近似ベイズ計算法を用いた生物数理モデルの構築と展望

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謝辞

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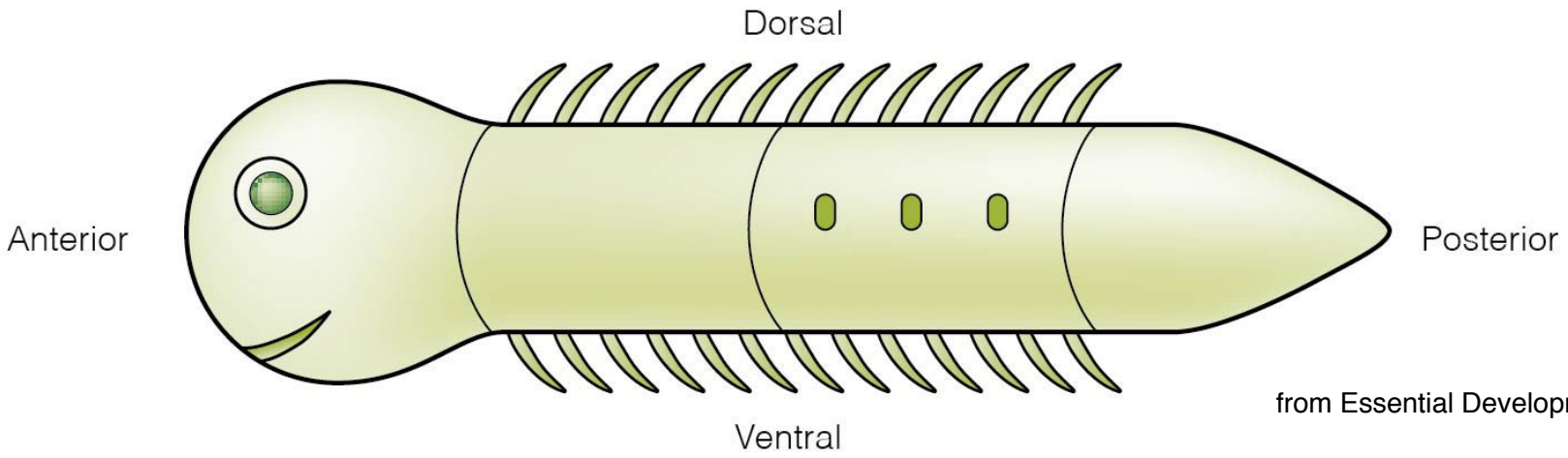
ライフサイエンスのチャレンジ

