How is information decoded in developmental systems?

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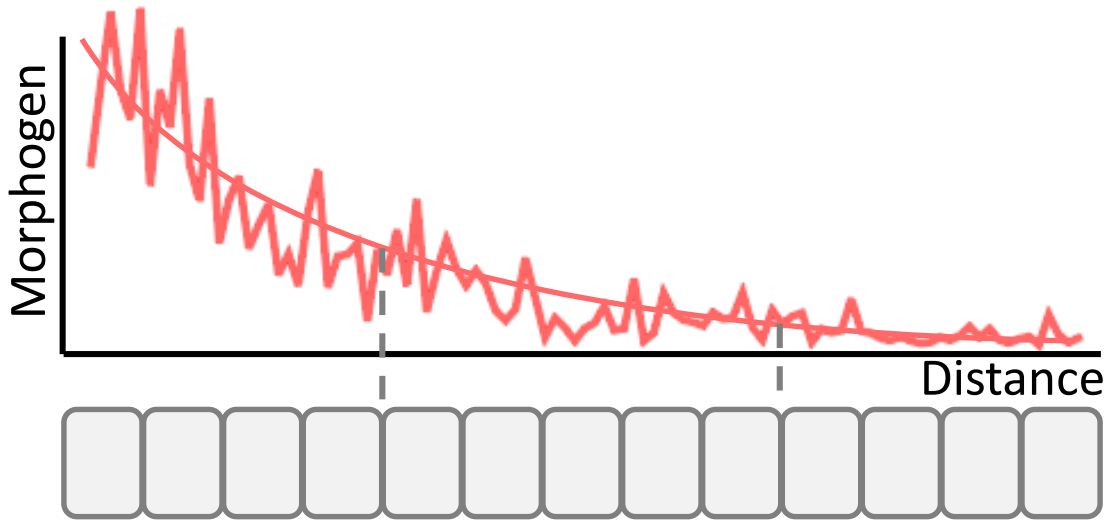
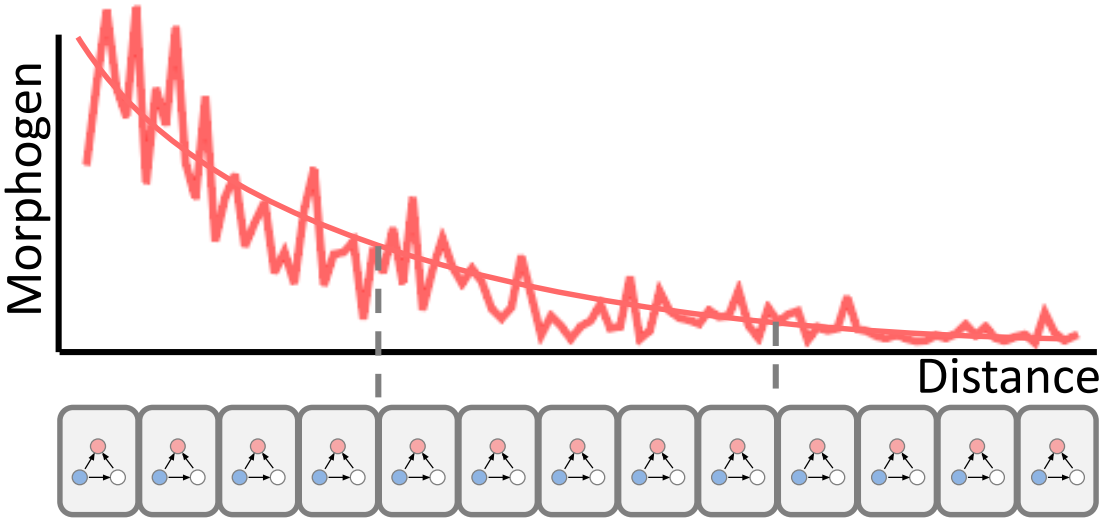
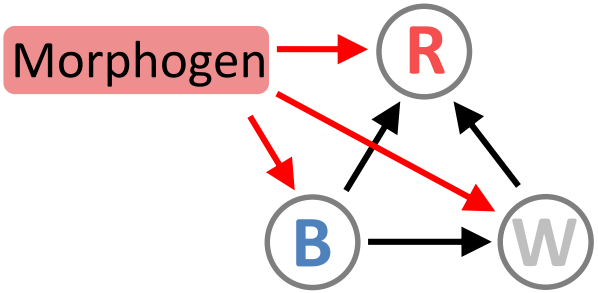
Morphogen gradients provide positional information establishing coordinate system for the developing tissue

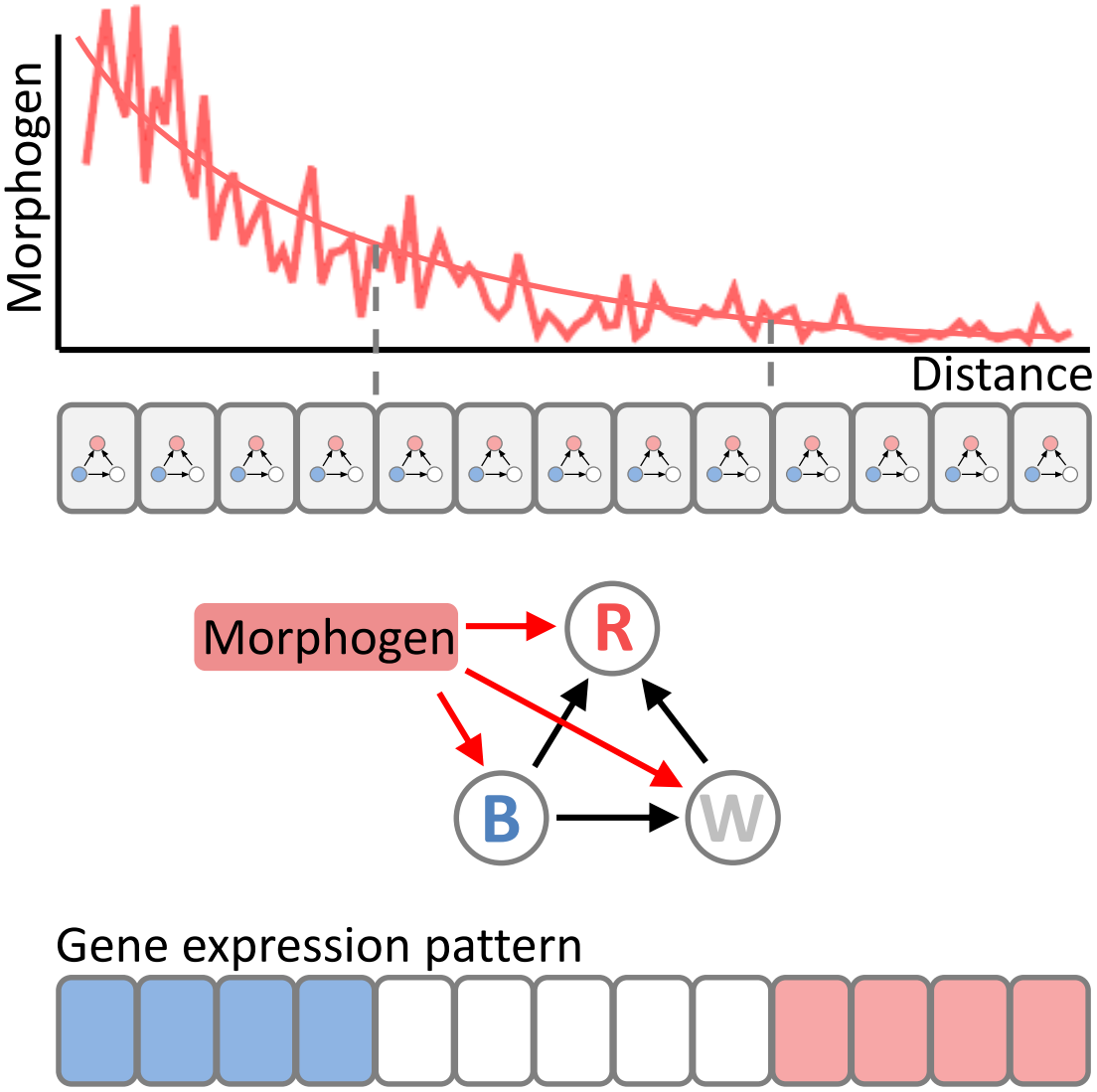


Morphogen gradients provide positional information establishing coordinate system for the developing tissue



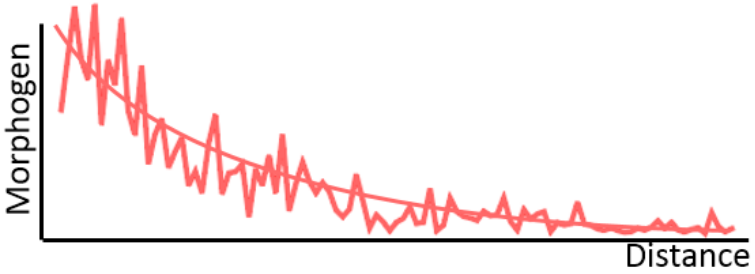


Morphogen gradients provide positional information establishing coordinate system for the developing tissue

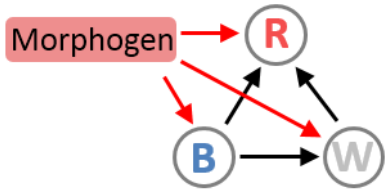


The gene regulatory network acts as an information decoder that specifies target pattern

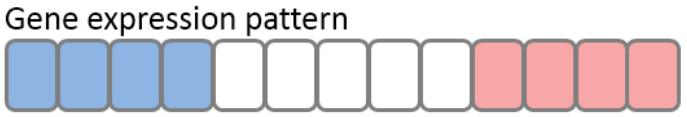
Input signal



Information decoder



Output signal

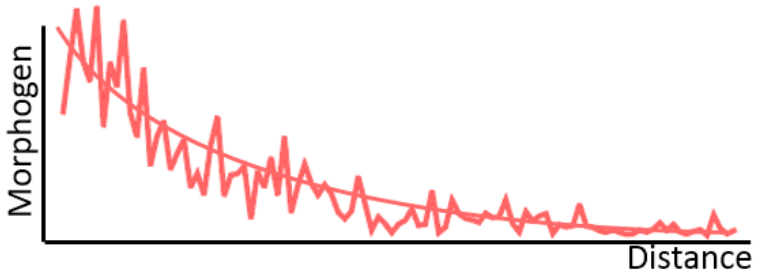


Optimal processing of information allows for pattern prediction without gene regulatory network

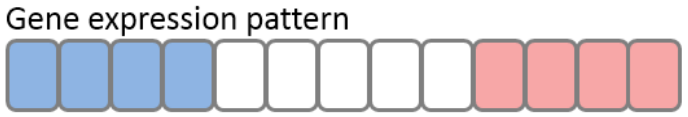
Input signal

Information decoder

Output signal



Optimal processing of positional information



Optimal decoder contains all the information that any cellular or computational mechanism could extract from input signals

Measured signal $\{g_i(x)\} = \{g_1(x), g_2(x), g_3(x), g_4(x)\}, \quad K = 4$

Signal distribution at every x

$$P(\{g_i\}|x) = \frac{1}{\sqrt{(2\pi)^K \det[\hat{C}(x)]}} \exp\left\{-\frac{1}{2}\sum_{i,j=1}^{K}(g_i - \bar{g}_i(x))(\hat{C}^{-1}(x))_{ij}(g_j - \bar{g}_j(x))\right\}$$

Optimal decoder from Bayes' rule

$$P(x^*|\{g_i\}) = \frac{1}{Z(\{g_i\})} P(\{g_i\}|x^*) P_X(x^*)$$

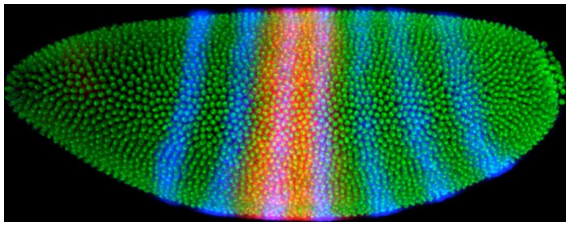
Decoding map

$$P^{\alpha}_{map}(x^*|x) = P(x^*|\{g_i\})\Big|_{\{g_i\}=\{g_i^{\alpha}(x)\}}$$

Tkacik et al., Genetics, 2015
Zagorski et al., Science, 2017
Petkova et al., Cell, 2019

In fruit fly decoding of input signals results in pattern specification with 1% positional error

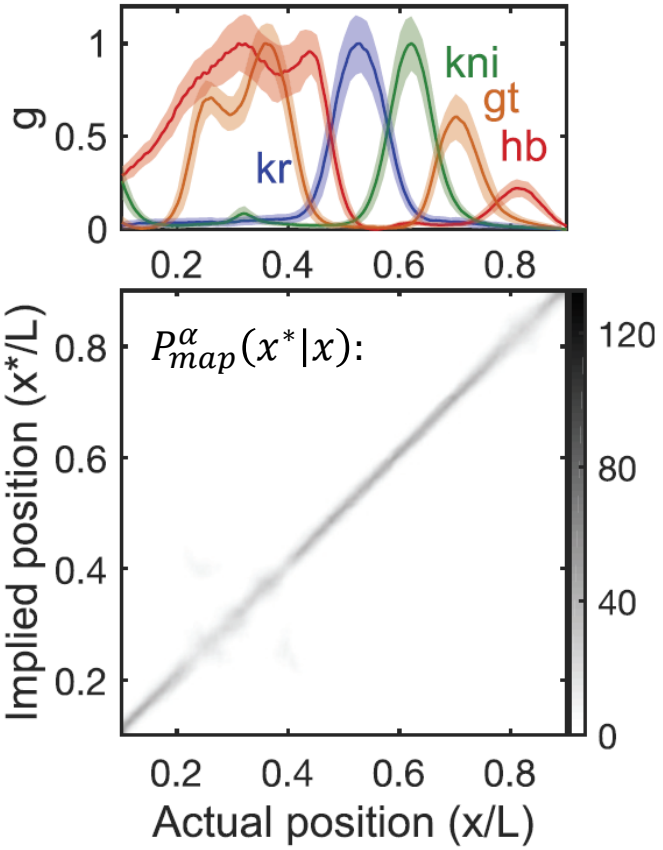
Pair-rule genes



ittakes30.files.wordpress.com/2010/06/drosophila-eve.jpg

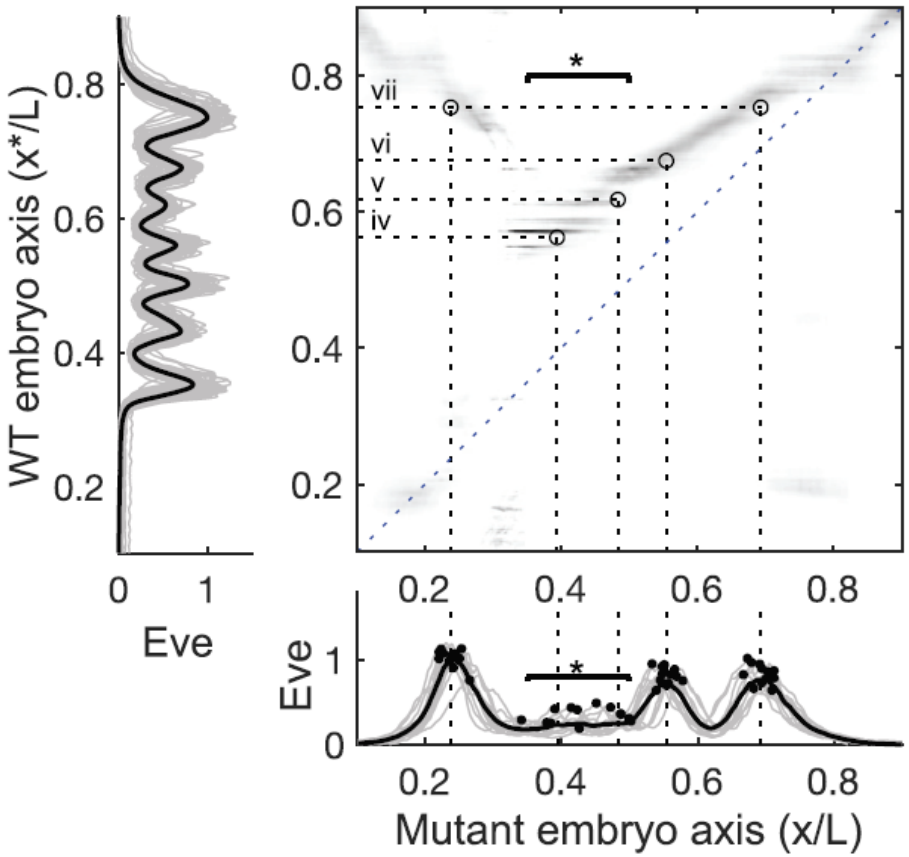
$\{g_i(x)\}$:

