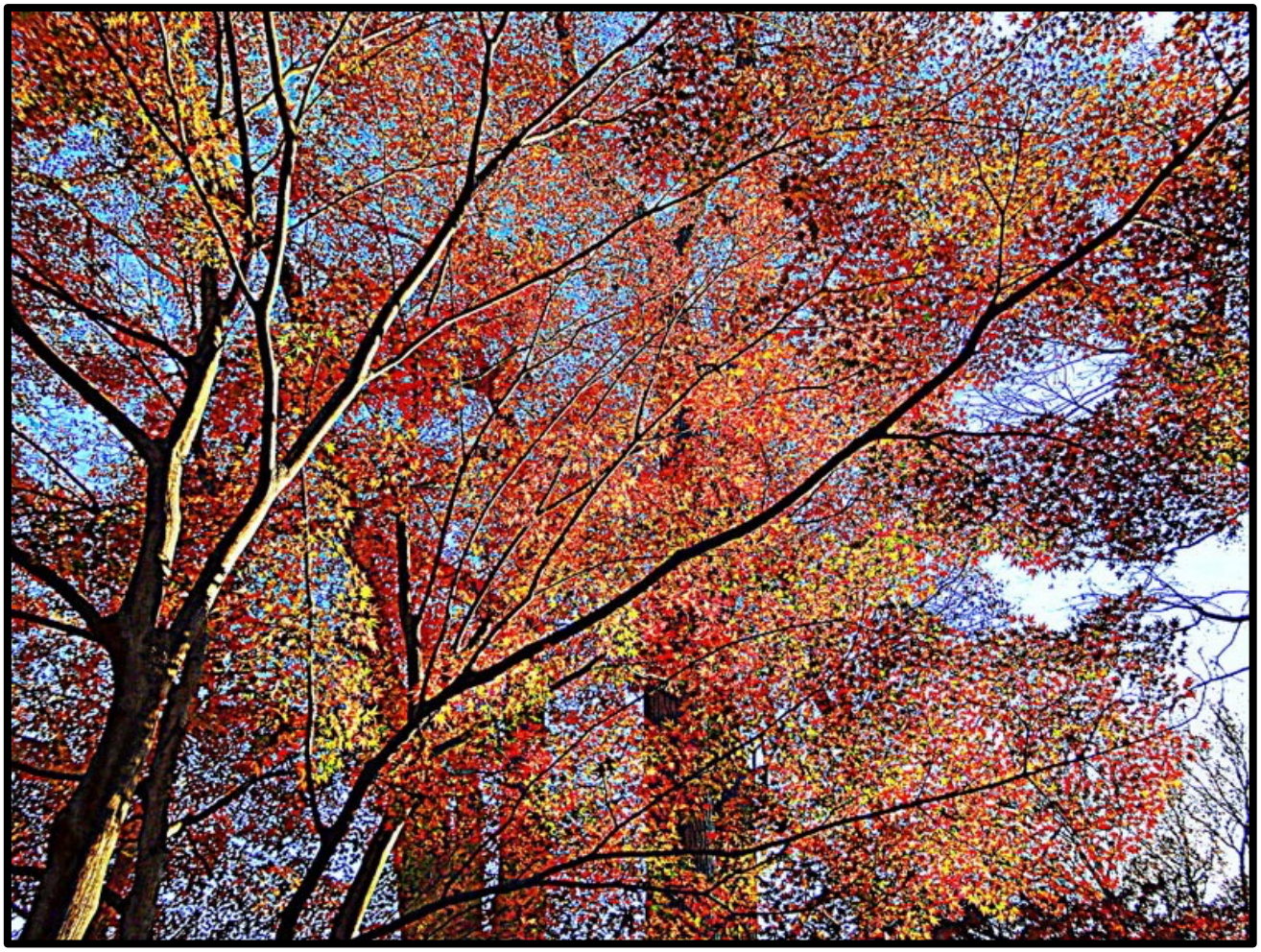
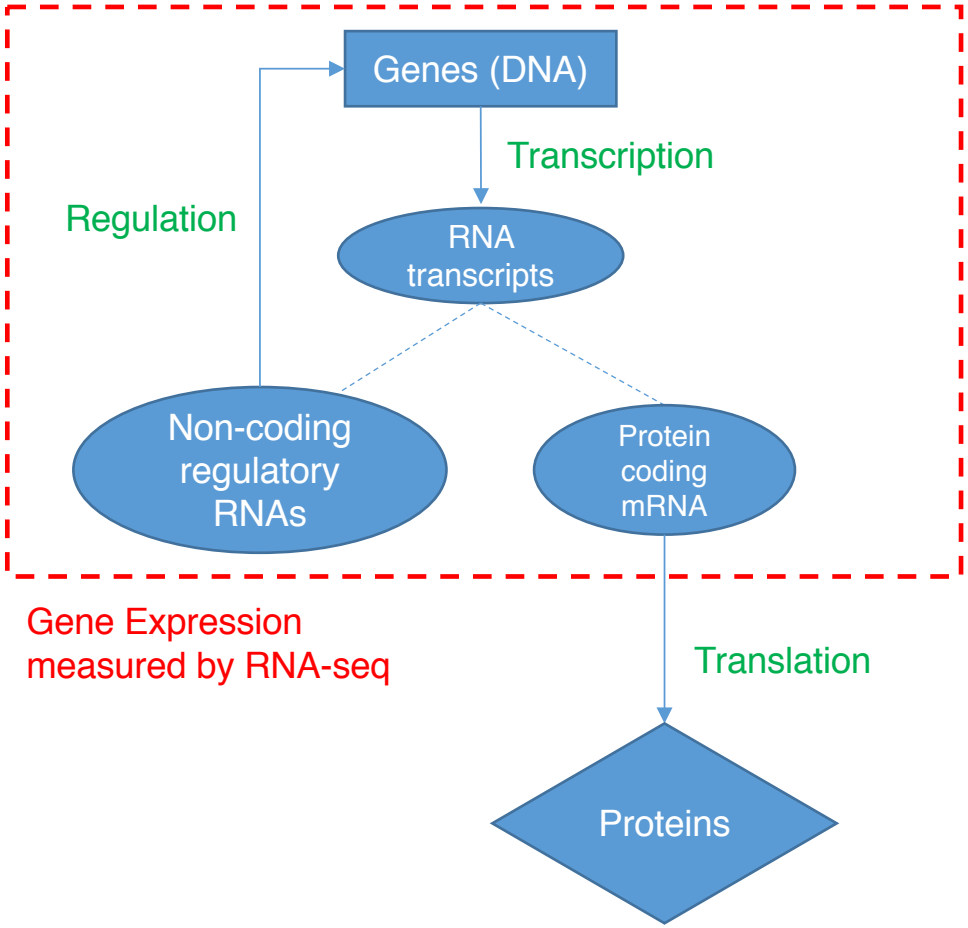
Transcriptome Mining:

Tackling core issues related to gene regulation
& also analyzing the "data exhaust" associated with this activity

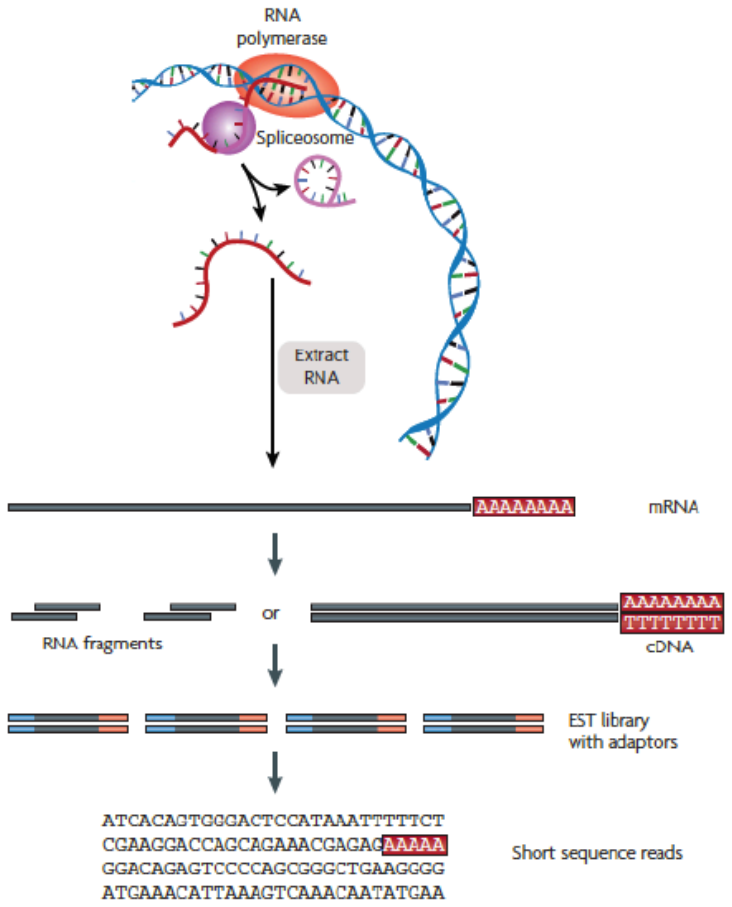


Mark Gerstein, Yale. Slides freely downloadable from **Lectures.GersteinLab.org** & “tweetable” (via **@markgerstein**). See last slide for more info.

Transcriptome = Gene Activity of All Genes in the Genome, usually quantified by RNA-seq



Gene Expression measured by RNA-seq



[*NATURE 459: 927; NAT. REV. GEN. 10: 57*]

Expression of genes is quantified by transcription:
RNA-Seq measures mRNA transcript amounts

RNA-Seq Overview

Successive steps of Data Reduction

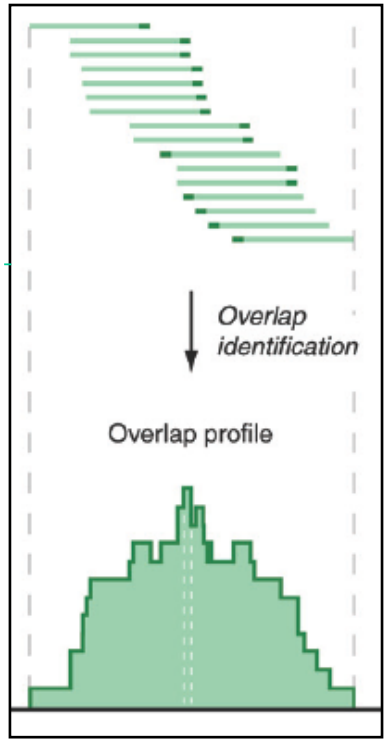
Fastq sequence files
~5-10 GB

```
ATACAAGCAAGTATAAGTTCGTATGCCGTCTT
GGAGGCTGGAGTTGGGGACGTATGCGGCATAG
TACCGATCGAGTCGACTGTAAACGTAGGCATA
ATTCTGACTGGTGTCATGCTGATGTACTTAAA
```

Index-building + Alignment to reference genome

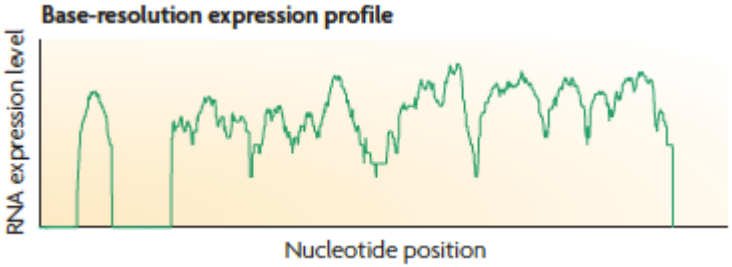
BAM files
~1-2-fold reduction

Conversion to signal track by overlapping reads



Reads => Signal

BigWig files
~25-fold reduction



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

Mapping to genes

Gene/Transcript expression matrix
~20-fold reduction

[*NAT. REV.* 10: 57; *PLOS CB* 4:e1000158; *PNAS* 4:107: 5254]

Activity Patterns

- RNA Seq. gives rise to activity patterns of genes & regions in the genome

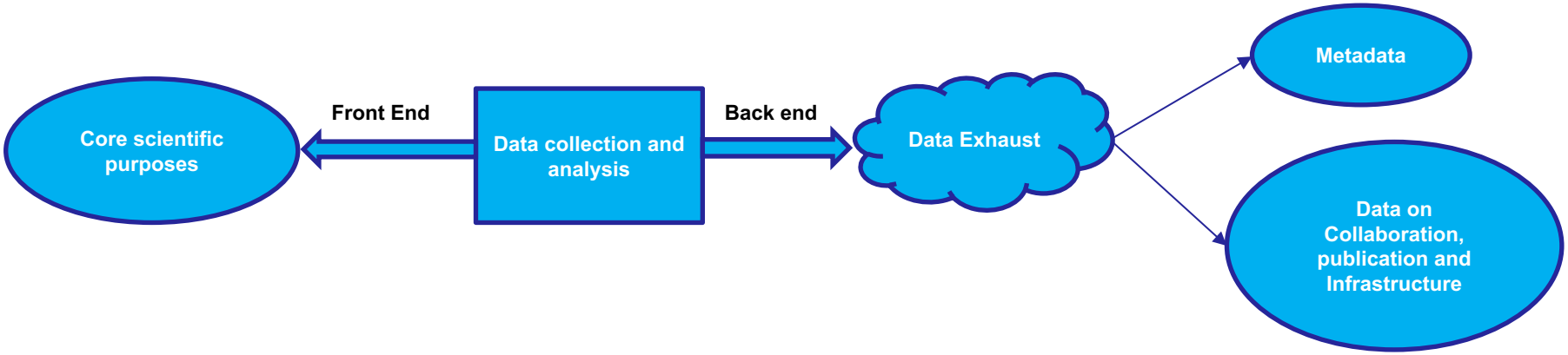
Some Core Science Qs Addressed by RNA-seq

- Gene activity as a function of:
  - **Developmental** stage: basic patterns of co-active genes across development
  - **Cell-type** & Tissue: relationship to specialized functions
  - **Evolutionary** relationships: behavior preserved across a wide range of organisms; patterns in model organisms in relation to those in humans
  - **Disease** phenotypes: disruption of patterns in disease

- Our overarching Qs:
  Are there core, ancient patterns of gene expression?
  Are they associated with development?
  Are they disrupted by disease?

Studying large-scale transcriptome data also produces

Data Exhaust



- Data Exhaust = Exploitable byproducts of big data collection and analysis
- Creative use of Data is key to Data Science !

[PHOTO: RELAXNEWS; from http://www.lapresse.ca]

Transcriptome Mining: Tackling core issues related to gene regulation & also analyzing the "data exhaust" associated with this activity

- *[Core-1]* **Expression Clustering**, Cross-species
  - Comparative ENCODE – Lots of worm-fly-human matched data & developmental timecourses
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  - Preponderance of OR gates in cancer v. cell-cycle (esp. for MYC)
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  - 2-sided nature of RNA-seq presents a particularly tricky privacy issue
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  - Instantiating a practical linking attack using extreme expression levels
- *[Exhaust-2]* **Publication Patterns** from data producing consortia
  - Co-authorship network statistics relate to publication rollouts & show gradual adoption by a diverse community
  - Key role of brokers in data dissemination

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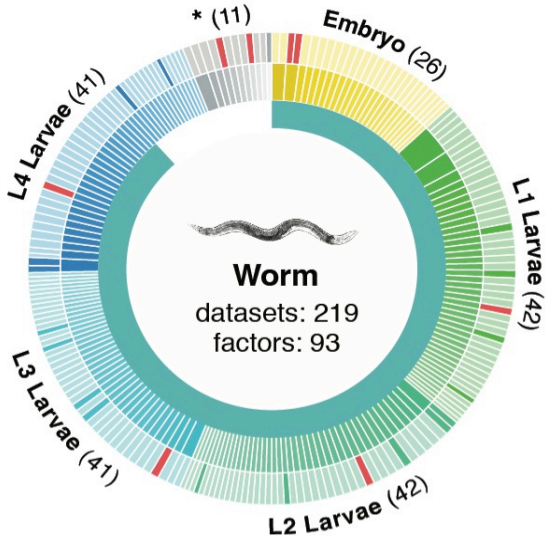
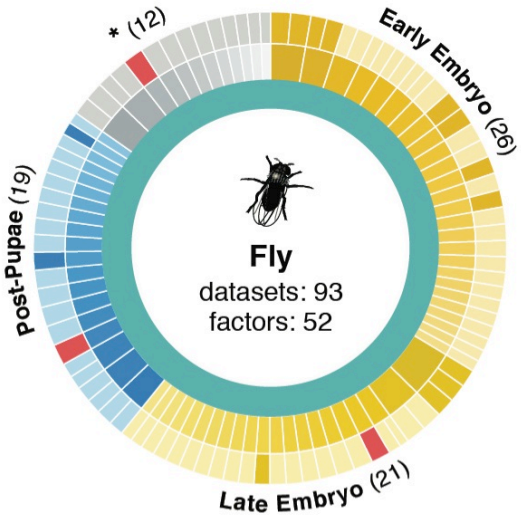
ENCODE Time-course gene expression data of worm & fly development + human conditions





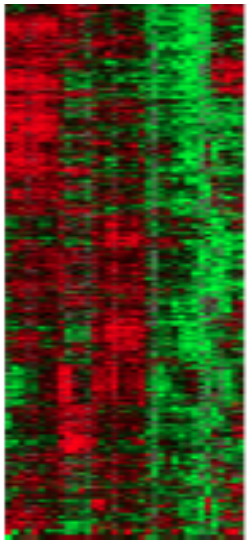
Comparative ENCODE Functional Genomics Resource (EncodeProject.org/comparative)

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

- Broad sampling of conditions across transcriptomes for human, worm & fly
  - embryo & ES cells
  - developmental time course (worm-fly)
- In total: ~3000 datasets (~130B reads)

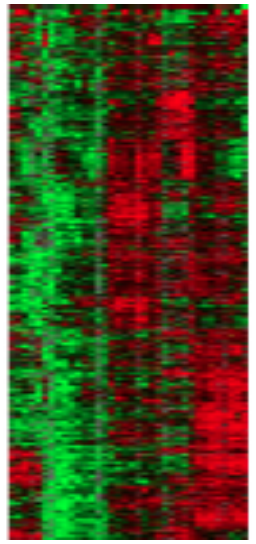
[*Nature* 512:445 ('14); doi: 10.1038/nature13424]

Expression clustering: revisiting an ancient problem



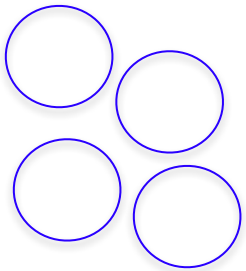
Species A

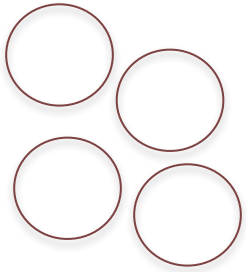
Species B



Clustering algorithm

Clustering algorithm



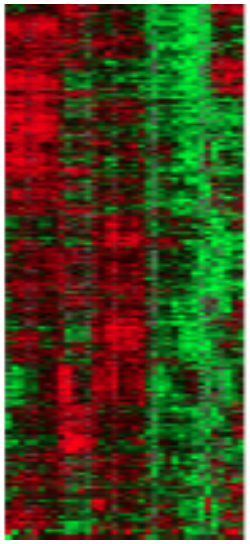


co-expressed genes responsible for the same function in a species

two independent sets of modules

Eisen MB et al. PNAS 1998
Langfelder P et al. BMC Bioinfo. 2008
Tamayo P et al. PNAS 1999
Kluger Y et al. Genome Res. 2003

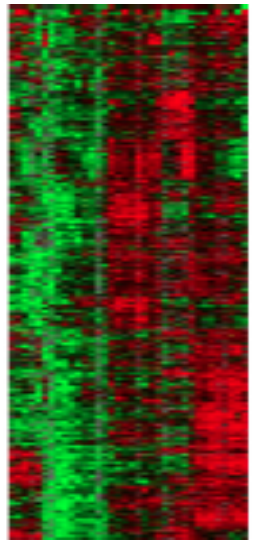
Expression clustering: revisiting an ancient problem



