

Systems Biology of *C. elegans*



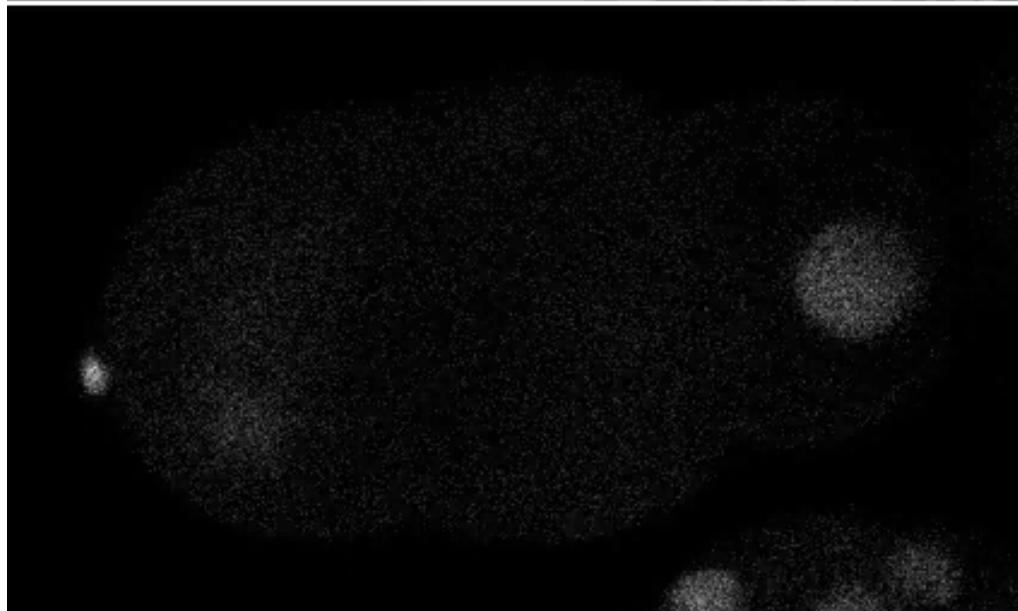
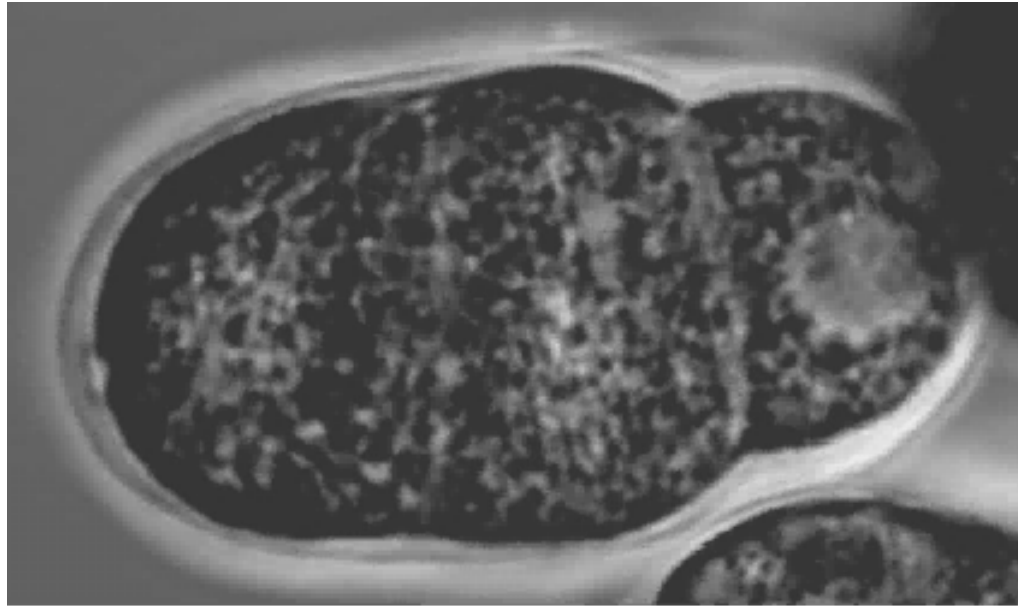
Stuart Kim
Stanford University

Overview

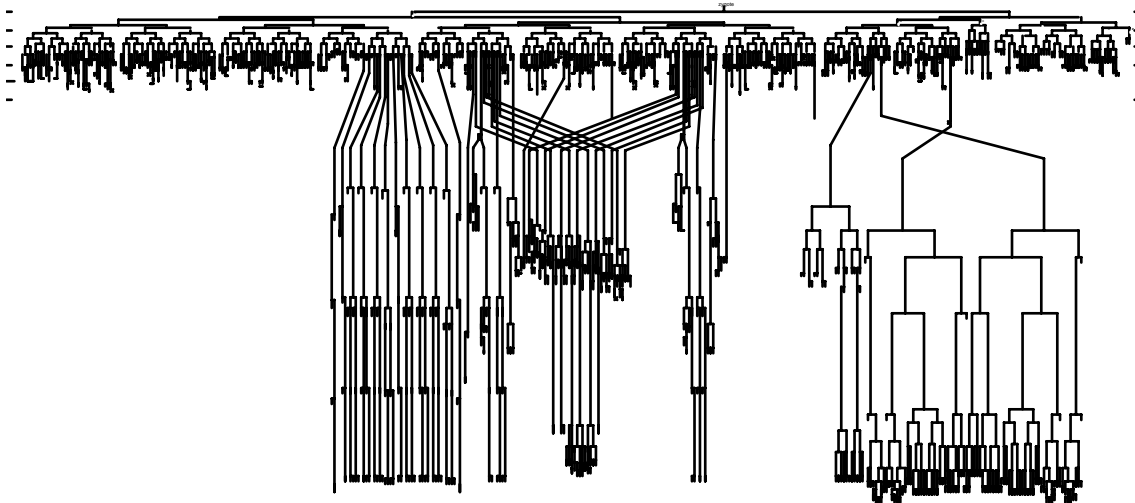
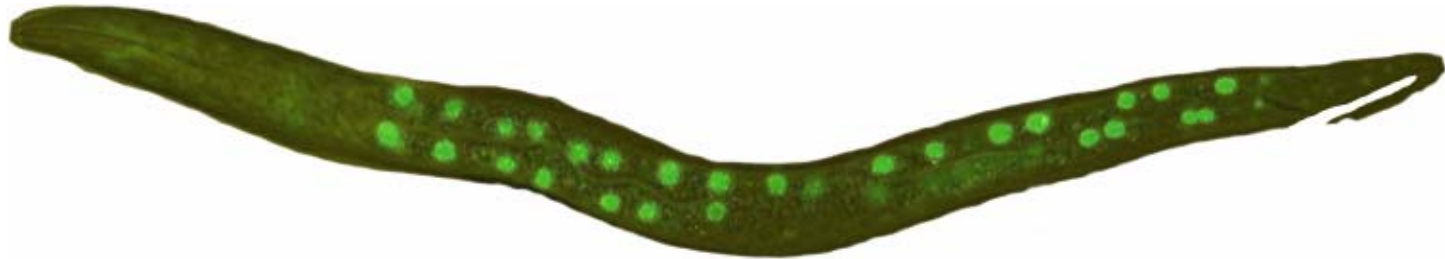
- Cell lineage
- Genome
- Mutant Phenotypes
- Protein interaction
- Gene Expression

Early cell divisions





C. elegans

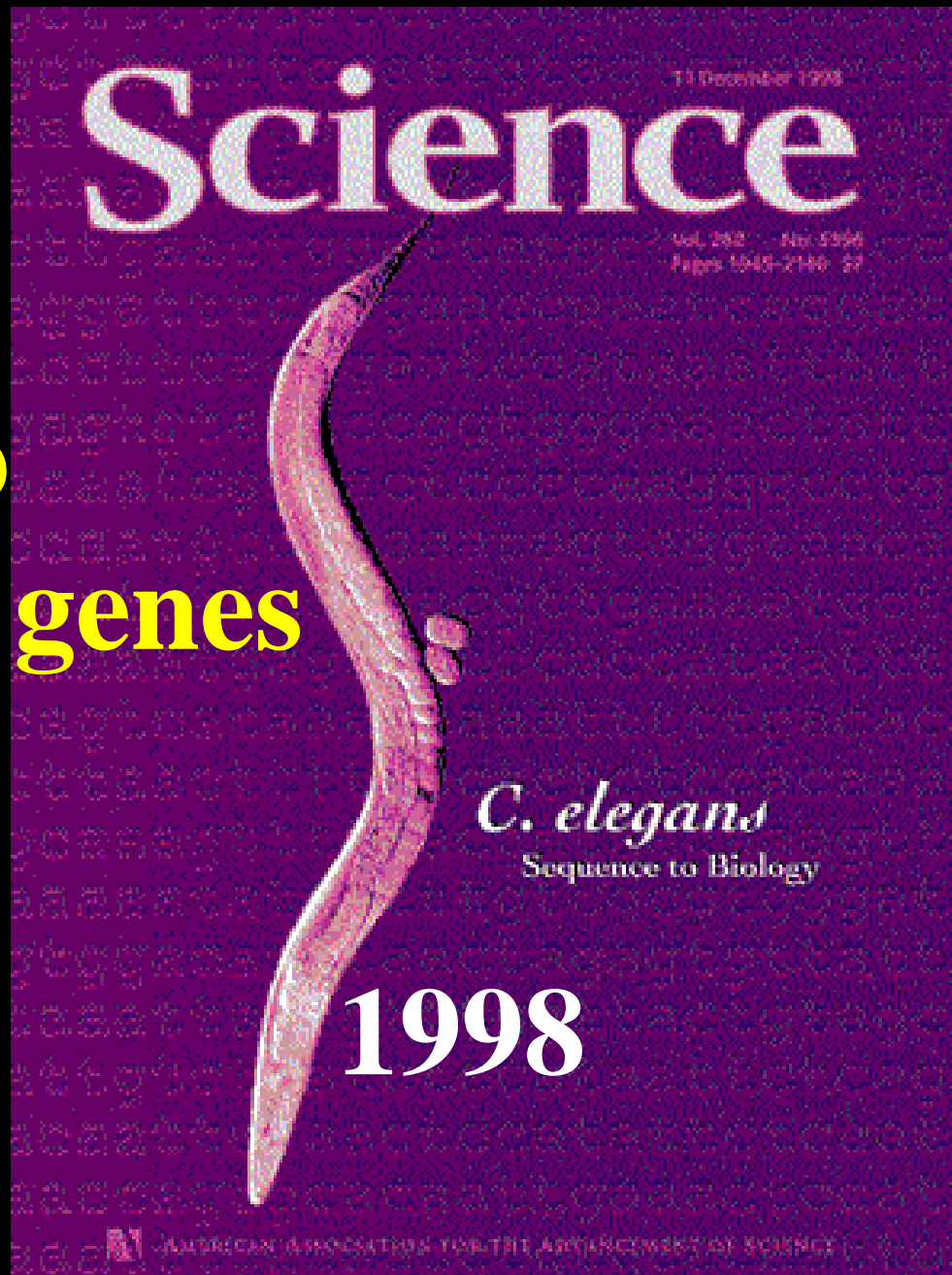


lineage of 959 cells

Overview

- Cell lineage
- **Genome**
- Mutant Phenotypes
- Protein interaction
- Gene Expression

100 Mb
~19735 genes



1998

Science

11 December 1998

Vol. 282 No. 5394
Pages 1045-2190 37



C. elegans
Sequence to Biology

1998



AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

“94% genes unknown” (~1998)

