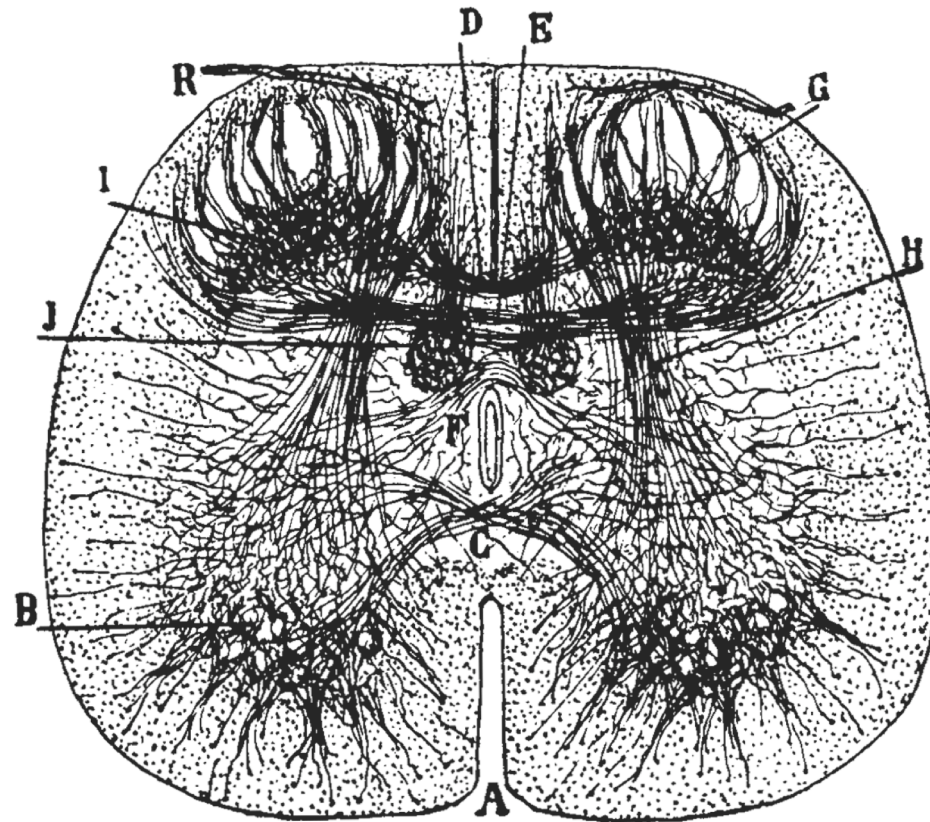


Dynamics of Neural Tube Development



Ramón-y-Cajal (Manual de Histología)

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Teresa Rayon Alonso
Andreas Sagner
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Anna Kicheva

Karen Page

Peter Sollich





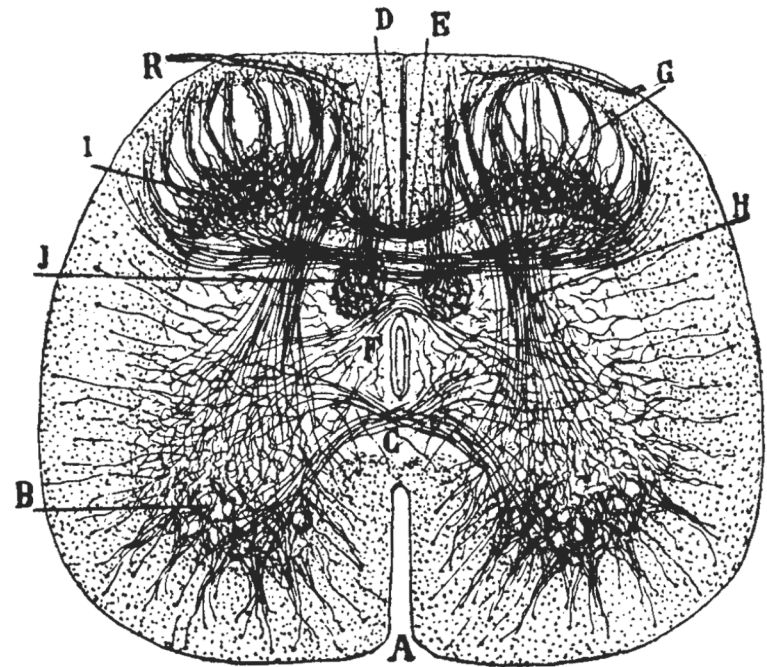
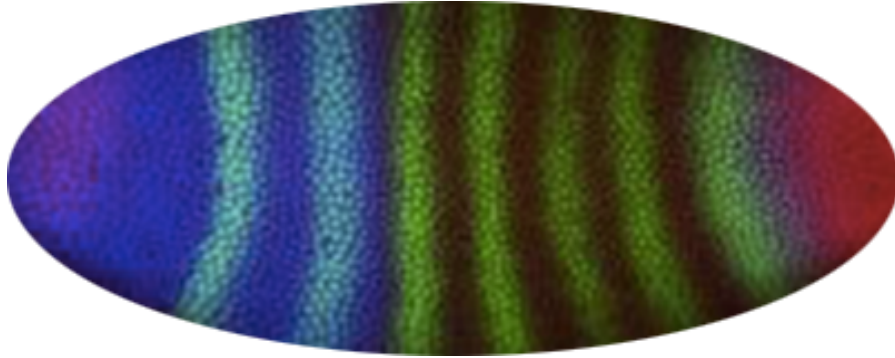
Development

For advances in developmental biology and stem cells

- created by scientists for scientists
- expert academic Editors
- scoop protection
- no page charges, no colour charges, no hidden fees
- free access to every paper after 6 months

supporting biologists inspiring biology

The problem

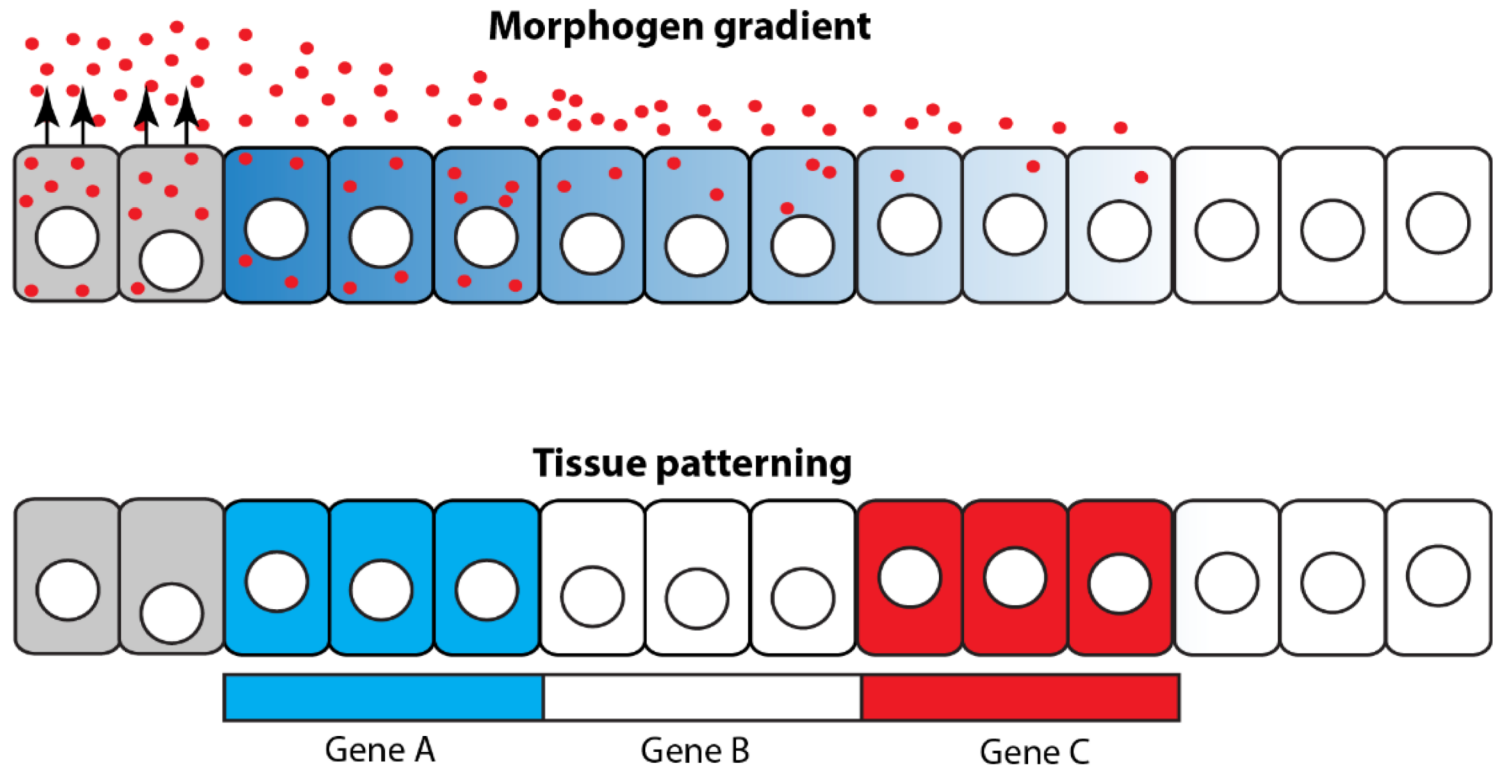


The 6 P's of developmental biology

- Position:** How do cells know their location?
- Pattern:** How do cells make decisions?
- Proportions:** How is growth controlled and coordinated?
- Precision:** How reliable and accurate is patterning?
- Pace:** What controls the tempo of development?
- Purpose:** What determines cell function?

Performance and Principles

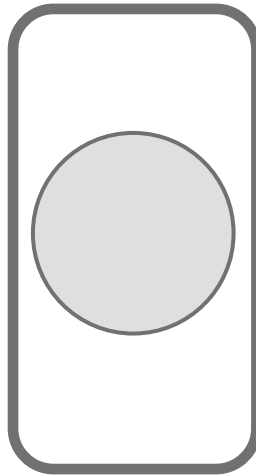
Morphogens



Sagner and Briscoe (2017) PMID:28319331

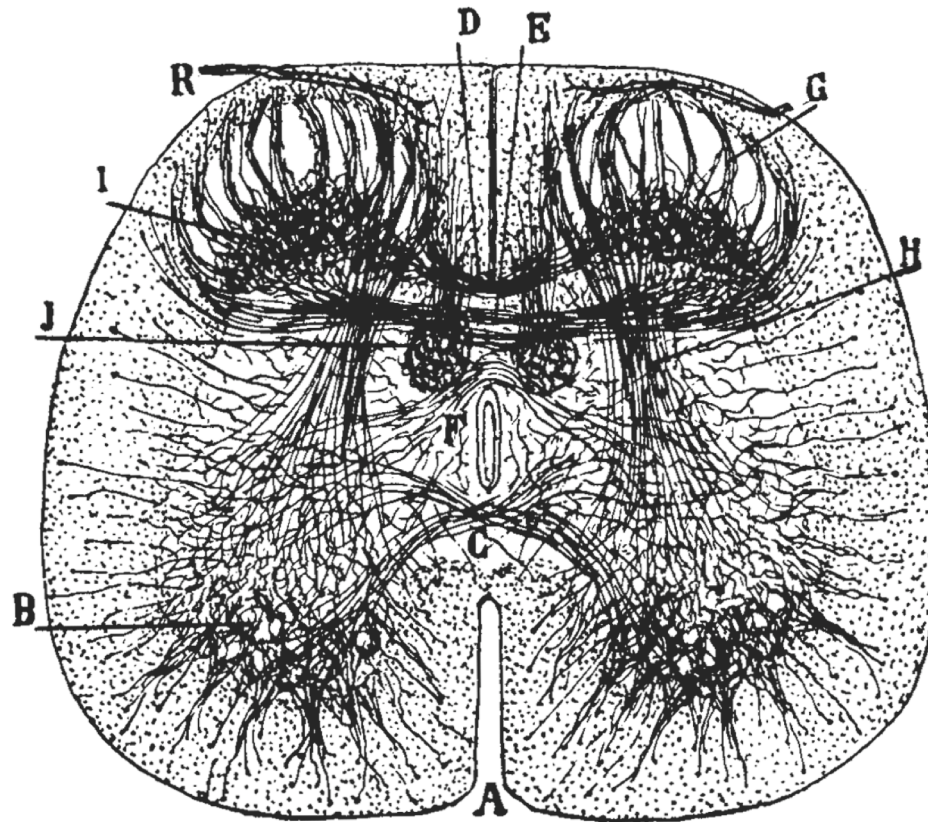
Cellular Information Processing

Input:
Morphogen



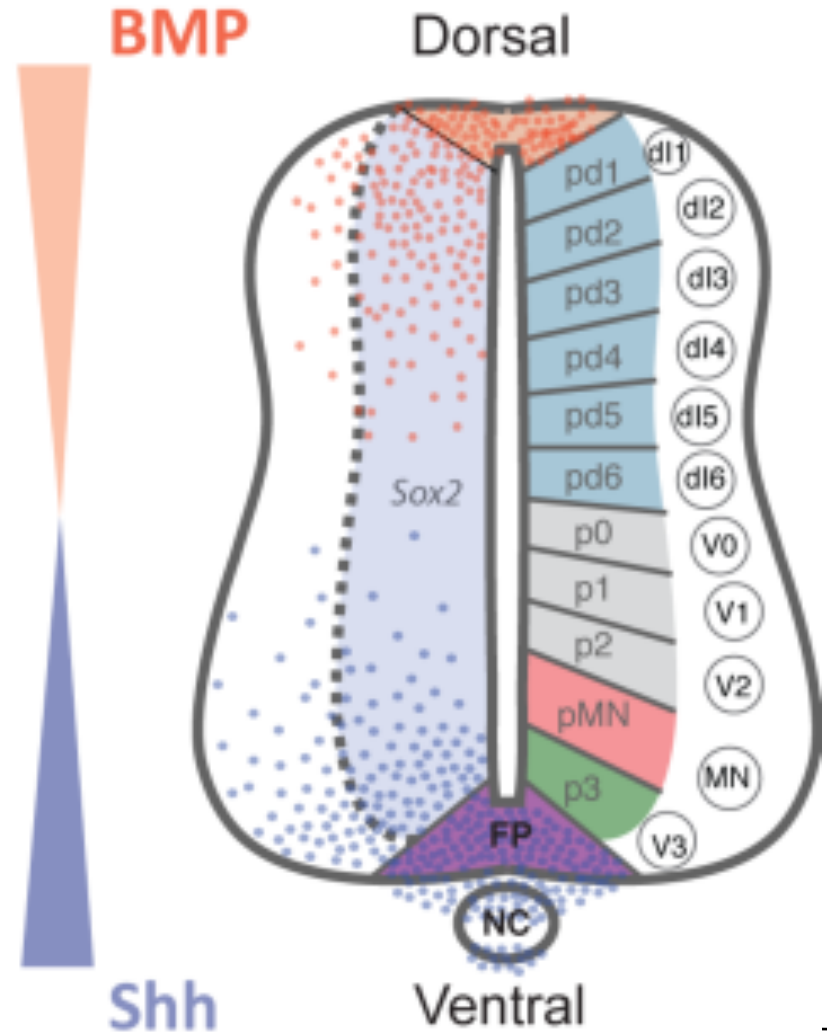
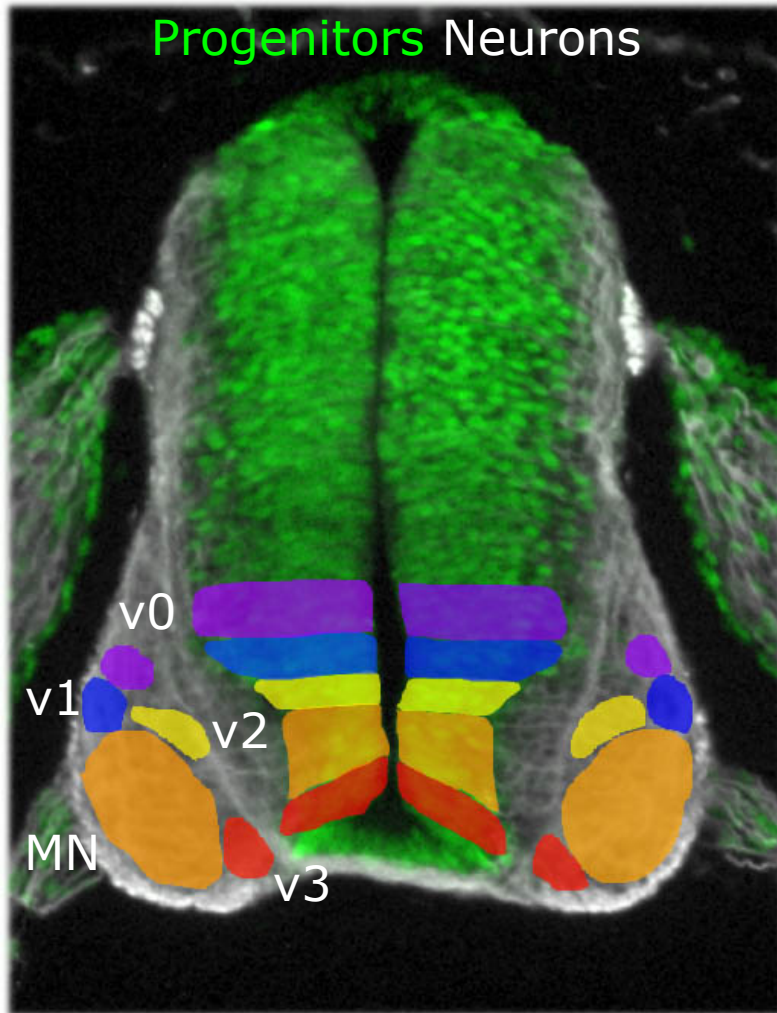
Output:
Cell Identity

The Neural Tube

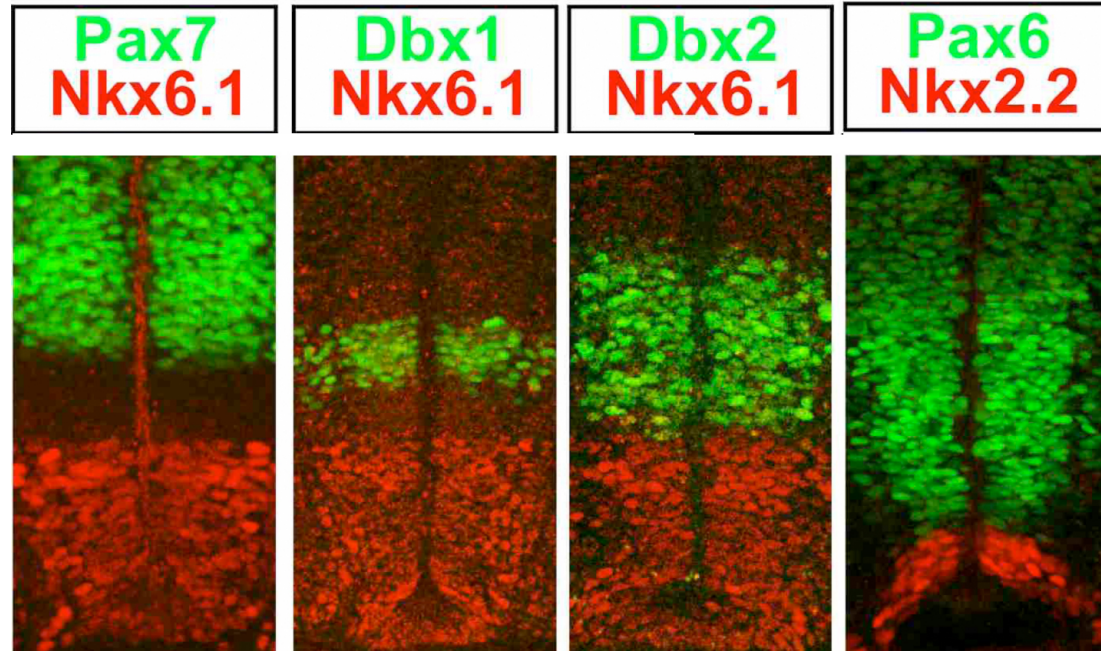
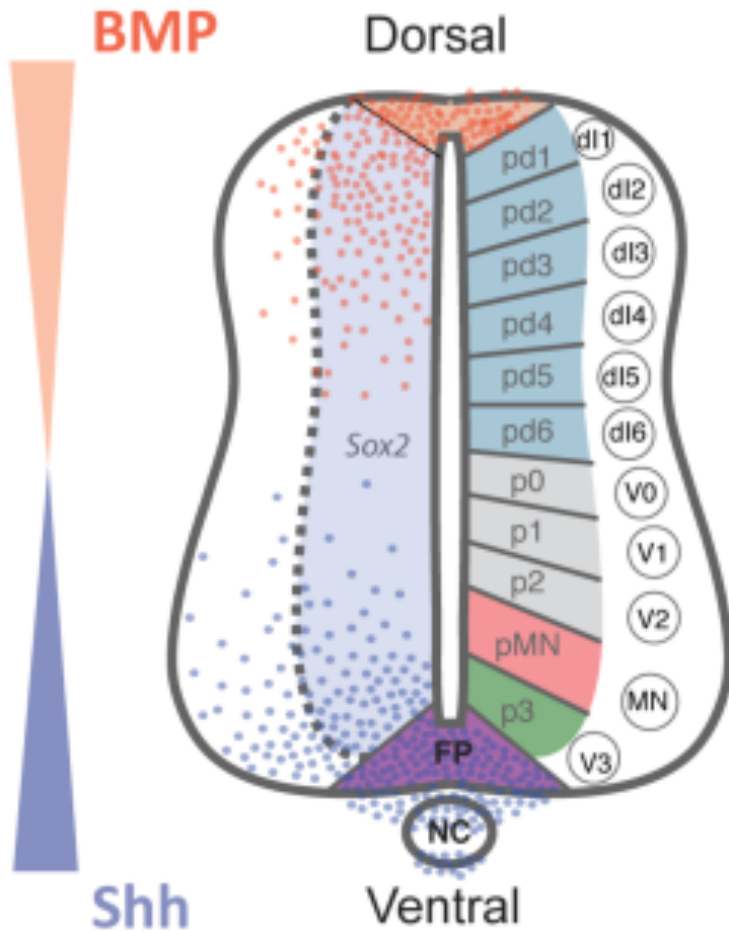


