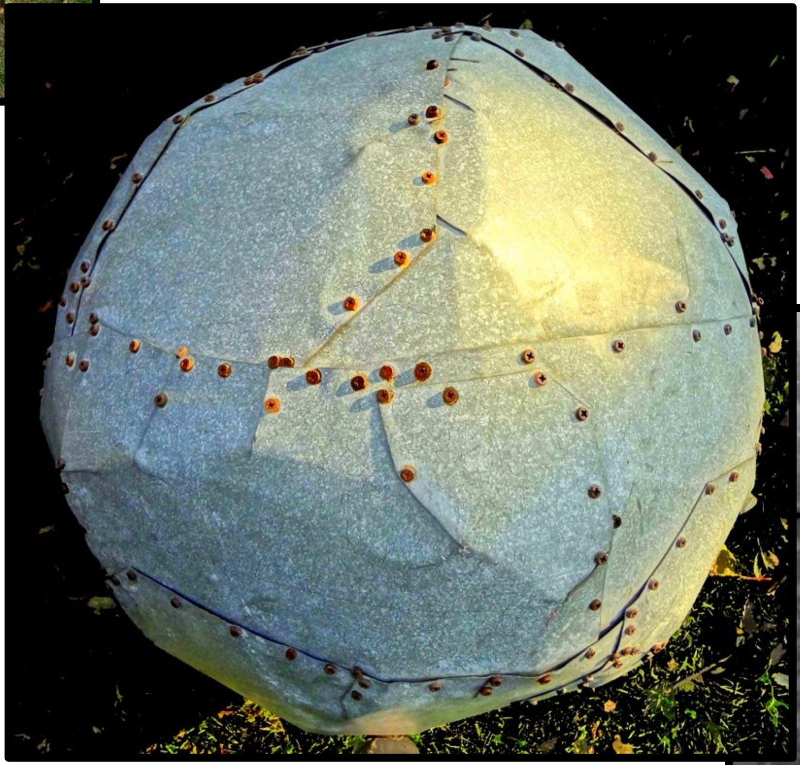
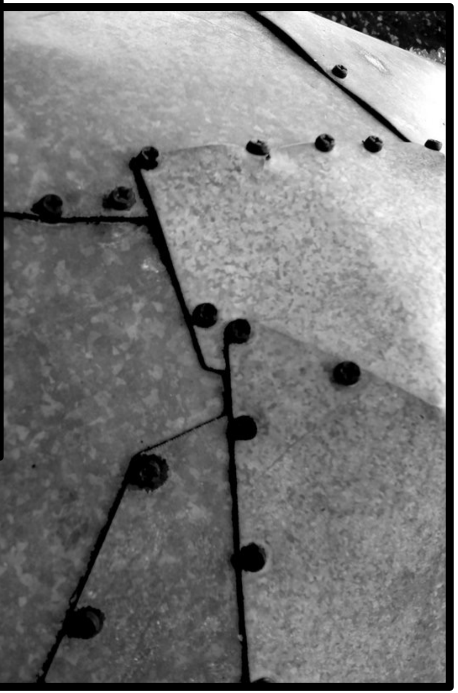
Comparative Genome Analysis:

Comparing Transcriptomes of Distant Organisms





M Gerstein, Yale

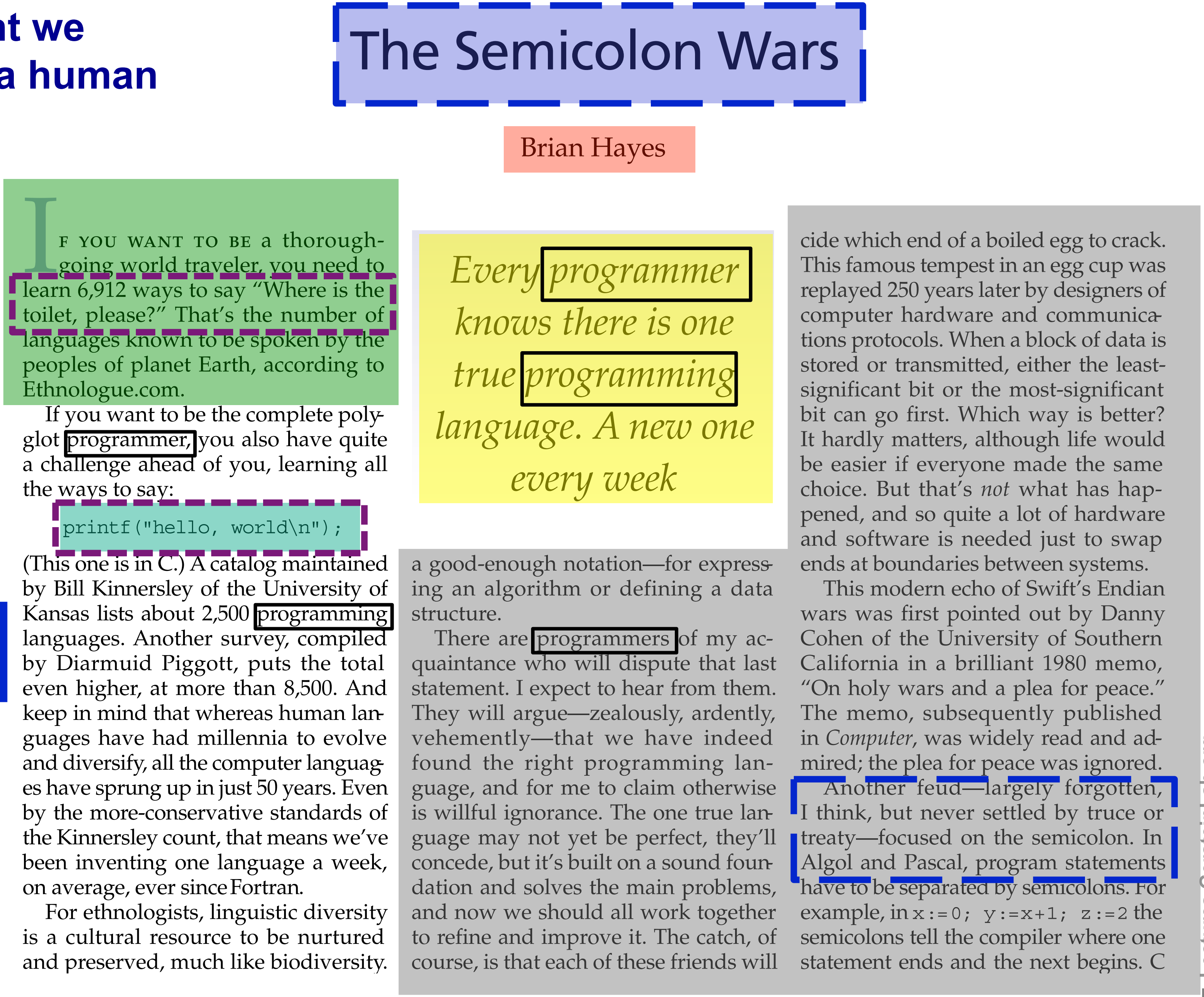
See last slide for
references & more info.

Slides freely downloadable from
Lectures.GersteinLab.org
& “tweetable” (via @markgerstein)

How might we annotate a human text?

Color is Function

Lines are Similarity



The Semicolon Wars

Brian Hayes

If you want to be a thorough-going world traveler, you need to learn 6,912 ways to say "Where is the toilet, please?" That's the number of languages known to be spoken by the peoples of planet Earth, according to Ethnologue.com.

If you want to be the complete polyglot programmer, you also have quite a challenge ahead of you, learning all the ways to say:

```
printf("hello, world\n");
```

(This one is in C.) A catalog maintained by Bill Kinnersley of the University of Kansas lists about 2,500 programming languages. Another survey, compiled by Diarmuid Piggott, puts the total even higher, at more than 8,500. And keep in mind that whereas human languages have had millennia to evolve and diversify, all the computer languages have sprung up in just 50 years. Even by the more-conservative standards of the Kinnersley count, that means we've been inventing one language a week, on average, ever since Fortran.

For ethnologists, linguistic diversity is a cultural resource to be nurtured and preserved, much like biodiversity.

> *Every programmer knows there is one true programming language. A new one every week*

a good-enough notation—for expressing an algorithm or defining a data structure.

There are programmers of my acquaintance who will dispute that last statement. I expect to hear from them. They will argue—zealously, ardently, vehemently—that we have indeed found the right programming language, and for me to claim otherwise is willful ignorance. The one true language may not yet be perfect, they'll concede, but it's built on a sound foundation and solves the main problems, and now we should all work together to refine and improve it. The catch, of course, is that each of these friends will

cide which end of a boiled egg to crack. This famous tempest in an egg cup was replayed 250 years later by designers of computer hardware and communications protocols. When a block of data is stored or transmitted, either the least-significant bit or the most-significant bit can go first. Which way is better? It hardly matters, although life would be easier if everyone made the same choice. But that's *not* what has happened, and so quite a lot of hardware and software is needed just to swap ends at boundaries between systems.

This modern echo of Swift's Endian wars was first pointed out by Danny Cohen of the University of Southern California in a brilliant 1980 memo, "On holy wars and a plea for peace." The memo, subsequently published in *Computer*, was widely read and admired; the plea for peace was ignored.

Another feud—largely forgotten, I think, but never settled by truce or treaty—focused on the semicolon. In Algol and Pascal, program statements have to be separated by semicolons. For example, in `x:=0; y:=x+1; z:=2` the semicolons tell the compiler where one statement ends and the next begins. C

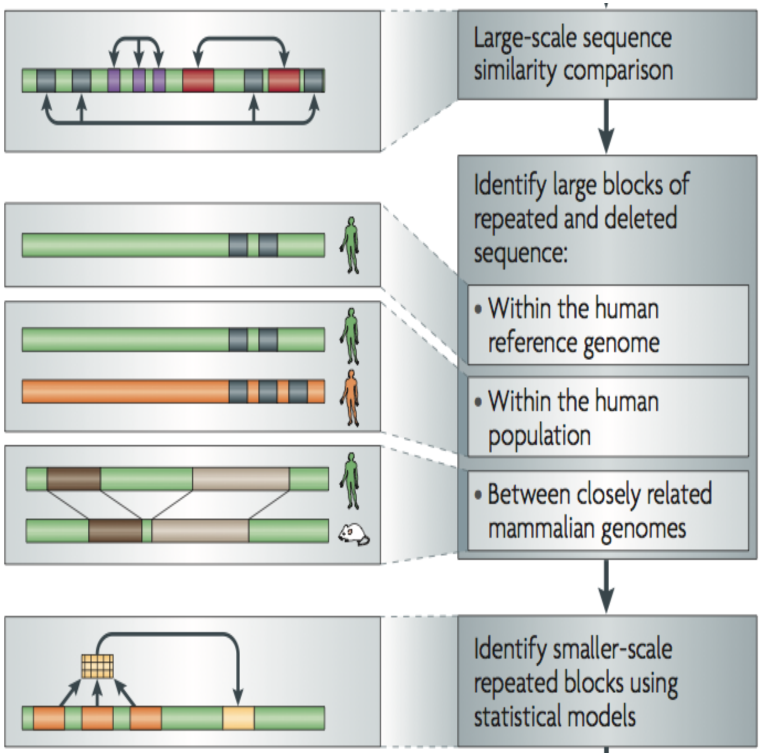
[B Hayes, Am. Sci. (Jul.- Aug. '06)]

Non-coding Annotations: Overview

There are several collections of information "tracks" related to non-coding features

Sequence features, incl. **Conservation**

Functional Genomics
ChIP-seq (Epigenome & seq. specific TF)
and ncRNA & un-annotated transcription

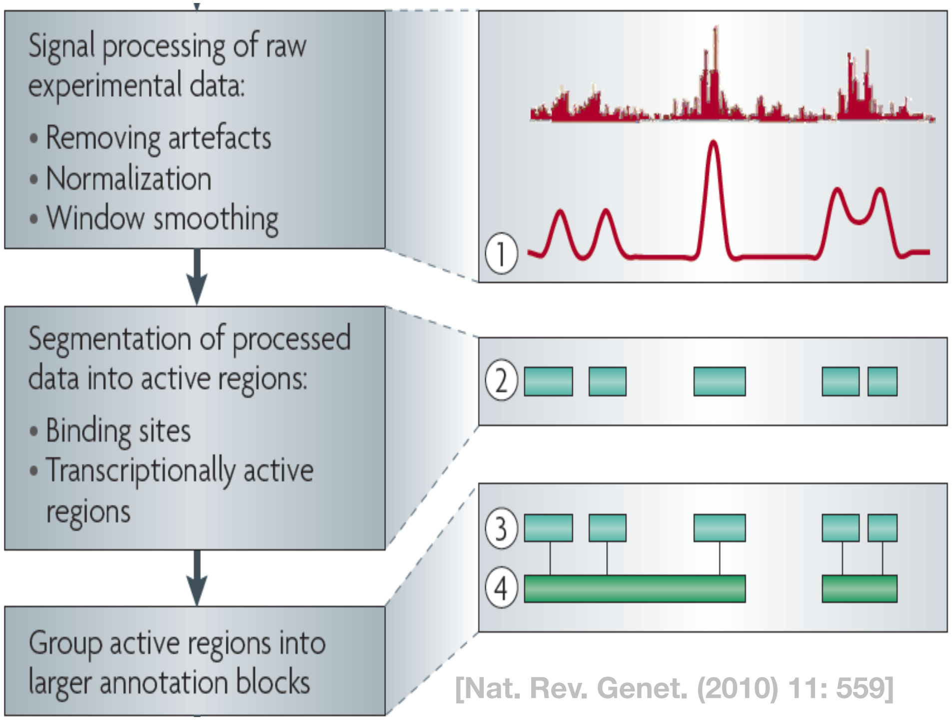


Large-scale sequence similarity comparison

Identify large blocks of repeated and deleted sequence:

- Within the human reference genome
- Within the human population
- Between closely related mammalian genomes

Identify smaller-scale repeated blocks using statistical models



Signal processing of raw experimental data:

- Removing artefacts
- Normalization
- Window smoothing

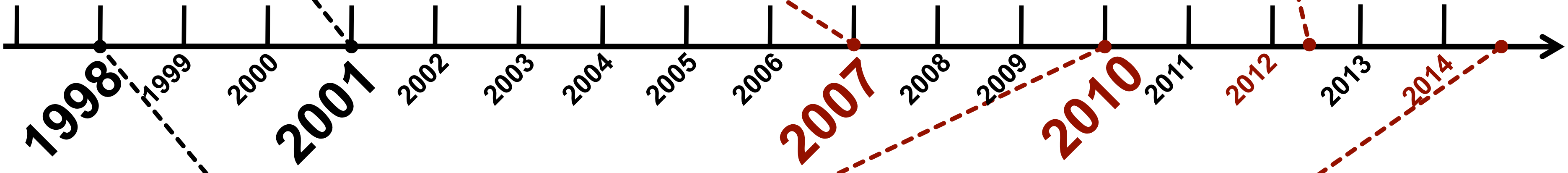
Segmentation of processed data into active regions:

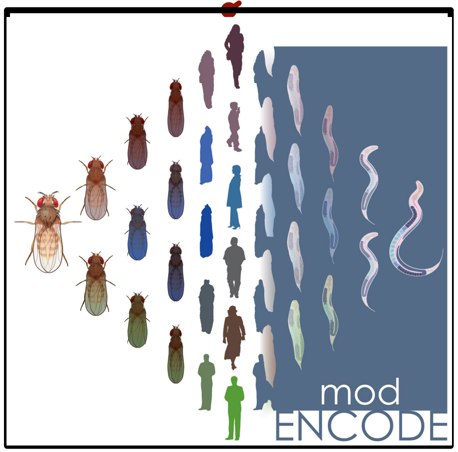
- Binding sites
- Transcriptionally active regions

Group active regions into larger annotation blocks

[Nat. Rev. Genet. (2010) 11: 559]

ENCODE Consortium & various annotation rollouts

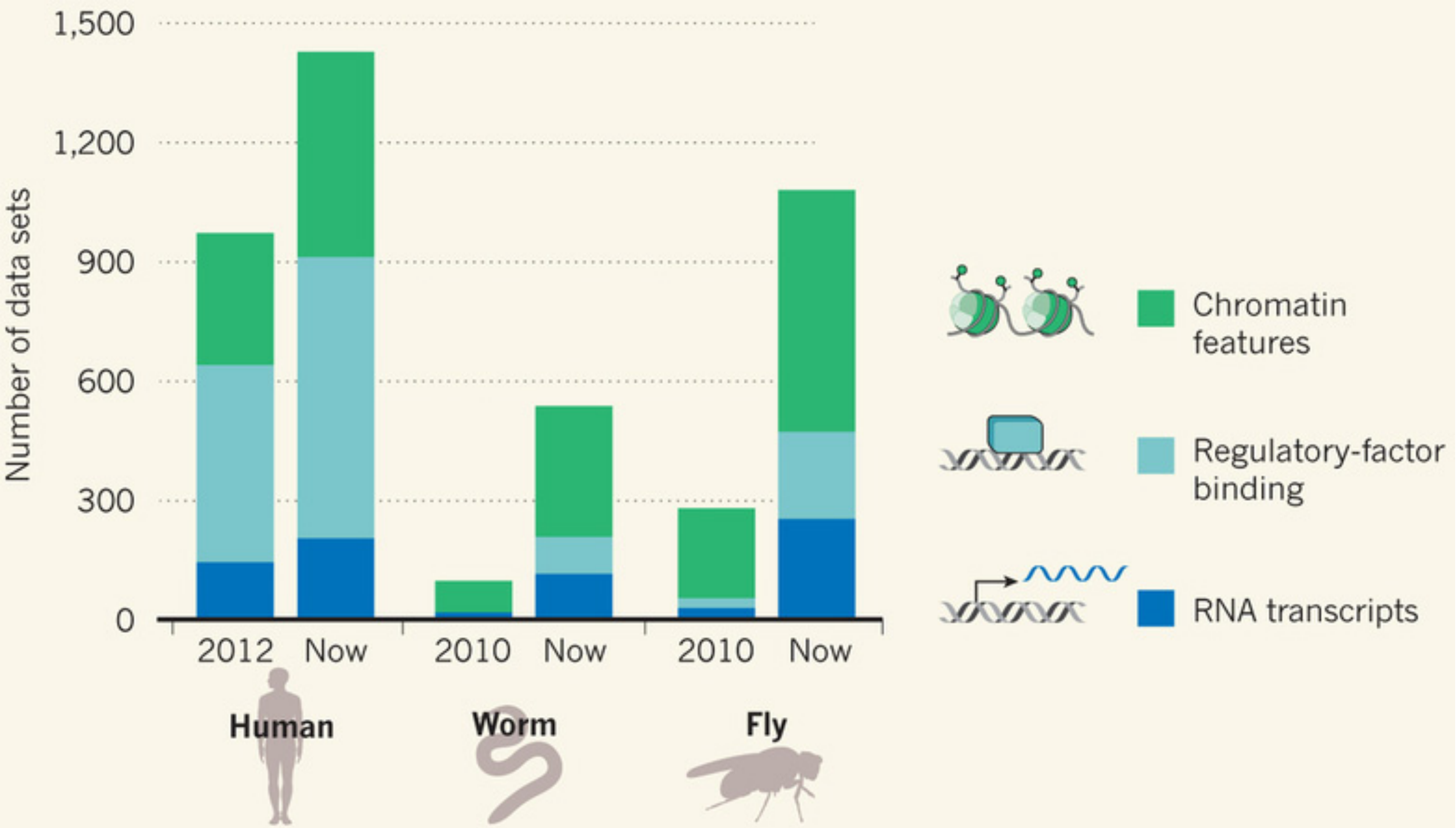




Comparative ENCODE Functional Genomics Resource

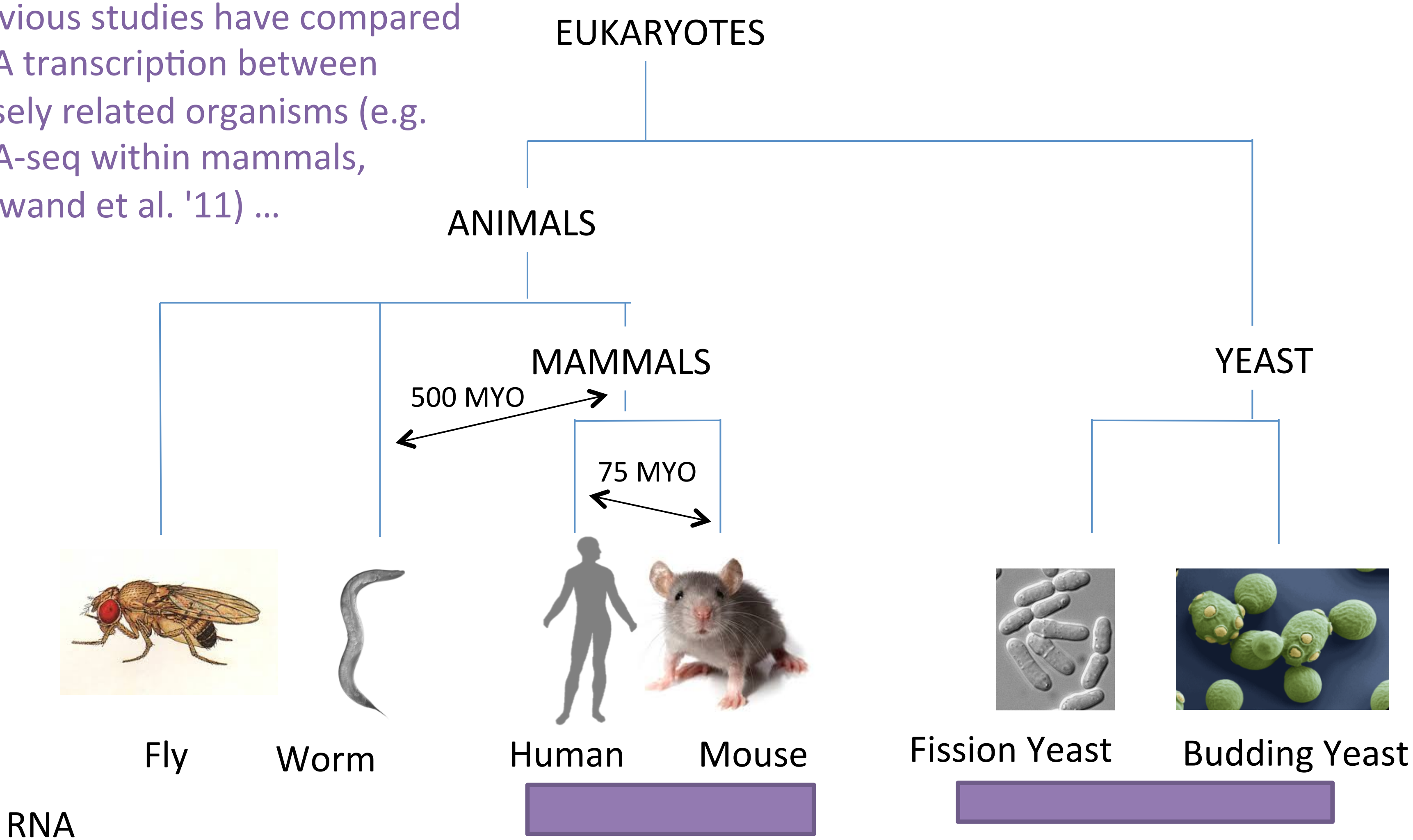
(EncodeProject.org/modENCODE.org)