Gap genes



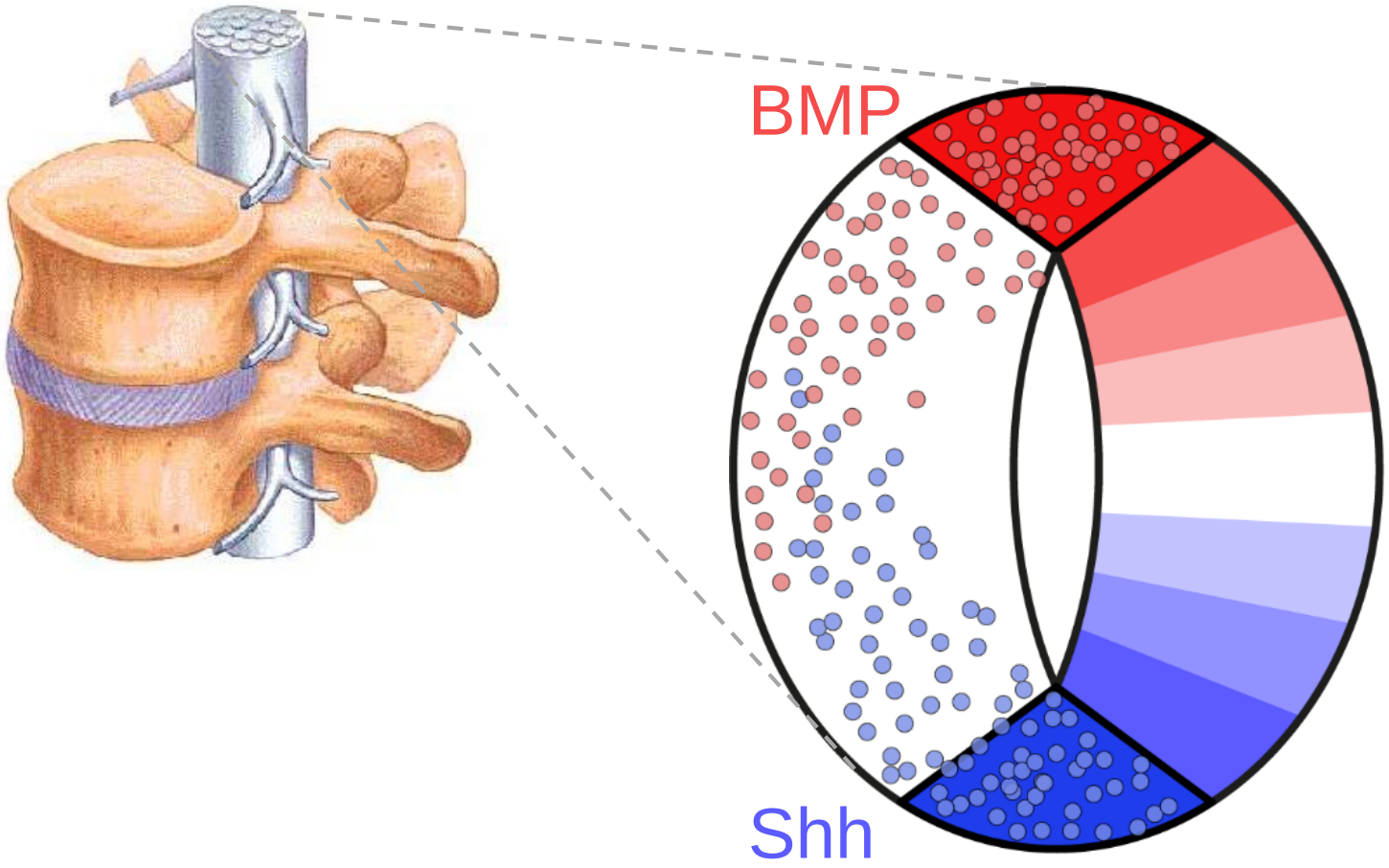
Petkova et al., Cell, 2019

The decoding map correctly predicts shifts, disappearance and duplications in 70 pair-rule stripes in mutant embryos

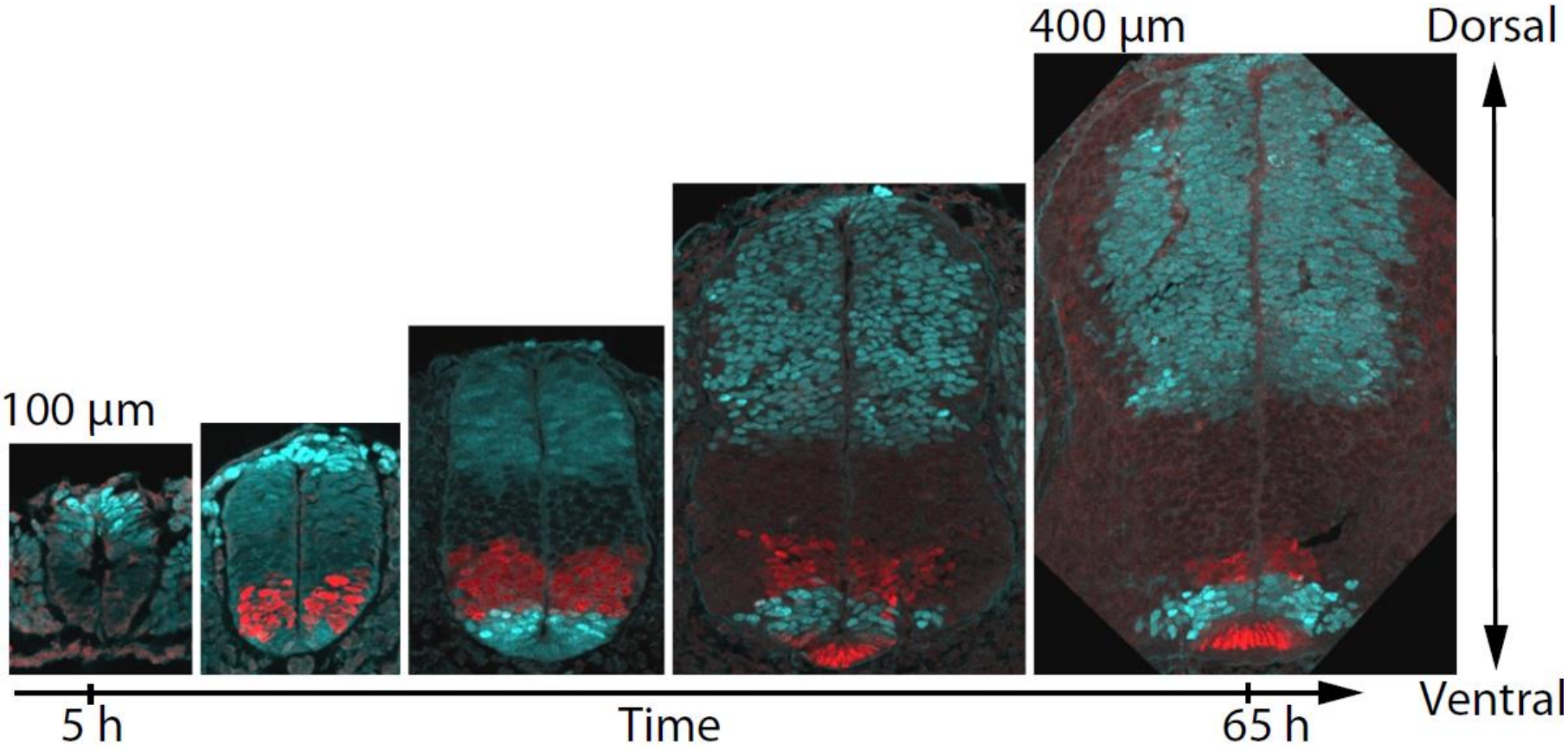


Petkova et al., Cell, 2019

Morphogen signaling gradients establish a striped pattern of neural progenitors

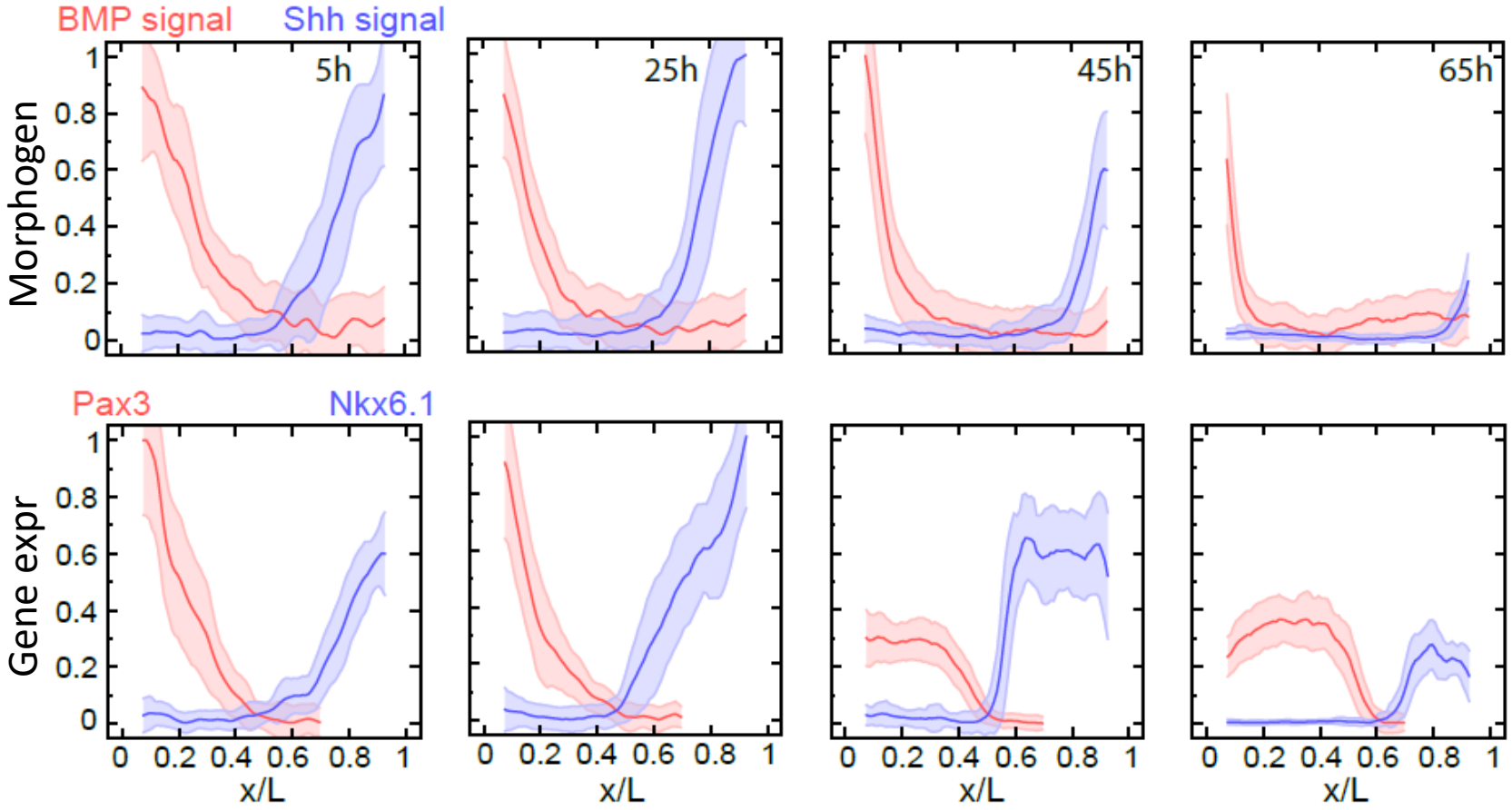


The striped pattern of gene expression domains is established progressively



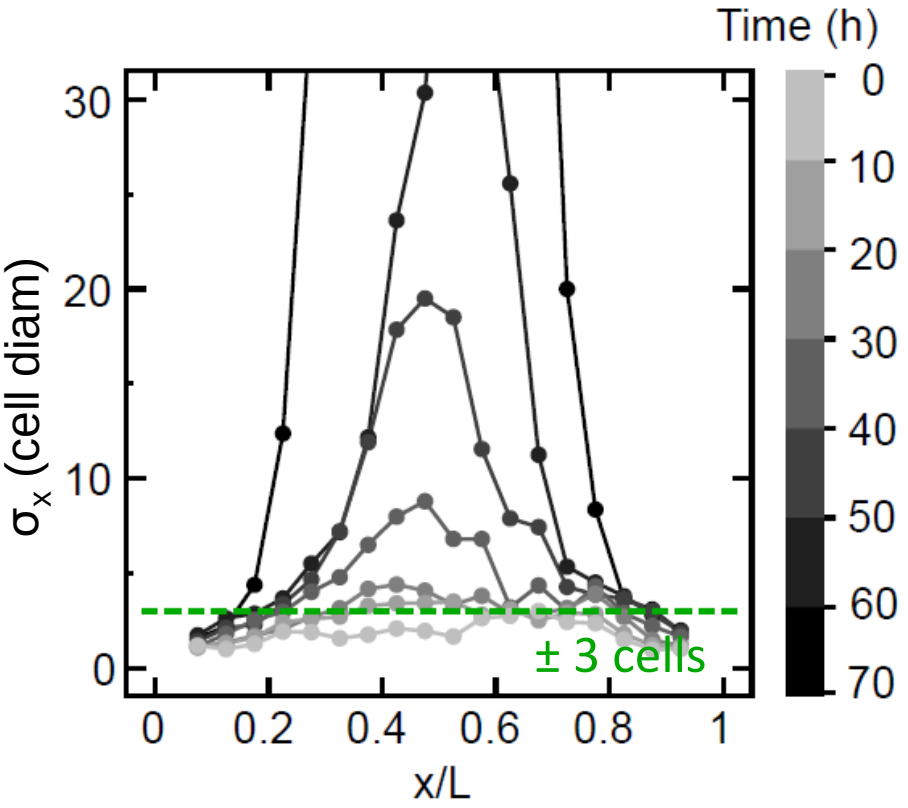
Zagorski et al., Science, 2017

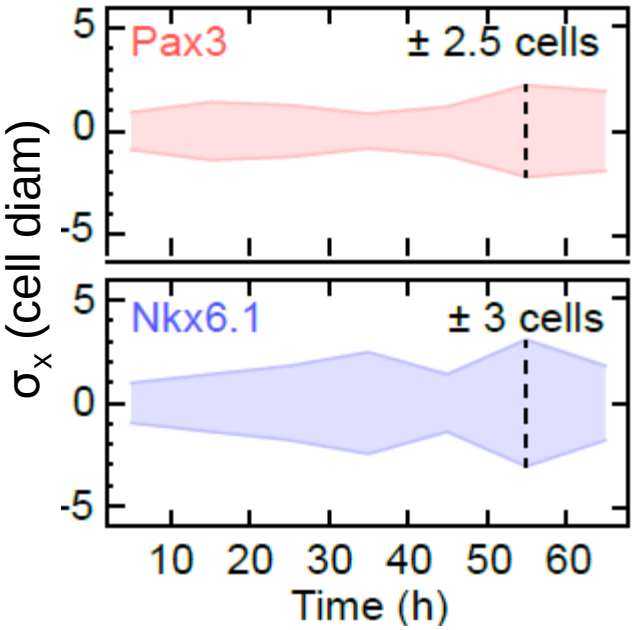
The morphogen signaling profiles do not scale with the embryo size



Zagorski et al., Science, 2017

The initial morphogen positional error corresponds to the boundary imprecision at later stages

