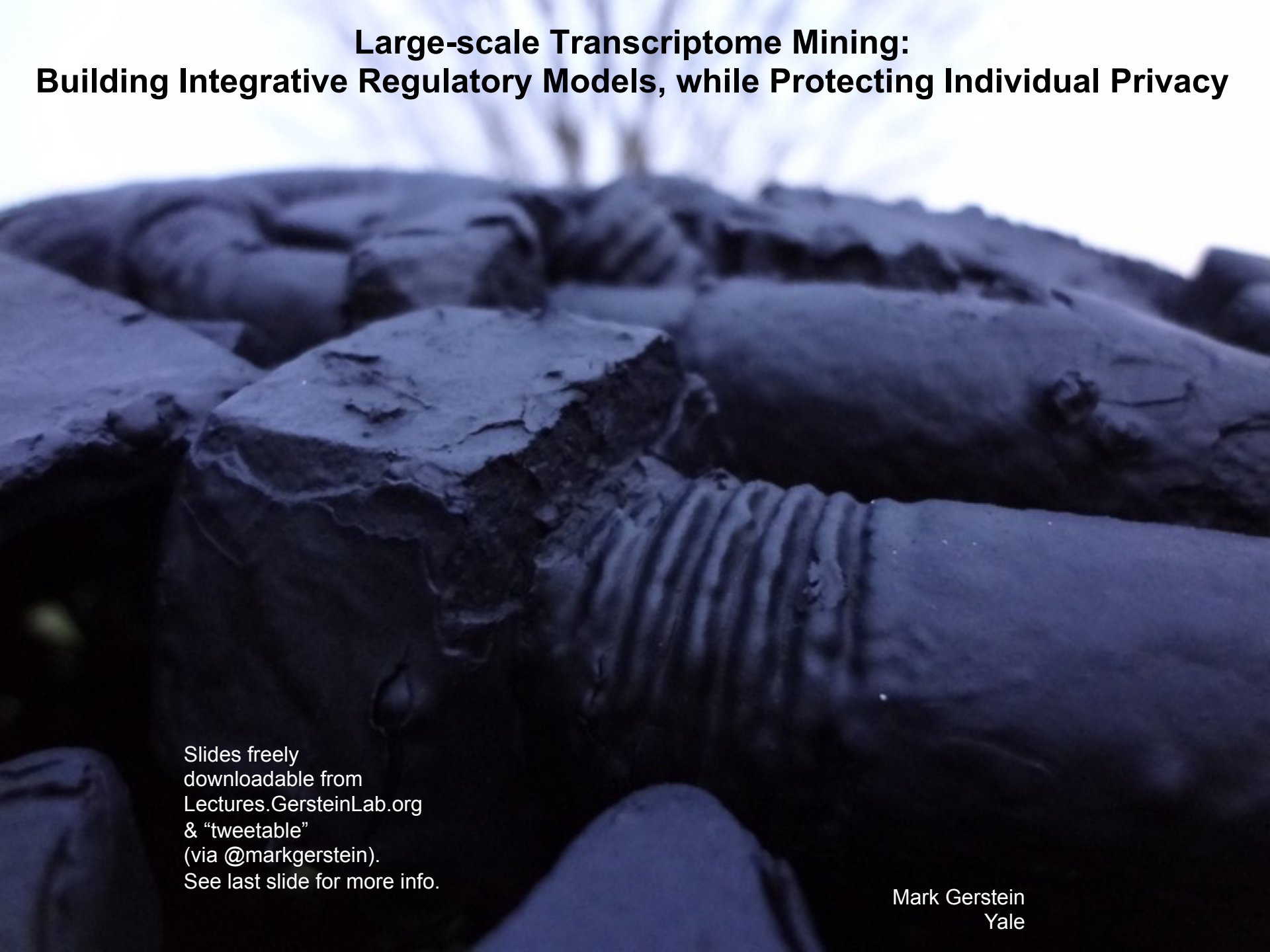
Large-scale Transcriptome Mining: Building Integrative Regulatory Models, while Protecting Individual Privacy

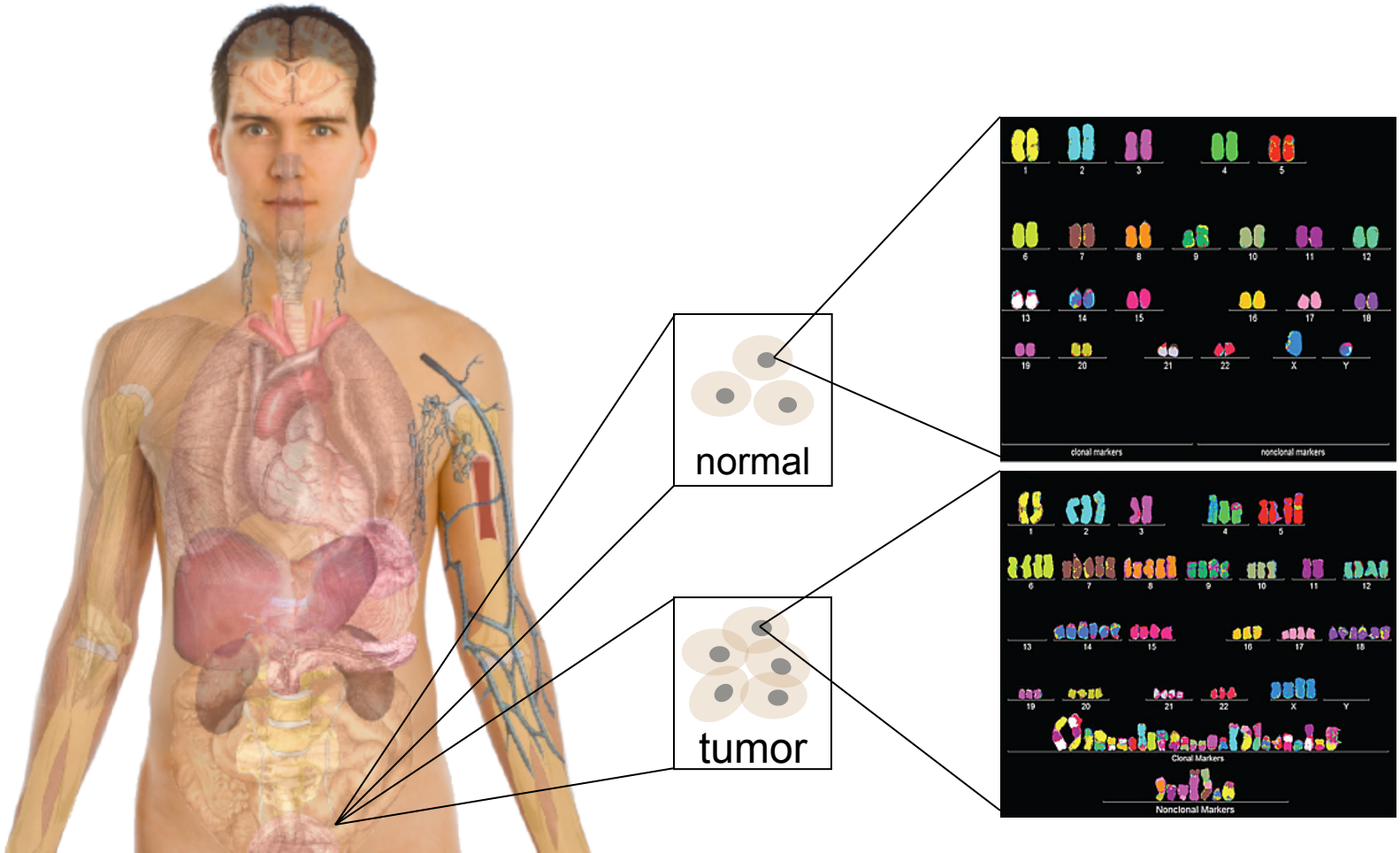


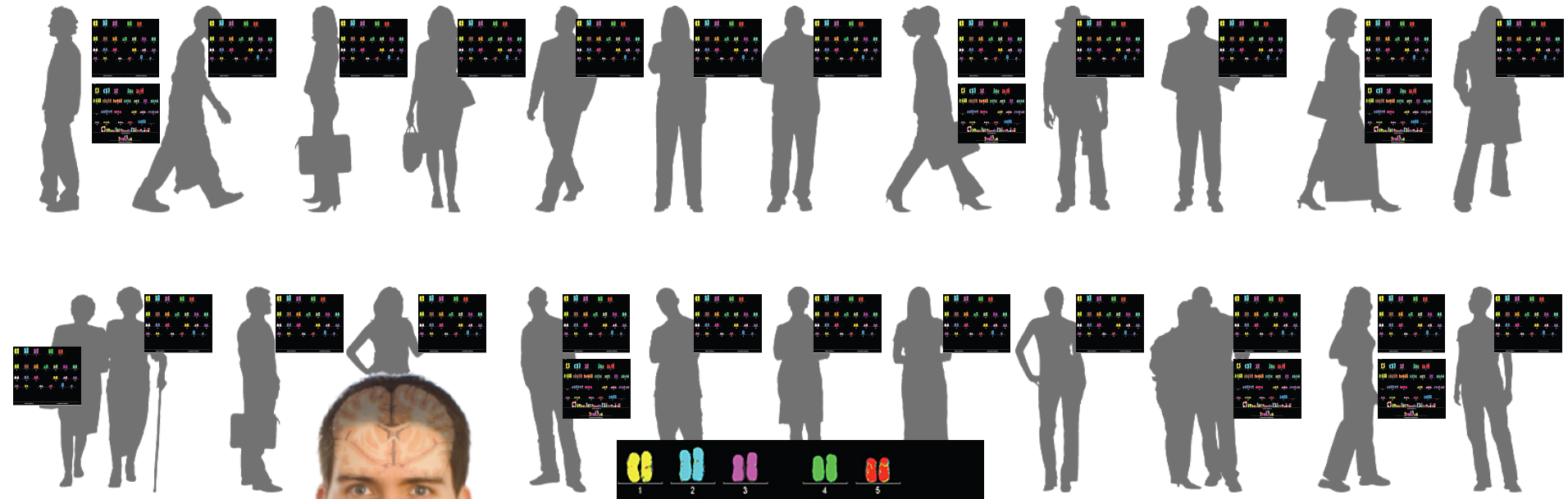
Slides freely downloadable from Lectures.GersteinLab.org & “tweetable” (via @markgerstein). See last slide for more info.

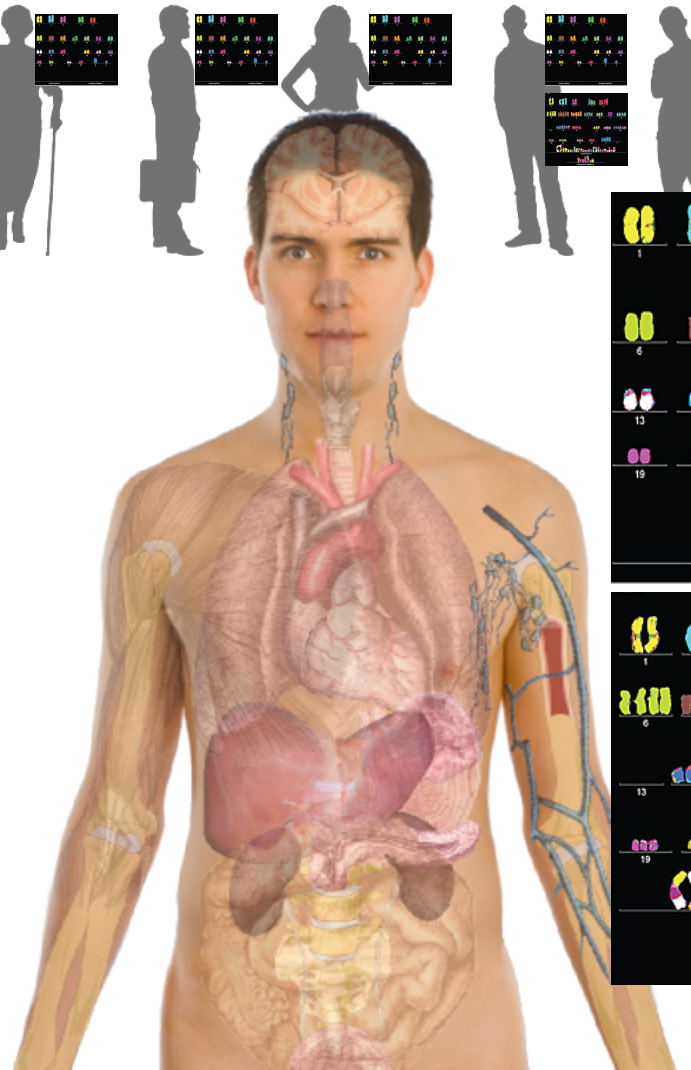
Mark Gerstein
Yale

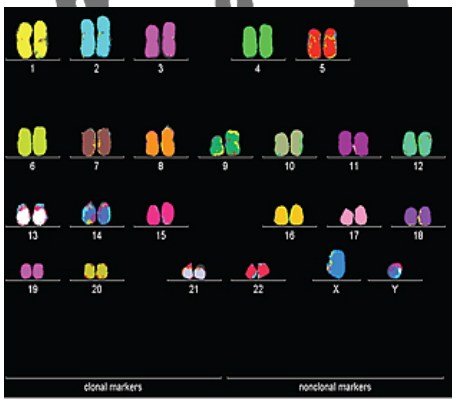
Personal Genomics & Transcriptomics as a Gateway into Biology

Personal genomes (& Transcriptomes) soon will become a commonplace part of medical research & eventually treatment (esp. for cancer).
They will provide a primary connection for biological science to the general public.



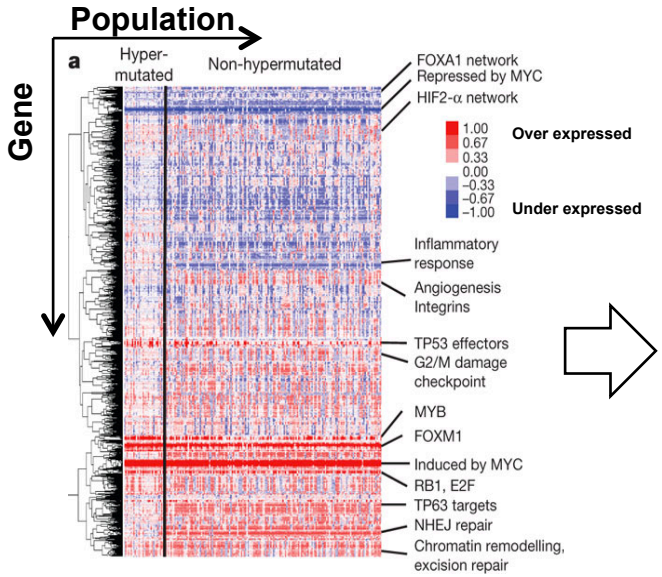






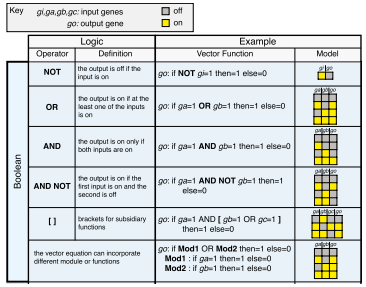
Placing the individual into the context of the population & using the population to build a interpretative model

Modeling for RNA-seq data across many samples & individuals… while still protecting individual privacy

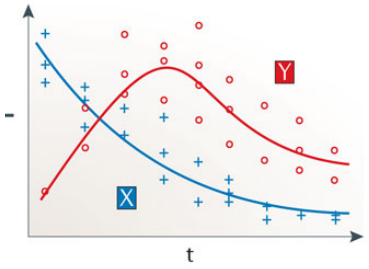


The Cancer Genome Atlas Network Nature 487, 330-337 (2012) doi:10.1038/nature11252

- Logical model



- Continuous model



$$\frac{dx_i}{dt} = \sum_{j=1}^{n} a_{i,j} x_j$$

- Probabilistic model

- Gene Regulatory Mechanisms

Istrail & Davidson, PNAS, '04 Nicolas Le Novère, Nature Reviews Genetics, '15

Large-scale Transcriptome Mining: Building Interpretative, Regulatory Models, while Protecting Individual Privacy

- **The Dilemma of Genomic Privacy**
  - Fundamental, inherited info that's very private v need for large-scale mining for med. research
  - Issues w/ current social & tech approaches: inconsistencies, burdensome security, various "hacks"
  - Strawman Hybrid Soc-Tech Proposal (Cloud Enclaves. Quantifying Leaks & Closely Coupled priv.-public datasets)
- **RNA-seq: How to Publicly Share Some of it**
  - Removing SNVs in reads w/ MRF
  - Quantifying & removing variant info from expression levels + eQTLs using ICI & predictability
  - Instantiating a practical linking attack using extreme expression levels
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  - Preponderance of OR gates in cancer v. cell-cycle (esp. for myc)
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  - Using dimensionality reduction to determine drivers and internal & external canonical dynamic patterns (iPDPs & ePDPs)
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The Conundrum of Genomic Privacy: Is it a Problem?