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



Comparative ENCODE

Previous studies have compared RNA transcription between closely related organisms (e.g. RNA-seq within mammals, Brawand et al. '11) …



Comparative ENCODE

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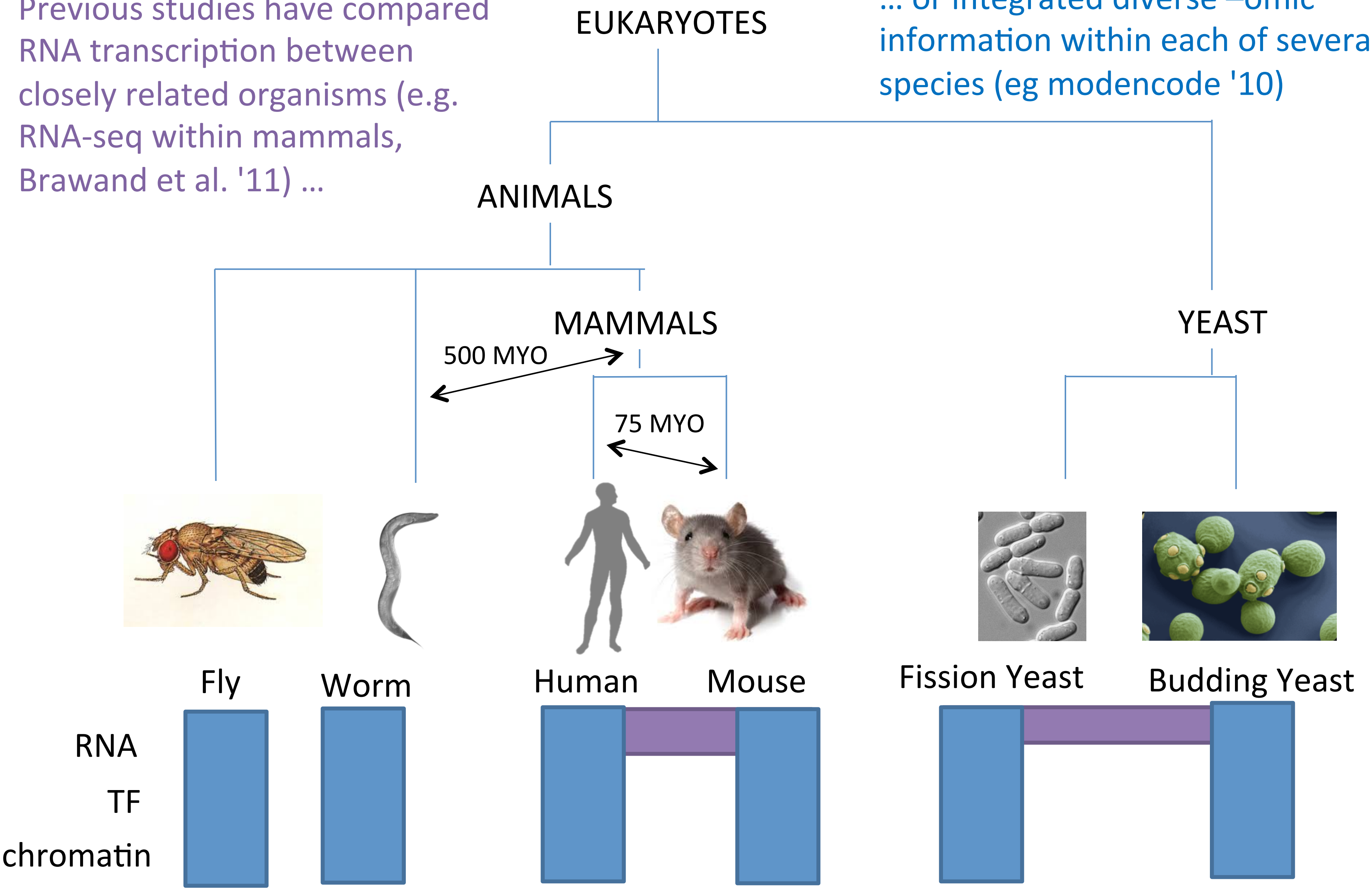
… or integrated diverse –omic information within each of several species (eg modencode '10)



EUKARYOTES

ANIMALS

MAMMALS

YEAST

500 MYO

75 MYO

Fly

Worm

Human

Mouse

Fission Yeast

Budding Yeast

RNA

TF

chromatin

Comparative ENCODE

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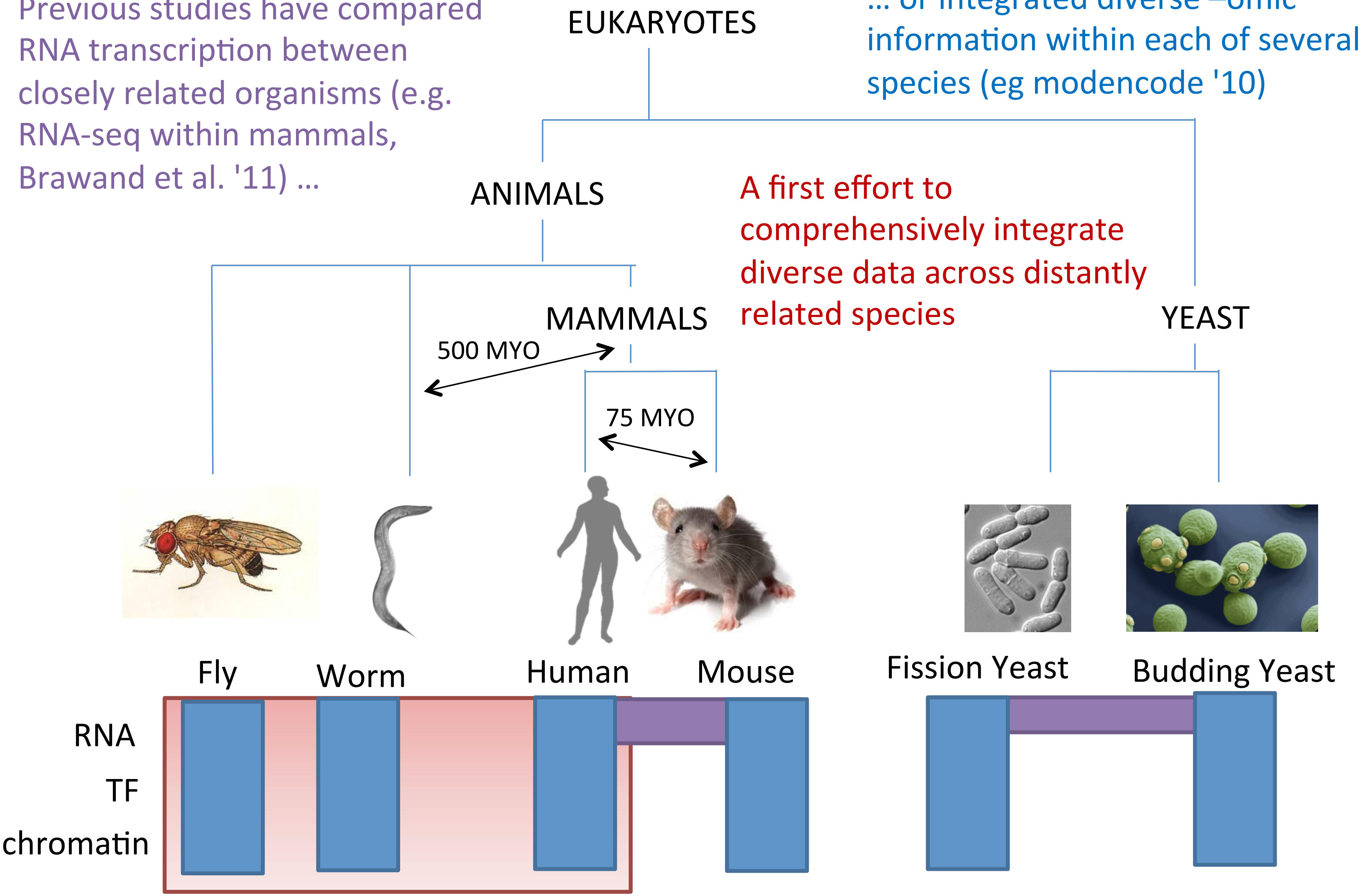
… or integrated diverse –omic information within each of several species (eg modencode '10)

A first effort to comprehensively integrate diverse data across distantly related species



Applications of Machine Learning for Comparing Transcriptomes of Distant Organisms

- **Intro to Comparative ENCODE**
  - Lots of Matched Data for Comparative Analysis
- **App. #1: Characterizing ncRNAs & TARs**
  - Not much news in canonical gene models
  - Simple contig search (TARs) finds uniform density of non-canonical transcription
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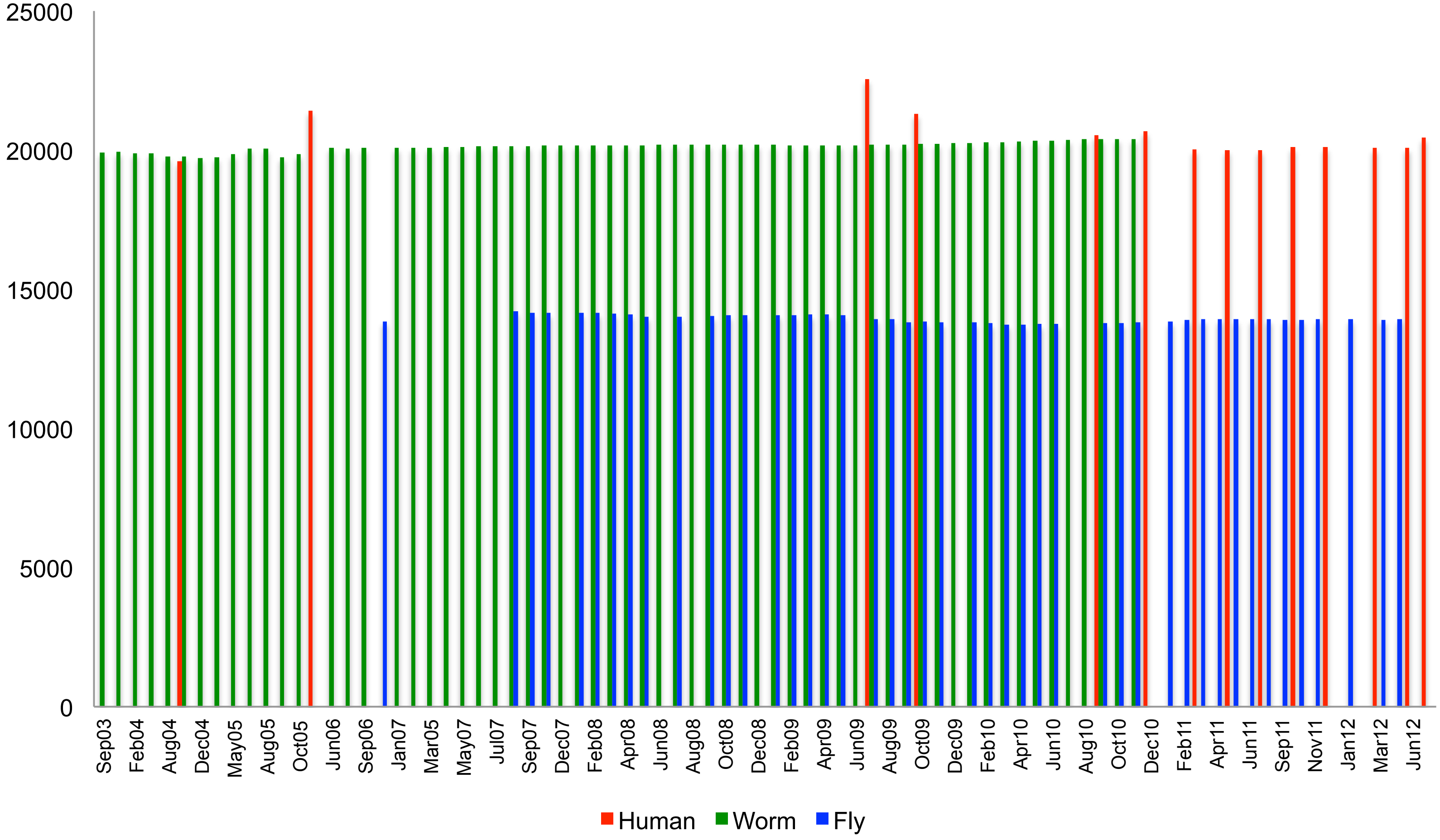
  - Surprisingly, a few TFs are quite predictive

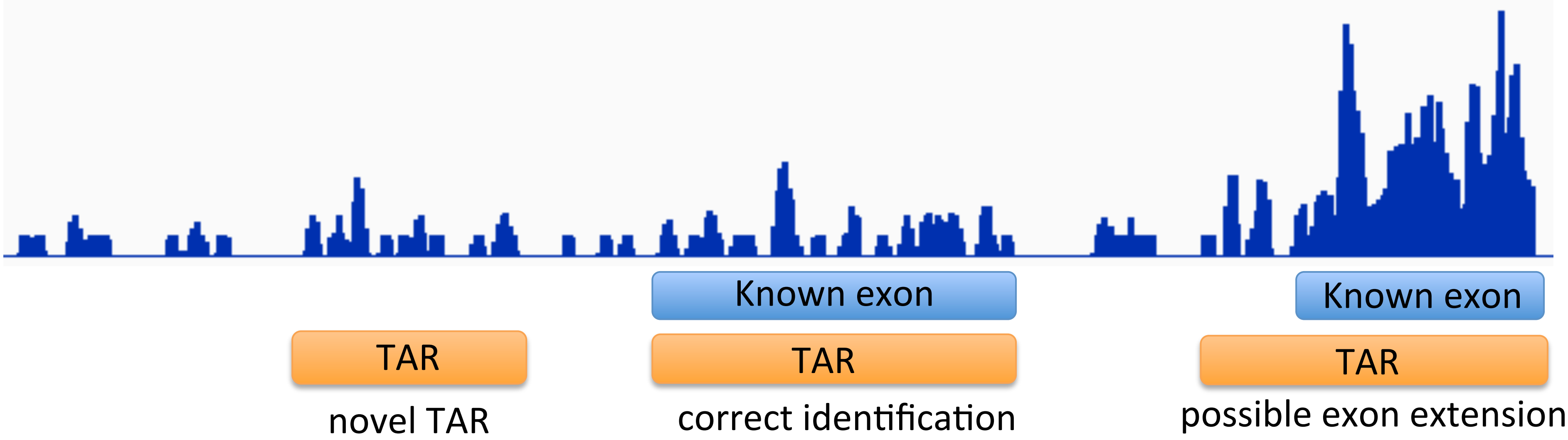
Protein-coding gene counts in worm, fly & human have stabilized & have remained fairly constant



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

Discovering Transcriptionally Active Regions (novel RNA contigs)

- Cluster reads setting minimum-run and maximum gap parameters for newly identified transcribed regions (TARs)
- Assess exon discovery rates for known genes and noncoding RNAs



Known exon

Known exon

TAR

TAR

TAR

novel TAR

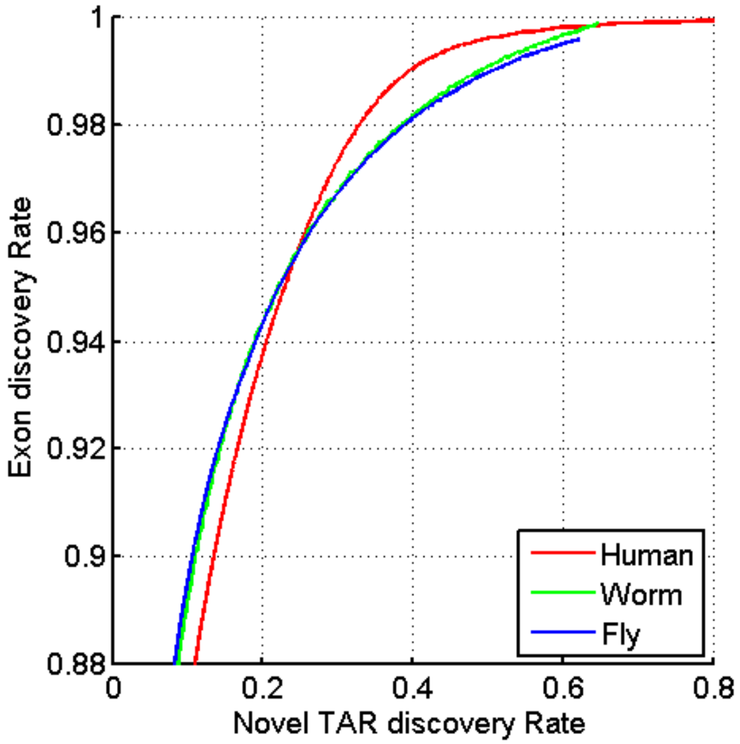
correct identification

possible exon extension

ENCODE RNA-Seq Data

Uniform Annotation of non-coding Elements

- Uniformly processed the RNA-seq expression compendium and for identification of pervasively transcribed regions



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

Annotated ncRNAs

			Human			**Worm**			**Fly**		
			Elements	**Genome Coverage**		**Elements**	**Genome Coverage**		**Elements**	**Genome Coverage**	
				Kb	**%**		**Kb**	**%**		**Kb**	**%**
mRNAs (exons)			20,007	86,560	3.0	21,192	34,437	34.3	13,940	35,970	28.0
Pseudogenes			11,216	27,089	0.95	881	1,343	1.3	145	155	0.12
Annotated ncRNAs	**Comparable ncRNAs**	**pri-miRNA**	58	1,158	0.04	44	16	0.02	43	300	0.23
		pre-miRNAs	1,756	162	0.006	221	20	0.02	236	22	0.02
		tRNAs	624	47	0.002	609	45	0.04	314	22	0.02
		snoRNAs	1,521	168	0.006	141	16	0.02	287	34	0.03
		snRNAs	1,944	210	0.007	114	14	0.01	47	7	0.006
		lncRNAs	10,840	10,581	0.37	233	184	0.18	852	868	0.68
	Other ncRNAs		5,411	3,268	0.11	40,104	2,329	2.3	376	2,103	1.6
		nc-piRNA loci	88	1,272	0.04	35,329	449	0.45	27	1,473	1.1
Total			22,154	17,770	0.62	41,466	2,611	2.6	2,155	3,279	2.6

Identify non-canonical transcription in regions of the genome excluding mRNA exons, pseudogenes or annotated ncRNAs.

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

& Non-Canonical Transcription

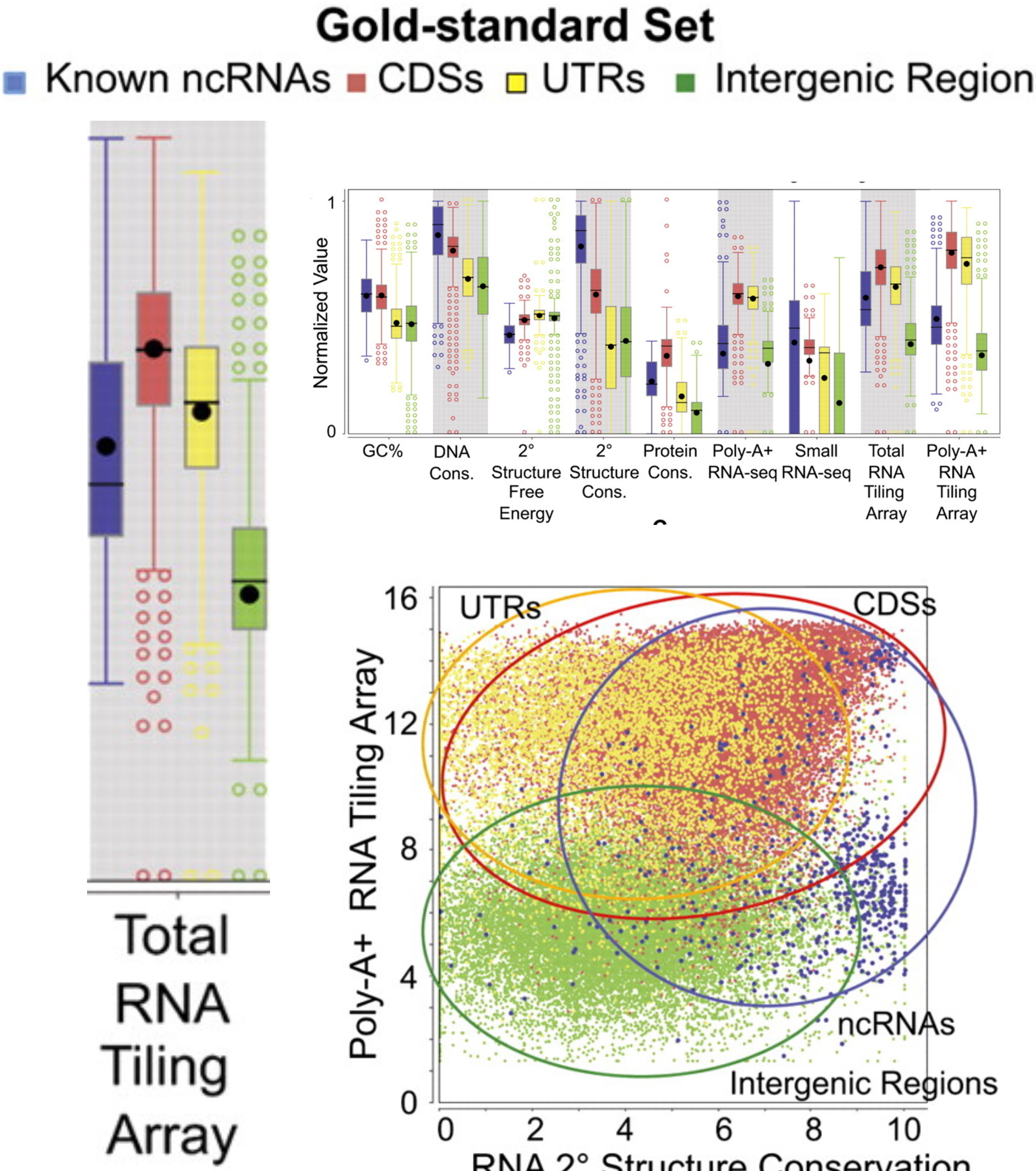
	Human			**Worm**			**Fly**		
	Elements	**Genome Coverage**		**Elements**	**Genome Coverage**		**Elements**	**Genome Coverage**	
		Kb	**%**		**Kb**	**%**		**Kb**	**%**
Total ncRNAs	22,154	17,770	0.62	41,466	2,611	2.6	2,155	3,279	2.6
Regions Excluding mRNAs, Pseudogenes or Annotated ncRNAs	283,816	2,731,811	95.5	143,372	63,520	63.3	60,108	89,445	69.6
Transcription Detected (TARs)	708,253	916,401	32.0	232,150	37,029	36.9	83,618	44,256	34.5
Supervised Predictions	104,016	13,835	0.48	2,525	392	0.39	599	164	0.13

- Similar fraction of non-canonical transcription of non-canonical transcription in human, worm and fly
  - 32-37% of each genome

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

lncRNA: Machine-learning Identification of many candidate ncRNAs through evidence integration

- No single feature (e.g. expr. expts., conservation, or sec. struc.) finds all known ncRNAs => combine features in stat. model
- 90% PPV, 13 of 15 tested validate

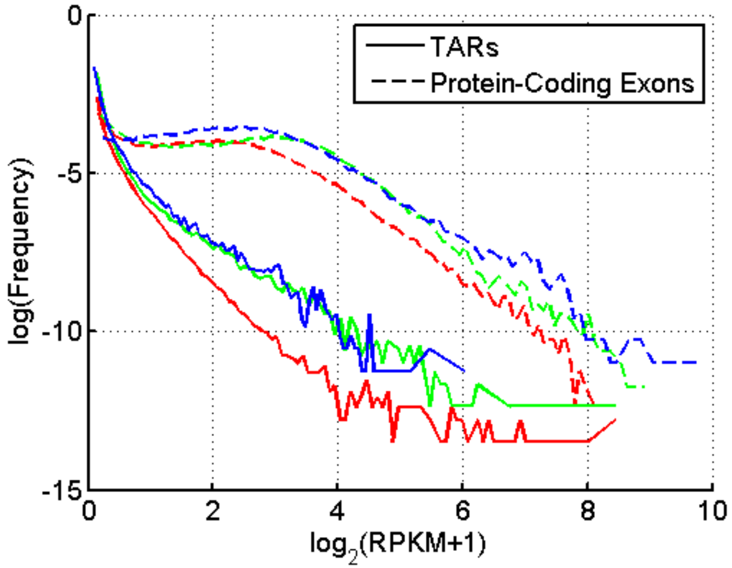


[Lu et al. Genome Res. 2011;21:276-285]

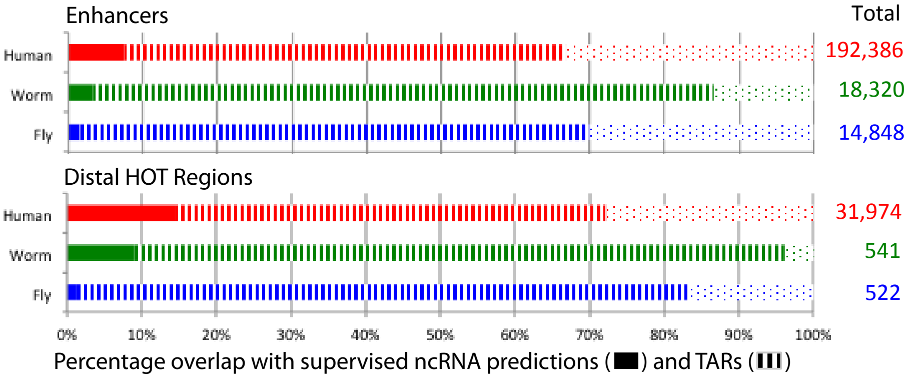
TAR Characterization

Non-canonical transcription (TARs):

- Mostly transcribed at lower levels than protein-coding genes.