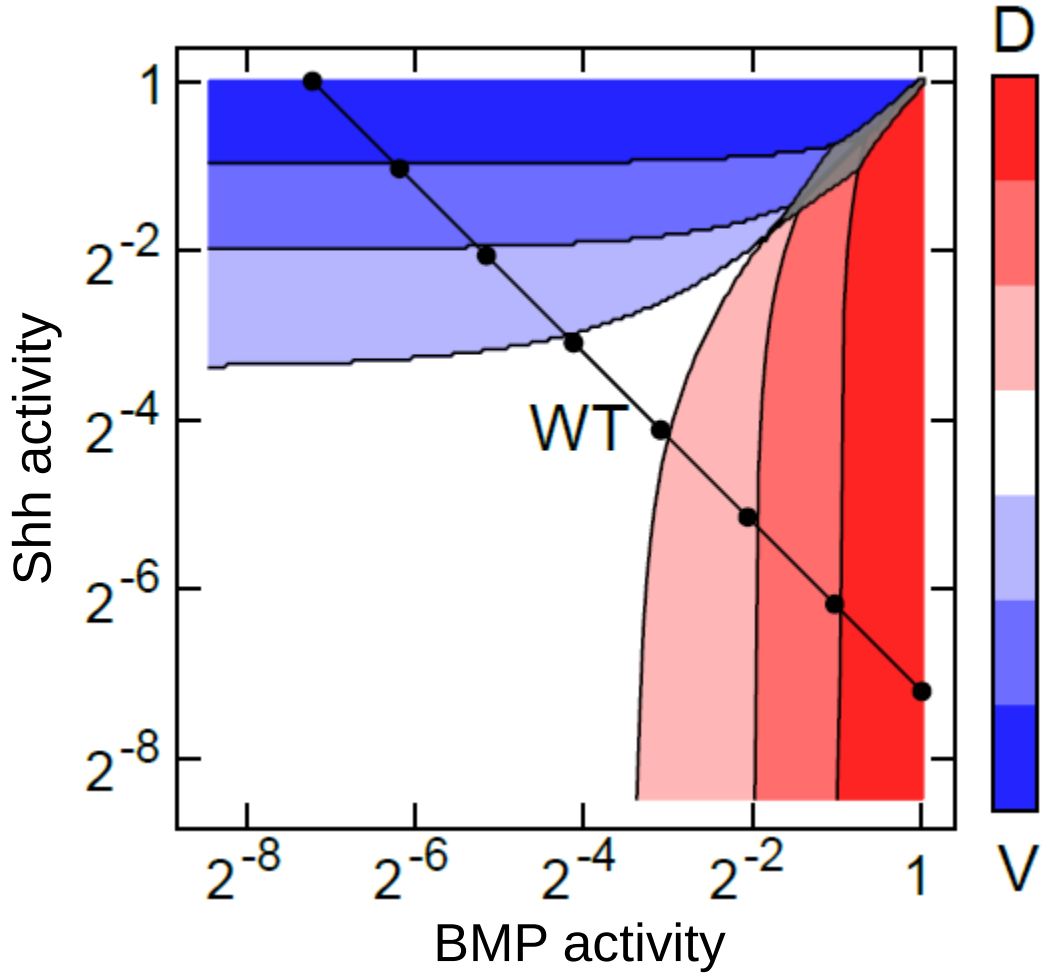




Zagorski et al., Science, 2017

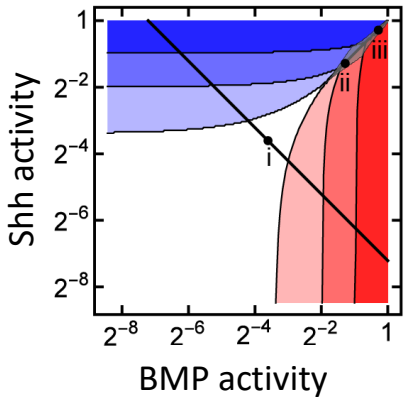
Cells interpret the opposing morphogen signals using an optimal decoding strategy

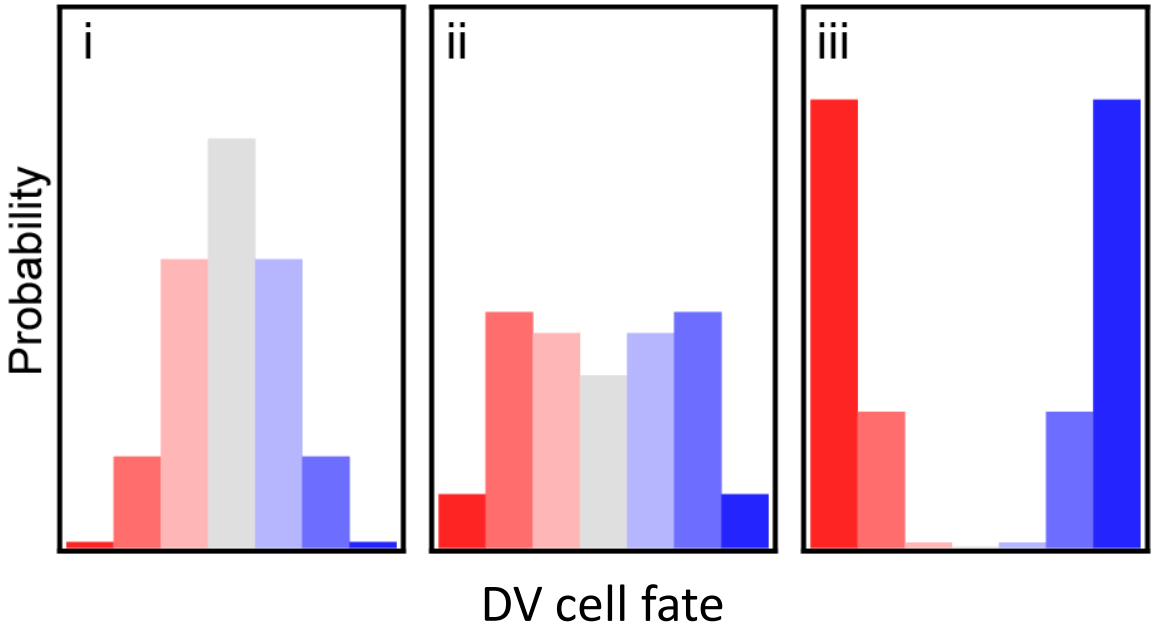
$P(x^*|\{g_1, g_2\})$:



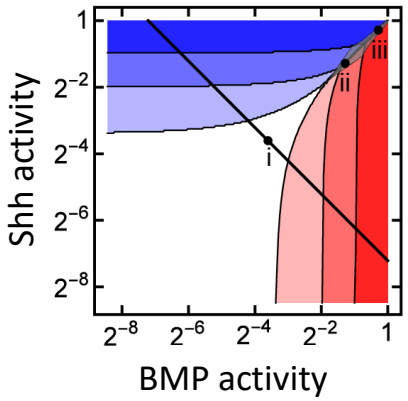
Zagorski et al., Science, 2017

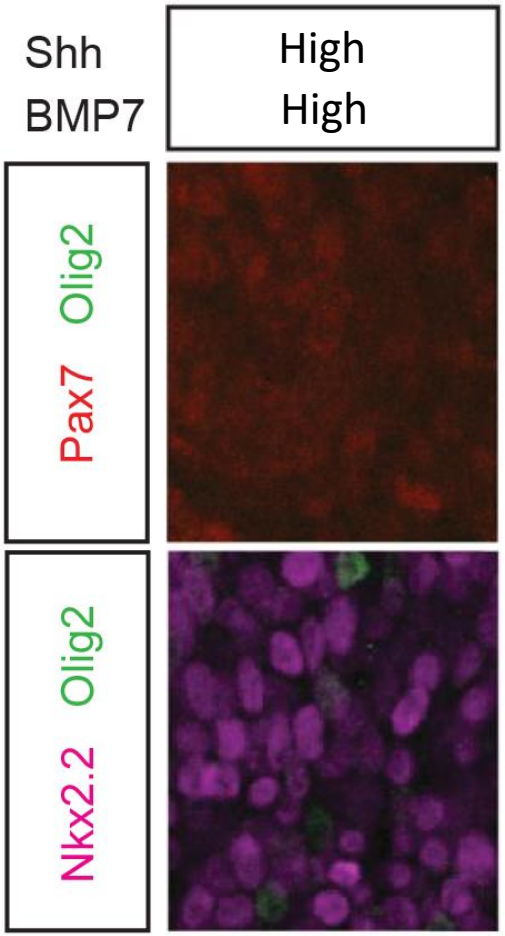
Decoding map predicts bimodal *posterior* distribution of cell fates for high morphogen concentrations





The predicted bimodal distribution of cell fates is consistent with explant experiments





Red cells: Dorsal fates

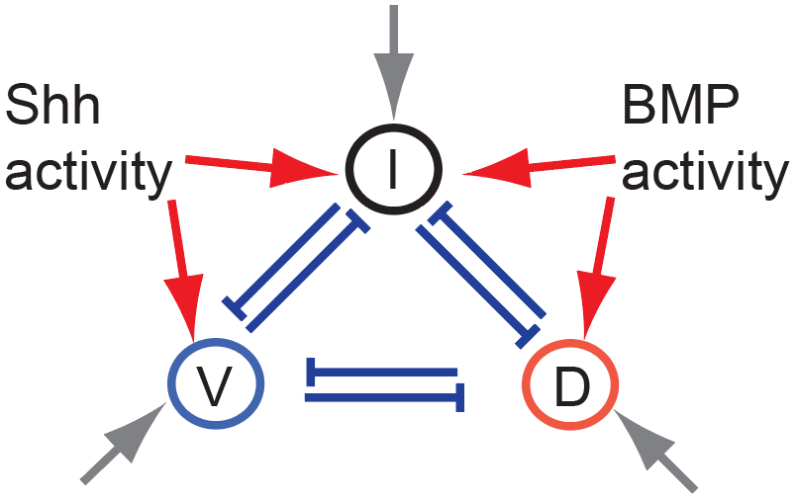
Green cells: Intermediate fates

Violet cells: Ventral fates

Green cells: Intermediate fates

Zagorski et al., Science, 2017

The morphogens activate gene regulatory network (GRN) to specify cell fate



$$\frac{d[D]}{dt} = \alpha_D \frac{\kappa_D + c_{B\to D}\kappa_D\,[BMP]}{(1 + K_{V\to D}[V])^{m_{V\to D}}(1 + K_{I\to D}[I])^{m_{I\to D}} + \kappa_D + c_{B\to D}\kappa_D\,[BMP]} - \gamma_D[D]$$

$$\frac{d[V]}{dt} = \alpha_V \frac{\kappa_V + c_{S\to V}\kappa_V\,[Shh]}{(1 + K_{D\to V}[D])^{m_{D\to V}}(1 + K_{I\to V}[I])^{m_{I\to V}} + \kappa_V + c_{S\to V}\kappa_V\,[Shh]} - \gamma_V[V]$$

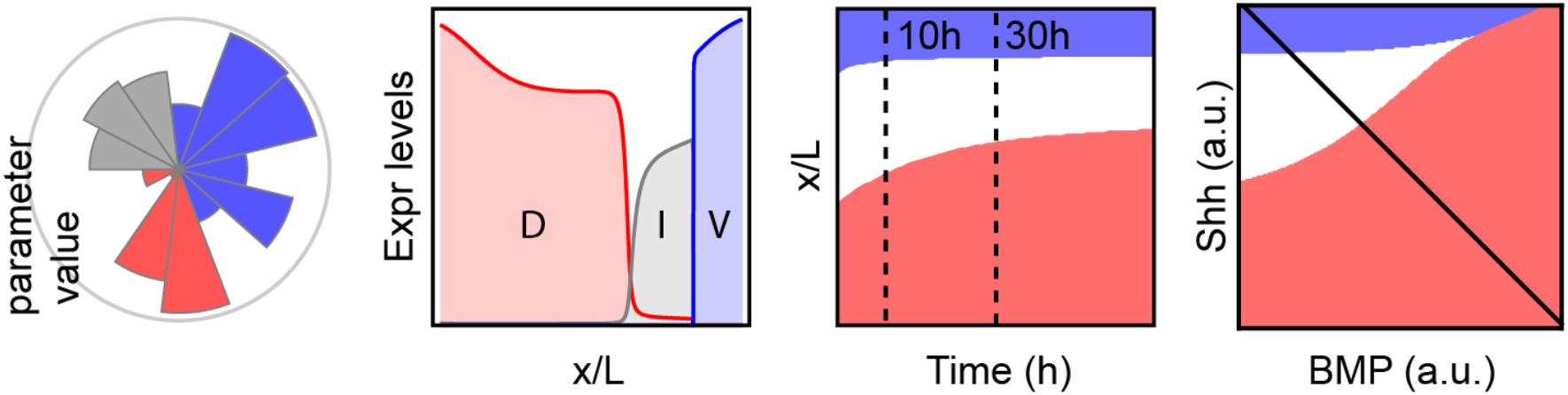
$$\frac{d[I]}{dt} = \alpha_I \frac{\kappa_I + c_{S\to I}\kappa_I\,[Shh] + c_{B\to I}\kappa_I\,[BMP]}{(1 + K_{D\to I}[D])^{m_{D\to I}}(1 + K_{V\to I}[I])^{m_{V\to I}} + \kappa_I + c_{S\to I}\kappa_I\,[Shh] + c_{B\to I}\kappa_I\,[BMP]} - \gamma_I[I]$$

Zagorski et al., Science, 2017

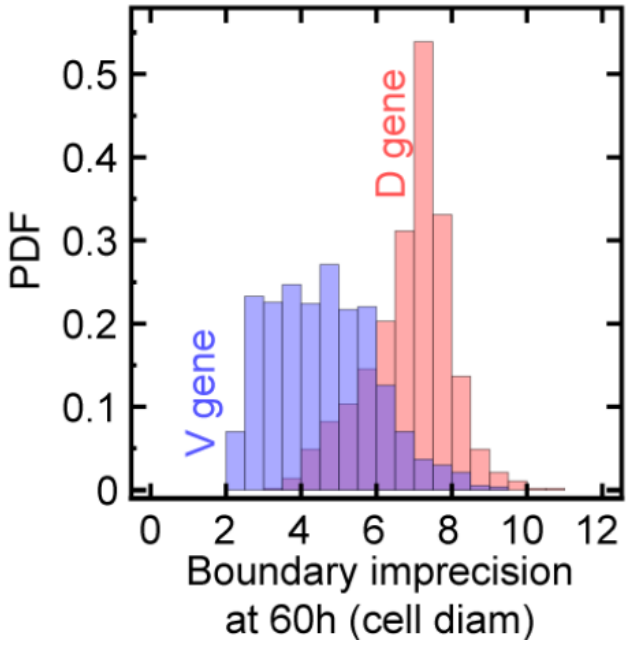
Computational screen resulted in a set of successful GRNs consistent with experimental observations

screen:

example:

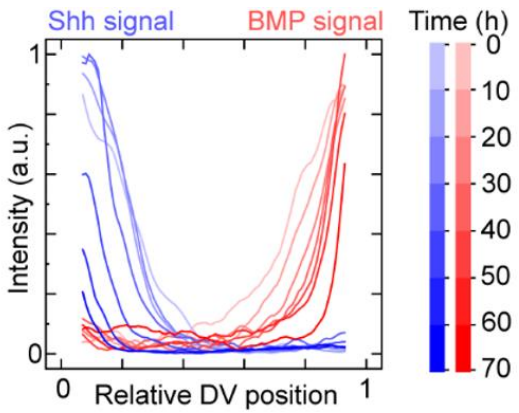


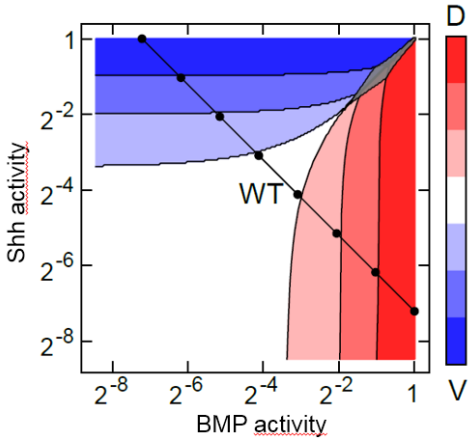
The target gene pattern established by GRNs resulted in a wide range of boundary imprecision

