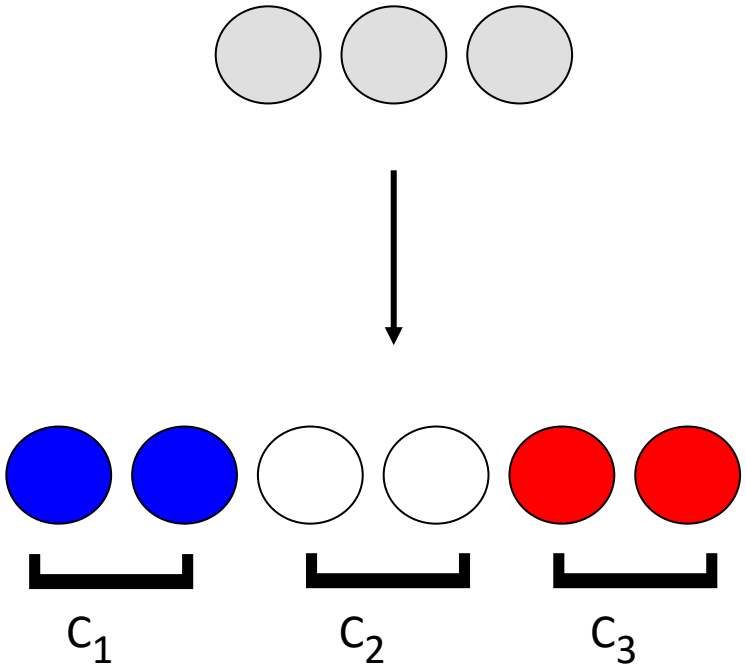
The Problem: Pattern Formation

Homogenous Progenitor Population



Different Differentiated Cell Types

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tw: @briscoejames
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The Problem: Pattern Formation

Different cell types = different gene expression profiles

Therefore problem is:

How is differential spatial pattern of gene expression controlled?

Requirement:

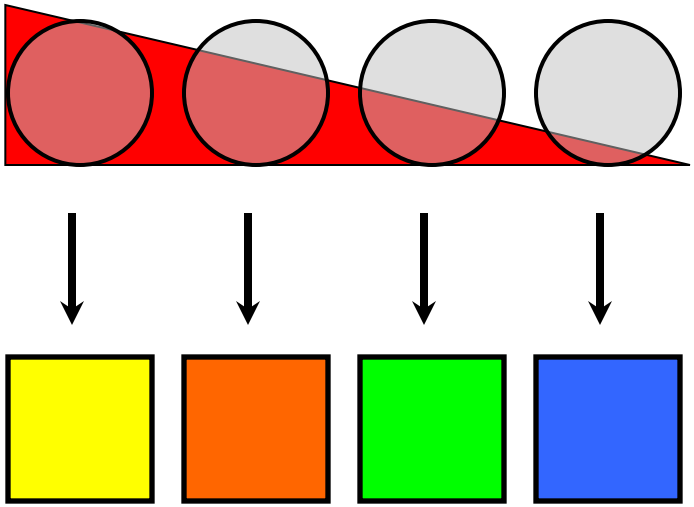
Symmetry breaking event to provide **spatial polarization**

Communication of position to cells to provide **positional information**

Conversion positional information to **discrete domains gene expression**

Morphogen gradients

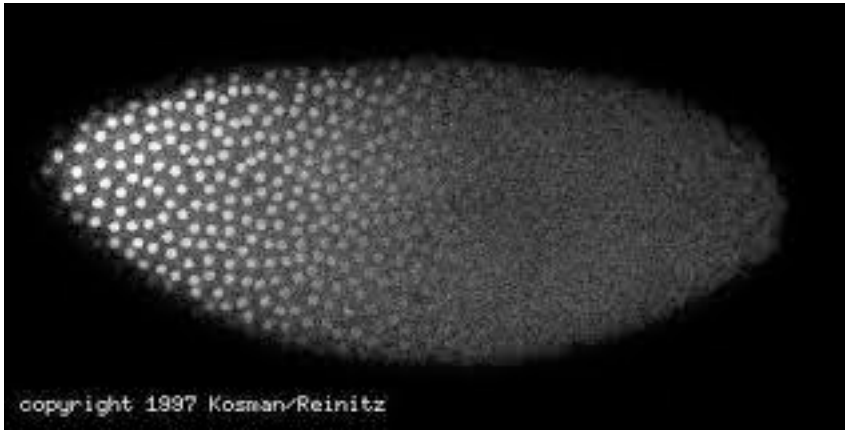
Long-range signal

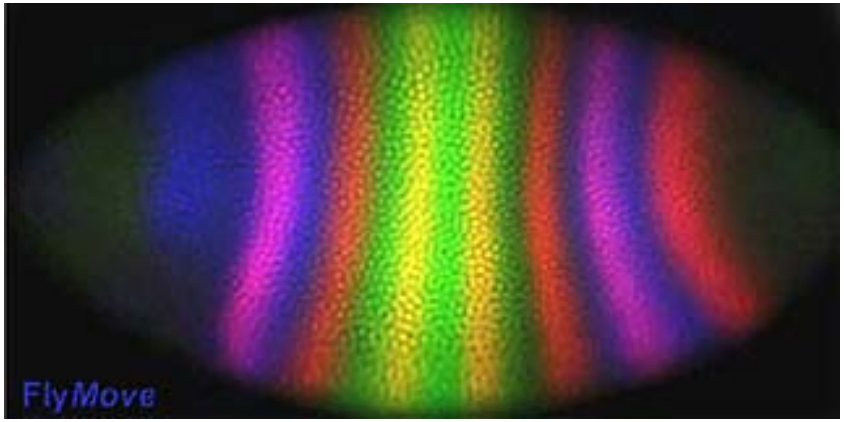


Concentration dependent

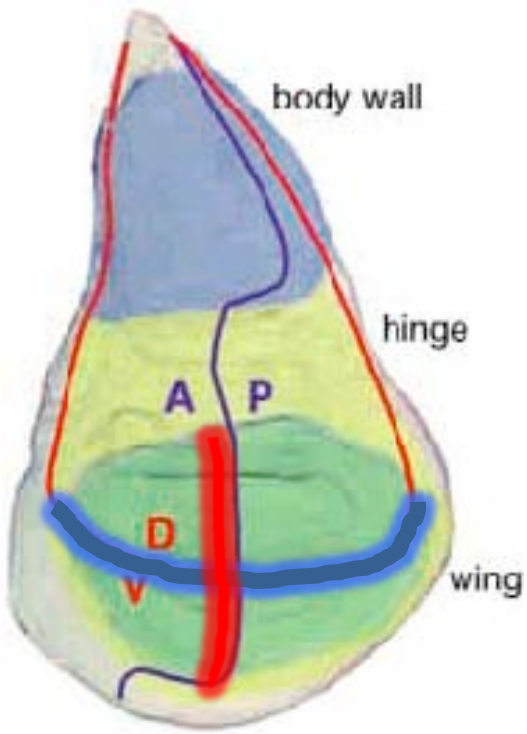
Determines cell fate

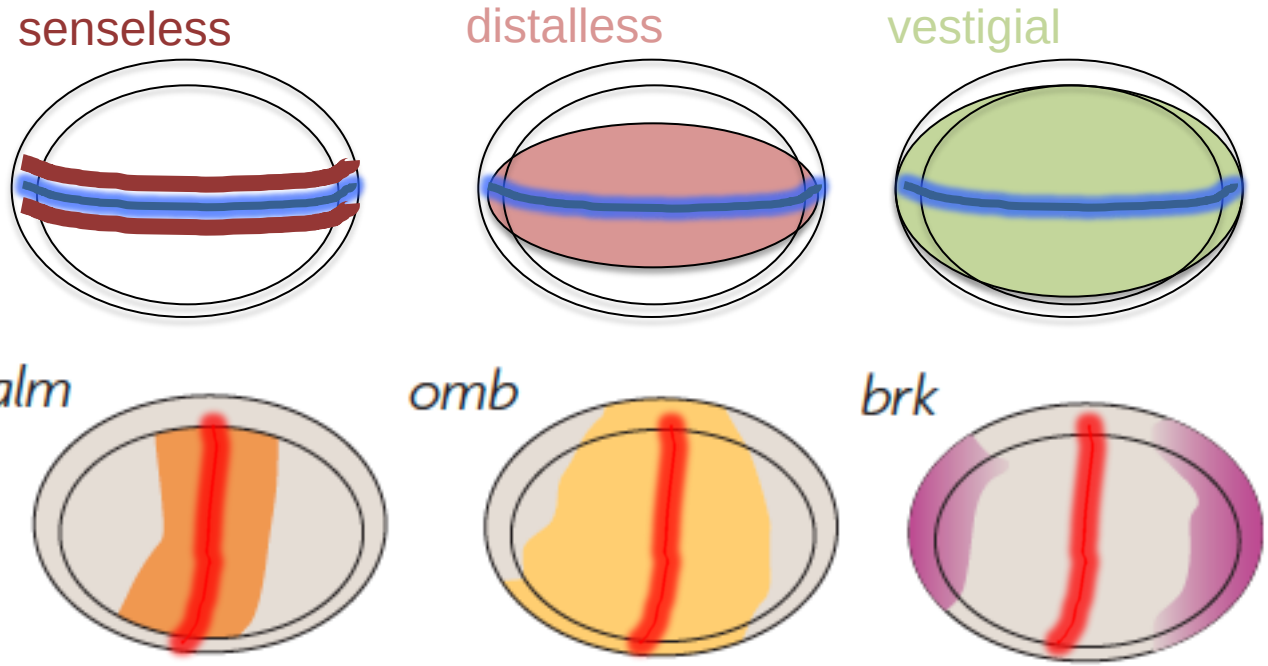
Responding cells perceive morphogen levels


copyright 1997 Kosman/Reinitz

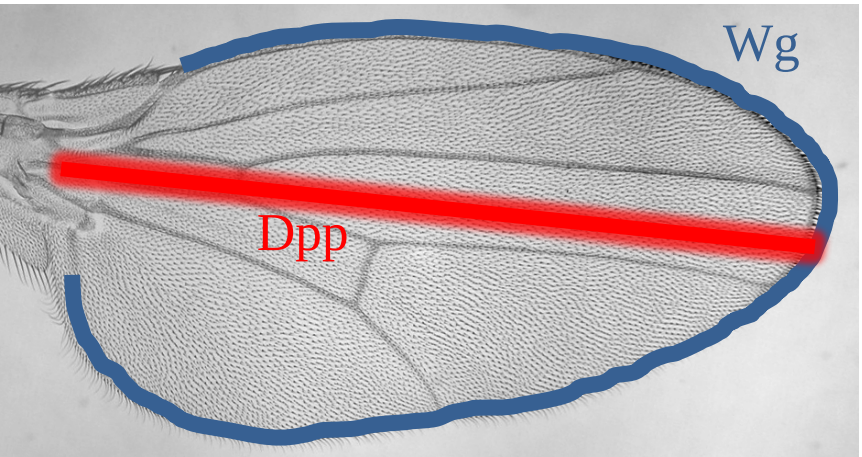

FlyMove

Wingless and Dpp in wing imaginal discs

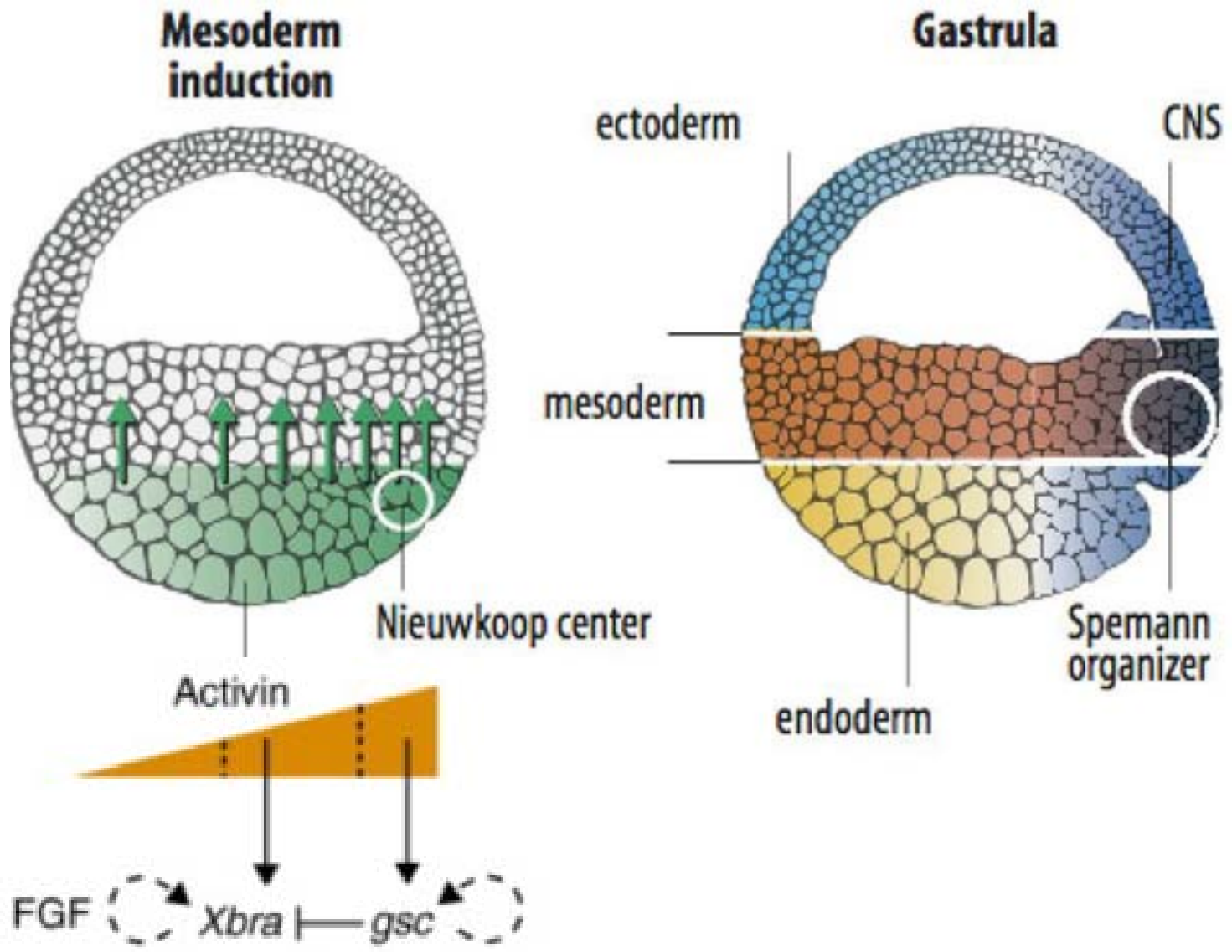




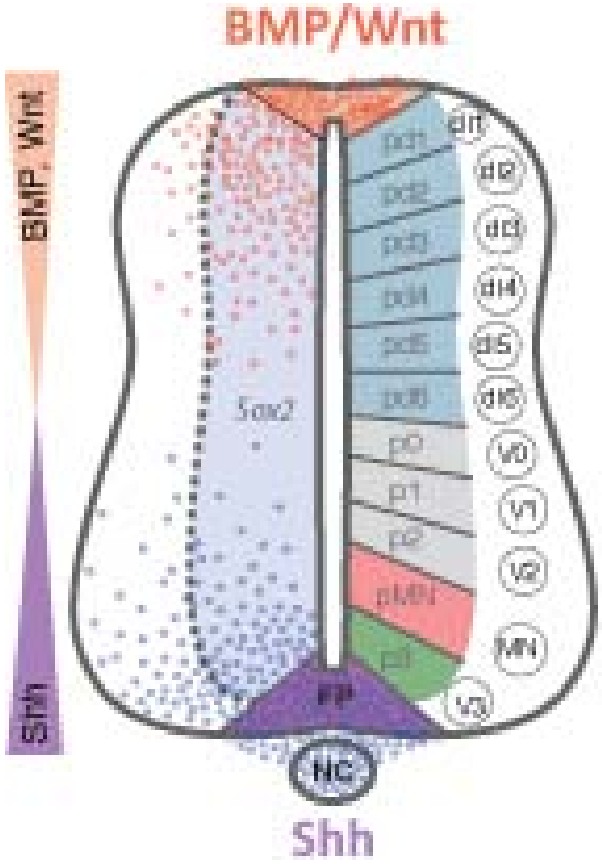
Adapted from Affolter and Basler

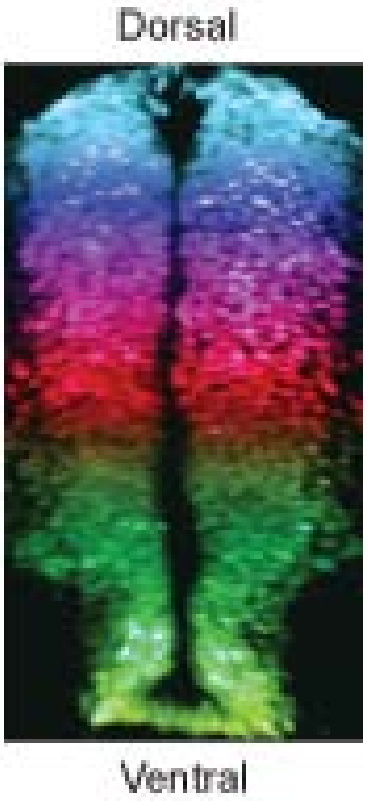


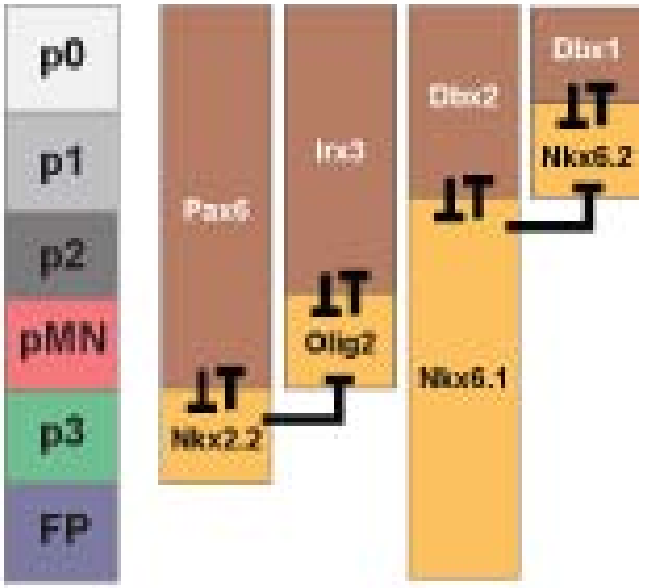
Graded signal transduction: Mesoderm



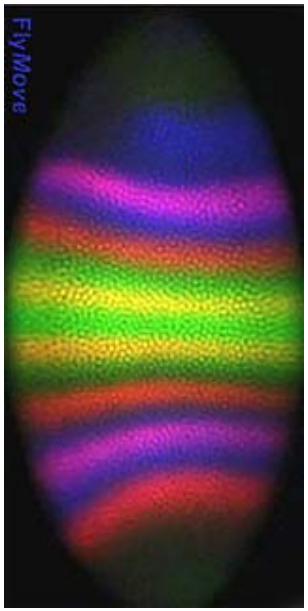
Neural tube patterning

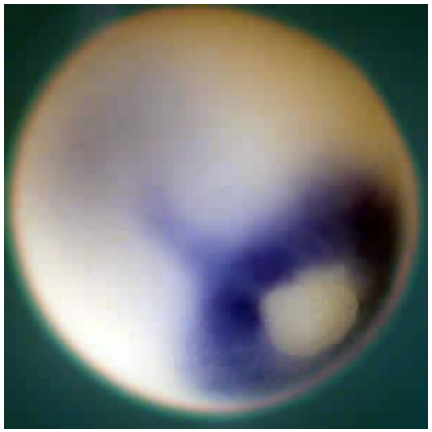


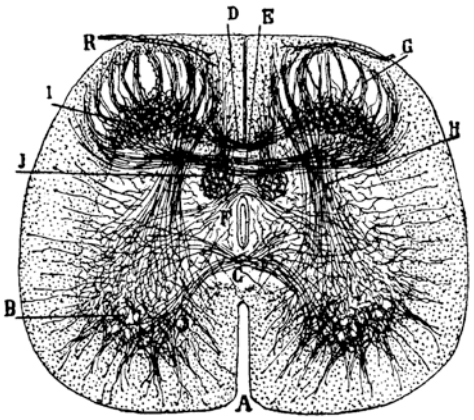




Different time scales of patterning







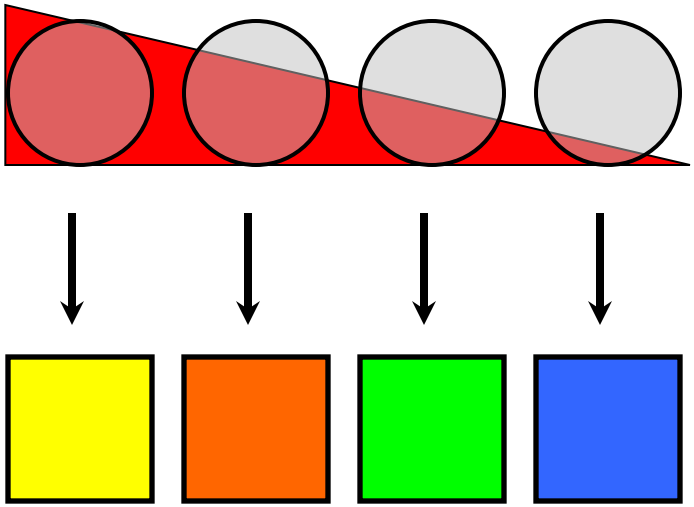
Minutes

Hours

Days

Morphogen gradients

Long-range signal



Concentration dependent

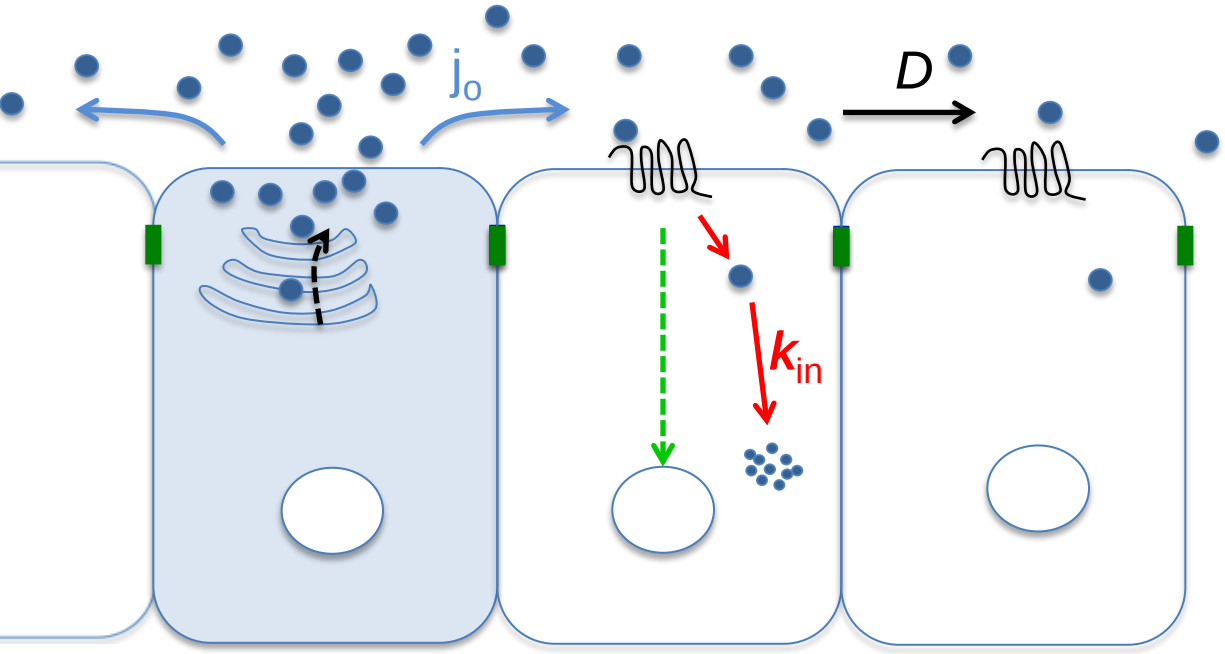
Determines cell fate

Responding cells perceive morphogen levels

Morphogens:

- Identification – what and where
- Formation - intercellular transmission
- Perception - signal transduction
- Interpretation - convert to discrete responses

Factors affecting the distribution of morphogens



Rate of secretion

-Current j_0 [molecules/(μm s)] at the source boundary

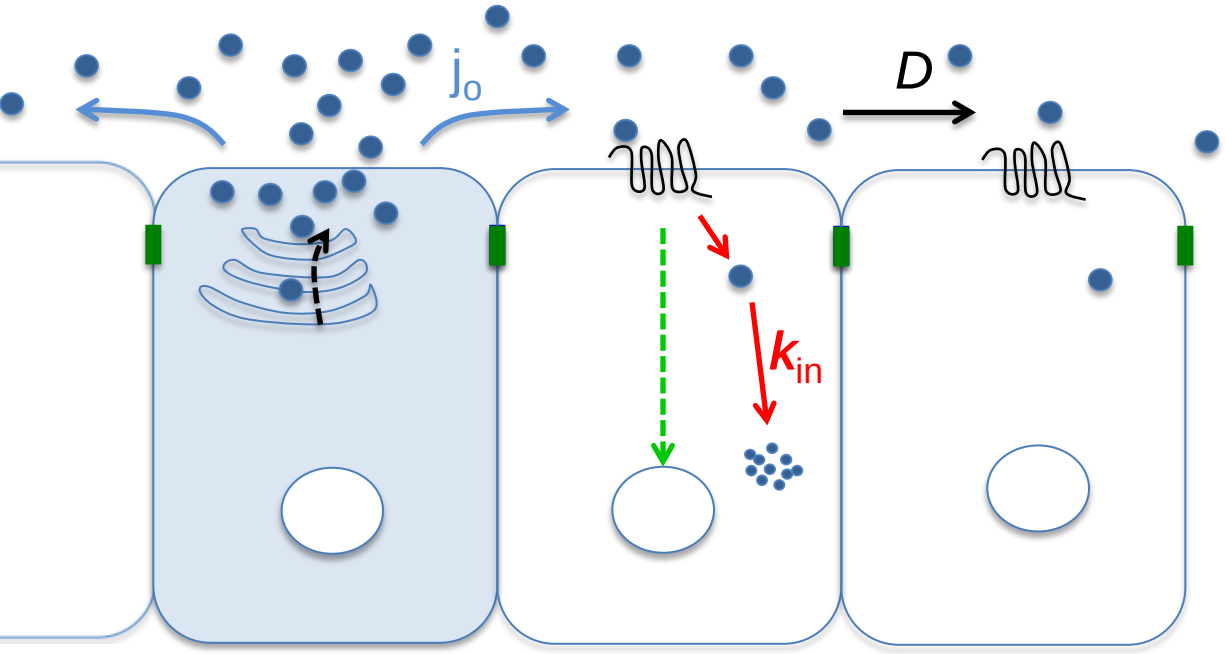
Diffusion or random walk process

-Effective diffusion coefficient D (mm^2/s).