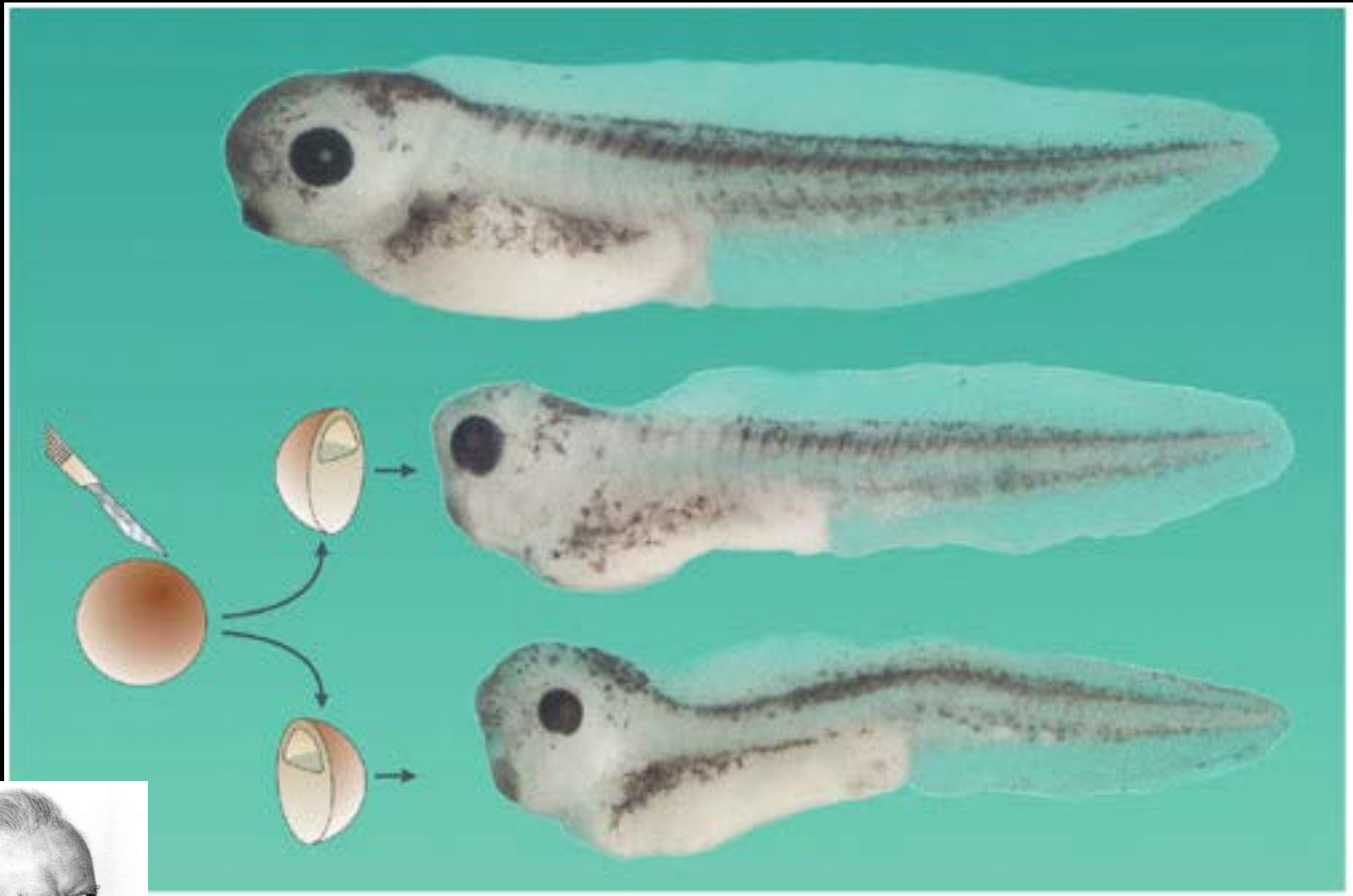
- 分子や相互作用の知識の蓄積
- 働きを理解するには不十分
- シミュレーションによる再構成 => 理解
- しかし、基礎方程式は不確実
- 数理モデル = 仮説の構築
- パラメータ値の不可知性

からだの基本的な３つの軸



from Essential Developmental Biology

- Anterior-Posterior (AP axis、前後軸)
- Dorsal-Ventral (DV axis、背腹軸)
- Left-Right (左右軸)

