Processing of biological information in developmental systems

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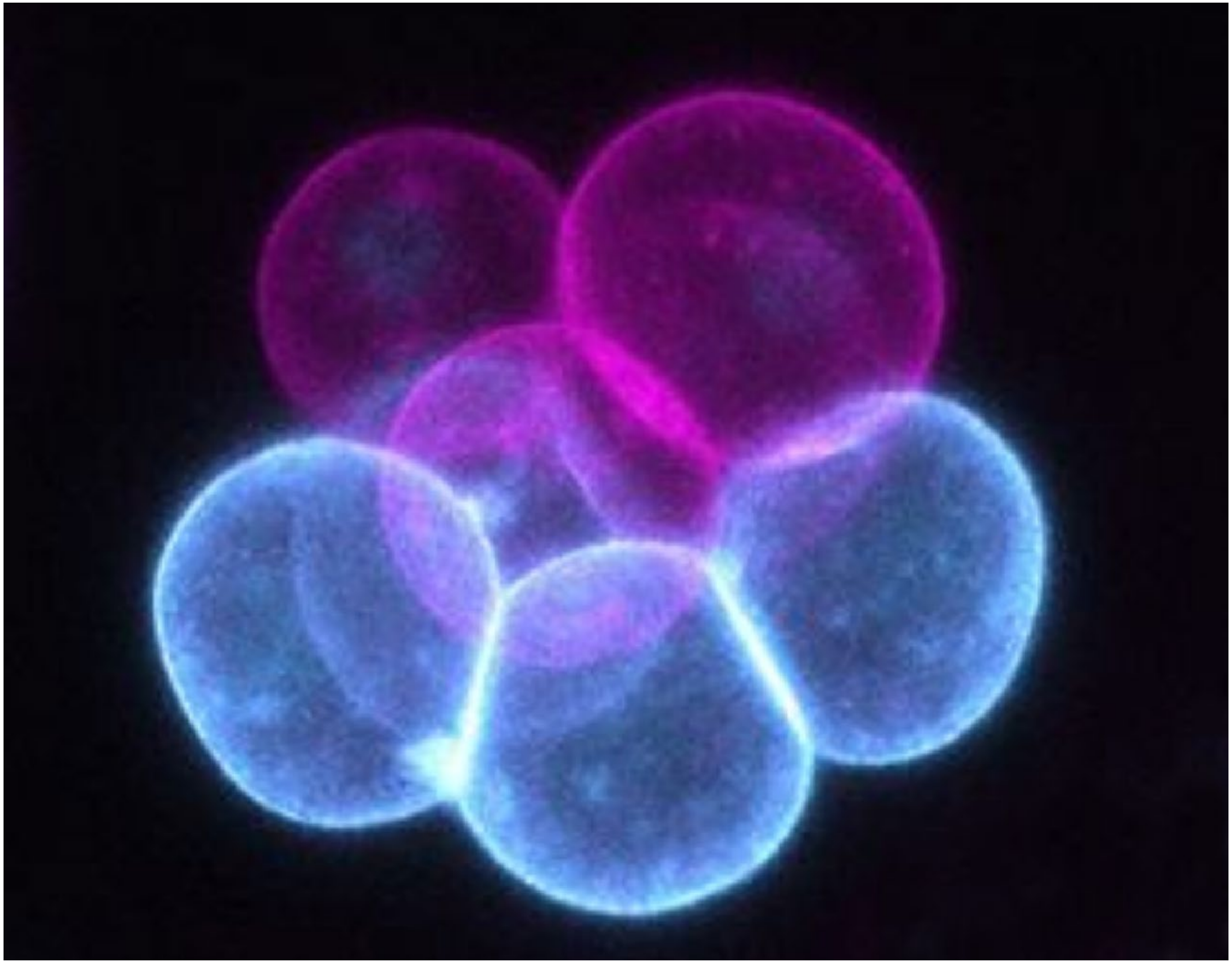
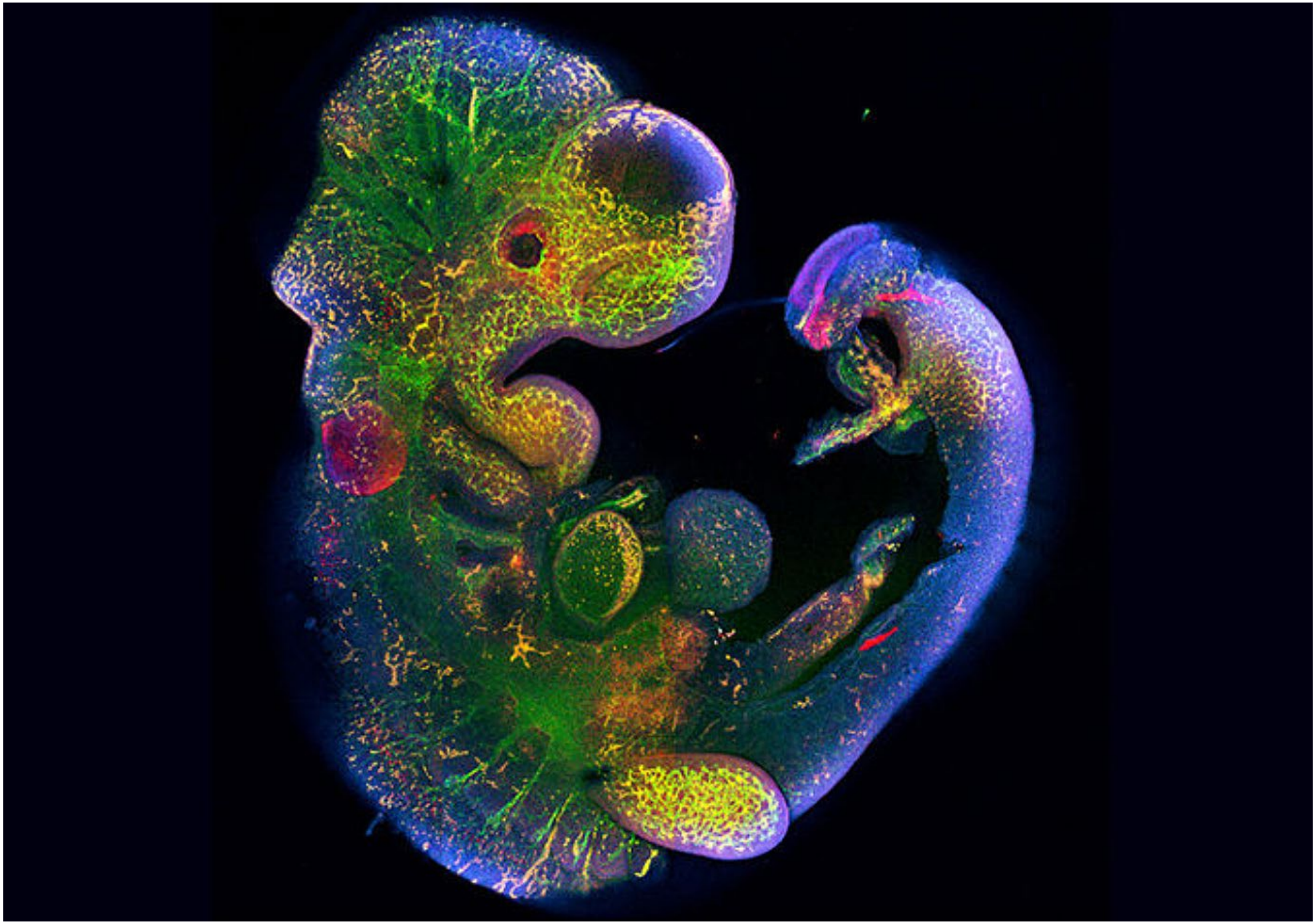
@wikipedia.org

Early stage mouse embryo with coloured daughter cells



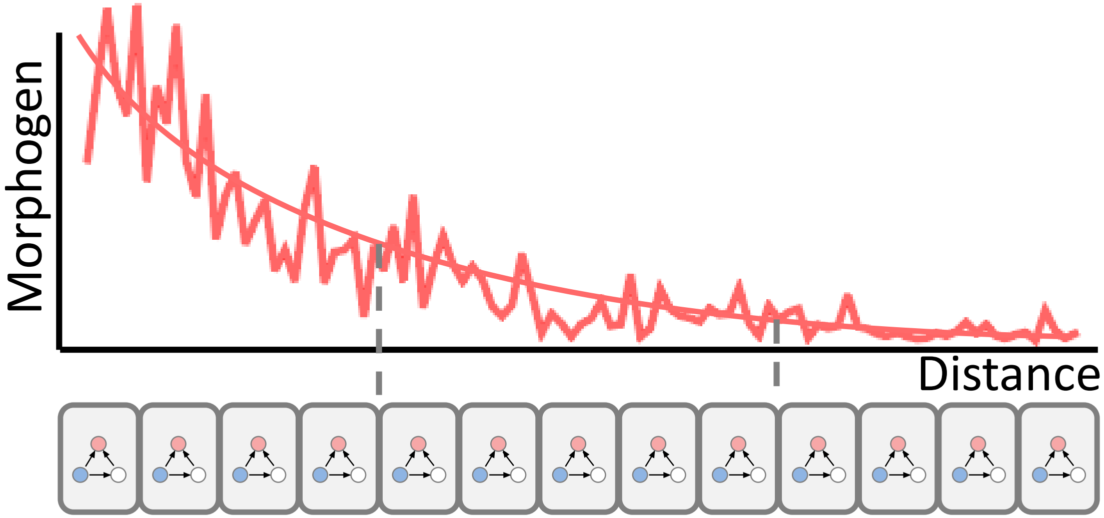
@Recher, Goolam, Zernicka-Goetz, University of Cambridge

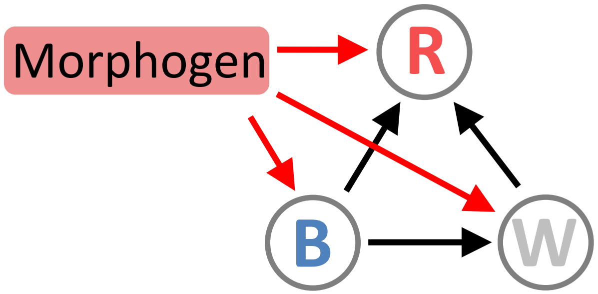
10.5-day mouse embryo with organs and body parts emerging



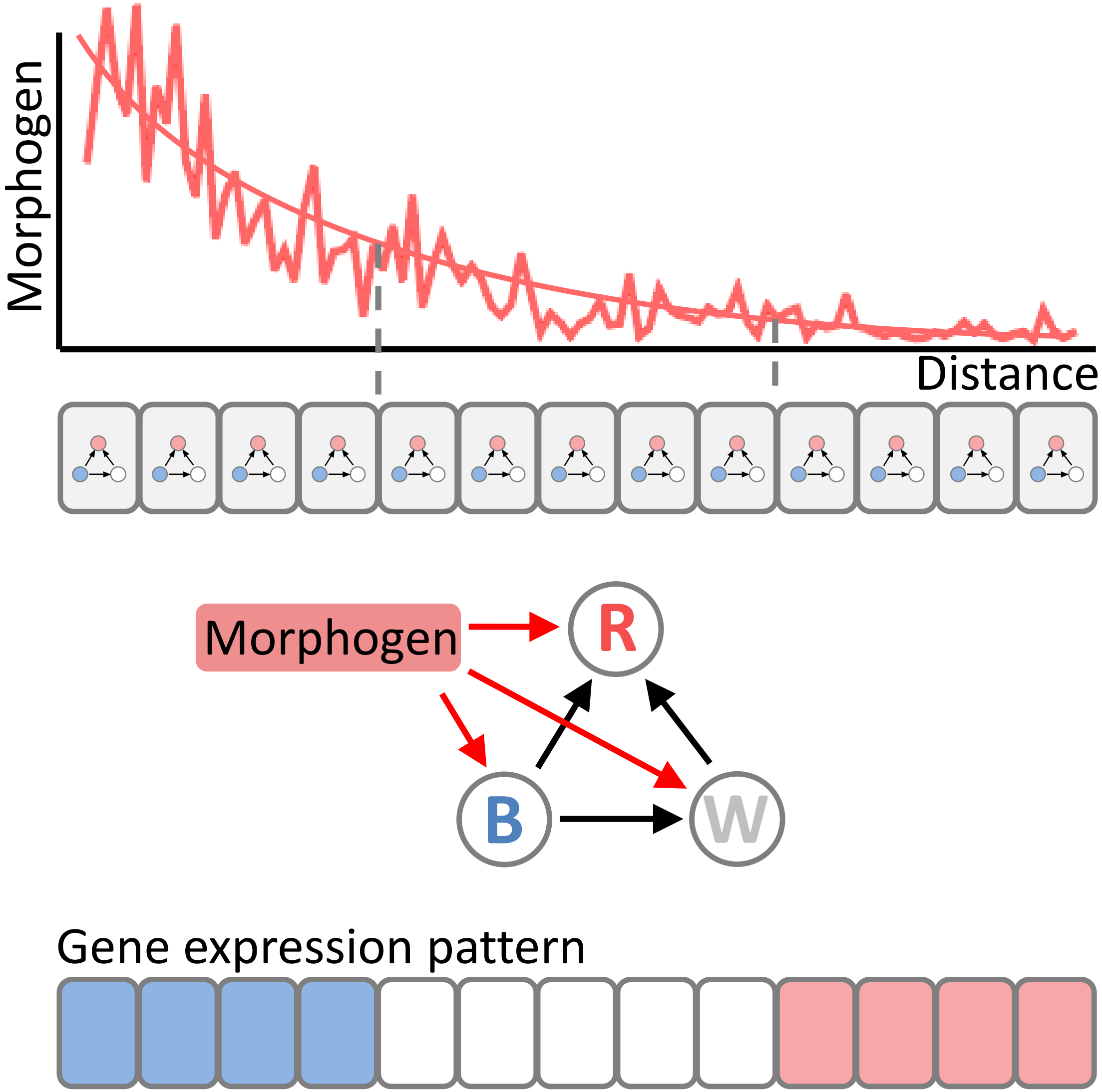
@Petersen, Miller. Marine Biological Laboratory in Woods Hole

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



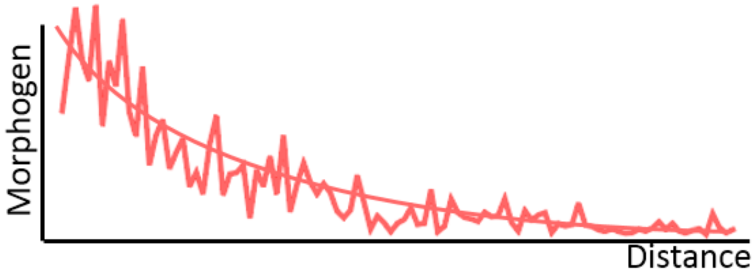


Morphogen gradients provide positional information establishing coordinate system for the developing tissue



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

Input signal



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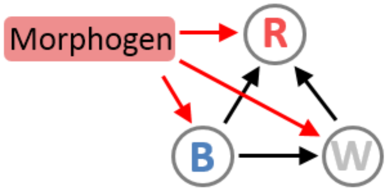
Information decoder



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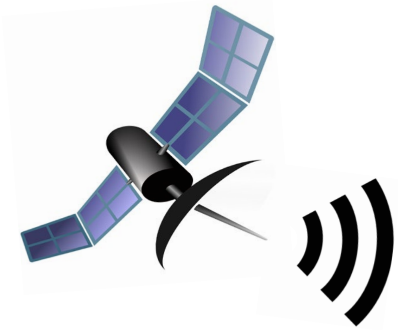
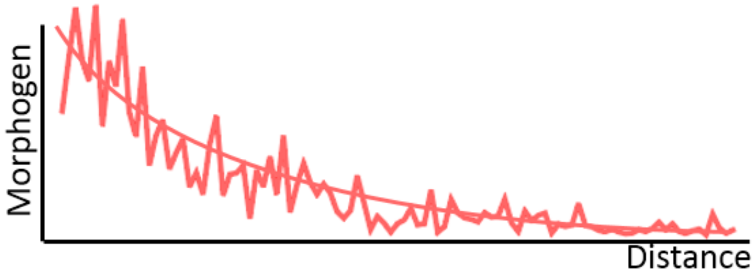
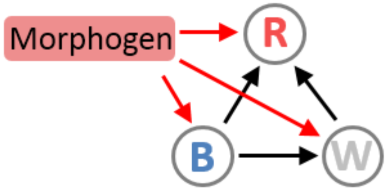
Output signal

Gene expression pattern

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







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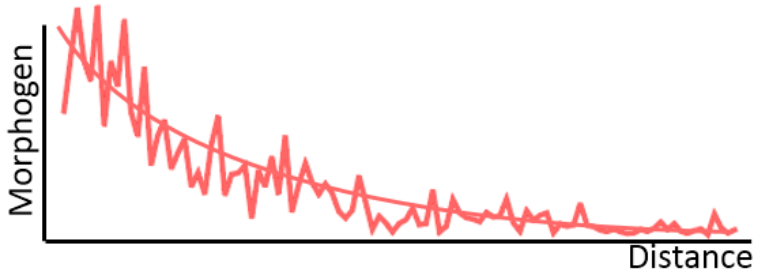
Gene expression pattern

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

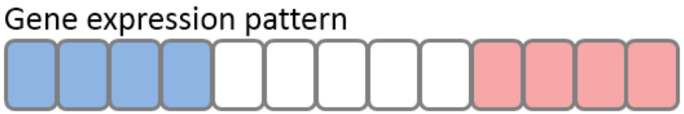
Input signal



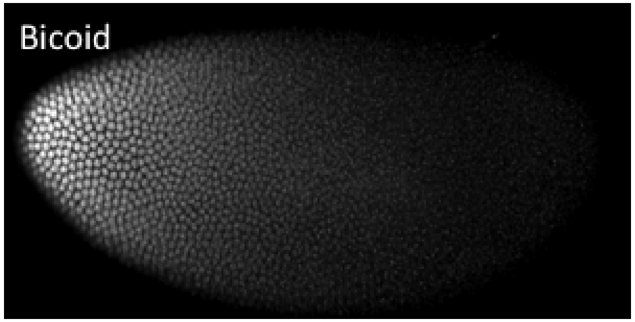
Information decoder

Optimal processing of positional information

Output signal

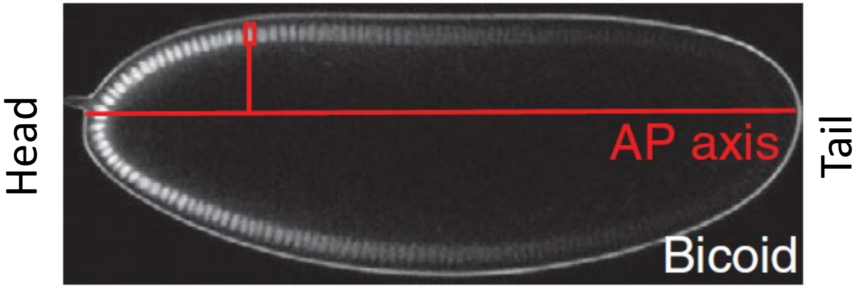


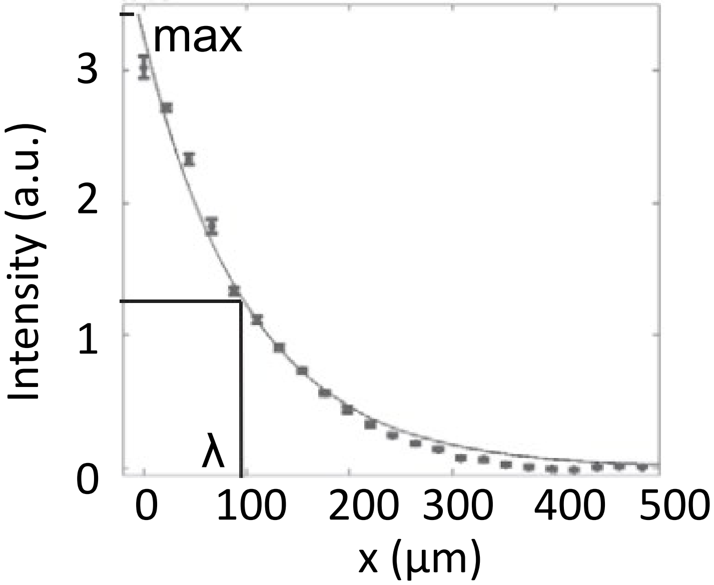
Bicoid proteins form a concentration gradient providing coordinate system for developing embryo