Ramón-y-Cajal (Manual de Histología)

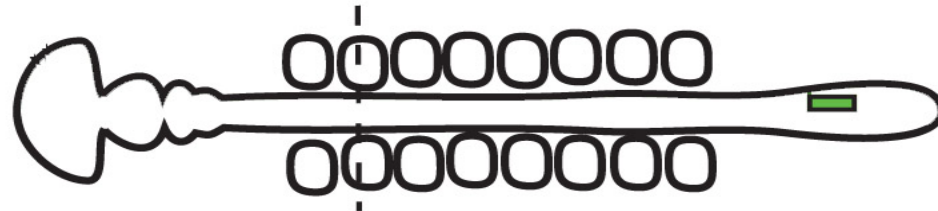
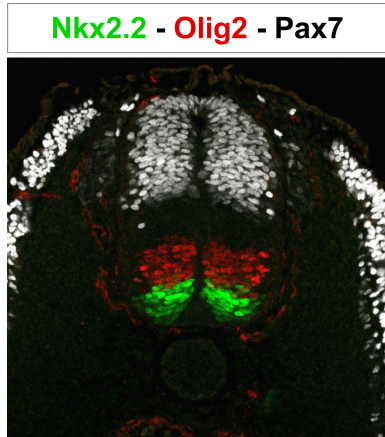
Organisation of the neural tube



Organisation of the neural tube



Concentration dependent response



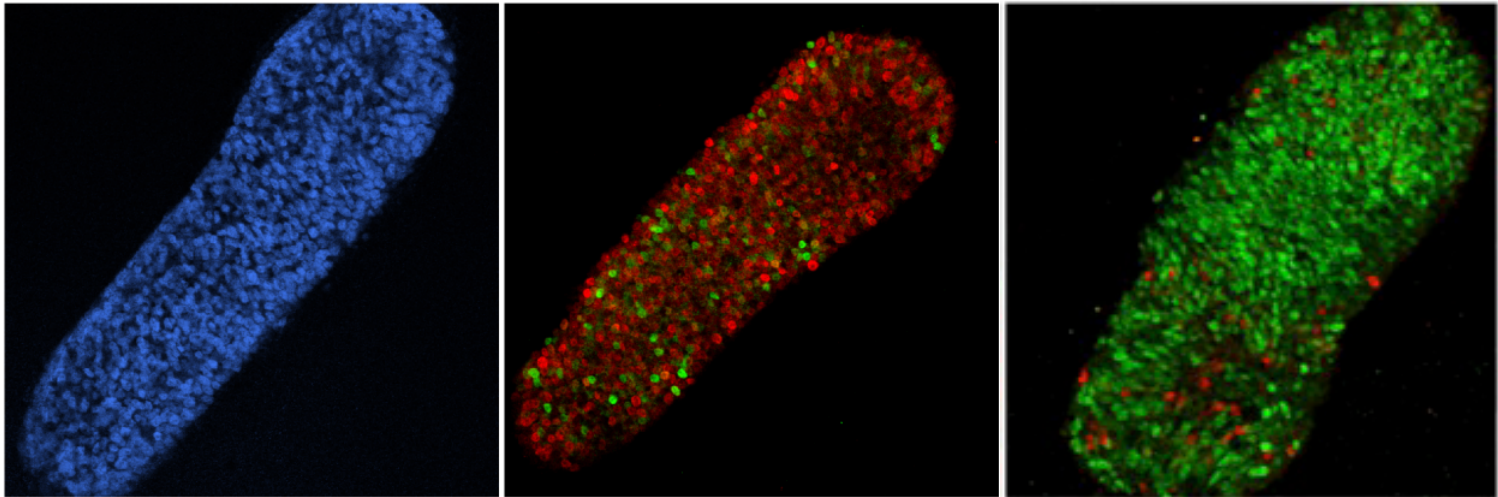
Shh concentration

0 nM

1 nM

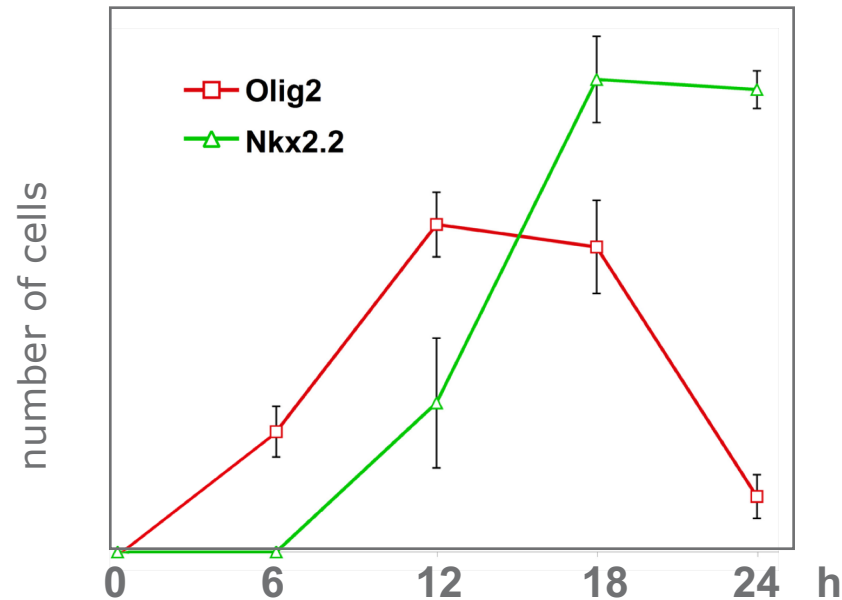
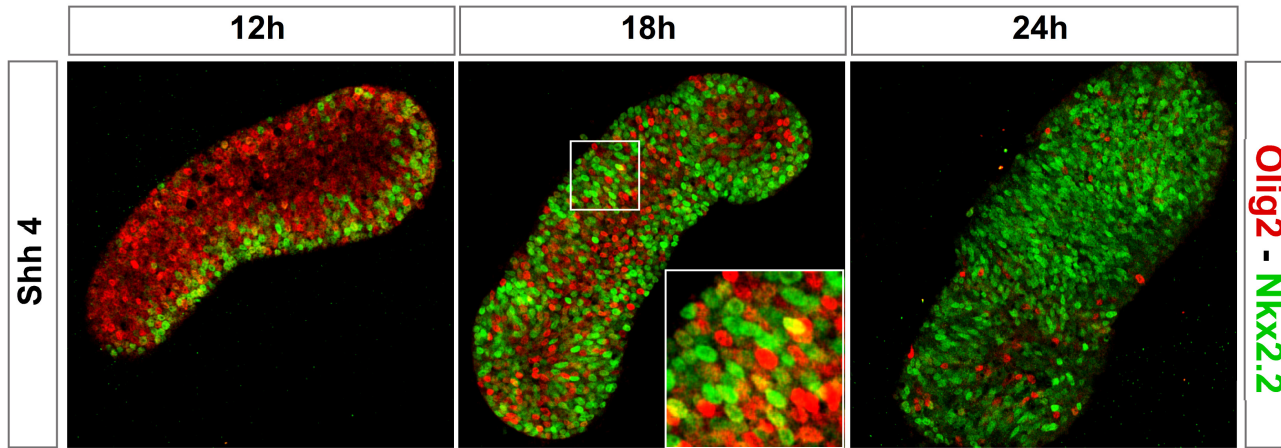
4 nM

Pax7 - Olig2 - Nkx2.2



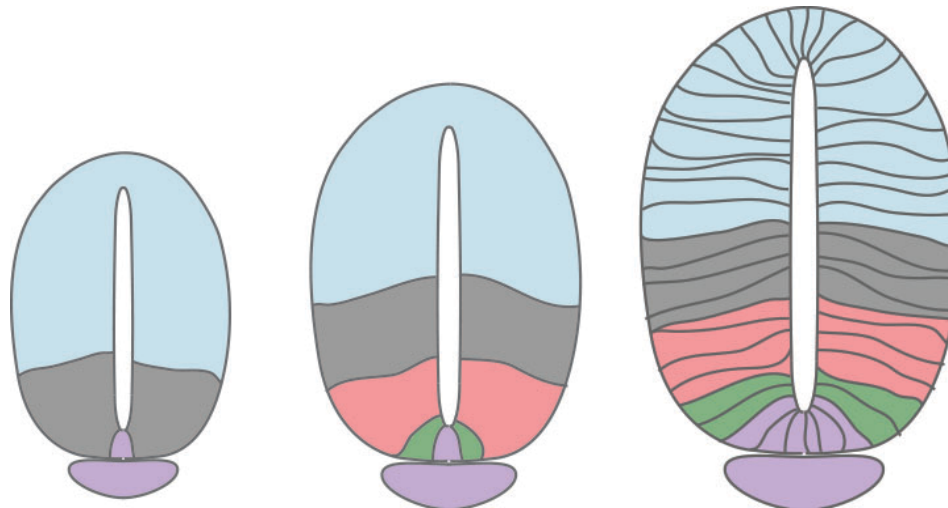
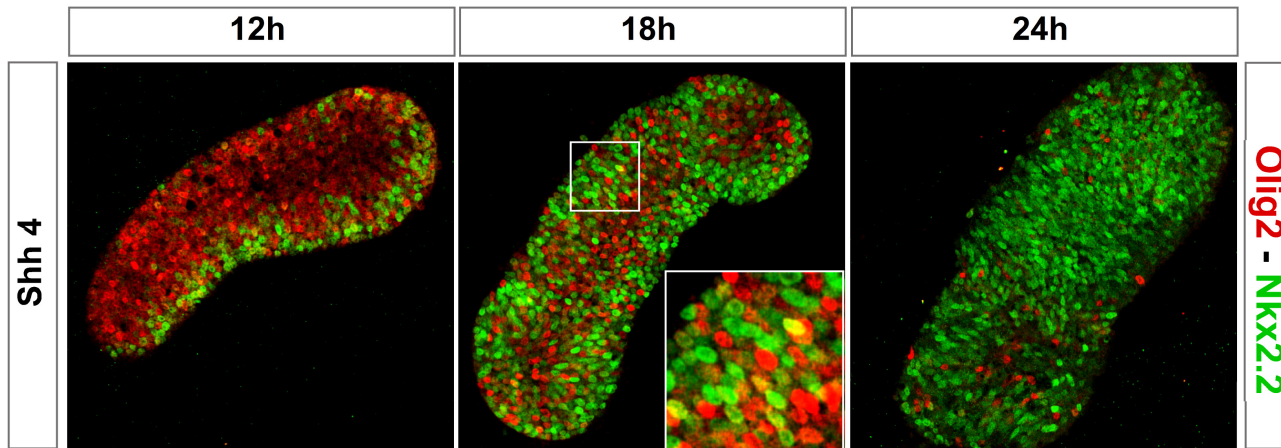
Dessaud et al (2007) PMID: 18046410

Duration dependent response



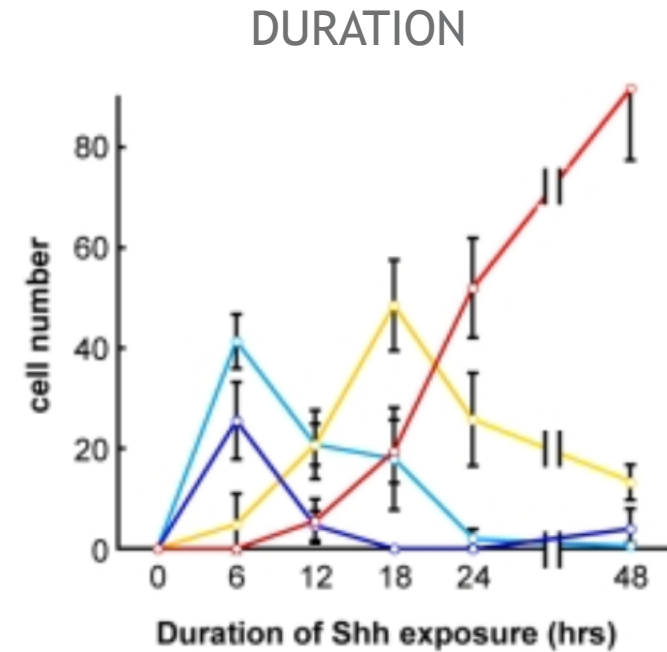
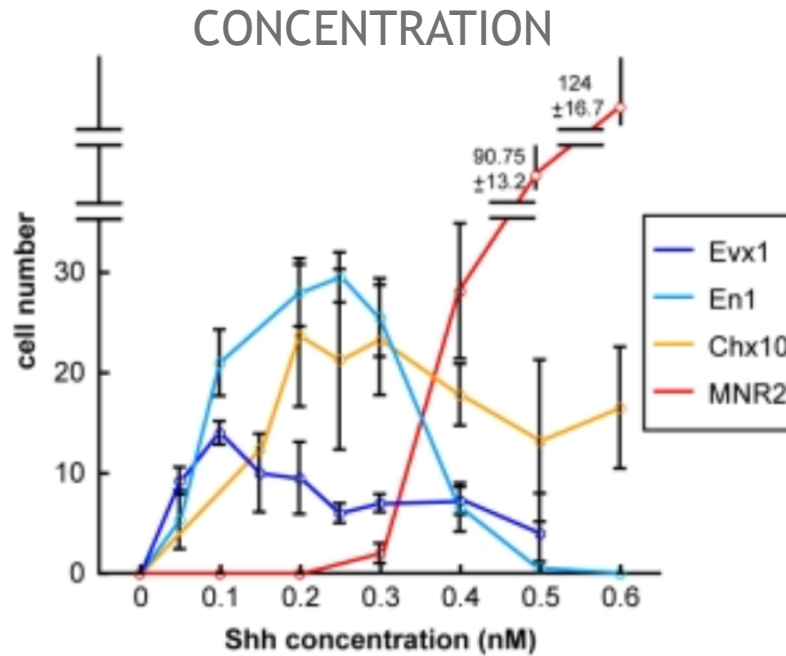
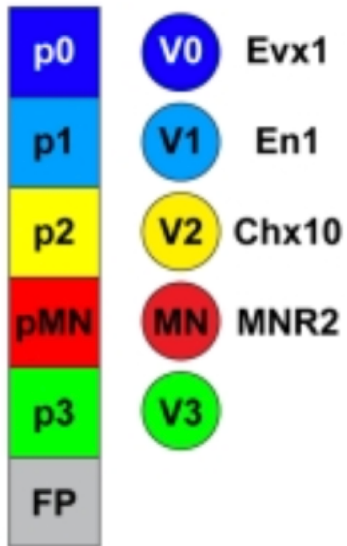
Dessaud et al
(2007)
PMID: 18046410

Duration dependent response



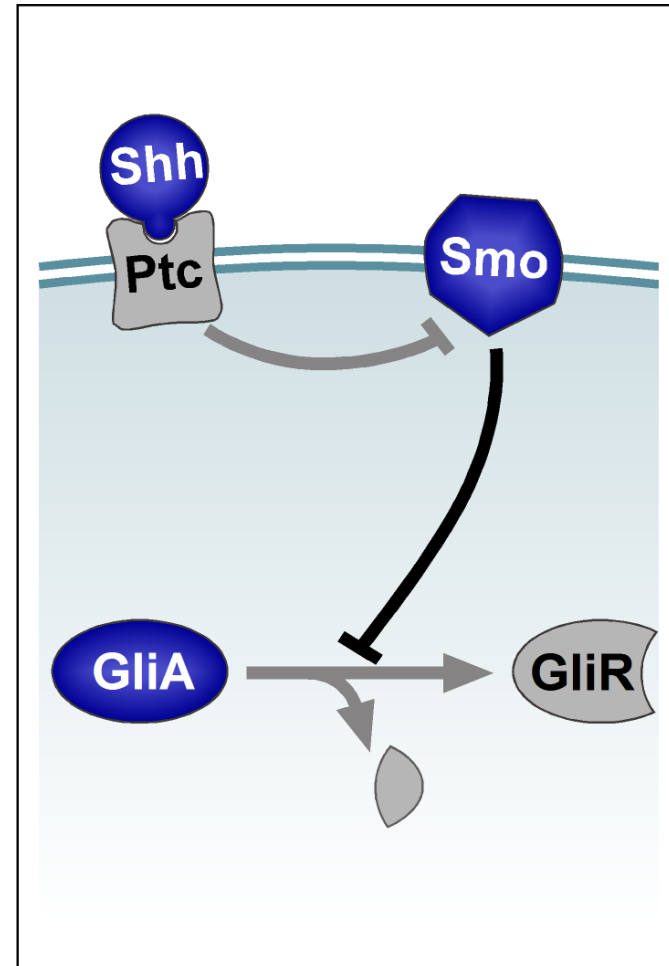
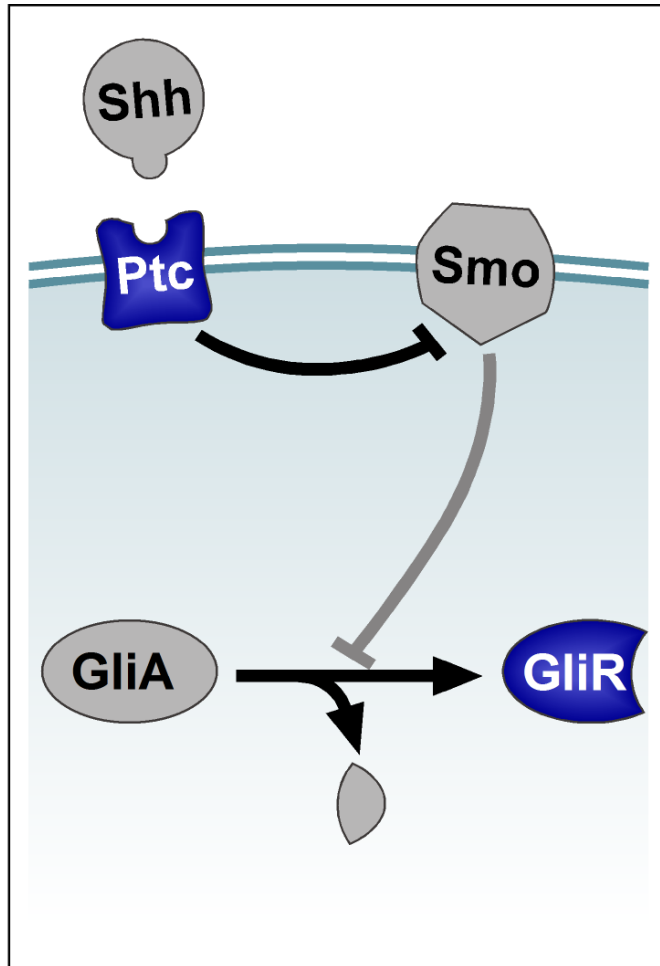
Dessaud et al
(2007)
PMID: 18046410

Concentration and duration pattern

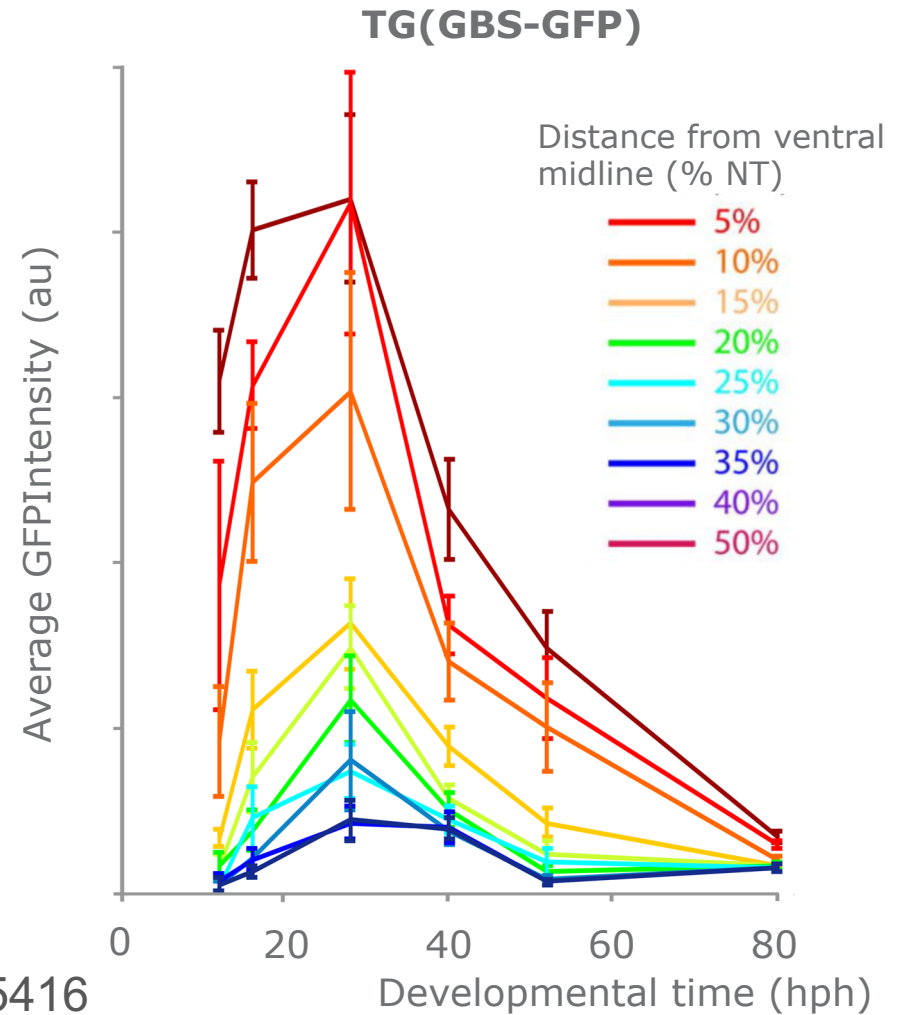
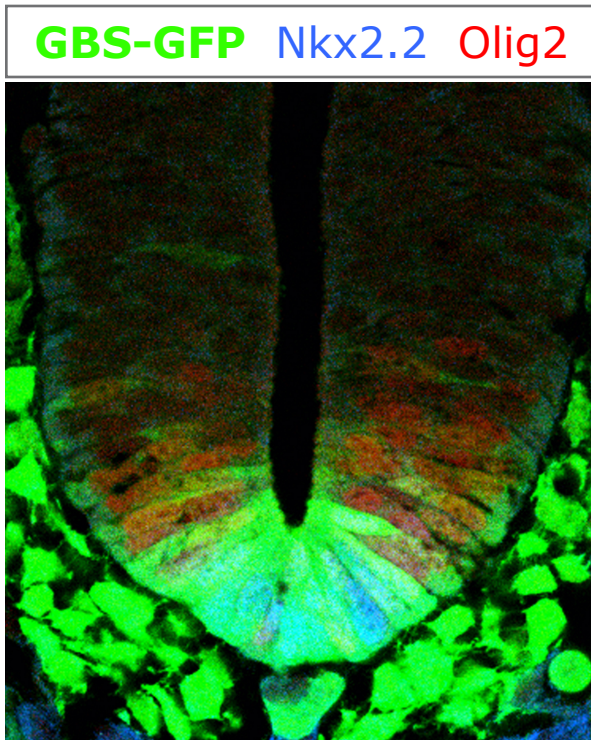


