How to make an organ: Specifying cell fate during development

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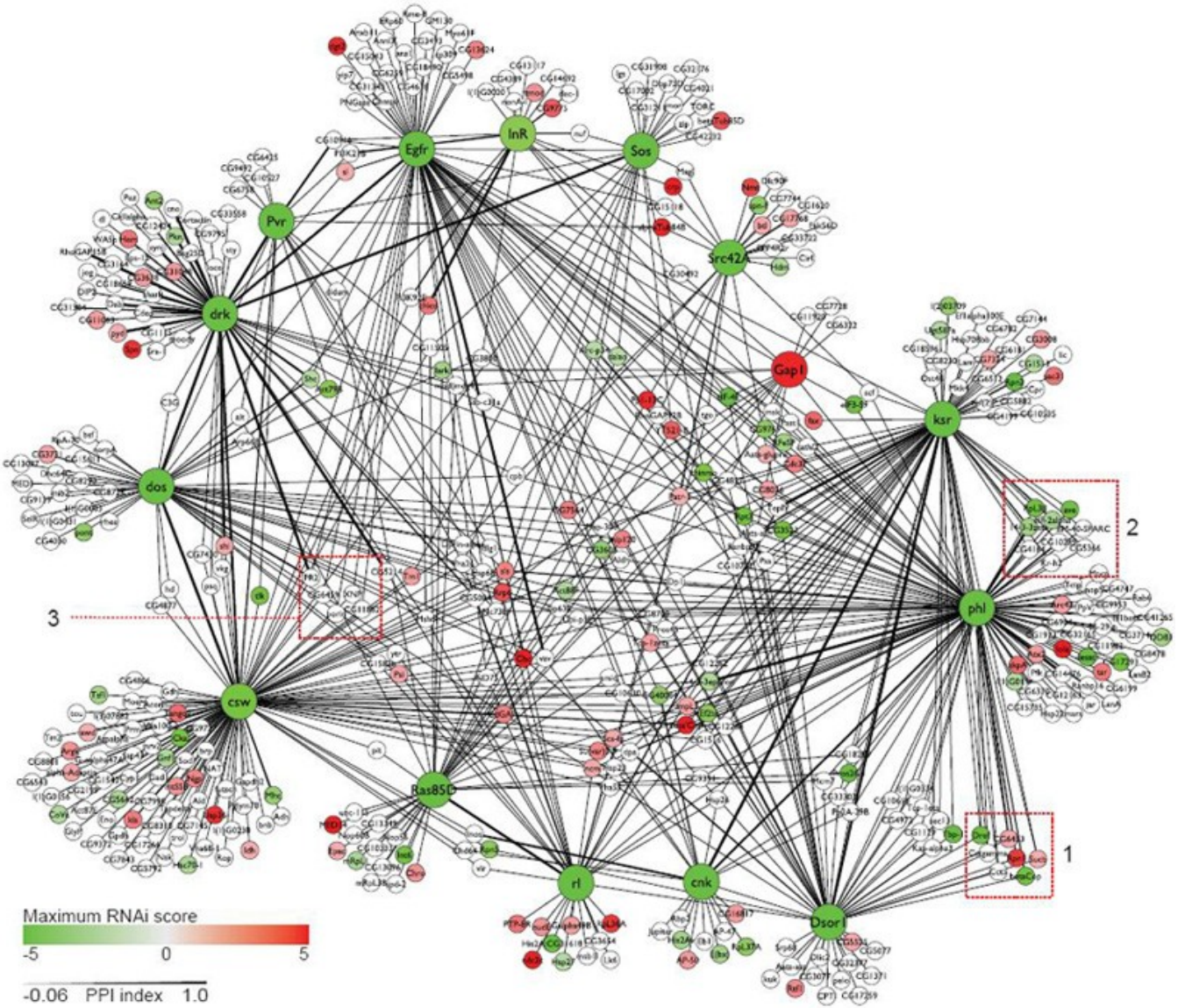
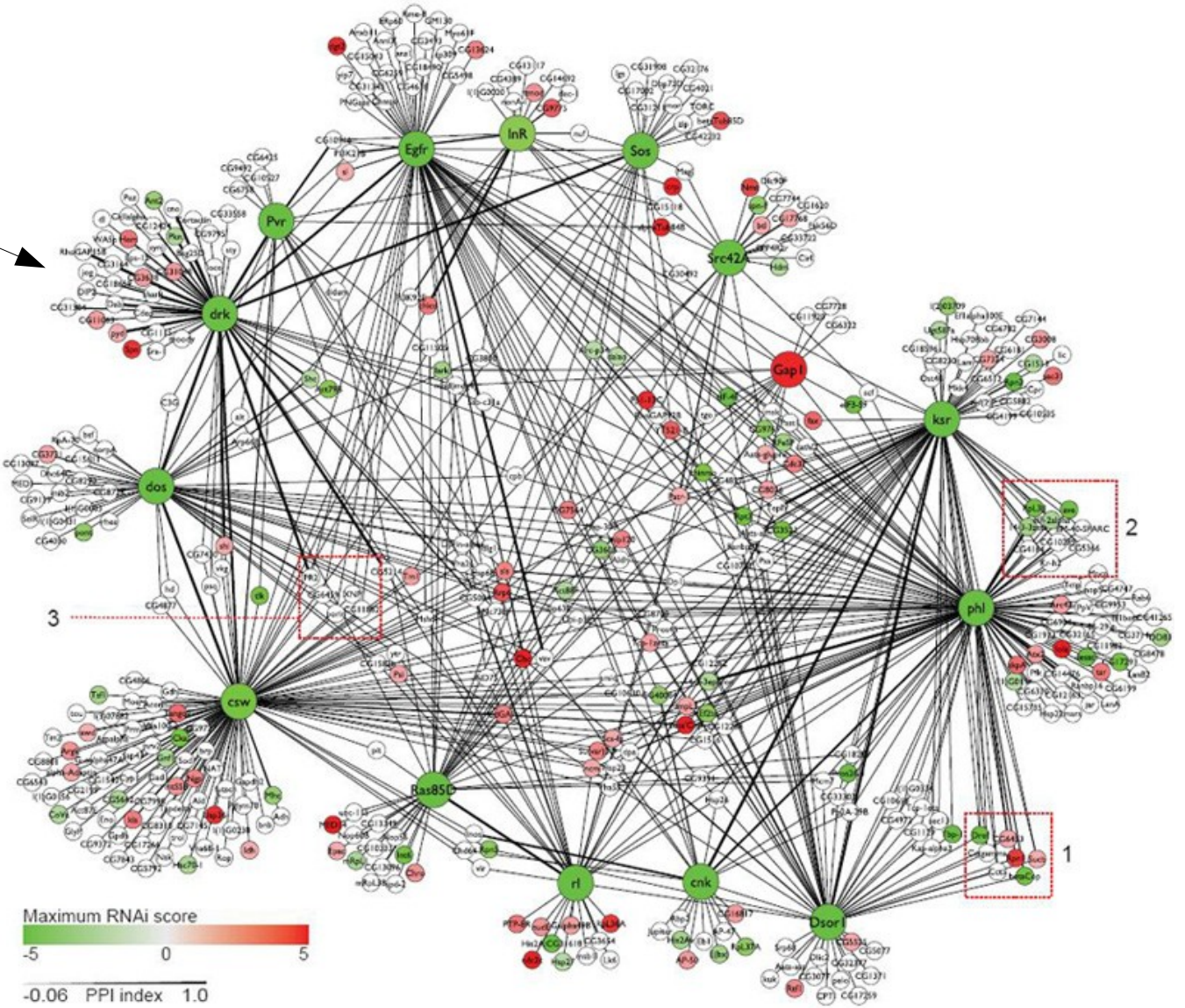
Signaling network determines output



