

Metrics for Comparing Cell Lineages

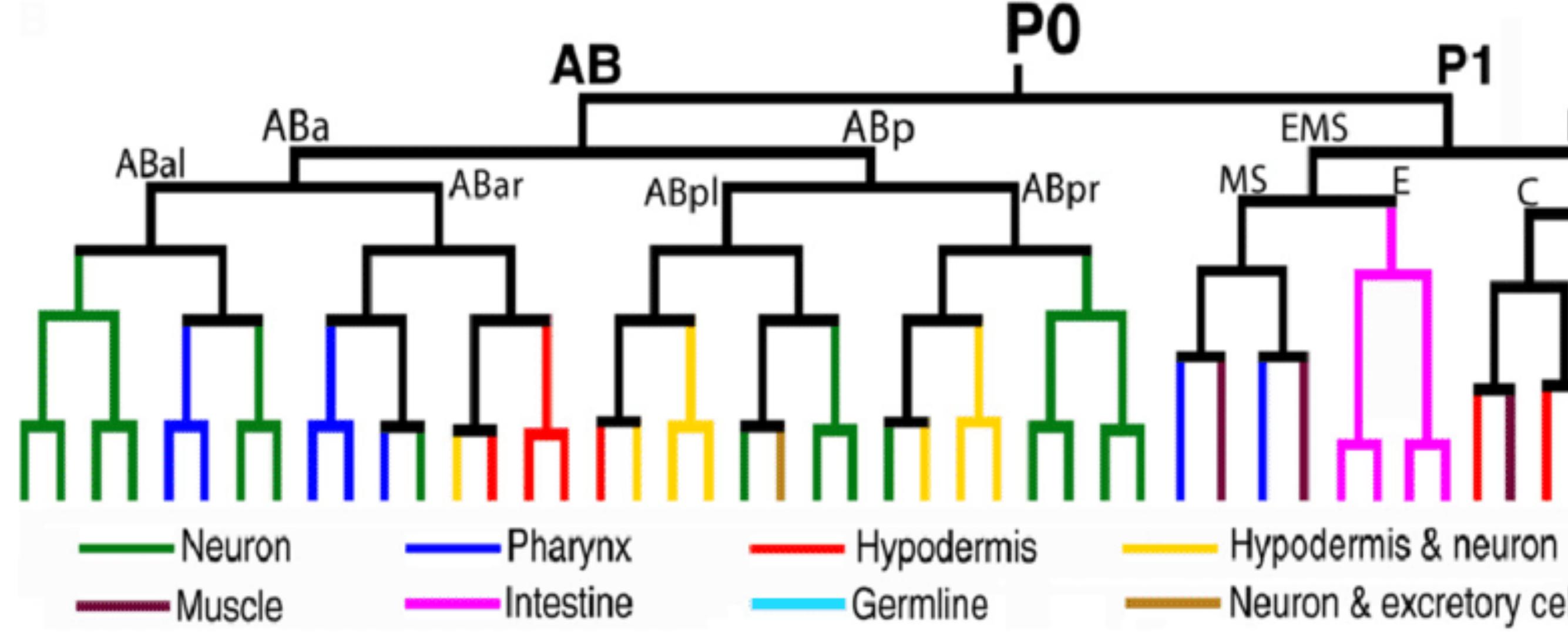
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BACKGROUND: All multicellular organisms develop through the proliferation and differentiation of a single progenitor cell. Here we propose a pair of metrics derived from graph theory to define distances between cell lineages recorded from developing embryos by live microscopy. Using a previously published resource of cell lineages recorded from wild-type and RNA-perturbed embryos of the nematode *C. elegans*, which possesses an invariant cell lineage, we demonstrate that our metrics can offer new insights into the structure of cell lineages as a phenotypic space.

OUR DATASET:

