



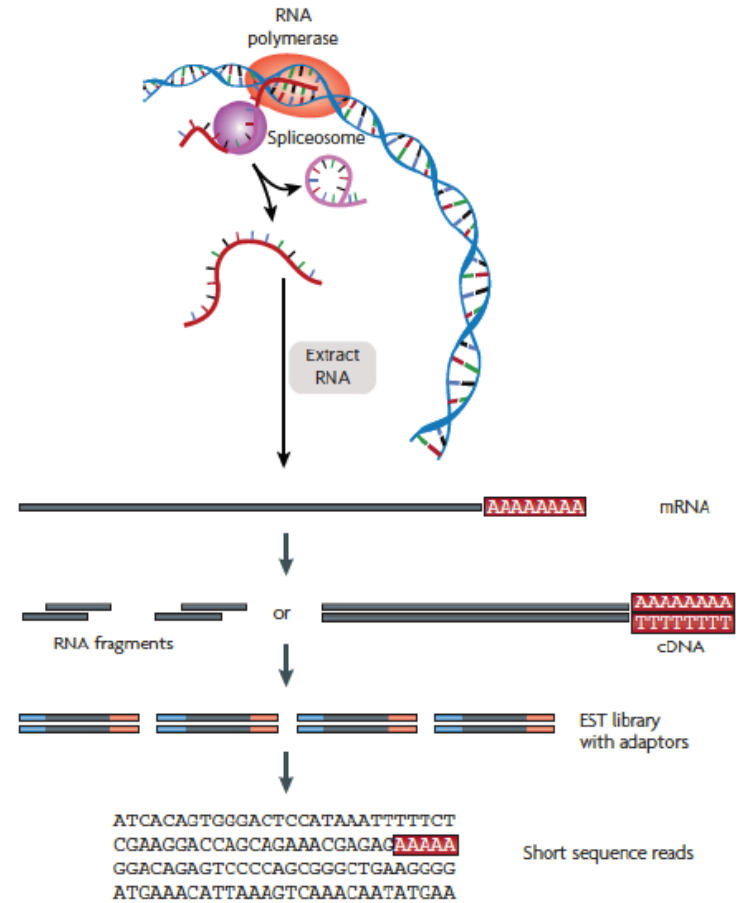
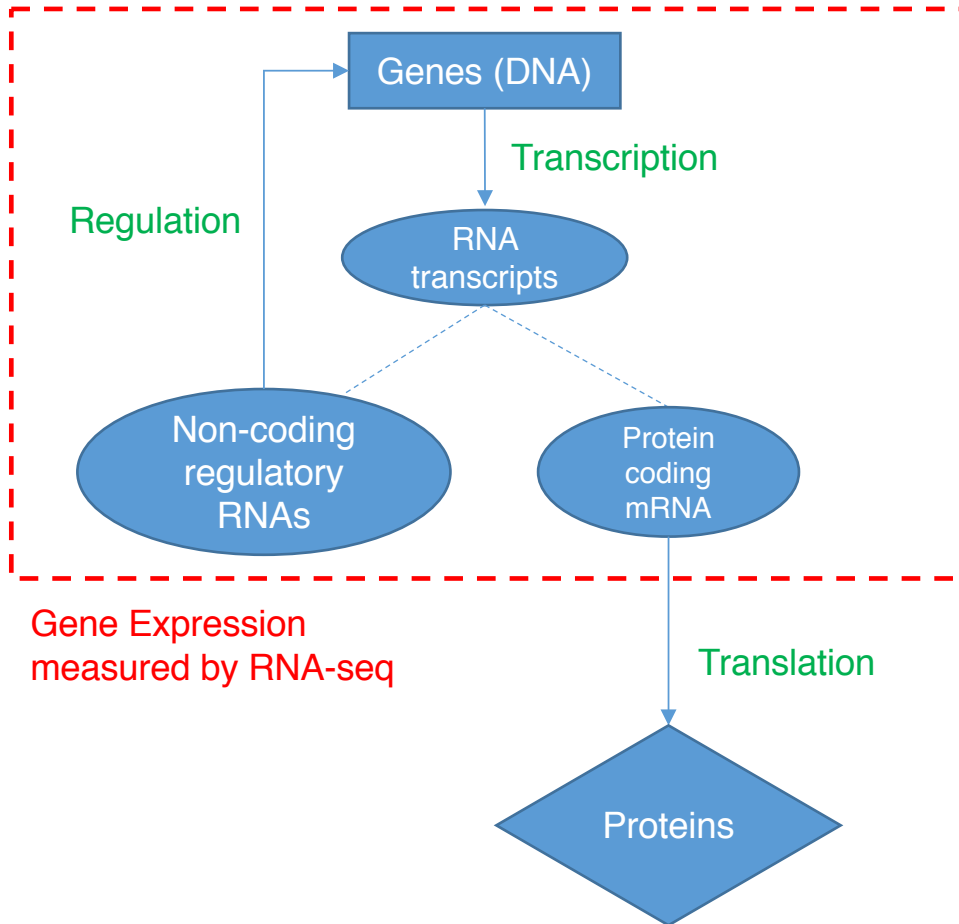
Transcriptome Mining:

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



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

RNA-Seq Overview

```
ATACAAGCAAGTATAAGTTCGTATGCCGTCTT
GGAGGCTGGAGTTGGGGACGTATGCGGCATAG
TACCGATCGAGTCGACTGTAAACGTAGGCATA
ATTCTGACTGGTGTTCATGCTGATGTACTTAAA
```

Fastq sequence files
~5-10 GB

Index-building + Alignment to reference genome

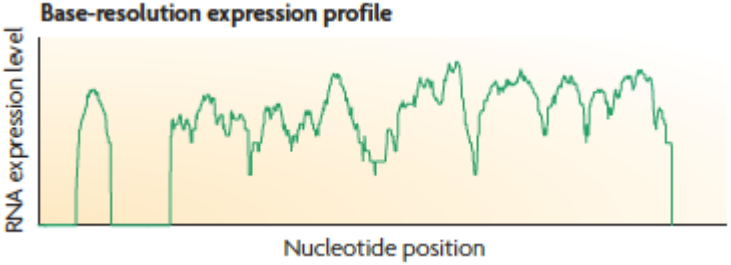
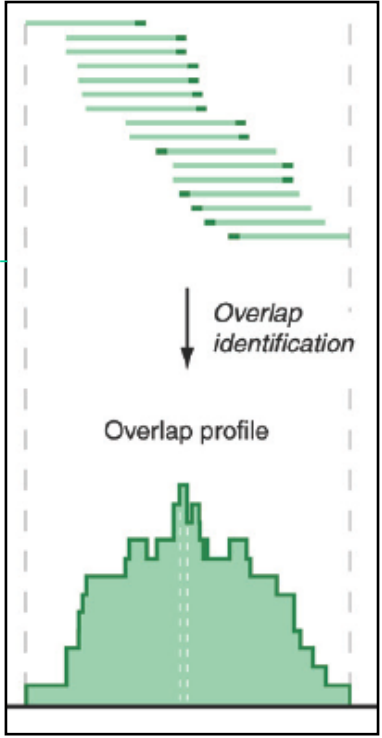
BAM files
~1-2-fold reduction

Conversion to signal track by overlapping reads

BigWig files
~25-fold reduction

Mapping to genes

Gene/Transcript expression matrix
~20-fold reduction



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

Successive steps of Data Reduction

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



Activity Patterns

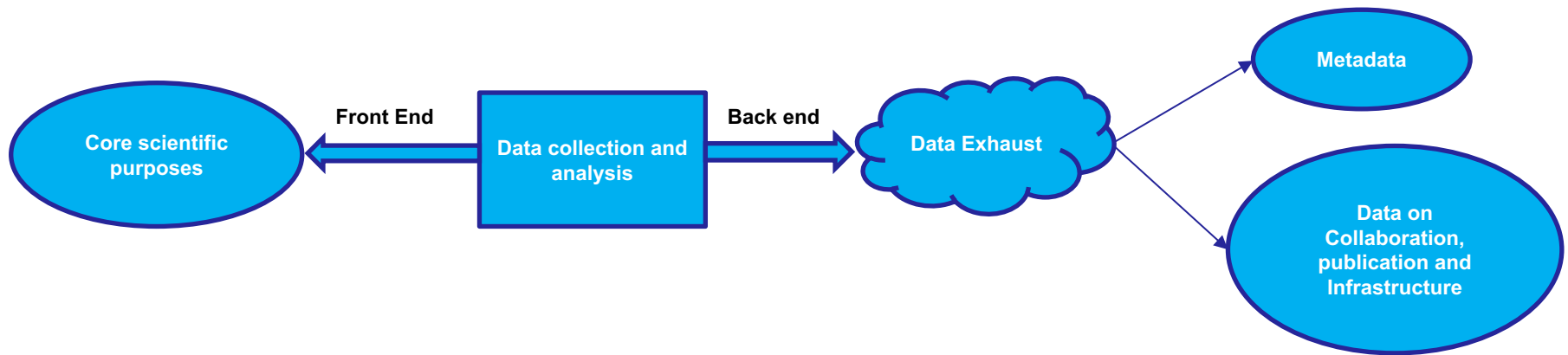
- RNA Seq. gives rise to activity patterns of genes & regions in the genome

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>]

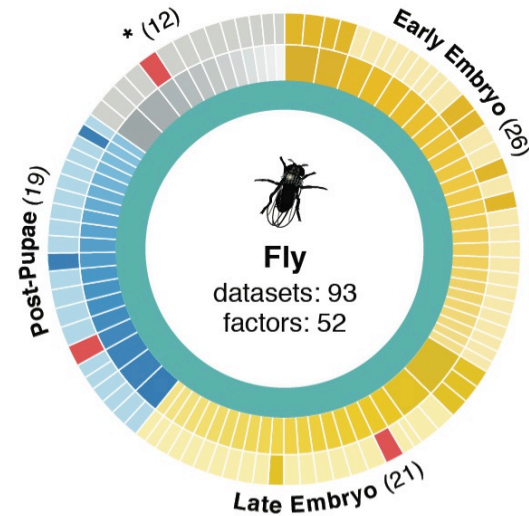
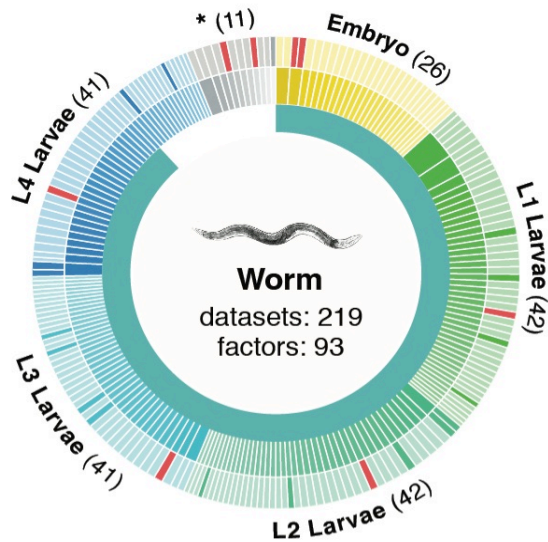
Transcriptome Mining: Tackling core issues related to gene regulation & also analyzing the "data exhaust" associated with this activity

- **[Core-1] Expression Clustering, Cross-species**
 - Comparative ENCODE – Lots of worm-fly-human matched data & developmental timecourses
 - Optimization gives 16 conserved co-expression modules, 12 w/ hourglass
- **[Core-2] State Space Models of Gene Expression**
 - Using dimensionality reduction to help determine internal & external drivers; Decoupling expression changes into those from conserved vs species-specific genes
 - Conserved genes have similar canonical patterns (iPDPs) in contrast to species specific ones (Ex of ribosomal v signaling genes)
- **[Core-3] Logic Gates Modeling**
 - Preponderance of OR gates in cancer v. cell-cycle (esp. for MYC)
- **[Exhaust-1] Genomic Privacy & RNA-seq**
 - The dilemma: The genome as fundamental, inherited info that's very private v need for large-scale mining for med. research
 - 2-sided nature of RNA-seq presents a particularly tricky privacy issue
 - Using file formats to remove obvious variants
 - Quantifying & removing further variant info from expression levels + eQTLs using ICI & predictability
 - 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

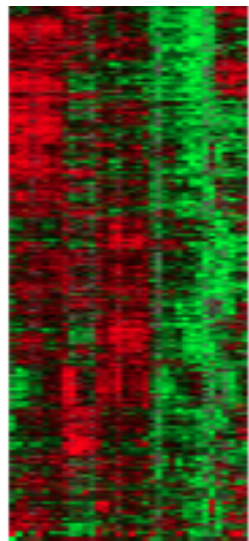


Comparative ENCODE Functional Genomics Resource
(EncodeProject.org/comparative)

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

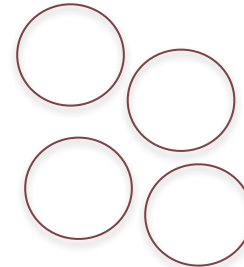
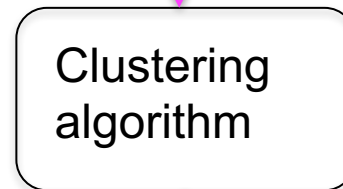
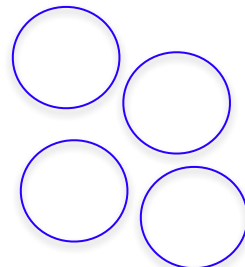
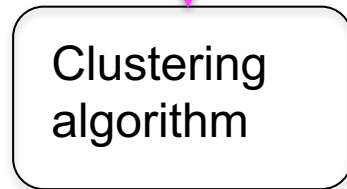
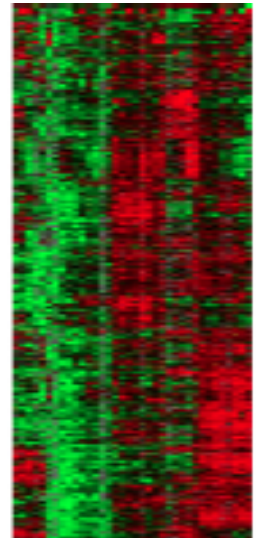
- Broad sampling of conditions across transcriptomes for human, worm & fly
 - embryo & ES cells
 - developmental time course (worm-fly)
- In total: ~3000 datasets (~130B reads)

Expression clustering: revisiting an ancient problem



Species A

Species B

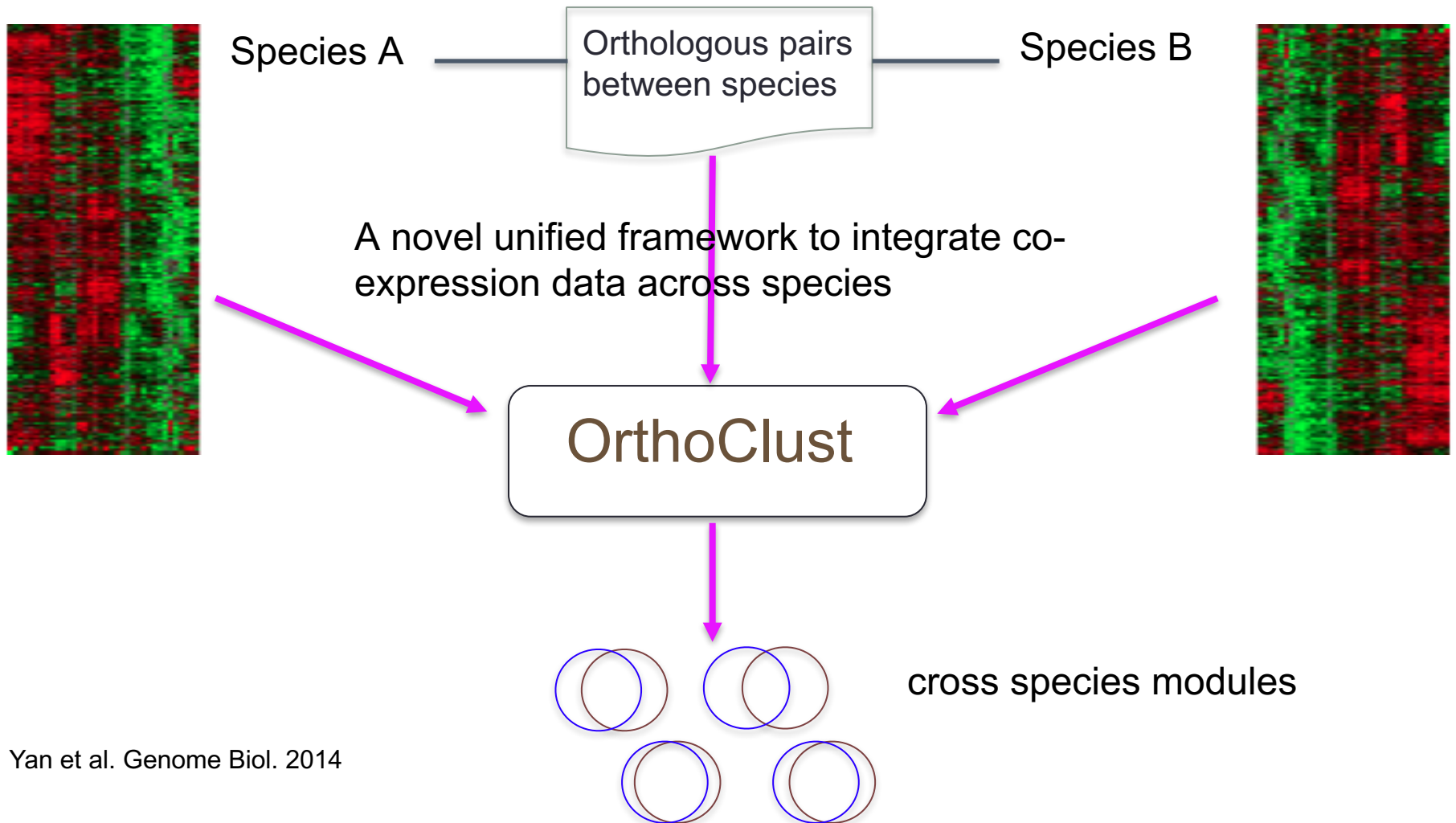


co-expressed genes
responsible for the same
function in a species

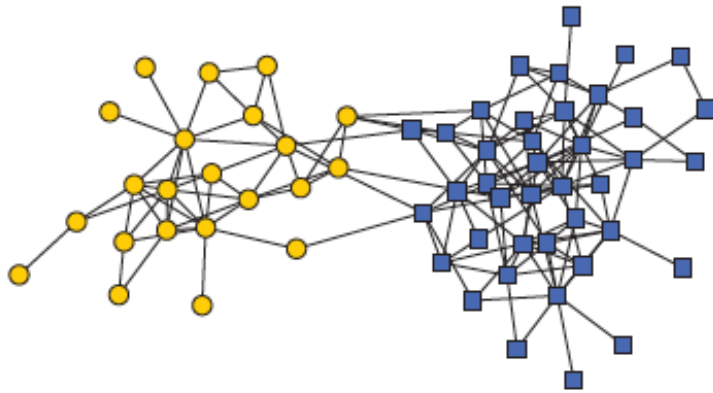
two independent sets
of modules

- 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

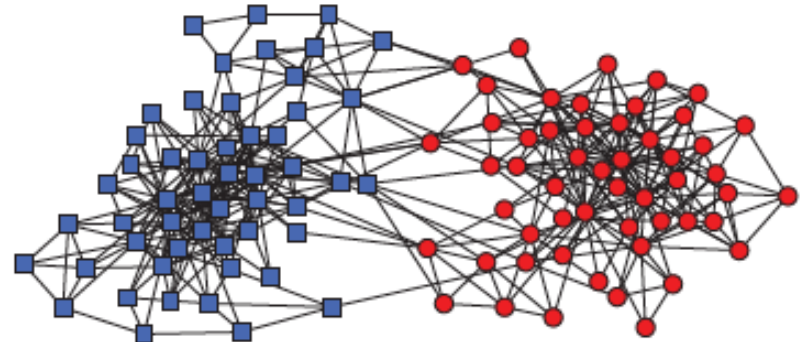
Expression clustering: revisiting an ancient problem