- Enrichment for overlap of TARs with ENCODE enhancers and distal HOT regions -> potential enhancer RNAs (eRNAs).



Human, **Worm** & **Fly**

[ENCODE-modencode Transcriptome paper, Nature (in press), doi: 10.1038/nature13424]

HOT Regions = High TF Co-occupancy

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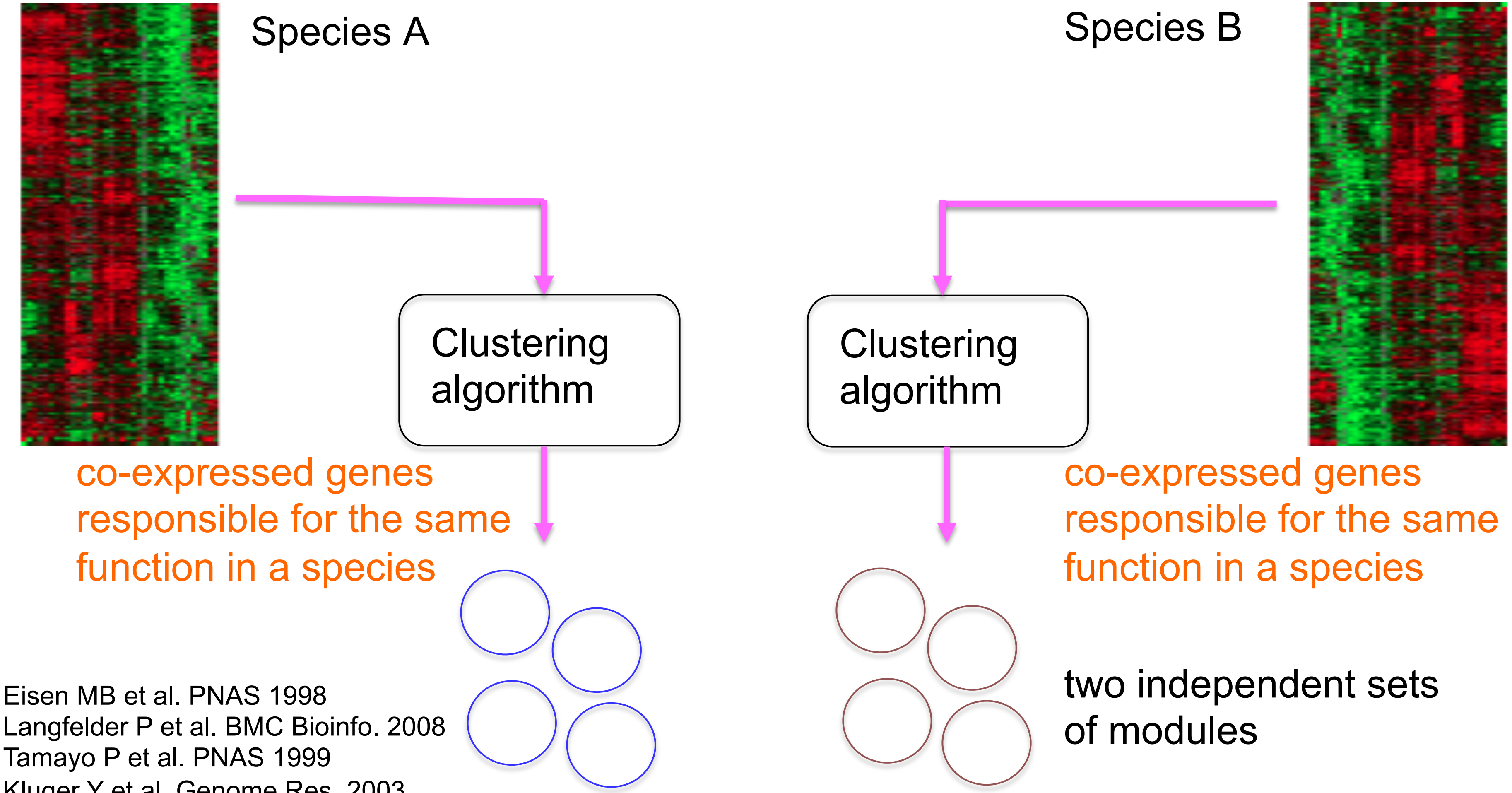
Expression clustering: revisiting an ancient problem



Species A

Species B

Clustering algorithm

Clustering algorithm

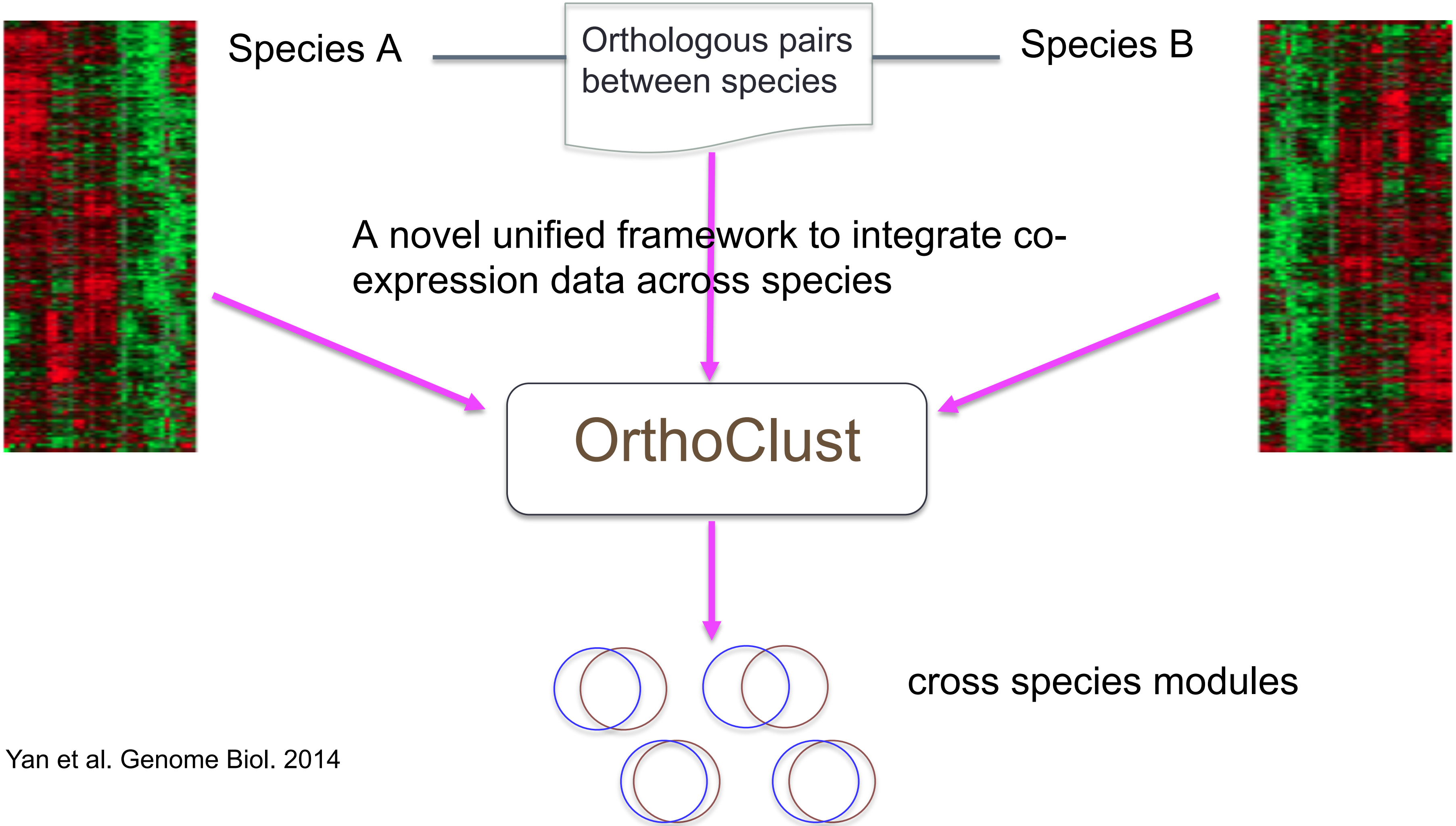
co-expressed genes responsible for the same function in a species

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

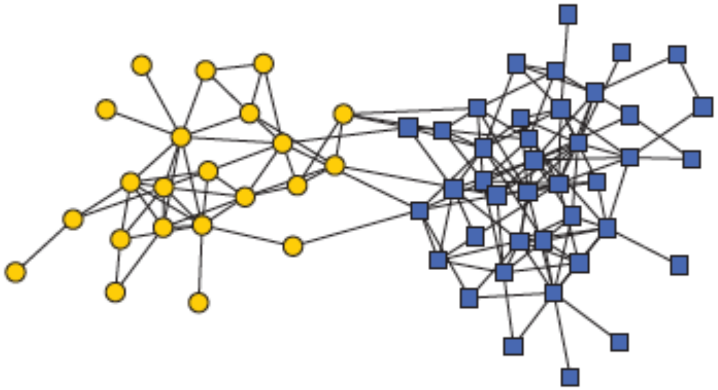
A novel unified framework to integrate co-expression data across species

OrthoClust

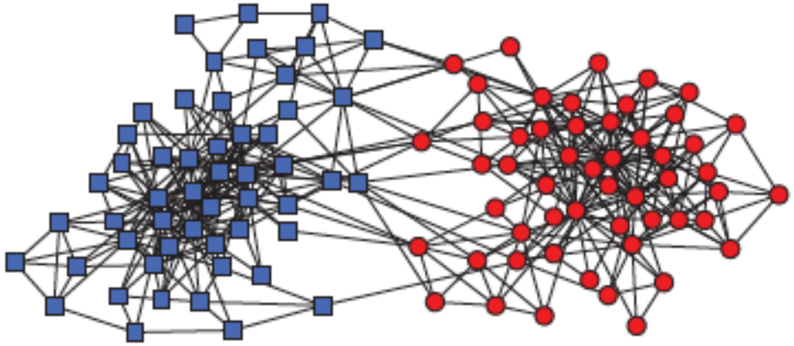
cross species modules

Yan et al. Genome Biol. 2014

Network modularity



Dolphin social network



Political books

Newman Phy. Rev. E 2013

degree of node i

adjacency matrix

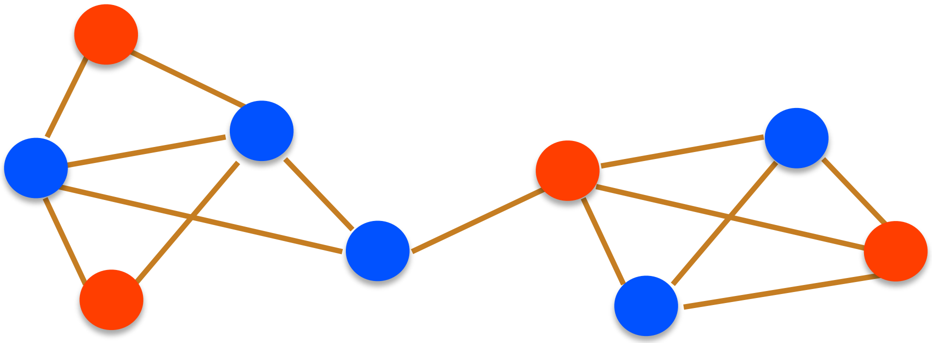
$$Q = \frac{1}{2m} \sum_{i,j} \left(W_{ij} - \boxed{\frac{k_i k_j}{2m}} \right) \delta_{\sigma_i \sigma_j}$$

whether or not
i, j are in the
same module

number of edges

expected number of
edges between i and j

Network modularity



$$Q \approx 0$$

degree of node i

adjacency matrix

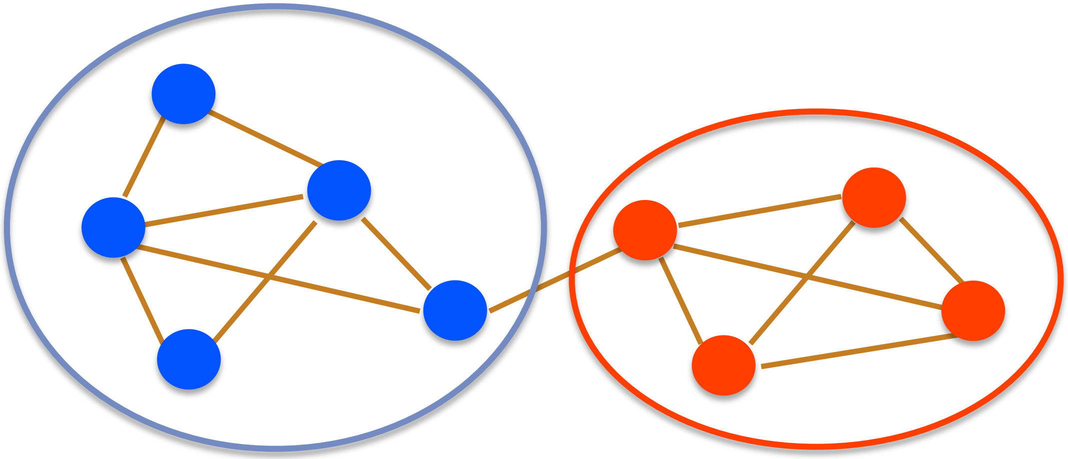
$$Q = \frac{1}{2m} \sum_{i,j} \left(W_{ij} - \boxed{\frac{k_i k_j}{2m}} \right) \delta_{\sigma_i \sigma_j}$$

whether or not i, j are in the same module

number of edges

expected number of edges between i and j

Network modularity



$$Q = Q_{max}$$

Optimization problem

degree of node i

adjacency matrix

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

whether or not
i, j are in the
same module

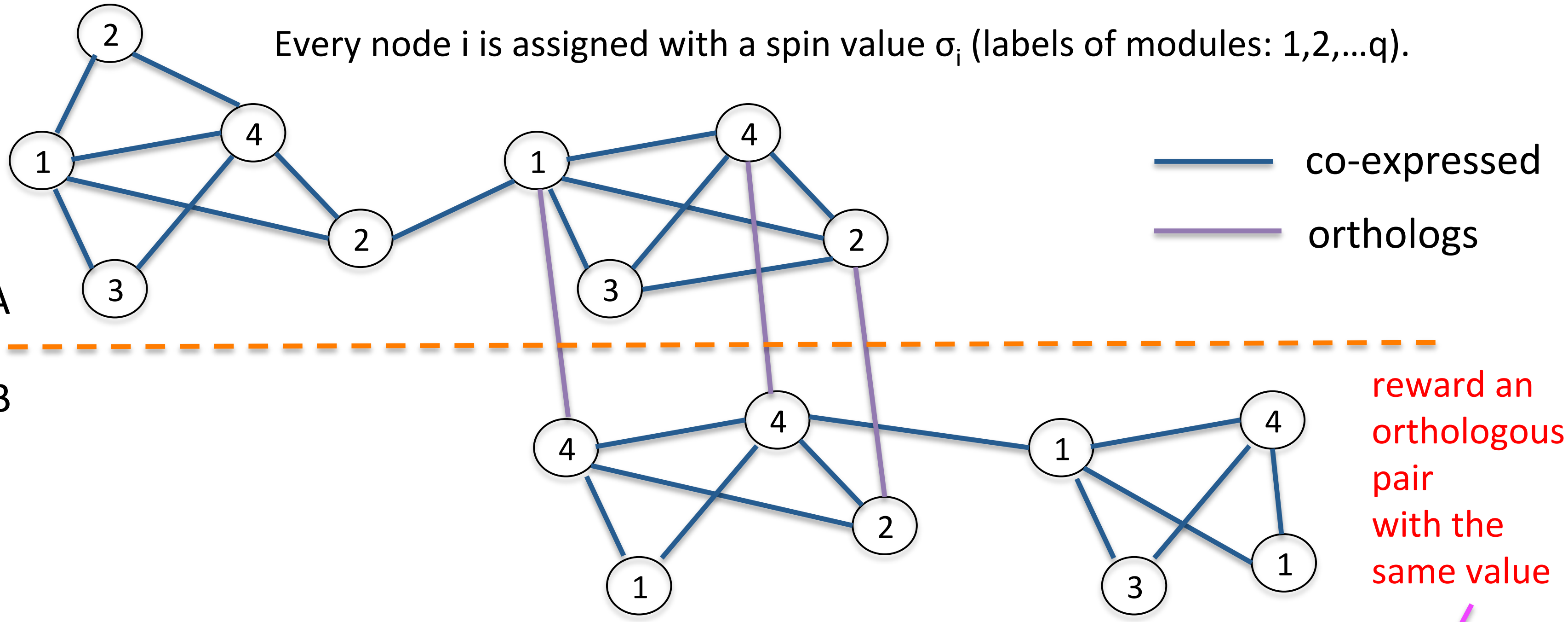
number of edges

expected number of
edges between i and j

[Yan et al. *GenomeBiol* 15:R100 ('14)]

A toy example [orthoclust]

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



Species A

Species B

reward an orthologous pair with the same value

$$H = \boxed{\sum_{i,j}\left(-W_{ij}^{(A)}+p_{ij}^{(A)}\right)\delta_{\sigma_i\sigma_j} + \sum_{i',j'}\left(-W_{i'j'}^{(B)}+p_{i'j'}^{(B)}\right)\delta_{\sigma_{i'}\sigma_{j'}}} - \kappa\boxed{\sum_{(i,j')\in Ortho}\delta_{\sigma_i\sigma_{j'}}}$$