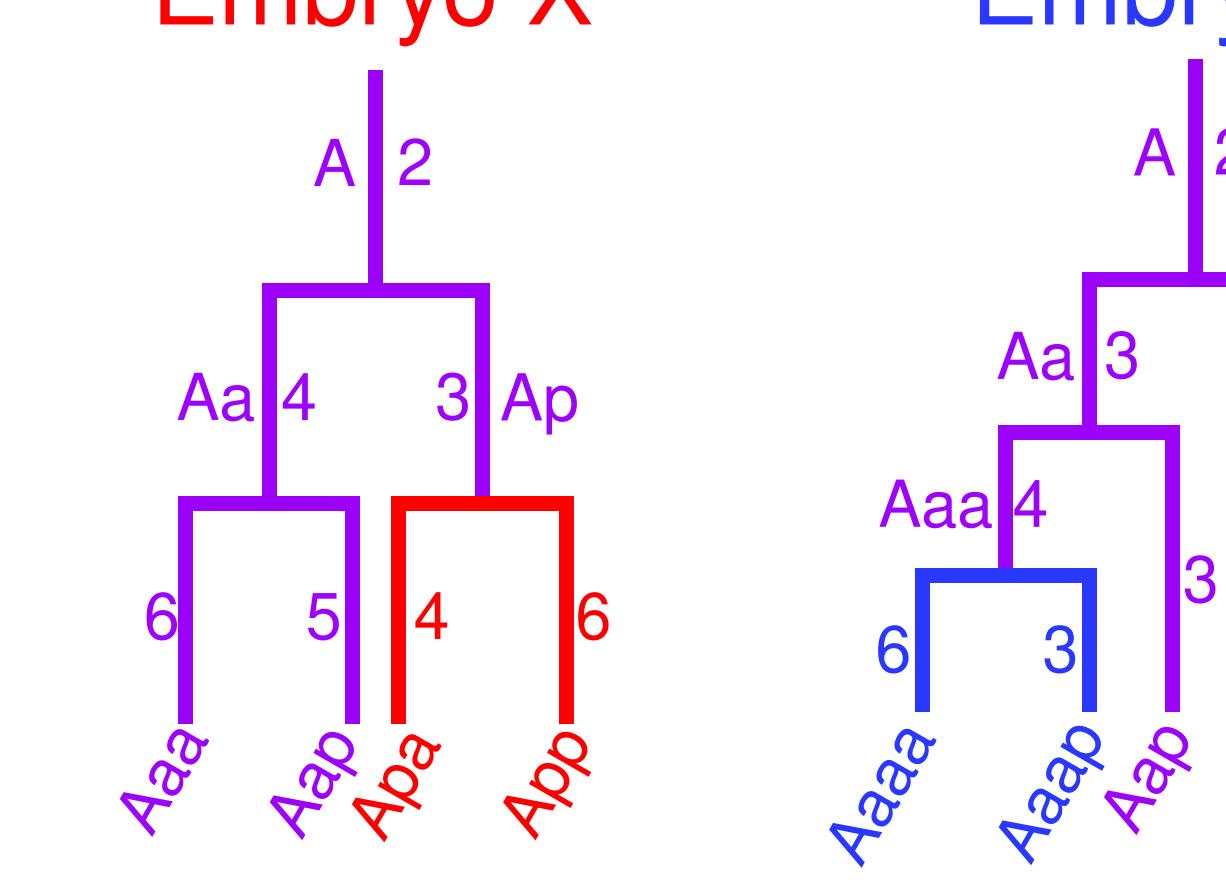
- Eutely in *C. elegans* indicates no variation in cell division, count, or identity.
- This has motivated extensive research in development and cell fate specification.
- *C. elegans* is an ideal candidate for evaluating novel metrics on tree structures, as it is topologically consistent and biologically well characterized.



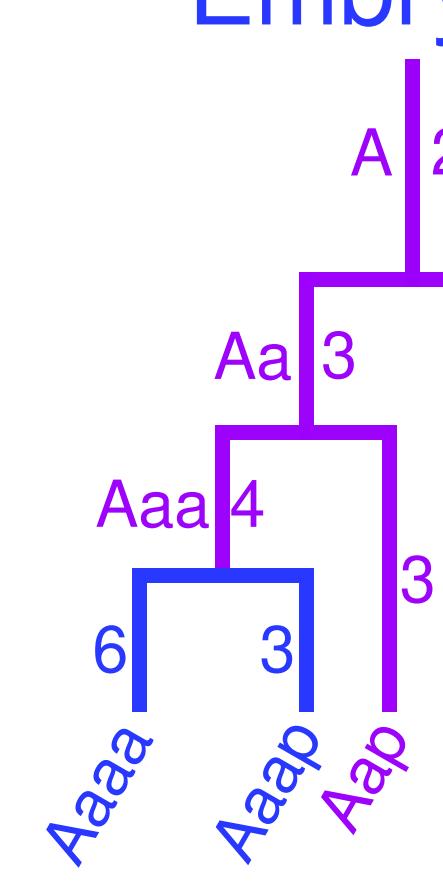
PROPOSED METRICS

We thus propose the usage of 3 unique graph metrics to compare these graphs.