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

www.sciencebuzz.com





Driever & Nüsslein-Volhard, Cell, 1988

Grimm et al., Development, 2010

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

Input signal

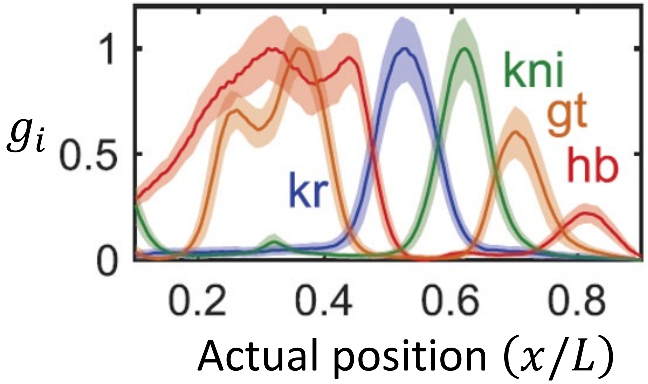
↓

Information decoder

↓

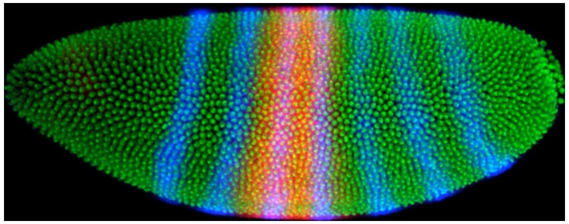
Output signal

Gap genes



Optimal decoder

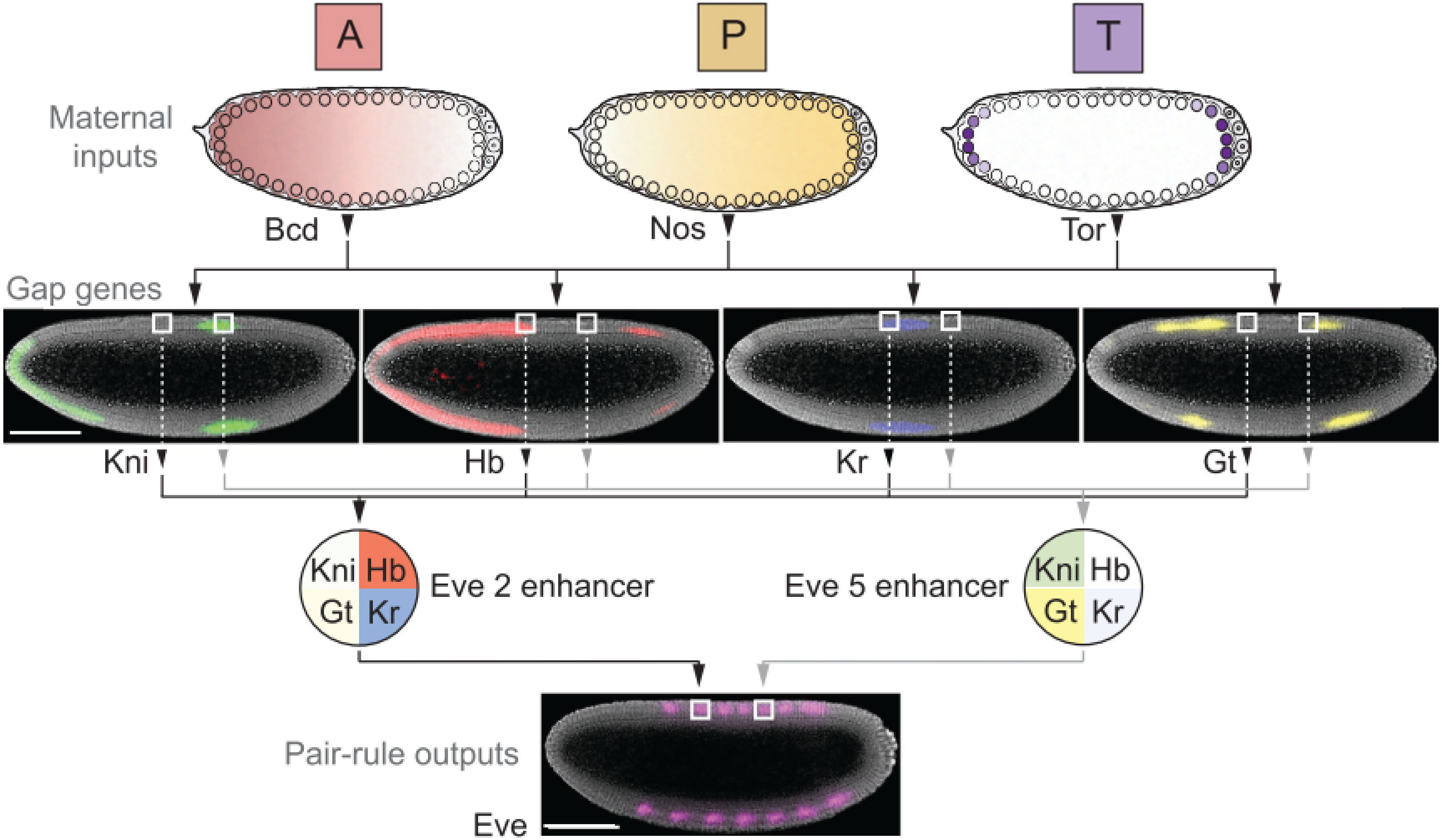
Pair-rule genes



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

Petkova et al., Cell, 2019

Decoding positional information in the early fruit fly embryo



Petkova et al., Cell, 2019

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

kr hb gt kni

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

Signal distribution at every x

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

Tkacik et al., Genetics, 2015:	formalism
Zagorski et al., Science, 2017:	spinal cord, K = 2
Petkova et al., Cell, 2019:	fruit fly, K = 4
Tkacik & Gregor, Development 2021:	review

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

Input signal

$$\{g_i(x)\} = \{\overset{\text{kr}}{g_1(x)}, \overset{\text{hb}}{g_2(x)}, \overset{\text{gt}}{g_3(x)}, \overset{\text{kni}}{g_4(x)}\}, \qquad K = 4$$

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Optimal decoder from Bayes' rule

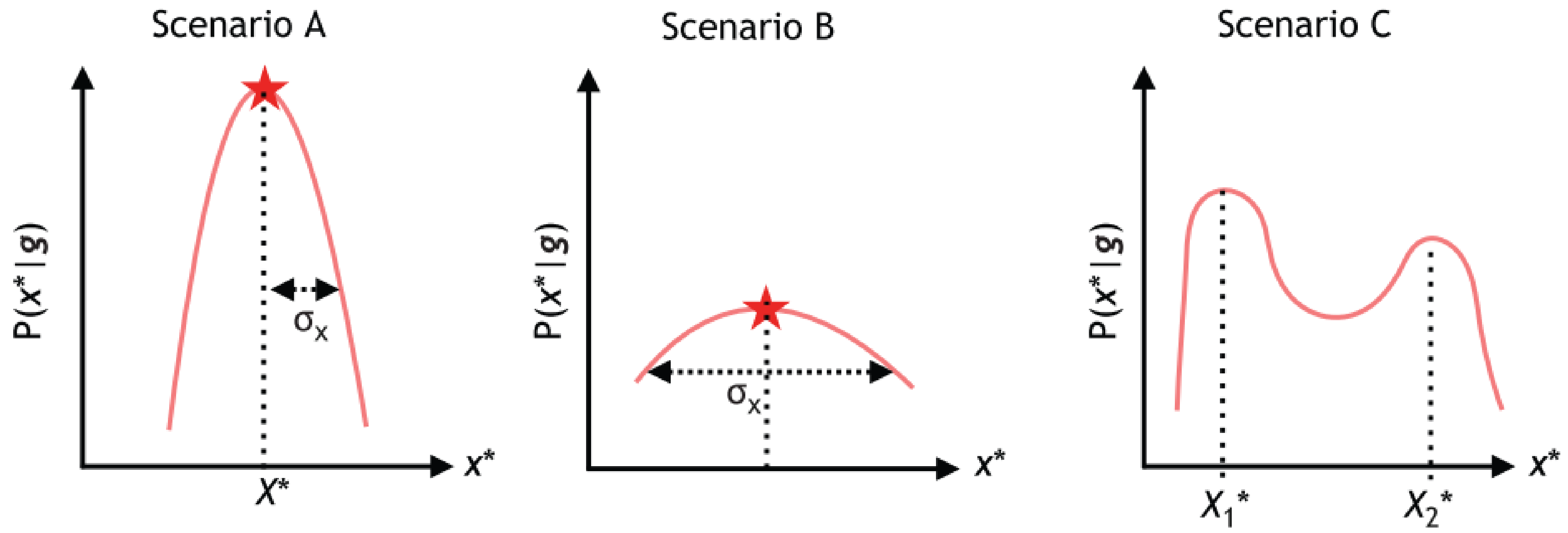
$$P(x^*|\{g_i\}) = \frac{1}{Z(\{g_i\})} P(\{g_i\}|x^*) P_X(x^*)$$

Decoding map

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

Tkacik et al., Genetics, 2015:	formalism
Zagorski et al., Science, 2017:	spinal cord, K = 2
Petkova et al., Cell, 2019:	fruit fly, K = 4
Tkacik & Gregor, Development 2021:	review

Good positional code has most likely position X^* sharply peaked



Unambiguous map
g → X^*,
small positional error σ_x

Unambiguous map,
large positional error σ_x

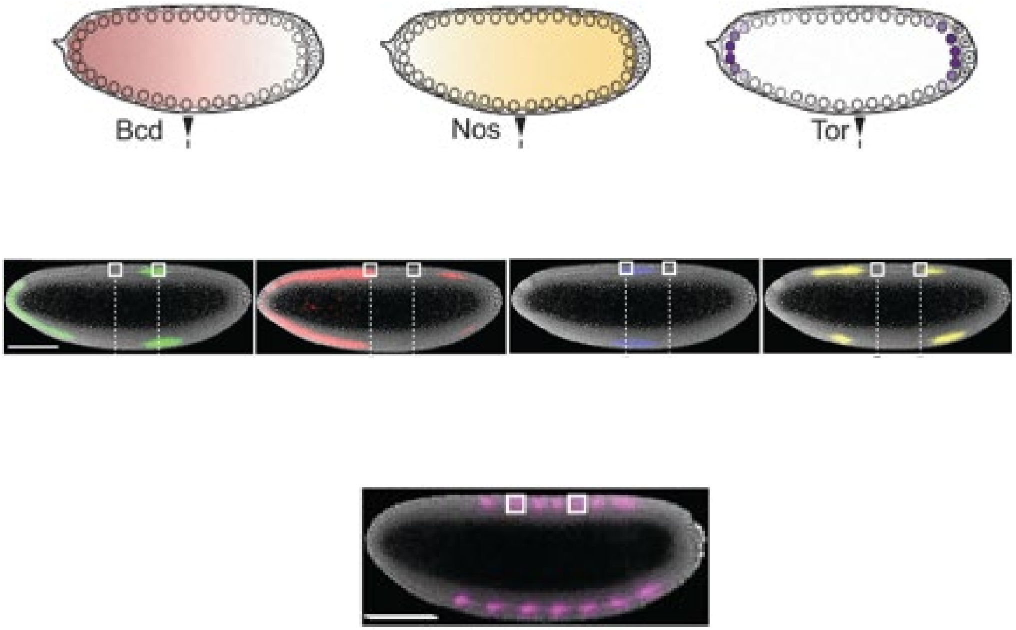
Ambiguous, **g**
maps to two positions

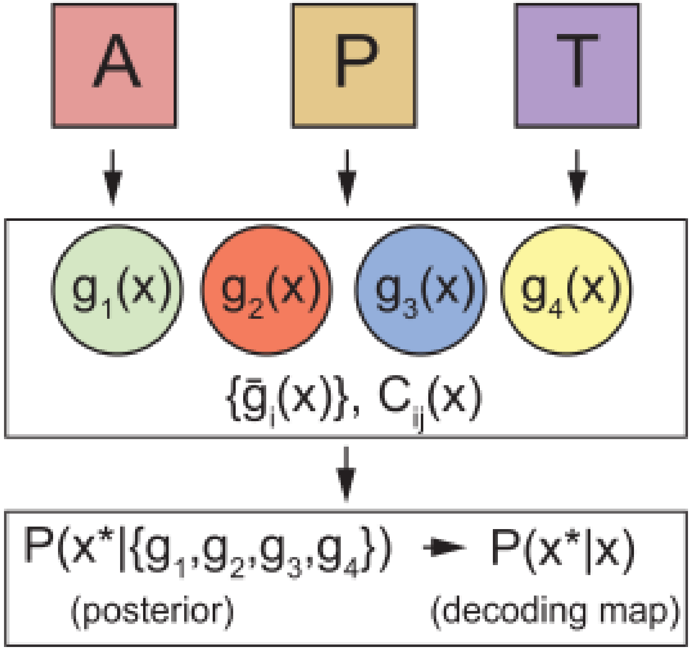
$$\sigma_x^2(x) = \int dx^* (x^* - X^*(x))^2 \; P(x^*|x)$$

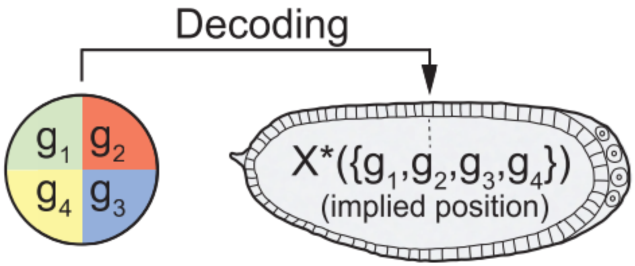
$$X^*(x) = \int dx^* \; x^* \; P(x^*|x)$$

Tkacik et al., Genetics, 2015
Petkova et al., Cell, 2019
Tkacik & Gregor, Development, 2021

GRN can be viewed as an input/output device that encodes physical location x in the embryo using concentrations g_i



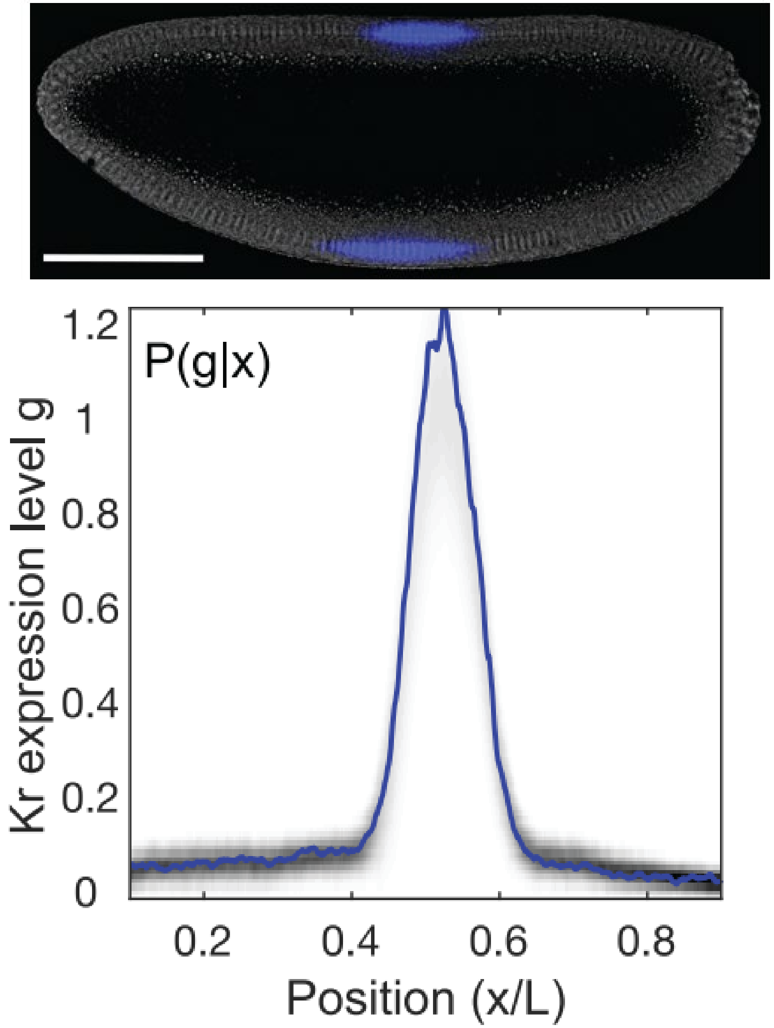




if $X^*=X^*_{str}$ → Pair-rule stripe

Petkova et al., Cell, 2019

Coding and decoding of position from a single input signal



Petkova et al., Cell, 2019

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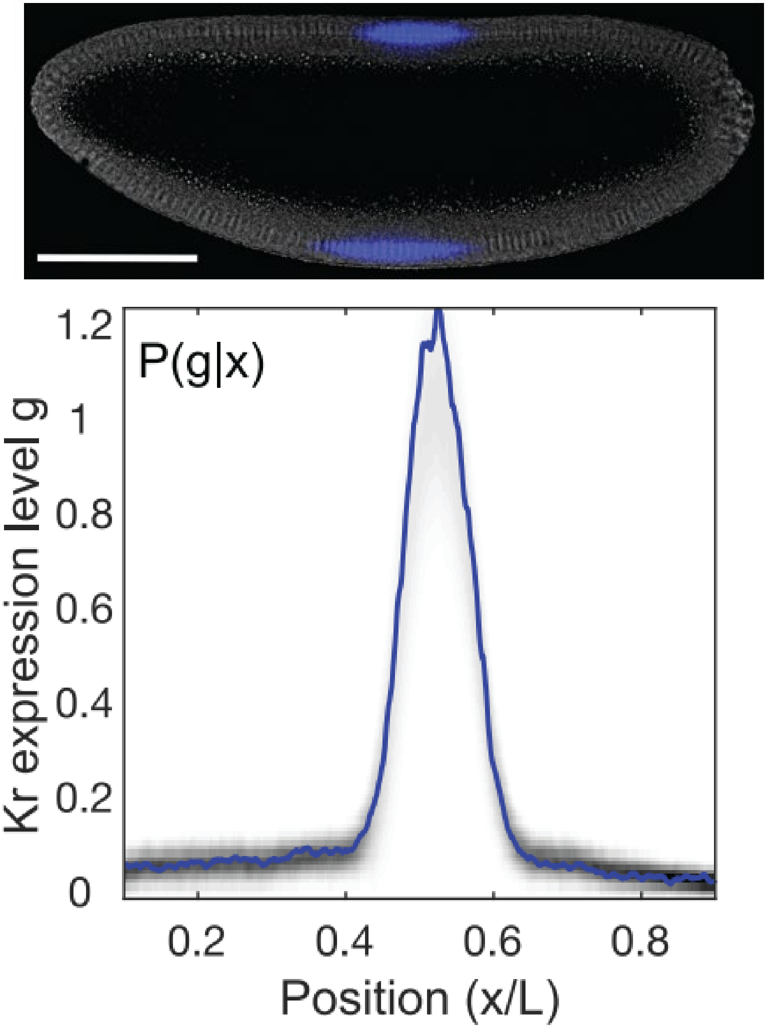

Petkova et al., Cell, 2019

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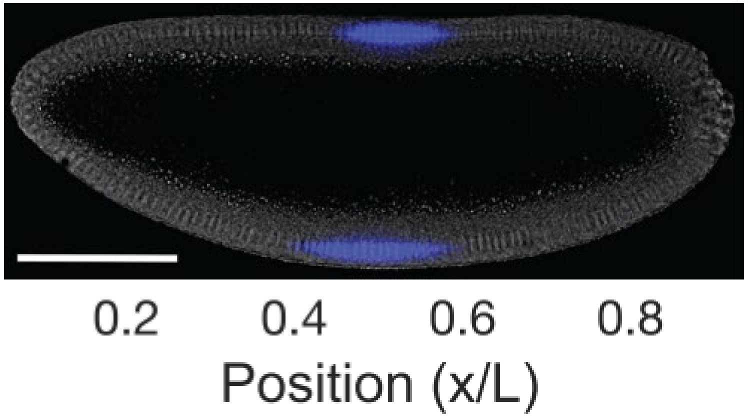