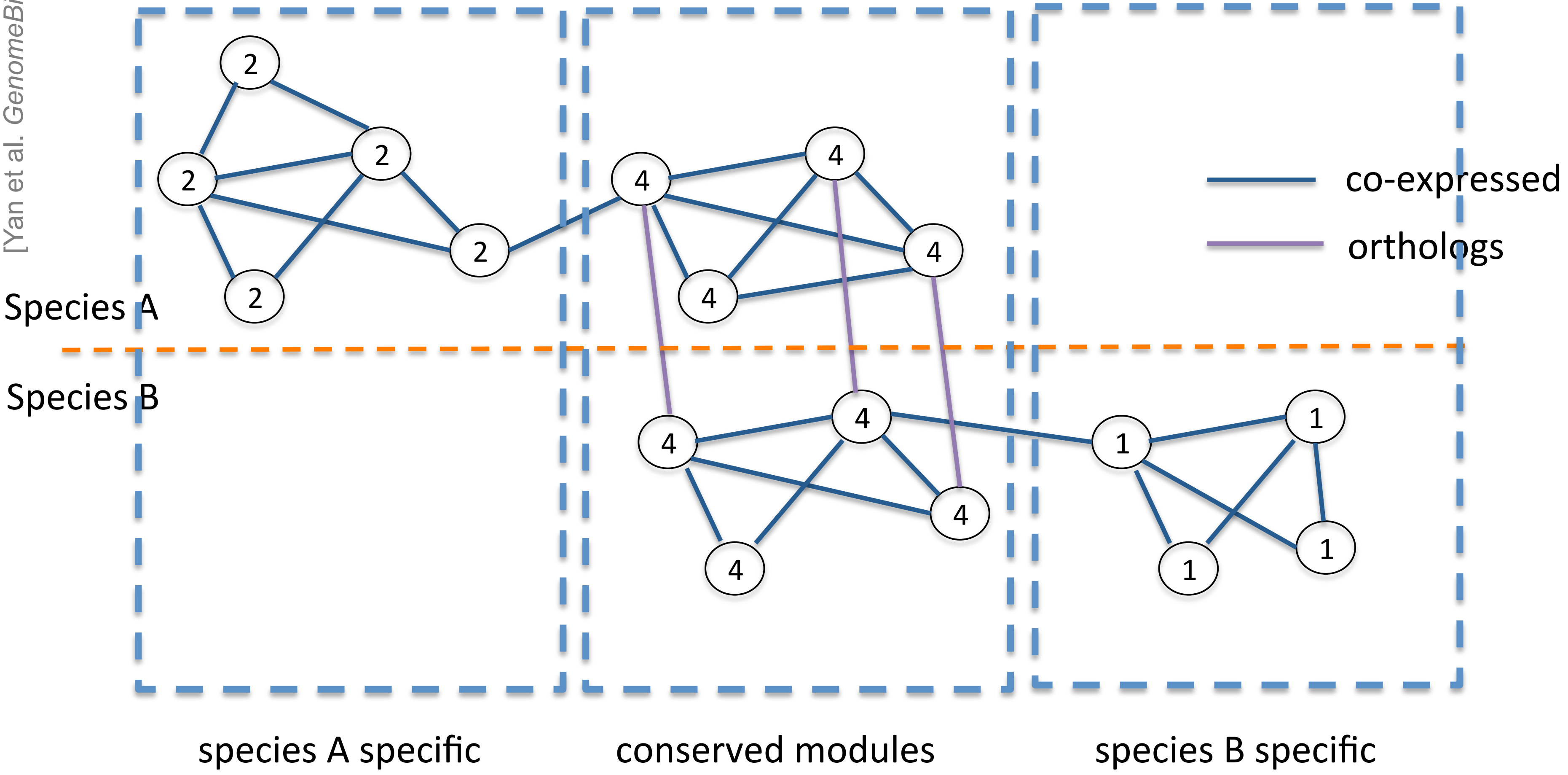
reward a co-expressed pair with the same value

punish a non co-expressed pair with the same value

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

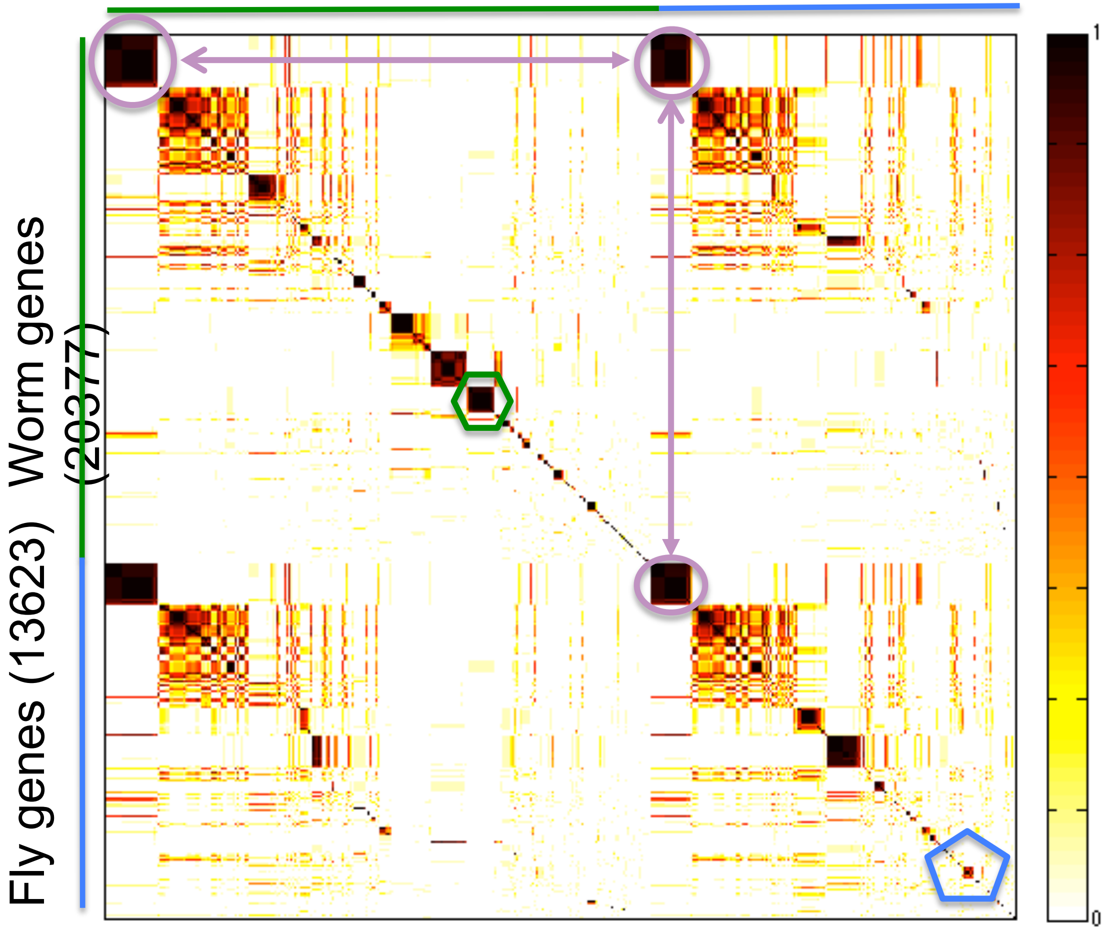
[Yan et al. *GenomeBiol* 15:R100 ('14)]

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.

Cross-species clusters for worm and fly



co-association frequency

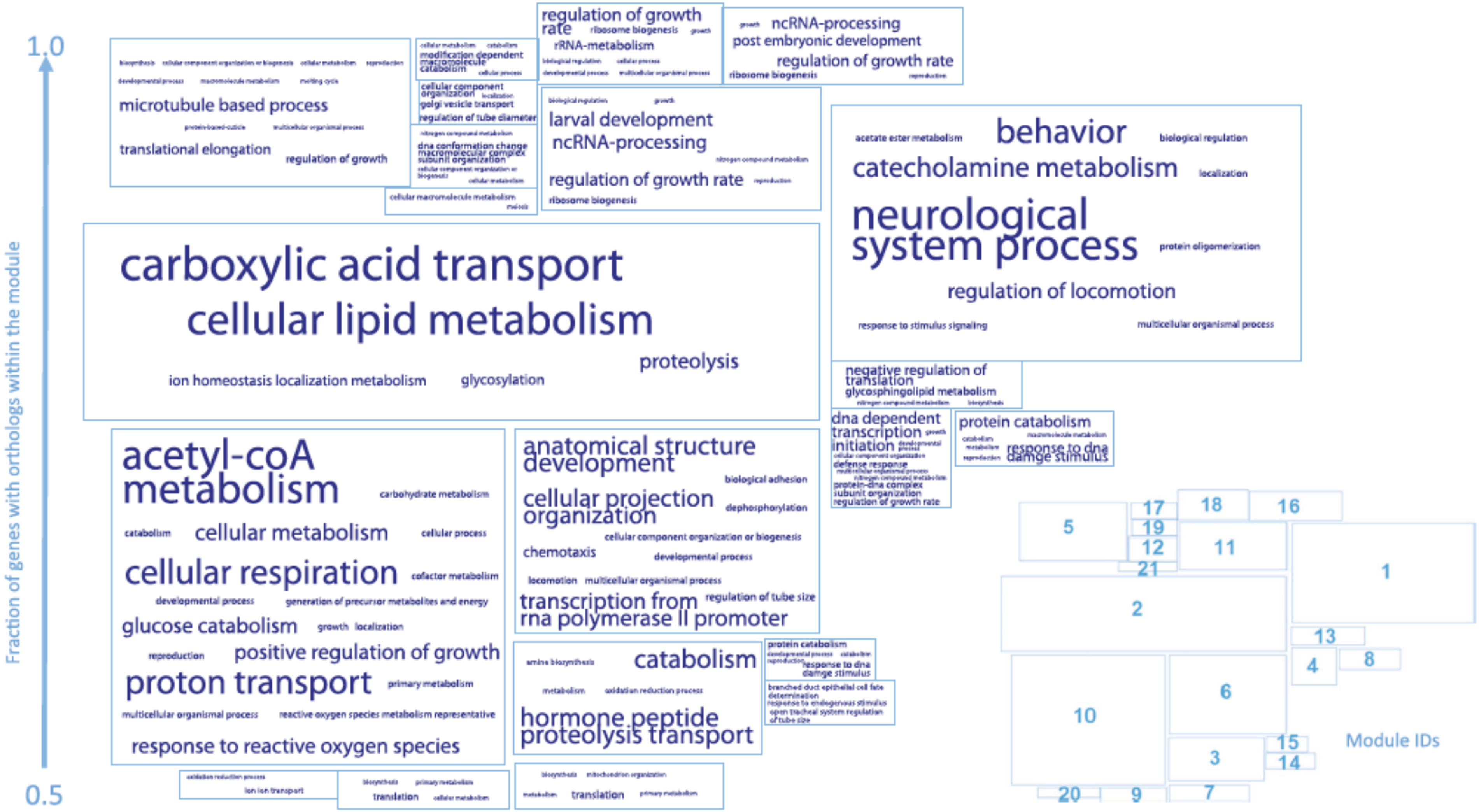
GO terms of conserved modules

GO terms of specific modules

worm specific	dauer entry
fly specific	chitin activities

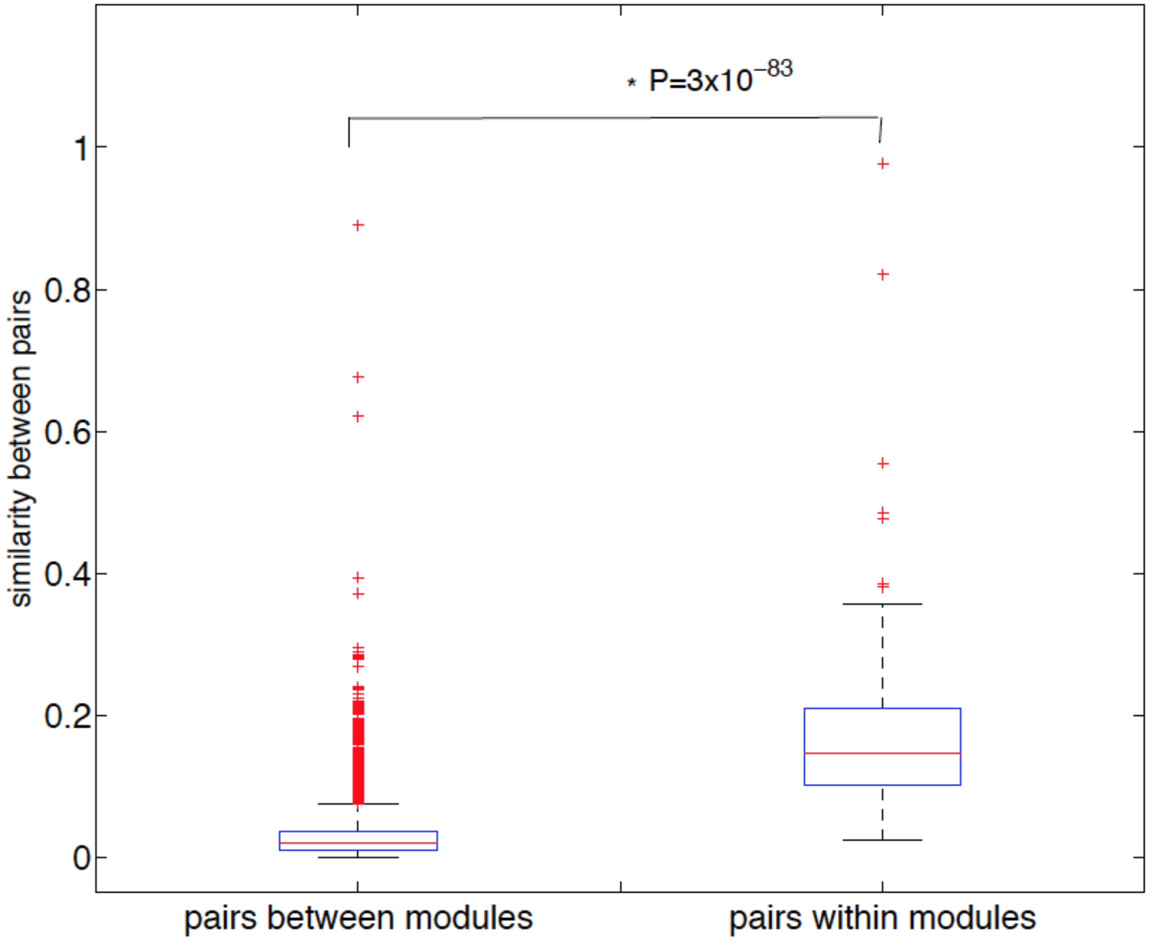
Yan KK et al. Genome Biology. 2014

More conserved modules



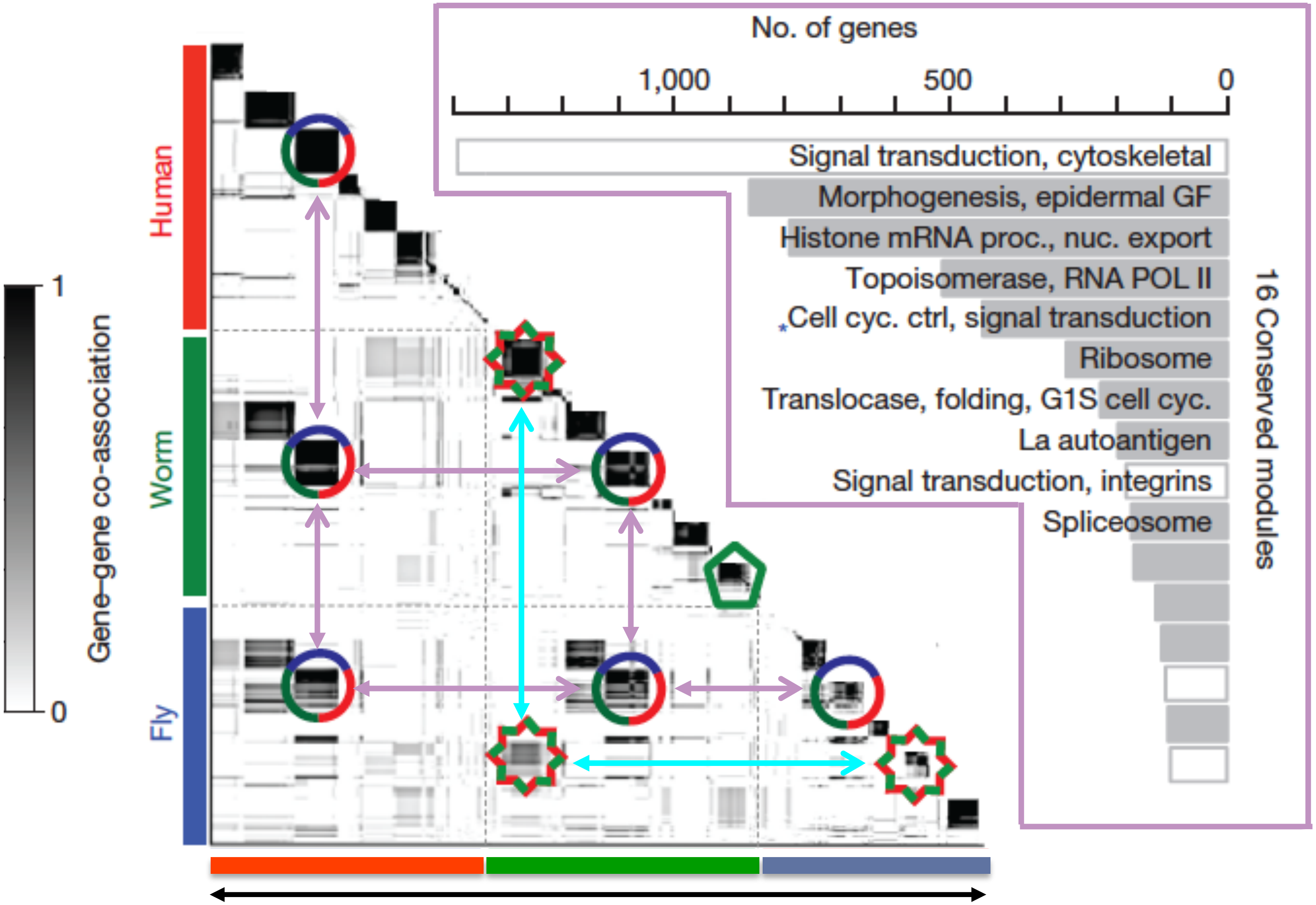
Yan KK et al. Genome Biology. 2014

Separation of modules in terms of GO



Yan KK et al. Genome Biology. 2014

Application for more than 2 species



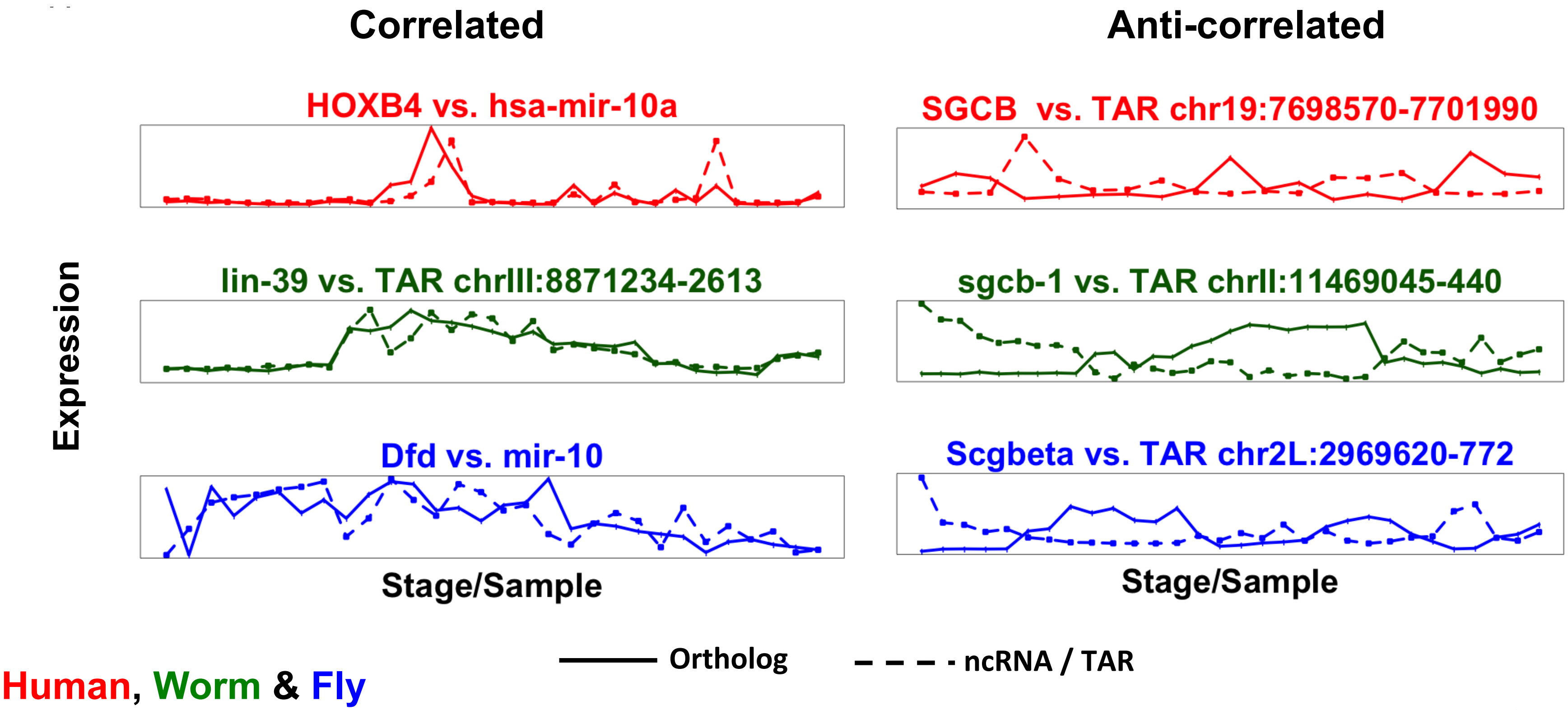
~55000 genes

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

ncRNAs associated with modules

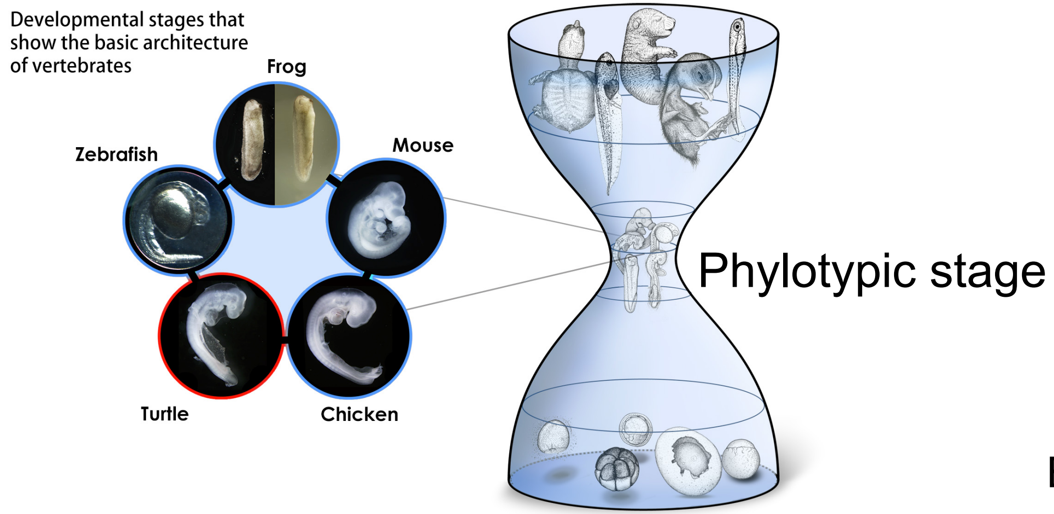
Non-canonical transcription (TARs):

- Identify TARs that are significantly correlated and anti-correlated with genes in the 16 modules.