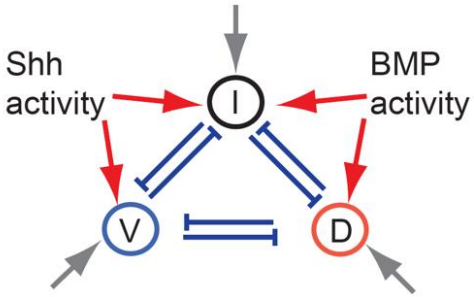


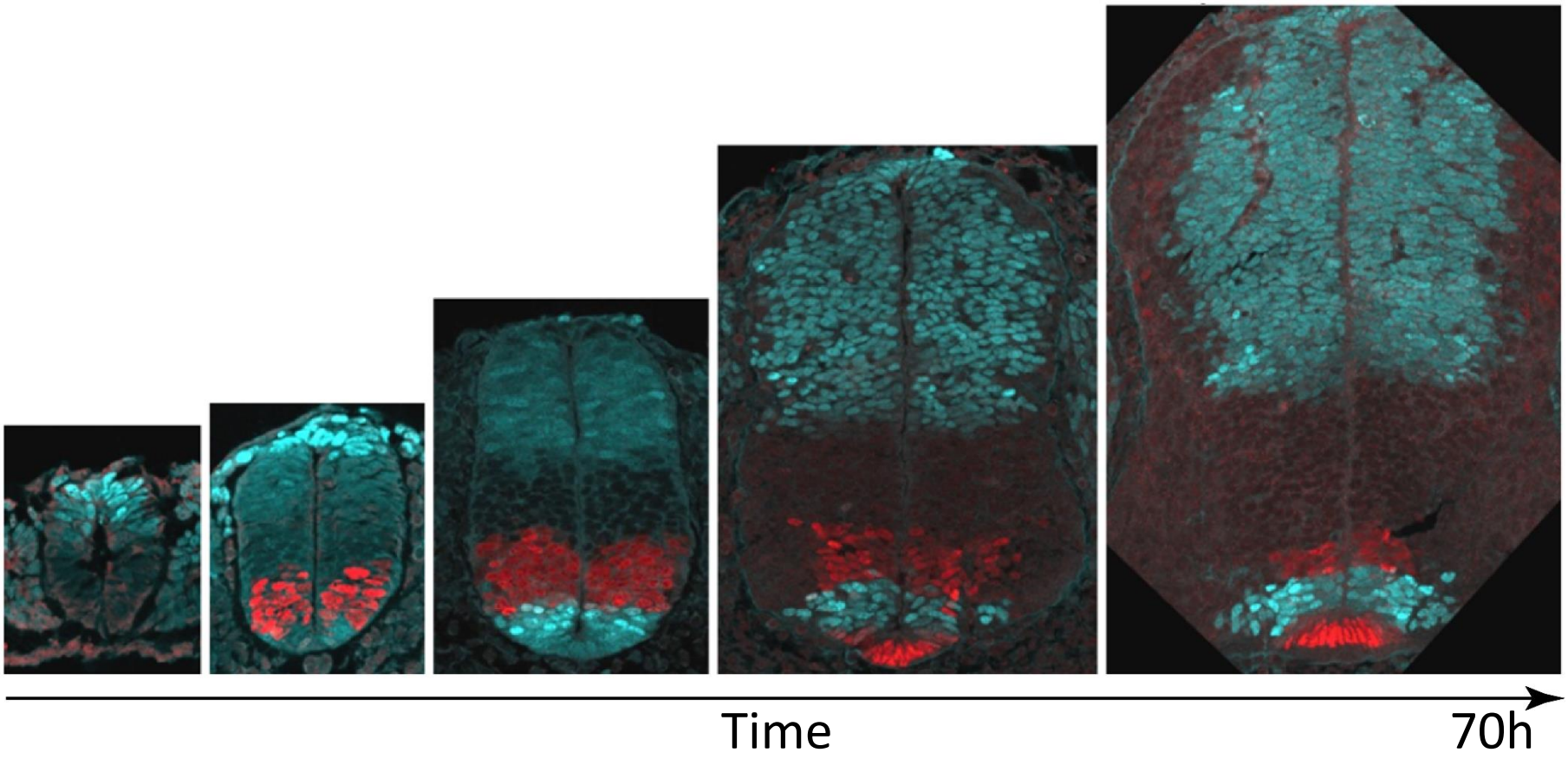
Summary

- Positional information is decoded with precision close to theoretical limit of decoding of noisy signals
- Regulatory mechanisms acting at the single cell level decode positional information
- Is the optimal decoding a fundamental principle characterizing pattern specification in developmental systems?









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National Science Centre Poland

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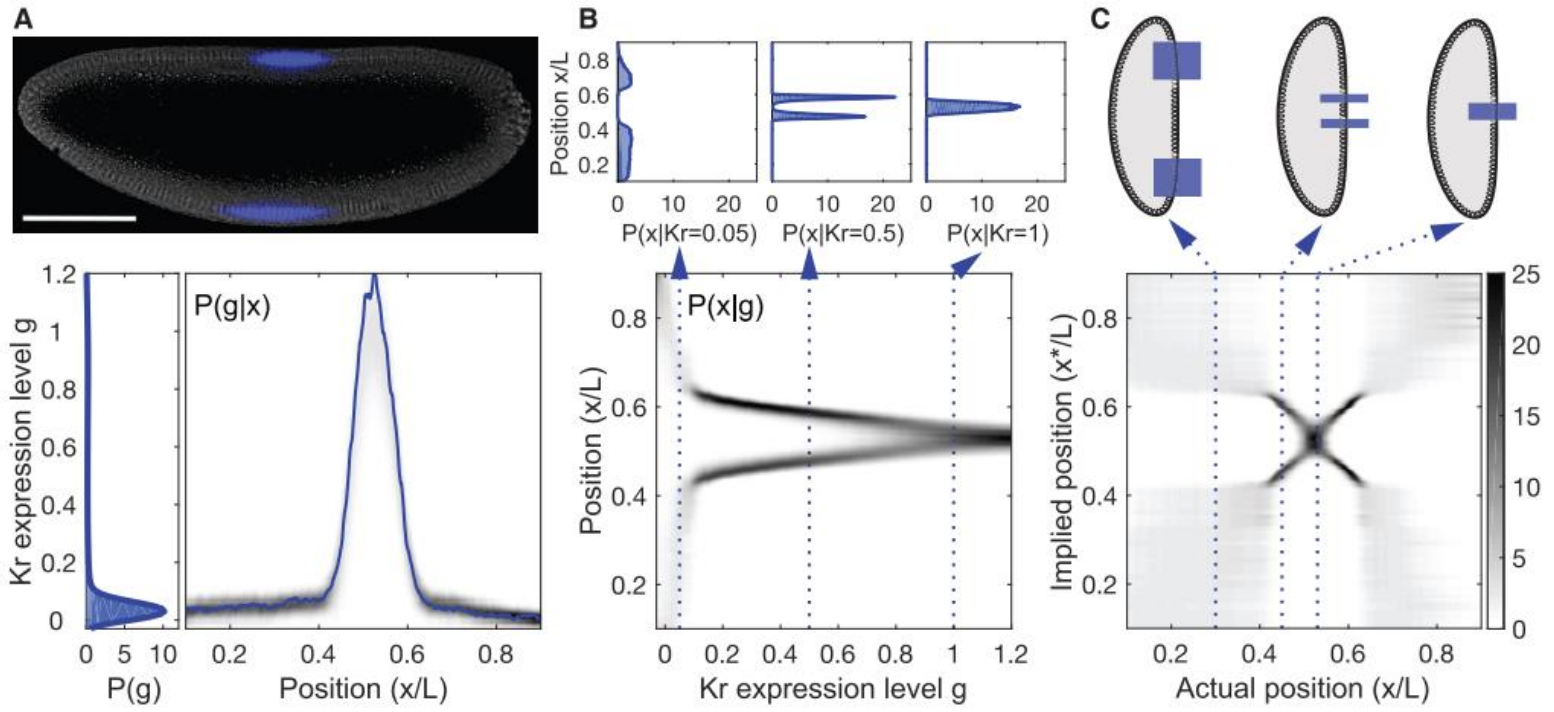
NAWA NARODOWA AGENCJA WYMIANY AKADEMICKIEJ

The project is financed by the Polish National Agency for Academic Exchange

Future directions

- To what extent the formation of the morphogen source regions affects morphogen profiles?
- What type of regulatory mechanisms affecting morphogen spreading are optimal for minimizing positional error?
- How does temporal progression of information decoding affect pattern decoding?
- Can self-organizing modes of pattern specification increase information capacity of morphogen decoding?

Coding and decoding positions in fly embryos



Petkova et al., Cell, 2019

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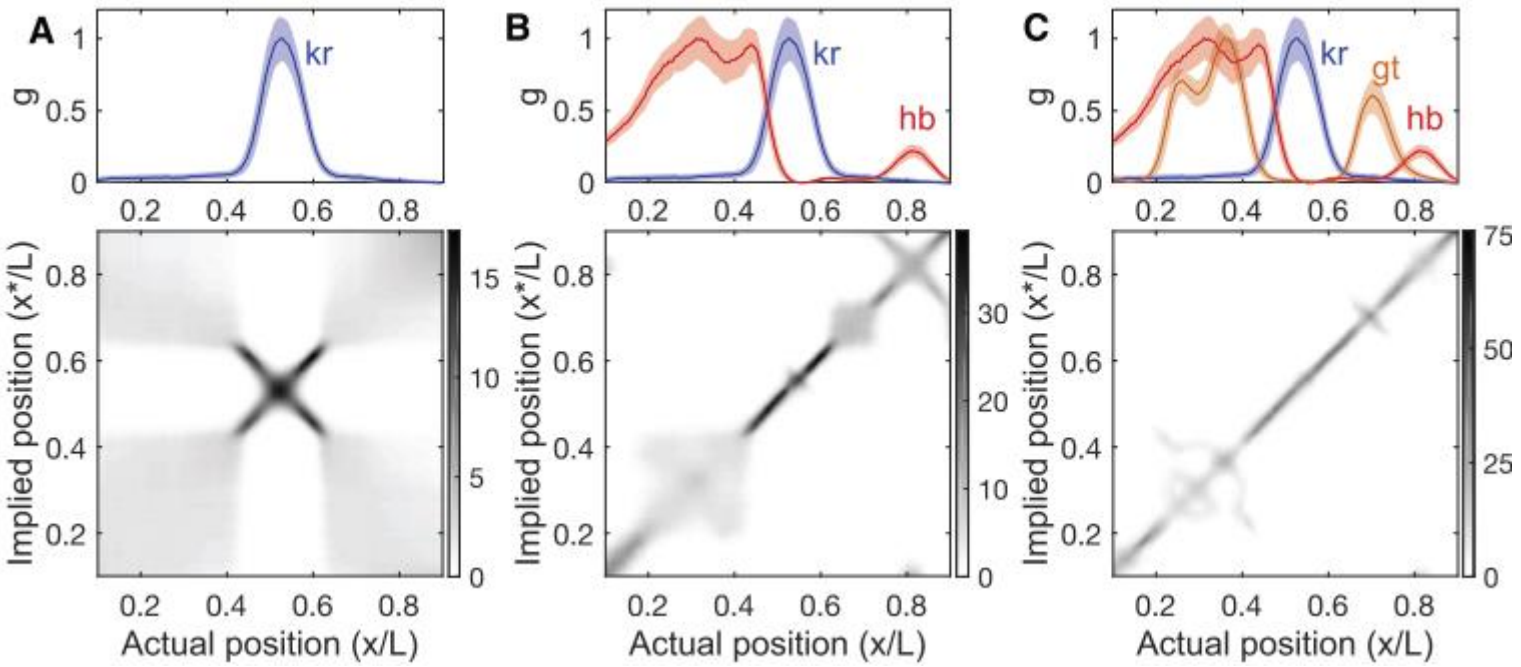
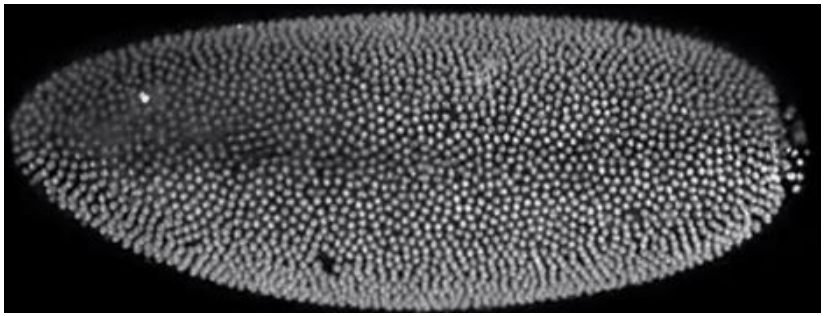


Petkova et al., Cell, 2019

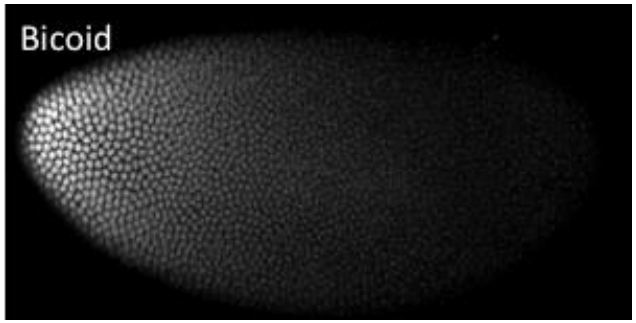
Cells acquire specific fates during organisms development



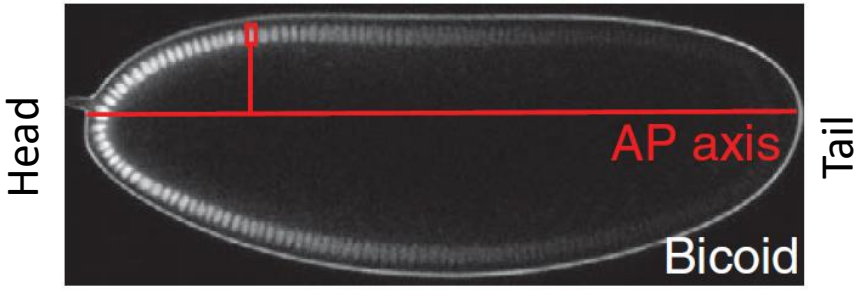
i.imgur.com/NKIMPmp.gif

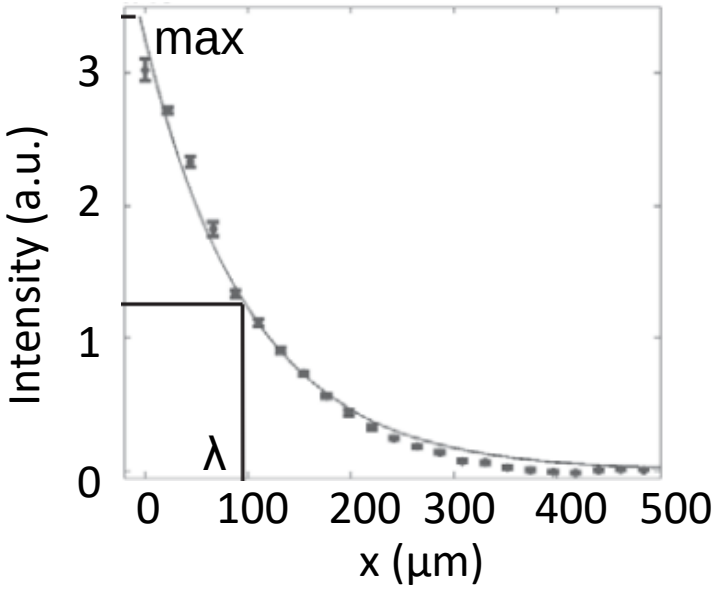
www.sciencebuzz.com

Bicoid proteins form a concentration gradient providing coordinate system for developing embryo



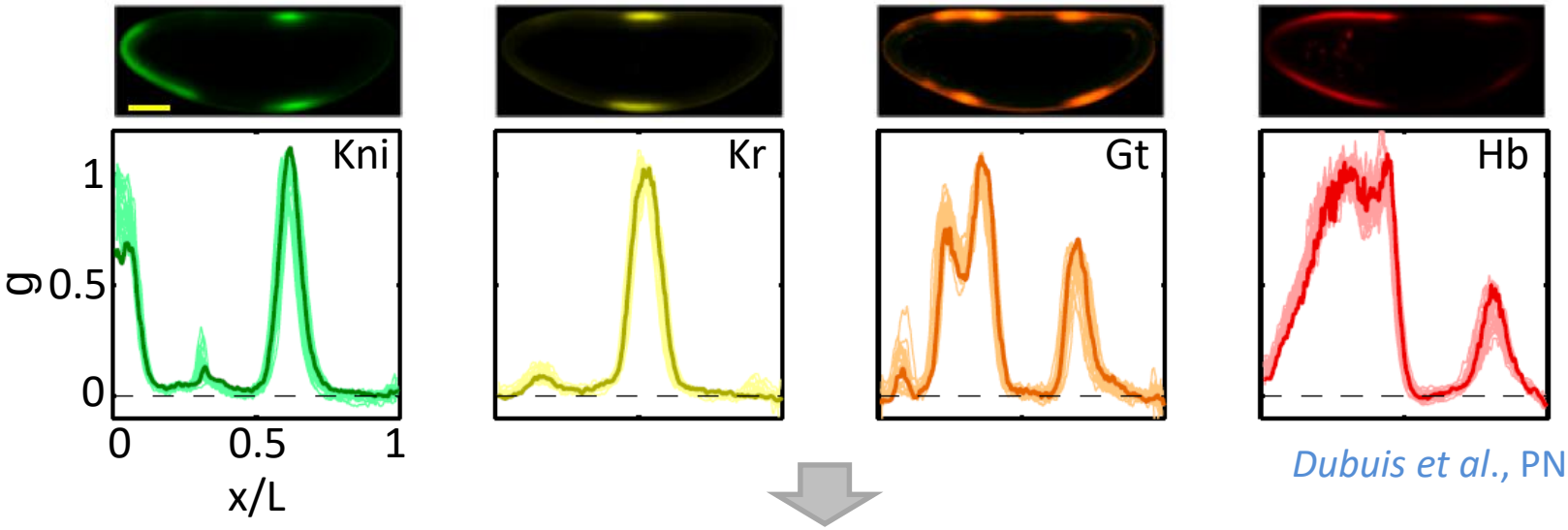
as.nyu.edu/faculty/stephen-small.html



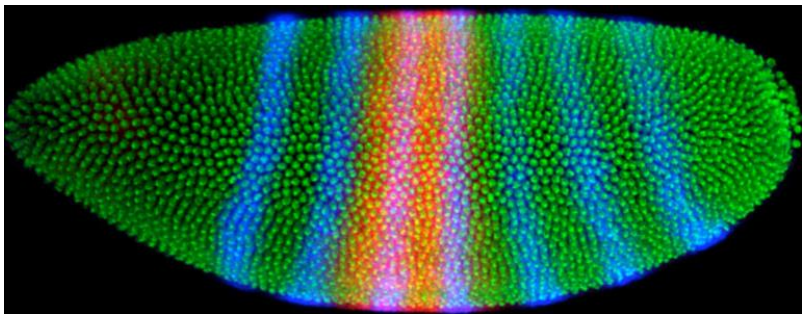


Grimm et al., Development, 2010

In fruit fly expression levels of 4 gap genes specify striped pattern of pair-rule genes