Yes

Genetic Exceptionalism :
genome is potentially very revealing about one's identity & characteristics

- Most discussion of Identification Risk but what about Characterization Risk?
  - Finding you were in study X vs identifying that you have trait Y from studying your identified genome

No

Shifting societal foci

No one really cares about *your* genes

You might not care

[Klitzman & Sweeney ('11), J Genet Couns 20:98l; Greenbaum & Gerstein ('09), New Sci. (Sep 23)]

Genomics has similar "Big Data" Dilemma in the Rest of Society

- Sharing & "peer-production" is central to success of many new ventures, with the same risks as in genomics
- We confront privacy risks every day we access the internet
- (...or is the genome more exceptional & fundamental?)

[Seringhaus & Gerstein ('09), *Hart. Courant* (Jun 5); Greenbaum & Gerstein ('11), *NY Times* (6 Oct)]

Tricky Privacy Considerations in Personal Genomics

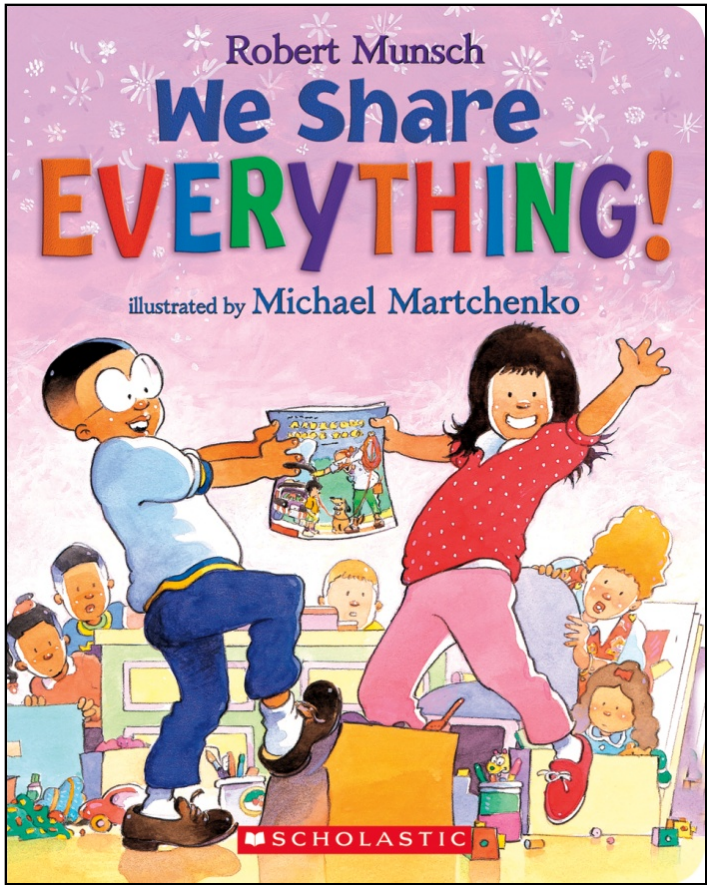
- Personal Genomic info. essentially meaningless currently but will it be in 20 yrs? 50 yrs?
  - Genomic sequence very revealing about one's children. Is true consent possible?
  - Once put on the web it can't be taken back
- Culture Clash: Genomics historically has been a proponent of "open data" but not clear personal genomics fits this
- Ethically challenged history of genetics

- Ownership of the data & what consent means (Hela)
  - Could your genetic data give rise to a product line?

[D Greenbaum & M Gerstein ('08). Am J. Bioethics; D Greenbaum & M Gerstein, Hartford Courant, 10 Jul. '08 ; SF Chronicle, 2 Nov. '08; Greenbaum et al. *PLOS CB* ('11) ; Greenbaum & Gerstein ('13), The Scientist; Photo from NY Times]

The Other Side of the Coin: Why we should share

- Sharing helps speed research
  - Large-scale mining of this information is important for medical research
  - Privacy is cumbersome, particularly for big data
- Sharing is important for reproducible research
- Sharing is useful for education



[Yale Law Roundtable ('10). Comp. in Sci. & Eng. 12:8; D Greenbaum & M Gerstein ('09). Am. J. Bioethics; D Greenbaum & M Gerstein ('10). SF Chronicle, May 2, Page E-4; Greenbaum et al. *PLOS CB* ('11)]

[Economist, 15 Aug '15]

The Dilemma

- The individual (harmed?) v the collective (benefits)
  - But do sick patients care about their privacy?
- Quantification
  - What is acceptable risk? What is acceptable data leakage? Can we quantify leakage?
    - Ex: photos of eye color
  - Cost Benefit Analysis: how helpful is identifiable data in genomic research v. potential harm from a breach?
- Maybe a we need a few "test pilots" (ala PGP)?
  - Sports stars & celebrities?

Current Social & Technical Solutions

- Consents
- “Protected” distribution of data (dbGAP)
- Local computes on secure computer

- Issues
  - Non-uniformity of consents & paperwork
    - Different international norms, leading to confusion
  - Encryption & computer security creates burdensome requirements on data sharing & large scale analysis
  - Many schemes get “hacked”

[Greenbuam et al ('04), Nat. Biotech; Greenbaum & Gerstein ('13), The Scientist]

Genomic Privacy Hacks, Mostly Focusing on Identification

- Early genomic studies were based on small cohorts
  - Individuals give consent to participate but request anonymity
    - HAPMAP, PGP, 1000 Genomes…
  - Focus on hiding the participation of individuals
  - Attacks aimed at detecting whether an individual with known genotypes participated a study
    - "Detection of genomes in a mixture" (Homer et al 2008, Im et al 2012)
- As more people are genotyped, more individuals are in large private genomic databases
  - Detection of an individual is irrelevant, as their participation is already known
    - Current EX: "An individual's genomic/phenotypic data is most certainly stored in their hospital"
    - Future: >1M people's health information is part of a NIH/PMI or NHS databases
- Identification attacks now focus on pinpointing individuals by cross-referencing large seemingly independent datasets
  - Illustrates that a leaked/hacker/stolen dataset, even when anonymized, can leak information
  - Sweeney et al 2013, Gymrek et al 2013

Gymrek et al, "Identifying Personal Genomes by Surname Inference" (2013)
Homer et al, "Resolving individuals contributing trace amounts of DNA to highly complex mixtures using high-density SNP genotyping microarrays." (2008)
Im et al, "On Sharing Quantitative Trait GWAS Results in an Era of Multiple-omics Data and the Limits of Genomic Privacy" (2012)
Sweeney et al, "Identifying Participants in the Personal Genome Project by Name" (2013)

Robust De-anonymization of Large Datasets (How to Break Anonymity of the Netflix Prize Dataset)

Arvind Narayanan and Vitaly Shmatikov

The University of Texas at Austin

February 5, 2008

Abstract

We present a new class of statistical de-anonymization attacks against high-dimensional micro-data, such as individual preferences, recommendations, transaction records and so on. Our techniques are robust to perturbation in the data and tolerate some mistakes in the adversary's background knowledge.

We apply our de-anonymization methodology to the Netflix Prize dataset, which contains anonymous movie ratings of 500,000 subscribers of Netflix, the world's largest online movie rental service. We demonstrate that an adversary who knows only a little bit about an individual subscriber can easily identify this subscriber's record in the dataset. Using the Internet Movie Database as the source of background knowledge, we successfully identified the Netflix records of known users, uncovering their apparent political preferences and other potentially sensitive information.

NetFlix challenge as an example of a "Linking Attack", characterizing already identified individuals in IMDB, with their (previously hidden) movie viewing habits

Cross correlated small set of identifiable IMDB rating records with large set of "anonymized" Netflix customer ratings, which were being used for a Machine Learning competition

Strawman Hybrid Social & Tech Proposed Solution?

- Fundamentally, researchers have to keep genetic secrets
  - Genetic Licensure & training for individuals (similar to medical license, drivers license)
- Technology to make things easier
  - Cloud computing & enclaves (eg solution of Genomics England)
- Technological barriers shouldn't create a social incentive for “hacking”

- **Quantifying Leakage & allowing a small amounts of it**
- **Careful separation & coupling of private & public data**
  - **Lightweight, freely accessible secondary datasets coupled to underlying variants**
  - Selection of stub & "test pilot" datasets for benchmarking
  - Develop programs on public stubs on your laptop, then move the program to the cloud for private production run

[D Greenbaum, M Gerstein (‘11). Am J Bioeth 11:39. Greenbaum & Gerstein, The Scientist ('13)]

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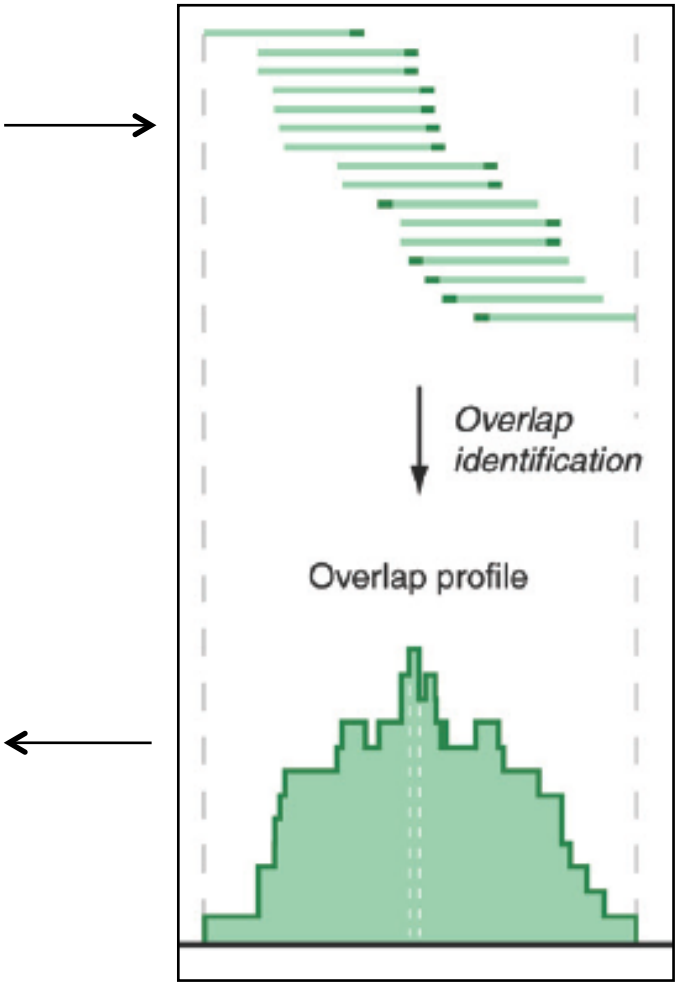
RNA-seq

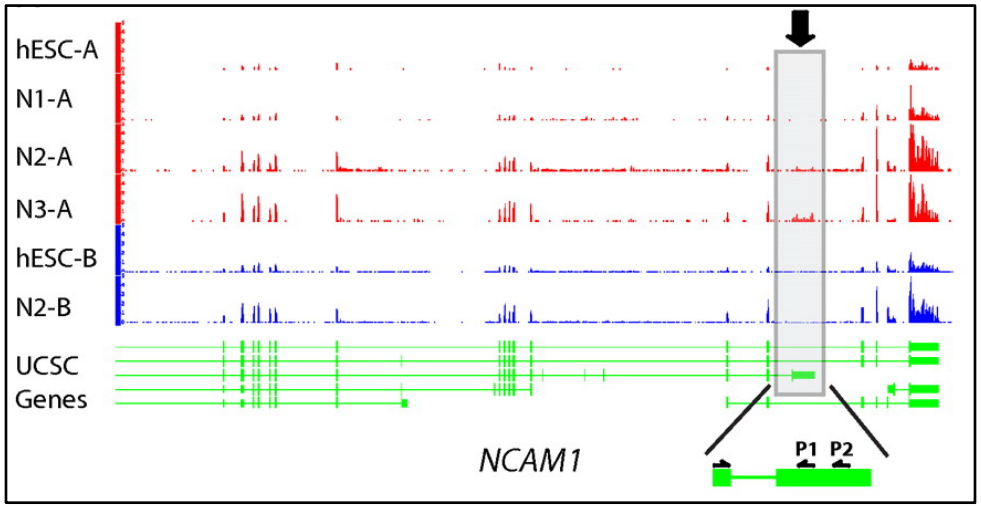
RNA-seq uses next-generation sequencing technologies to reveal RNA presence and quantity within a biological sample.

```
ATACAAGCAAGTATAAGTTCGTATGCCGTCTT
GGAGGCTGGAGTTGGGGACGTATGCGGCATAG
TACCGATCGAGTCGACTGTAAACGTAGGCATA
ATTCTGACTGGTGTCATGCTGATGTACTTAAA
```

Reads (fasta)
- Quality scores (fastq)
- Mapping (BAM)
- Contain variant information in transcribed regions



Reads => Signal

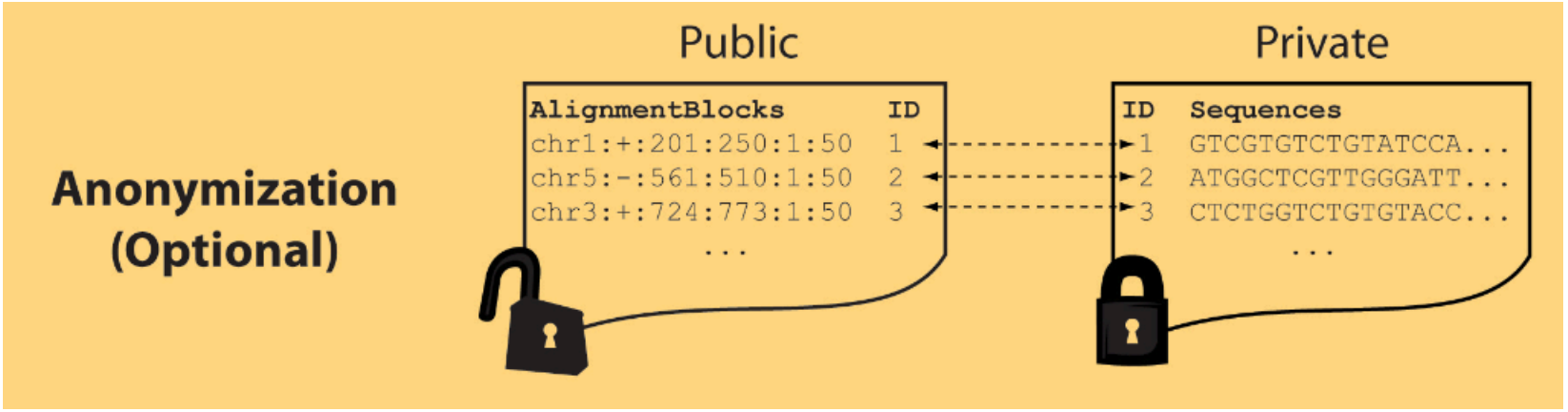


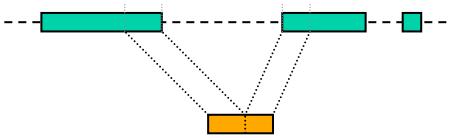
Quantitative information from RNA-seq signal: average signals at exon level (RPKMs)