Extracellular protease or lysosomal targeting

-Uniform degradation with a rate k (s^{-1})

Factors affecting the distribution of morphogens



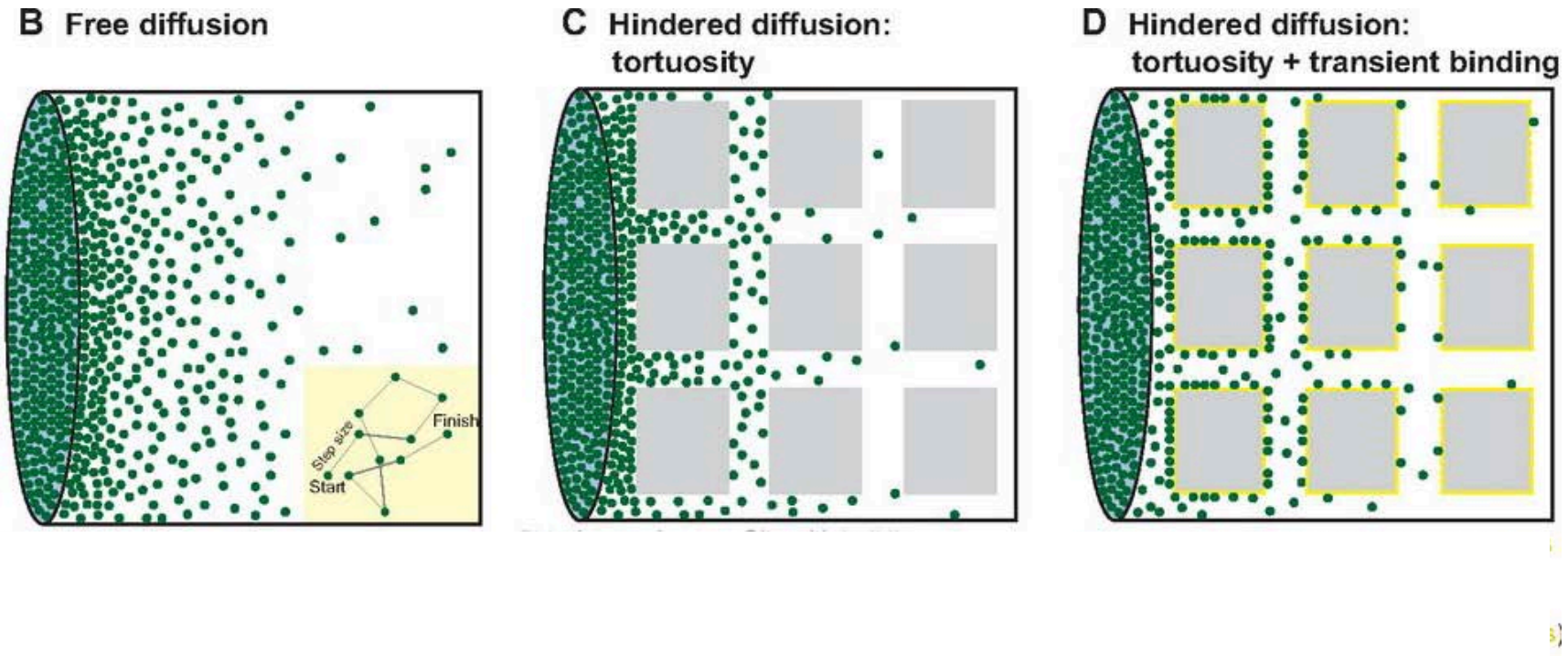
$$\frac{\partial C}{\partial t} = j_0(x) + D\frac{\partial^2 C}{\partial x^2} - kC$$

$$C = C_0\, e^{-x/\lambda}$$

Wartlick, O., Kicheva, A. & González-Gaitán, M.. Cold Spring Harb. Perspect. Biol. 1: a001255 (2009).

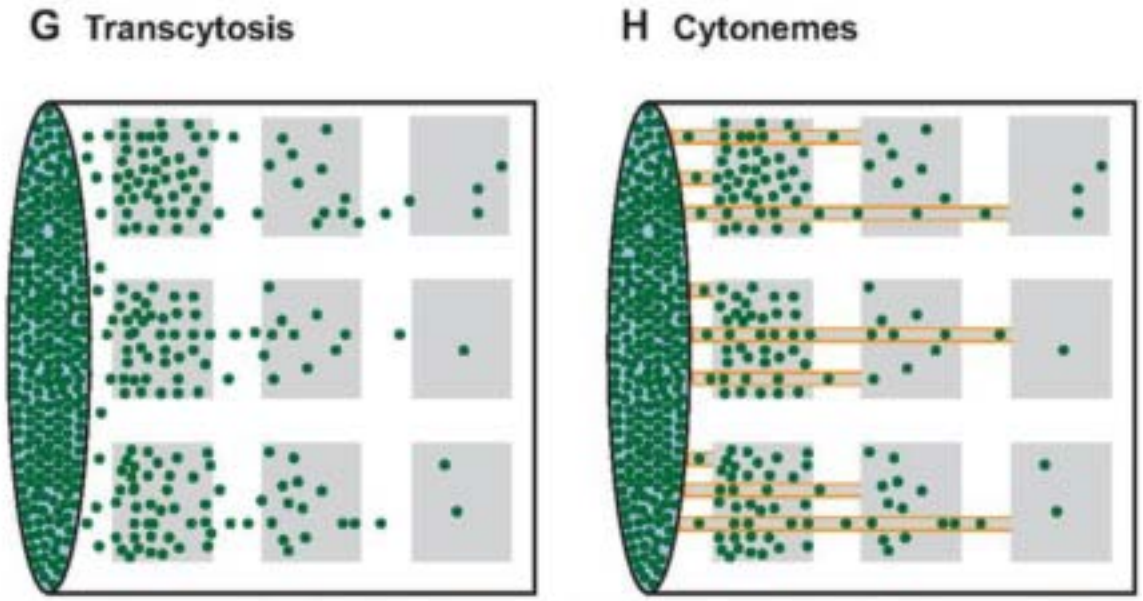
$$c_0 = \frac{j_0}{\sqrt{Dk}} \qquad \lambda = \sqrt{\frac{D}{k}}$$

Mechanism of spread



Müller P et al. Development 2013;140:1621-1638

Mechanism of spread

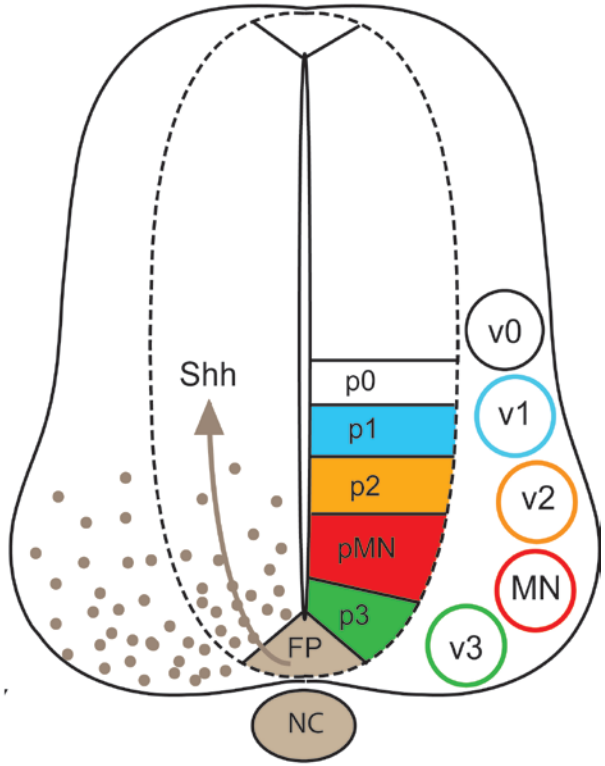


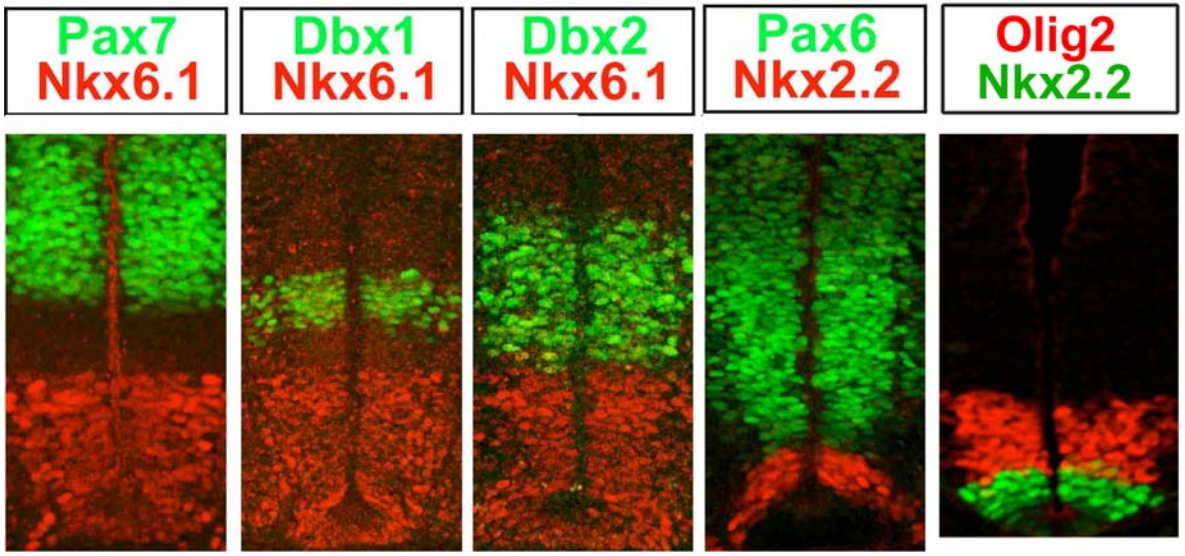
Müller P et al. Development 2013;140:1621-1638

Morphogens:

- Identification – what and where
- Formation - intercellular transmission
- Perception - signal transduction
- Interpretation - convert to discrete responses

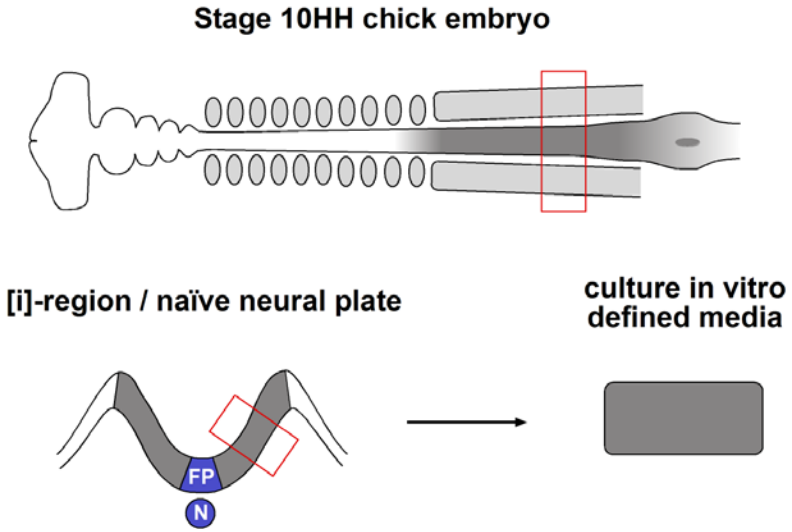
Transcriptional code identifies progenitor domains

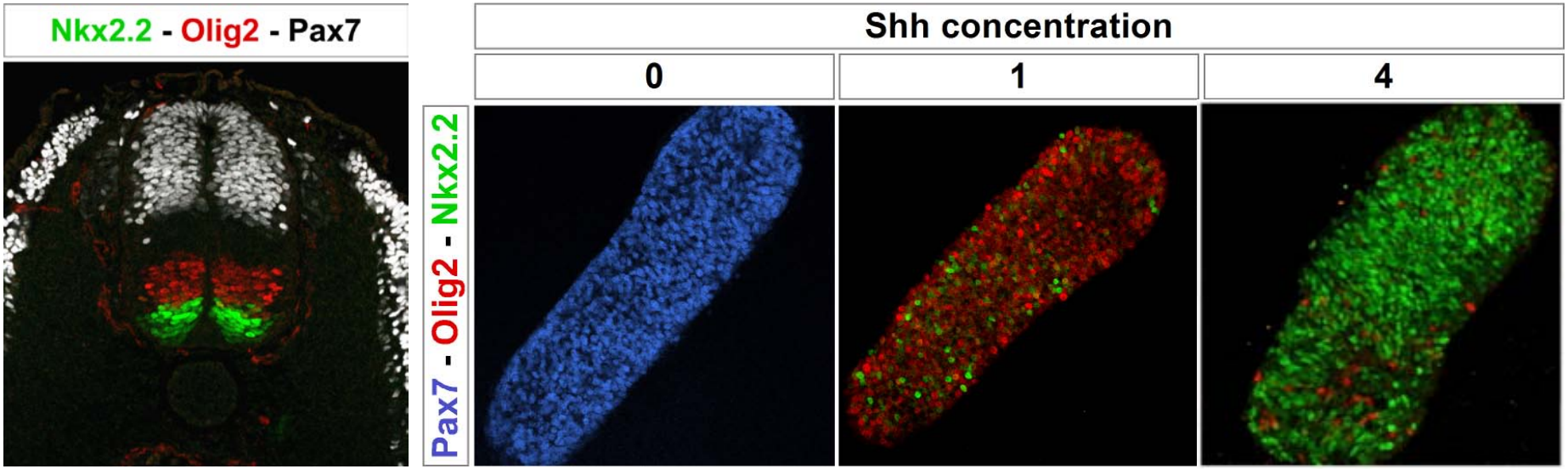




Dessaud, E., McMahon, A. P. & Briscoe, J. Development 135, 2489–2503 (2008).

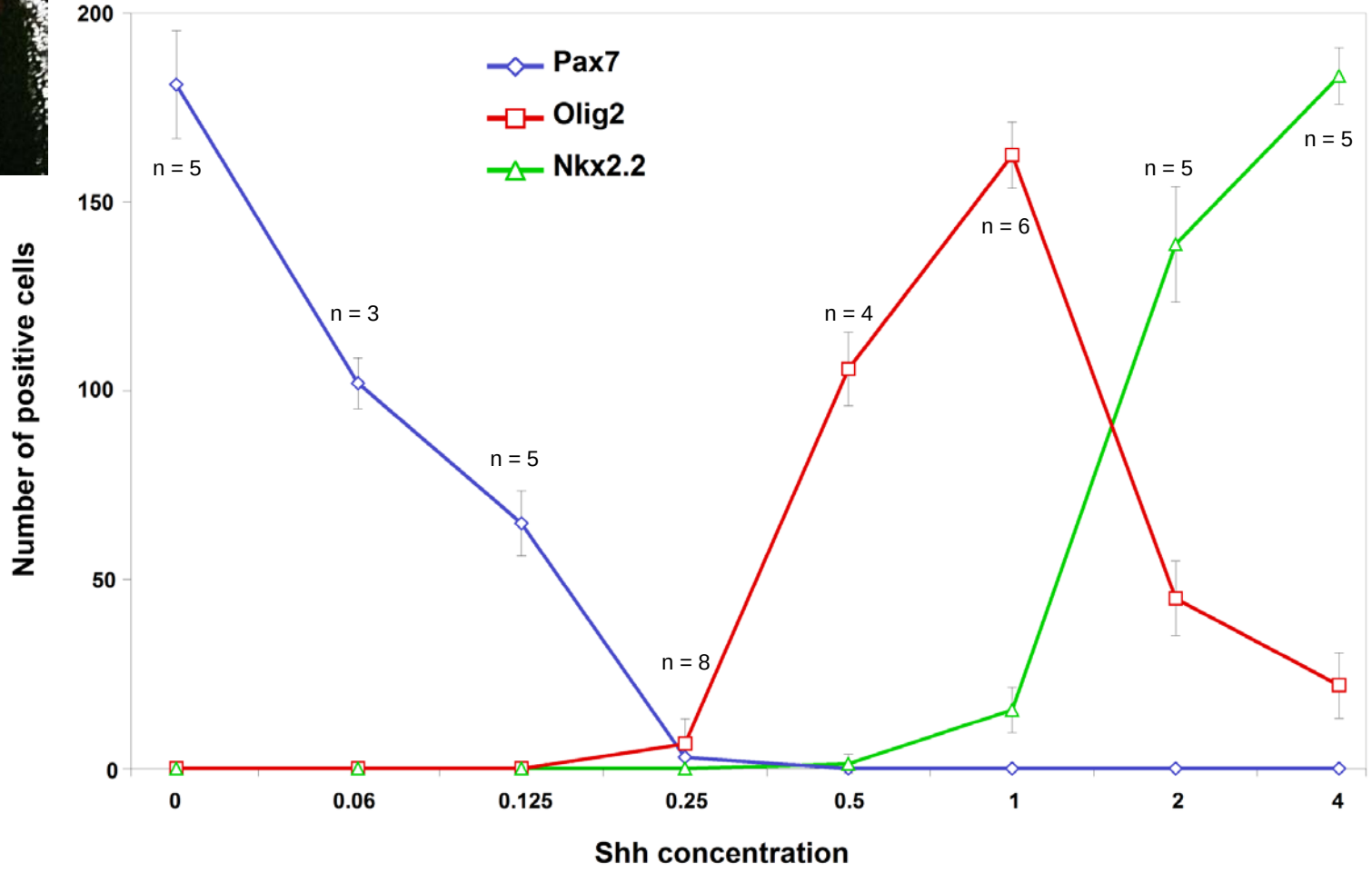
Ex vivo model to analyse of graded Shh response





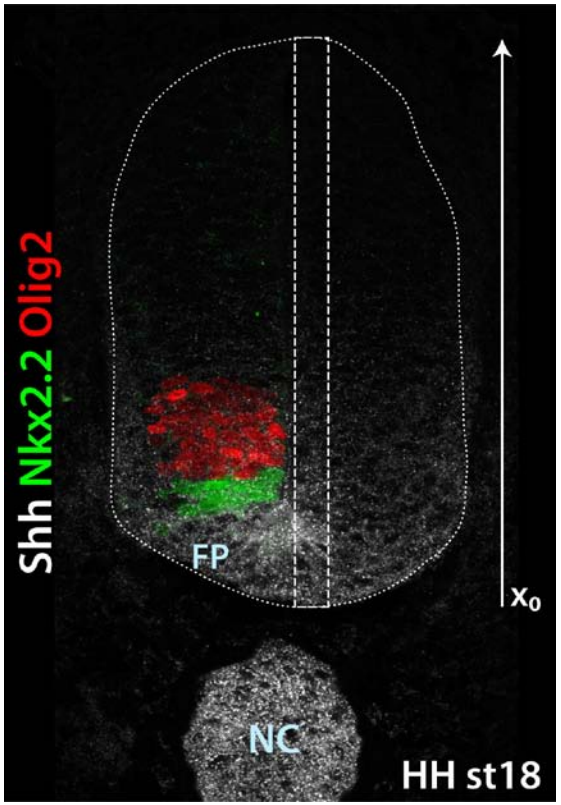
Eric Dessaud

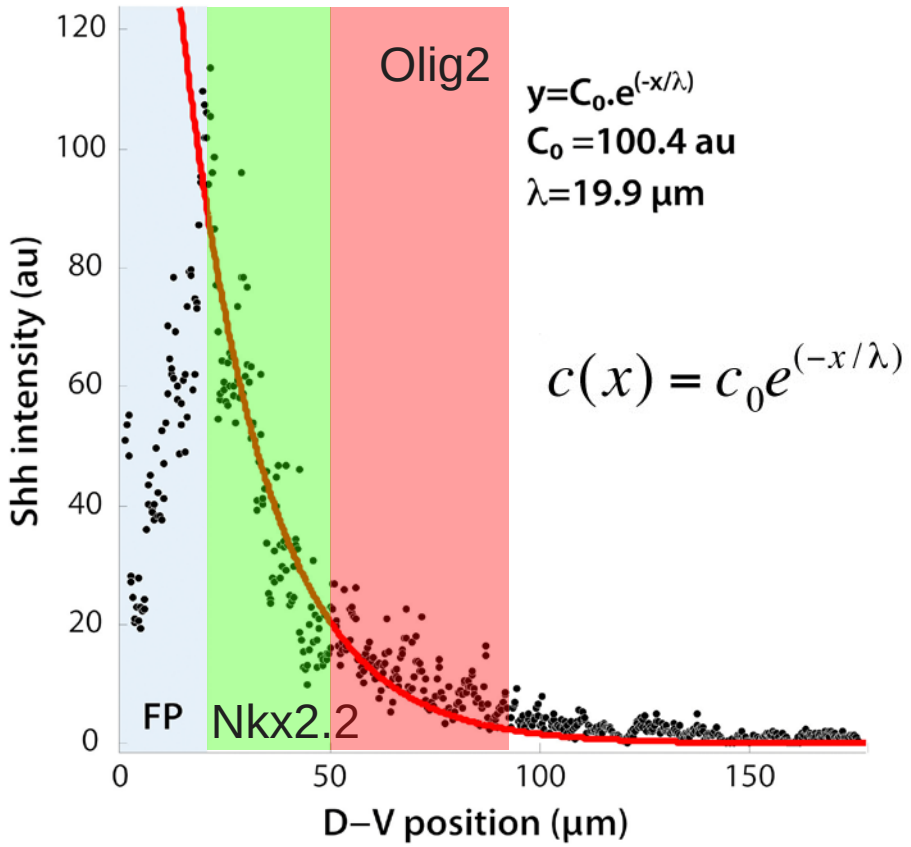
Shh controls progenitor cell fates in a concentration-dependent manner



Dessaud, E. et al. Nature 450, 717–720 (2007).

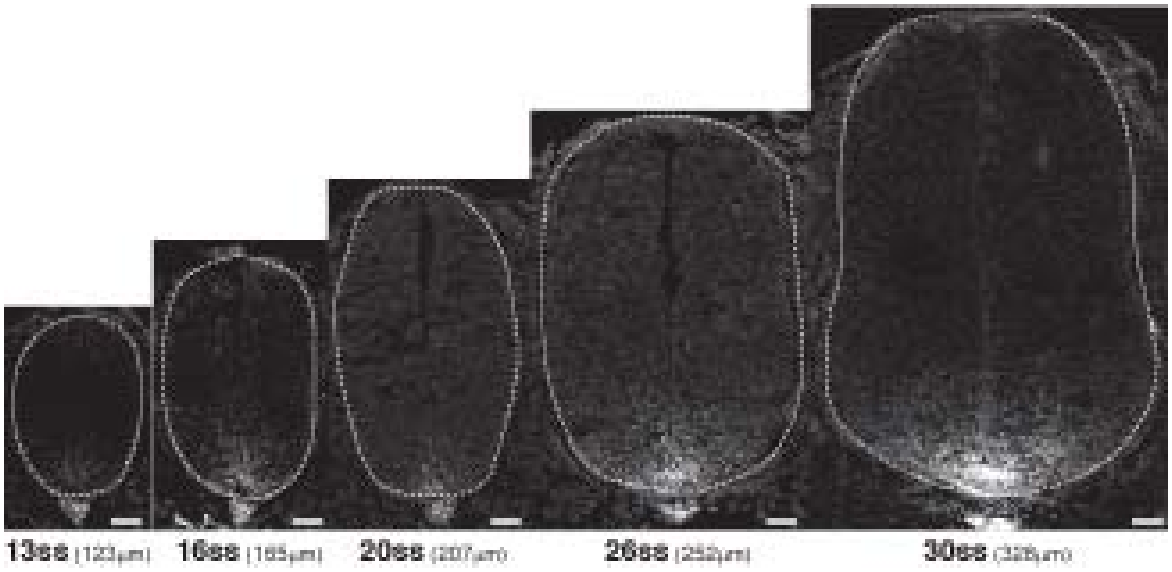
[Shh] in vivo is graded

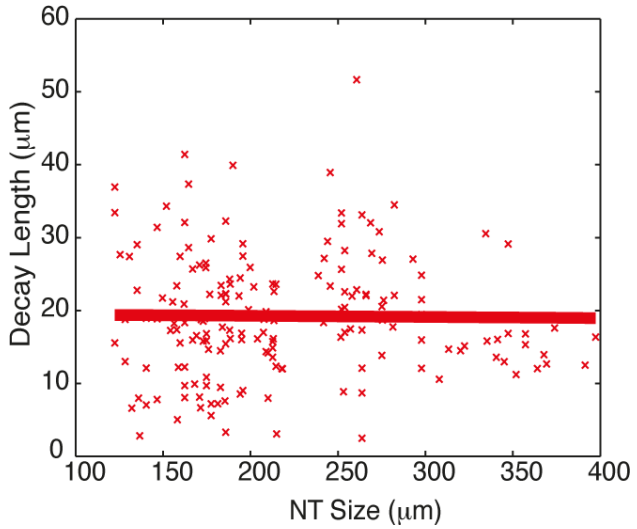


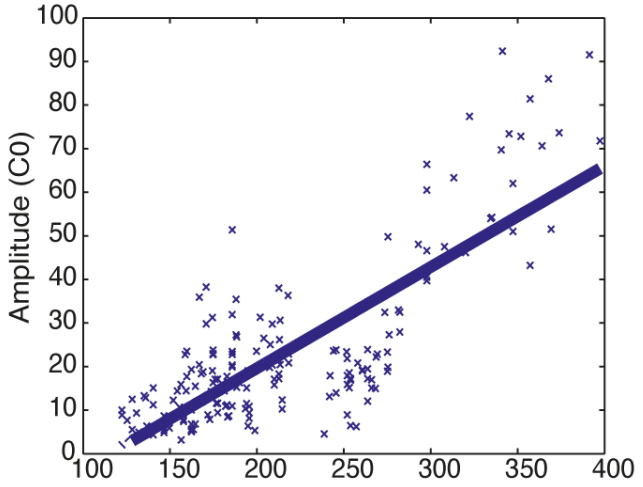


Cohen, M. et al. Nat. Commun. 6, 6709 (2015).

[Shh] is dynamic

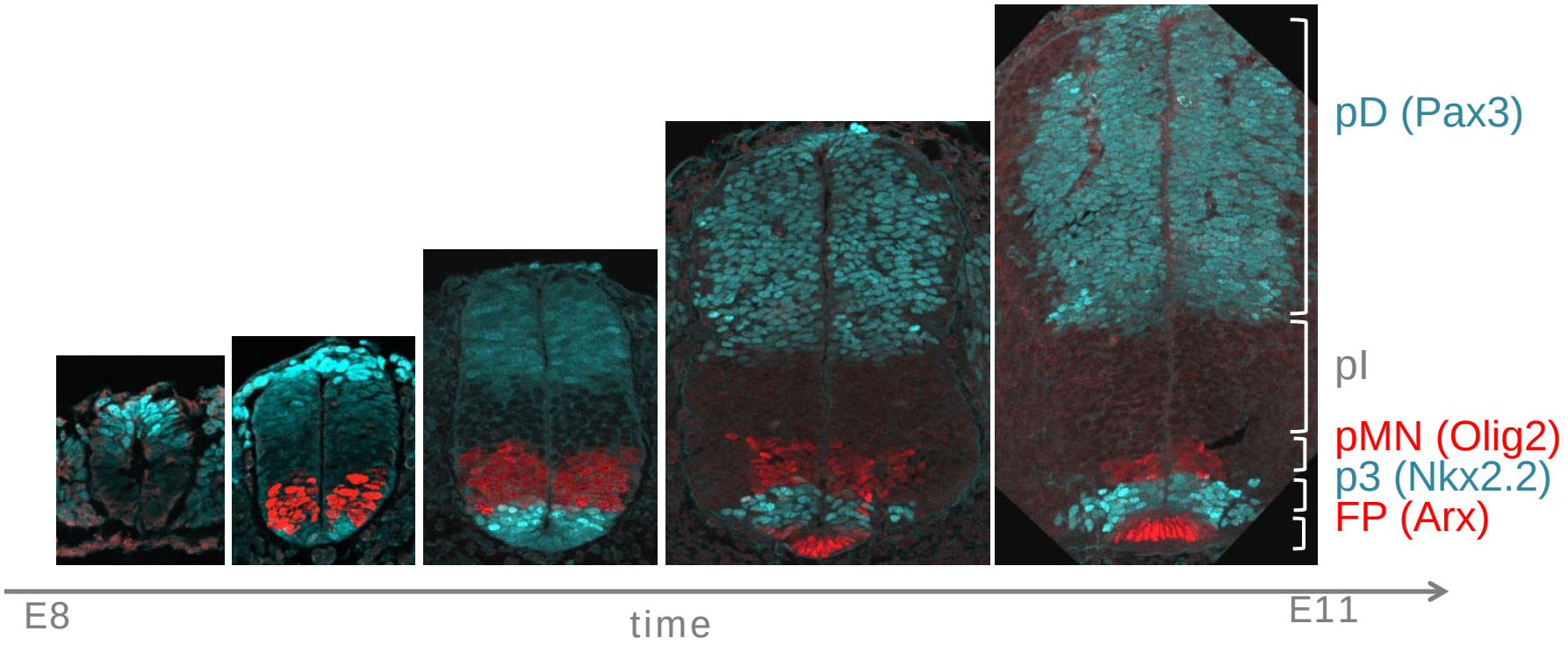






Cohen, M. et al. Nat. Commun. 6, 6709 (2015).