Species A

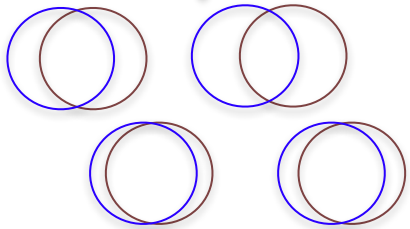
Orthologous pairs between species

Species B



A novel unified framework to integrate co-expression data across species

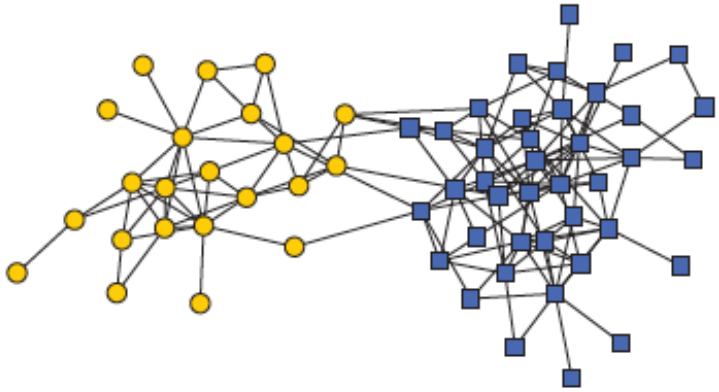
OrthoClust



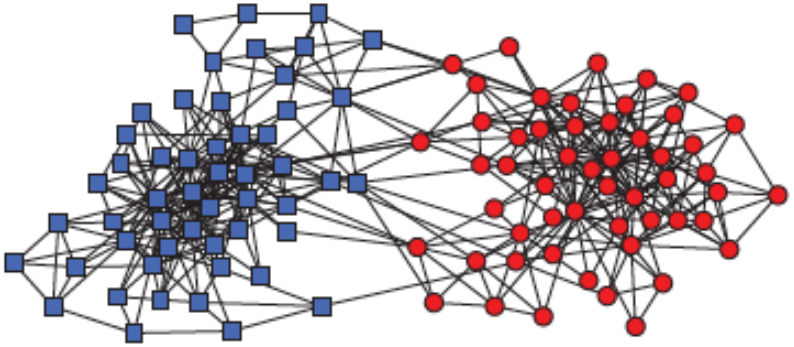
cross species modules

Yan et al. Genome Biol. 2014

Network modularity



Dolphin social network



Political books

Newman Phy. Rev. E 2013

$$Q = \frac{1}{2m} \sum_{i,j} \left(W_{ij} - \frac{k_i k_j}{2m} \right) \delta_{\sigma_i \sigma_j}$$

adjacency matrix

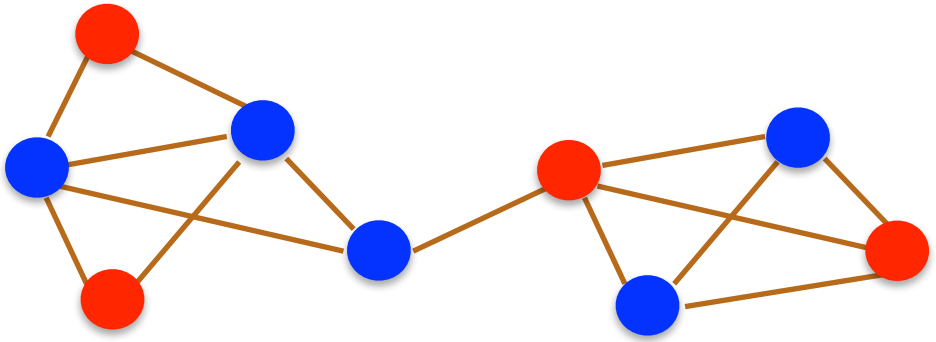
degree of node i

number of edges

expected number of edges between i and j

whether or not i, j are in the same module

Network modularity



$$Q \approx 0$$

$$Q = \frac{1}{2m} \sum_{i,j} \left(W_{ij} - \frac{k_i k_j}{2m} \right) \delta_{\sigma_i \sigma_j}$$

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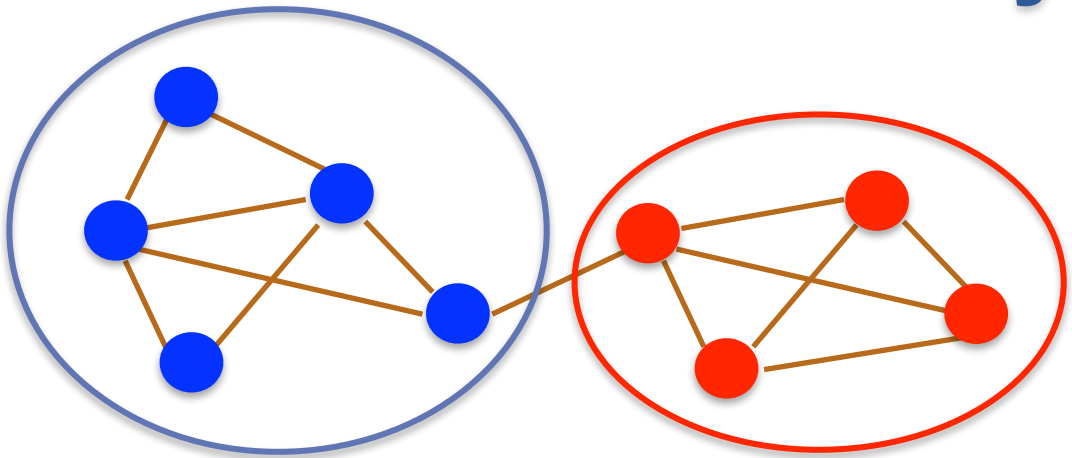

$$Q = Q_{max}$$

Optimization problem for sim. annealing

$$Q = \frac{1}{2m} \sum_{i,j} \left(W_{ij} - \frac{k_i k_j}{2m} \right) \delta_{\sigma_i \sigma_j}$$

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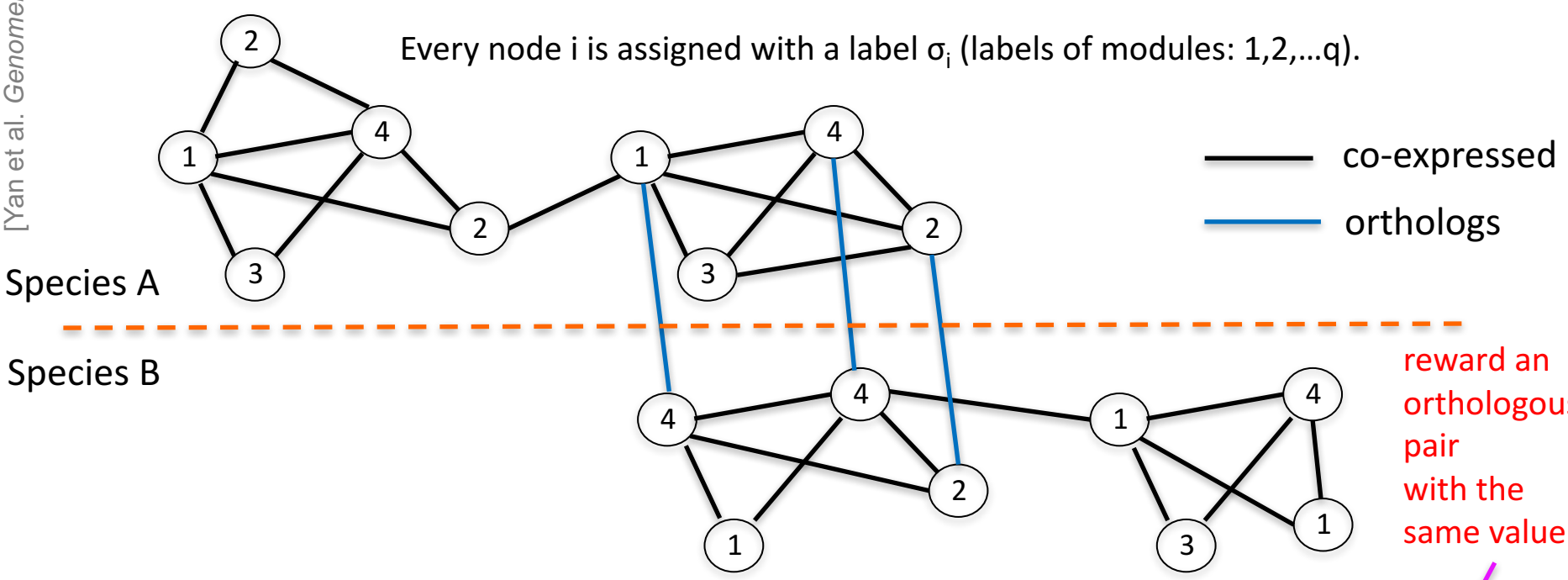
A toy example [orthoclust]

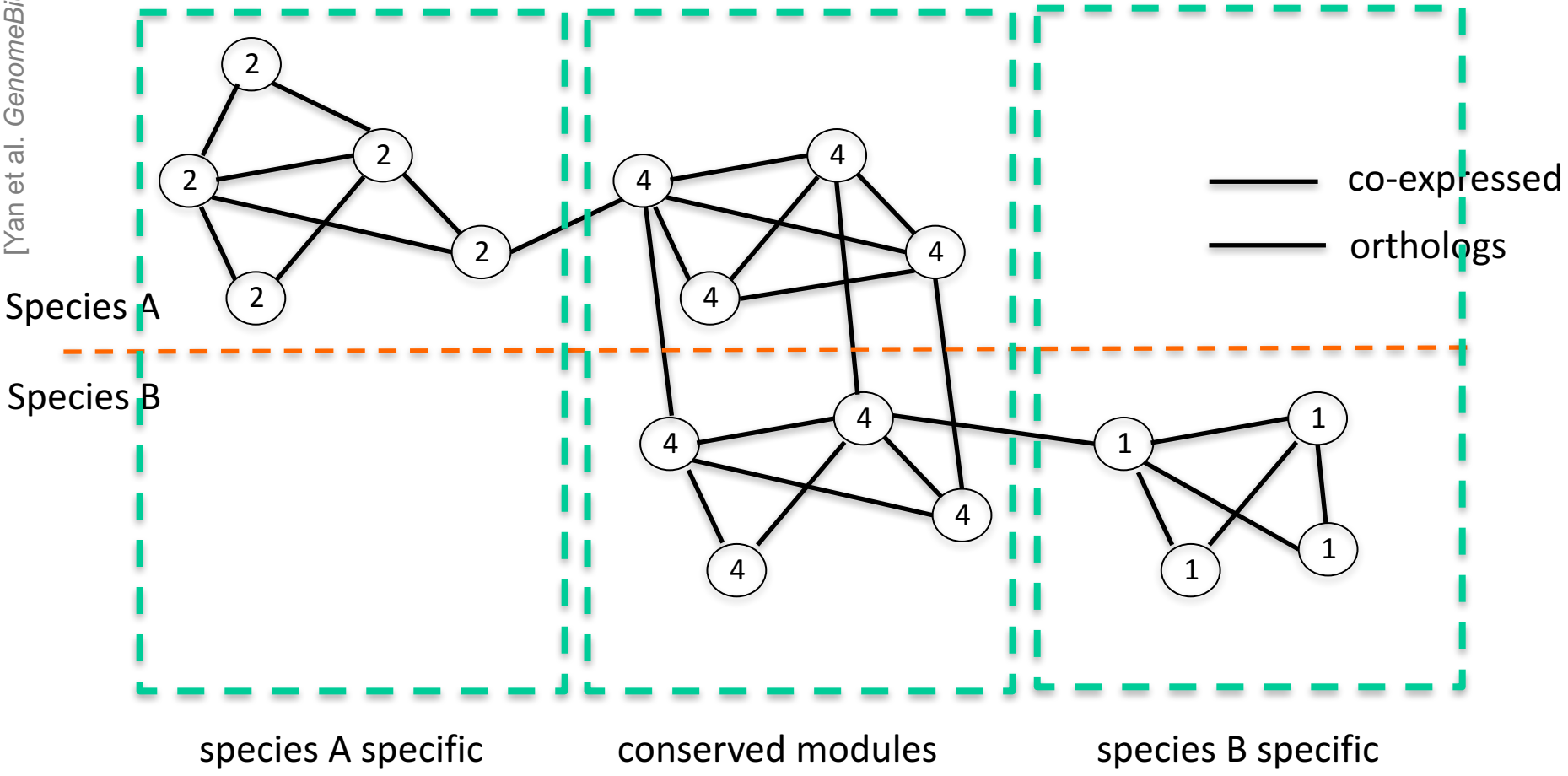
Every node i is assigned with a label σ_i (labels of modules: 1,2,…q).



$$H = \boxed{Q(\text{for all } \sigma_i \text{ in A}) \quad + \quad Q(\text{for all } \sigma_i \text{ in B})} + \kappa \boxed{\sum_{(i,j')\in Ortho} \delta_{\sigma_i \sigma_{j'}}}$$

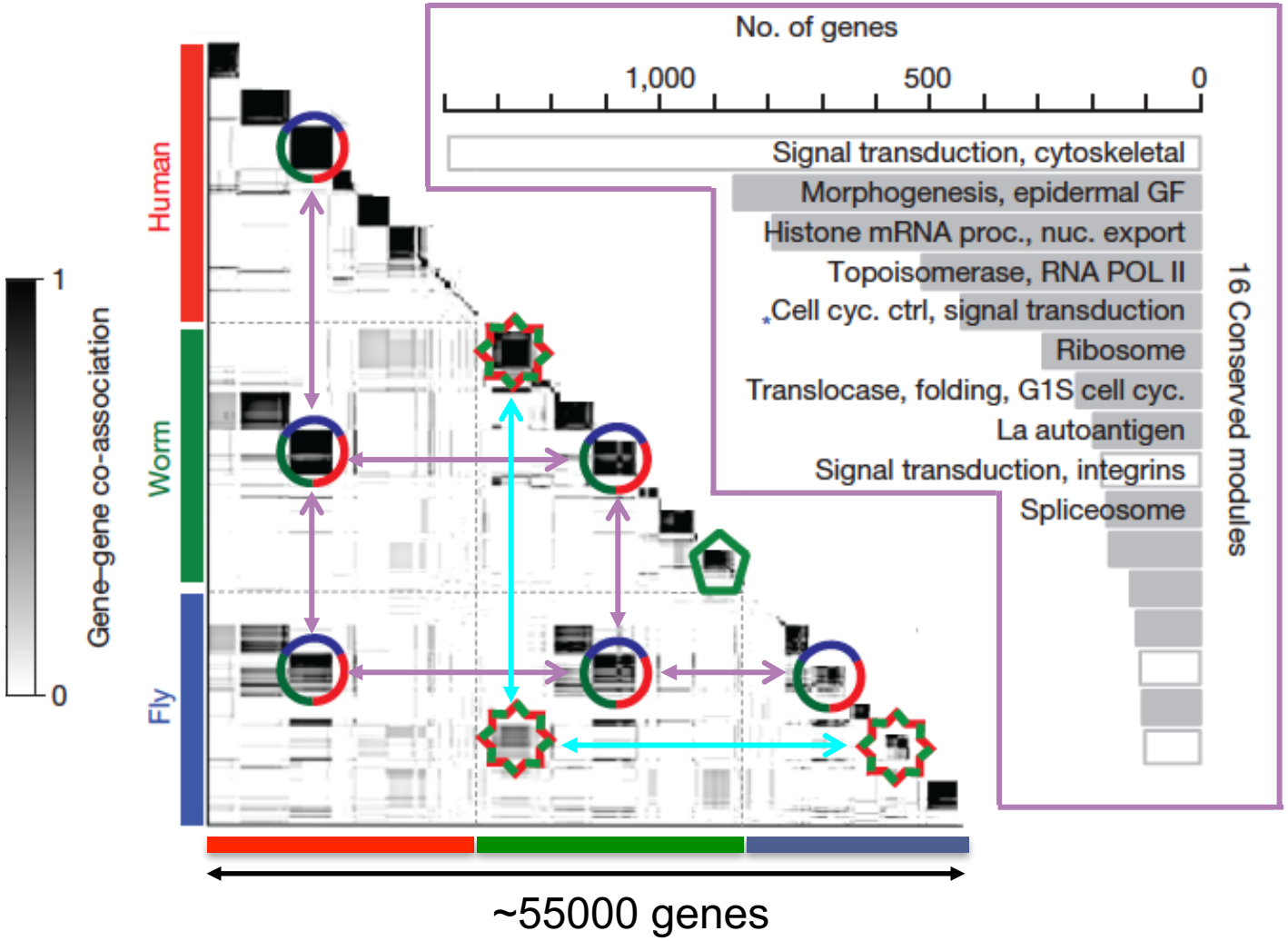
Favorableness = "Modularity" in species A + "Modularity" in species B + consistency betw. A & B

A toy example [orthoclust]



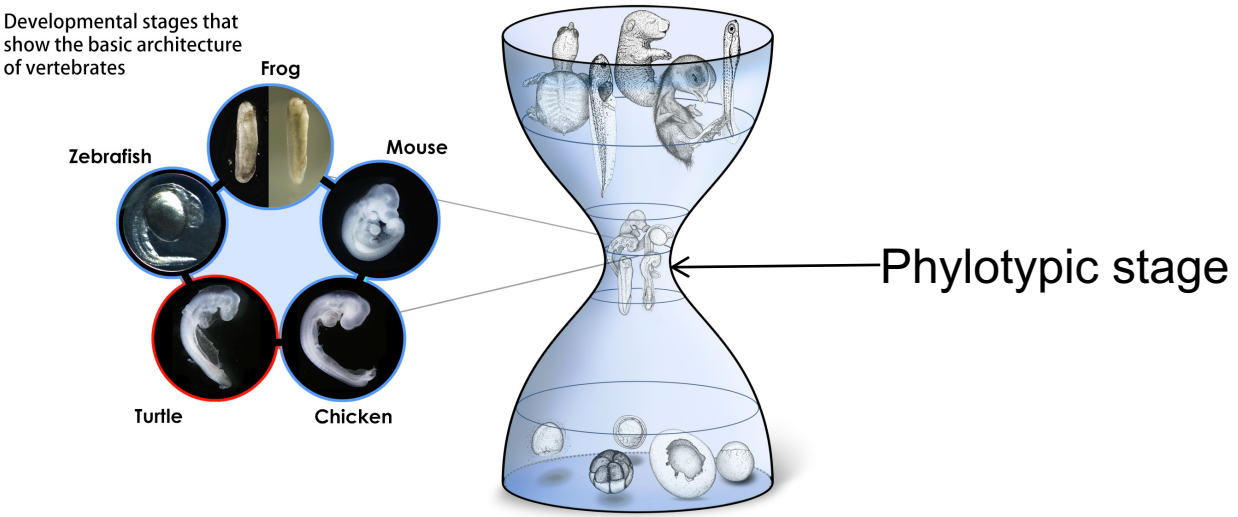
Use Potts model (generalized Ising model) to simultaneously cluster co-expressed genes within an organism as well as orthologs shared between organisms. Here, the ground state configuration correspond to three modules: 1, 2, 4.

