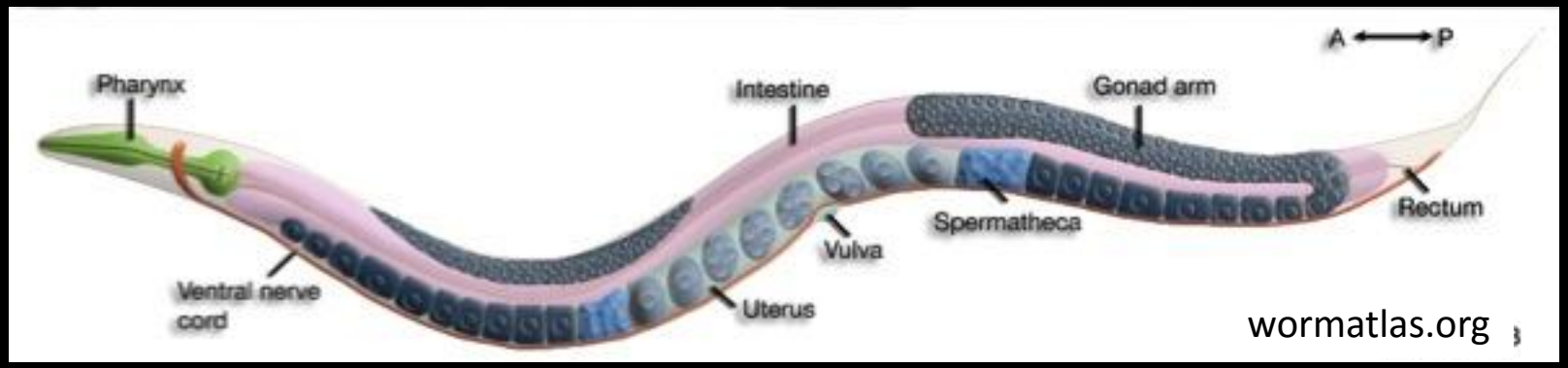
The making of a worm: genes, cells and the organism

Zhirong Bao
鲍志戎
baoz@mskcc.org

Memorial Sloan-Kettering Cancer Center
The Best Cancer Care. Anywhere.

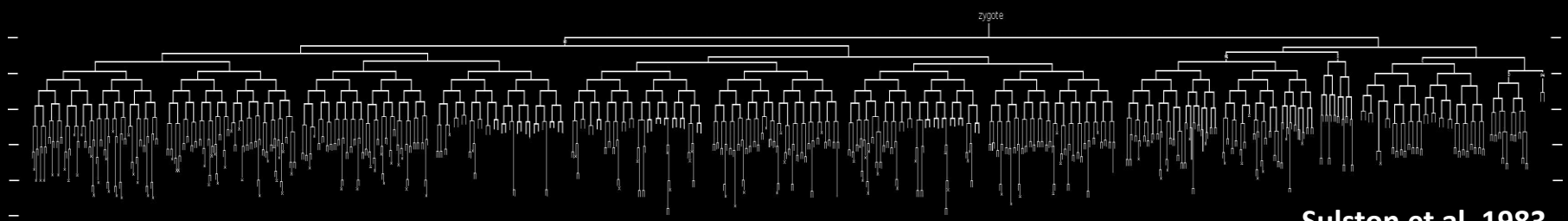
C. elegans as a Model Organism



Nematode
round worm
worm

Courtesy of Allyson McCormick
& Jim Thomas

The Invariant Cell Lineage of *C. elegans*



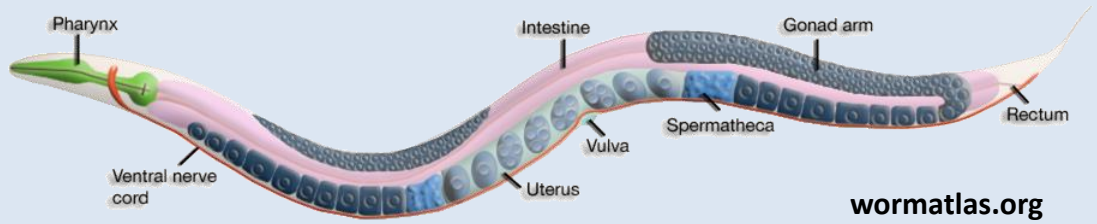
Sulston et al, 1983

Goldstein Lab

Deppe et al, 1978, PNAS
Schnabel et al, 1997, Dev Biol
Henriksson et al, 2013 Nat Methods
Boyle et al, 2006, BMC Bioinformatics

Hamahashi et al, 2005, BMC Bioinformatics
Bao et al, 2006, PNAS
Giurumescu et al, 2013, Development
Mace et al, 2013, G3
Chen et al, 2013, BMC Bioinformatics