Science

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C. elegans

Sequence to Biology

1998



AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

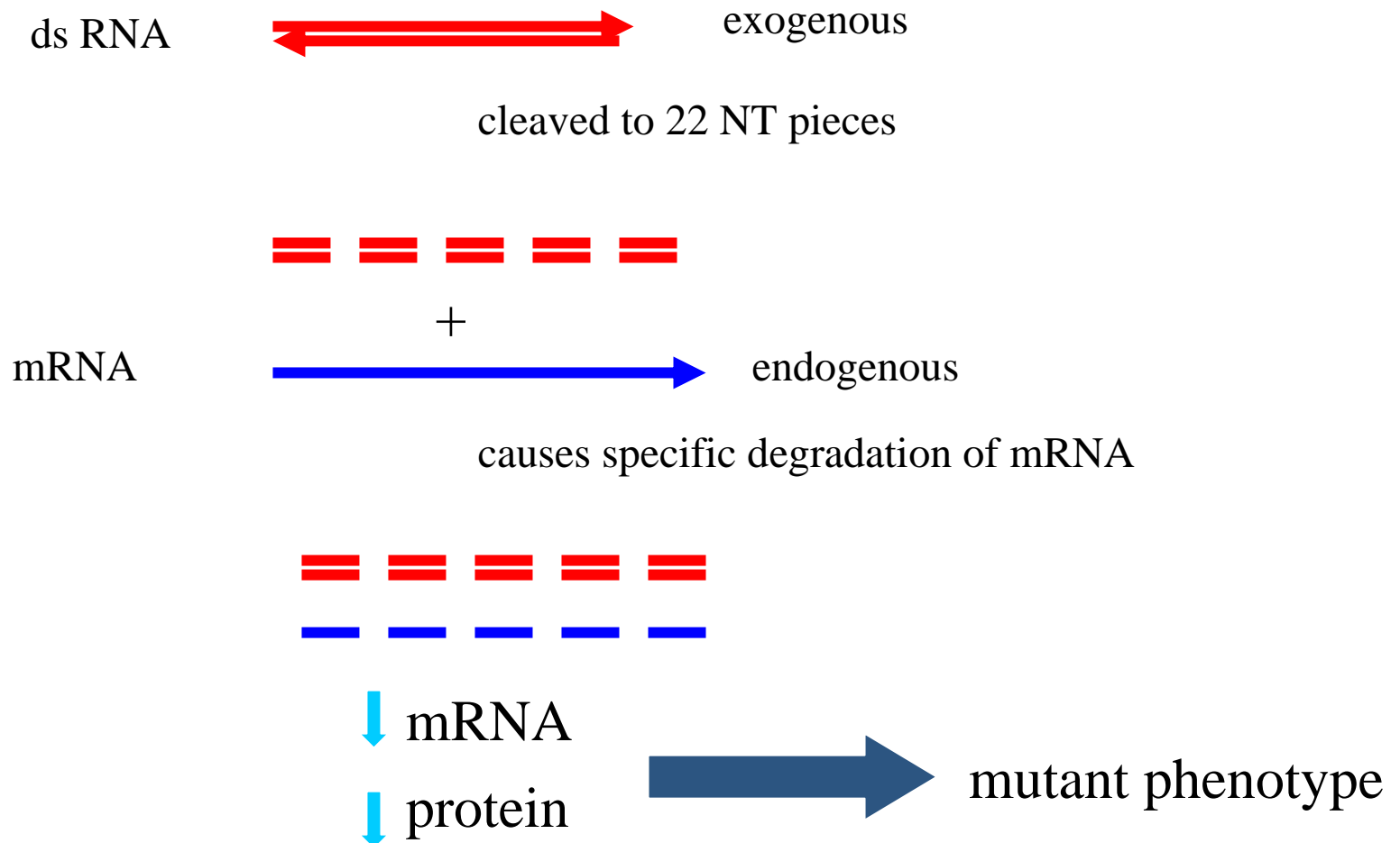
“94% genes unknown” (~1998)

“interactions for 92% of genes” (~2001)

Overview

- Cell lineage
- Genome
- **Mutant Phenotypes**
- Protein interaction
- Gene Expression

RNA mediated interference (RNAi)

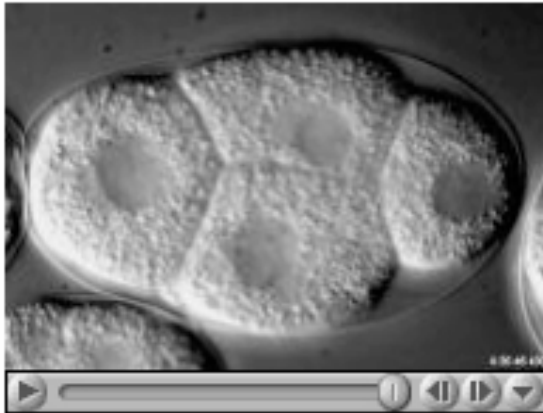


RNAi in *C. elegans*



- Feed worms strains of *E. coli* expressing ds RNA

wild-type



mcm-5



<http://mpi-web.embl-heidelberg.de/dbScreen>

<http://www.wormbase.org>

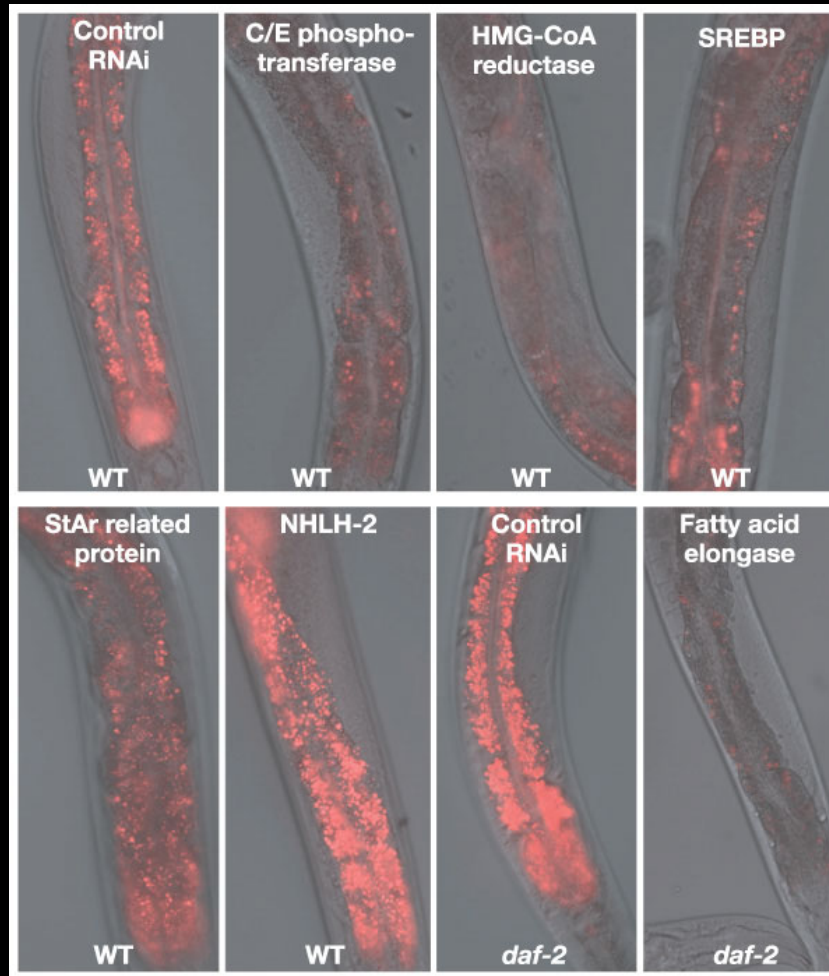
www.rnai.org

http://watson.genes.hib.ac.jp/db/rnai_s/index.html

Mutant cell divisions



RNAi screen for 417 fat genes



- RNAi screens in *C. elegans* (*last two years*)

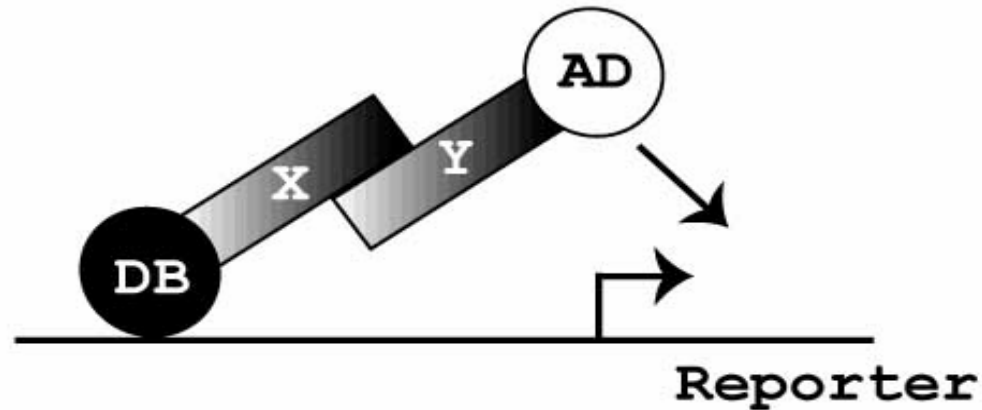
- No mapping/cloning etc.
- Order bacterial strain set and do experiments yourself.
- Examples of screens:
 - ~500 longevity
 - 417 fat genes
 - Genes needed for RNAi
 - Embryonic polarity
 - synaptic function

Overview

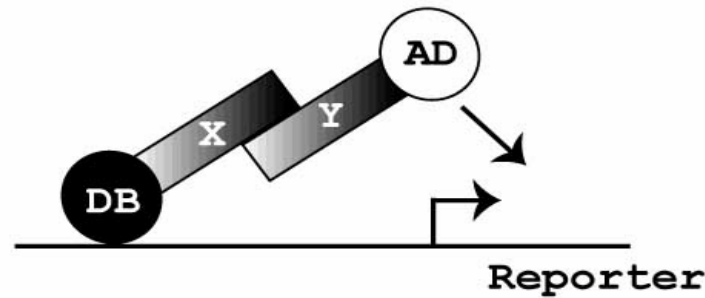
- Cell lineage
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Global Yeast Two Hybrid

Subclone all ORFs into Yeast two hybrid system
Systematically describe potential protein-protein interactions



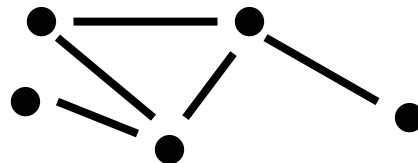
Global Yeast Two Hybrid



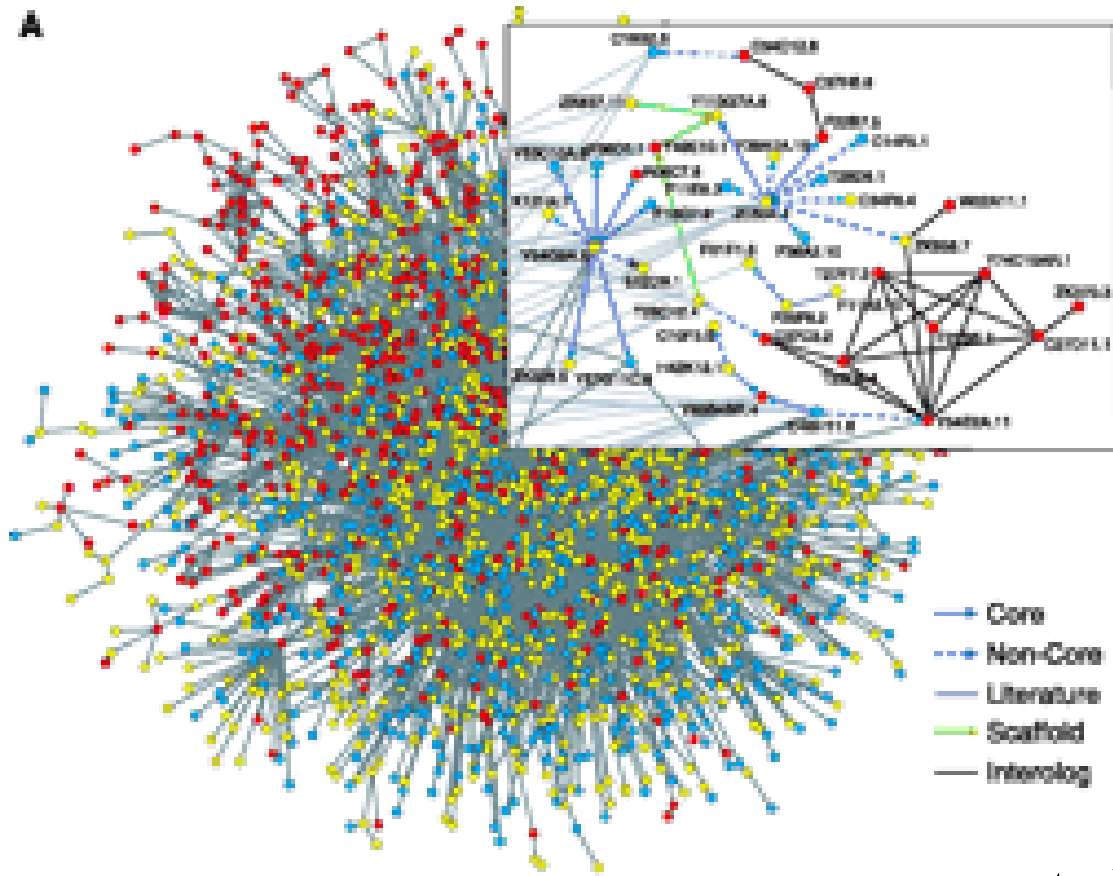
Sons, Ltd.