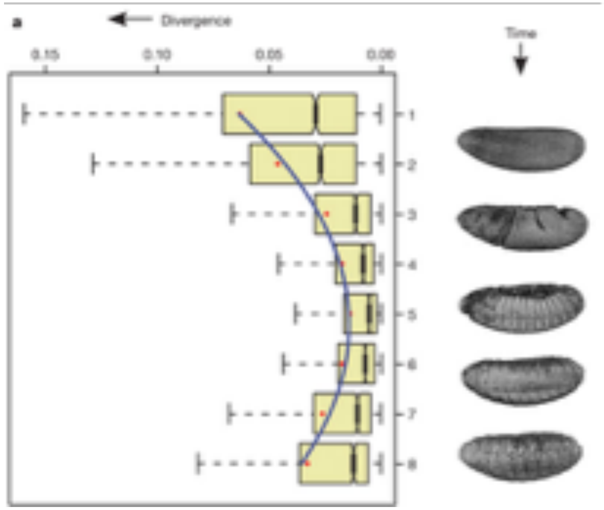


[*Nature* 512:445 ('14); doi: 10.1038/nature13424]

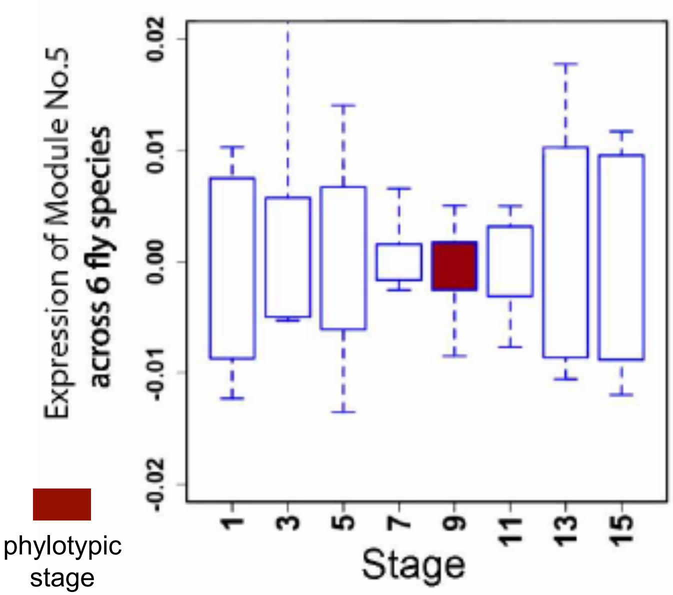
Conserved modules exhibit canonical hourglass behavior



Illustrations courtesy Naoki Irie



Expression divergence across species is minimized during phylotypic stage (Kalinka et al. Nature 2010)



<u>Canonical Inter-organism Behavior</u>

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

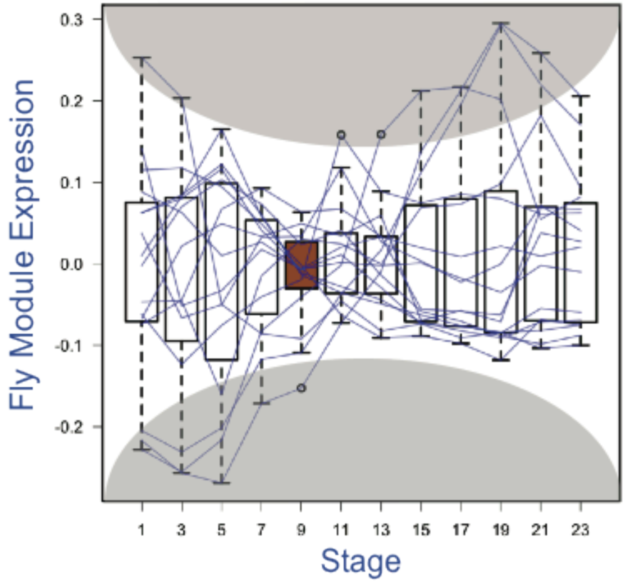
[*Nature* 512:445 ('14); doi: 10.1038/nature13424]

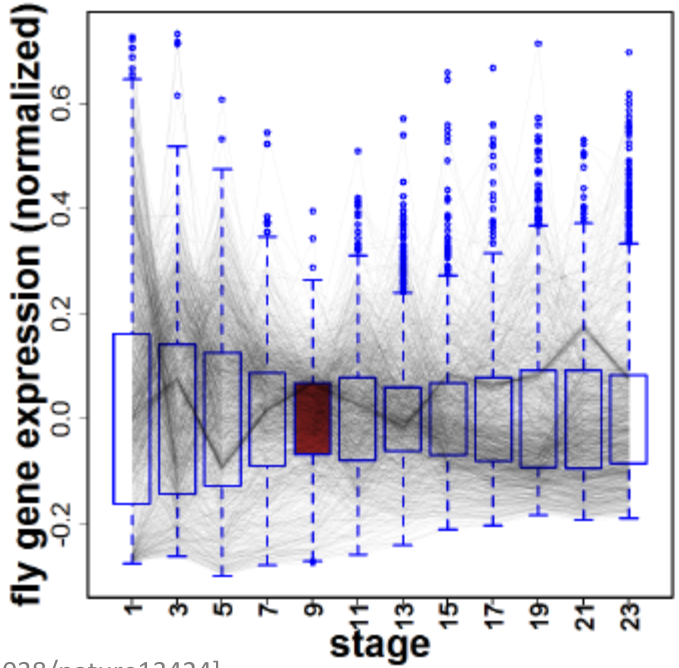
Hourglass Behavior

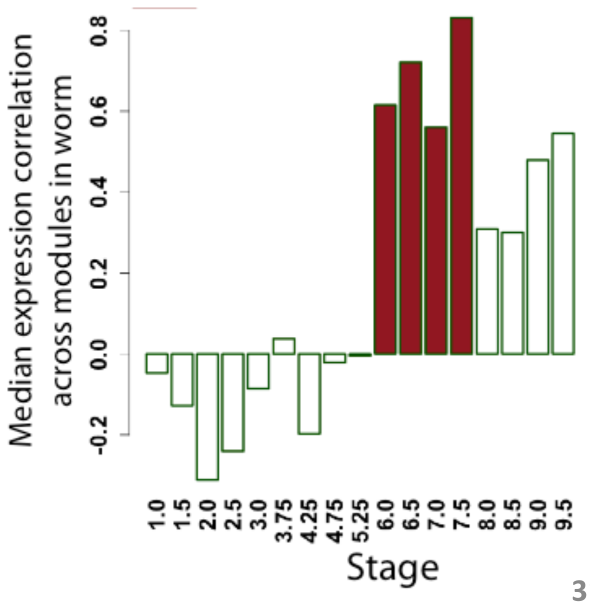
🟥 **phylotypic stage**

Intra-organism Behavior also Present

- We observe that the expression of genes across 12 modules are the most tightly coordinated at the phylotypic stage (fly).
- Strongly correlated correlation at phylotypic stage (worm).

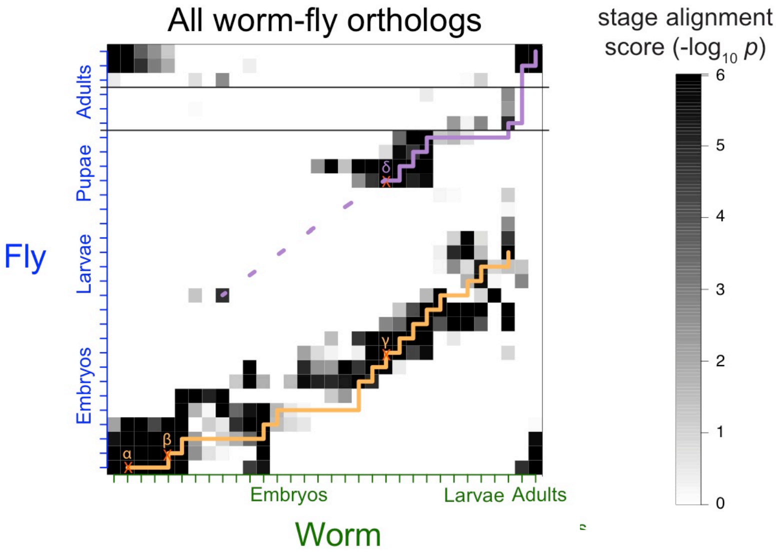






[*Nature* 512:445 ('14); doi: 10.1038/nature13424]

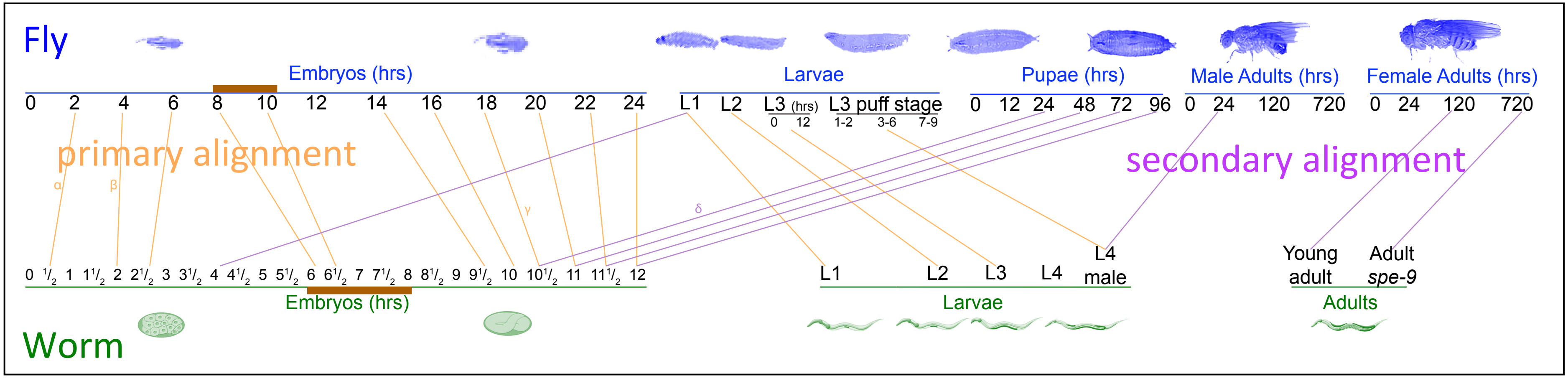
Alignment of Developmental Time-Course



For worm & fly find stage-specific genes

We can align developmental stages using fraction of shared orthologs between worm and fly amongst these

Reuse of genes from LE in worm in fly pupa



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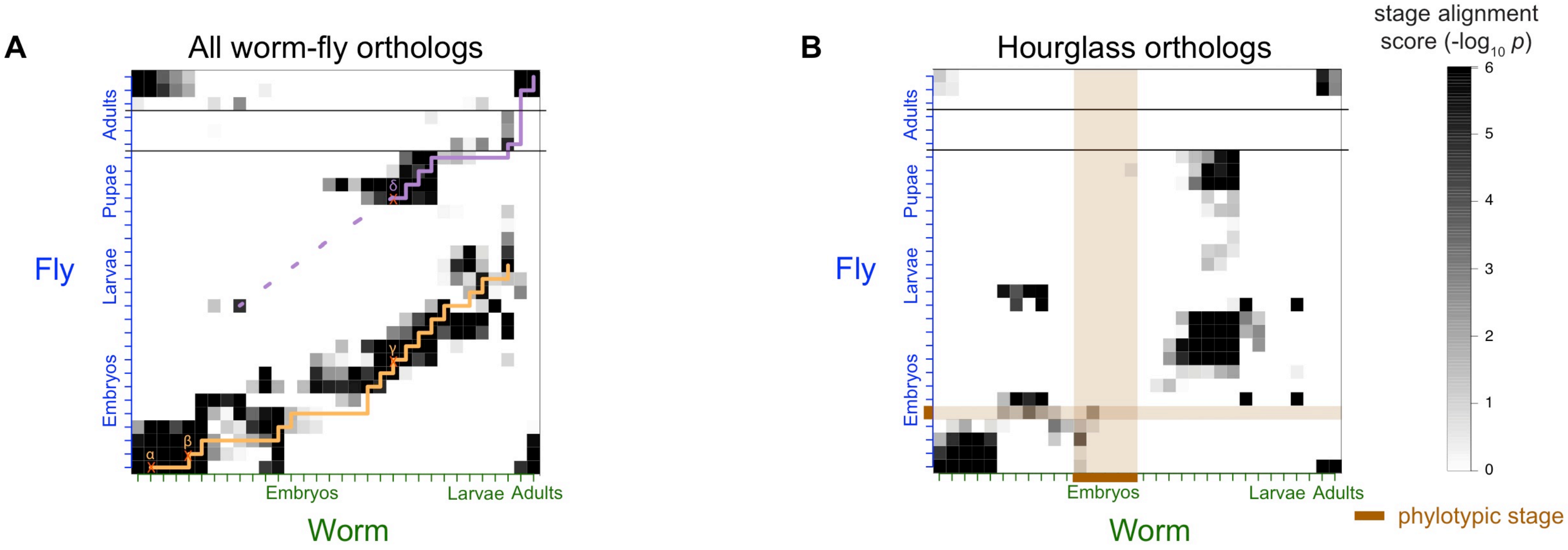
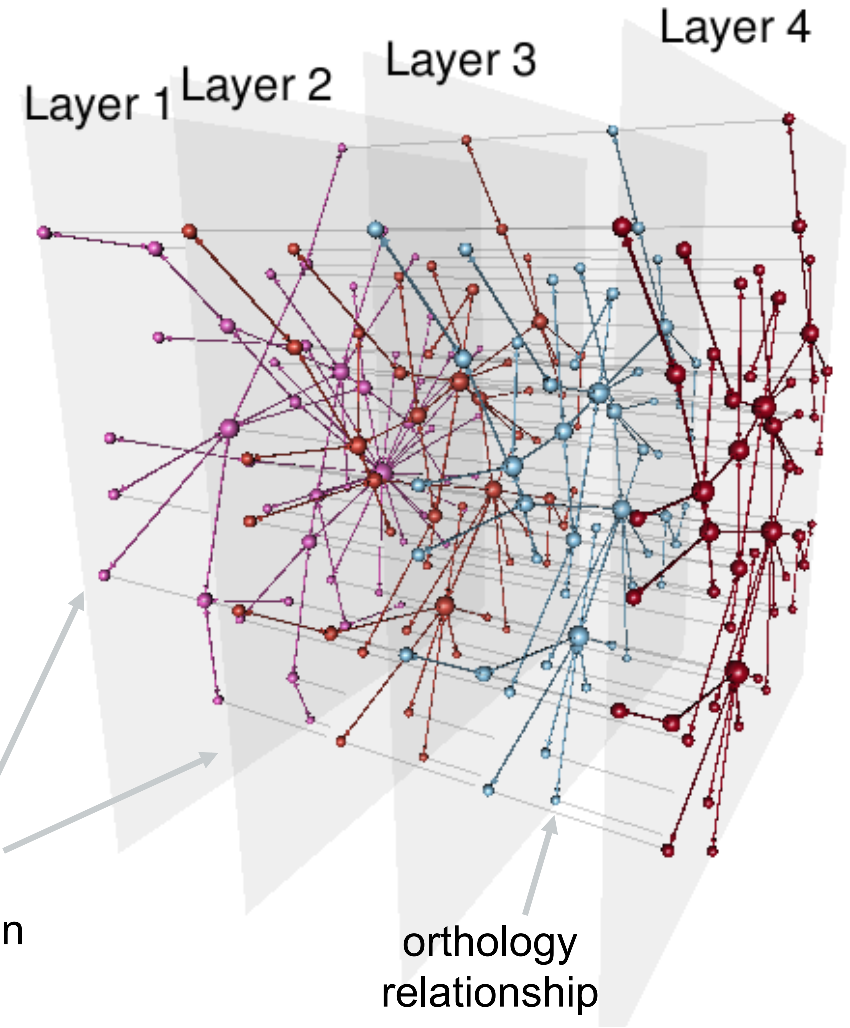


Using only orthologs in 12 "hourglass" modules show stronger alignment except for absence of genes at the phylotypic stage

- By definition genes in hourglass modules are not phylotypic stage specific, hence the gap

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

Other applications and generalizations

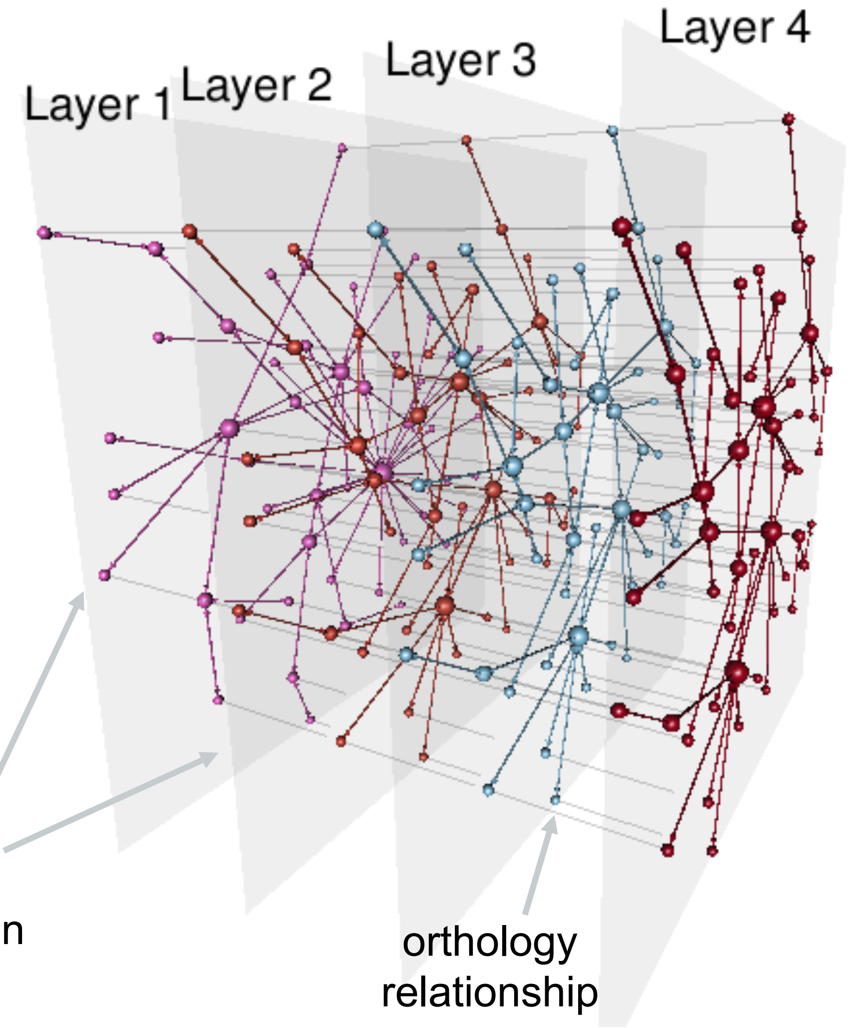


expression networks:
- worm vs fly vs human

orthology relationship

image courtesy http://muxviz.net/

Other applications and generalizations



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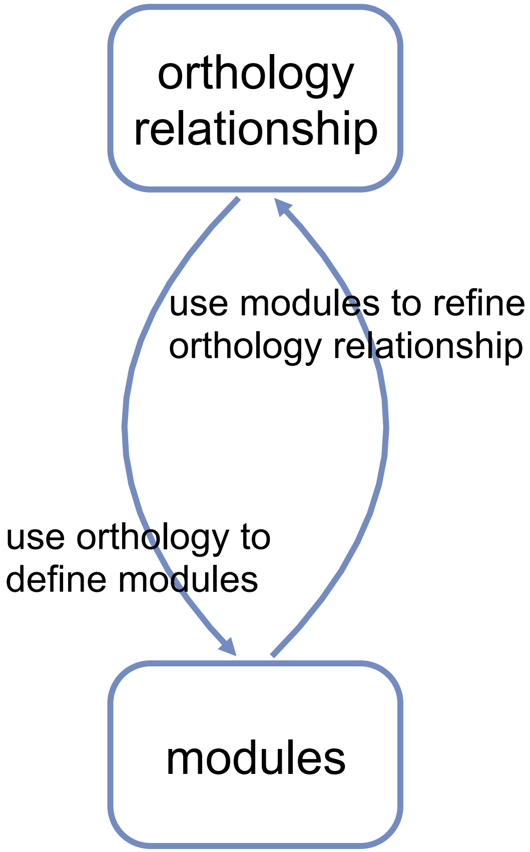


orthology relationship

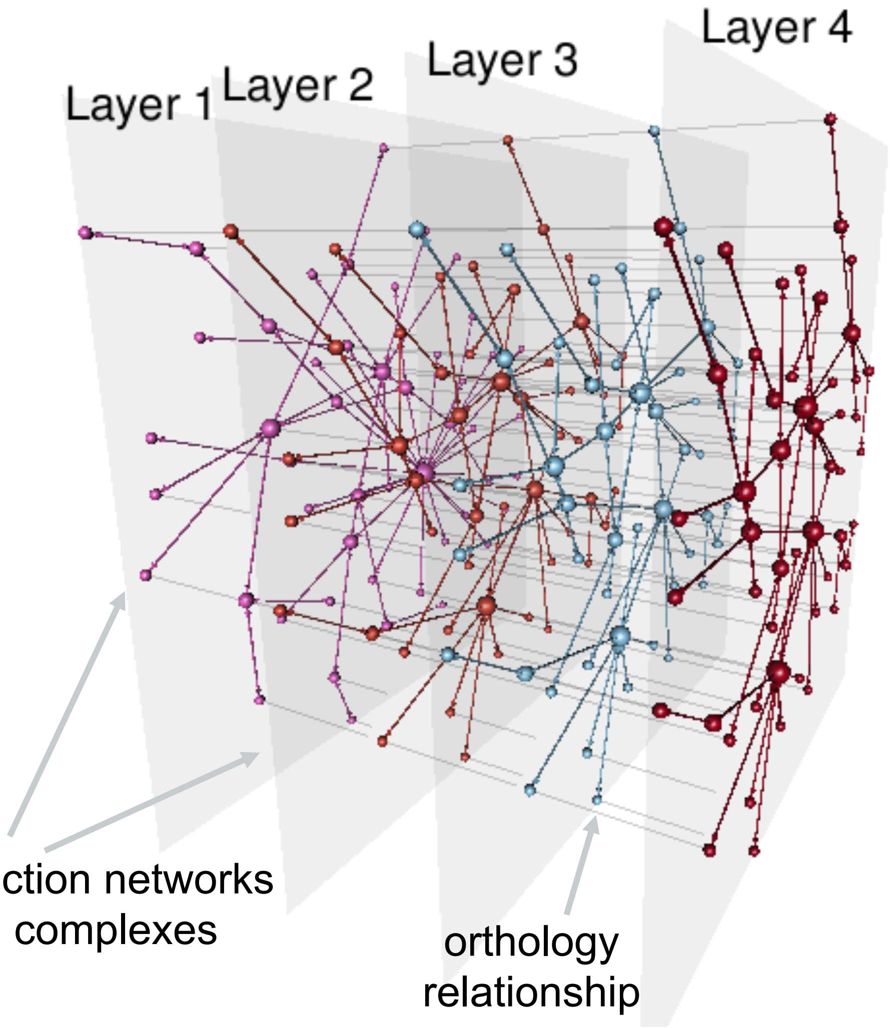
use modules to refine orthology relationship