[*PLOS CB* 4:e1000158; *PNAS* 4:107: 5254 ; *IJC* 123:569]

Light-weight formats

- Some lightweight format clearly separate public & private info., aiding exchange
- Files become much smaller
- Distinction between formats to compute on and those to archive with – become sharper with big data





Mapping coordinates without variants (MRF)

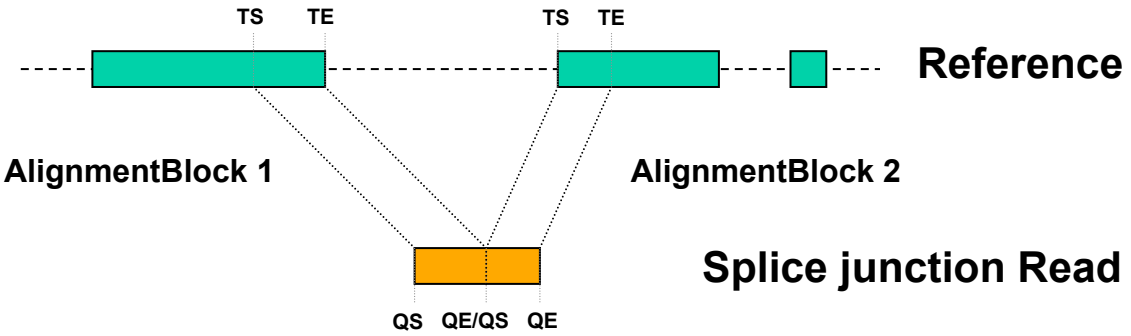
Reads (linked via ID, 10X larger than mapping coord.)

[*Bioinformatics* 27: 281]

MRF Examples

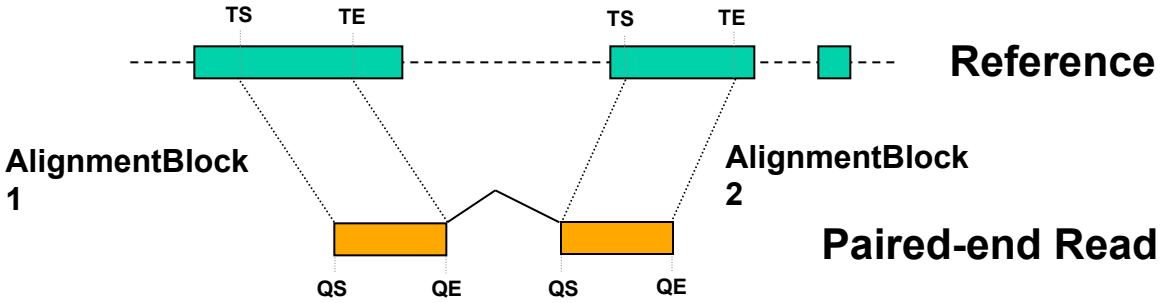
Reference based compression **(ie CRAM)** is similar but it stores actual variant beyond just position of alignment block

`chr2:+:601:630:1:30,chr2:+:921:940:31:50`



Legend: TS = TargetStart, TE = TargetEnd, QS = QueryStart, QE = QueryEnd

`chr9:+:431:480:1:50|chr9:+:945:994:1:50`



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[Habegger et al., Bioinformatics ('11)]

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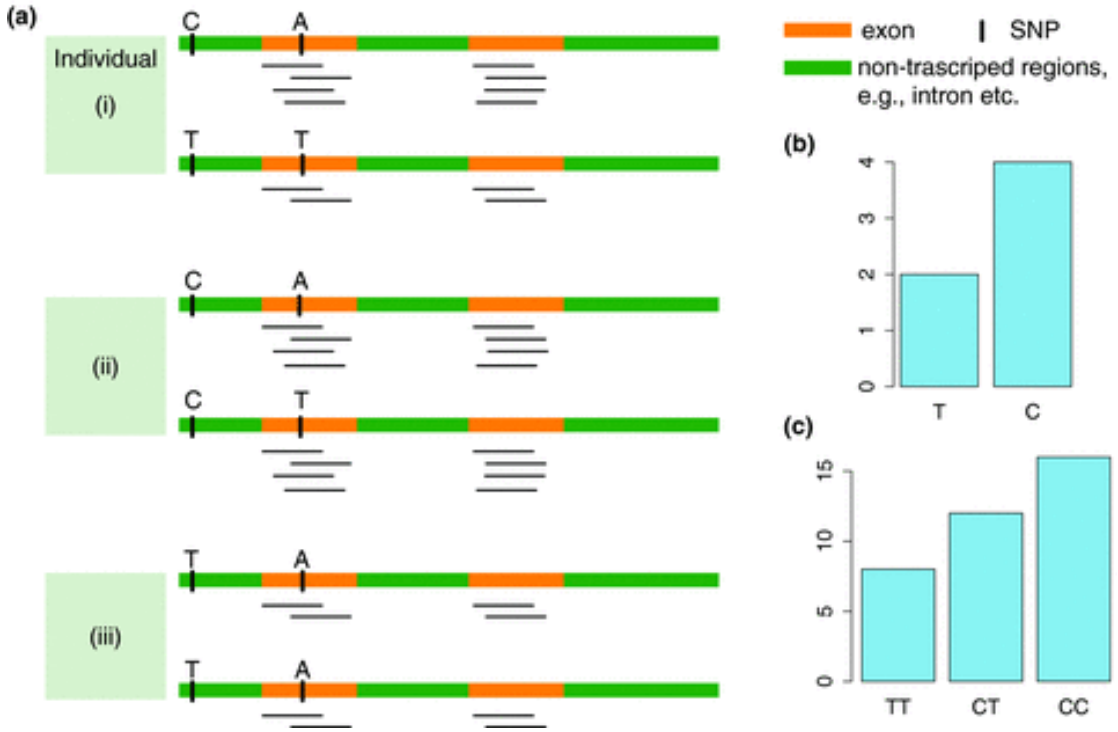
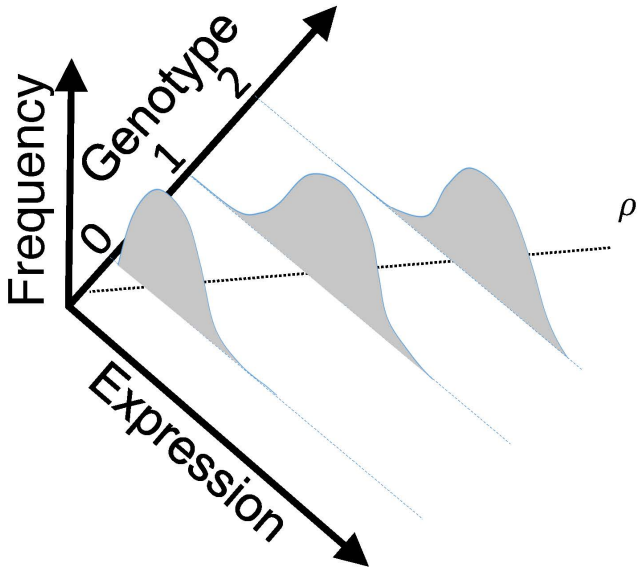


[*Biometrics 68(1) 1–11*]

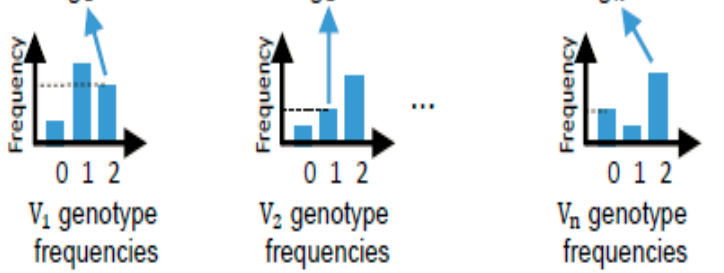


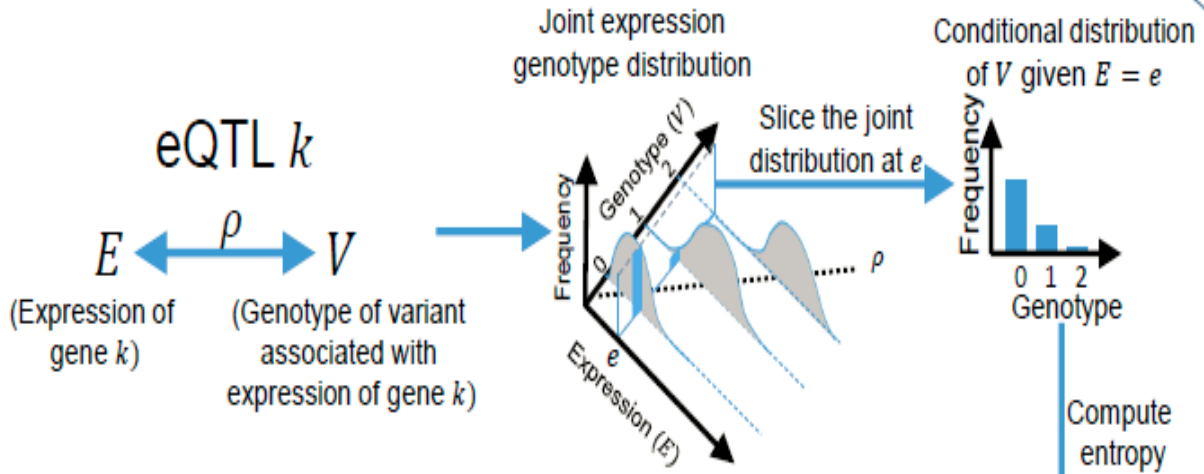
eQTL Mapping Using RNA-Seq Data

- eQTLs are genomic loci that contribute to variation in mRNA expression levels
- eQTLs provide insights on transcription regulation, and the molecular basis of phenotypic outcomes
- eQTL mapping can be done with RNA-Seq data

Information Content and Predictability

$$ICI\left(\begin{array}{c}\text{Individual has variant}\\ \text{genotypes } g_1, g_2, \ldots, g_n\\ \text{for variants } V_1, V_1, \ldots, V_n\end{array}\right) = \log\left(\frac{1}{\text{Frequency of } V_1 \text{ genotype } g_1 = 2}\right) + \log\left(\frac{1}{\text{Frequency of } V_2 \text{ genotype } g_2 = 1}\right) + \ldots + \log\left(\frac{1}{\text{Frequency of } V_n \text{ genotype } g_n = 2}\right)$$



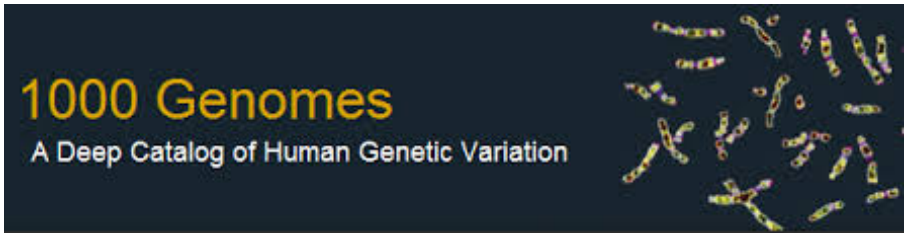


$$\pi\left(V \mid E = e\right) = e^{-H\left(V \mid E = e\right)}$$

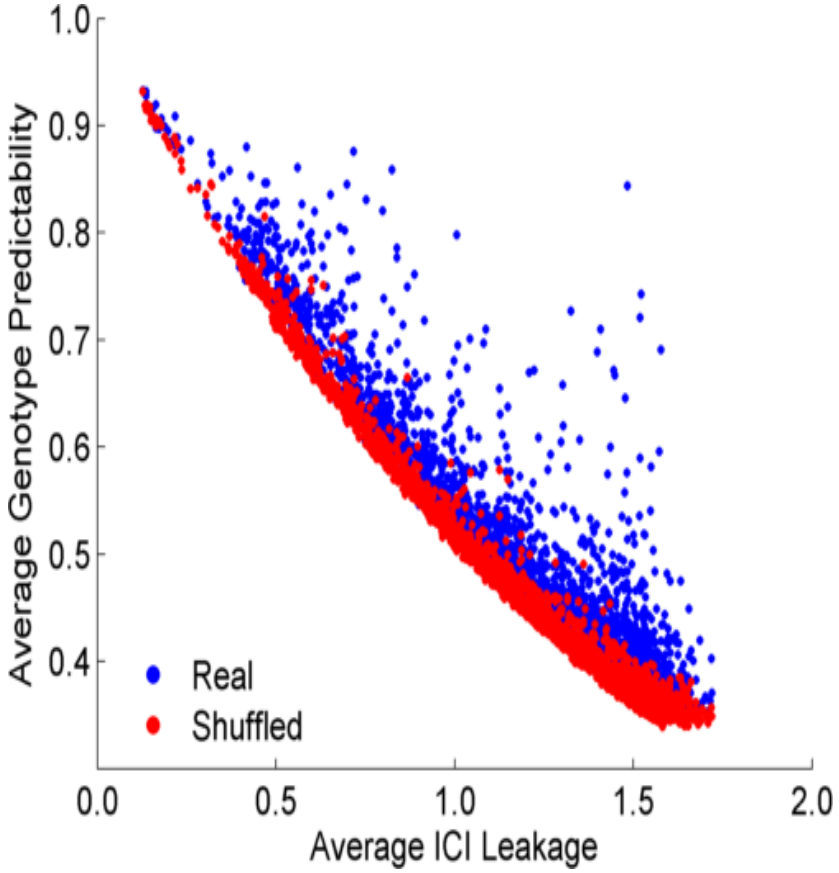
[Harmanciet al. Nat. Meth. (in revision)]