2898 nodes connected by 5460 edges



Protein interaction network



et al. Vidal, 2004

Overview

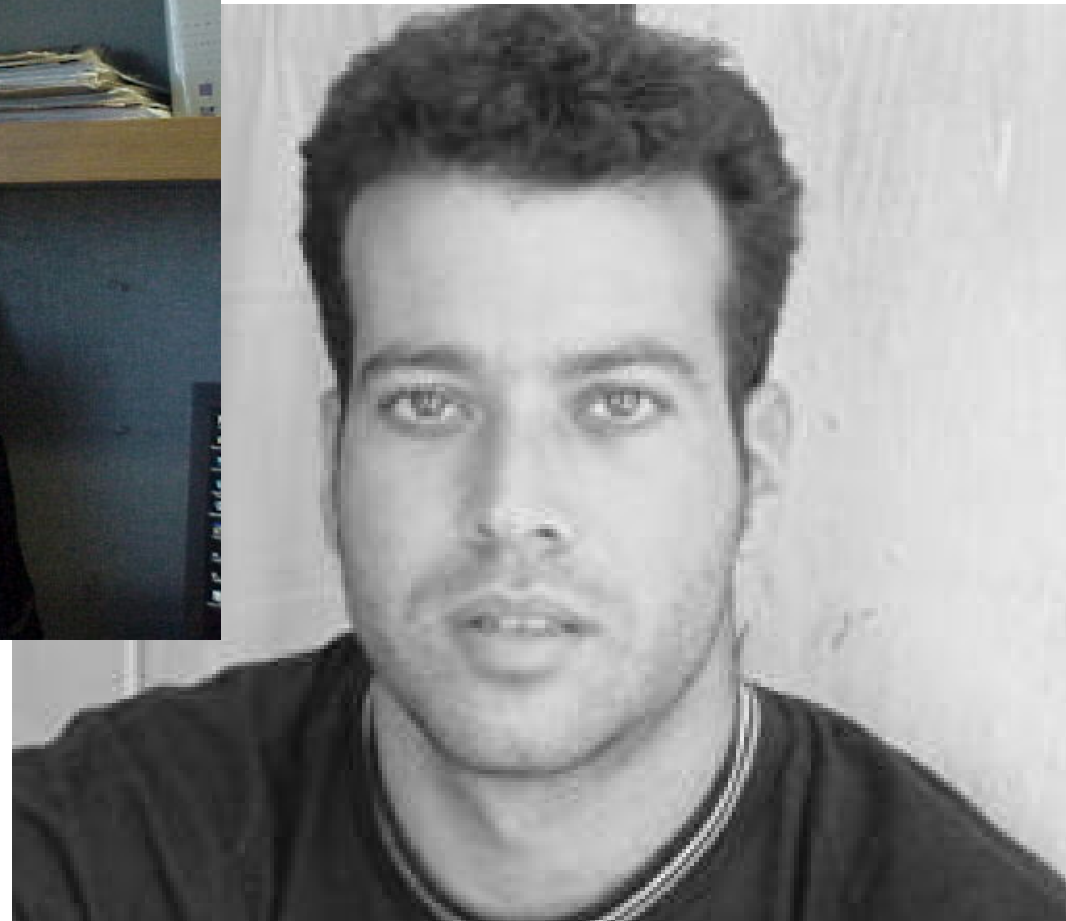
- Cell lineage
- Genome
- Mutant Phenotypes
- Protein interaction
- **Gene Expression**

Gene expression Networks

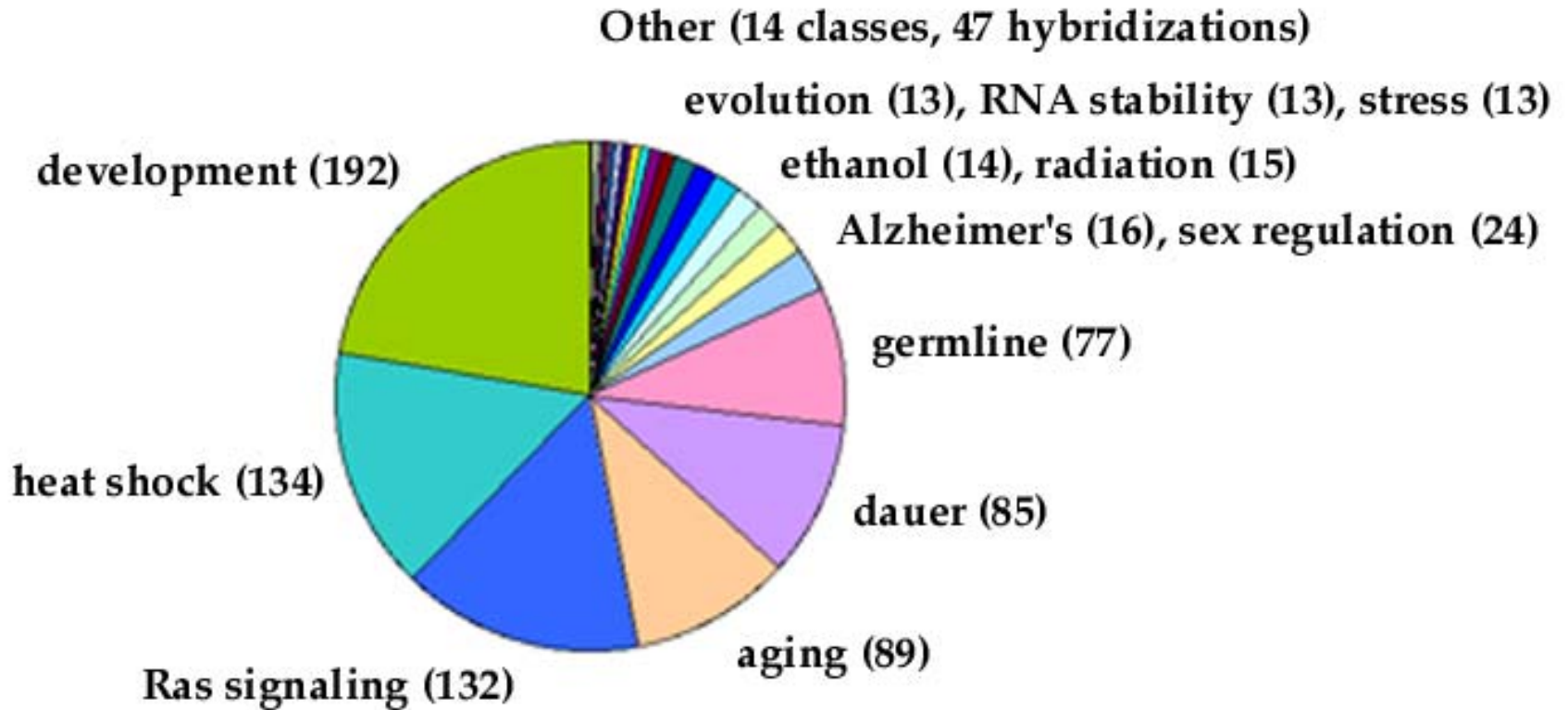
Eran Segal
(Weizmann)



Josh Stuart (UCSC)