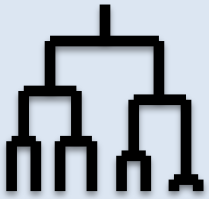
(Systems) Biology of *C. elegans*



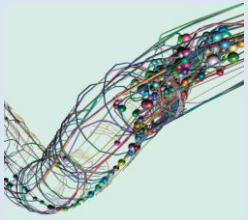
wormatlas.org

Genome

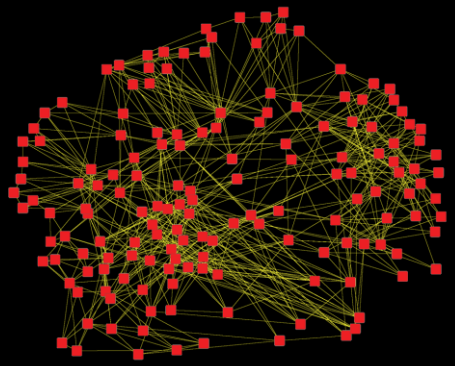
Cell Lineage



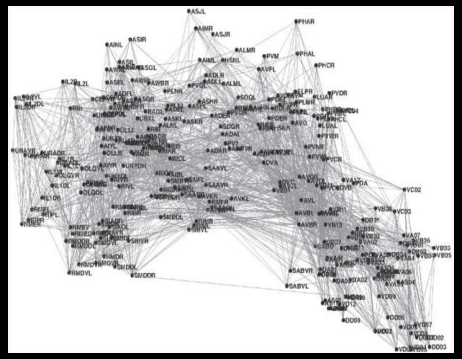
Connectome

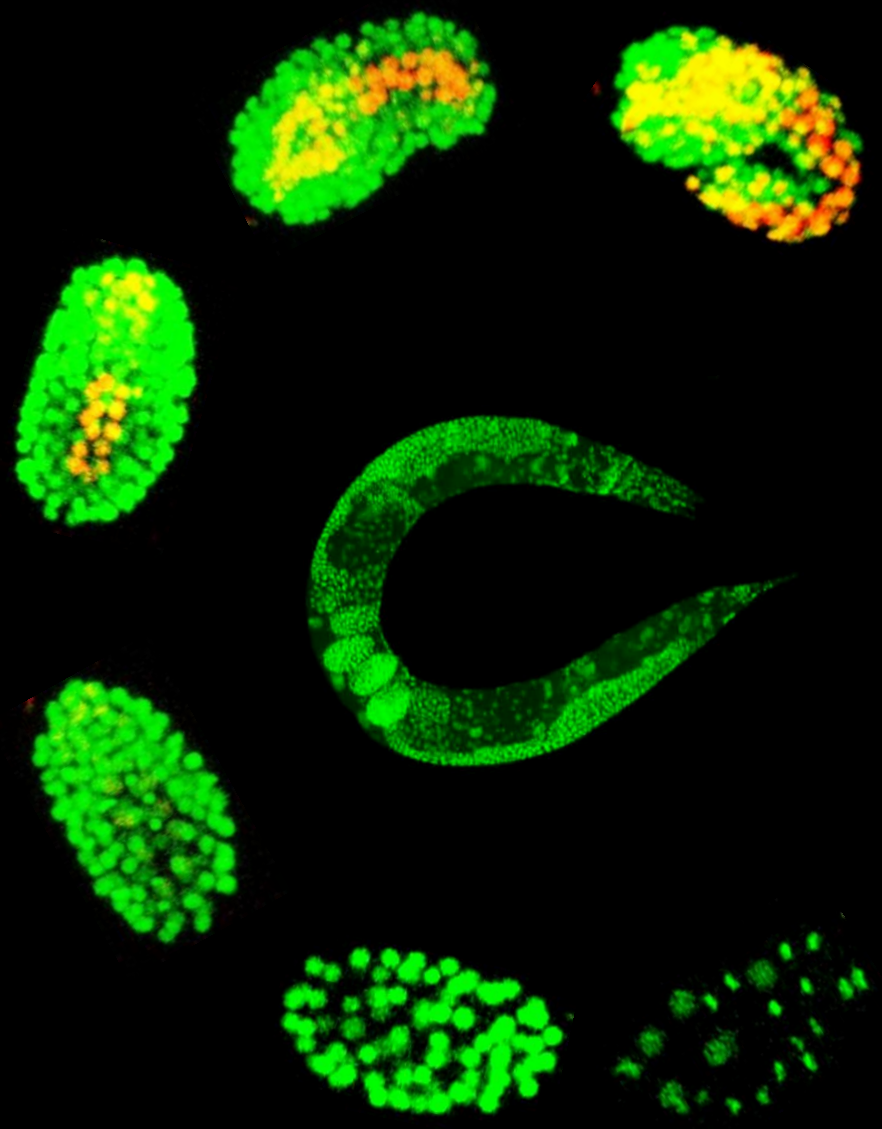


Molecular Networks



Cellular Networks





***in toto* imaging**

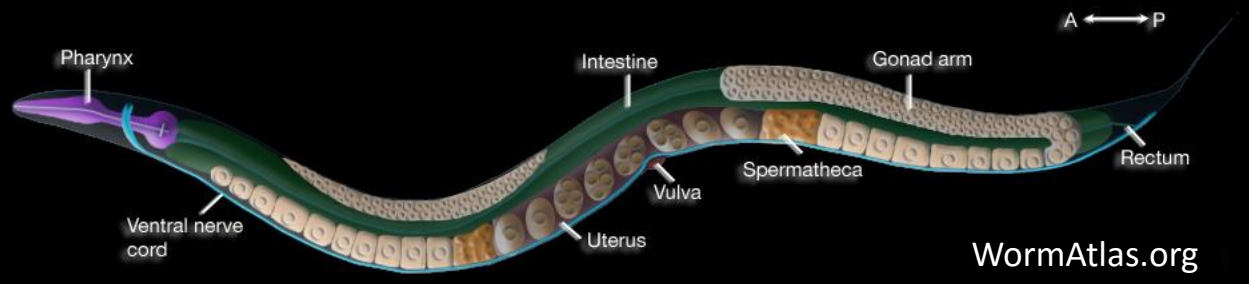
↓

Developmental phenotypes

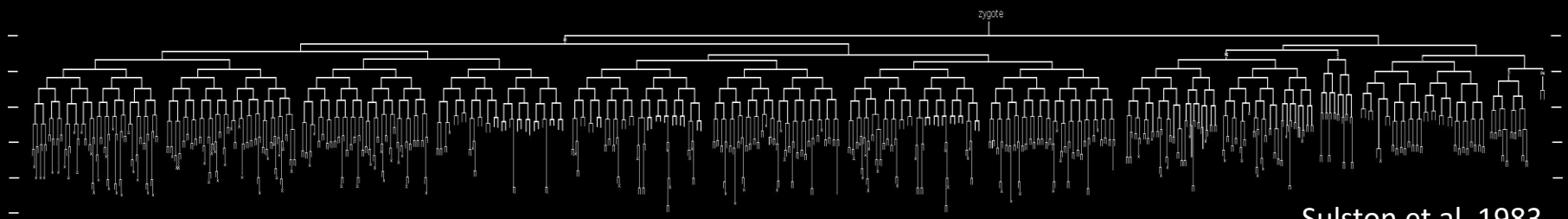
↓

Developmental mechanisms

The Invariant Cell Lineage of *C. elegans*

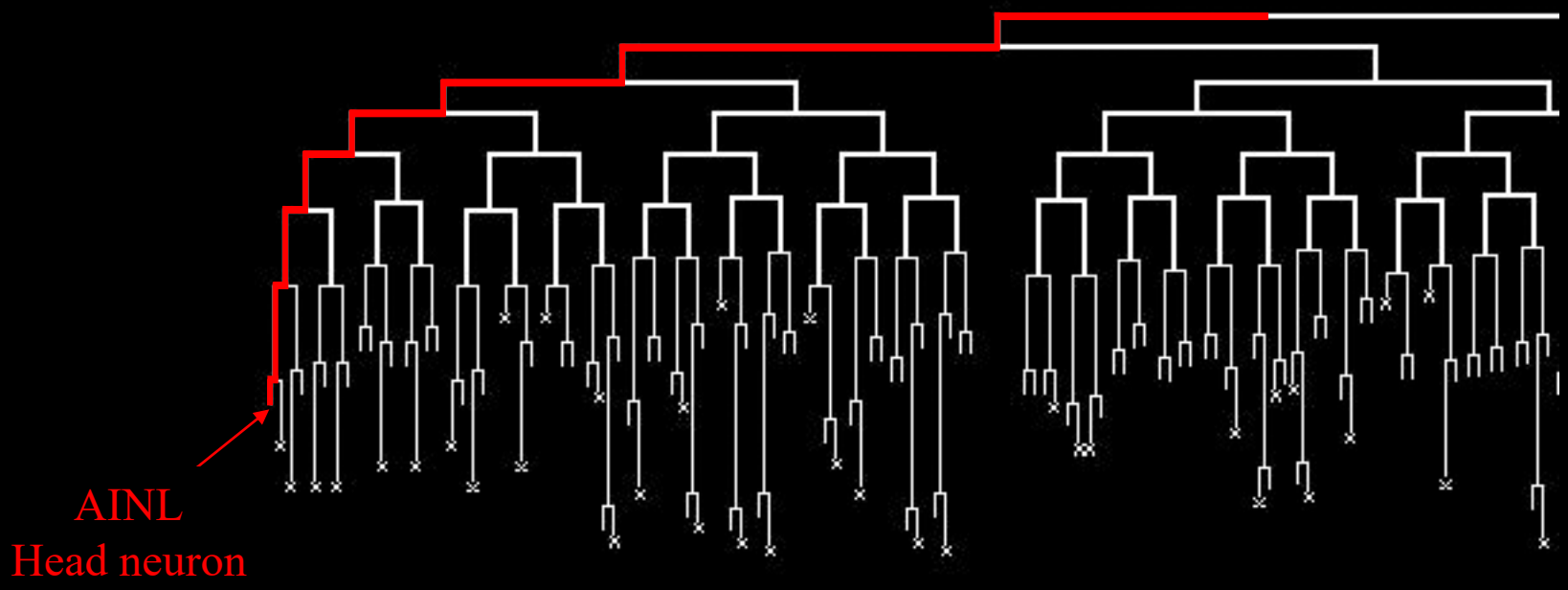


WormAtlas.org



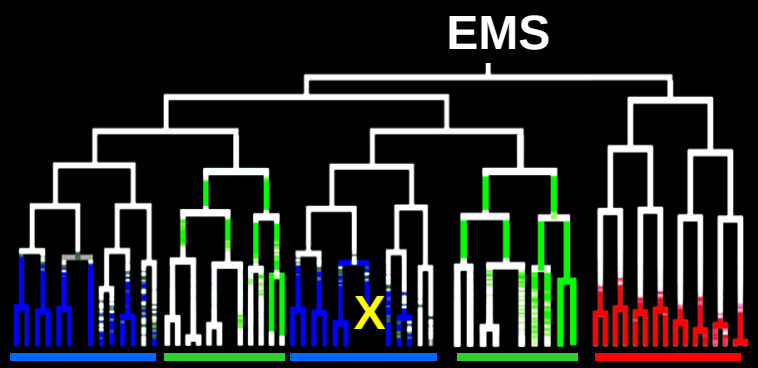
Sulston et al, 1983

The Invariant Cell Lineage of *C. elegans*



Invariability of Embryogenesis

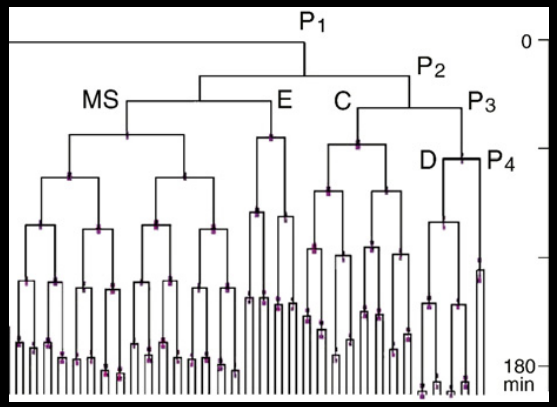
Differentiation



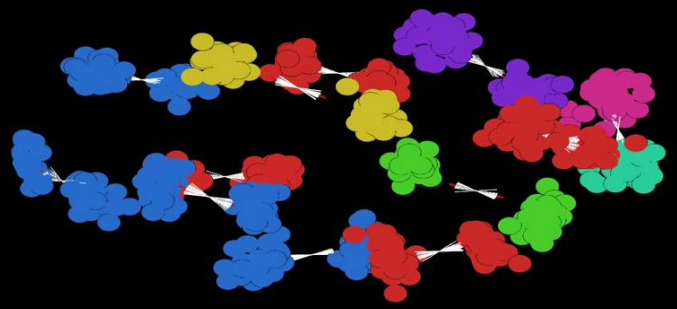
pharynx/*pha-4* muscle/*hnd-1*
X: cell death gut/*elt-2*