Representative Expression, Genotype, eQTL Datasets

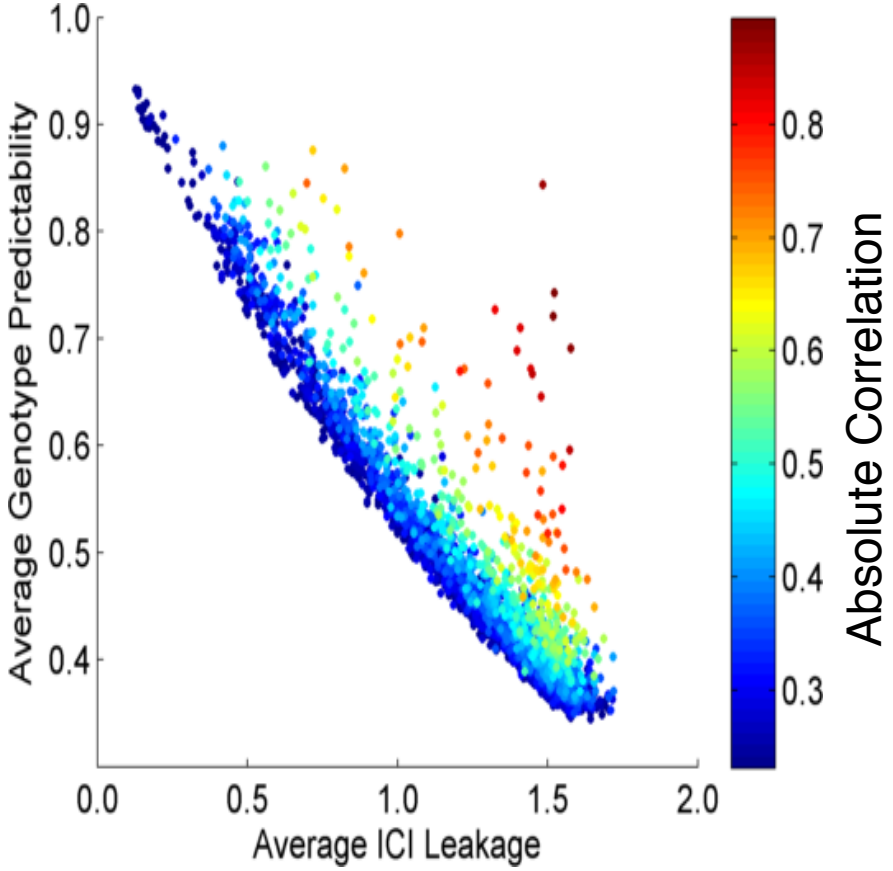
- Genotypes are available from the 1000 Genomes Project
- mRNA sequencing for 462 individuals
  - Publicly available quantification for protein coding genes
- Approximately 3,000 cis-eQTL (FDR<0.05)



Per eQTL and ICI Cumulative Leakage versus Genotype Predictability

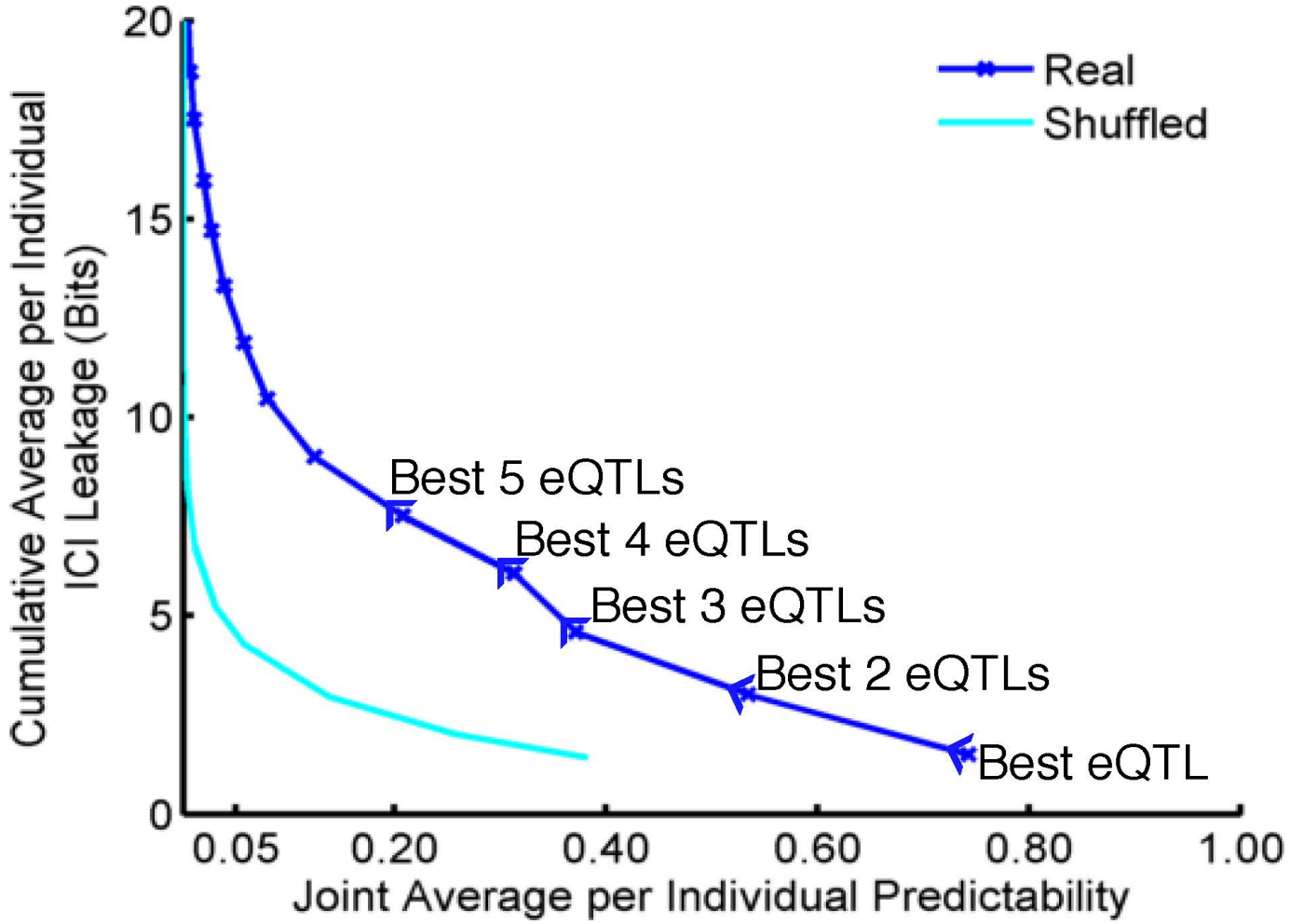


Colors by absolute correlation



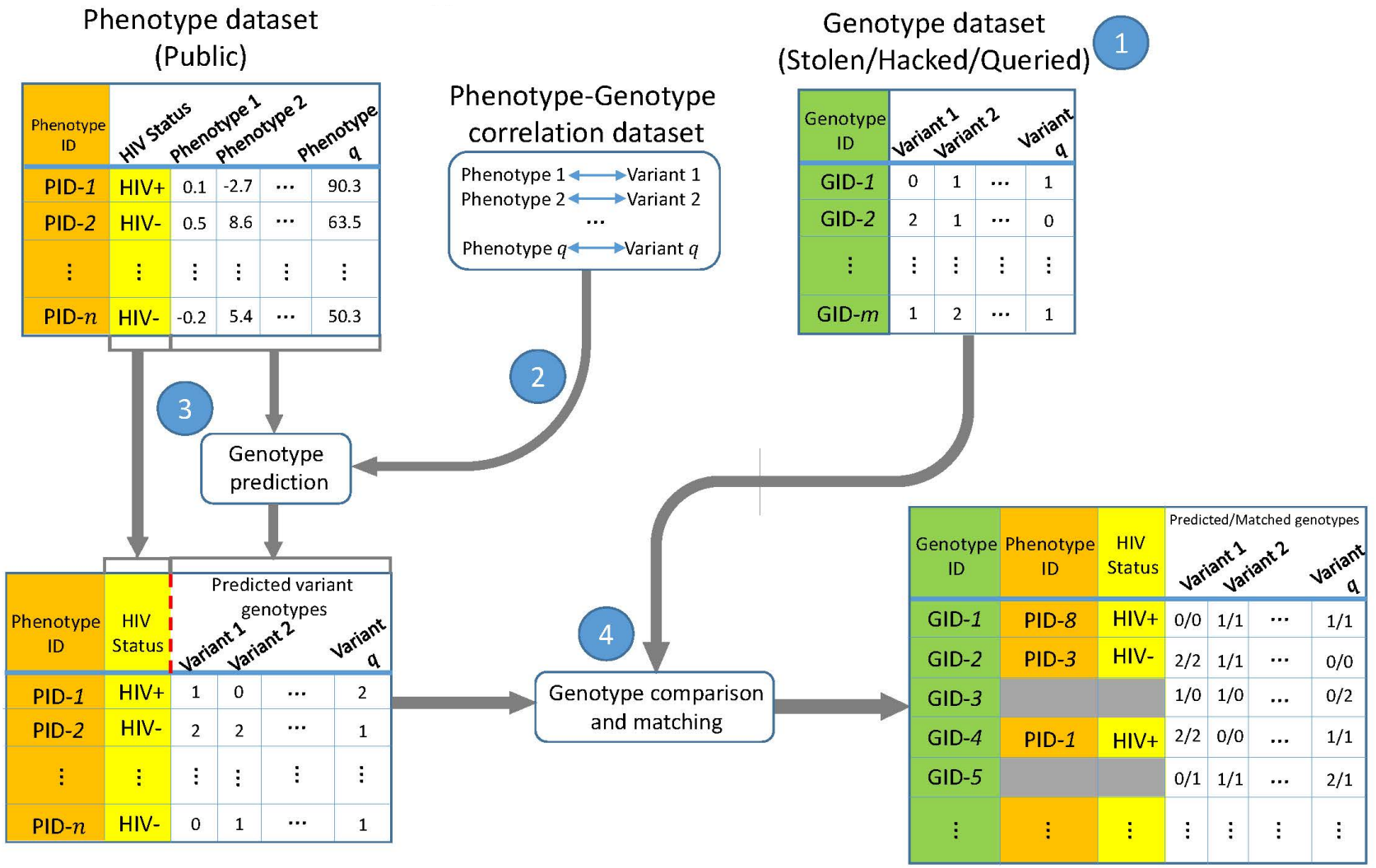
[Harmanciet al. Nat. Meth. (in revision)]

Cumulative Leakage versus Joint Predictability



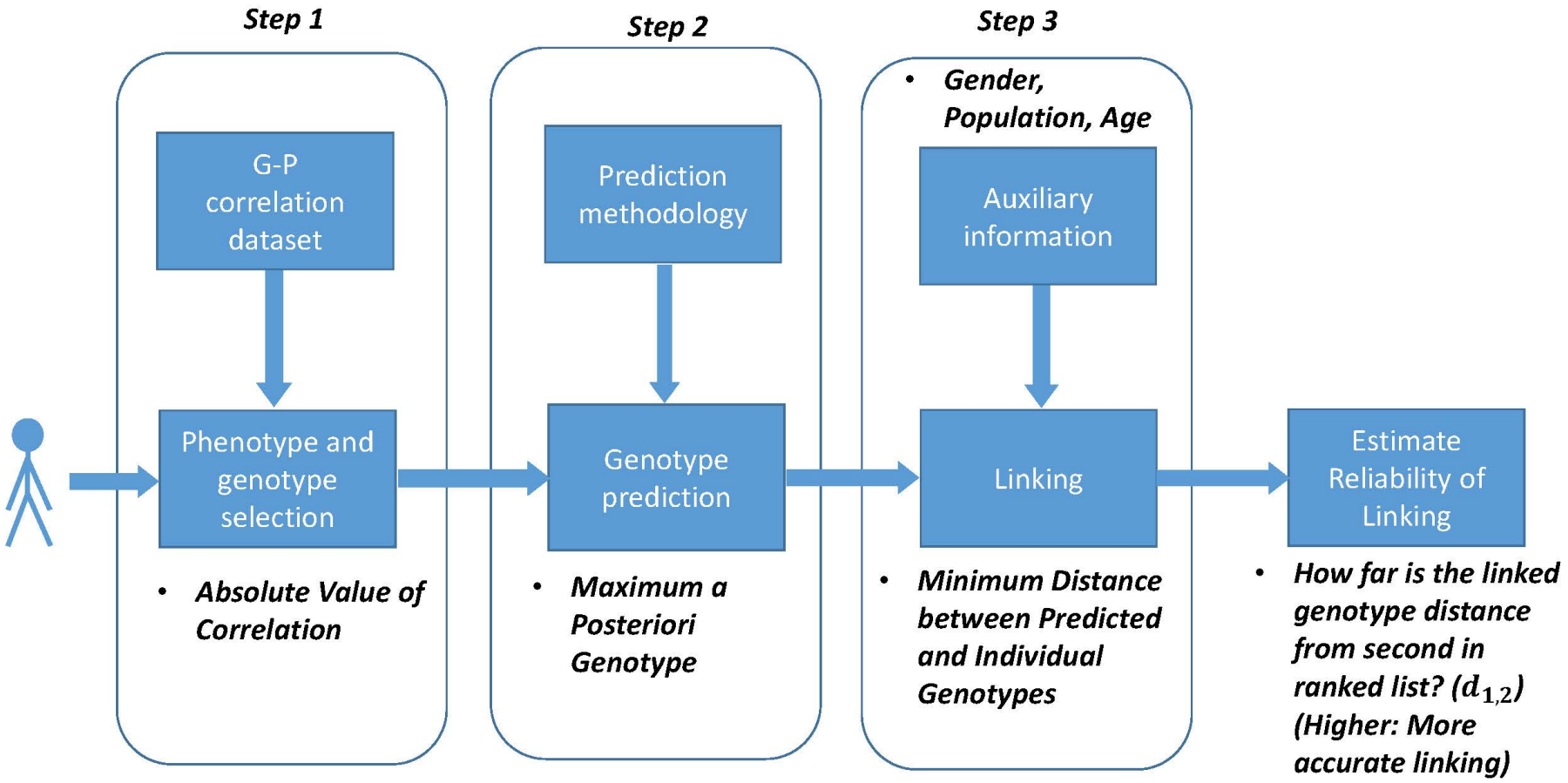
[Harmanciet al. Nat. Meth. (in revision)]

Linking Attack Scenario



[Harmanciet al. Nat. Meth. (in revision)]