use orthology to define modules

modules

image courtesy http://muxviz.net/

Other applications and generalizations

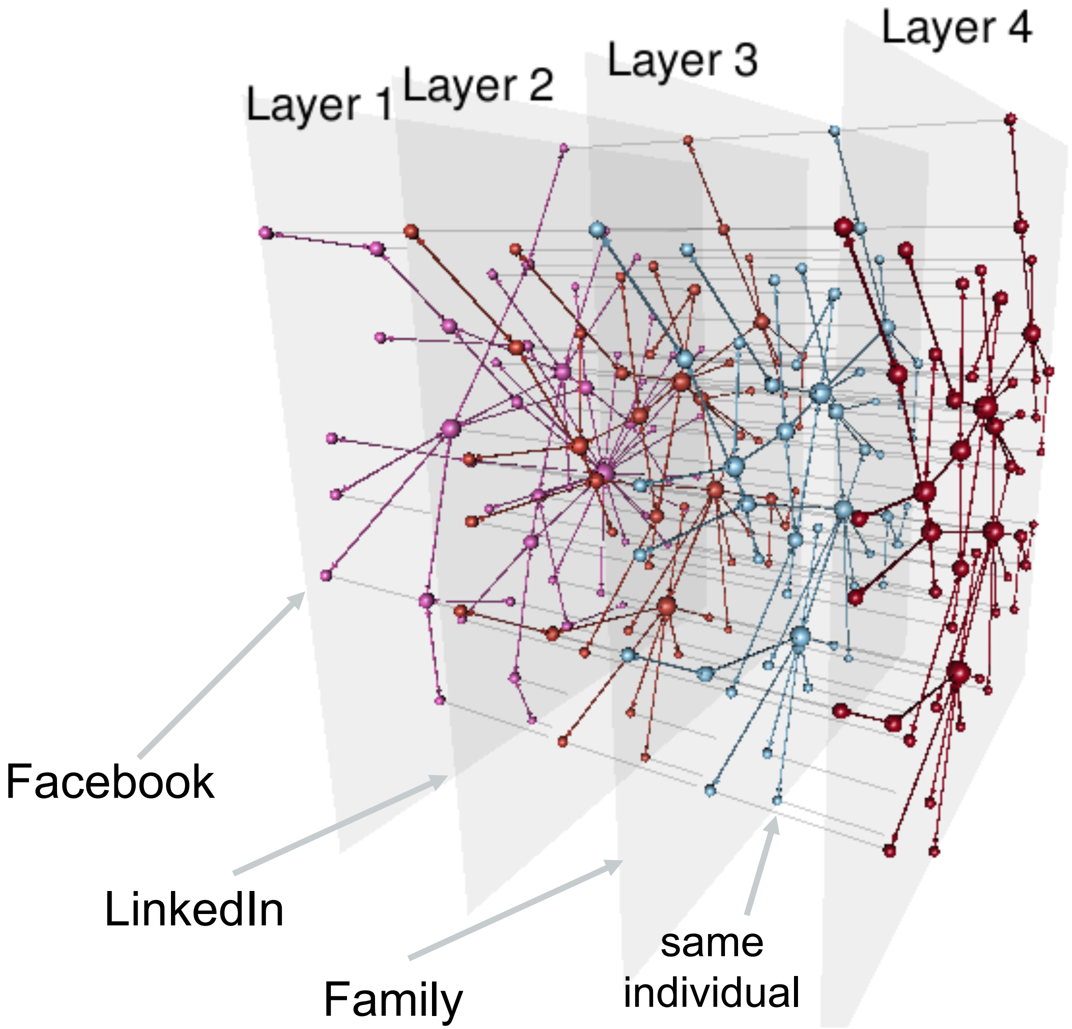


protein-protein interaction networks
- evolution of protein complexes

orthology relationship

image courtesy http://muxviz.net/

Other applications and generalizations



Facebook

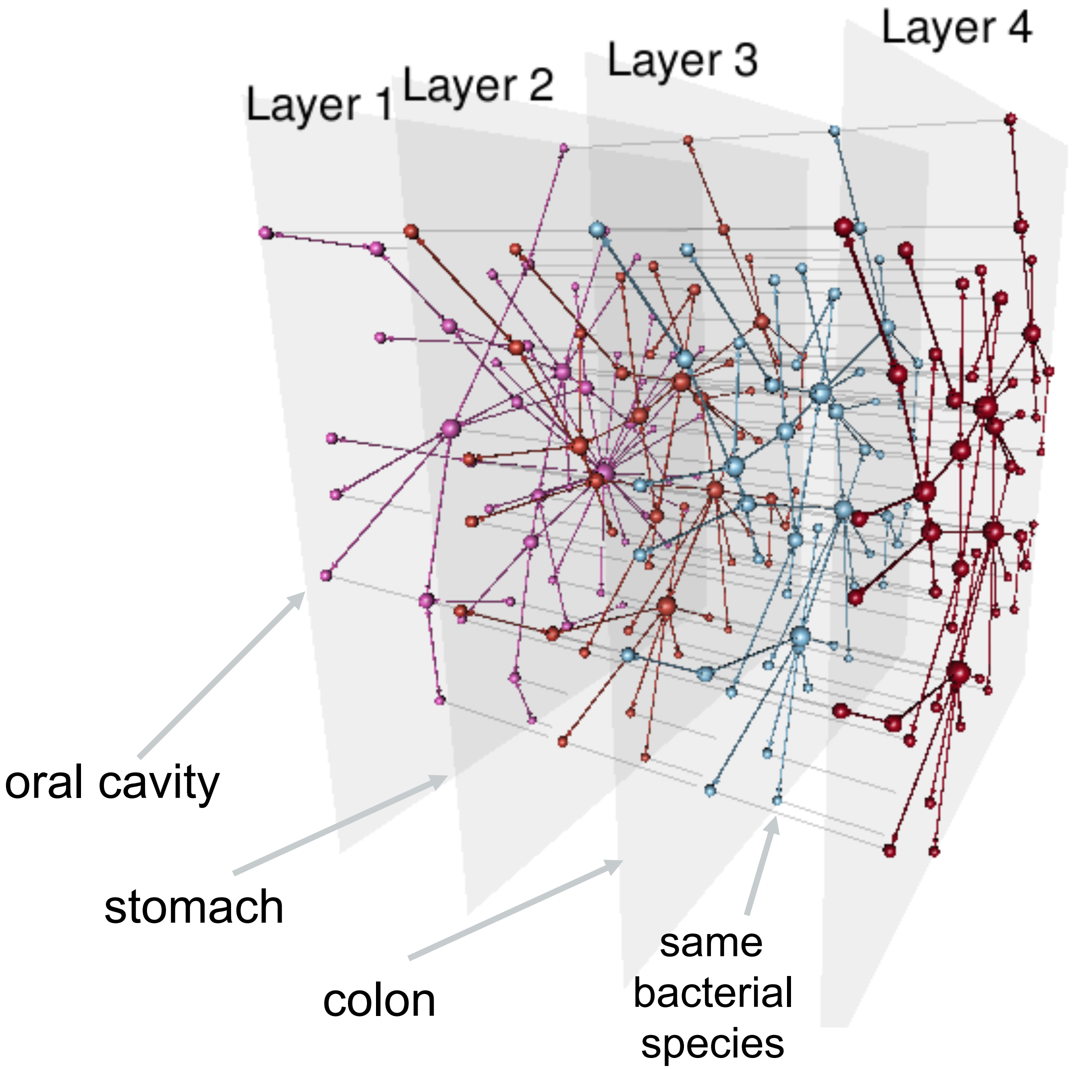
LinkedIn

Family

same individual

image courtesy http://muxviz.net/

Other applications and generalizations



oral cavity

stomach

colon

same bacterial species

image courtesy http://muxviz.net/

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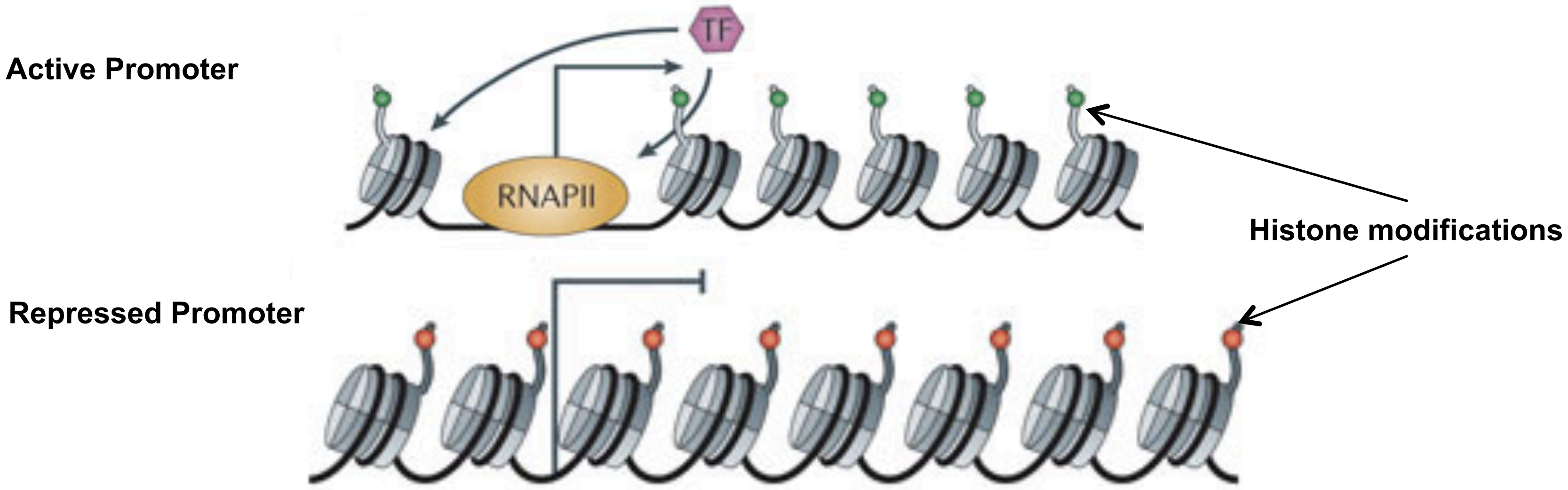
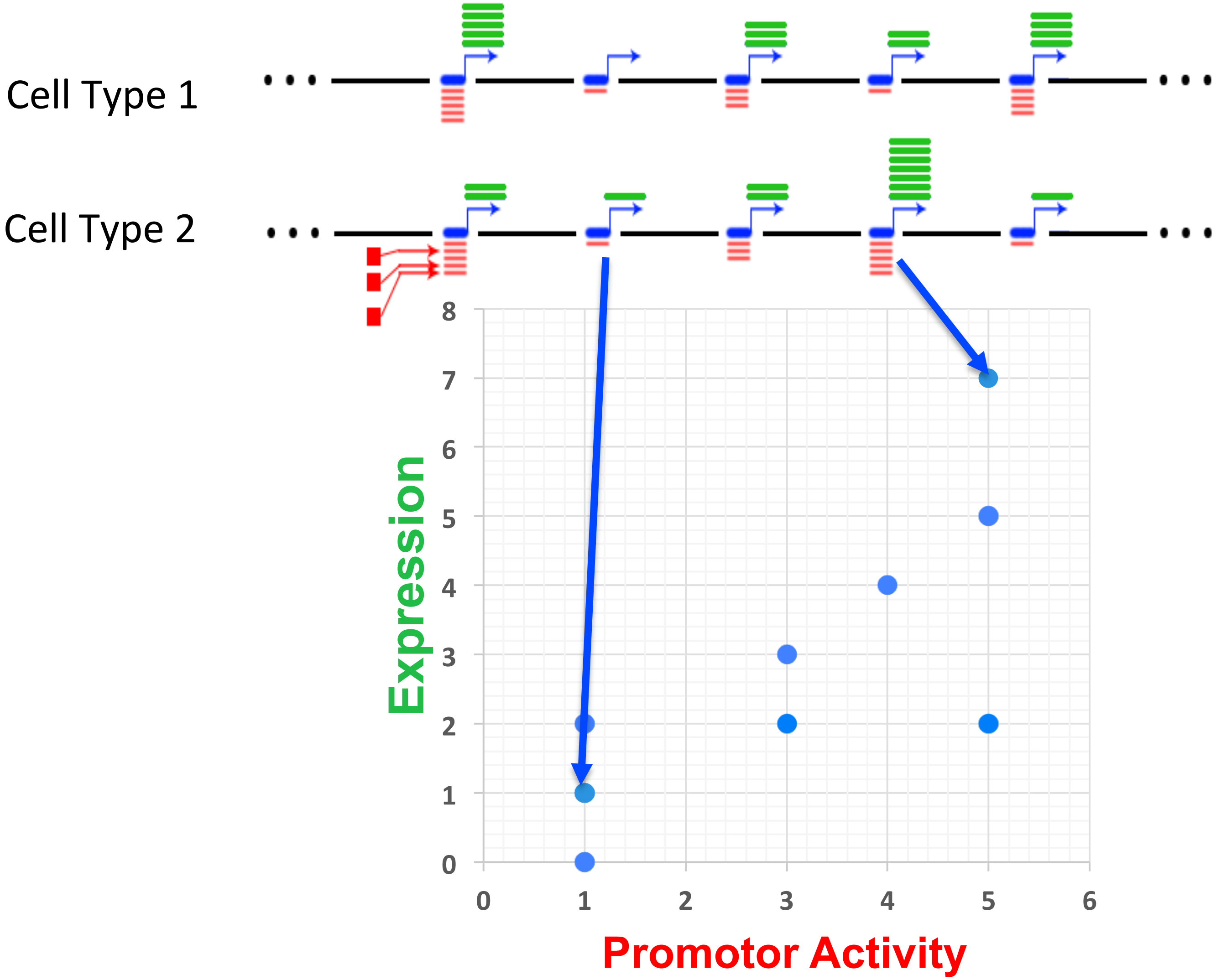
Focus on Promoters

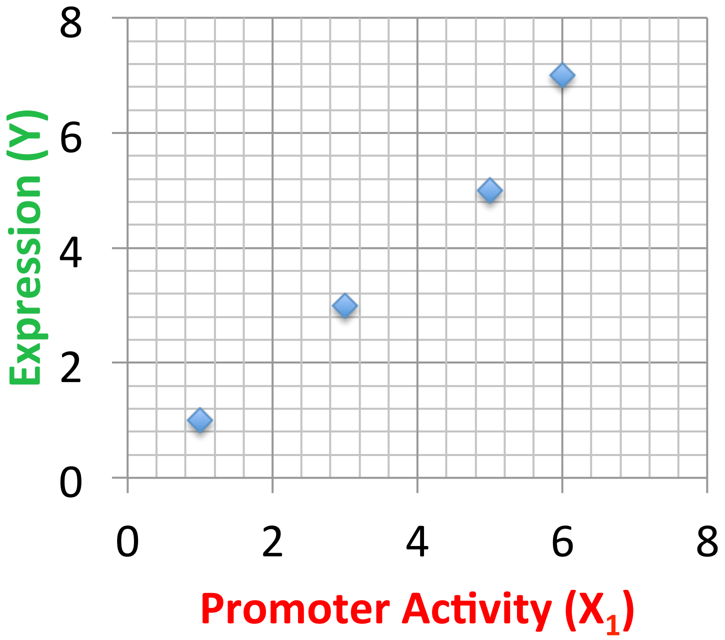


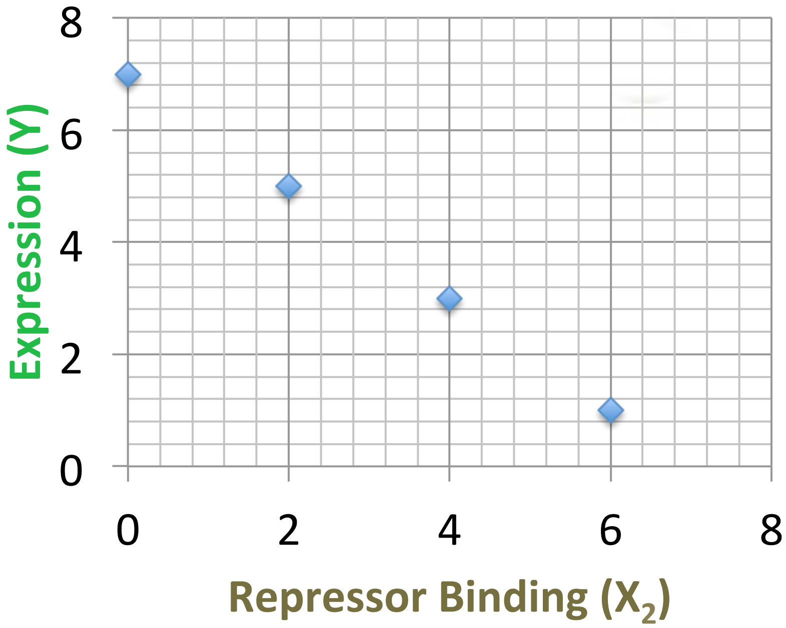
- Key Questions
  - – How do we define the active regions of promoter?
  - – For an active promoter, how do we relate it bound TFs, its epigenetic marks & its chromatin state to the level of transcription?
  - – Are these definitions & relationships conserved between very different species?

Zhou *et al. Nat. Rev. Genetics* 2011

Relating Genomic Inputs to Outputs

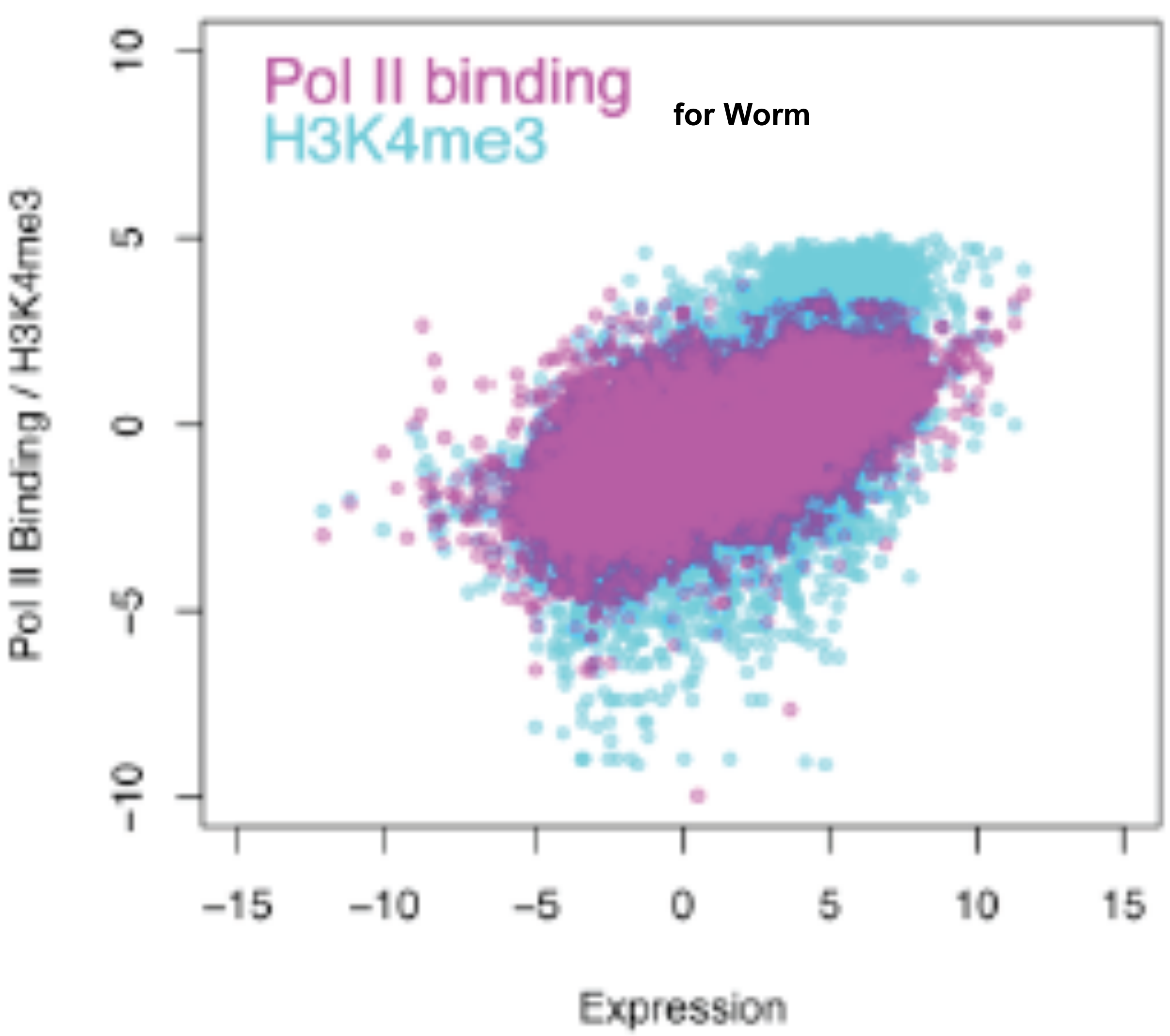



8
6
4
2
0
Expression (Y)
0
2
4
6
8
Promoter Activity (X_1)


8
6
4
2
0
Expression (Y)
0
2
4
6
8
Repressor Binding (X_2)

$$Y = aX_1 + bX_2 + c$$

Inputs v Outputs: Upstream Binding/Modification v Expression



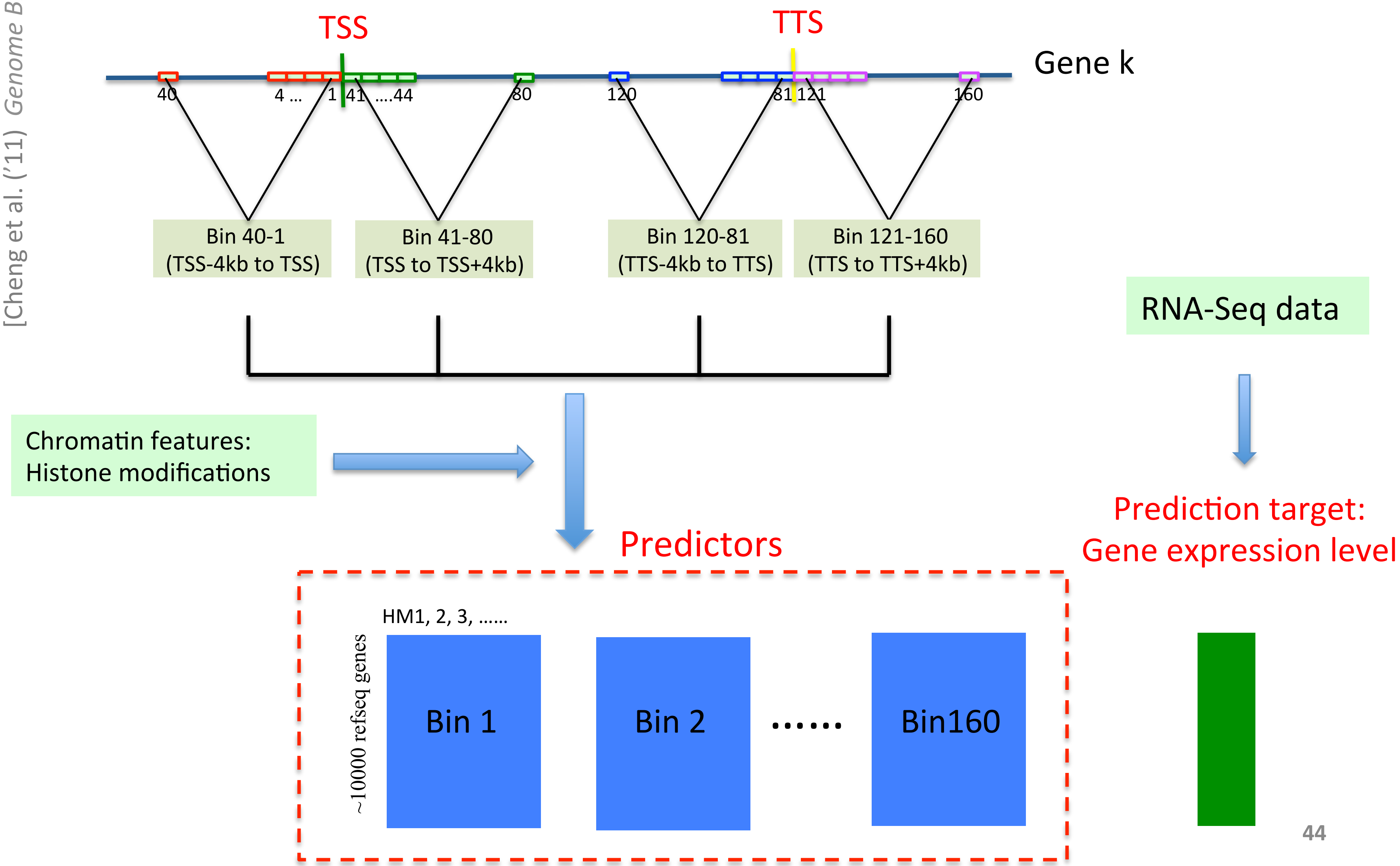
for Worm

PCC: Pol II,
0.33;
H3K4me3,
0.28

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

Histone Modification (HM) model

[Cheng et al. ('11) *Genome Biol.* 12: R15]



Bin 40-1
(TSS-4kb to TSS)

Bin 41-80
(TSS to TSS+4kb)

Bin 120-81
(TTS-4kb to TTS)

Bin 121-160
(TTS to TTS+4kb)

RNA-Seq data

Chromatin features:
Histone modifications

Predictors

Prediction target:
Gene expression level

Bin 1

Bin 2

……

Bin160

His. mods around TSS & TTS are clearly related to level of gene expression, in a position-dependent fashion