Friedman et al (2011) *Sci Signal*

Signaling network determines output

External signal

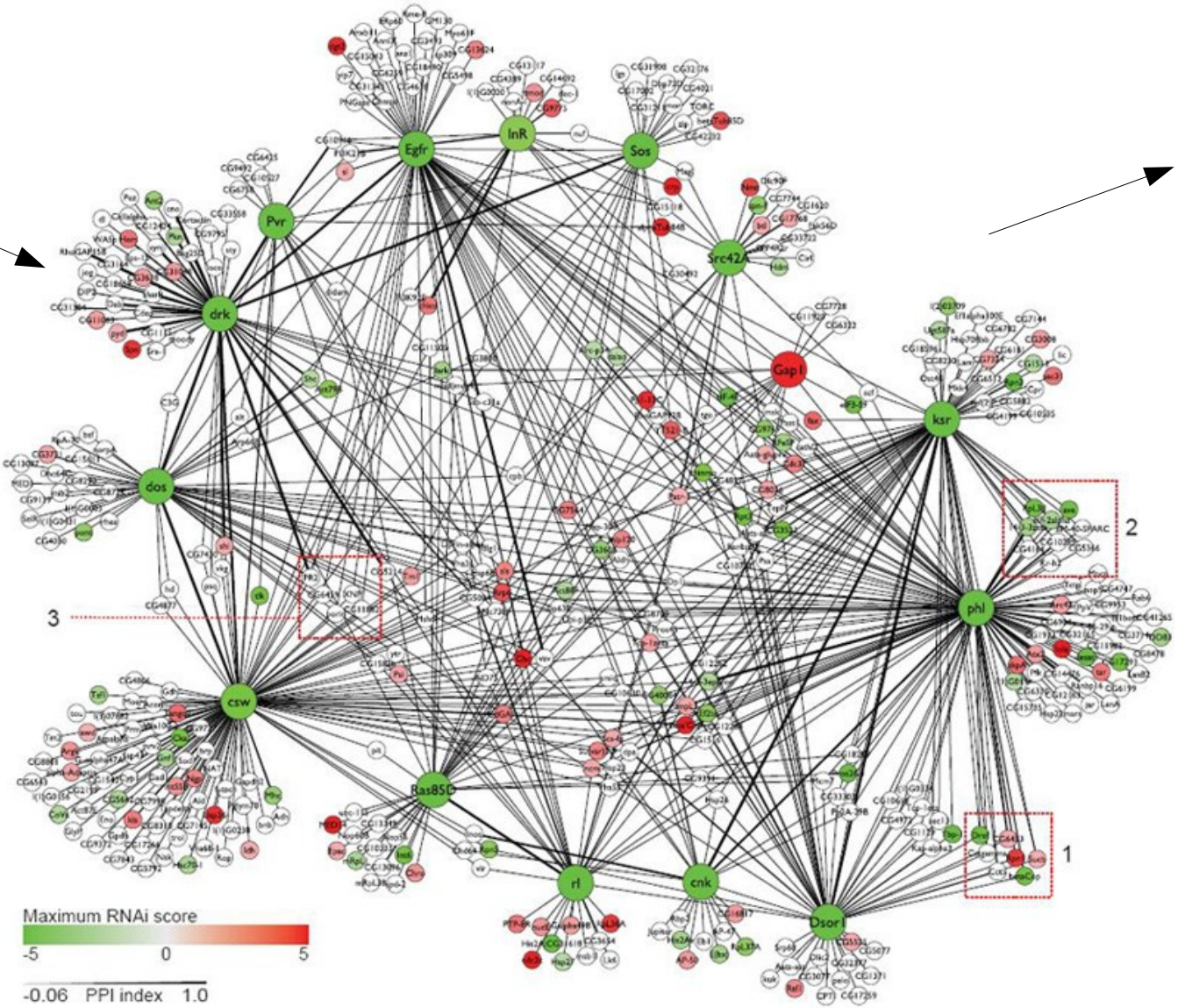


Friedman et al (2011) *Sci Signal*

Signaling network determines output

External signal

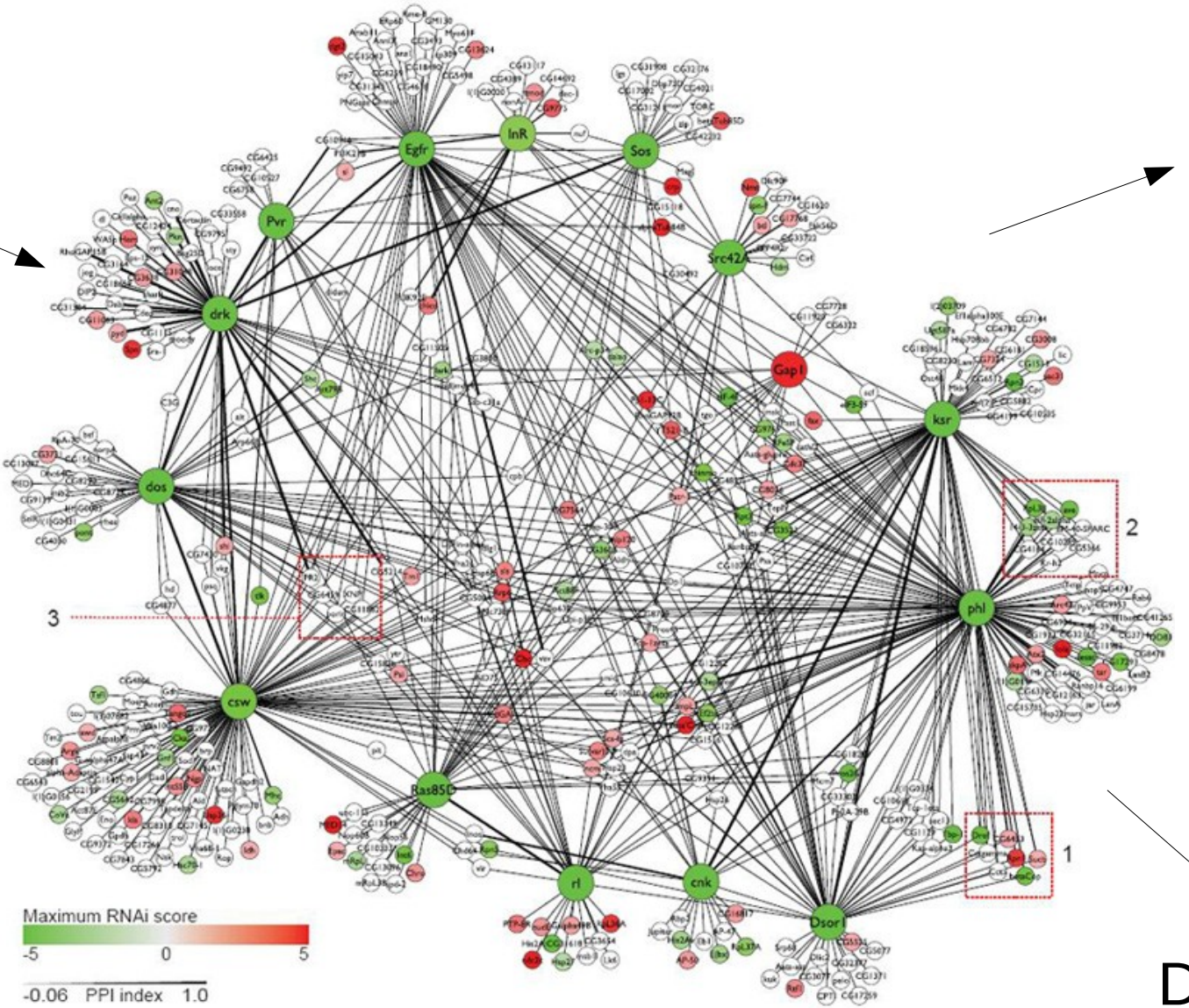
Division



Friedman et al (2011) *Sci Signal*

Signaling network determines output

External signal



Division

Death

Friedman et al (2011) *Sci Signal*

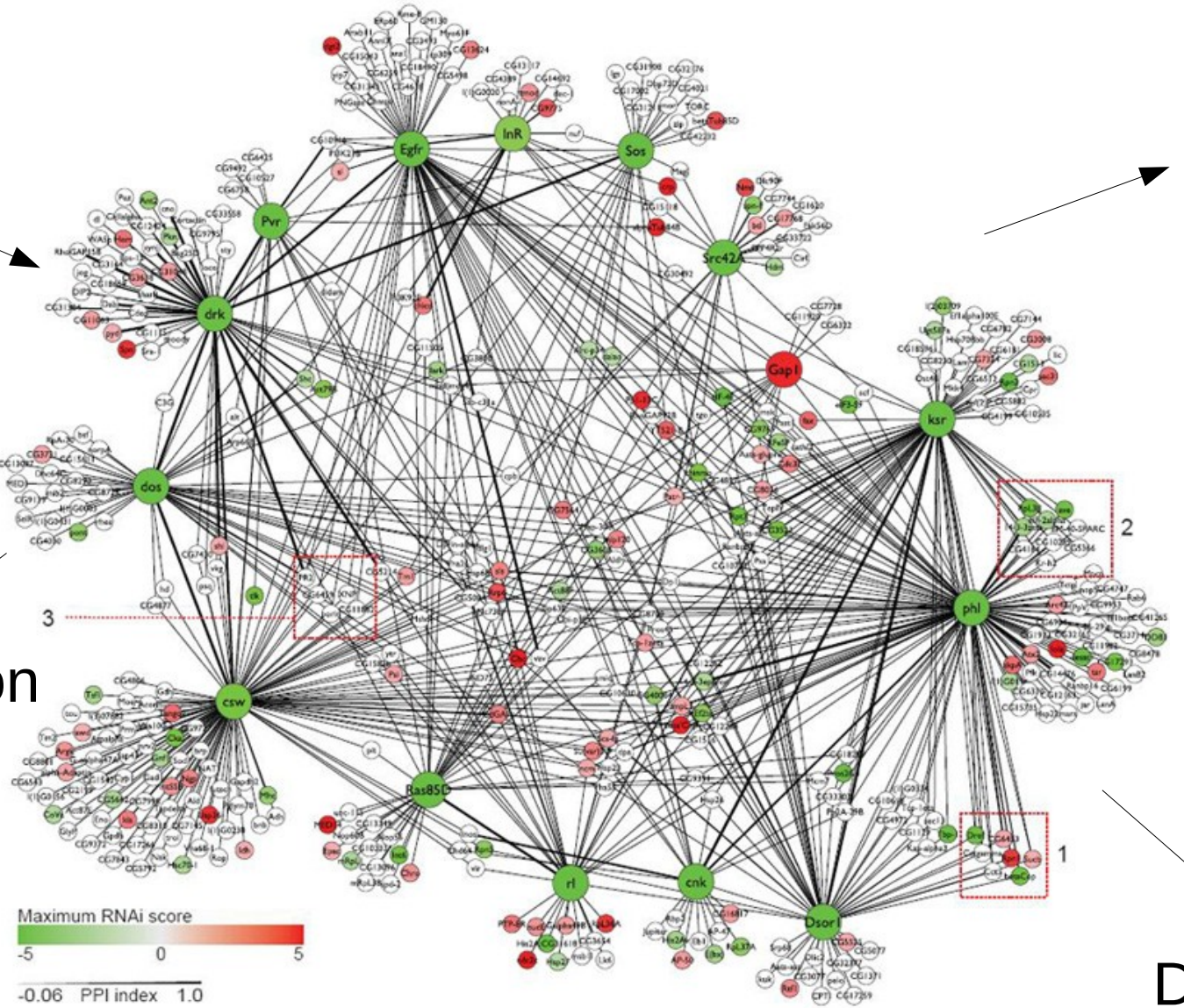
Signaling network determines output

External signal

Division

Differentiation

Death



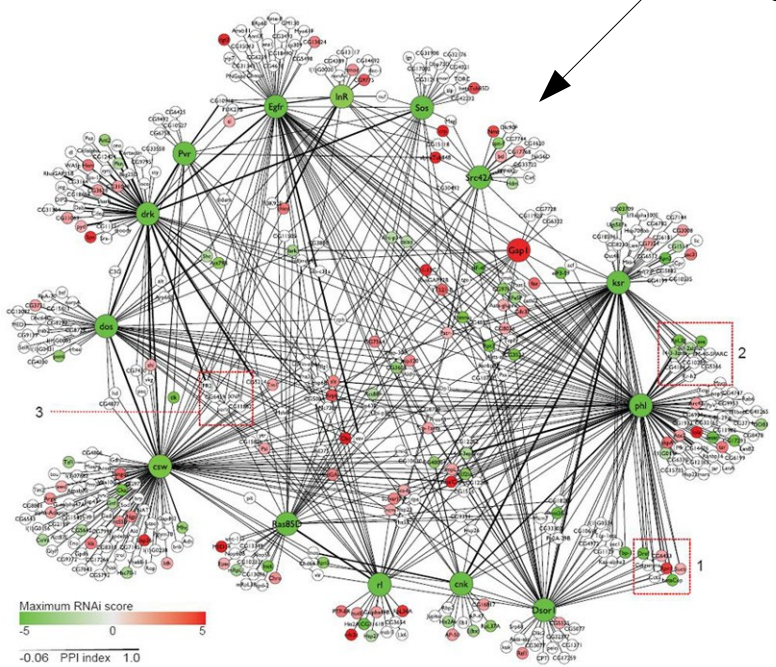
Friedman et al (2011) *Sci Signal*

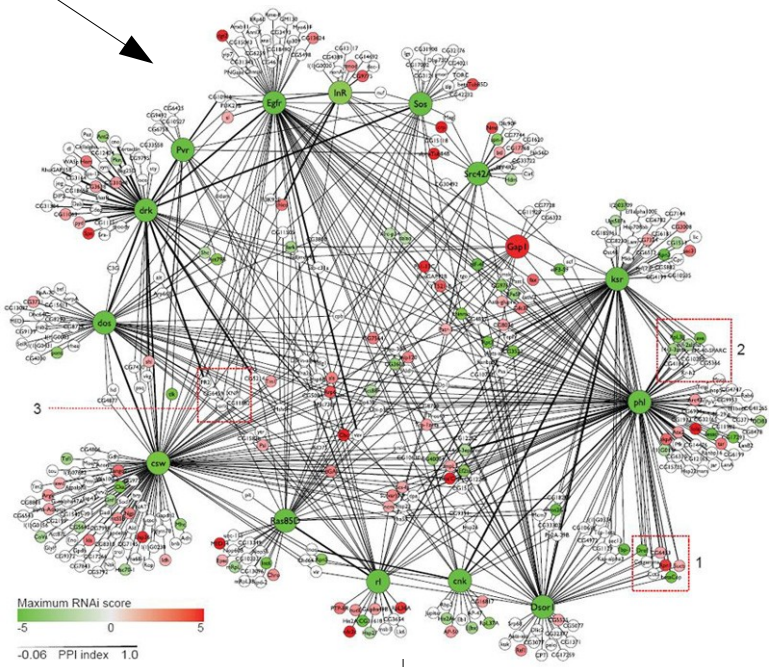
Tissue-specific response

Tissue A

External signal

Tissue B





Output A

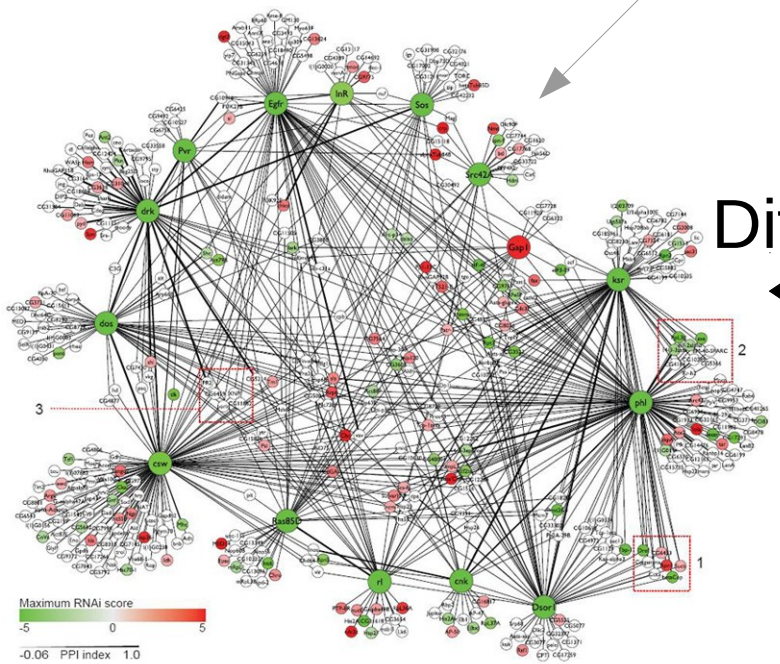