Steps in Instantiation of a (Mock) Linking Attack



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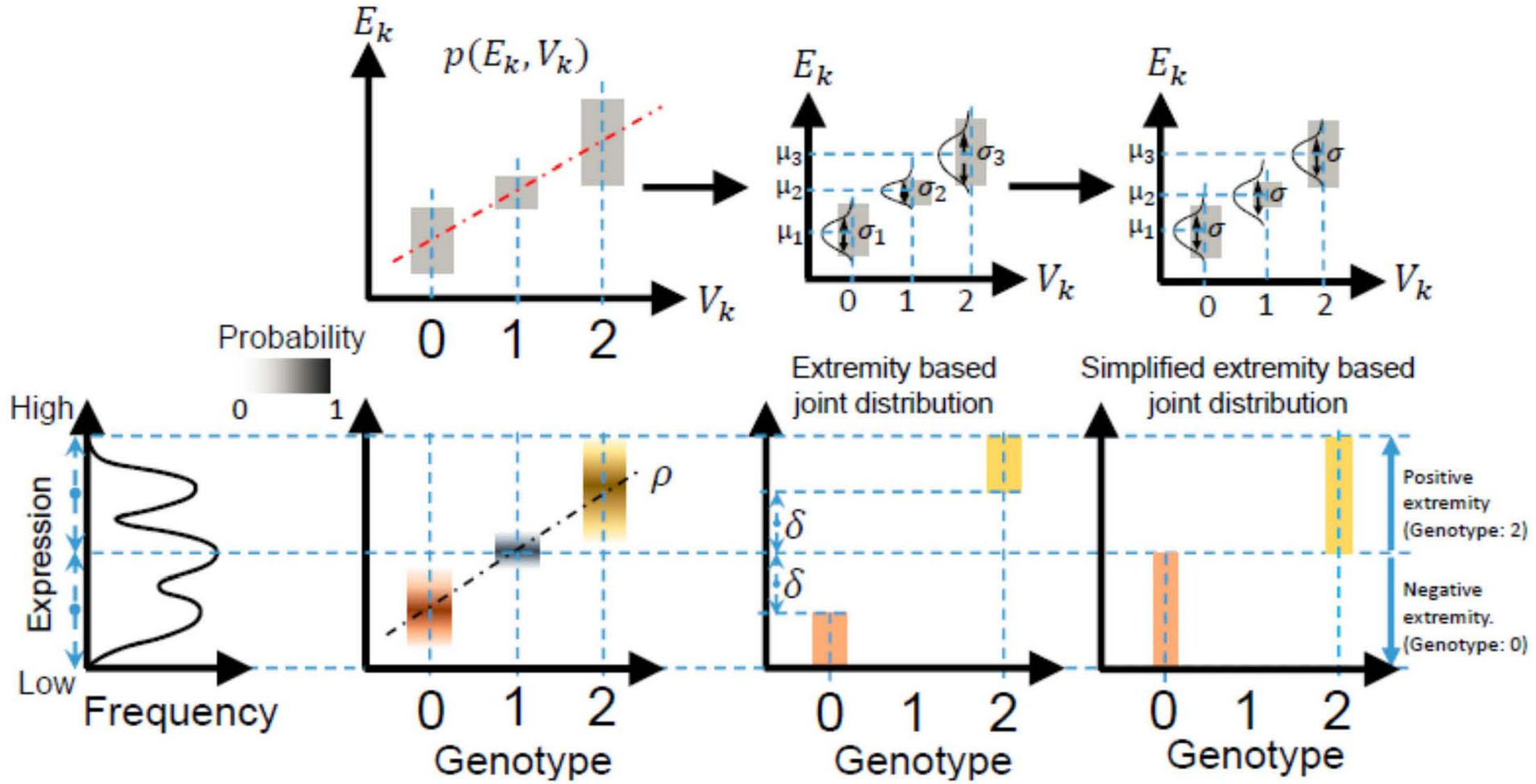
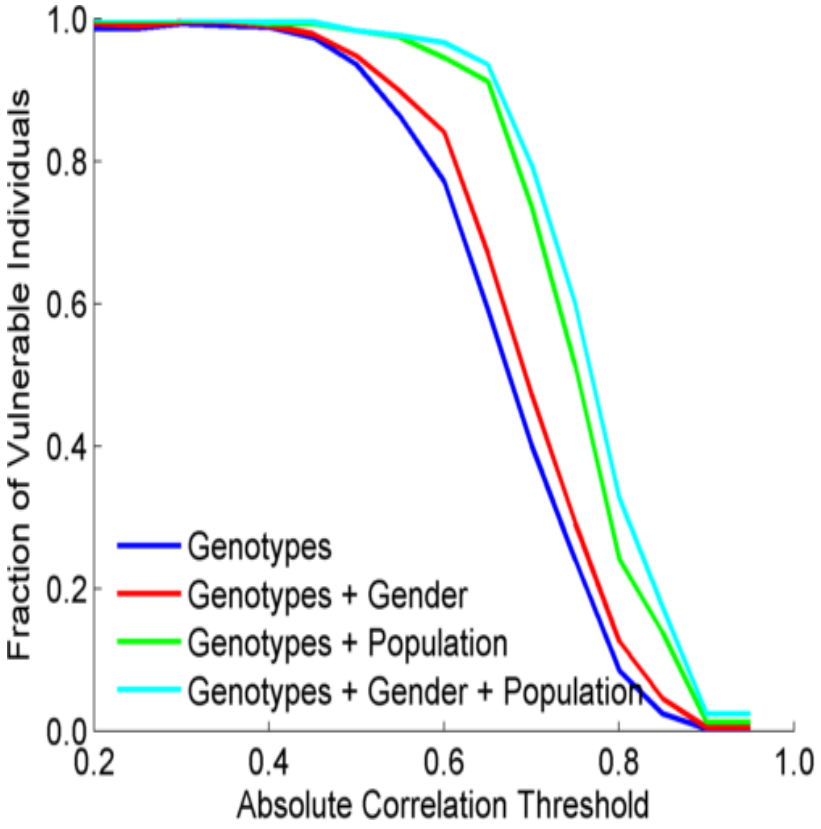
Levels of Expression-Genotype Model Simplifications

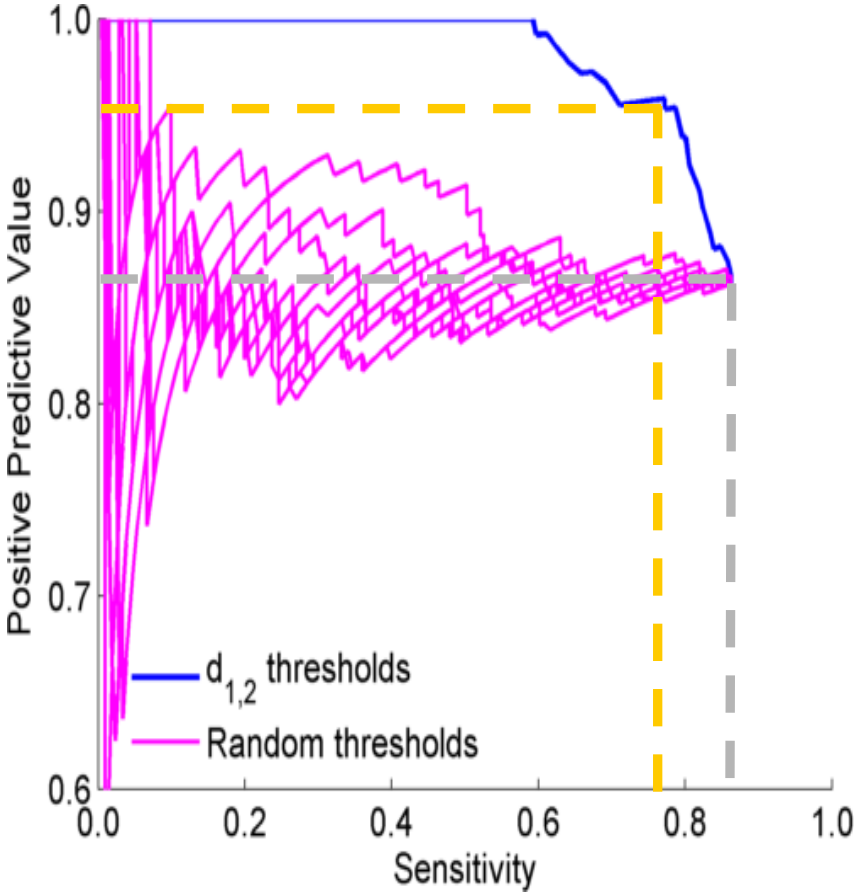


[Harmanciet al. Nat. Meth. (in revision)]

Extremity based linking with homozygous genotypes



Attacker can estimate the reliability of linkings



Sensitivity: Fraction of correctly linked Individuals among all individuals

PPV: Fraction of correctly linked individuals among selected individuals

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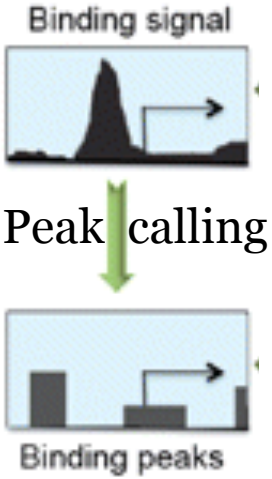
A gene can be regulated by multiple gene regulatory factors

Next generation sequencing techniques (e.g., ChIP-seq, CLIP-seq) predict **gene regulatory factors (RFs)** and their target genes

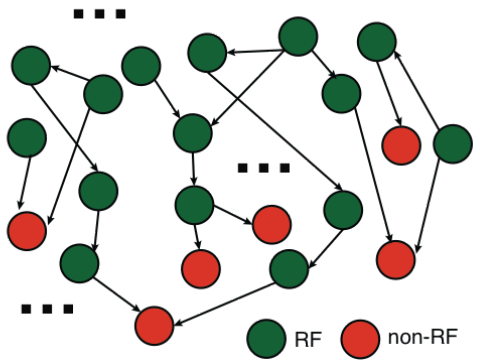
- transcription factors (TFs)
- micro-RNAs

…



Gene regulatory network

Regulatory Factor (RF)	Target (T)
TF 1	Gene 1
TF 2	Gene 1
TF 3	Gene 2
miRNA 1	Gene 1
miRNA 2	Gene 3
miRNA 3	Gene 2
…	…



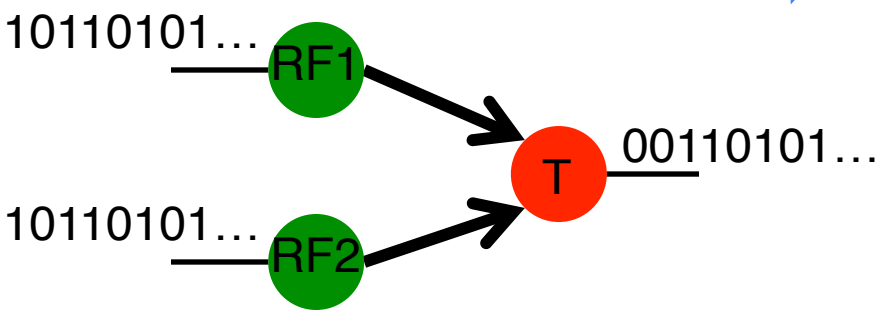
Many genes are regulated by multiple RFs.
How RFs coordinate to regulate target gene expression?

- cooperative?
- competitive?
- independent?

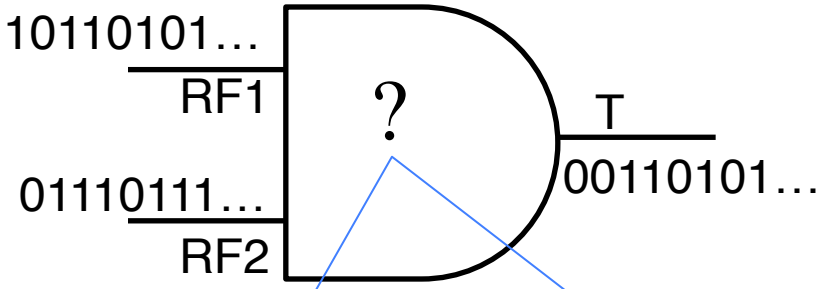
…

Modeling cooperativity between RFs to target gene using logic gates

A regulatory triplet



2-input-1-output logic gate

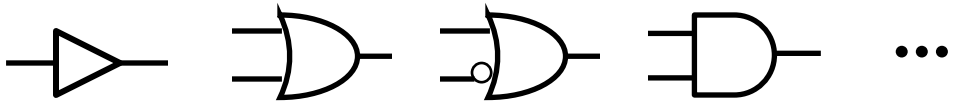


0 – gene off
1 – gene on
after binarizing gene expression data*

Input type (RF1, RF2)	RF1	0	0	1	1
	RF2	0	1	0	1
Output	T	*X*	*X*	*X*	*X*

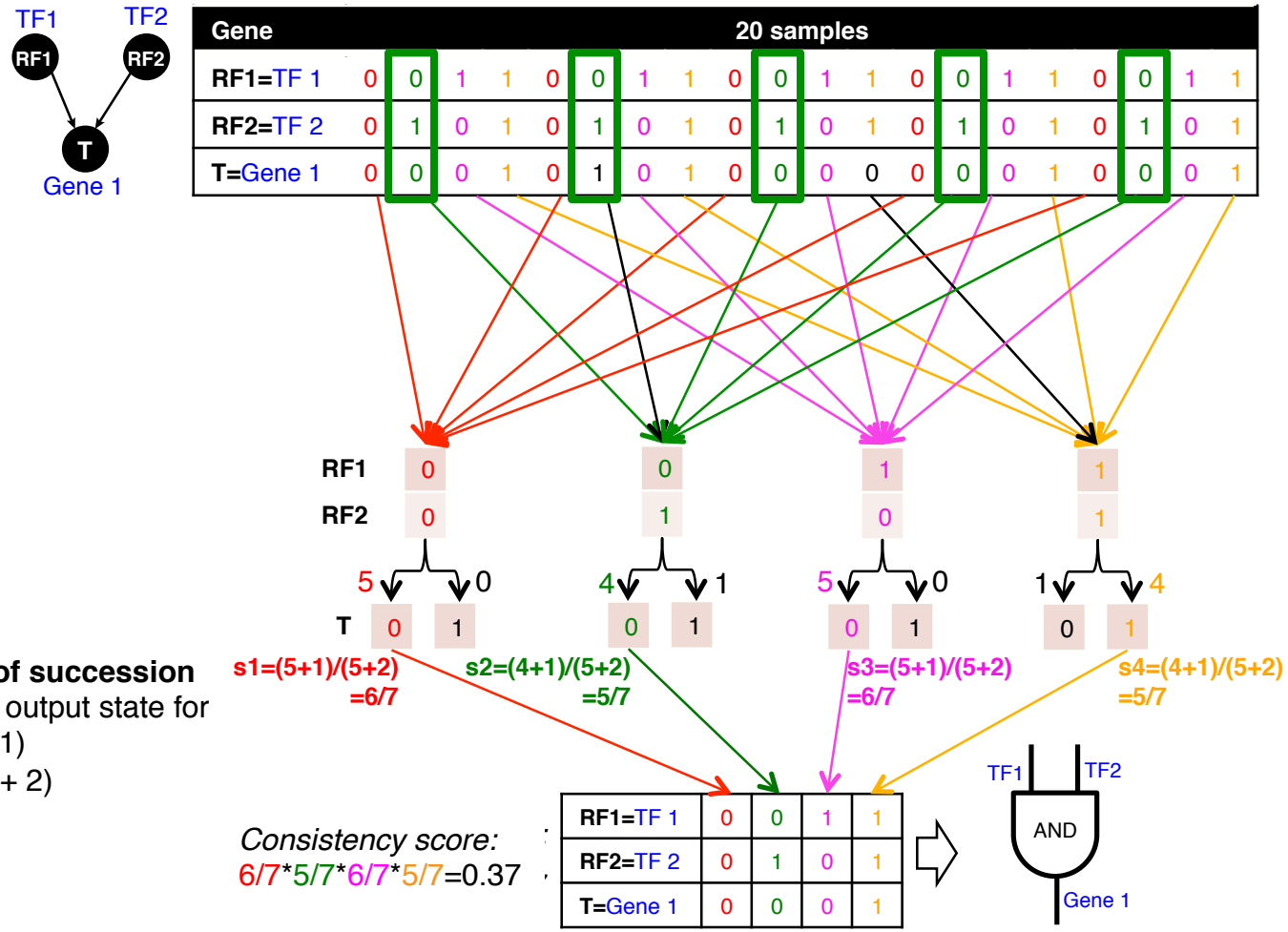
Binarized expression

X can be 0 or 1, so there are 2^4=16 possible output combinations, each of which corresponds to a unique 2-input-1-output logic gate



*BoolNet, R package

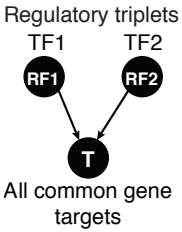
An example: selection of the best-matched logic gate



Laplace's rule of succession
s=(# of selected output state for the input type + 1)
/(# of input type + 2)