Network modularity



Dolphin social network



Political books

Newman *Phy. Rev. E* 2013

adjacency matrix

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

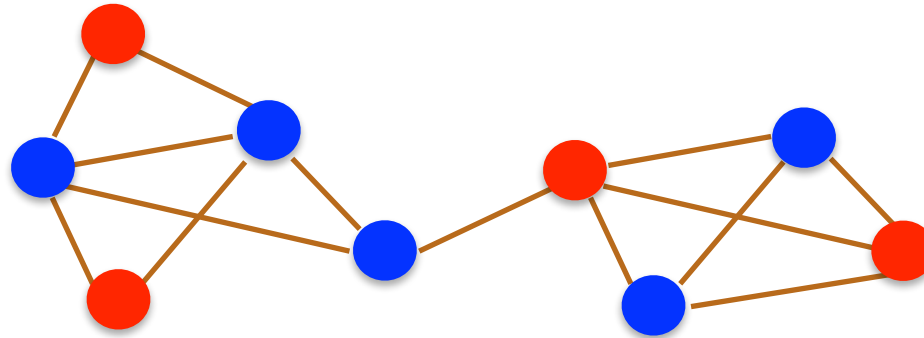
number of edges

degree of node i

whether or not i, j are in the same module

expected number of edges between i and j

Network modularity

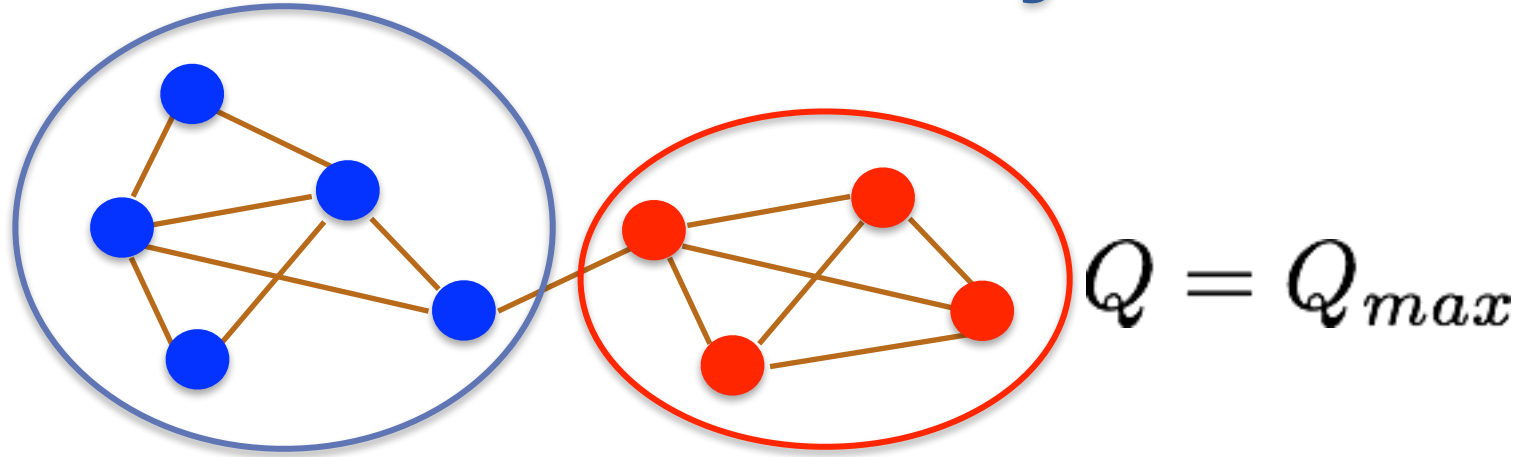


$$Q \approx 0$$

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

adjacency matrix W_{ij}
 degree of node i k_i
 number of edges $2m$
 expected number of edges between i and j $\frac{k_i k_j}{2m}$
 whether or not i, j are in the same module $\delta_{\sigma_i \sigma_j}$

Network modularity

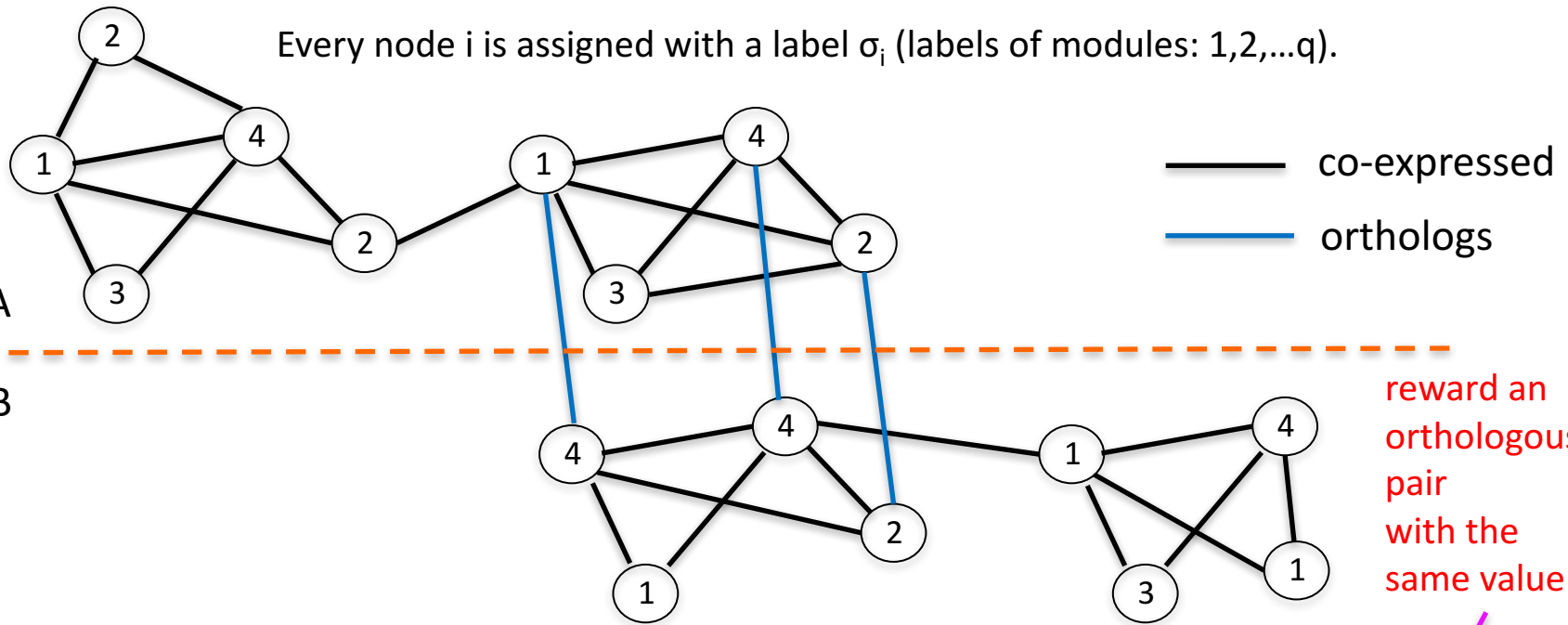


Optimization
problem
for sim.
annealing

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

adjacency matrix W_{ij}
 degree of node i k_i
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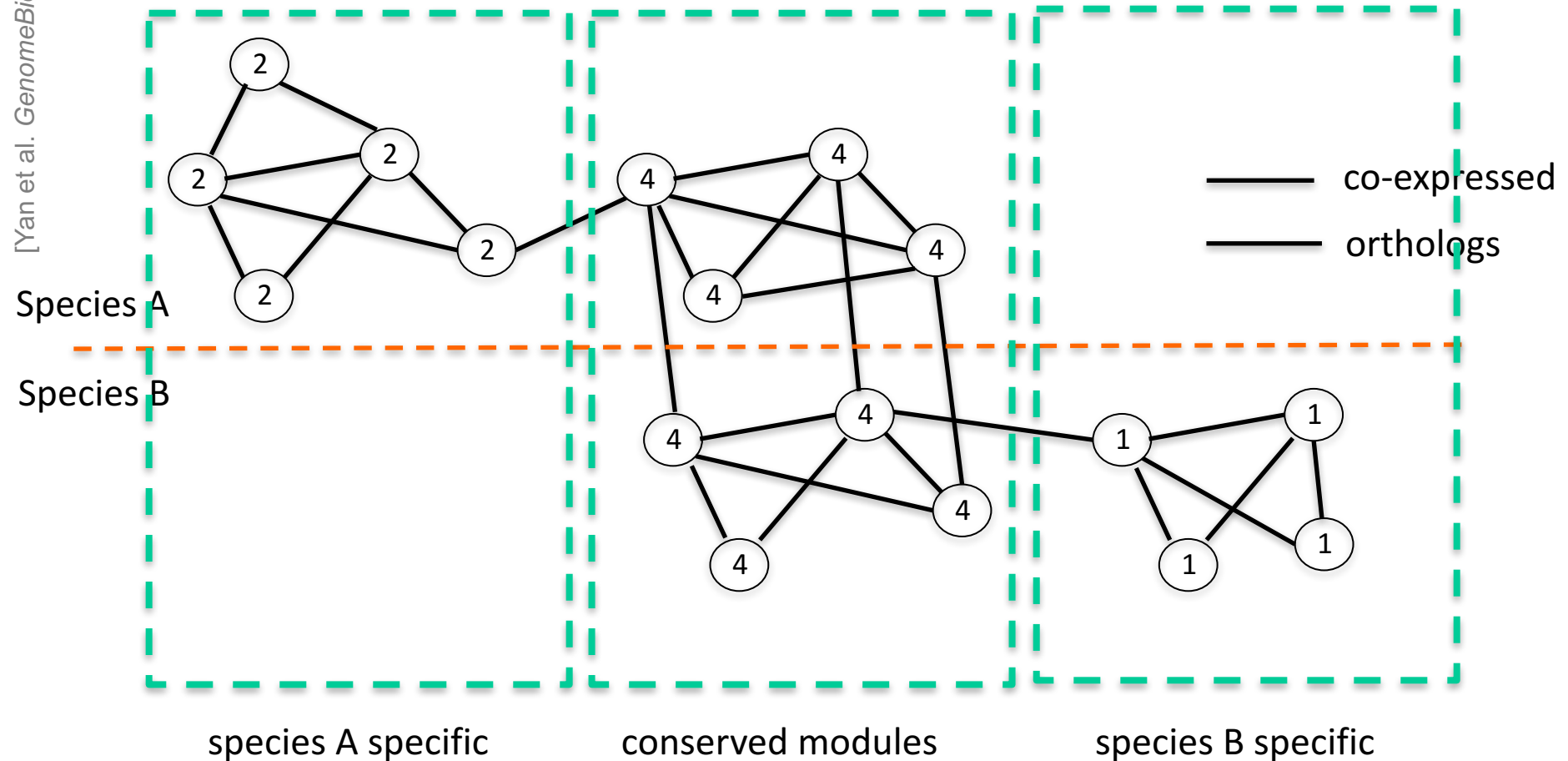
A toy example [orthoclust]



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

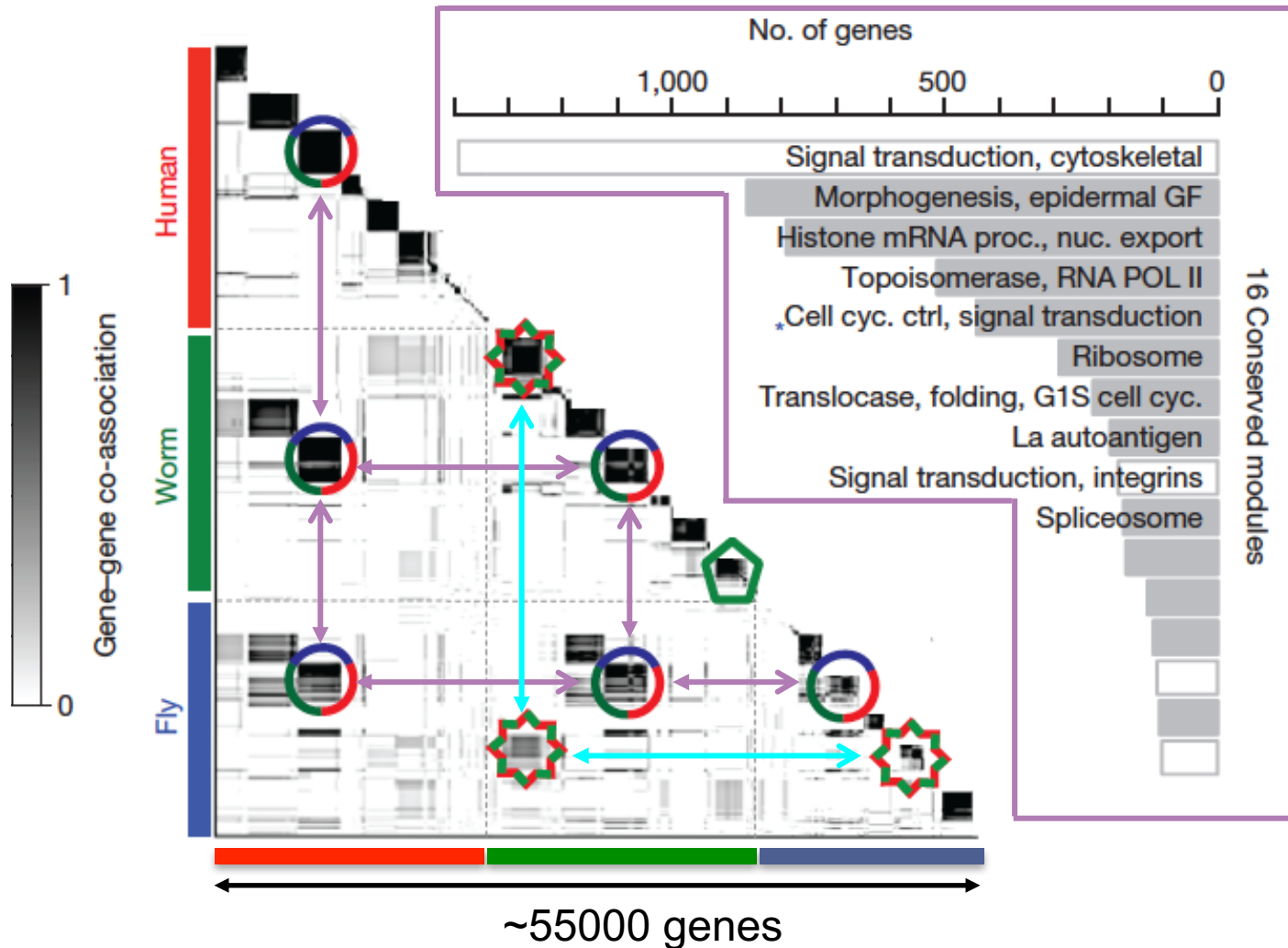
Favorableness = "Modularity" in species A + "Modularity" in species B + consistency betw. A & B

A toy example [orthoclust]

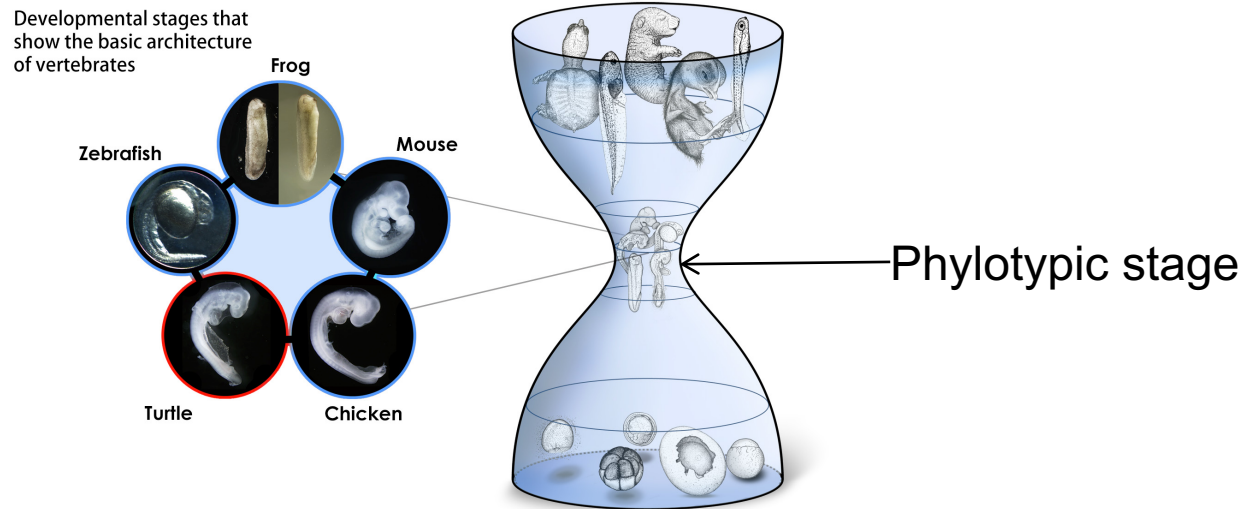


Use Potts model (generalized Ising model) to simultaneously cluster co-expressed genes within an organism as well as orthologs shared between organisms. Here, the ground state configuration correspond to three modules: 1, 2, 4.

Application for more than 2



Conserved modules exhibit canonical hourglass behavior



Illustrations courtesy Naoki Irie

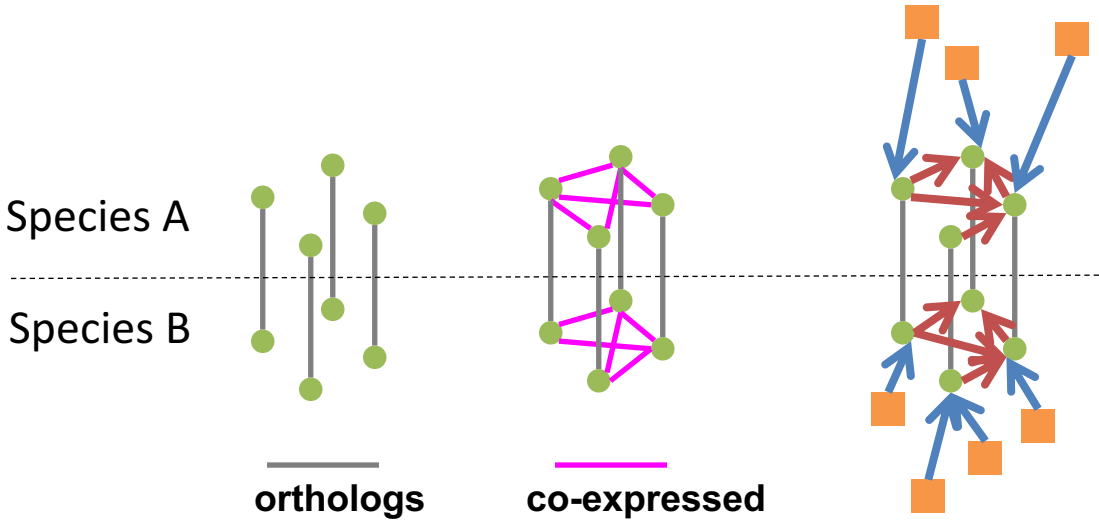
Canonical Inter-organism Behavior

- “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**

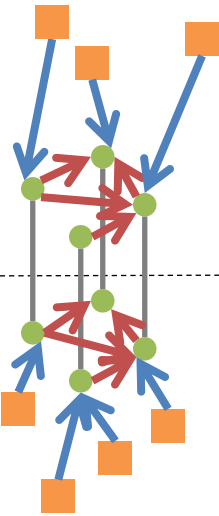
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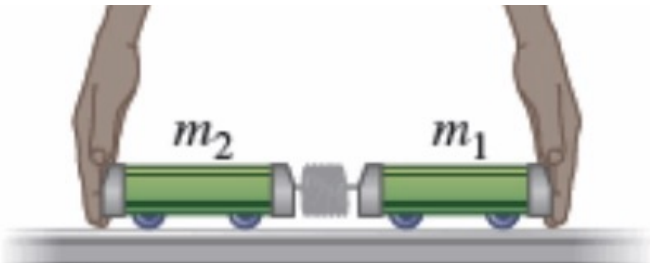
Is gene regulation among orthologs conserved?