number of cells

Proliferation

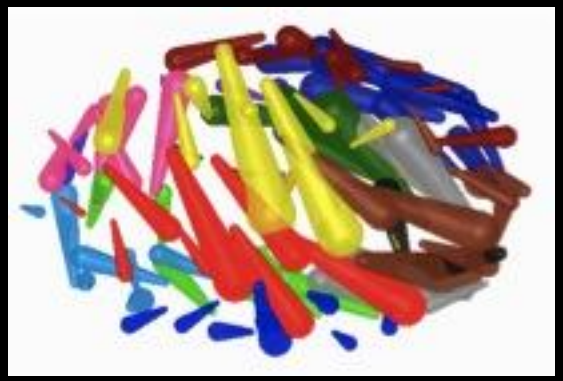


Cell Position



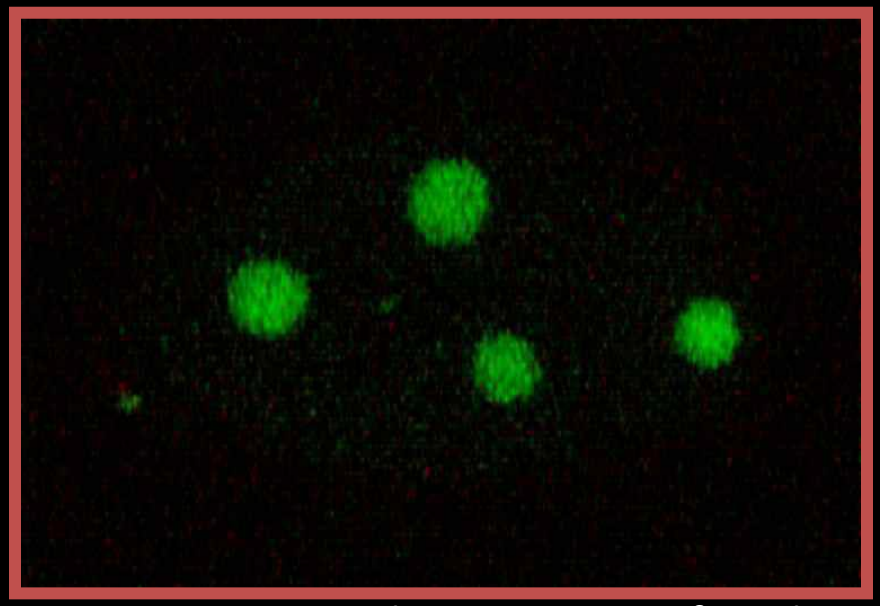
35 embryos aligned

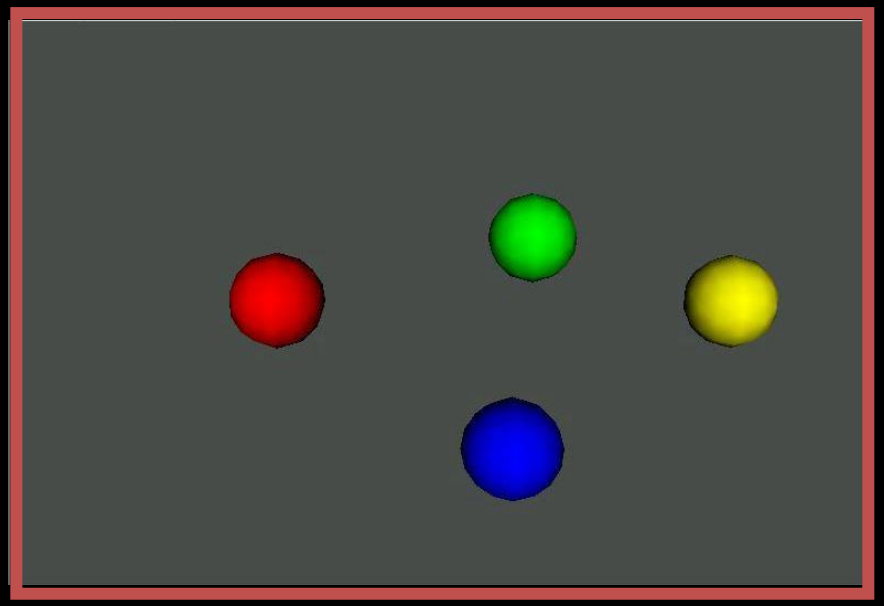
Migration



Moore et al 2013 Development

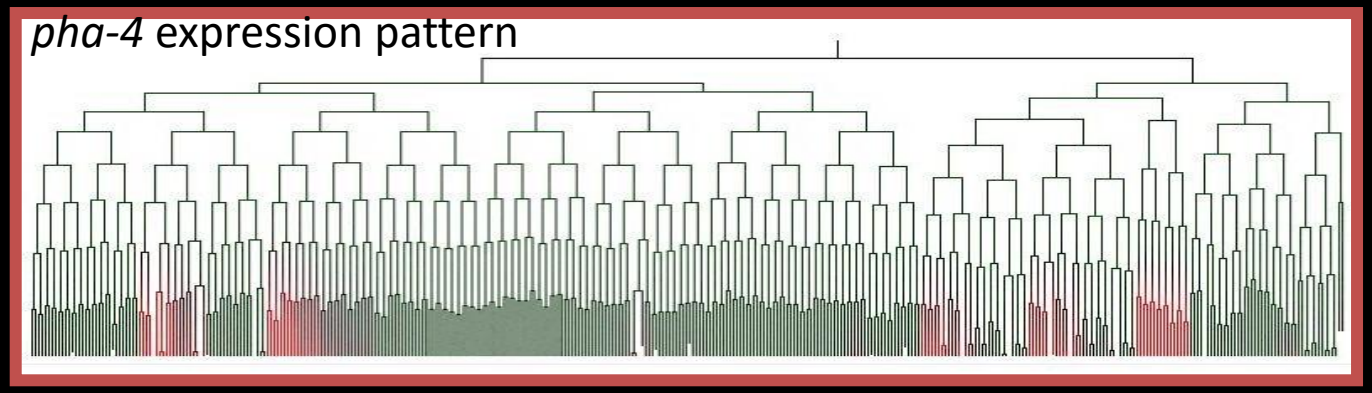
Automated Lineaging





30 plane every min for 7 hrs

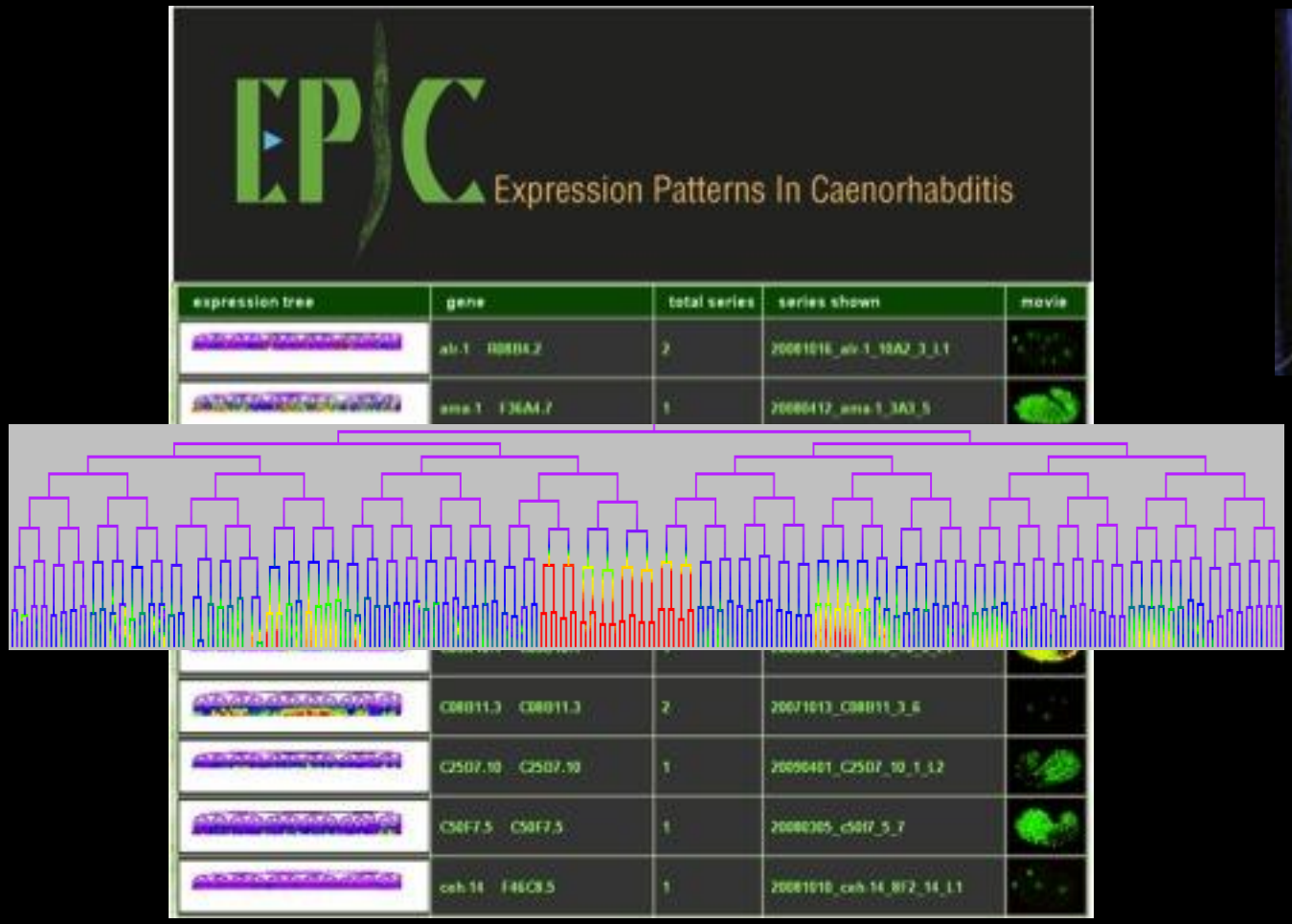
Starrynite



Bao et al, 2006, PNAS; Murray et al, 2008, Nat Methods

Systematic Single-Cell Analysis: Gene Expression

http://epic.gs.washington.edu

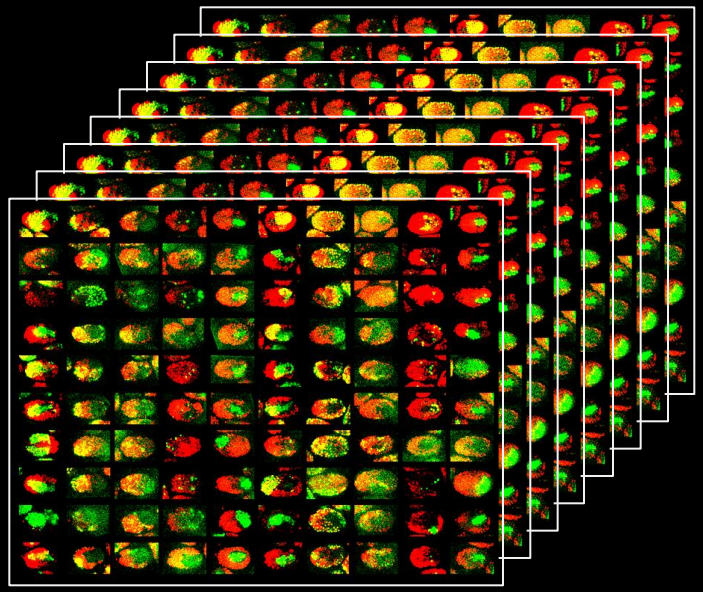


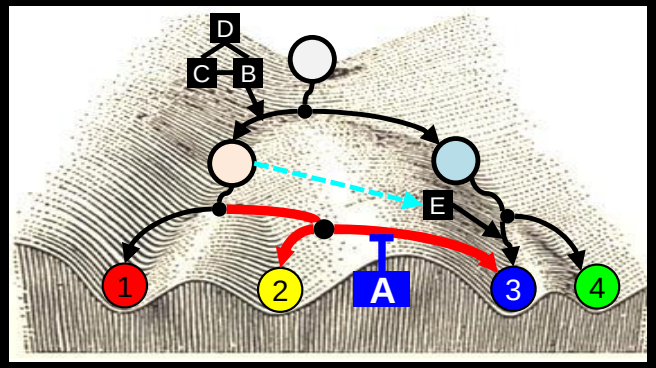
Bob Waterston, UW

John Murray, UPenn

Murray et al, 2012, Genome Res