Dessaud et al (2010) PMID: 20532235

Shh signal transduction

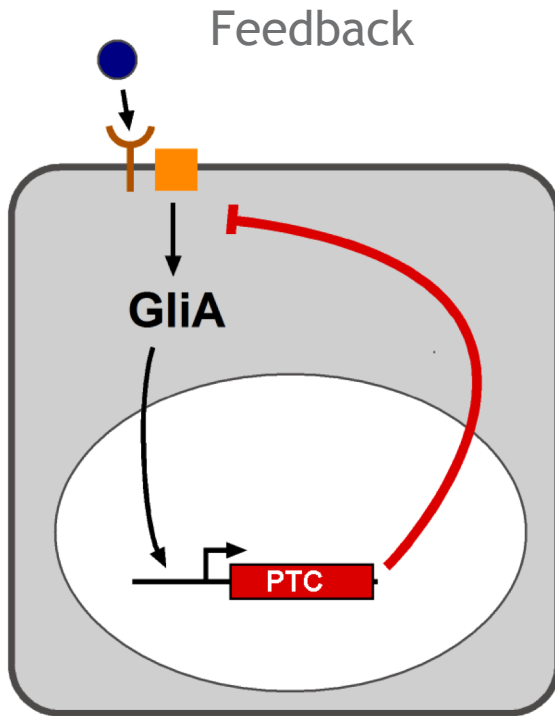


Shh signalling adapts over time

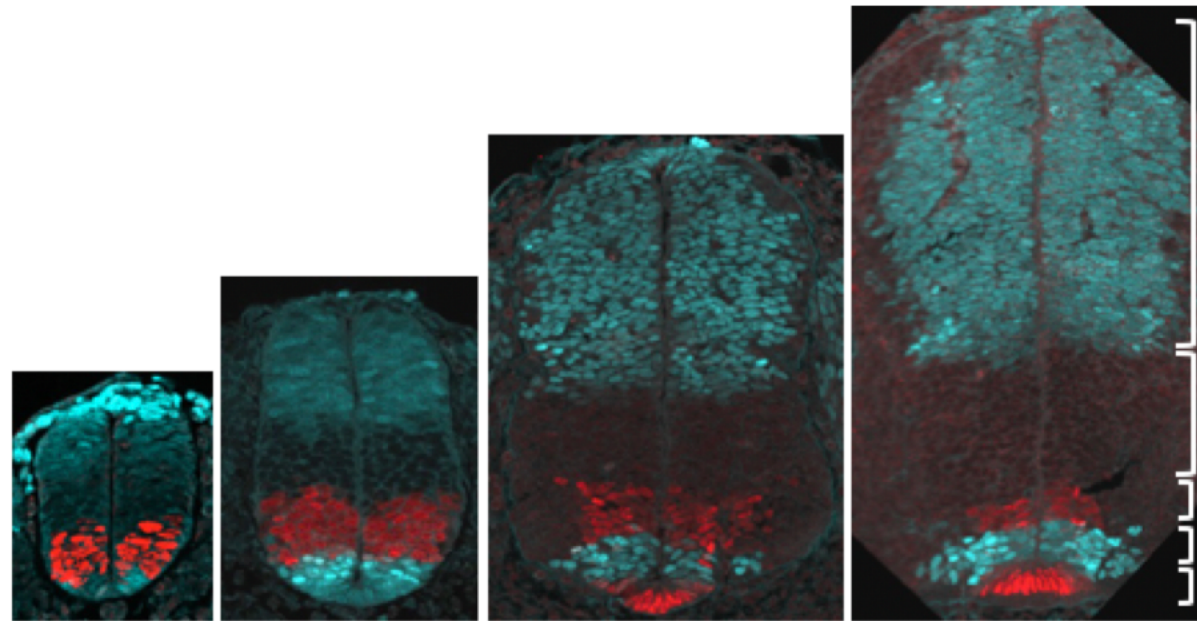


Balaskas et al (2012) PMID: 22265416

Shh signalling adapts over time



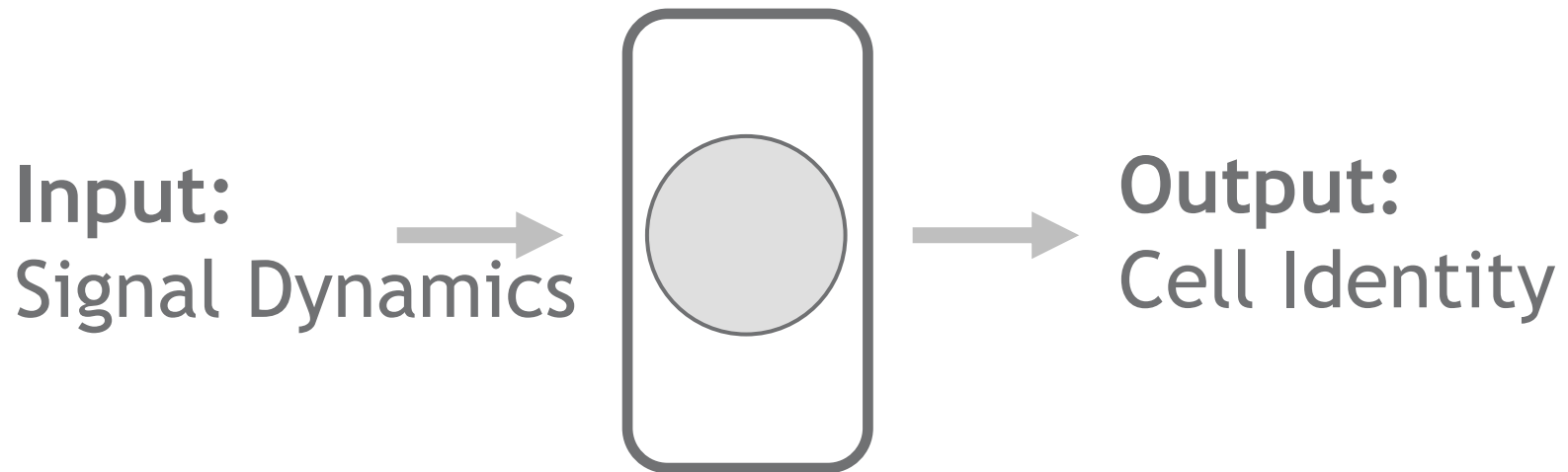
Growth



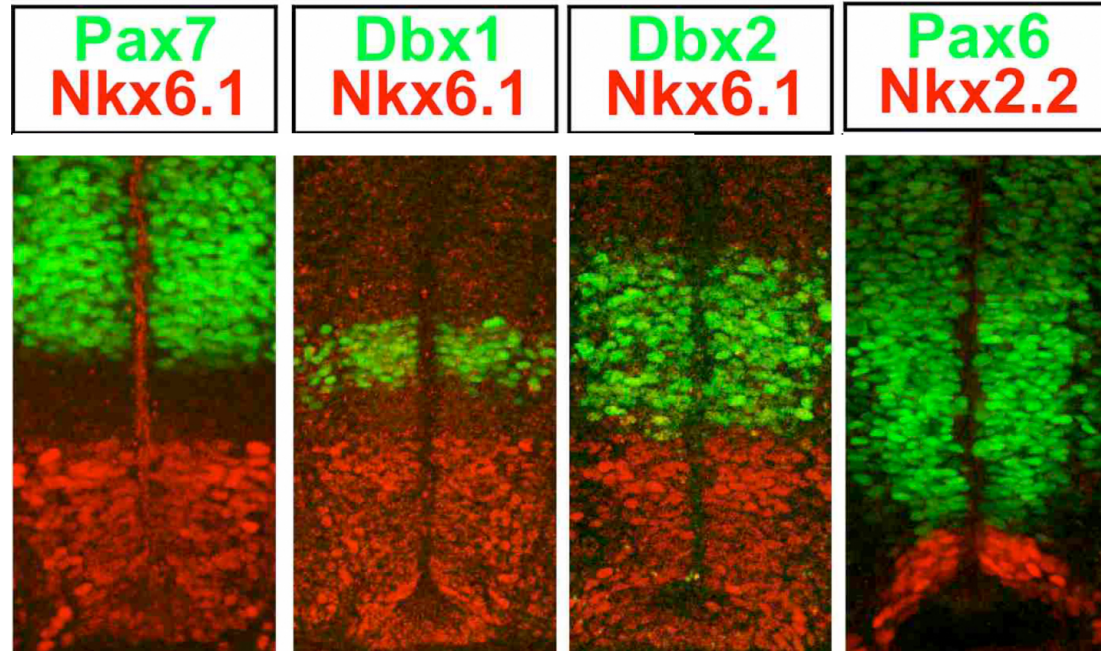
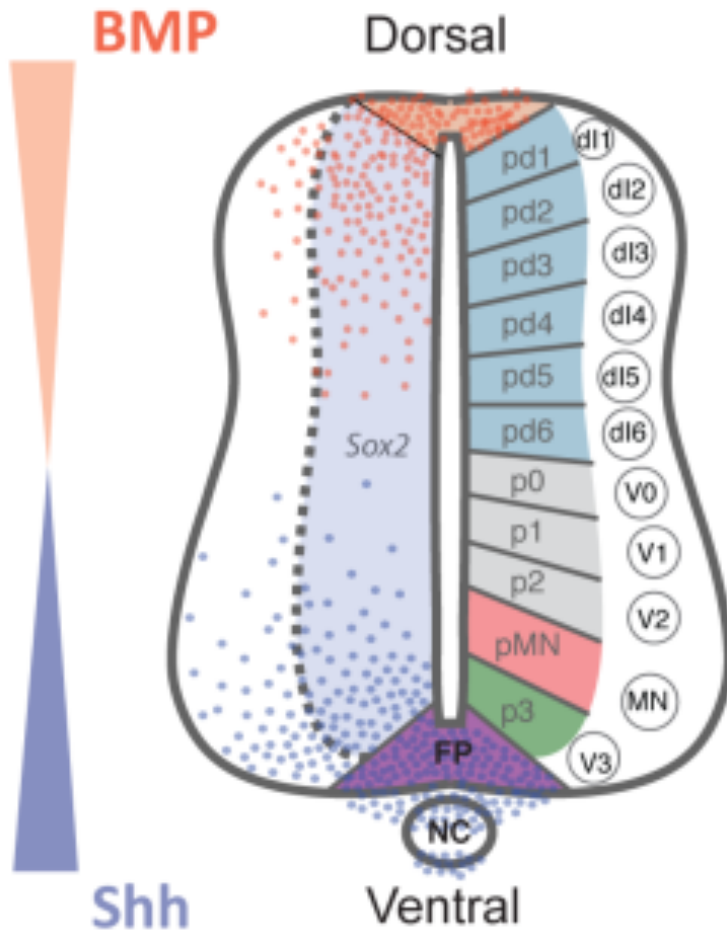
● Shh ■ Smo Y Ptc1

Kicheva et al (2014) PMID: 25258086

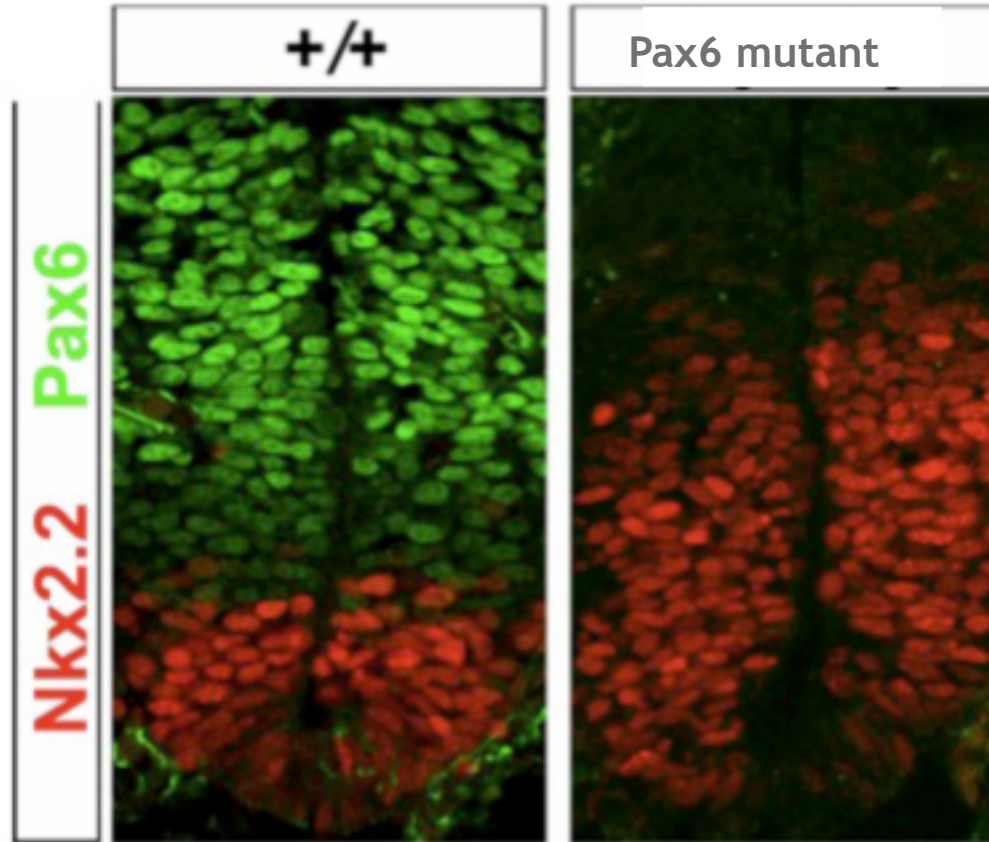
Cellular Information Processing



Shh directs a gene regulatory network

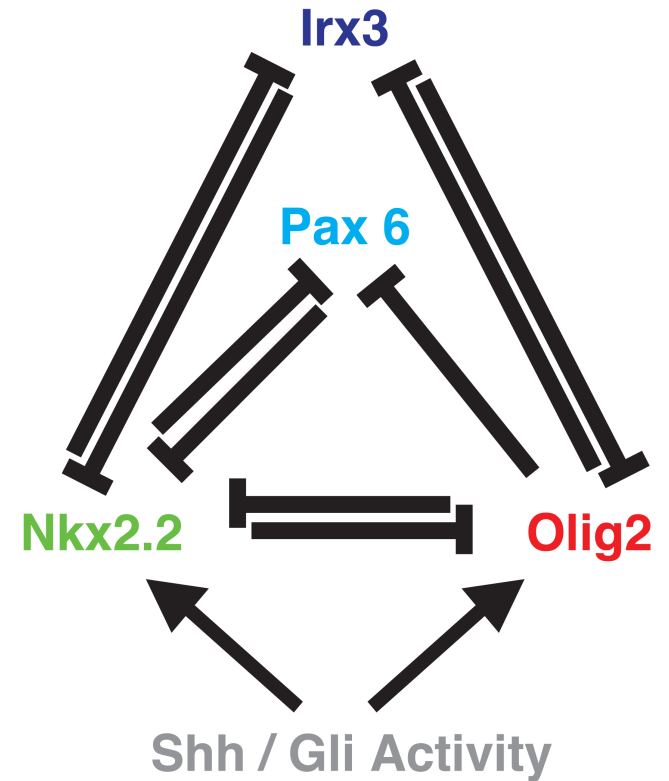
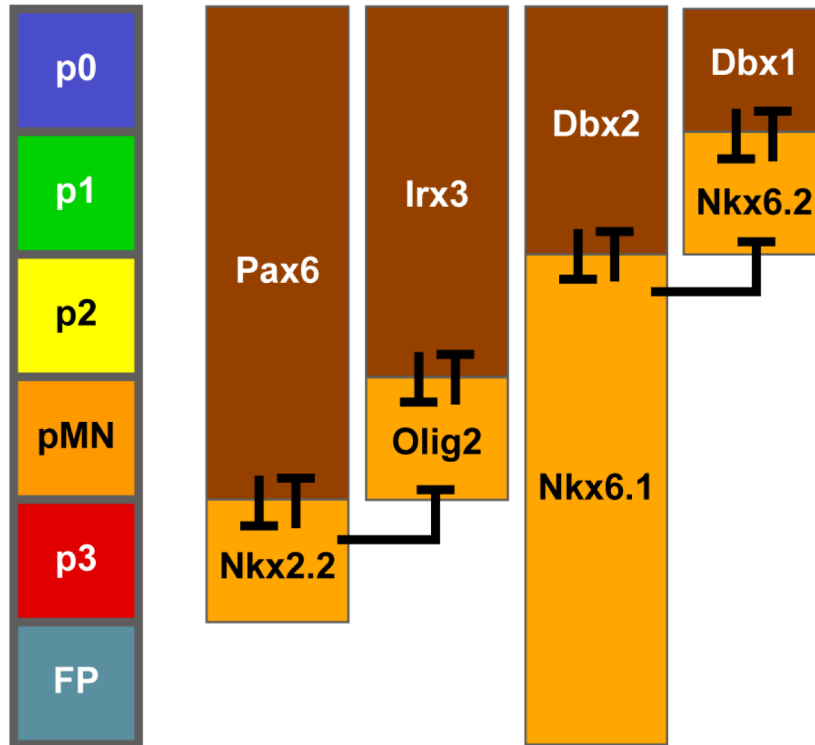


Pax6 represses Nkx2.2

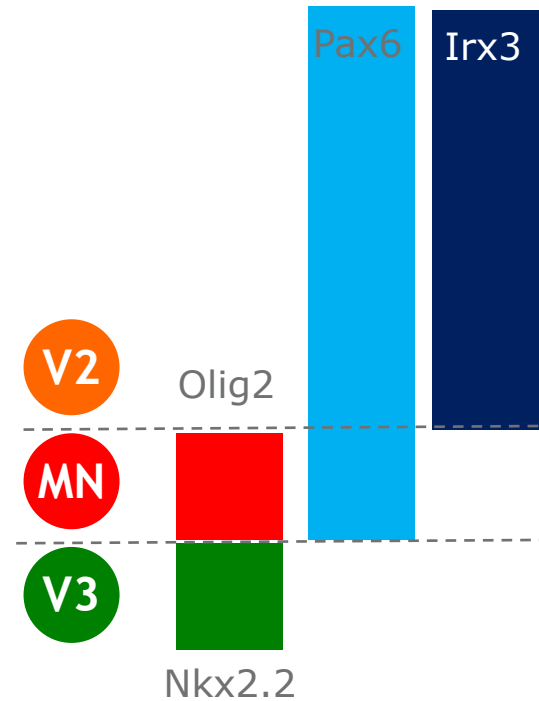
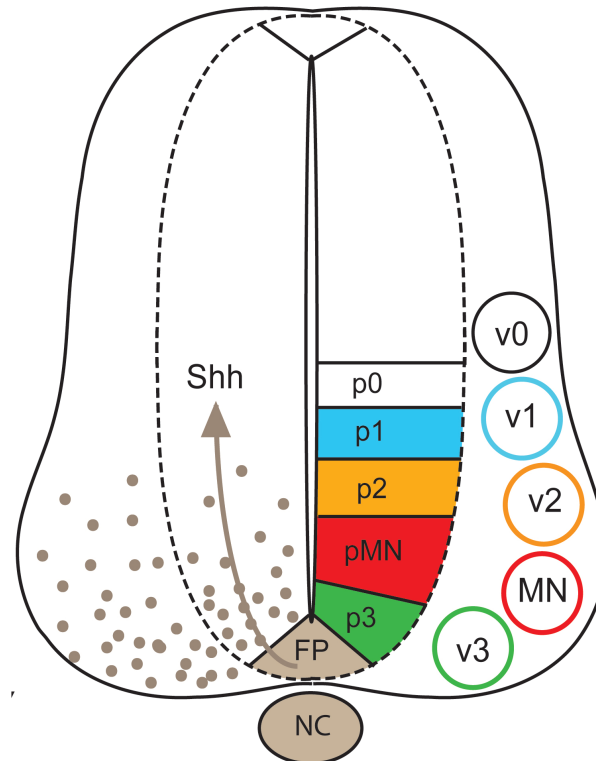
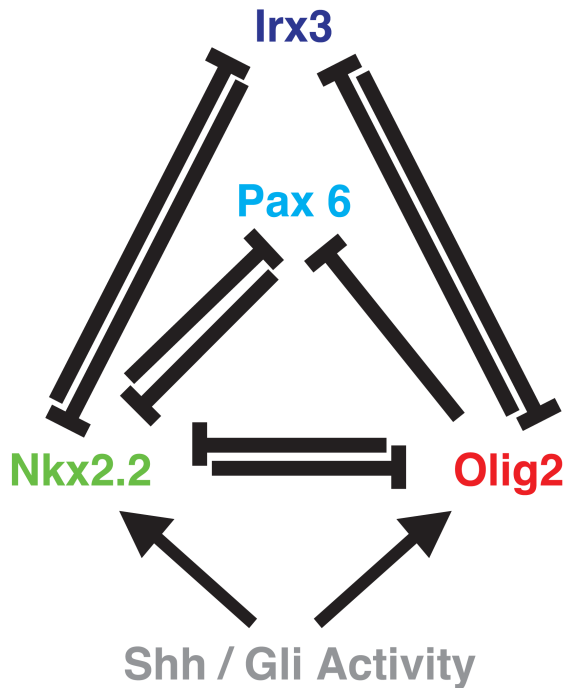