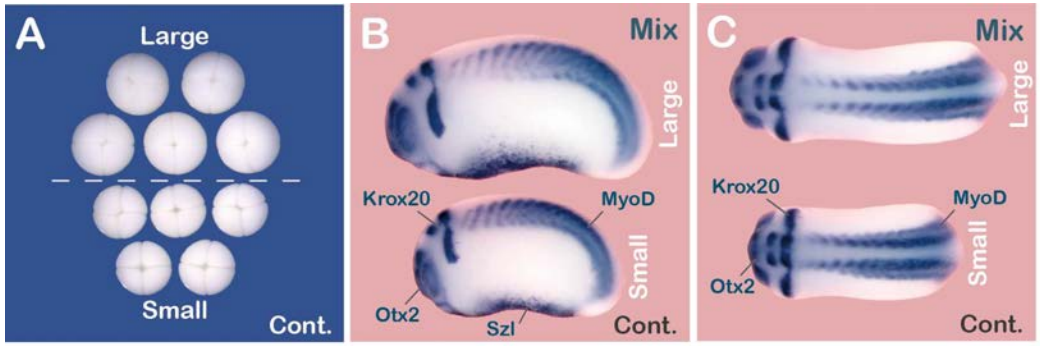


Nature Reviews | Molecular Cell Biology

Hans Spemann

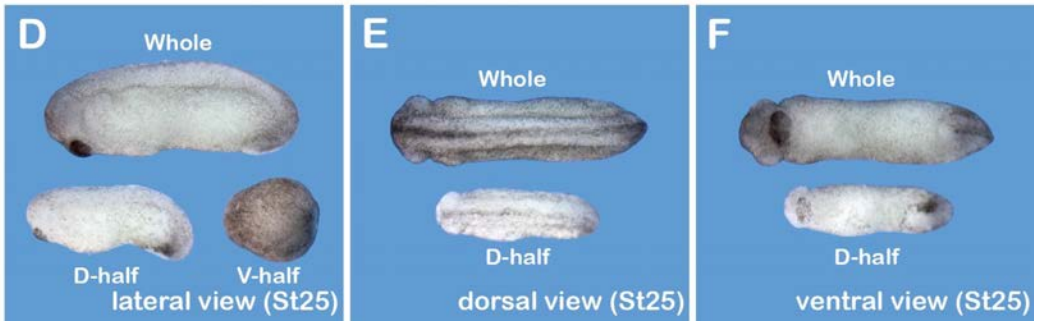
背腹軸パタン形成のスケーリング性

Xenopus laevis



whole

Bisection



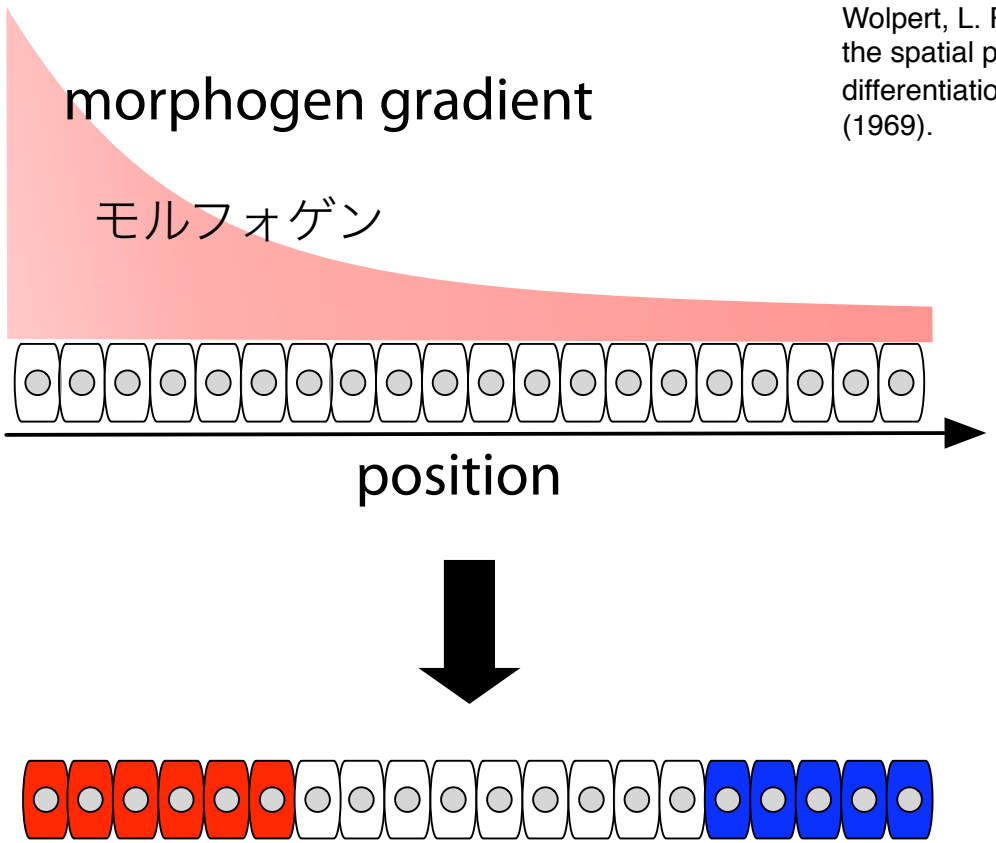
- 胚のサイズの違いにもかかわらず、背腹軸のパタン形成はプロポーションが維持されている。
- 背腹軸のパターンを体のサイズに適応させる仕組みは何か？
- 「スケーリング性のあるパタン形成」

実験結果については→ Inomata, H., Shibata, T., Haraguchi, T., & Sasai, Y. (2013). Cell, 153(6), 1296–1311.