Embryo X



Embryo Y



Tree edit distance:

counts the number of topological differences in nodes between two trees

$$N_x = \{A, Aa, \dots, App\}$$

$$N_y = \{A, Aa, \dots, Aaap\}$$

$$TED = |N_x \Delta N_y| =$$

$$|\{App, App, Aaaa, Aaap\}|$$

Intersection Branch Distance: L2 norm

between shared node values of trees

$$\{N_\alpha \cap N_\beta\} = \{A, Aa, Ap, Aaa, Aap\}$$

$$\{A, Aa, Ap, Aaa, Aap\}$$

$$V_x = [2, 4, 3, 6, 5, 4, 6, 0, 0]$$

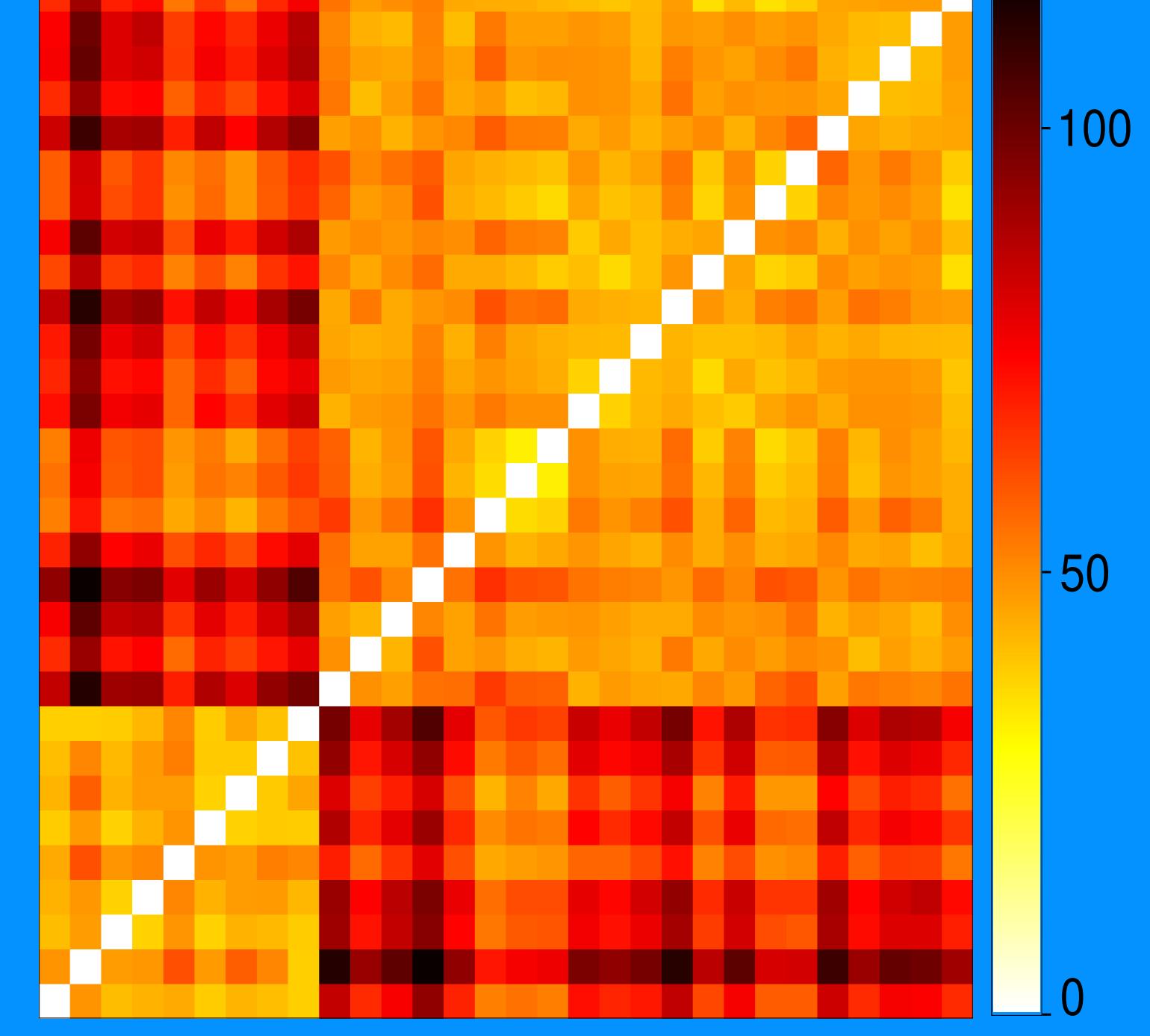