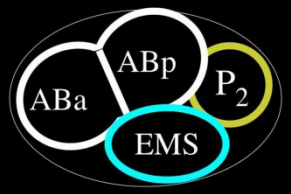
From Images to Mechanisms

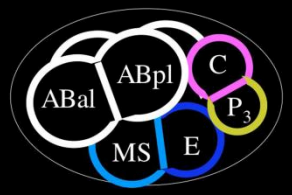




Du et al, 2014, Cell

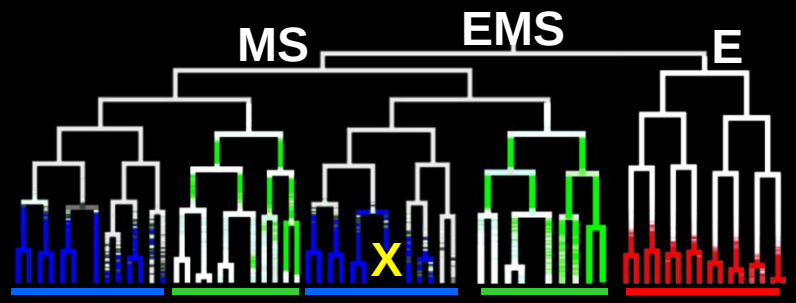
Self-Renewal of the EMS Blastomere



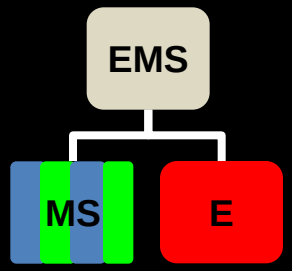


wormbook.org

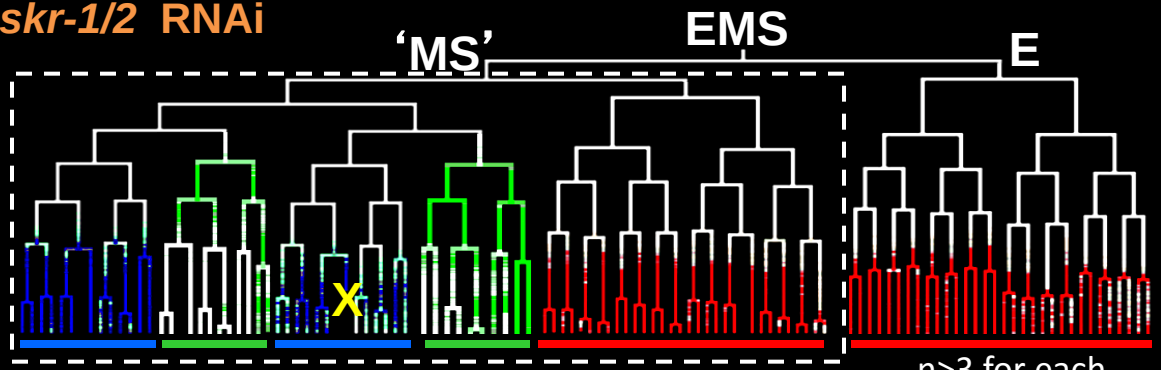
WT



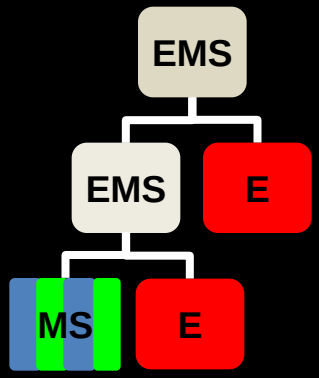
Pharynx Muscle Gut Cell Death n=5

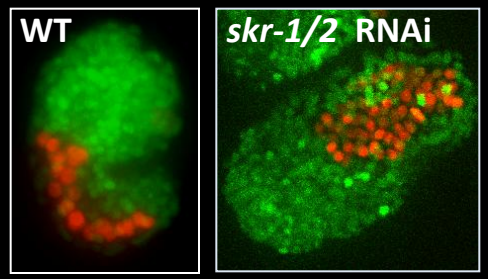


***skr-1/2* RNAi**

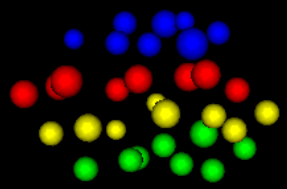


n>3 for each



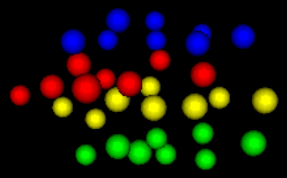


● All cells ● Gut cells



WT MS

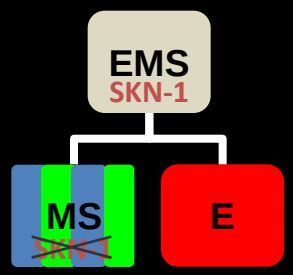
≈

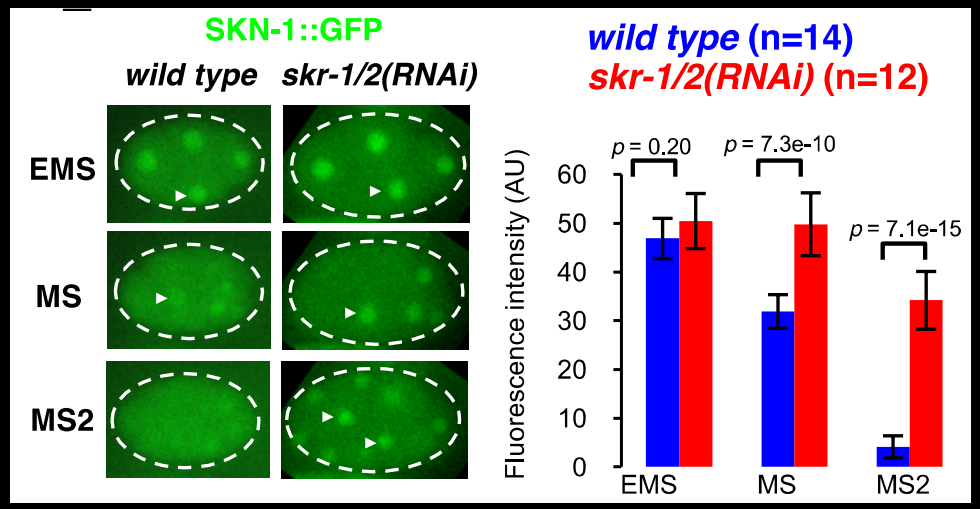


Renewed 'MS'