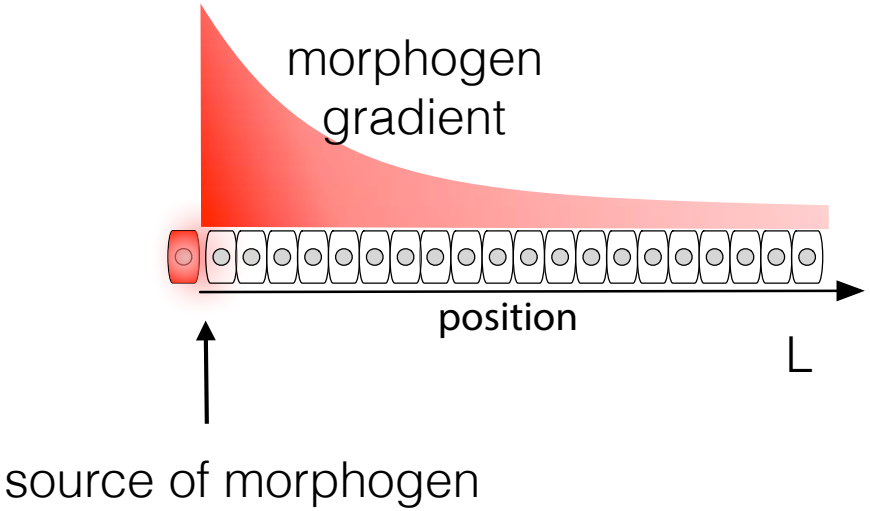
濃度勾配が位置情報を与える

Wolpert's "French flag" model

Wolpert, L. Positional information and the spatial pattern of cellular differentiation. J Theor Biol 25, 1–47 (1969).



拡散係数と分解レートが濃度勾配を決める



$$\frac{\partial c}{\partial t} = -\lambda c + D\frac{\partial^2 c}{\partial x^2}$$

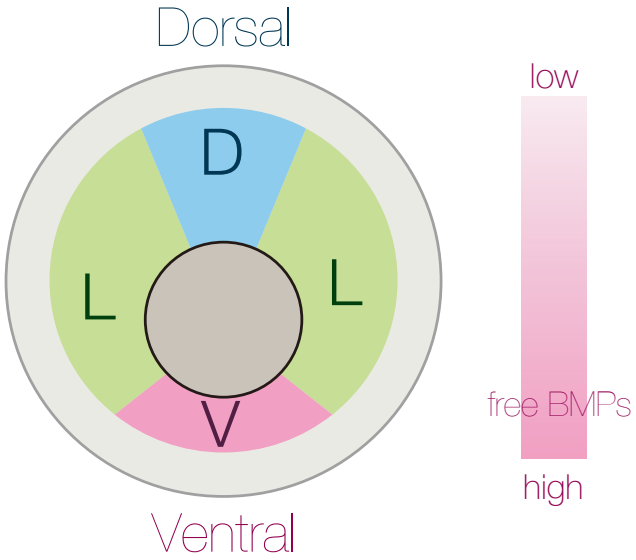
$$D\frac{\partial c}{\partial x}\bigg|_{x=0} = -J$$