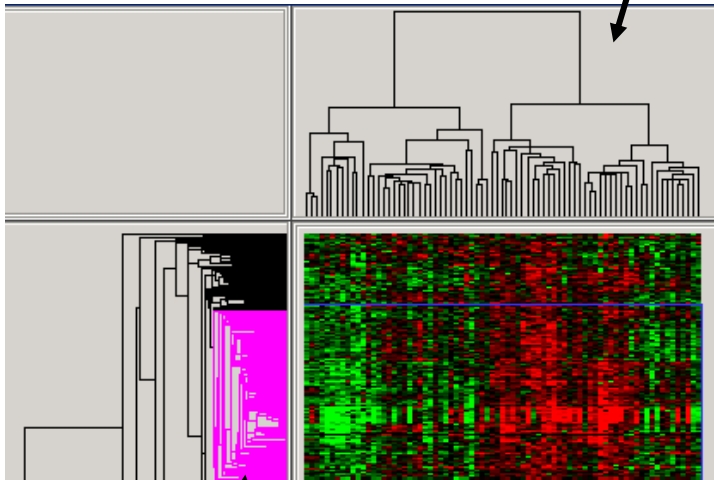
C. elegans gene expression database



553 DNA microarray expts X ~ 19,000 genes

Cluster of co-expressed genes from DNA microarray experiments

553 DNA microarray experiments



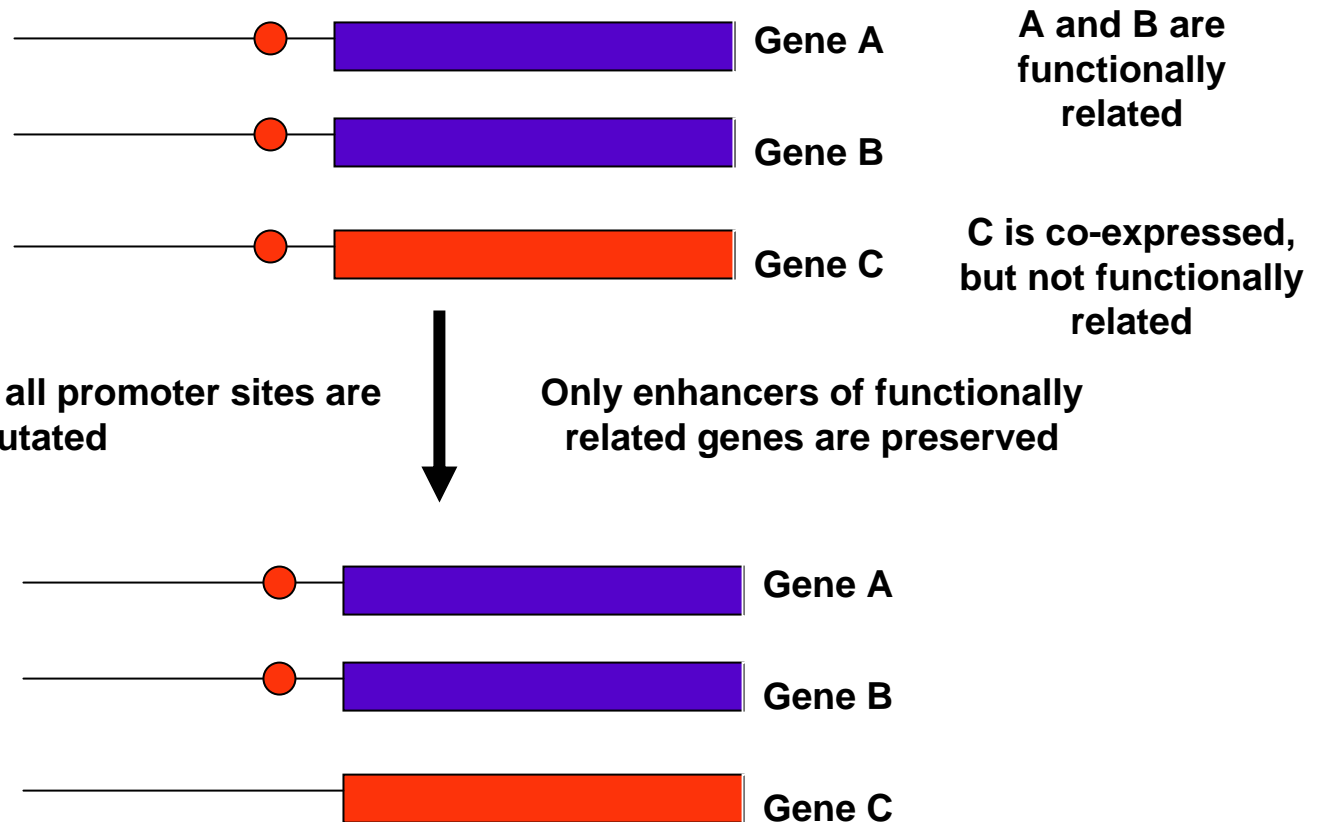
~20,000 genes

Expressed together

Which are functionally related?

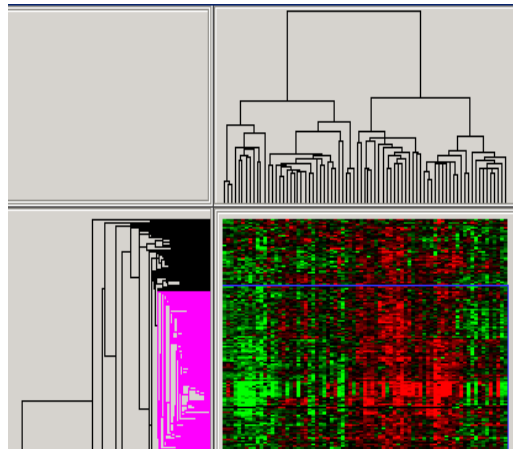
Which are physiologically relevant?

Evolutionary conservation implies functional interaction



Conserved co-expression

human



YFG

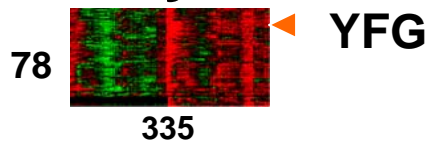
Functionally related to YFG?

Selective advantage for co-expression

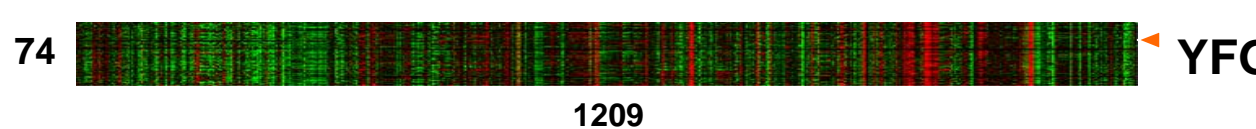
Evolutionarily conserved

May see co-expression in:

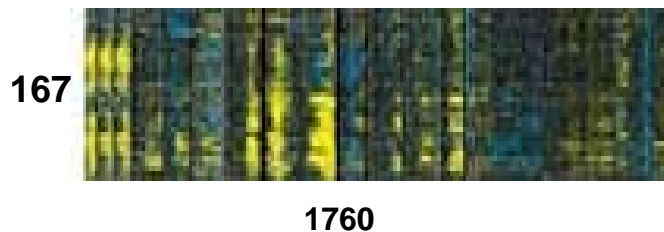
Fly



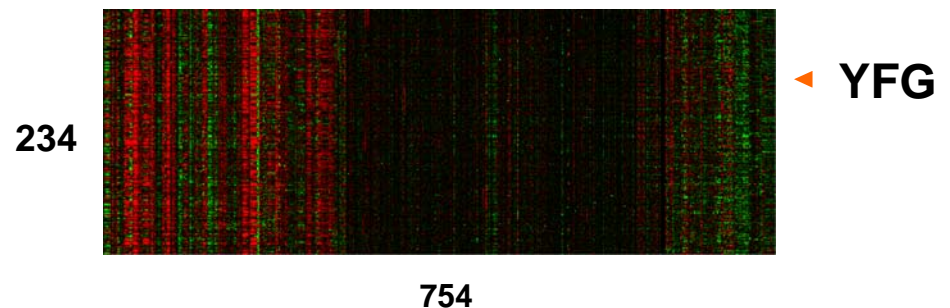
Worm

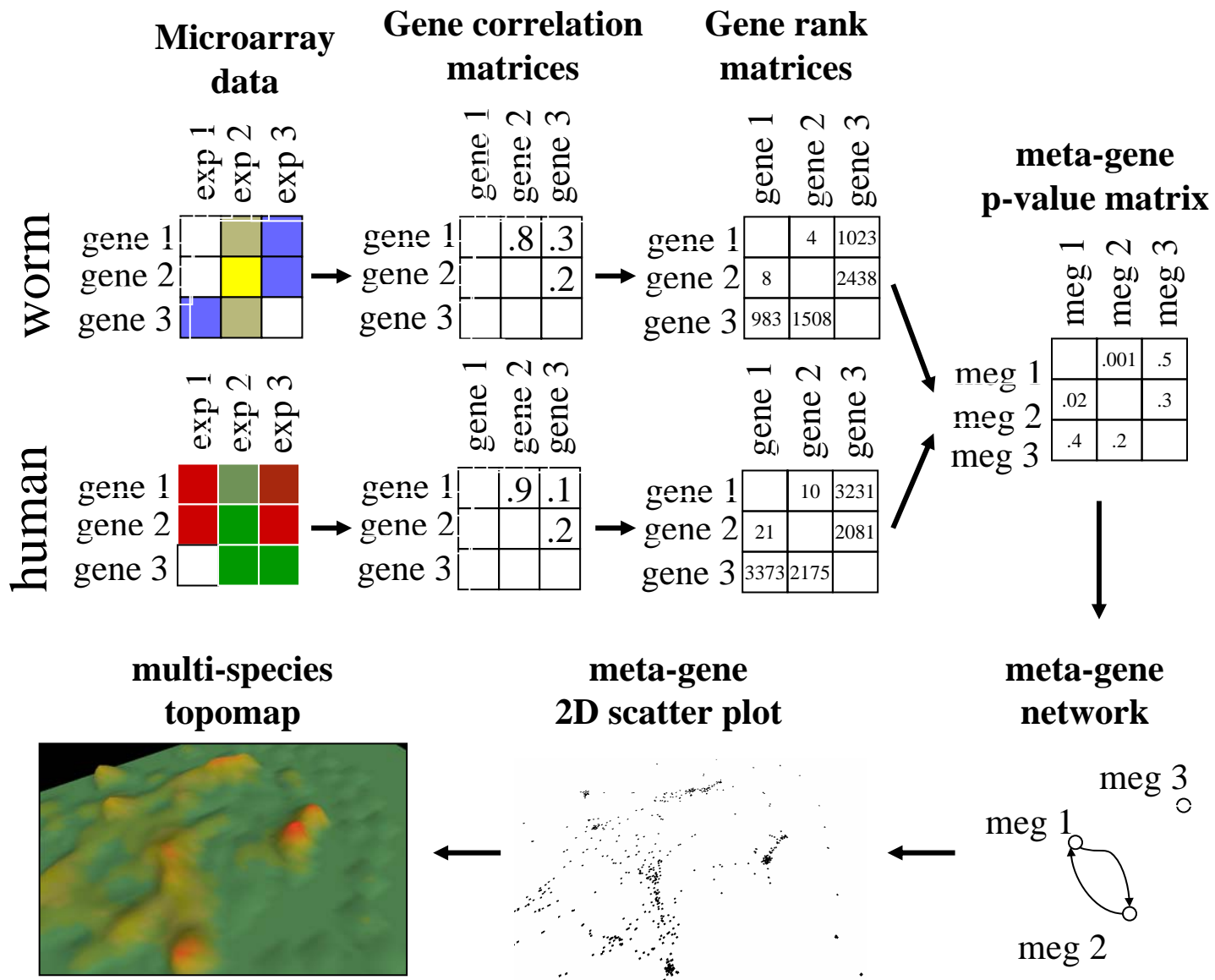


Mouse

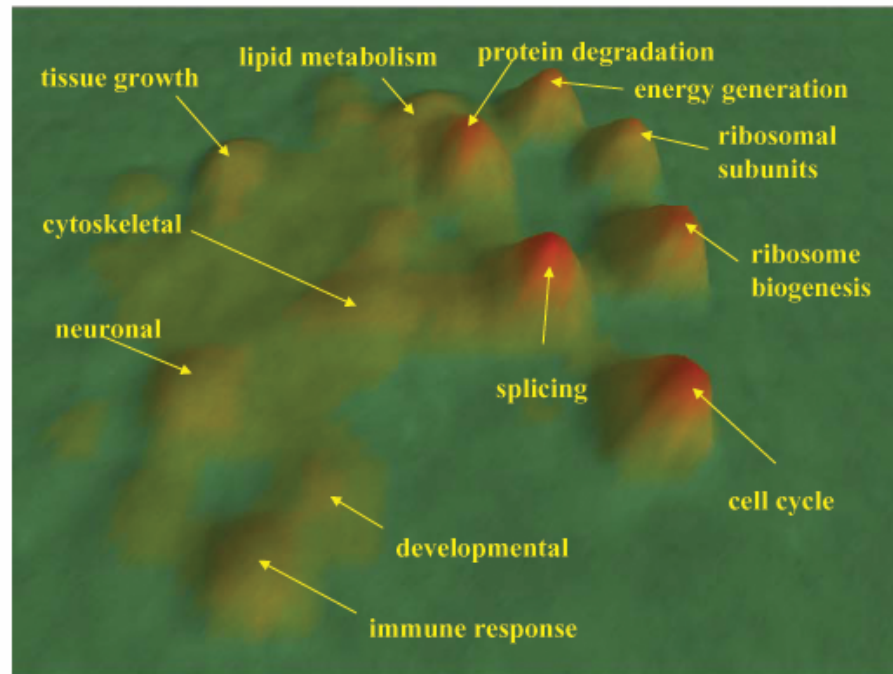
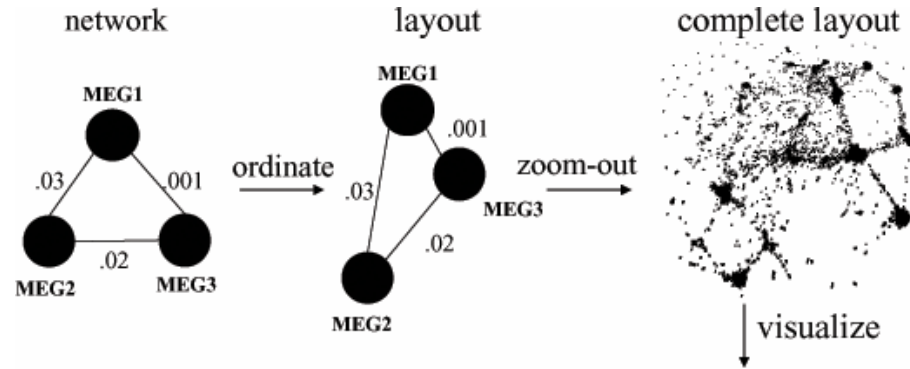