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



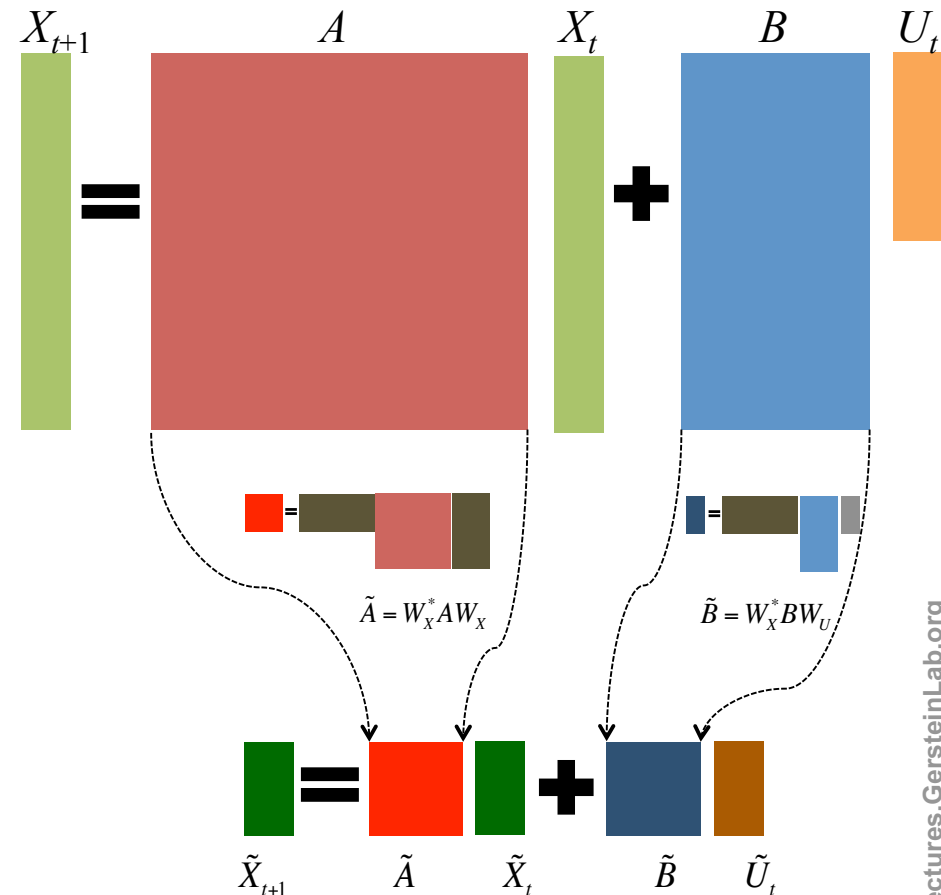
With External force



Purely Internal Dynamics

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



State-space model for internal and external gene regulatory networks

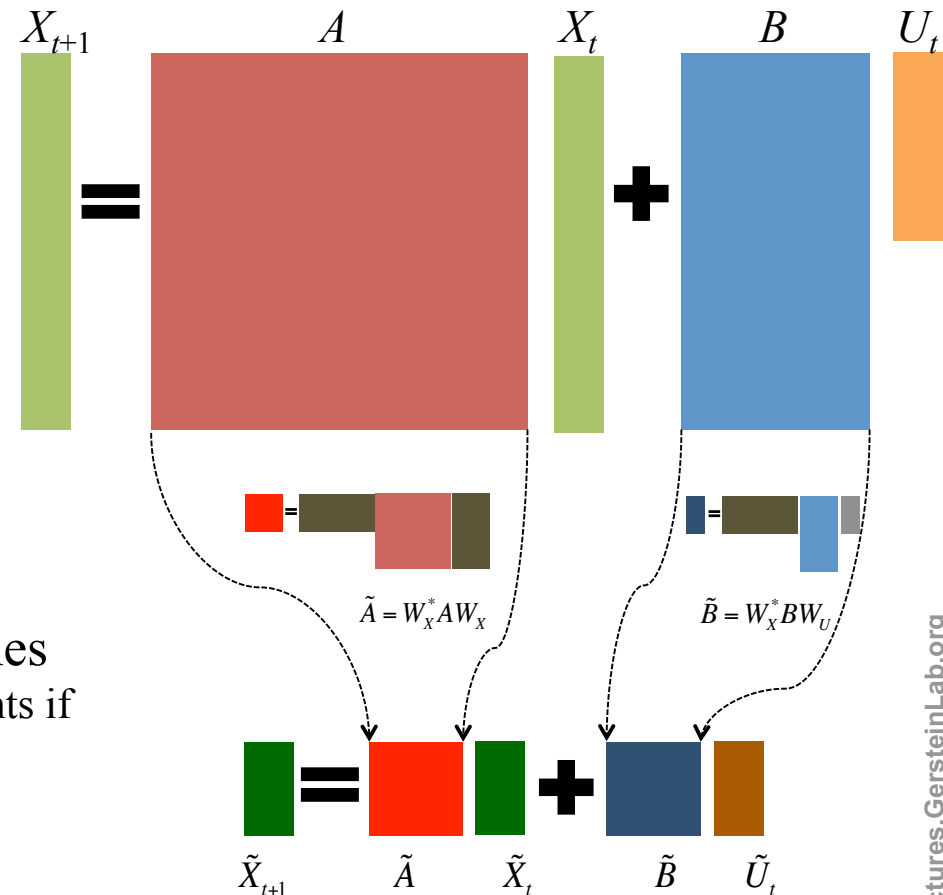
Not enough data to estimate state space model for genes
(e.g., 25 time points per gene to estimate 4 million elements of A or B for 2000 genes)



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)



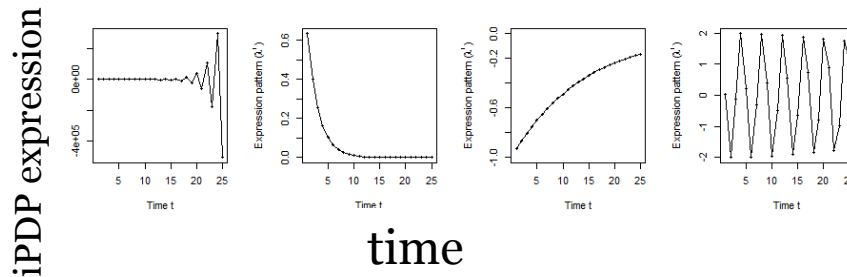
Canonical temporal expression trajectories from effective state space model

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

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

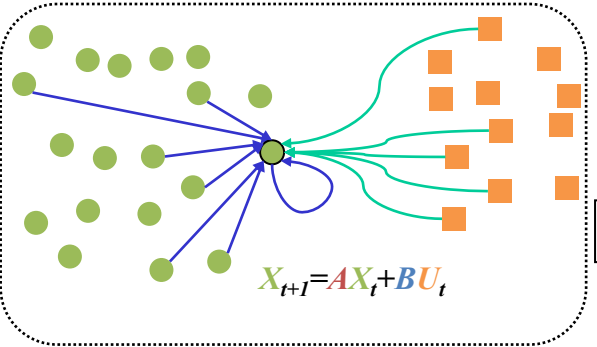
p^{th} internal principal dynamic pattern (iPDP): $[\lambda_p^1, \lambda_p^2, \dots, \lambda_p^T]$, where λ_p is p^{th} eigenvalue of \tilde{A} .

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

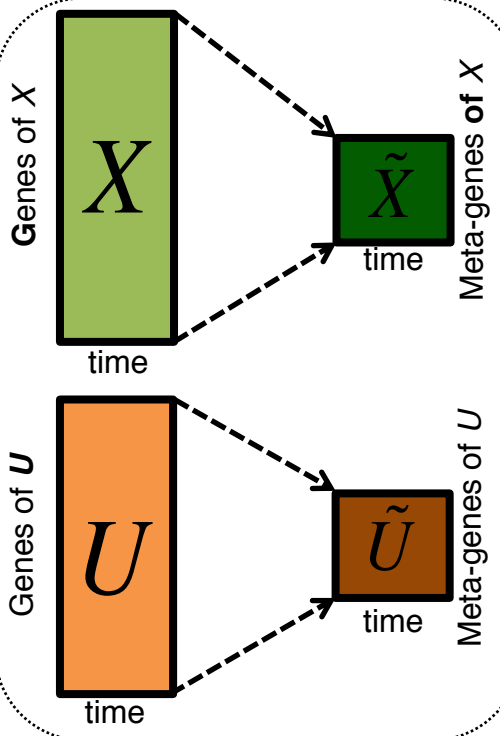


Flowchart

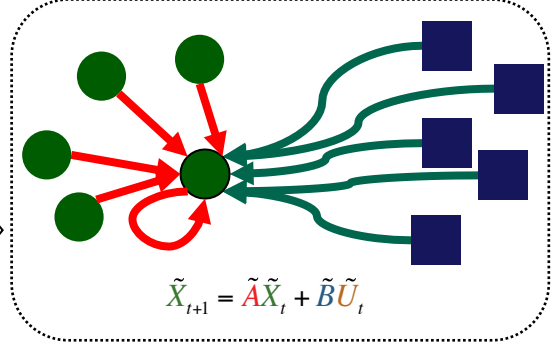
A. Gene state-space model



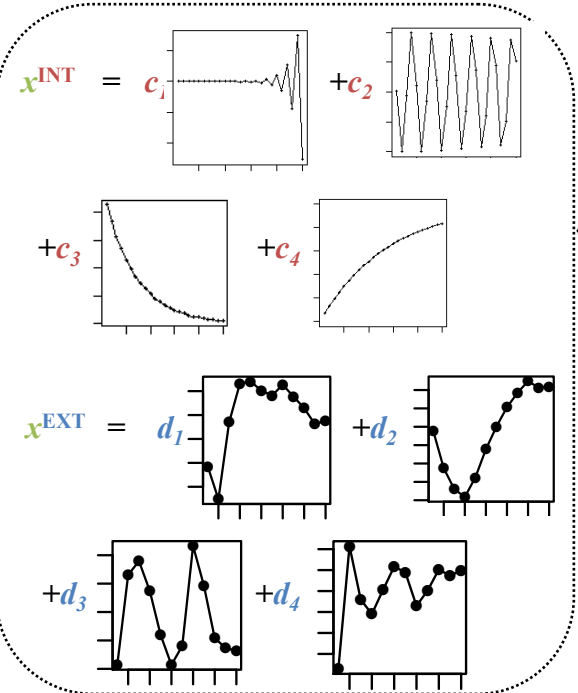
B. Dimensionality Reduction



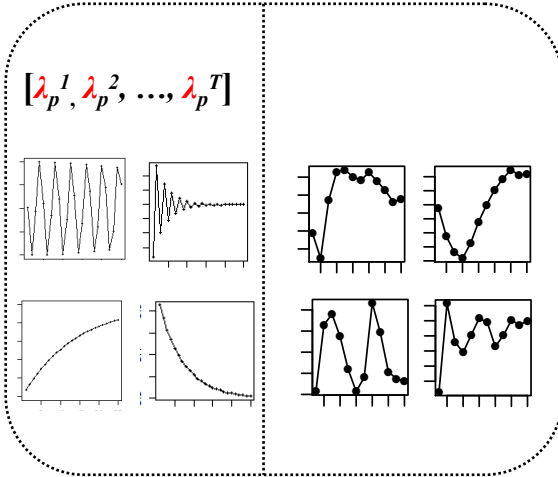
C. Meta-gene state-space model



E. Gene's internal (INT) and external (EXT) driven expression dynamics composed of PDPs

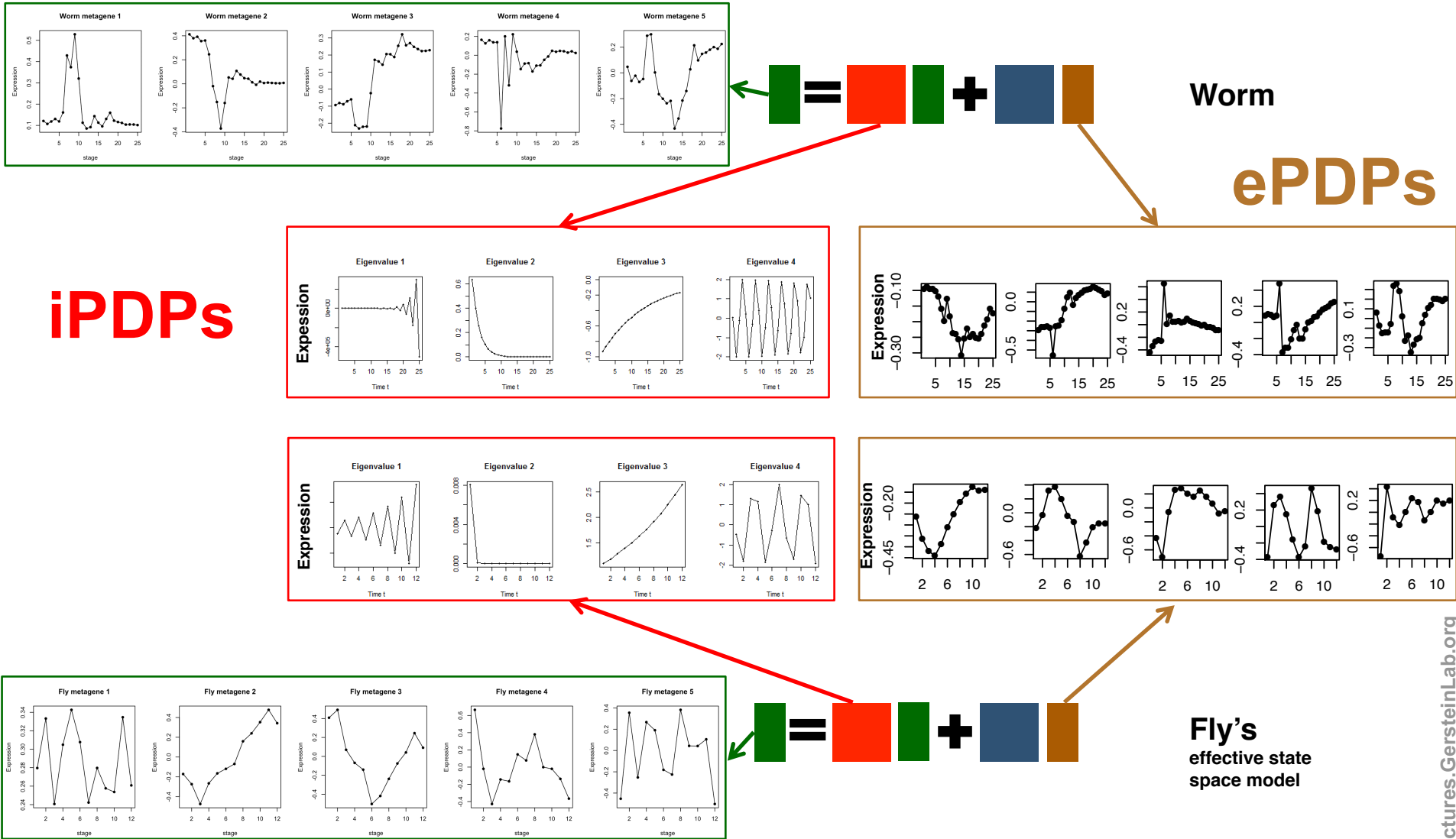


D. Internal/External Principal Dynamic Patterns (PDPs)



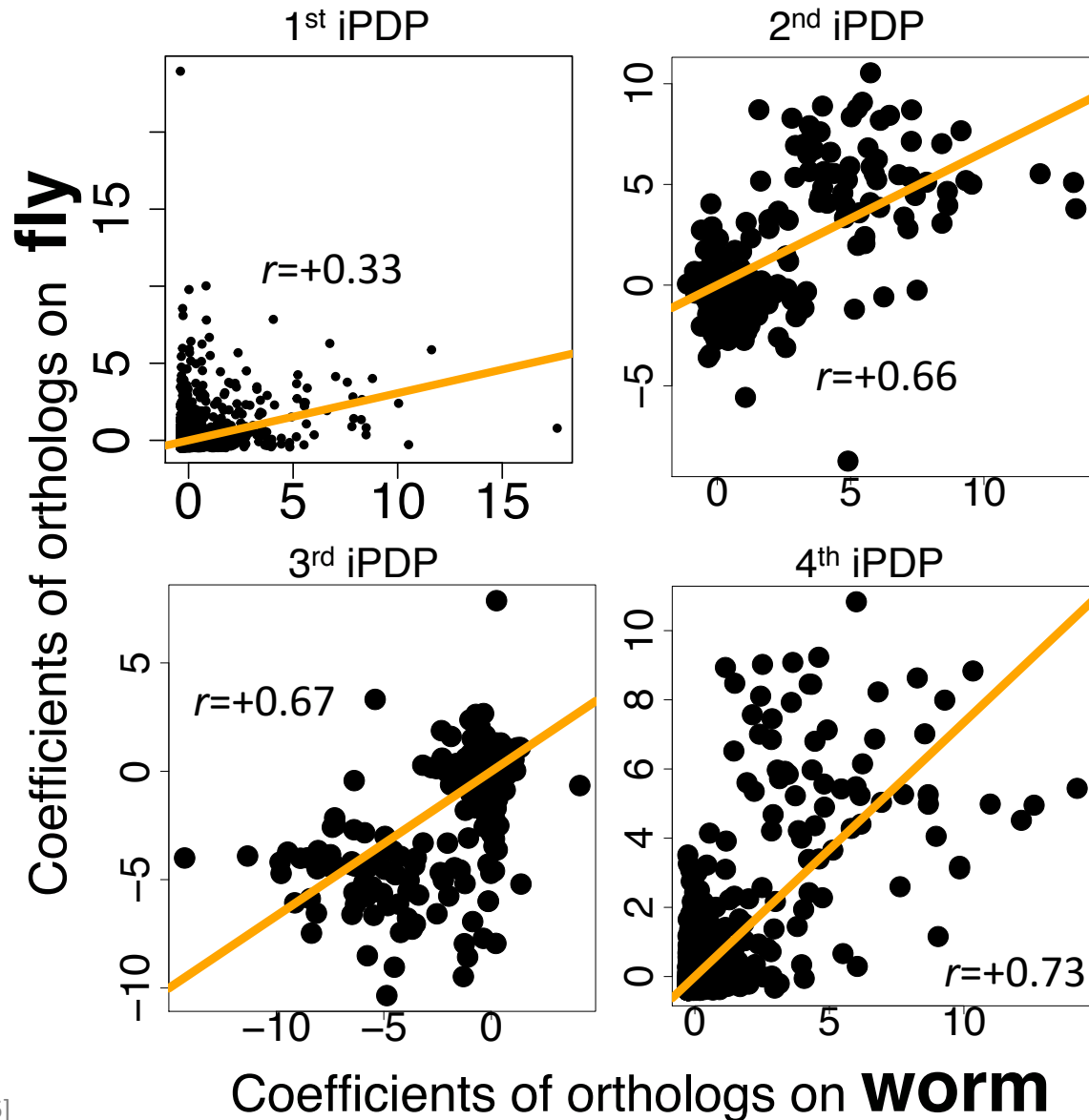
- ← Internal regulation among internal genes/meta-genes by A/\tilde{A}
- ← External regulation from external genes/meta-genes to internal genes/meta-genes in Group X by B/\tilde{B}
- Internal genes/meta-genes
- External genes/meta-genes

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

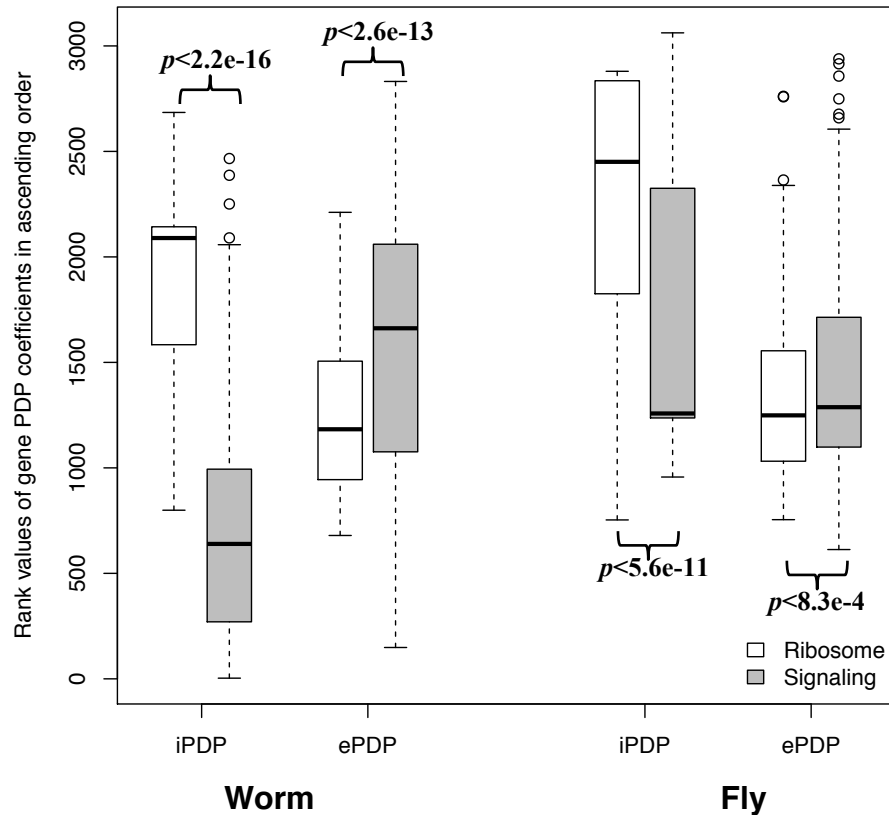


Meta-genes

Orthologs have correlated iPDP coefficients



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

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.