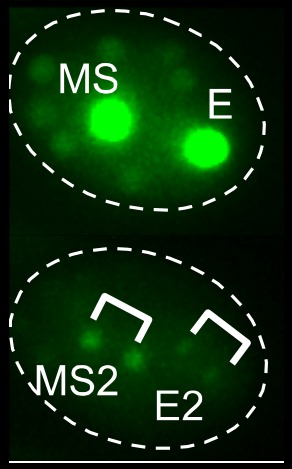
SKN-1 Turnover Regulates self-renewal

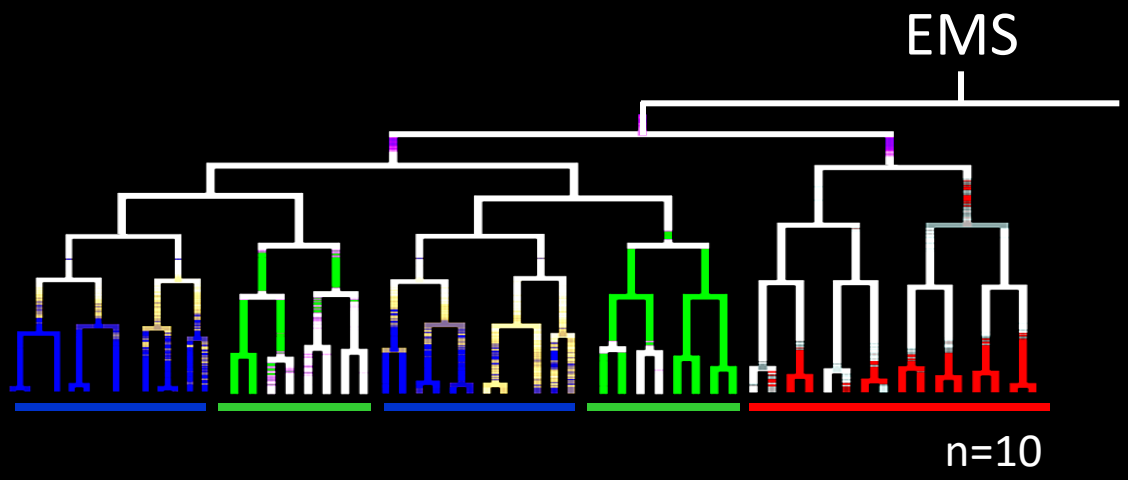
WT

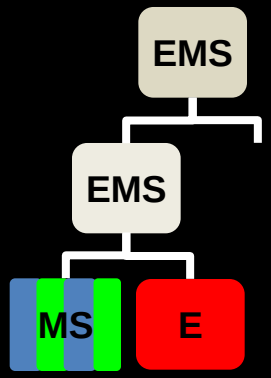




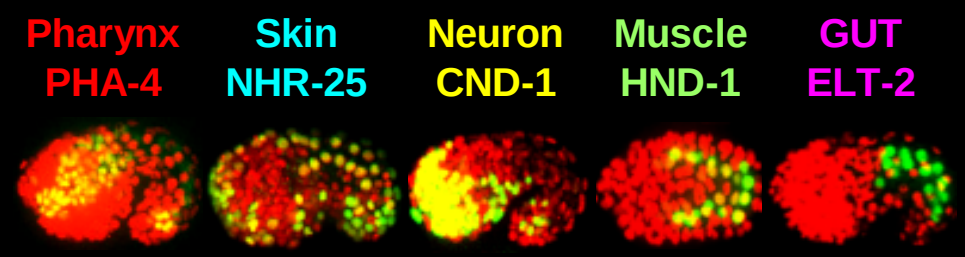
HS SKN-1

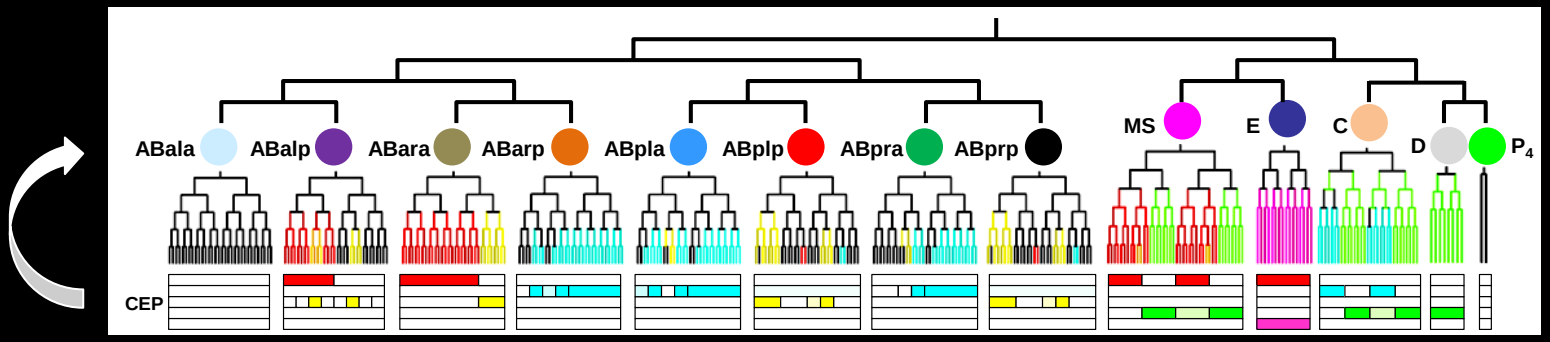


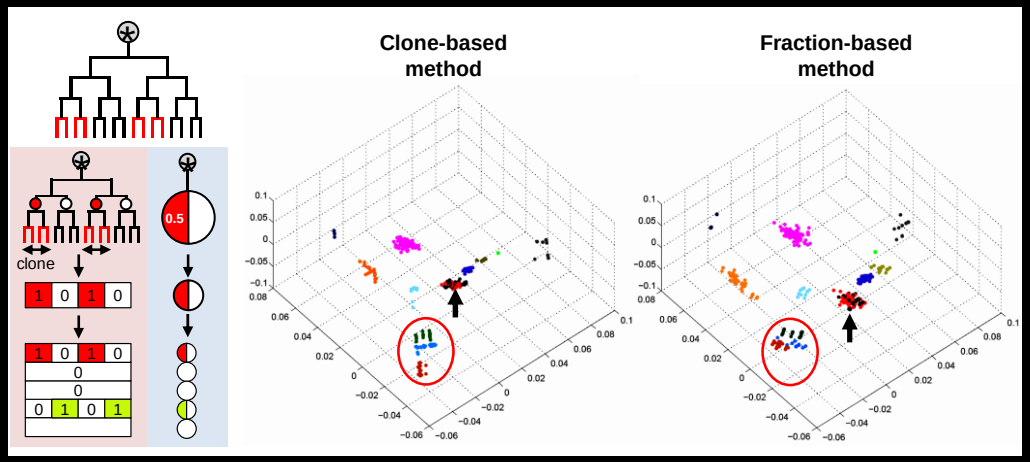




From Terminal Cell Fates to Progenitors

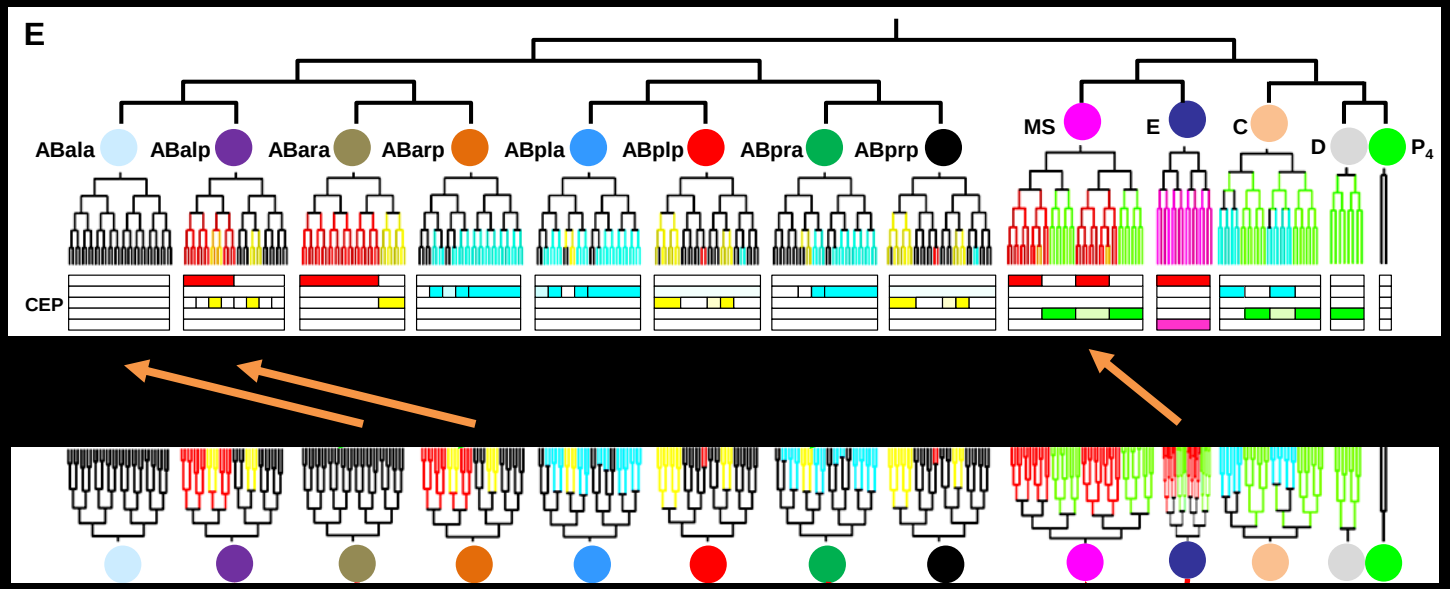




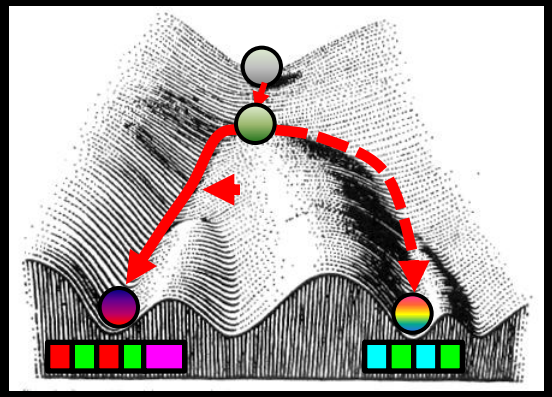


Fate Transformations as Key Phenotype

wild type

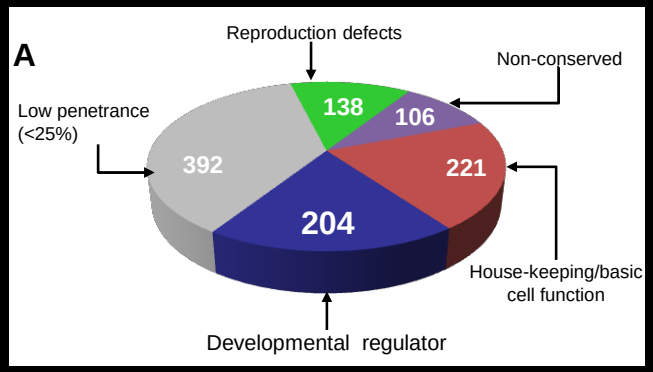


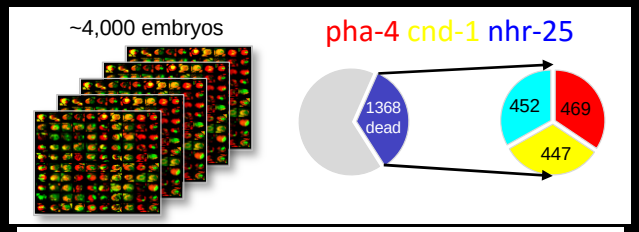
mom-2/Wnt (RNAi)