Ericson et al (1997) PMID: 9230312

Reconstructing the GRN

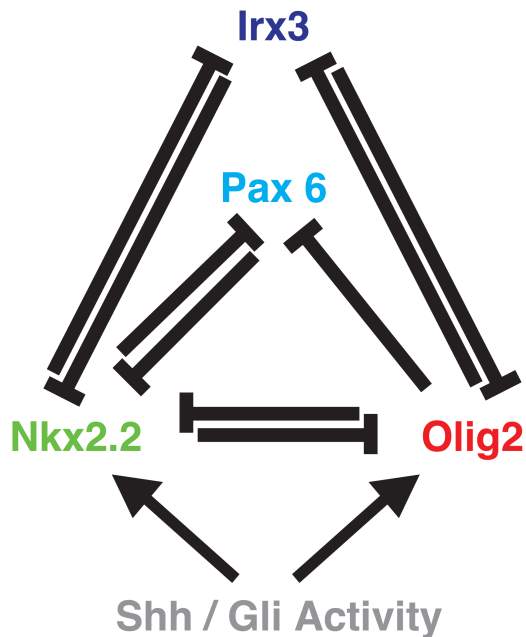


A circuit defining two boundaries



An ODE description of the circuit

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



After Shea and Ackers

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

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

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

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

Cohen et al (2014)
PMID: 25294939

$$Z_{Pax} = K_{P_Pax}[P] + (1 + 2K_{O_Pax}[O] + (K_{O_Pax}[O])^2)(1 + 2K_{N_Pax}[N] + (K_{N_Pax}[N])^2)$$

$$Z_{Irx} = K_{P_Irx}[P] + (1 + 2K_{O_Irx}[O] + (K_{O_Irx}[O])^2)(1 + 2K_{N_Irx}[N] + (K_{N_Irx}[N])^2)$$

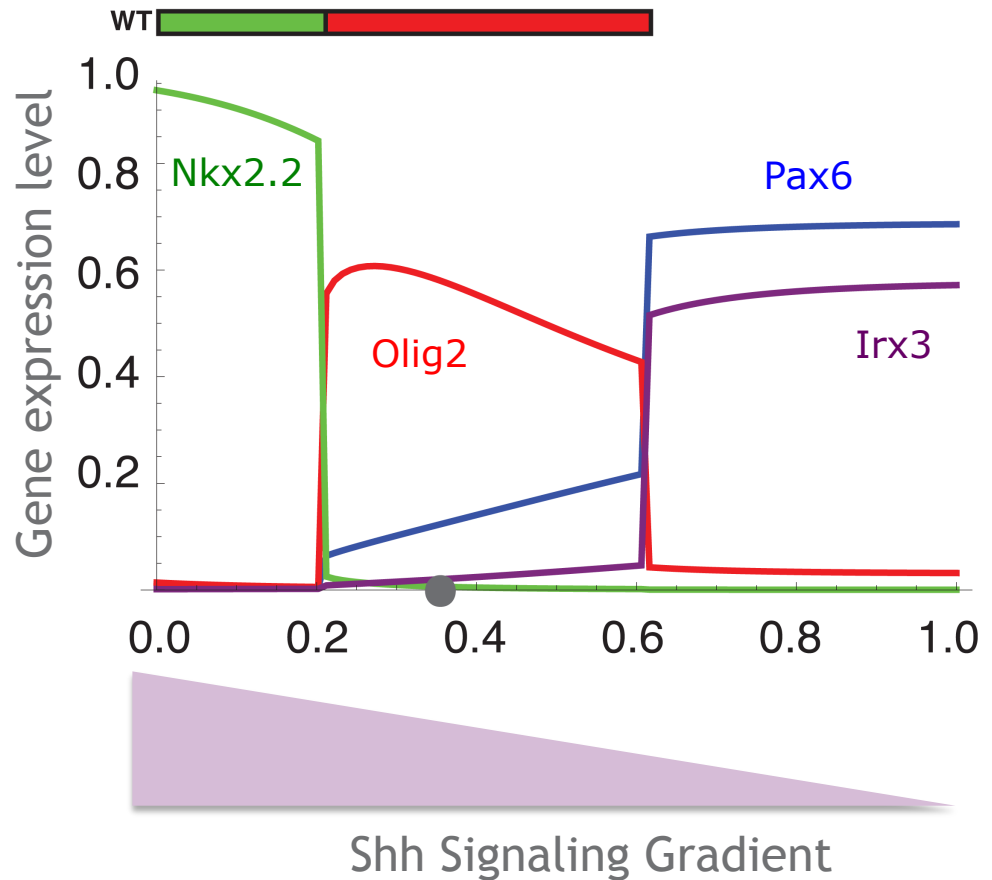
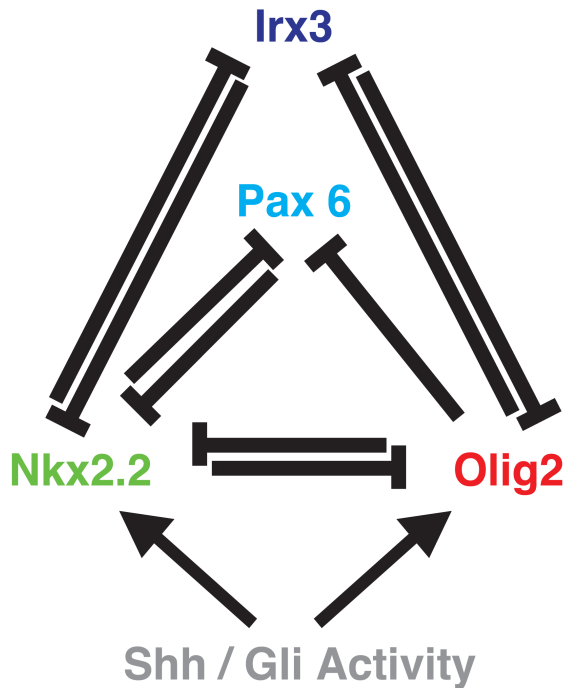
$$Z_O = K_{P_O}[P] + c_{AP}K_{P_O}[P]K_A[A] + (1 + K_{G_O}[R] + K_{G_O}[A])$$

$$(1 + 2K_{N_O}[N] + (K_{N_O}[N])^2)(1 + 2K_{Irx_O}[Irx] + (K_{Irx_O}[Irx])^2)$$

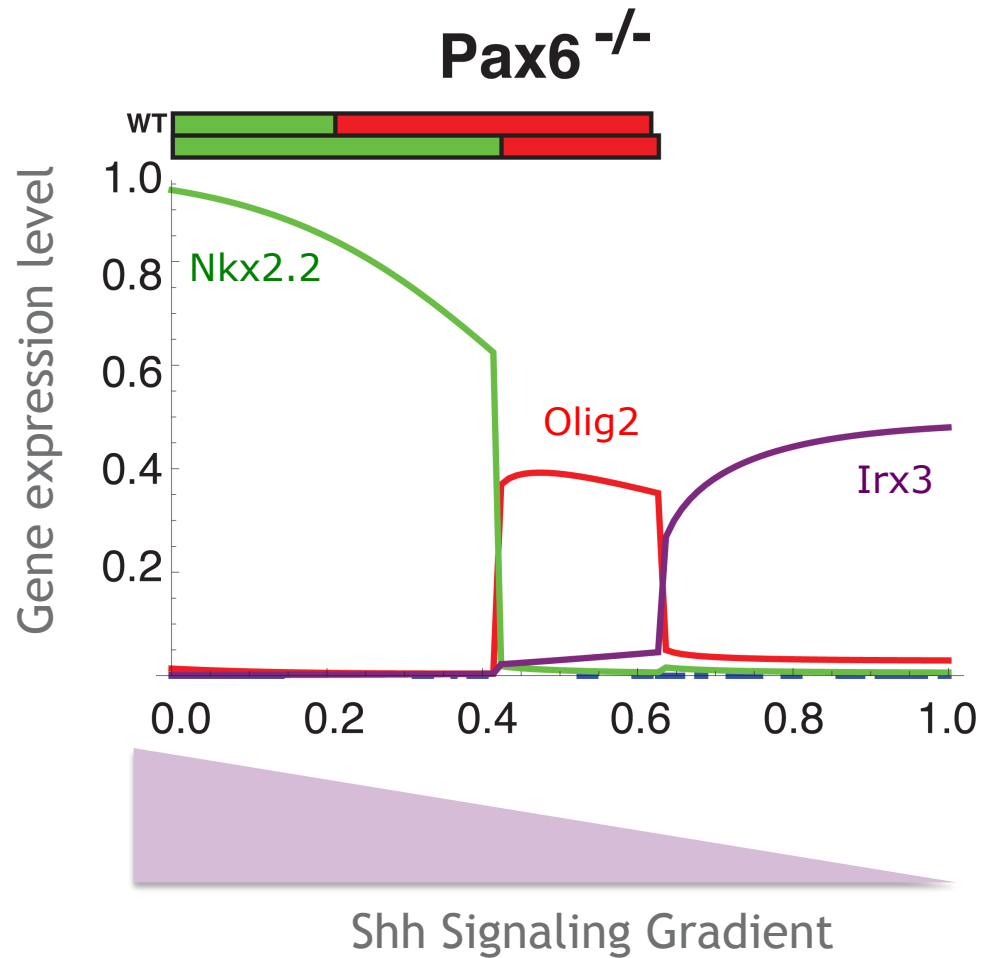
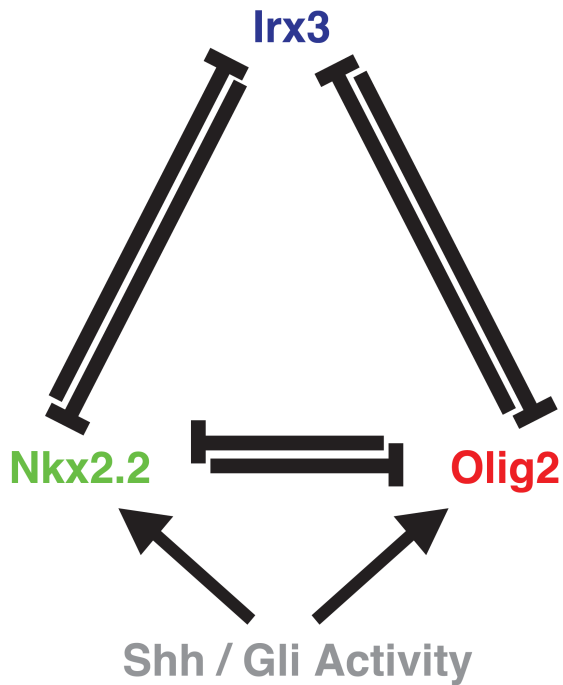
$$Z_N = K_{P_N}[P] + c_{AP}K_{P_N}[P]K_A[A] + (1 + K_{G_N}[R] + K_{G_N}[A])(1 + 2K_{O_N}[O] + (K_{O_N}[O])^2)$$

$$(1 + 2K_{Irx_N}[Irx] + (K_{Irx_N}[Irx])^2)(1 + 2K_{Pax_N}[Pax] + (K_{Pax_N}[Pax])^2)$$

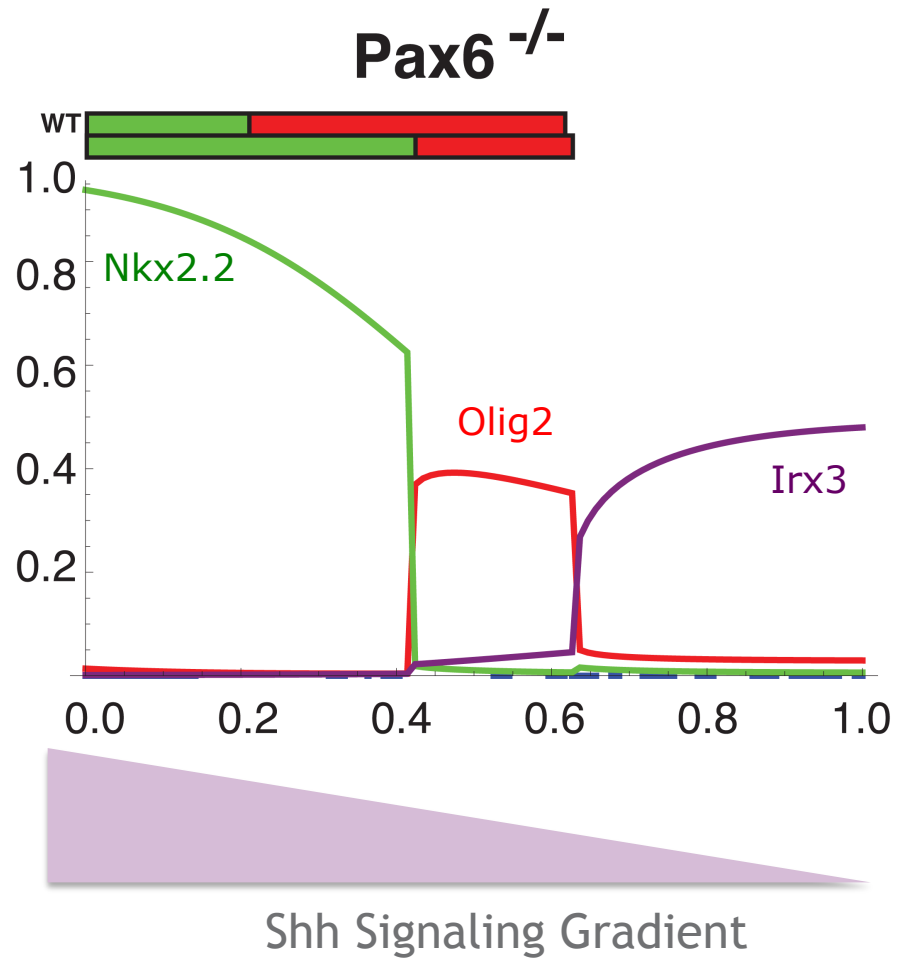
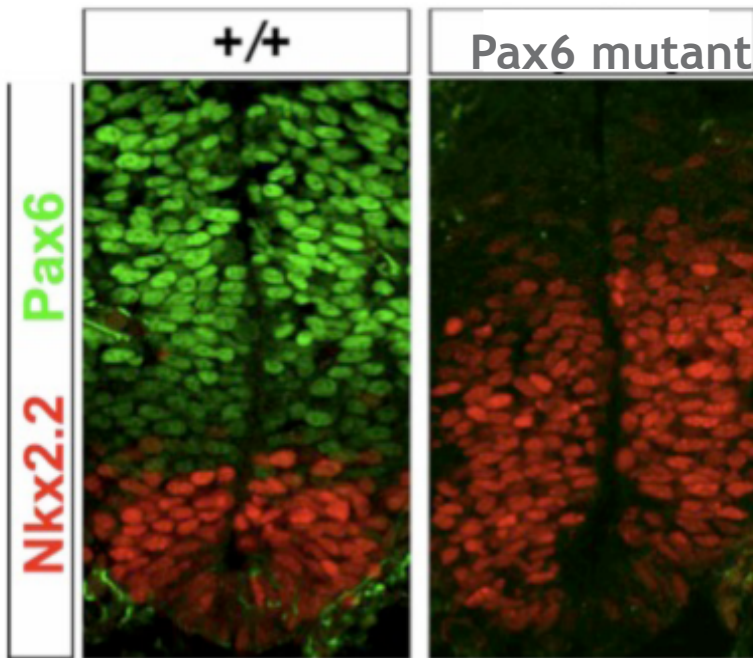
Network generates morphogen response



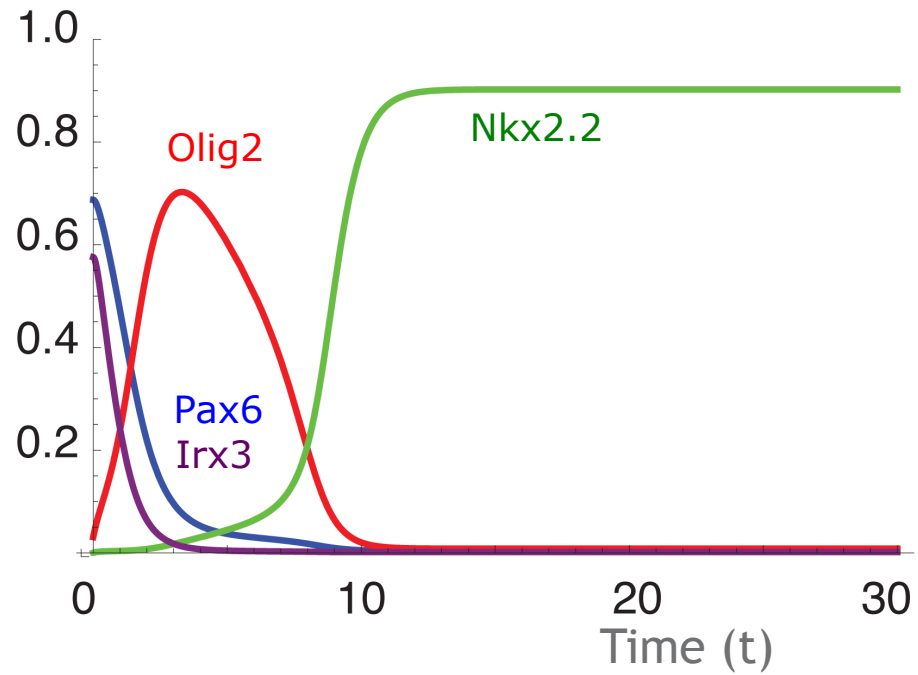
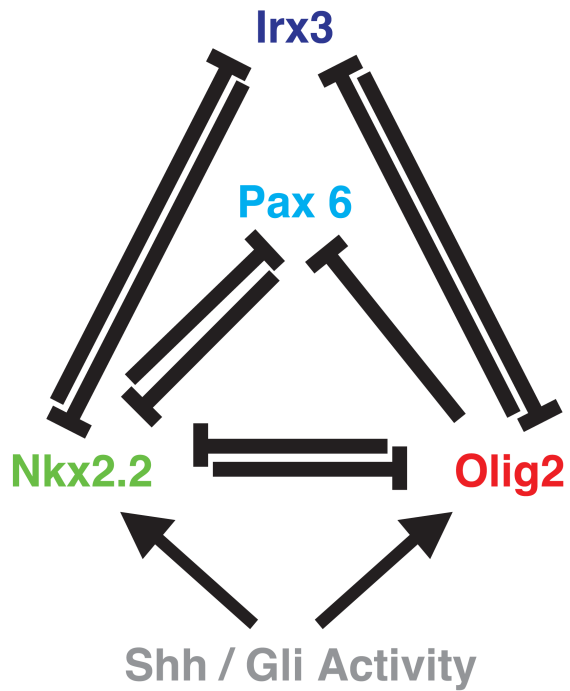
Network generates morphogen response



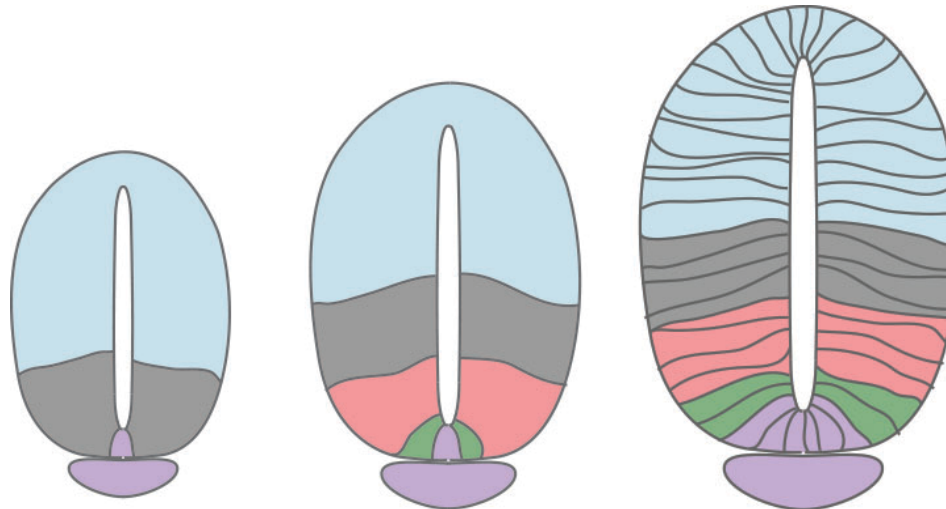
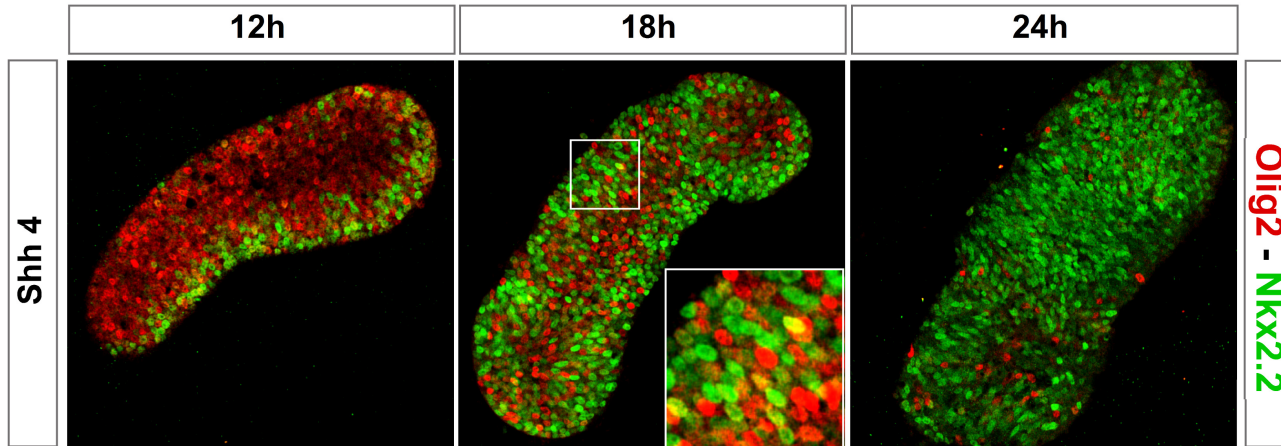
Network generates morphogen response