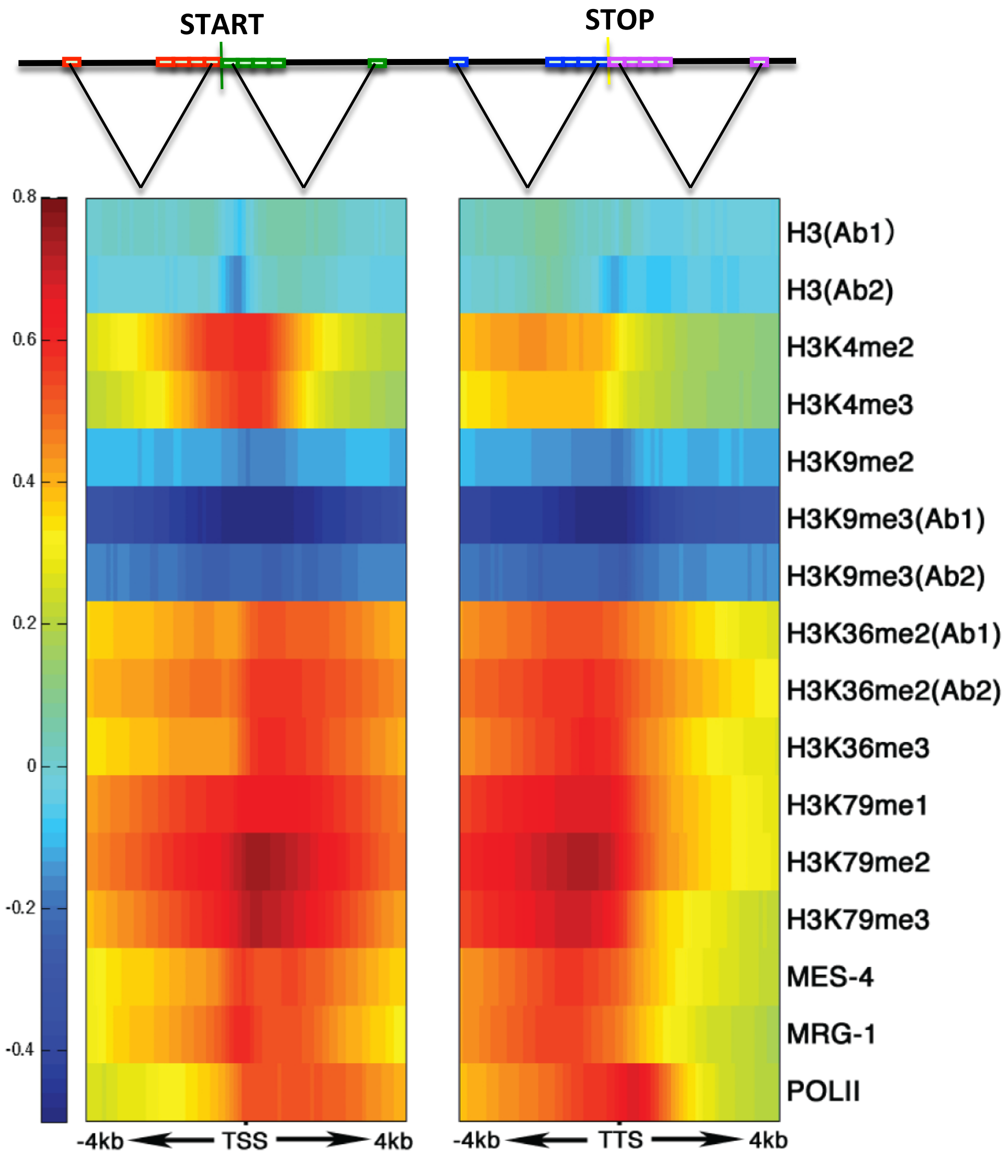
Early work in '09/'10

Science 330:6012
[here]

Also:

Ouyang, Zhou, Wong
('09) *PNAS*;

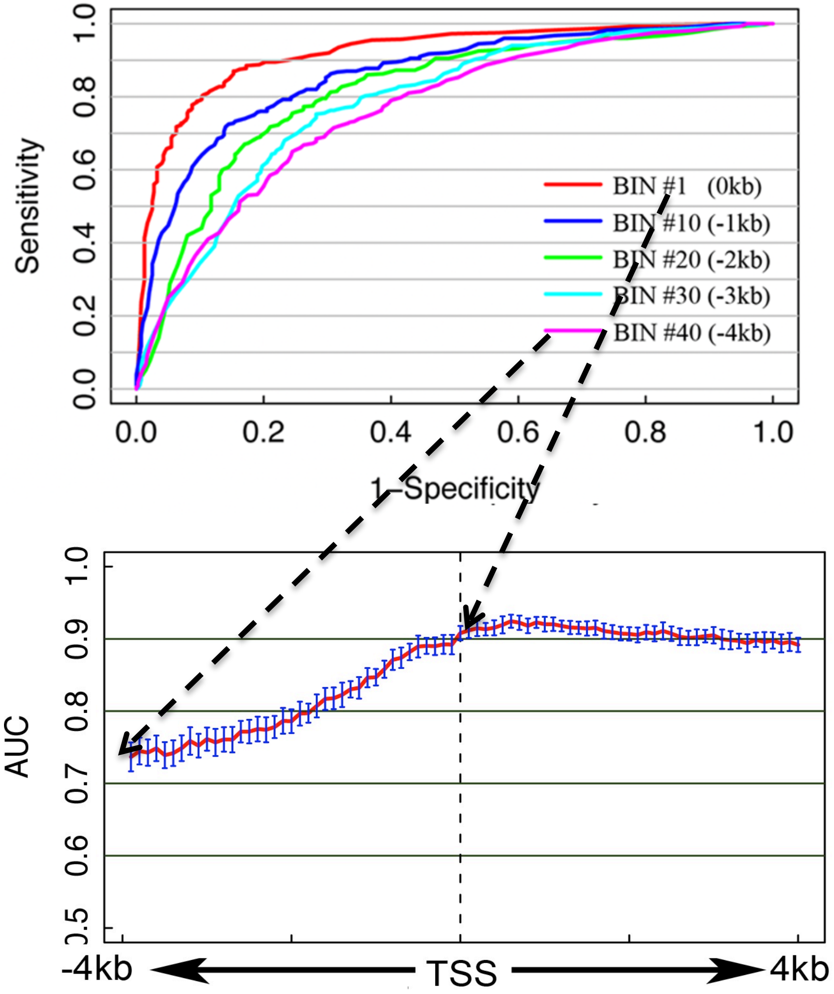
Karlic et al. & Vingron
('10) *PNAS*



[Cheng et al. ('11) *Genome Biol.* 12: R15]

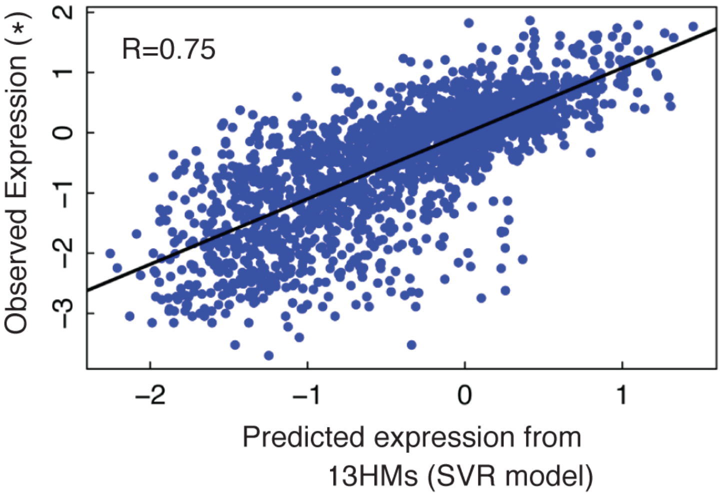
Integrate all histone modifications to predict gene expression levels

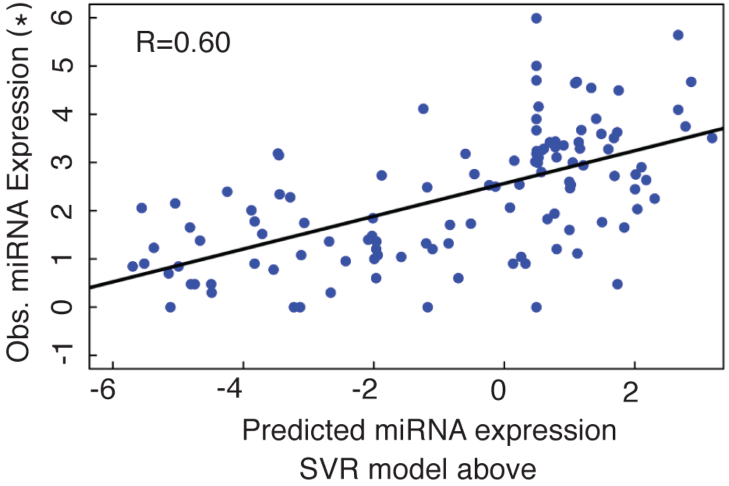
Classify H/L genes (SVM)



Magnitude of Prediction from a "bin" around the TSS

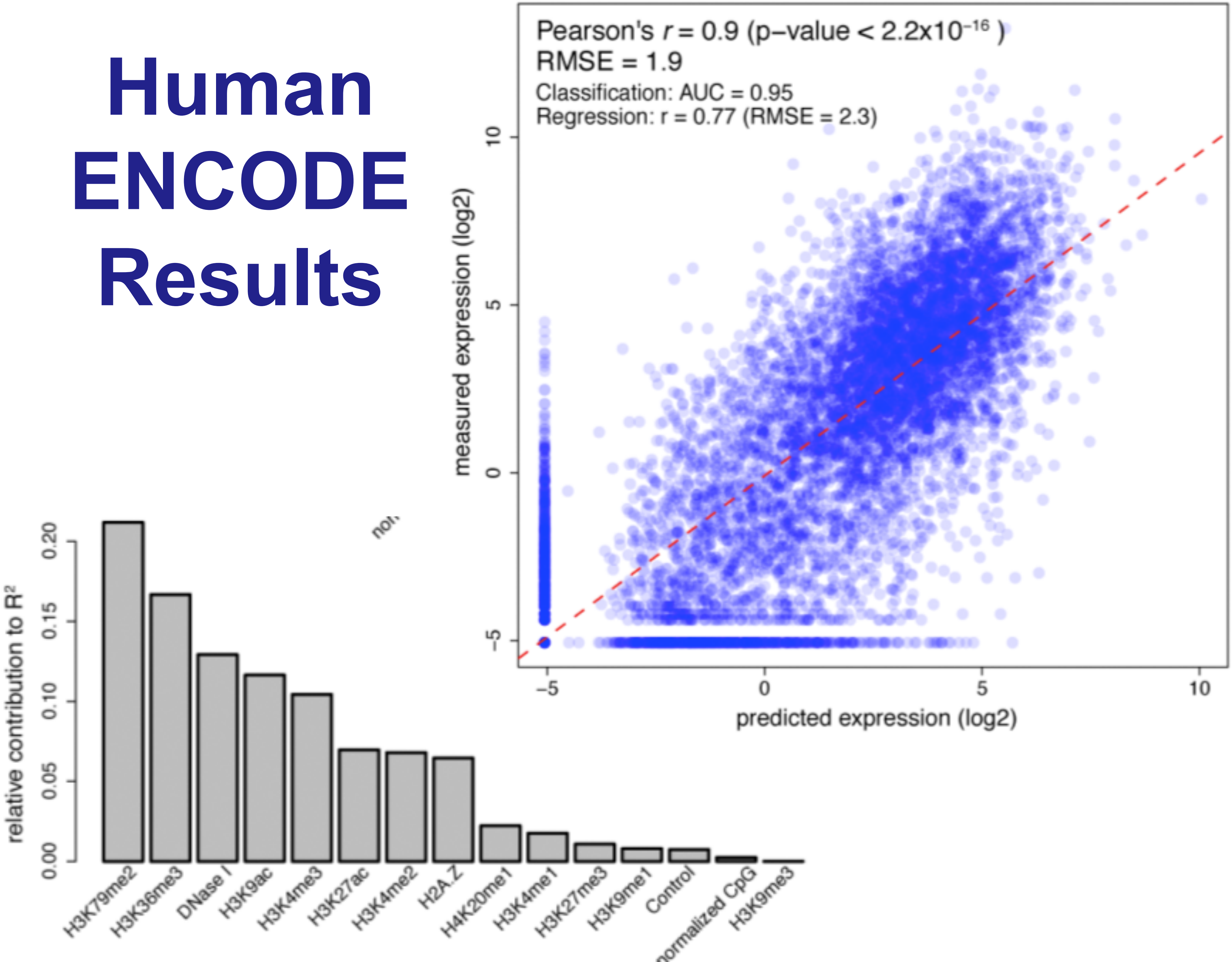
Predict expression values





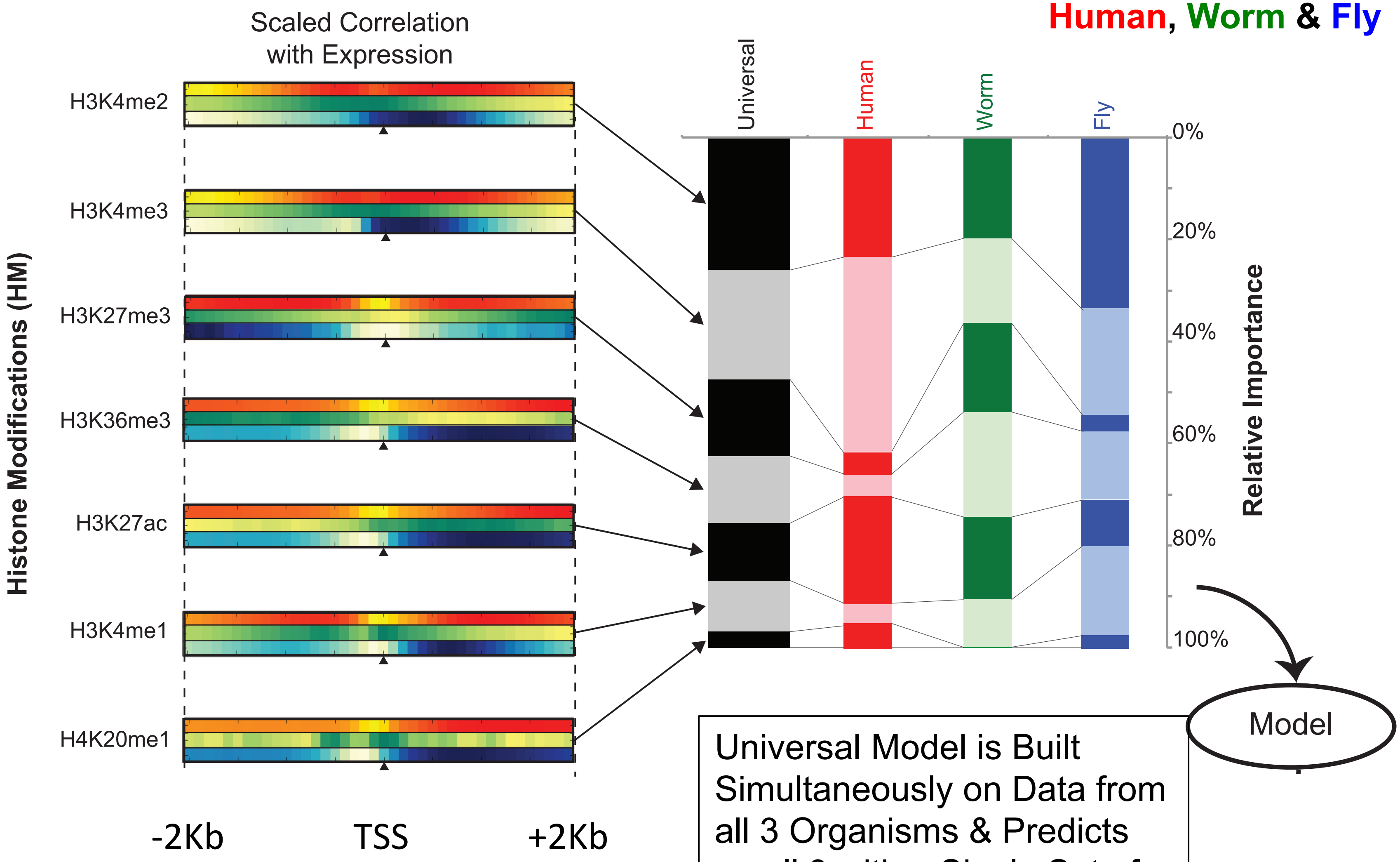
$*$ = $LOG_{10}RPKM$

Human ENCODE Results



[Encode Consortium, *Nature* ('12)]

Comparison of Models for Gene Expression, Building a Universal Model



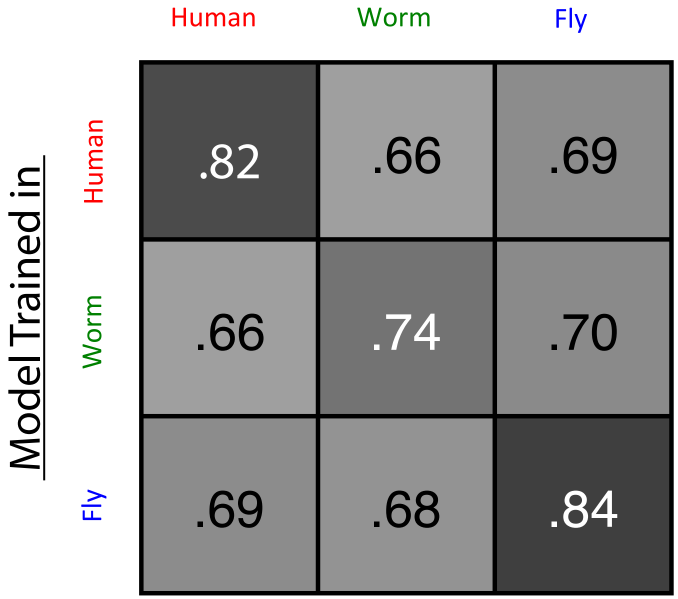
Universal Model is Built Simultaneously on Data from all 3 Organisms & Predicts on all 3 with a Single Set of Parameters

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

Performance of Universal, cross-organism Model

- works almost as well as species specific models
- works for both mRNAs and ncRNAs

Prediction Accuracy for Protein-coding Genes



Model Trained in	Human	Worm	Fly
Human	.82	.66	.69
Worm	.66	.74	.70
Fly	.69	.68	.84

Prediction Accuracy of Universal Model

Protein coding	.80	.73	.83
ncRNA	.69	.51	.60

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

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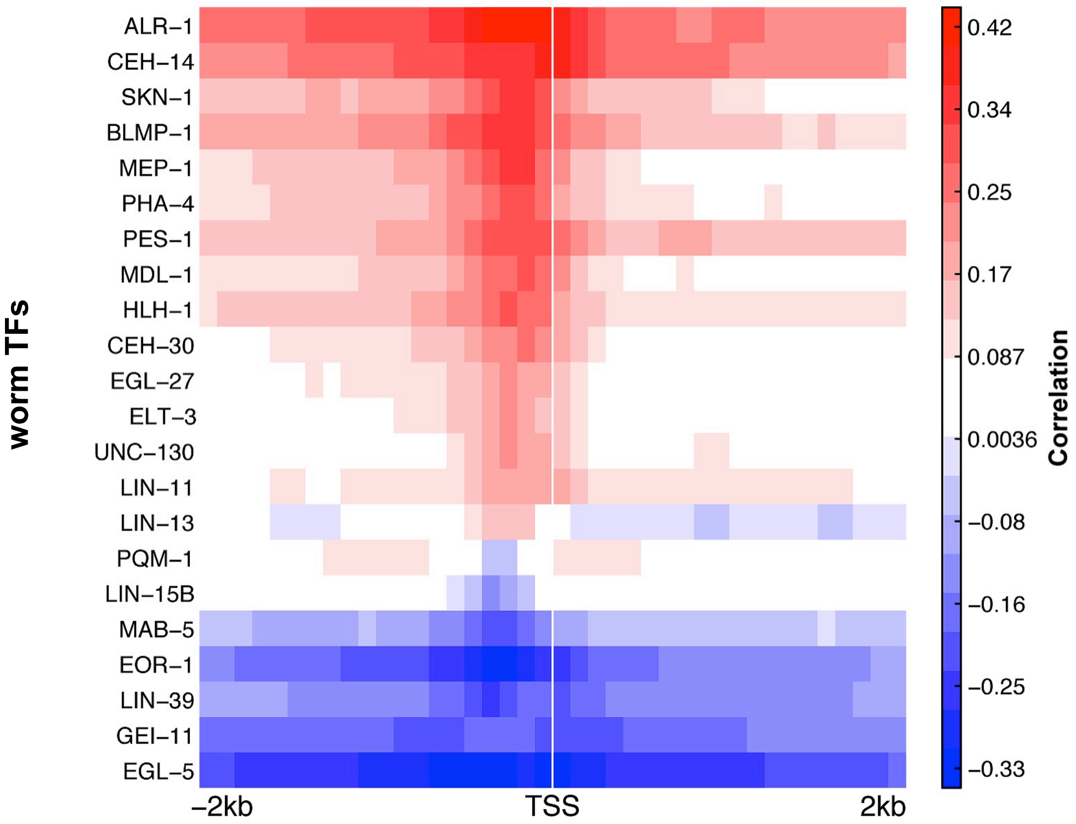
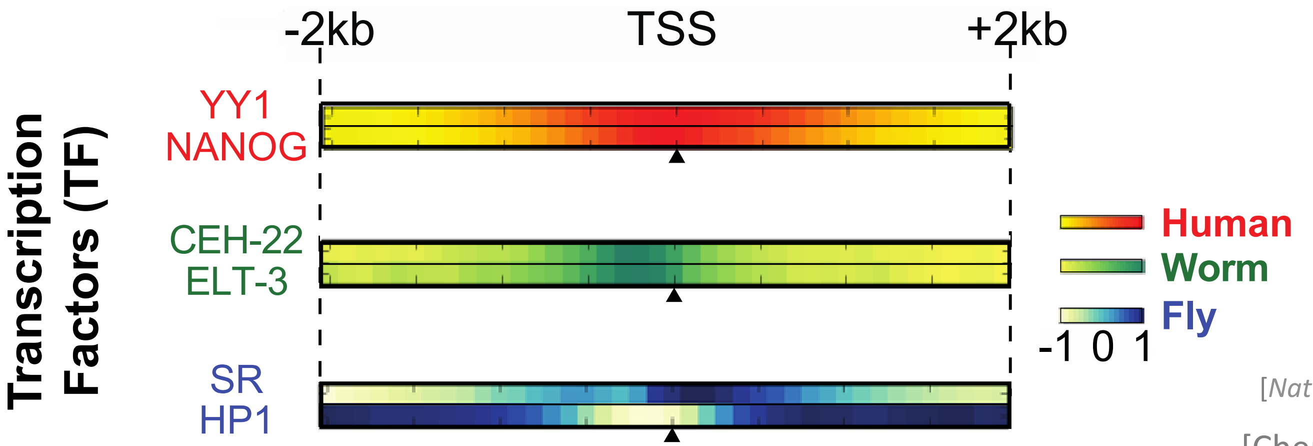
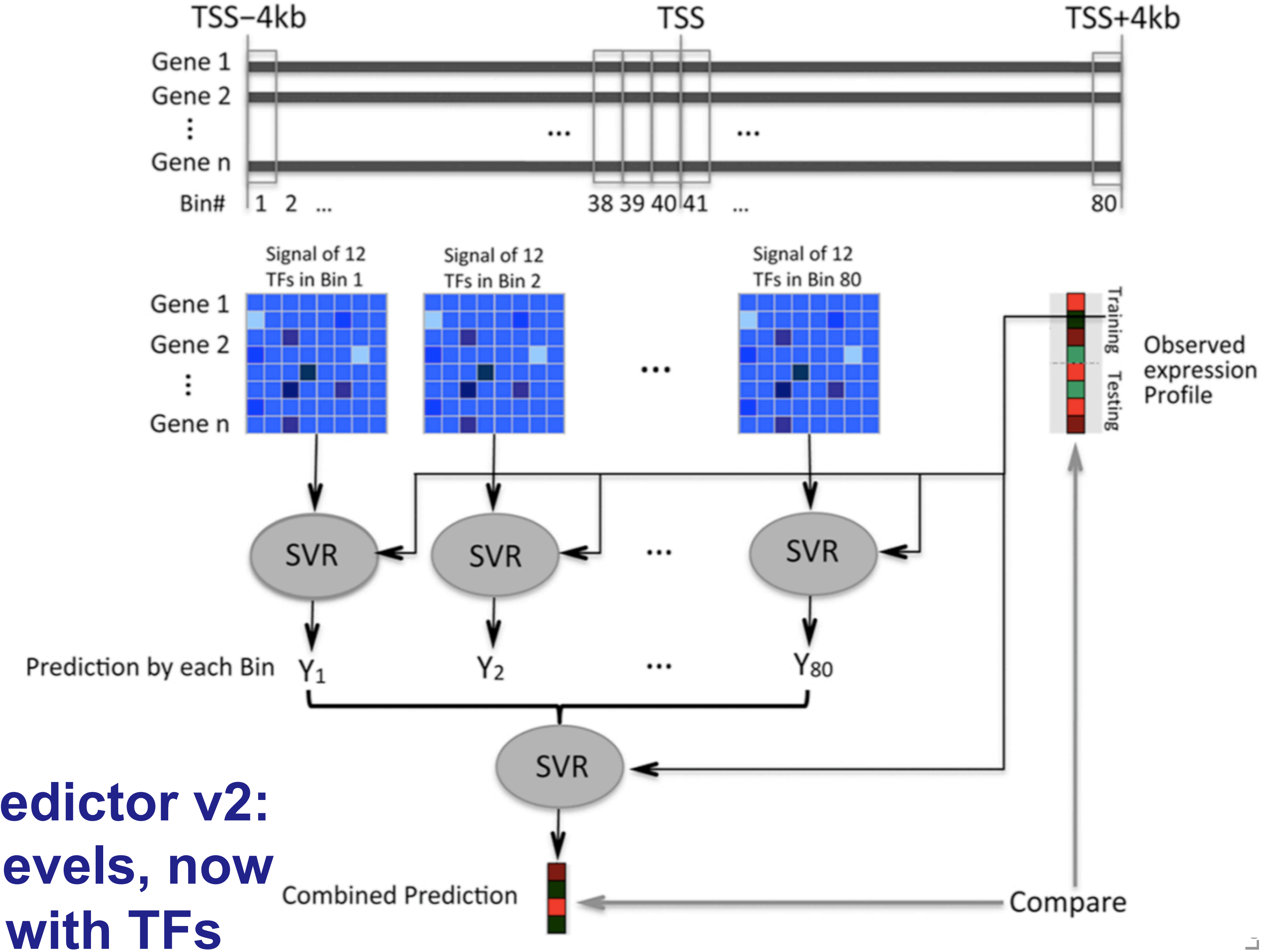
Doing a Model with TFs: Positive and negative regulators from correlating TF signal at TSS with gene expression