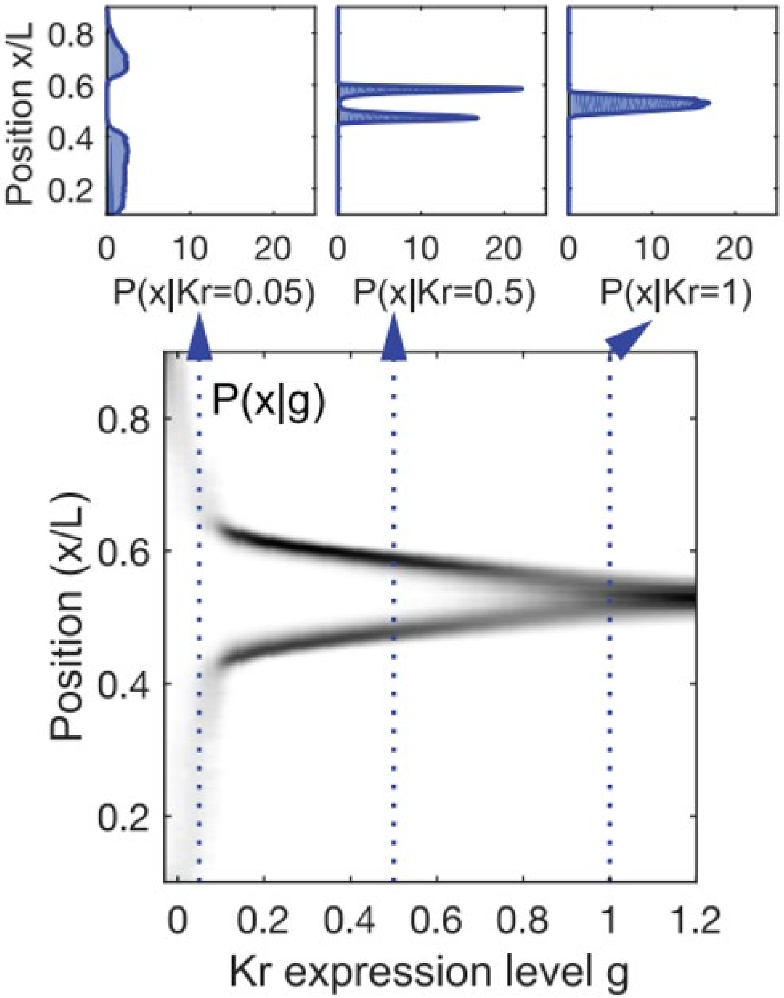

Petkova et al., Cell, 2019

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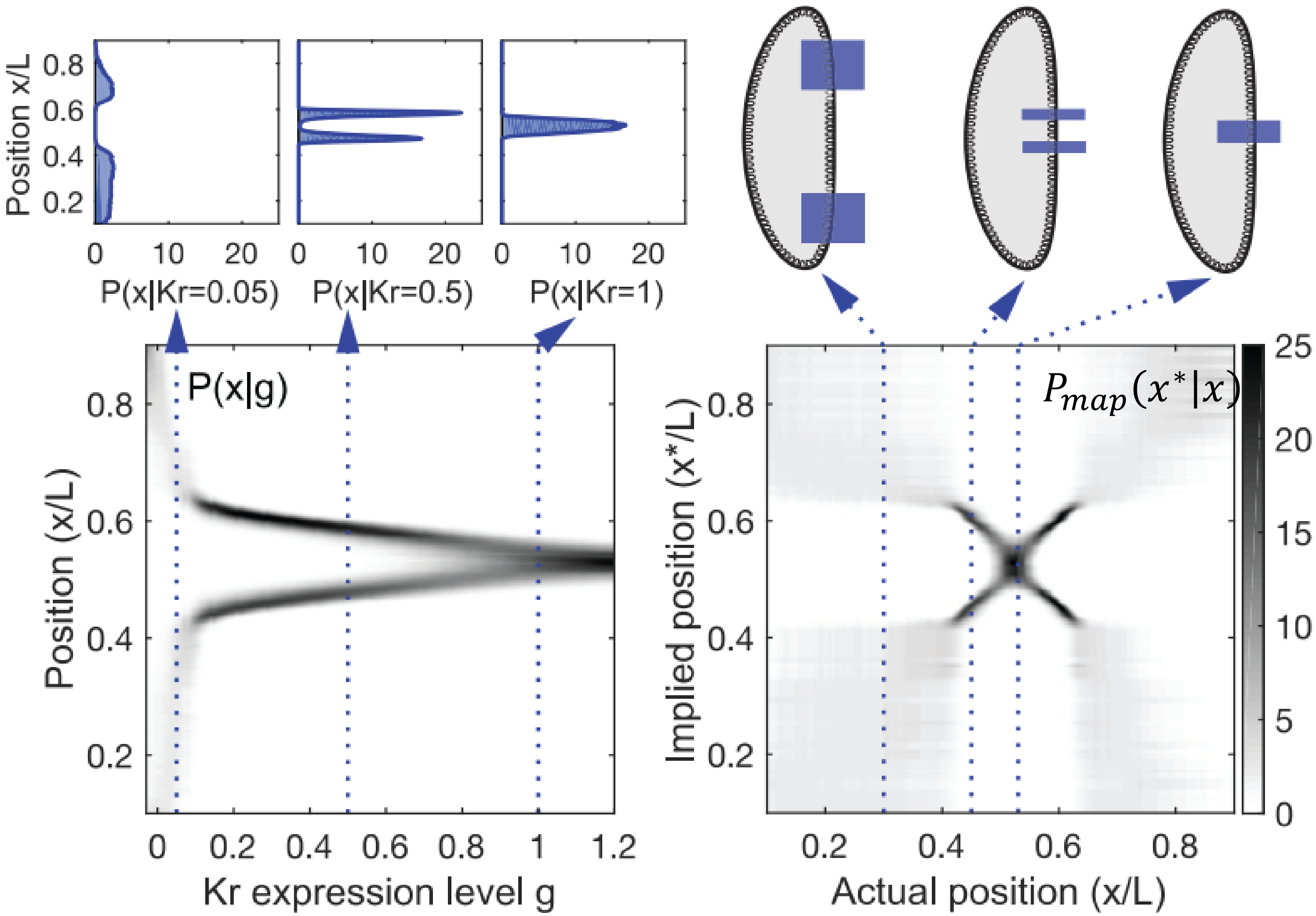
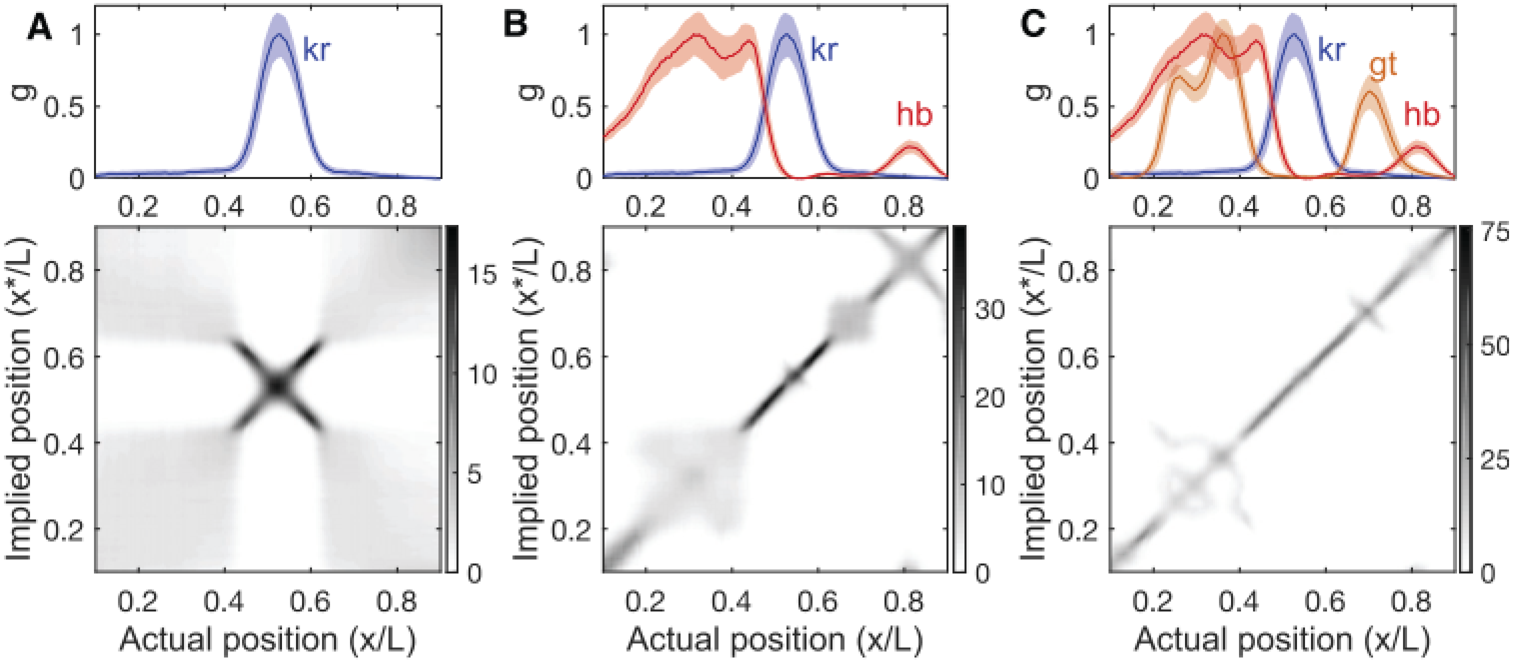


Petkova et al., Cell, 2019

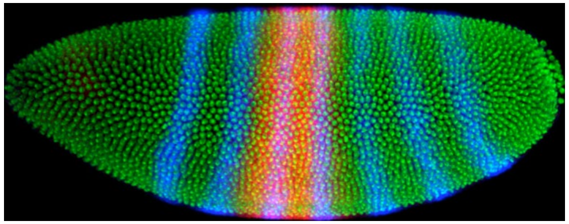
High accuracy of pattern specification requires decoding of signals from all 4 gap genes



Petkova et al., Cell, 2019

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

Pair-rule genes



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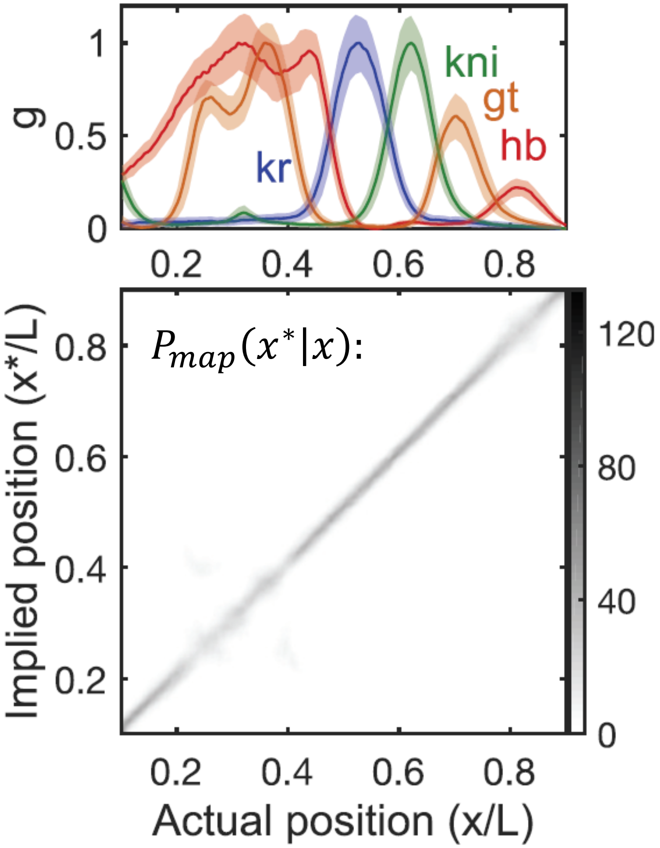
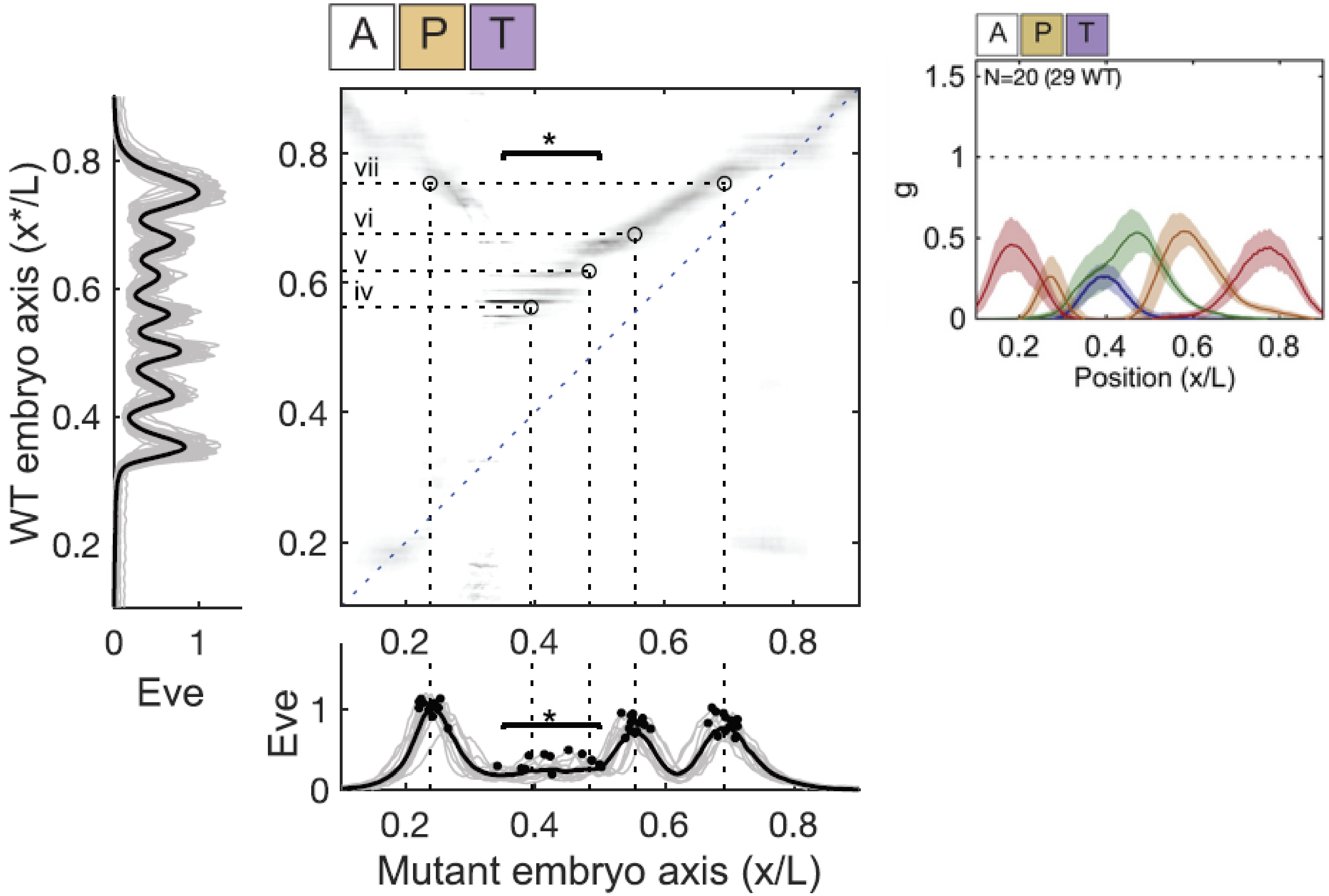
Gap genes

$\{g_i(x)\}$:



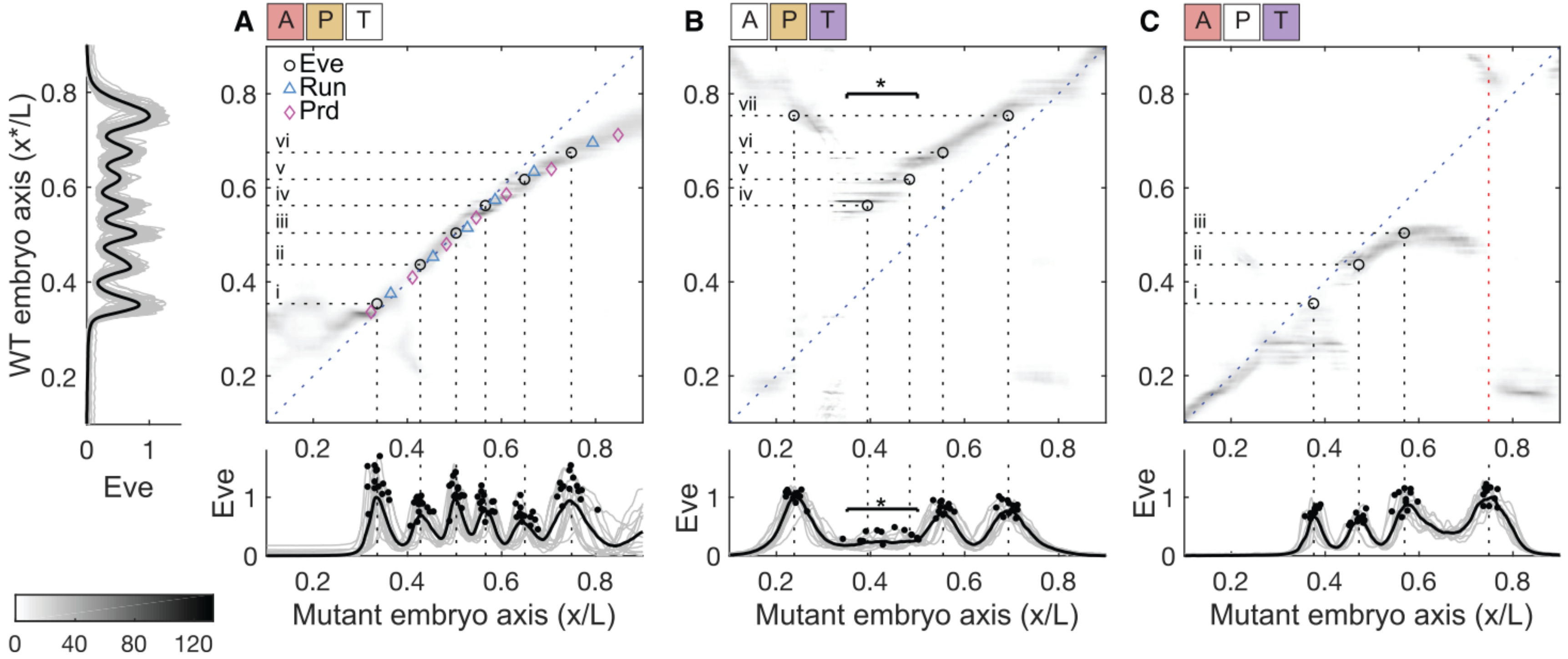
Petkova et al., Cell, 2019

The decoding map correctly predicts shifts, disappearance and duplications in different mutation backgrounds



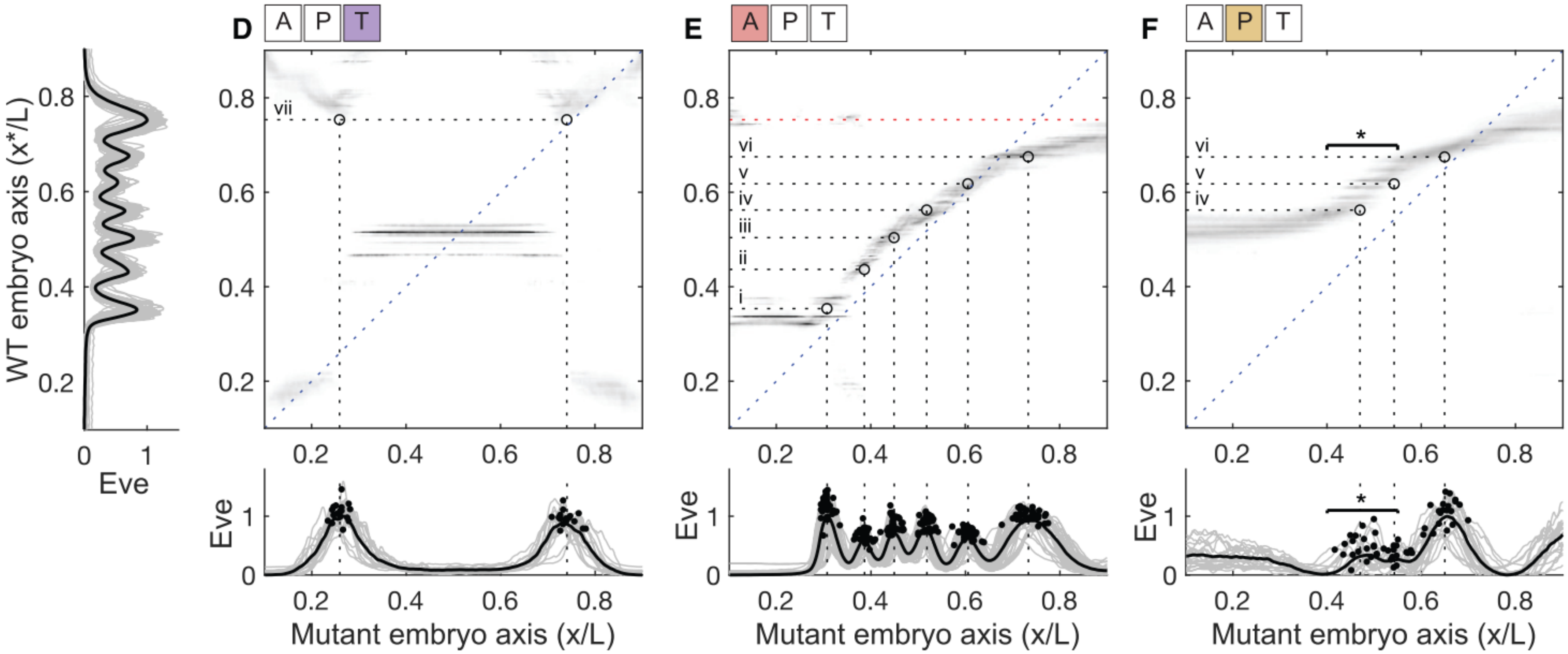
Petkova et al., Cell, 2019

The average decoding maps for mutation backgrounds with one maternal system perturbed



