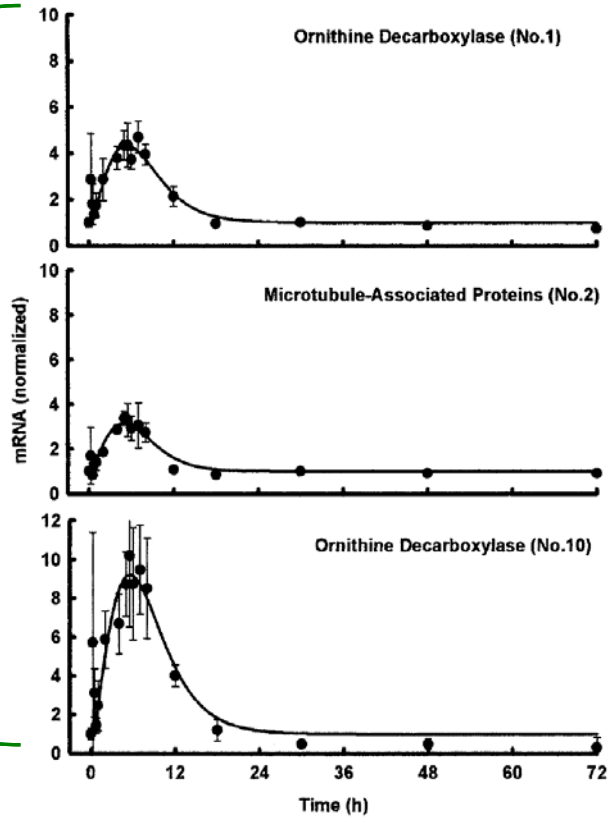
PLoS ONE, 4(7):e5992, 2009

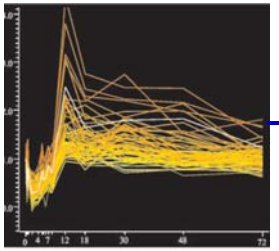


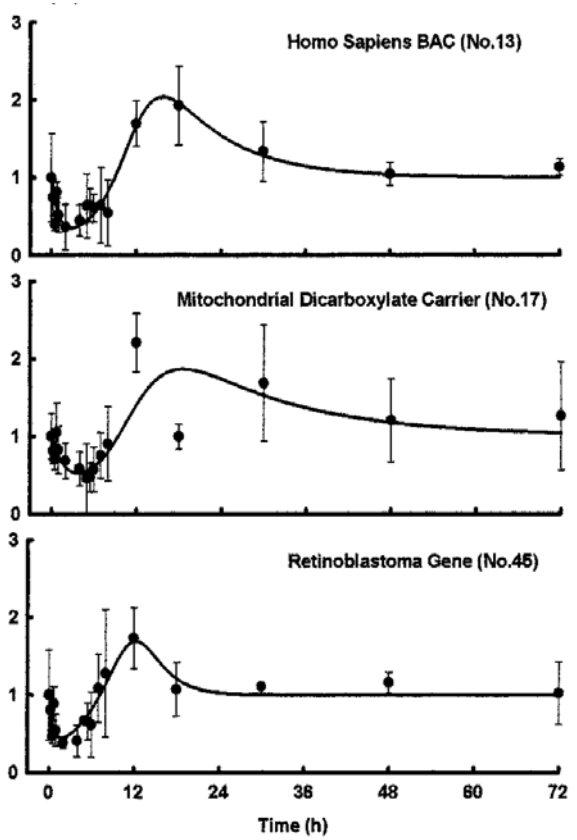
OMICS, 19(2):80, 2015

Diversity across responses









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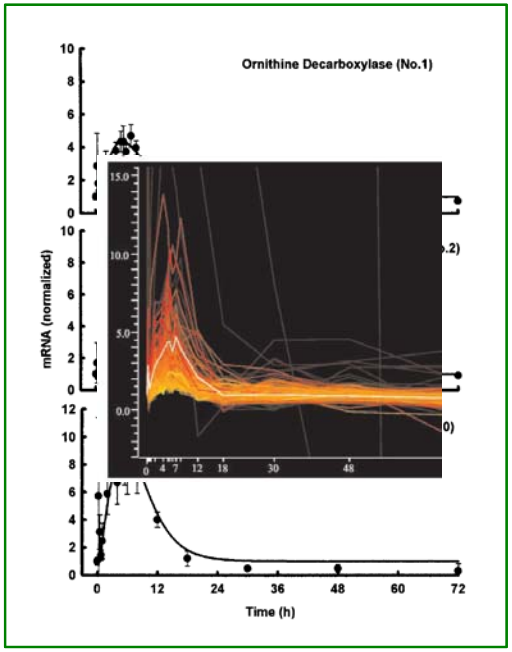
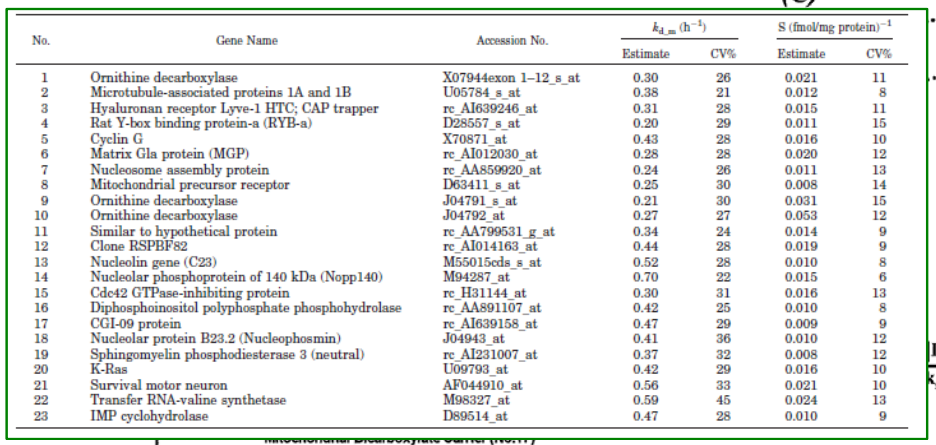
Model-based grouping of transcriptional profiles

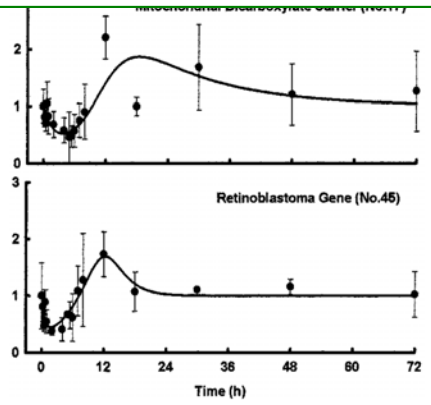
The mechanism is the element connecting the data

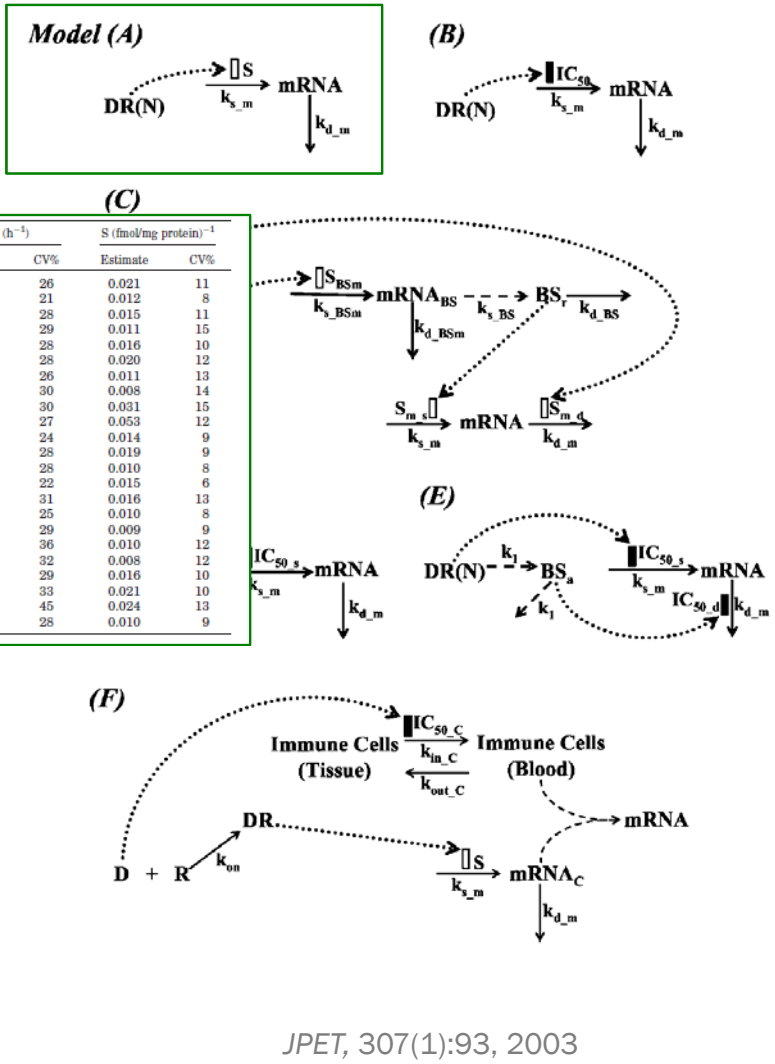
$$\frac{\mathrm{dmRNA}}{\mathrm{dt}} = k_{s\_m} \cdot (1 + S \cdot DR(N)) - k_{d\_m} \cdot \mathrm{mRNA}$$





No.	Gene Name	Accession No.	k_{d_m} (h^{-1})		S (fmol/mg protein)$^{-1}$	
			Estimate	CV%	Estimate	CV%
1	Ornithine decarboxylase	X07944exon 1–12_s_at	0.30	26	0.021	11
2	Microtubule-associated proteins 1A and 1B	U05784_s_at	0.38	21	0.012	8
3	Hyaluronan receptor Lyve-1 HTC; CAP trapper	rc_AI639246_at	0.31	28	0.015	11
4	Rat Y-box binding protein-a (RYB-a)	D28557_s_at	0.20	29	0.011	15
5	Cyclin G	X70871_at	0.43	28	0.016	10
6	Matrix Gla protein (MGP)	rc_AI012030_at	0.28	28	0.020	12
7	Nucleosome assembly protein	rc_AA859920_at	0.24	26	0.011	13
8	Mitochondrial precursor receptor	D63411_s_at	0.25	30	0.008	14
9	Ornithine decarboxylase	J04791_s_at	0.21	30	0.031	15
10	Ornithine decarboxylase	J04792_at	0.27	27	0.053	12
11	Similar to hypothetical protein	rc_AA799531_g_at	0.34	24	0.014	9
12	Clone RSPBF82	rc_AI014163_at	0.44	28	0.019	9
13	Nucleolin gene (C23)	M55015cds_s_at	0.52	28	0.010	8
14	Nucleolar phosphoprotein of 140 kDa (Nopp140)	M94287_at	0.70	22	0.015	6
15	Cdc42 GTPase-inhibiting protein	rc_H31144_at	0.30	31	0.016	13
16	Diphosphoinositol polyphosphate phosphohydrolase	rc_AA891107_at	0.42	25	0.010	8
17	CGI-09 protein	rc_AI639158_at	0.47	29	0.009	9
18	Nucleolar protein B23.2 (Nucleophosmin)	J04943_at	0.41	36	0.010	12
19	Sphingomyelin phosphodiesterase 3 (neutral)	rc_AI231007_at	0.37	32	0.008	12
20	K-Ras	U09793_at	0.42	29	0.016	10
21	Survival motor neuron	AF044910_at	0.56	33	0.021	10
22	Transfer RNA-valine synthetase	M98327_at	0.59	45	0.024	13
23	IMP cyclohydrolase	D89514_at	0.47	28	0.010	9





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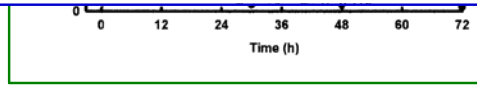
$$\frac{\mathrm{dmRNA}}{\mathrm{dt}} = k_{s\_m} \cdot (1 + S \cdot \mathrm{DR(N)}) - k_{d\_m} \cdot \mathrm{mRNA}$$

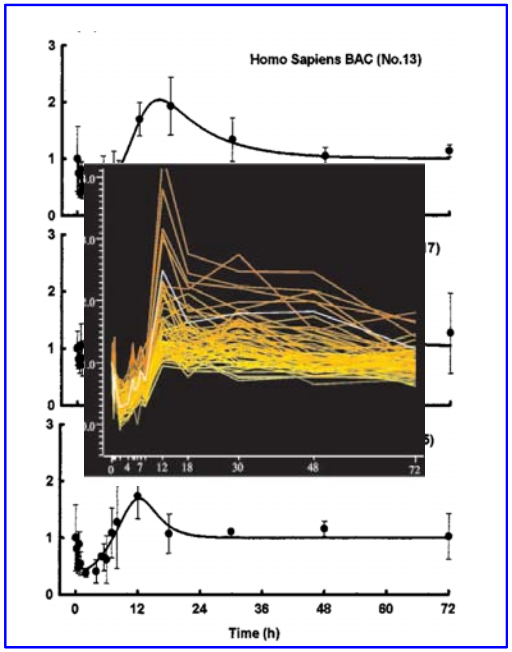
$$\frac{\mathrm{dBS_a}}{\mathrm{dt}} = k_1 \cdot (\mathrm{DR(N)} - \mathrm{BS_a})$$

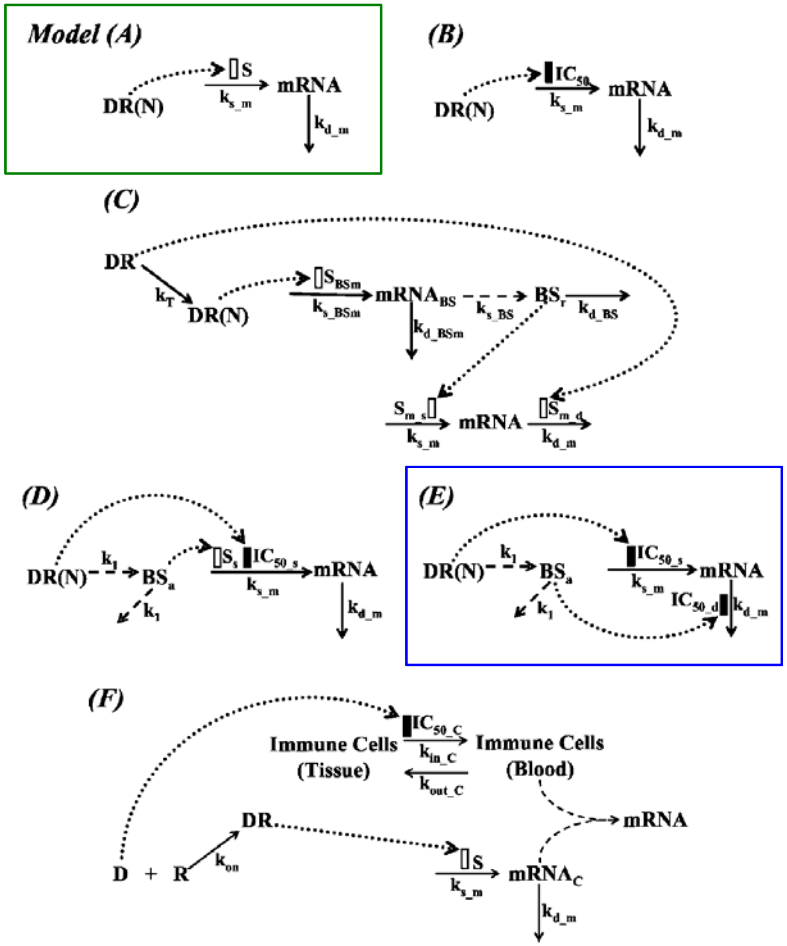
$$\frac{\mathrm{dmRNA}}{\mathrm{dt}} = k_{s\_m} \cdot \left(1 - \frac{\mathrm{DR(N)}}{\mathrm{IC_{50\_s}} + \mathrm{DR(N)}}\right) - k_{d\_m} \cdot \left(1 - \frac{\mathrm{BS_a}}{\mathrm{IC_{50\_d}} + \mathrm{BS_a}}\right) \cdot \mathrm{mRNA}$$