$$V_y = [2, 3, 6, 4, 3]$$

$$IBD = \|V_x - V_y\|_2$$

$$UBD = \|U_x - U_y\|_2$$

Graph based Analysis of Embryonic Lineages

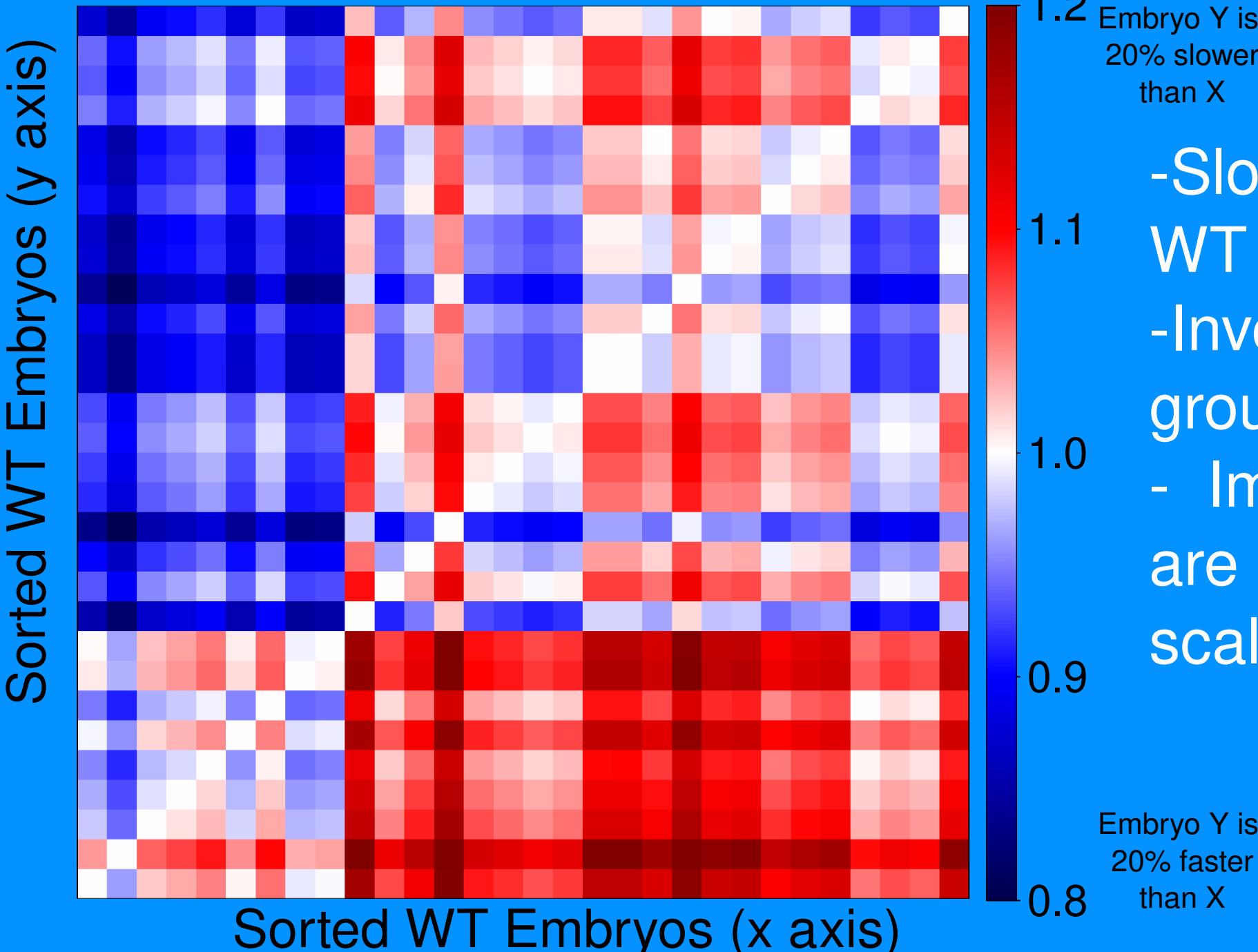
Branch Distances between Embryos (minutes)



Branch Distance detects batch effects in wild type embryogenesis due to global scaling

- Clustering Branch Distance between 30 WT embryos reveals two distinct groups,
- Data shows more variation in the developmental clock than expected