Application for more than 2



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

Conserved modules exhibit canonical hourglass behavior



Illustrations courtesy Naoki Irie

Canonical Inter-organism Behavior

- "Hourglass hypothesis": all organisms go through a particular stage in embryonic development ("phylotypic" stage) where inter-organism expression differences of orthologous genes are smallest.
- **12 out of our 16 modules have this behavior**

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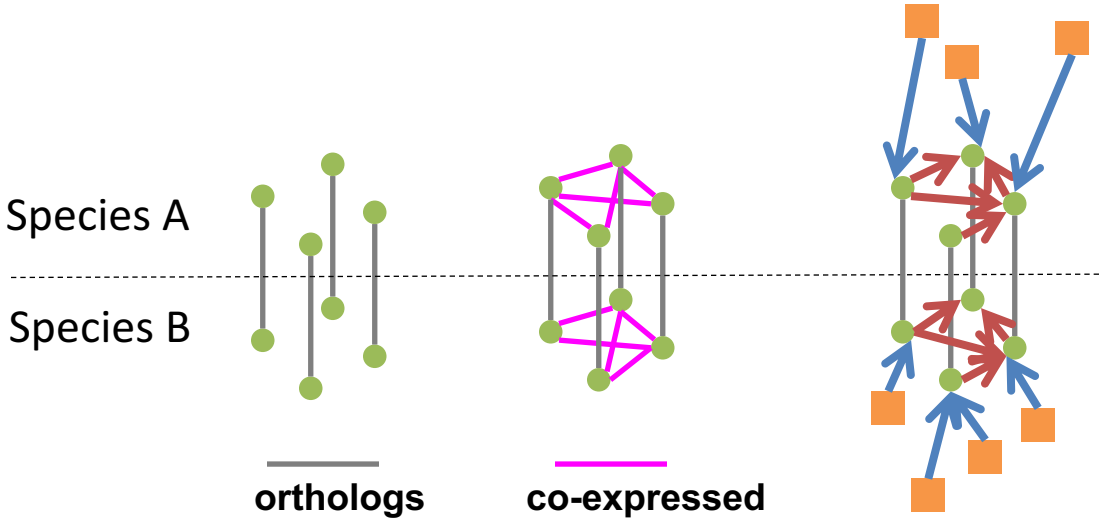
Is gene regulation among orthologs conserved?



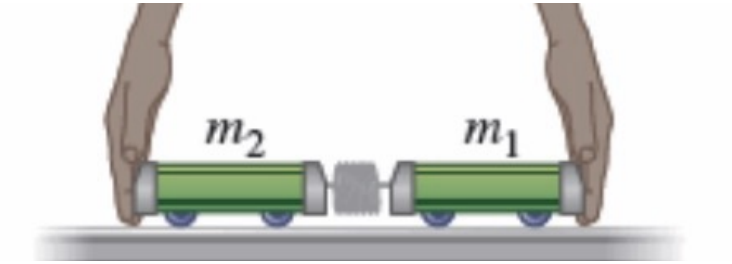
To what degree can't ortholog expression levels be predicted due to species-specific regulation?

Regulation among orthologs (**internal**)

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

Orthologous genes (orthologs)

Species-specific transcription factors



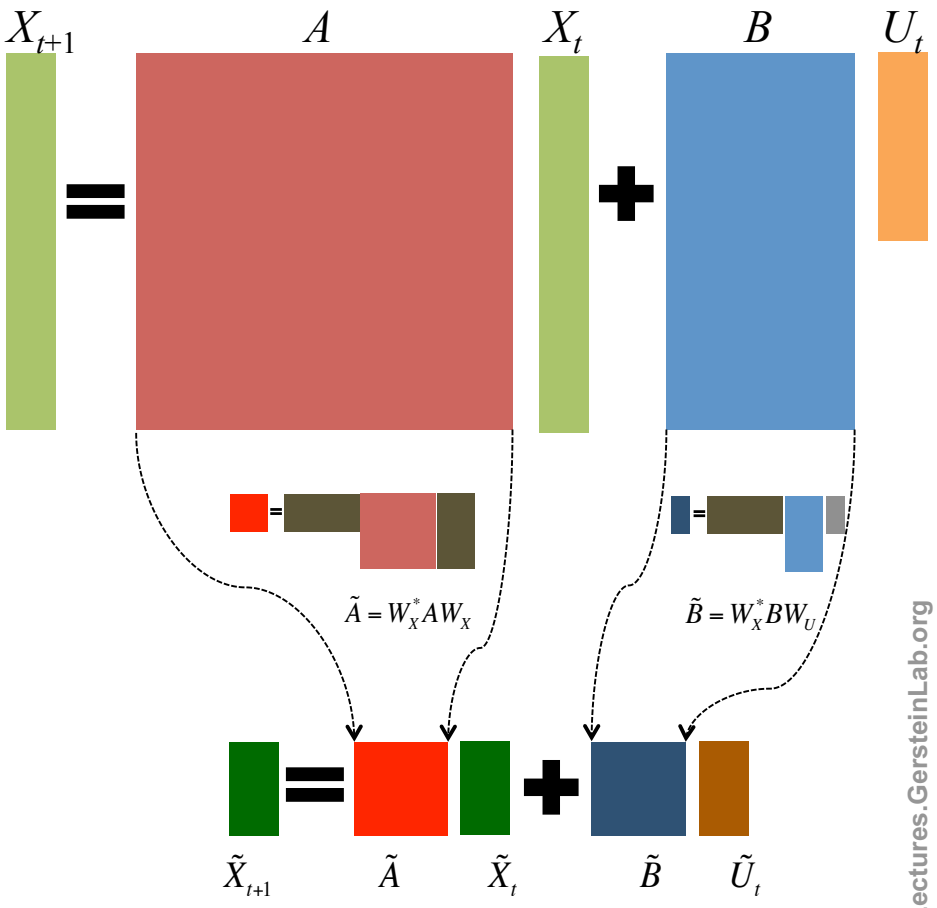
With External force

Purely Internal Dynamics

[Wang et al. *PLOS CB*, '16]

State-space model for internal and external gene regulatory networks

- **State X_t:** Gene expression vector of internal group at time t
- A_{ij} captures temporal casual influence from Gene i to Gene j in internal group
- B_{kl} captures temporal casual influence from external factor k to Gene l in internal group
- **Control U_t:** Gene expression vector of external factors at time t



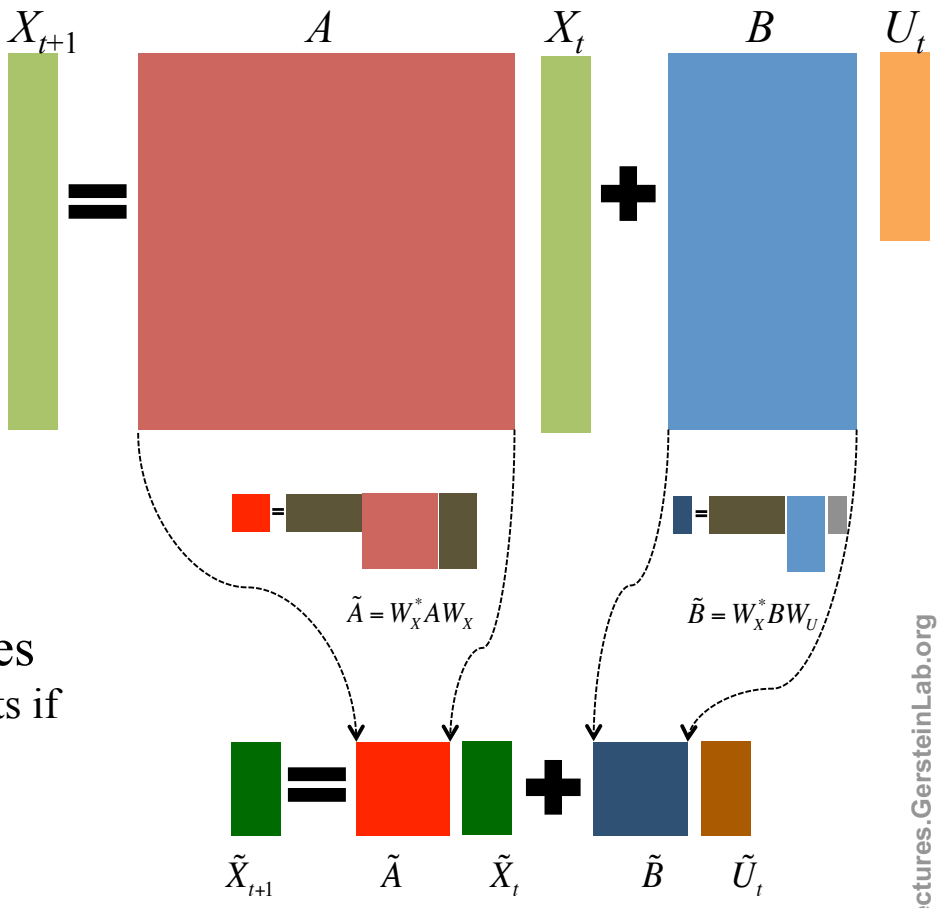
[Wang et al. *PLOS CB*, '16]

State-space model for internal and external gene regulatory networks

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)

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)



[Wang et al. *PLOS CB*, '16]

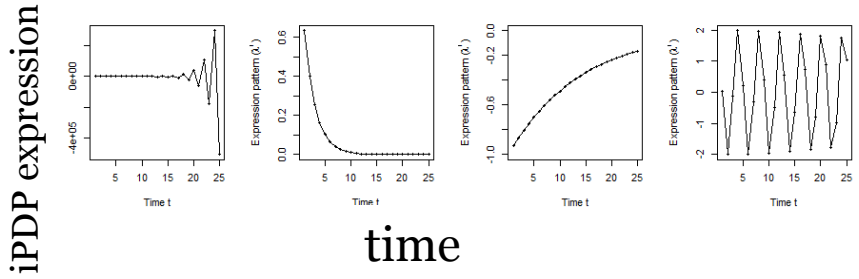
Canonical temporal expression trajectories from effective state space model

Is a std. 1st order homogeneous matrix difference equation. It can solved by diagonalizing A giving….

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

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 $\tilde{A}$.

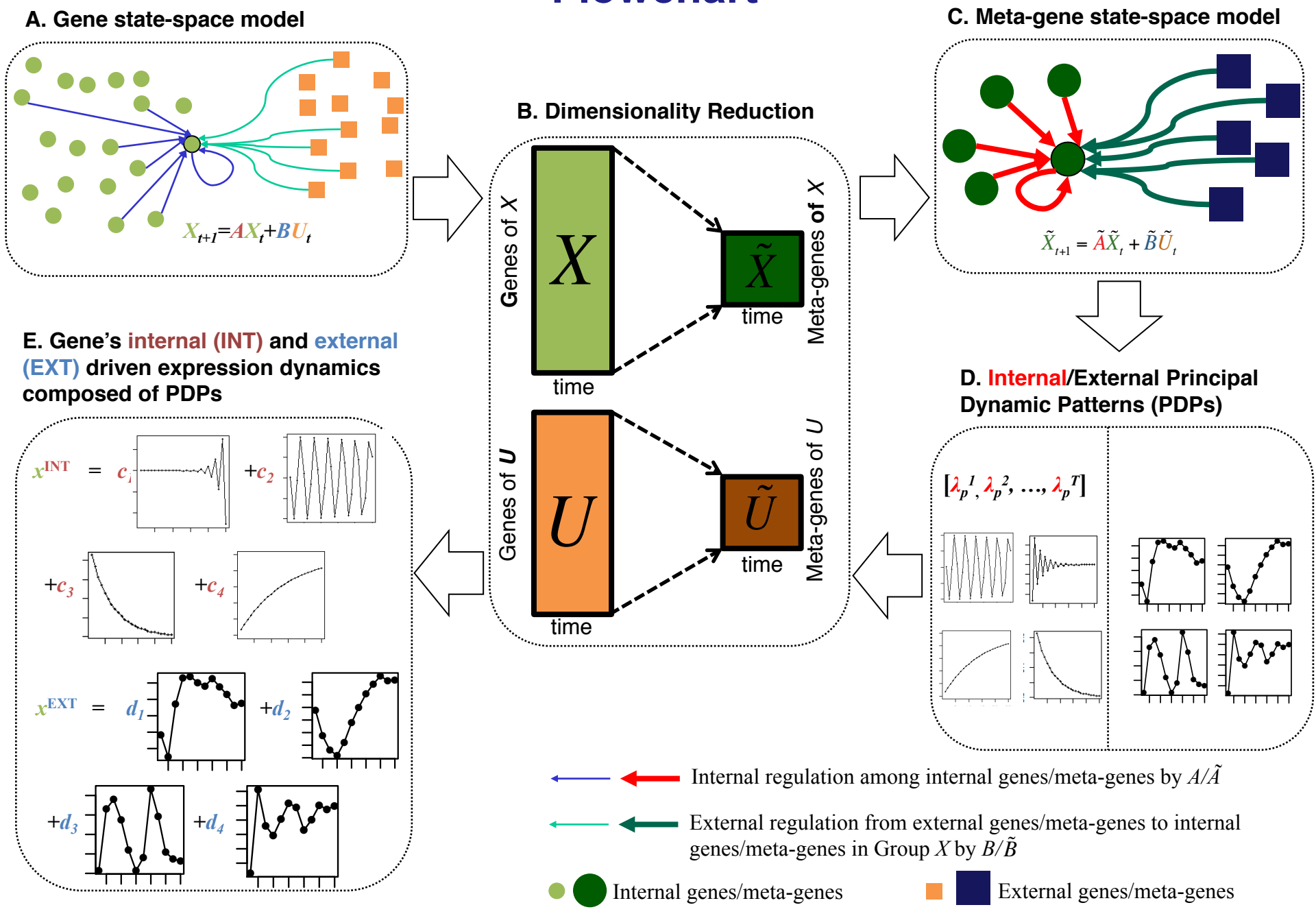
Canonical temporal expression trajectories
(e.g., degradation, growth, damped oscillation, etc.)



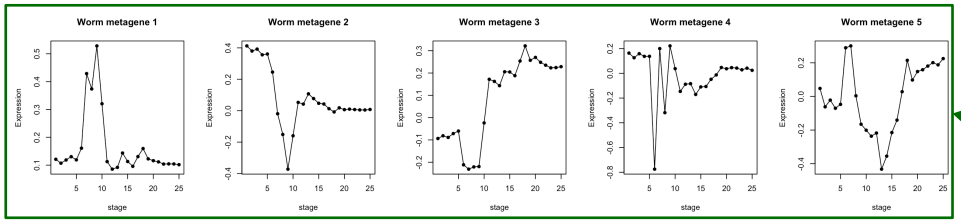
[Wang et al. *PLOS CB*, '16]

[Wang et al. *PLOS CB*, '16]

Flowchart



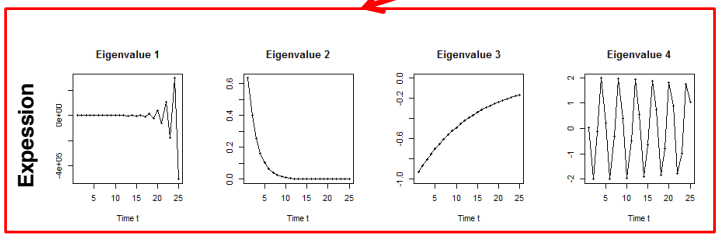
Orthologs have similar internal but different external dynamic patterns during embryonic development

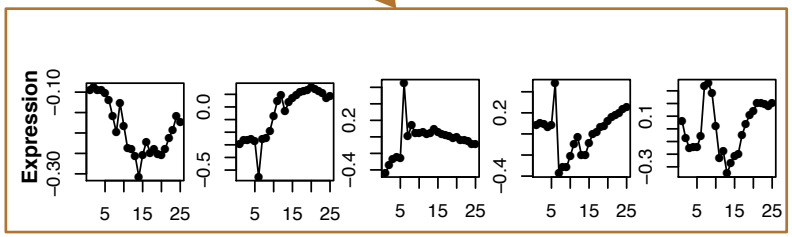


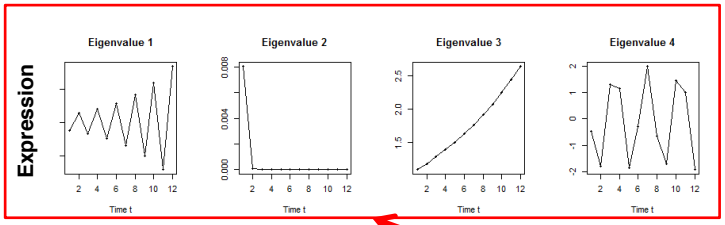
Worm

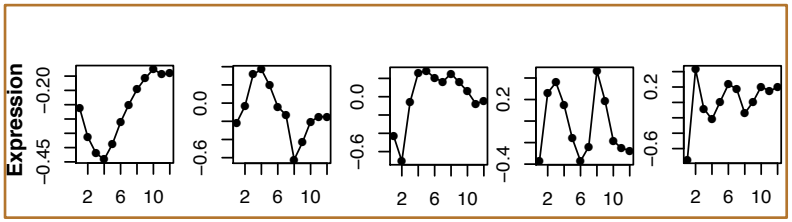
ePDPs

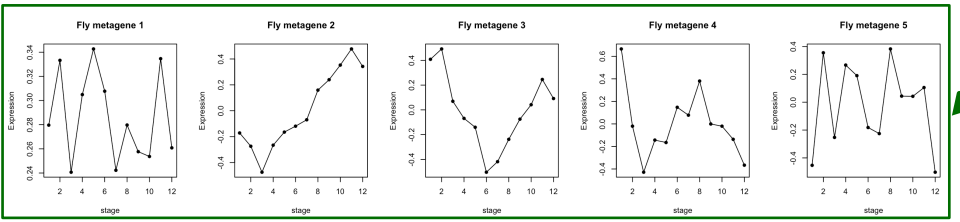
iPDPs











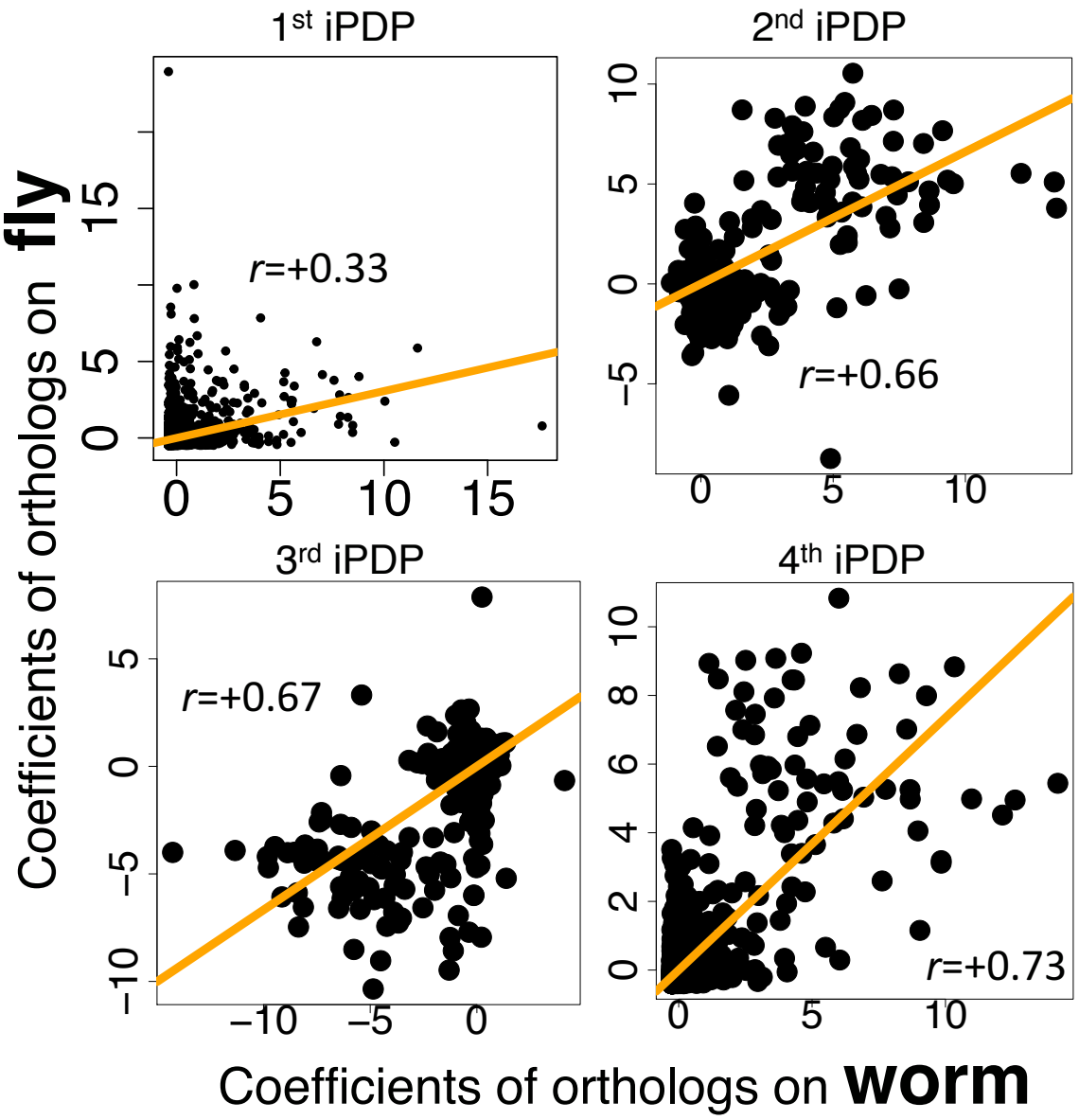
Fly's
effective state space model

Meta-genes

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

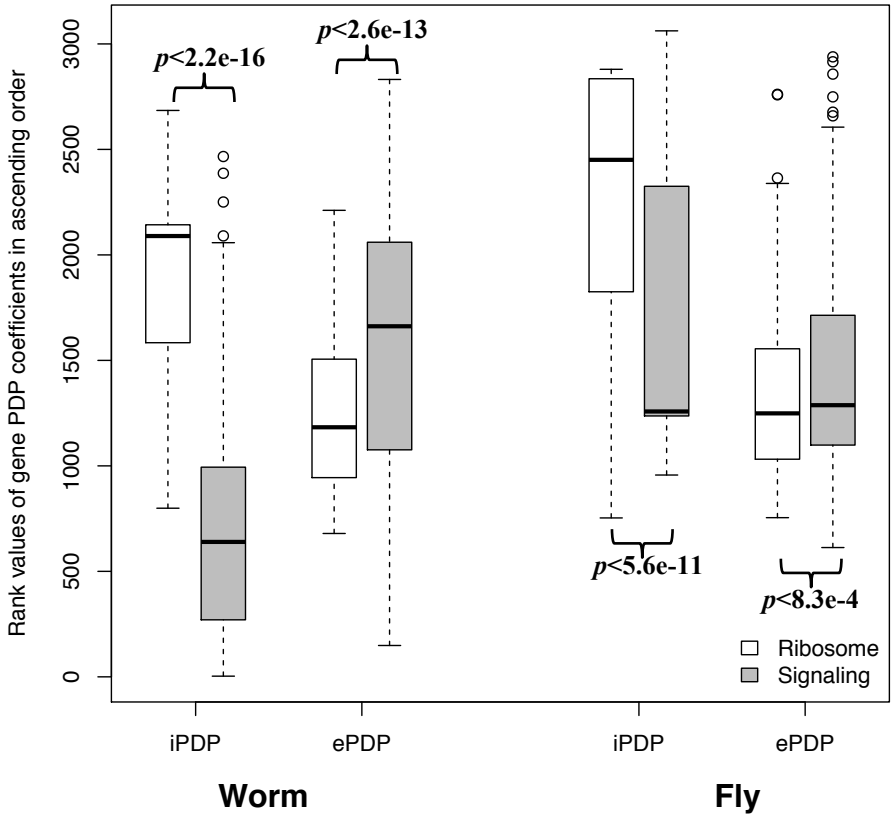
[Wang et al. *PLOS CB*, '16]