Cluster 4 Genes Fitted by Model D:

No.	Gene Name	Accession No.	k_1 (h^{-1}) Estimate	k_1 CV%	k_{d_m} (h^{-1}) Estimate	k_{d_m} CV%	IC_{50_s} (fmol/mg protein) Estimate	IC_{50_s} CV%	S_s (fmol/mg protein)$^{-1}$ Estimate	S_s CV%
1	Hydroxysteroid sulfotransferase	D14988_f_at	0.011	209	1.09	88	35.7	219	0.046	145
2	Hydroxysteroid sulfotransferase	D14987_f_at	0.016	156	1.01	79	38.3	194	0.031	94
3	Hydroxysteroid sulfotransferase	rc_AA817987_f_at	0.026	156	1.09	96	42.8	217	0.017	90
4	Hydroxysteroid sulfotransferase	D14989_f_at	0.014	195	1.27	98	33.9	228	0.033	146
5	Hydroxysteroid sulfotransferase	rc_AA818122_f_at	0.014	279	1.41	88	37.1	180	0.022	213
6	Hydroxysteroid sulfotransferase	M31363mRNA_f_at	0.016	159	1.66	81	34.2	155	0.017	210
7	Hydroxysteroid sulfotransferase	X63410cds_f_at	0.014	105	0.55	80	41.5	208	0.079	66
8	Hydroxysteroid sulfotransferase	rc_AA945050_f_at	0.015	110	0.64	93	37.0	266	0.079	66
9	Hydroxysteroid sulfotransferase	rc_AI169695_f_at	0.0092	272	1.33	97	30.7	235	0.051	215
10	Hydroxysteroid sulfotransferase a (STa)	M33329_f_at	0.018	124	0.50	114	35.5	377	0.072	68
11	Calcium/calmodulin-dependent protein kinase I	L24907_at	0.0072	348	1.45	75	29.3	164	0.038	270
12	GABA transporter GAT-2	M95762_at	0.020	95	0.59	61	35.7	199	0.032	51
14	Glucuronosyltransferase precursor	J02589mRNA#2_at	0.034	36	1.15	33	21.7	112	0.023	28
15	Retinoblastoma gene (RB)	D25233cds_at	0.051	90	13.90	213	50.9	67	0.0075	63
16	c-Raf protooncogene	M15427_s_at	0.056	49	0.92	31	15.0	127	0.010	49
18	D44494_at	D44494_at	0.015	548	1.25	81	37.9	180	0.0079	352
19	NF1-like DNA-binding protein	X13167cds_s_at	0.020	184	0.93	88	33.8	239	0.020	106
20	Liver UDP-glucuronosyltransferase	M13506_at	0.014	93	0.27	64	26.5	277	0.077	54
21	Aldehyde dehydrogenase	rc_AA996484_g_at	0.082	89	1.27	40	16.6	141	0.0054	96
22	α-1B adrenergic receptor	M60655_at	0.023	219	1.19	64	58.2	109	0.0082	121
24	Zinc transporter ZnT-1	U17133_at	0.033	81	0.39	65	49.4	207	0.022	40
25	3-Hydroxyanthranilate 3,4-dioxygenase	D28339_s_at	0.033	139	0.89	59	34.6	174	0.0090	89
27	Nuclear factor 1 (NFI-A2)	D78018_s_at	0.034	249	1.25	95	48.4	185	0.0063	121
29	Syndecan in vascular smooth muscle	X60651mRNA_s_at	0.041	147	1.63	85	83.7	101	0.0065	70
30	Mitochondrial phosphoprotein	AB000098_g_at	0.023	56	0.81	37	31.7	92	0.021	31
32	Glycogen storage disease type 1b protein	AF080468_g_at	0.043	36	1.50	34	12.2	100	0.014	30
35	*N*-Acetylglucosaminyl transferase I (GnT-I)	rc_AA957132_s_at	0.083	77	1.07	53	28.6	152	0.0050	91
38	Aldo-keto reductase	rc_AA892821_g_at	0.071	59	1.11	38	23.4	123	0.0066	65
42	Glucose-6-phosphate transporter	AF080468_at	0.042	61	1.39	29	8.8	136	0.012	59
43	Potassium channel 2 subunit (I2RF5)	rc_H33656_at	0.052	59	0.75	48	40.2	125	0.010	29
44	Aldo-keto reductase	rc_AA892821_at	0.087	67	0.89	30	18.6	126	0.0061	75
47	Mus musculus, clone RP23-181H5	rc_AA893289_at	0.157	170	2.07	53	61.1	—[a]	0.0022	109
48	Cytochrome P450 (CYP2B14P)	U33540exon_f_at	0.051	66	0.66	36	34.3	118	0.0075	49
49	Dicarboxylate carrier (DIC)	AJ223355_at	0.036	121	0.51	74	61.1	173	0.013	55
50	CTP:Phosphoethanolamine cytidylyltransferase	AF080568_g_at	0.050	62	0.96	26	90.8	—[a]	0.0061	51
53	Liver nonspecific lipid transfer protein	M58287_s_at	0.032	72	0.33	41	42.2	145	0.016	34
54	Protoporphyrinogen oxidase	rc_AA859700_g_at	0.040	44	0.48	35	25.8	127	0.015	26
55	Cytochrome *c* oxidase subunit VIa (rCOXVIa)	X72757_at	0.054	36	0.51	46	69.2	—[a]	0.014	26
57	Cathepsin H (RCHII)	M38135_at	0.121	44	0.85	25	53.6	—[a]	0.0052	31
58	RIKEN cDNA 2410142G14 gene	rc_AA859933_at	0.038	67	0.78	51	26.9	165	0.014	42
61	RAB8 LMW GTP-binding protein	M83675_at	0.100	47	1.37	31	56.8	—[a]	0.0070	34







JPET, 307(1):93, 2003

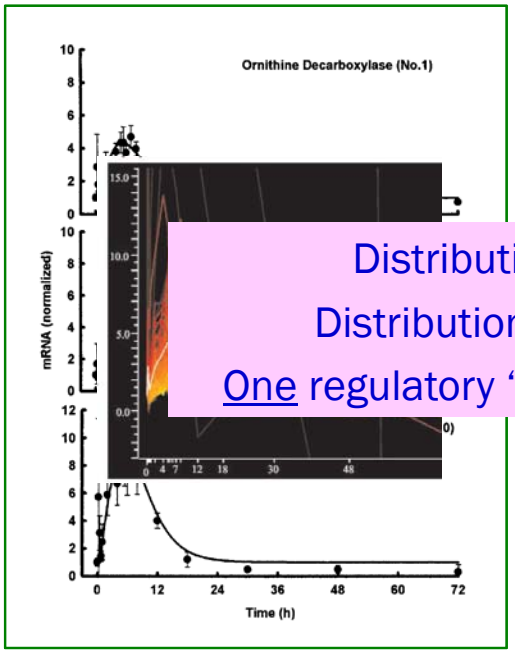
Model-based grouping of transcriptional profiles

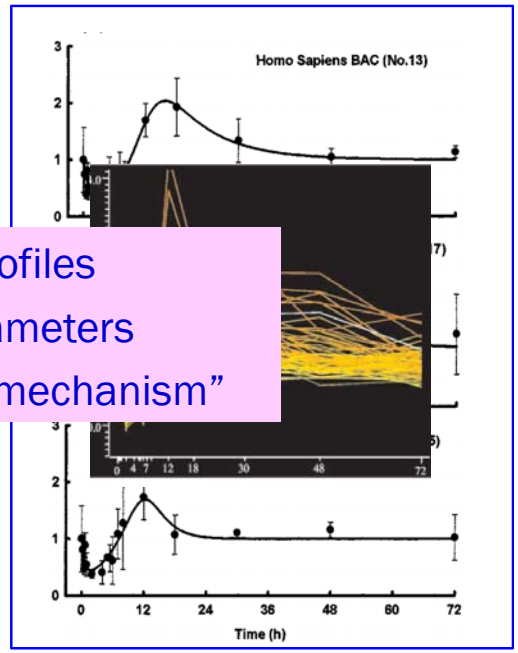
The mechanism is the element connecting the data

$$\frac{\mathrm{dmRNA}}{\mathrm{dt}} = k_{s\_m} \cdot (1 + \mathrm{S} \cdot \mathrm{DR(N)}) - k_{d\_m} \cdot \mathrm{mRNA}$$

$$\frac{\mathrm{dBS_a}}{\mathrm{dt}} = k_1 \cdot (\mathrm{DR(N)} - \mathrm{BS_a})$$

$$\frac{\mathrm{dmRNA}}{\mathrm{dt}} = k_{s\_m} \cdot \left(1 - \frac{\mathrm{DR(N)}}{\mathrm{IC_{50\_s}} + \mathrm{DR(N)}}\right) - k_{d\_m} \cdot \left(1 - \frac{\mathrm{BS_a}}{\mathrm{IC_{50\_d}} + \mathrm{BS_a}}\right) \cdot \mathrm{mRNA}$$

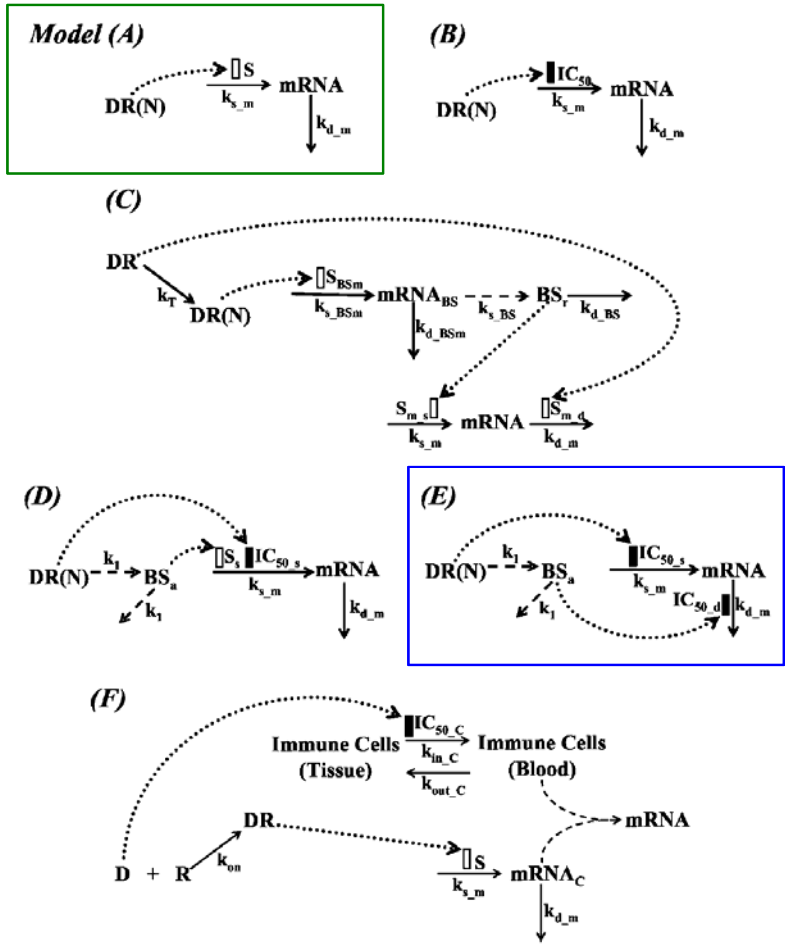




Distribution of profiles

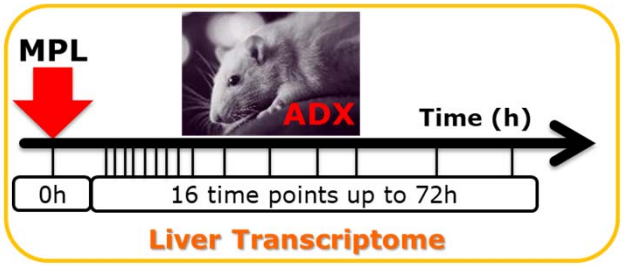
Distribution of parameters

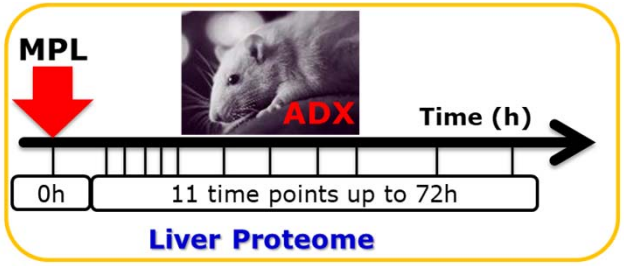
One regulatory “model/mechanism”