Wang, et al., *PLoS Computational Biology*, 2015

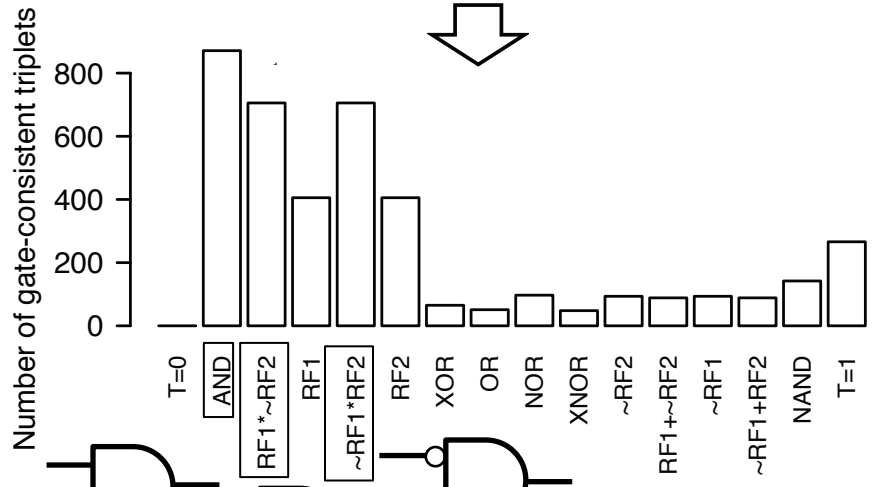
Application 1 – transcription factor cooperativity in Yeast cell cycle



Target gene	2464
TF	176
Triplet	39,011
Time point	59

Yeast Cell Cycle

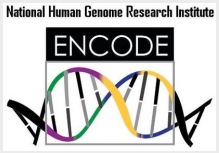
Triplet ID	RF1	RF2	Common Target Gene (T)	Matched logic gate
1	YHR084W	YBR083W	YBR082C	AND
2	YKL112W	YIL131C	YMR198W	OR
…	…	…	…	…
39011	YOR113W	YBL103C	YDR042C	XOR



AND-like gates

Wang, et al., *PLoS Computational Biology*, 2015

Application 2 – transcription factor cooperativity in Acute Myeloid Leukemia (AML)

Target gene	1824	ENCODE Data (K562, ChIP-seq) http://encodenets.gersteinlab.org/
TF	70	
Regulatory triplet	50,865	TCGA Data (AML, level 3, RNA-seq) https://tcga-data.nci.nih.gov/tcga/tcgaDownload.jsp
Patient sample	197	

Wang, et al., *PLoS Computational Biology*, 2015

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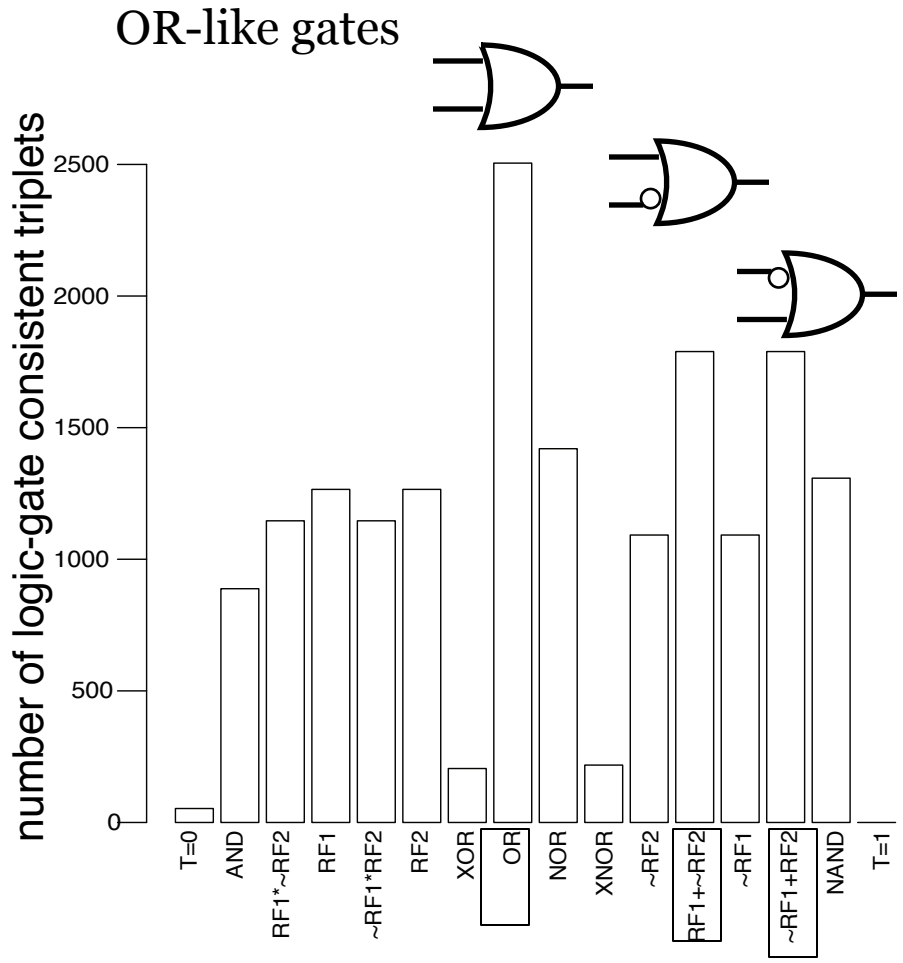
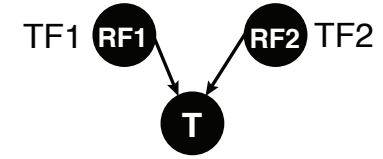


Human TF-TF-target

RF1	RF2	Common Target Gene (T)	Matched logic gate
ATF3	BDP1	YPEL1	AND
MYC	BCL3	BCR	T=RF1
ATF3	BRF2	AIF1L	AND
…	…	…	…

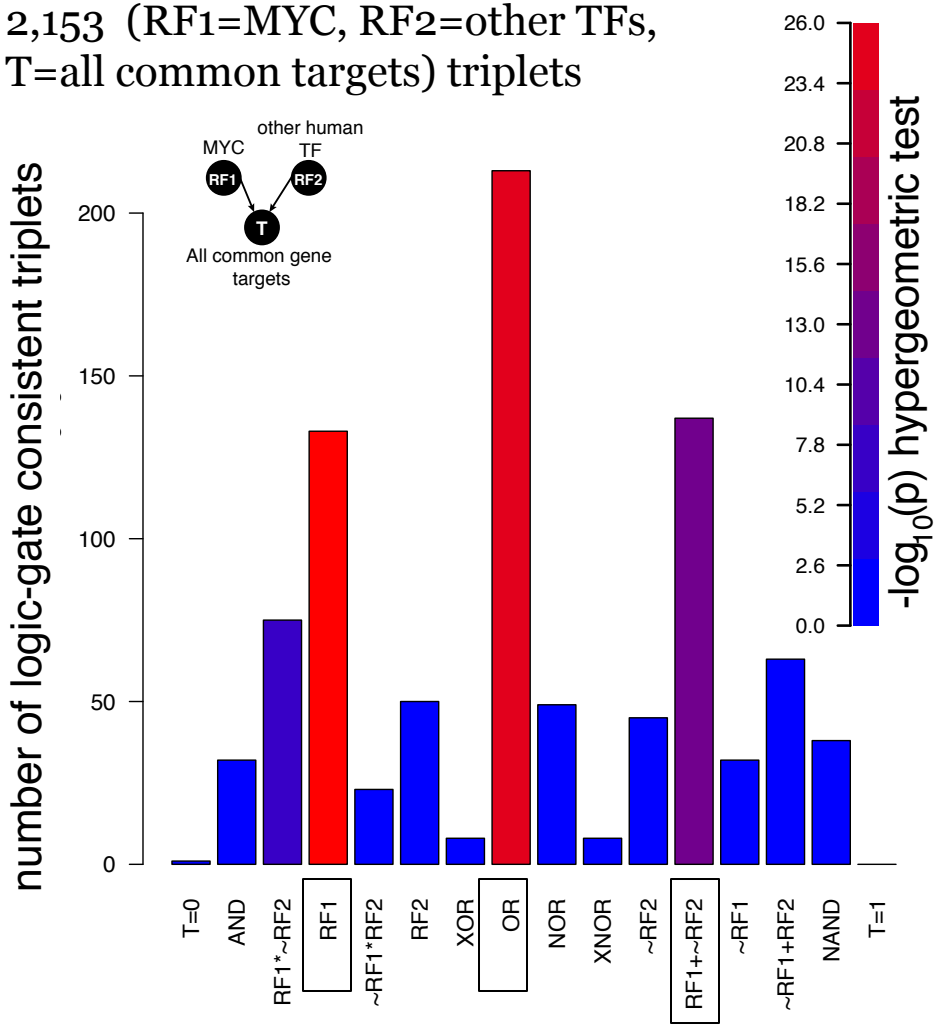


All common gene targets

Wang, et al., *PLoS Computational Biology*, 2015

Cancer-related TF, MYC universally amplifies target expression

2,153 (RF1=MYC, RF2=other TFs, T=all common targets) triplets



- RF1
- **OR**(RF1, RF2)
- **OR**(RF1, **NOT** RF2)

High expression of MYC is sufficient for high target gene expression

c-Myc Is a Universal Amplifier of Expressed Genes in Lymphocytes and Embryonic Stem Cells

Cell

Zuqin Nie,[1,6] Gangqing Hu,[2,6] Gang Wei,[2] Kairong Cui,[2] Arito Yamane,[3] Wolfgang Resch,[3] Ruoning Wang,[4] Douglas R. Green,[4] Lino Tessarollo,[5] Rafael Casellas,[3] Keji Zhao,[2,*] and David Levens[1,*]

Wang, et al., *PLoS Computational Biology*, 2015

Large-scale Transcriptome Mining: Building Interpretative, Regulatory Models, while Protecting Individual Privacy

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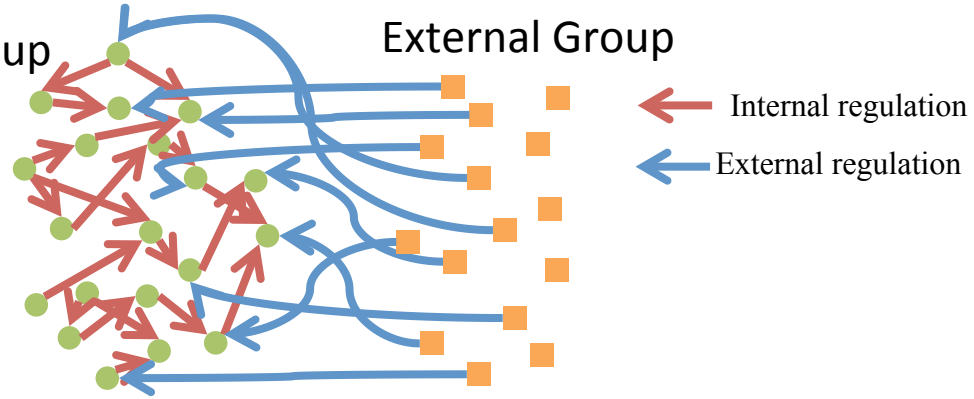
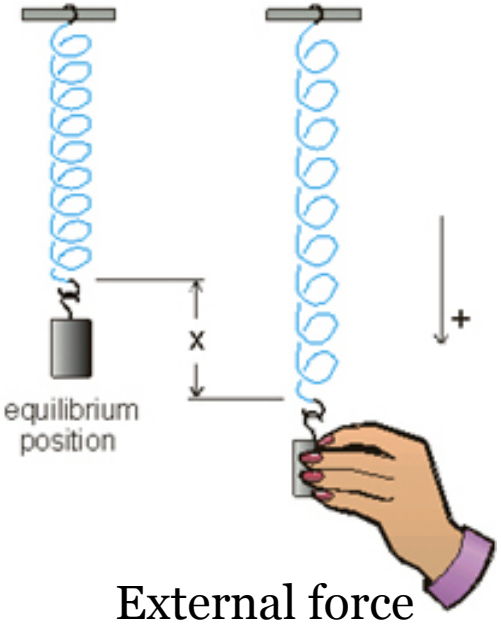
Internal and external gene regulatory networks

How to identify gene expression dynamics driven by internal/ external regulation?



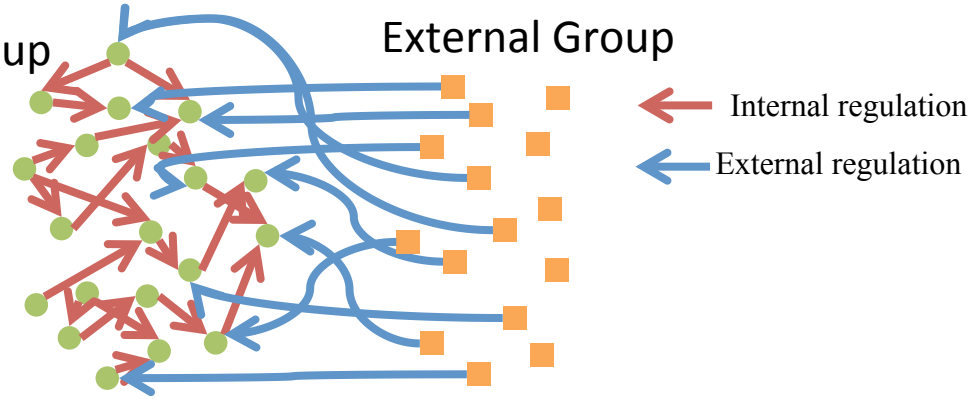


Interested system	Internal regulatory network	External regulatory network
Cross-species conserved genes	Conserved transcriptional factors (TFs)	Non-conserved TFs
Protein-coding genes	TFs	micro-RNAs
Individual's protein coding genes	Wild-type TFs	Somatic mutated TFs
Protein-coding genes in brain	Commonly expressed TFs	Brain-specific expressed TFs
Protein-coding genes in development	House-keeping TFs	Developmental TFs

[Wang et al. *PLOS CB* (in revision, '15)]

State-space model for internal and external gene regulatory networks

How to identify gene expression dynamics driven by internal/ external regulation?