Slope (y/x) of regression between Embryos

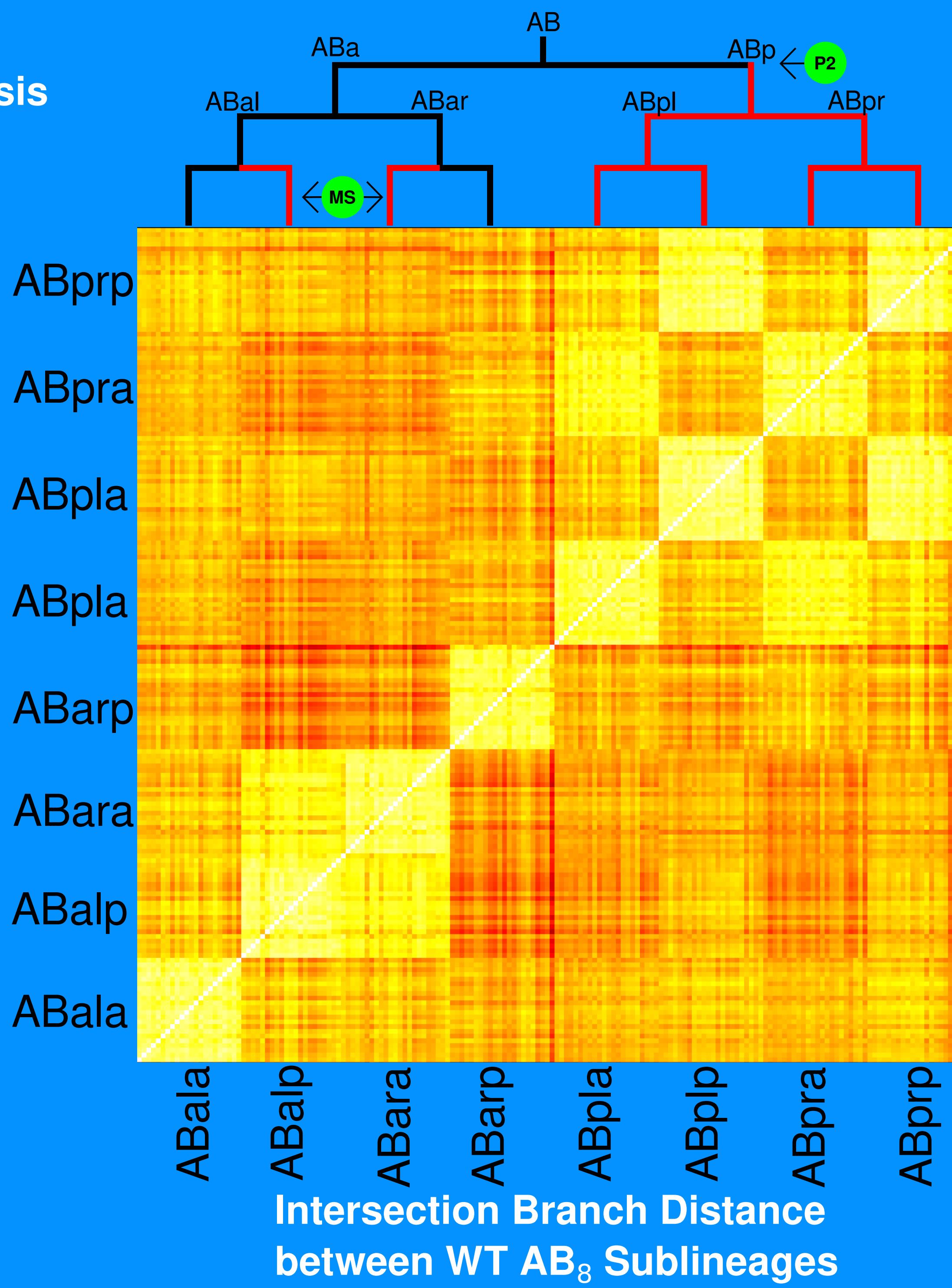


Embryo Y is 20% slower than X

- Slope between cell cycles in WT embryos are compared
- Inverted slope between groups suggest linear scaling
- Implying global clock rates are modified through linear scaling