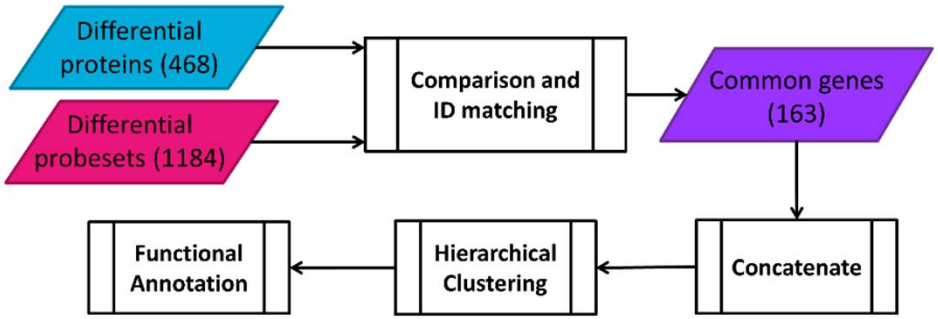
JPET, 307(1):93, 2003

Simultaneous transcriptomic and proteomic analyses

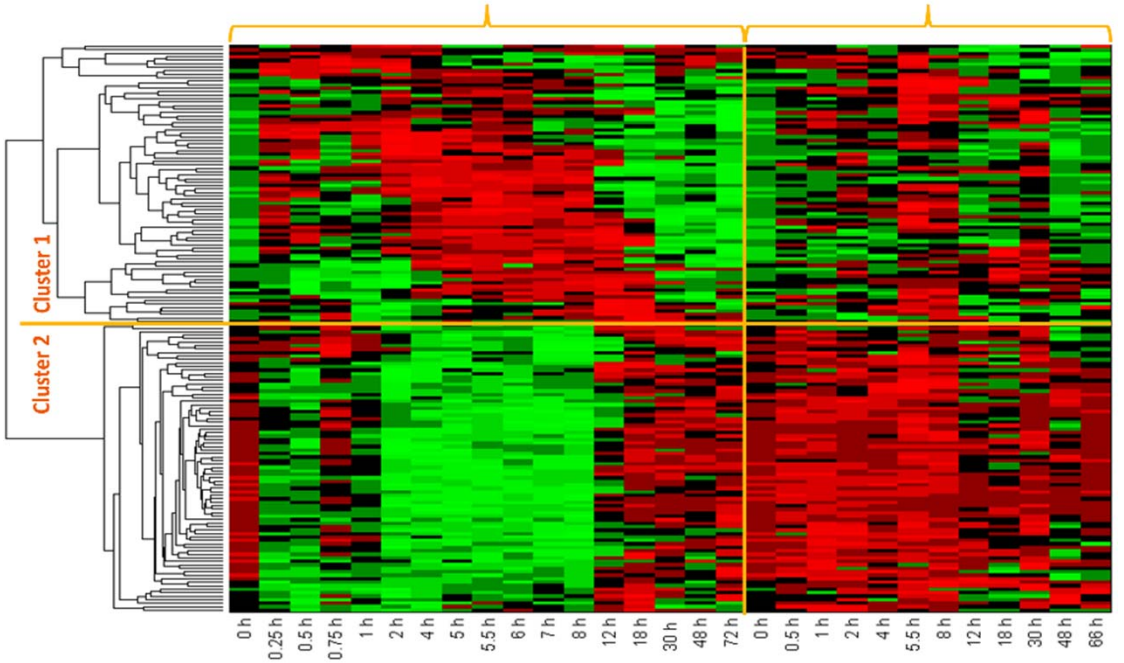




Anal Chem, 86(16):8149, 2014

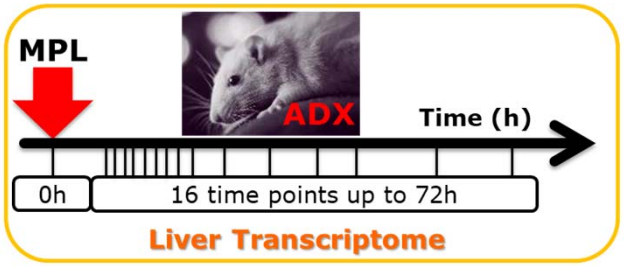


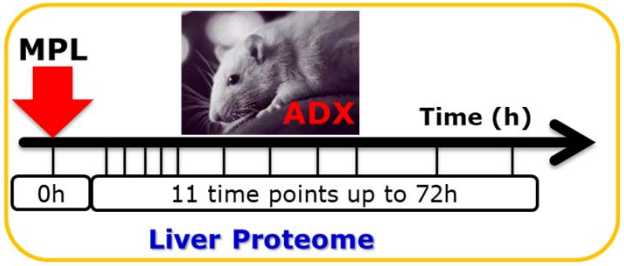
This is getting even "bigger"



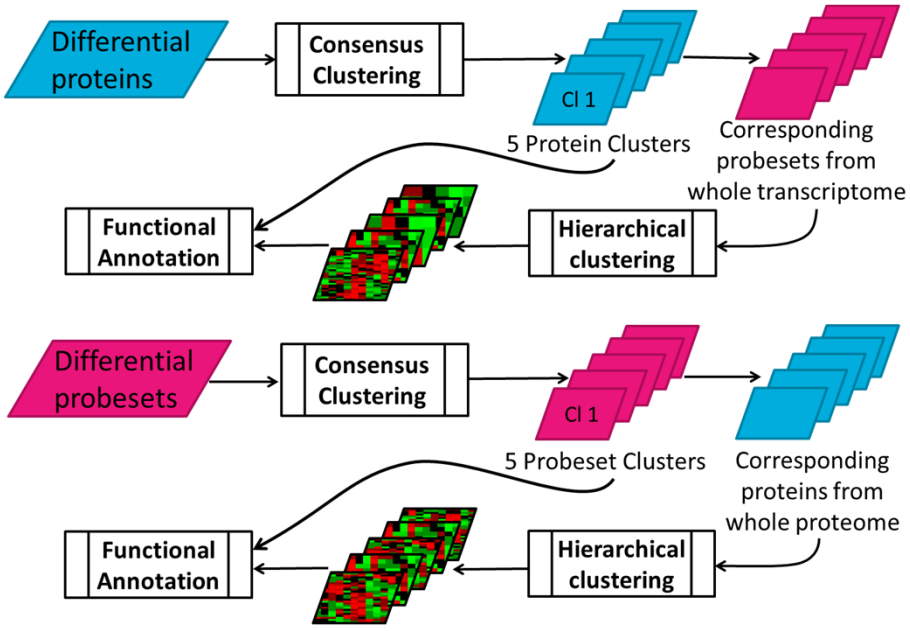
OMICS, 19(2):80, 2015

Simultaneous transcriptomic and proteomic analyses

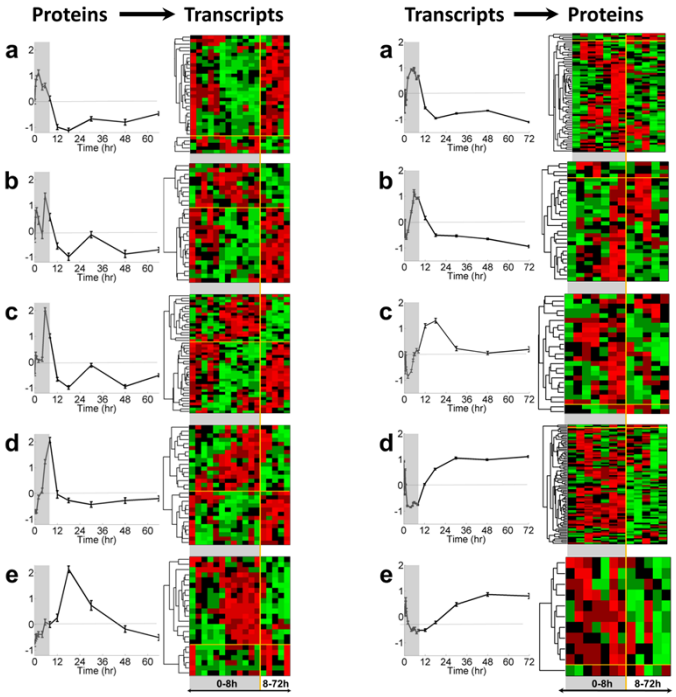




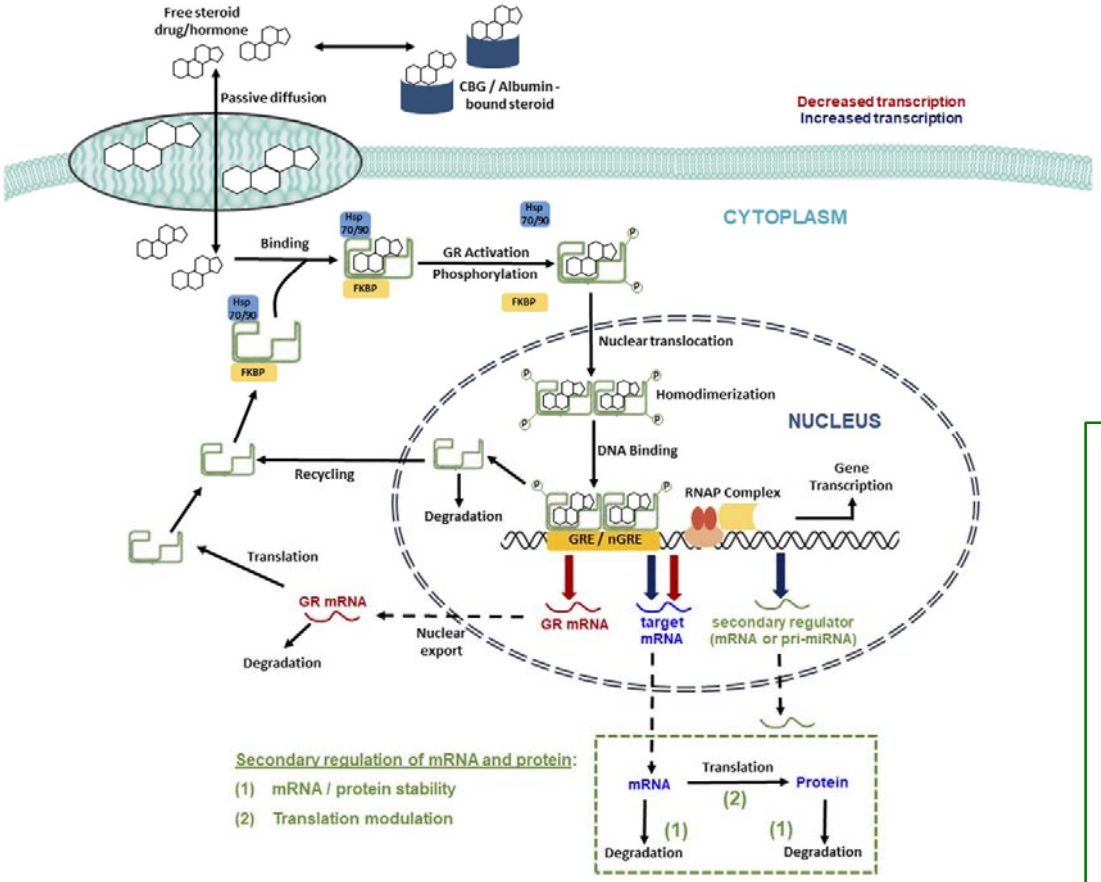
Anal Chem, 86(16):8149, 2014



OMICS, 19(2):80, 2015



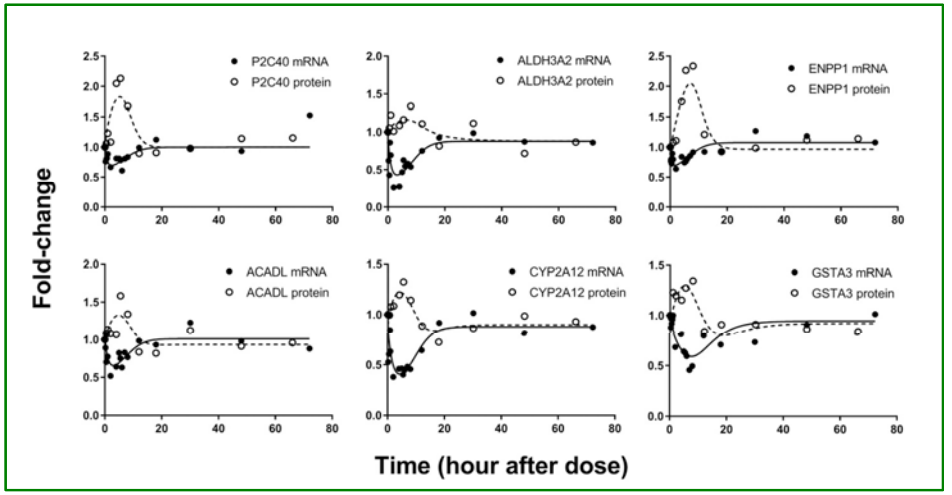
Individual transcription/translation models based on –*omics* data



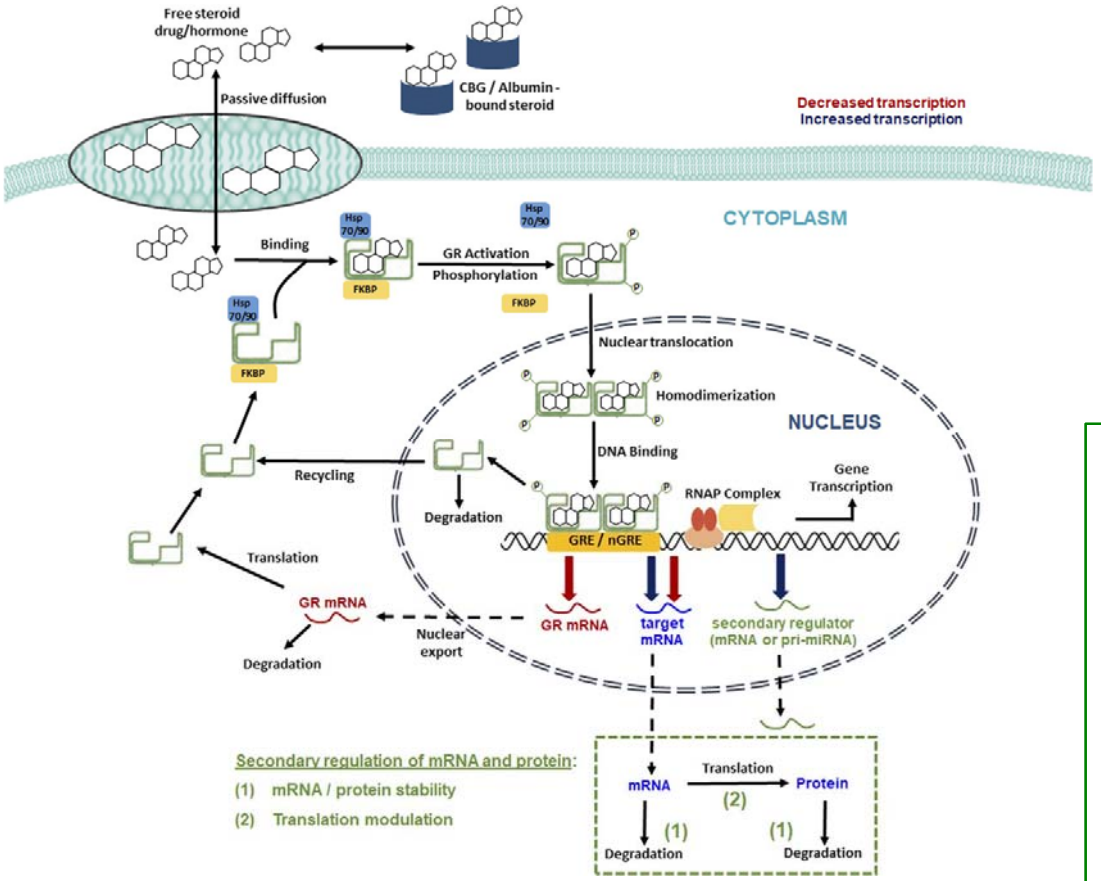
JPET, 367(1):168, 2018

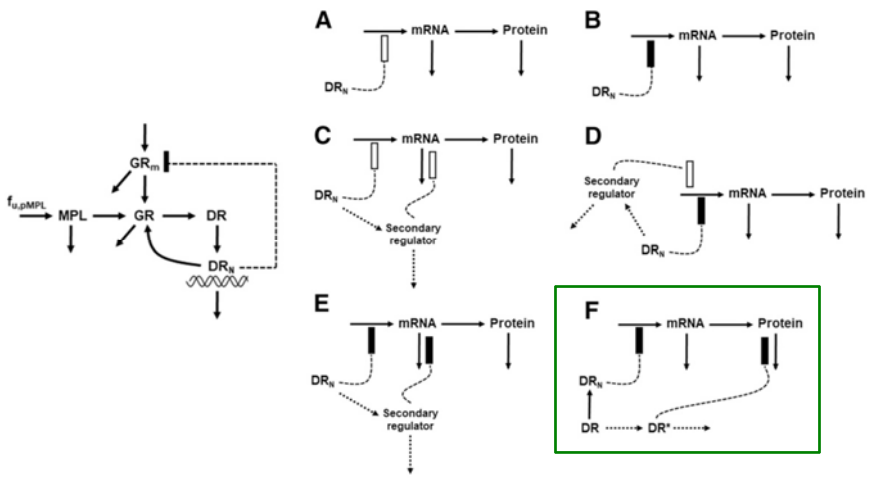
High throughput –*omics* can generate large volumes on mRNA and protein abundance data