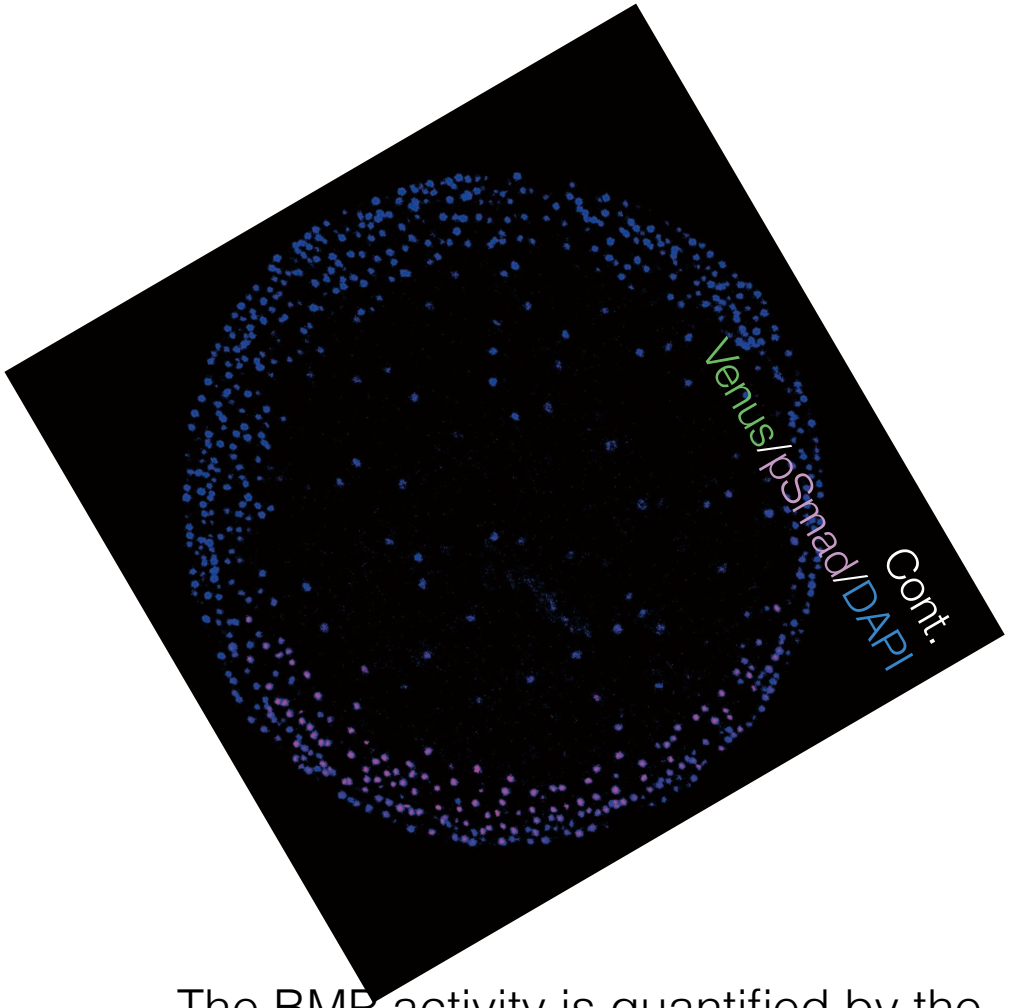
The morphogen gradient: $C(x) = \frac{J}{\sqrt{D\lambda}} e^{-\frac{x}{\sqrt{D/\lambda}}}$