Yeast





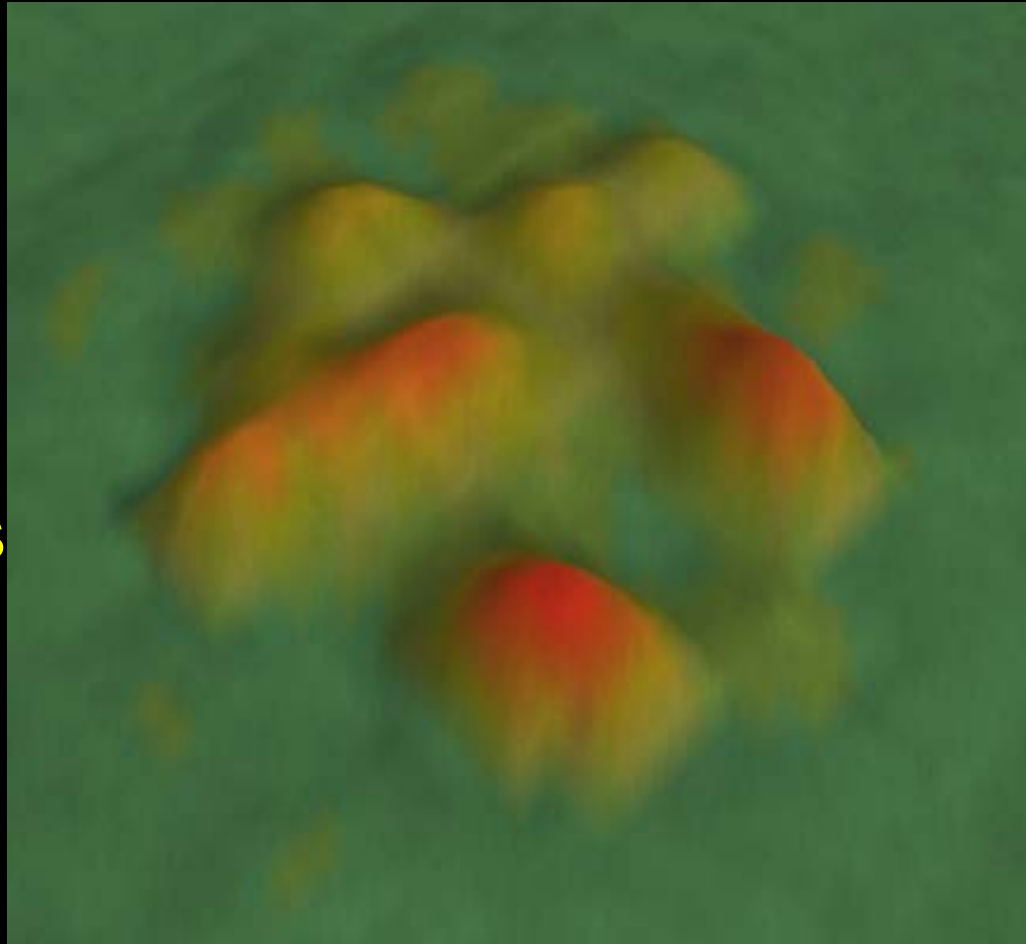
Gene Expression Network



Gene Expression Topomap

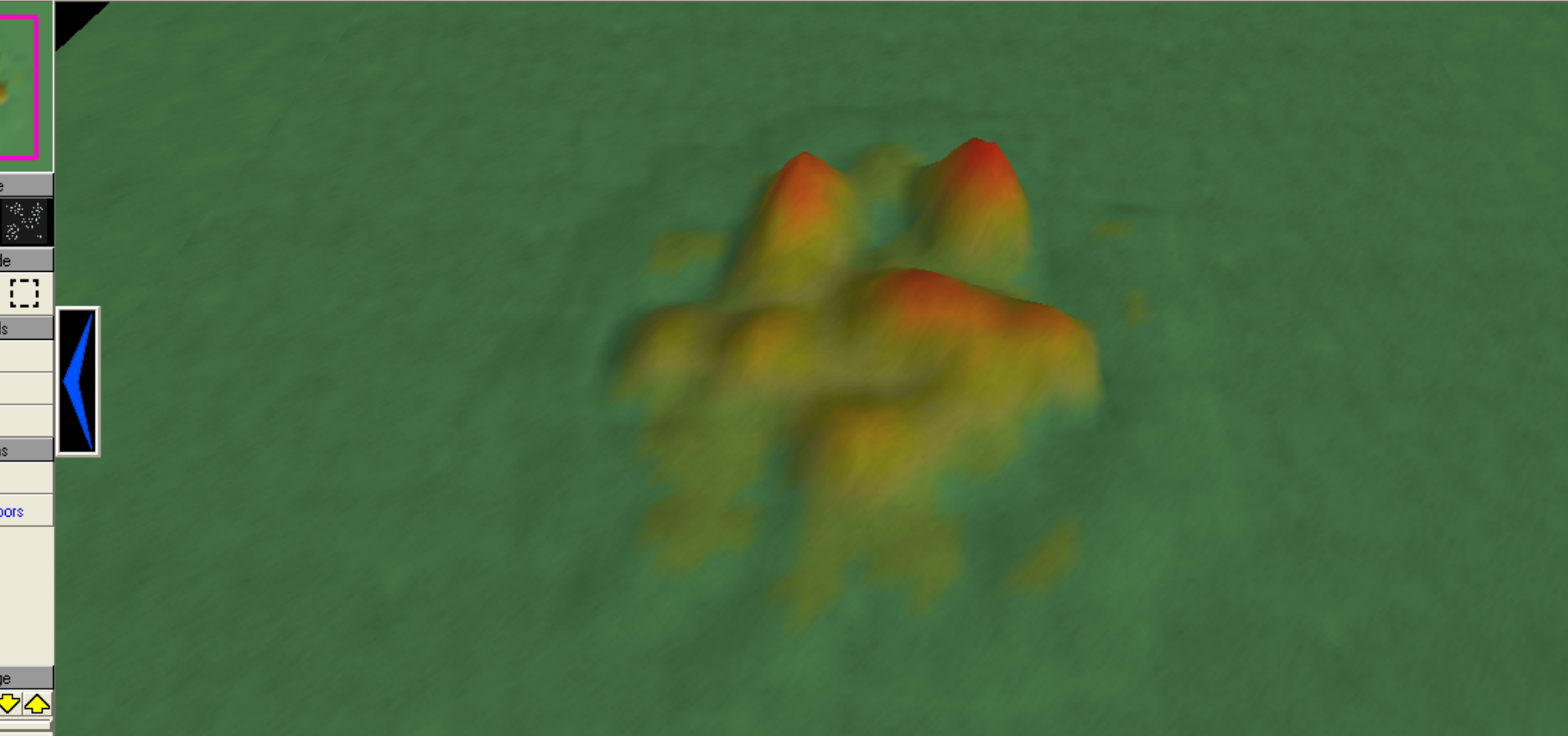
6886
meta-genes

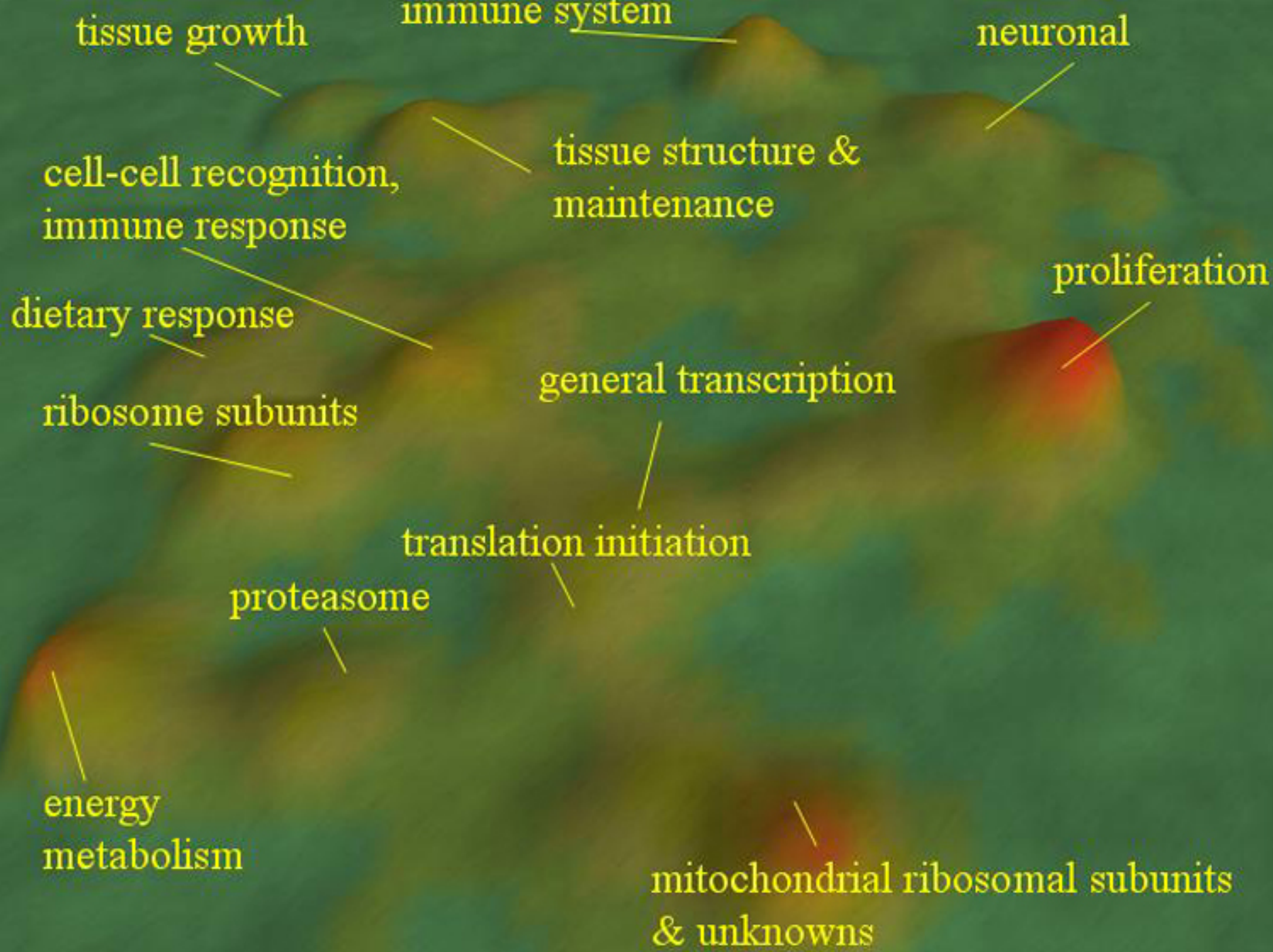
>1000
unknown



Ribosomal subunits

Short





A gene expression microscope

- Plan A = microarrays



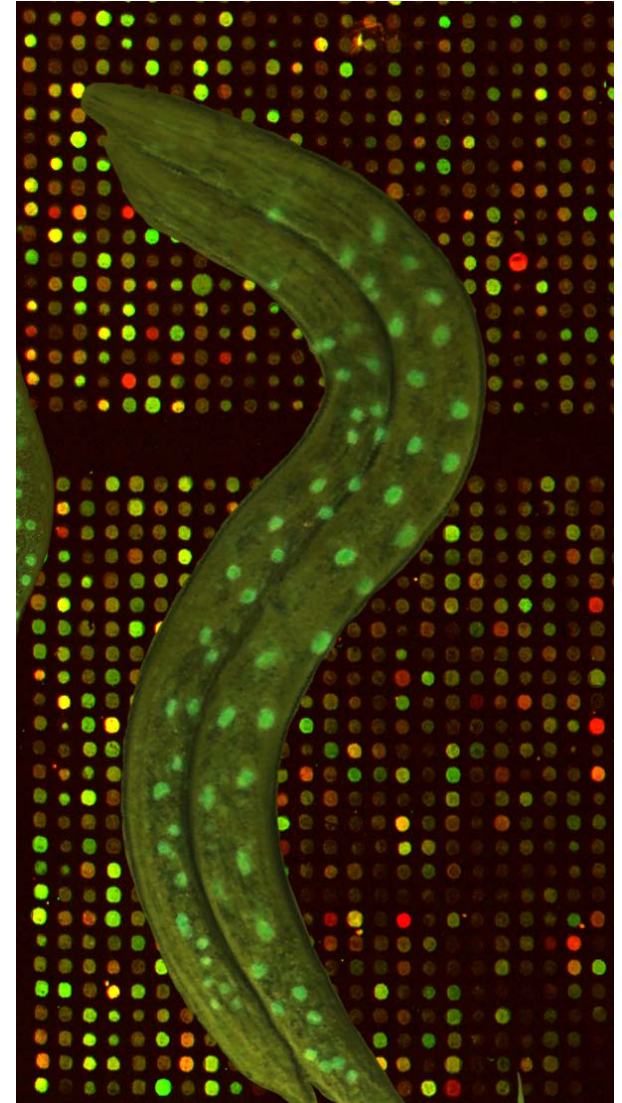
Flo Pauli

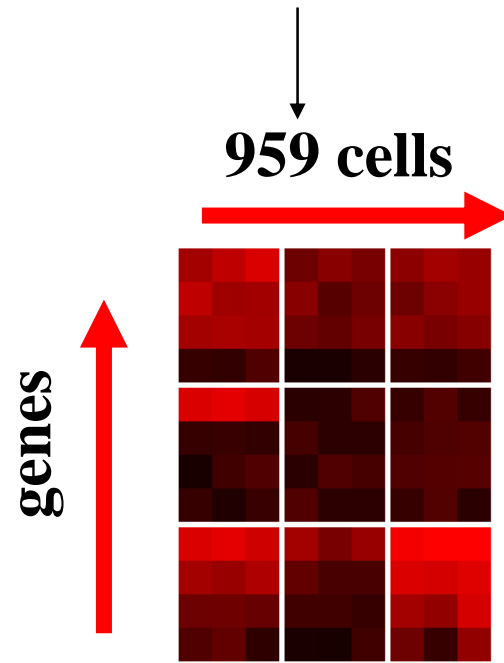
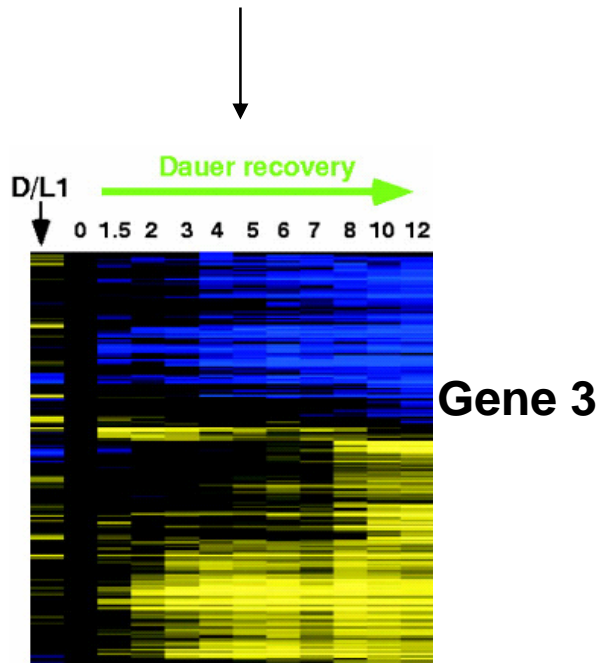
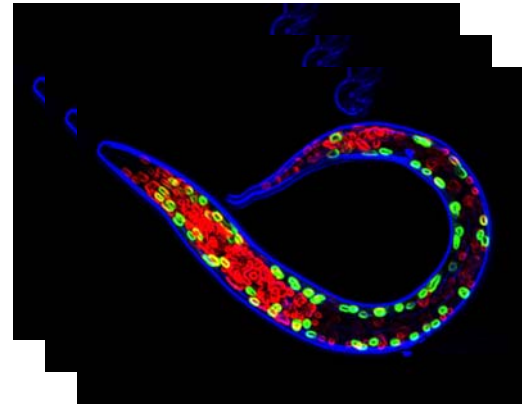
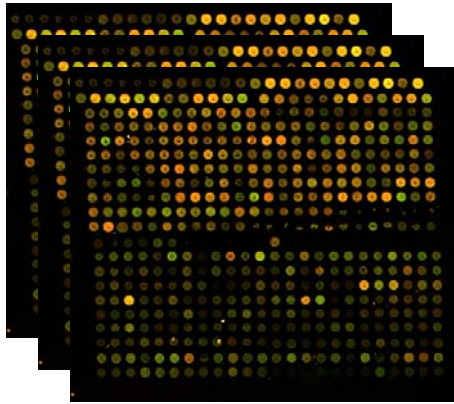
- Plan B = GFP reporters