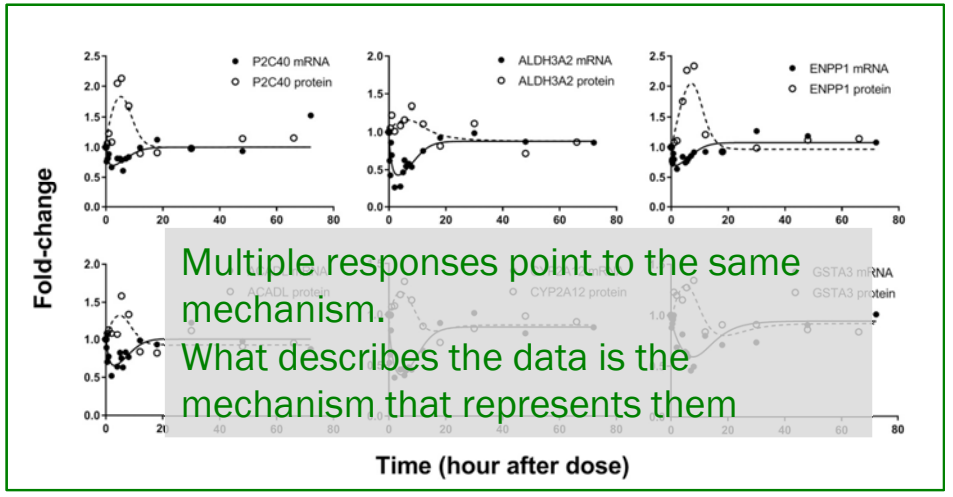
What was done for TAT can be done at a much larger scale



Individual transcription/translation models based on –omics data



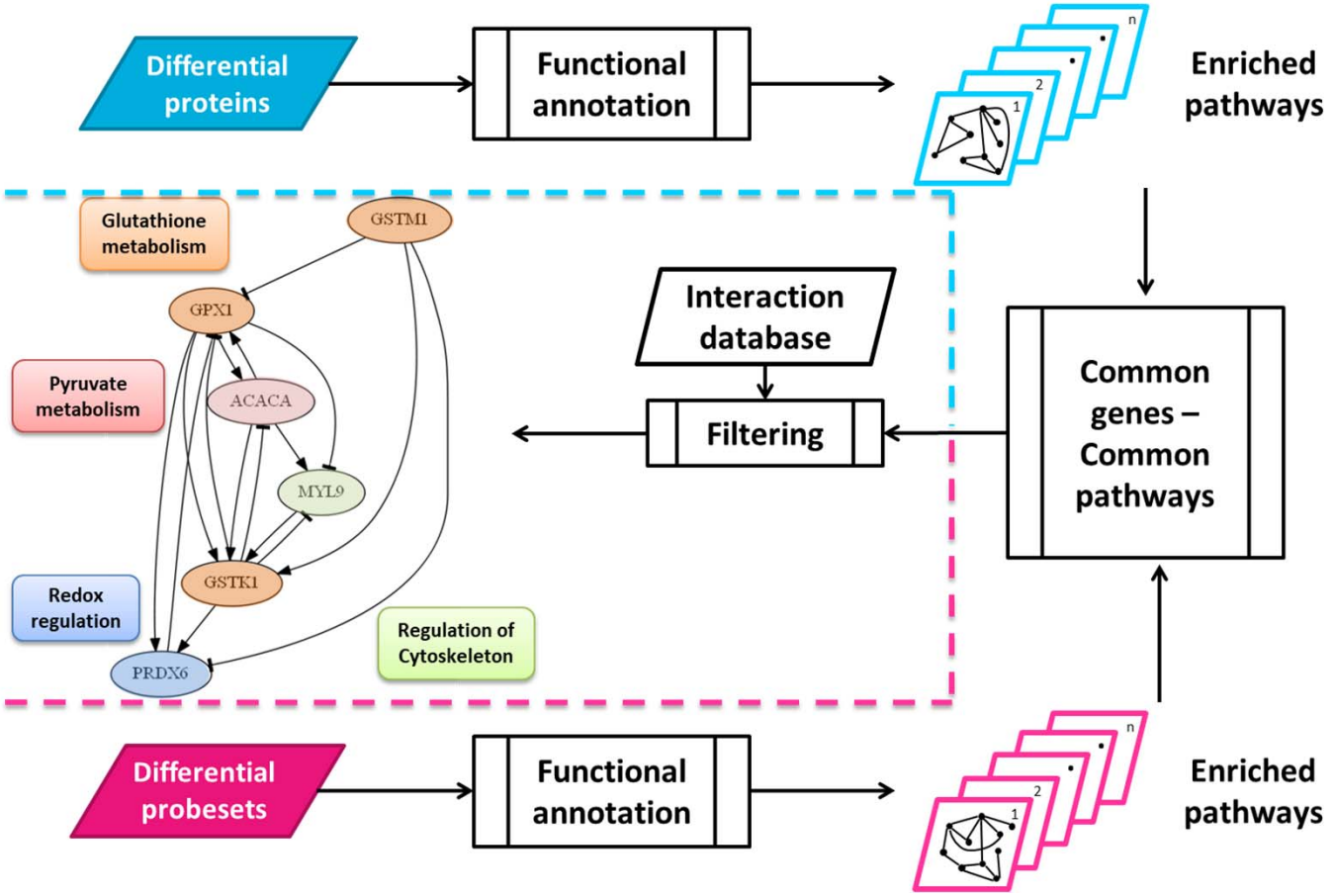




Multiple responses point to the same mechanism.
What describes the data is the mechanism that represents them

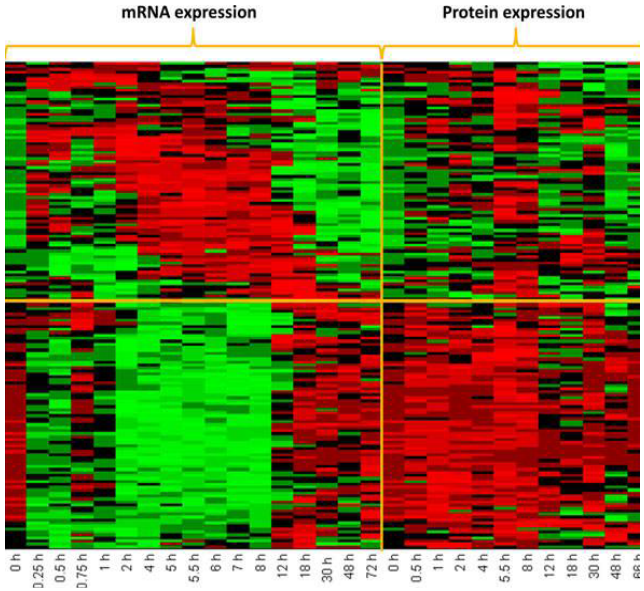
JPET, 367(1):168, 2018

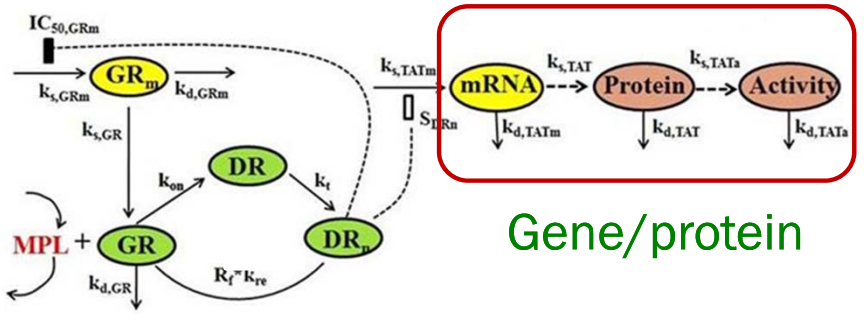
Towards network models



Front Pharmacol, 8:91, 2017

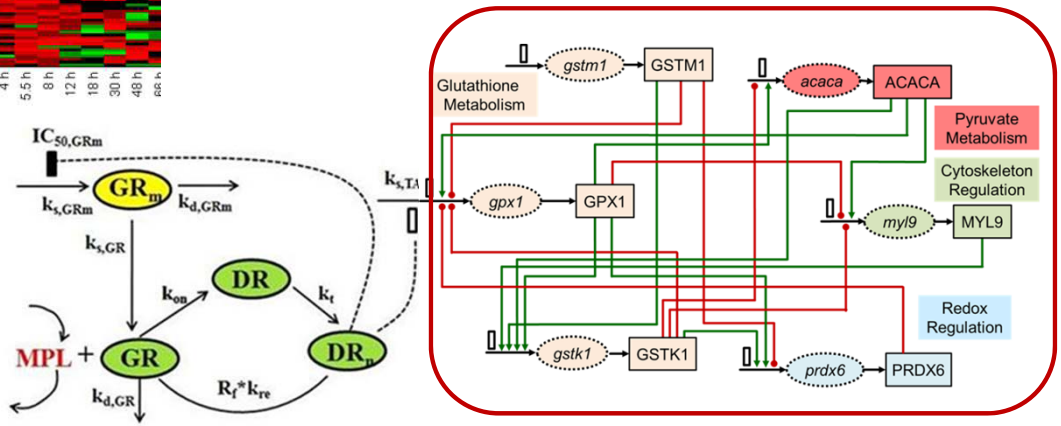
Modeling network dynamics

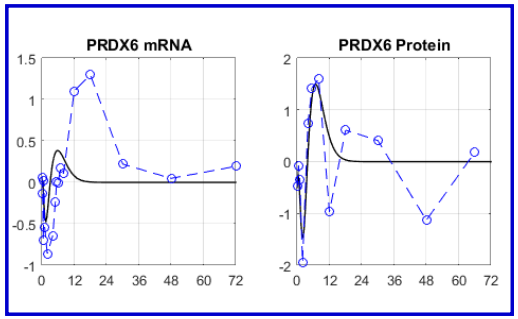


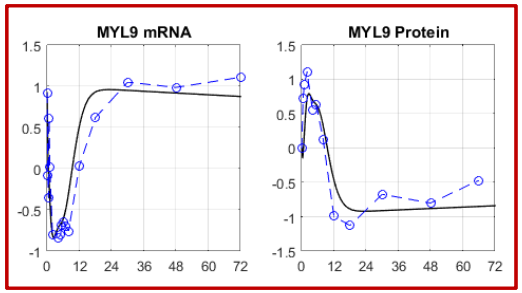


Gene/protein

Network







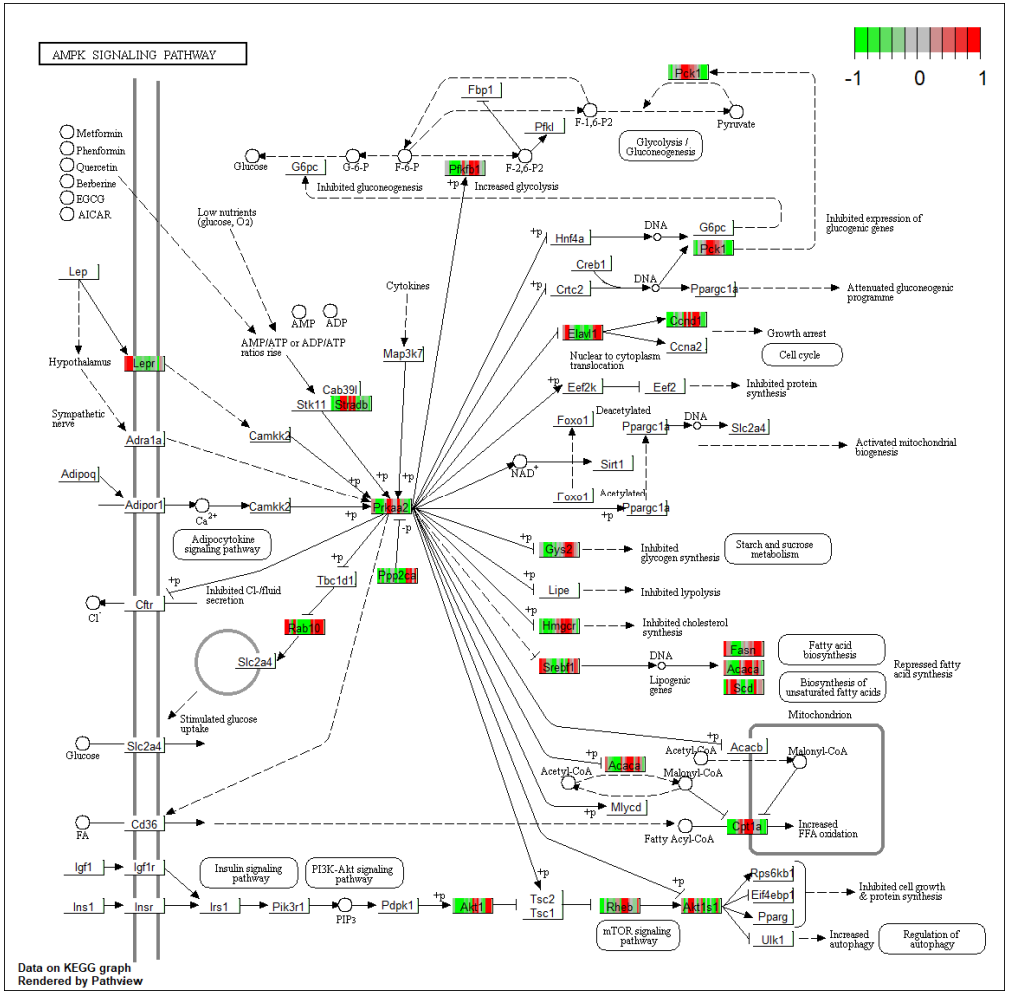
Front Pharmacol, 8:91, 2017

From elements to groups

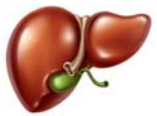
Everything discussed up to this point, whether small or big(ger) data, always comes down to considering individual elements

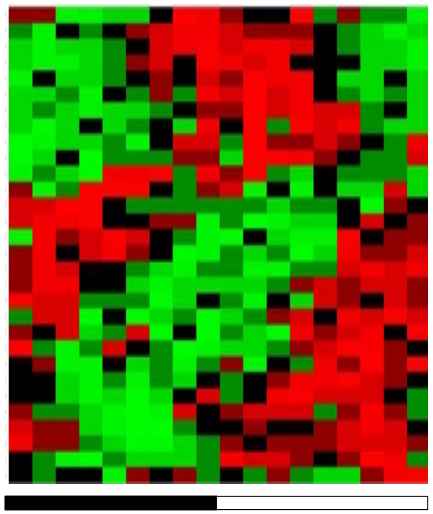
One of the advantages of big(er) data is that they allow us to look at “the big(er) picture”

Question: what if we were to look at a functional grouping of related elements as opposed to individual elements?