Embryo Y is 20% faster than X

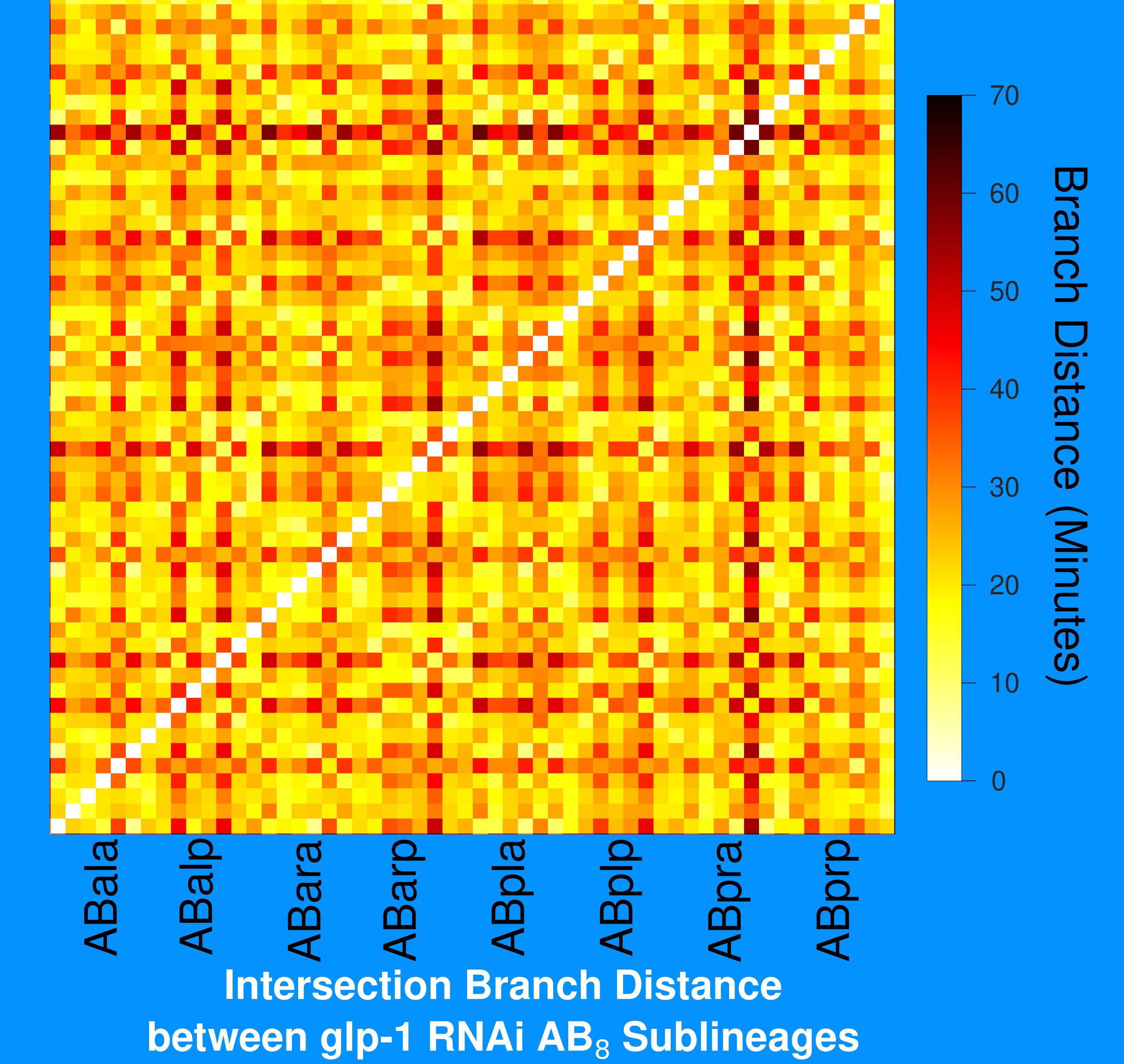
Notch Signaling in WT AB Sublineage



Intersection Branch Distance between WT AB₈ Sublineages

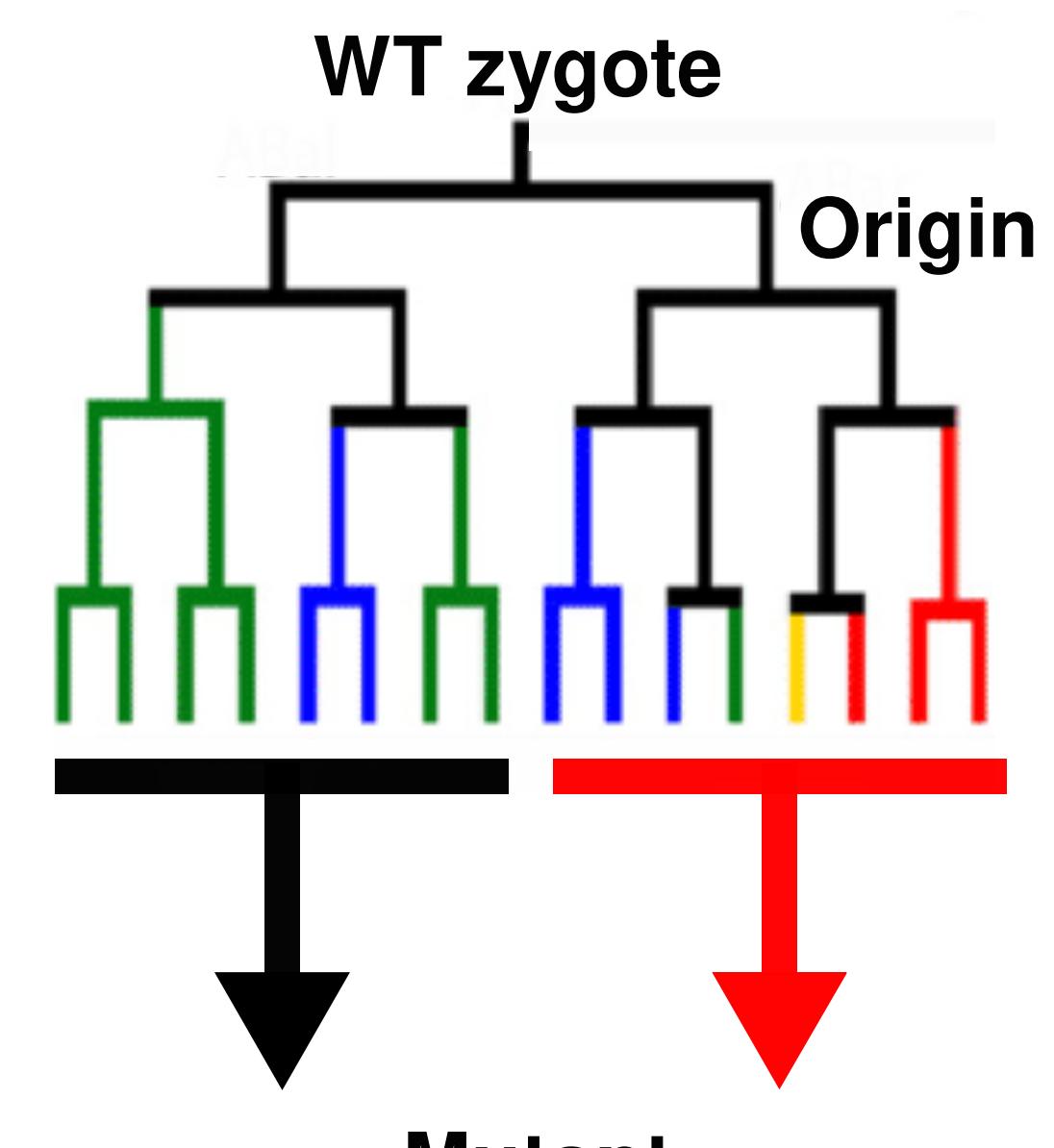
Notch Signaling in glp-1 RNAi AB Sublineage

- Contrasting WT, there is no notch signaling in glp-1 RNAi embryos.
- Effects of notch (left figure) are not shown below, instead showing underlying wnt signals



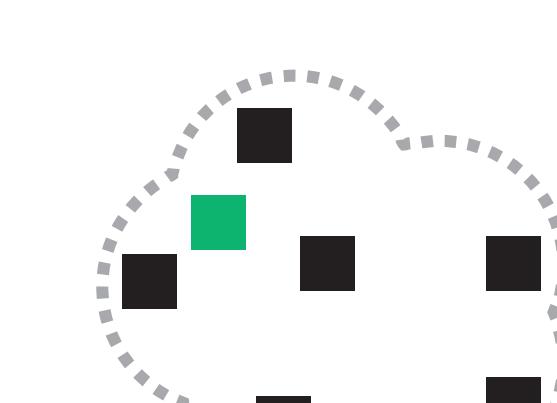
Intersection Branch Distance between glp-1 RNAi AB₈ Sublineages

DEFINING FATE TRANSFORMATIONS



- **Unperturbed:** Phenotypes of a Mutant sublineage is unchanged from WT counterpart
- **Transformed:** phenotypes of Mutant sublineage is different from WT counterpart (Origin) and corresponds to different WT sublineage (Destination)