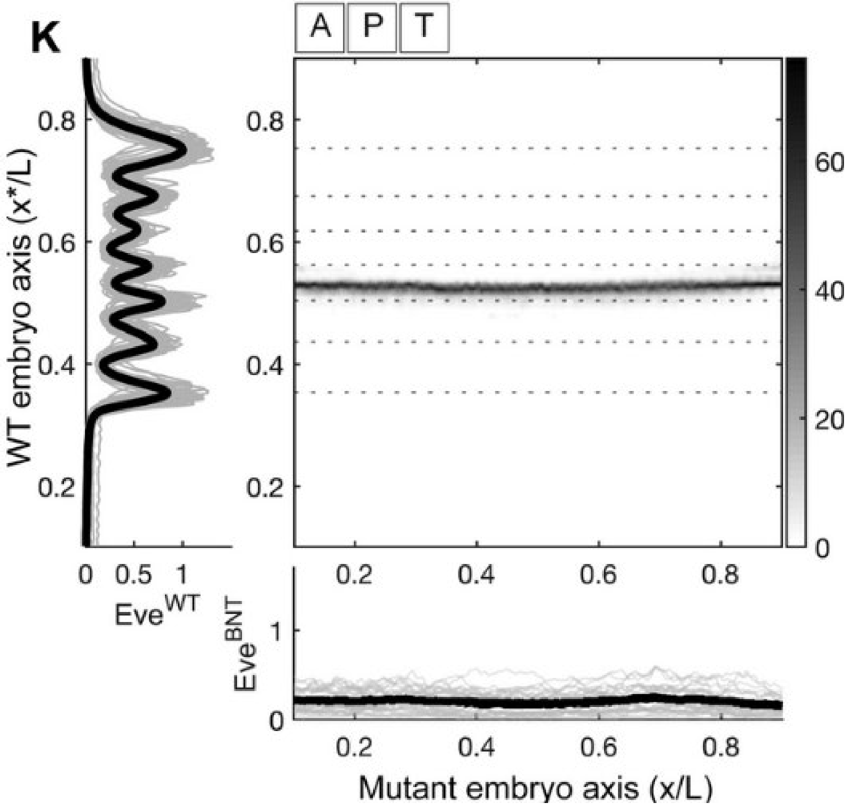
Petkova et al., Cell, 2019

The average decoding maps for mutation backgrounds with two maternal systems perturbed



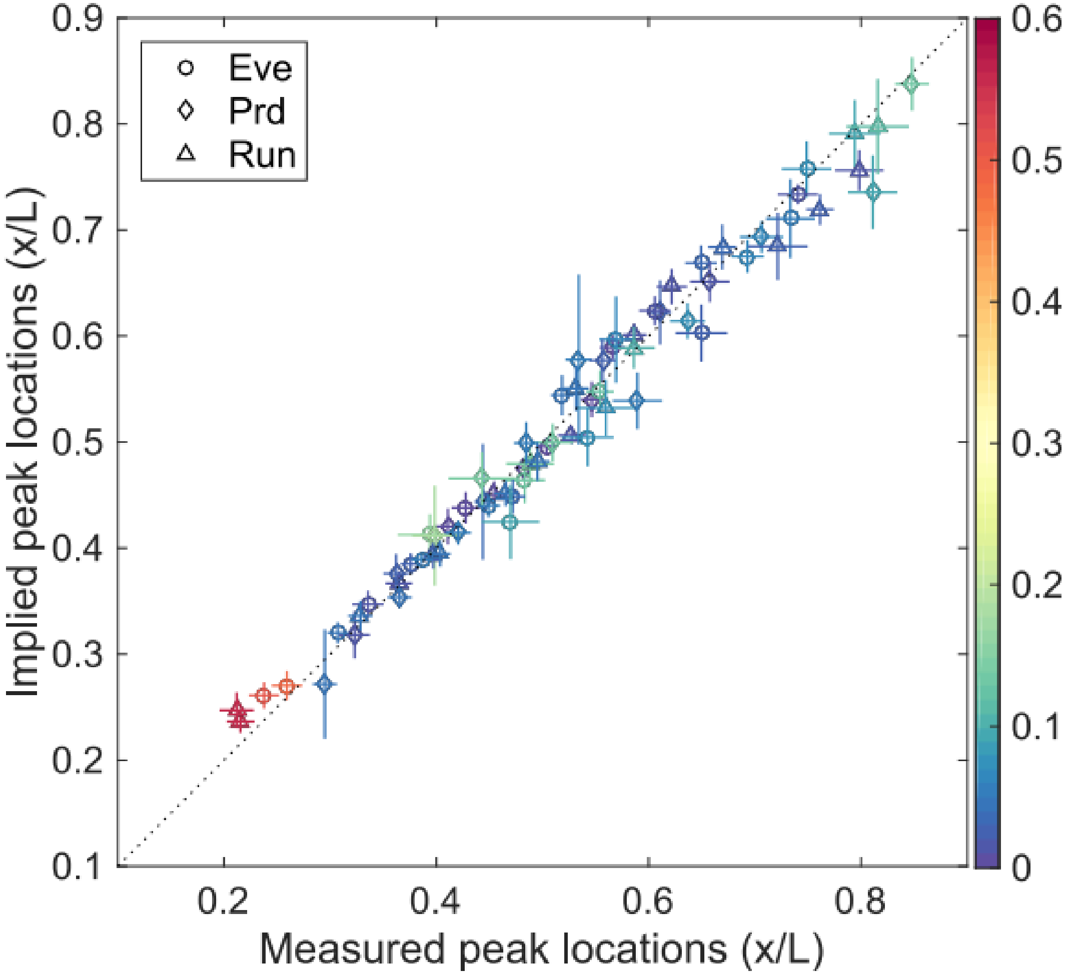
Petkova et al., Cell, 2019

Deleting all three maternal inputs removes AP positional information completely



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

What is positional information?

Positional information (**PI**) measures any kind of statistical dependence between position x and morphogen concentrations $\{g_i\}$.

When a change in random variable, X, leads with some probability to a change in another random variable, Y, we say that X 'has information' about Y. This information would allow us to infer (or predict) the value of Y if we knew the value of X, and vice versa.

Claude Shannon identified mutual information, $I(X;Y)$, as the unique measure that mathematically captures such a statistical dependence between X and Y.

Tkacik & Gregor, Development, 2021

What is positional information?

Mutual information is derived from a more basic quantity, the ‘entropy’ $S(X) = -\Sigma\, P(X) \log_2 P(X)$, where the summation extends over all values of X that happen with probability $P(X)$.

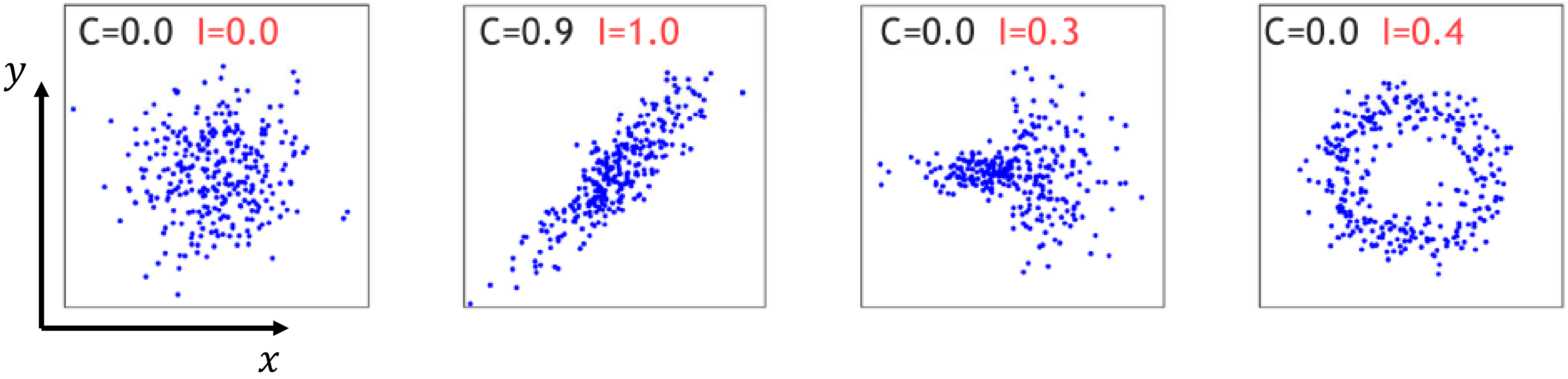
Entropy measures the dynamic range of the distribution, and is conceptually related to its variance.

Mutual information is $I(X;Y) = S(X) + S(Y) - S(X,Y)$, or the difference in entropy of X and Y taken separately and jointly.

For independent X and Y, $S(X,Y) = S(X) + S(Y)$, hence $I(X;Y) = 0$

Tkacik & Gregor, Development, 2021

Mutual information captures any statistical dependence between X and Y

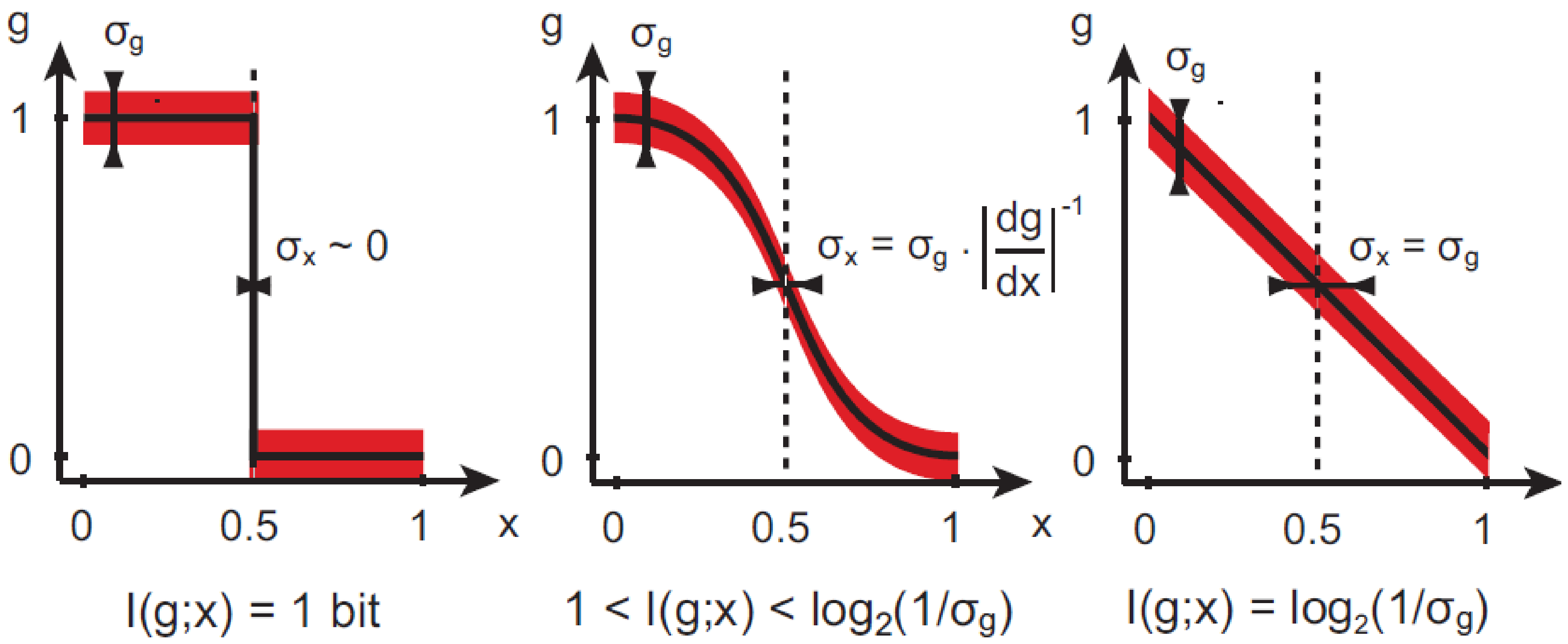


C is linear Pearson correlation coefficient

I mutual information (in bits) between x and y.

Tkacik & Gregor, Development, 2021

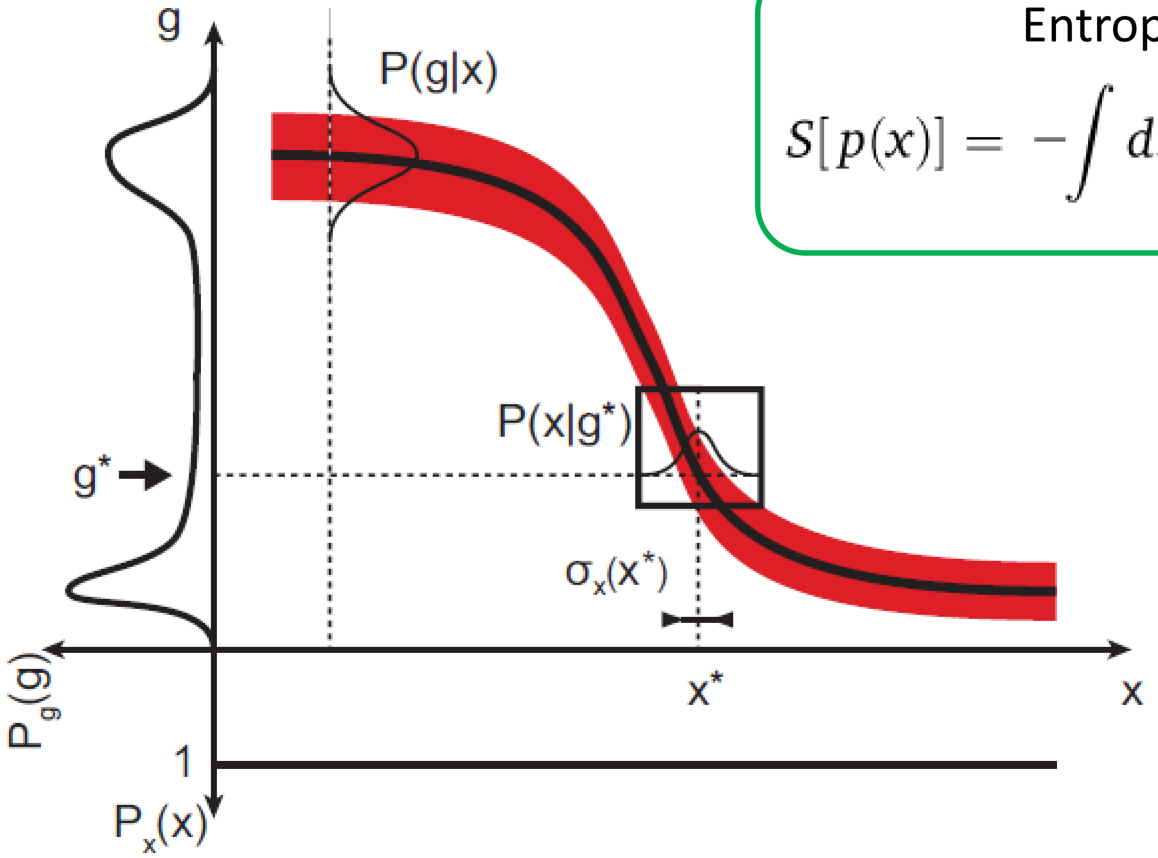
Positional information encoded by a single gene can be quantified in bits



- Step-function specifies up to 2 gene states: “on” and “off”.
- Widening the boundary results in more distinguishable gene states possible $2^{I(g;x)}$

Tkacik et al., Genetics, 2015

PI measures the average reduction in uncertainty about position due to morphogen signal observation



Entropy

$$S[p(x)] = -\int dx\, p(x) \log_2 p(x)$$

$$\boxed{I(\{g_i\};x)} = \boxed{S\left[P_g(\{g_i\})\right]} - \boxed{\left\langle S[P(\{g_i\}|x)] \right\rangle_x}$$

Mutual information | Total entropy | Noise entropy

Tkacik et al., Genetics, 2015

Positional information encoded by a single gene can be quantified in bits

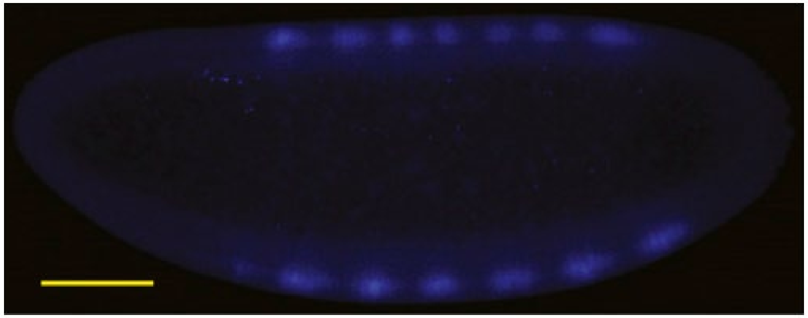
Mutual information $\boxed{I(\{\mathrm{g_i}\};\ x)} = \boxed{\mathrm{S}\left[P_{\mathrm{g}}(\{\mathrm{g}_i\})\right]} - \boxed{\langle S[P(\{\mathrm{g}_i\}|x)]\rangle_x}$

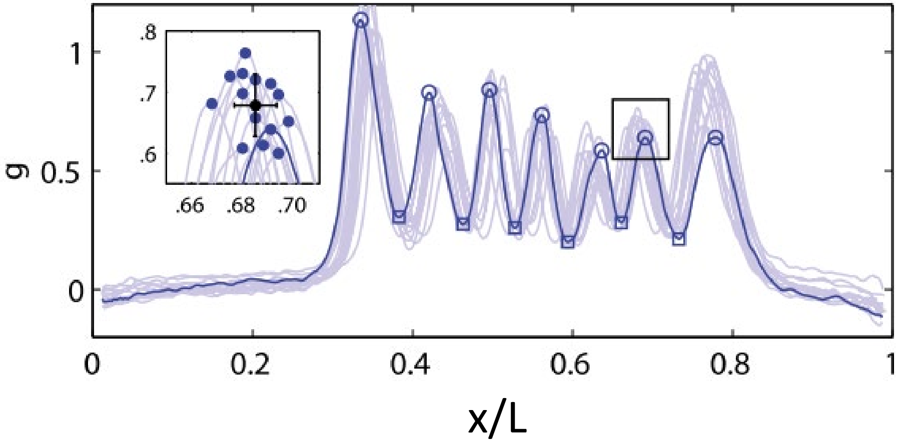
Entropy $\mathrm{S}[p(x)] = -\int dx\, p(x) \log_2 p(x)$

$I(\{\mathrm{g_i}\};\ x)$	**useful part** (the mutual information) that describes systematic modulation of g with position *x*
$\mathrm{S}\left[P_{\mathrm{g}}(\{\mathrm{g}_i\})\right]$	„**total entropy**” measures the range of gene expression available across the whole embryo.
$\langle S[P(\{\mathrm{g}_i\}|x)]\rangle_x$	**pure noise** that carries no information about position, quantifies variability in g that remains even at constant position x

Tkacik et al., Genetics, 2015

Is positional information conveyed in the input signal sufficient to specify the output pattern?





Dubuis et al., PNAS, 2011

PI is an upper bound to the information between true and implied positions

Data Processing Inequality (DPI)

PI is always greater or equal to the mutual information between the true locations and the best estimates of position.