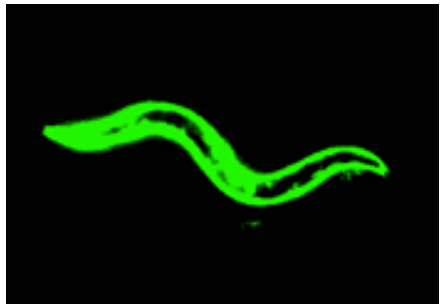


Xiao Liu

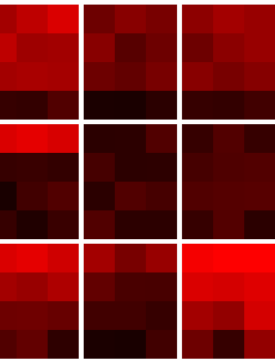
(Fuhui Long, Hanchuan Peng, Gene Myers)







959 cells



A large number of GFP-reporter transgenic worms



3-D confocal data stack



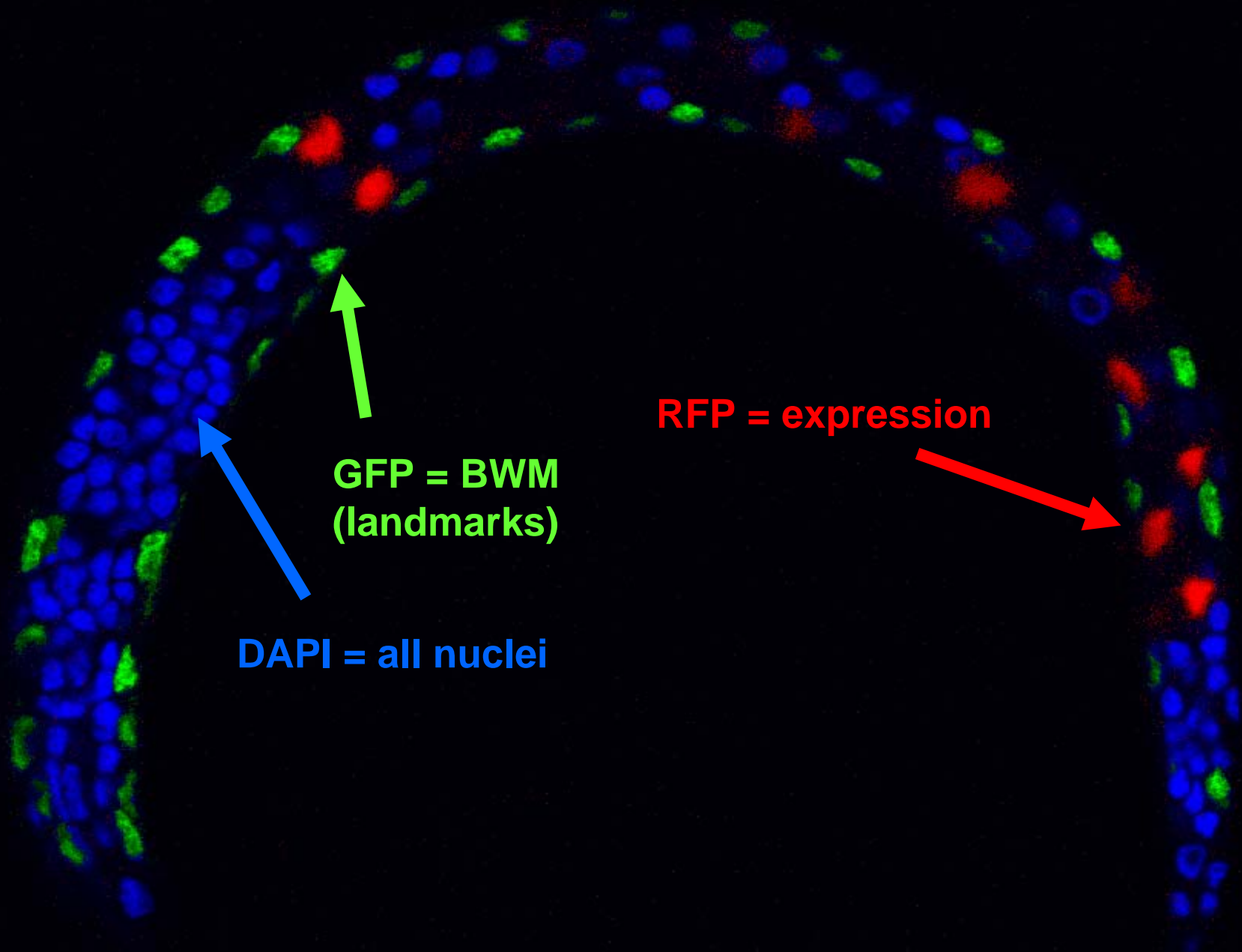
Automatic cell lineage analyzer



Quantitative measurement of GFP expression at the level of single cells

Long Term Plan

- Construct a imaging system to automate cell identification of *C. elegans*
- Generate GFP-reporter strains in a large scale
- Use this GFP analysis system to study aging