Output B

What accounts for observed differences?

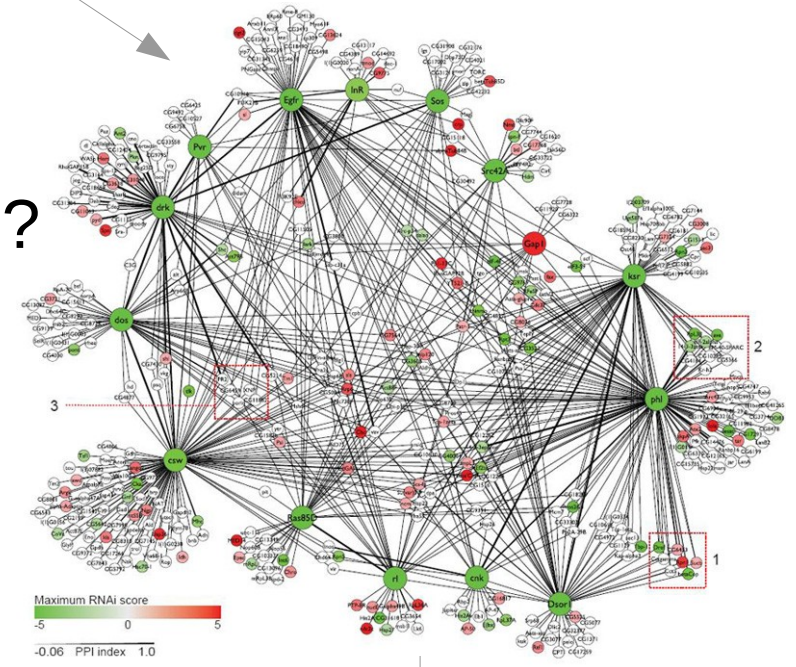
Tissue A

External signal

Tissue B



Differences?



Output A

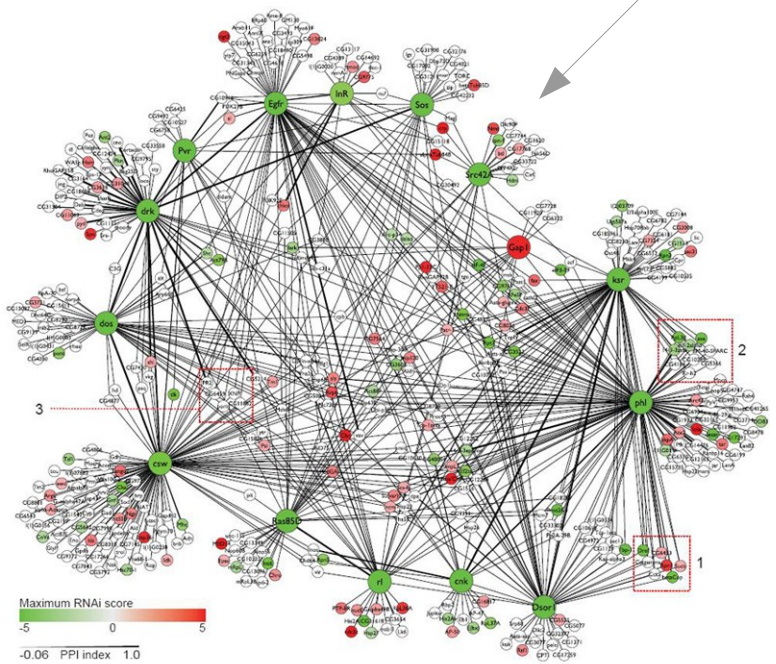
Output B

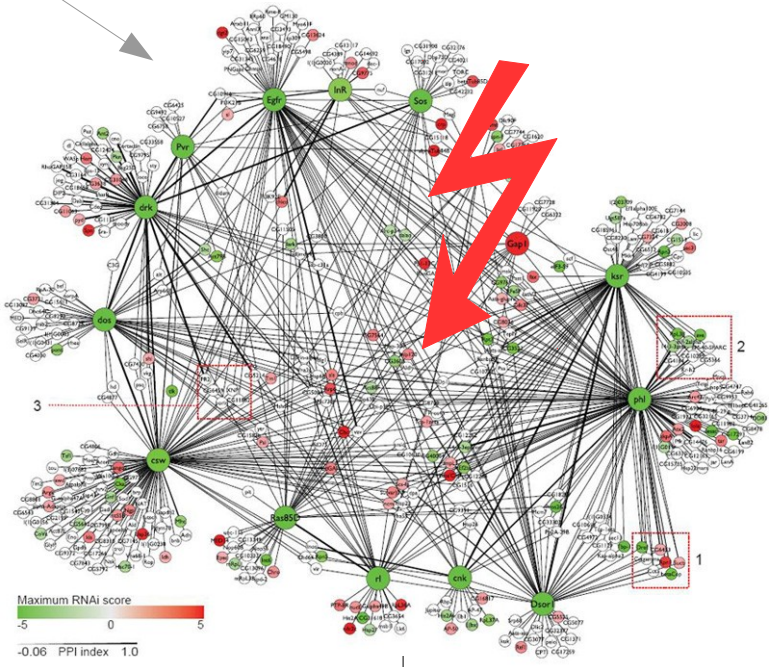
Tune output by targeted manipulations?

Tissue A

External signal

Tissue B

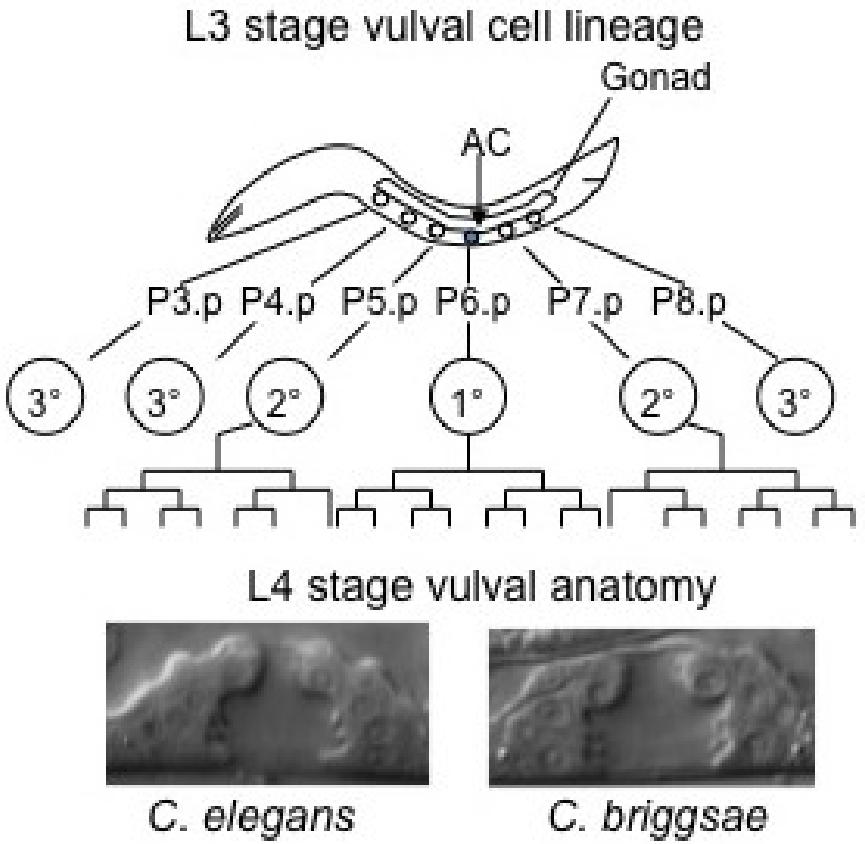




Output A

Output A

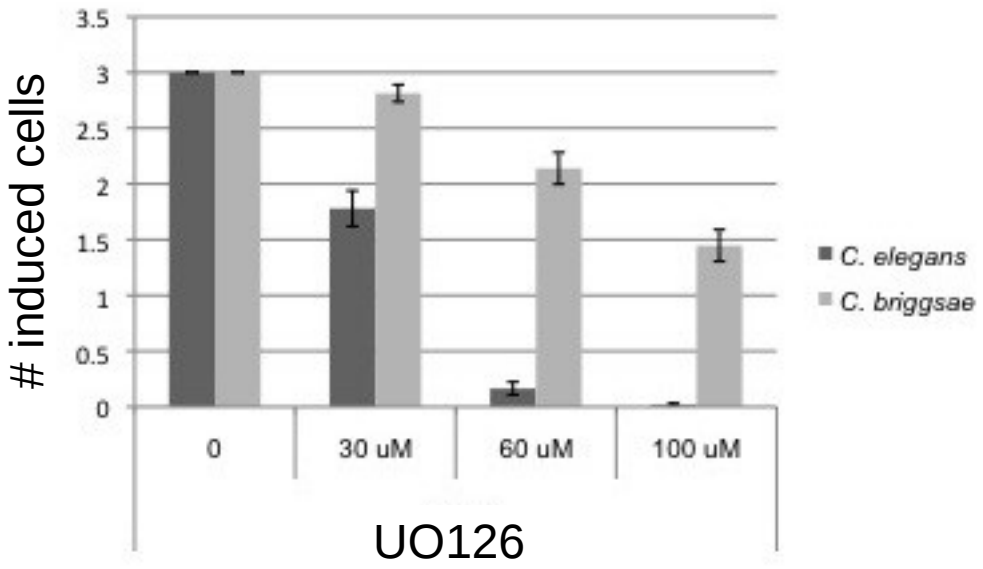
Vulval development in *Caenorhabditis*



- Egg laying structure
- VPC = Vulval Precursor Cell
- Anchor Cell (AC): signal source
- 1^{o}, 2^{o}: Induced
- 3^{o}: Not induced
- Identical WT development in *C. elegans* and *C. Briggsae*
- Conservation of process and factors: EGF (inductive signal), Notch (lateral signal) and Wnt