Brunel & Nadal, Neural Comp, 1998

Relating positional error to PI

Dependency chain: $x \rightarrow \{g_i\} \rightarrow x^*$

From DPI: $I(\{g_i\};\, x) \geq I(x^*;\, x)$

$$I(x^*; x) = S[P_x(x^*)] - \left\langle S[P(x^*|x)] \right\rangle_{P_x(x)}$$

Positional error determines the lower bound on information between true and implied positions

Relating positional error to PI

$$I(\{g_i\};\, x) \geq\, I(x^*;\, x)$$

$$I(x^*;x) = S[P_x(x^*)] - \Big\langle S[P(x^*|x)] \Big\rangle_{P_x(x)}$$

$S[P_x(x^*)]$ entropy of uniform distribution $P_x(x^*) = 1/L$

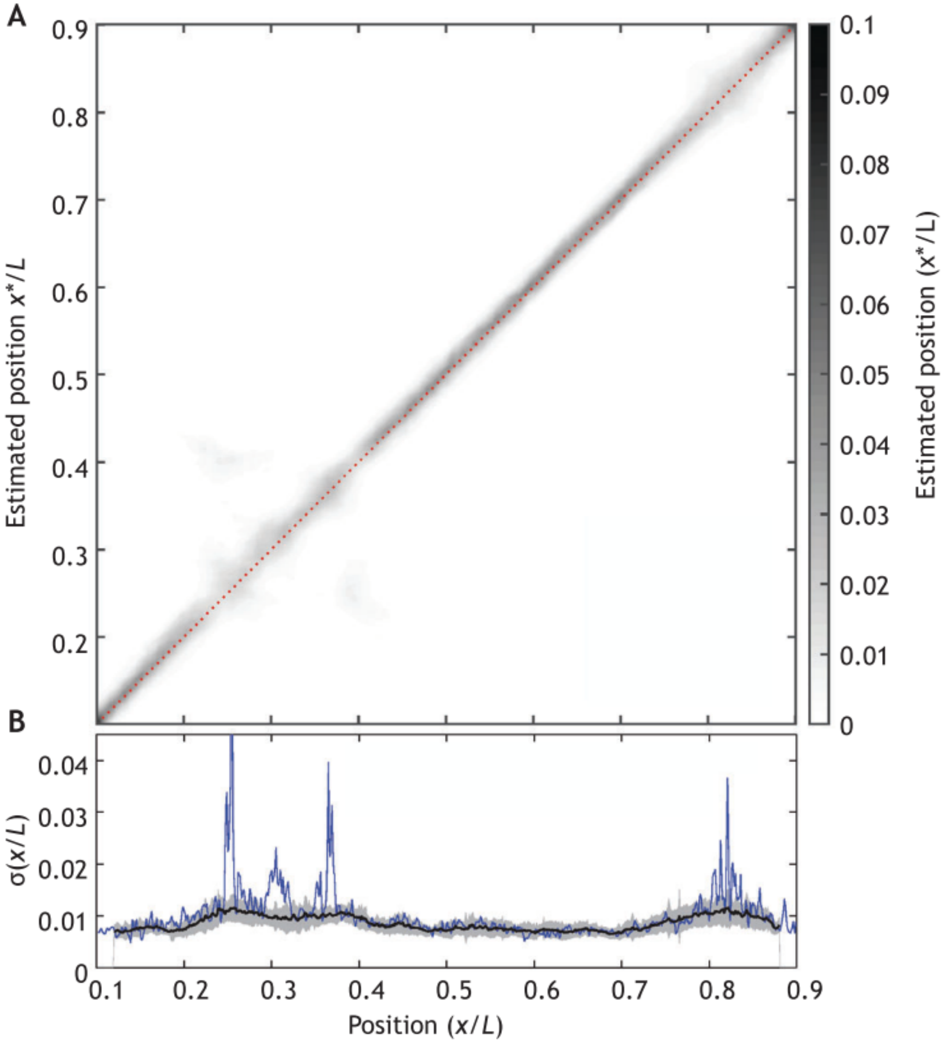
We do not know exact $P_x(x^*|x)$, but we know its variance $\sigma_x^2(x)$

The entropy of $P_x(x^*|x)$ must be $\leq$ to the entropy of the Gaussian distribution of the same variance

$$S[P_x(x^*|x)] = \log_2 \sqrt{2\pi e \sigma_x^2(x)}$$

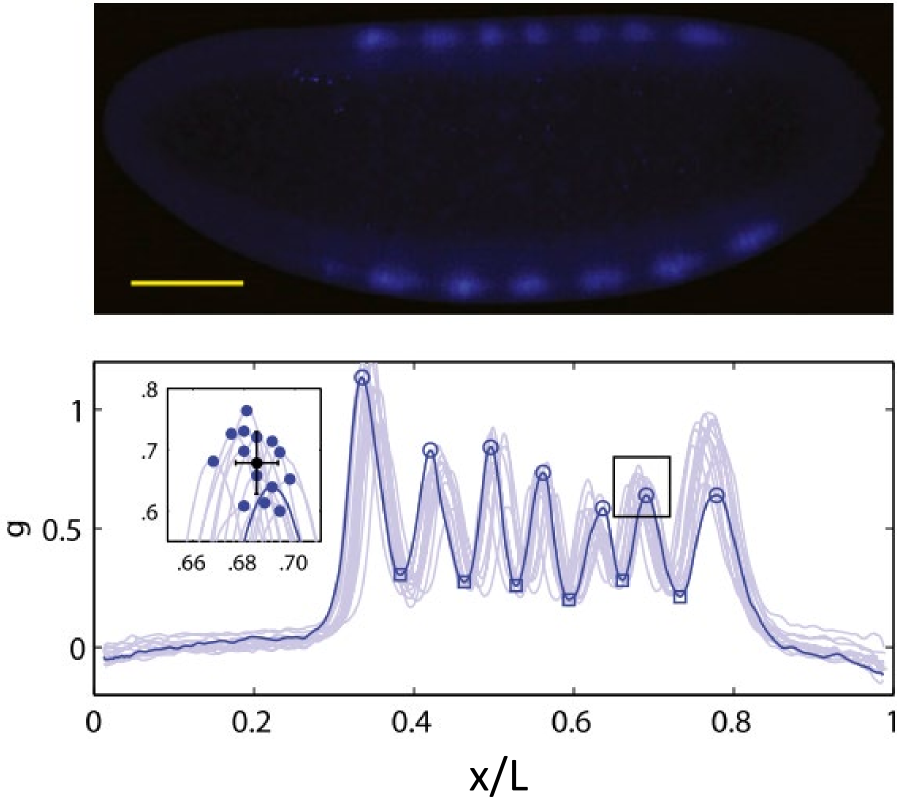
$$I(x^*;x) = -\left\langle \log_2 \sqrt{2\pi e \sigma_x^2(x)/L^2} \right\rangle_x$$

Precise decoding from four Drosophila morphogens: equivalence between the decoding map and positional error



Petkova et al., Cell, 2019
Tkacik & Gregor, Development, 2021

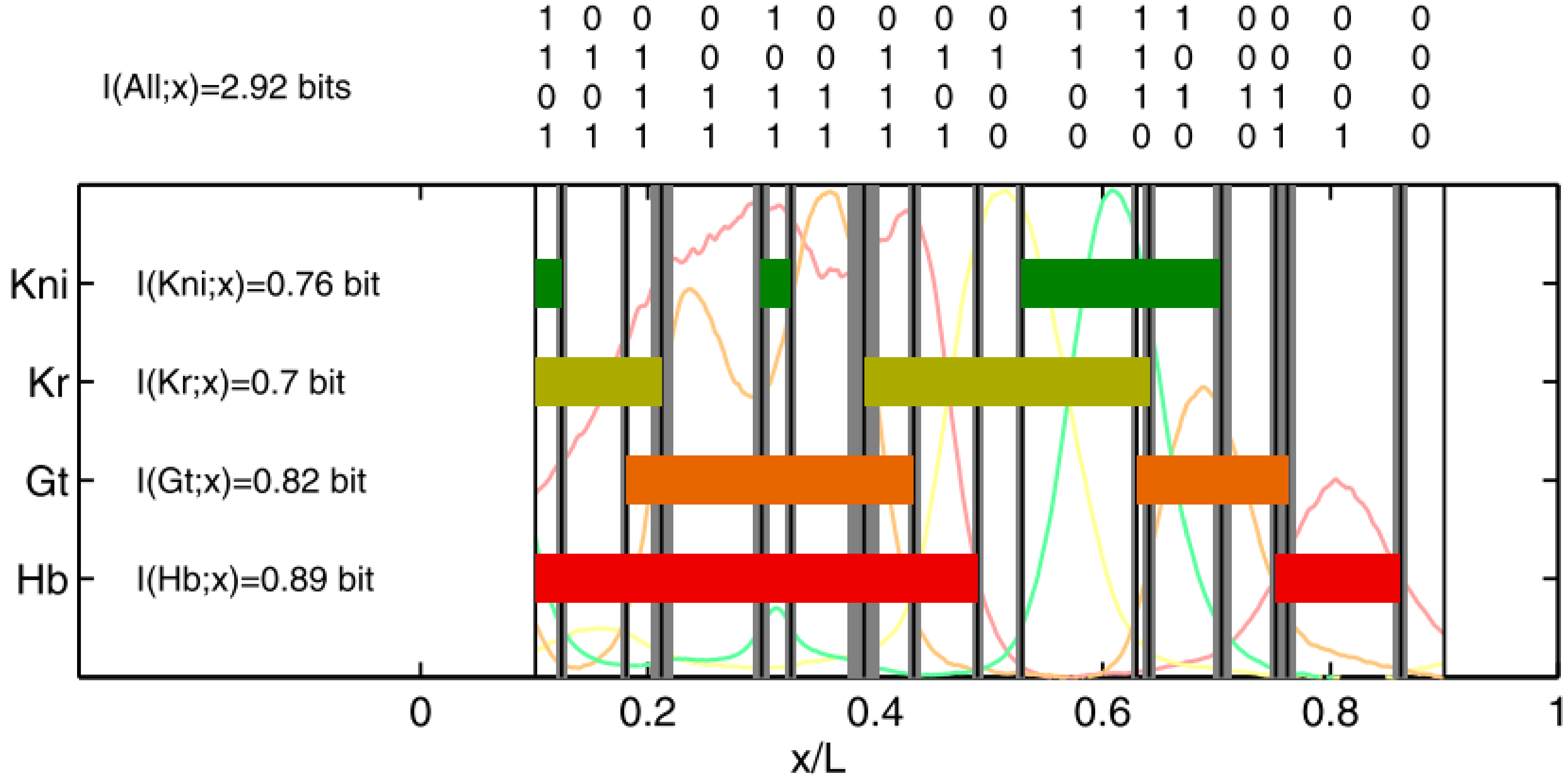
The information conveyed in the input signal is sufficient to specify output pattern