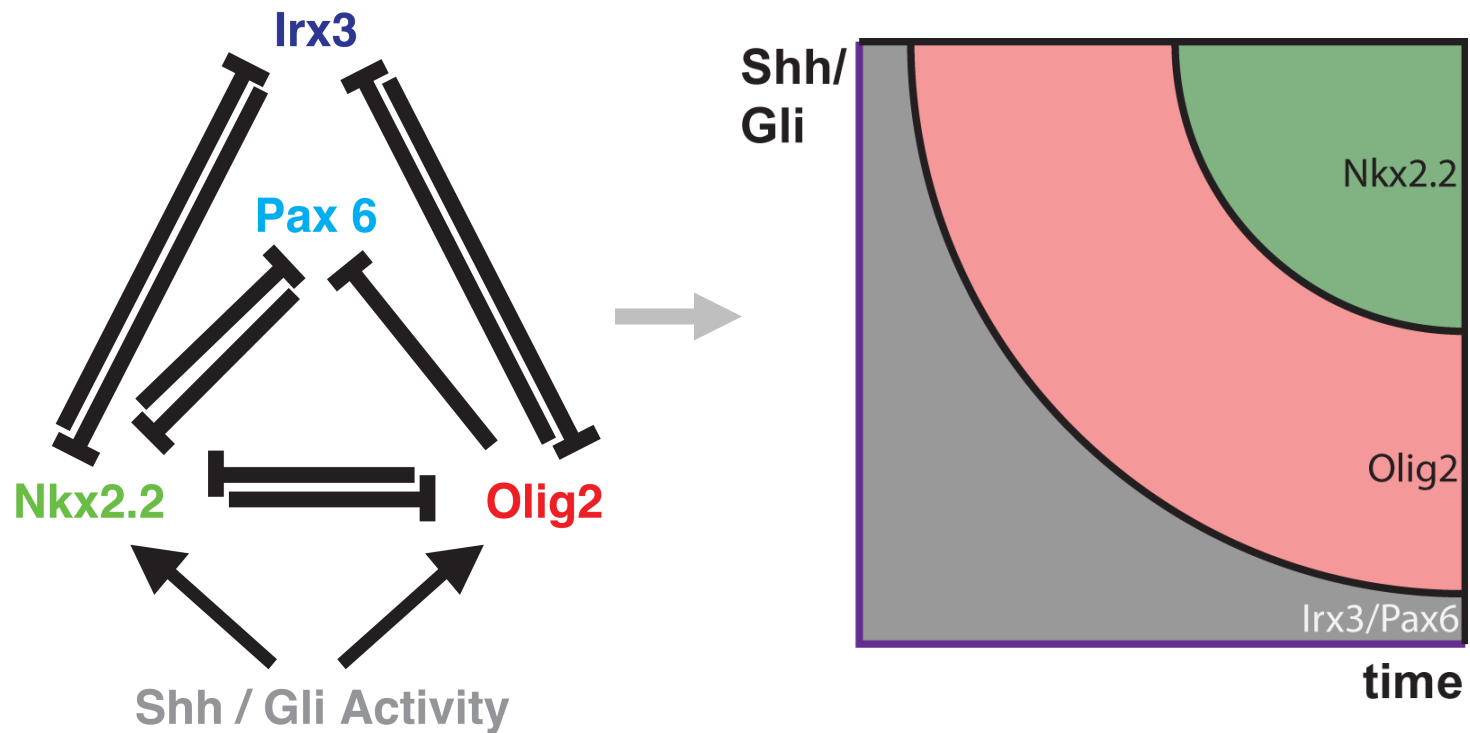
Network generates temporal response



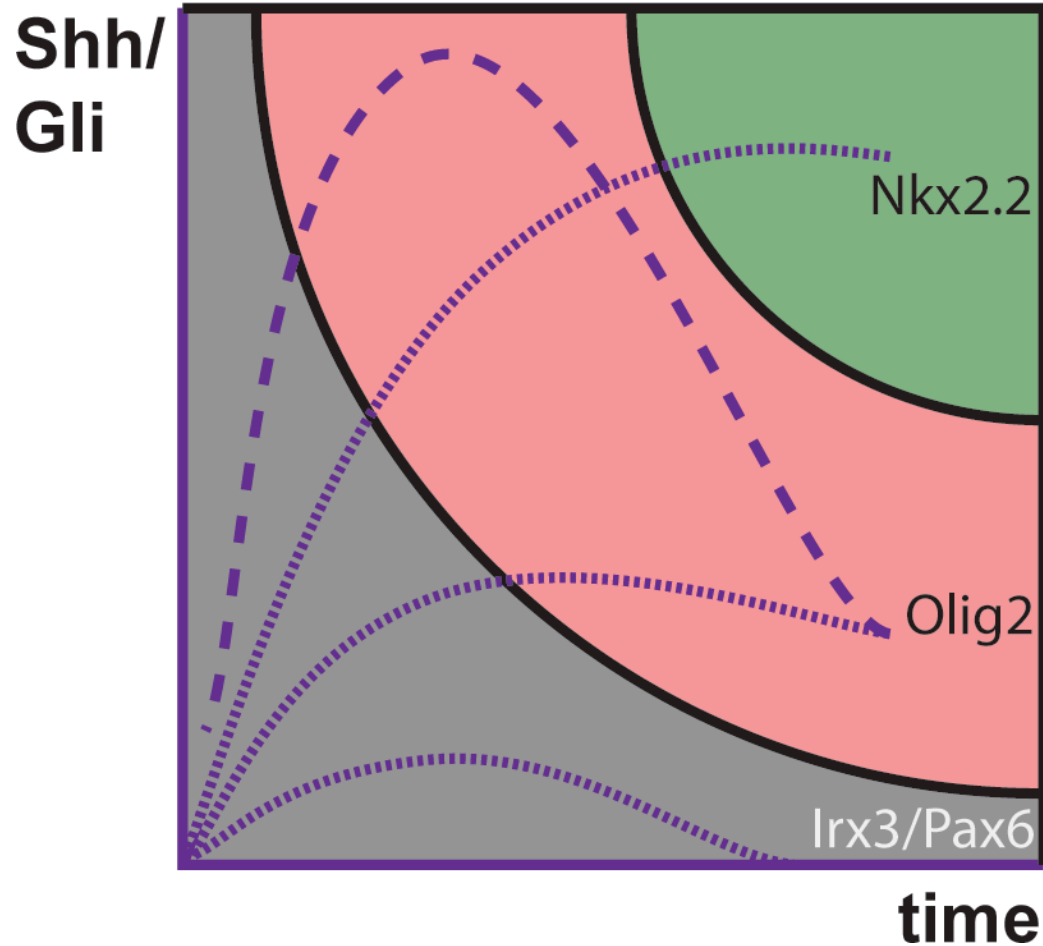
Network generates temporal response



Network generates morphogen response

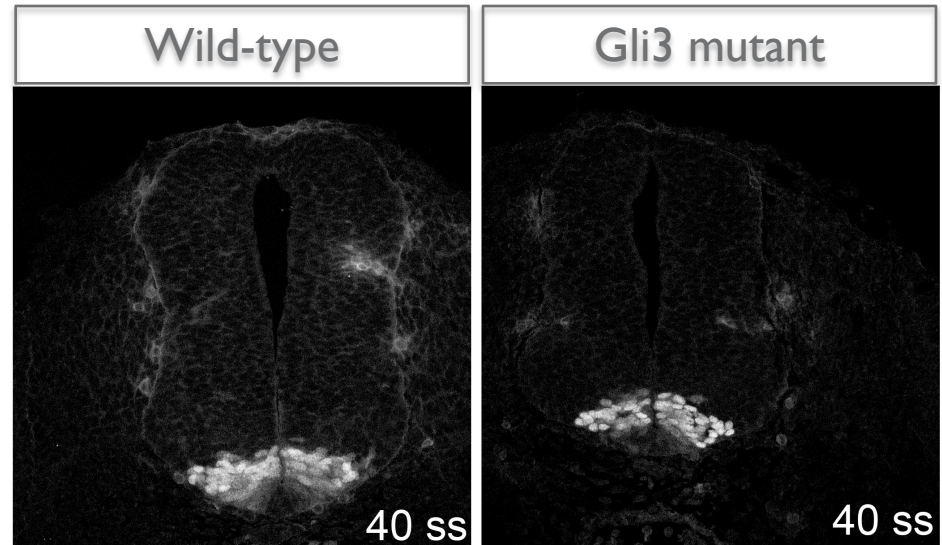
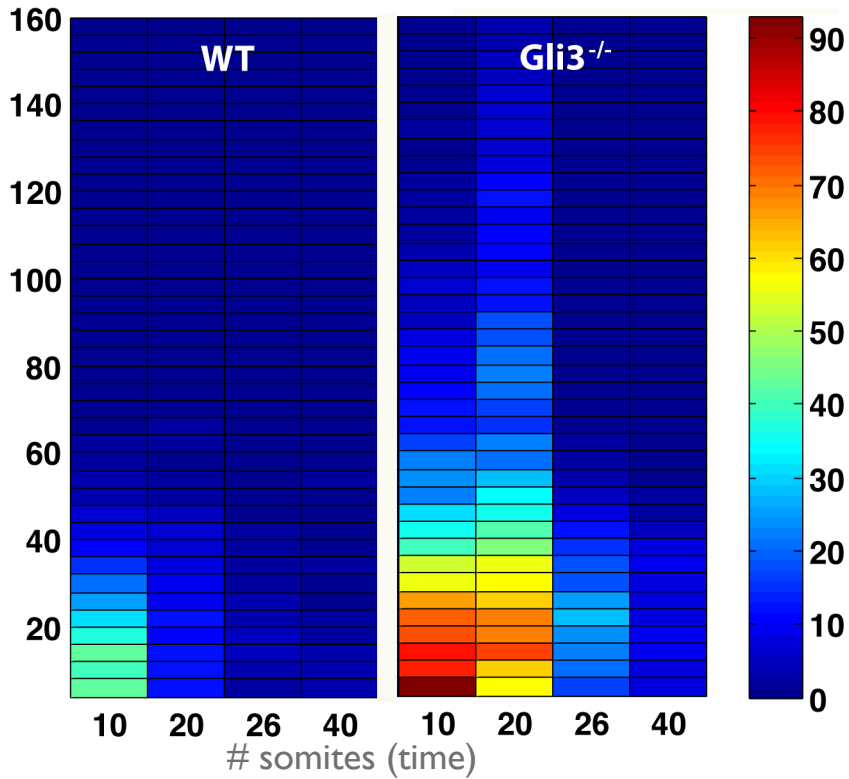


Network confers robustness to signal dynamics



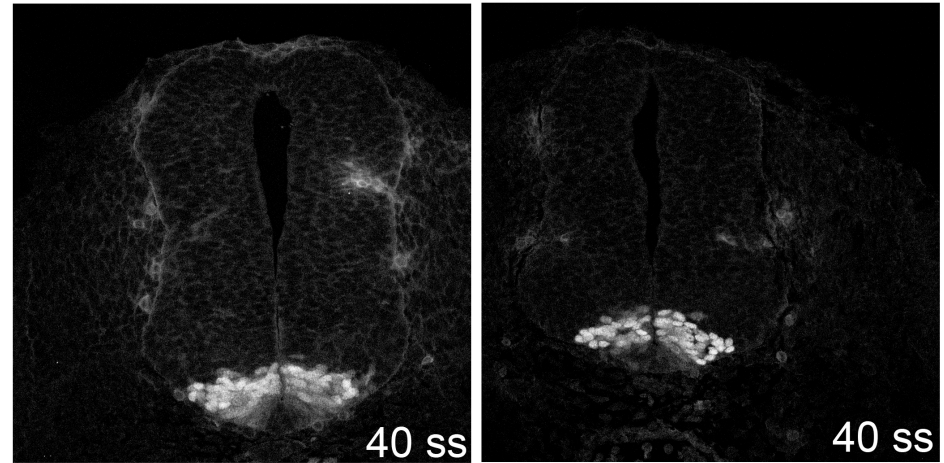
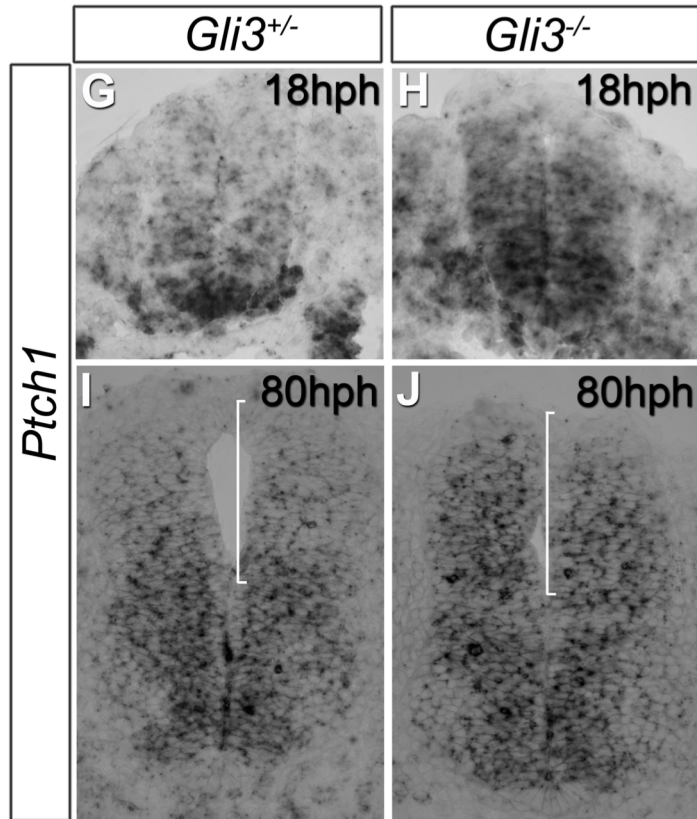
Transient increase in Shh signalling does not affect patter

Gli activity in vivo



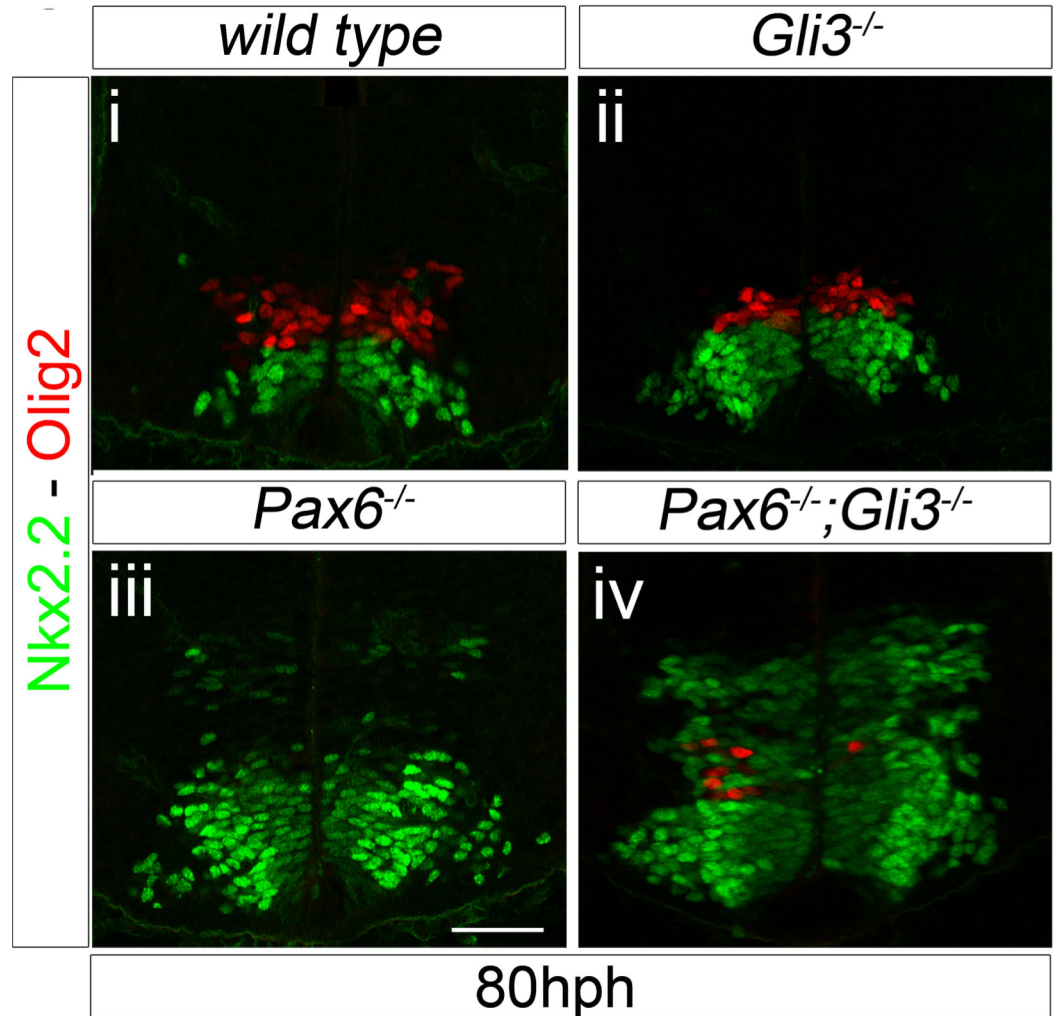
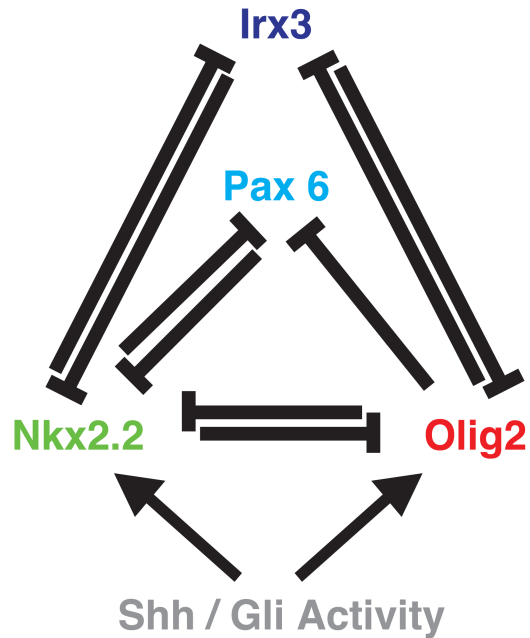
Balaskas et al (2012) PMID: 22265416

Negative feedback buffers increased signaling



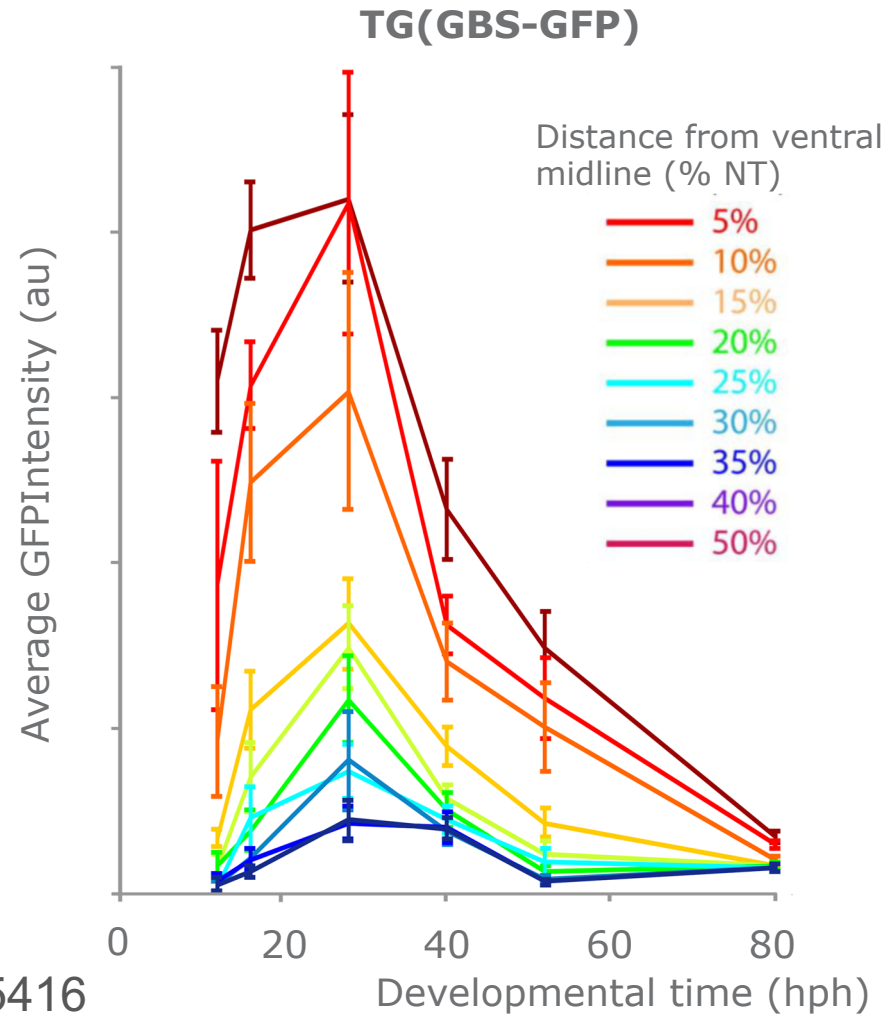
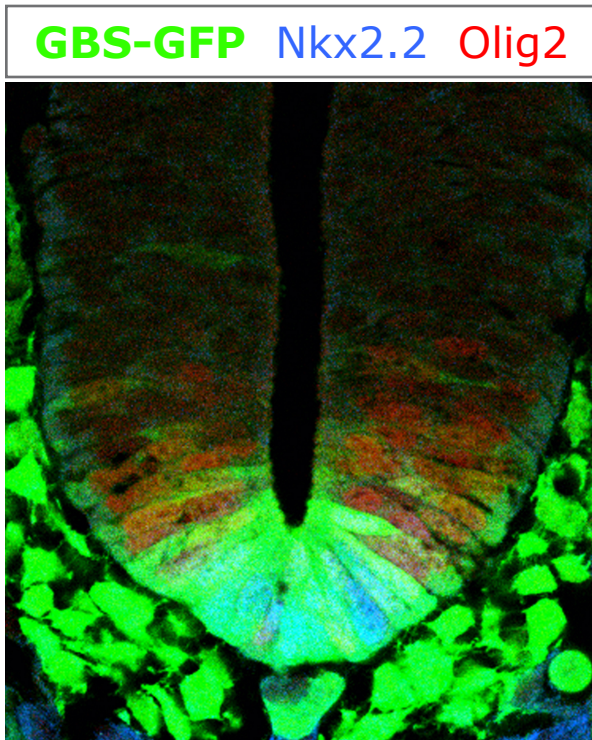
Balaskas et al (2012) PMID: 22265416