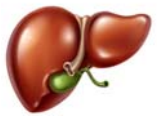


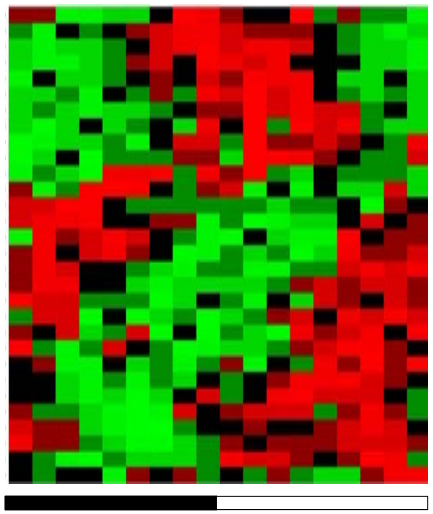
Many genes

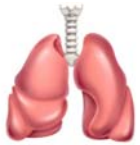


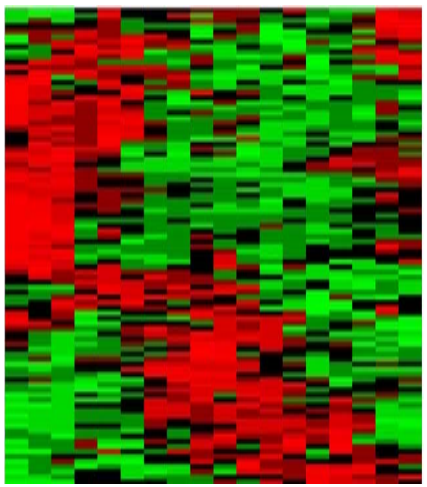


Many genes in many tissues

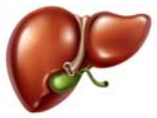


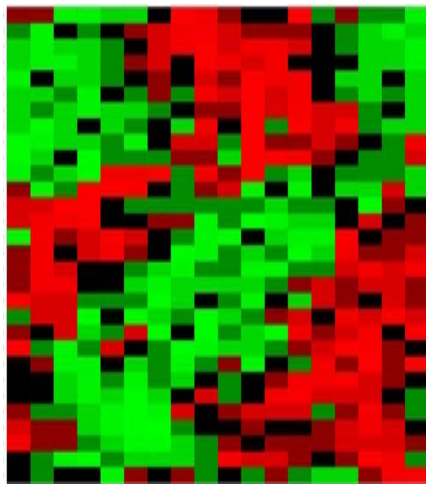


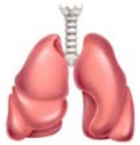


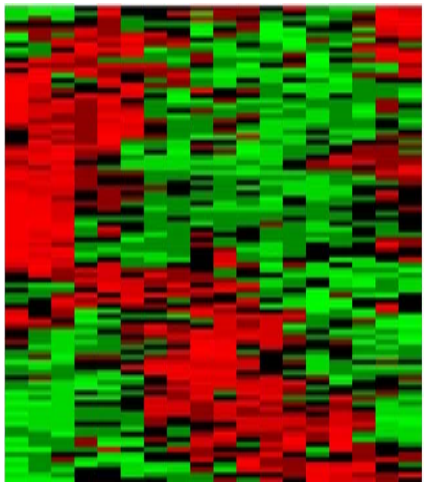


Many genes in many tissues in many species

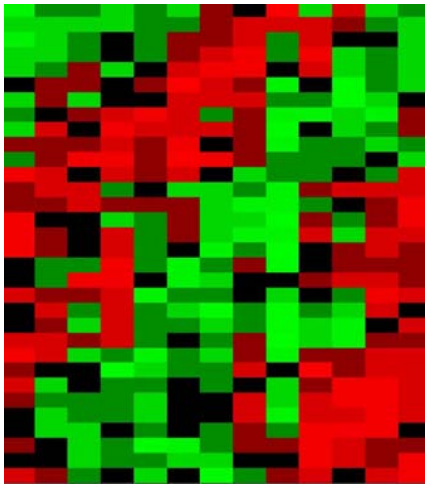


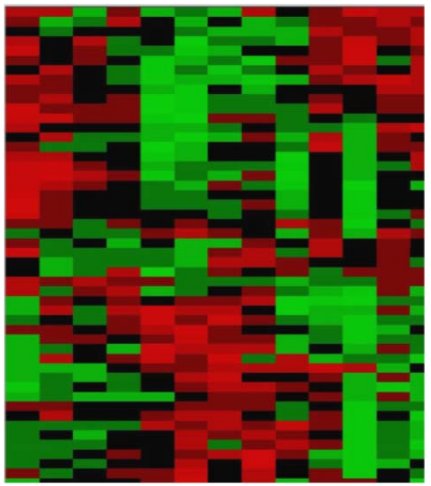






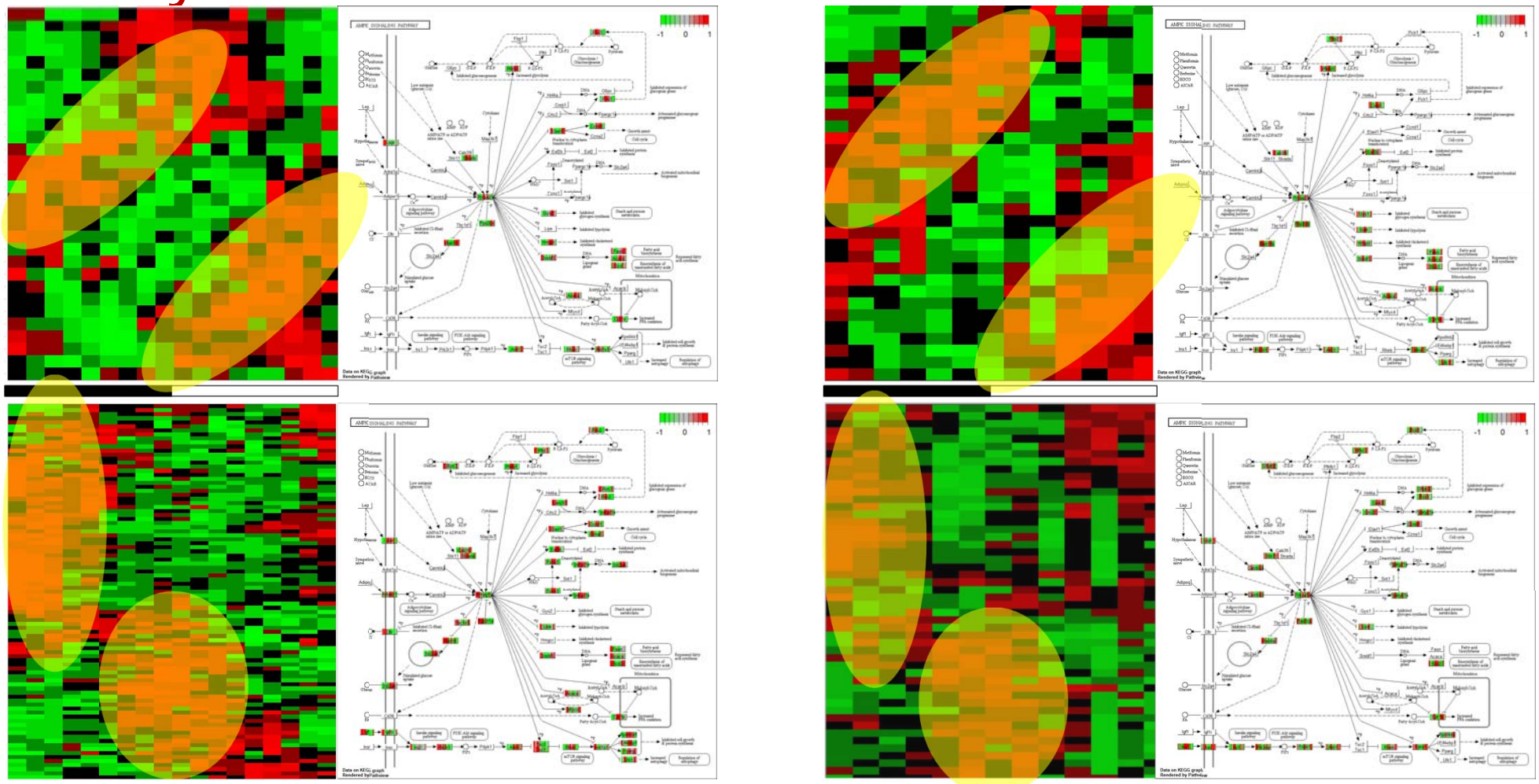
PLoS ONE, 13(5):0197258, 2018





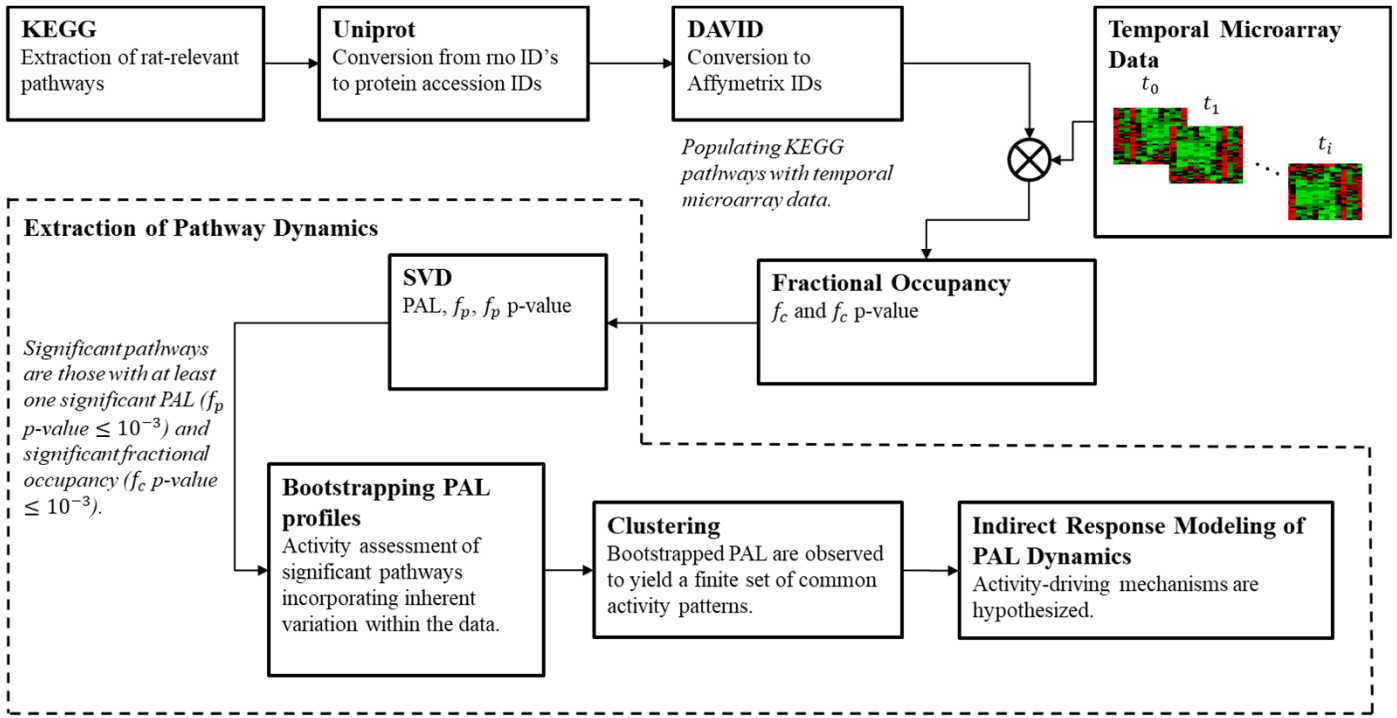
PNAS, 111(45):16219, 2014

Heterogeneity pointing to common functional activity



From multi-dimensional data to functional group dynamics

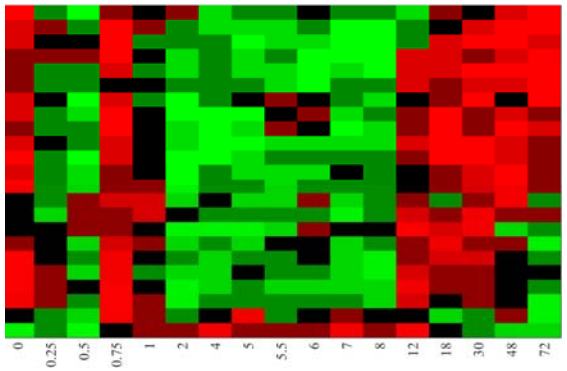
Does a functionally related grouping of components (metabolic, signaling or disease pathway) exhibit a coherent emergent dynamic response irrespective of individual contributions? If so how can this be captured and quantified?

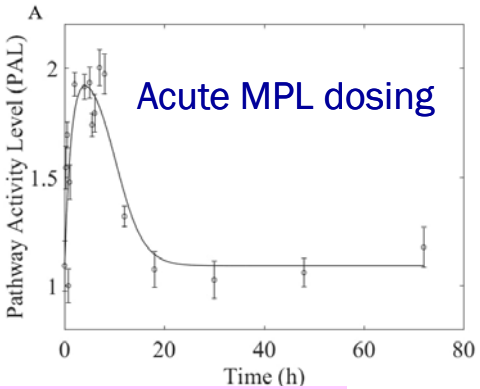


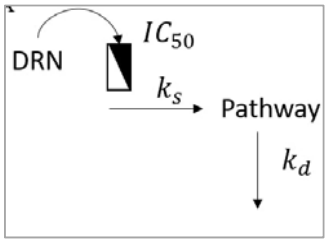
BMC Bionf, 11:540, 2010, *Gene Reg & Sys Biol, under review*

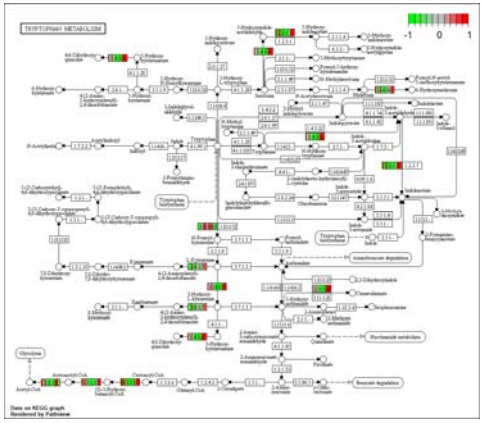
Pathway dynamics as an emergent property – The population dynamic network

Network dynamics is an emergent property, resulting from component interactions

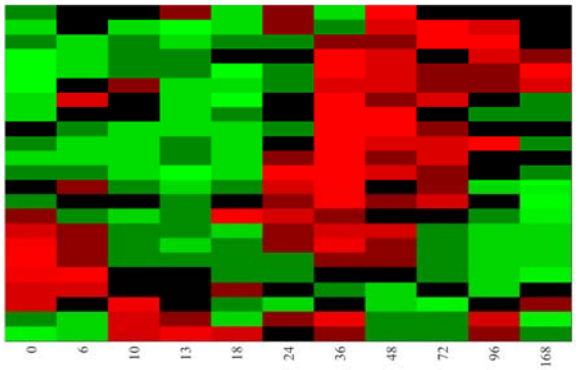


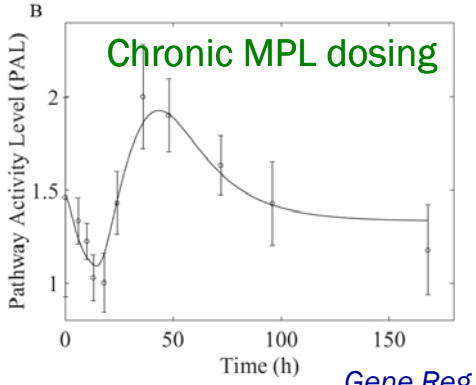


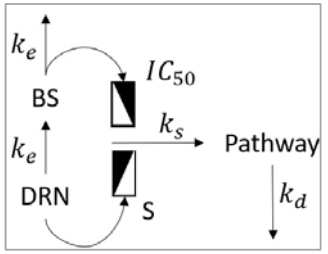


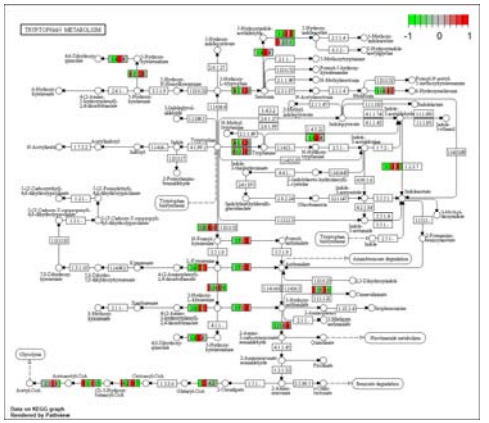


From TAT to a group!