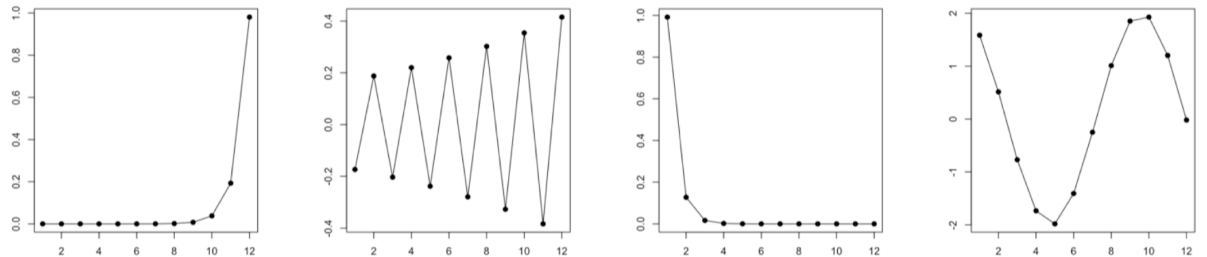
- INT = conserved human genes

- ~1100 H-F-W orthologs
- follow normal cell cycle

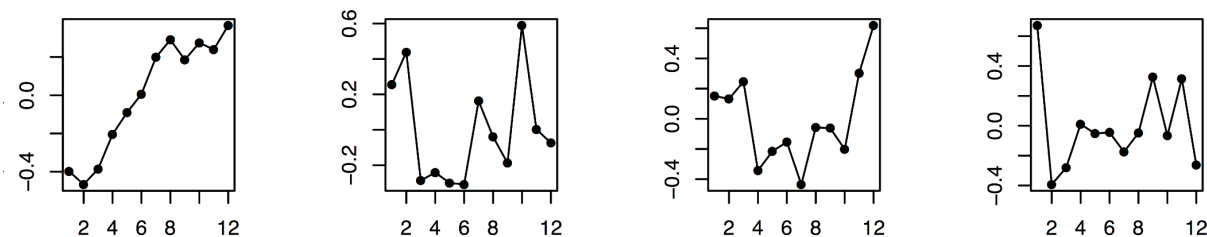
- EXT = human spec TFs

- diff from above
- perhaps responding to stimulation

iPDPs



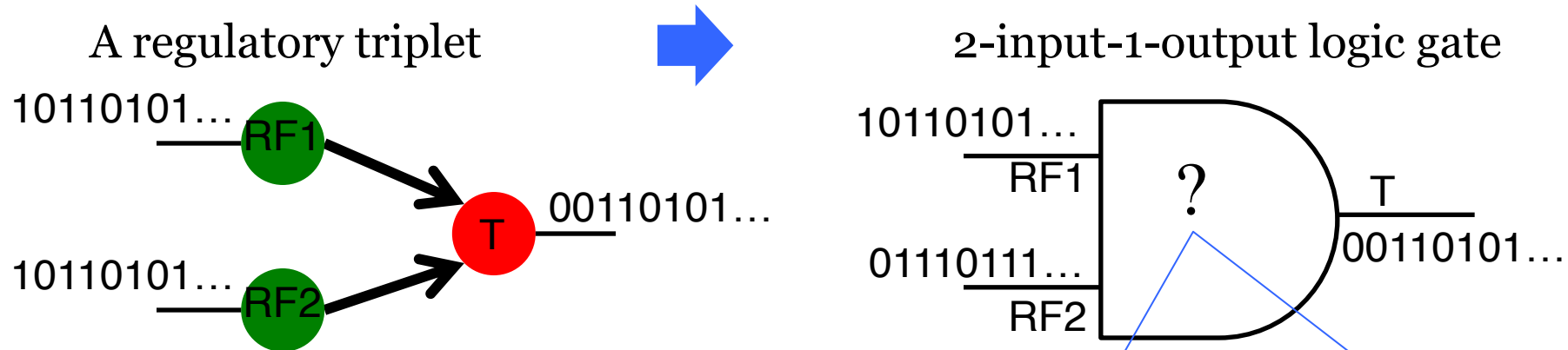
ePDPs



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Modeling cooperativity between TFs to target gene using logic gates



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

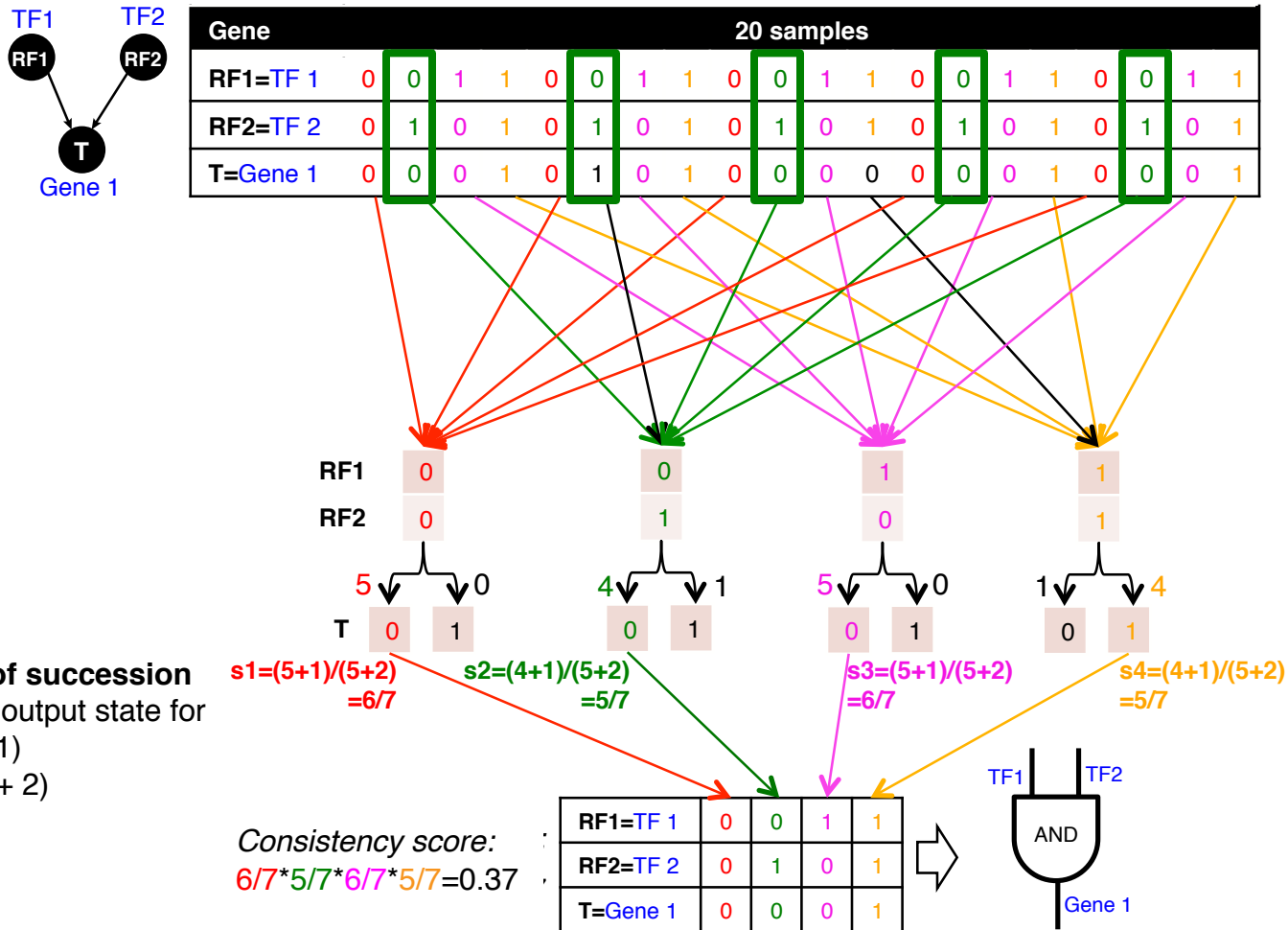
Input type (RF1, RF2)	RF1	0	0	1	1	} Binarized expression
	RF2	0	1	0	1	
Output	T	X	X	X	X	

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

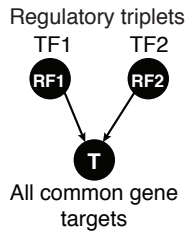


*BoolNet, R package

An example: selection of the best-matched logic gate

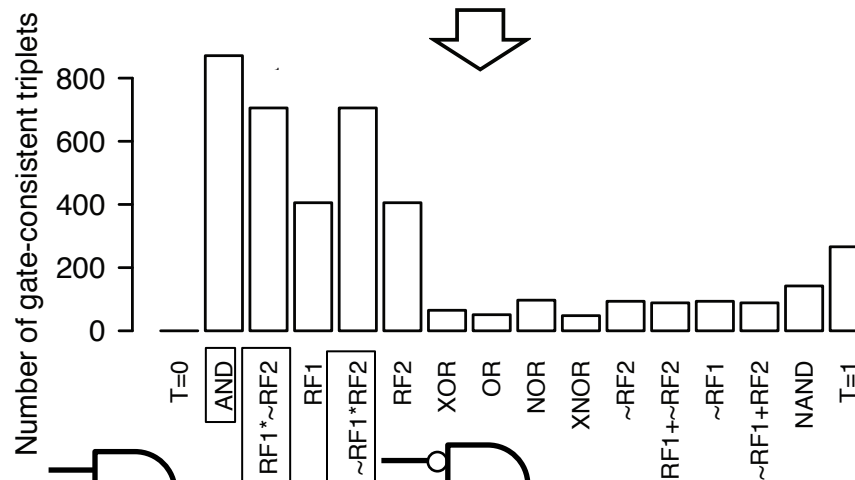


App. 1 – TF cooperativity in the cell cycle

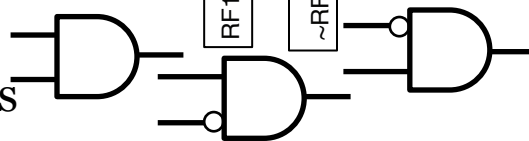


Target gene	2464
TF	176
Triplet	39,011
Time point	59

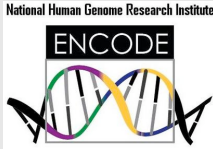

Triplet ID	RF1	RF2	Common Target Gene (T)	Matched logic gate
1	YHR084W	YBR083W	YBR082C	AND
2	YKL112W	YIL131C	YMR198W	OR
...
39011	YOR113W	YBL103C	YDR042C	XOR



AND-like gates

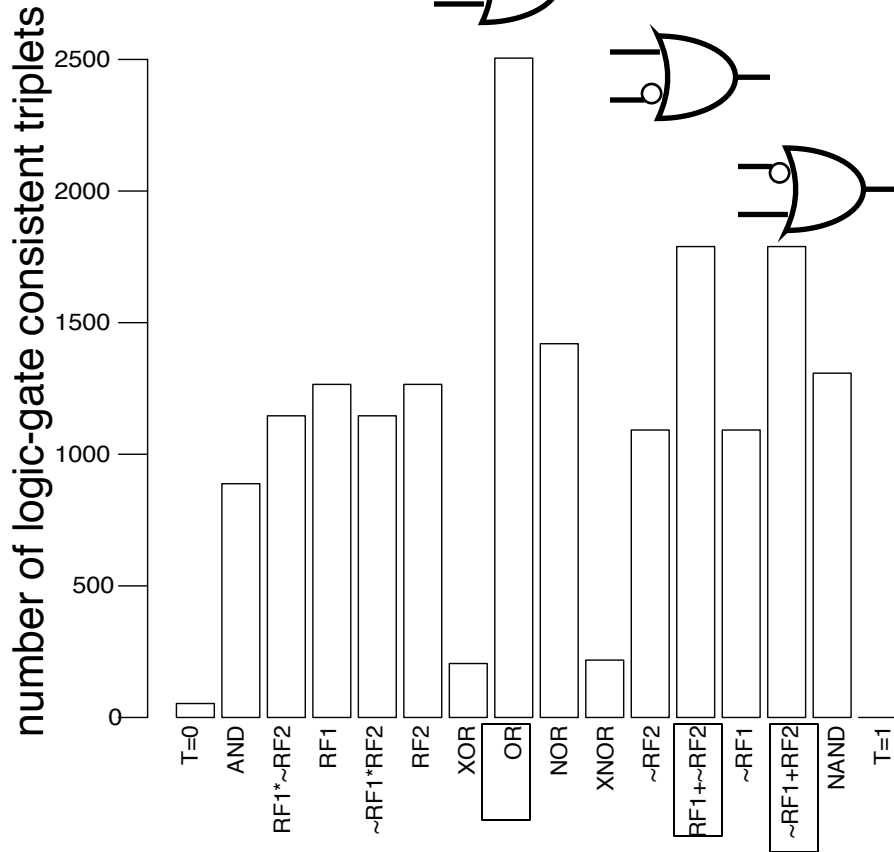
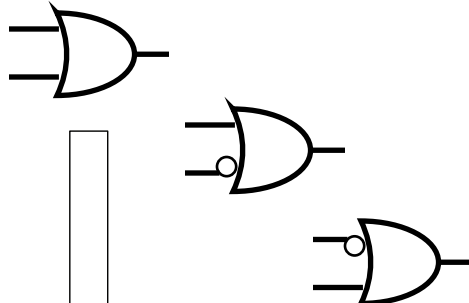


Acute Myeloid Leukemia (AML)

Target gene	1824	ENCODE Data (K562, ChIP-seq)
TF	70	 The logo for the ENCODE project, featuring a stylized DNA double helix in purple and yellow, with the word "ENCODE" in a black box above it. Above the logo is the text "National Human Genome Research Institute".
Regulatory triplet	50,865	TCGA Data (AML, level 3, RNA-seq) https://tcga-data.nci.nih.gov/tcga/tcgaDownload.jsp
Patient sample	197	 The logo for The Cancer Genome Atlas (TCGA), featuring a stylized DNA double helix in purple and yellow, with the text "THE CANCER GENOME ATLAS" and a globe icon below it.

App. 2 – TF cooperativity in AML

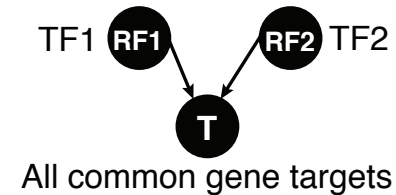
OR-like gates



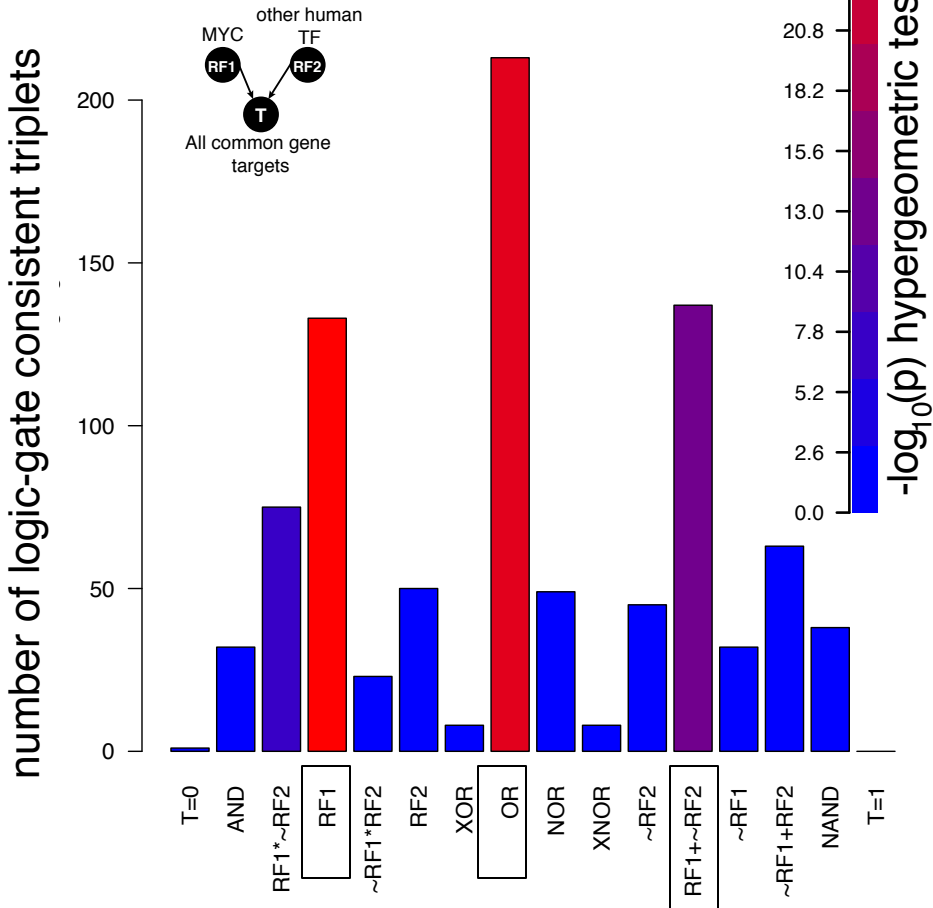
Regulatory triplet from ENCODE	50,865
Patient sample for TCGA AML expression data	197

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
...



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

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,*}



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
 - Optimization gives 16 conserved co-expression modules, 12 w/ hourglass
- *[Core-2]* **State Space Models** of Gene Expression
 - Using dimensionality reduction to help determine internal & external drivers; Decoupling expression changes into those from conserved vs species-specific genes
 - Conserved genes have similar canonical patterns (iPDPs) in contrast to species specific ones (Ex of ribosomal v signaling genes)
- *[Core-3]* **Logic Gates** Modeling
 - Preponderance of OR gates in cancer v. cell-cycle (esp. for MYC)
- *[Exhaust-1]* **Genomic Privacy & RNA-seq**
 - The dilemma: The genome as fundamental, inherited info that's very private v need for large-scale mining for med. research
 - 2-sided nature of RNA-seq presents a particularly tricky privacy issue
 - Using file formats to remove obvious variants
 - Quantifying & removing further variant info from expression levels + eQTLs using ICI & predictability
 - 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

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

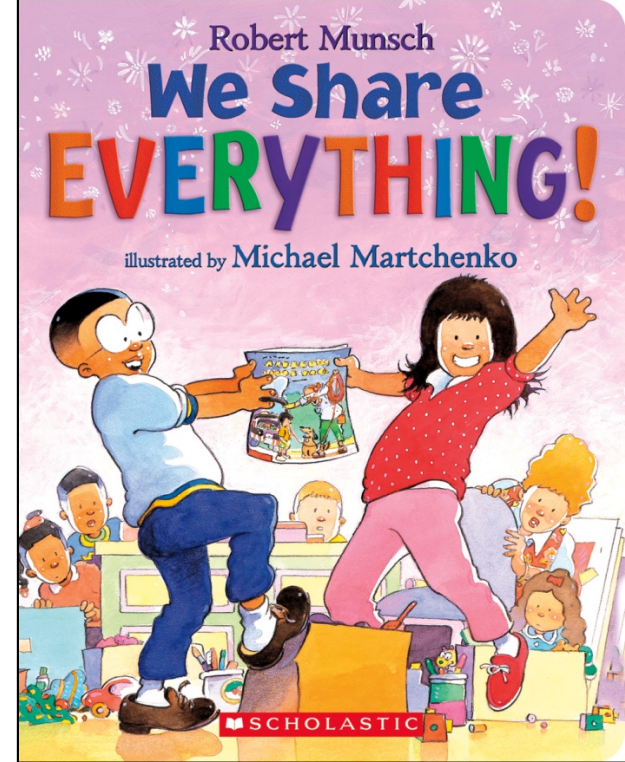
Tricky Privacy Considerations in Personal Genomics

- **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?