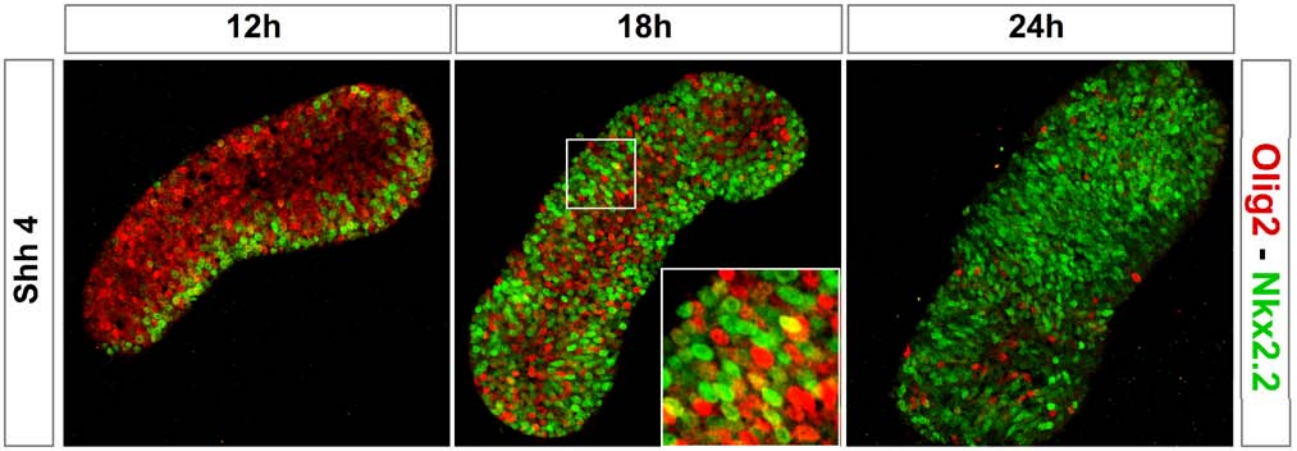
Patterning is progressive as neural tube grows

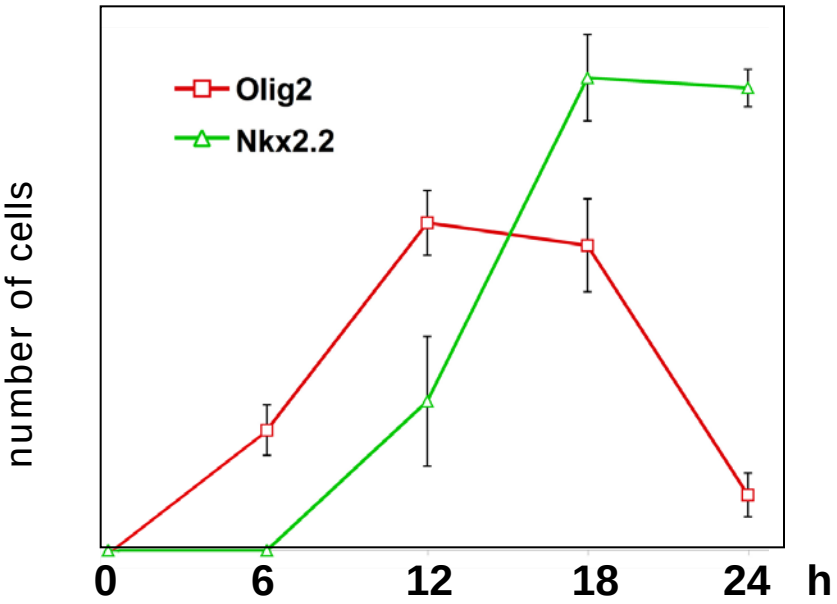


Kicheva, A. et al.. Science (80-.). 345, 1254927 (2014).

Ani Kicheva

Duration of signalling influences pattern

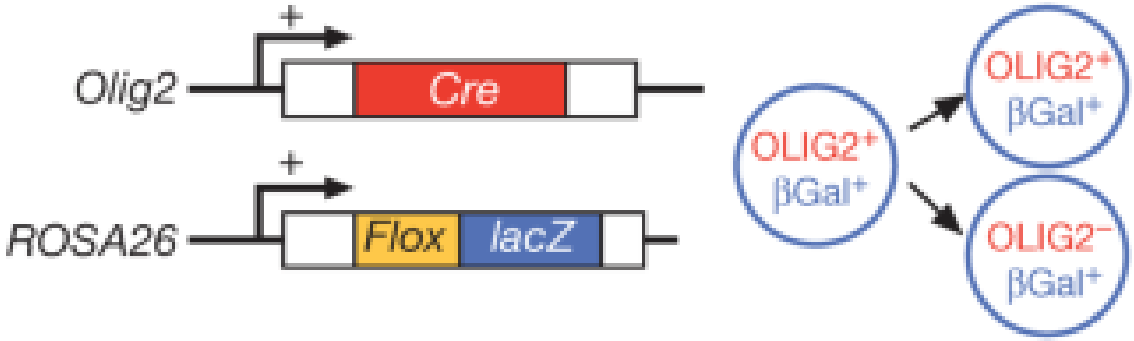


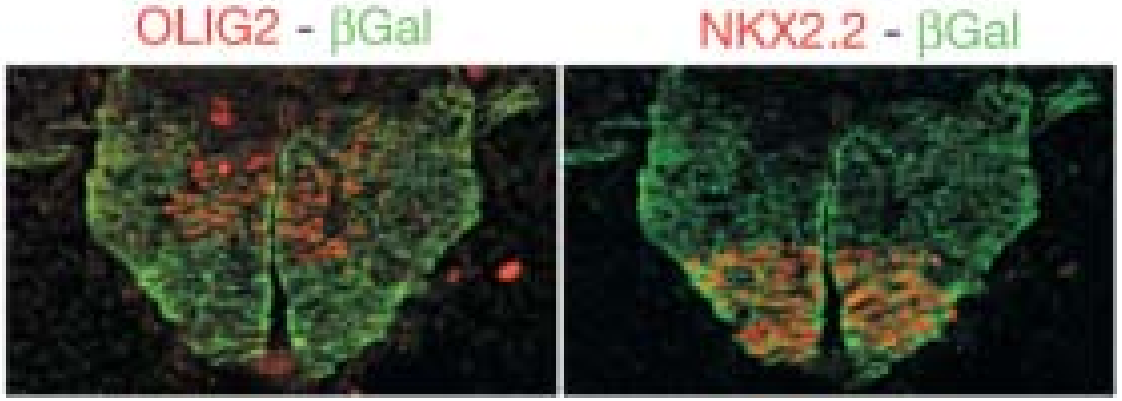


Dessaud, E. *et al*. *Nature* **450,** 717–720 (2007).

Eric Dessaud

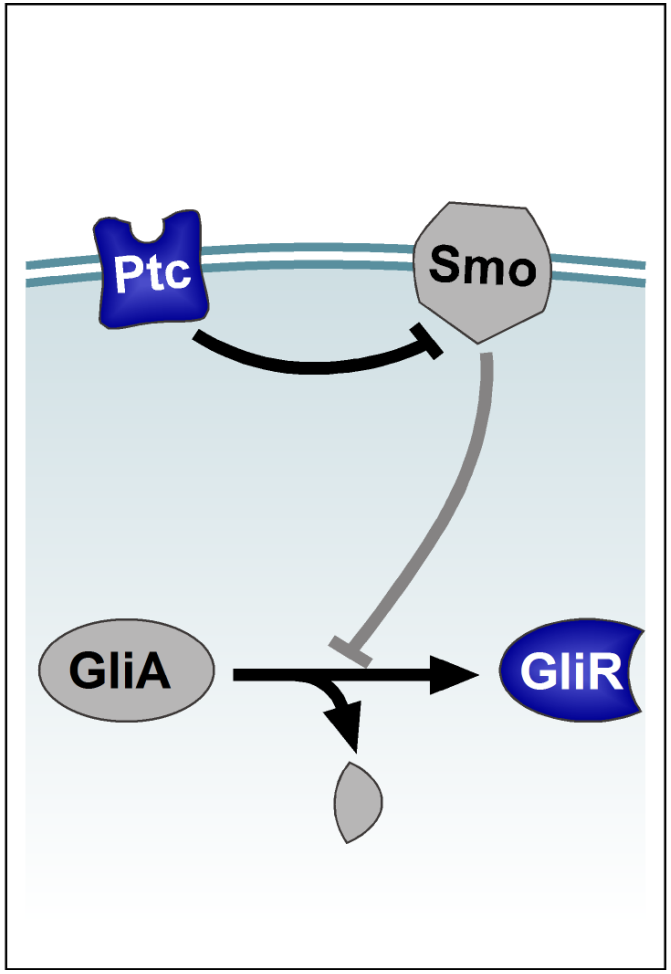
Sequential induction in vivo

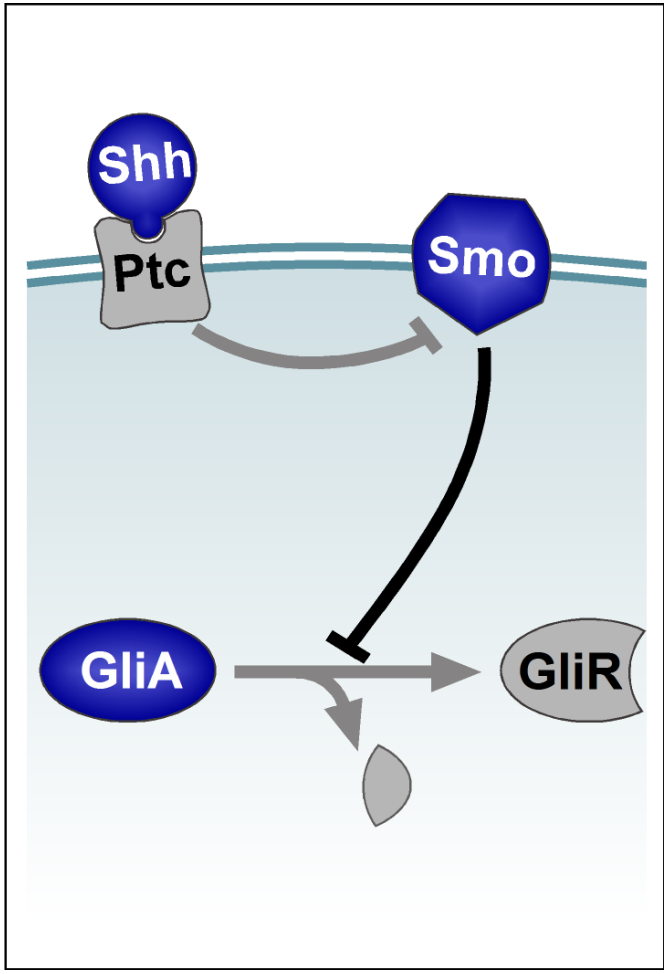




Eric Dessaud

Intracellular signaling

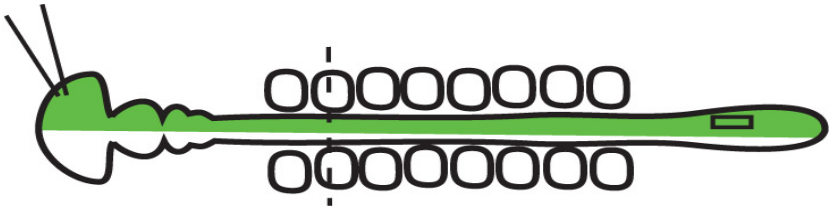


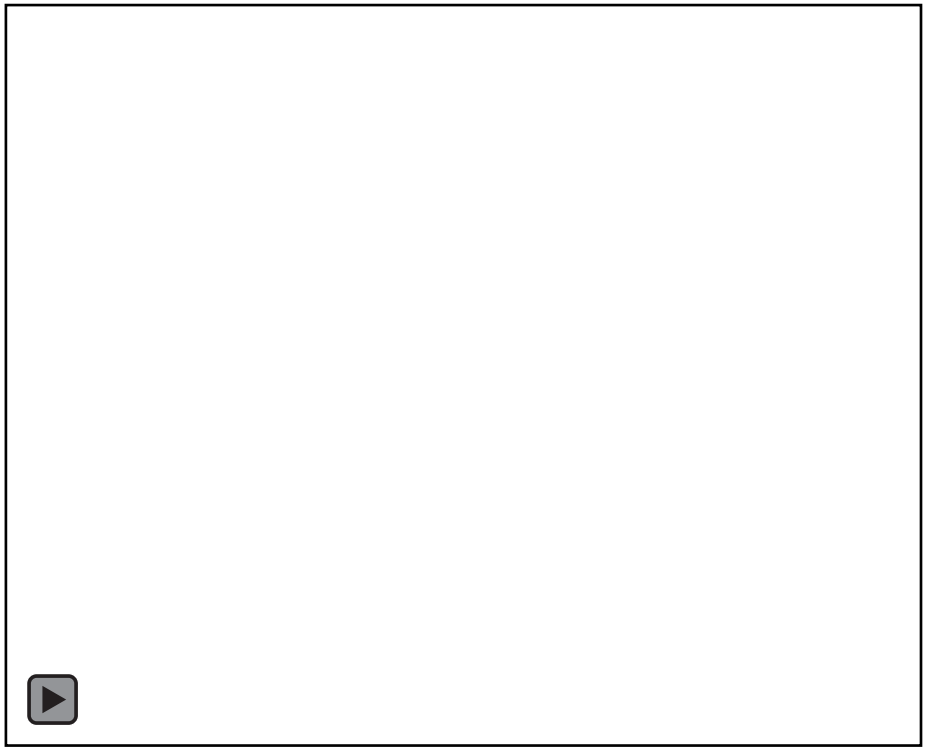


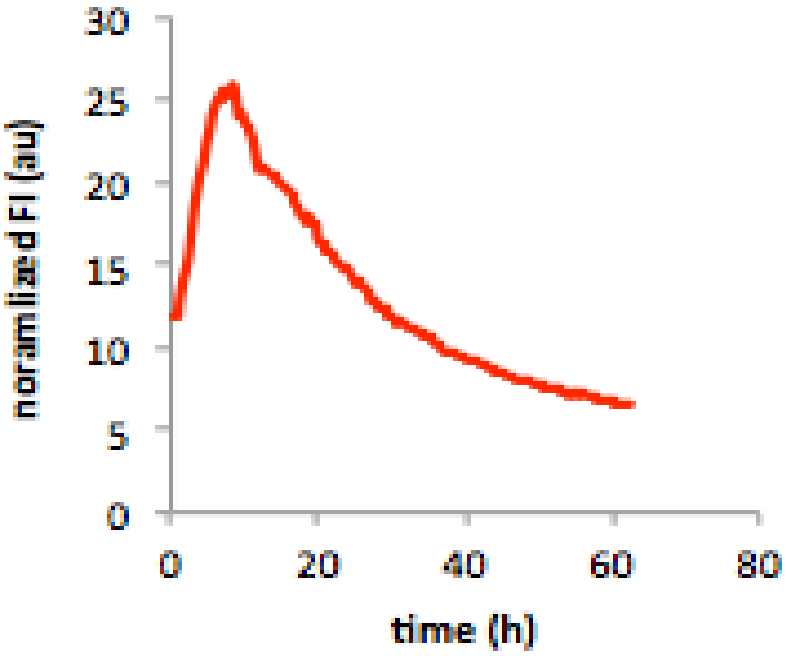
Gli activity is dynamic

GBS-nlsVenus

Control FP

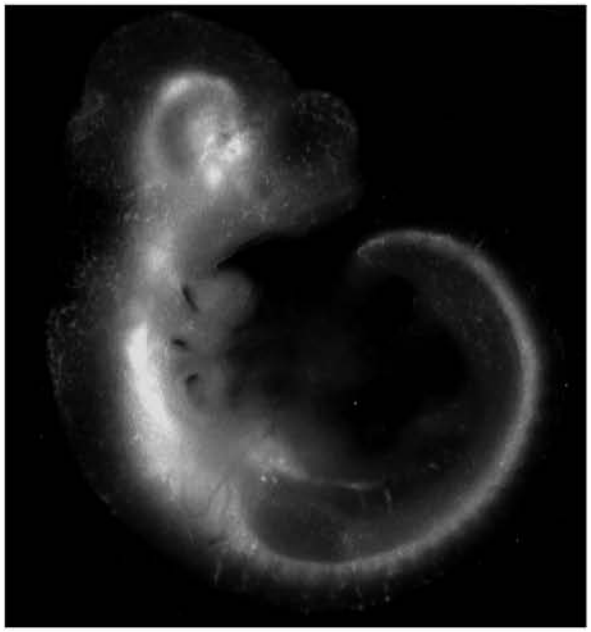


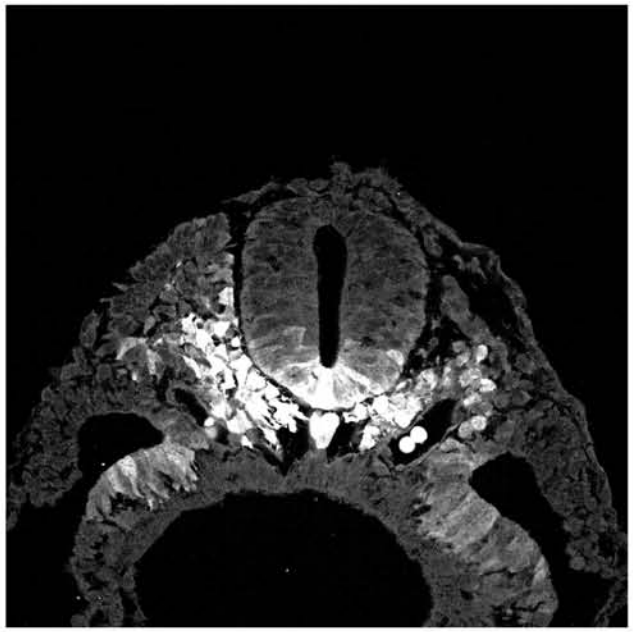


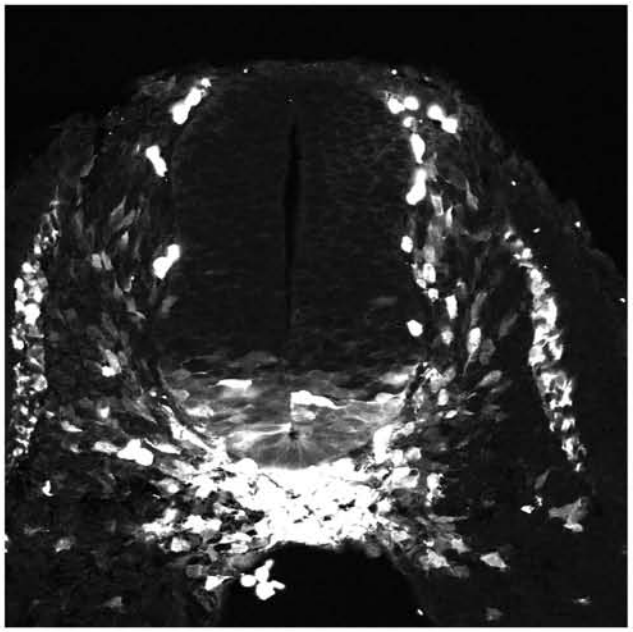


Ani Kicheva

Gli activity is dynamic



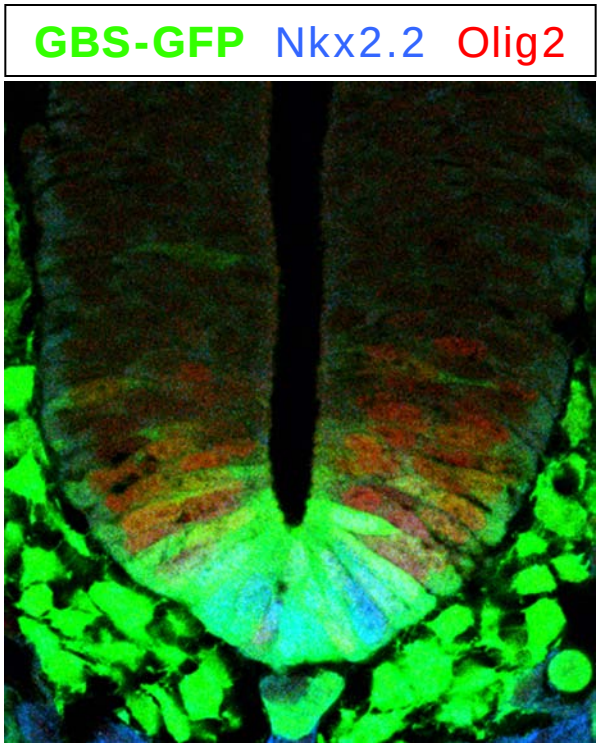


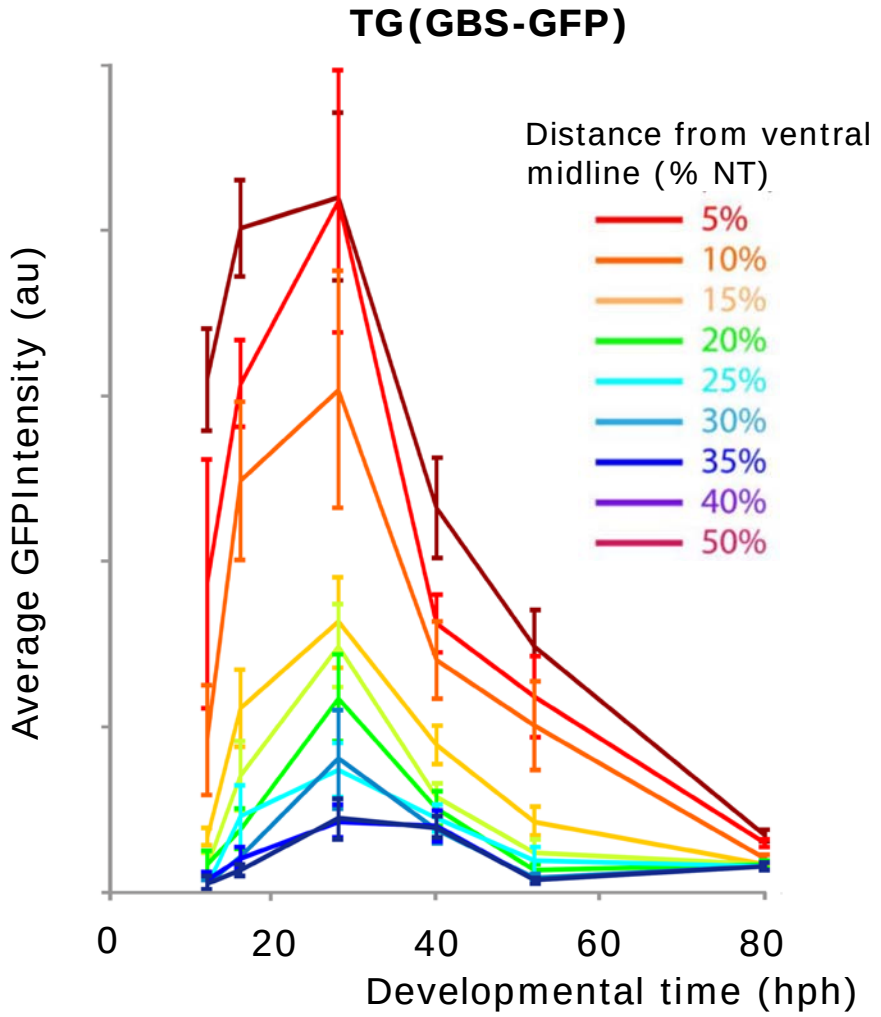


Balaskas, N. *et al. Cell* **148,** 273–284 (2012).