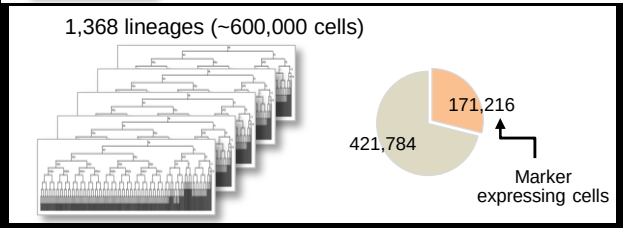


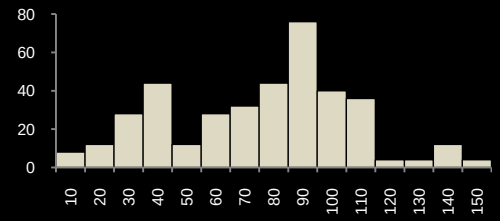
penetrance
pleiotropy
primary site

Systematic Perturbation of Development





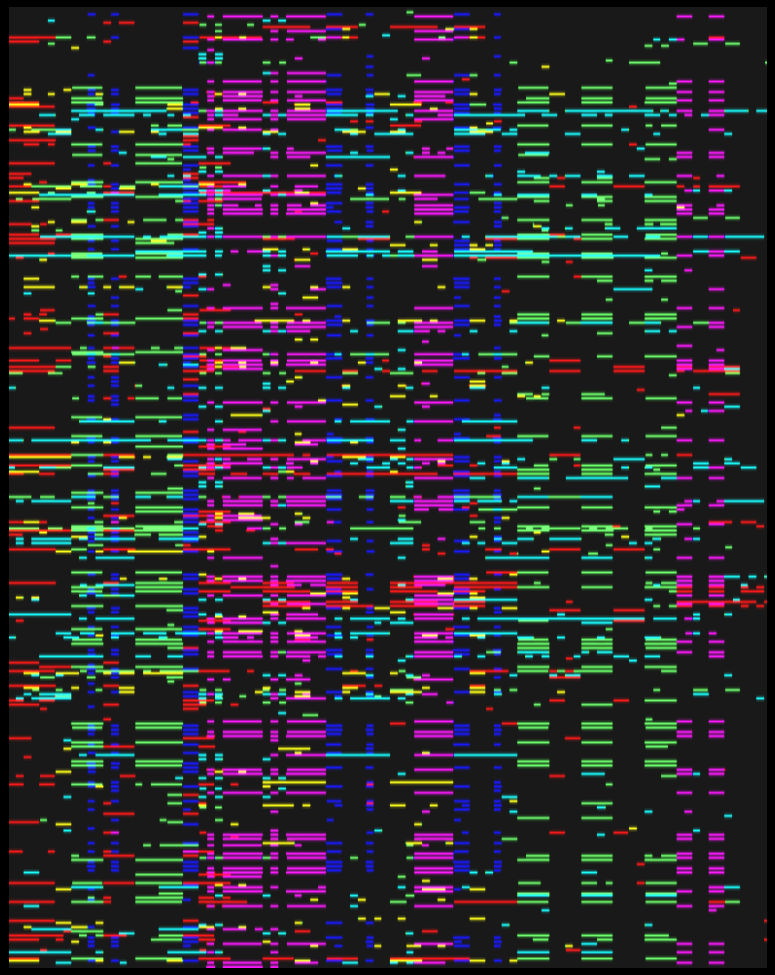




# of changes/cell

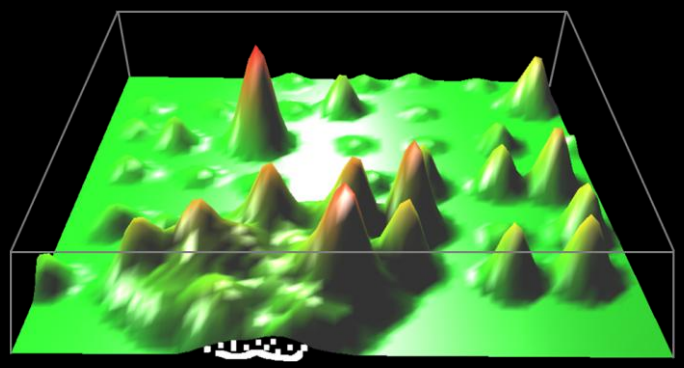
350 terminal cells

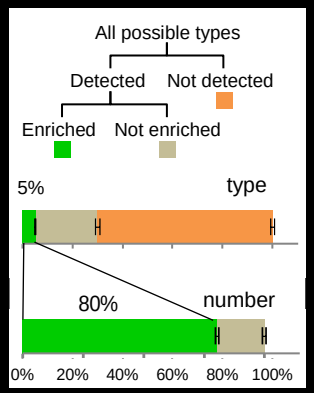
204 genes 1368 embryos

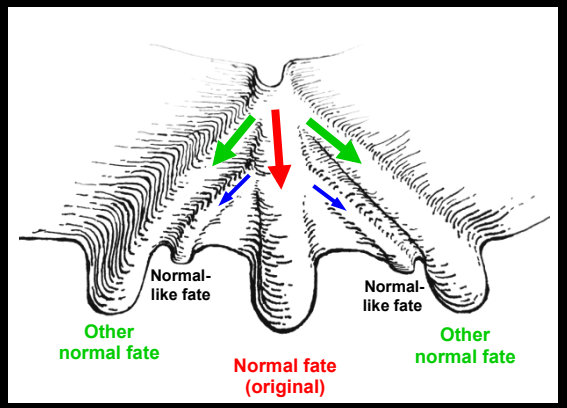


Du et al, 2015, Dev Cell

Canalized Landscape of Cell Lineage Differentiation

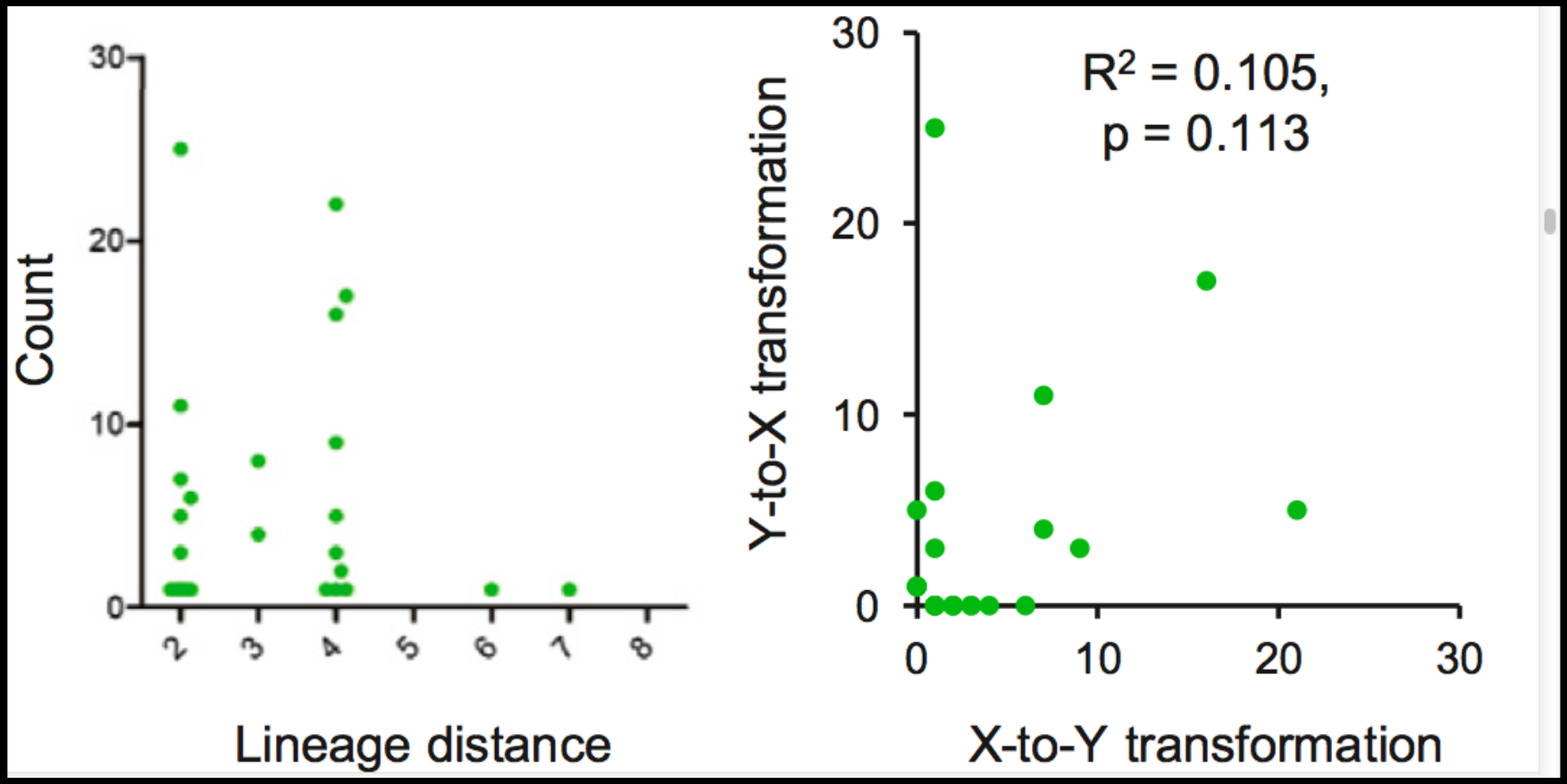




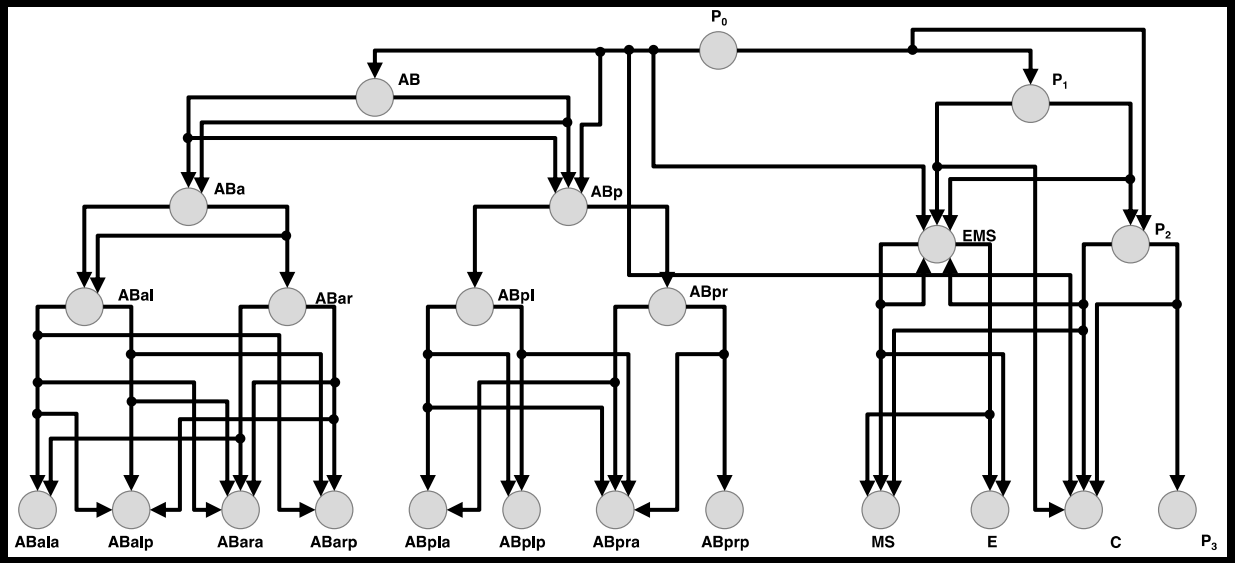


- Enriched types:
  - Normal fates used by other cells (homeotic transformations)
  - Patterns similar to normal fates

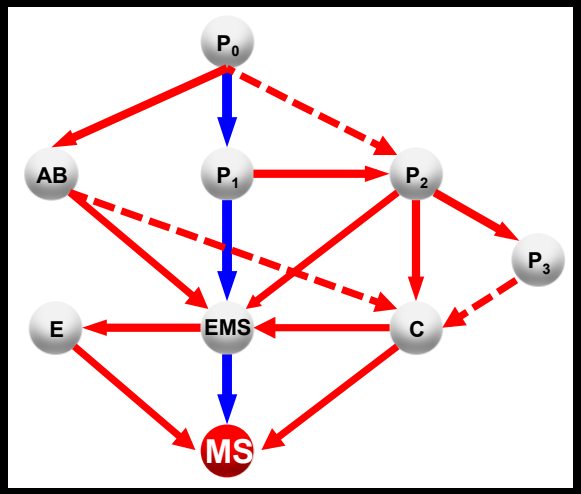
What do frequencies mean?



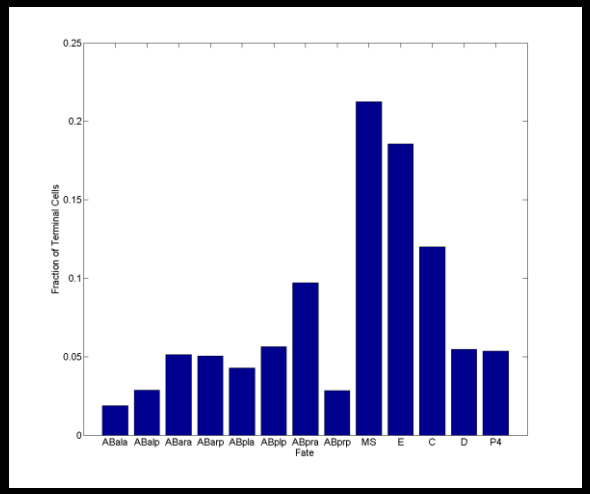
Trajectories of Cell Fate Differentiation