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)]

CARL ZIMMER'S
GAME OF GENOMES
SEASON 1





The Dilemma

[Economist, 15 Aug '15]

- 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**

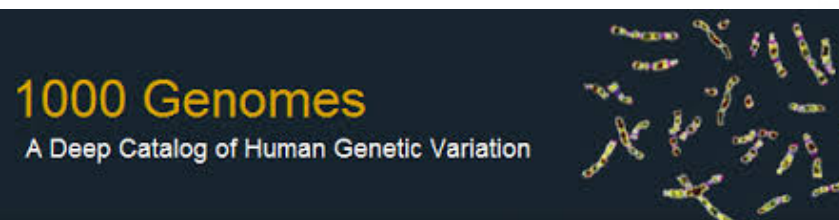
- Genomic “test pilots” (ala PGP)?
 - Sports stars & celebrities?
- Some public data & data donation is helpful but is this a realistic solution for an unbiased sample of ~1M

Strawman Hybrid **Social** & **Tech** Proposed Solution?

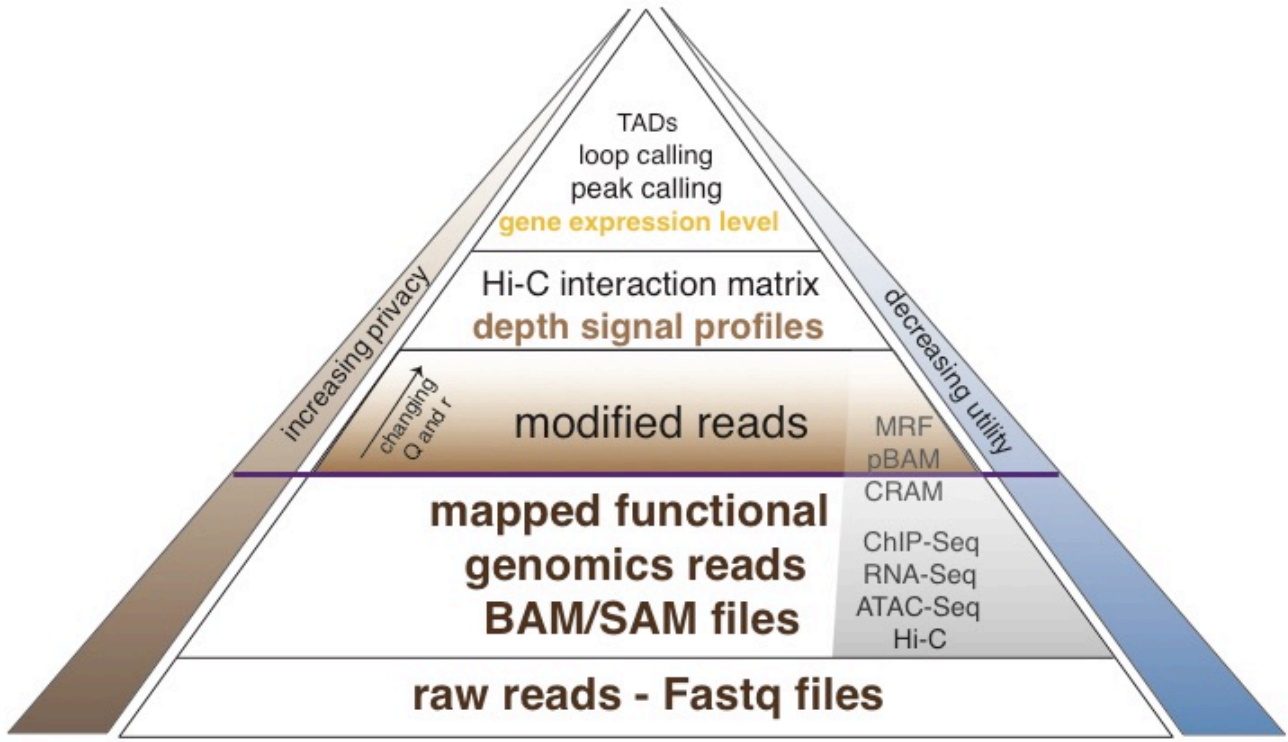
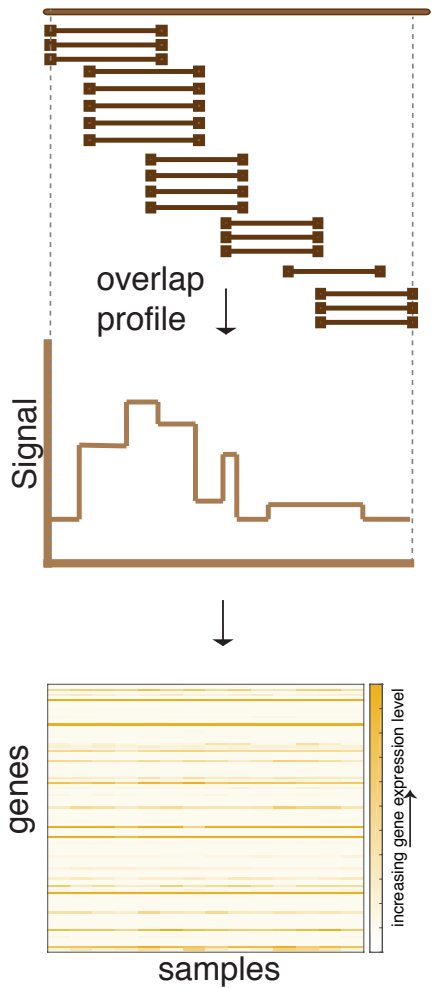
- Fundamentally, researchers have to keep genetic secrets.
 - **Need for an (international) legal framework**
 - Genetic Licensure & training for individuals (similar to medical license, drivers license)
- Technology to make things easier
 - Cloud computing & enclaves (eg solution of Genomics England)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

Representative Functional Genomics, 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
- Functional genomics data (ChIP-Seq, RNA-Seq, Hi-C) available from ENCODE
- Approximately 3,000 cis-eQTL (FDR<0.05)



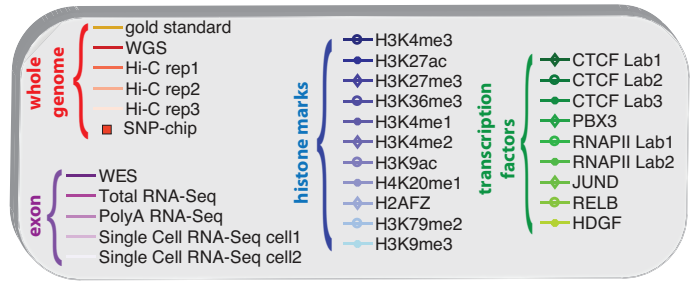
- Functional genomics data comes with a great deal of sequencing
 - **NA12878 as case study - 1000 genomes variants are used as gold standard**
- We can quantify amount of leakage at every step of the data summarization process.



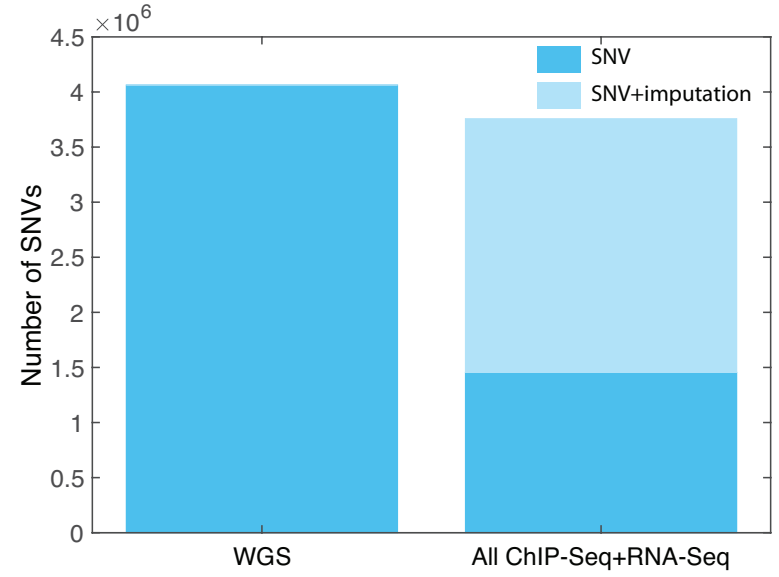
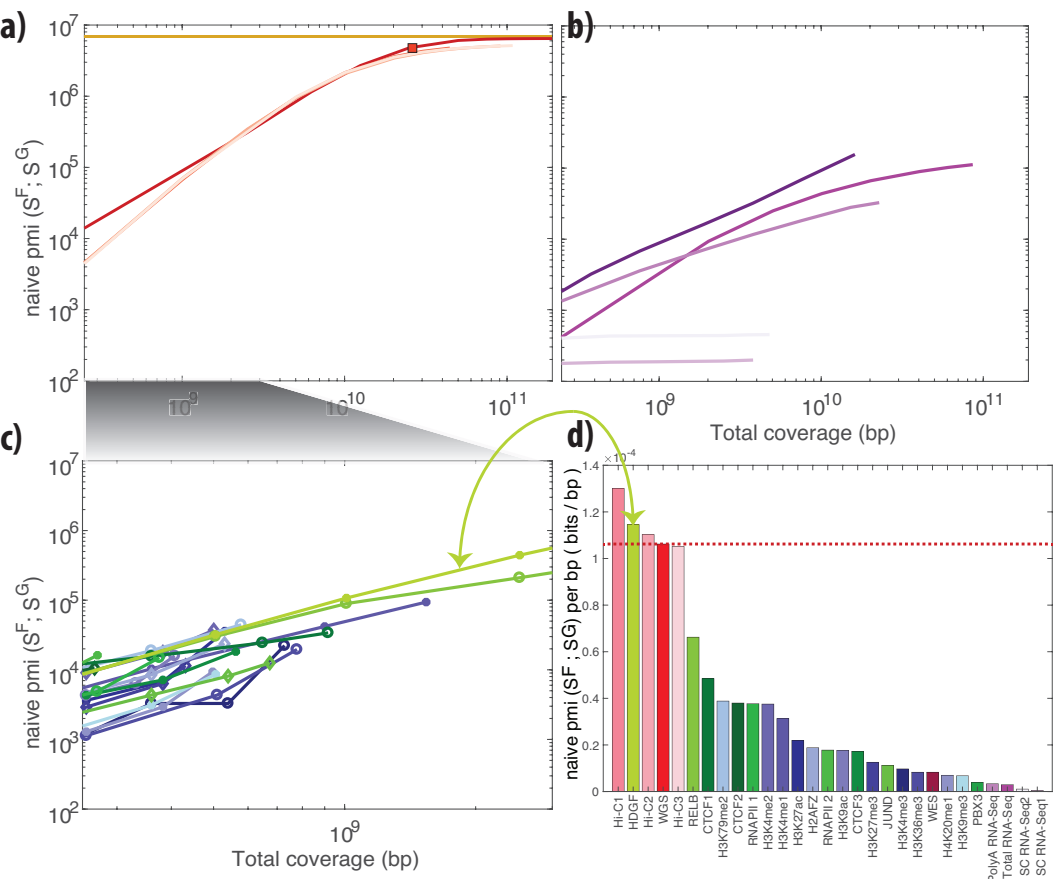
Leakage Source	Leaking Variants	# of potential variants	Average leakage per variant (bits)	Maximum leakage per variant (bits)	# of accessible variants	Total leakage (bits)
Raw reads	Exonic variants	2,682,417	0.10 ± 0.28	9.88 ± 2.12	246,893	24,689
Modified reads Q = {indels}	Exonic SNVs	2,607,969	0.09 ± 0.27	9.95 ± 2.02	231,031	207,92
Modified reads Q = {mismatches}	Exonic indels	51,408	0.33 ± 0.47	7.64 ± 2.42	15,862	5234
Signal profiles	Exonic deletions	48,019	0.29 ± 0.45	7.97 ± 2.42	1,067	298
Gene expression quantification	eQTLs	3,175	1.19 ± 0.36	4.00 ± 1.92	158	188

[Gursoy et al, Bioarxiv]

- How much information, for example, do RNA-Seq reads (or ChIP-Seq) reads contain? Does that information enough to identify individuals?

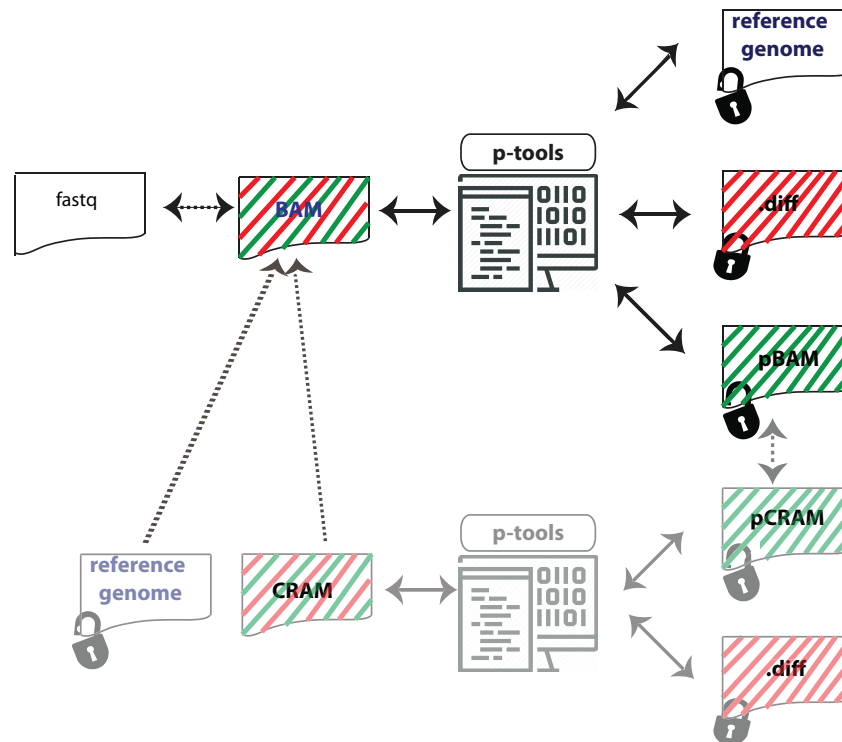


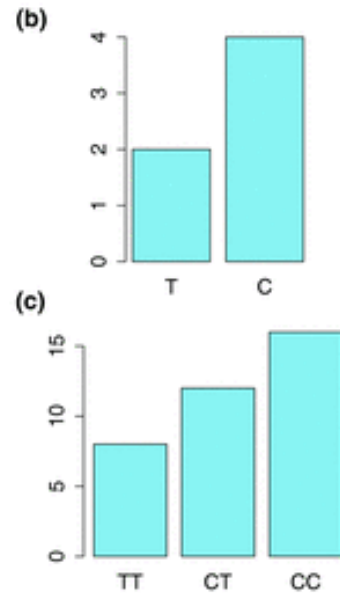
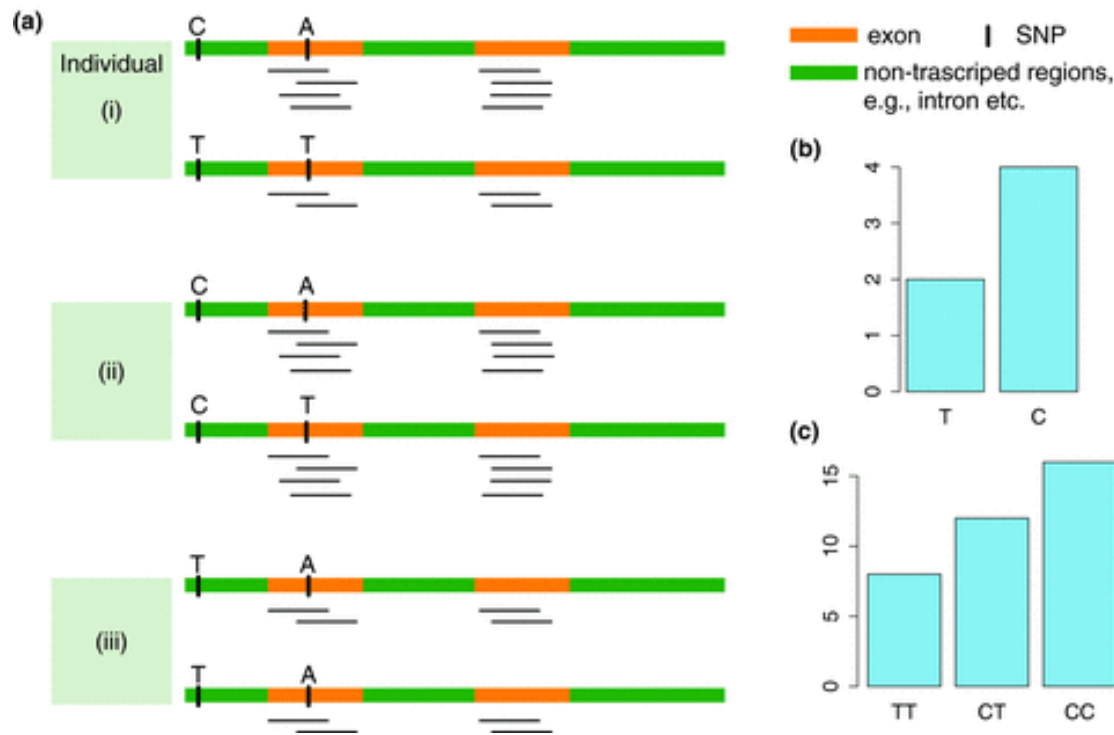
- It might seem like we don't infer much information from single ChIP-Seq and RNA-Seq experiments compared to WGS
 - However putting 10 different ChIP-Seq experiments and RNA-Seq together with imputation provides a great deal of information about the individual



Privacy-aware file formats that hide the variants but recover signal

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

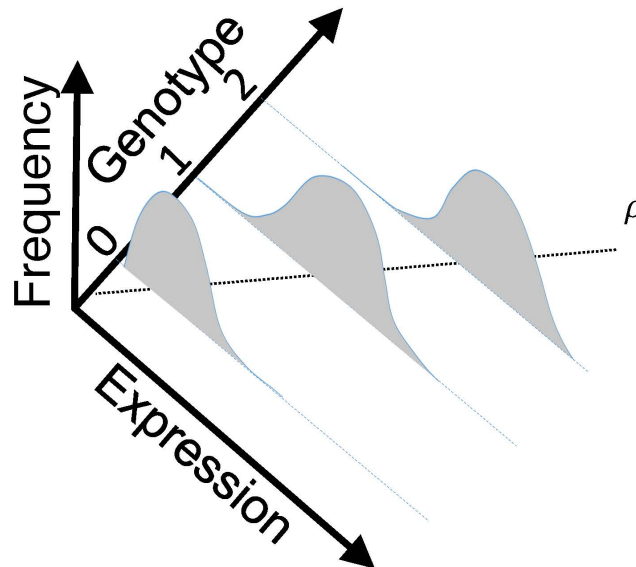




eQTL Mapping Using RNA-Seq Data

- 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

[*Biometrics* 68(1) 1–11]