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

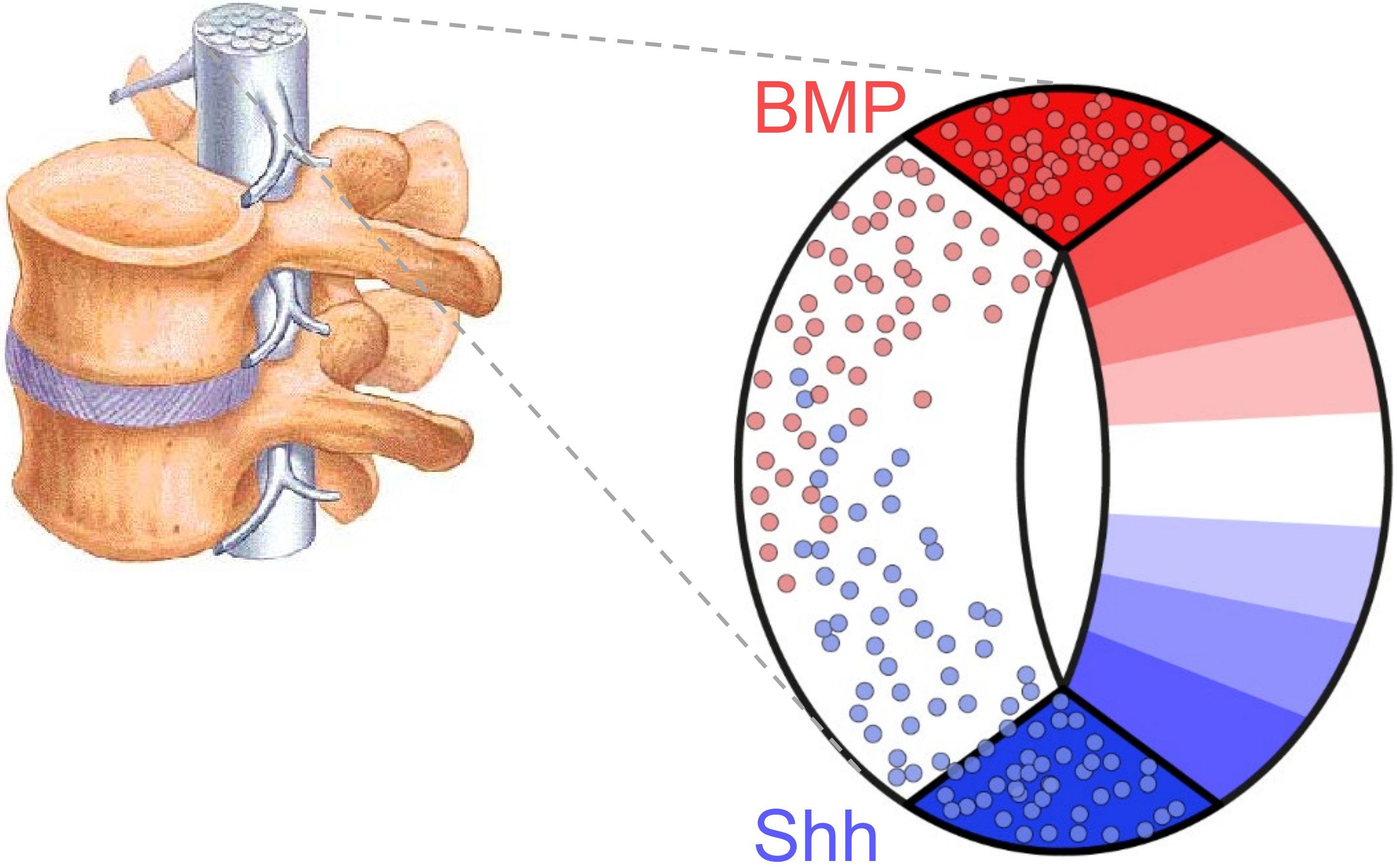
Dubuis et al., PNAS, 2011

Binary encoding of information is not sufficient to explain output pattern

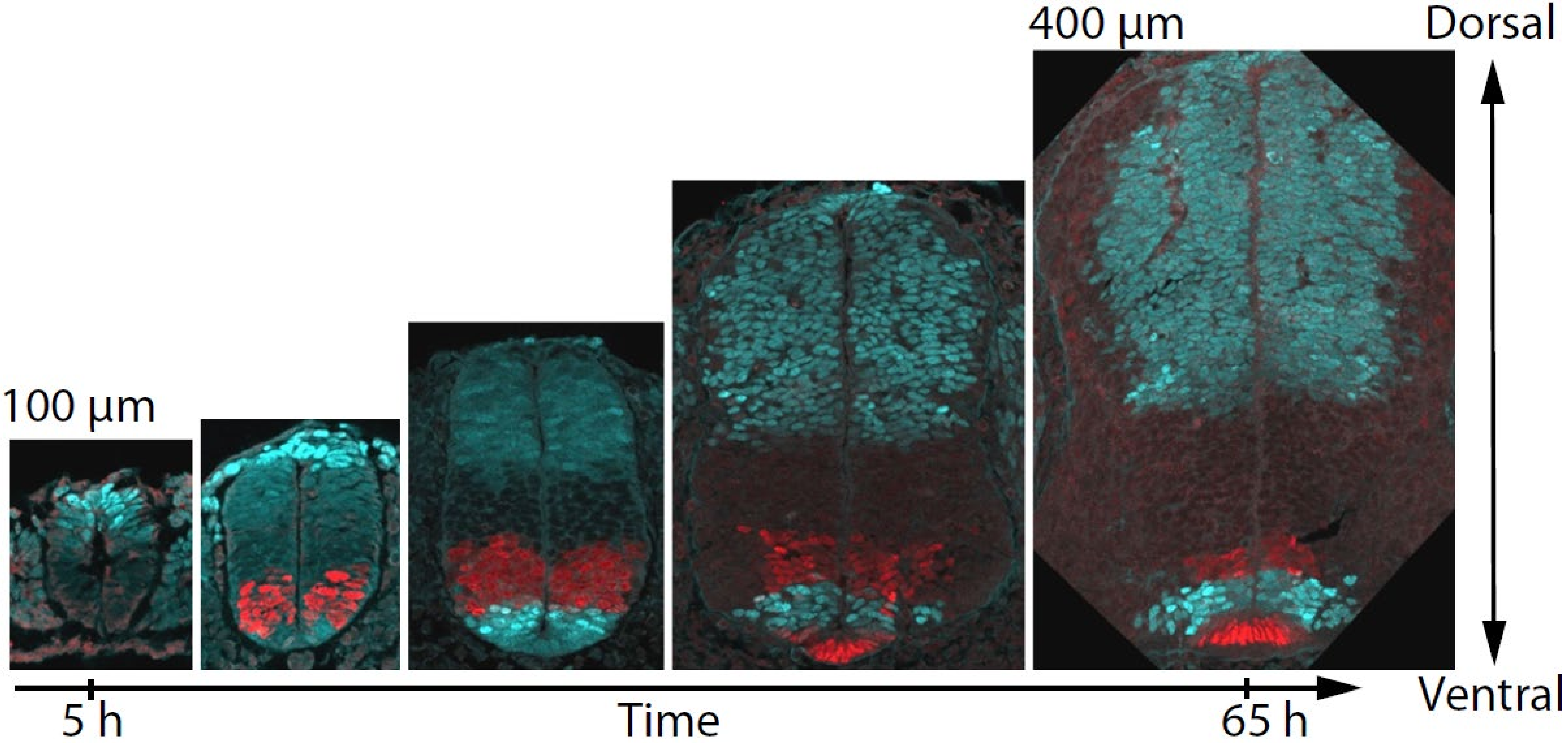


Dubuis et al., PNAS, 2011

Morphogen signaling gradients establish a striped pattern of neural progenitors

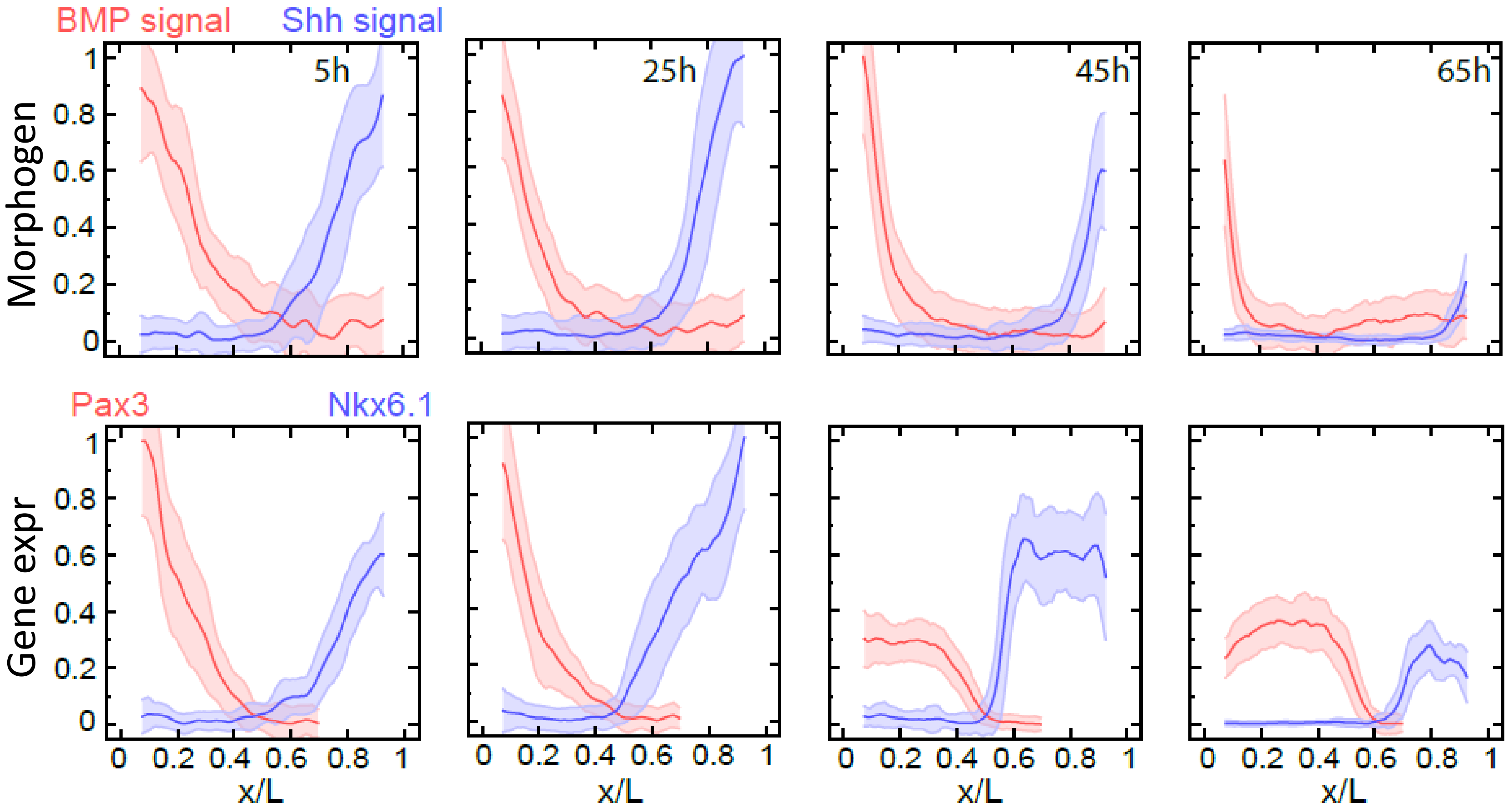


The striped pattern of gene expression domains is established progressively



Zagorski et al., Science, 2017

The morphogen signaling profiles do not scale with the embryo size



Zagorski et al., Science, 2017

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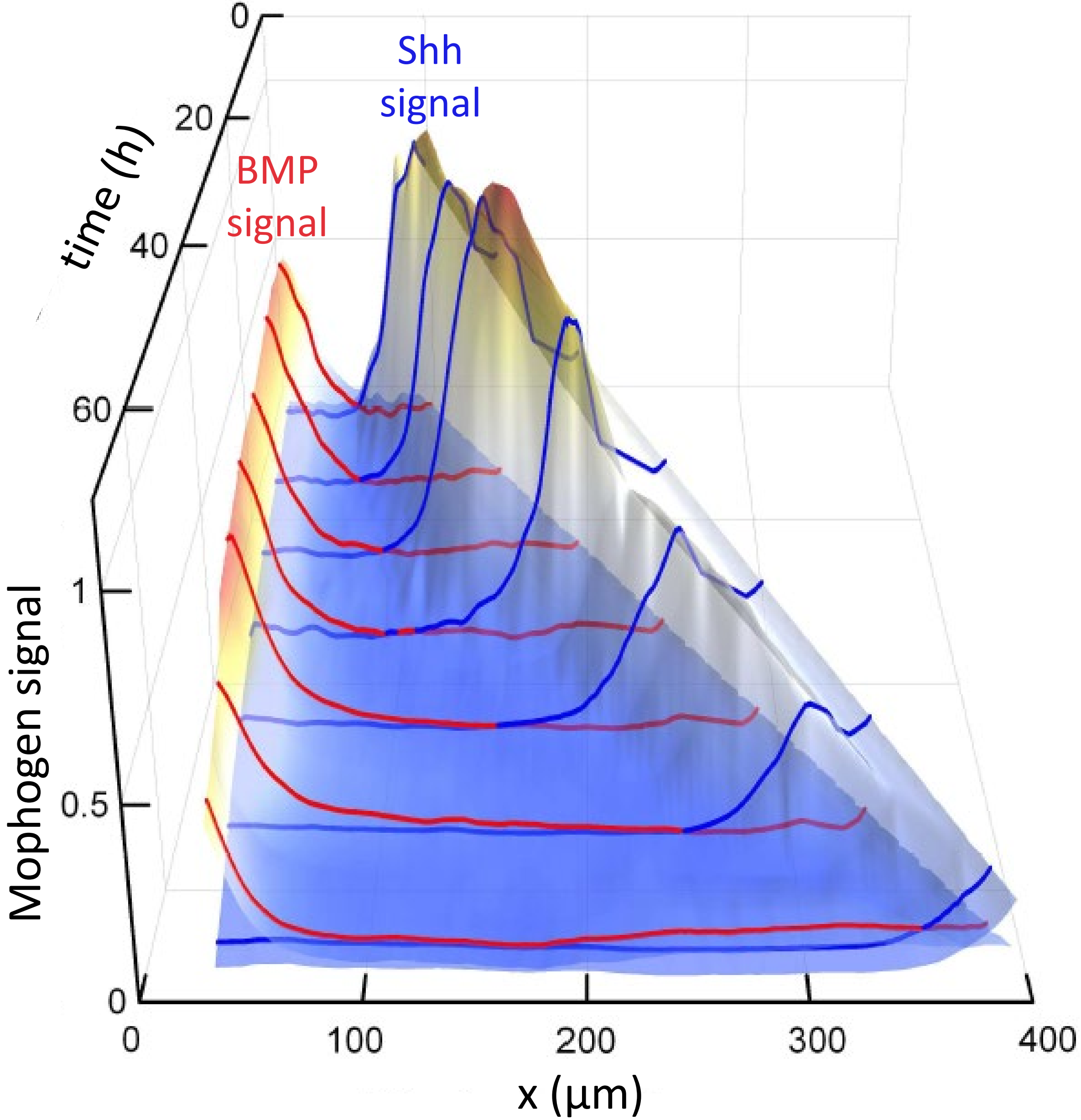
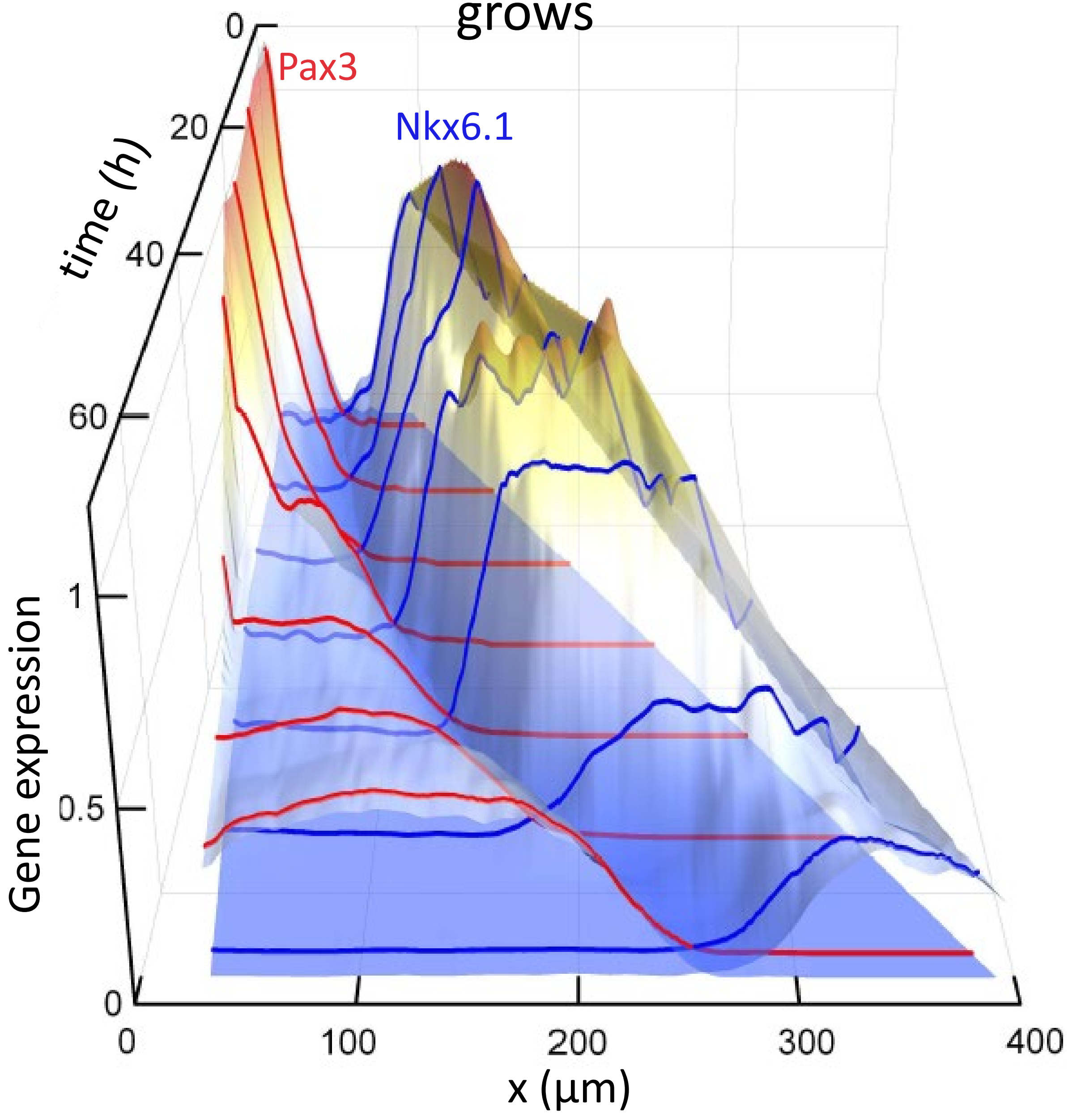
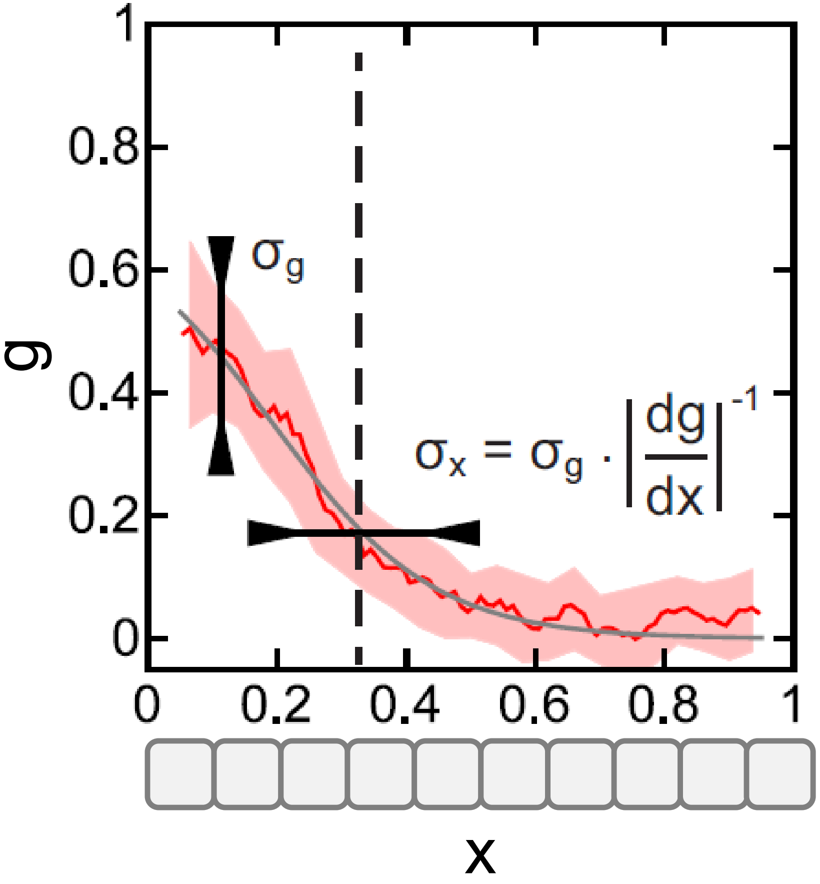


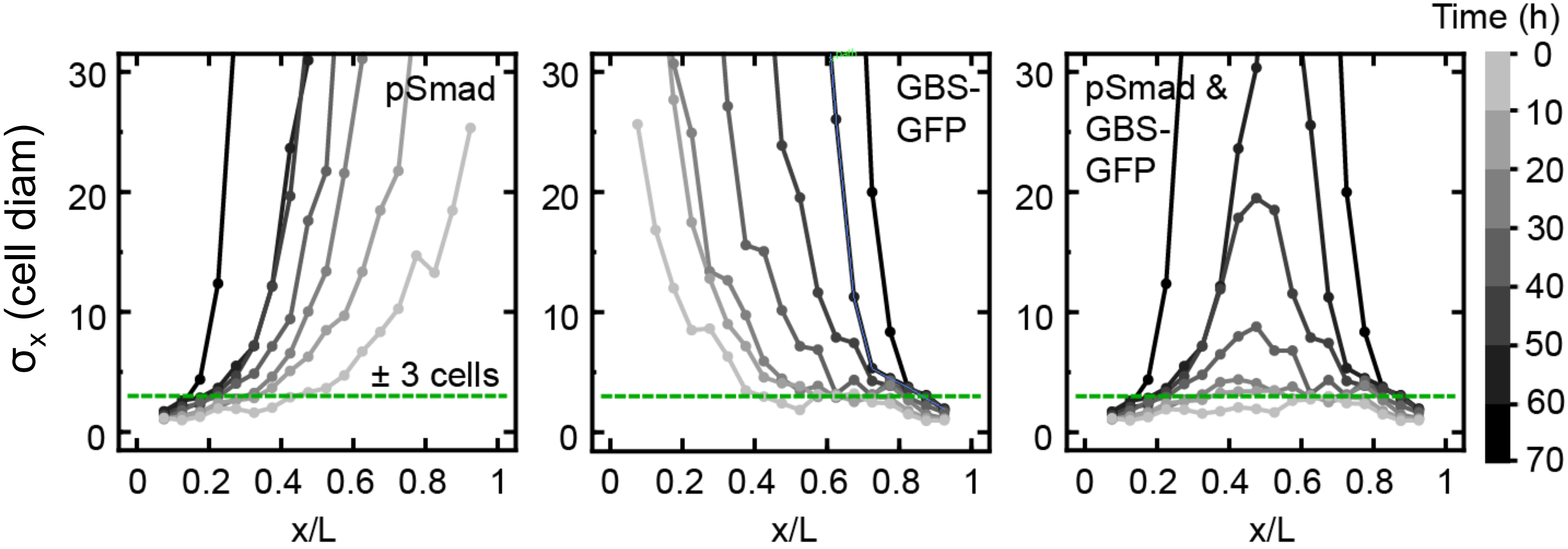
The gene expression boundaries are formed and shift as embryo grows



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



Both morphogen signals are needed to provide positional information across the DV axis

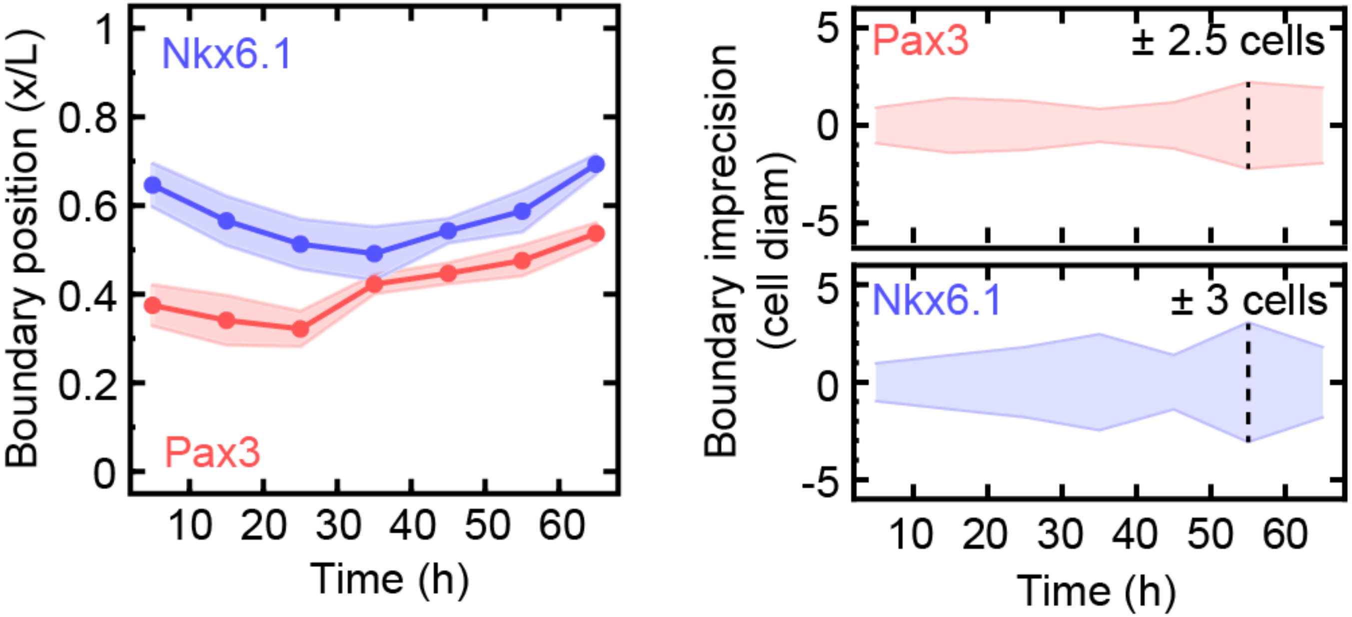


BMP signal: pSmad
Shh signal: GBS-GFP

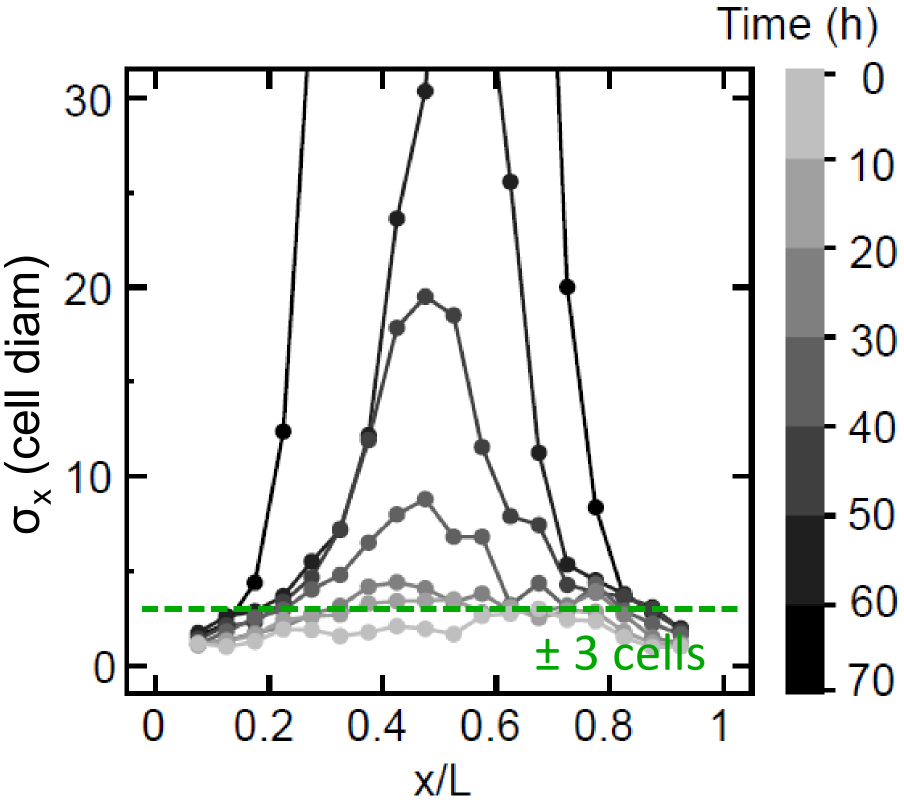
$$\sigma_x(x) = \left[\left(\frac{d[BMP]}{dx}\right)^2 \sigma_{BMP}^{-2} + \left(\frac{d[Shh]}{dx}\right)^2 \sigma_{Shh}^{-2}\right]^{-\frac{1}{2}}$$

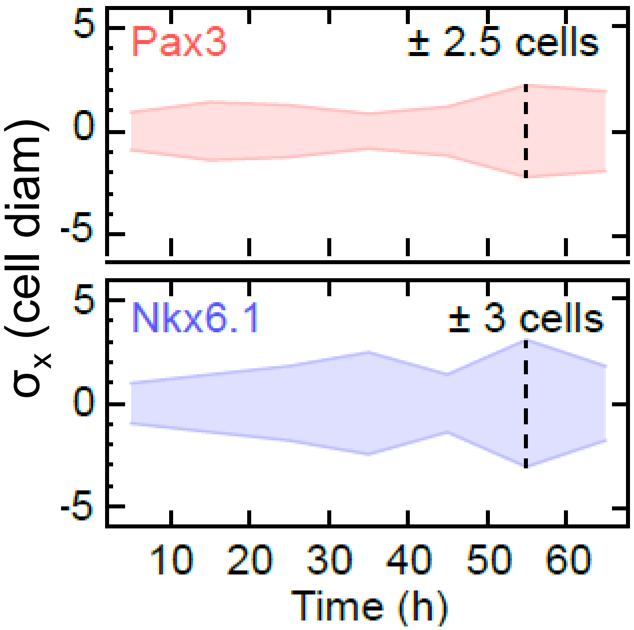
Zagorski et al., Science, 2017

Boundary imprecision of gene expression domains remains low also at latter stages



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





$$\sigma_x(x) = \left[\left(\frac{d[BMP]}{dx}\right)^2 \sigma_{BMP}^{-2} + \left(\frac{d[Shh]}{dx}\right)^2 \sigma_{Shh}^{-2}\right]^{-\frac{1}{2}}$$

Zagorski et al., Science, 2017

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

Input signal

$$\{g_i(x)\} = \{\overset{\text{BMP}}{g_1(x)}, \overset{\text{Shh}}{g_2(x)}\}, \qquad K = 2$$