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

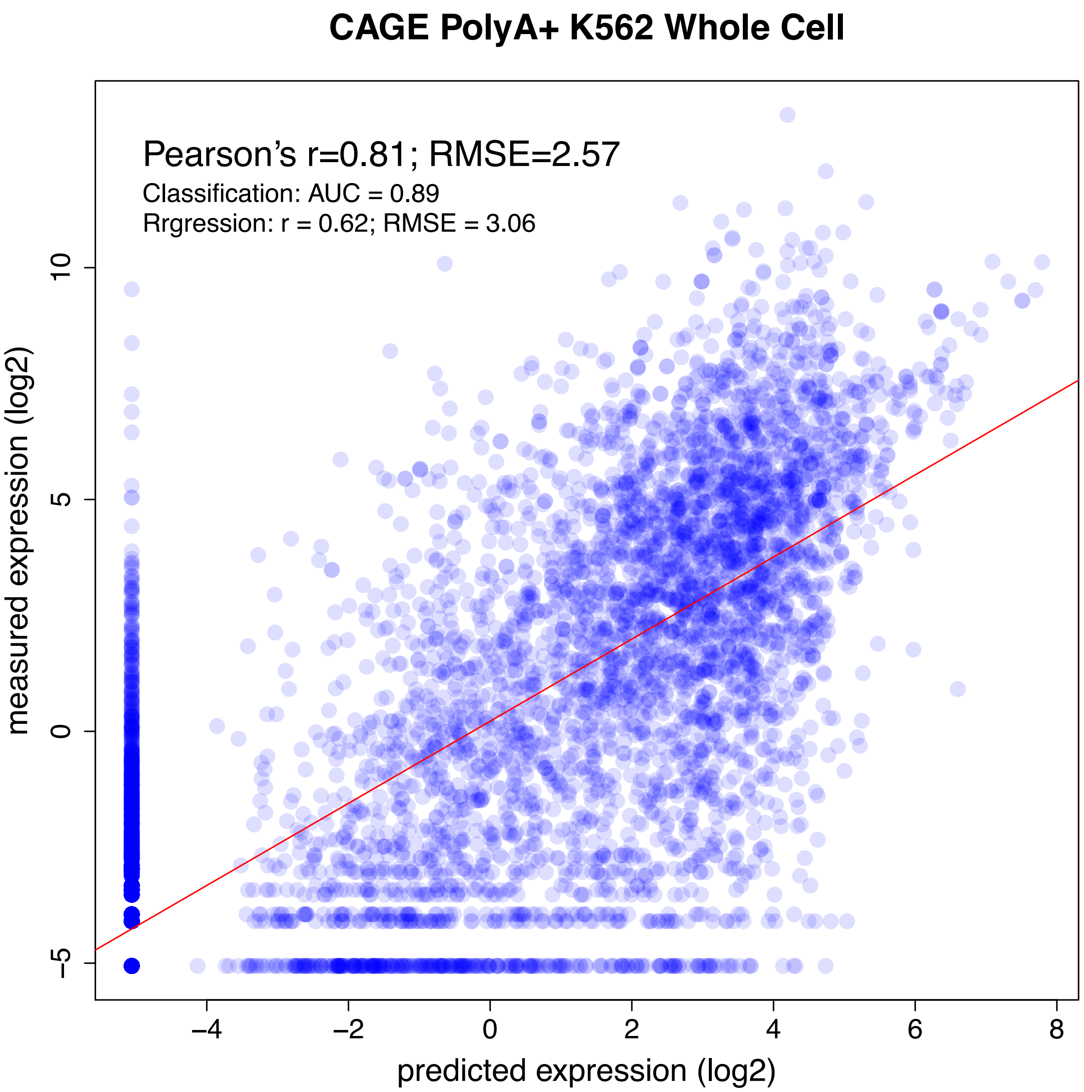
[Cheng et al. ('11) *PLOS CB*]



Predictor v2: 2-levels, now with TFs

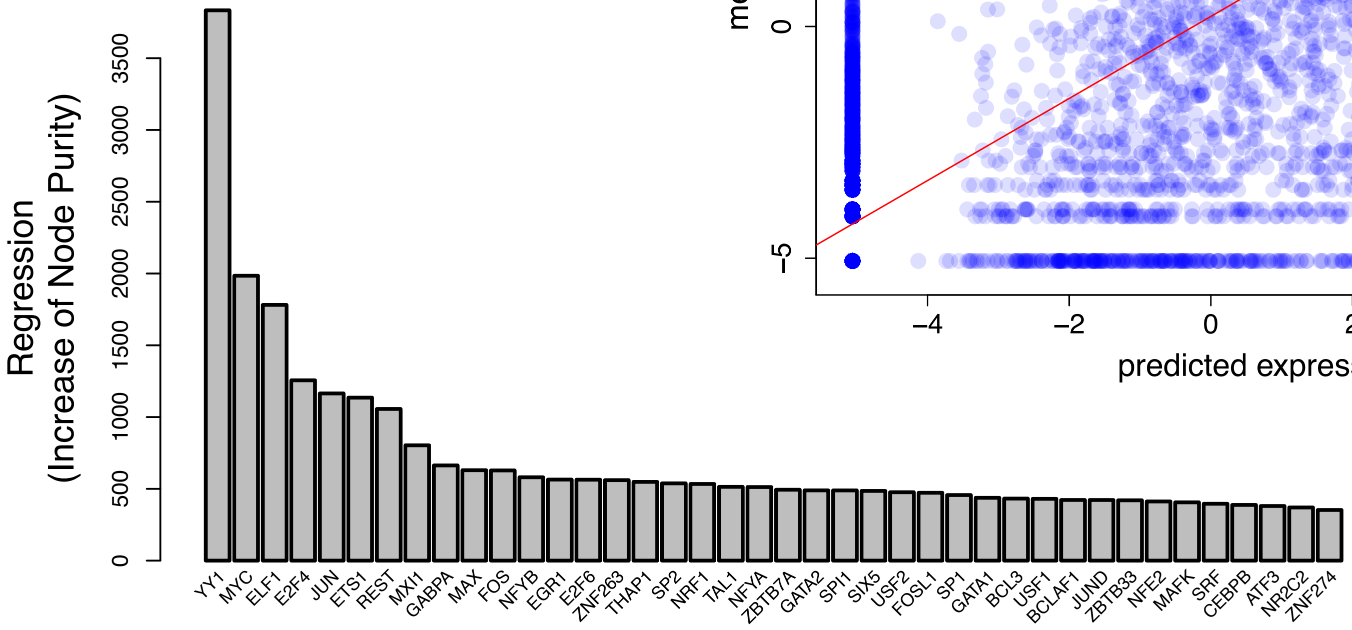
[Cheng et al. *NAR* ('11)]

Human Results



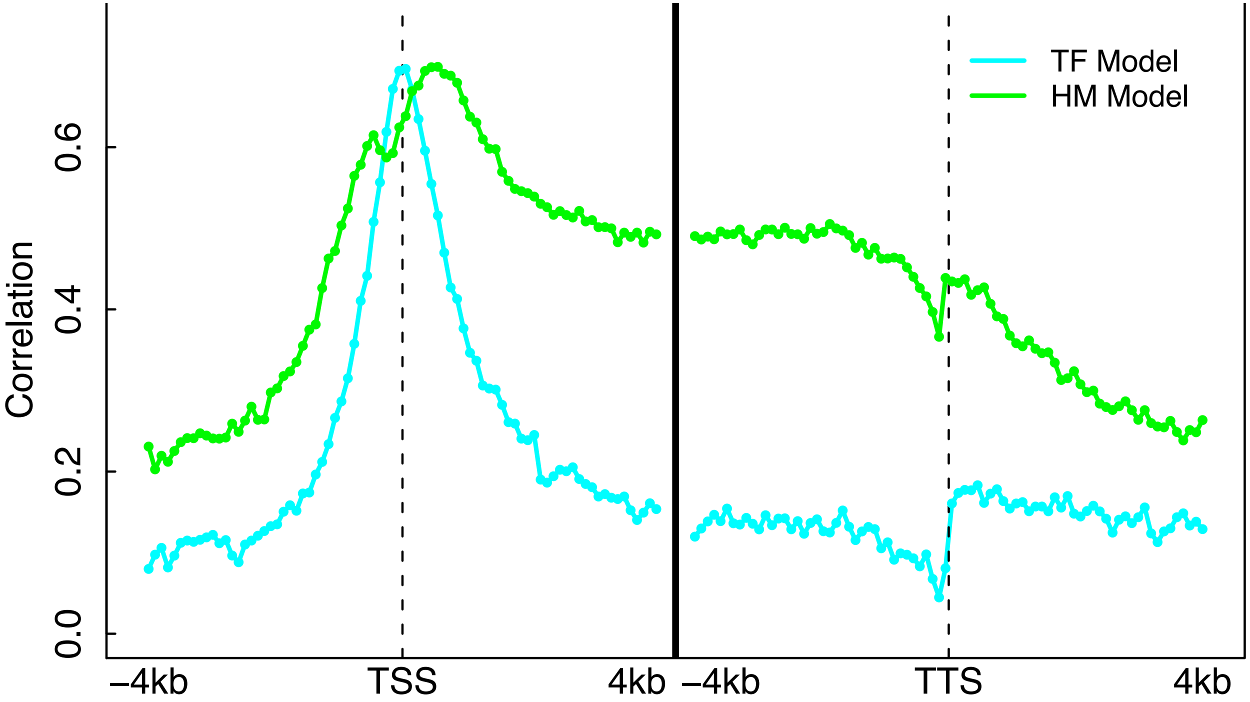
CAGE PolyA+ K562 Whole Cell

Pearson's r=0.81; RMSE=2.57
Classification: AUC = 0.89
Rrgression: r = 0.62; RMSE = 3.06

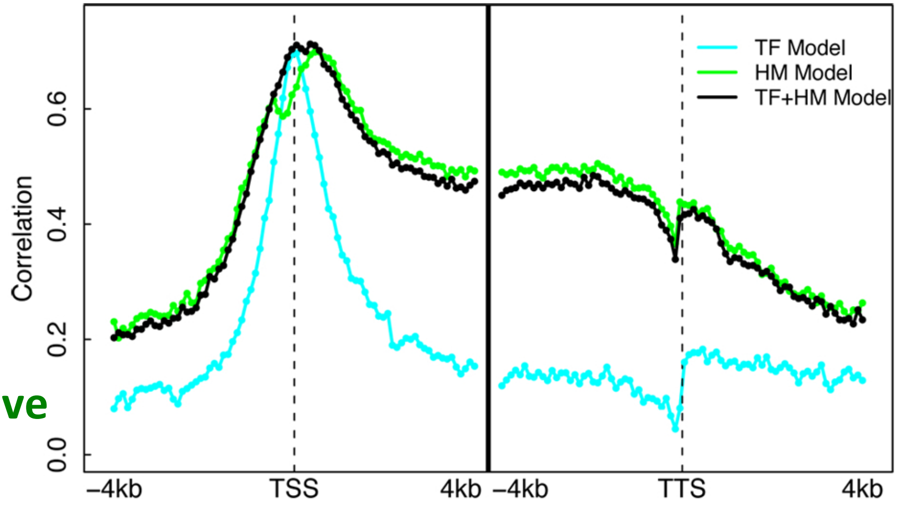


[Encode Consortium, *Nature* ('12)]

Models Illuminates Different Regions of Influence for TFs vs HMs



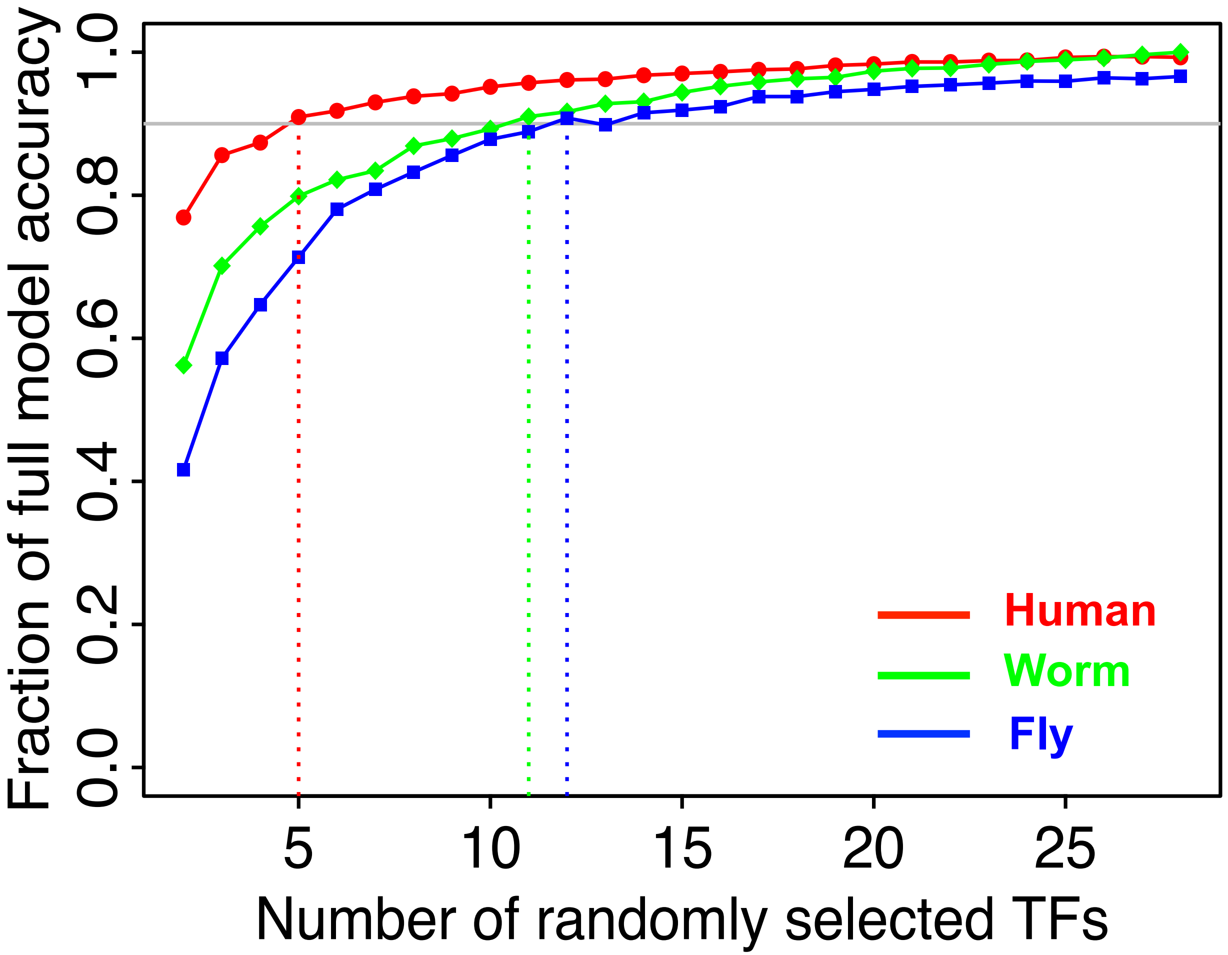
- Datasets
  - ChIP-Seq for 12 TFs (Chen et al. 2008)
  - ChIP-Seq for 7 HMs (Meissner et al.'08; Mikkelsen et al. '07)
  - RNA-Seq (Cloonan et al. 2008)



A TF+HM model that combine TF and HM features does NOT improve accuracy!

Cheng et al. 2011, Nucleic Acids Res.

TF model accuracy only needs a small number of TFs for high accuracy (>90%)



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Acknowledgements

modENCODE/ENCODE Transcriptome subgroup

Joel Rozowsky, Koon-Kiu Yan, Daifeng Wang, Chao Cheng, James B. Brown, Carrie A. Davis, LaDeana Hillier, Cristina Sisu**, Jingyi Jessica Li,** Baikang Pei, Arif O. Harmanci, Michael O. Duff, Sarah Djebali, Roger P. Alexander, Burak H. Alver, Raymond K. Auerbach, Kimberly Bell, Peter J. Bickel, Max E. Boeck, Nathan P. Boley, Benjamin W. Booth, Lucy Cherbas, Peter Cherbas, Chao Di, Alex Dobin, Jorg Drenkow, Brent Ewing, Gang Fang, Megan Fastuca, Elise A. Feingold, Adam Frankish, Guanjun Gao, Peter J. Good, Phil Green, Roderic Guigó, Ann Hammonds, Jen Harrow, Roger A. Hoskins, Cédric Howald, Long Hu, Haiyan Huang, Tim J. P. Hubbard, Chau Huynh, Sonali Jha, Dionna Kasper, Masaomi Kato, Thomas C. Kaufman, Rob Kitchen, Erik Ladewig, Julien Lagarde, Eric Lai, Jing Leng, **Zhi Lu,** Michael MacCoss, Gemma May, Rebecca McWhirter, Gennifer Merrihew, David M. Miller, Ali Mortazavi, Rabi Murad, Brian Oliver, Sara Olson, Peter Park, Michael J. Pazin, Norbert Perrimon, Dmitri Pervouchine, Valerie Reinke, Alexandre Reymond, Garrett Robinson, Anastasia Samsonova, Gary I. Saunders, Felix Schlesinger, Anurag Sethi, Frank J. Slack, William C. Spencer, Marcus H. Stoiber, Pnina Strasbourger, Andrea Tanzer, Owen A. Thompson, Kenneth H. Wan, Guilin Wang, Huaien Wang, Kathie L. Watkins, Jiayu Wen, Kejia Wen, Chenghai Xue, Li Yang, Kevin Yip, Chris Zaleski, Yan Zhang, Henry Zheng, **Steven E. Brenner, Brenton R. Graveley, Susan E. Celniker, Thomas R Gingeras, Robert Waterston**

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TF-v-expr:

Cheng C, Yan KK, Hwang W, Qian J, Bhardwaj N, Rozowsky J, Lu ZJ, Niu W, Alves P, Kato M, Snyder M

worm-HM:

Cheng C, Yan KK, Yip KY, Rozowsky J, Alexander R, Shou C

ENCODE:

Chao Cheng, Roger Alexander, **Renqiang Min**, Kevin Y. Yip, Jing Leng, Joel Rozowsky, Koon-kiu Yan, Xianjun Dong, Sarah Djebali, Yijun Ruan, Carrie A Davis, Piero Carninci, Timo Lassman, Thomas R. Gingeras, Roderic Guigó Serra, Ewan Birney, Zhiping Weng, Michael Snyder

Orthoclust :

KK Yan, D Wang, J Rozowsky, H Zheng, C Cheng

Models Acknowledgements

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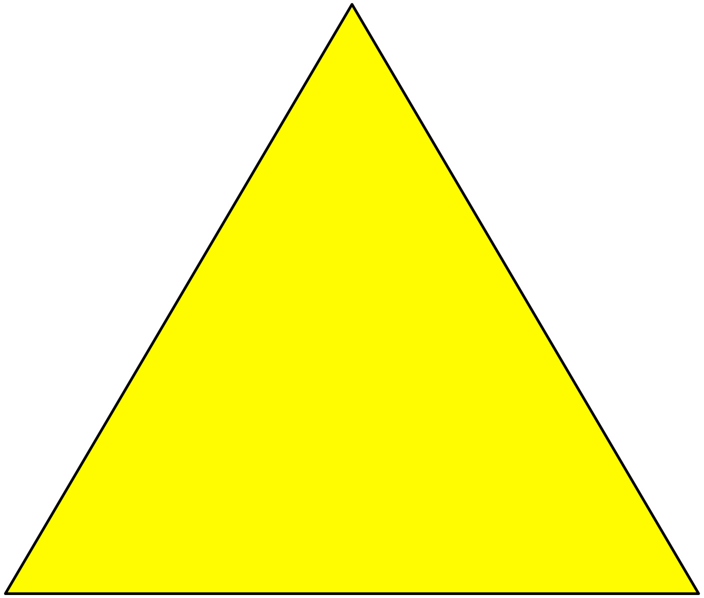
  - Level 2



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