Vanessa Ribes

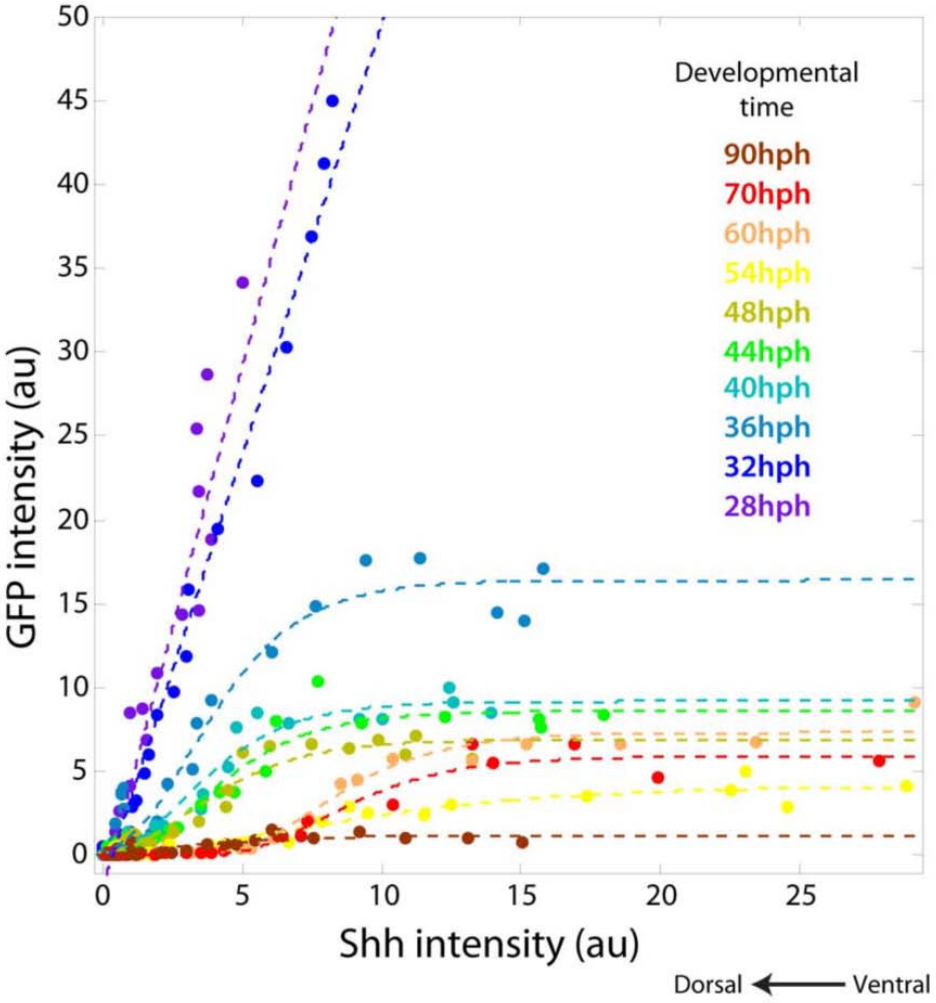
Gli activity is dynamic





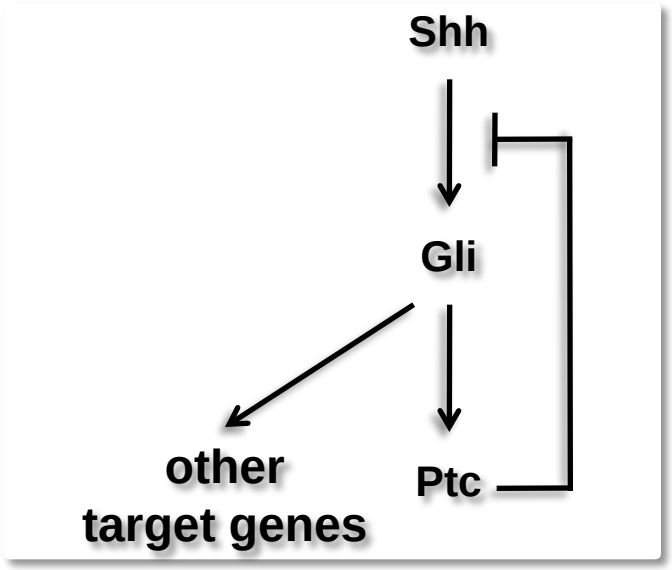
Vanessa Ribes/Ana Ribeiro

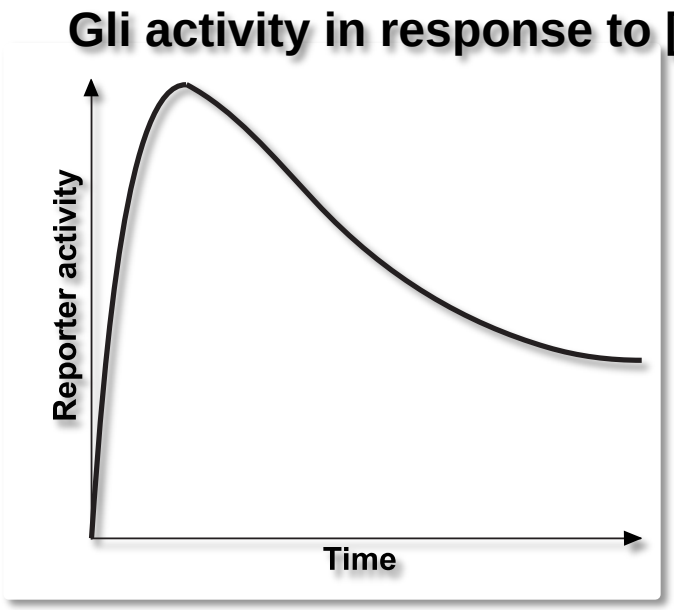
Adaptation in vivo



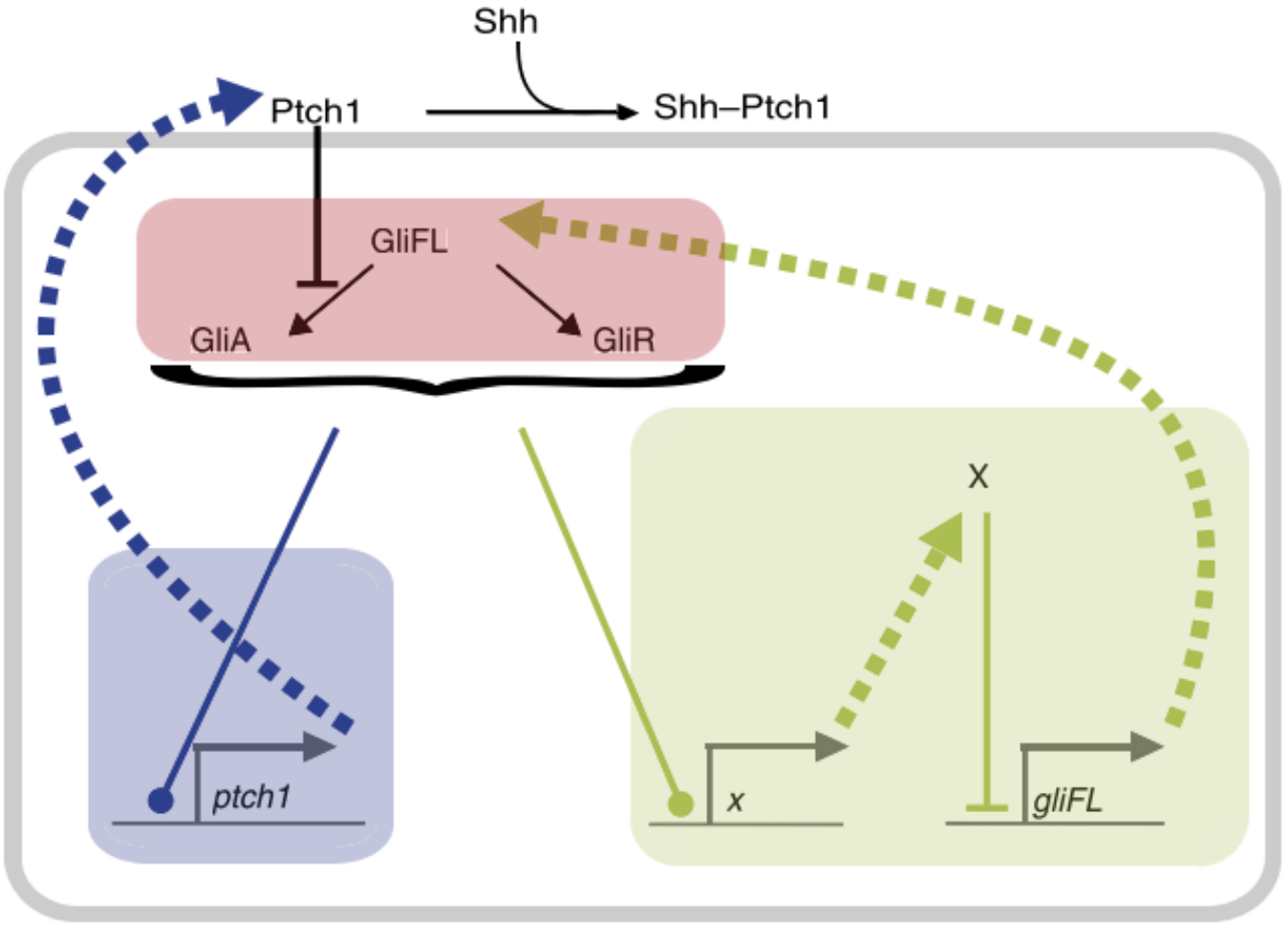
Ana Ribeiro

Adaptation shapes response



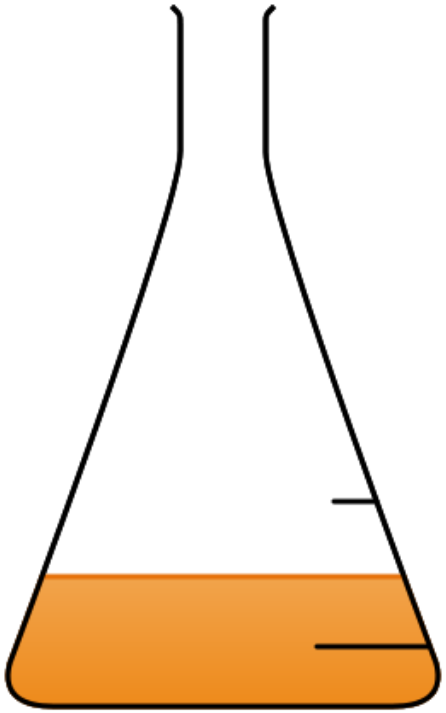


Adaptation shapes response

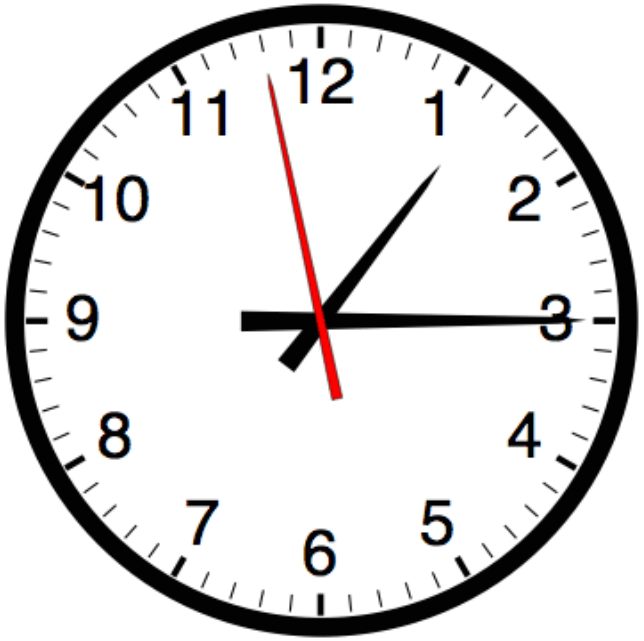


Cohen, M. et al. Nat. Commun. 6, 6709 (2015).

Concentration converted to time

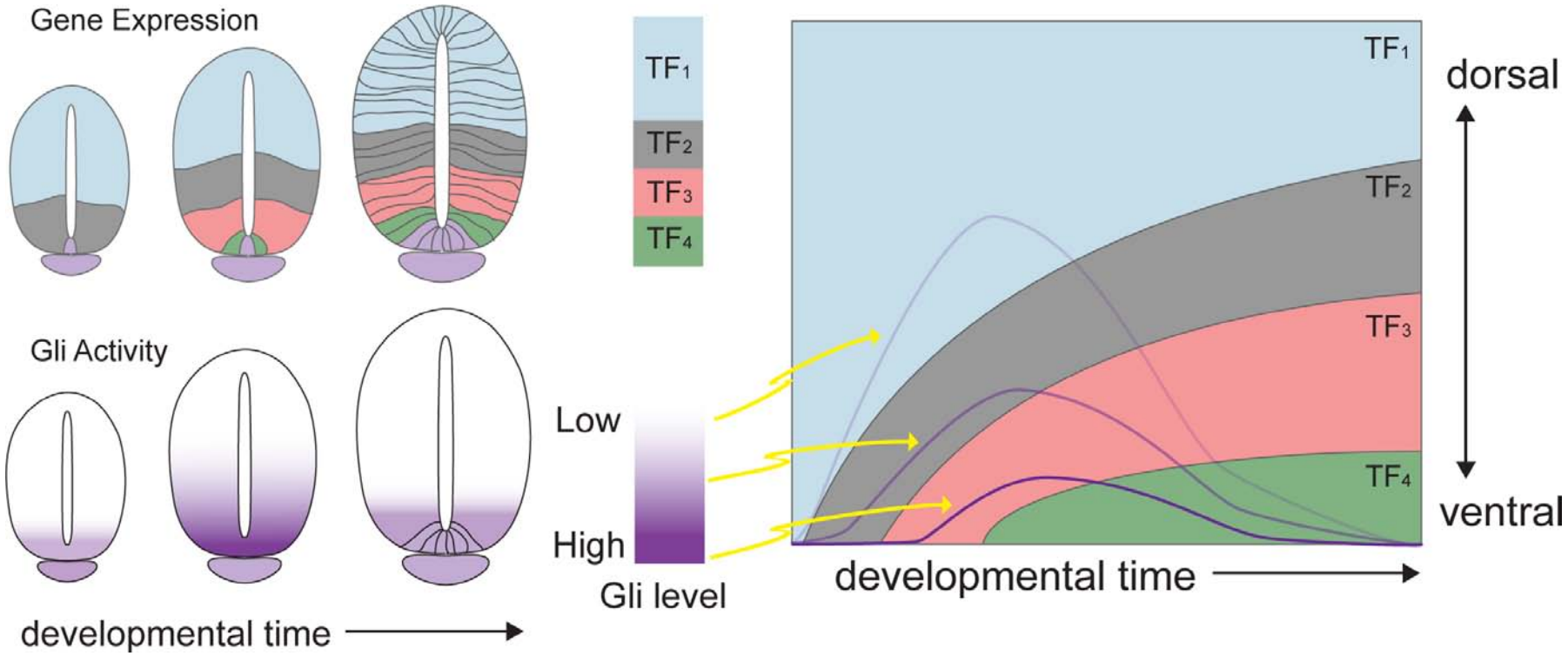


[Shh]



Gli Activity

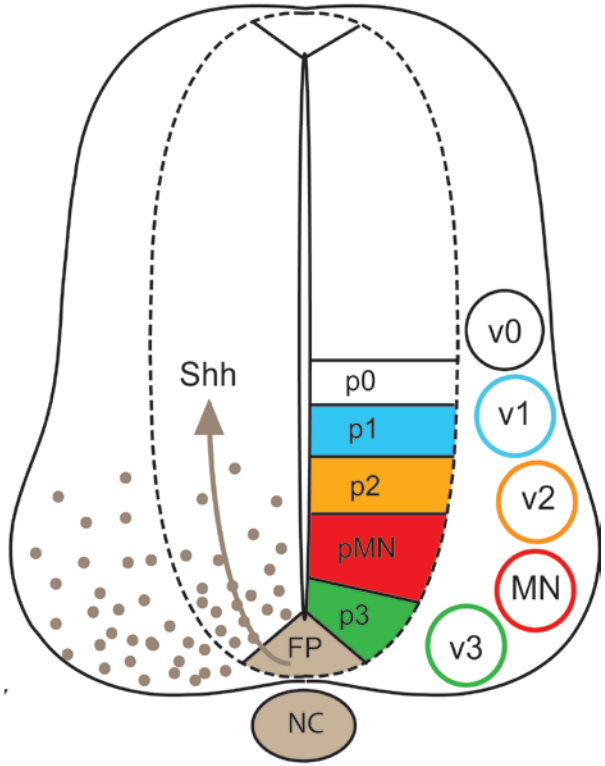
Dynamics of signal and pattern

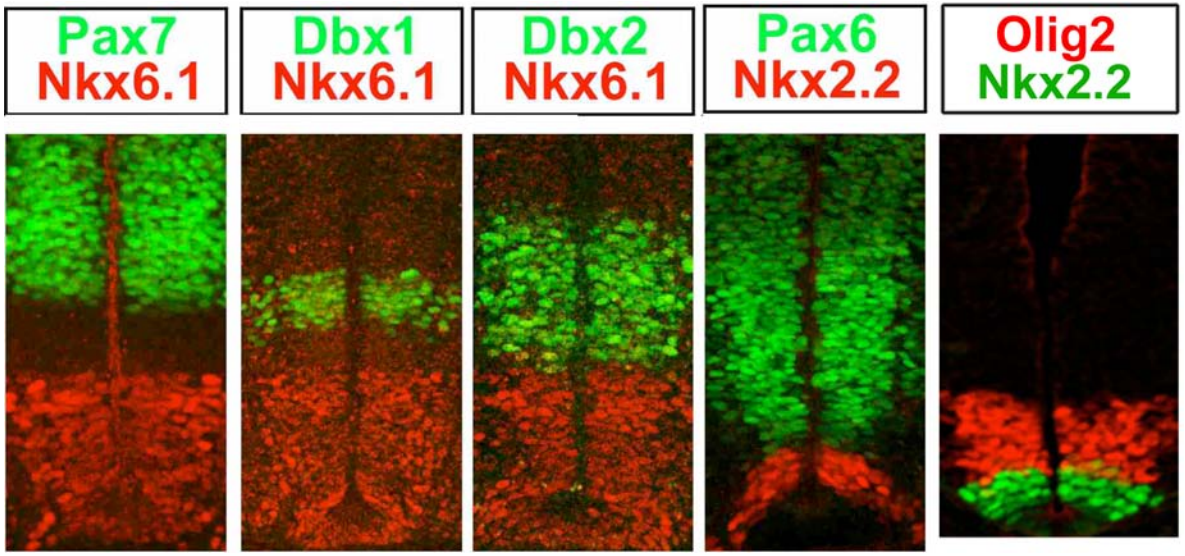


Shh morphogen interpretation

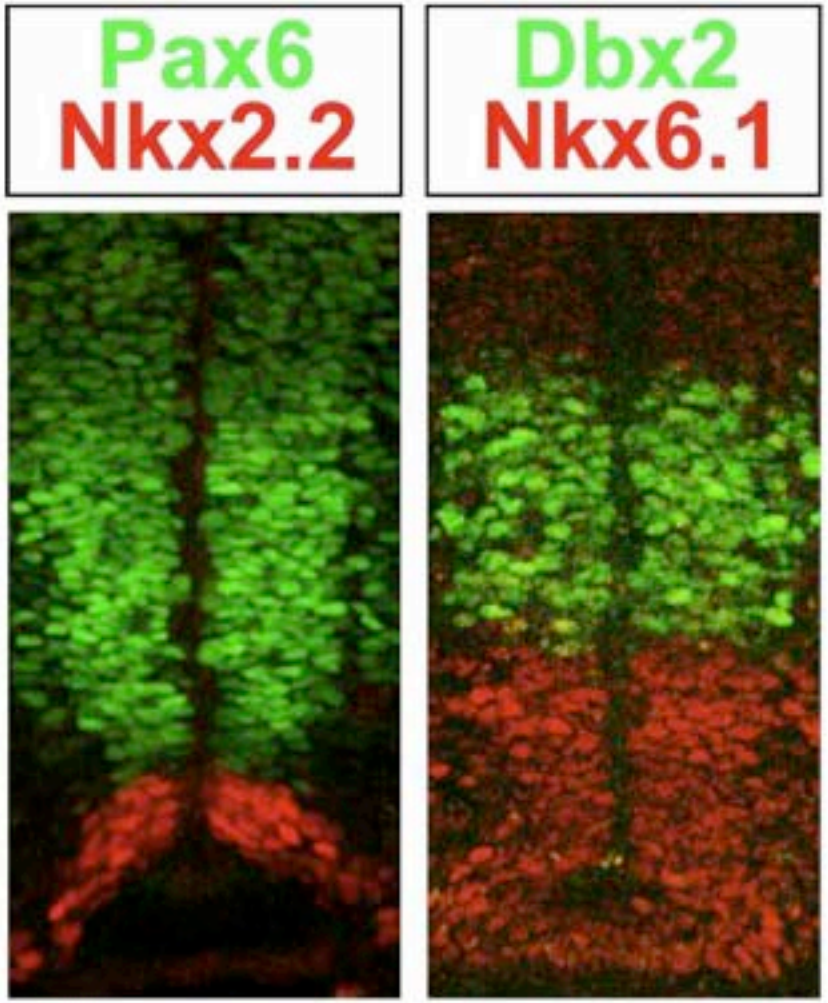
- Complicated relationship between [Shh] and Gli activity
- Both concentration and duration affects response
- Gli activity adapts to signal over time
- Gene expression boundaries are sharp and accurate

Shh directs a transcriptional network





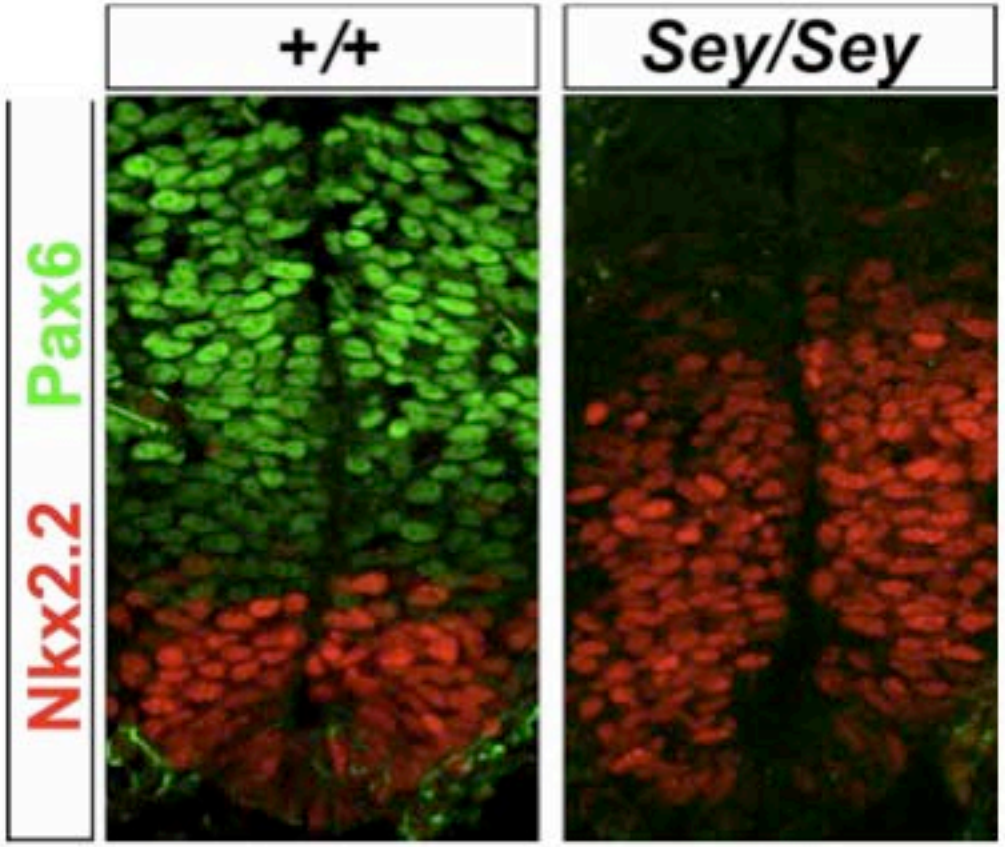
Cross repression between specific pairs of TFs required for gradient interpretation



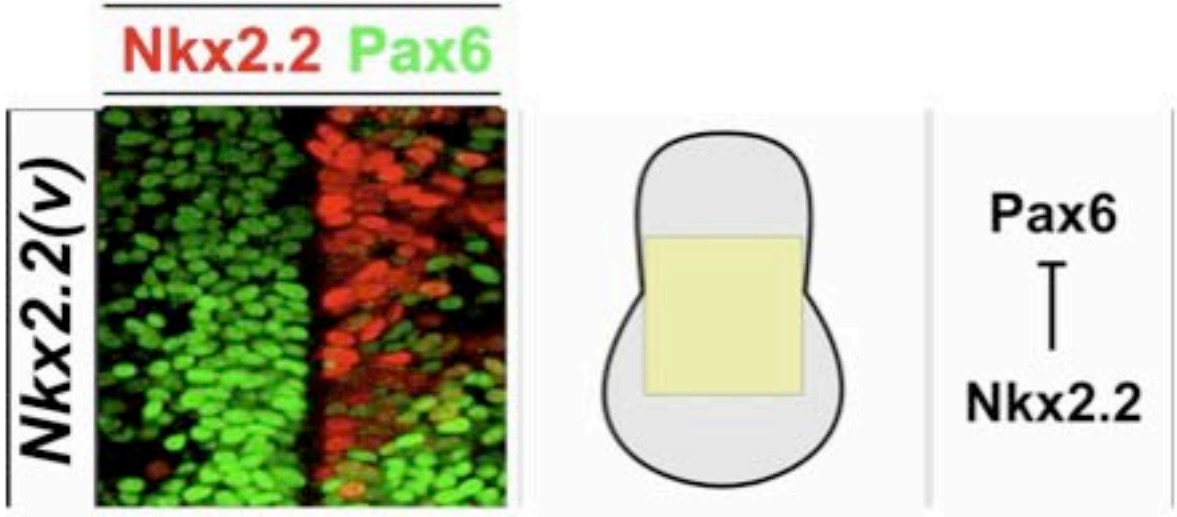
Pax6 and Nkx2.2 cross repress each other and establish a boundary between the progenitor giving rise to the MN and the V3 inter neurons

Pax6 represses Nkx2.2

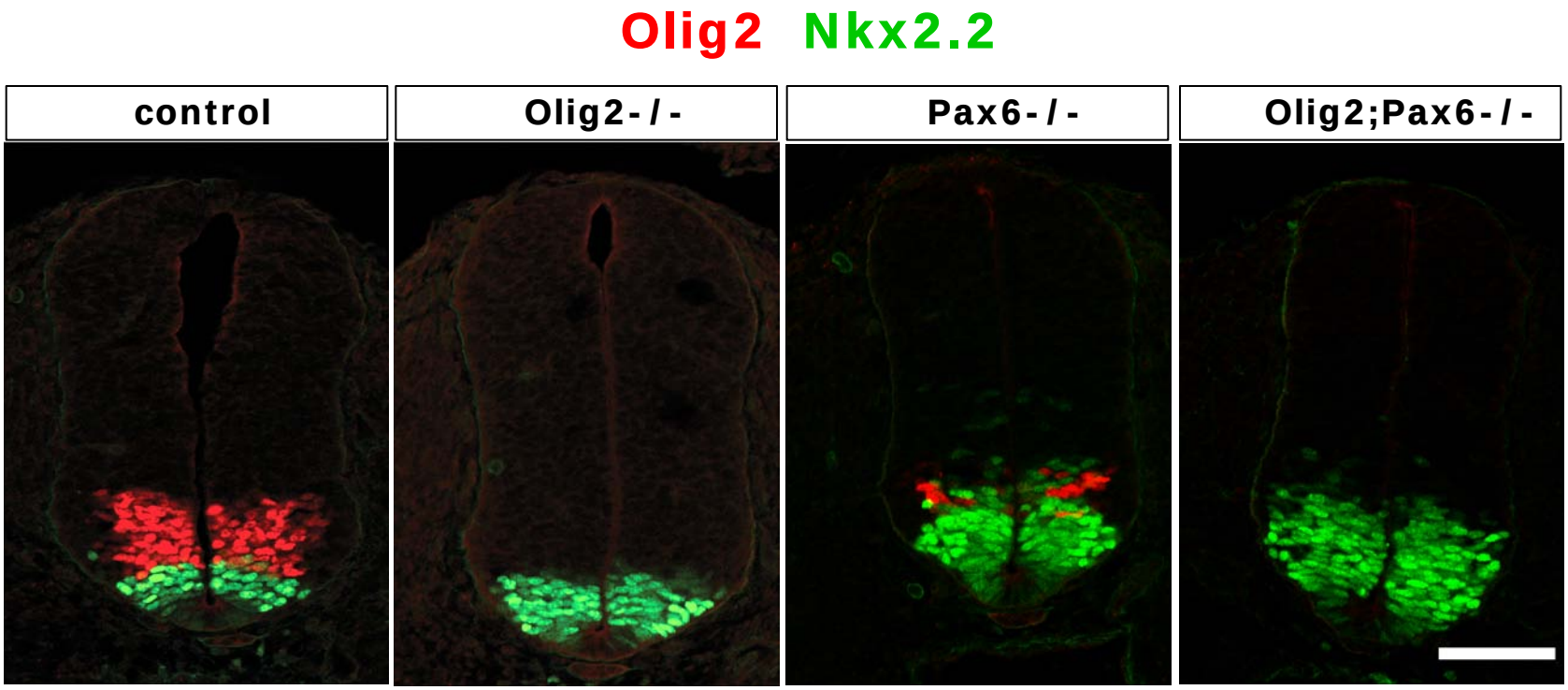
Embryos lacking Pax6



Nkx2.2 represses Pax6



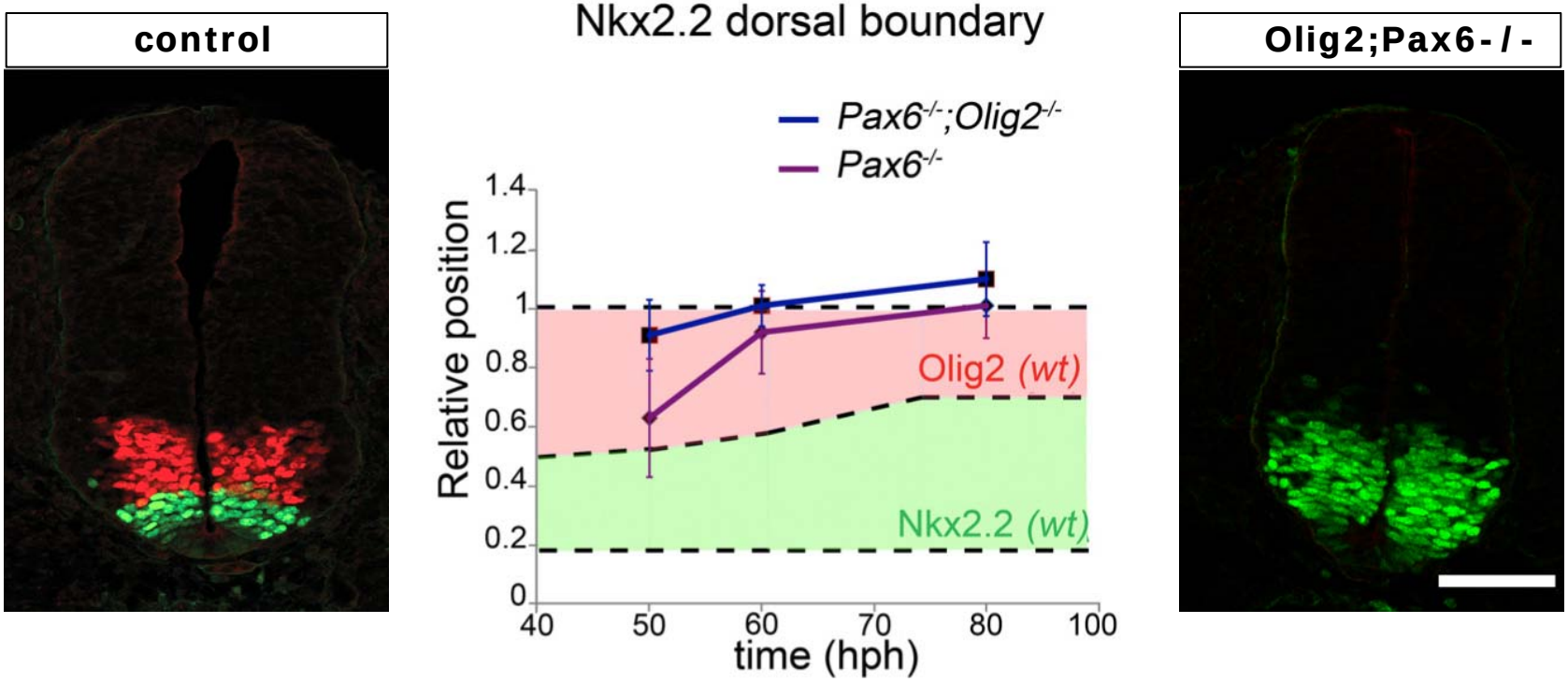
Pax6 and Olig2 repress Nkx2.2



Balaskas, N. *et al. Cell* **148,** 273–284 (2012).