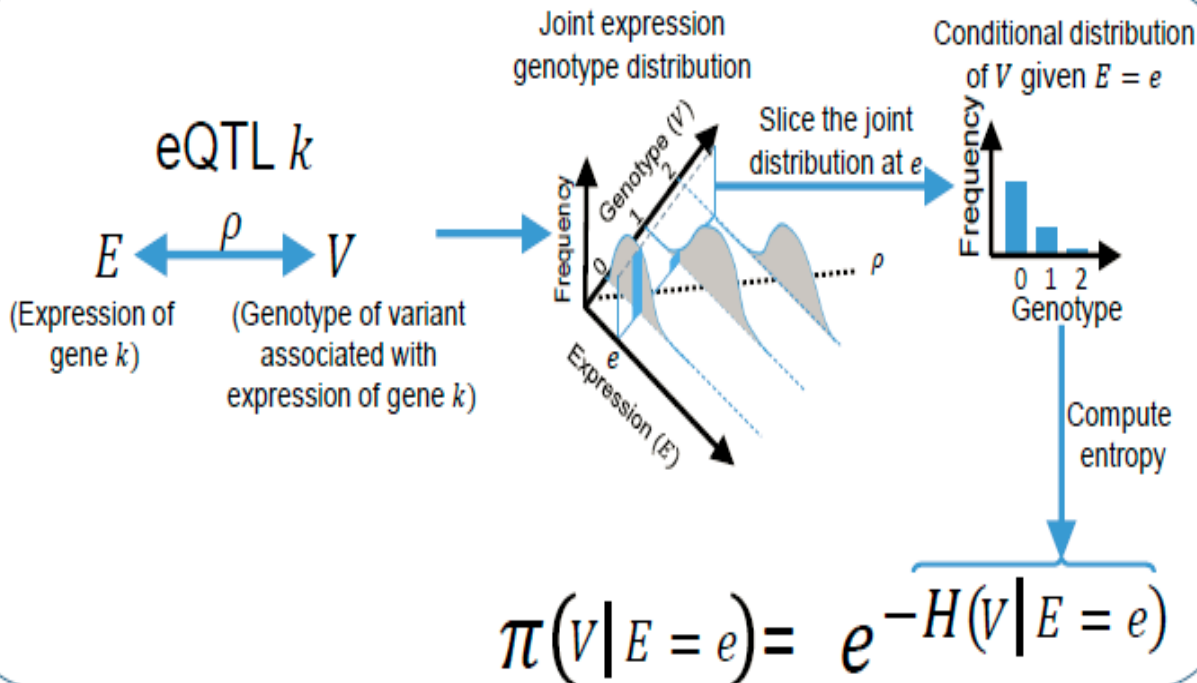
Information Content and Predictability

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

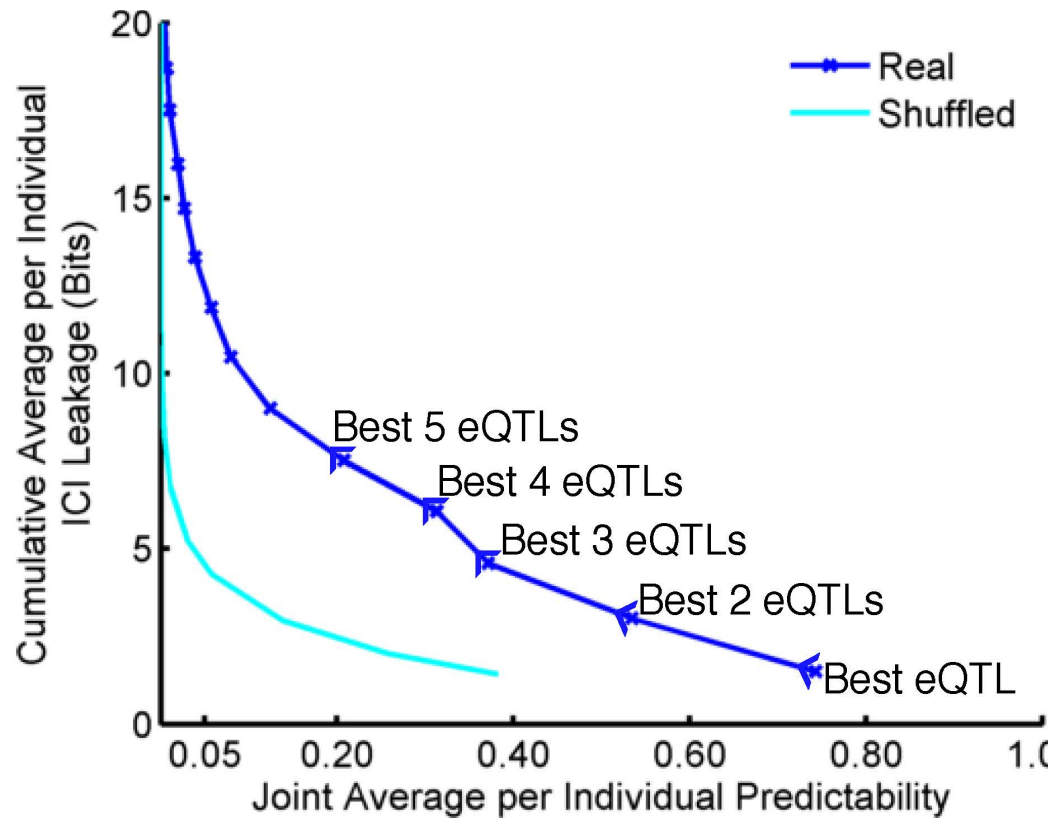
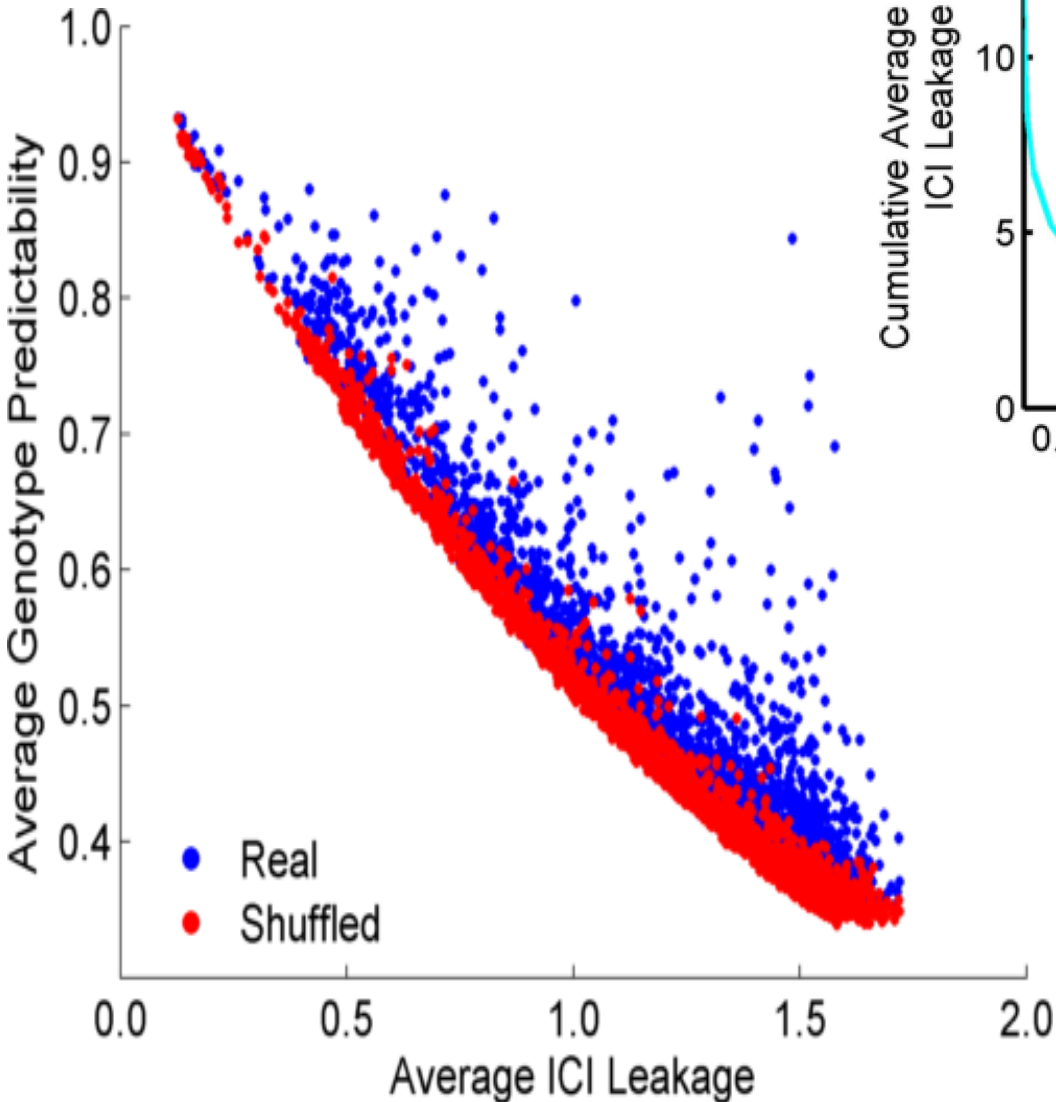
$g_1 = 2$ $g_2 = 1$ $g_n = 2$

V_1 genotype frequencies V_2 genotype frequencies V_n genotype frequencies

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

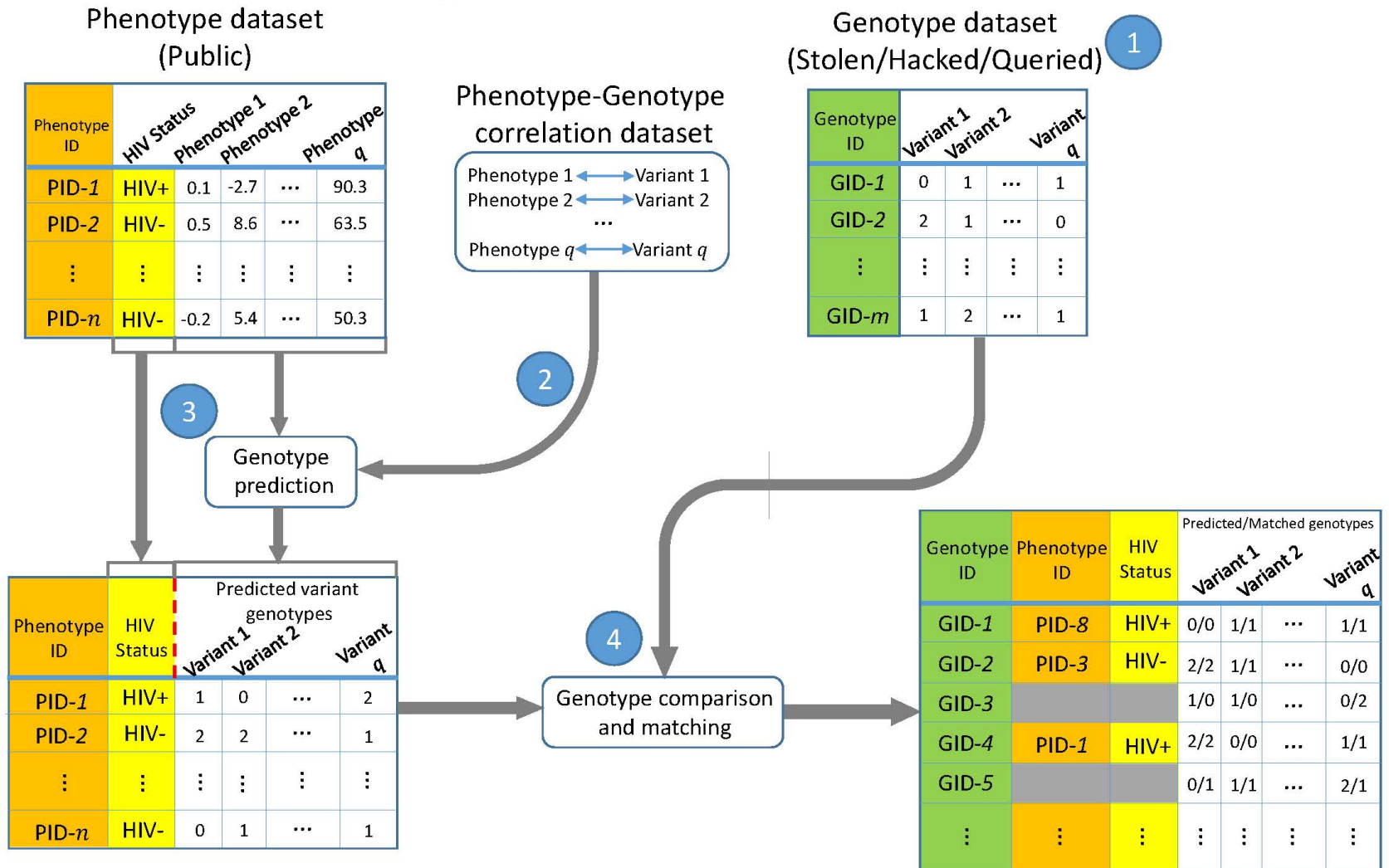


- Condition specific entropy
- Higher cond. entropy: Lower predictability
- Additive for multiple eQTLs



ICI Leakage versus Genotype Predictability

Linking Attack Scenario



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	-
...
...
...

- 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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...
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- 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

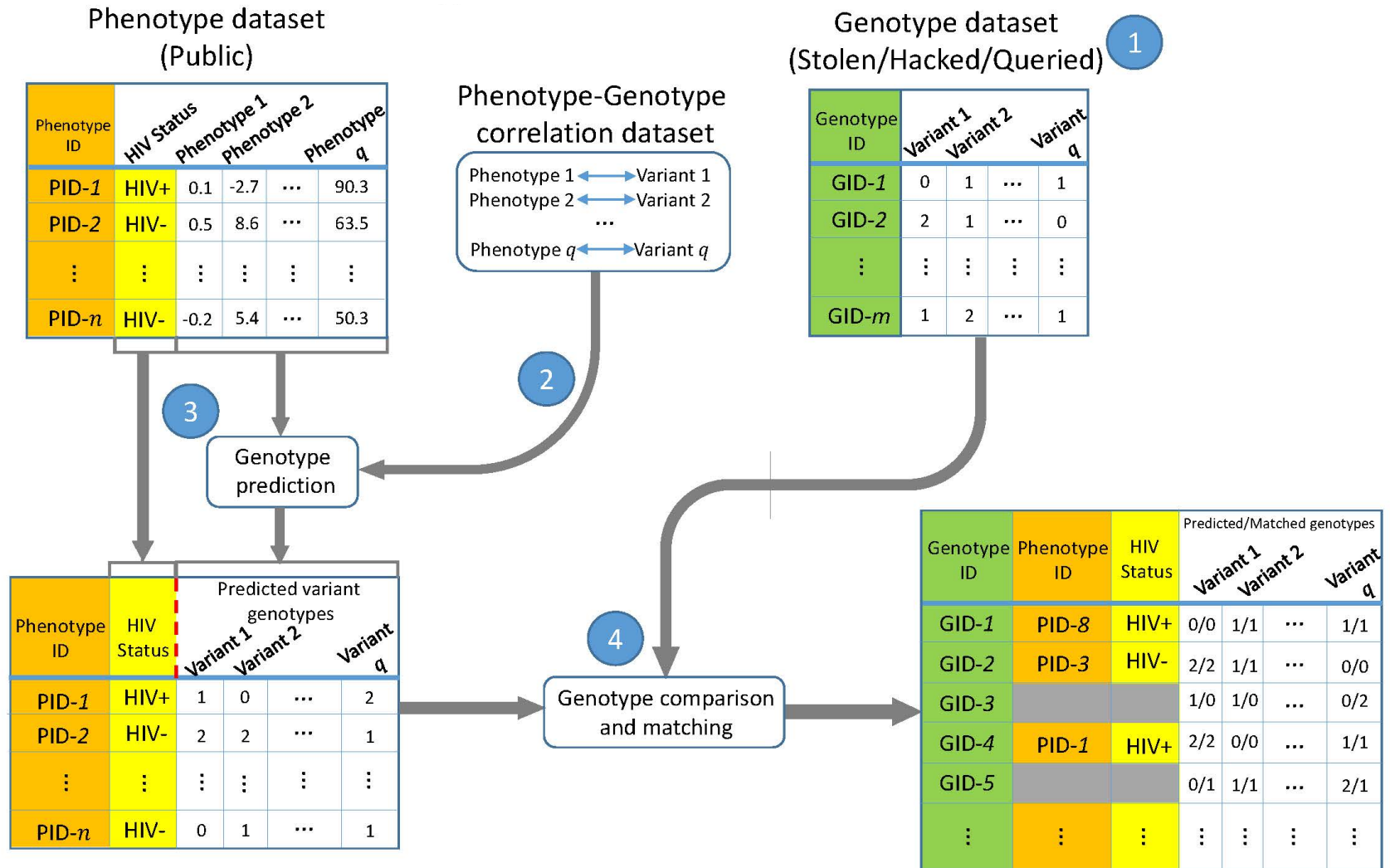


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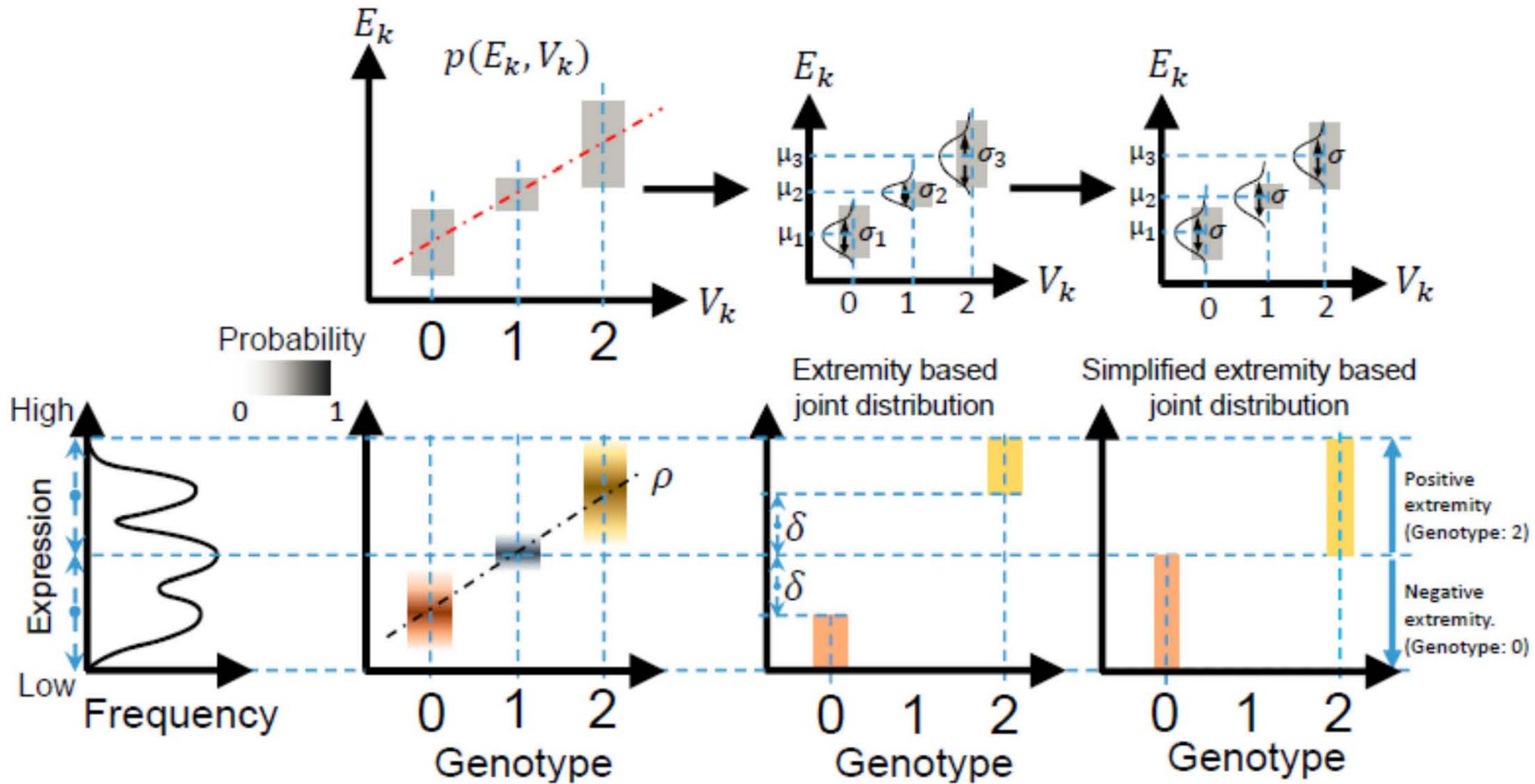
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Linking Attack Scenario