The diffusion distance $\ell = \sqrt{D/\lambda}\ (\mu m)$

- 体のサイズは濃度勾配に影響しない！

BMP の濃度勾配が背腹軸を決めている

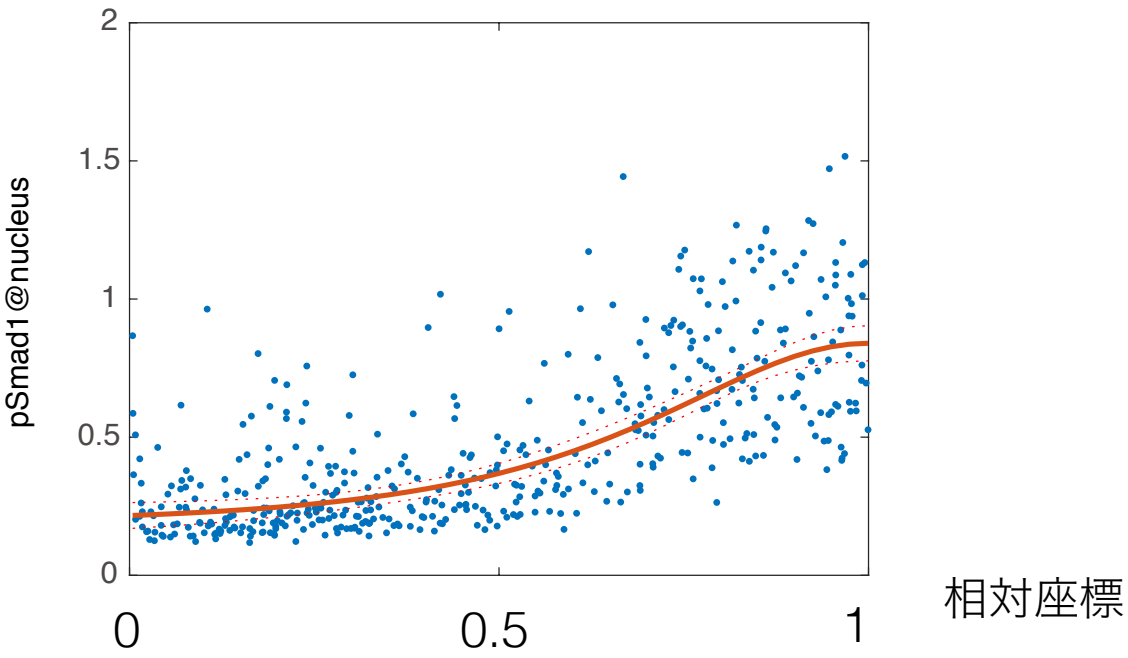




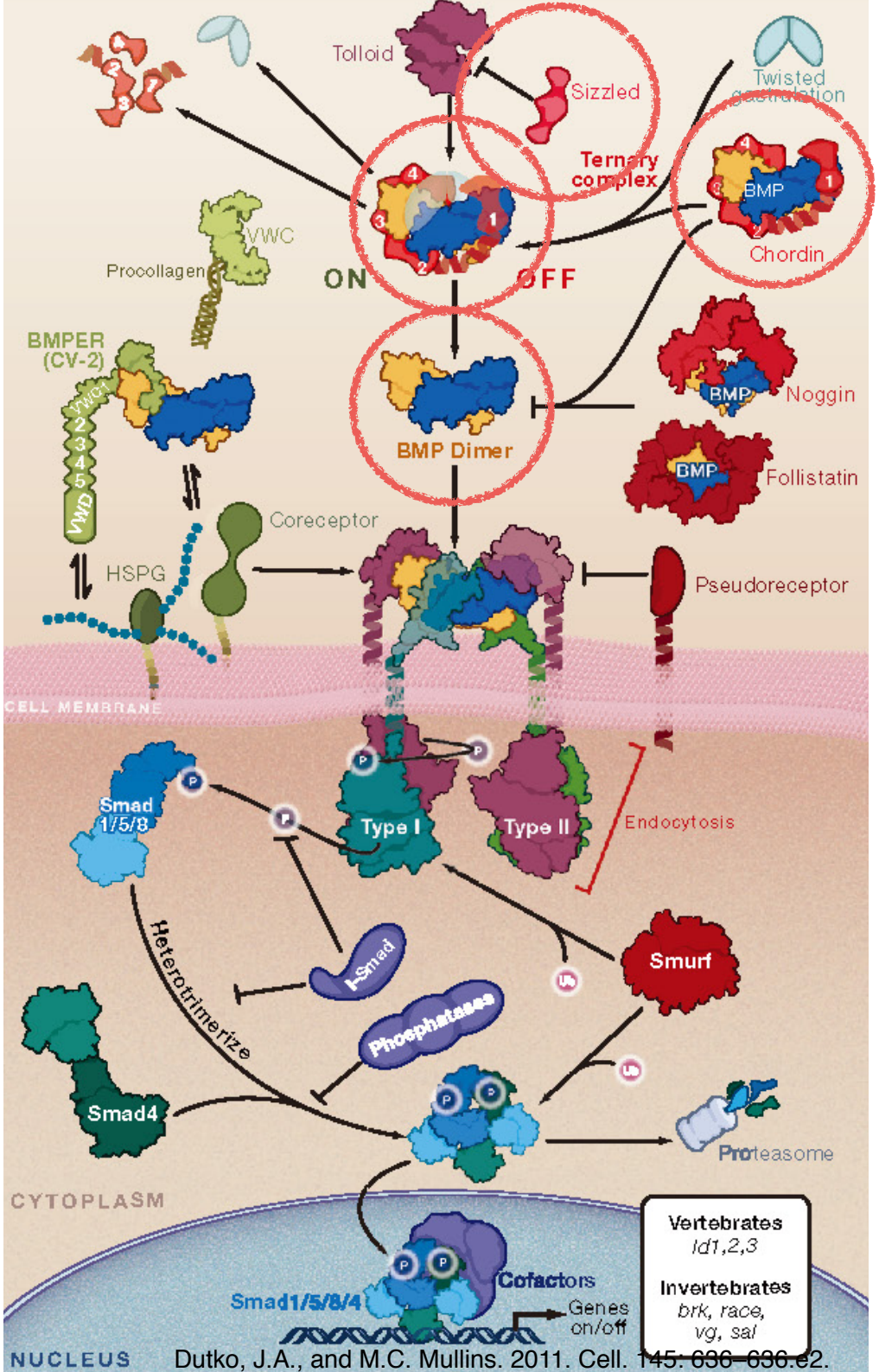
The BMP activity is quantified by the nuclear phospho-Smad1 (pSmad1) signal.