Orthologs have correlated iPDP coefficients



[Wang et al. *PLOS CB*, '16]

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



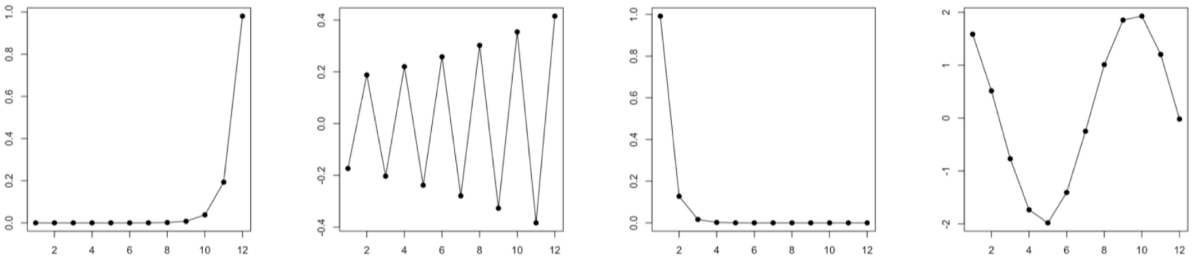
Ribosomal genes have significantly larger coefficients for the internal than external PDPs, but signaling genes exhibit the opposite trend

[Wang et al. *PLOS CB*, '16]

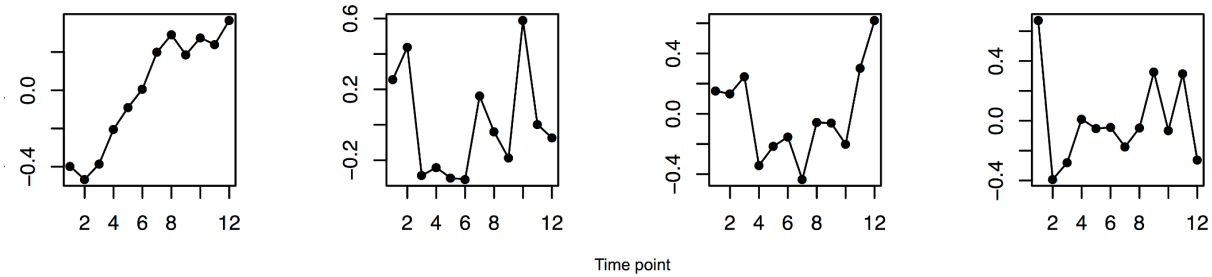
Human-specific TFs respond more strongly to hormonal stimulation during cell-cycle than conserved genes in breast cancer cell

- Applied to Breast Cancer Cell Cycle (2 periods) under hormonal stim.
  - **INT = conserved human genes**
    - ~1100 H-F-W orthologs
    - follow normal cell cycle
  - **EXT = human spec TFs**
    - diff from above
    - perhaps responding to stimulation

iPDPs



ePDPs



Transcriptome Mining: Tackling core issues related to gene regulation & also analyzing the "data exhaust" associated with this activity

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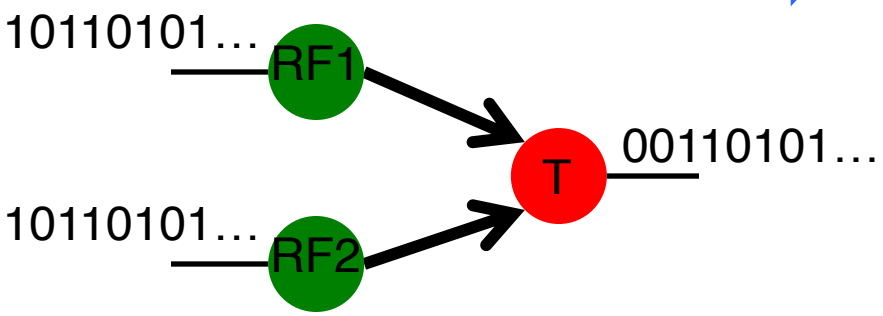
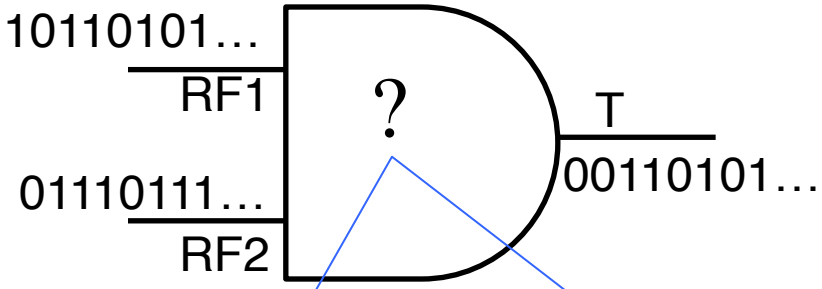
  - Key role of brokers in data dissemination

Modeling cooperativity between TFs to target gene using logic gates

A regulatory triplet



2-input-1-output logic gate

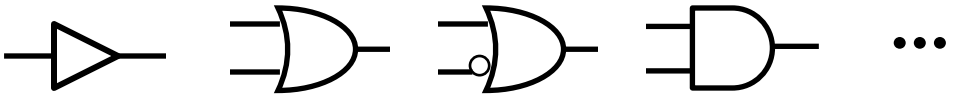


0 – gene off
1 – gene on
after binarizing gene expression data*

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

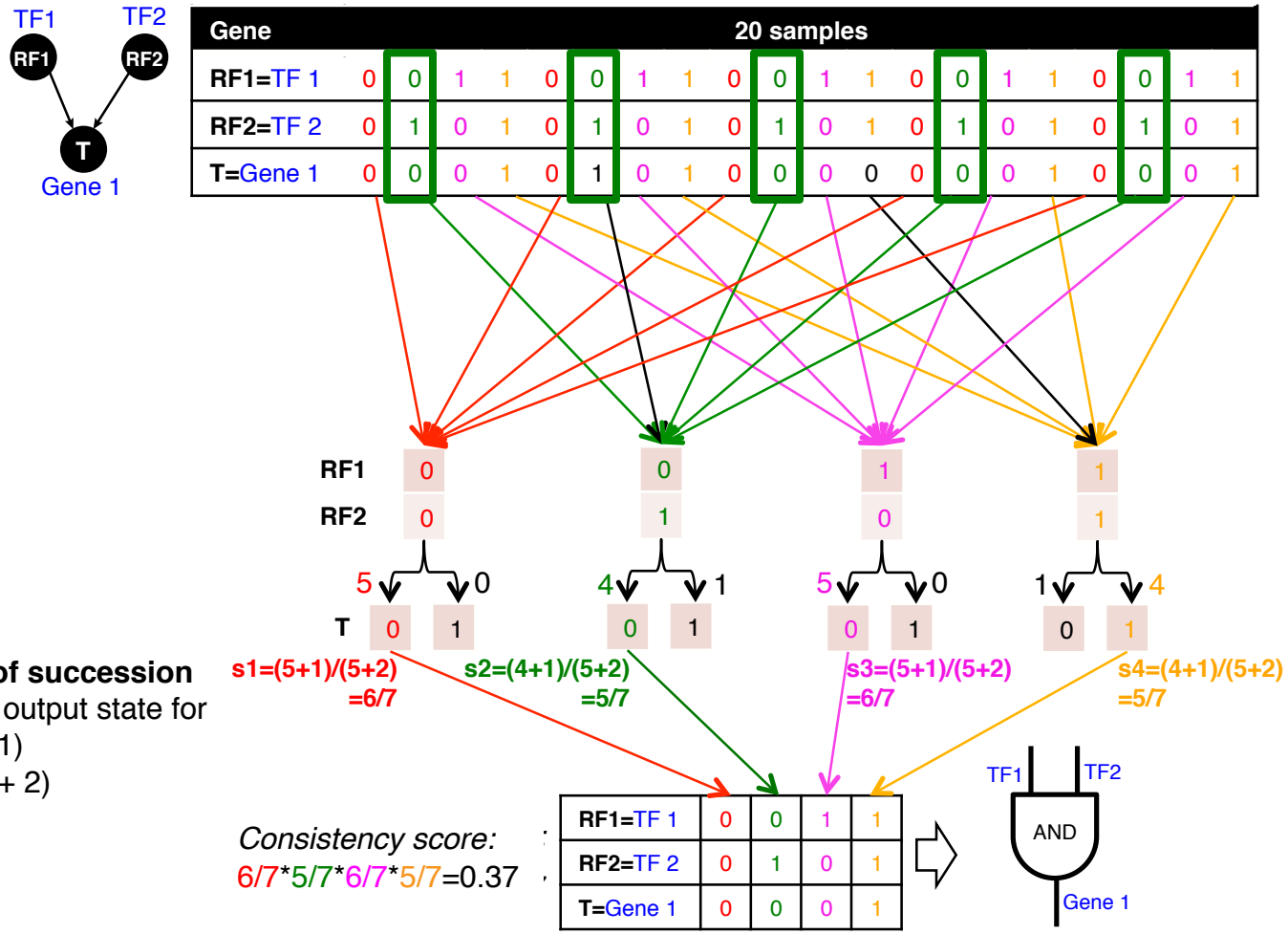
Binarized expression

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

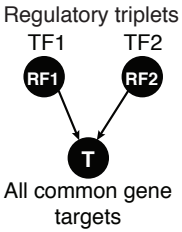
An example: selection of the best-matched logic gate



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

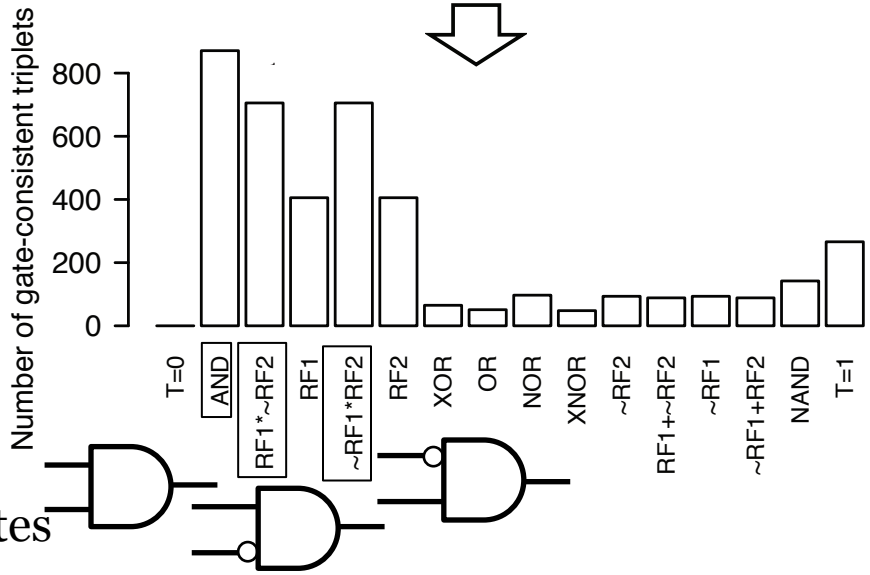
App. 1 – TF cooperativity in the cell cycle



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

Yeast Cell Cycle

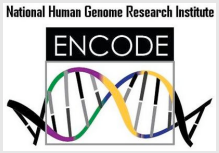
Triplet ID	RF1	RF2	Common Target Gene (T)	Matched logic gate
1	YHR084W	YBR083W	YBR082C	AND
2	YKL112W	YIL131C	YMR198W	OR
…	…	…	…	…
39011	YOR113W	YBL103C	YDR042C	XOR



AND-like gates

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

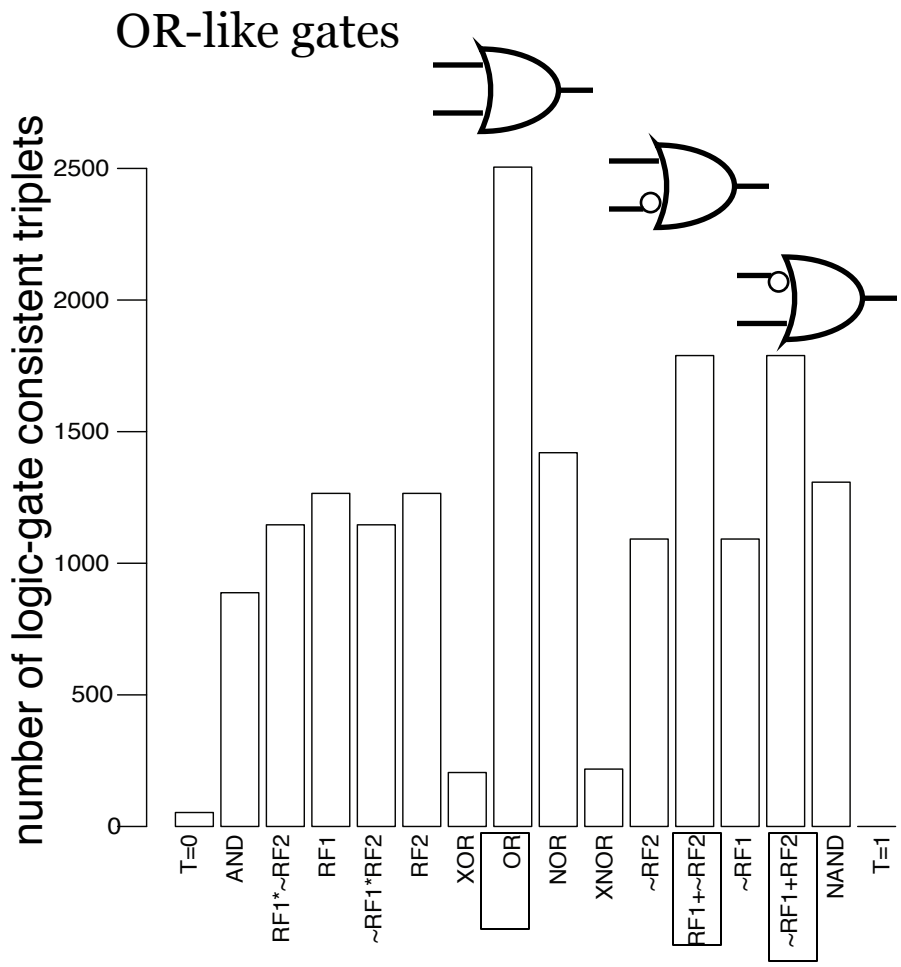
Acute Myeloid Leukemia (AML)

Target gene	1824	ENCODE Data (K562, ChIP-seq)
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

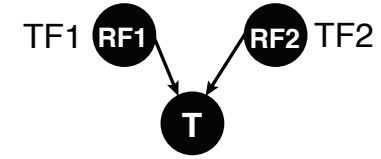
App. 2 – TF cooperativity in AML

Regulatory triplet from ENCODE	50,865
Patient sample for TCGA AML expression data	197



Human TF-TF-target

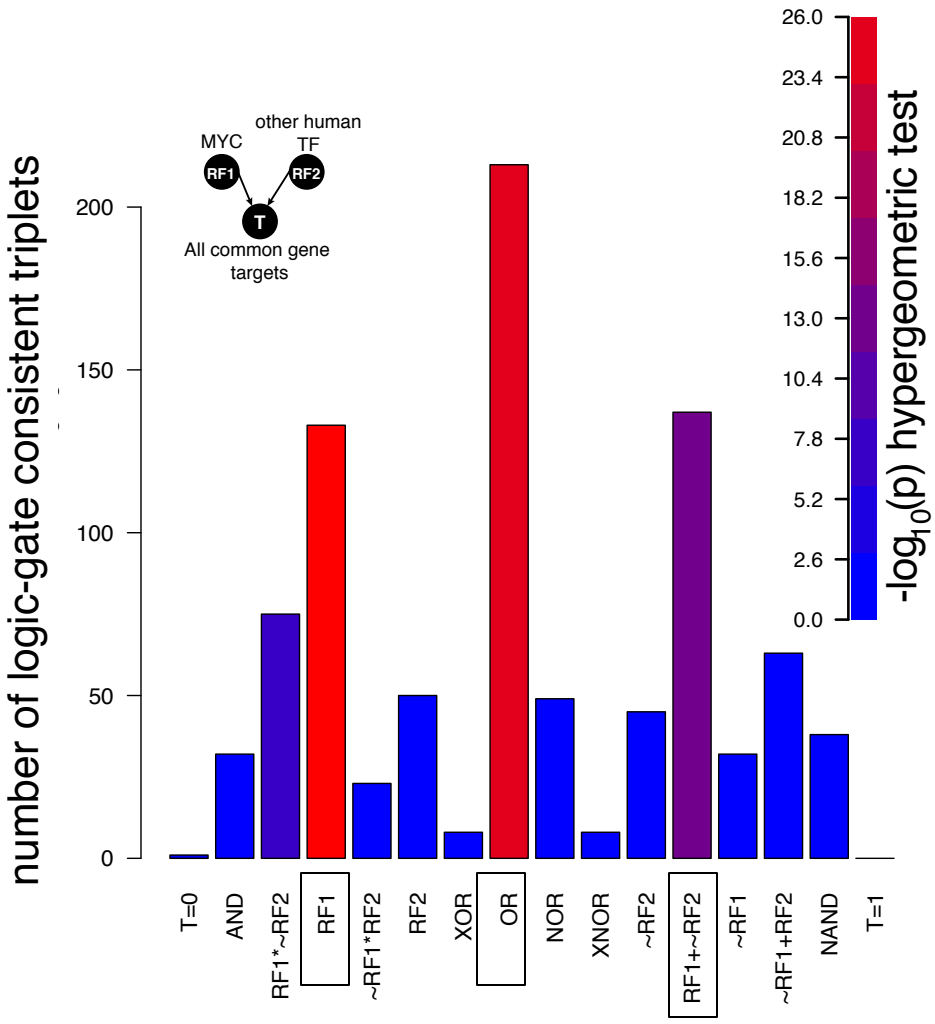
RF1	RF2	Common Target Gene (T)	Matched logic gate
ATF3	BDP1	YPEL1	AND
MYC	BCL3	BCR	T=RF1
ATF3	BRF2	AIF1L	AND
…	…	…	…