Dubuis et al., PNAS, 2013



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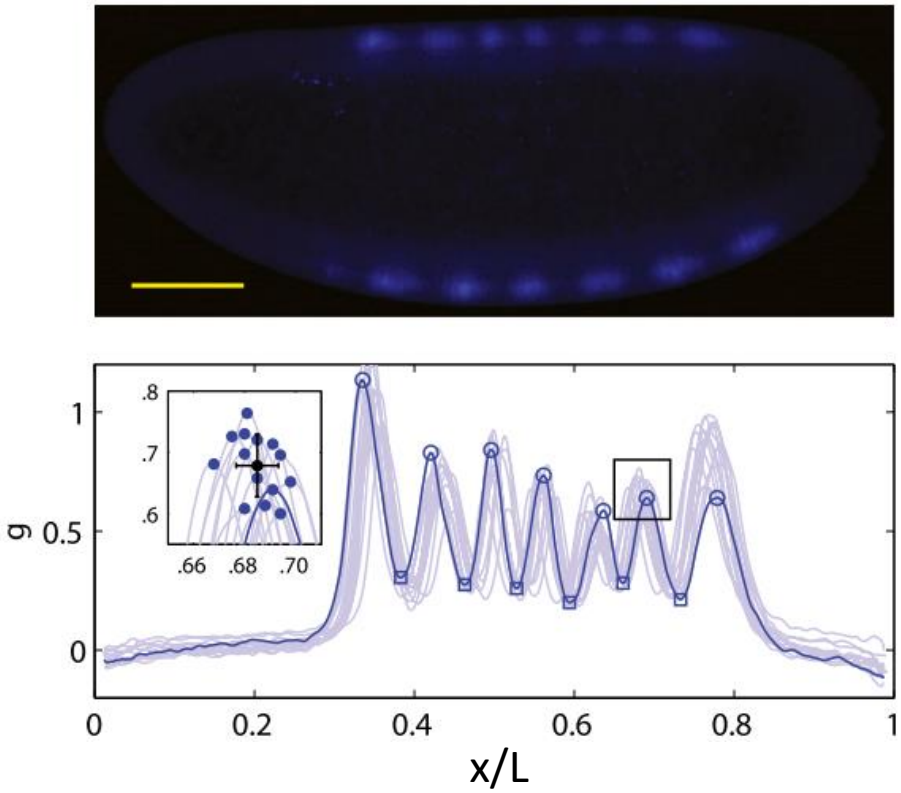
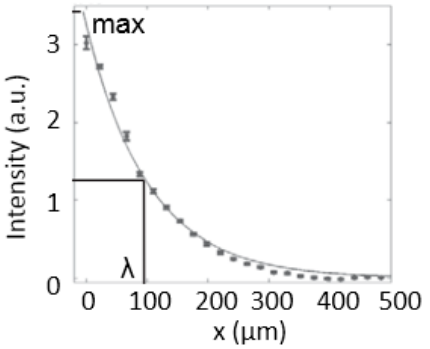
The information is decoded to specify gene expression pattern; output



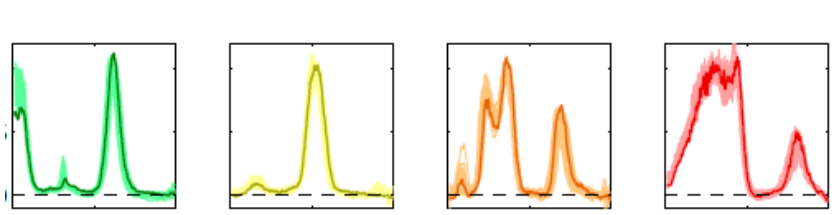
- Input: I = 4.1 ±0.2 bits, Output: I = 4.3 bits.

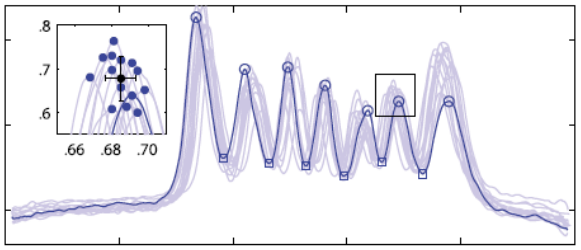
Interim summary

- Morphogens provide a coordinate system for patterning of developing tissues



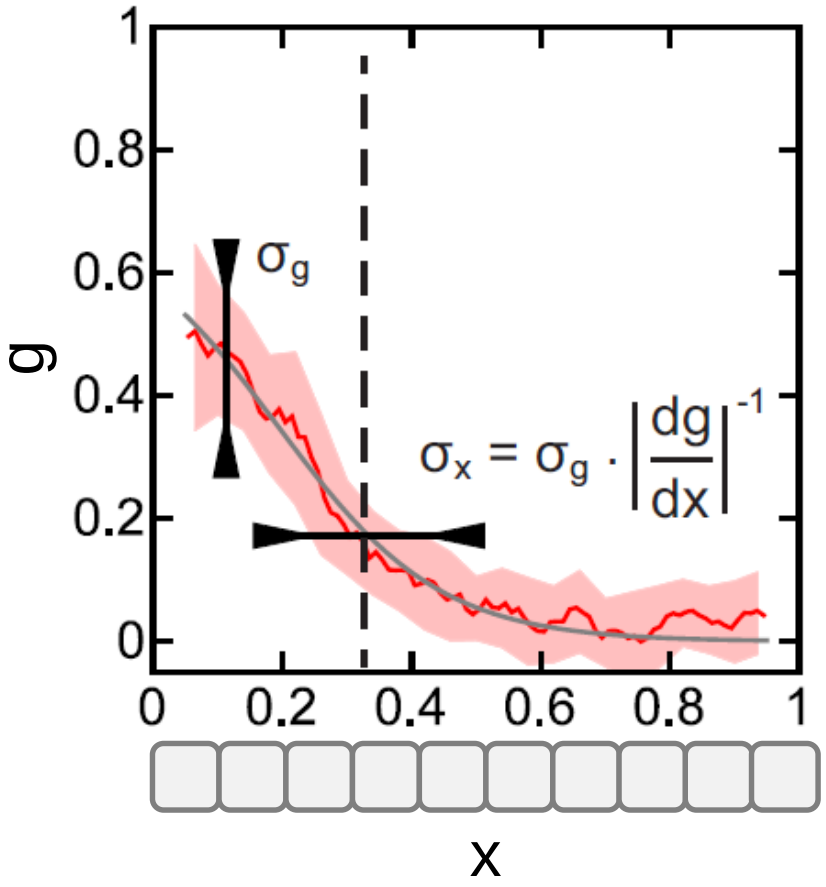
- Positional information conveyed in the input signals corresponds to positional imprecision in the output
- Positional error is about 1 cell diameter and equally distributed along the anterior-posterior axis



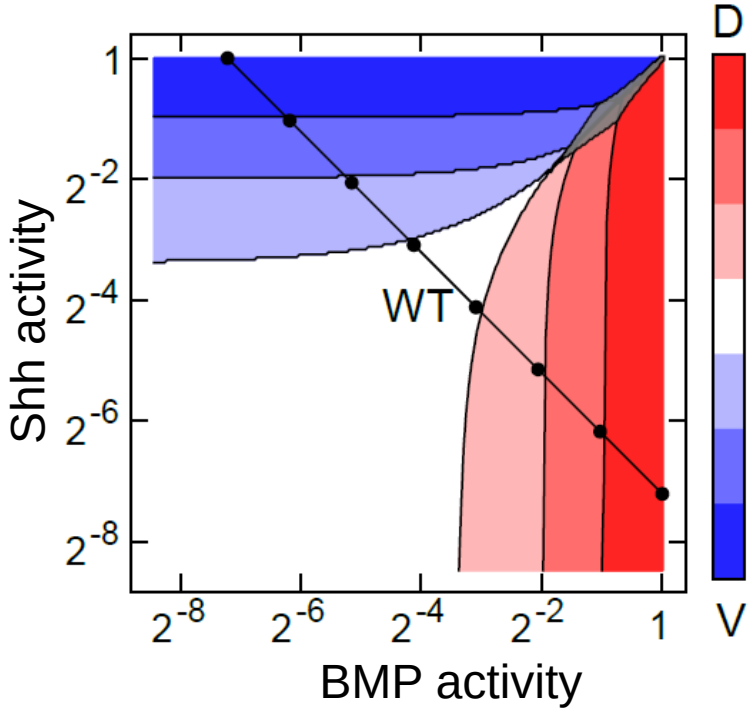


What are the principles of information decoding in development?

Positional error quantifies uncertainty in cell fate specification at a given position



Cells interpret the opposing morphogen signals using an optimal decoding strategy

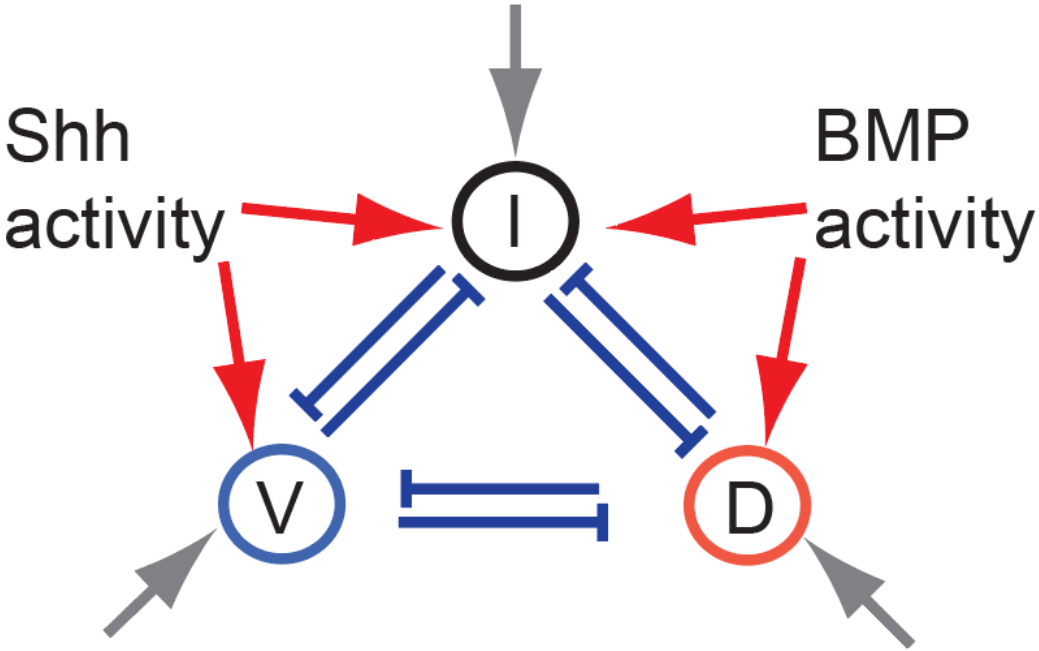


$$P(c_B, c_S|x) = \frac{1}{2\pi\sigma_B(x)\sigma_S(x)} \exp\left\{-\frac{1}{2}\left[\frac{\left(c_B - c_B(x)\right)^2}{\sigma_B^2(x)} + \frac{\left(c_S - c_S(x)\right)^2}{\sigma_S^2(x)}\right]\right\}$$

$$\hat{x}(c_B, c_S) = \mathrm{argmax}_x\, P(c_B, c_S|x)$$

Morishita & Yoh, PRE, 2009
Tkacik et al., Genetics, 2015
Zagorski et al., Science, 2017

The morphogens activate gene regulatory network (GRN) to specify cell fate

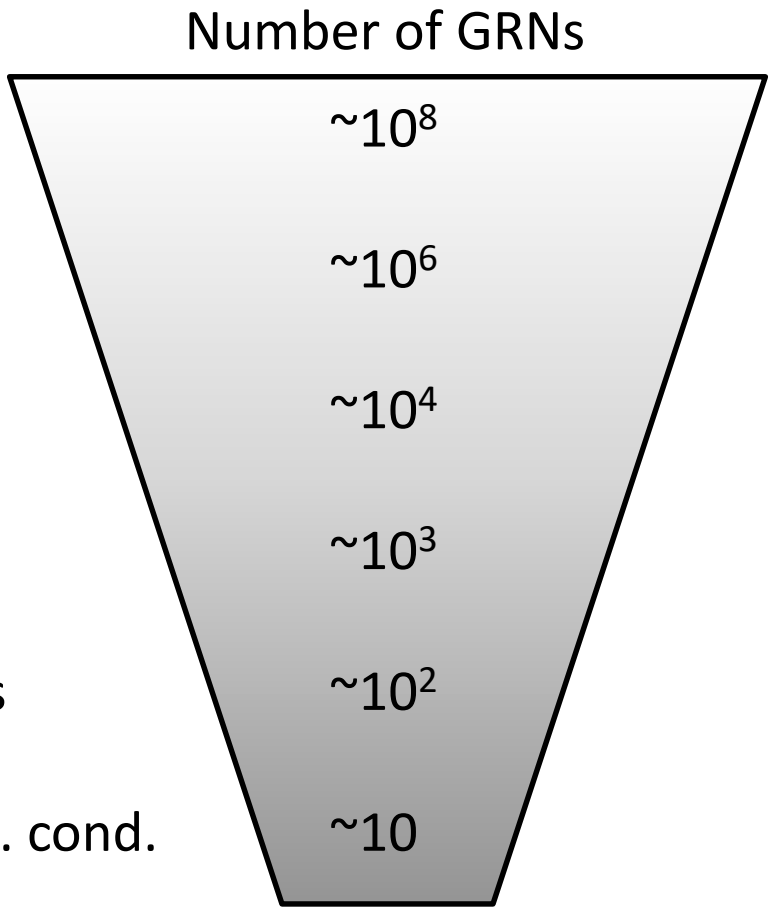


D: Pax3
I: Dbx2
V: Nkx6.1

Zagorski et al., Science, 2017

Numerical screening through GRNs with experimentally motivated criteria

1. Stable gene domains
2. Stripped gene pattern
3. Correct shifts in WT pattern
4. Consistent shifts in Shh mutant
5. High heterogeneity for high signal levels
6. Robustness towards perturbation in init. cond.