DAPI = all nuclei

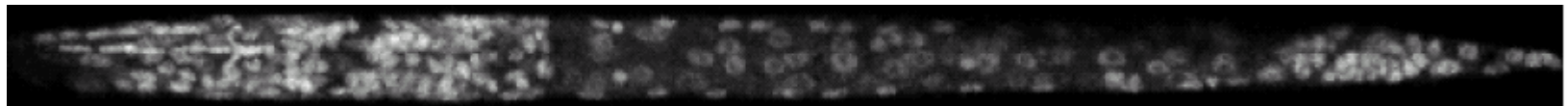
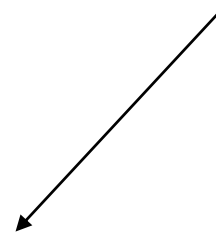
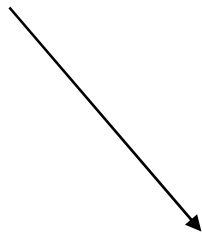
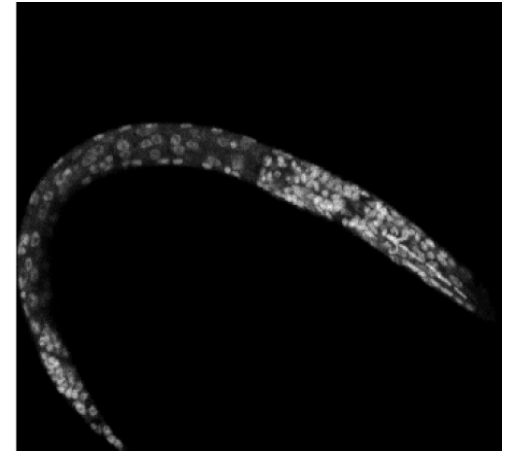
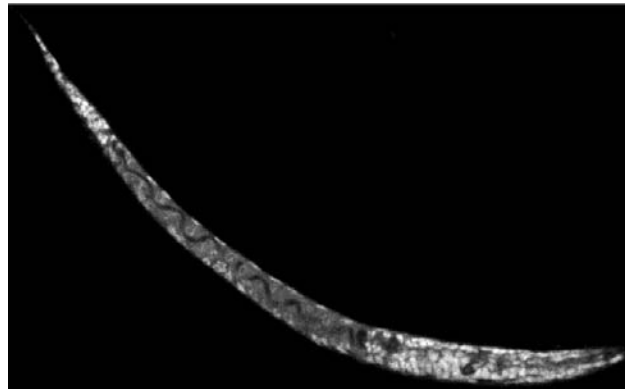
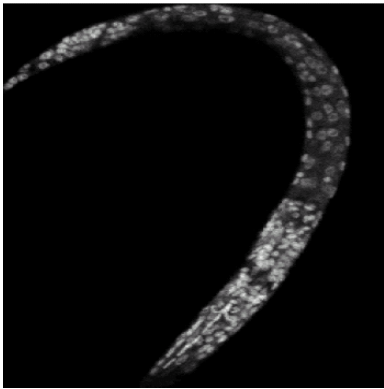
GFP = BWM
(landmarks)

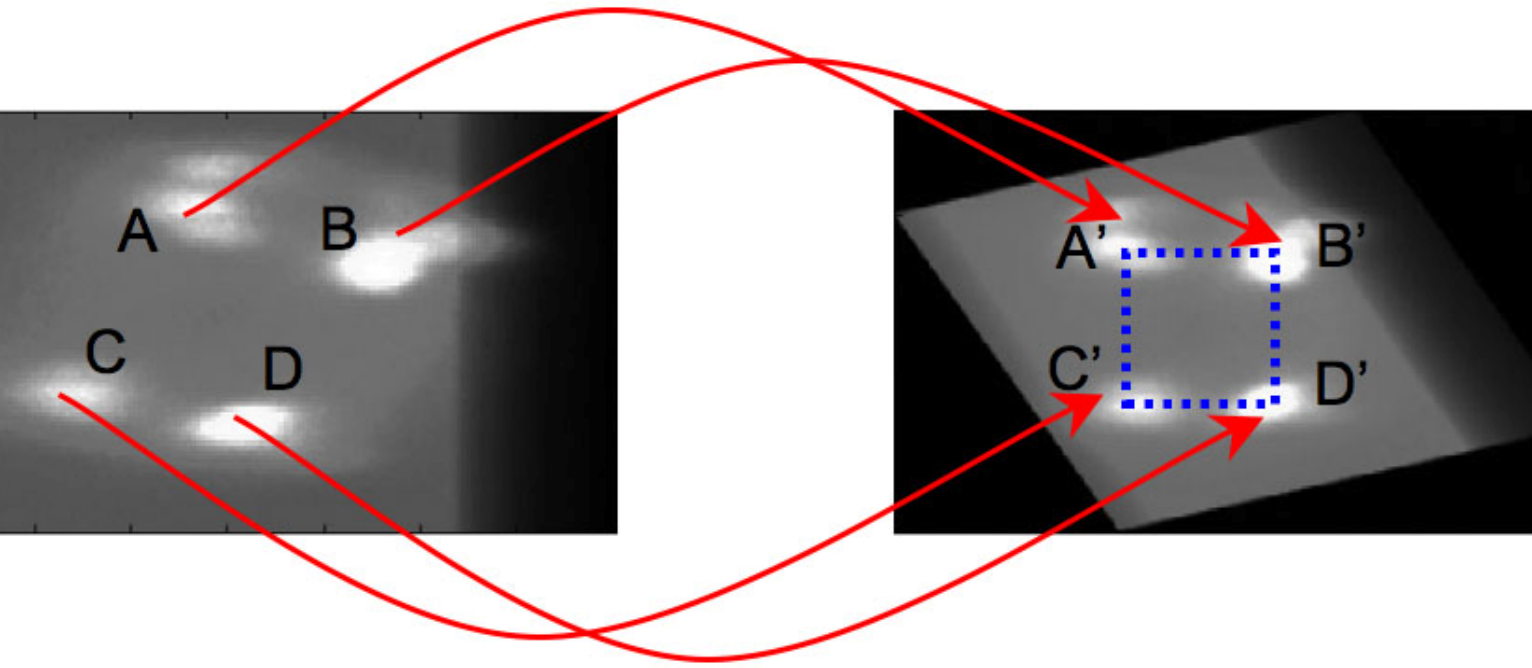
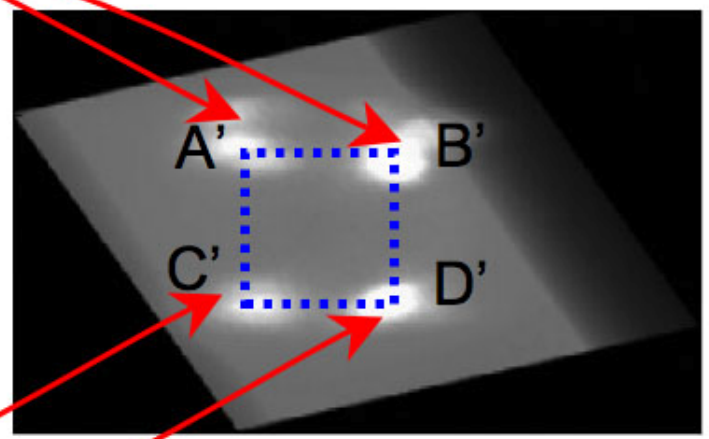
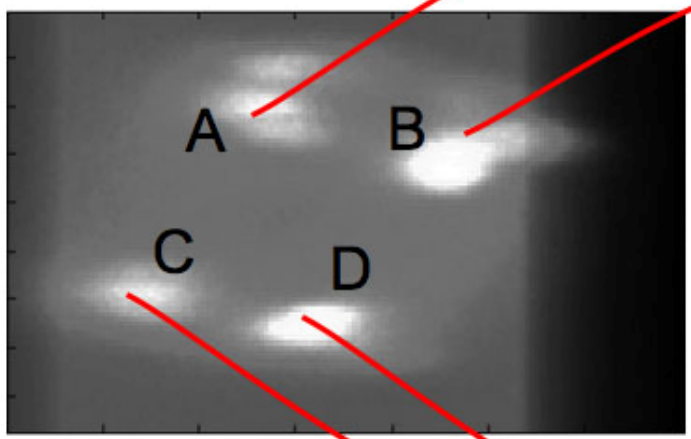
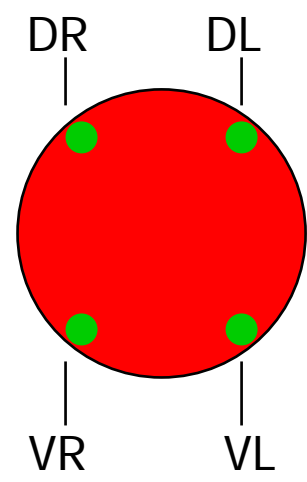
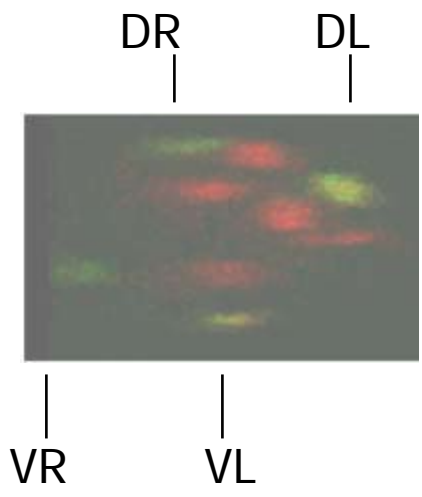
RFP = expression

Automatic GFP analyzer

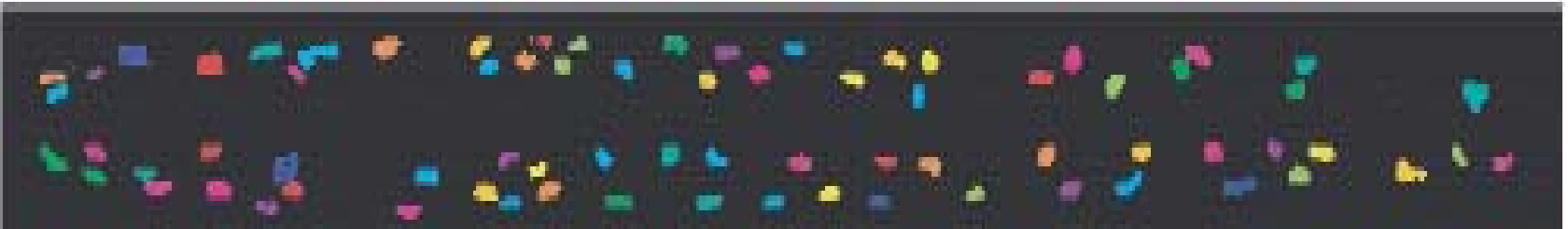
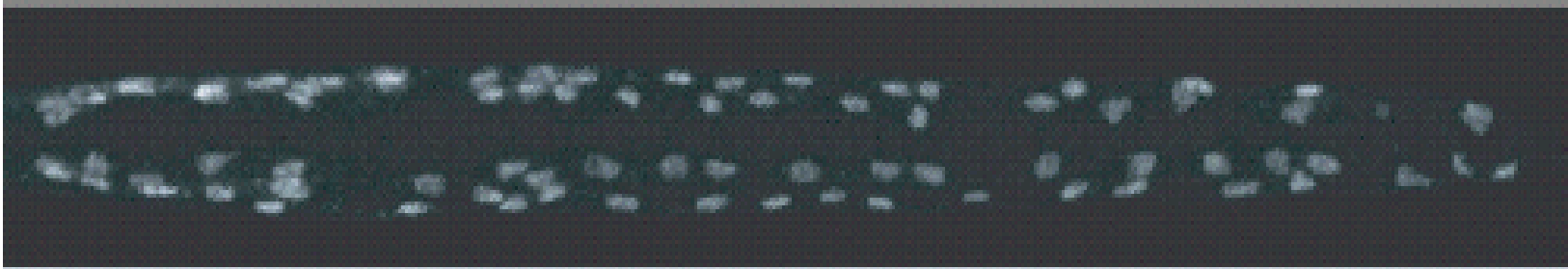
- Registration = align the image to a standard virtual worm model
- Segmentation = find the nuclei
- Recognition = name the nuclei
- Expression = measure GFP levels in each nucleus