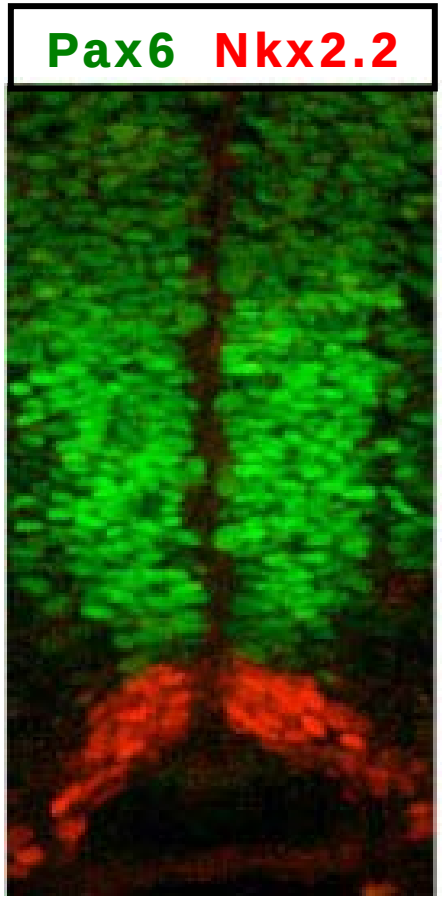
Nikos Balaskas

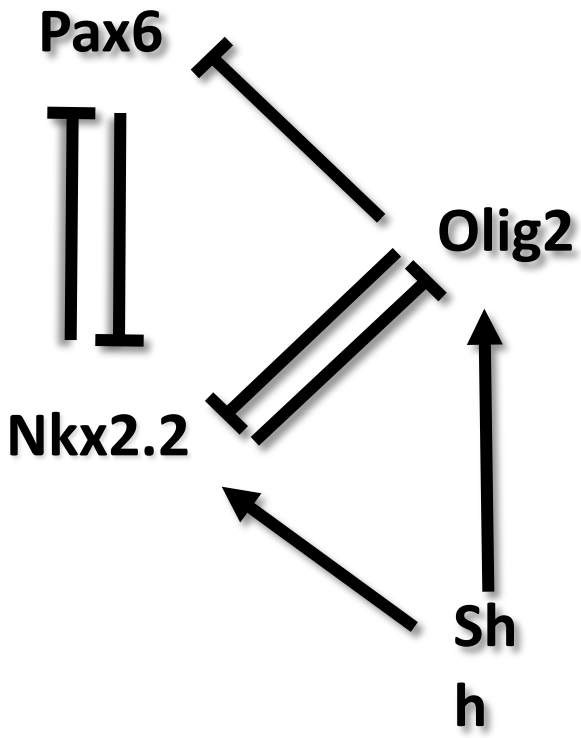
Pax6 and Olig2 repress Nkx2.2

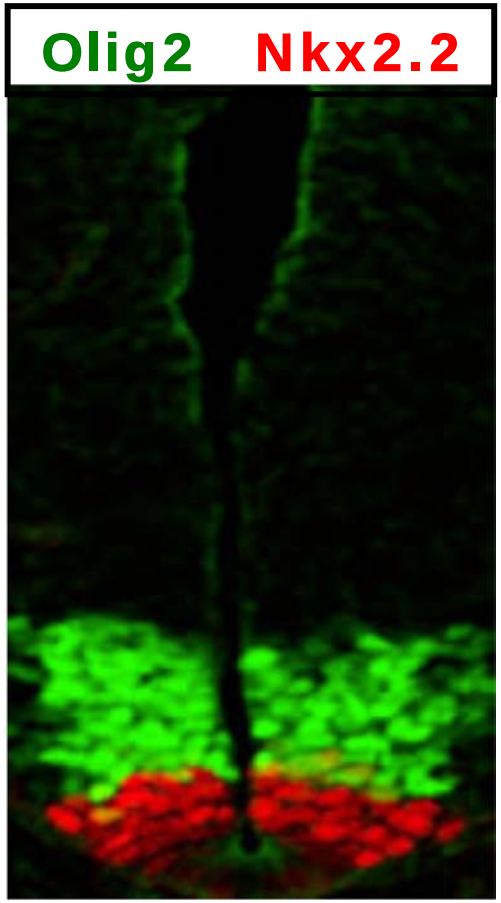


Nikos Balaskas

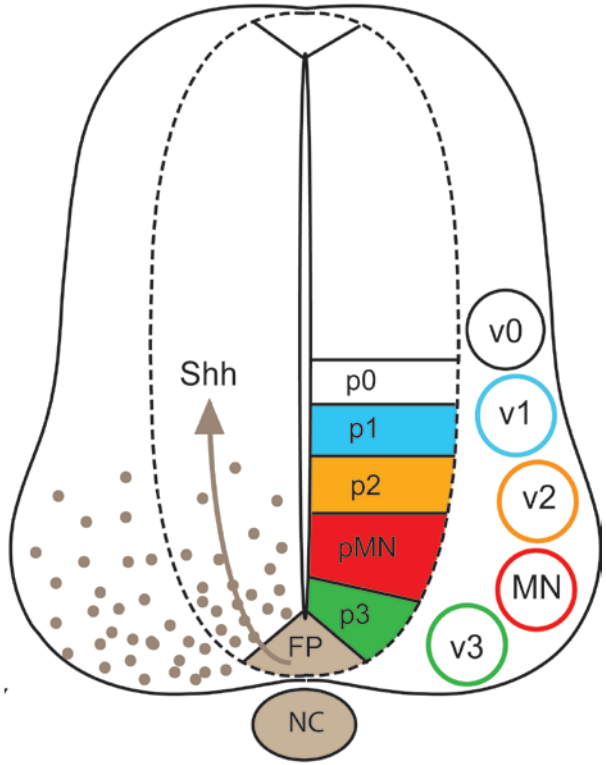
A transcriptional circuit for morphogen interpretation

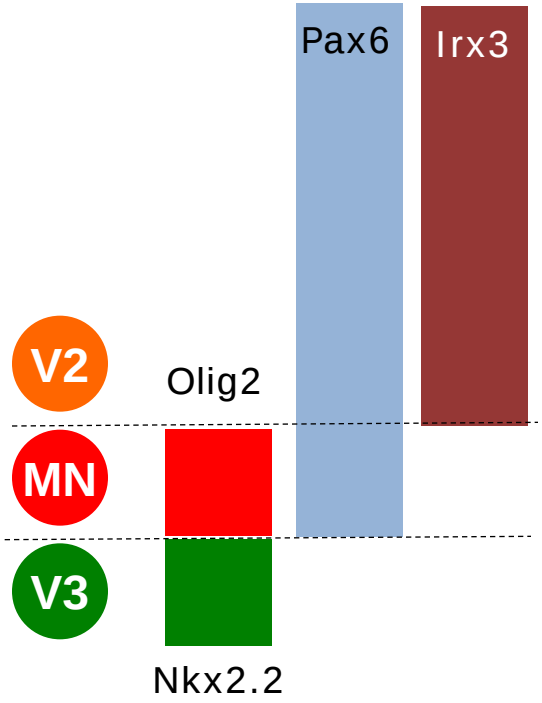


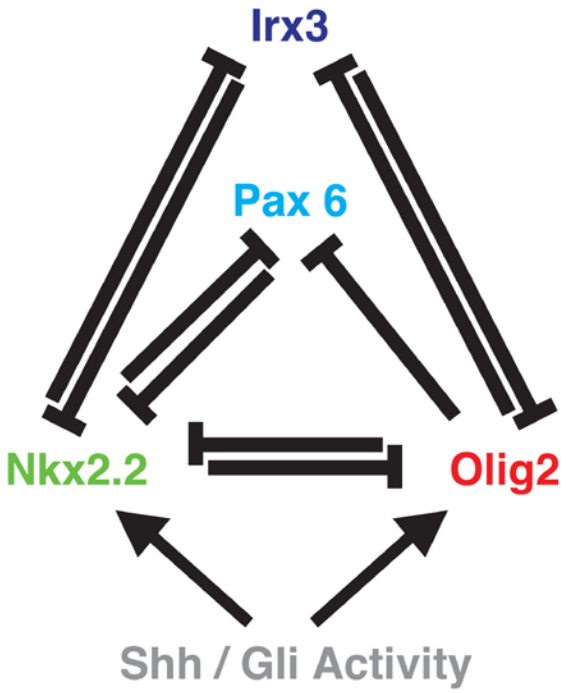




A transcriptional circuit for morphogen interpretation

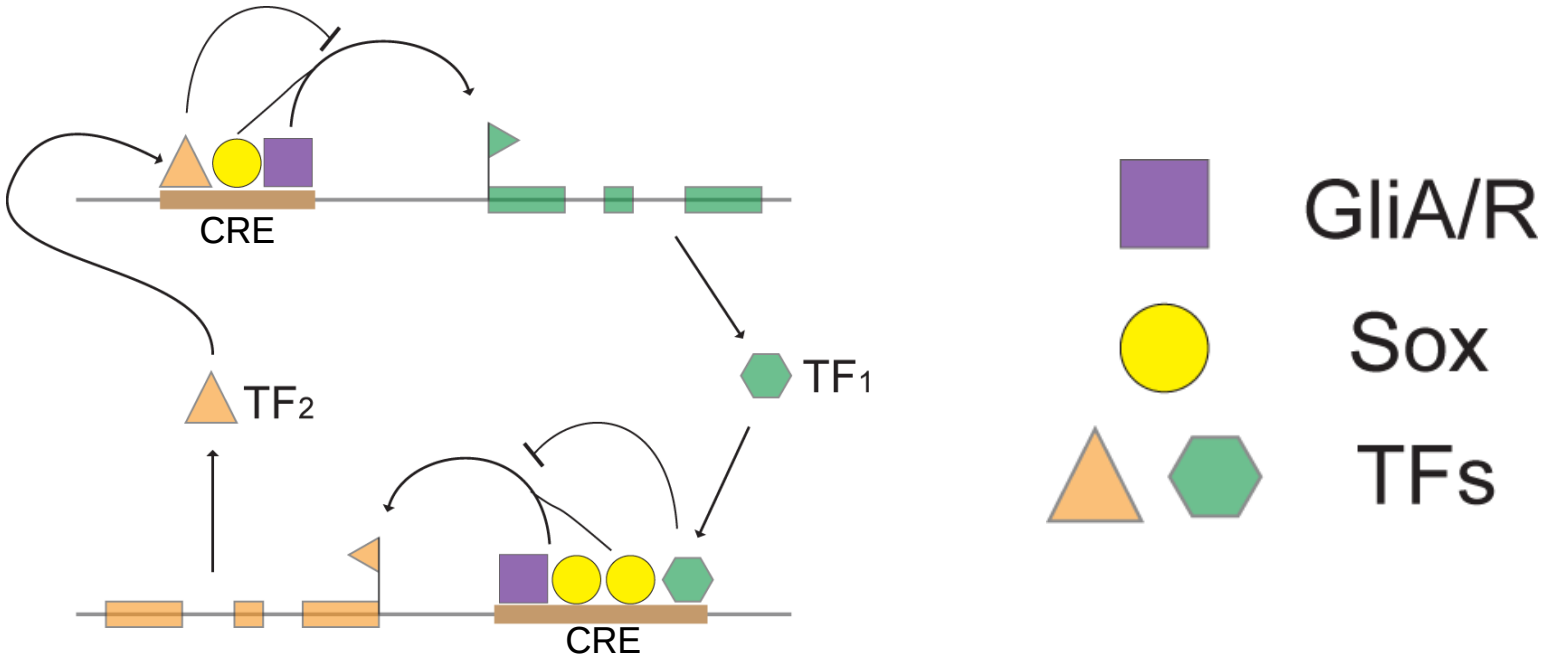






Michael Cohen

Three Components to Gene Regulation

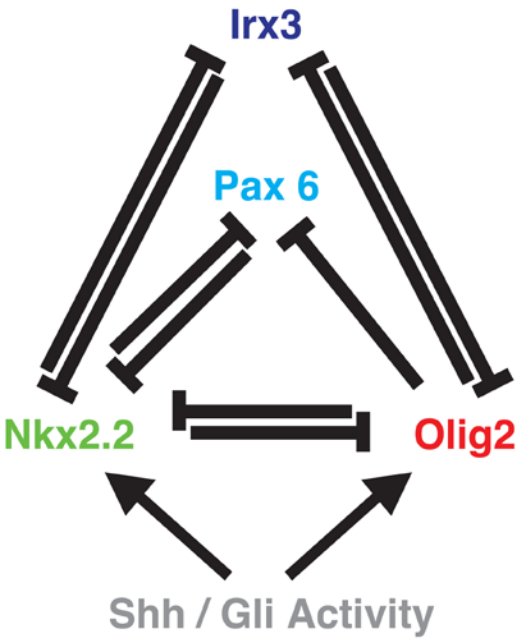


Oosterveen, T., Kurdija, S., Alekseenko, Z., Uhde, C.W., Bergsland, M., Sandberg, M., Andersson, E., Dias, J.M., Muhr, J., and Ericson, J. (2012).
Mechanistic Differences in the Transcriptional Interpretation of Local and Long-Range Shh Morphogen Signaling.
Dev. Cell *23*, 1006–1019.

Peterson, K.A., Nishi, Y., Ma, W., Vedenko, A., Shokri, L., Zhang, X., McFarlane, M., Baizabal, J.M., Junker, J.P., van Oudenaarden, A., et al. (2012).
Neural-specific Sox2 input and differential Gli-binding affinity provide context and positional information in Shh-directed neural patterning.
Genes Dev. *26*, 2802–2816.

Statistical thermodynamic description of gene regulation

$$d\frac{[TF]}{dt} = \alpha\phi_{TF} - \beta[TF]$$



$$\phi_{Pax} = \frac{K_{P\_Pax}[P]}{Z_{Pax}}$$

$$\phi_{Irx} = \frac{K_{P\_Irx}[P]}{Z_{Irx}}$$

$$\phi_O = \frac{K_{P\_O}[P] + c_{AP}K_{P\_O}[P]K_{G\_O}[A]}{Z_O}$$

$$\phi_N = \frac{K_{P\_N}[P] + c_{AP}K_{P\_N}[P]K_{G\_N}[A]}{Z_N}$$

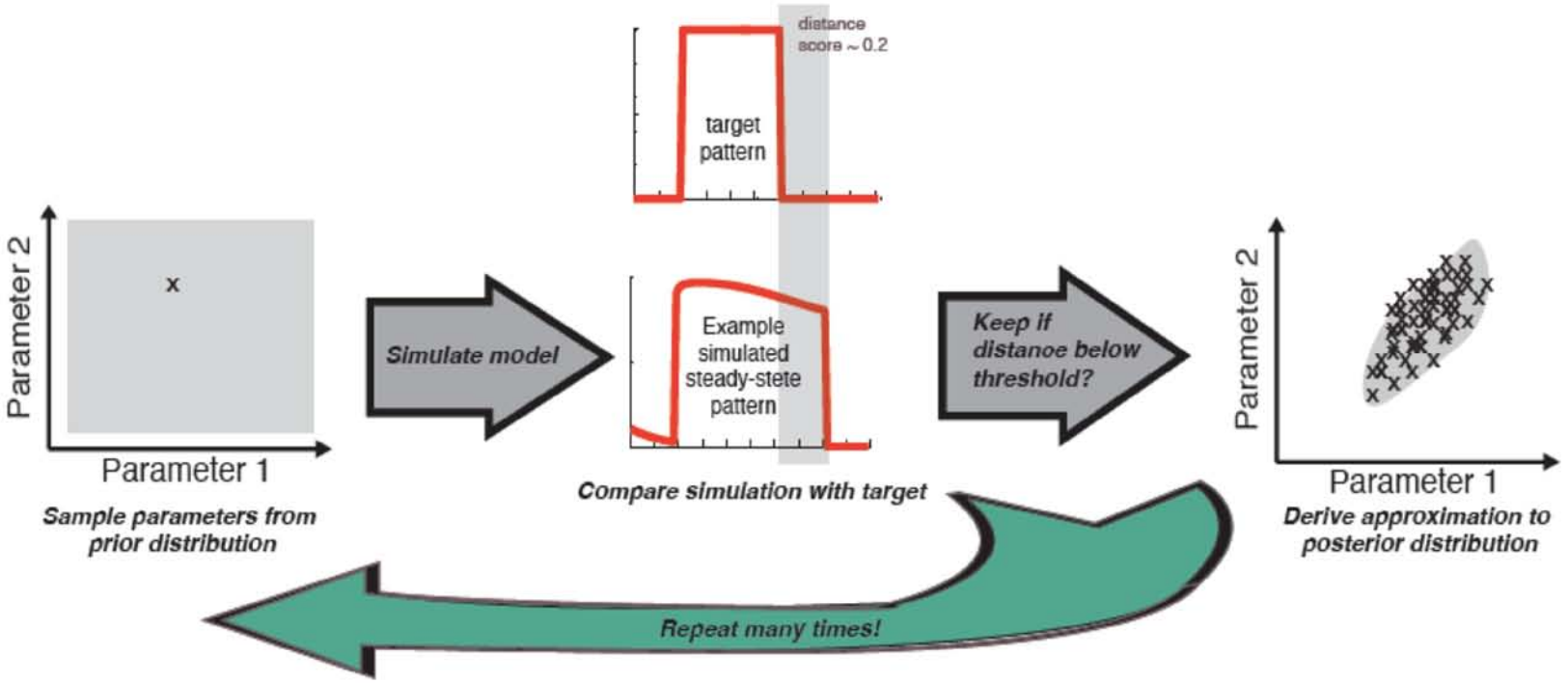
$$Z_{Pax} = K_{P\_Pax}[P] + (1 + 2K_{O\_Pax}[O] + (K_{O\_Pax}[O])^2)(1 + 2K_{N_{Pax}}[N] + (K_{N_{Pax}}[N])^2)$$

$$Z_{Irx} = K_{P\_Irx}[P] + (1 + 2K_{O\_Irx}[O] + (K_{O\_Irx}[O])^2)(1 + 2K_{N_{Irx}}[N] + (K_{N_{Irx}}[N])^2)$$

$$Z_O = K_{P_O}[P] + c_{AP}K_{P_O}[P]K_A[A] + (1 + K_{G_O}[R] + K_{G_O}[A])$$
$$(1 + 2K_{N\_O}[N] + (K_{N\_O}[N])^2)(1 + 2K_{Irx\_O}[Irx] + (K_{Irx\_O}[Irx])^2)$$

$$Z_N = K_{P_N}[P] + c_{AP}K_{P_N}[P]K_A[A] + (1 + K_{G_N}[R] + K_{G_N}[A])(1 + 2K_{O_N}[O] + (K_{O_N}[O])^2)$$
$$(1 + 2K_{Irx\_N}[Irx] + (K_{Irx\_N}[Irx])^2)(1 + 2K_{Pax\_N}[Pax] + (K_{Pax\_N}[Pax])^2)$$

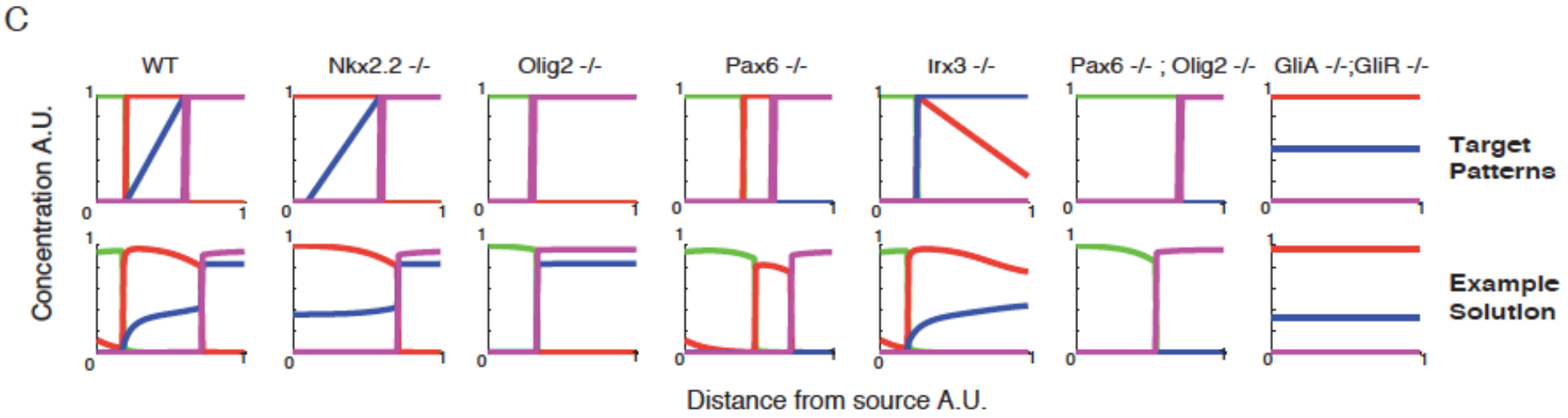
Approximate Bayesian Computation



Parameter screen and optimization by ABC

Chris Barnes

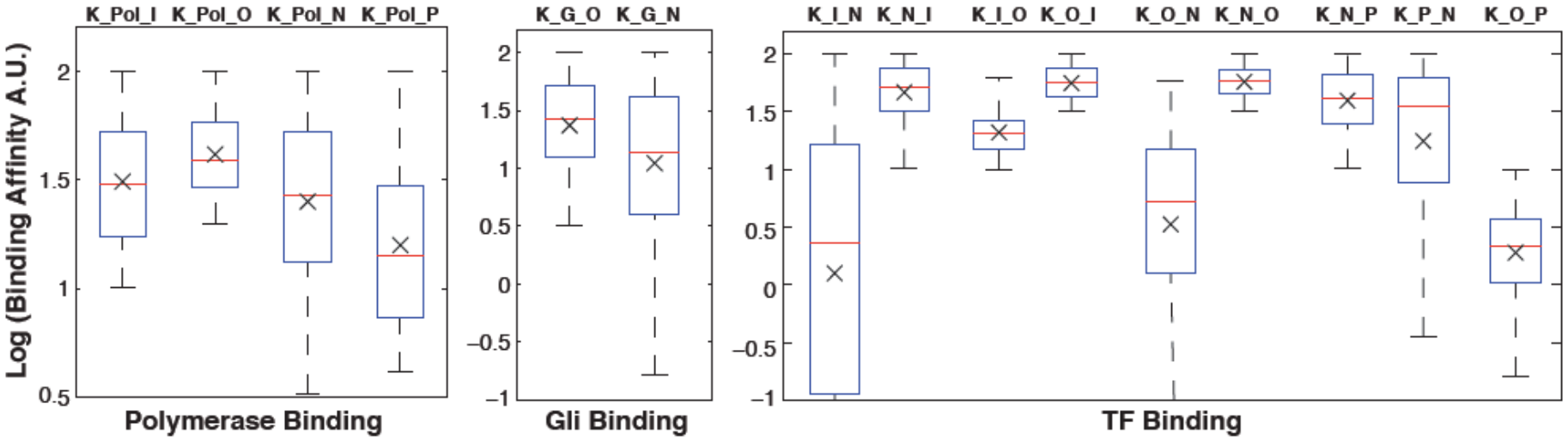
Approximate Bayesian Computation



Cohen, M., Page, K. M., Perez-Carrasco, R., Barnes, C. P. & Briscoe, J. *Development* **141,** 3868–3878 (2014).