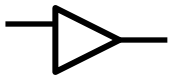
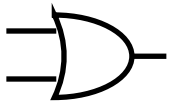
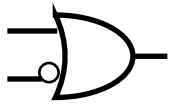
All common gene targets

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

Cancer-related TF, MYC, universally amplifies target expression



Restrict to RF1=MYC, giving 2,153 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

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2-sided nature of functional genomics data: Analysis can be very General/Public or Individual/Private

- **General quantifications** related to overall aspects of a condition – ie gene activity as a function of:
  - Developmental stage, Evolutionary relationships, Cell-type, Disease

- **Above are not tied to an individual's genotype. However, data is derived from individuals & tagged with their genotypes**

- (Note, a few calculations aim to use explicitly genotype to derive general relations related to sequence variation & gene expression - eg allelic activity)

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
  - **EG web search**: Large-scale mining essential

- We confront privacy risks every day we access the internet

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

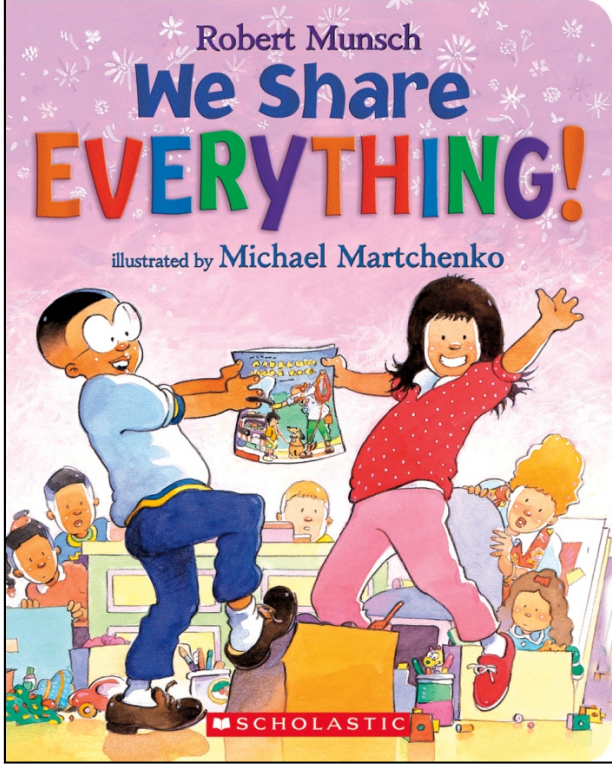
Tricky Privacy Considerations in Personal Genomics

- **Genetic Exceptionalism :** The Genome is very fundamental data, potentially very revealing about one's identity & characteristics
- **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.
  - Clinical Medline has a very different culture.
- **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**
  - More fun to study a known person's genome
    - Eg Zimmer's Game of Genomes in STAT



[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?
- How to balance risks v rewards - Quantification
  - What is acceptable risk?
    Can we quantify leakage?
    - Ex: photos of eye color
  - Cost Benefit Analysis

Current Social & Technical Solutions

- **Closed Data** Approach
  - Consents
  - "Protected" distribution via dbGAP
  - Local computes on secure computer
- Issues with Closed Data
  - 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"

- **Open Data**
  - Genomic "test pilots" (ala PGP)?
    - Sports stars & celebrities?
  - Some public data & data donation is helpful but is this a realistic solution for an unbiased sample of ~1M

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

Strawman Hybrid Social & Tech Proposed Solution?

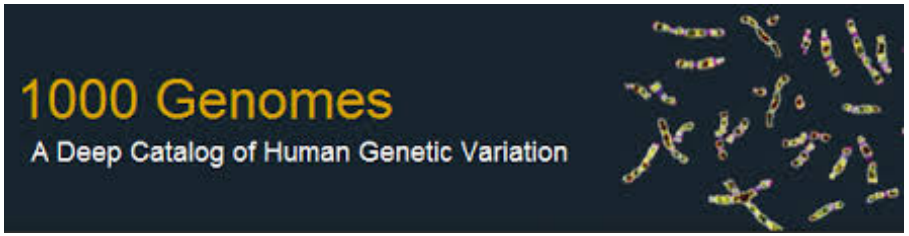
- Fundamentally, researchers have to keep genetic secrets.
  - **Need for an (international) legal framework**
  - Genetic Licensure & training for individuals (similar to medical license, drivers license)
- Technology to make things easier
  - Cloud computing & enclaves (eg solution of Genomics England)
- 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)]

Representative Expression, Genotype, eQTL Datasets

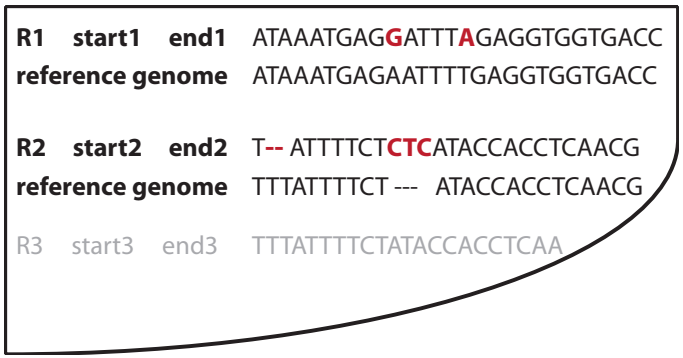
- Genotypes are available from the 1000 Genomes Project
- mRNA sequencing for 462 individuals from gEUVADIS and ENCODE
  - Publicly available quantification for protein coding genes
- Approximately 3,000 cis-eQTL (FDR<0.05)

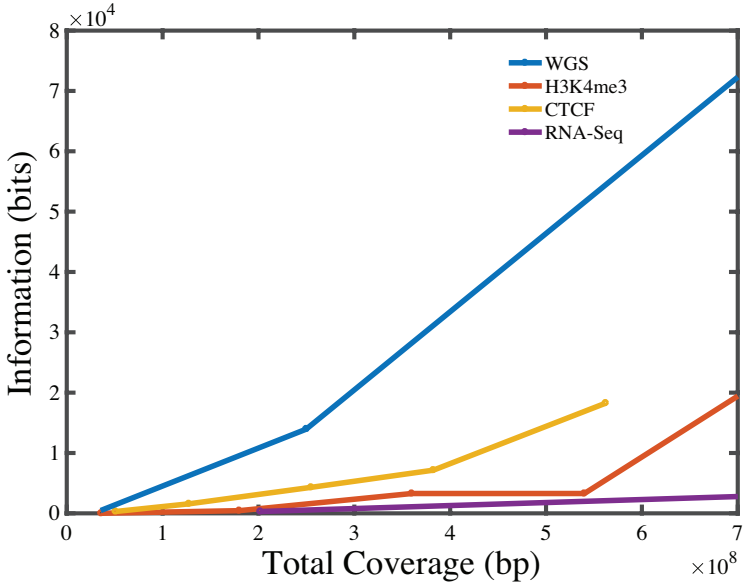


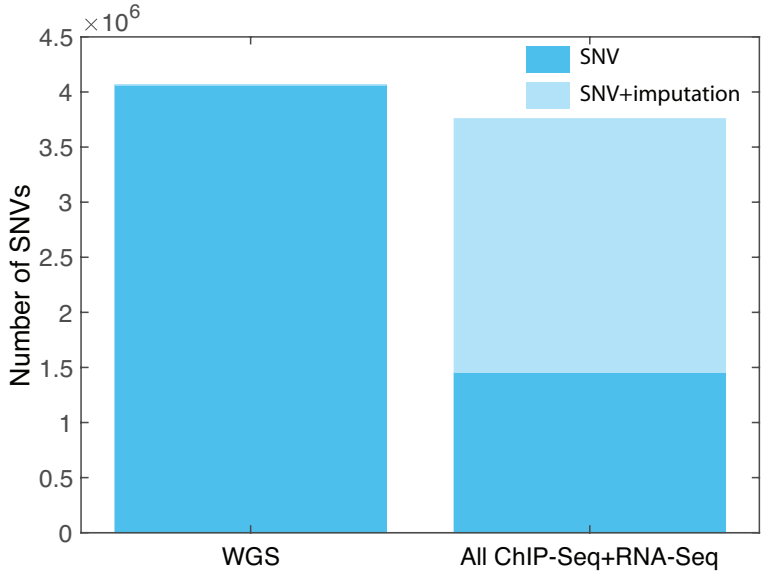
Variants directly in the reads

- Functional genomics data comes with a great deal of sequencing
  - NA12878 as case study - 1000 genomes variants are used as gold standard
- How much information, for example, do RNA-Seq reads (or ChIP-Seq) reads contain? Does that information enough to identify individuals?

Variants from RNA-Seq reads



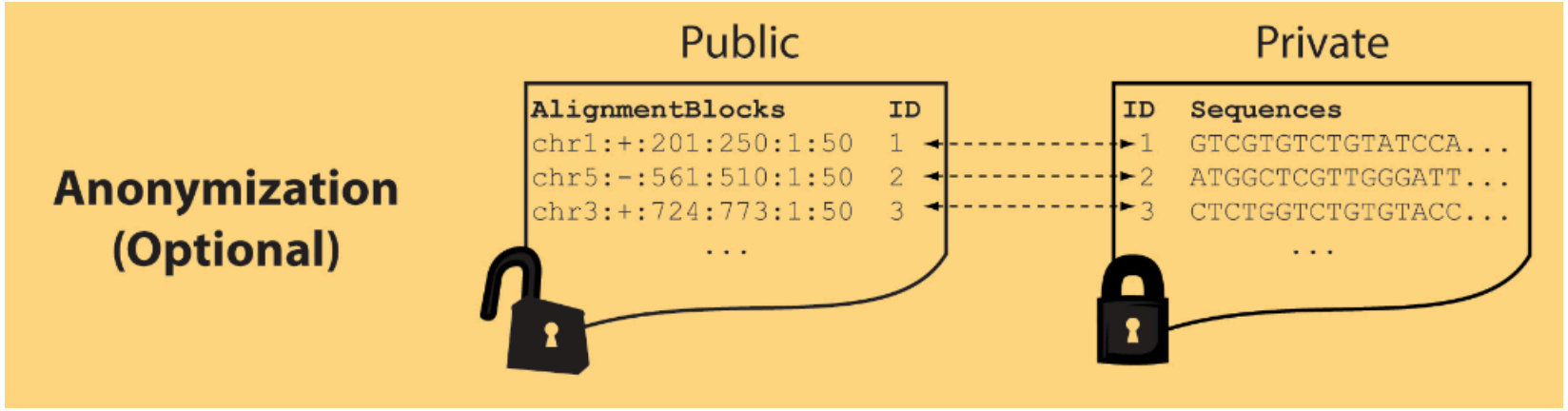


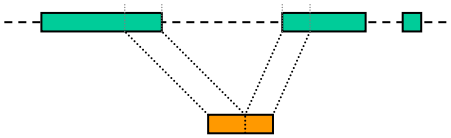


- It might seem like we don't infer much information from single ChIP-Seq and RNA-Seq experiments compared to WGS
  - However putting 10 different ChIP-Seq experiments and RNA-Seq together with imputation provides a great deal of information about the individual

Light-weight formats to Hide Most of the Read Data (Signal Tracks)

- 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

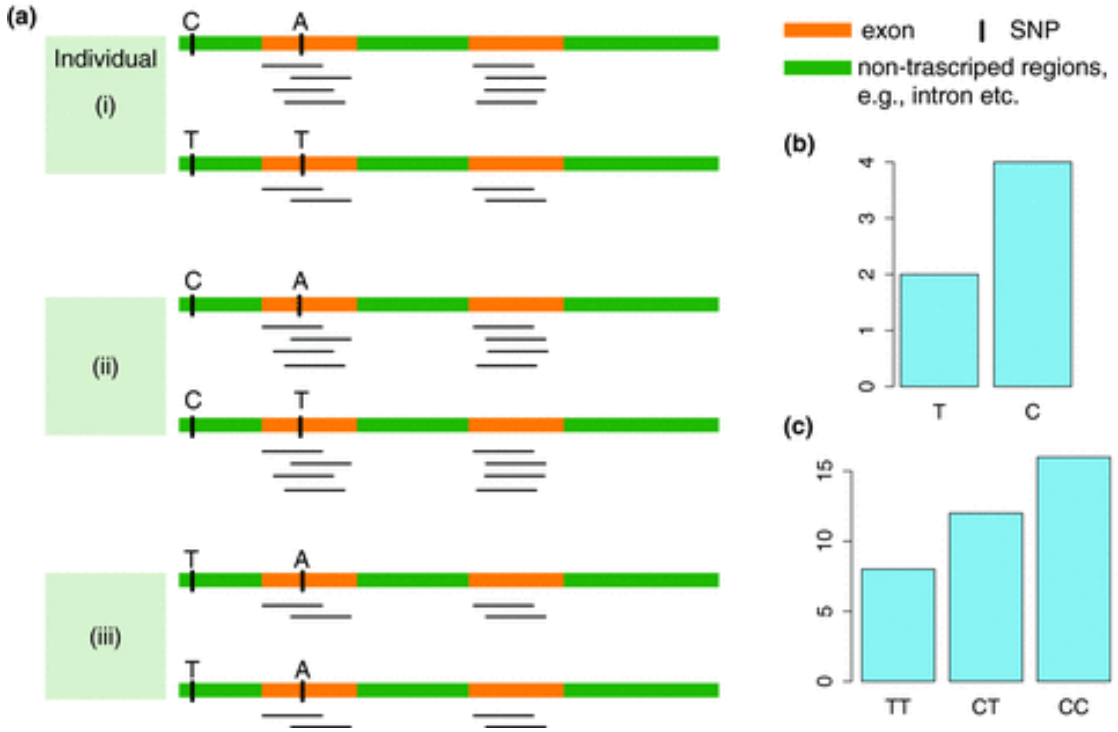




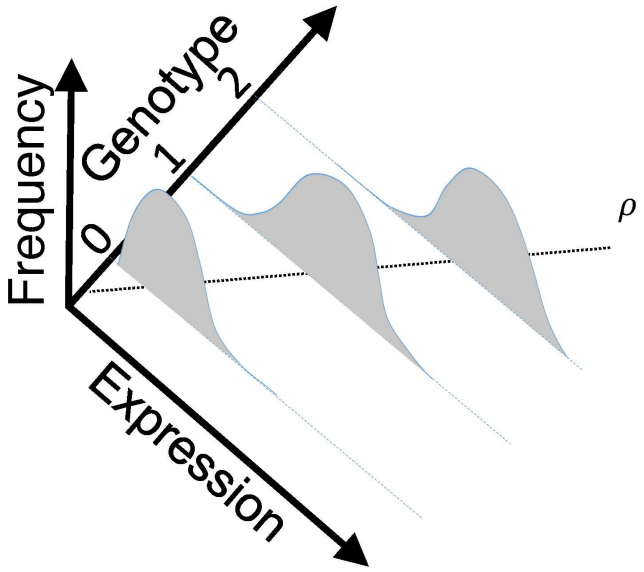
Mapping coordinates without variants (MRF)

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

[*Bioinformatics* 27: 281]



[*Biometrics 68(1) 1–11*]

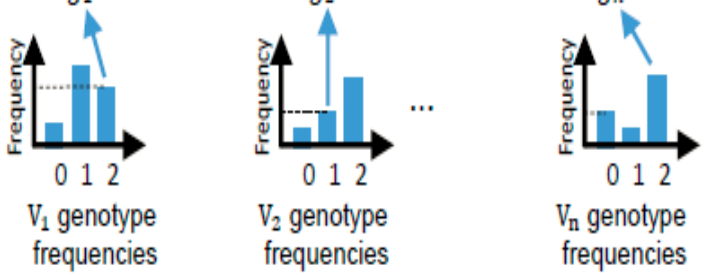


eQTL Mapping Using RNA-Seq Data

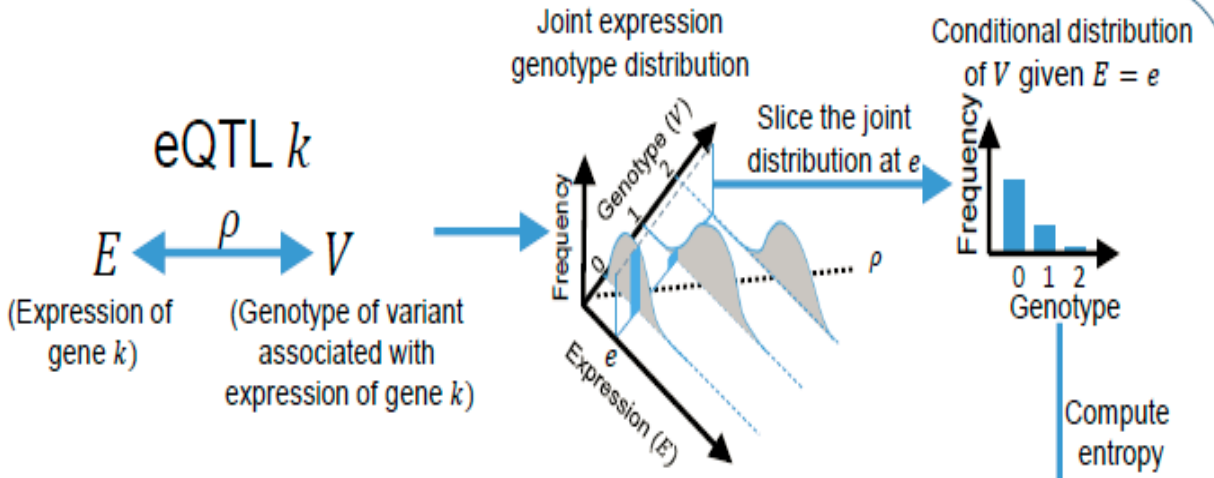
- eQTLs are genomic loci that contribute to variation in mRNA expression levels
- eQTLs provide insights on transcription regulation, and the molecular basis of phenotypic outcomes
- eQTL mapping can be done with RNA-Seq data

Information Content and Predictability

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



- Naive measure of information (no LD, distant correlations, pop. struc., &c)
- Higher frequency: Lower ICI
- Additive for multiple variants