Unperturbed RNAi lineage



Neighborhood of WT origin lineage

Transformed RNAi lineage

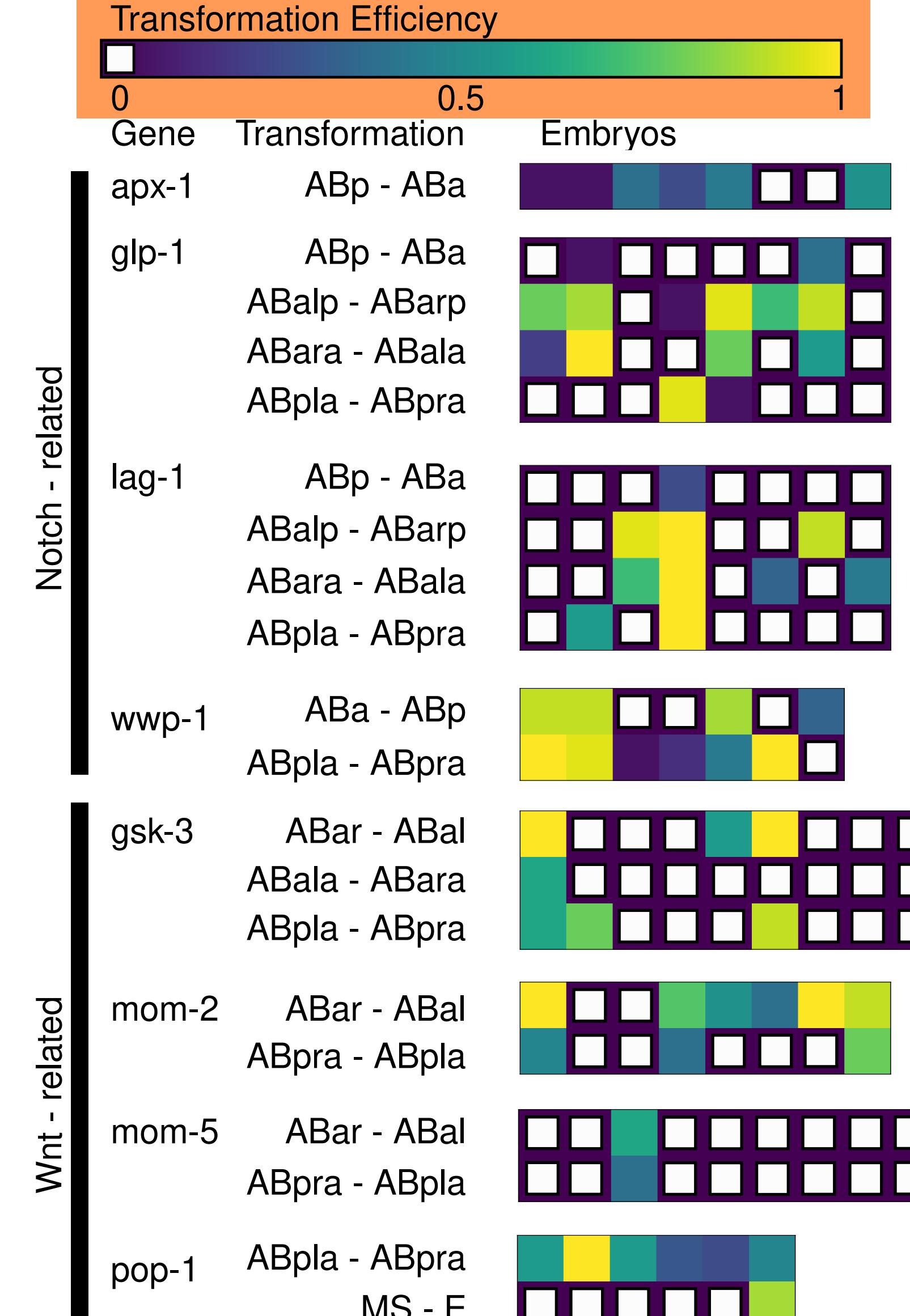
Transformed RNAi lineage



Neighborhood of WT destination lineage

The marker based approach to fate analysis can be reimplemented in high dimensional vector space, with point clouds representing aggregate WT phenotypes, and distances from Mutant Ito WT lineages representing degrees of transformation

GENE MEDIATED FATE TRANSFORMATIONS



REFERENCES

- Du, Zhuo, et al. "The Regulatory Landscape of Lineage Differentiation in a Metazoan Embryo." *Developmental Cell*, vol. 34, no. 5, 2015, pp. 592–607, <https://doi.org/10.1016/j.devcel.2015.07.014>.
- Schwarz, Stefan et al. "A New Perspective on the Tree Edit Distance." *ISAP* (2017).
- Johnson, S.C. "Hierarchical clustering schemes." *Psychometrika* 32 (1967): 241-254.
- Scikit-learn: Machine Learning in Python, Pedregosa et al., JMLR 12, pp. 2825-2830, 2011.
- Harris, C.R., Millman, K.J., van der Walt, S.J., et al. Array programming with NumPy. *Nature* 585, 357–362 (2020). DOI: [10.1038/s41586-020-6492-2](https://doi.org/10.1038/s41586-020-6492-2)
- Pauli Virtanen et al., and SciPy 1.0 Contributors. (2020) SciPy 1.0: Fundamental Algorithms for Scientific Computing in Python. *Nature Methods*, 17(3), 261-272.

Transformation Efficiency:

Count of number of WT Destination nodes in proximity of Mutant Sublineage. Larger number indicates greater degree of transformation