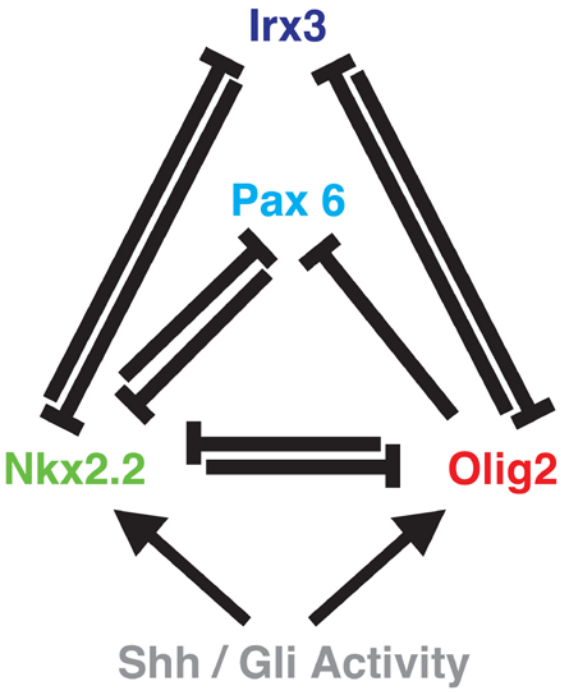
Chris Barnes

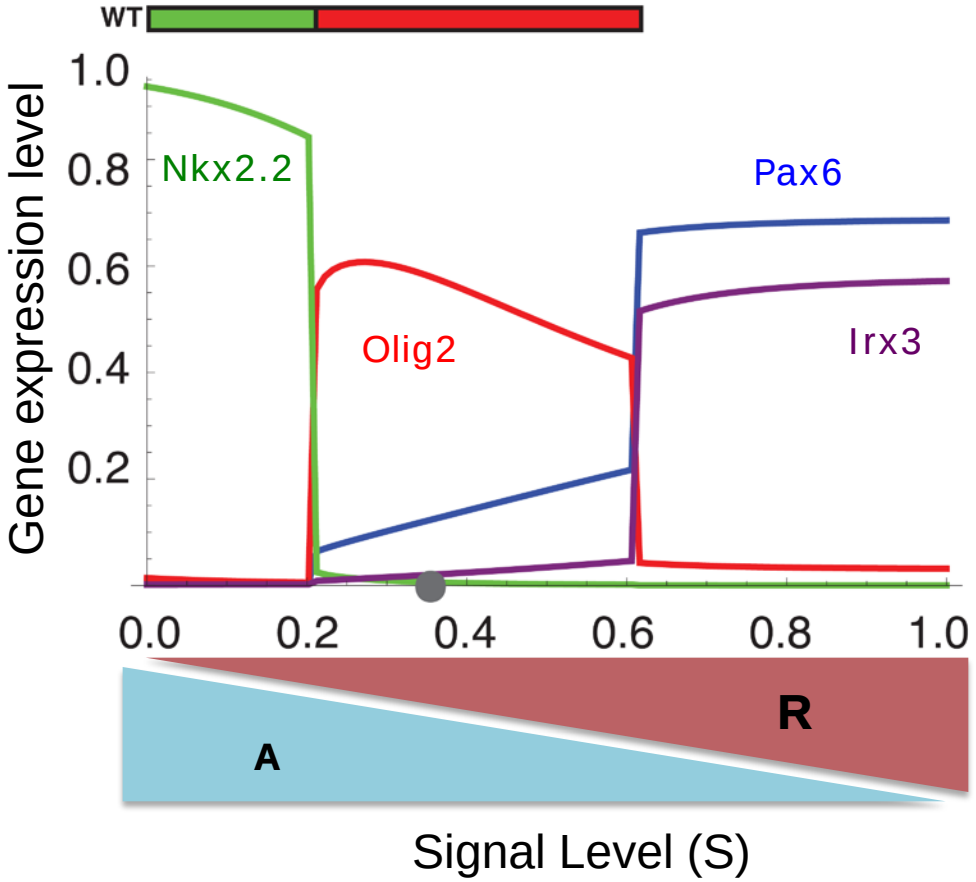
Posterior Distributions of Parameters from ABC



Cohen, M., Page, K. M., Perez-Carrasco, R., Barnes, C. P. & Briscoe, J. *Development* **141,** 3868–3878 (2014).

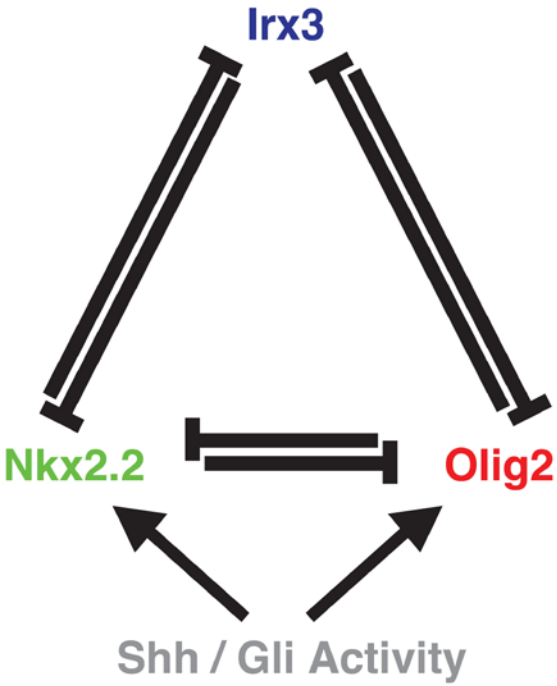
Network generates morphogen response

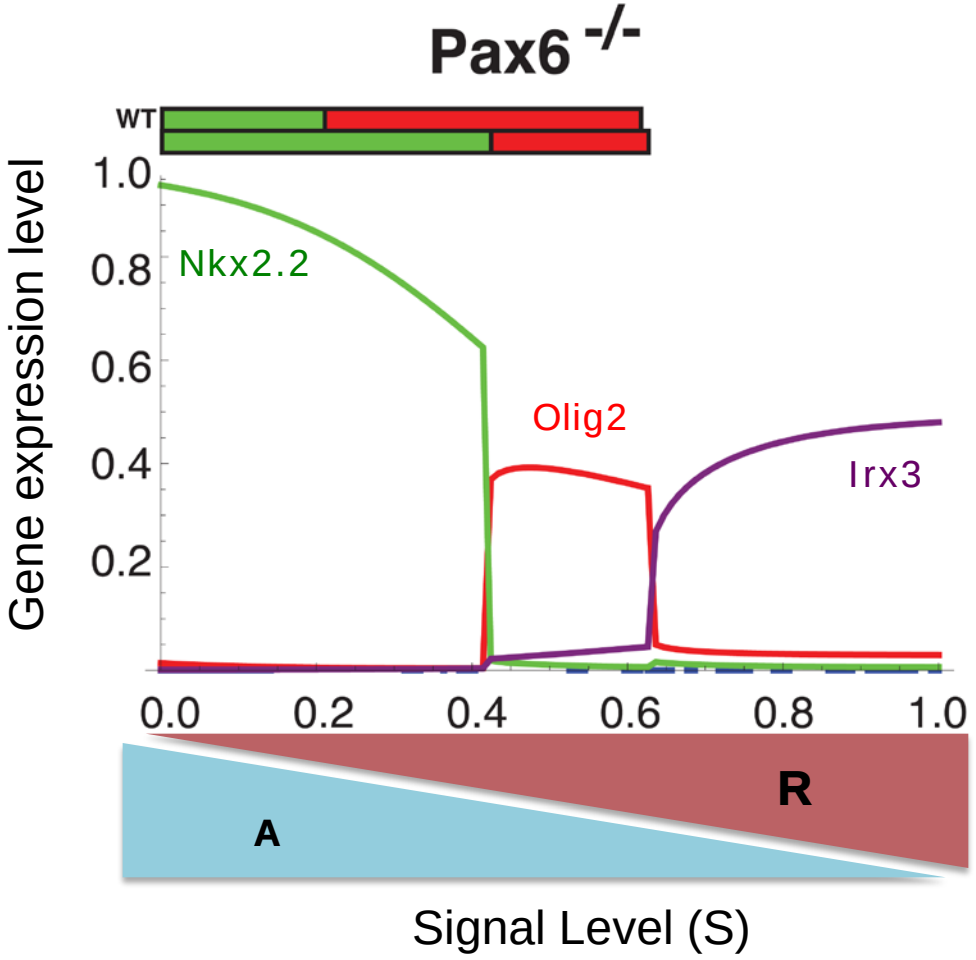




Michael Cohen

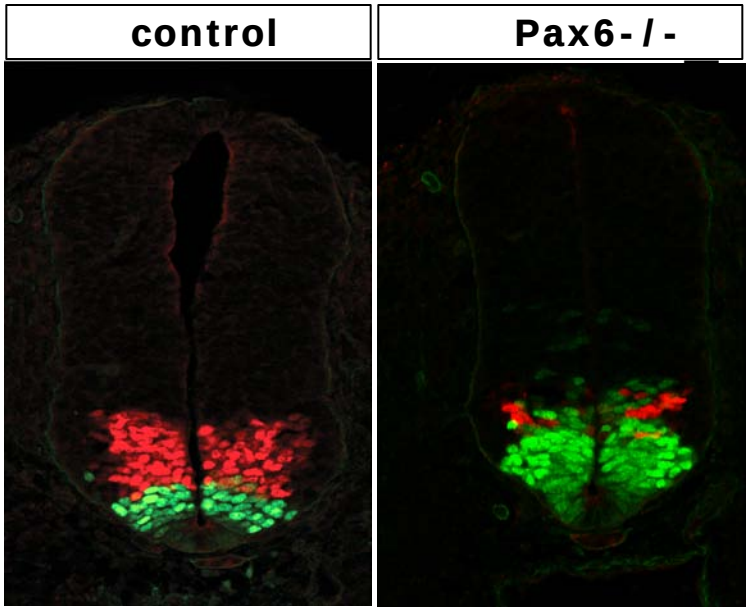
Network generates morphogen response

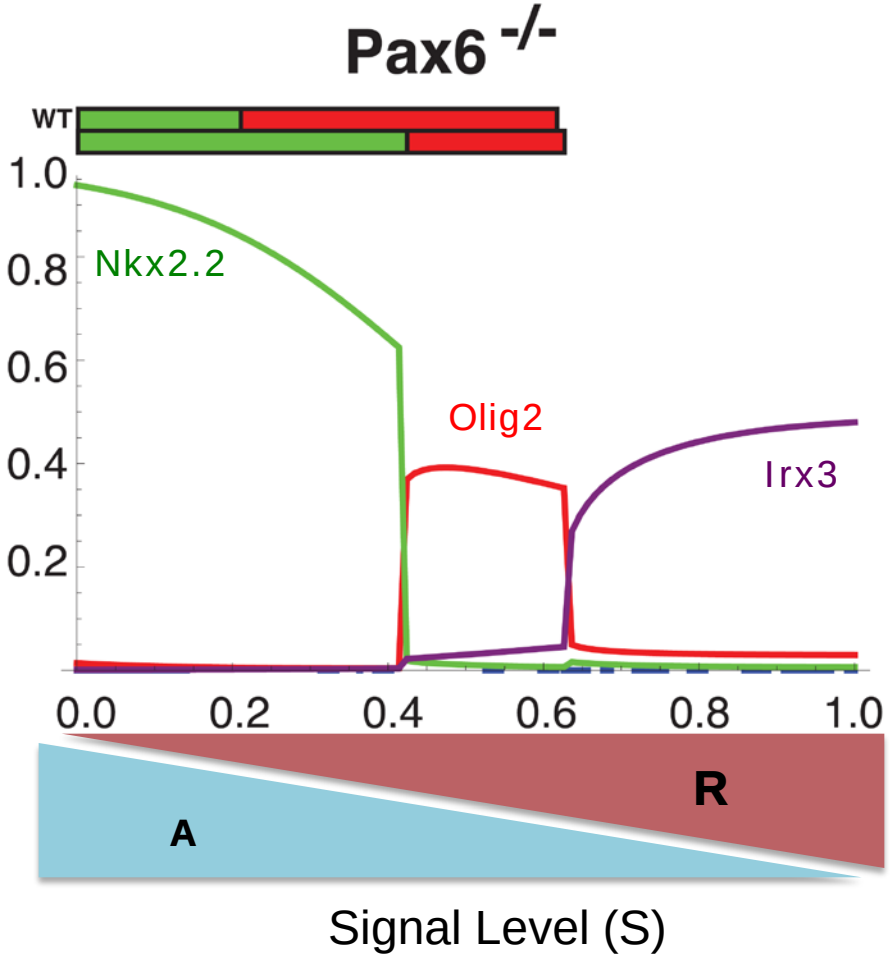




Michael Cohen

Network generates morphogen response





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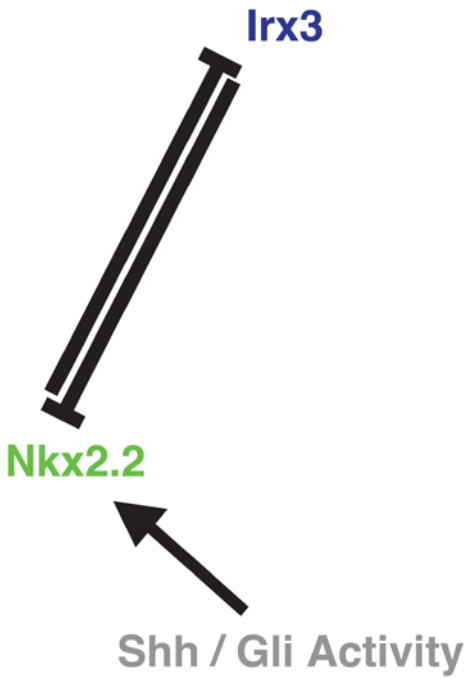
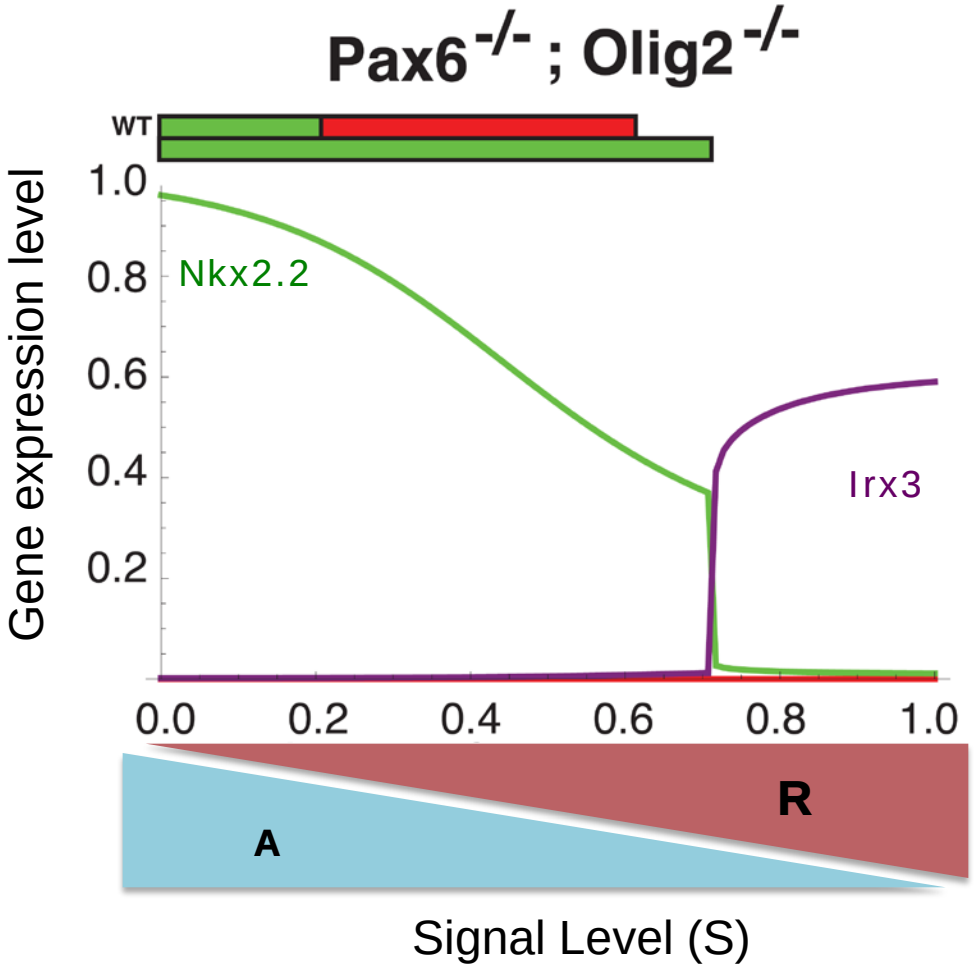
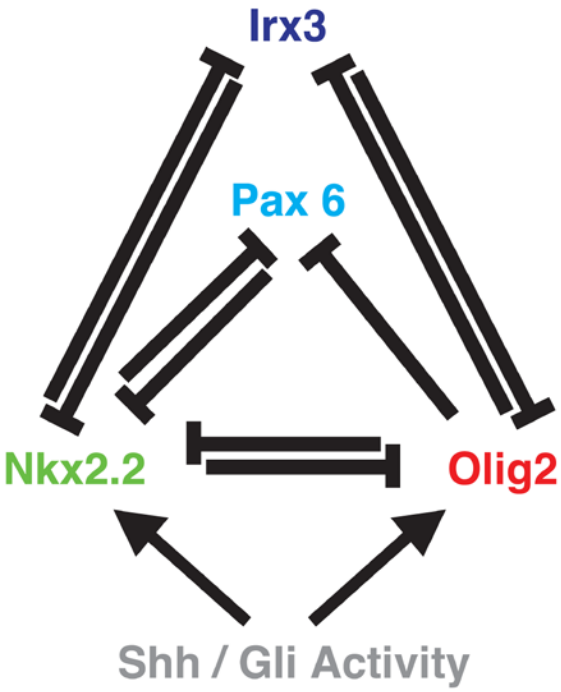
Network generates morphogen response

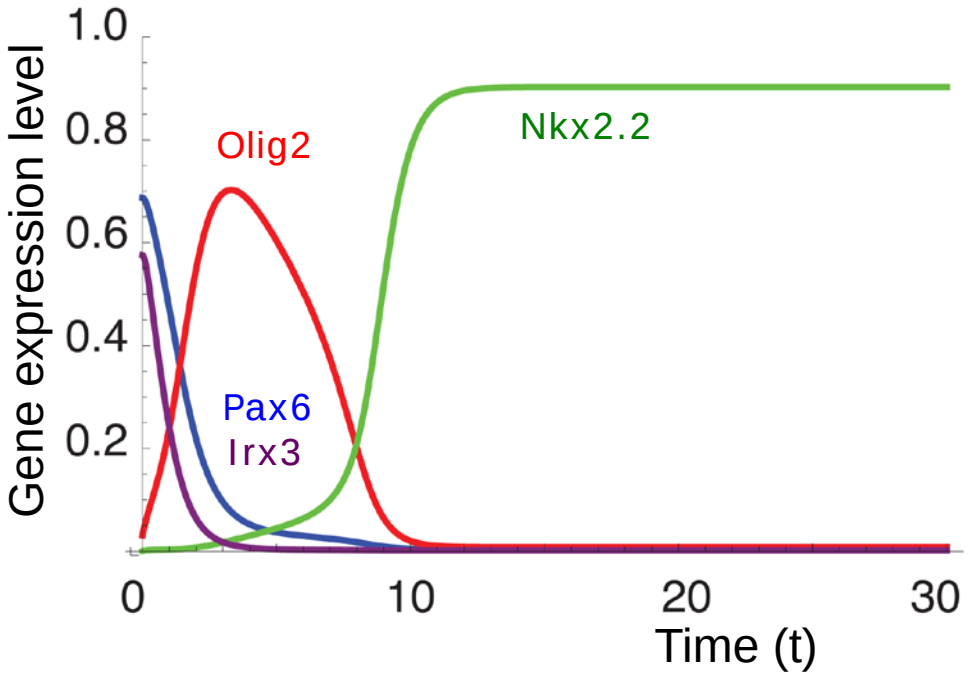




Michael Cohen

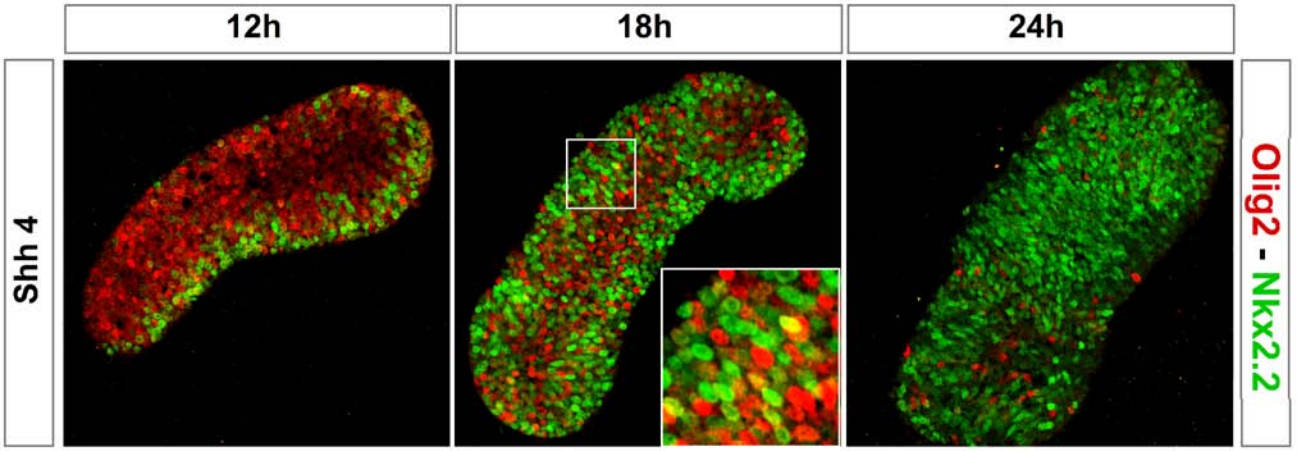
Network generates **temporal** response

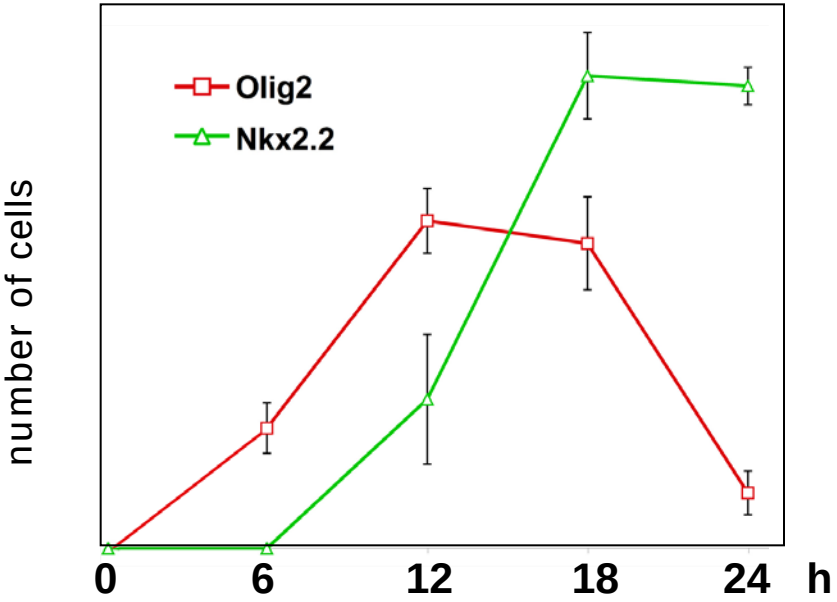




Michael Cohen

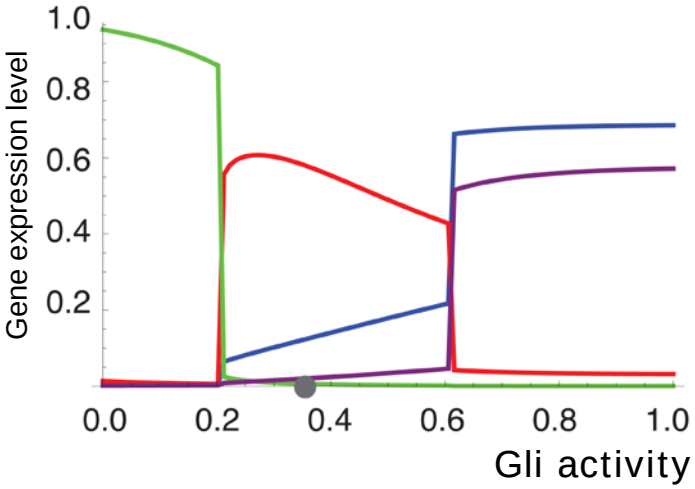
Duration of signalling influences pattern

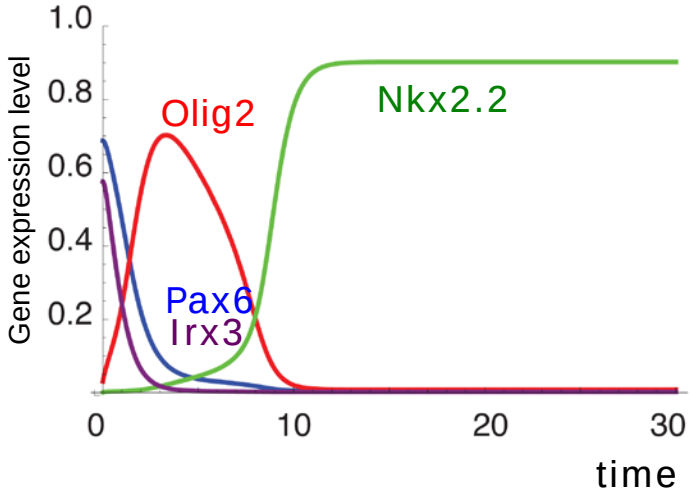


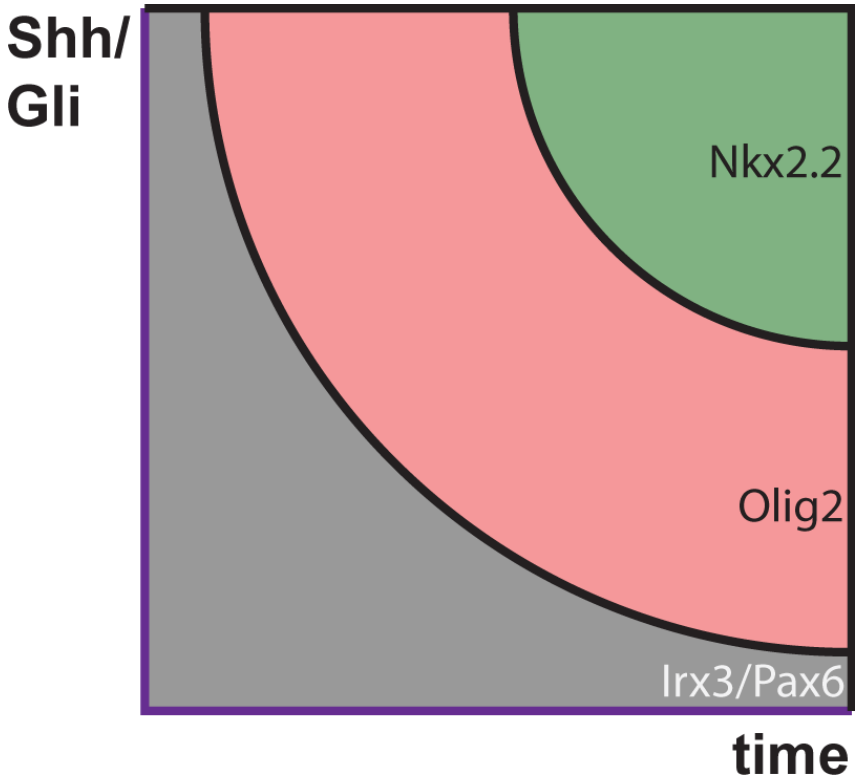


Eric Dessaud

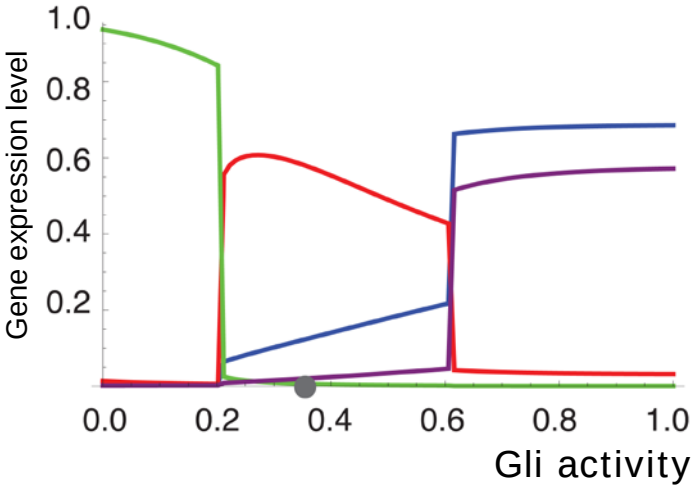
Network explains equivalency of time and level