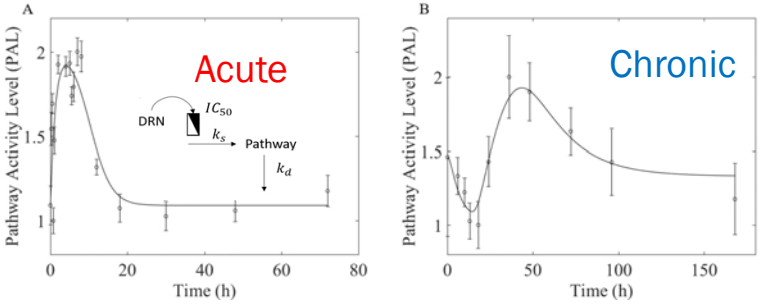




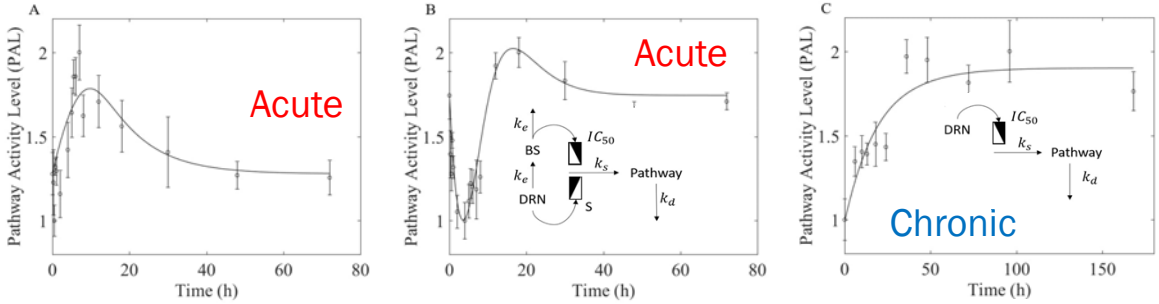
Gene Reg & Sys Biol, under review

Same Drug, Same Pathway
Different Dosing, Different Pathway Activity

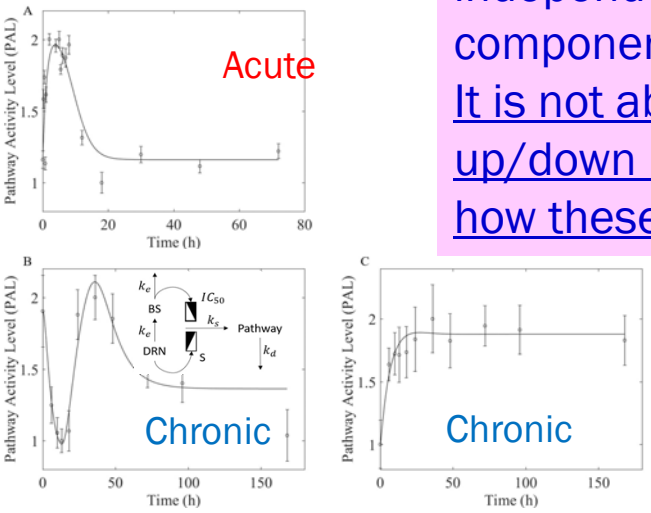
Tryptophan Metabolism



Arginine Biosynthesis

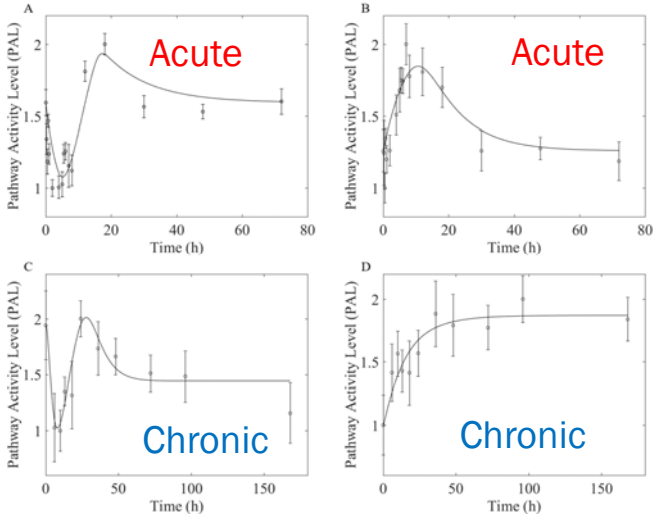


Peroxisome Response



The dynamics of the pathway are independent of the individual components of the pathway
It is not about which element is up/down regulated, but rather about how these elements come together

Cysteine and Methionine Metabolism



Gene Reg & Sys Biol, under review

Looking forward…

Can we tease out the individual from the bulk?

1) Using the function and not the component
2) Using the response dynamics

Personalized perturbation of pathways - The *personalized* static network

- Human studies (asthma, Parkinson and Huntington's disease) indicated extremely few if any genes to be consistently upregulated across all patients!
- The technical and biological variability, the genetic diversity and the heterogeneity of complex disease indicate that molecular mechanisms act differently in patients with the same phenotype
- Despite high level of individual component variability, complex diseases arise from common disruptions at the pathway/function level complex
- The fraction of perturbed components was a personalized predictor of disease, rather than a specific component

Menche *et al.*, *NPJ Syst Biol Appl, 3(10)* 2017

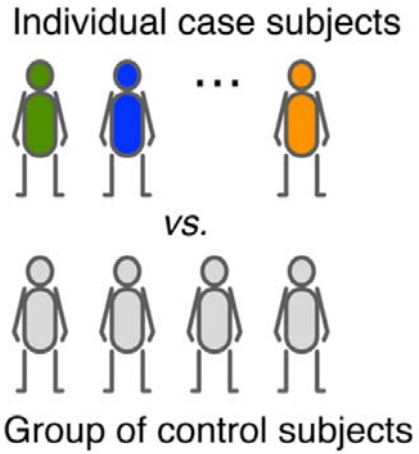
Personalized perturbation of pathways - The *personalized* static network

The heterogeneity of complex diseases leads to the possibility that partially overlapping molecular mechanisms act on patients with the same phenotype

➔Different genes could correspond to regulation checkpoints within the pathway

➔Searching for similarities across patients may be futile

Disease and/or drug treatment result in consistent disease/drug-specific pathway activation despite “inconsistent” component changes



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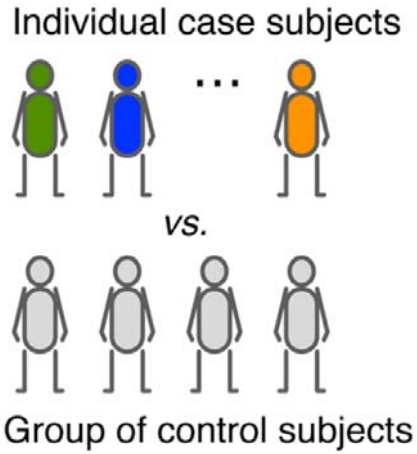

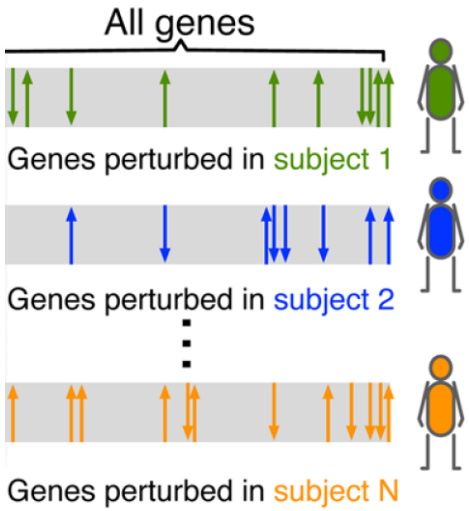

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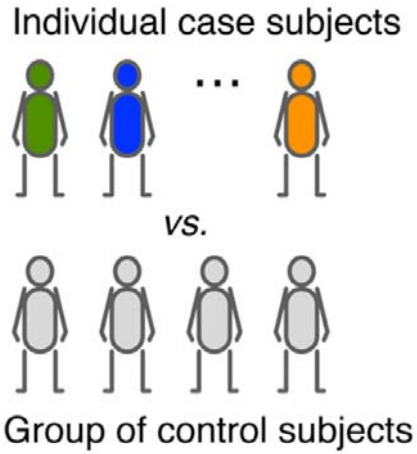

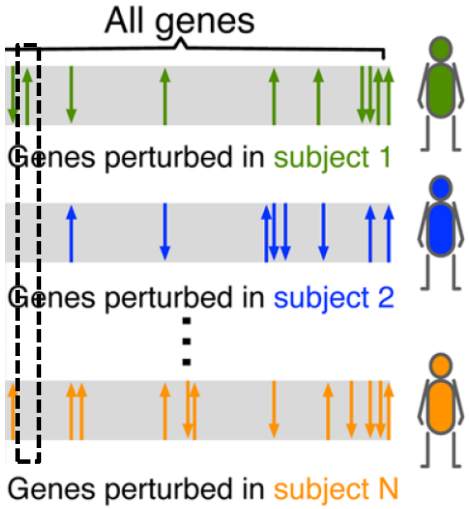

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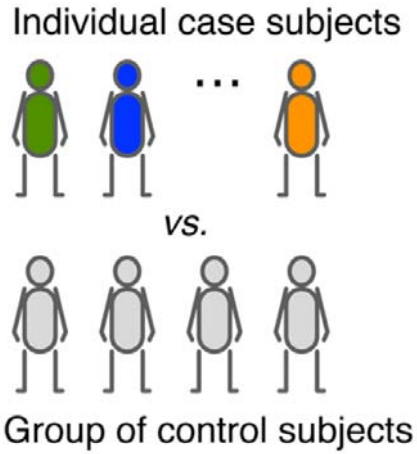

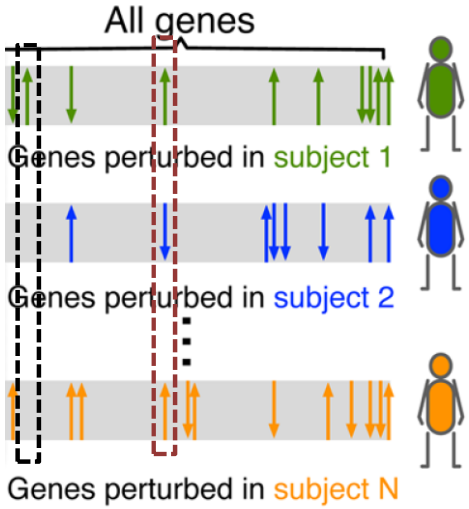

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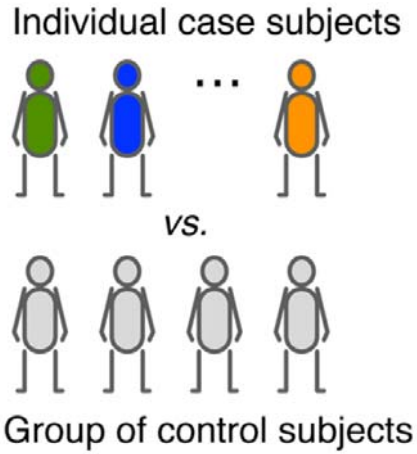

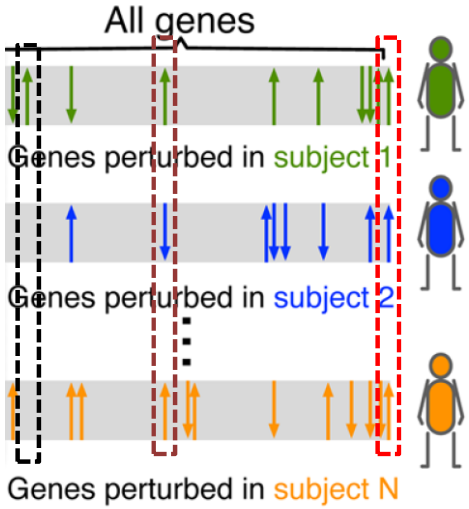

NPJ Syst Biol Appl, 3(10) 2017

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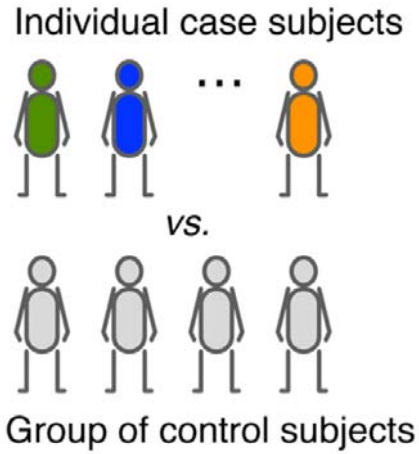
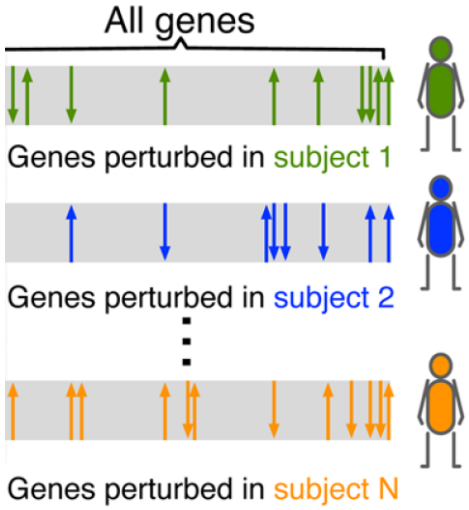
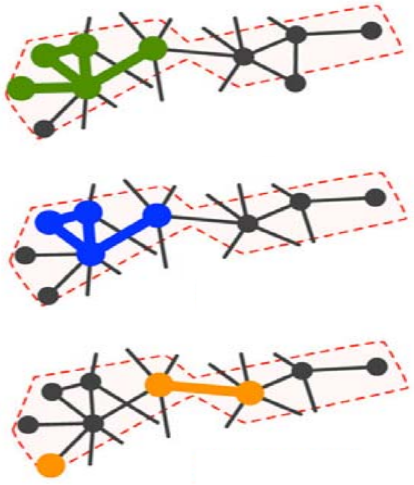
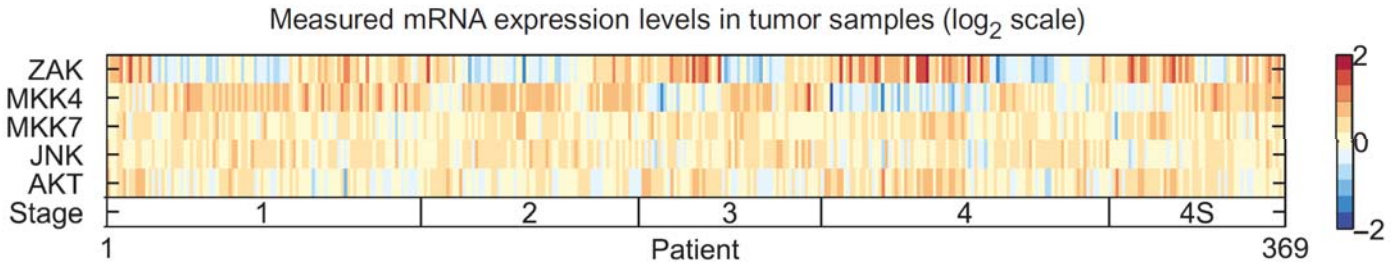