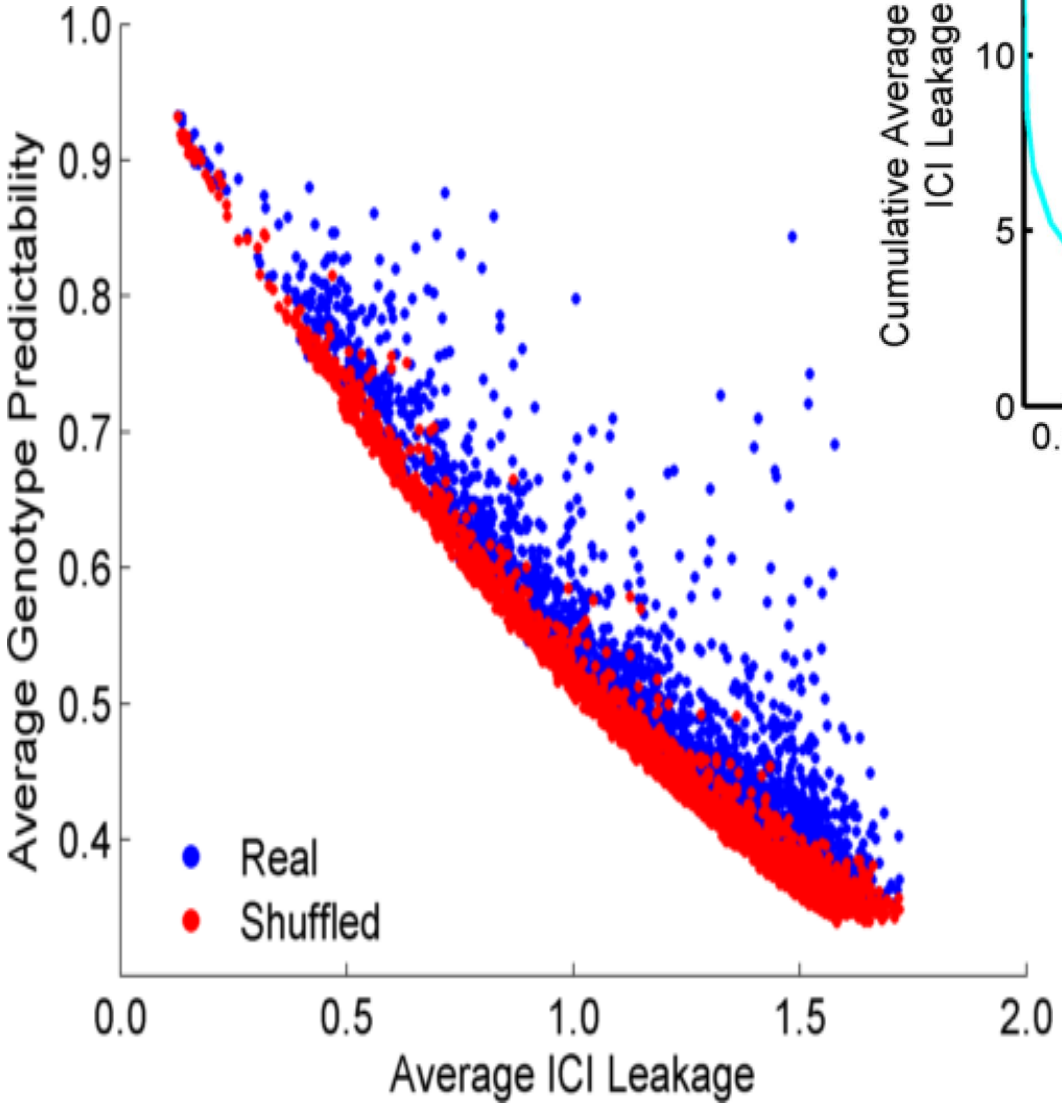


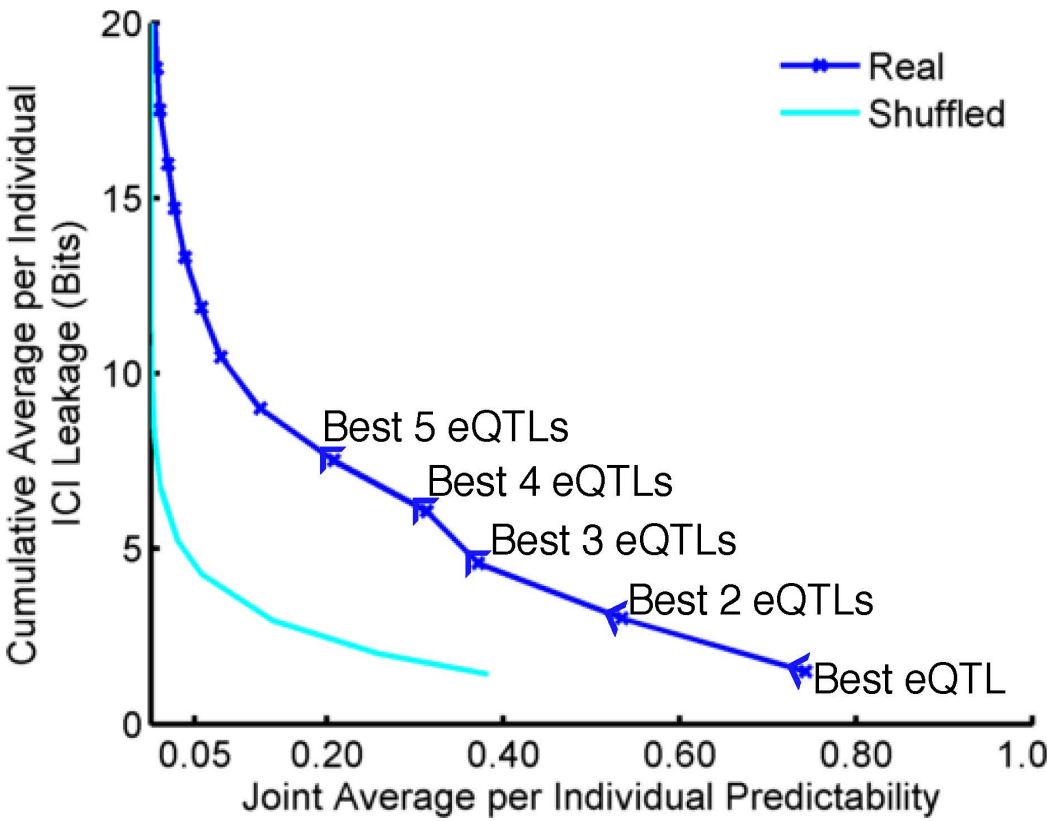
$$\pi\left(V \mid E = e\right) = e^{-H\left(V \mid E = e\right)}$$

- Condition specific entropy
- Higher cond. entropy: Lower predictability
- Additive for multiple eQTLs

[Harmanci et al. Nat. Meth. 2016]

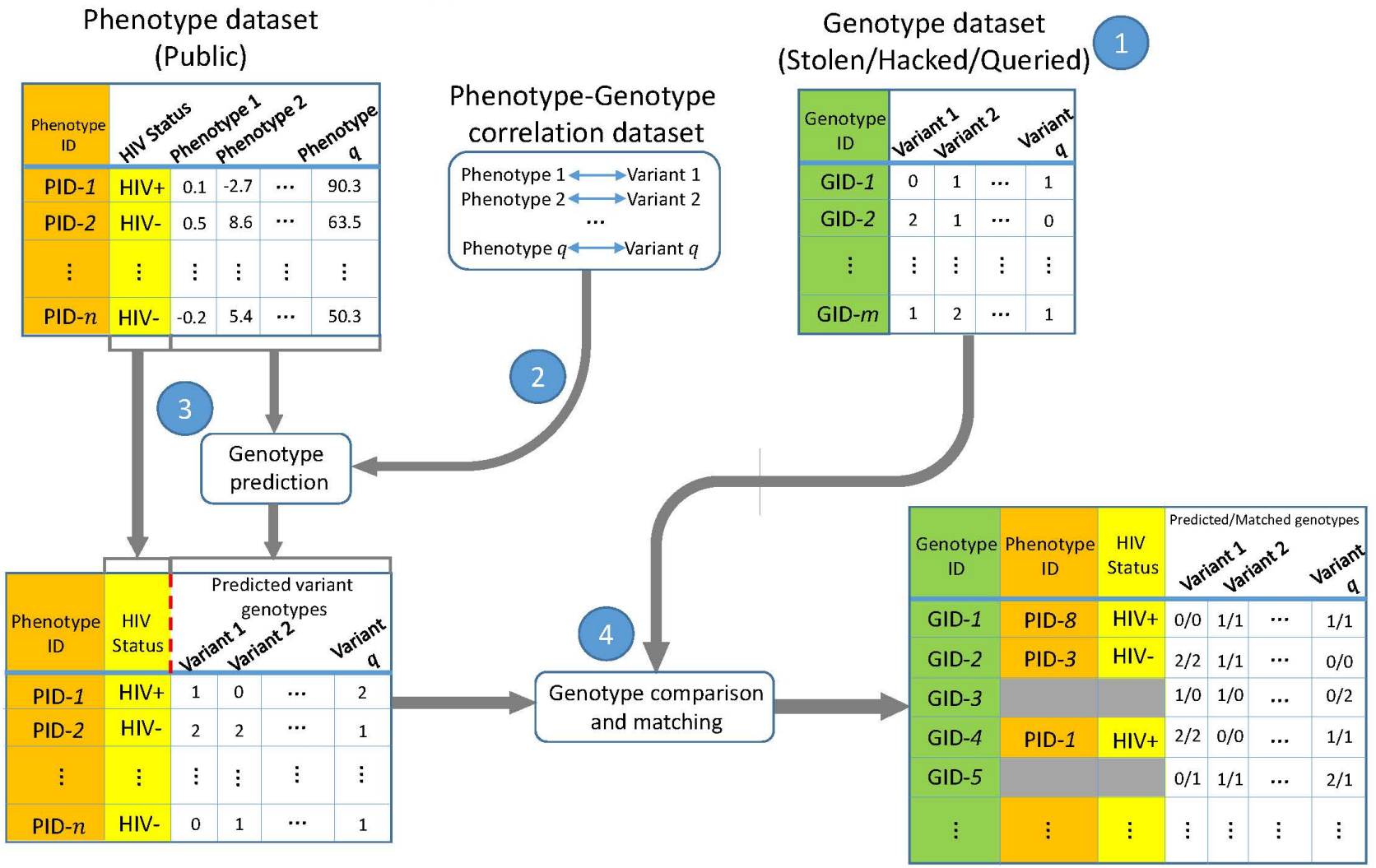
[Harmanciet al. Nat. Meth. (‘16]





ICI Leakage versus Genotype Predictability

Linking Attack Scenario



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

Linking Attacks: Case of Netflix Prize

User (ID)	Movie (ID)	Date of Grade	Grade [1,2,3,4,5]
NTFLX-0	NTFLX-19	10/12/2008	1
NTFLX-1	NTFLX-116	4/23/2009	3
NTFLX-2	NTFLX-92	5/27/2010	2
NTFLX-1	NTFLX-666	6/6/2016	5
…	…	…	…
…	…	…	…

Names available for many users!

User (ID)	Movie (ID)	Date of Grade	Grade [0-10]
IMDB-0	IMDB-173	4/20/2009	5
IMDB-1	IMDB-18	10/18/2008	0
IMDB-2	IMDB-341	5/27/2010	-
…	…	…	…
…	…	…	…
…	…	…	…

- **Many users are shared**
- **The grades of same users are correlated**
- **A user grades one movie around the same date in two databases**

Anonymized Netflix Prize Training Dataset made available to contestants

Linking Attacks: Case of Netflix Prize

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…	…	…	…
…	…	…	…
…	…	…	…

- **Many users are shared**
- **The grades of same users are correlated**
- **A user grades one movie around the same date in two databases**

- **IMDB users are public**

- **NetFLIX and IMdB moves are public**

Linking Attacks: Case of Netflix Prize

Names available for many users!

User (ID)	Movie (ID)	Date of Grade	Grade [1,2,3,4,5]
NTFLX-0	NTFLX-19	10/12/2008	1
NTFLX-1	NTFLX-116	4/23/2009	3
NTFLX-2	NTFLX-92	5/27/2010	2
NTFLX-1	NTFLX-666	6/6/2016	5
…	…	…	…
…	…	…	…

User (ID)	Movie (ID)	Date of Grade	Grade [0-10]
IMDB-0	IMDB-173	4/20/2009	5
IMDB-1	IMDB-18	10/18/2008	0
IMDB-2	IMDB-341	5/27/2010	-
…	…	…	…
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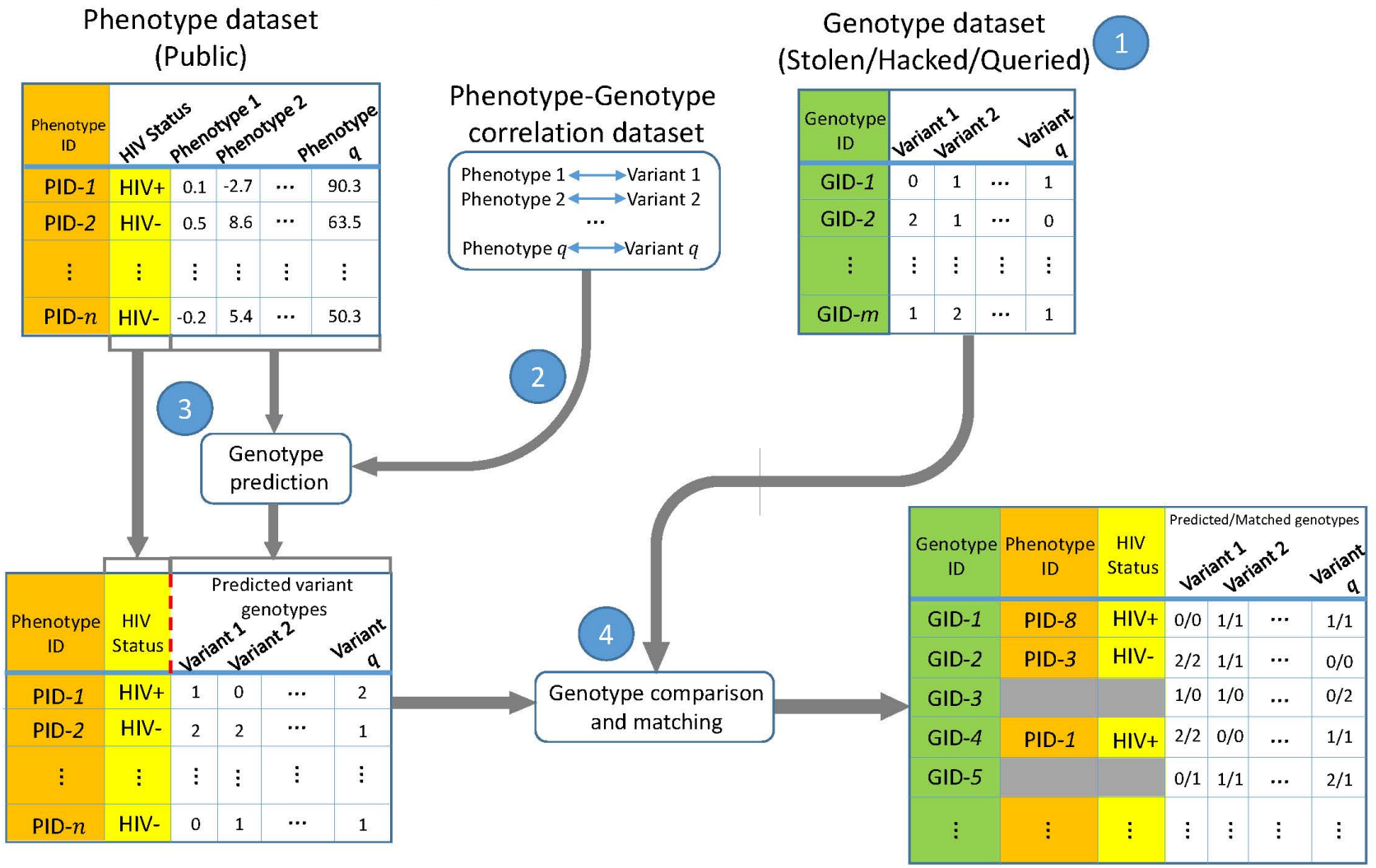
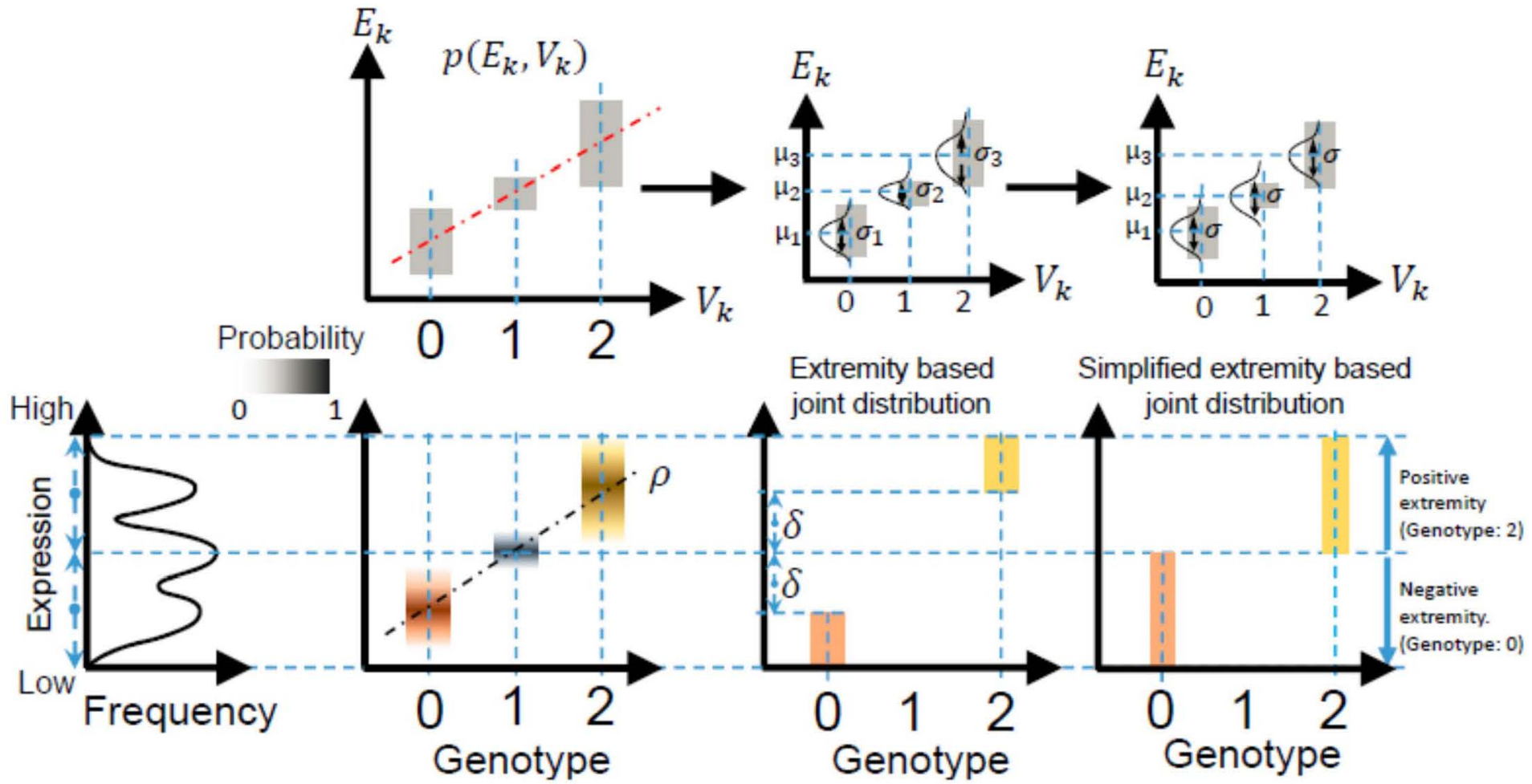
Linking Attack Scenario