3-node regulatory network model

$$\frac{\mathrm{d[Msx]}}{\mathrm{dt}} = \alpha_{Msx}\frac{\kappa_{Msx} + c_{B\to M}\kappa_{Msx}\,[\mathrm{BMP}]}{(1+K_{N\to M}[\mathrm{Nkx}])^{m_{N\to M}}(1+K_{D\to M}[\mathrm{Dbx}])^{m_{D\to M}} + \kappa_{Msx} + c_{B\to M}\kappa_{Msx}\,[\mathrm{BMP}]} - \gamma_{Msx}[\mathrm{Msx}]$$

$$\frac{\mathrm{d[Nkx]}}{\mathrm{dt}} = \alpha_{Nkx}\frac{\kappa_{Nkx} + c_{S\to N}\kappa_{Nkx}\,[\mathrm{Shh}]}{(1+K_{M\to N}[\mathrm{Msx}])^{m_{M\to N}}(1+K_{D\to N}[\mathrm{Dbx}])^{m_{D\to N}} + \kappa_{Nkx} + c_{S\to N}\kappa_{Nkx}\,[\mathrm{Shh}]} - \gamma_{Nkx}[\mathrm{Nkx}]$$

$$\frac{\mathrm{d[Dbx]}}{\mathrm{dt}} = \alpha_{Dbx}\frac{\kappa_{Dbx} + c_{S\to D}\kappa_{Dbx}\,[\mathrm{Shh}] + c_{B\to D}\kappa_{Dbx}\,[\mathrm{BMP}]}{(1+K_{M\to D}[\mathrm{Msx}])^{m_{M\to D}}(1+K_{N\to D}[\mathrm{Dbx}])^{m_{N\to D}} + \kappa_{Dbx} + c_{S\to D}\kappa_{Dbx}\,[\mathrm{Shh}] + c_{B\to D}\kappa_{Dbx}\,[\mathrm{BMP}]} - \gamma_{Dbx}[\mathrm{Dbx}]$$

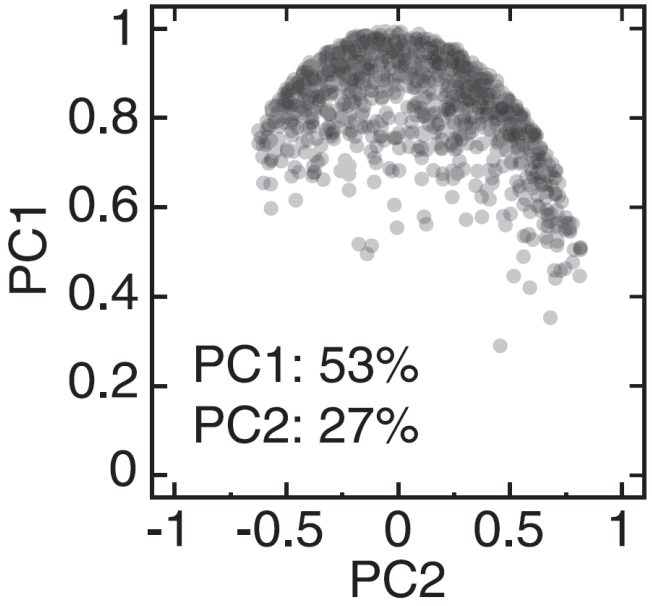
Exhaustive and/or random screen for 3+6+4=13 parameters

$\kappa_{Msx}, \kappa_{Nkx}, \kappa_{Dbx}$	uniform activation, range [0, 5]
$K_{N\to M}, K_{M\to N}, K_{N\to D}, K_{D\to N}, K_{M\to D}, K_{D\to M}$	repressor binding affinity, range [0, 100]
$c_{B\to M}, c_{B\to D}, c_{S\to N}, c_{S\to D}$	morphogen activation, range [0, 20]

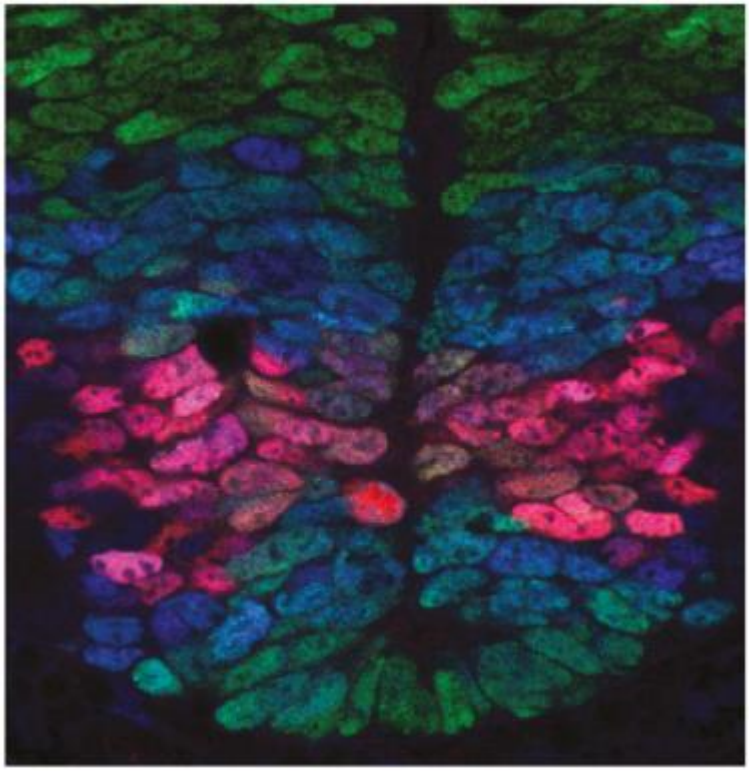
Fixed during screen

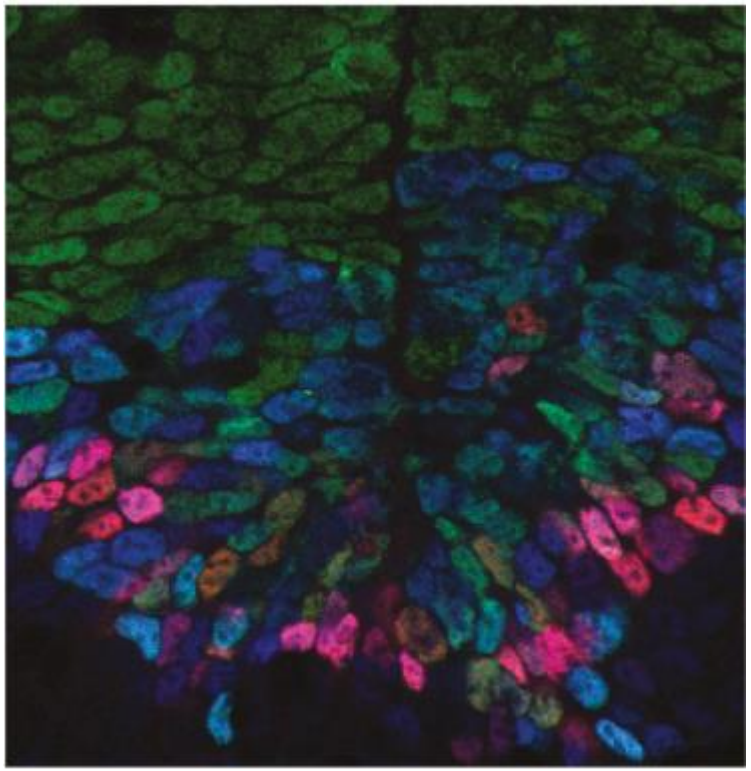
$\alpha_{Msx} = \alpha_{Nkx} = \alpha_{Dbx} = 1\ (h^{-1})$	production rate
$\gamma_{Msx} = \gamma_{Nkx} = \gamma_{Dbx} = 0.2\ (h^{-1})$	degradation rate
$m_{N\to M} = m_{M\to N} = m_{N\to D} = m_{D\to N} = m_{M\to D} = m_{D\to M} = 2$	Hill coefficients

Successful GRNs formed a single cluster in the parameter space



The pattern is established with less than 3 cell

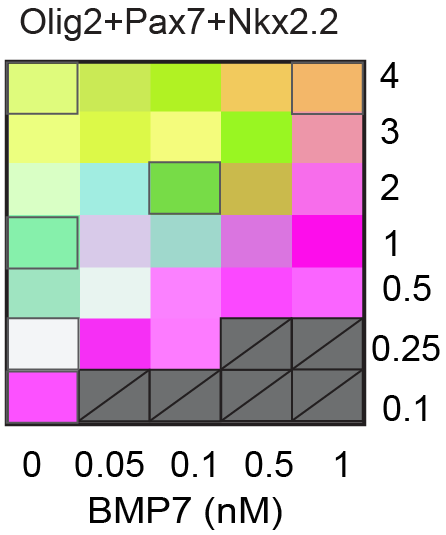


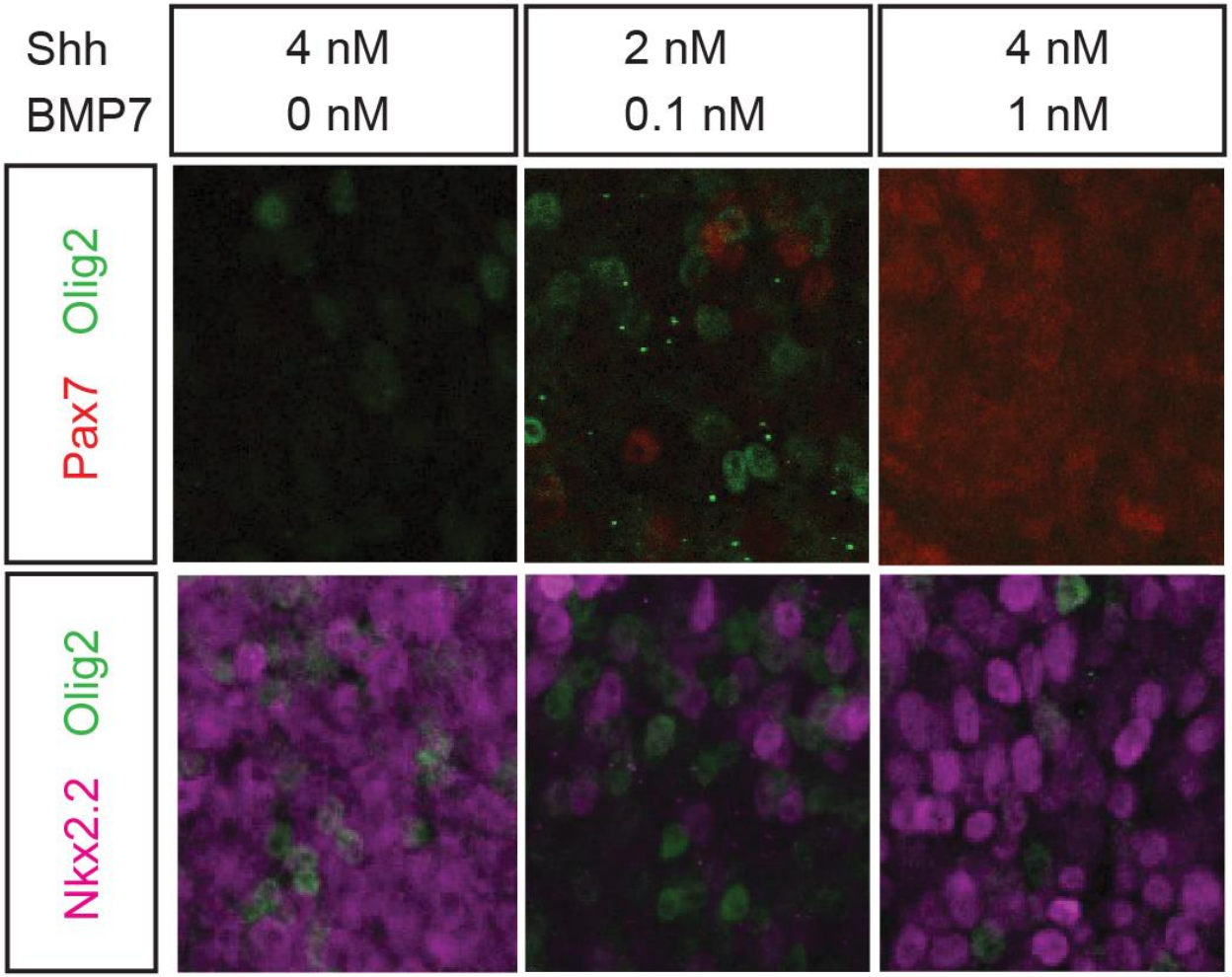


- Regulatory mechanisms; To what extent the FP size affects the resulting Shh morphogen profile?

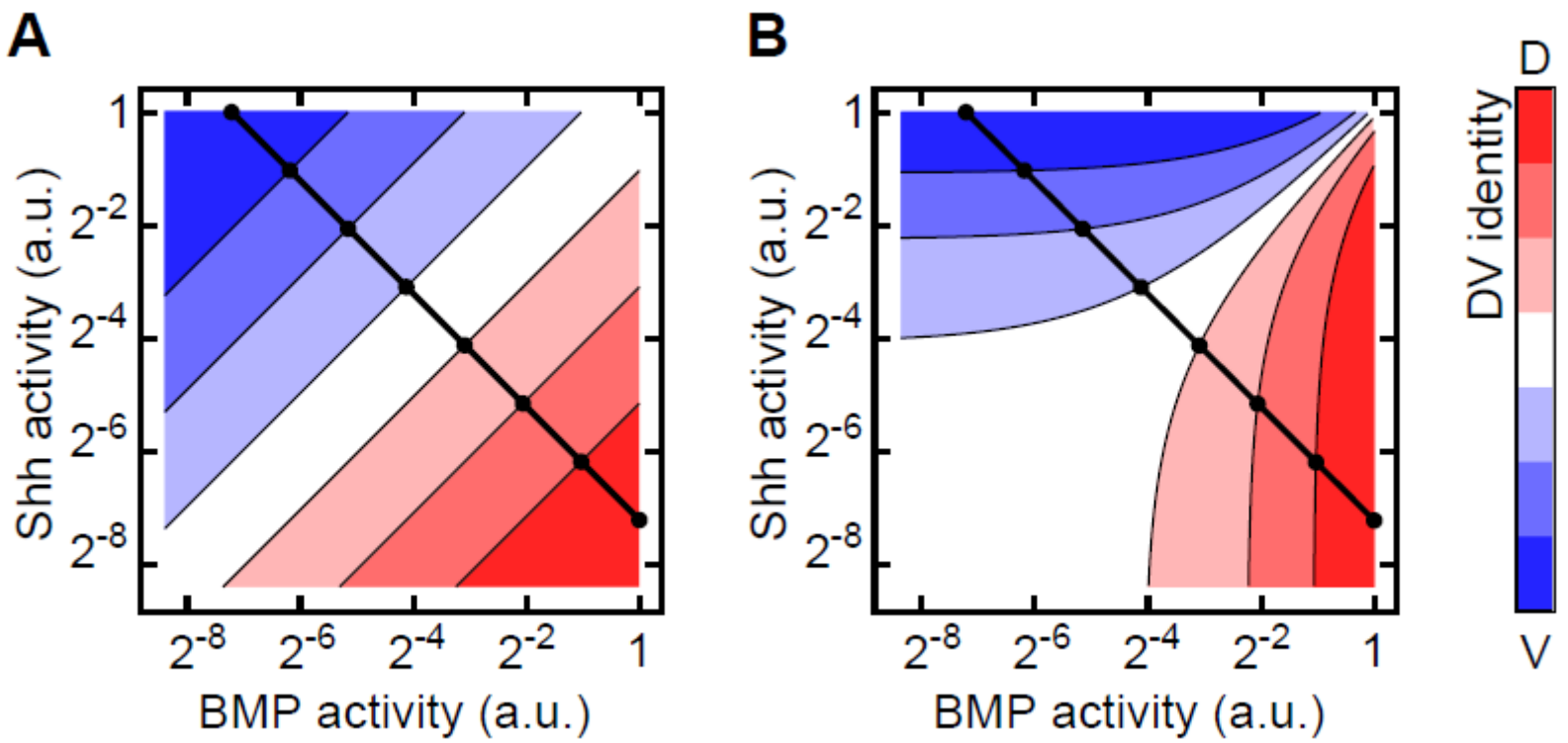
Source: Zagorski et al., Science 356, 2017

Decoding map reconstructed from explant experiment is consistent with ML predictions