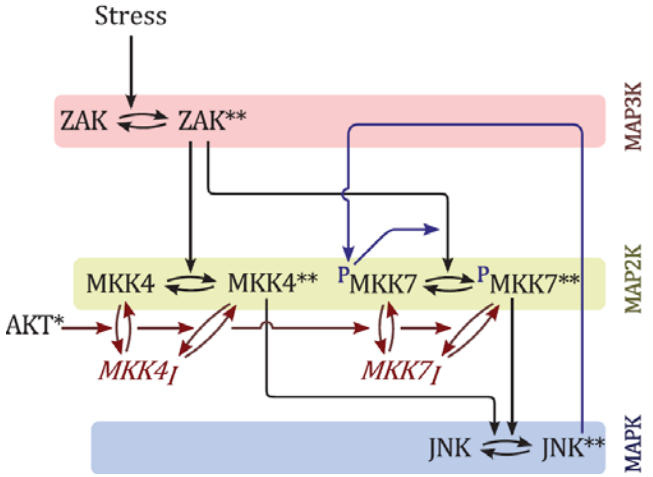


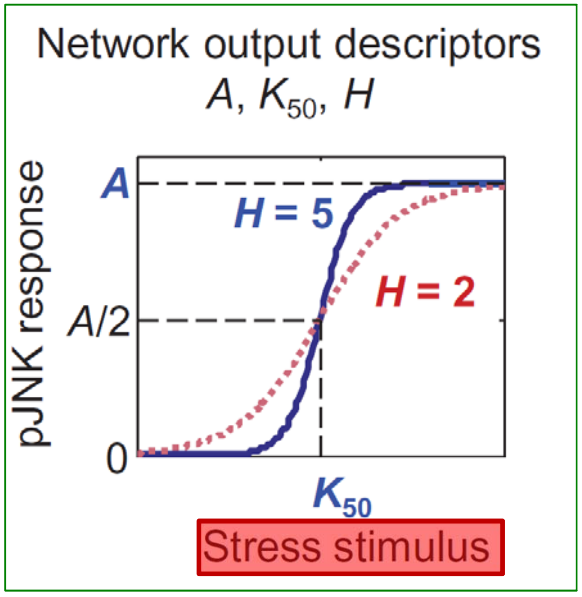


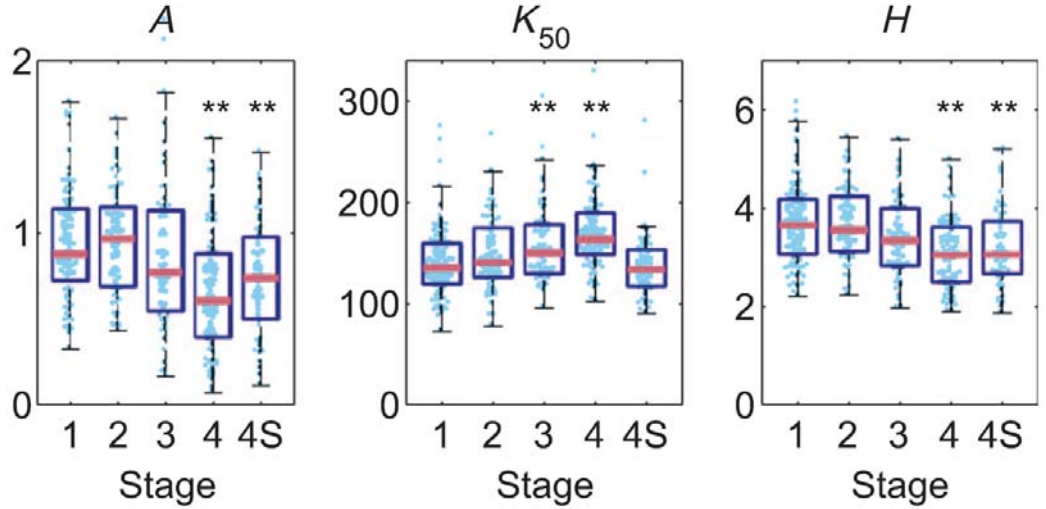
NPJ Syst Biol Appl, 3(10) 2017

Response dynamics of personalized networks – The *personalized* dynamic network









Sci Signaling, ***8***(408):1, 2015

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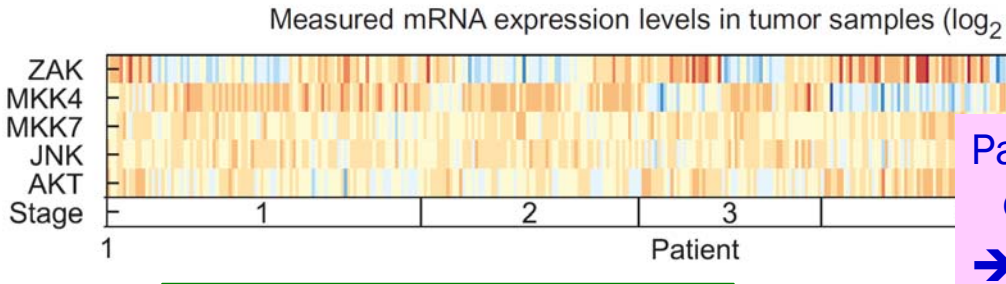
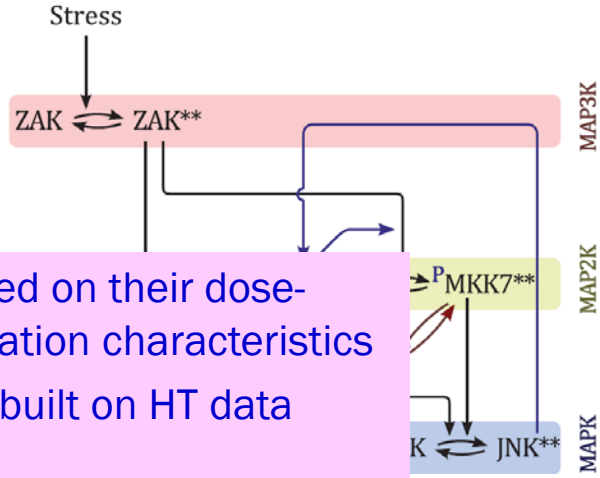
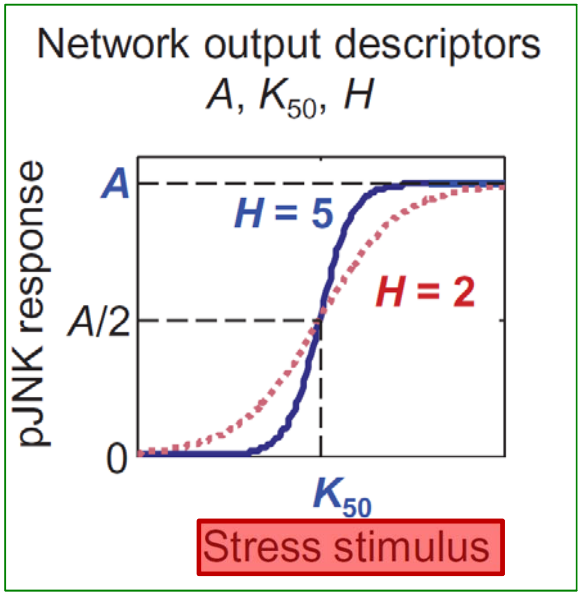
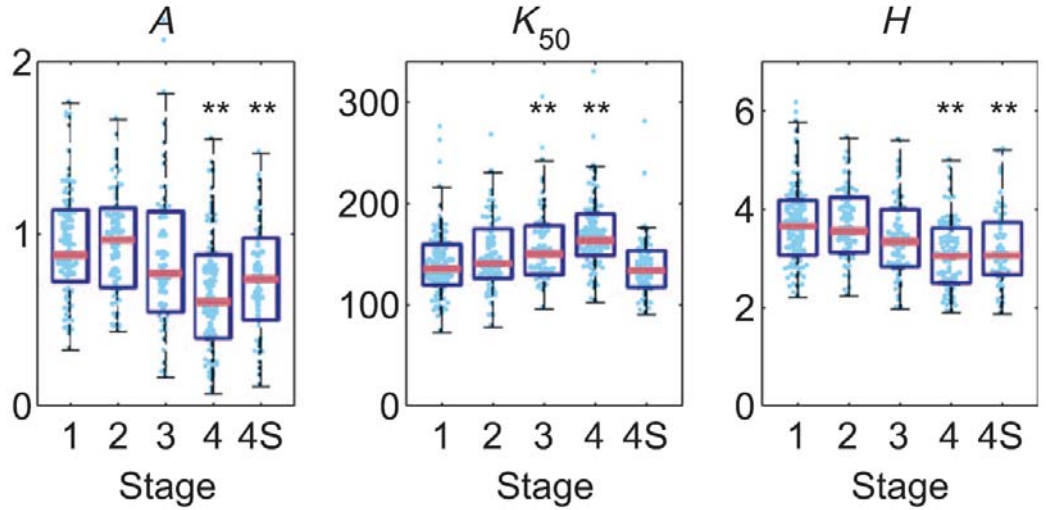




Patients are stratified based on their dose-dependent (model) activation characteristics

➔Dynamics of the model built on HT data becomes the biomarker





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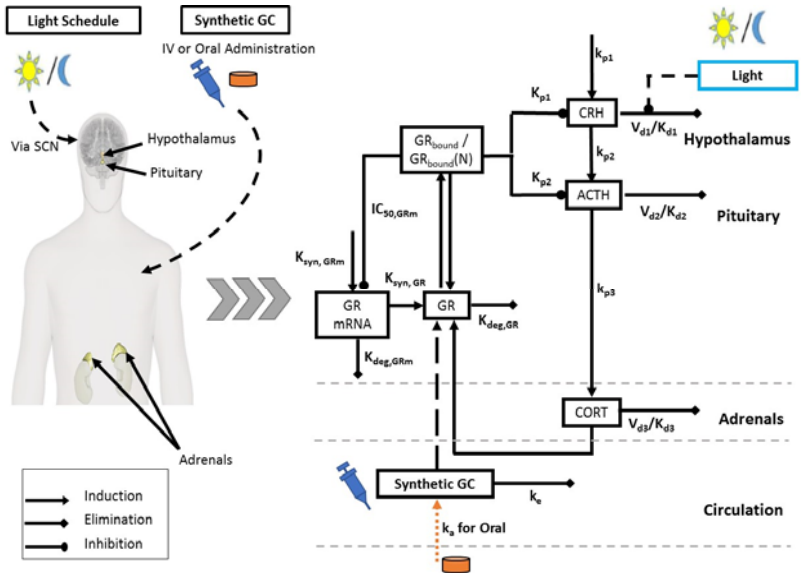
Average response of an *in silico* population



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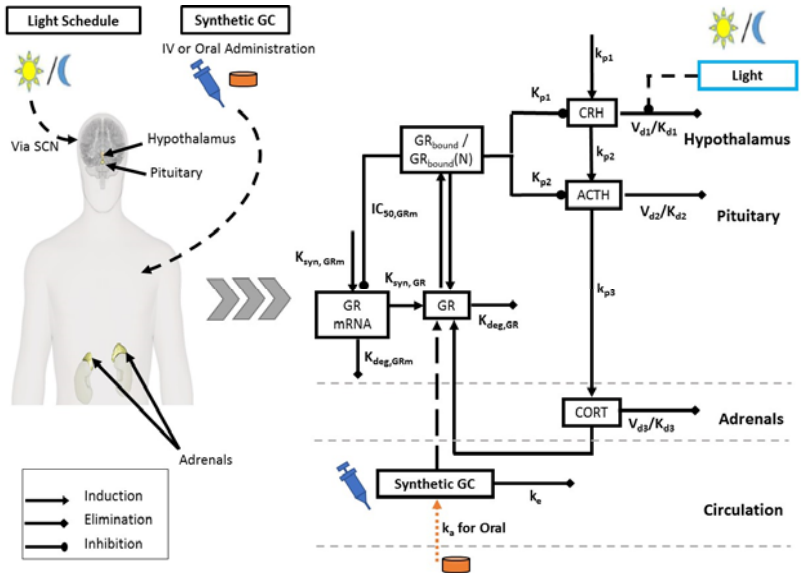
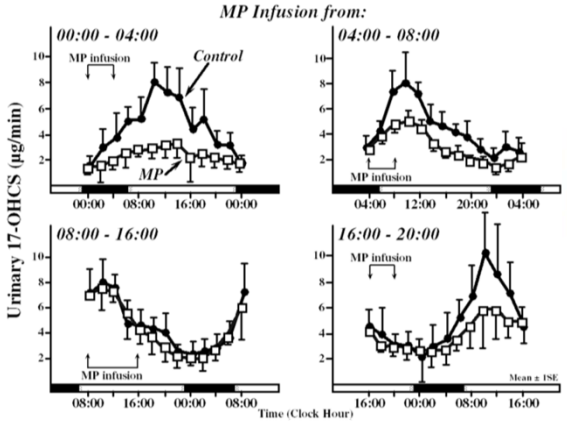
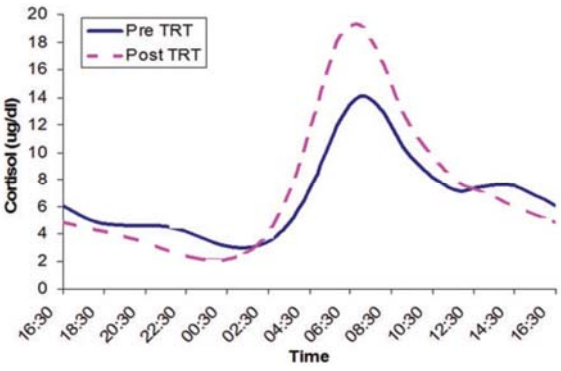