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

Levels of Expression-Genotype Model Simplifications for Genotype Prediction



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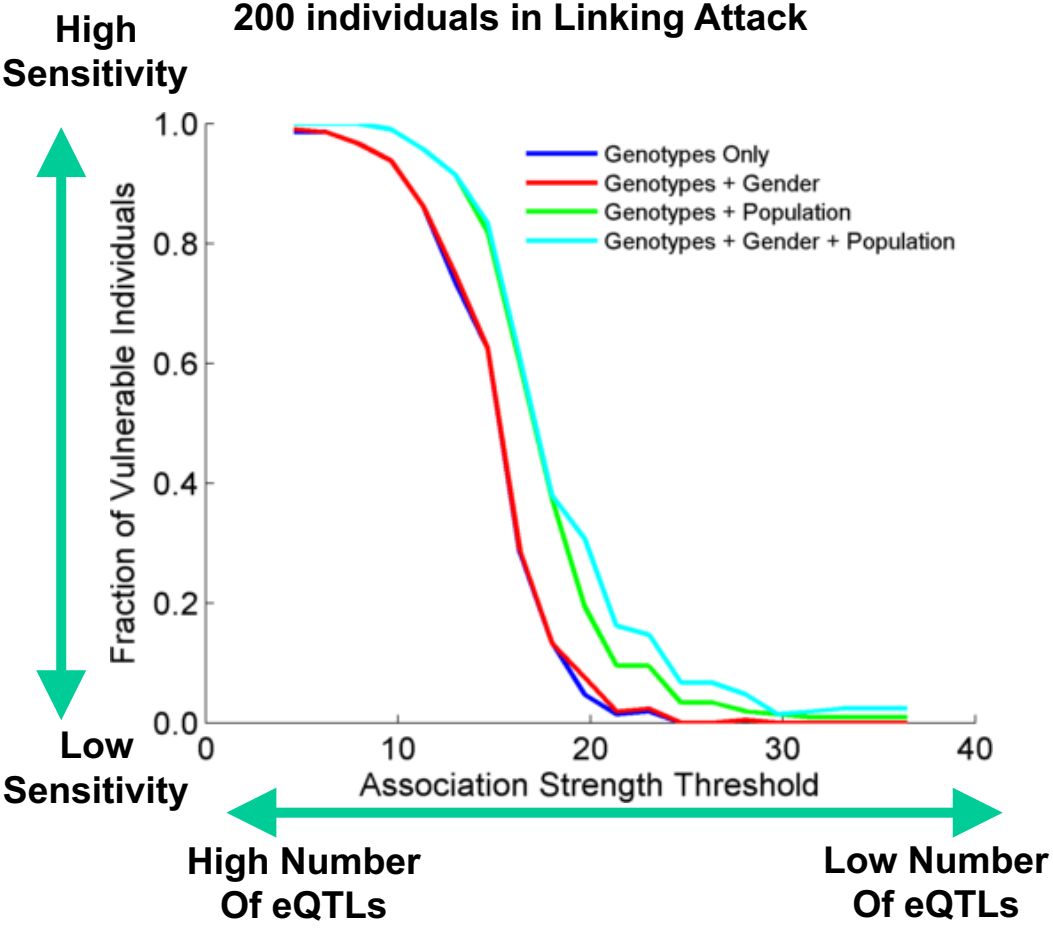
Success in Linking Attack with Extremity based Genotype Prediction

200 individuals eQTL Discovery
200 individuals in Linking Attack



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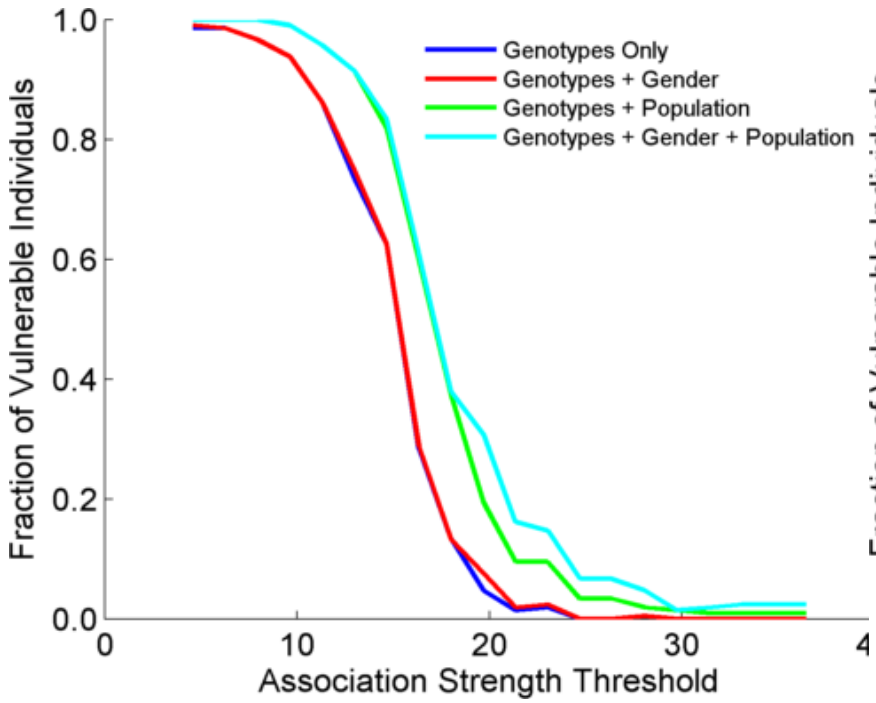
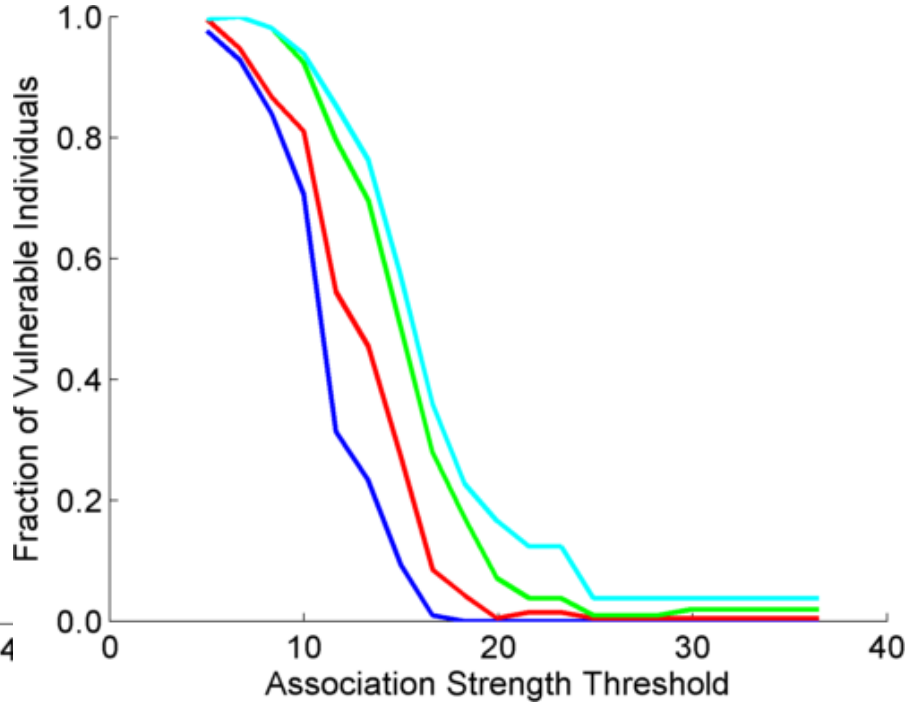


200 individuals eQTL Discovery
100,200 individuals in Linking Attack



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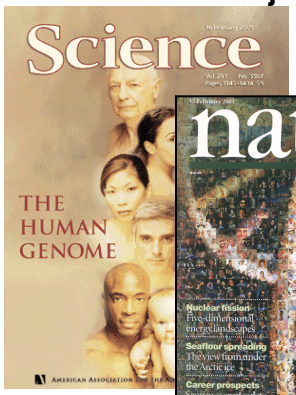
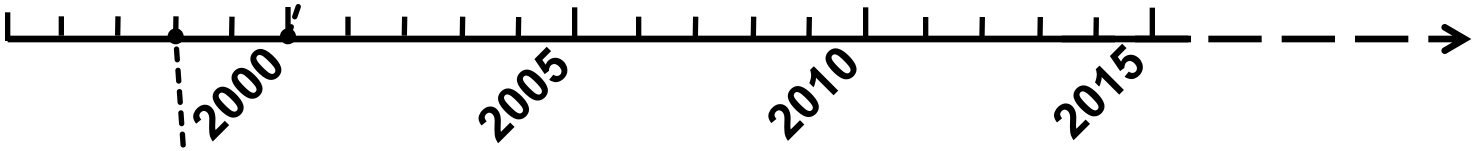
The Human Genome Project



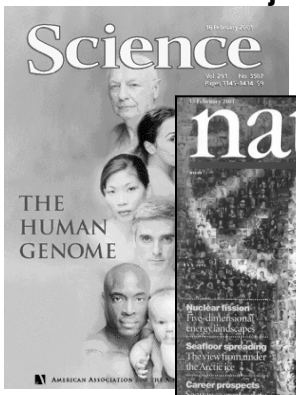


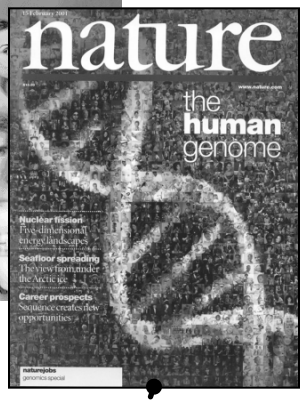
Worm Genome

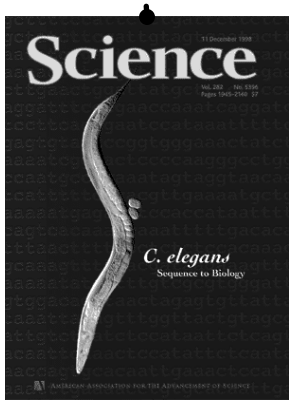
The Human Genome Project

ENCODE Pilot

ENCODE Production







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modENCODE

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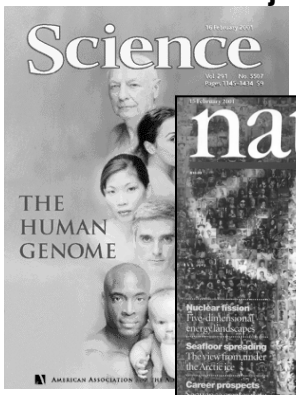
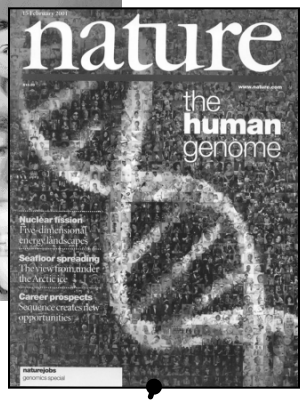
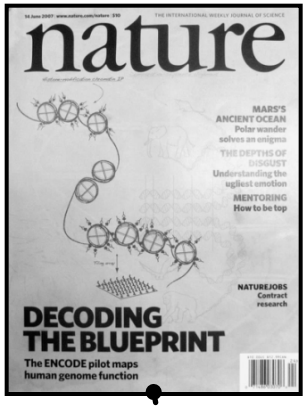
Comparative ENCODE





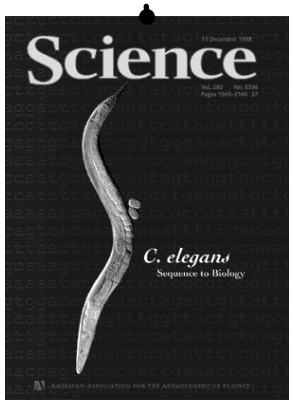


2000

2005

2010

2015



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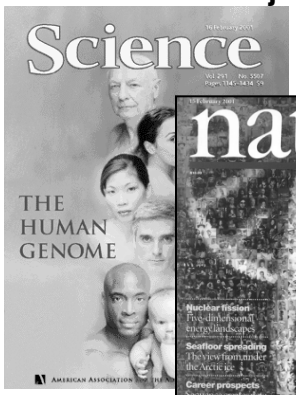

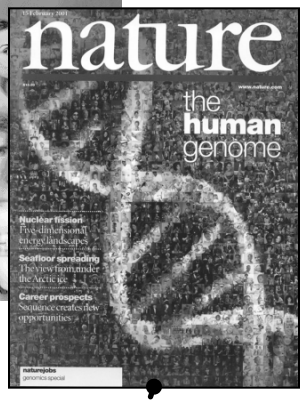

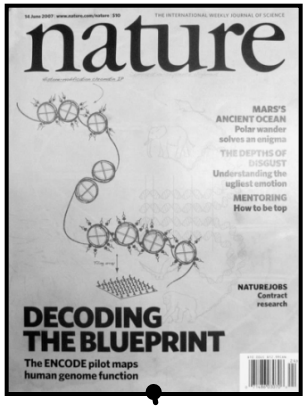

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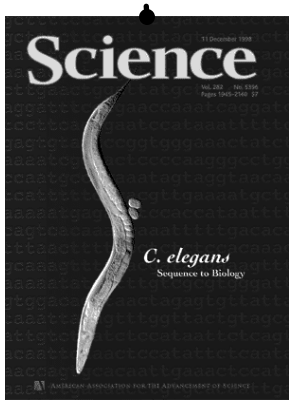

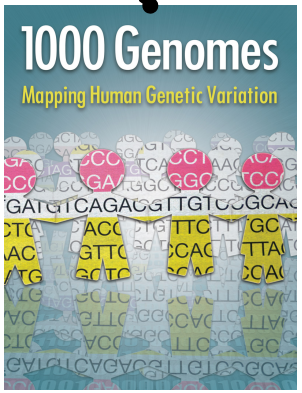

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modENCODE

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1000 Genomes Production

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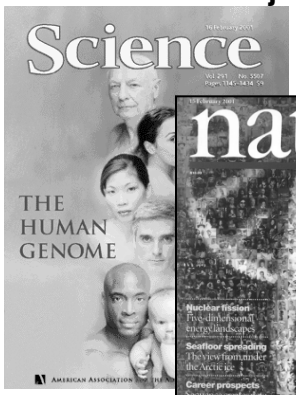
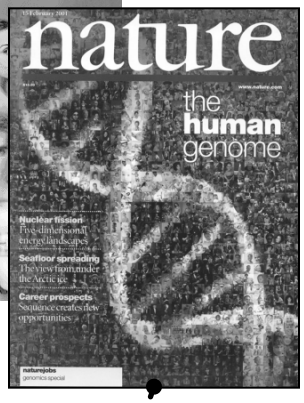
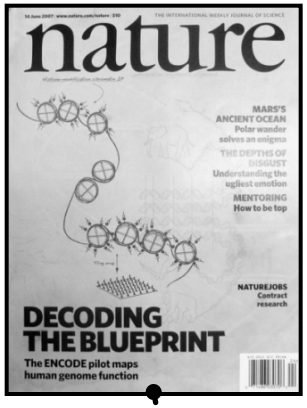
Comparative ENCODE

Epigenome Roadmap







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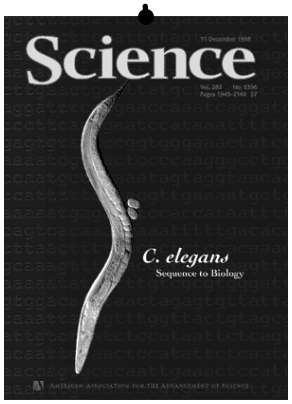

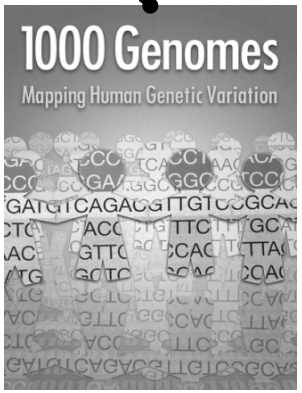

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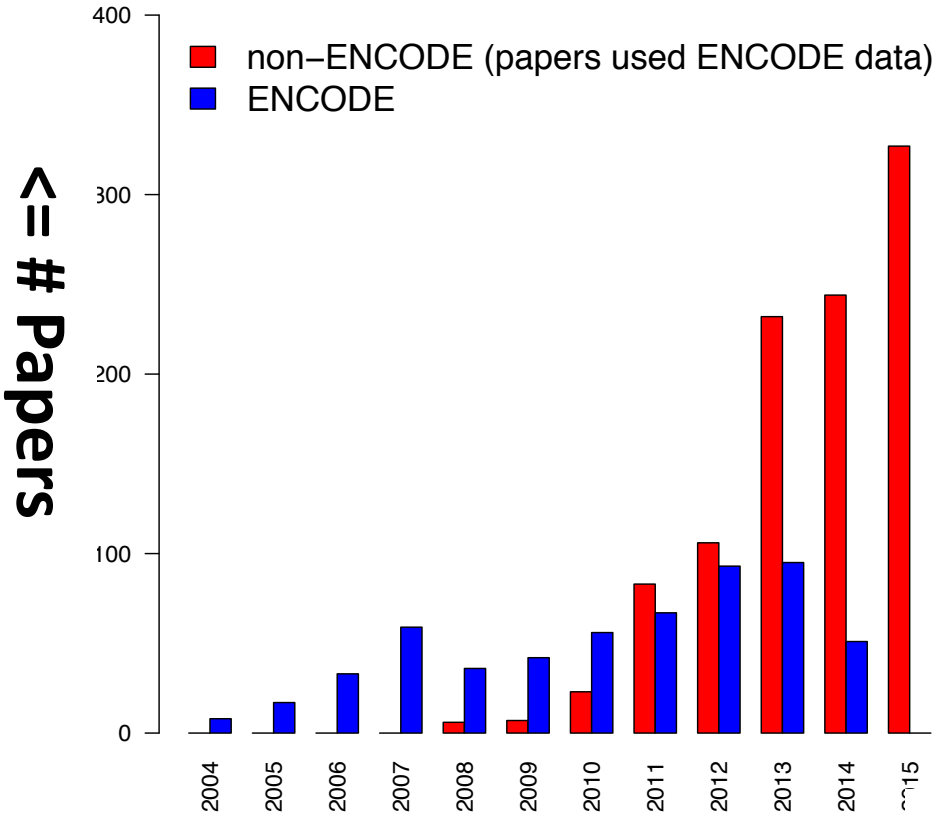
GTEx

With help of M Pazin at NHGRI, identified: 702 community papers that used ENCODE data but were not supported by ENCODE funding &
558 consortium papers supported by ENCODE funding
(https://www.encodeproject.org/search/?type=Publication for up-to-date query)
Then identified 1,786 ENCODE members & 8,263 non-members .

non–ENCODE (papers used ENCODE data) ENCODE



 # Authors

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Yr. ('04 to '15)

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- non-member
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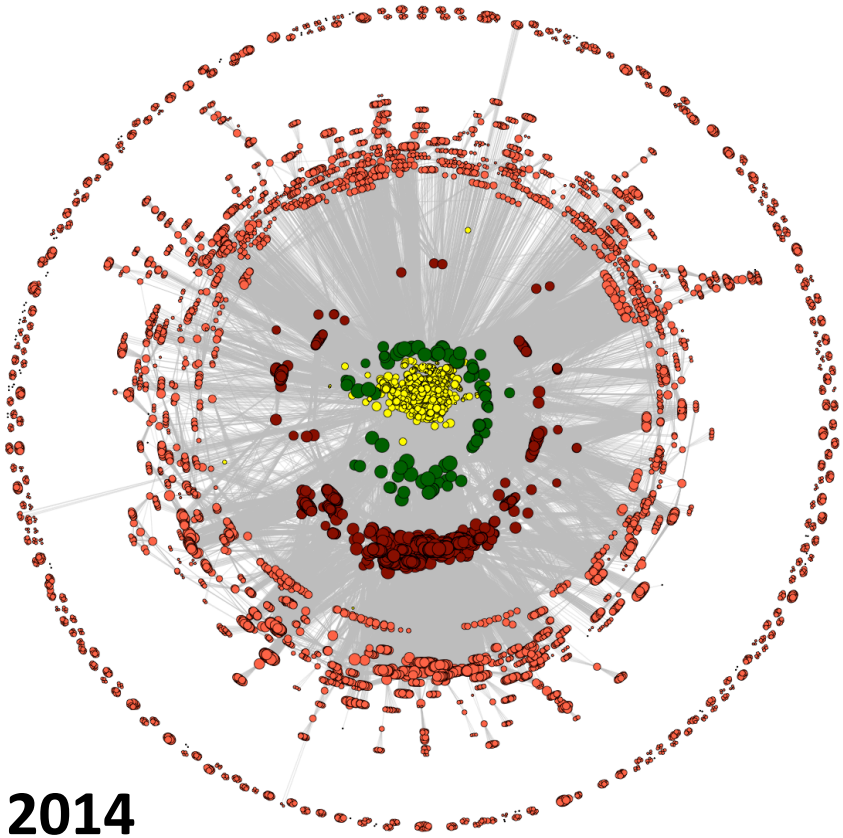
co-authorship