Registration = align image to a standard virtual worm model

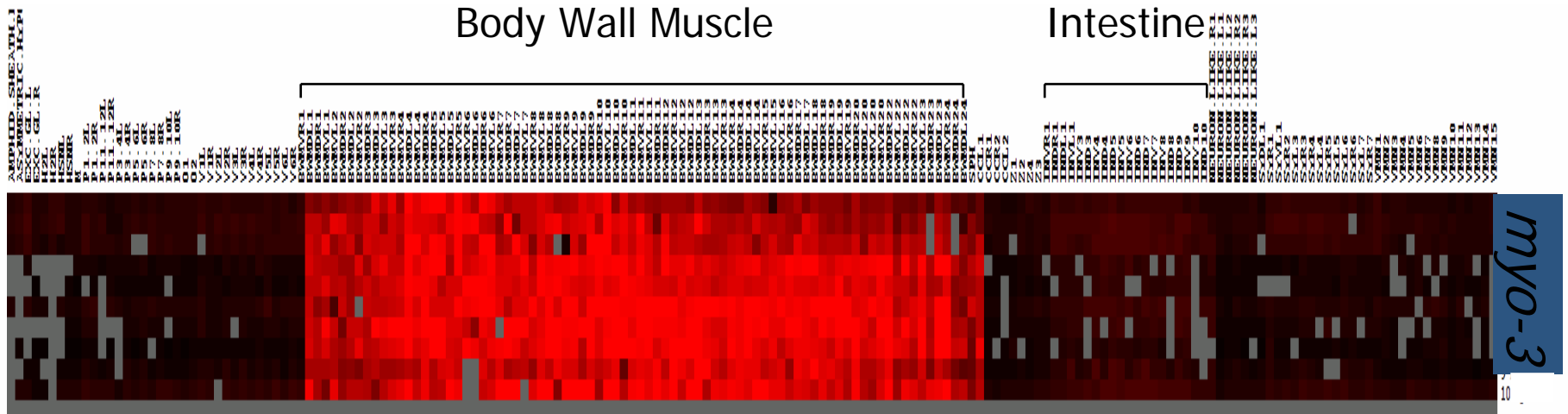




Segmentation = find the nuclei

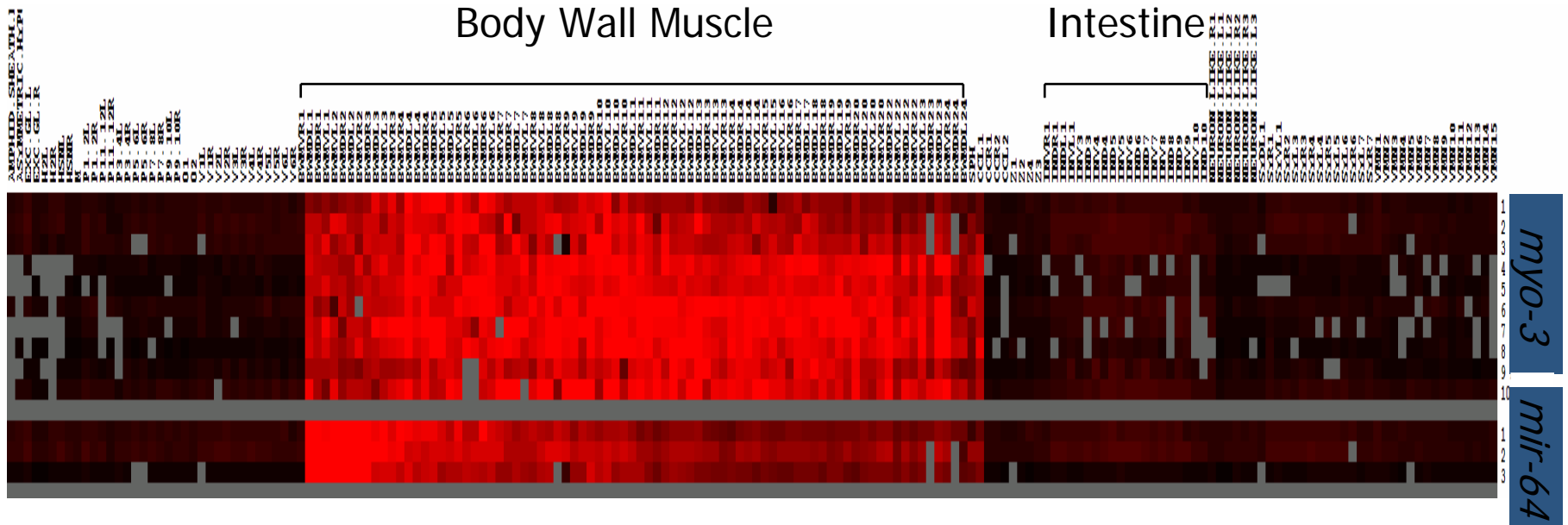


Gene expression profile at the level of single cells



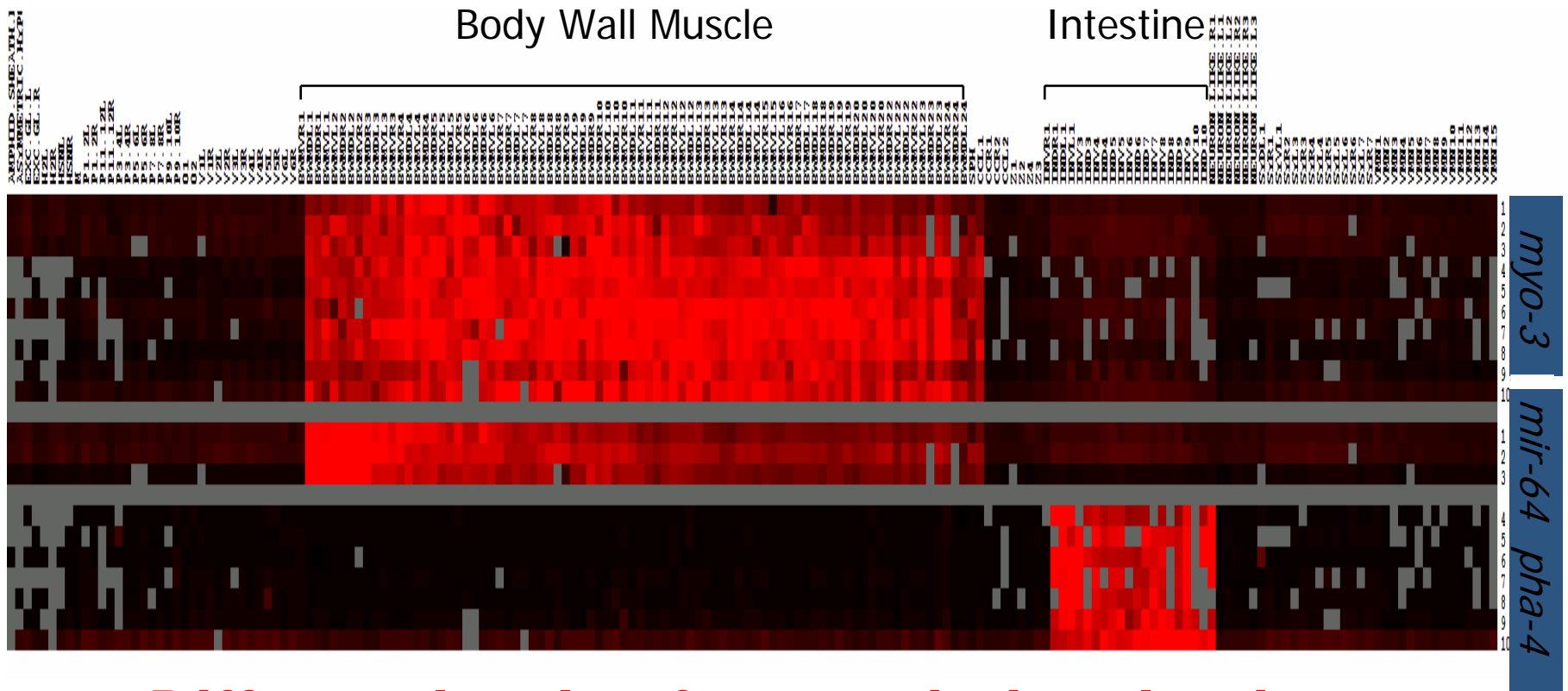
Tissue Specificity

Gene expression profile at the level of single cells

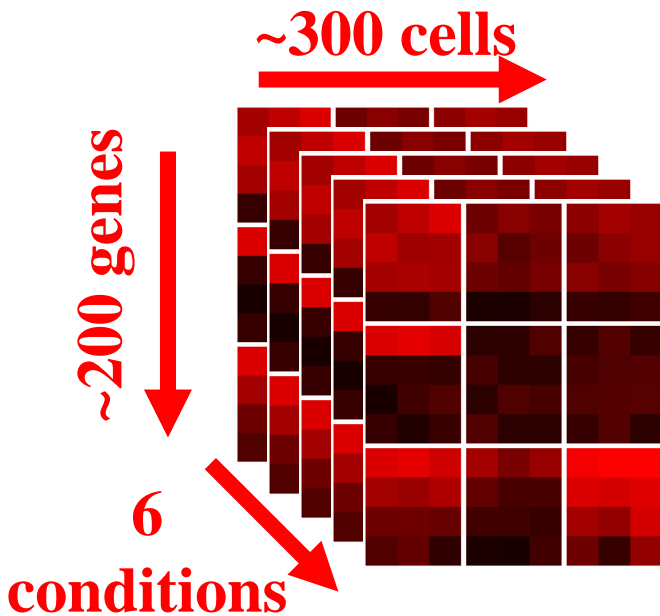
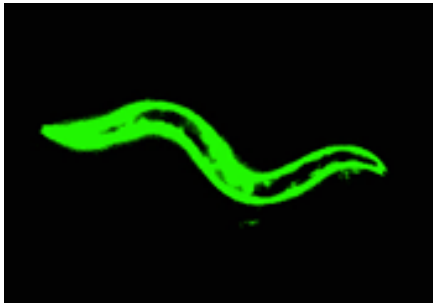


Gradient of gene expression

Gene expression profile at the level of single cells



Different levels of transcriptional noise



~200 GFP-reporter transgenic worms/yr



3-D confocal data stacks



6 developmental time points

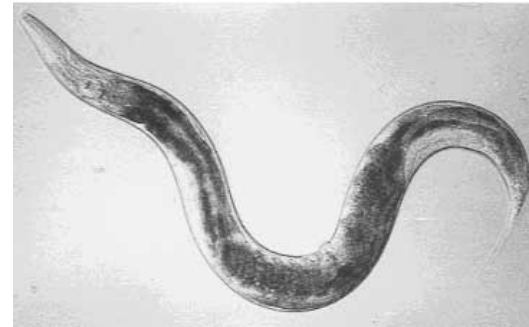
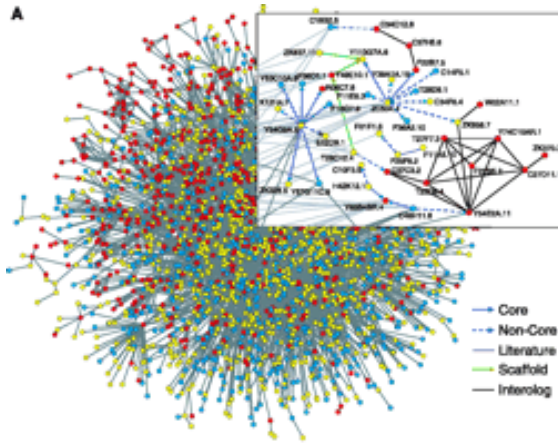


Automatic cell lineage analyzer



Quantitative measurement of GFP expression at the level of single cells

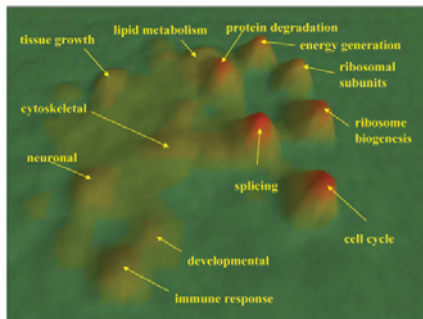
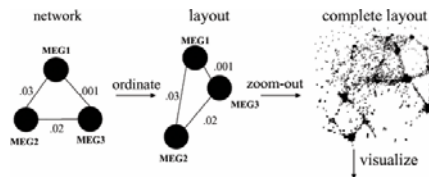
Systems Biology



+



OR



Systems Biology of *C. elegans*

- Conserved gene expression modules
 - Josh Stuart
 - Eran Segal (Daphne Koller)
- Automatic GFP lineage analyzer
 - Xiao Liu
 - Fuhui Long
 - Hanchuan Peng
 - Gene Myers