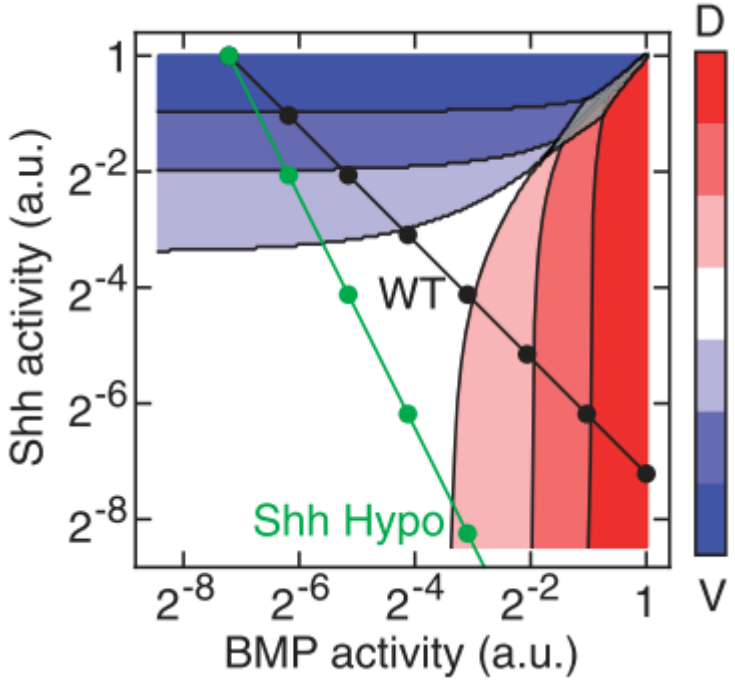


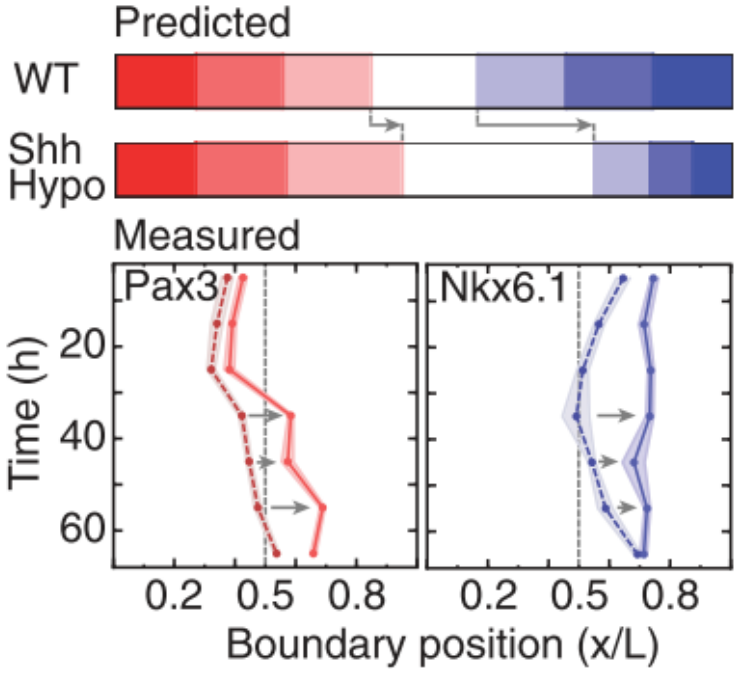


Alternative decoding maps: signal ratio and signal difference

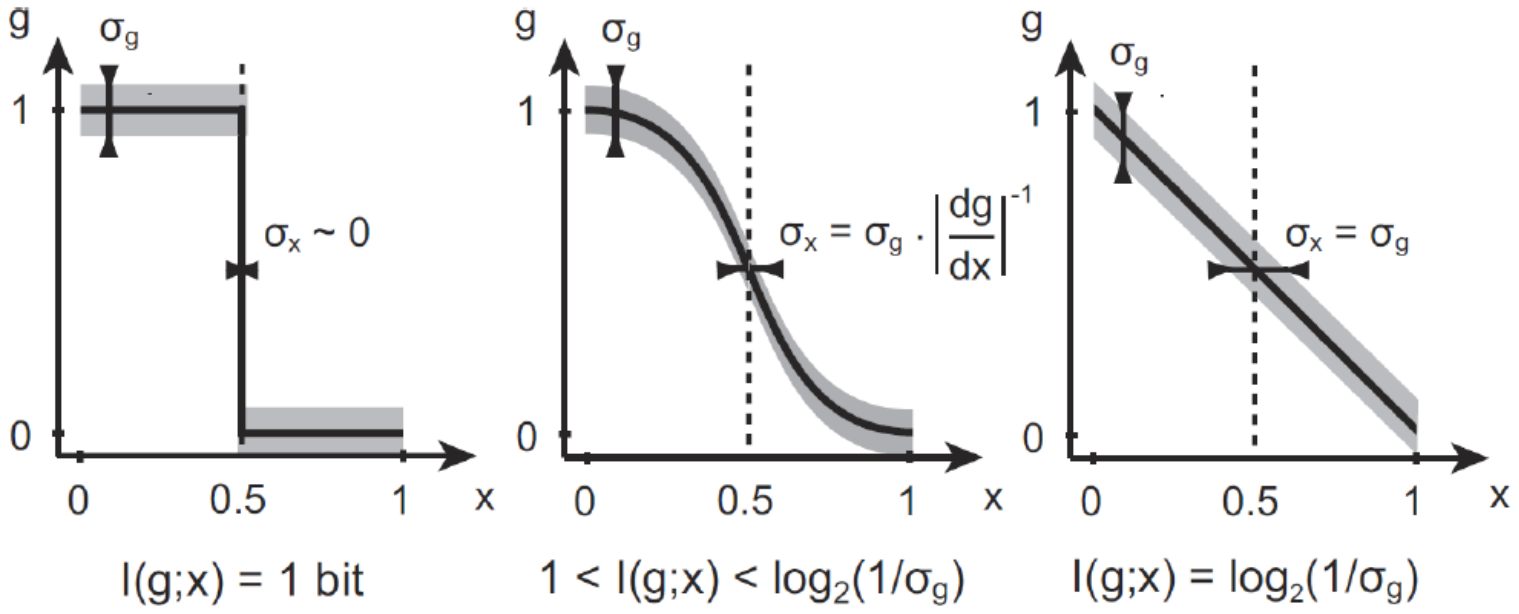


Predictions for Shh deficient mutant (Shh hypomorph)





Positional information in bits



$$I(x \to \{g_i\}) = \int dx P_x(x) \int d^N\mathbf{g} P(\{g_i\}|x) \log_2 \frac{P(\{g_i\}|x)}{P_g(\{g_i\})}$$

Tkacik et al., Genetics, 2015

Positional information in bits

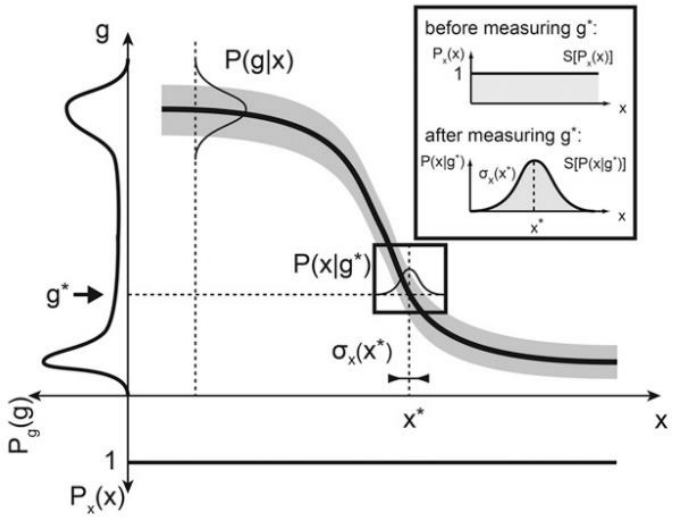
$$S[P_x(x)] = -\int dx\, P_x(x)\log_2\left[P_x(x)\right]$$

$$I(g) = S\left[P_x(x)\right] - S\left[P(x|g)\right]$$

$$I_{g\to x} = \int dg\, P_g(g)\left(S[P_x(x)] - S[P(x|g)]\right),$$

$$= \int dg \int dx\, P(g,x)\log_2\left[\frac{P(g,x)}{P_g(g)P_x(x)}\right]$$

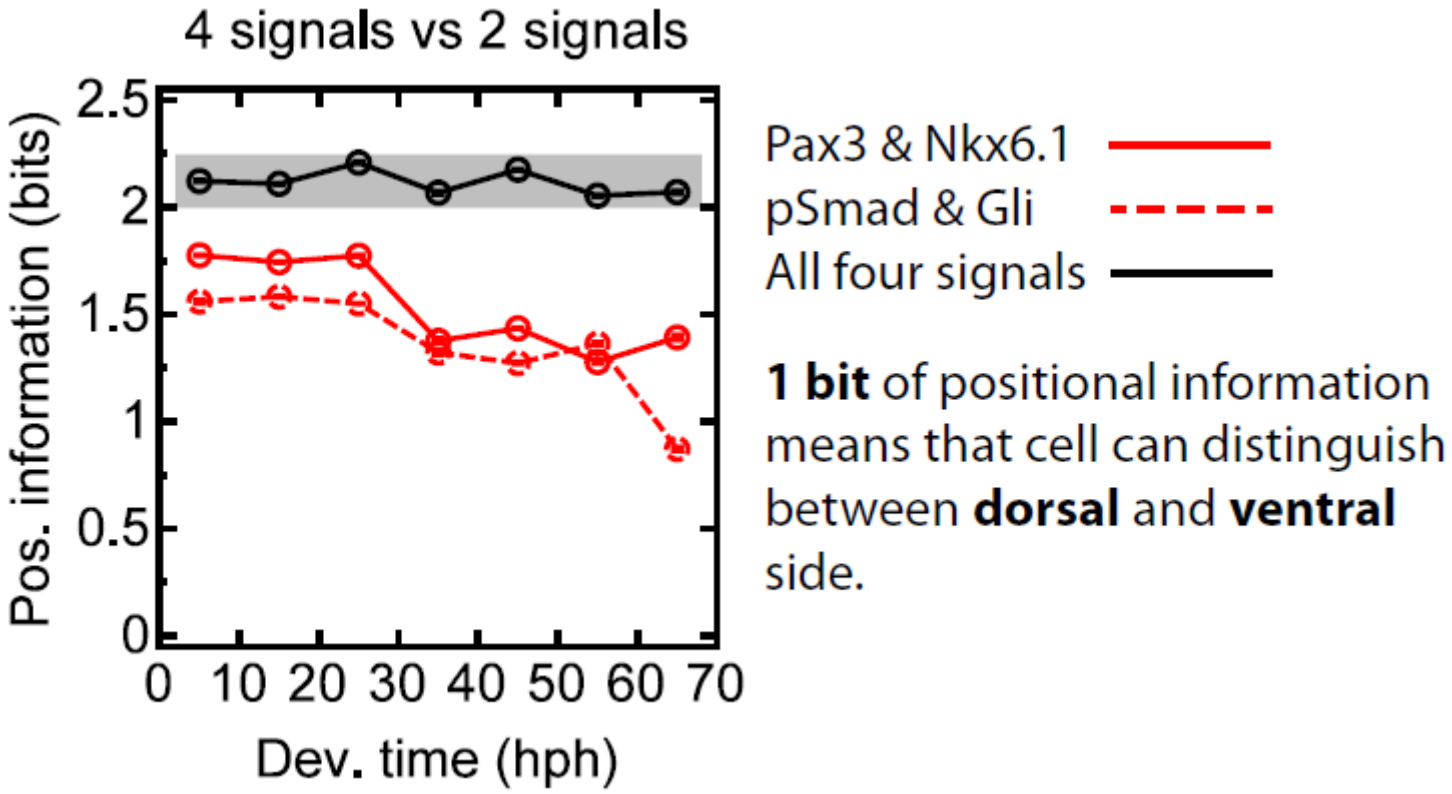
$$I_{g\to x} = \int dx\, P_x(x)\left(S\left[P_g(g)\right] - S[P(g|x)]\right)$$



Dubuis et al., PNAS, 2013

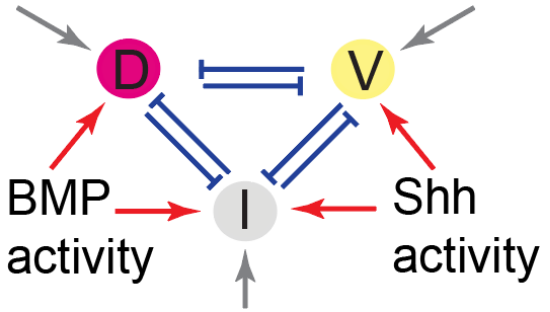
Tkacik et al., Genetics, 2015

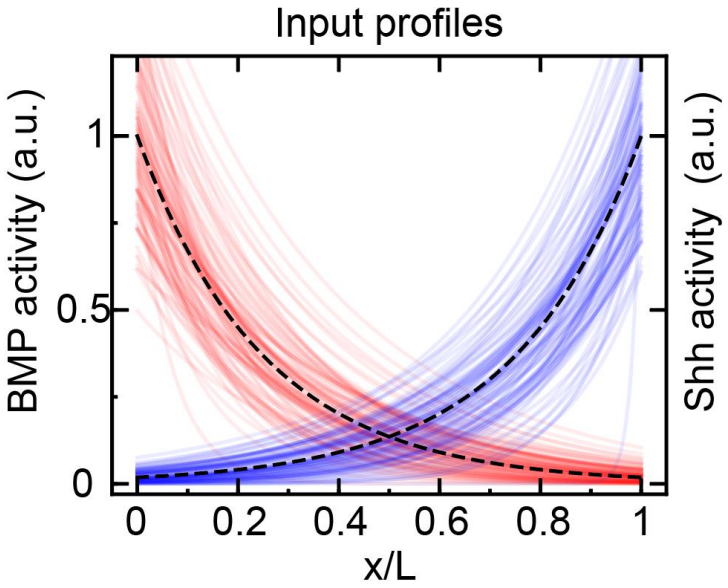
Total positional information is conserved

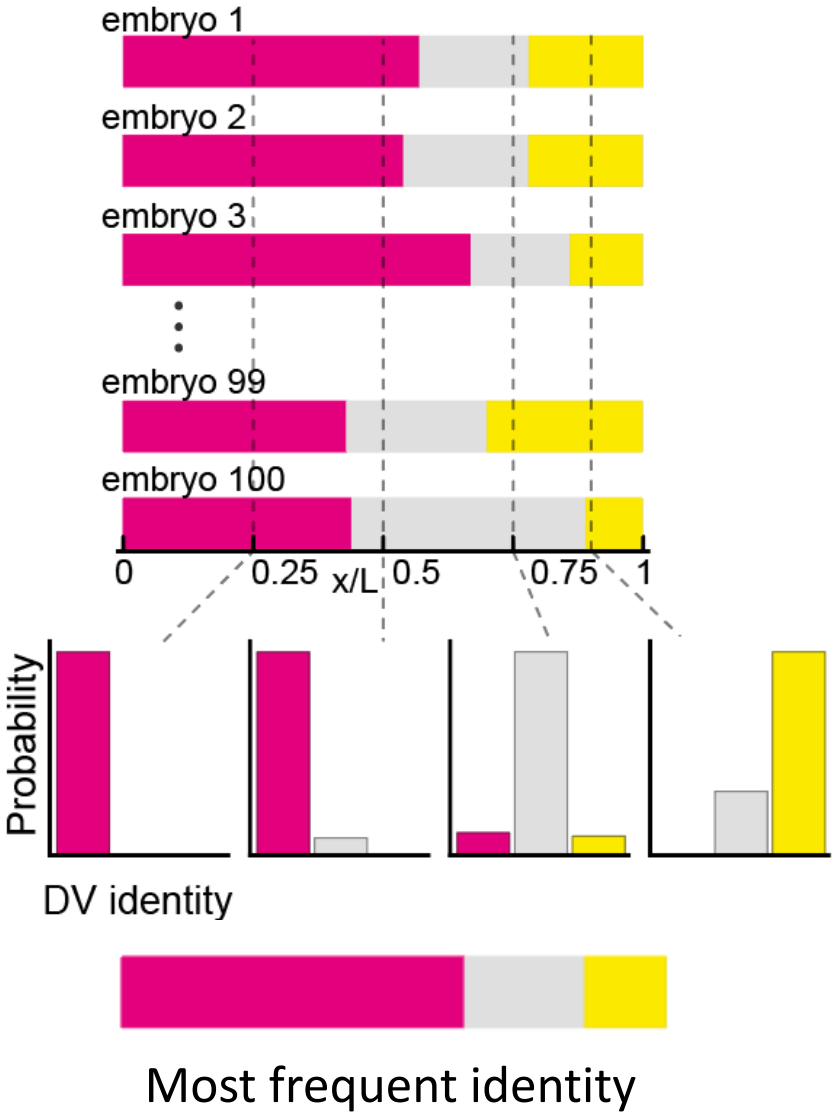


- Information is transferred from morphogen signals to their target genes at early stages