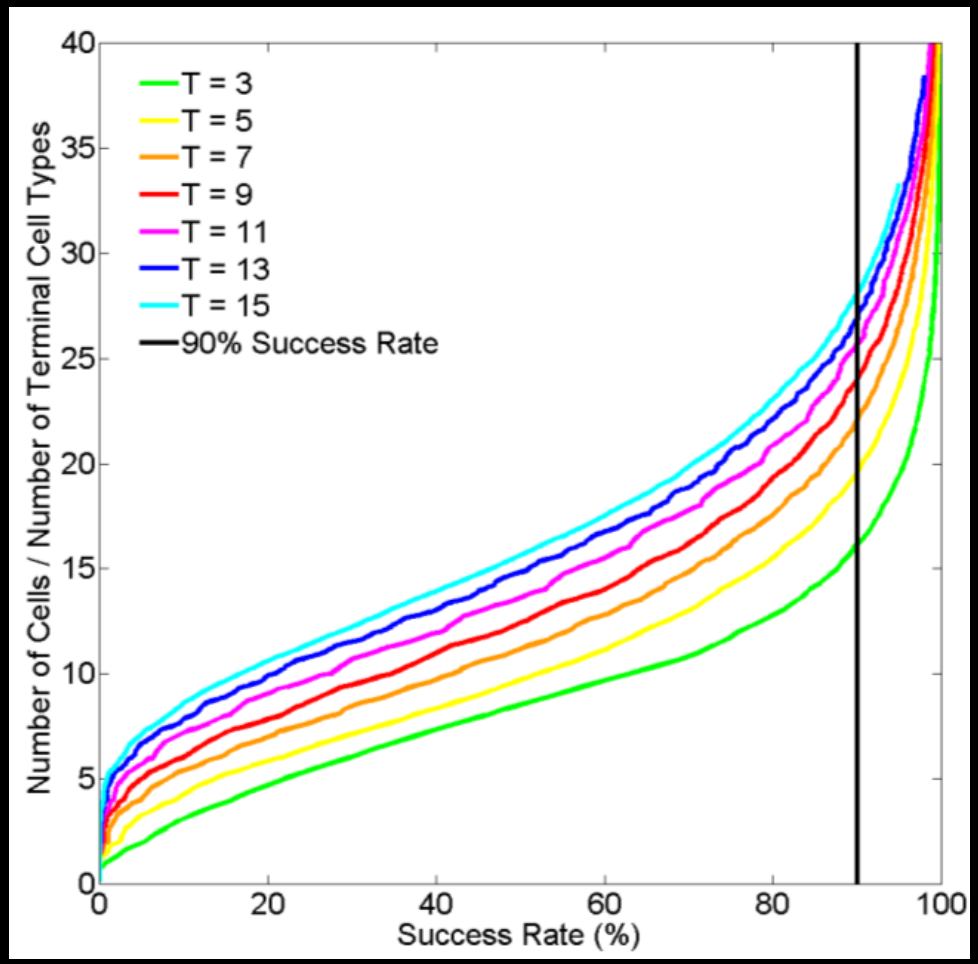
Alternative paths to MS



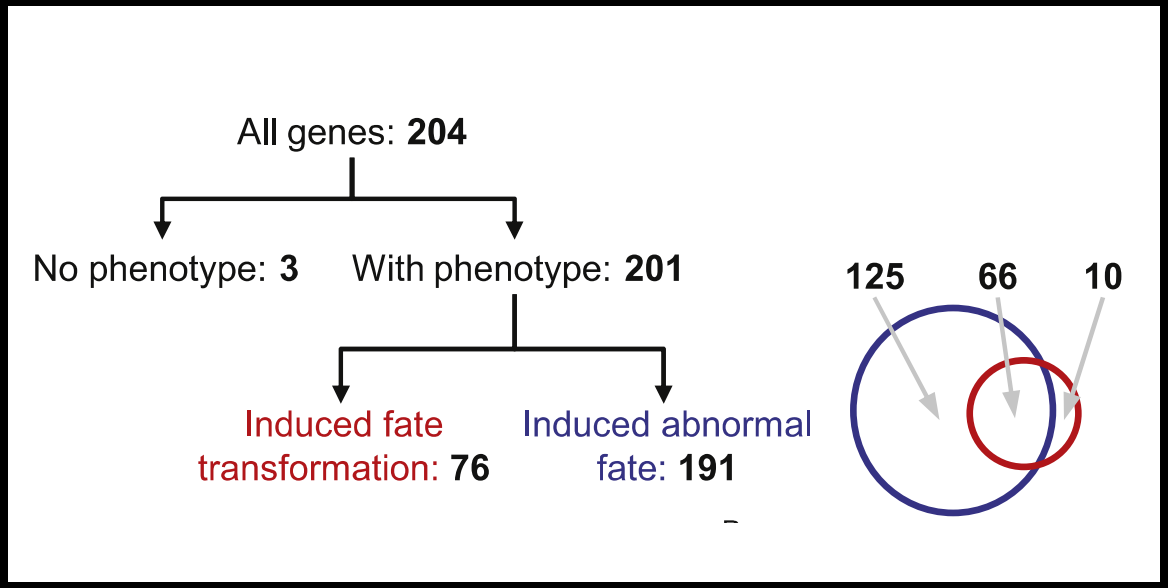
Inherent Propensity



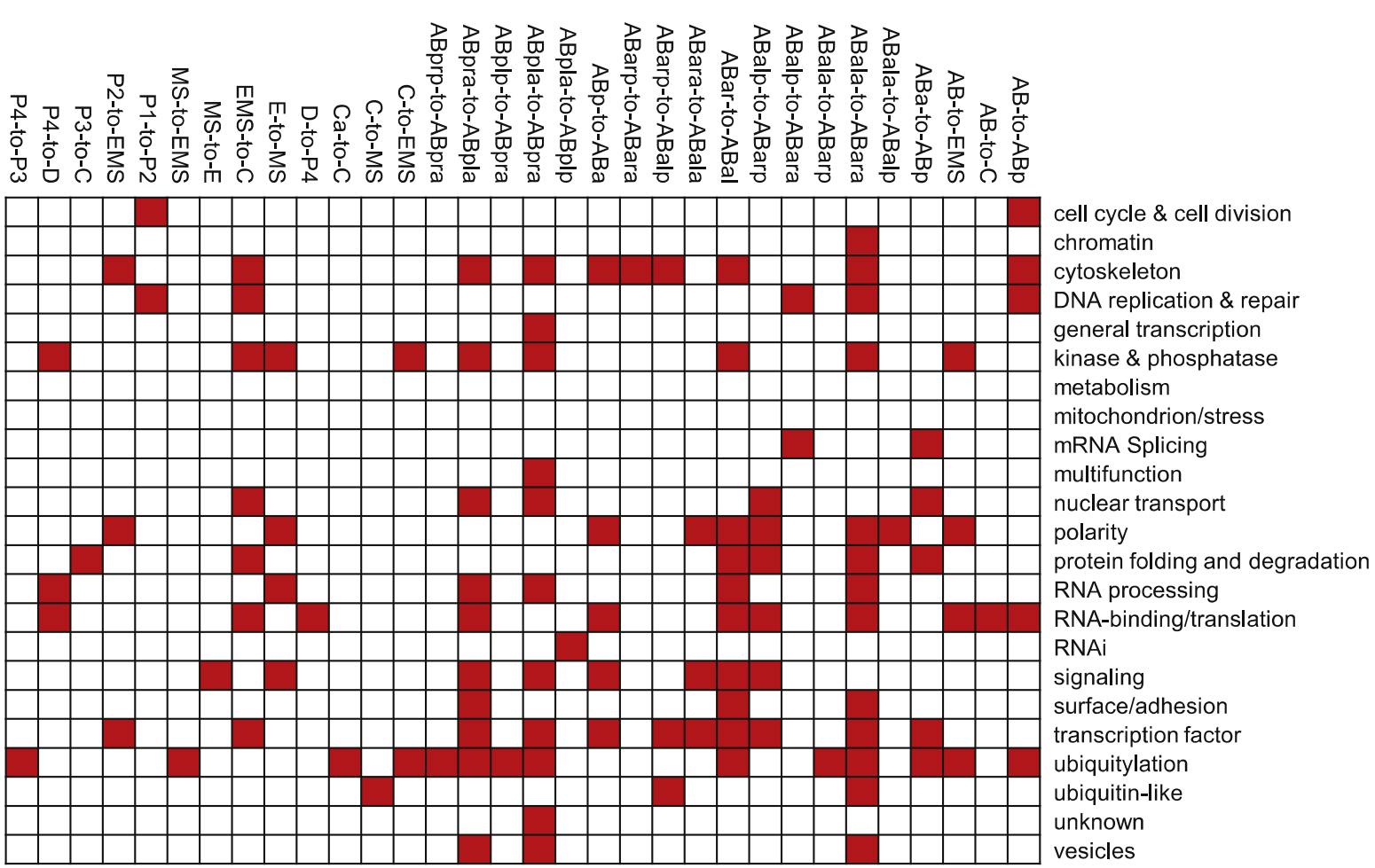
When is There Room for Random Fate Decisions?