State space model

$$X_{t+1} = A X_t + B U_t$$

State: Gene expression vector of Group X at time t+1

A_{ij} captures temporal casual influence from Gene i to Gene j in internal group

State: Gene expression vector of internal group at time t

Control: Gene expression vector of external factors at time t

B_{kl} captures temporal casual influence from external factor k to Gene l in internal group

[Wang et al. *PLOS CB* (in revision, '15)]

Effective state space model for meta-genes

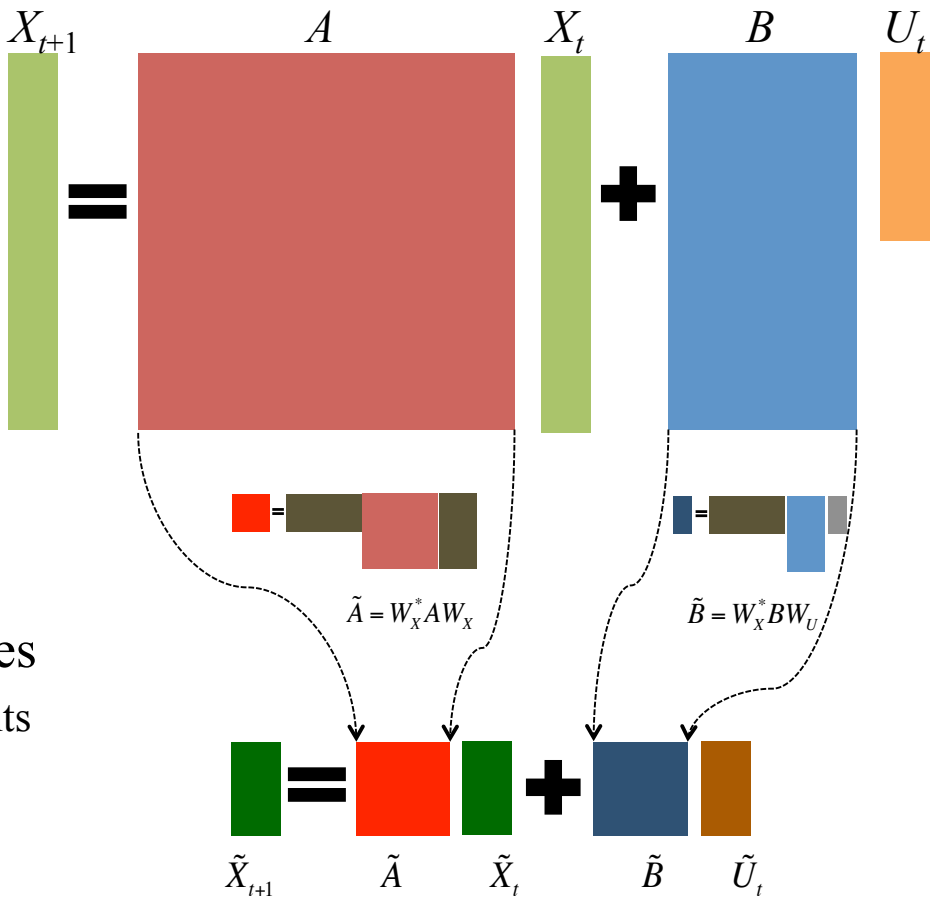
Not enough data to estimate state space model for genes
(e.g., 25 time points per gene to estimate 4 million elements of A or B for 2000 genes)

$$X_{t+1} = AX_t + BU_t$$

Dimensionality reduction from genes to meta-genes (e.g., SVD)

Effective state space model for meta-genes
(e.g., 250 time points to estimate 50 matrix elements if 5 meta-genes)

$$\tilde{X}_{t+1} = \tilde{A}\tilde{X}_t + \tilde{B}\tilde{U}_t$$



[Wang et al. *PLOS CB* (in revision, '15)]

Canonical temporal expression trajectories from effective state space model

$$\tilde{X}_{t+1} = \tilde{A}\,\tilde{X}_t + \tilde{B}\,\tilde{U}_t$$

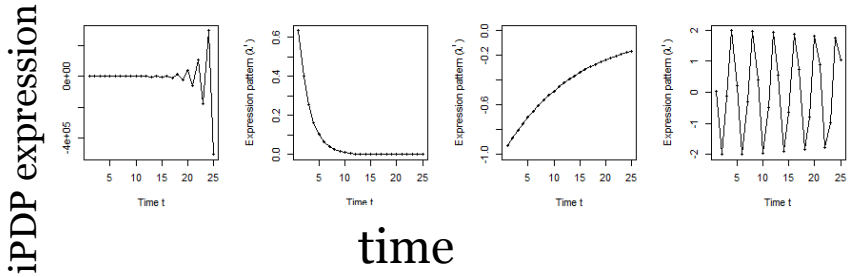
Internal driven dynamics

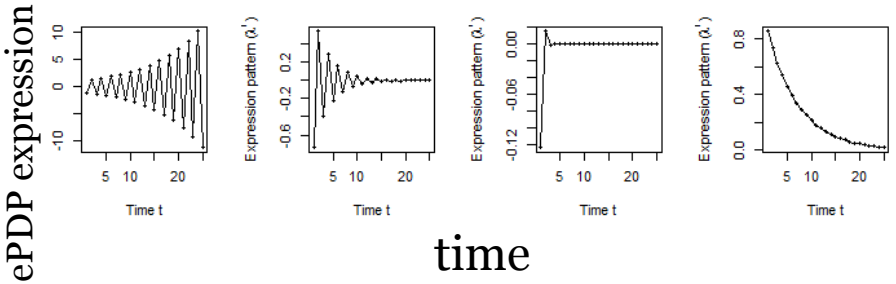
p^{th} internal principal dynamic pattern (iPDP): $[\lambda_p{}^1, \lambda_p{}^2, \ldots, \lambda_p{}^T]$, where λ_p is p^{th} eigenvalue of $\tilde{A}$.

Externally driven dynamics

q^{th} external principal dynamic pattern (ePDP): $[\sigma_q{}^1, \sigma_q{}^2, \ldots, \sigma_q{}^T]$, where σ_q is q^{th} eigenvalue of $\tilde{B}$.

Canonical temporal expression trajectories
(e.g., degradation, growth, damped oscillation, etc.)

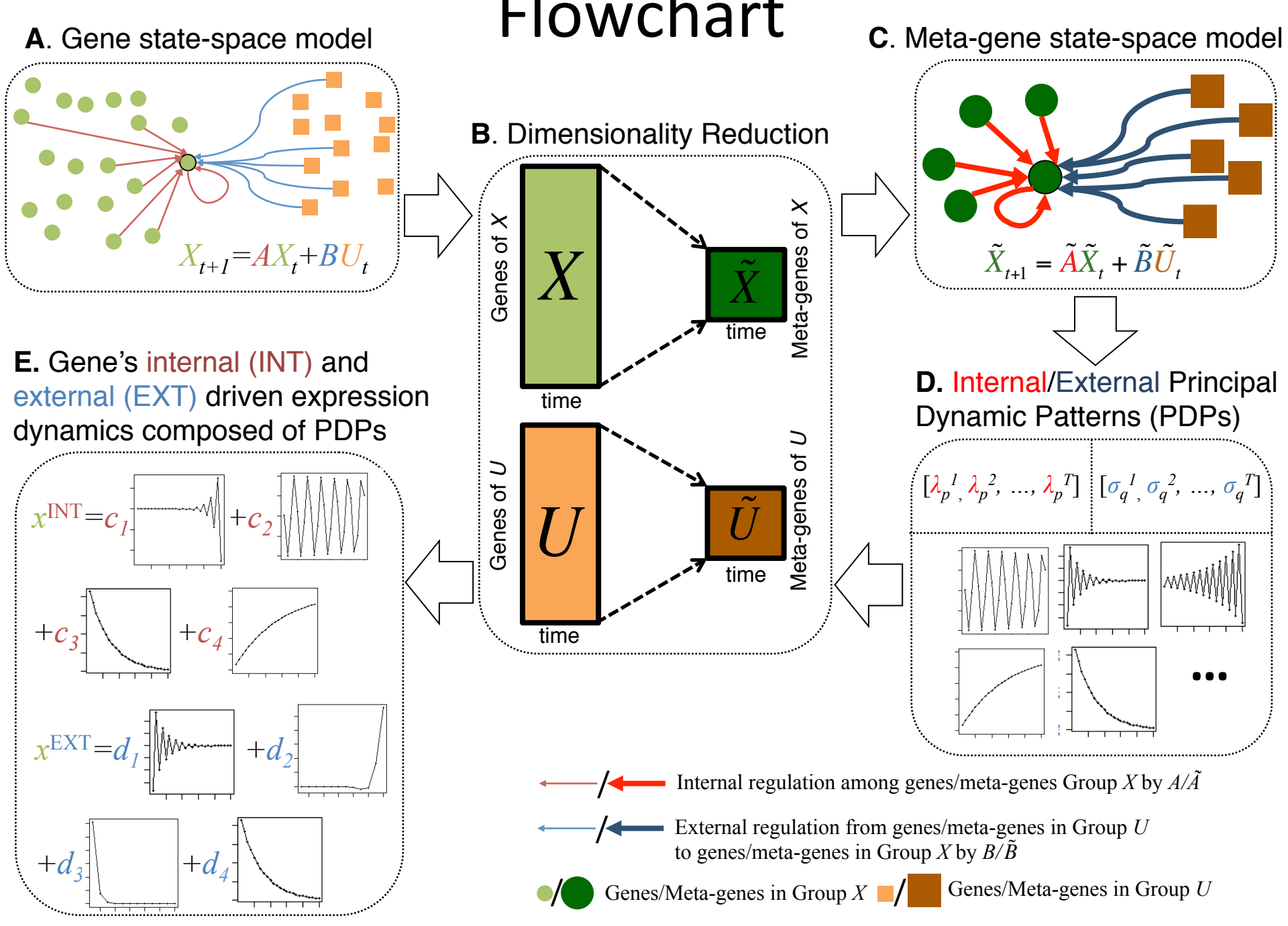




[Wang et al. *PLOS CB* (in revision, '15)]

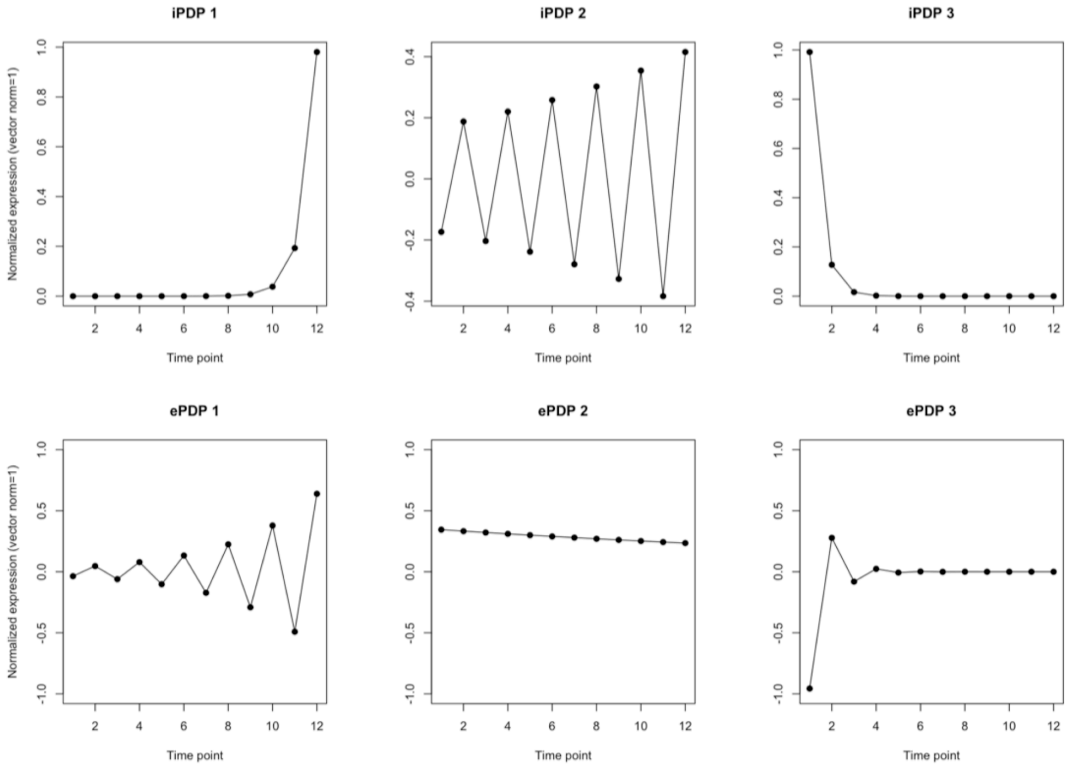
[Wang et al. *PLOS CB* (in revision, '15)]

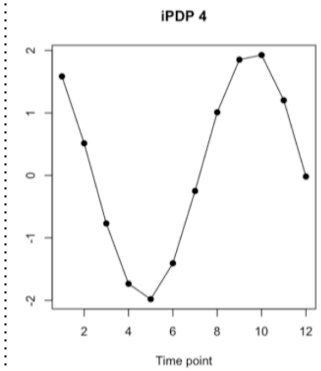
Flowchart



Breast cancer cell cycle (under hormonal stimulation):
Conserved genes & TFs have dynamic pattern matching cell-cycle period; Non-conserved ones, do not

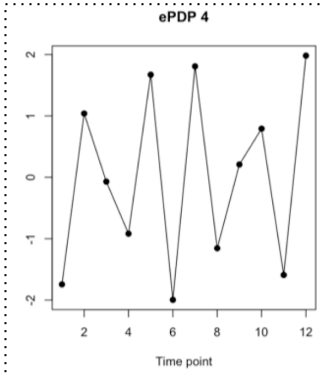
Dataset	Group *X* (internal)	Group *U* (external)	Time samples of a full cell cycle
Human breast cancer cell cycle under hormonal stimulation	1132 metazoan conserved genes incl. 150 orthologous TFs	1870 non-conserved metazoan transcription factors	T=12 time points: 0, 4, 6, 8, 12, …, 28, 32 hours





Oscillated iPDP by conserved TFs

a full cell cycle

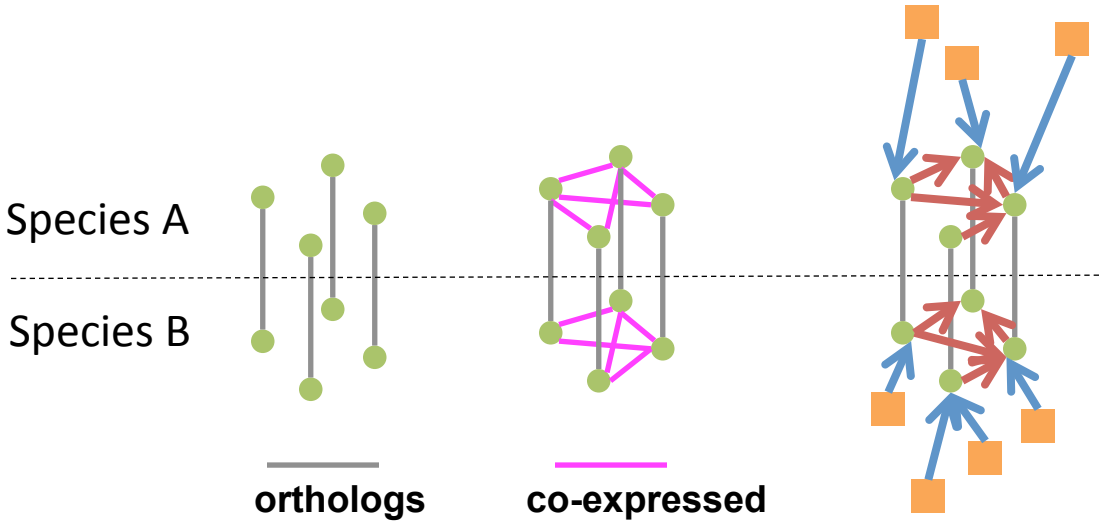


Oscillated ePDP by non-conserved TFs

faster cycle due to hormone

[Wang et al. *PLOS CB* (in revision, '15)]

Are gene regulations among orthologs conserved across species?



Are gene regulatory networks among orthologs conserved across species?