Bull NYU Hosp Jt Dis, **70**:3, 2012



Ann NY Acad Sci, **1193**:127, 2010

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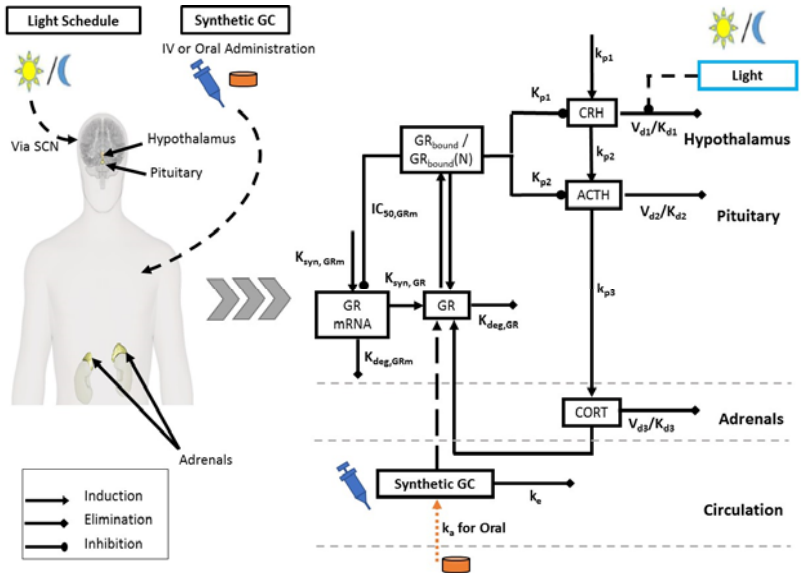

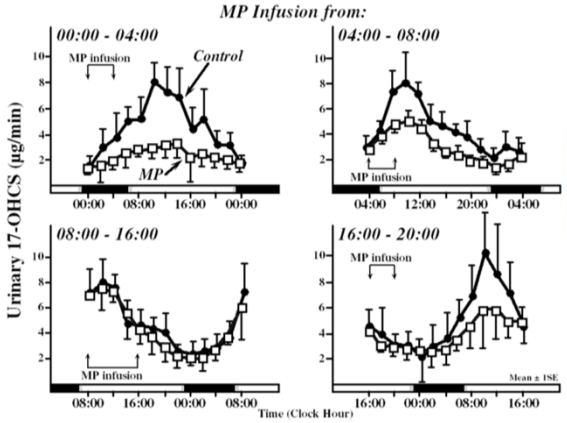

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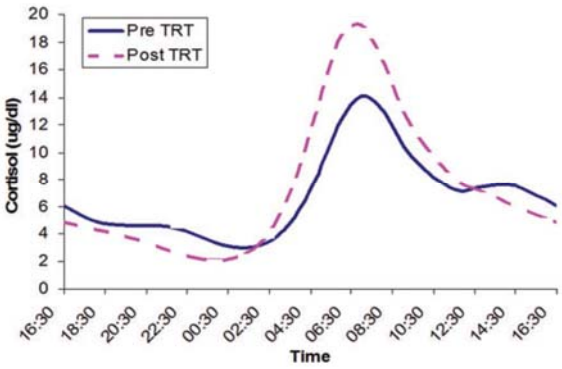

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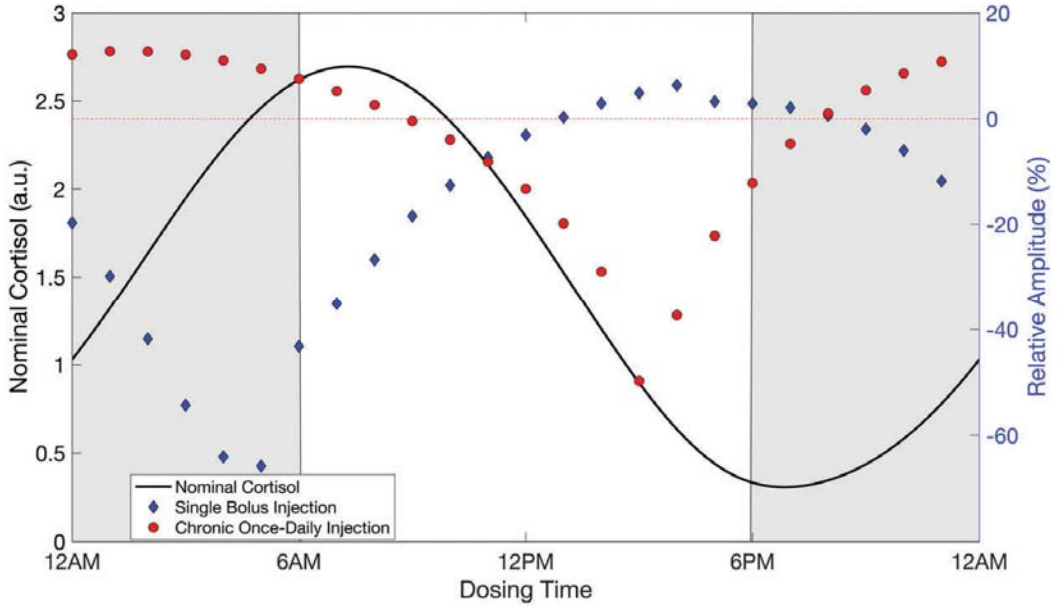
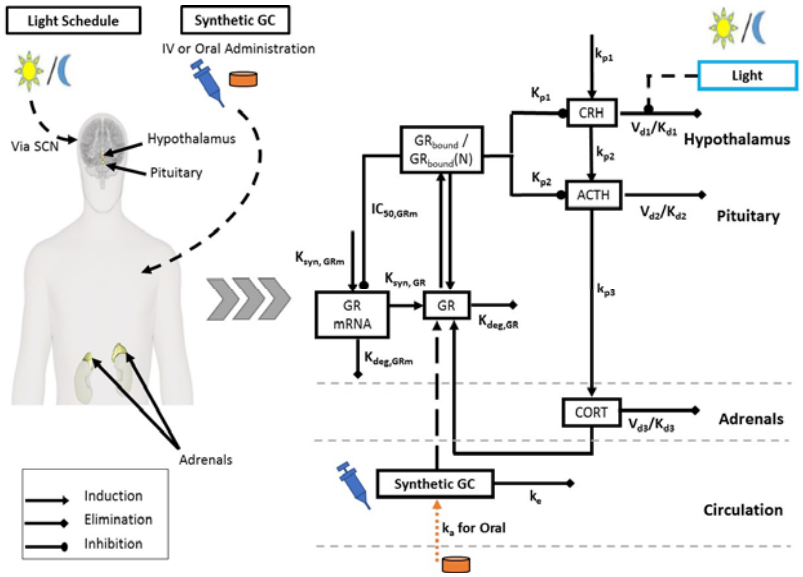
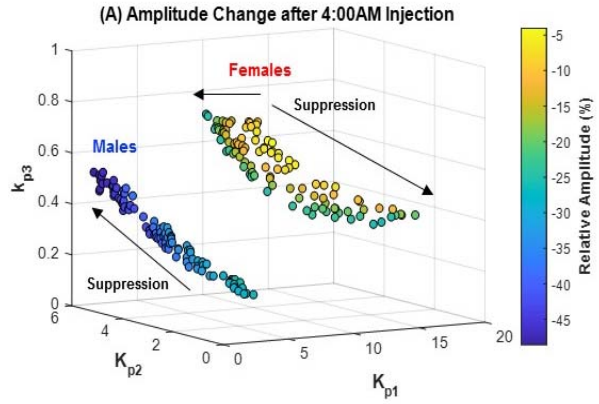
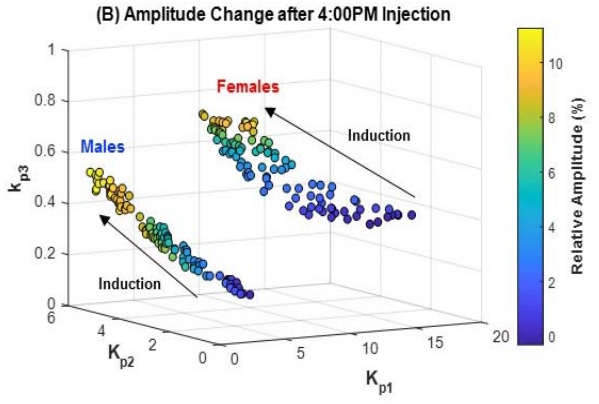


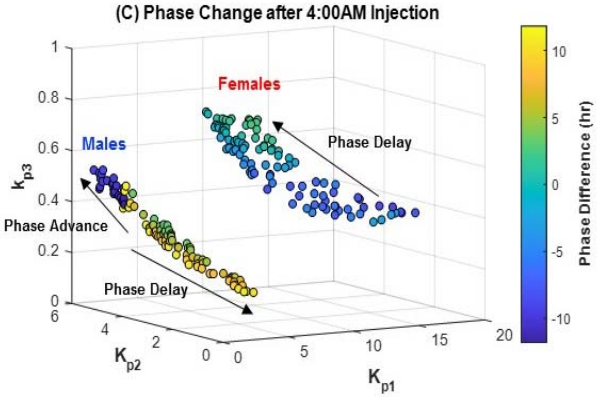
Chronobiol Int, **35**(12):1618, 2018

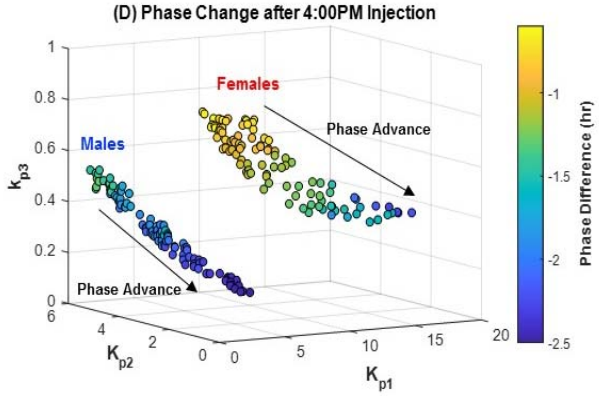
Individualized response of an *in silico* population





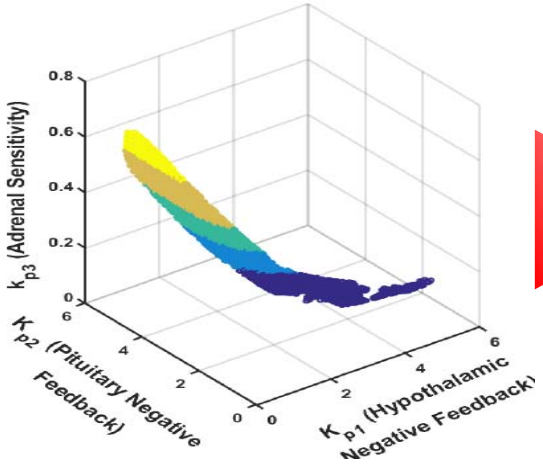


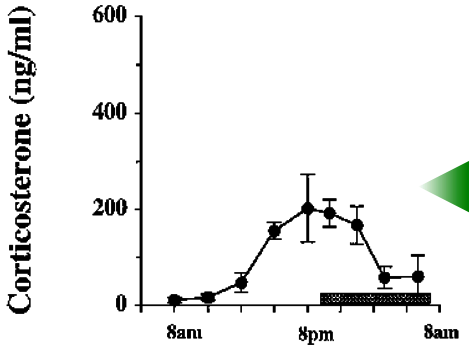




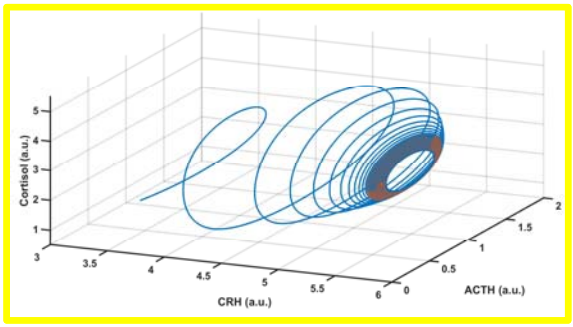
(under review)

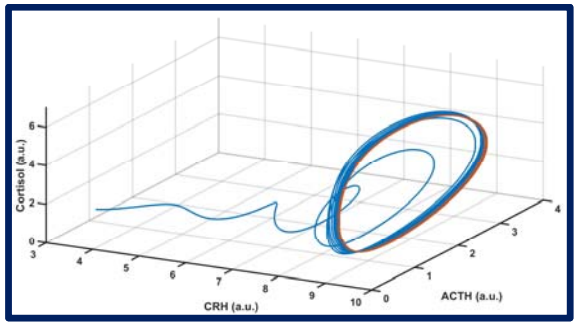
From genotypic plasticity to phenotypic similarity to response diversity

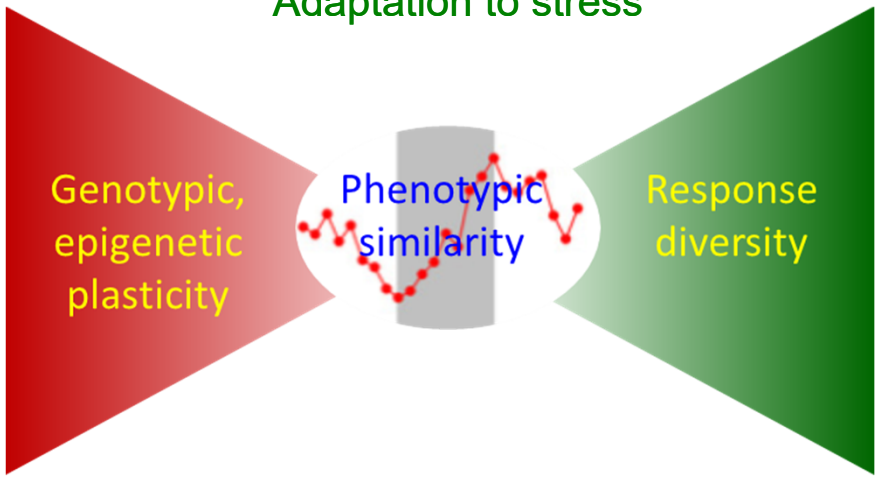




Response to acute stress
Adaptation to stress







Endocrinology, 158(11):4017, 2017

Some final thoughts

1) HT big(er) data enable us to look not at more things but move us towards a more "functional" view of the system: gene → pathway

   We can begin to tease out not just more individual components, but rather how multiple components come together in the form a "function"

1) Explore the idea of higher-level modeling . This does not imply simply writing models with more variables and equations, but rather, i.e., modeling at the level of some higher level "function" (what is that the components do)

2) Meta-analysis of the model becomes the "biomarker": structure, response to perturbations, others?

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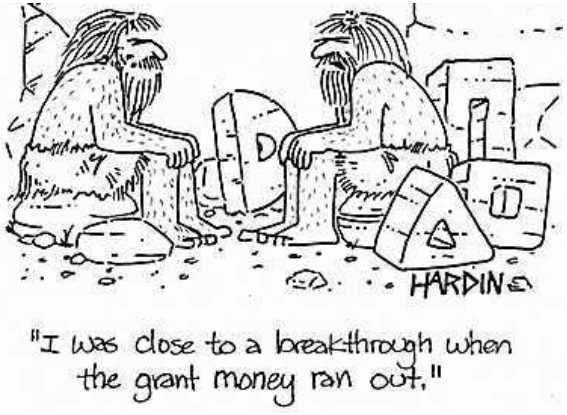

NATIONAL INSTITUTES OF HEALTH

William J. Jusko
SUNY Buffalo