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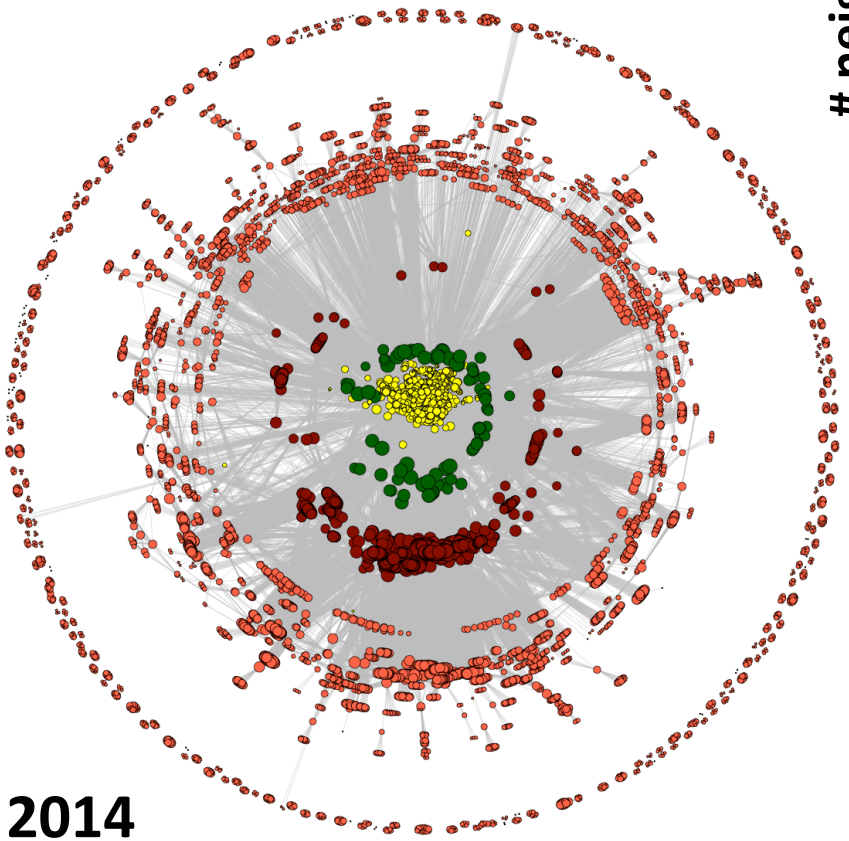

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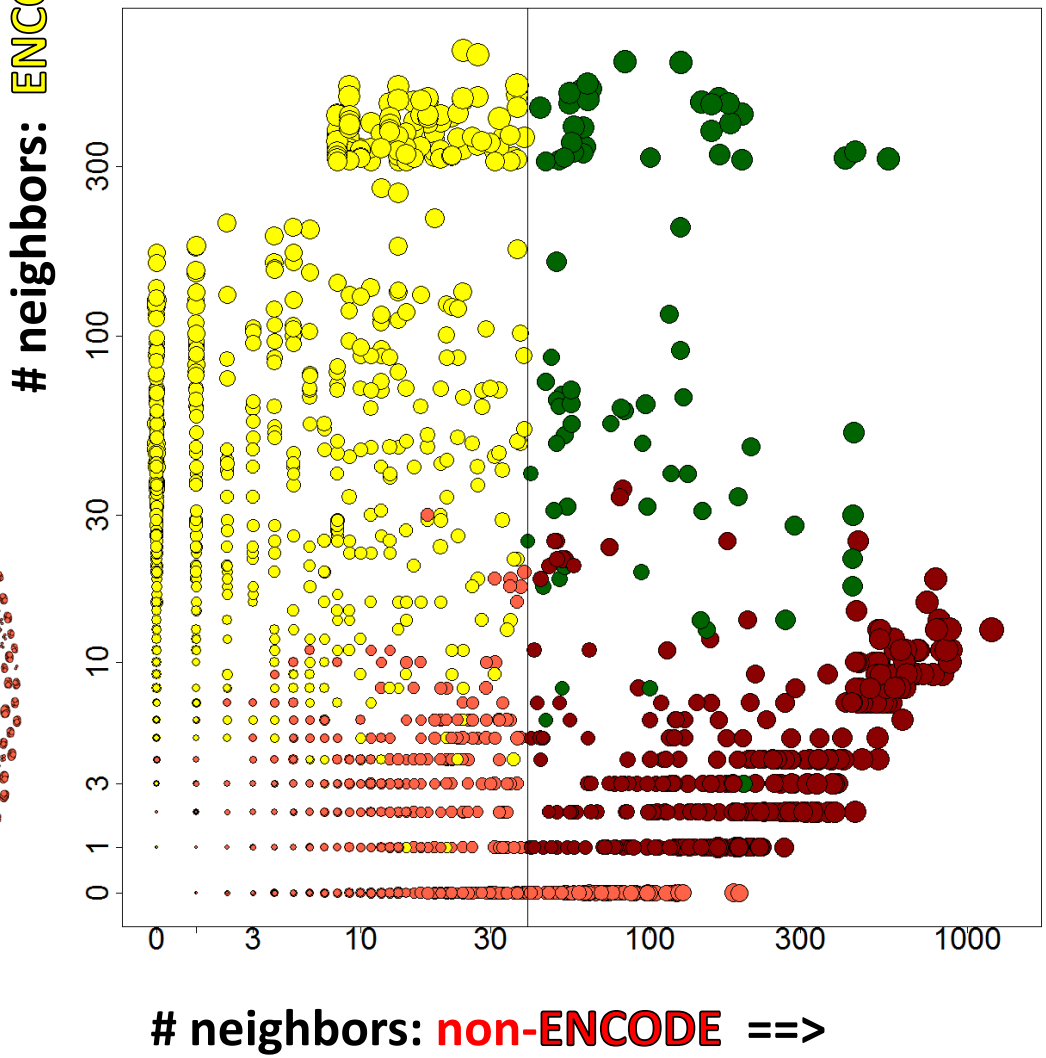

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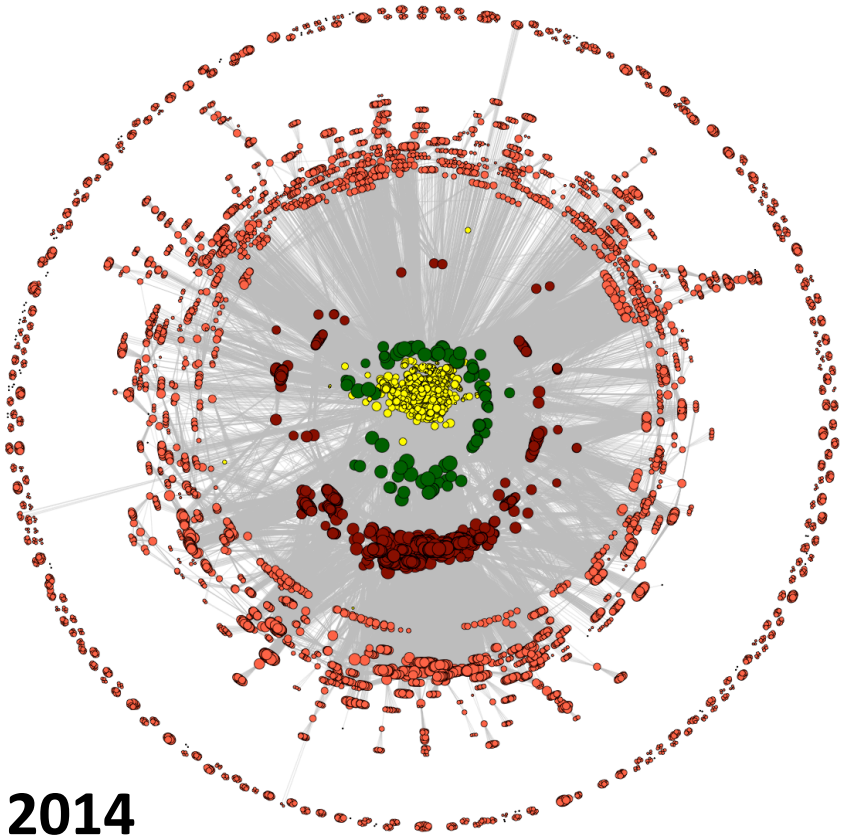

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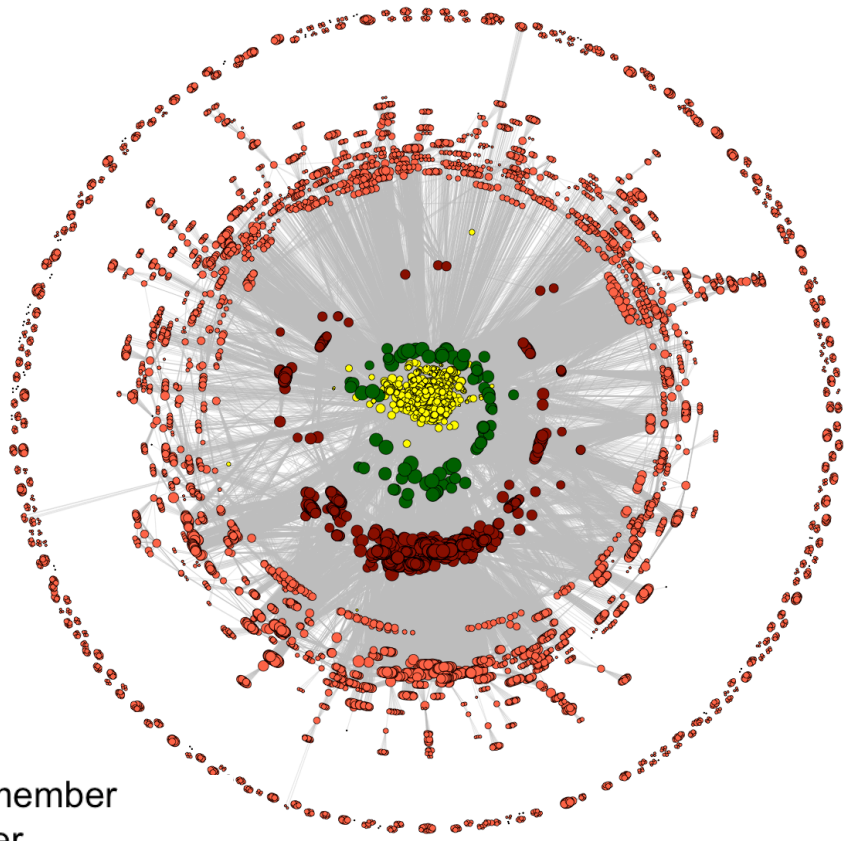

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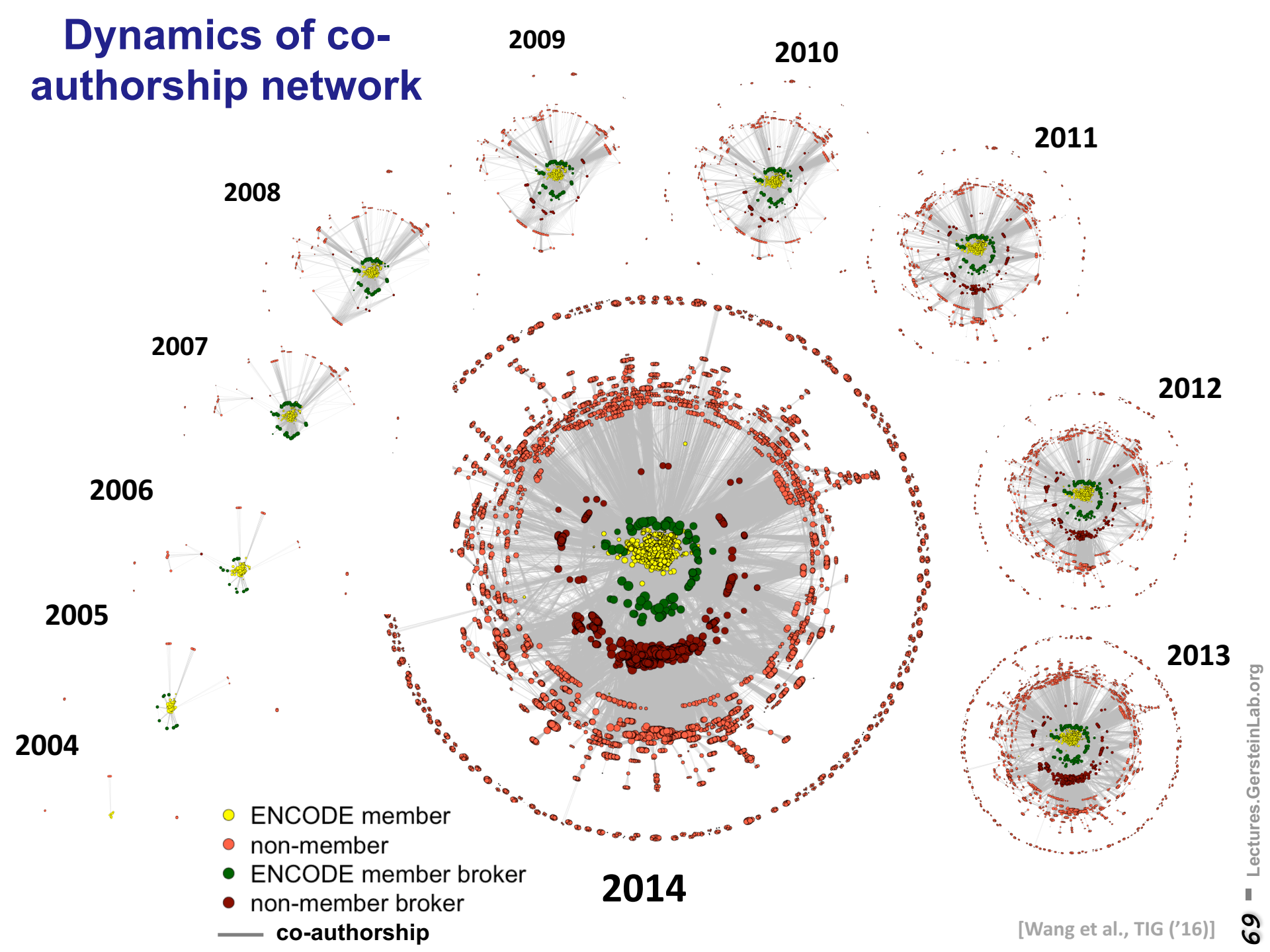

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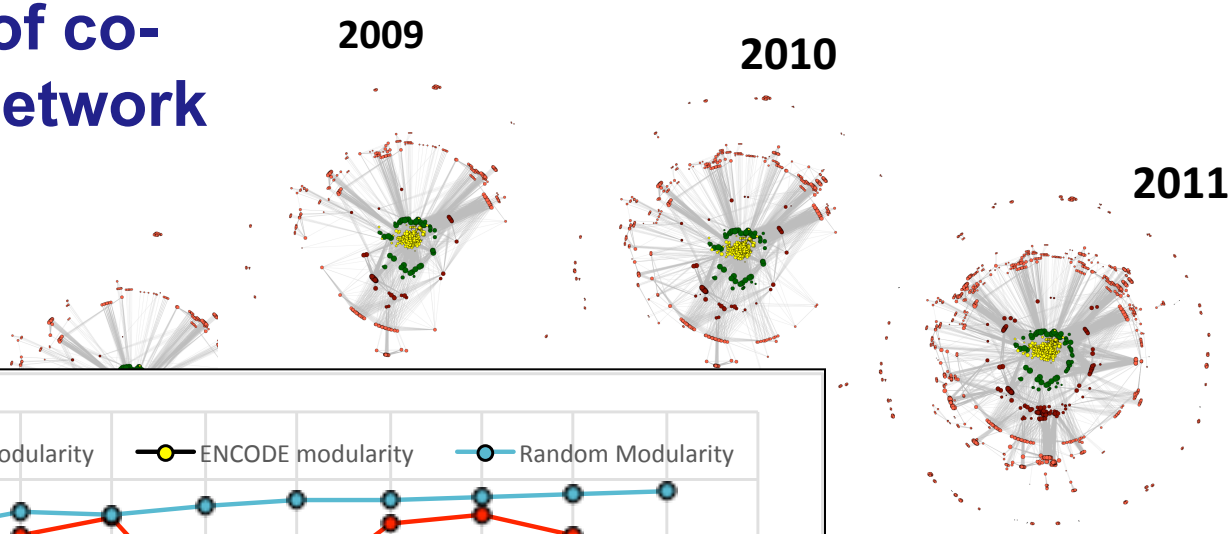

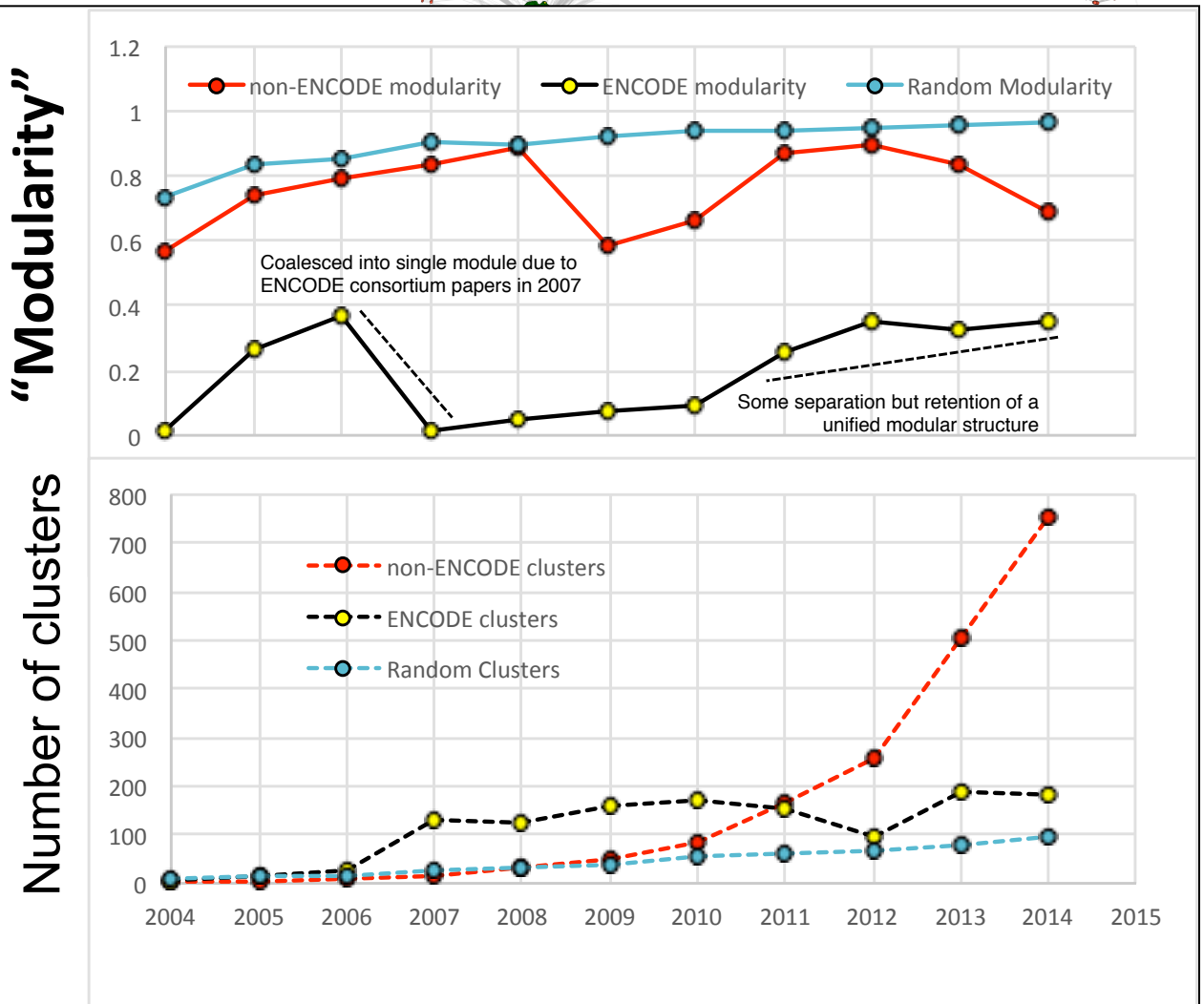

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Steven E. Brenner, Brenton R. Graveley, Susan E. Celniker, Thomas R Gingeras, Robert Waterston

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A **Harmanci**, G Gürsoy, F Navarro

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K **Yan**, D Wang, J Rozowsky, H Zheng, C Cheng

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