Inomata, H., Shibata, T., Haraguchi, T., & Sasai, Y. (2013). Cell, 153(6), 1296–1311.

背腹軸に沿ったモルフォゲン濃度勾配



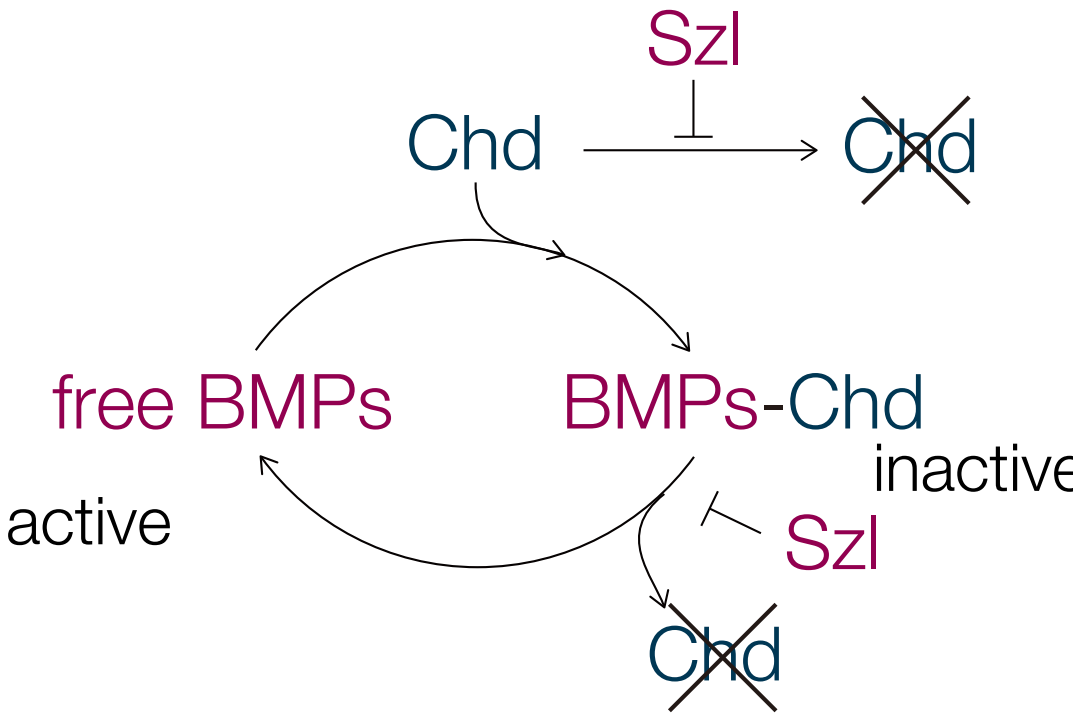
- 疑問：体のサイズに対して、いつも同じ割合で変化する濃度勾配は、どのように作られるか？



Dutko, J.A., and M.C. Mullins. 2011. Cell. 145: 636–636.e2.