VPC response to perturbation

- Drug treatment: gradual reduction in target activity
- Species-specific response
- Control: UO126 affects other processes

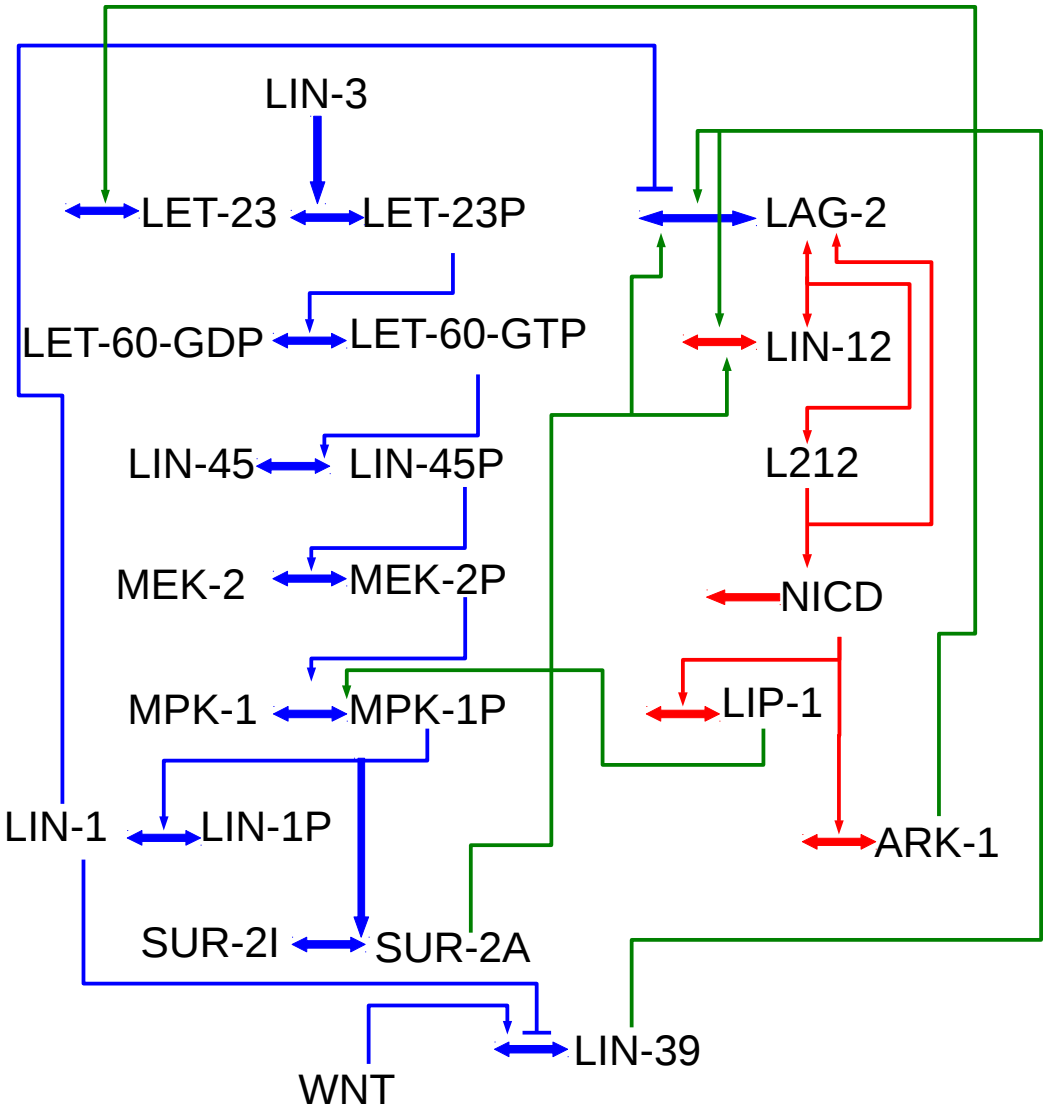


Big Question #1

What factors are responsible for the species-specific response?

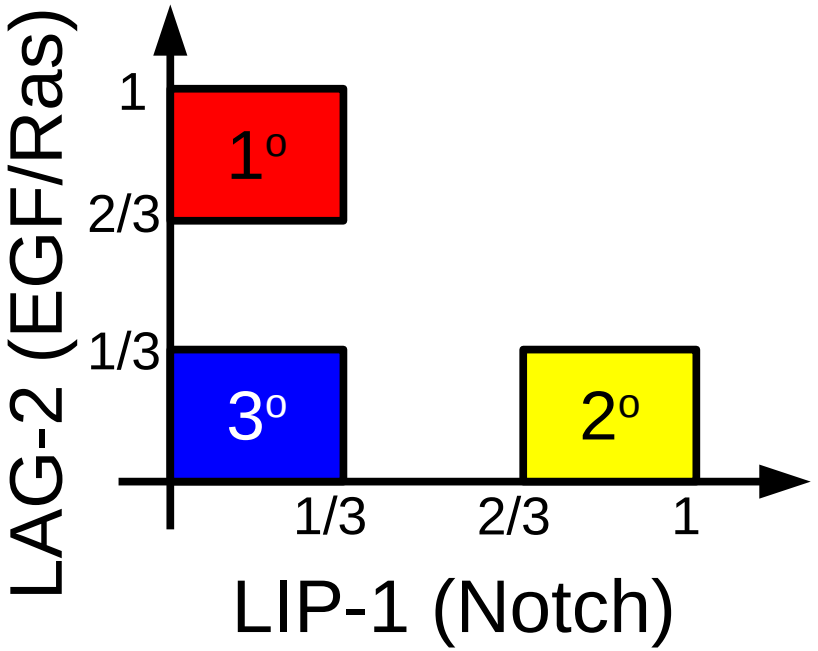
Biologically based model

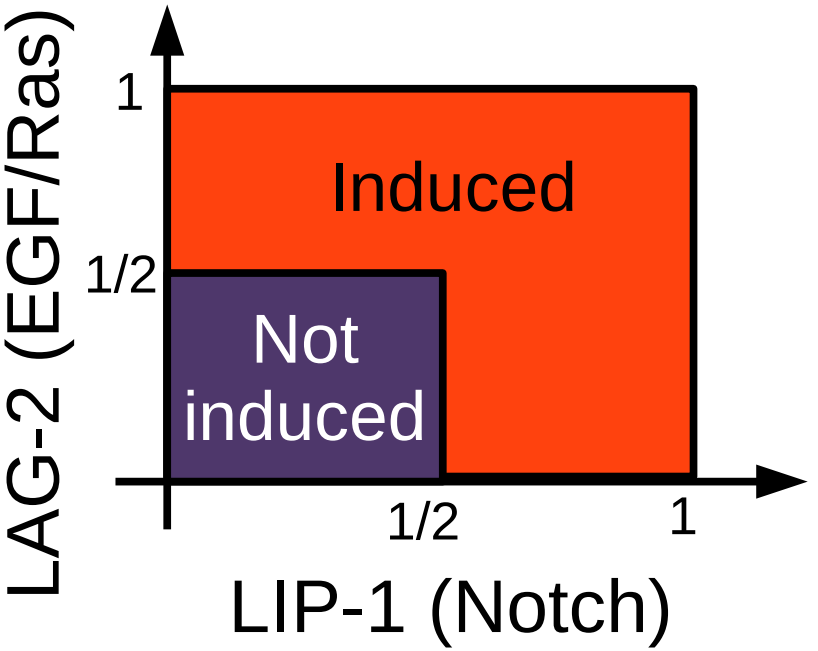
- Most data from *C. elegans:* conservation
- **Blue = EGF/Ras**
- **Red = Notch**
- **Green = Crosstalk**
- Identical system of equations implemented in each VPC (6 x 15 eqns, 71 params)
- Spatially varying EGF, Wnt signal



Model Assumptions

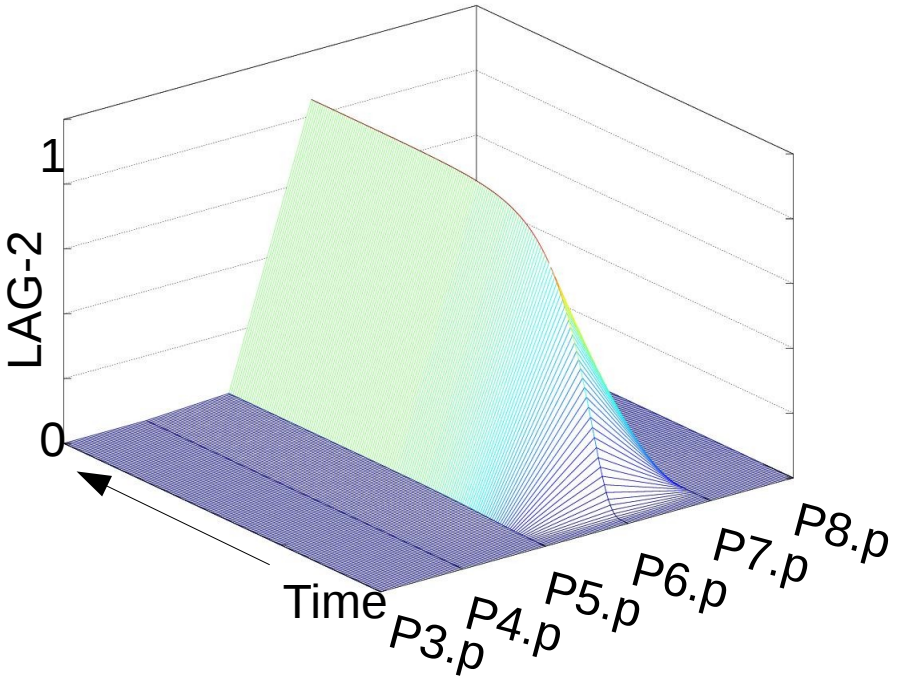
- Kinase/phosphatase activity follows Hill-type dynamics (saturating)
- All other dynamics linear/mass-action
- Cell fate determination:



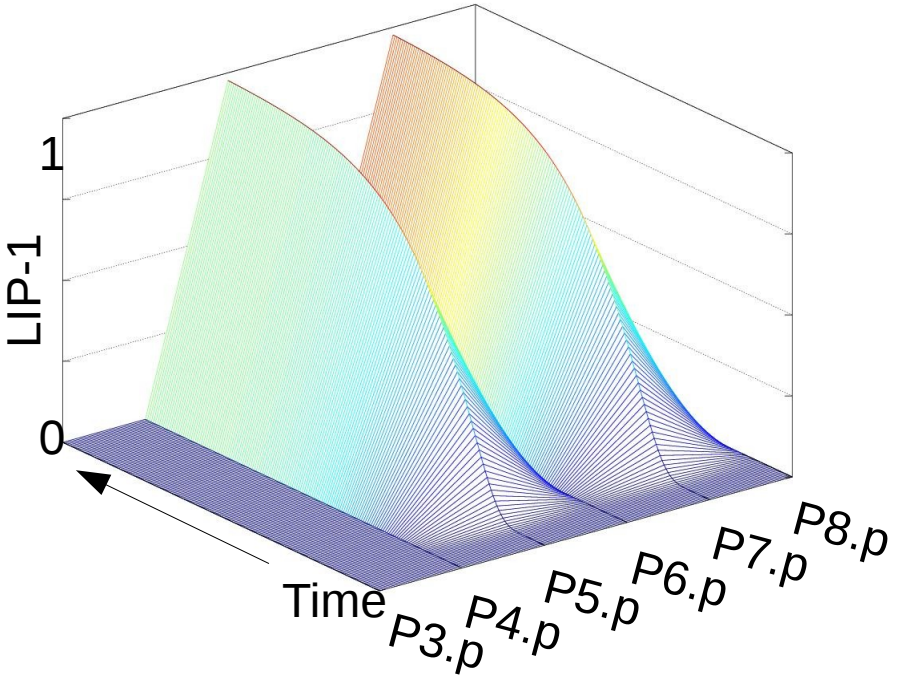


Model recapitulates wild-type time course

EGF/Ras output

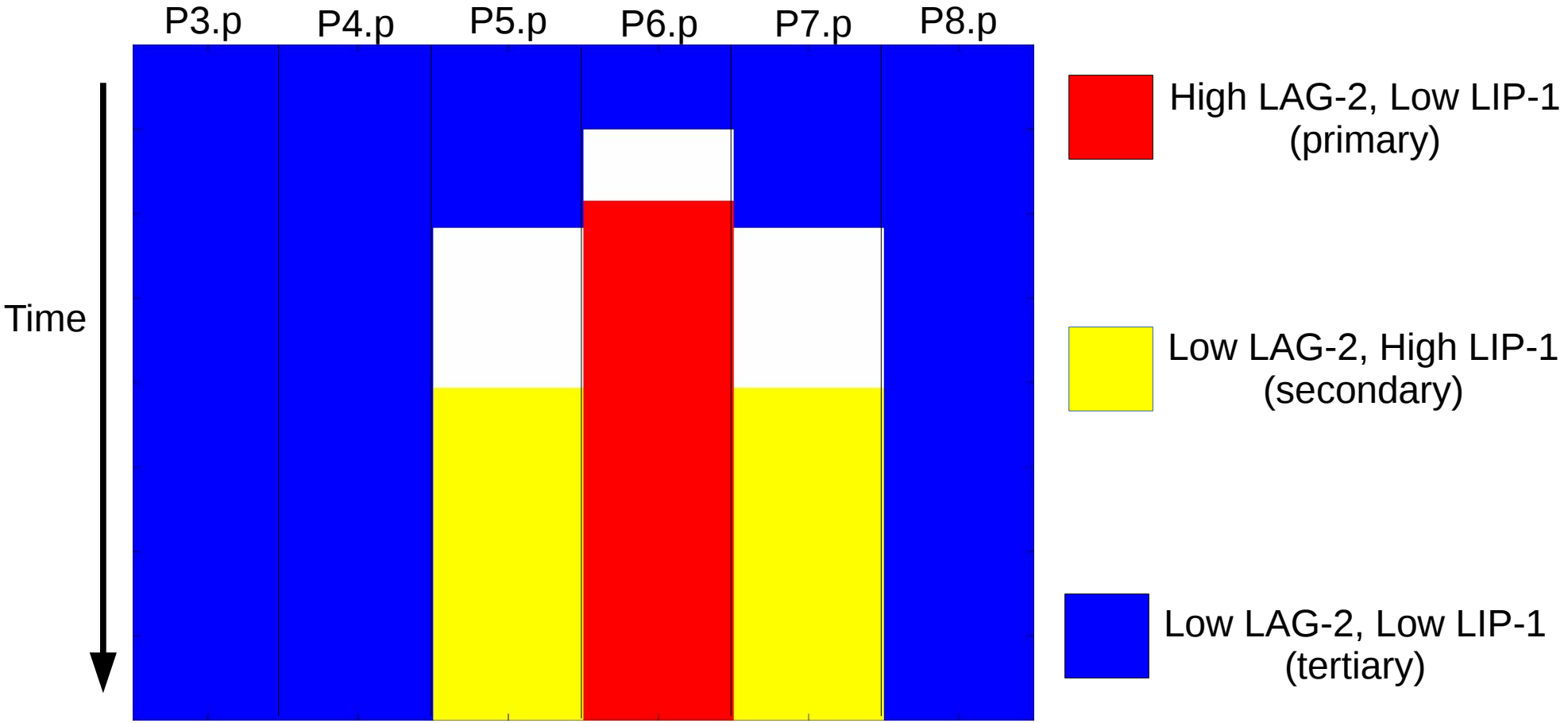


Notch output



	Primary	Secondary	Tertiary
LAG-2	↑	↓	↓
LIP-1	↓	↑	↓

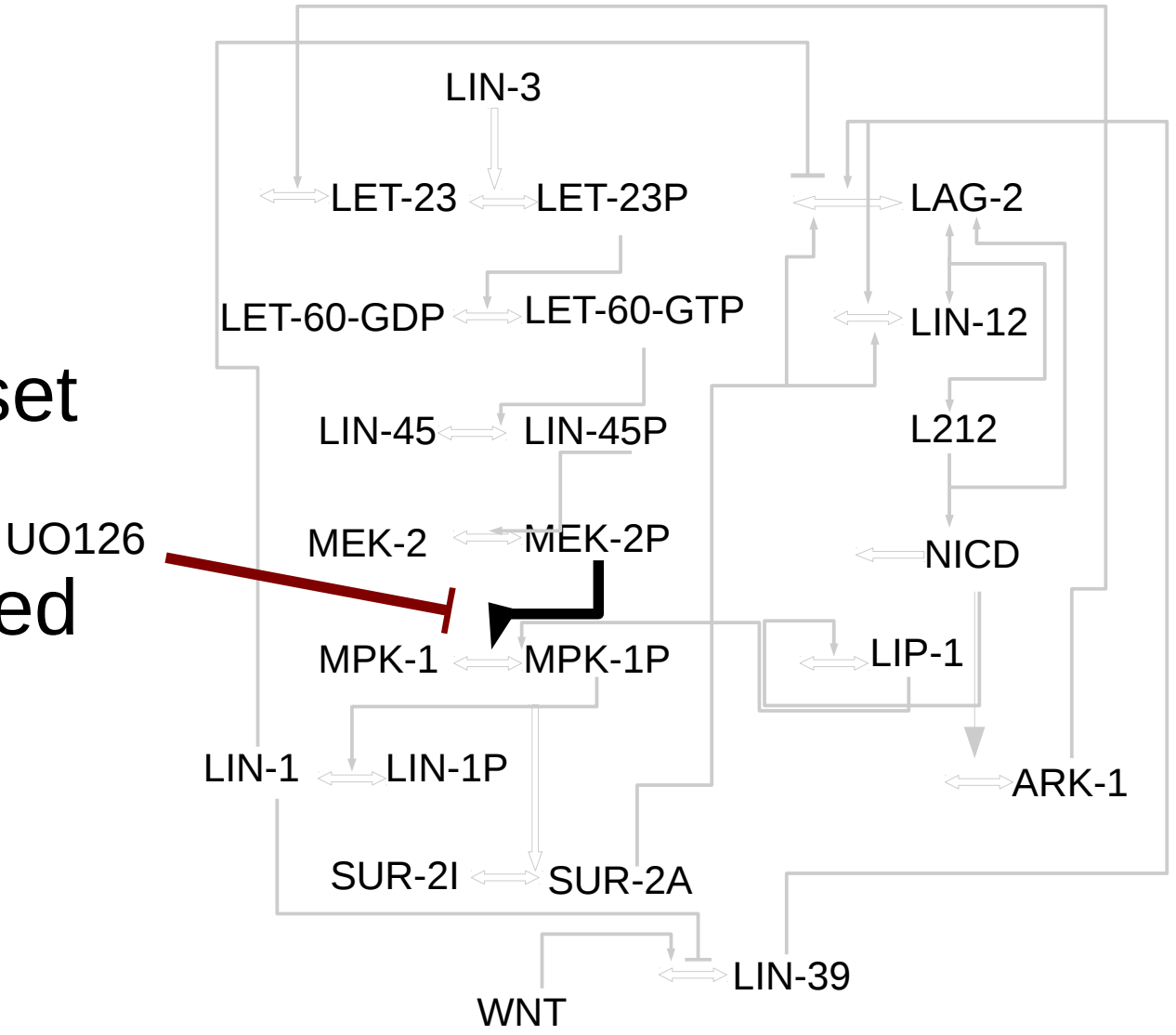
WT time course



Role of UO126

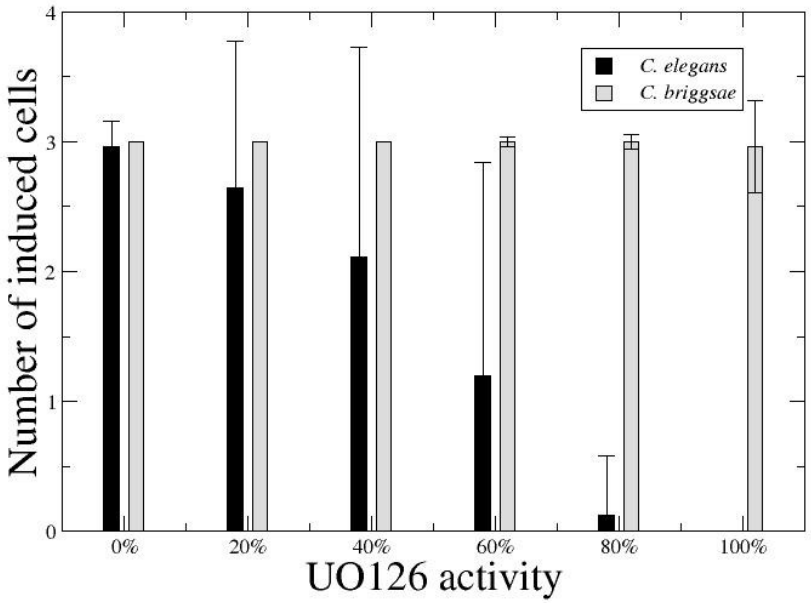
- MEK-2 inhibitor
- Prevents MPK-1 phosphorylation
- Test parameter set responses:

  number of induced cells

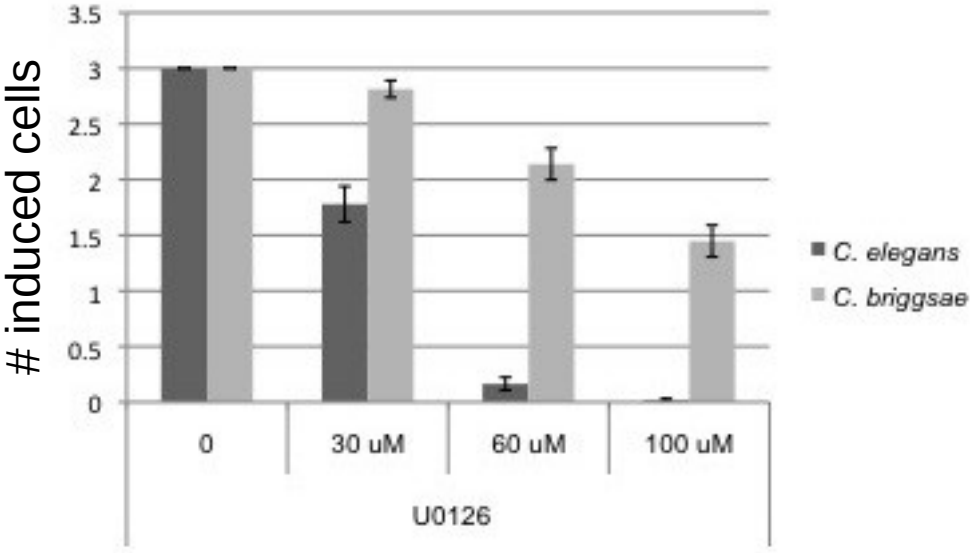


Simulations replicate response to UO126

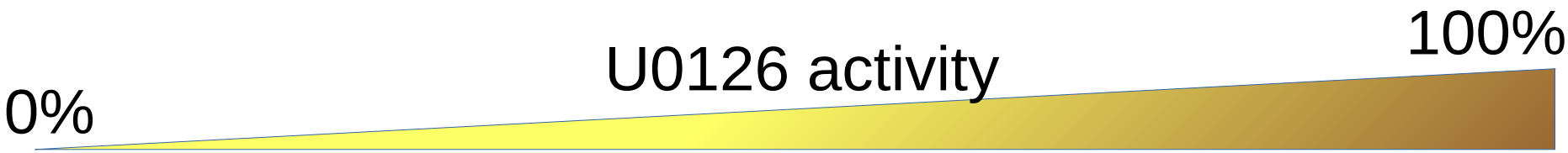
Numerical data



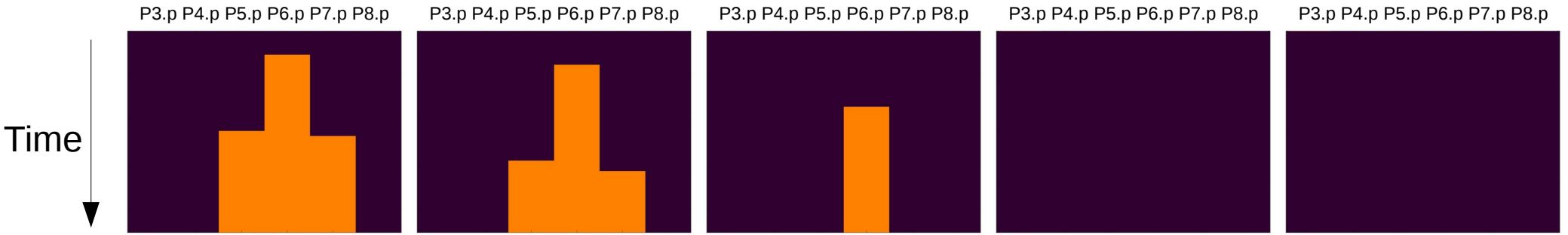
Experimental data



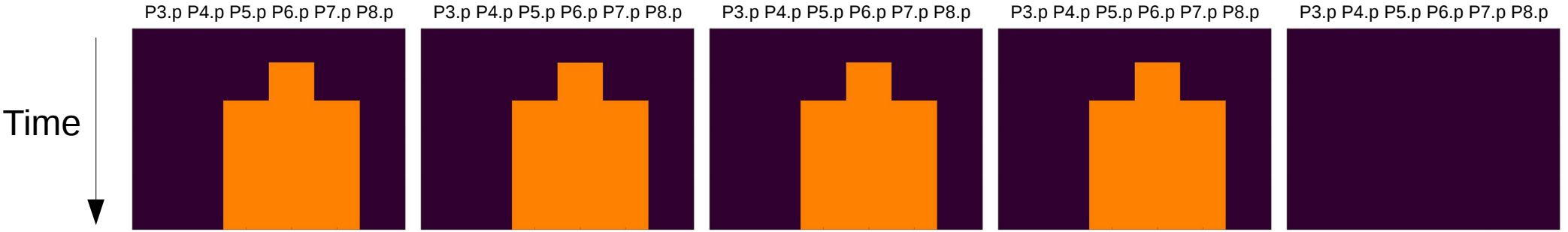
Simulated response to UO126



C. elegans

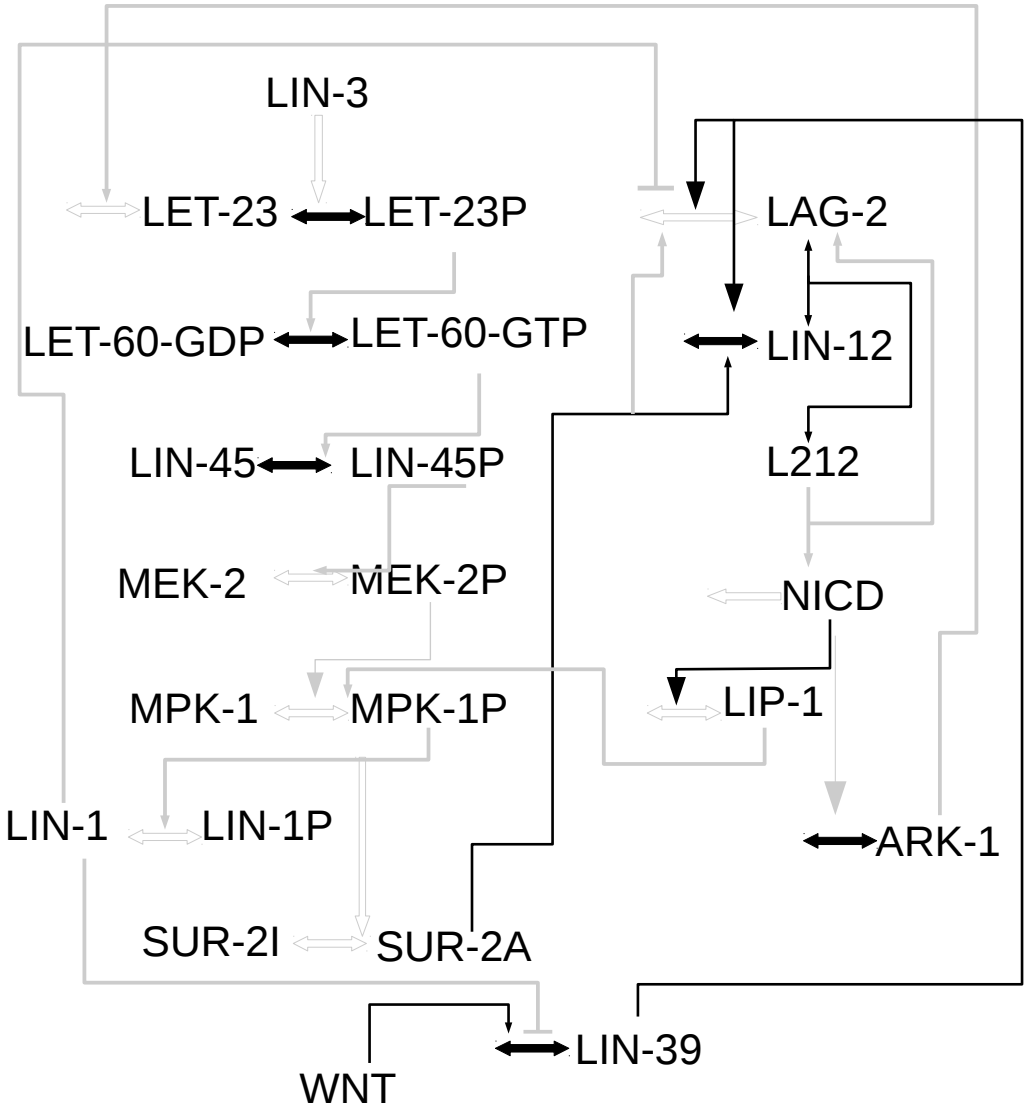


C. briggsae



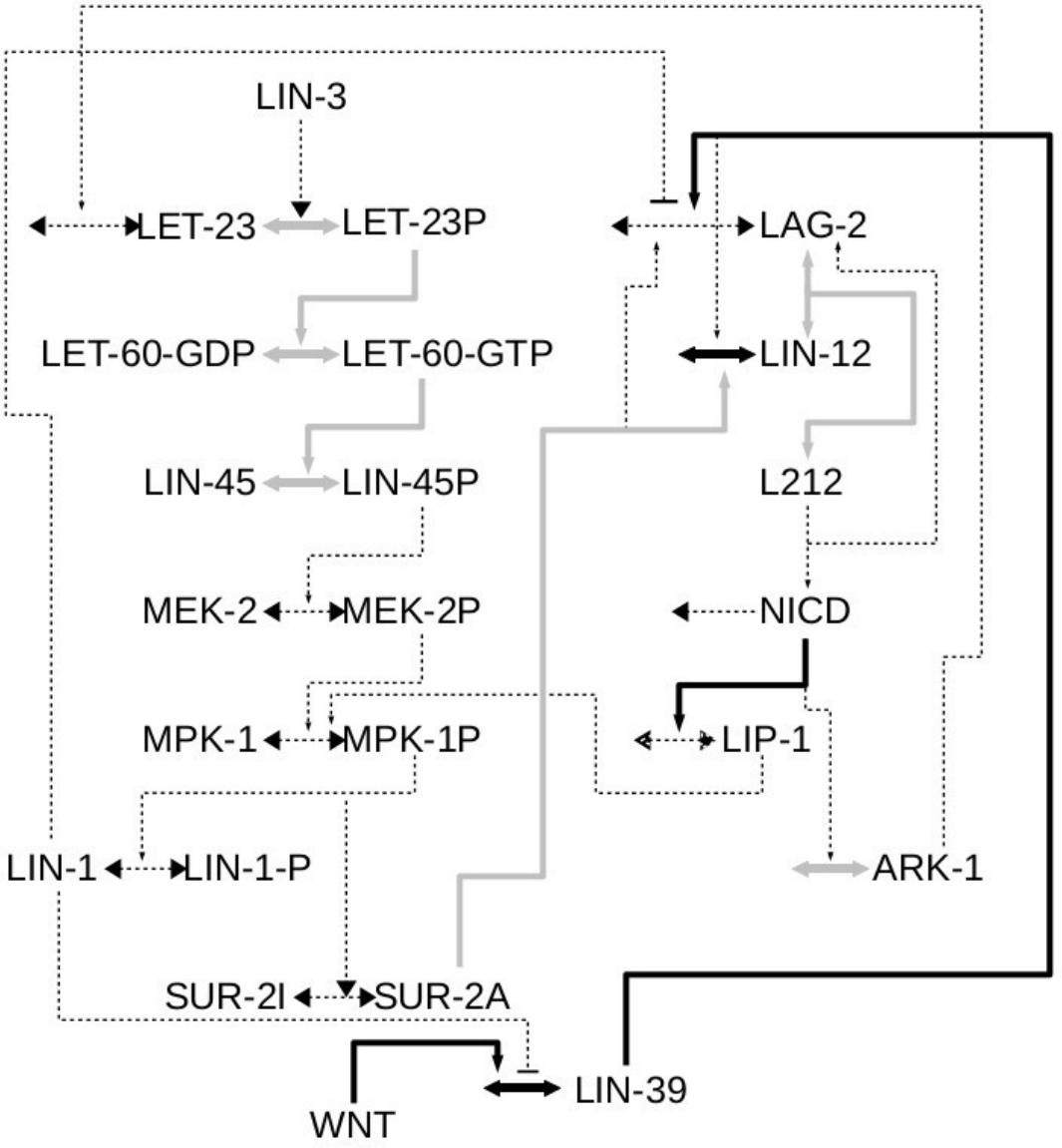
Parameter differences in EGF synthesis, Notch activation