Signal distribution at every x

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

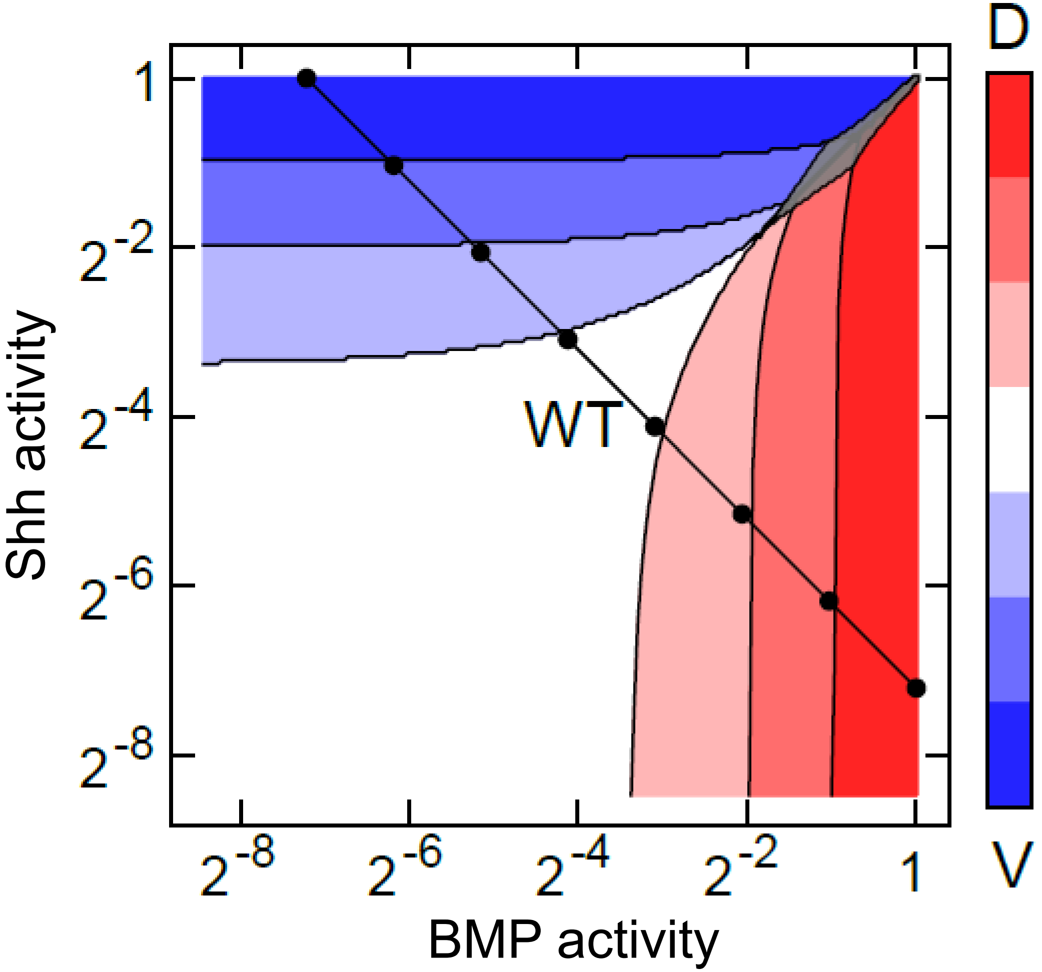
Optimal decoder from Bayes' rule

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

Tkacik et al., Genetics, 2015: formalism
Zagorski et al., Science, 2017: mouse spinal cord, K = 2
Petkova et al., Cell, 2019: fruit fly, K = 4

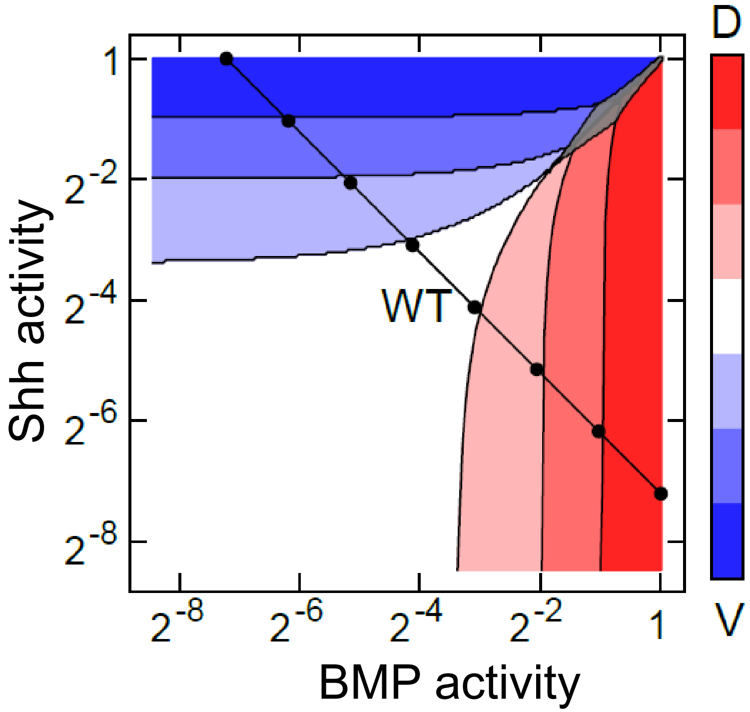
Cells interpret the opposing morphogen signals using an optimal decoding strategy

$P(x^*|\{g_B, g_S\})$:



Zagorski et al., Science, 2017

Cells interpret the opposing morphogen signals using an optimal decoding strategy

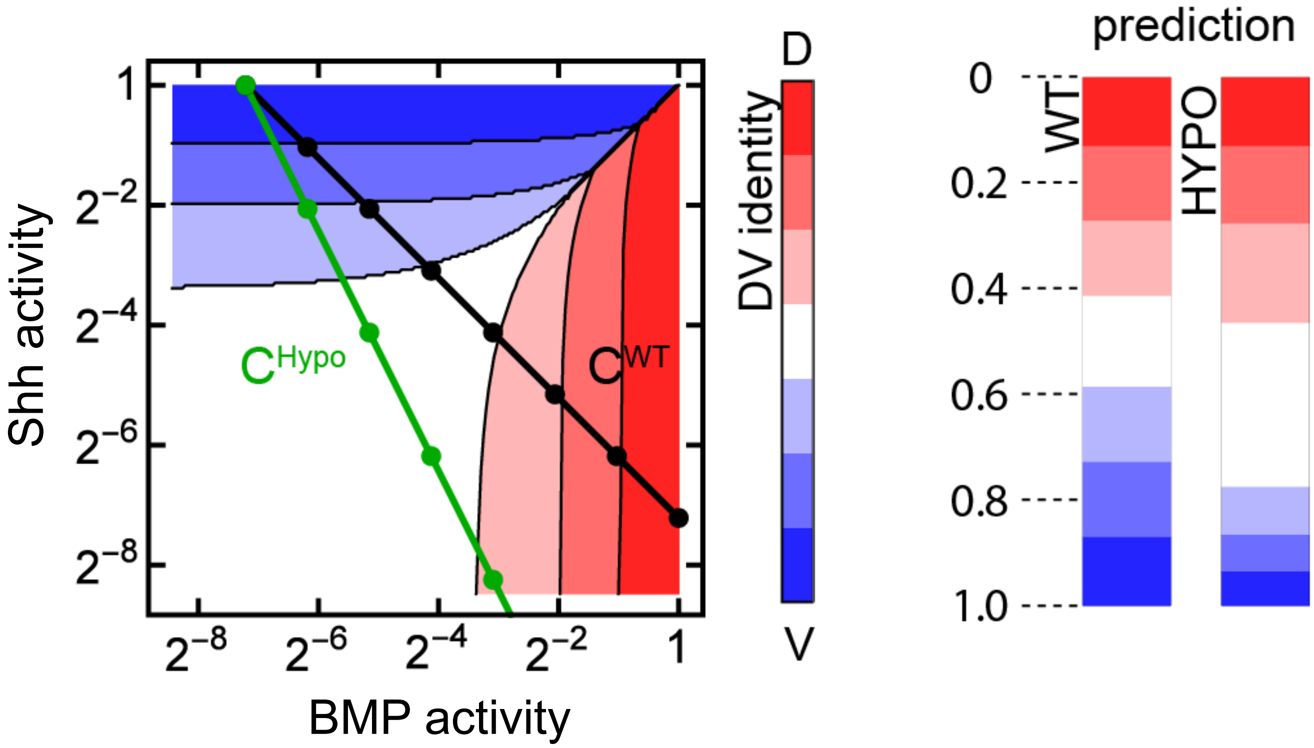


$$P(\{g_B, g_S\}|x) = \frac{1}{2\pi\sigma_B(x)\sigma_S(x)} \exp\left\{-\frac{1}{2}\left[\frac{\left(g_B - g_B(x)\right)^2}{\sigma_B^2(x)} + \frac{\left(g_S - g_S(x)\right)^2}{\sigma_S^2(x)}\right]\right\}$$

$$x^*(g_B, g_S) = \mathrm{argmax}_x\, P(\{g_B, g_S\}|x)$$

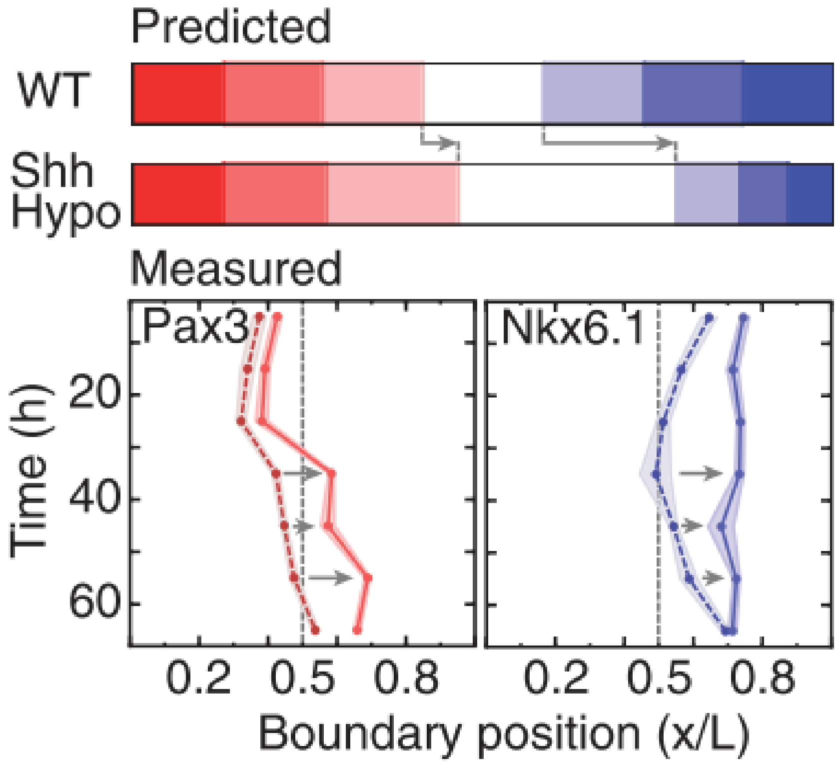
Zagorski et al., Science, 2017

The decoding map predicts the correct shifts of gene expression domains in mutant with reduced Shh



Zagorski et al., Science, 2017

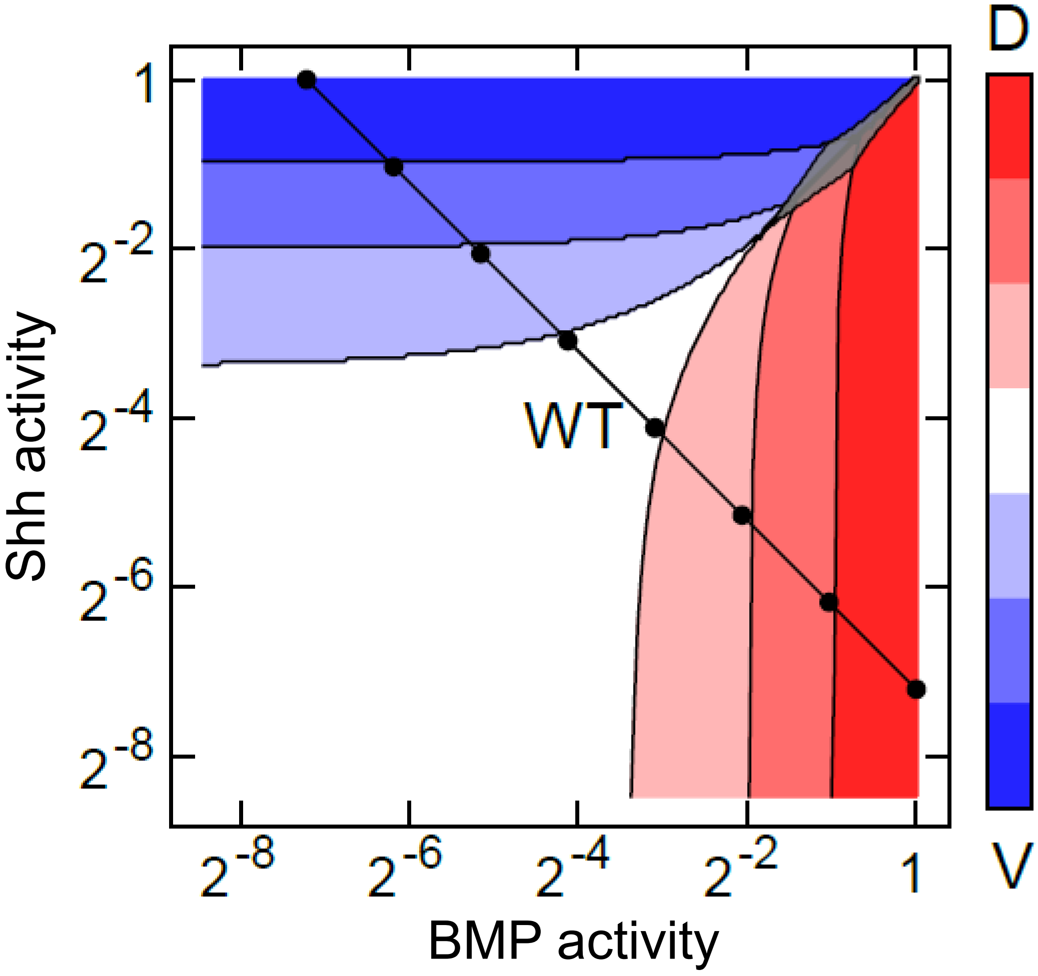
The measured gene expression boundaries are shifted ventrally relative to the wild type



Zagorski et al., Science, 2017

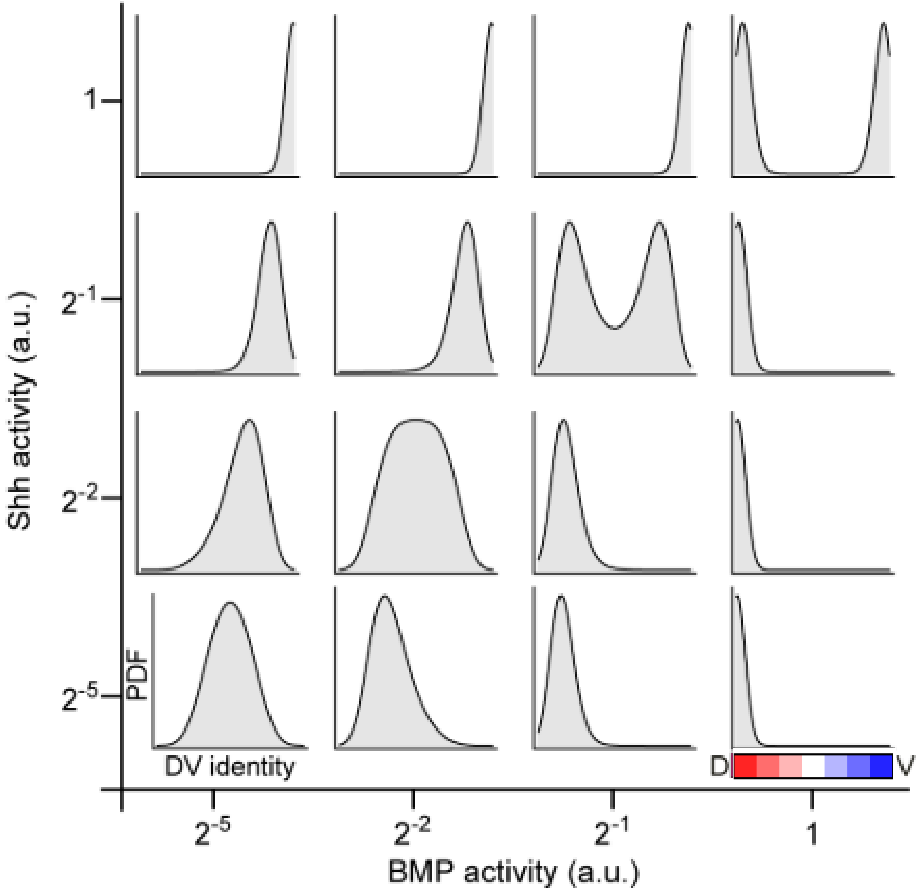
Cells interpret the opposing morphogen signals using an optimal decoding strategy

$P(x^*|\{g_B, g_S\})$:



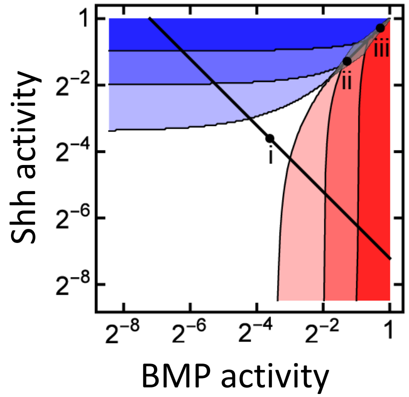
Zagorski et al., Science, 2017

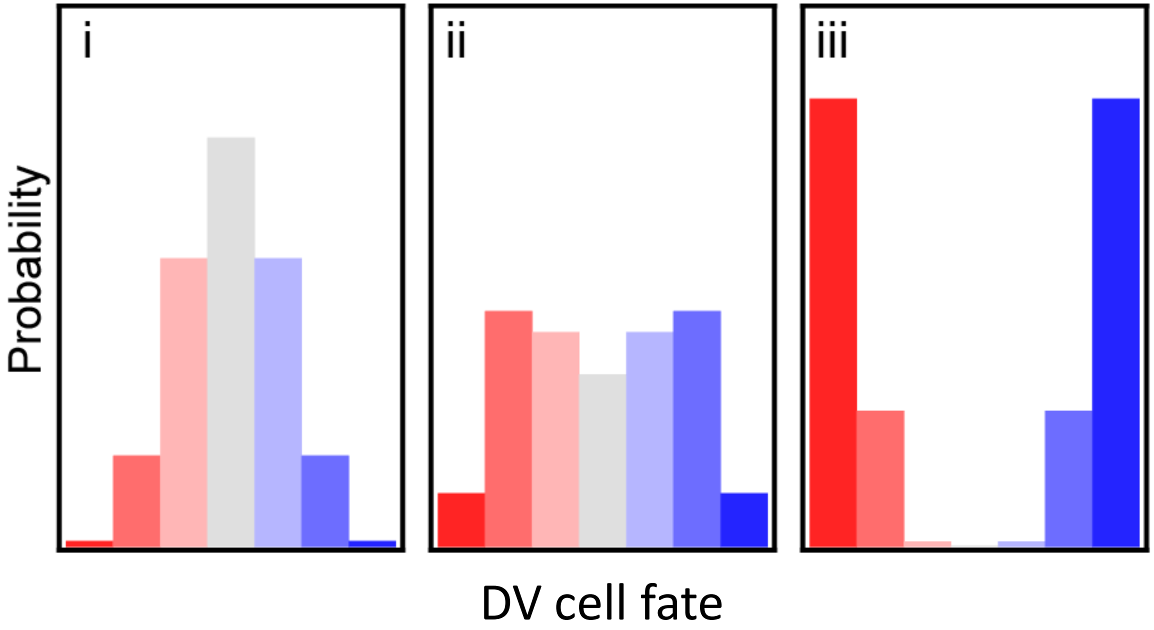
Decoding map predicts bimodal *posterior* distribution of cell fates for high morphogen concentrations and unimodal elsewhere