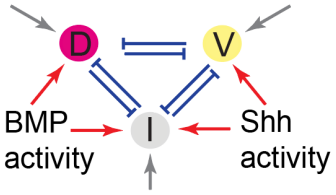
Noise affects resulting striped pattern



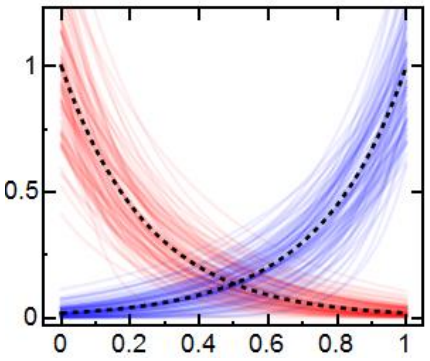


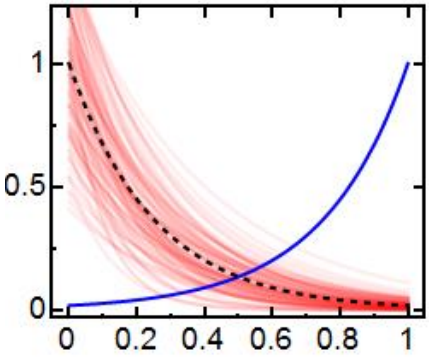


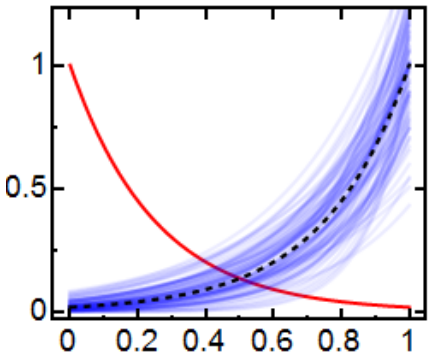
Boundary imprecision for a set of GRNs

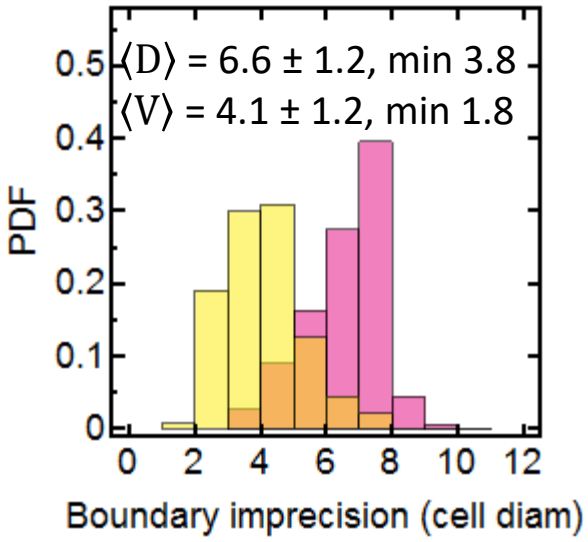


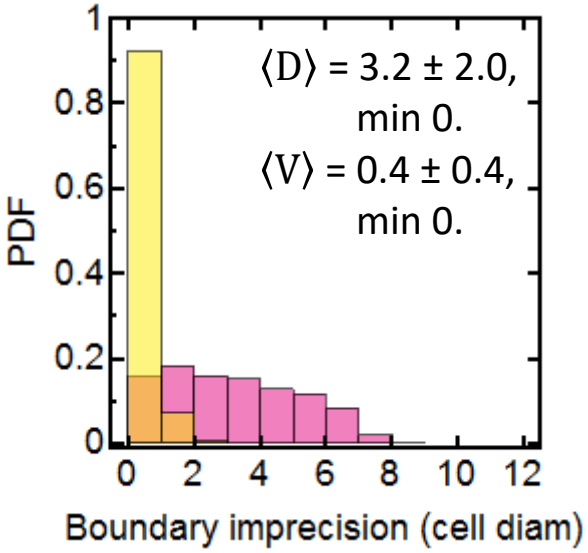
- 1221 GRNs consistent with experimental observations

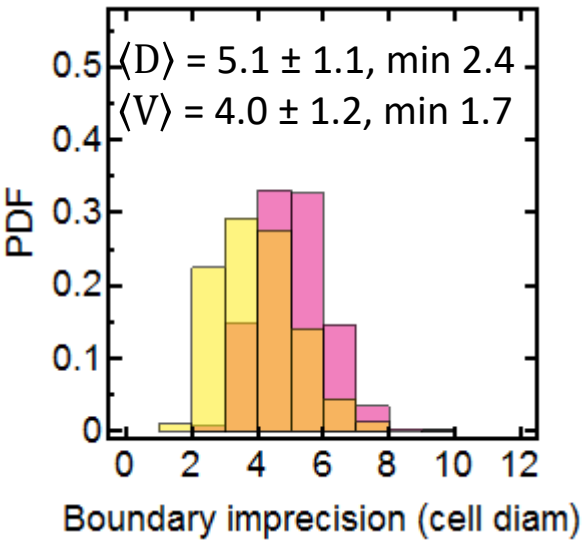




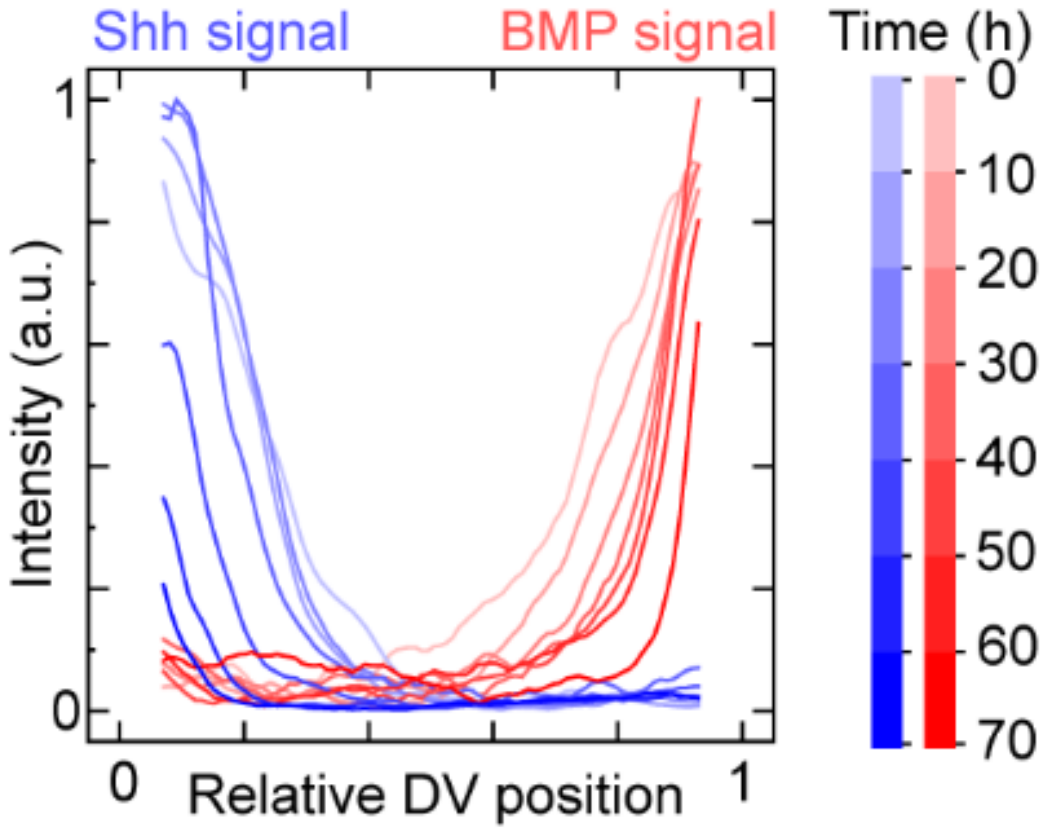






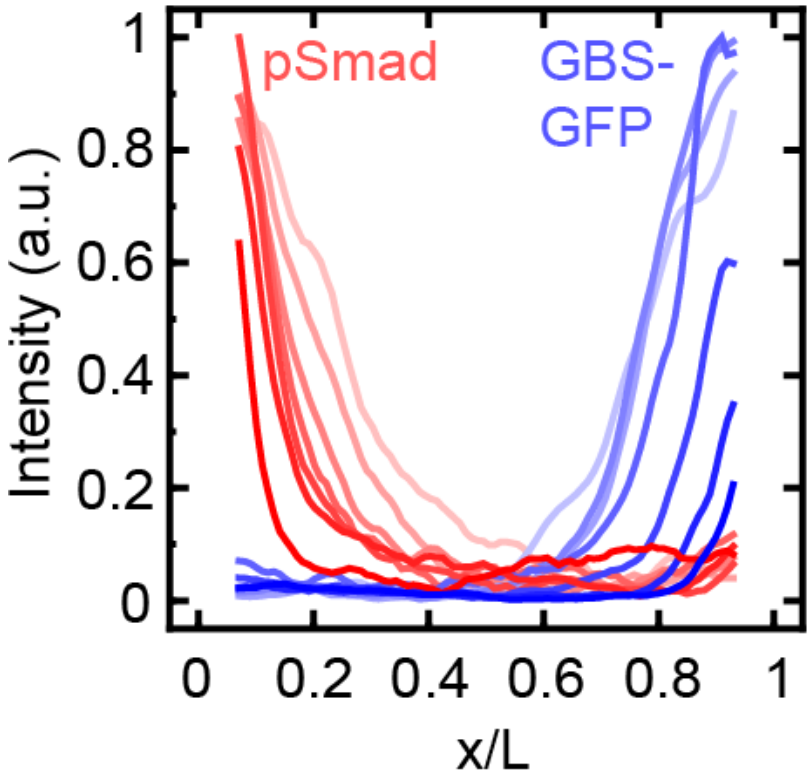


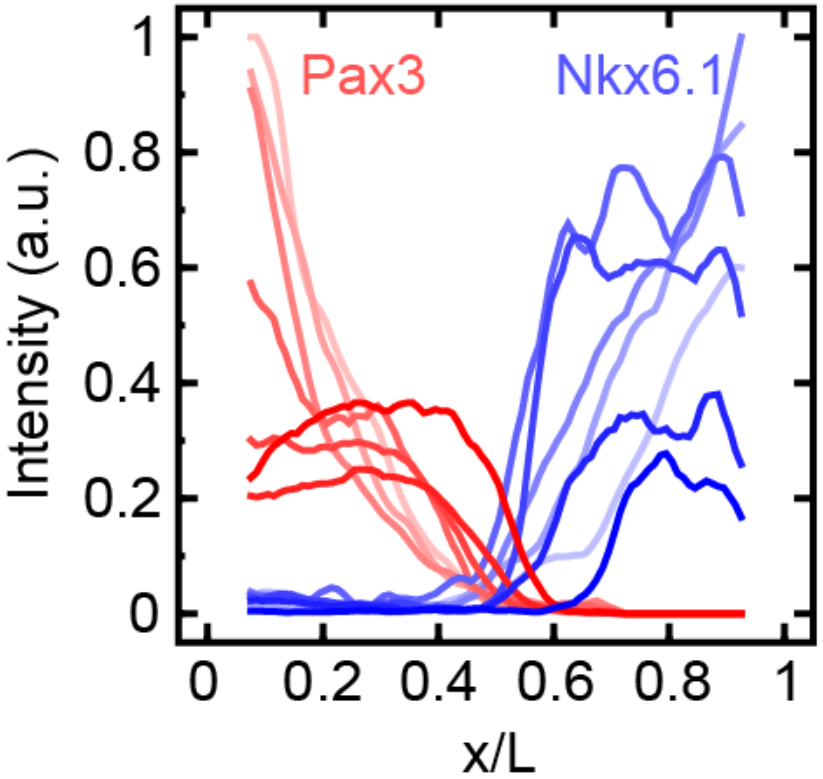
The morphogen signaling profiles do not scale with the embryo size



Zagorski et al., Science, 2017

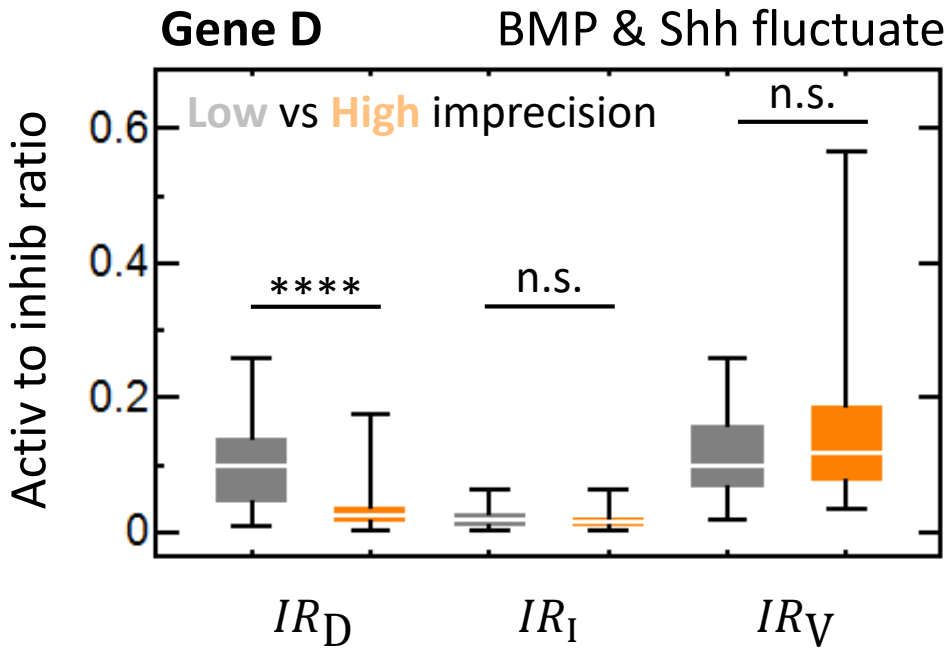
Sharp gene domain boundaries are formed after 30h





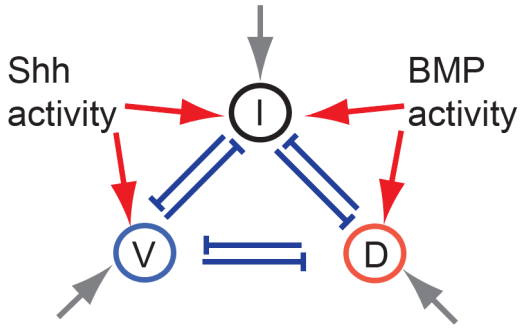
- Are morphogen signals sufficiently precise to specify the positions of target gene expression domains?

Ratio of activatory to inhibitory input of D gene affects boundary imprecision

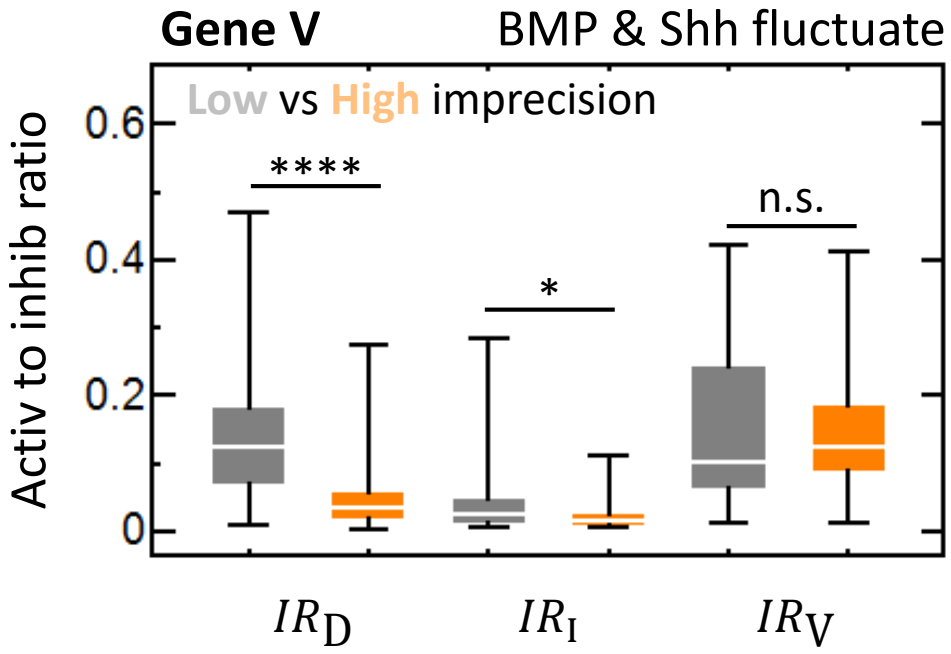


$$IR_{\mathrm{gene}} = \frac{\sum \mathrm{gene}_{activation}}{\sum \mathrm{gene}_{inhibition}}$$

$$IR_{\mathrm{D}} = \frac{c_{\mathrm{B}\to\mathrm{D}}}{K_{\mathrm{V}\to\mathrm{D}} + K_{\mathrm{I}\to\mathrm{D}}}$$

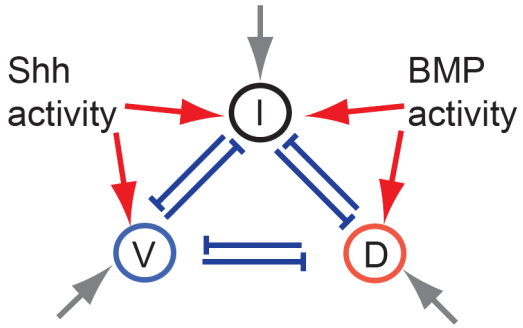


Ratio of activatory to inhibitory input of D gene affects boundary imprecision



$$IR_{\mathrm{gene}} = \frac{\sum \mathrm{gene}_{activation}}{\sum \mathrm{gene}_{inhibition}}$$

$$IR_{\mathrm{D}} = \frac{c_{\mathrm{B}\to\mathrm{D}}}{K_{\mathrm{V}\to\mathrm{D}} + K_{\mathrm{I}\to\mathrm{D}}}$$



Ratio of activ to inhib input in GRNs results in different imprecision for only BMP or BMP & Shh fluctuations