Network buffers against transient increase in signal



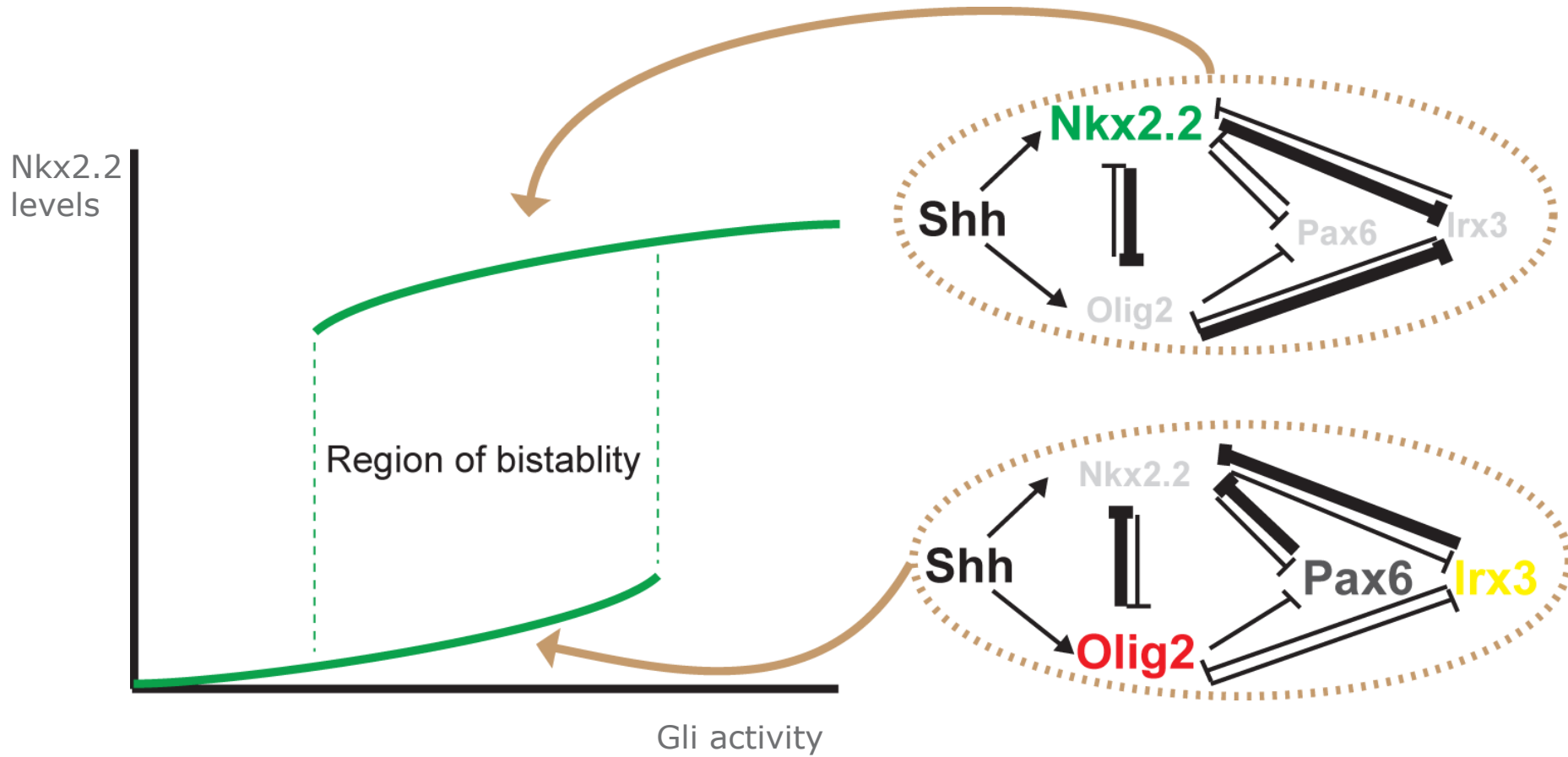
Balaskas et al (2012)
PMID: 22265416

Shh signalling adapts over time

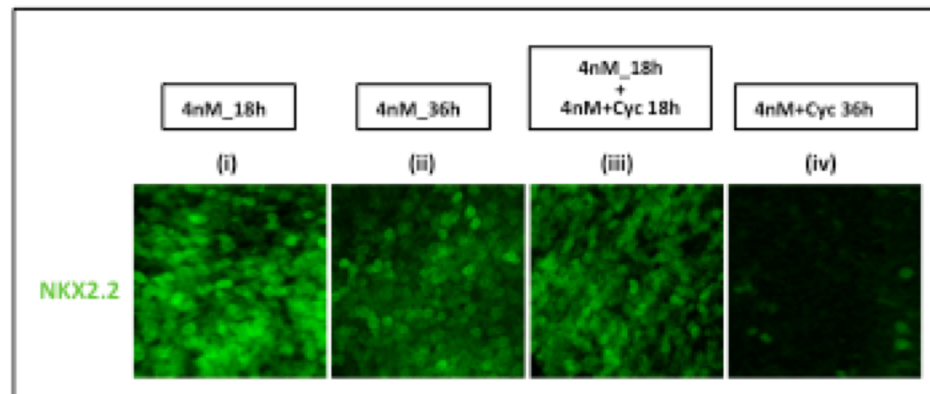
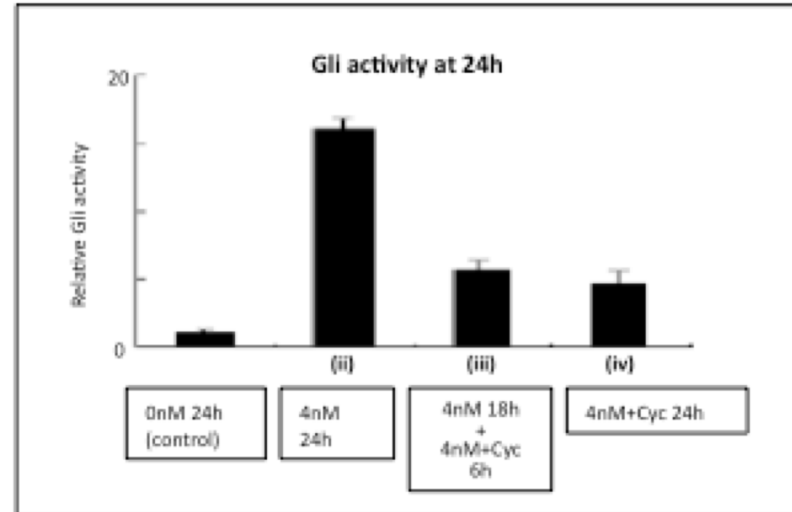
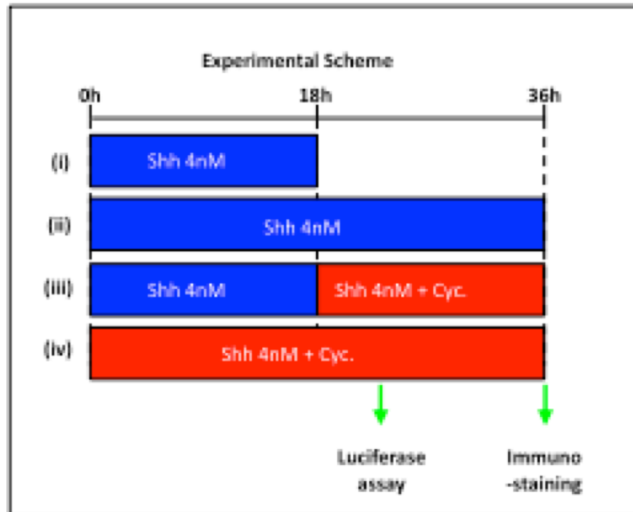


Balaskas et al (2012) PMID: 22265416

Network provides hysteresis

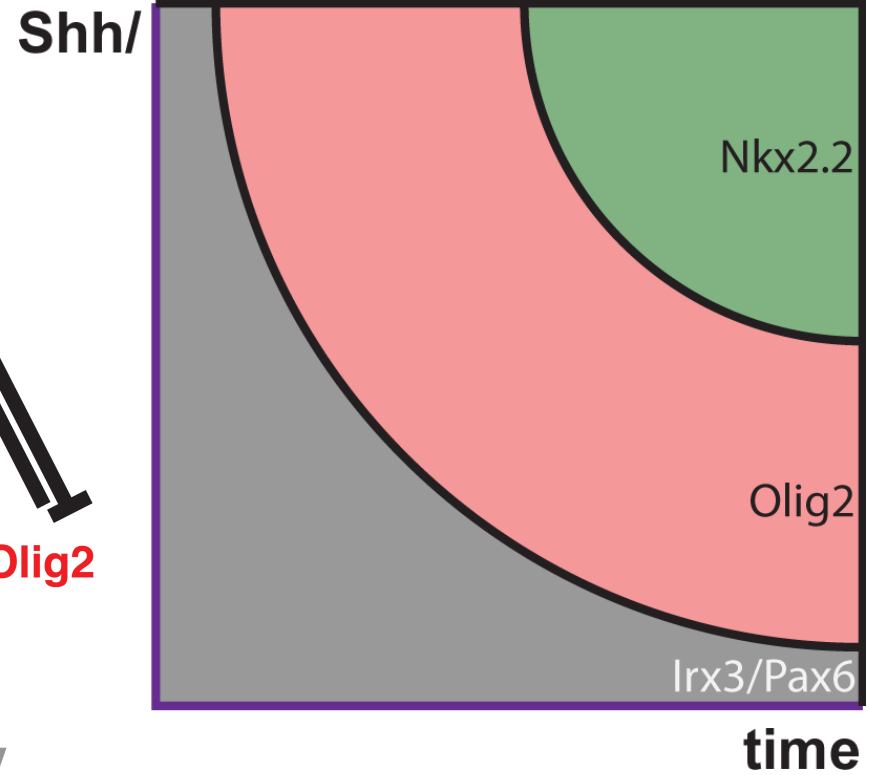
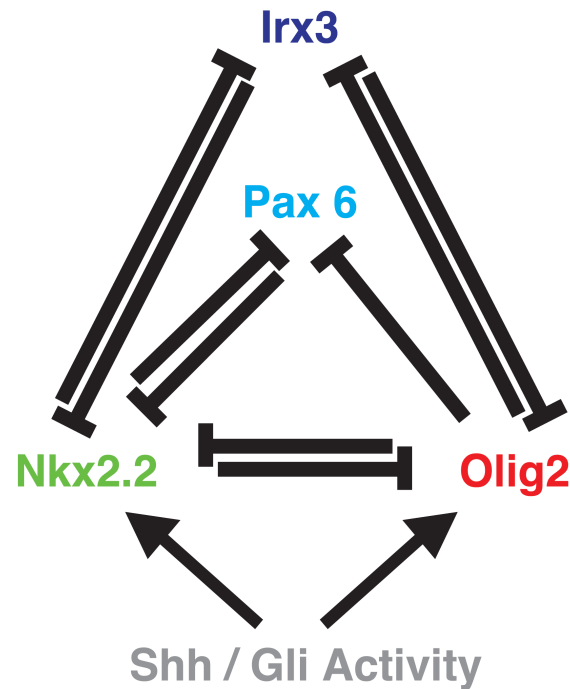
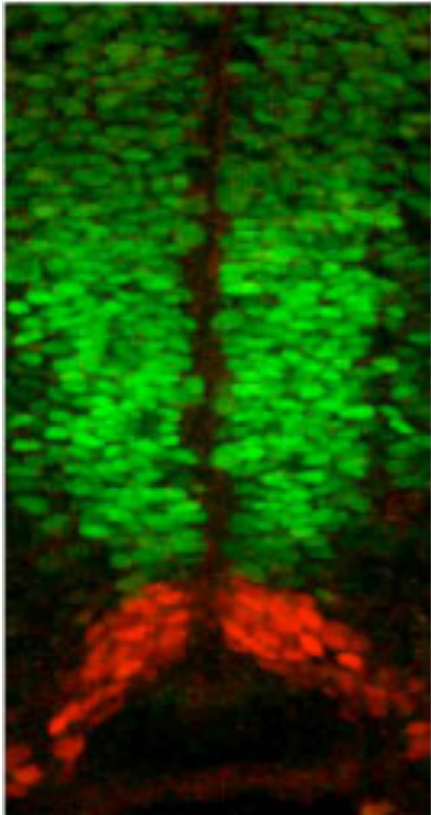


Network provides hysteresis

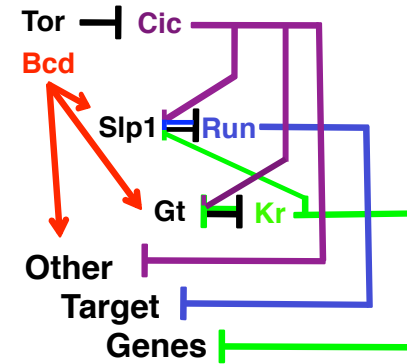
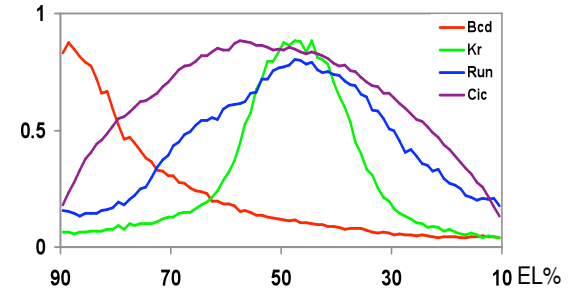
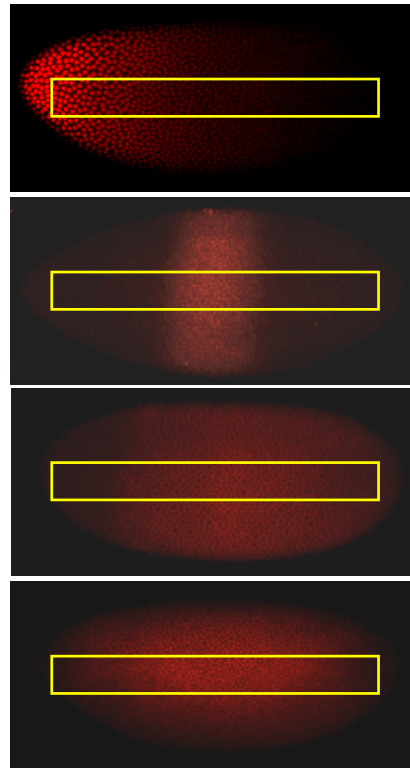
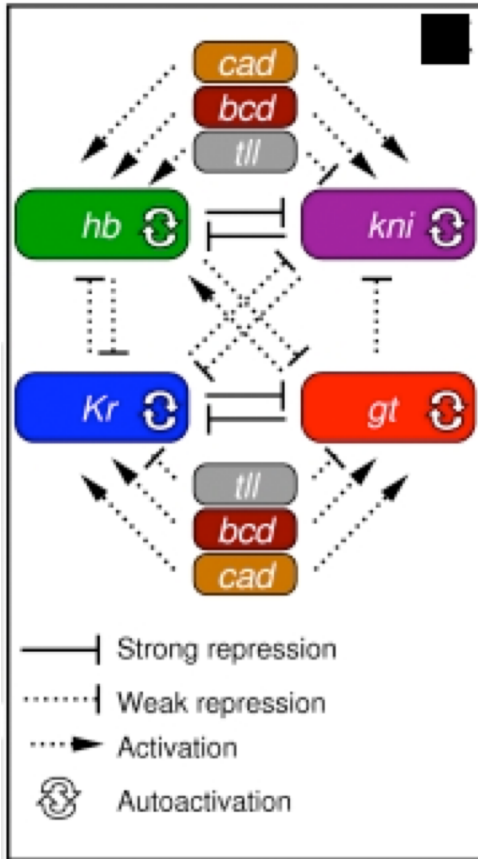


Balaskas et al
(2012) PMID:
22265416

A transcriptional circuit for morphogen interpretation

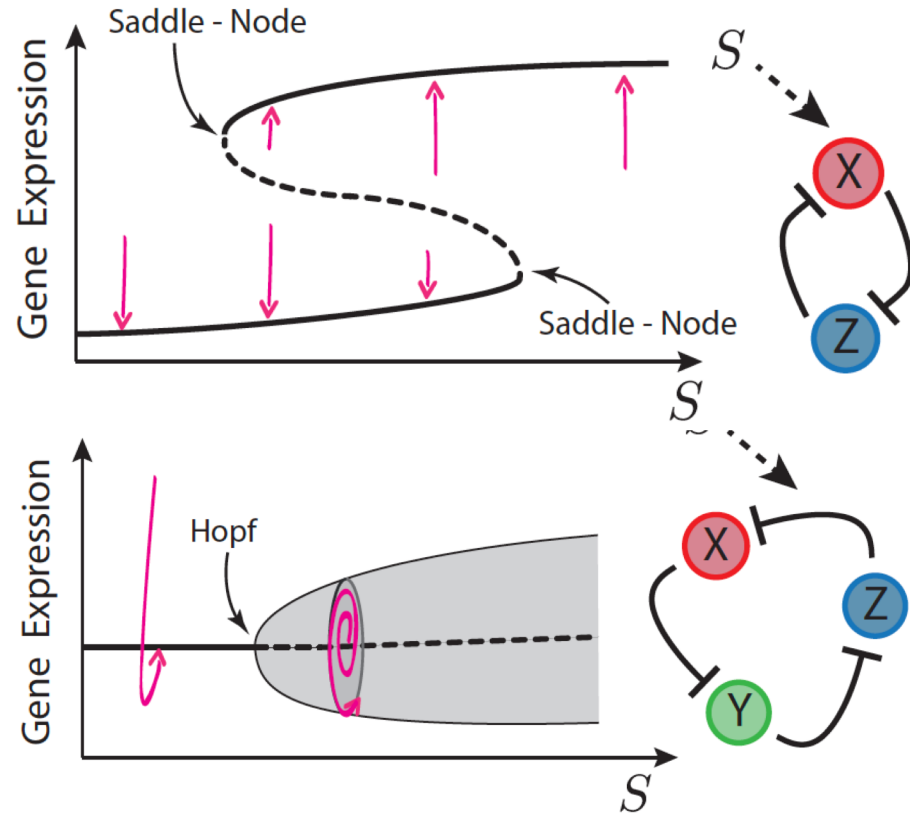
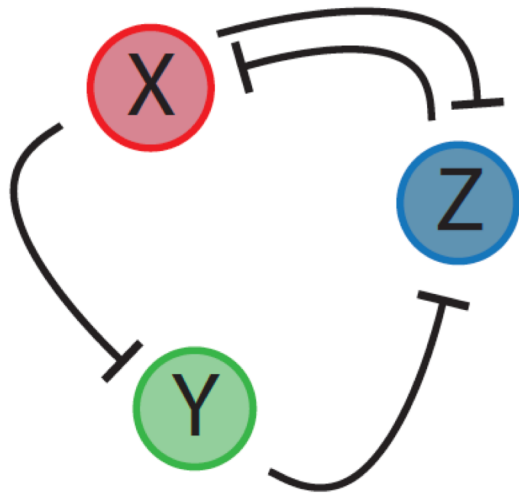