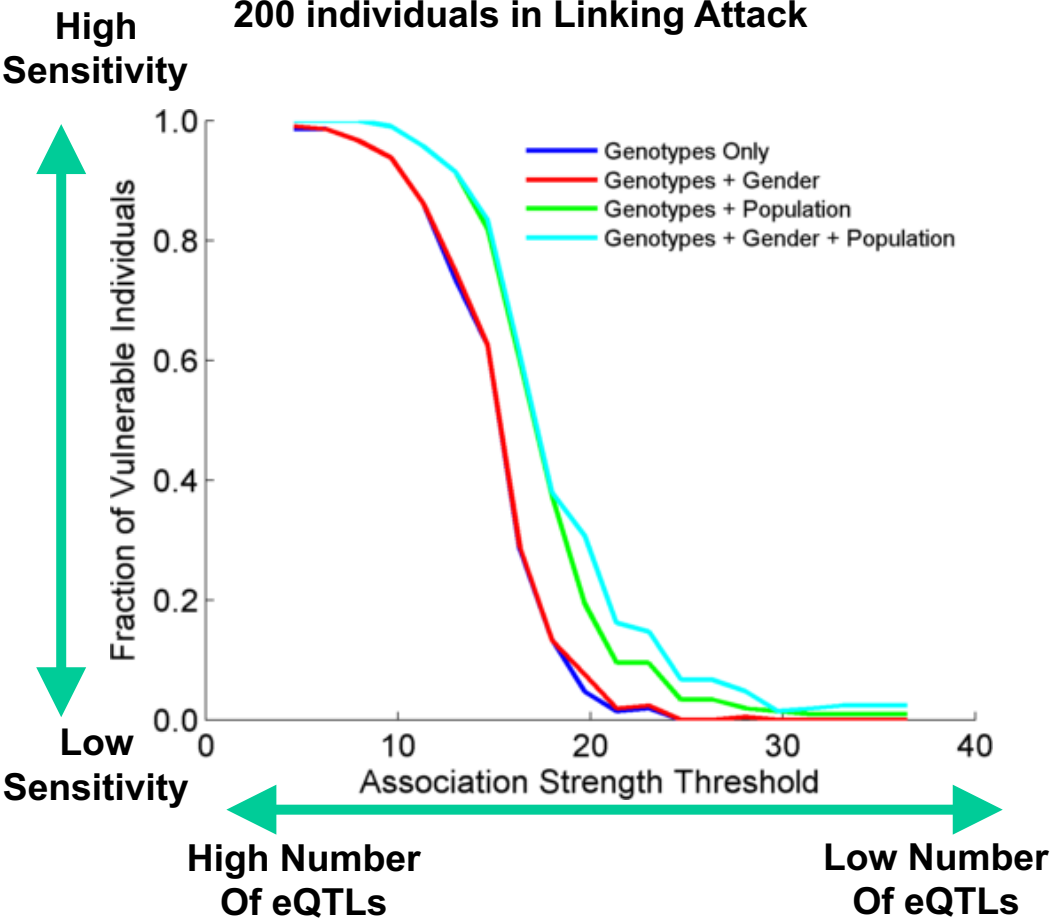


Levels of Expression-Genotype Model Simplifications for Genotype Prediction



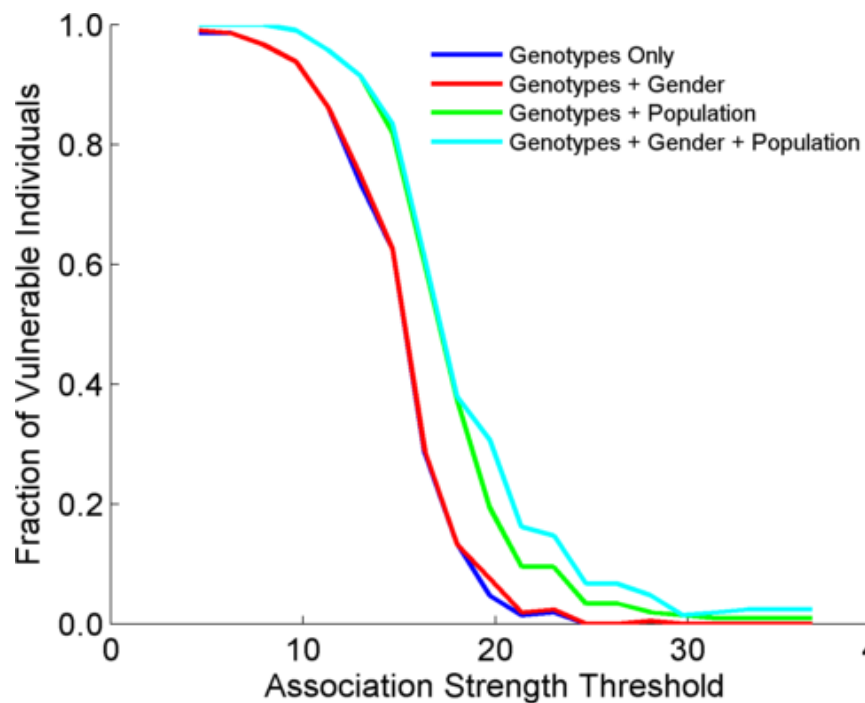
Success in Linking Attack with Extremity based Genotype Prediction

200 individuals eQTL Discovery
200 individuals in Linking Attack

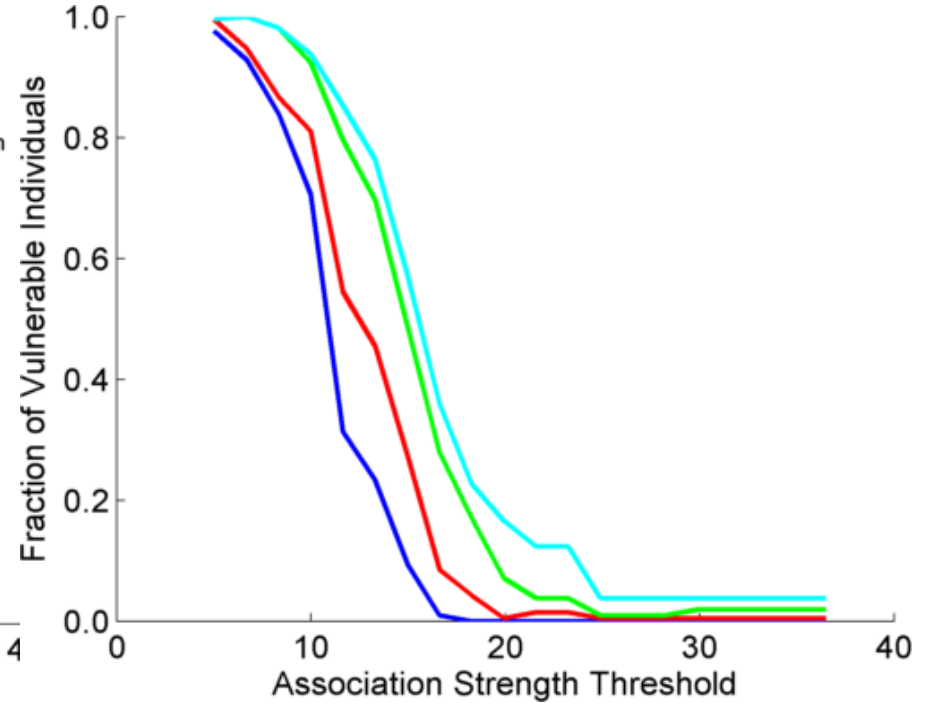


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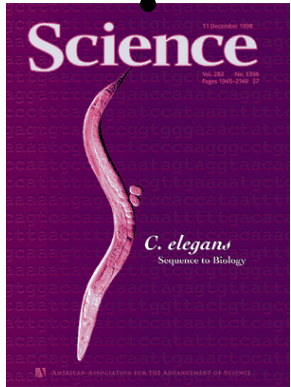
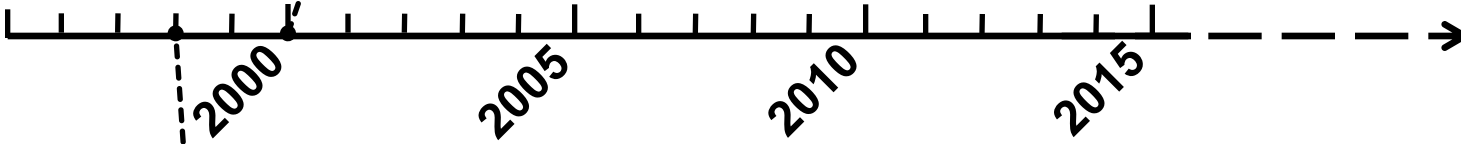
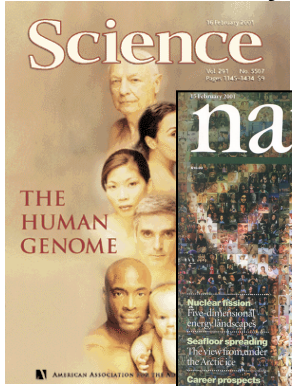
200 individuals eQTL Discovery
100,200 individuals in Linking Attack



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

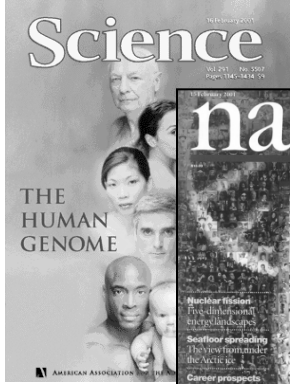
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The Human Genome Project



Worm Genome

The Human Genome Project



ENCODE Pilot



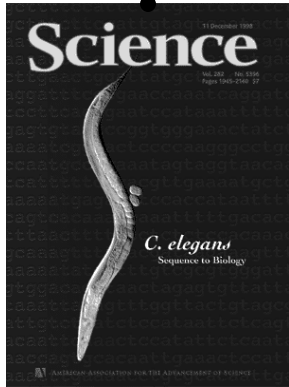
ENCODE Production



2000

2005

2010



Worm Genome



modENCODE

The Human Genome Project



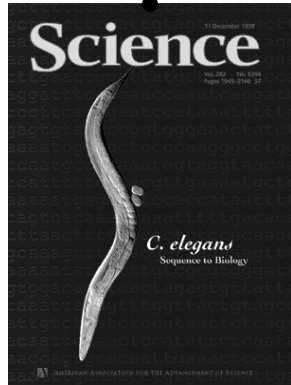
ENCODE Pilot



ENCODE Production



Comparative ENCODE



Worm Genome



modENCODE

The Human Genome Project



ENCODE Pilot



ENCODE Production



Comparative ENCODE

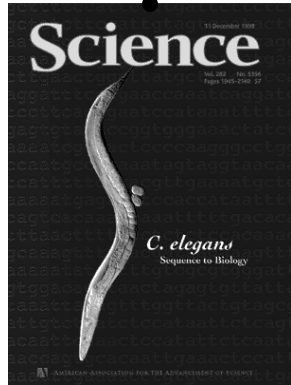


2000

2005

2010

2015



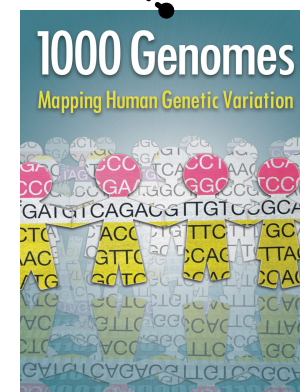
Worm Genome



modENCODE



1000 Genomes Pilot



1000 Genomes Production

The Human Genome Project



ENCODE Pilot



ENCODE Production



Comparative ENCODE



Epigenome Roadmap

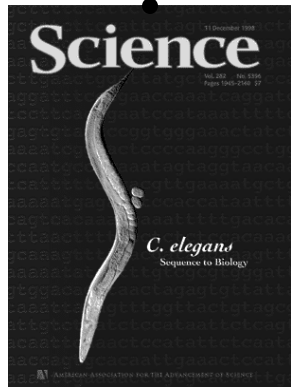


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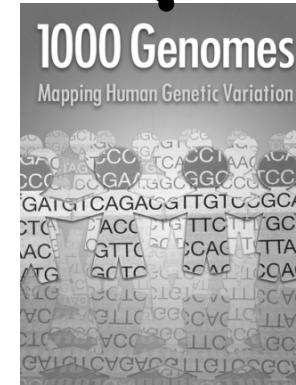
Worm Genome



modENCODE



1000 Genomes Pilot



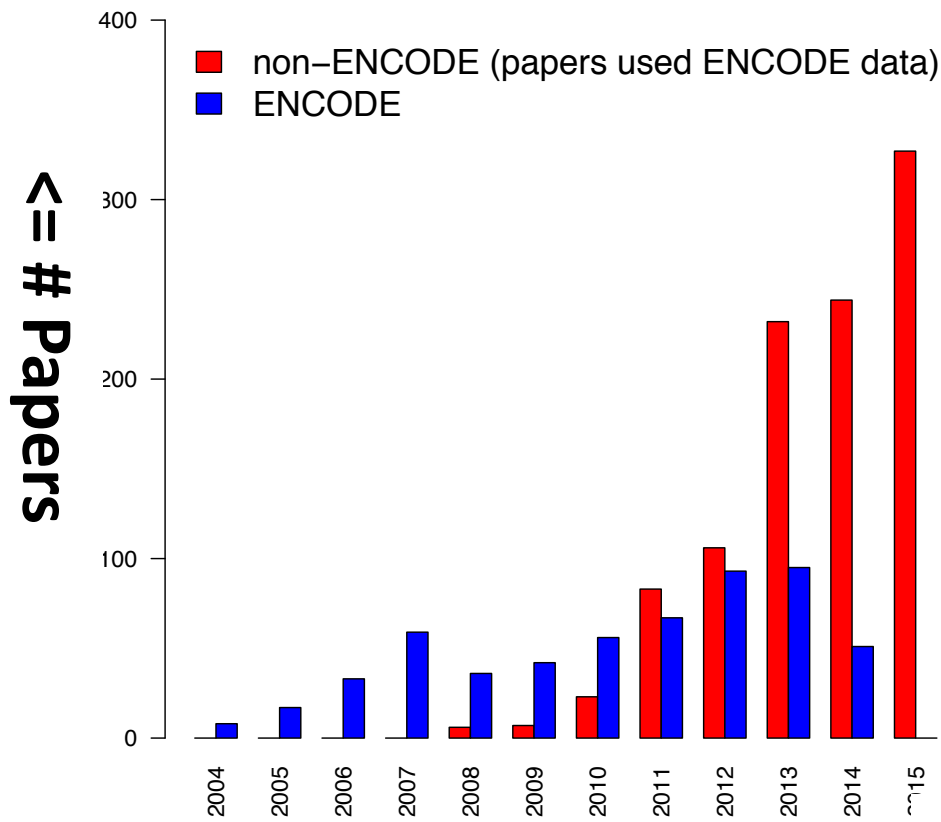
1000 Genomes Production



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



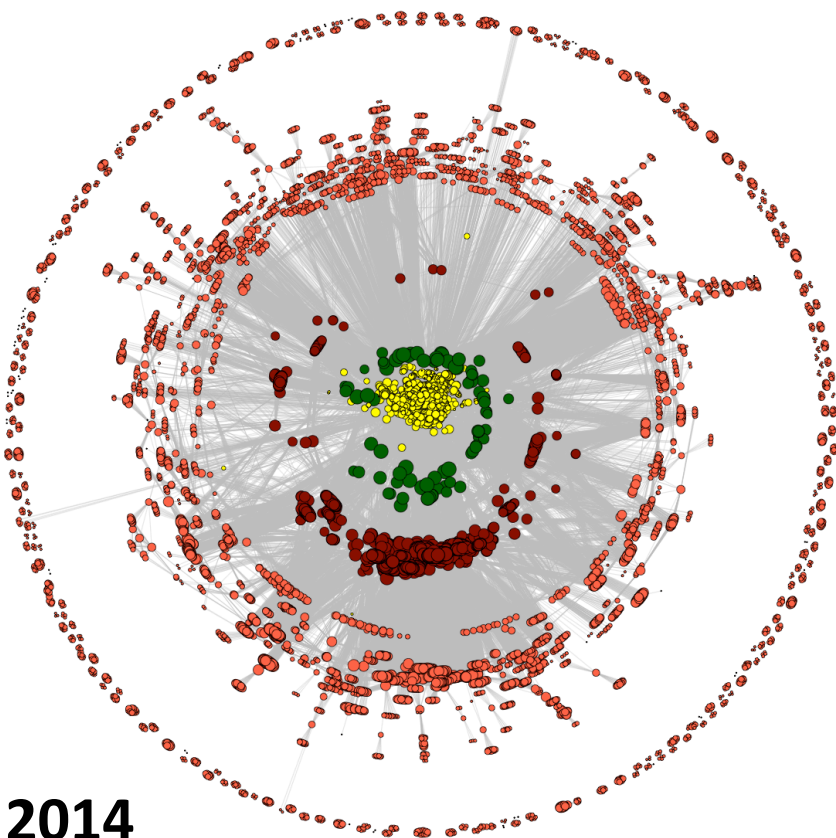
Authors

[Wang et al., TIG ('16)]

Yr. ('04 to '15)

Co-authorship Network of ENCODE members & Data Users

- ENCODE member
- non-member
- ENCODE member broker
- non-member broker
- co-authorship

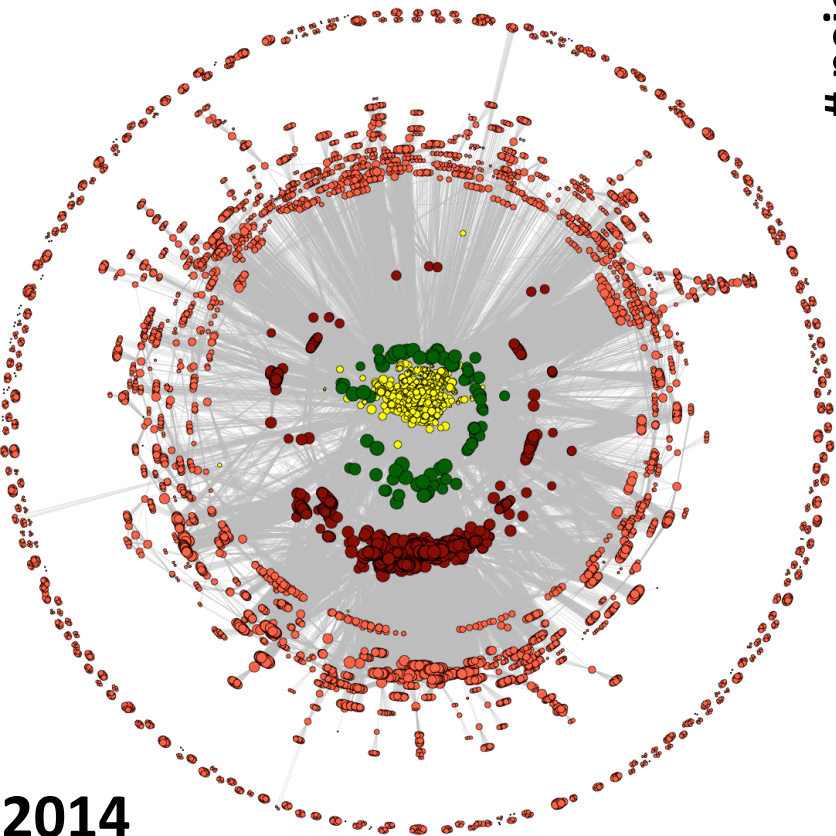


2014

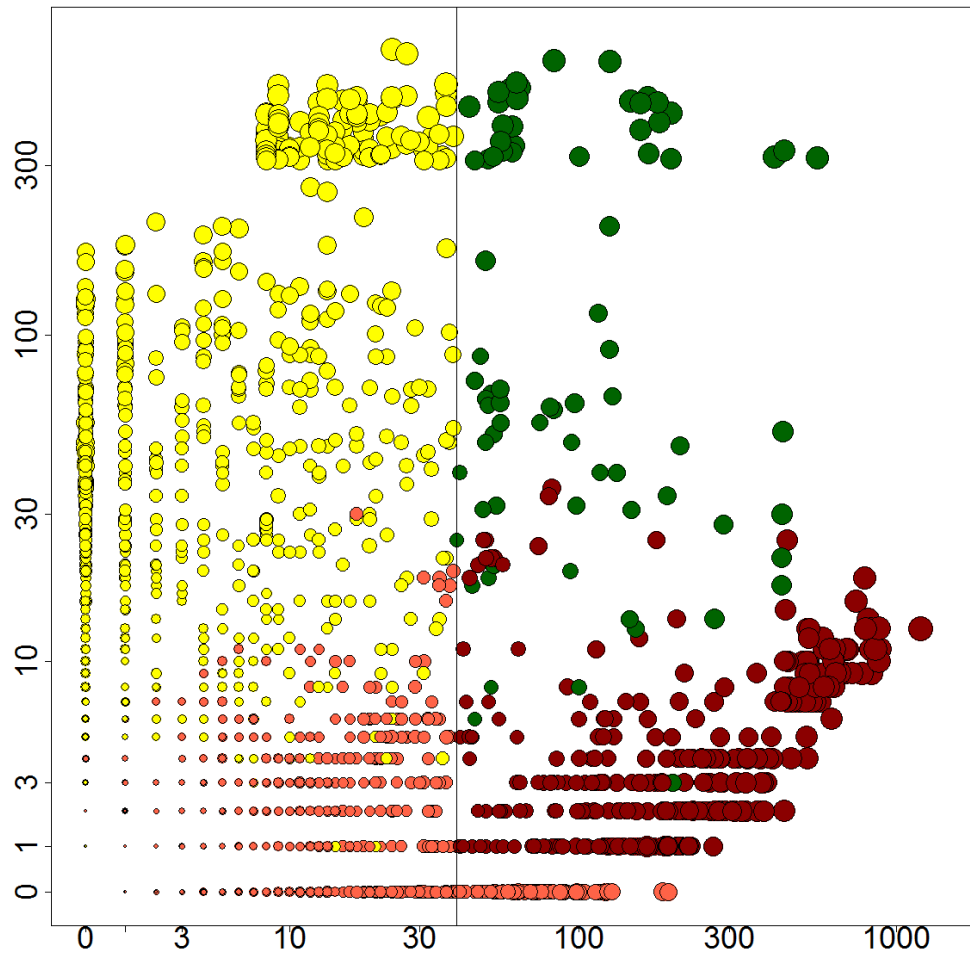
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neighbors: ENCODE ==>