- Two sample t-test between *C. elegans* and *C. briggsae*-like sets



Phenotype “switching” by key parameters

- Parameters modulated one at a time and response tested



Results #1

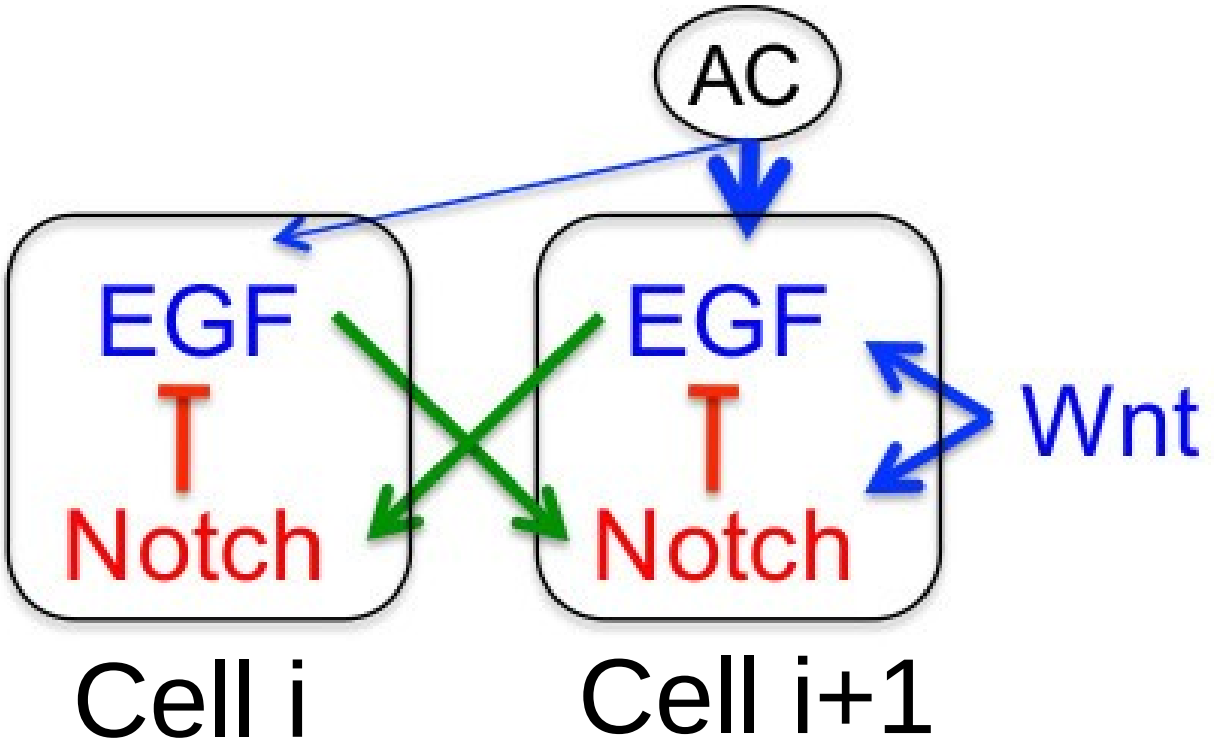
- Constructed biologically based based model that recapitulates wild-type behaviour
- External Wnt signal identified as key parameter for species-specific response

Big Question #2

How is the Wnt signal affecting cell fates?

Carly Williamson

Simplified network



Model equations

$$\textit{Notch} \quad \frac{dN_i}{dt} = W_i f\left(\bar{E}\right) - N_i$$

$$\textit{EGF} \quad \frac{dE_i}{dt} = \gamma\left(\lambda_i g\left(N_i\right) - E_i\right)$$

$$\textit{where} \quad \bar{E}_i = \frac{1}{m}\sum_j E_j$$

$$f(\sigma) = \frac{\sigma^k}{\alpha + \sigma^k}$$

$$g(\sigma) = \frac{1}{1 + \beta\sigma^h}$$

Model equations

$$\textit{Notch} \quad \frac{dN_i}{dt} = W_i f(\bar{E}) - N_i$$

$$\textit{EGF} \quad \frac{dE_i}{dt} = \gamma(\lambda_i g(N_i) - E_i)$$

$$\gamma = \frac{k_E}{k_N}$$

$$\textit{where} \quad \bar{E}_i = \frac{1}{m}\sum_j E_j$$

$$f(\sigma) = \frac{\sigma^k}{\alpha + \sigma^k}$$

$$g(\sigma) = \frac{1}{1 + \beta\sigma^h}$$

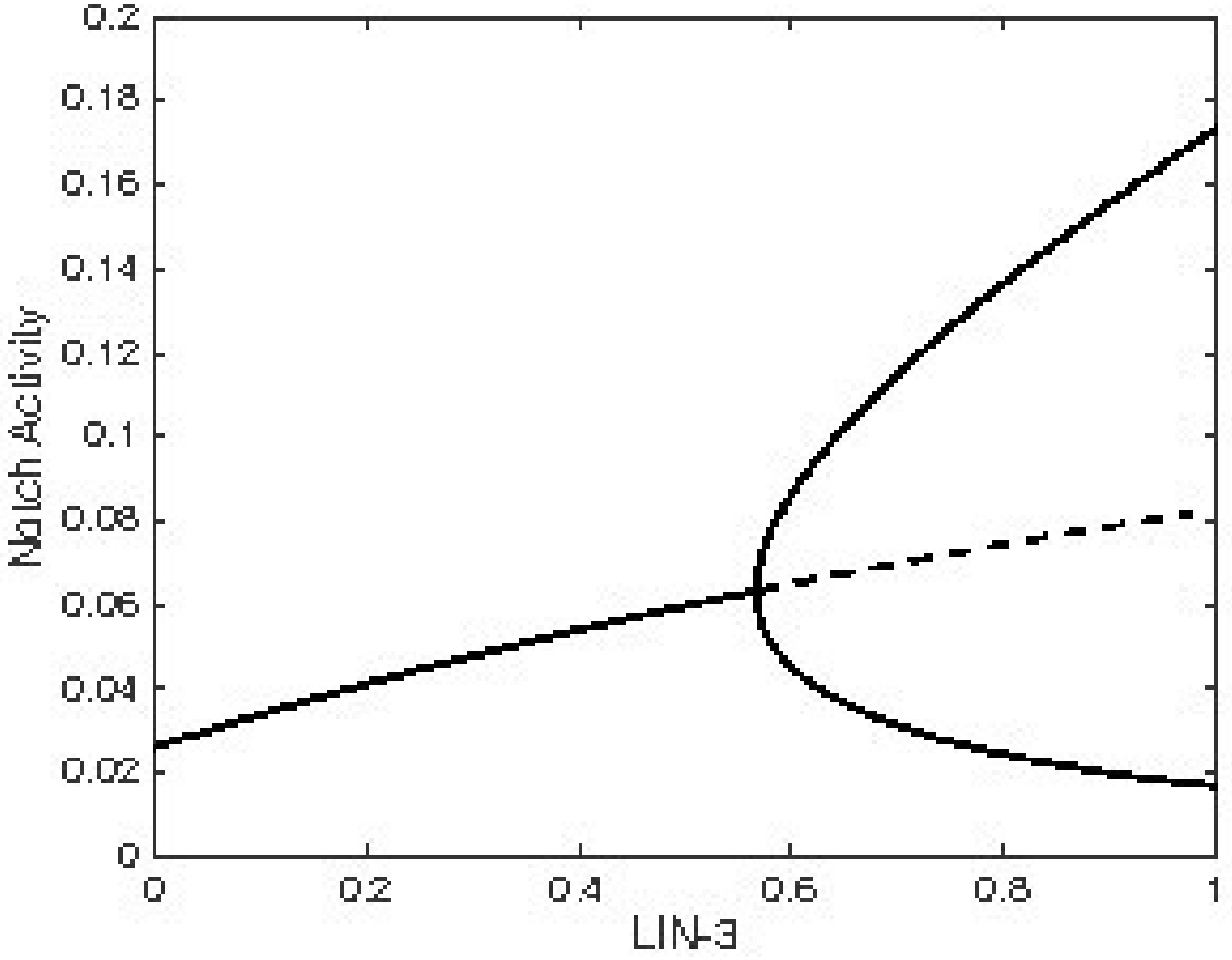
Linear stability analysis

- Solve for steady state E*, N*
- Linearize system of equations and find eigenvalues
- Bifurcation point:

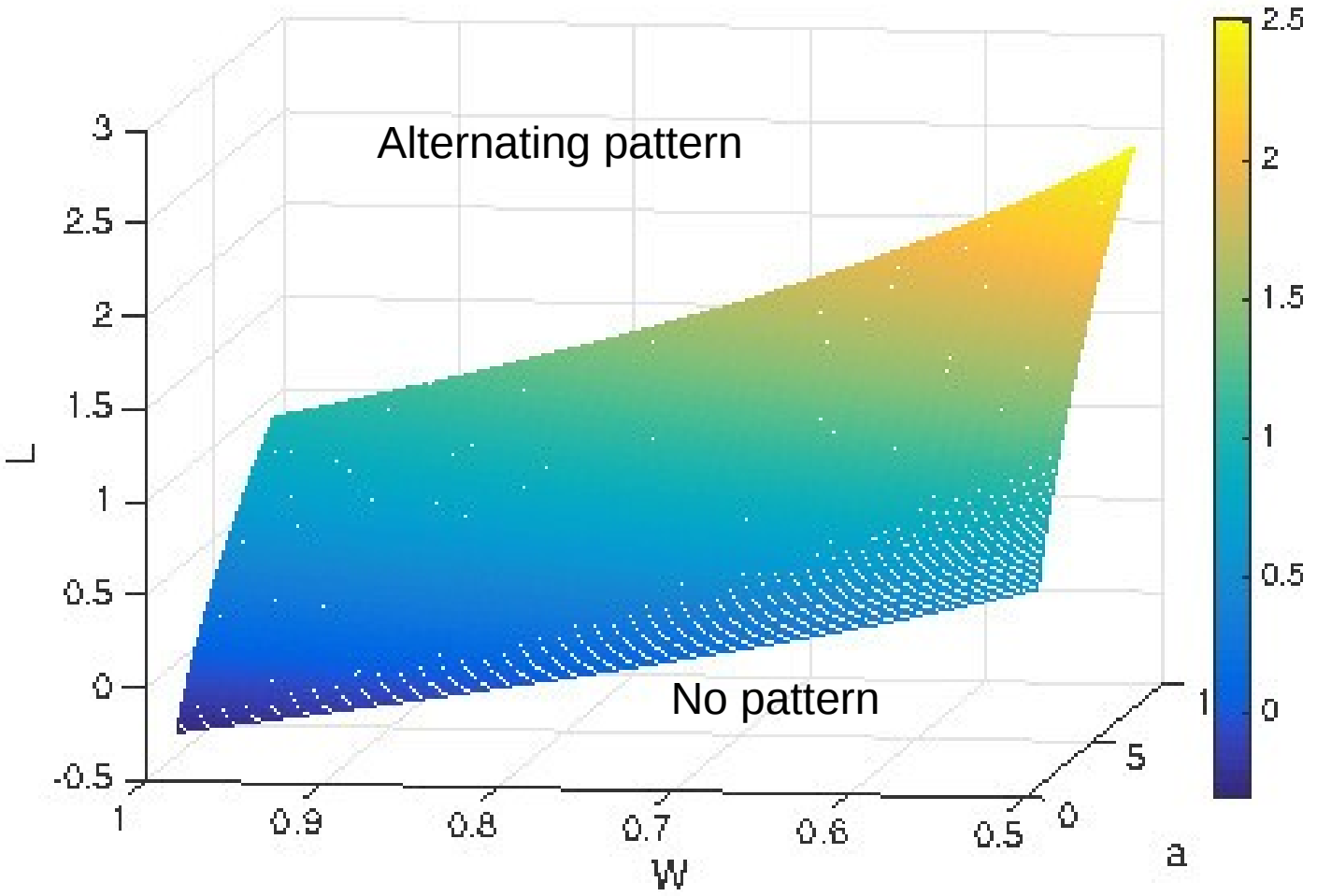
$$L = \frac{-1}{\mu}\left(\frac{\mu+1}{W f'(E^*) g'(N^*)} + W\right)$$

Bifurcation diagram

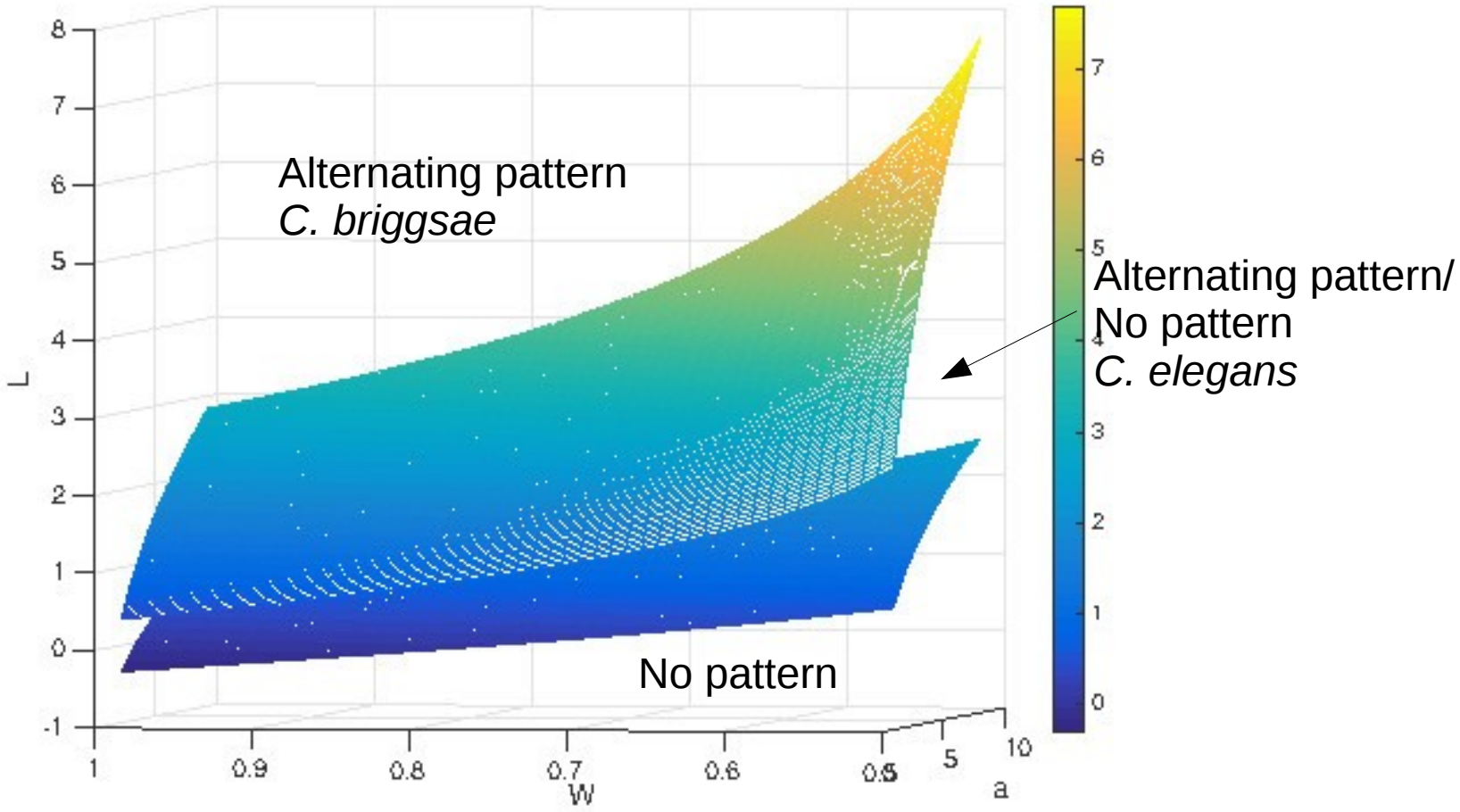
- Supercritical pitchfork bifurcation



Bifurcation plane



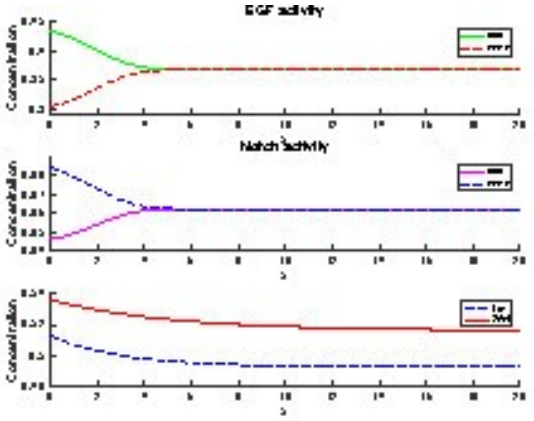
Bifurcation plane with EGF knock down



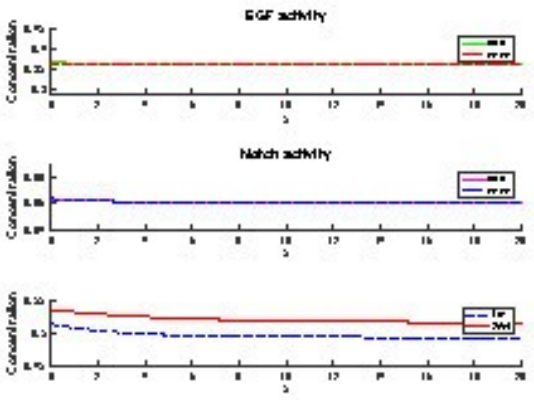
Asymptotics about bifurcation point

$$L = l + \delta^2 L(x)$$
$$W = w + \delta^2 W(x)$$

C. briggsae



C. elegans



Results #2

- Simplified model recapitulates loss of pattern
- Interrelationship between LIN-3, Wnt and sensitivity to external signals dictates loss of pattern
- Tuning Wnt signal can rescue alternating pattern

Open questions

- What if γ is very large?
- Consider $\varepsilon \rightarrow 0$

$$
\begin{aligned}
Notch \quad & \frac{dN_i}{dt} = W_i f\left(\bar{E}\right) - N_i \\
EGF \quad & \frac{dE_i}{dt} = \gamma\left(\lambda_i g\left(N_i\right) - E_i\right) \\
\Rightarrow \quad & \frac{dN_i}{dt} = W_i f\left(\bar{E}\right) - N_i \\
& \epsilon \frac{dE_i}{dt} = \lambda_i g\left(N_i\right) - E_i
\end{aligned}
$$

Open questions

- Does this system satisfy conditions of Tikhonov's theorem?
- How does small parameter assumption affect bifurcation dynamics? Asymptotics?
- Do we gain new insight into the system dynamics by taking the limit?

Acknowledgments

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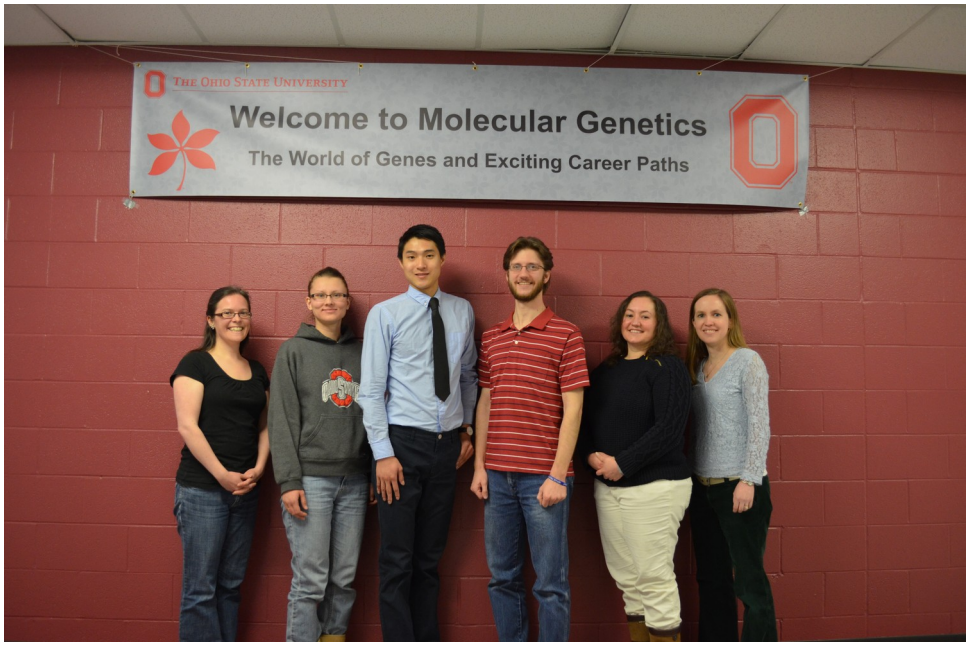
Carly Williamson

Chamberlin Lab



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