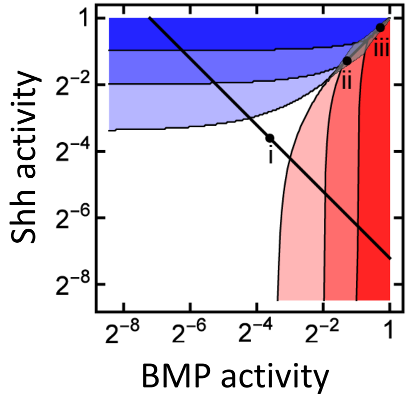
Zagorski et al., Science, 2017

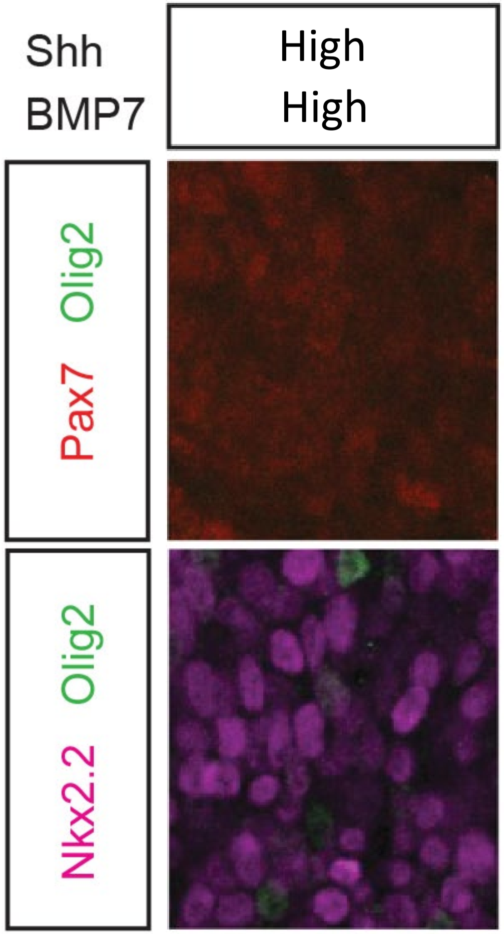
Decoding map predicts bimodal *posterior* distribution of cell fates for high morphogen concentrations





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





Red cells: Dorsal fates

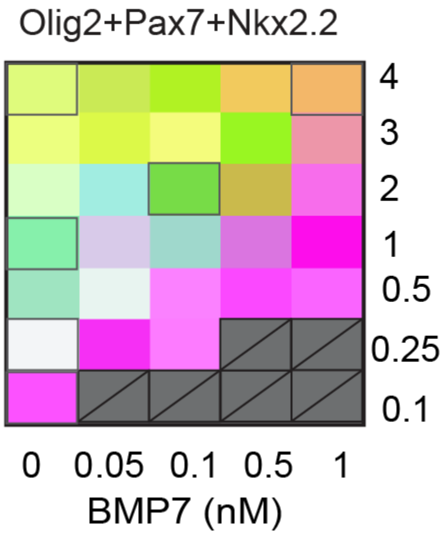
Green cells: Intermediate fates

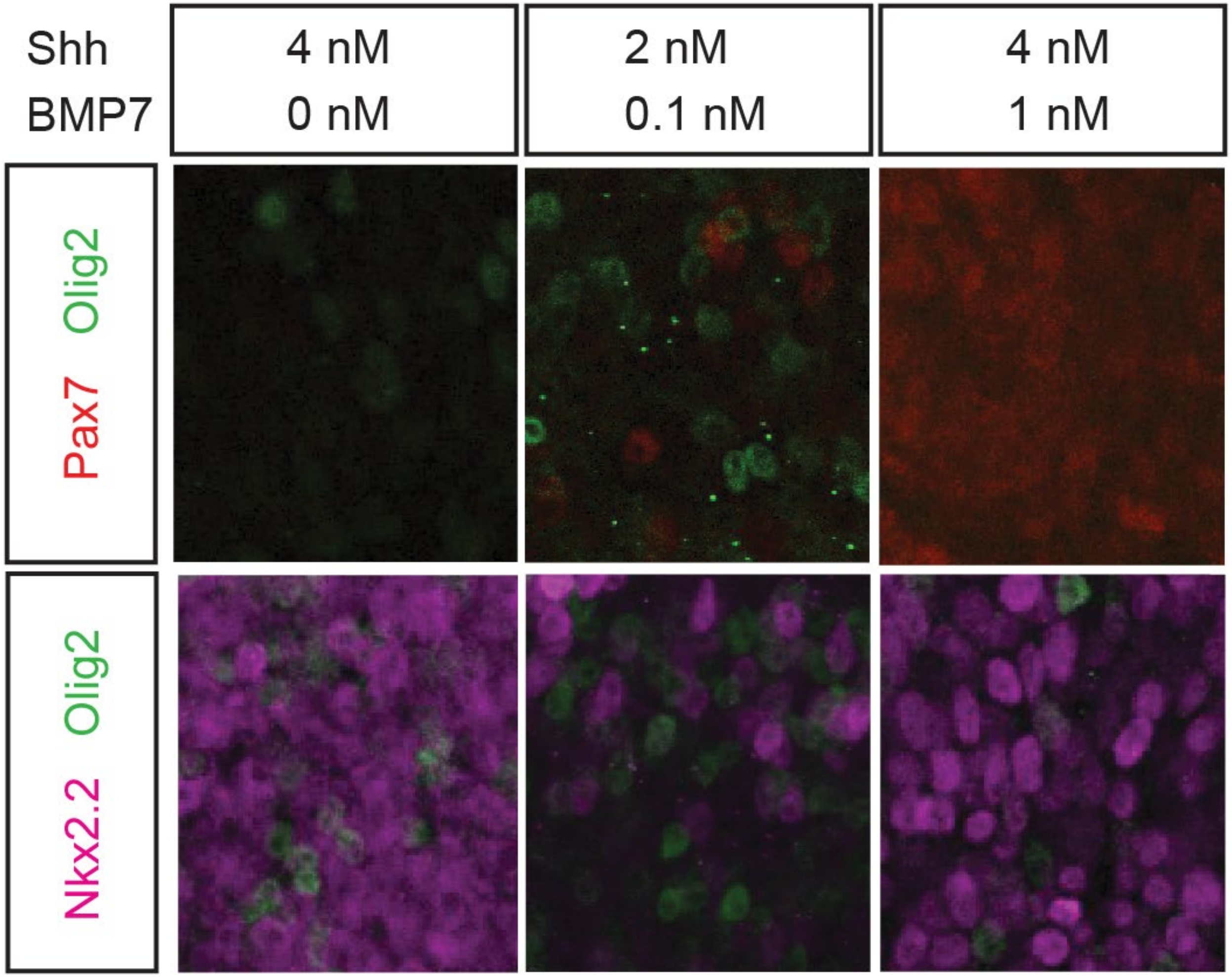
Violet cells: Ventral fates

Green cells: Intermediate fates

Zagorski et al., Science, 2017

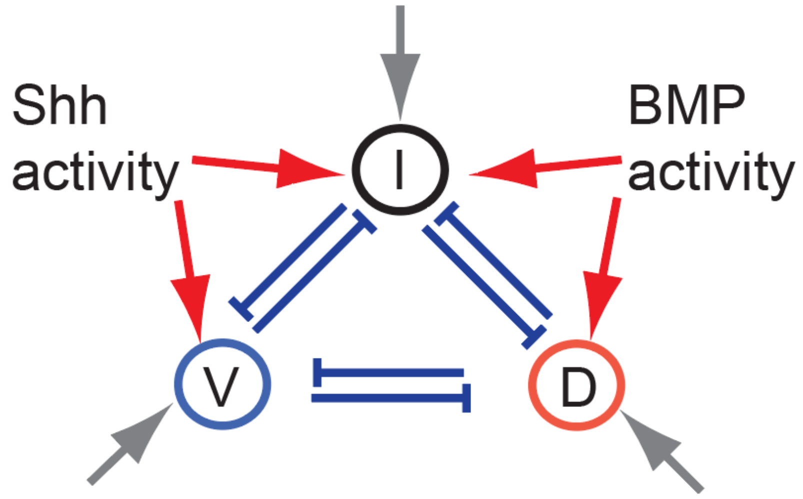
Decoding map reconstructed from explant experiment is consistent with maximum likelihood predictions





Zagorski et al., Science, 2017

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



D: Pax3
I: Dbx2
V: Nkx6.1

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

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

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

Zagorski et al., Science, 2017

3-node regulatory network model

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

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

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

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

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

Fixed during screen

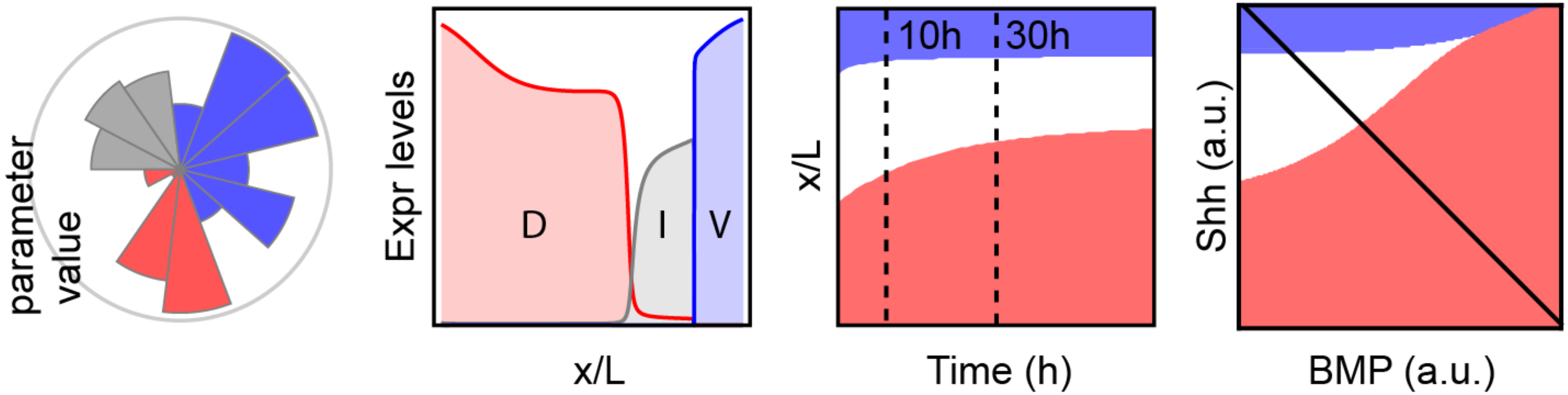
$\alpha_{Msx} = \alpha_{Nkx} = \alpha_{Dbx} = 1\ \ (h^{-1})$	production rate
$\gamma_{Msx} = \gamma_{Nkx} = \gamma_{Dbx} = 0.2\ \ (h^{-1})$	degradation rate
$m_{N\to M} = m_{M\to N} = m_{N\to D} = m_{D\to N} = m_{M\to D} = m_{D\to M} = 2$	Hill coefficients

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

screen:

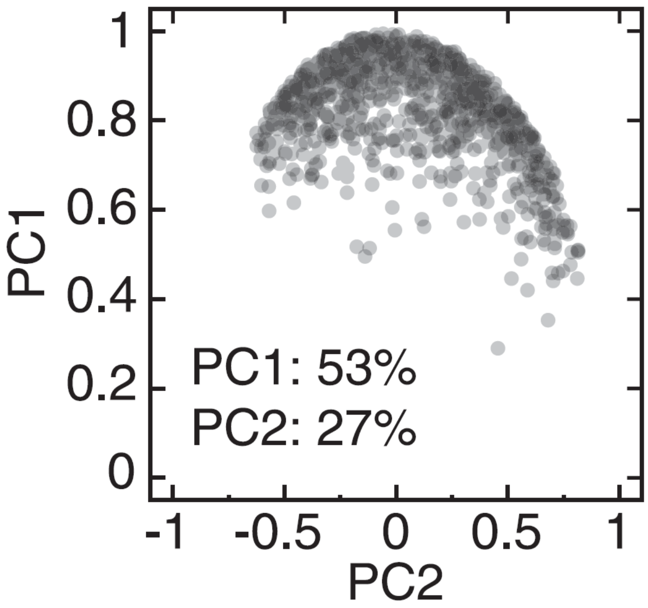
13 parameters 6×10^8 sets → Spatial pattern 4×10^6 sets → Temporal pattern 2×10^4 sets → Decoding map $\sim 10^3$ sets

example:



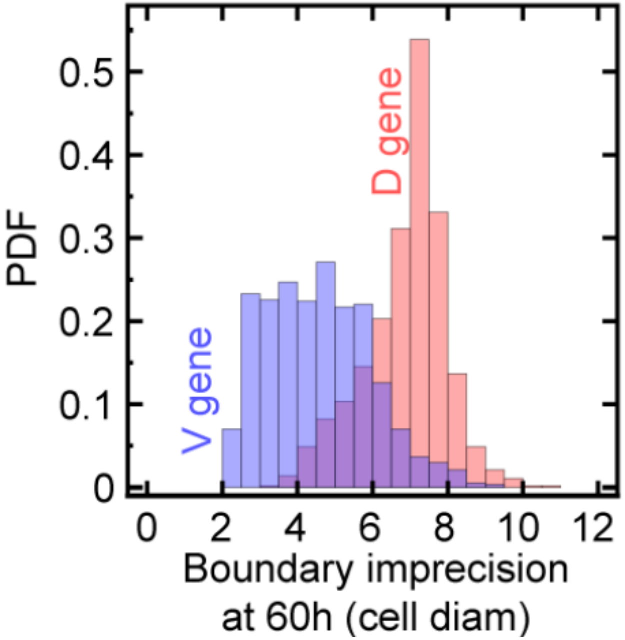
Zagorski et al., Science, 2017

Successful GRNs formed a single cluster in the parameter space



Zagorski et al., Science, 2017

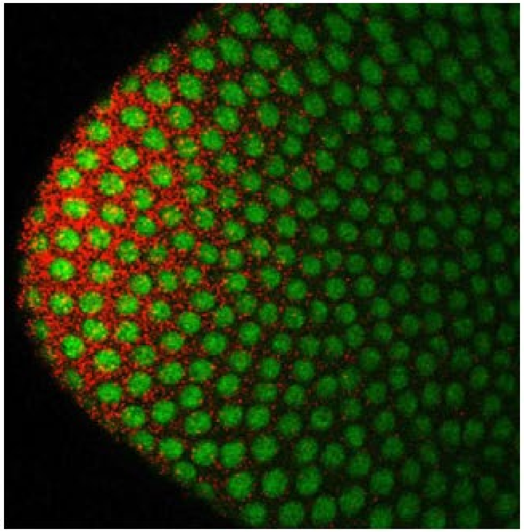
The target gene pattern established by GRNs resulted in a wide range of boundary imprecision



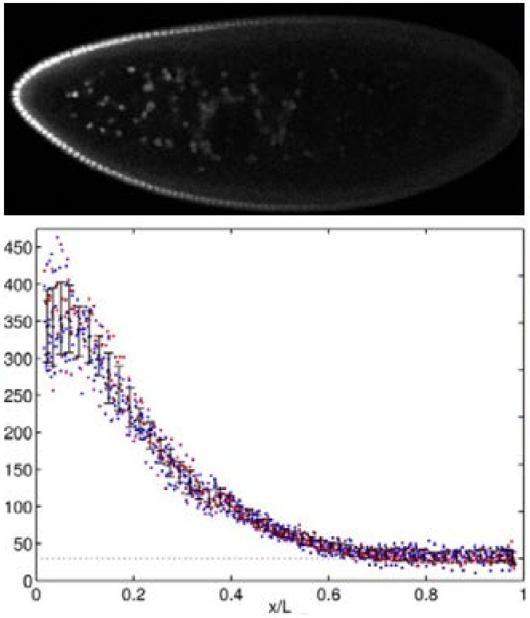
Zagorski et al., Science, 2017

Summary of positional information decoding scheme in developmental systems (part I)

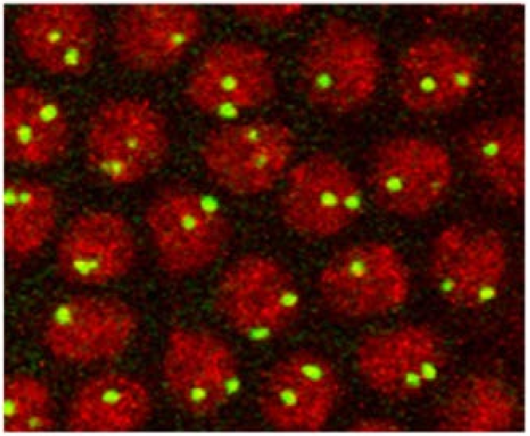
(1) Encoding
Mechanisms of Bcd gradient establishment



(2) PI in I(Bcd;x)



(3) Recoding
Mechanisms of Hb regulation by Bcd (can involve multiple steps)



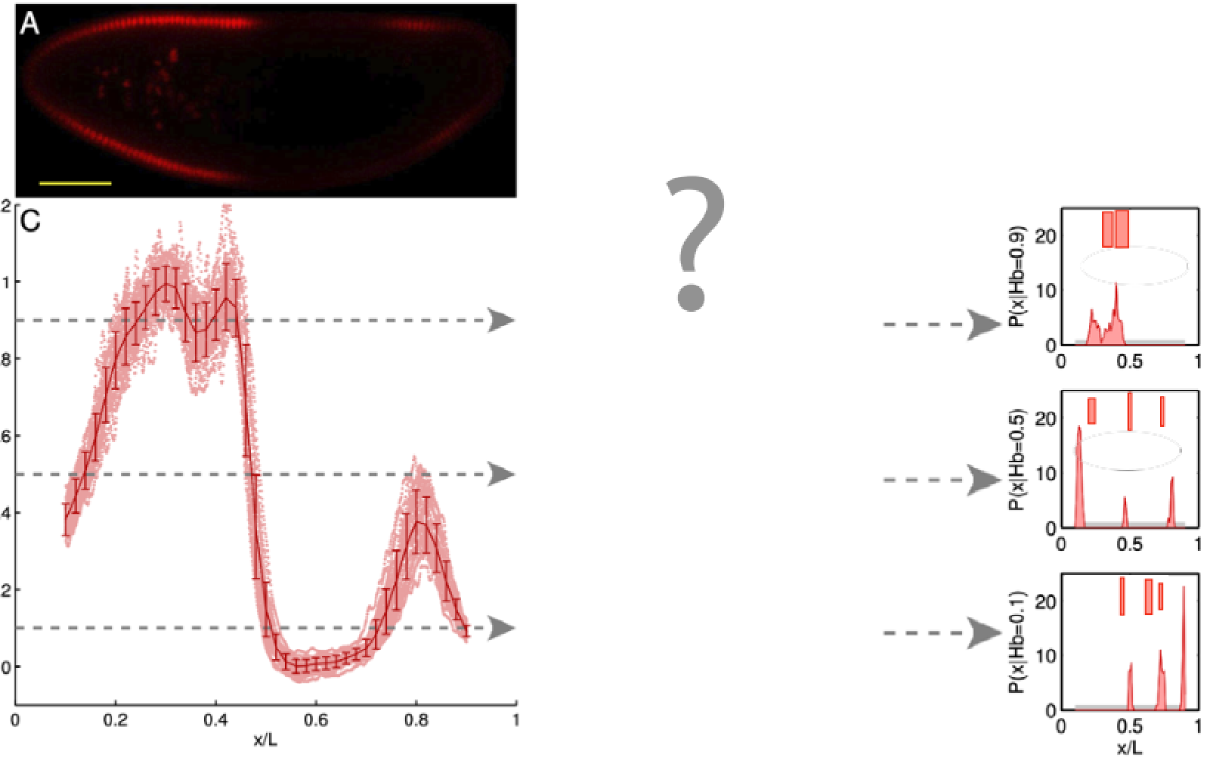
Tkacik & Gregor, Development, 2021

Summary of positional information decoding scheme in developmental systems (part II)

(4) PI in I(Hb;x)

(5) Decoding
Positional fate determination

(6) Optimal decoding

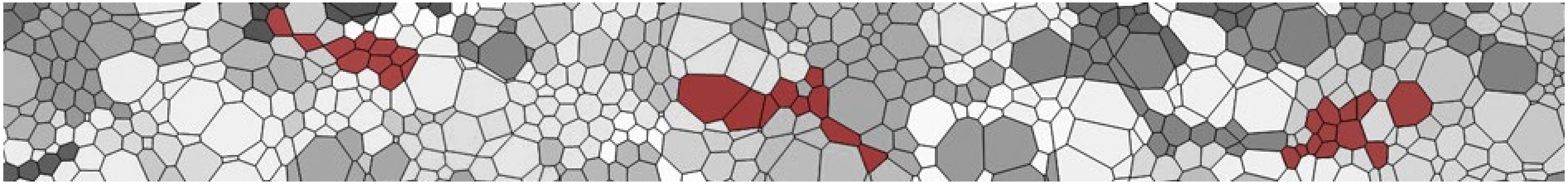


Tkacik & Gregor, Development, 2021

Open questions and future directions

- How far did evolution drive patterning systems towards theoretically optimal patterns that maximize PI?
- Is PI encoded by temporal dynamics of developmental genes?
- Is PI 'produced' during development?
- Why is PI transformed and how are the different representations related to developmental networks?
- How is PI related to robustness?
- Can PI be related to cell fate and canalization?
- Is the optimal decoding a fundamental principle characterizing the pattern specification in developmental systems?

Tkacik & Gregor, Development, 2021



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