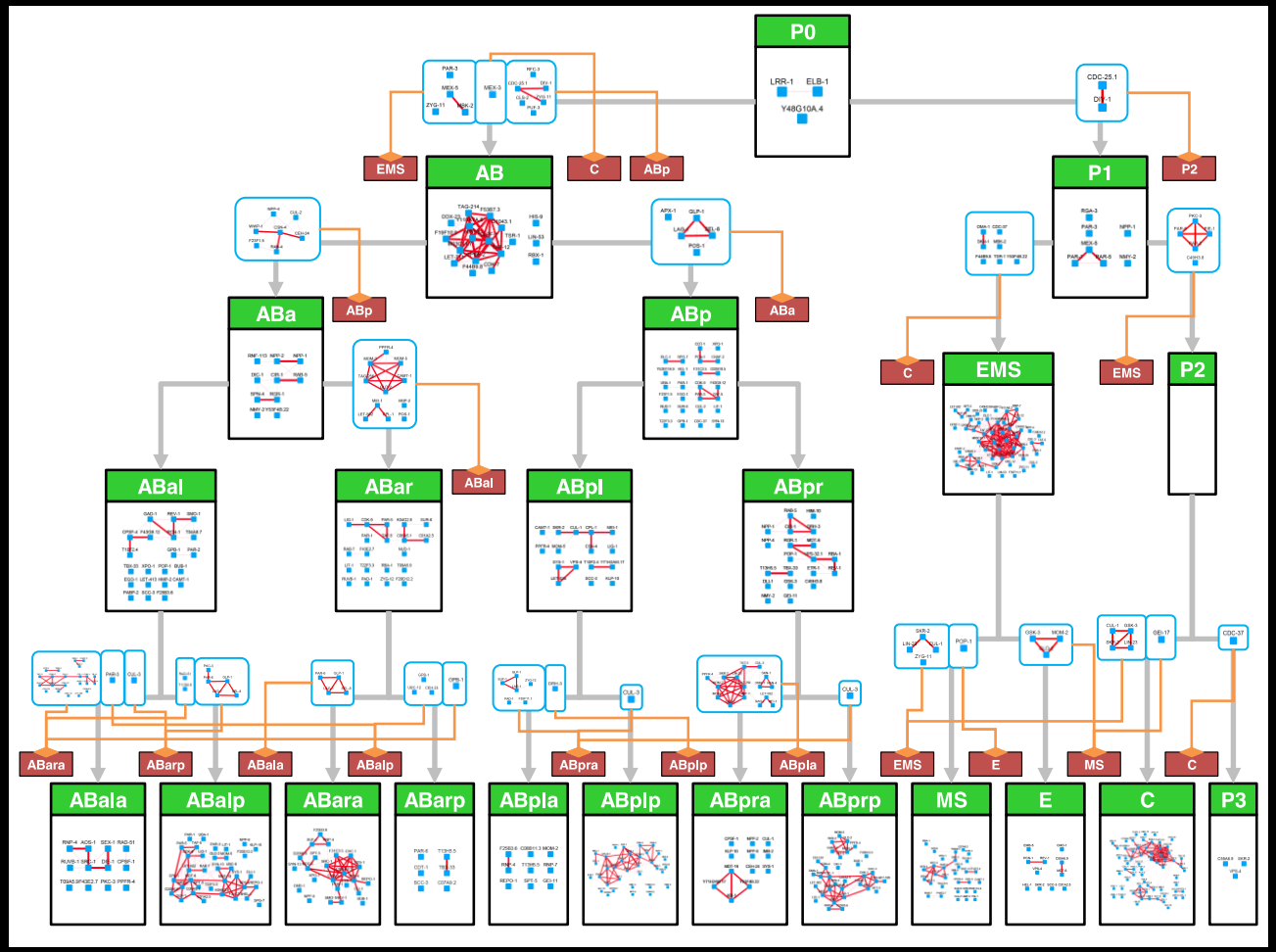
“Pure” fate switch genes are rare



Many pathways contribute to fate choice

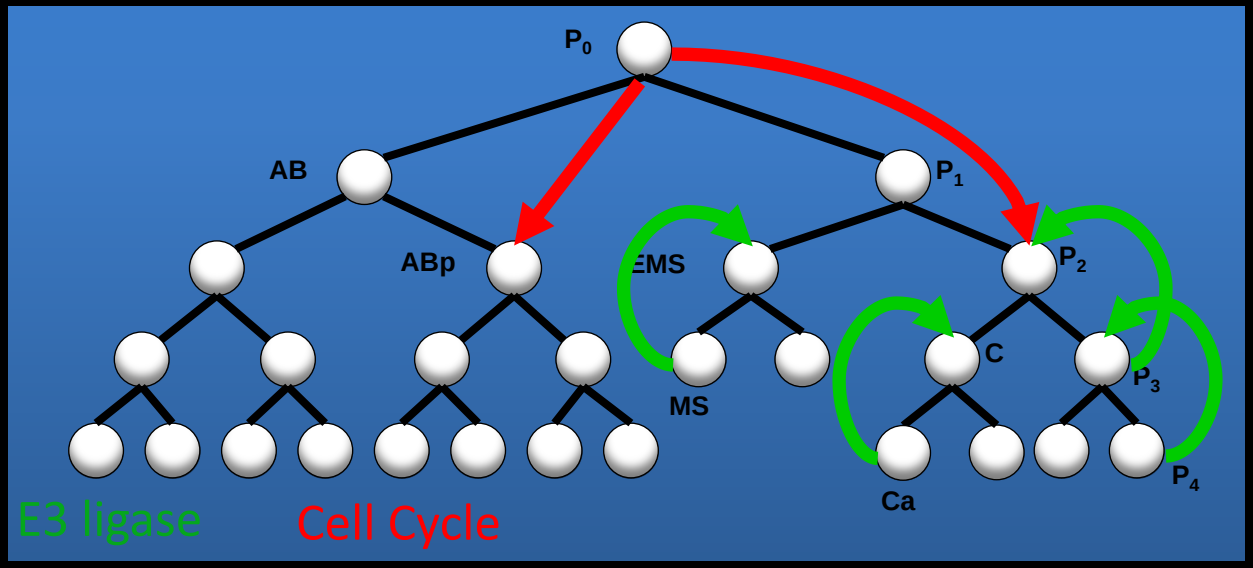


Integrated Model



http://digital-development.org

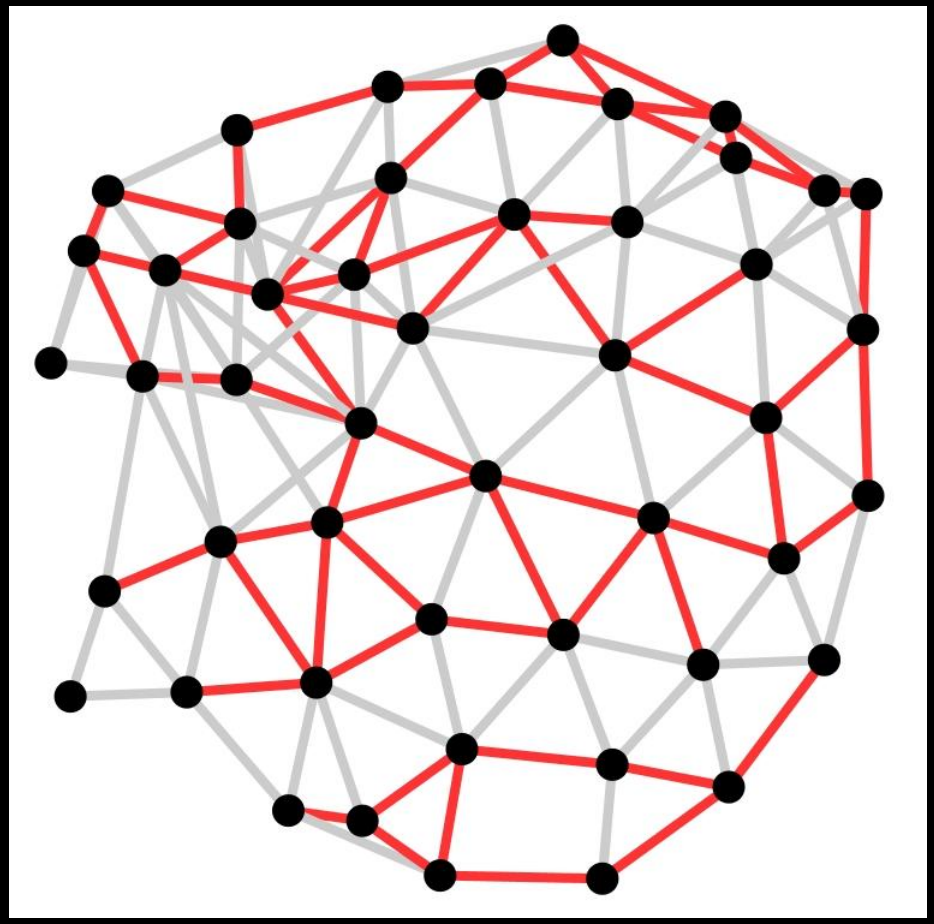
Flexibility of Fate Restriction



Reproducible Cell Positions

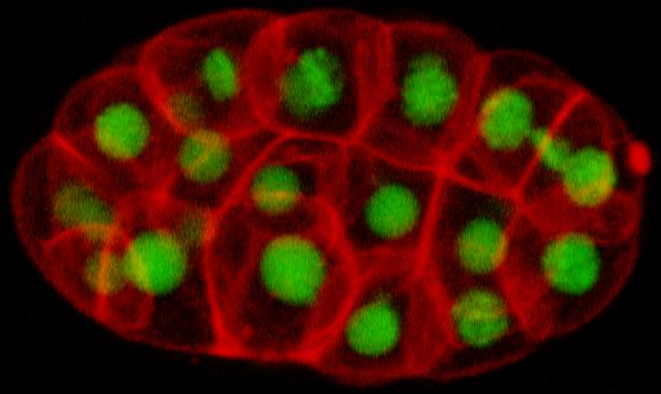
Cell Position

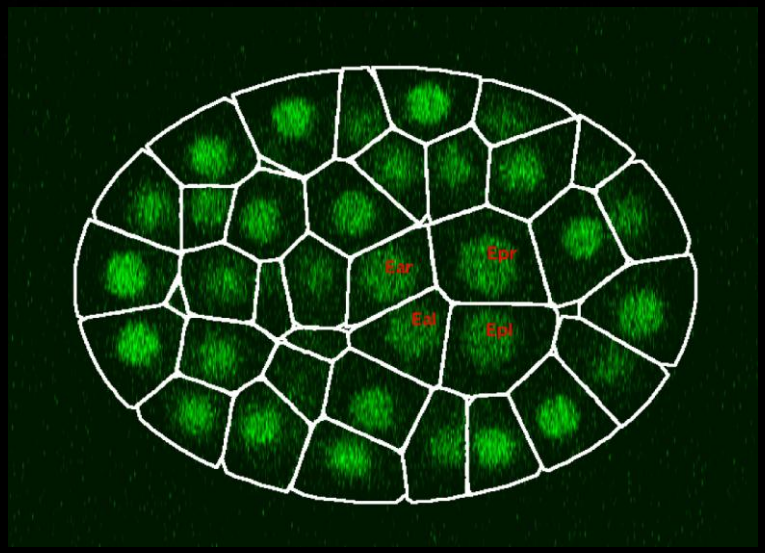
Constant Neighbors



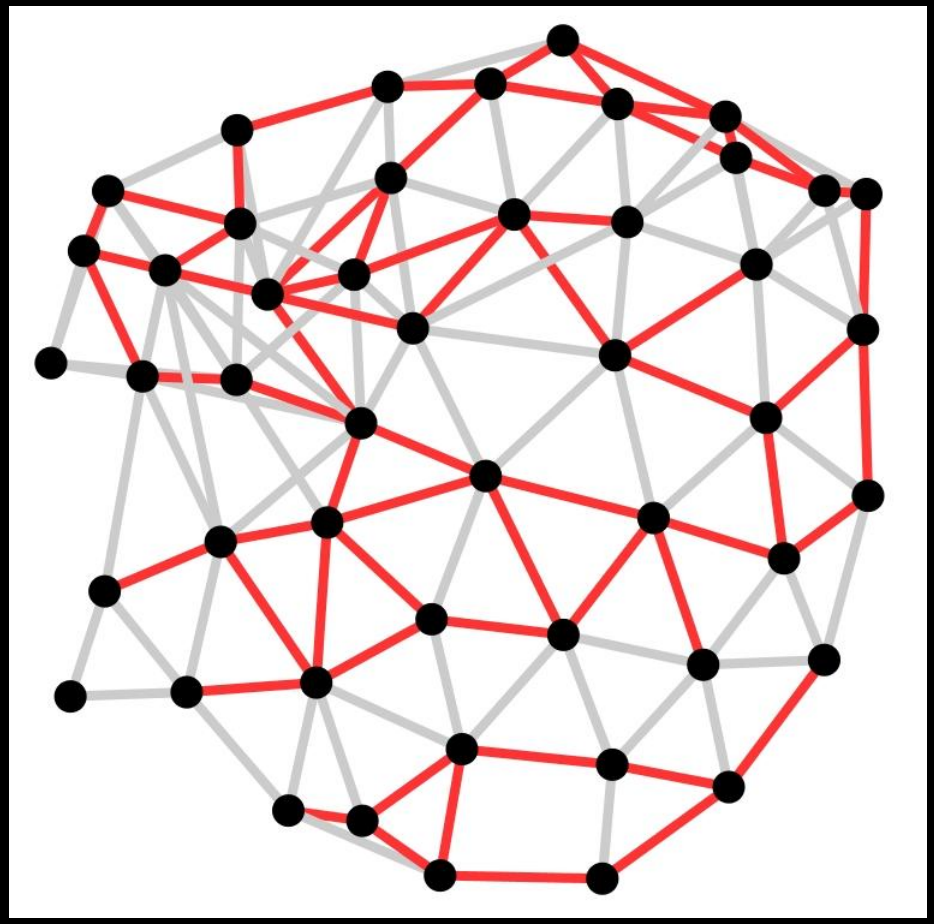
Migration

Reproducible Cell Positions





Constant Neighbors



Lab Members

Anthony Santella
Pavak Shah
Fan Li
Yichi Xu
Kris Barnes
Hong Shao
Raul Catena

Undergrad Assistants
Doris Tang
Katie Tran
Braden Katzman
Benjamin De Leon
Allison Chen
David Cohen

NIGMS

Eunice Kennedy Shriver NICHD
National Institute of Child Health & Human Development

NIH
ORIP