Regulation among orthologs (**internal**)

Regulation from species-specific factors (**external**)

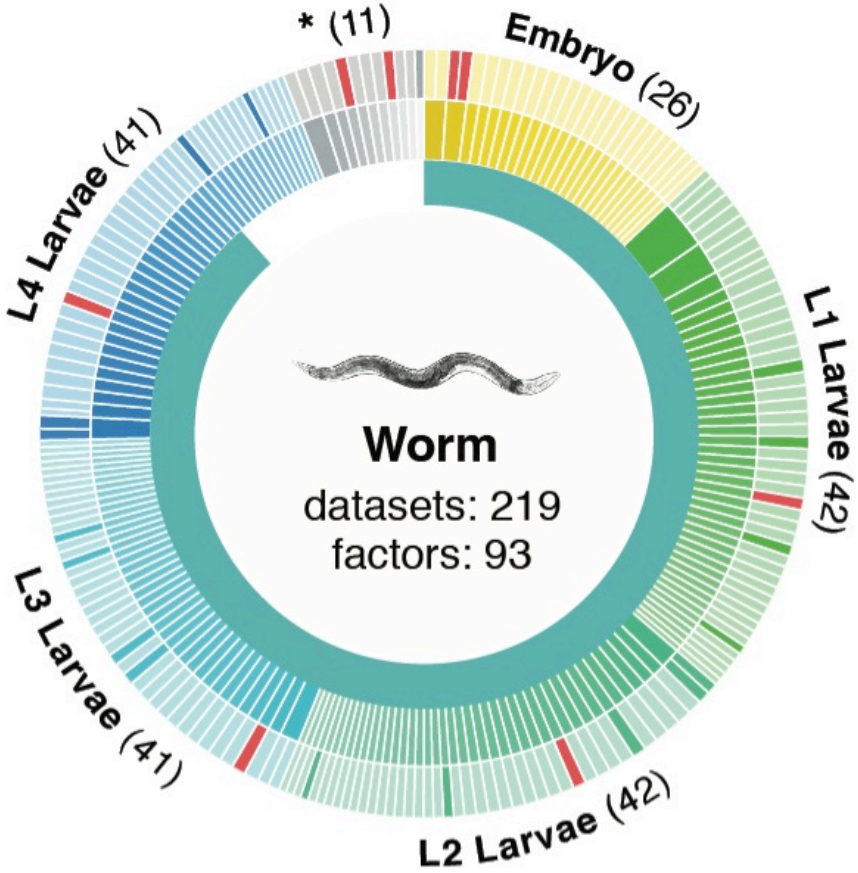
Orthologous genes (orthologs)

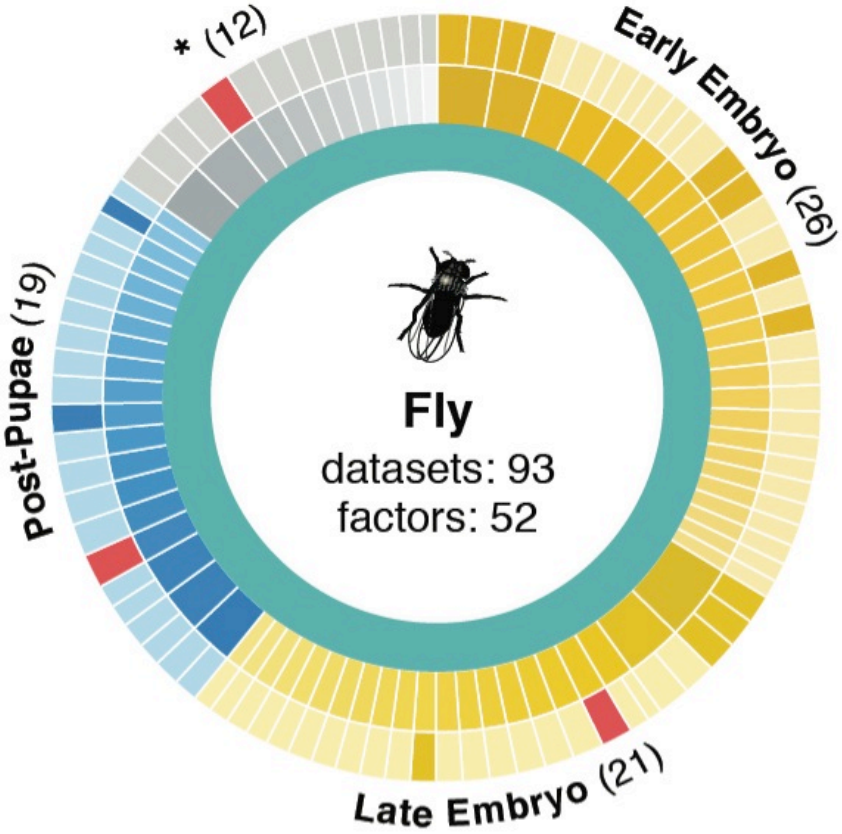
Species-specific transcription factors

To what degree can't ortholog expression levels be predicted due to species-specific regulation

[Wang et al. *PLOS CB* (in revision, '15)]

Time-course gene expression data of worm & fly development, from modENCODE





Organism	Major developmental stages
worm (*C. elegans*)	33 stages: 0, 0.5, 1, …, 12 hours, L1, L2, L3, L4, …, Young Adults, Adults
fly (*D. mel.*)	30 stages: 0, 2, 4, 6, 8,…, 20, 22 hours, L1-L4, Pupaes, Adults

[*Nature* 512:445 ('14); doi: 10.1038/nature13424]

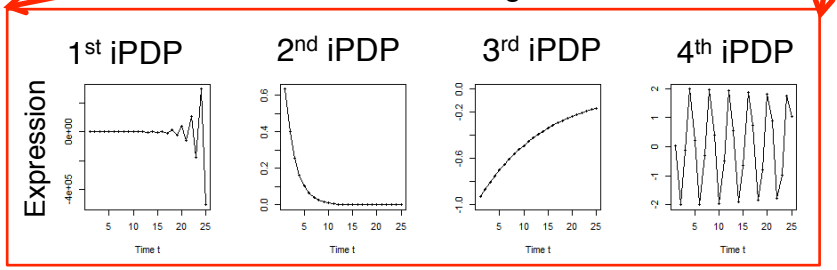
Orthologs have similar internal but different external dynamic patterns during embryonic development

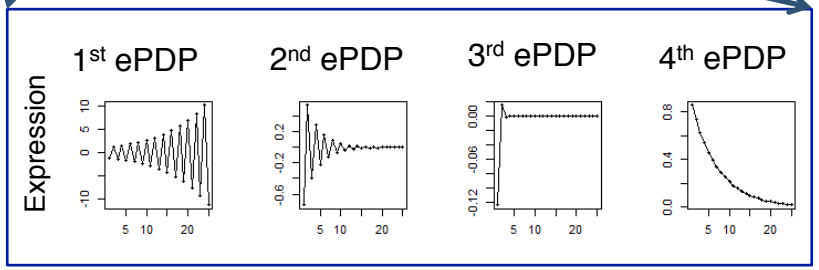
Worm's effective state space model

$$\tilde{X}_{t+1} = \tilde{A}\tilde{X}_t + \tilde{B}\tilde{U}_t$$

iPDPs: time exponentials of $\tilde{A}$ eigenvalues in worm

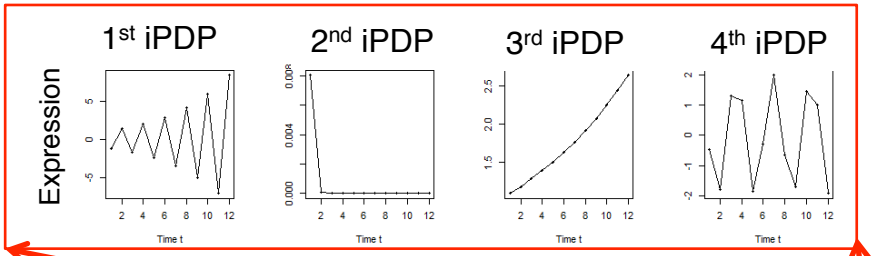
ePDPs: time exponentials of $\tilde{B}$ eigenvalues in worm

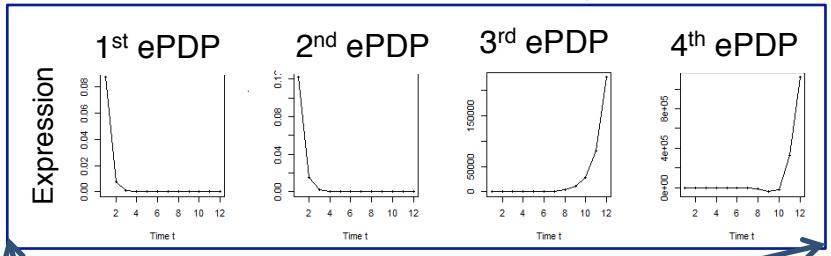




Similar iPDP canonical trajectories

Different ePDP canonical trajectories





iPDPs: time exponentials of $\tilde{A}$ eigenvalues in fly

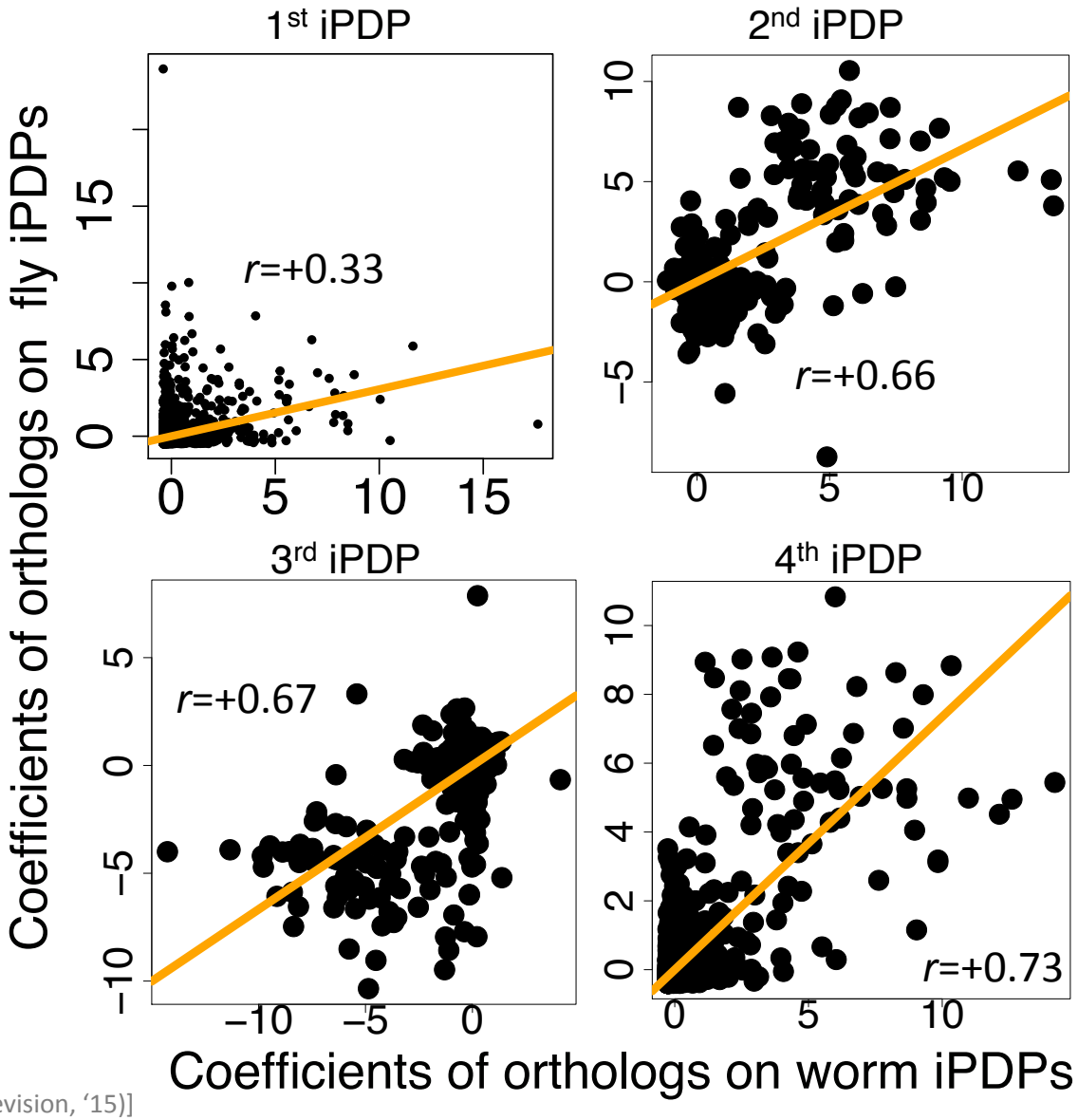
ePDPs: time exponentials of $\tilde{B}$ eigenvalues in fly

Fly's effective state space model

$$\tilde{X}_{t+1} = \tilde{A}\tilde{X}_t + \tilde{B}\tilde{U}_t$$

[Wang et al. *PLOS CB* (in revision, '15)]

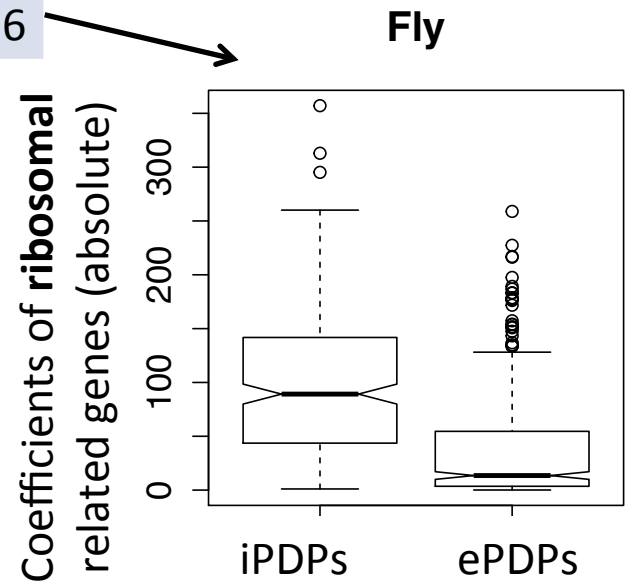
Orthologs have correlated iPDP coefficients



[Wang et al. *PLOS CB* (in revision, '15)]

Evolutionarily conserved and younger genes exhibit the opposite internal and external PDP coefficients

iPDP coeffs > ePDP coeffs	Worm	Fly
Ribosomal genes	$p<0.001$	$p<2.2e-16$



Ribosomal genes have significantly larger coefficients for the internal than external PDPs, but signaling genes exhibit the opposite trend

iPDP coeffs < ePDP coeffs	Worm	Fly
Signaling genes	$p<7e-4$	$p<6e-4$

* *p*-values from KS-test

[Wang et al. *PLOS CB* (in revision, '15)]

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Acknowledgements

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D Greenbaum

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Loregic.gersteinlab.org [github]

D Wang,

KK Yan, C Sisu, C Cheng, J Rozowsky, W Meyerson

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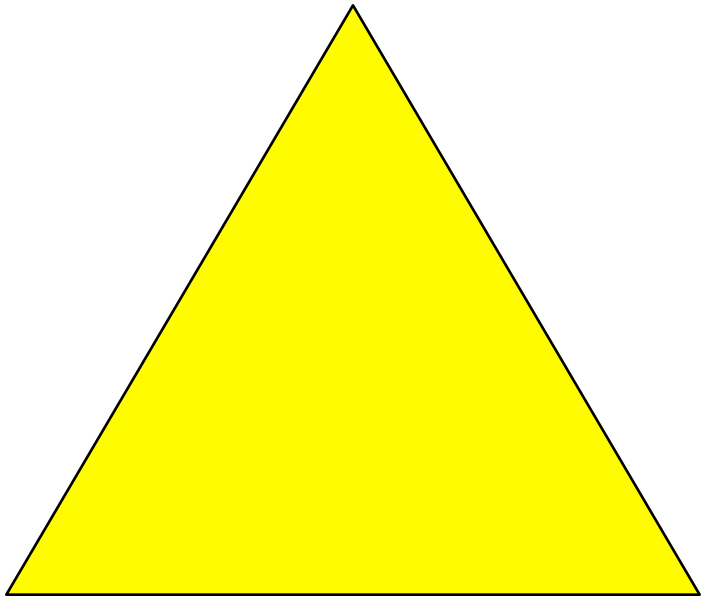
Default Theme

- Default Outline Level 1
  - Level 2



More Information on this Talk

SUBJECT: Networks

DESCRIPTION:

NOTES:
This PPT should work on mac & PC. Paper references in the talk were mostly from Papers.GersteinLab.org.

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