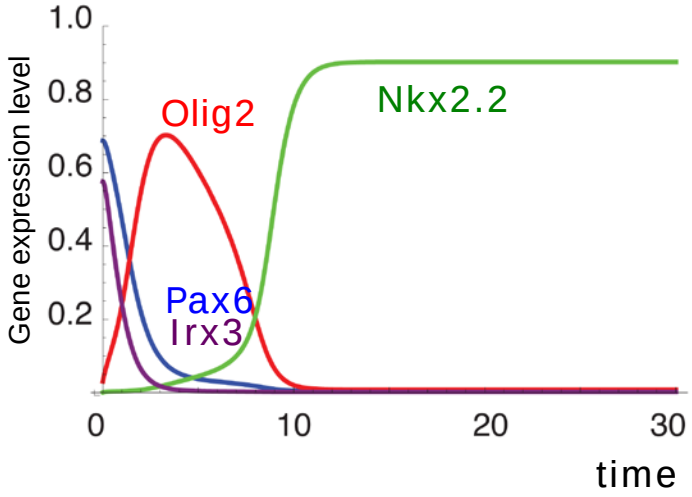


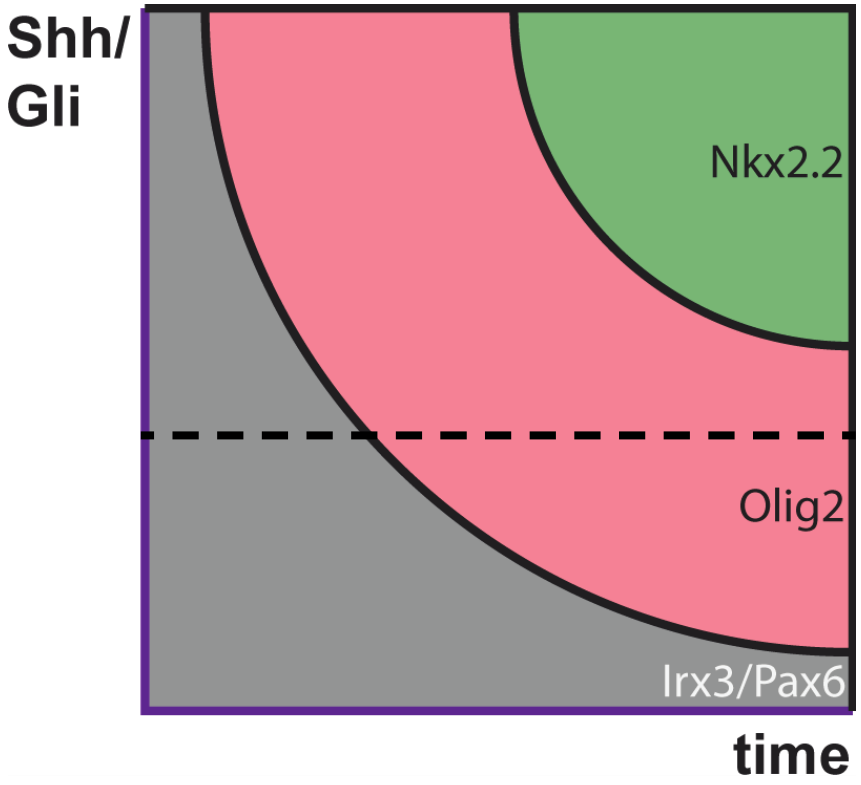




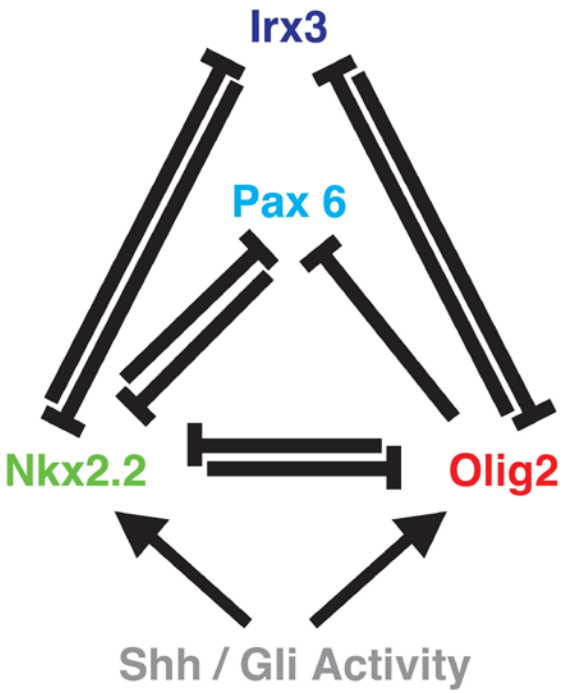
Network explains equivalency of time and level

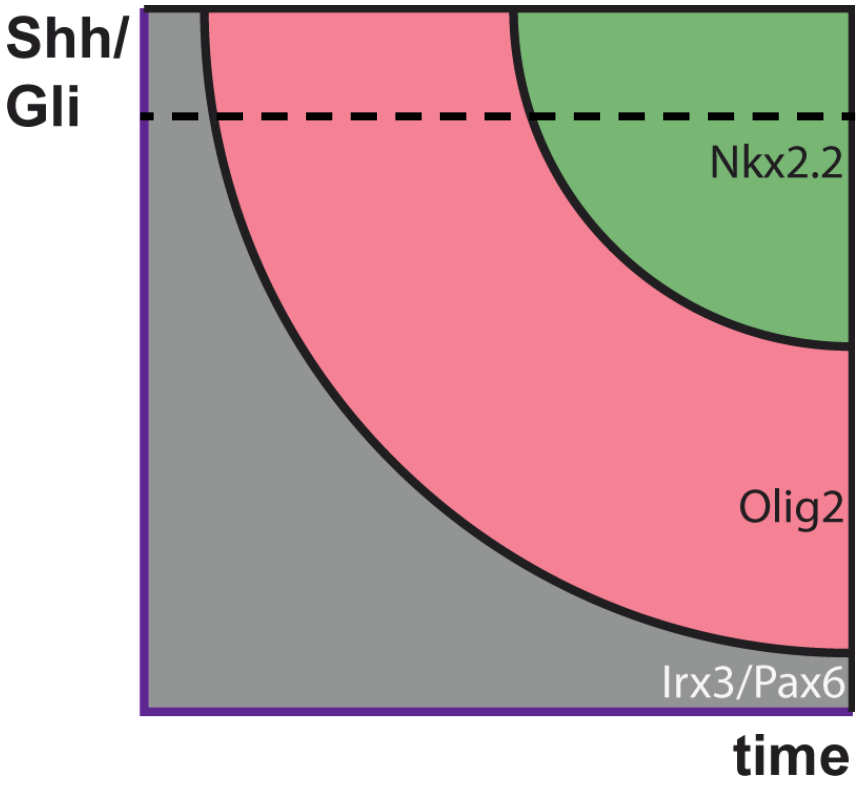




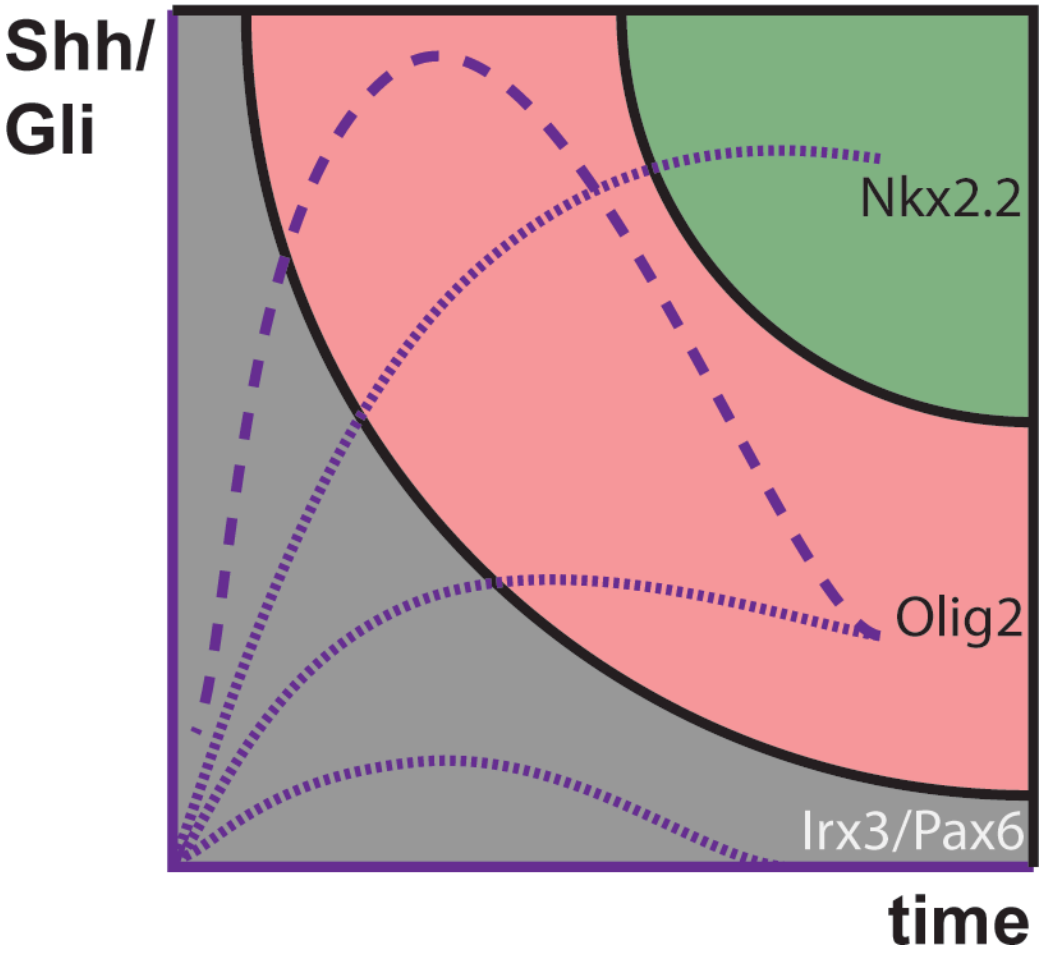


Network explains equivalency of time and level

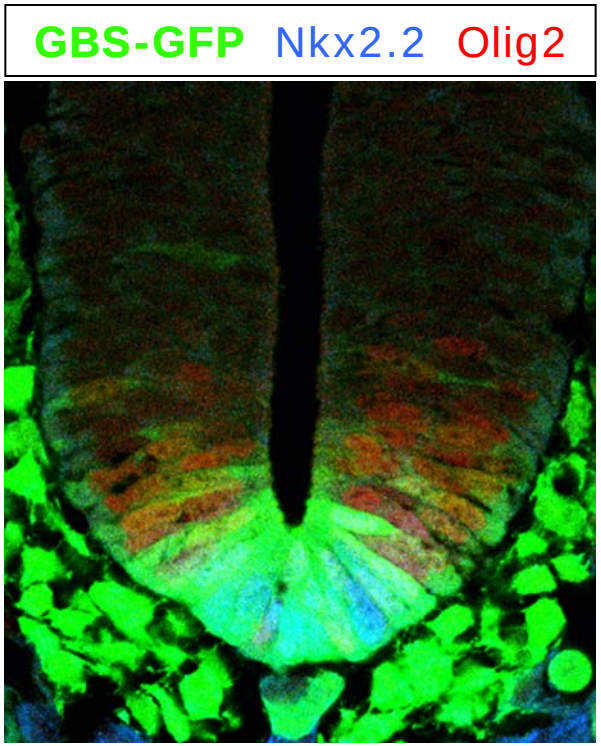


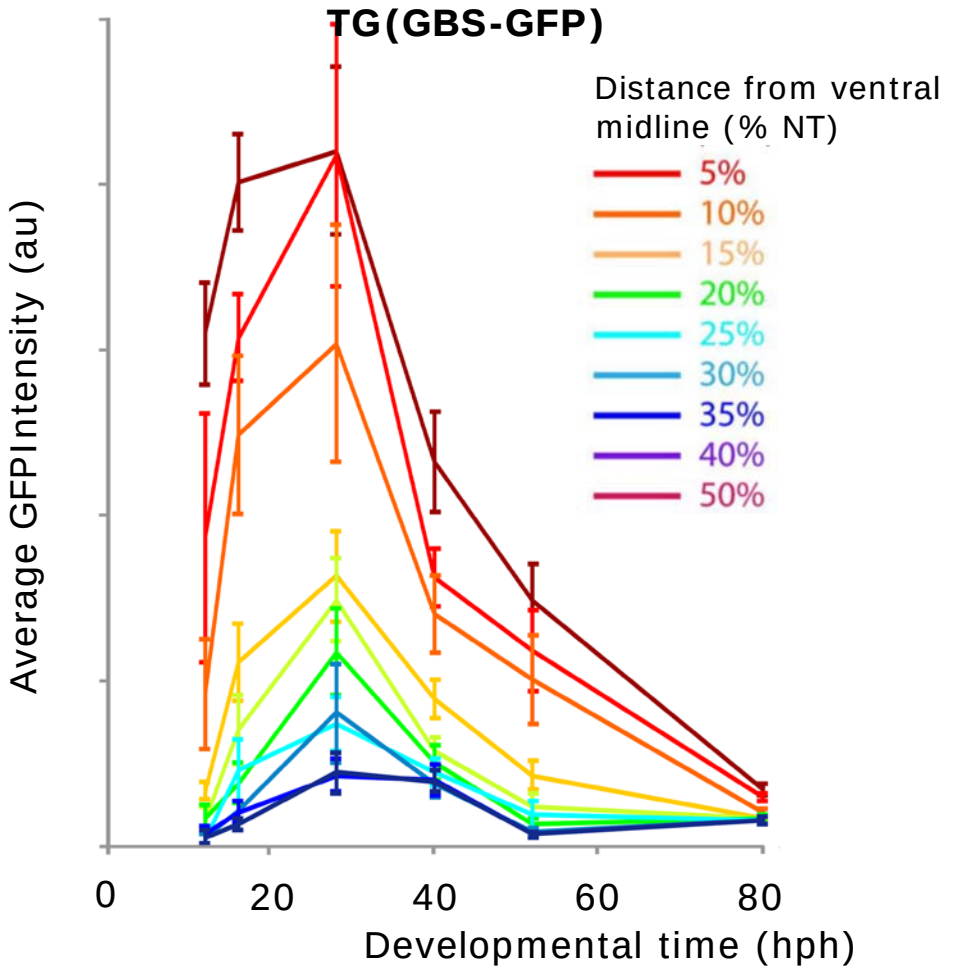


Dynamics explains robustness to temporary increases



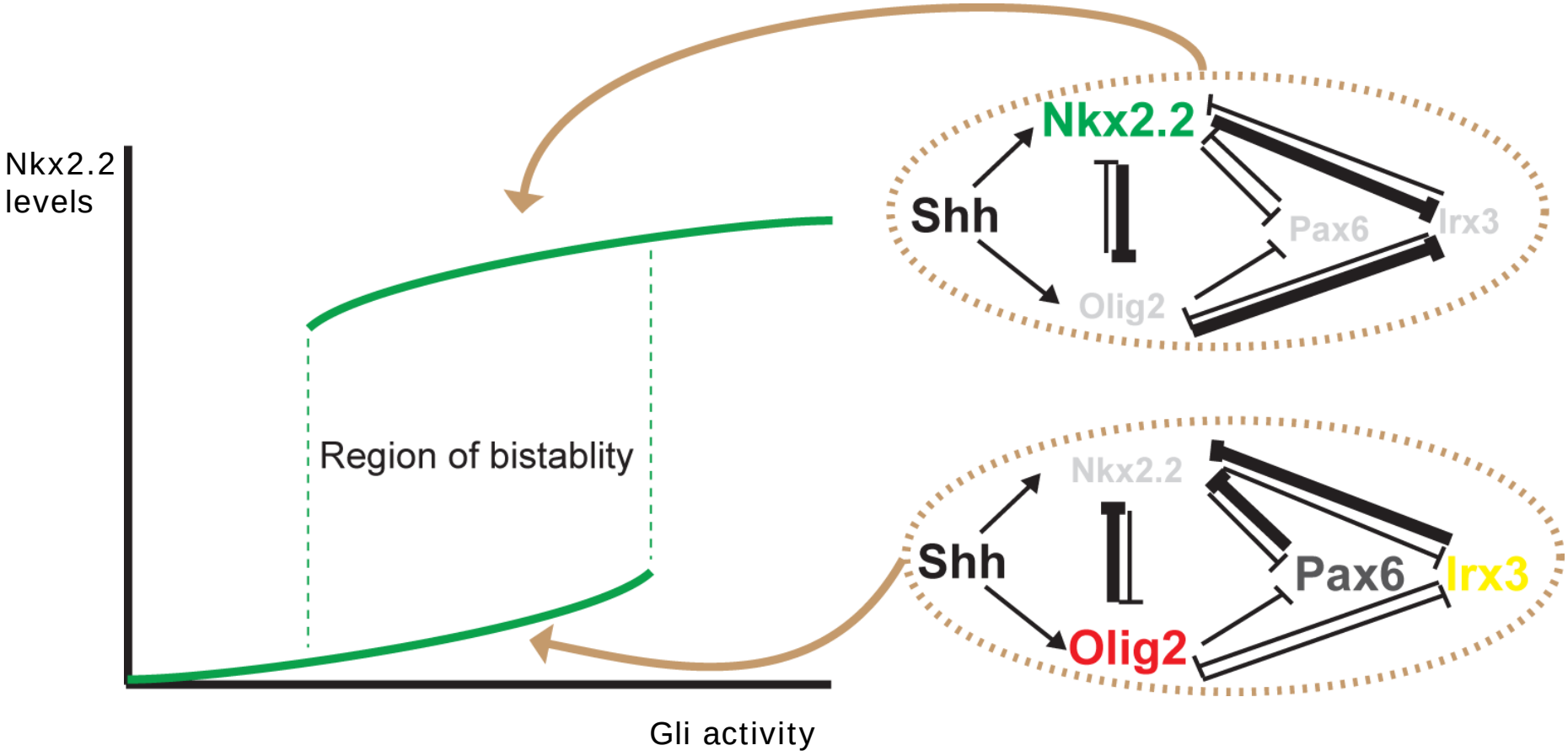
Gli activity is dynamic





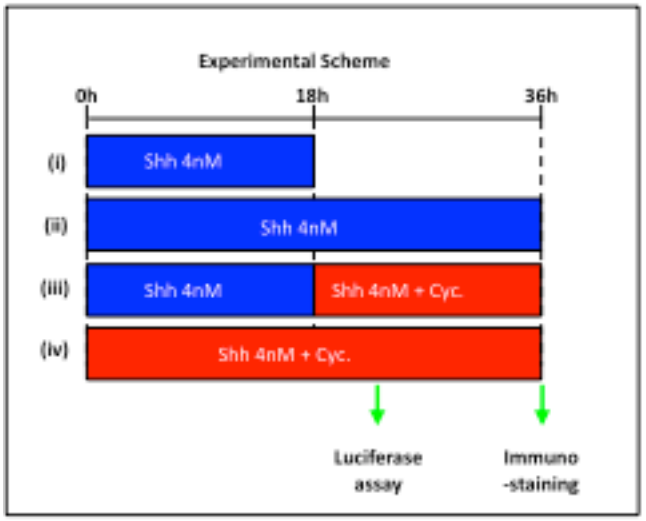
Vanessa Ribes/Ana Ribeiro

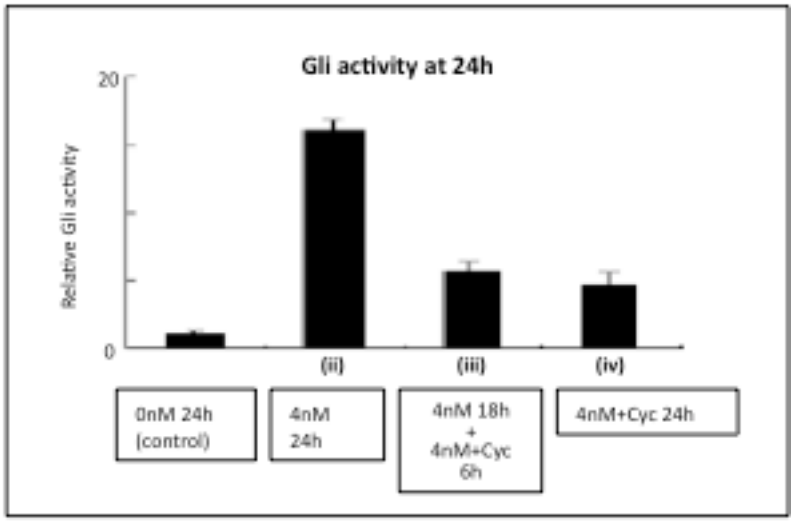
Network confers hysteresis

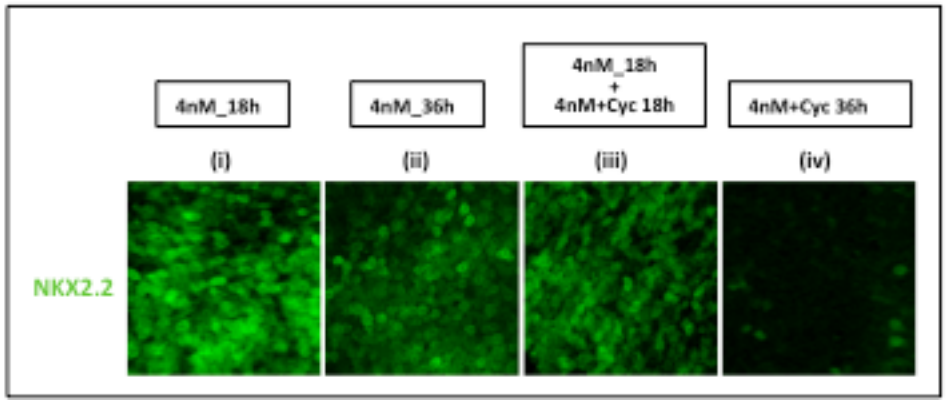


Ruben Perez

Network confers hysteresis



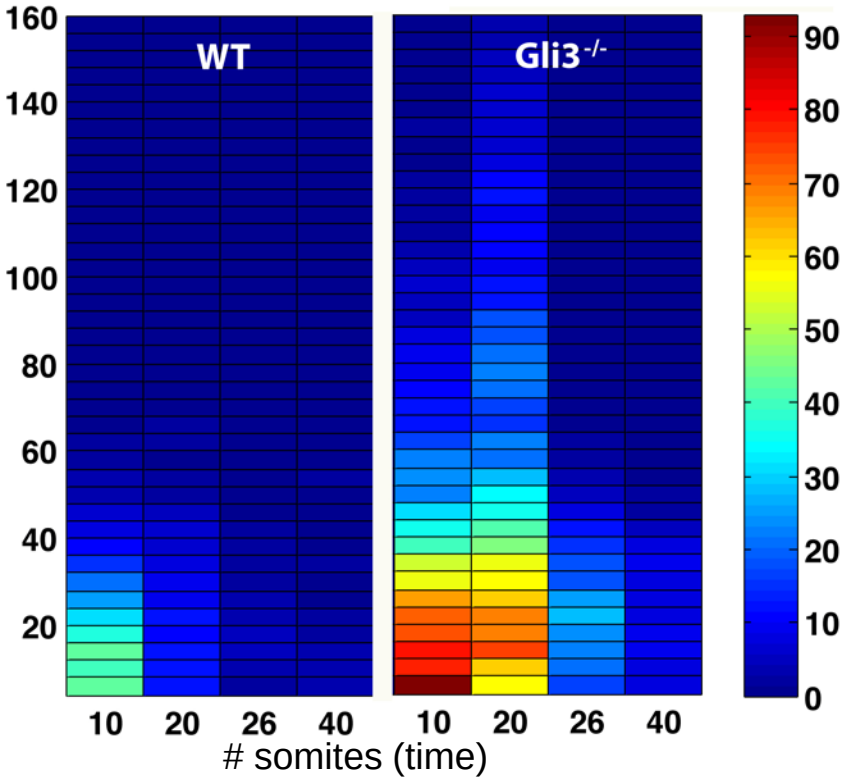


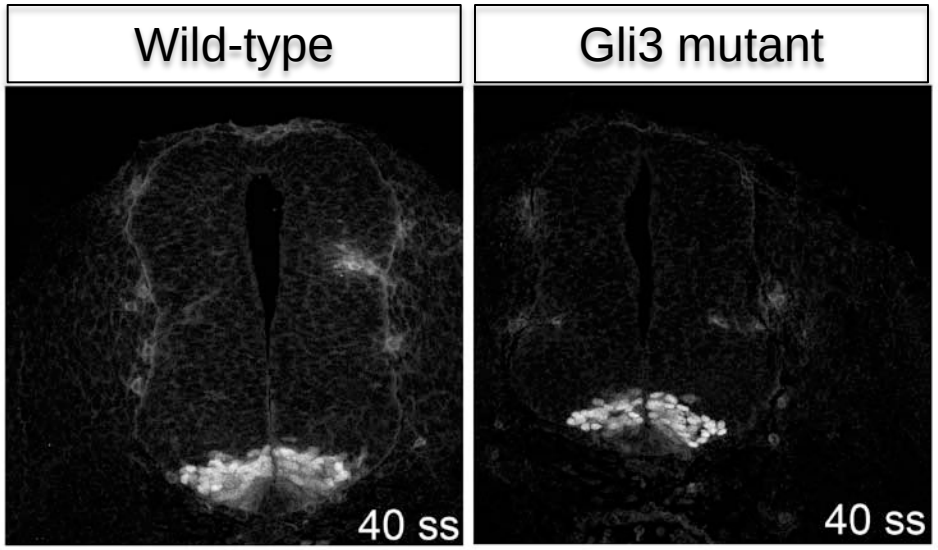


Noriaki Sasai

Transient increase in Gli activity does not change pattern

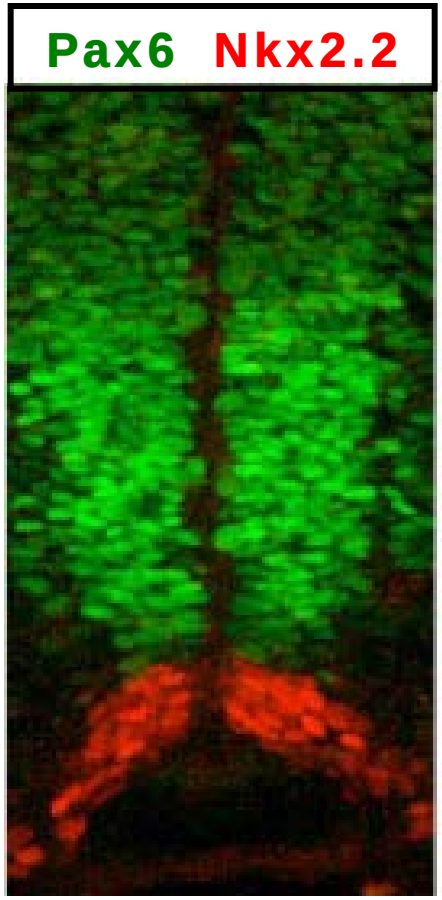
Gli activity in vivo

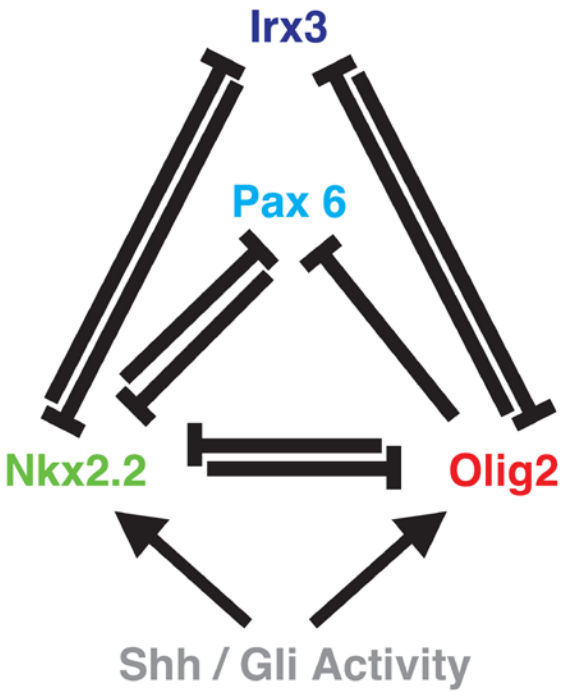


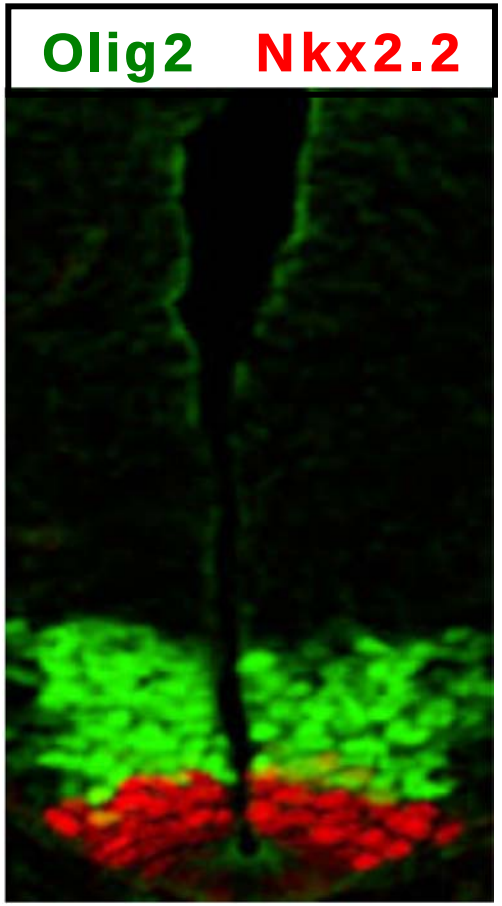


Vanessa Ribes

A transcriptional circuit for morphogen interpretation







Heaviside simplification of the circuit

$$\frac{dP}{dt} = \frac{\alpha}{1 + \left(\frac{N}{N_{critP}}\right)^{h1} + \left(\frac{O}{O_{critP}}\right)^{h2}} - k_1 P$$

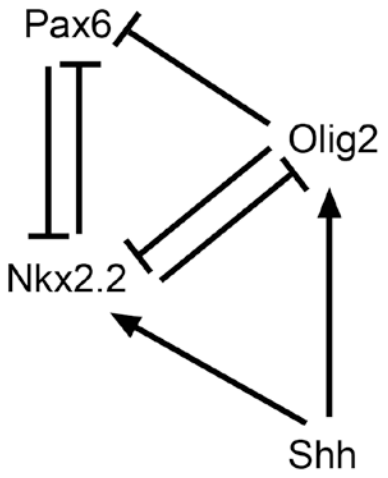
Pax6 (P)

$$\frac{dO}{dt} = \frac{\beta S}{1+S} \times H(N_{crit1} - N) - k_2 O$$

Olig2 (0)

$$\frac{dN}{dt} = \frac{\gamma S}{1+S} \times H(O_{crit1} - O) H(P_{crit1} - P) - k_3 N$$

Nkx2.2 (N)



Panovska-Griffiths, J., Page, K. M. & Briscoe, J. *Journal of The Royal Society Interface* **10,** 20120826 (2013).