Morphogen interpretation by GRNs



Yogi Jaeger, Manu, John Reinitiz , Steve Small et al

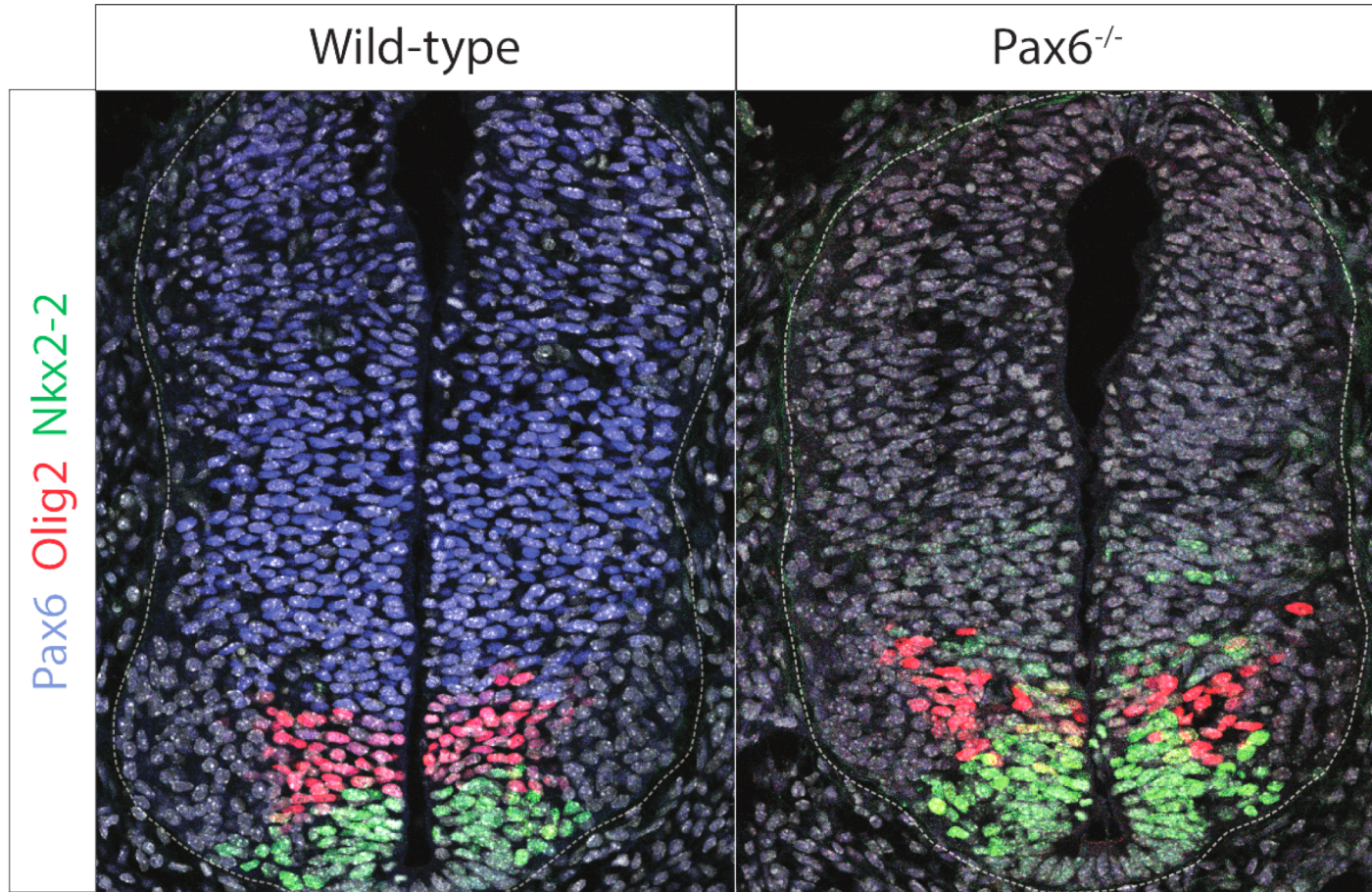
A multifunctional network motif



Panovska-Griffiths et al (2012) PMID: 23235261

Perez-Carrasco et al (2017) PMID: 29574056

Pax6 affects precision of pattern

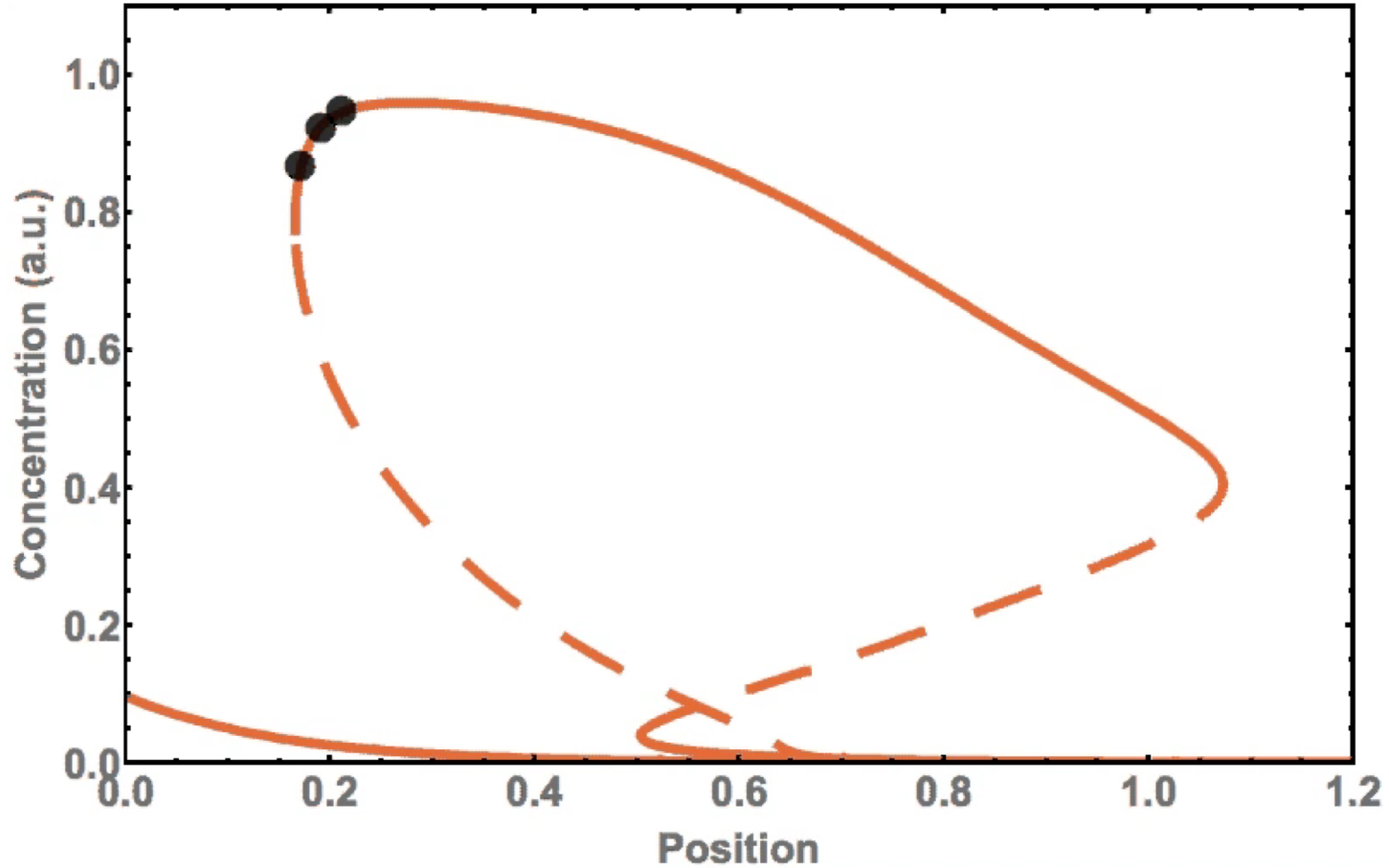


Exelby, Herrera-Delgado et al (2019) BioRxiv

Stochastic fluctuations



Noise driven cell fate transitions



Pax6 affects precision of pattern

$$d\frac{[TF]}{dt} = \alpha\phi_{TF} - \beta[TF] + \Omega^{-1/2}\xi_{TF}(t)$$

$$\langle \xi_i(t)\xi_j(t') \rangle = \delta_{ij}\delta(t-t')(\alpha\phi_j + \beta[TF])$$

Wild-type

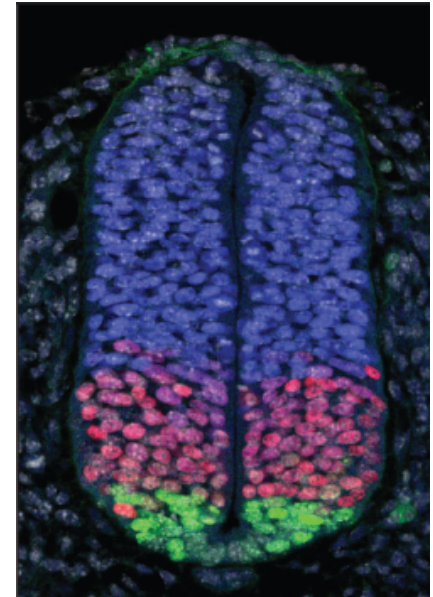
Pax6 mutant



Pax6

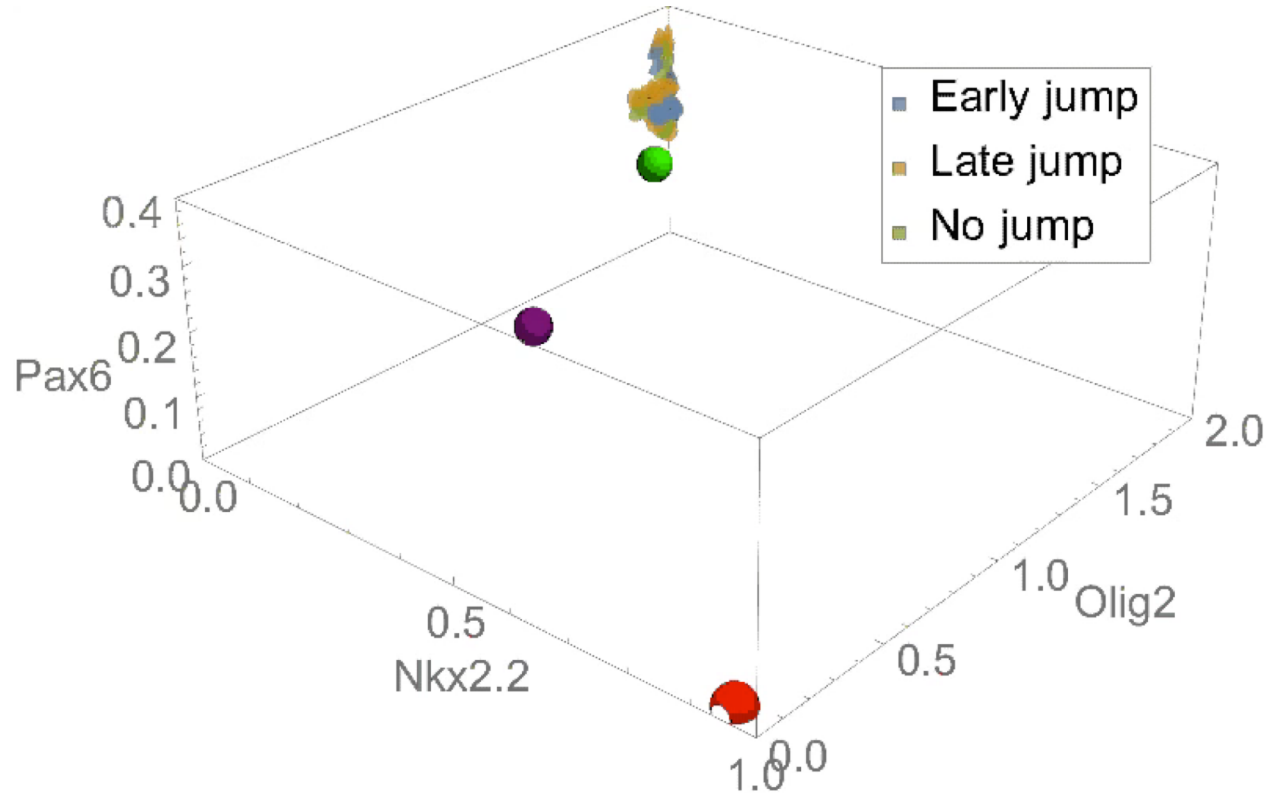
Olig2

Nkx2.2



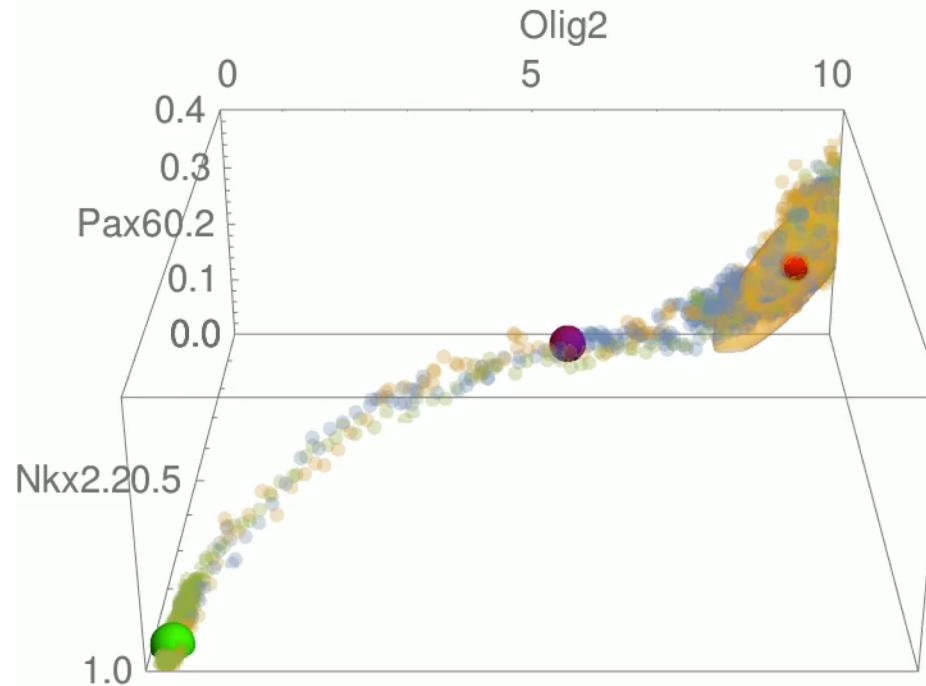
Exelby, Herrera-Delgado et al (2019) BioRxiv

Pax6 angles fluctuations away from transition point



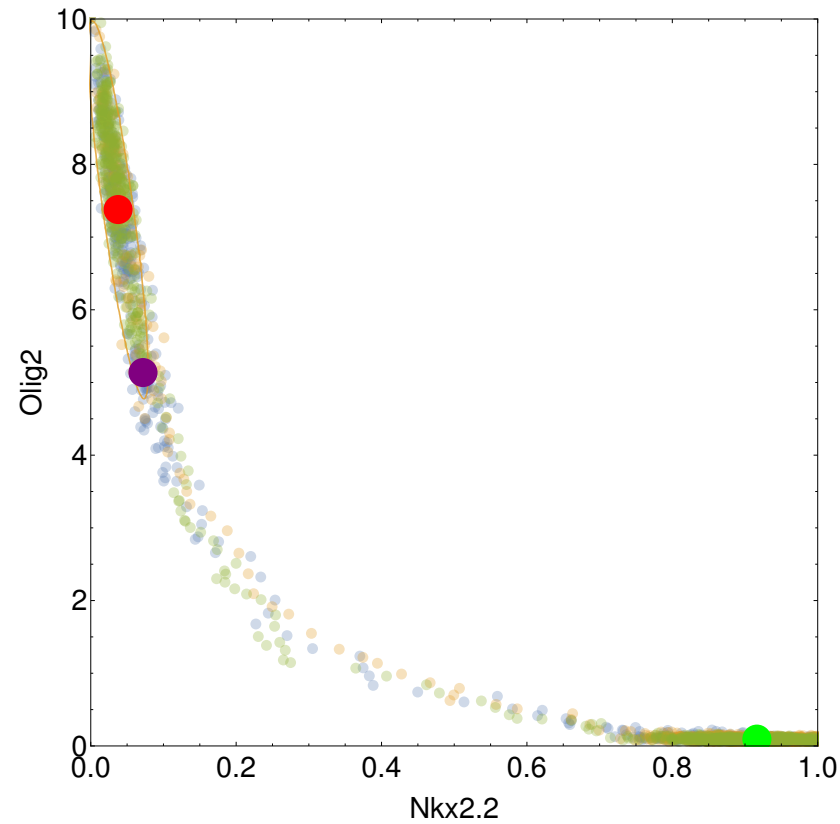
Exelby, Herrera-Delgado et al (2019) BioRxiv

Pax6 angles fluctuations away from transition point



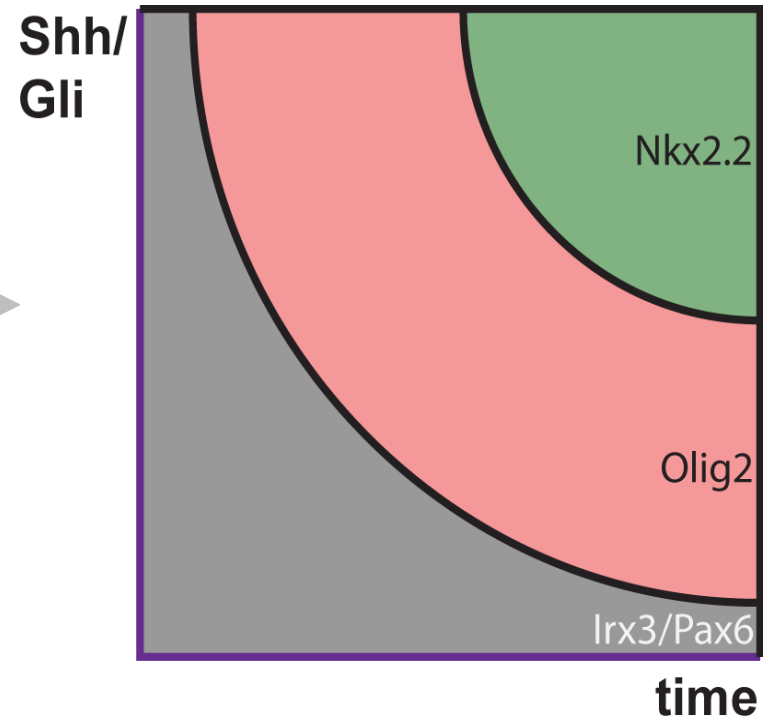
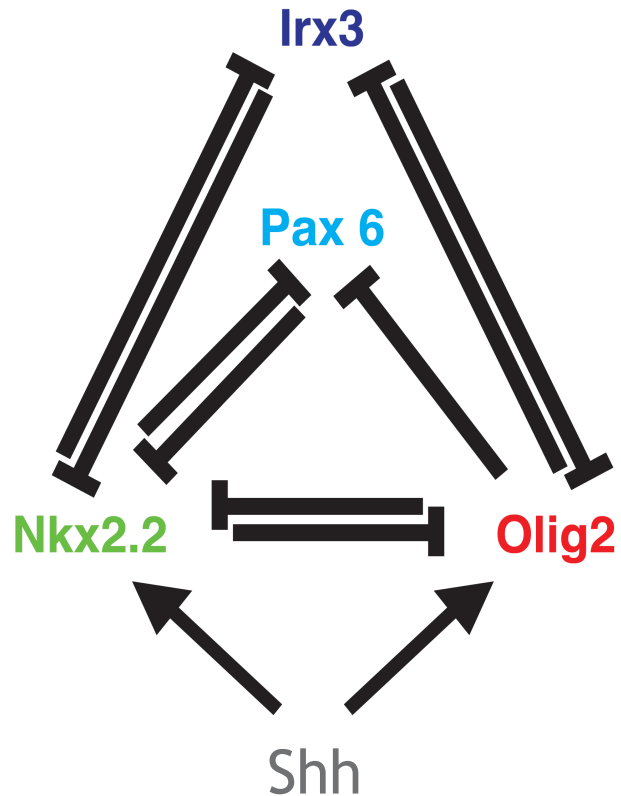
Exelby, Herrera-Delgado et al (2019) BioRxiv

Pax6 angles fluctuations away from transition point

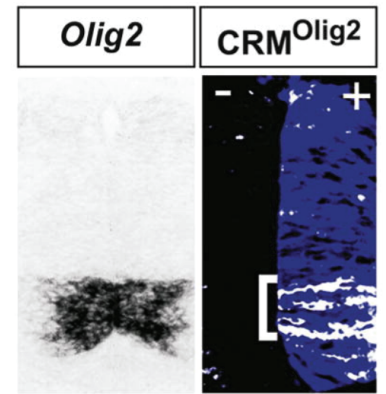
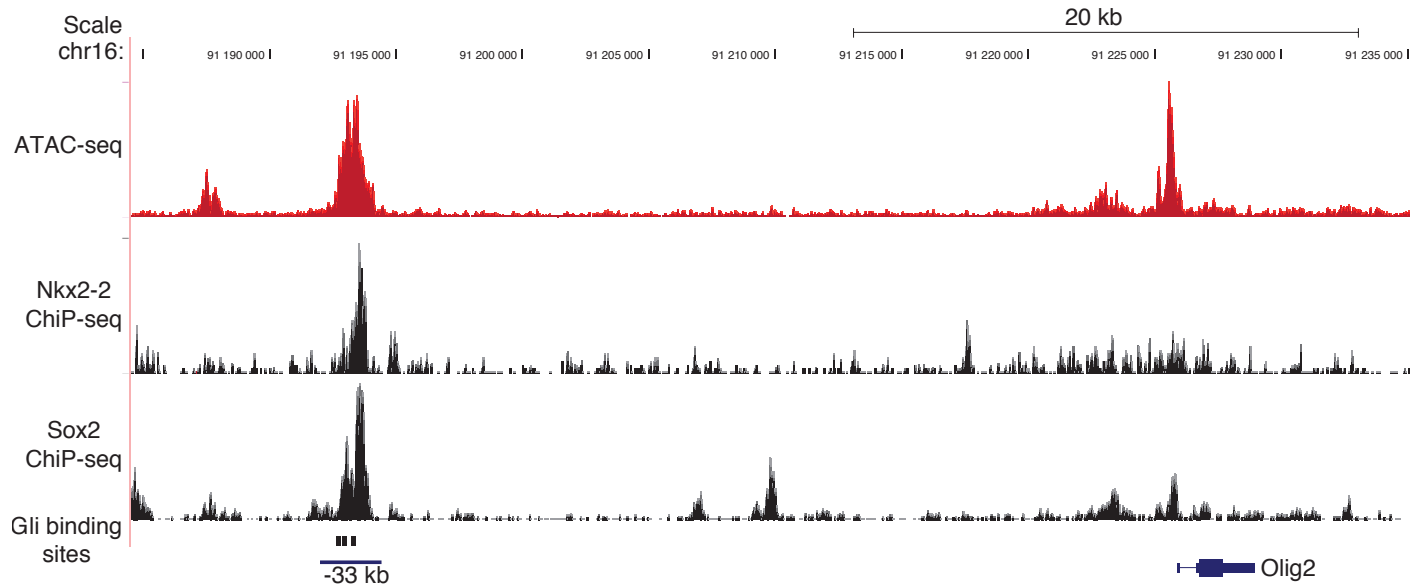


Exelby, Herrera-Delgado et al (2019) BioRxiv

Precision: Morphogen controlled txn network

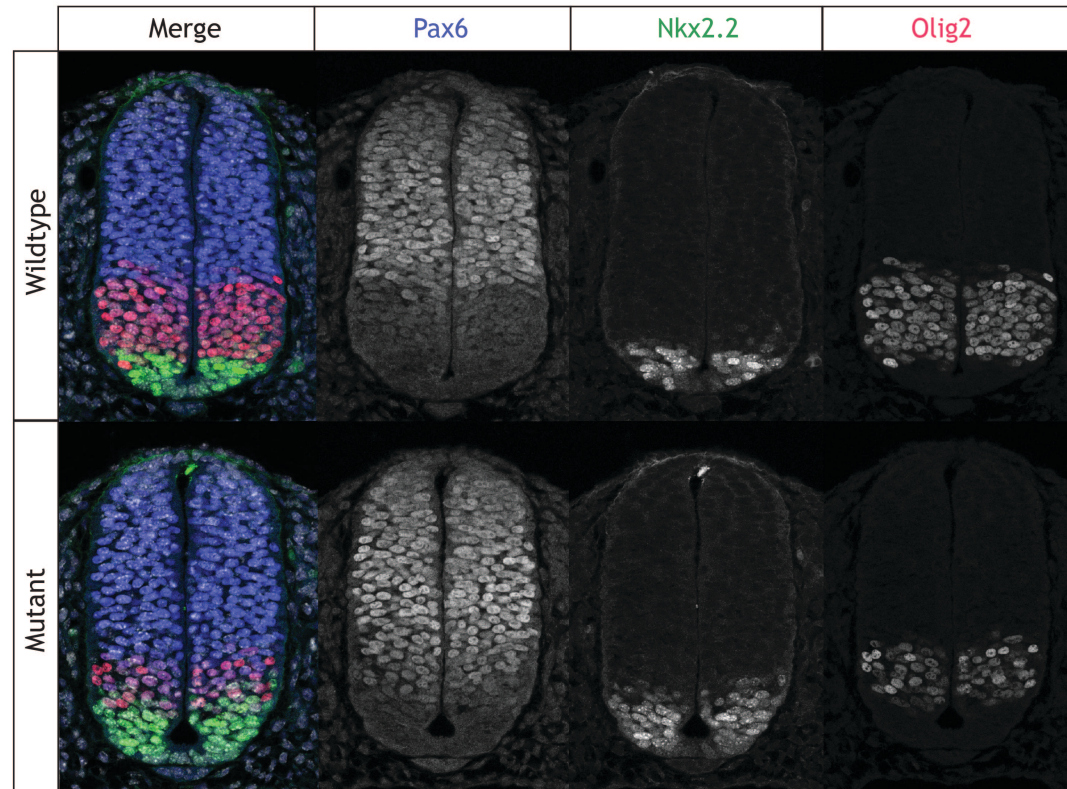
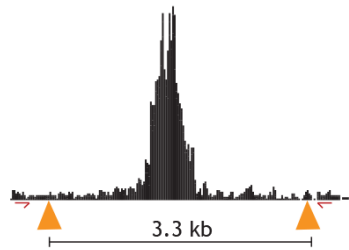