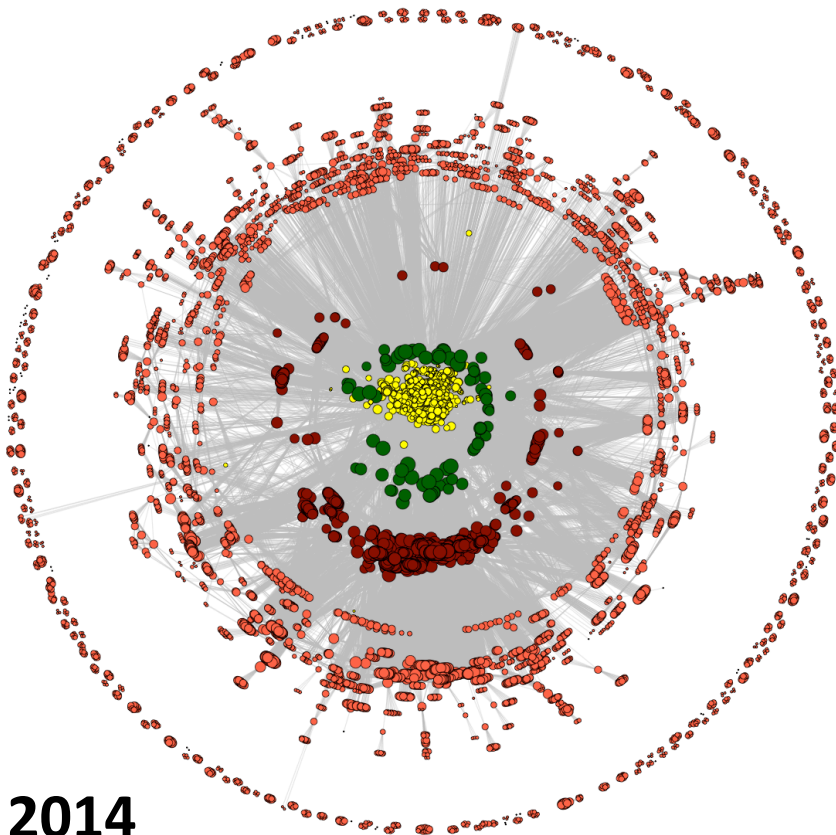


neighbors: non-ENCODE ==>

2014

Co-authorship Network of ENCODE members & Data Users

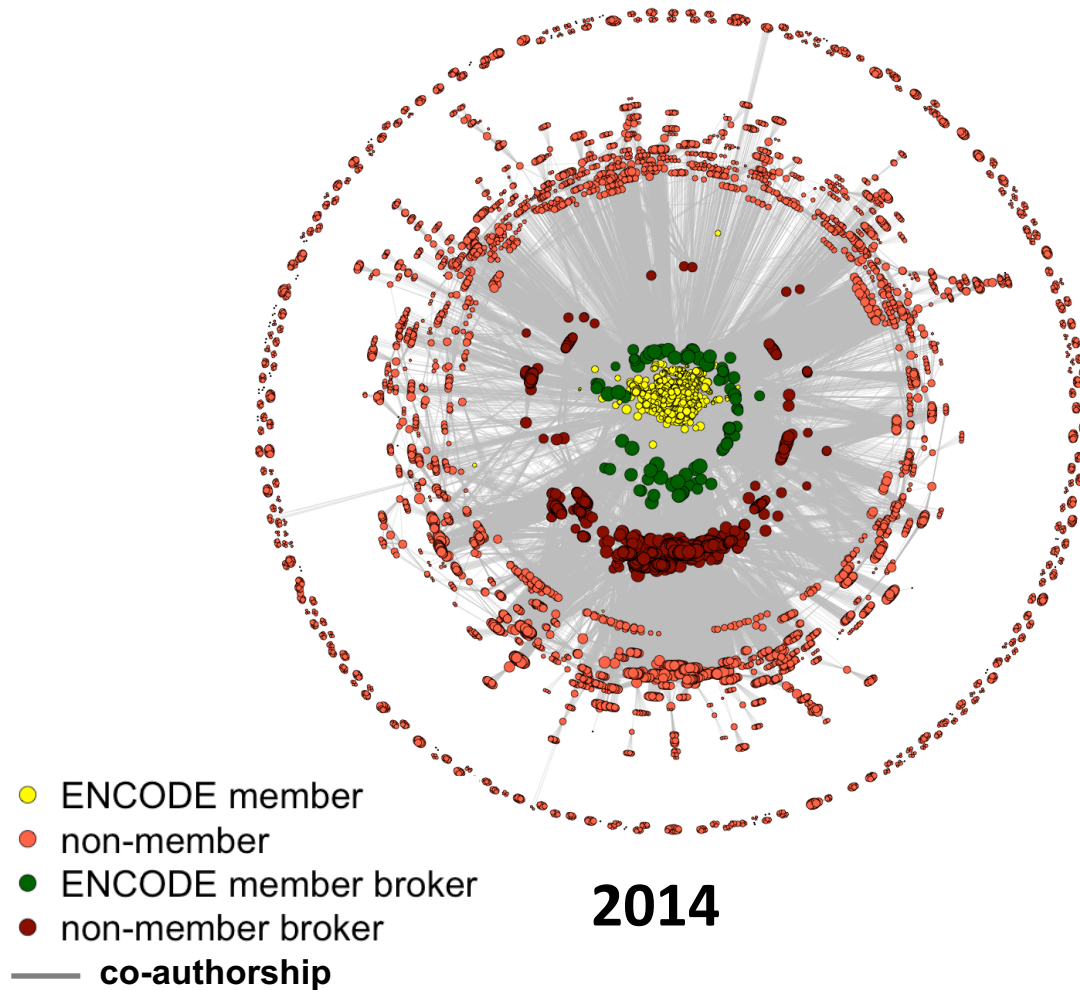
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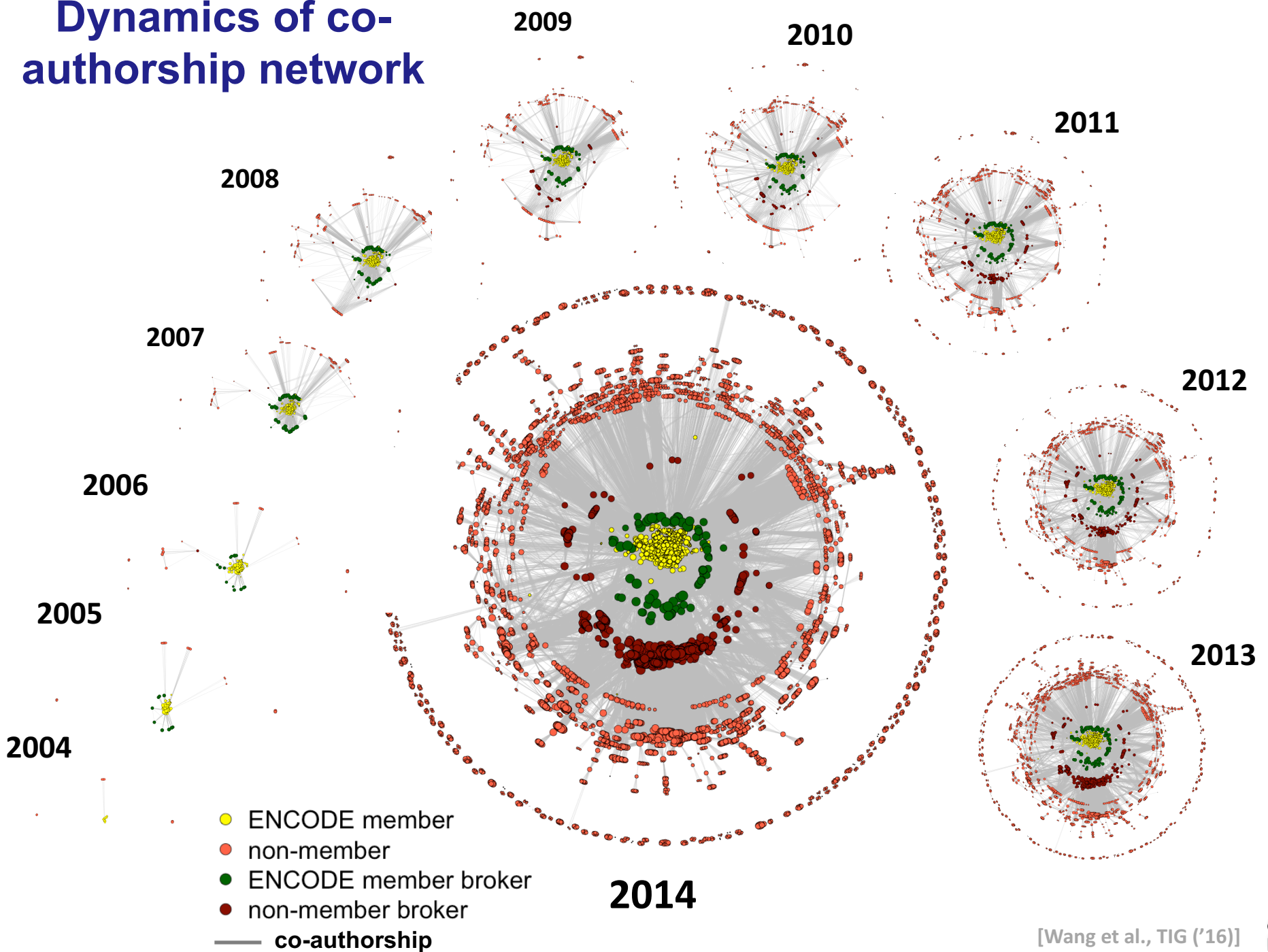
2014

[Wang et al., TIG ('16)]

Dynamics of co-authorship network



Dynamics of co-authorship network



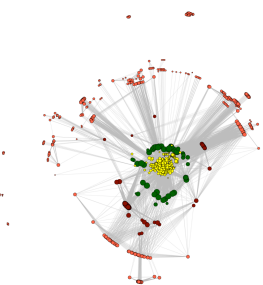
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Dynamics of co-authorship network

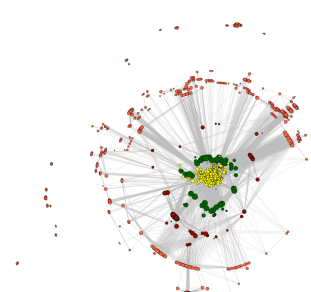
2008



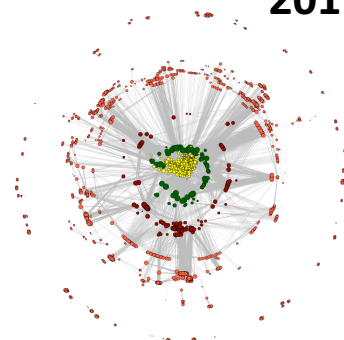
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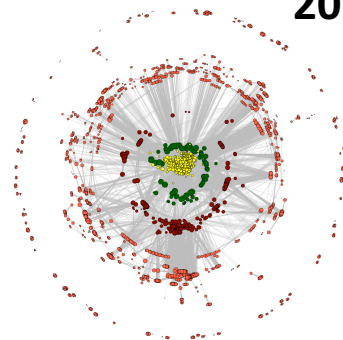
2010



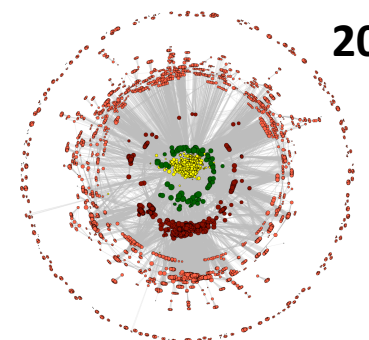
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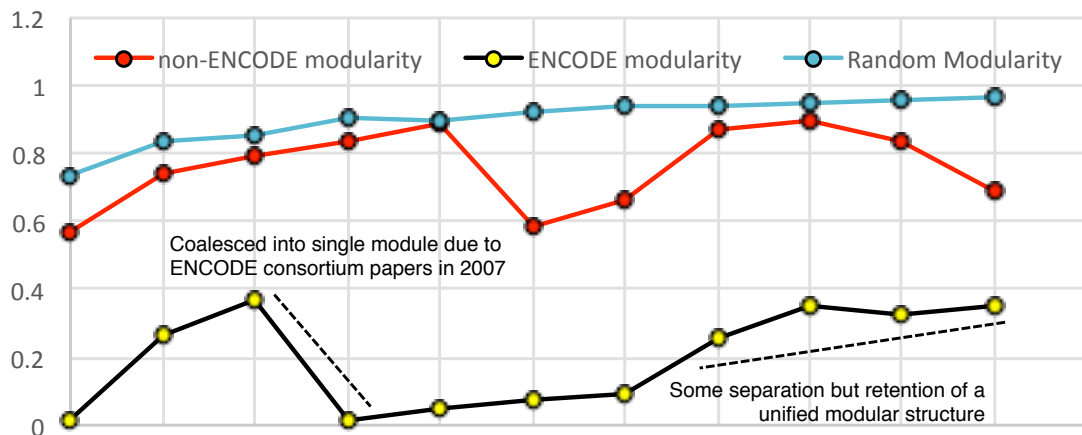
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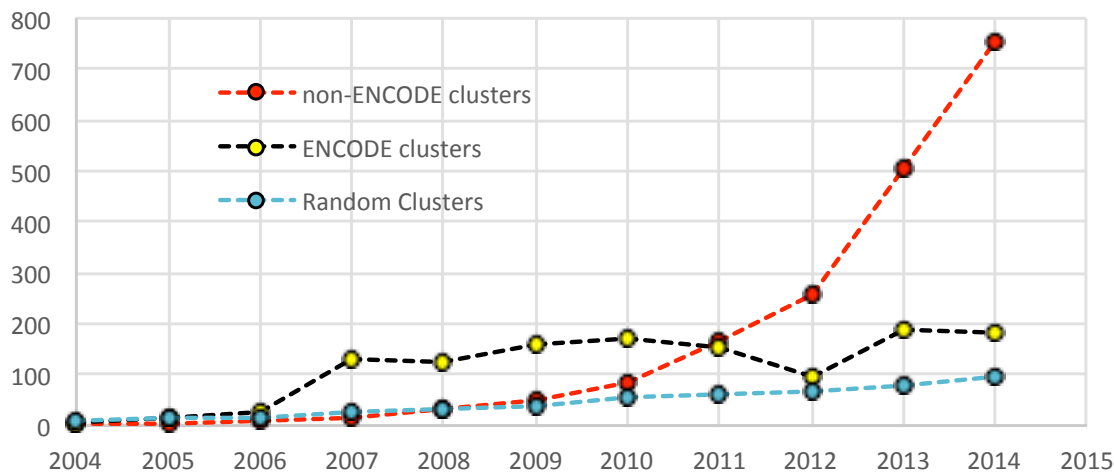
2013



“Modularity”



Number of clusters



[Wang et al., TIG ('16)]

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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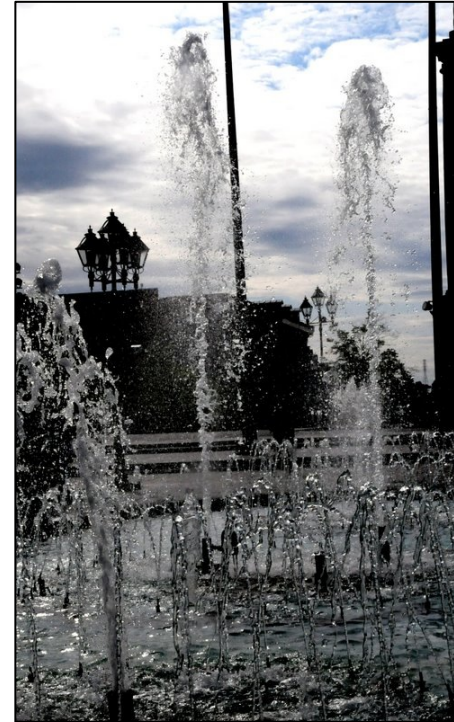
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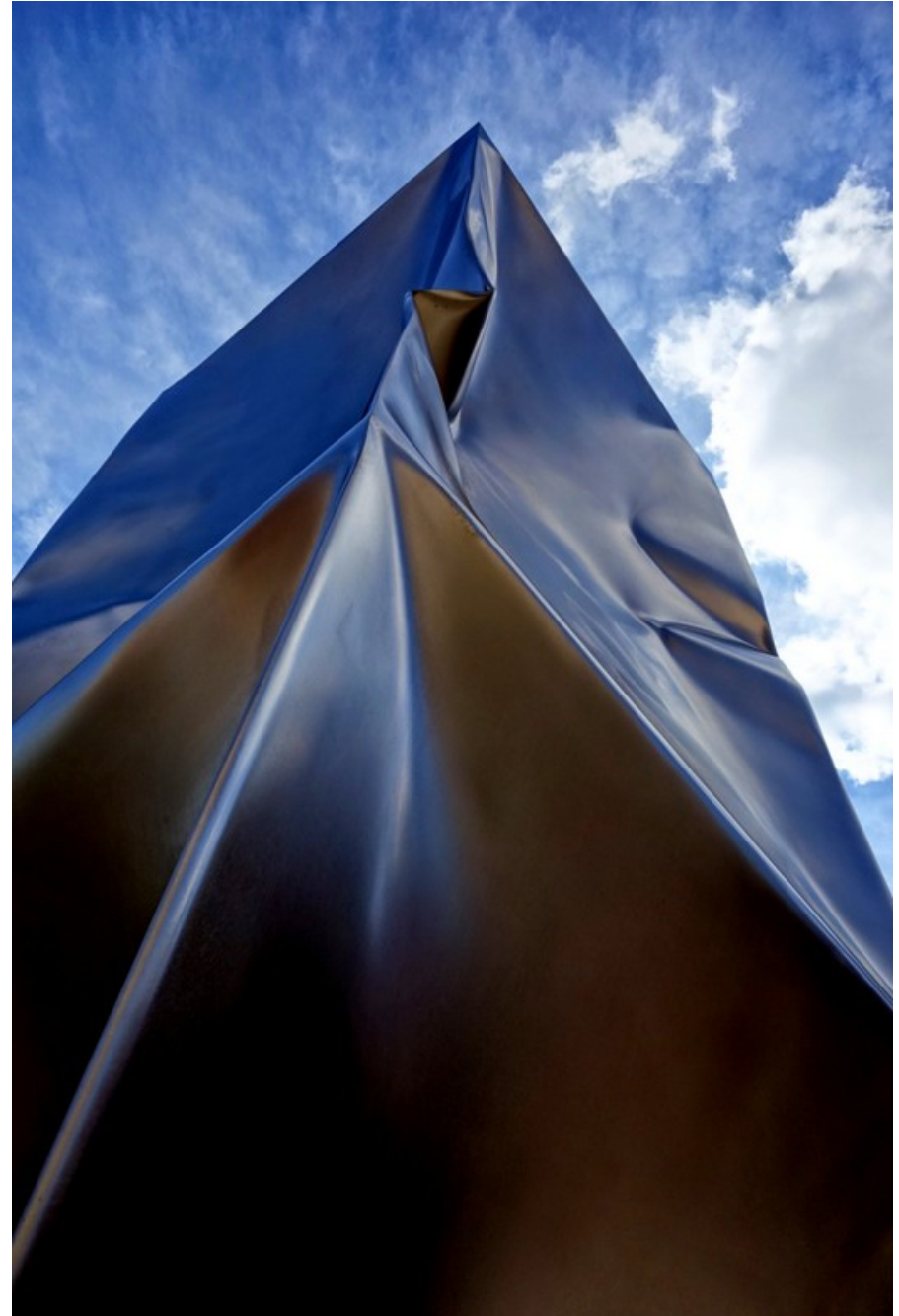
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Publication patterns [“encode authors”]

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