Steady state solutions

- Three possible steady states:
  - $\mathbf{B_1}$ no Nkx2.2; Olig2 increases & Pax6 decreases with S
  - $\mathbf{B_2}$ no Olig2; Nkx2.2 increases & Pax6 decreases with S
  - $\mathbf{B_3}$ both Nkx2.2 and Olig2 increase and Pax6 decreases with S

- Each state is stable when it exists.
- Criteria for existence are simple inequalities in parameter values.
- Each state varies with S, so that, for example, for low S, all of the states correspond to Pax6 high.

Steady state solutions – oscillation vs. bistability

Biological behaviour involves:

B1 -> B2 as S increases

As the signal increases - either overlap or gap in stability of steady states

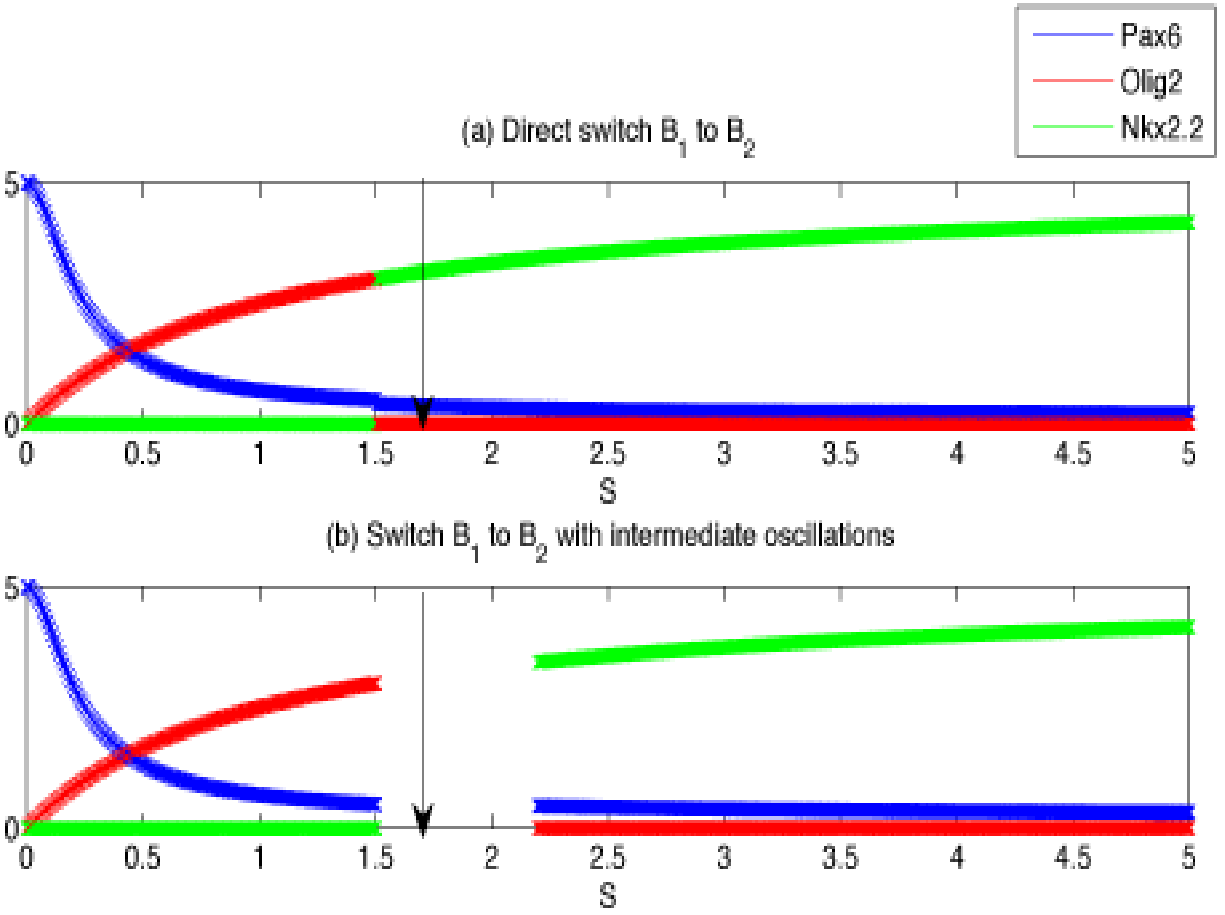
Overlap = hysteresis in S
Gap = a range of S for which get oscillations.

Gap if:

$$\left(\frac{N_{\max} O_{crit}}{N_{crit} 0_{\max}}\right)^{h_1 h_2} < \left(\frac{P_{\max}}{P_{crit}}\right)^{h_2 - h_1}$$

Otherwise coexistence and bistablity

Steady state solutions – oscillation vs. bistability



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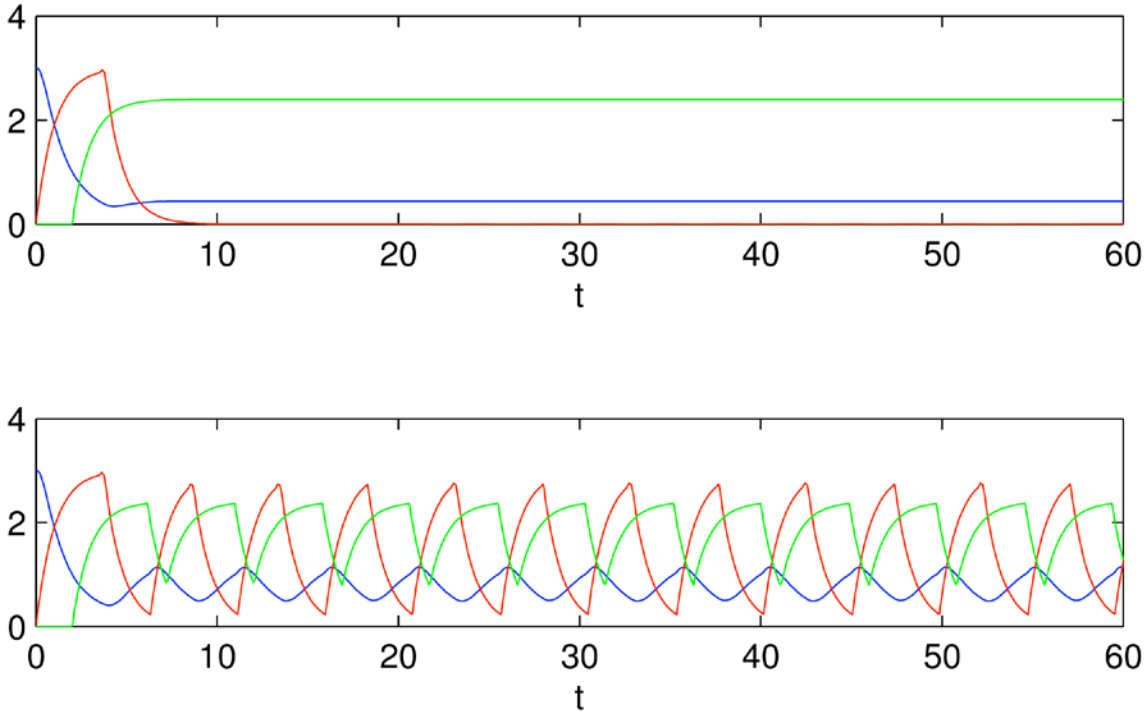
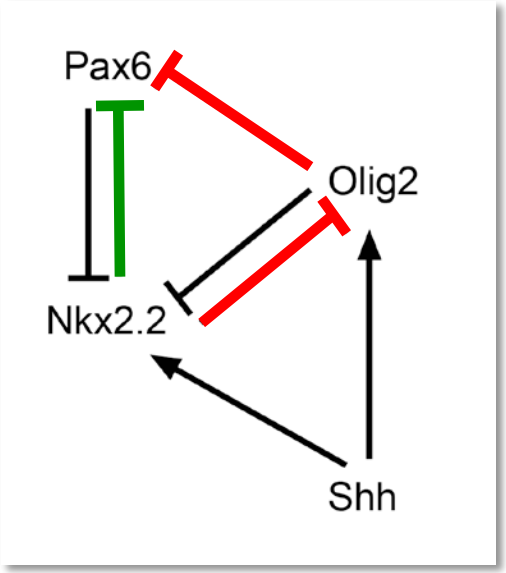
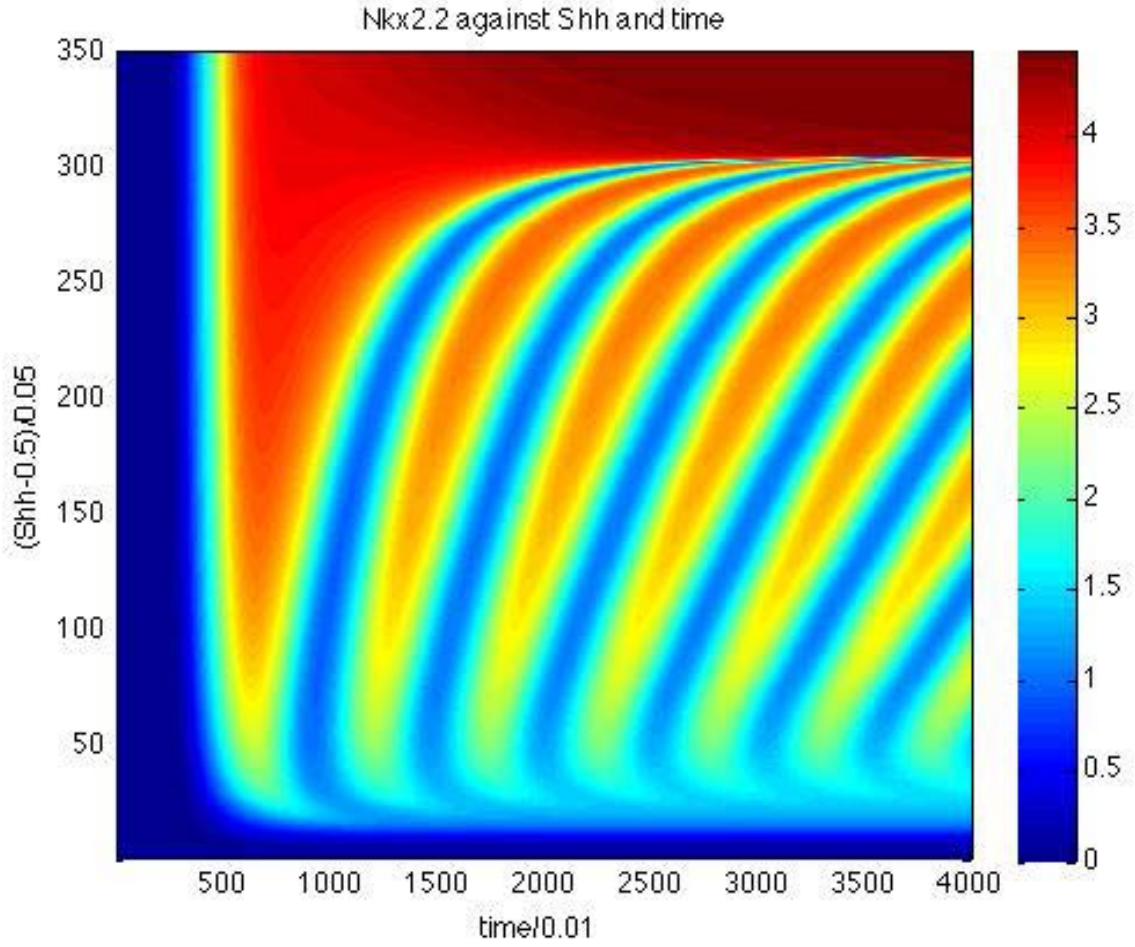
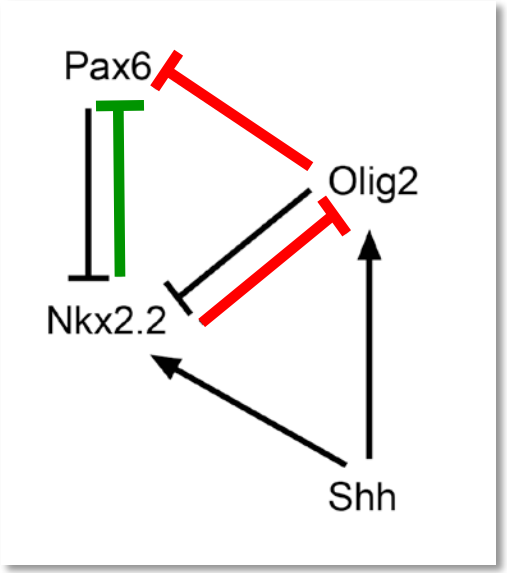
Dynamics- oscillation vs. bistability





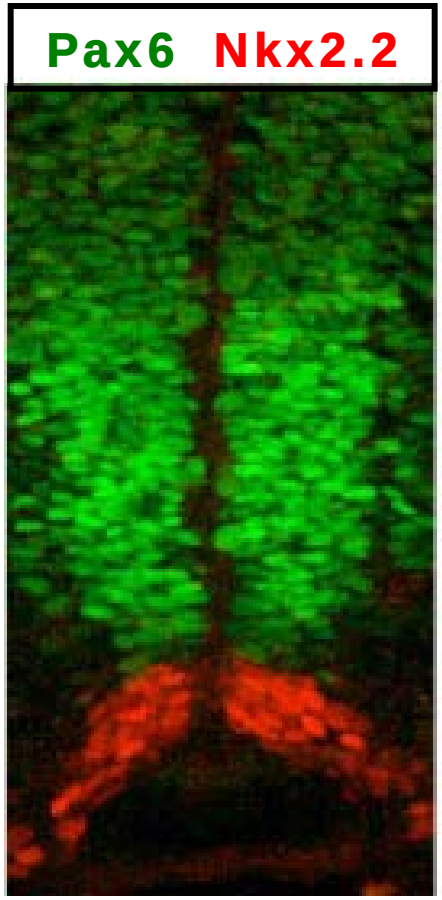
Dynamics- oscillation

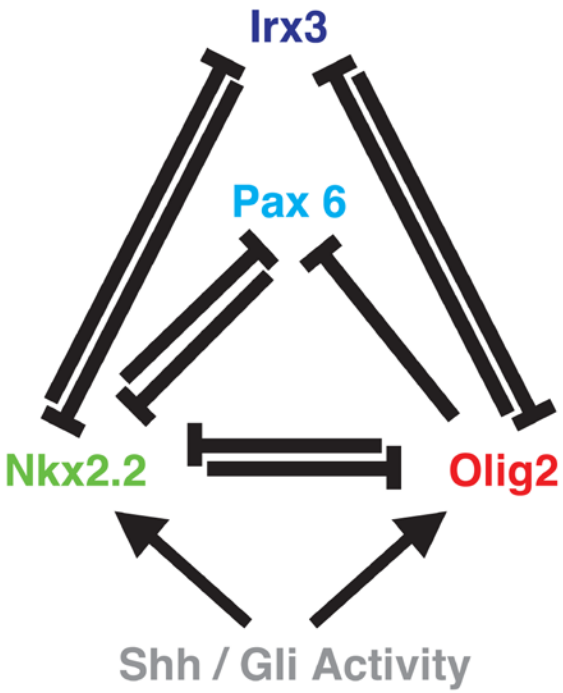


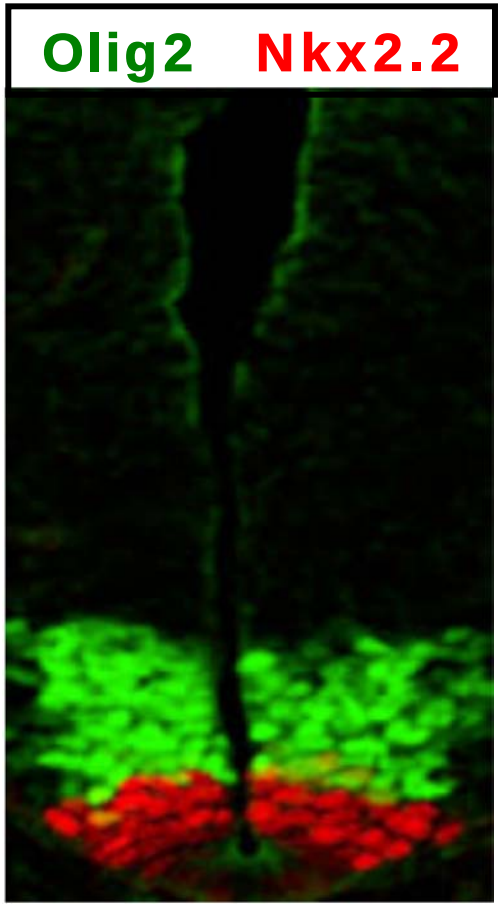



AC/DC
LET THERE BE ROCK

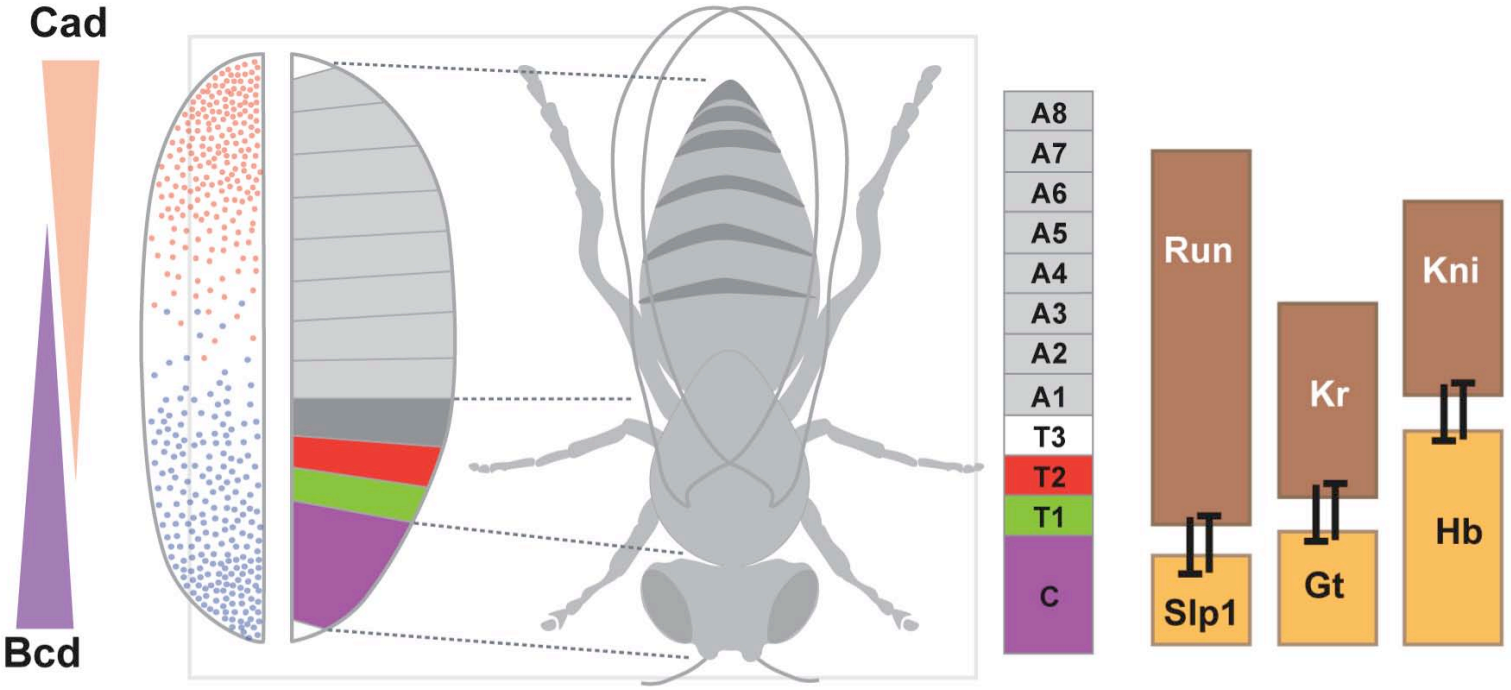
A transcriptional circuit for morphogen interpretation







The patterning power of transcriptional networks



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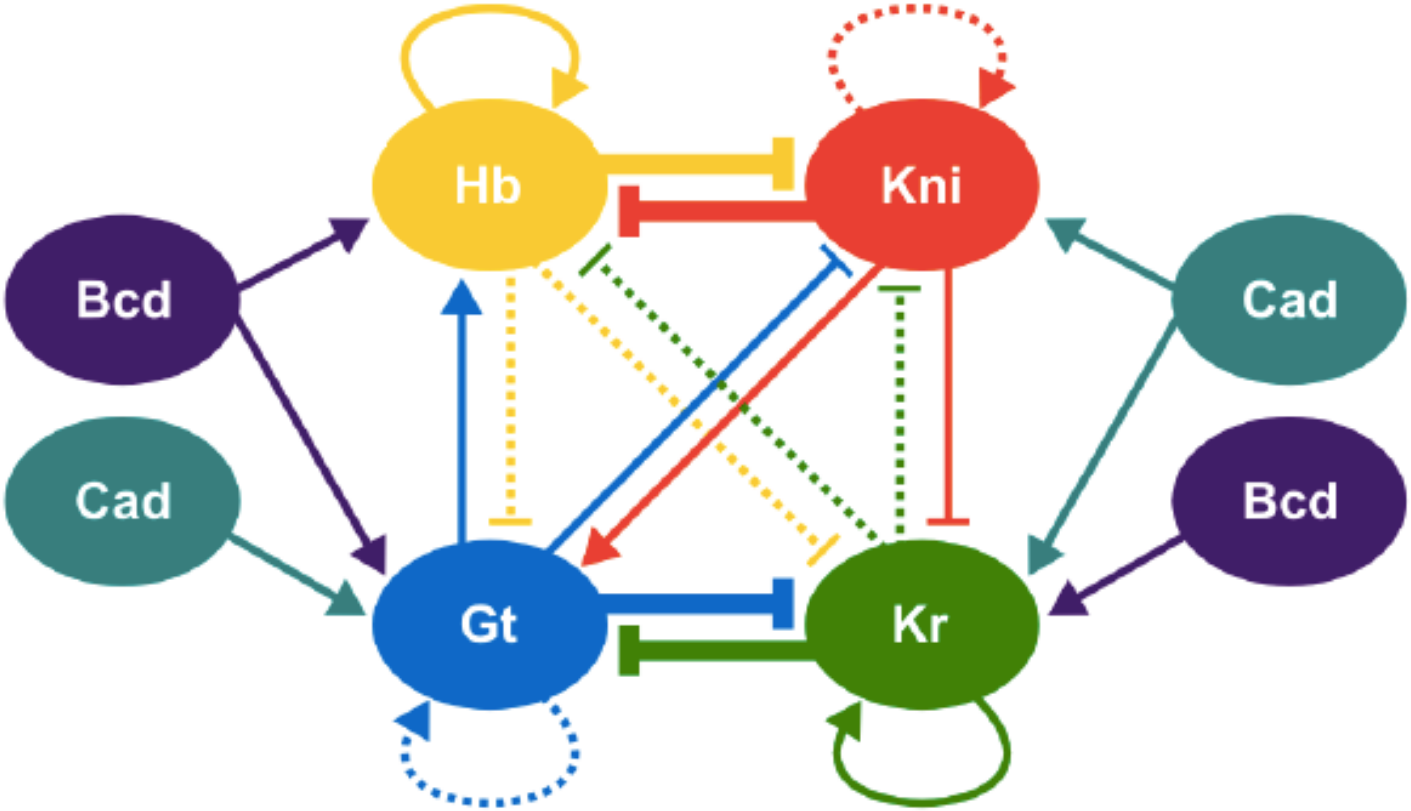
The patterning power of transcriptional networks



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