Regulatory elements as network edges



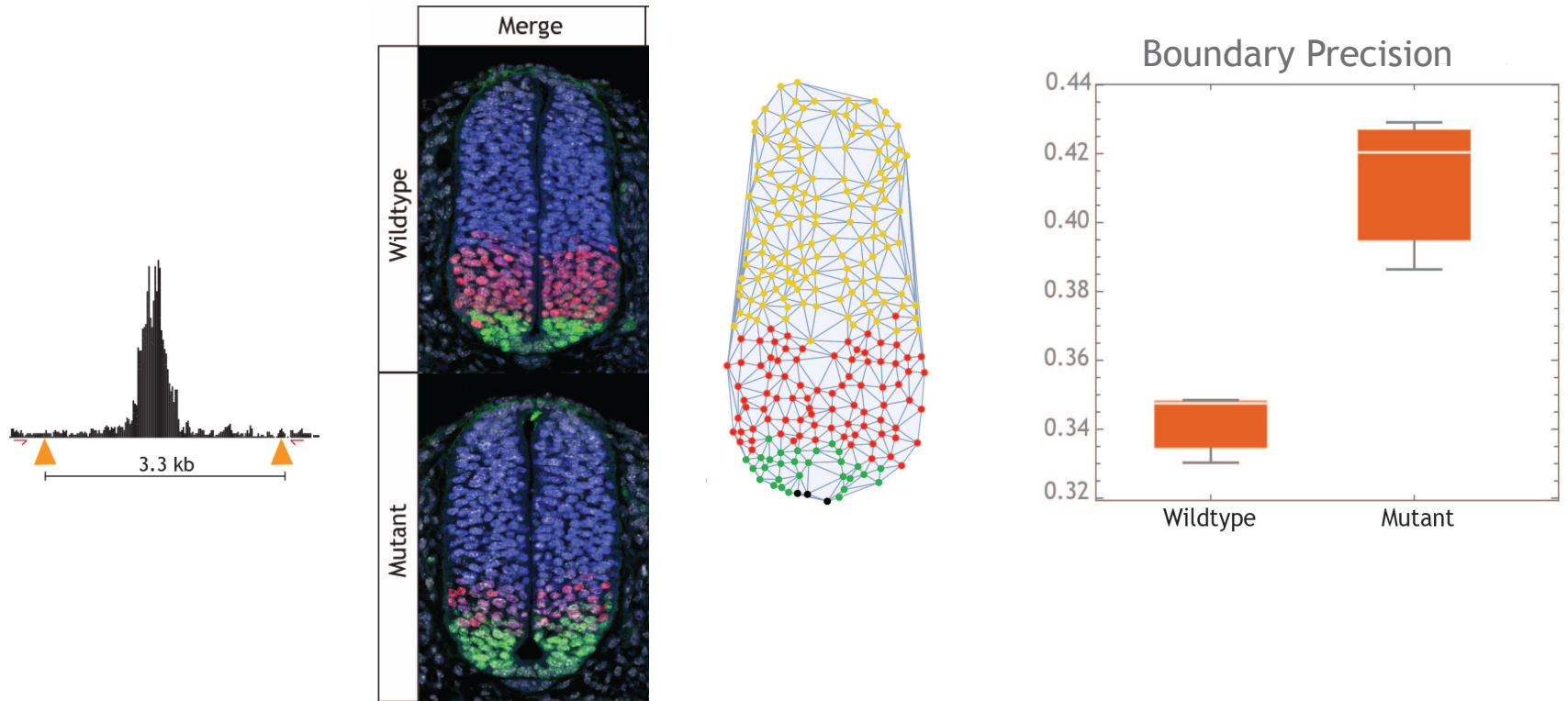
Oosterveen et al., 2012

O2e33 influences precision of Nkx2.2 boundary



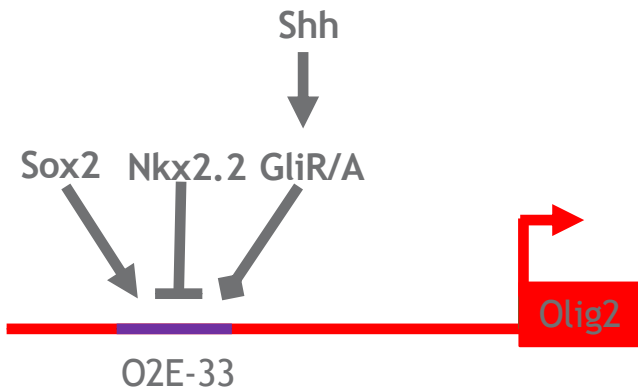
Exelby, Herrera-Delgado et al (2019) BioRxiv

O2e33 influences precision of Nkx2.2 boundary



Exelby, Herrera-Delgado et al (2019) BioRxiv

Stochastic simulations predict pattern alterations



$$d\frac{[TF]}{dt} = \alpha\phi_{TF} - \beta[TF] + \Omega^{-1/2}\xi_{TF}(t)$$

$$\langle \xi_i(t)\xi_j(t') \rangle = \delta_{ij}\delta(t-t')(\alpha\phi_j + \beta[TF])$$

Wild-type



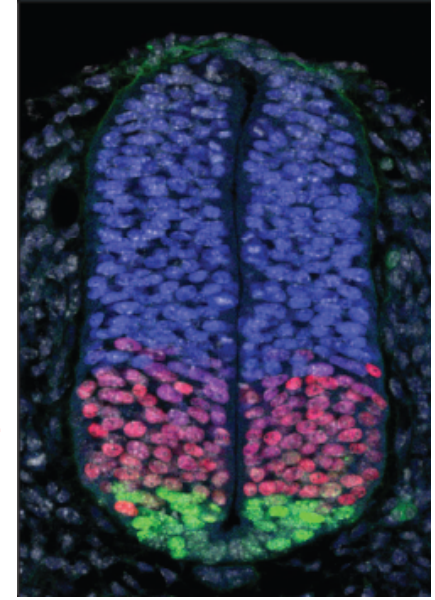
O2e-33 mutant



Pax6

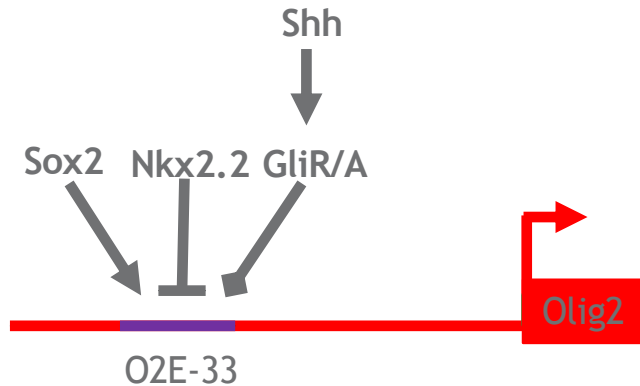
Olig2

Nkx2.2



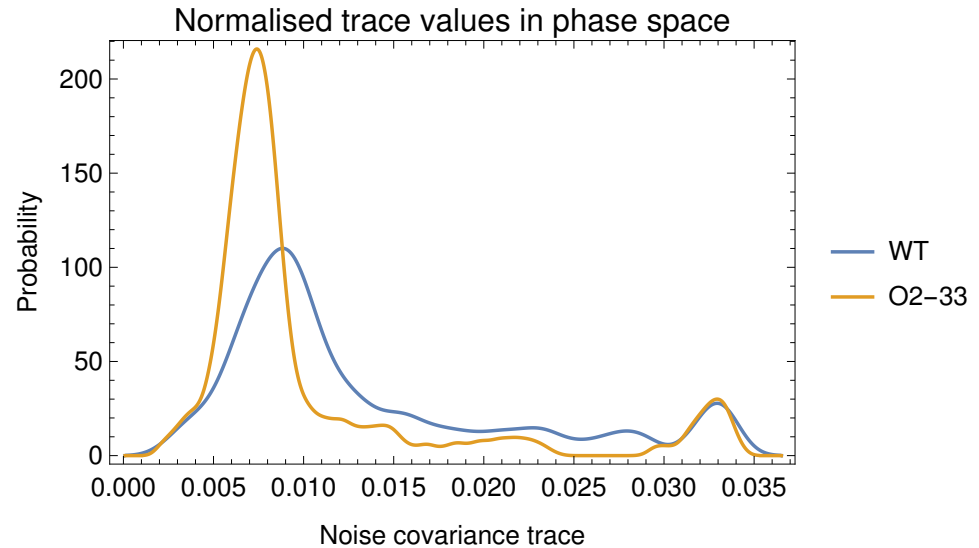
Exelby, Herrera-Delgado et al (2019) BioRxiv

Stochastic simulations predict pattern alterations



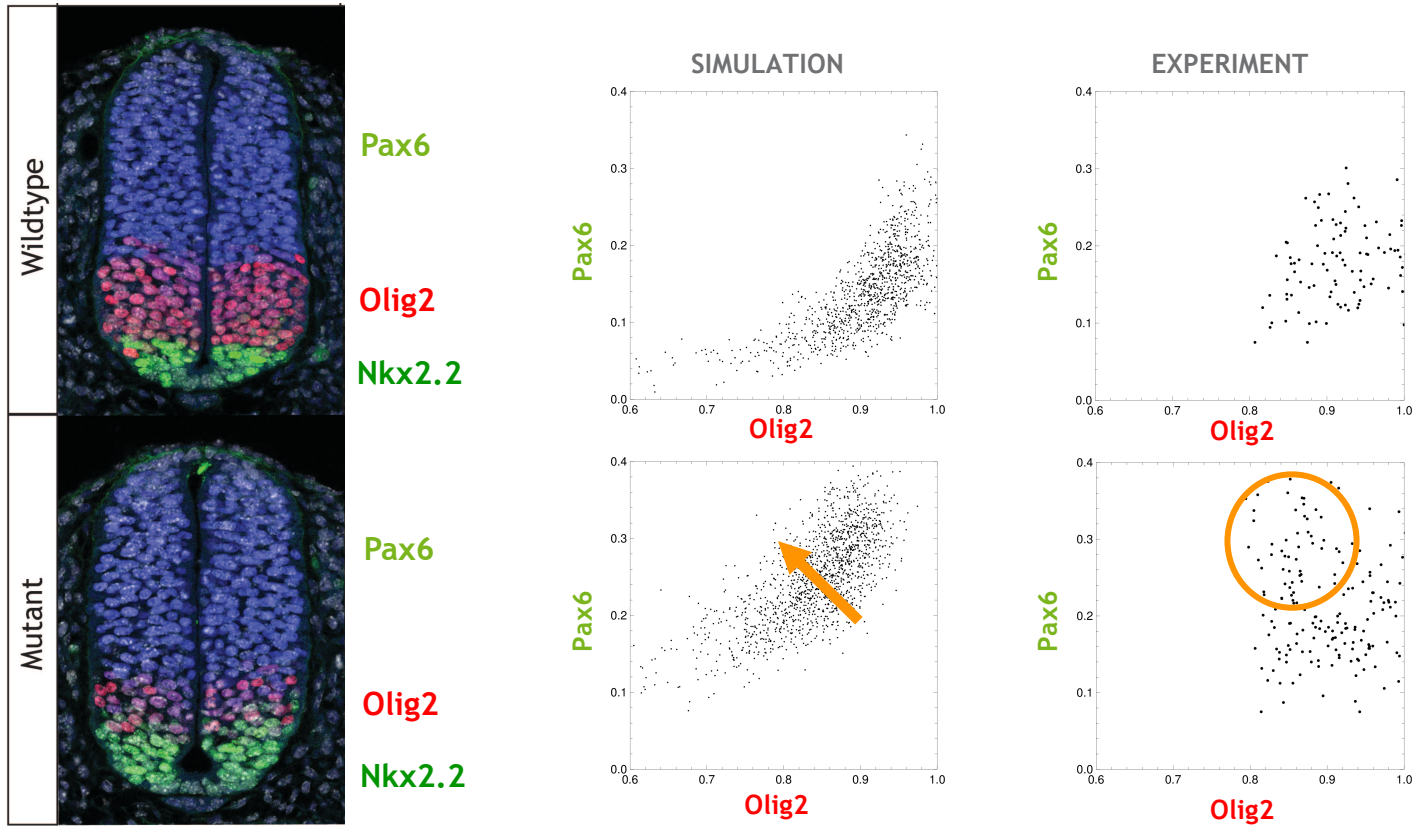
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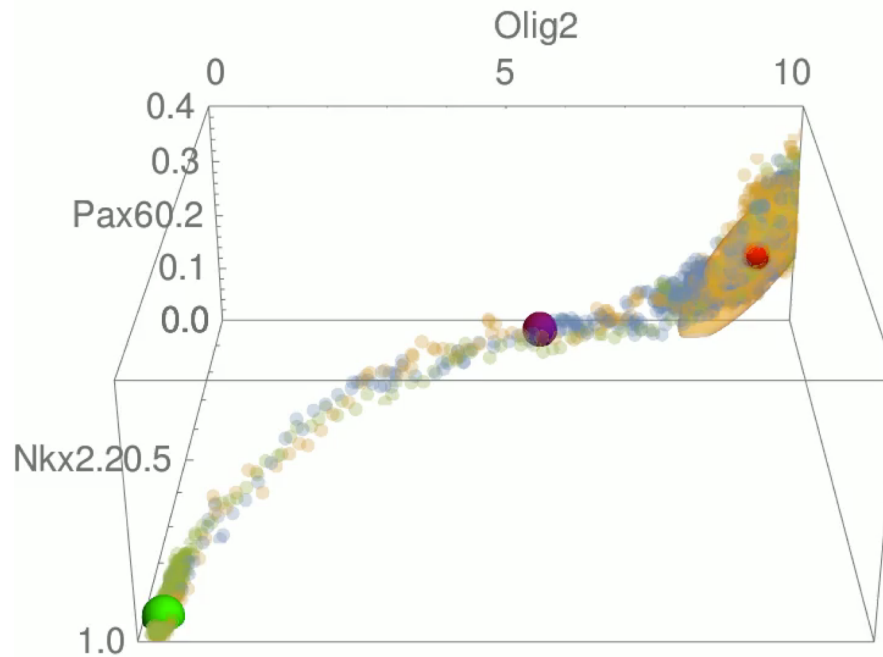
Exelby, Herrera-Delgado et al (2019) BioRxiv

Structure of fluctuations altered in O2e33



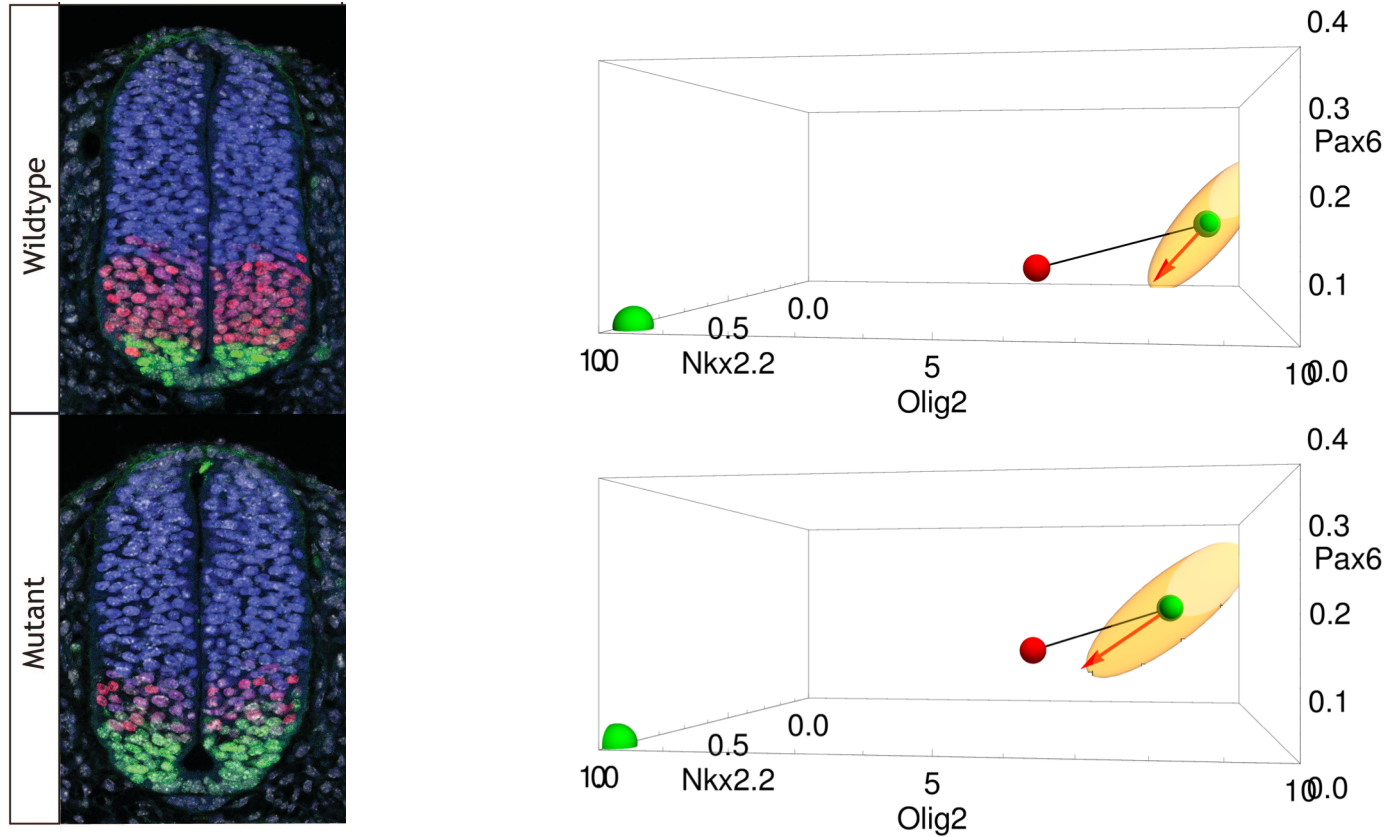
Exelby, Herrera-Delgado et al (2019) BioRxiv

Pax6 angles fluctuations away from transition point



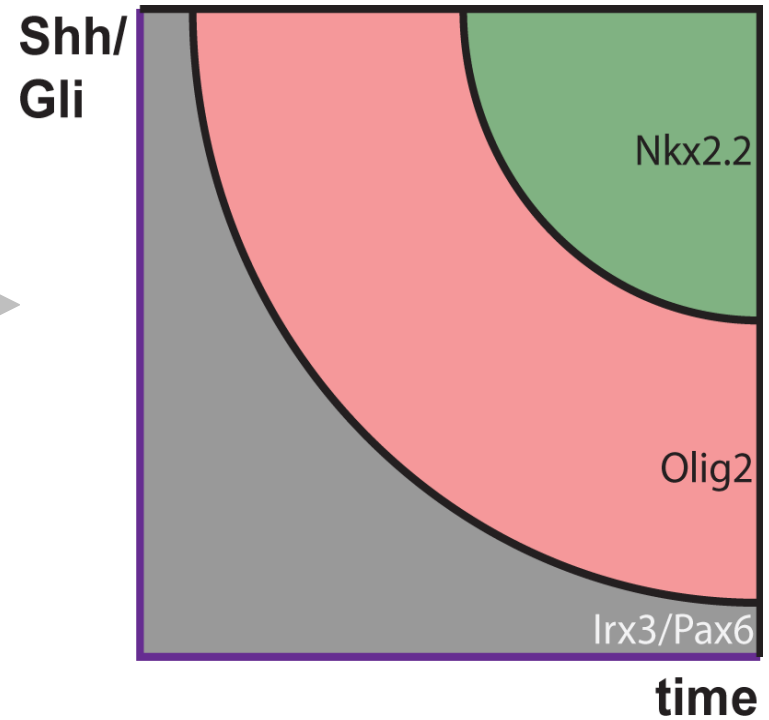
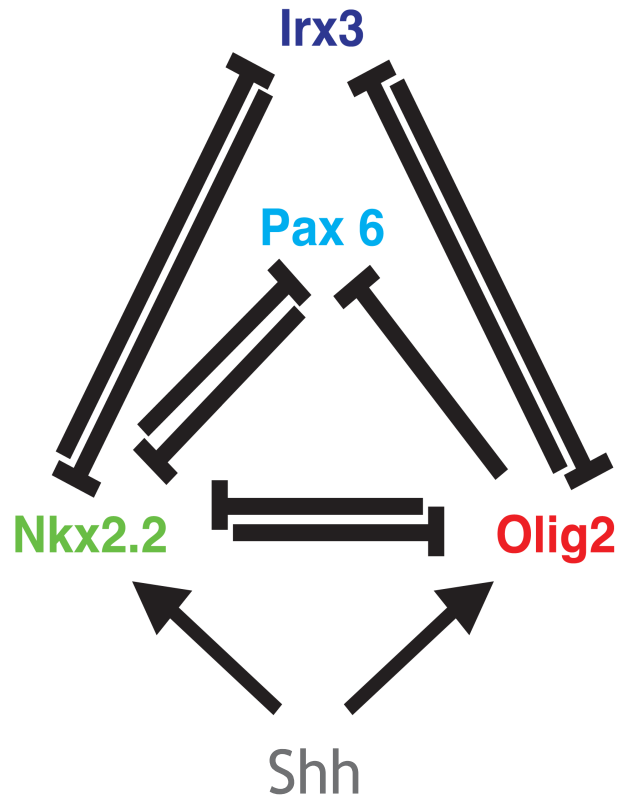
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Fluctuations more permissive in O2e33



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Precision: Morphogen controlled txn network



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