BMP濃度勾配を調節する分子ネットワーク

Sizzled, a inhibitor for Chordin protease, stabilizing Chordin and BMPs-Chd complexes



Inomata, H., Shibata, T., Haraguchi, T., & Sasai, Y. (2013). Cell, 153(6), 1296–1311.

背腹軸パタン形成の数理モデル

(***A***) ADMP
(***C***) Chordin
(***AC***) ADMP-Chd
(***BC***) BMP4-Chd
(***B***) BMP4
(***S***) Sizzled

(1) BMP-dependent production

(2) Degradation

(3) Association between BMPs & Chordin

(4) Sizzled-regulated Chordins degradation

(5) Diffusion

(6) Chd production at dorsal end

$$\frac{\partial C}{\partial t} = V_C \frac{K_C^{h_C}}{K_C^{h_C} + (A+B)^{h_C}} - \lambda_C \frac{C}{1 + S/K_i + (C+BC+AC)/K_m} - k_{chdbmp} C \cdot B - kC \cdot A + D_{chd} \Delta C$$

$$\frac{\partial B}{\partial t} = V_B \frac{(A+B)^{h_B}}{K_B^{h_B} + (A+B)^{h_B}} - \lambda_B B + \lambda_C \frac{BC}{1 + S/K_i + (C+BC+AC)/K_m} - k_{chdbmp} C \cdot B + D_{bmp} \Delta B$$

$$\frac{\partial A}{\partial t} = V_A \frac{K_A^{h_A}}{K_A^{h_A} + (A+B)^{h_A}} - \lambda_B A + \lambda_C \frac{AC}{1 + S/K_i + (C+BC+AC)/K_m} - k_{chdadmp} C \cdot A + D_{admp} \Delta$$

$$\frac{\partial S}{\partial t} = V_S \frac{(A+B)^{h_S}}{K_S^{h_S} + (A+B)^{h_S}} - \lambda_S S + D_{szl} \Delta S$$

$$\frac{\partial BC}{\partial t} = -\lambda_C \frac{BC}{1 + S/K_i + (C+BC+AC)/K_m} + k_{chdbmp} C \cdot B + D_{chdbmp} \Delta BC$$

$$\frac{\partial AC}{\partial t} = -\lambda_C \frac{AC}{1 + S/K_i + (C+BC+AC)/K_m} + k_{chdadmp} C \cdot A + D_{chdadmp} \Delta AC$$

$$D\nabla C|_{x=0} = -J_C$$

$$D\nabla B|_{x=0} = D\nabla A|_{x=0} = D\nabla S|_{x=0} = D\nabla BC|_{x=0} = D\nabla S|_{x=0} = 0$$

$$D\nabla C|_{x=L} = D\nabla B|_{x=L} = D\nabla A|_{x=L} = D\nabla S|_{x=L} = D\nabla BC|_{x=L} = D\nabla S|_{x=L} = 0$$

Inomata, H., Shibata, T., Haraguchi, T., & Sasai, Y. (2013). Cell, 153(6), 1296–1311.

パラメータ

$$\left.\begin{array}{r} V_c, K_c, h_c \\ V_B, K_B, h_B \\ V_A, K_A, h_A \\ V_s, K_s, h_s \end{array}\right\} \cdots\cdots\cdots\cdots$$

(1) BMP-dependent production rate, Hill coefficient, threshold

$\lambda_{\mathrm{B}}, \lambda_{\mathrm{S}}$ ..... (2) Degradation

k_{BC} ..... (3) Association between BMPs & Chordin

$\lambda_{\mathrm{C}}, K_m, K_i$ ..... (4) Sizzled-regulated Chordins degradation

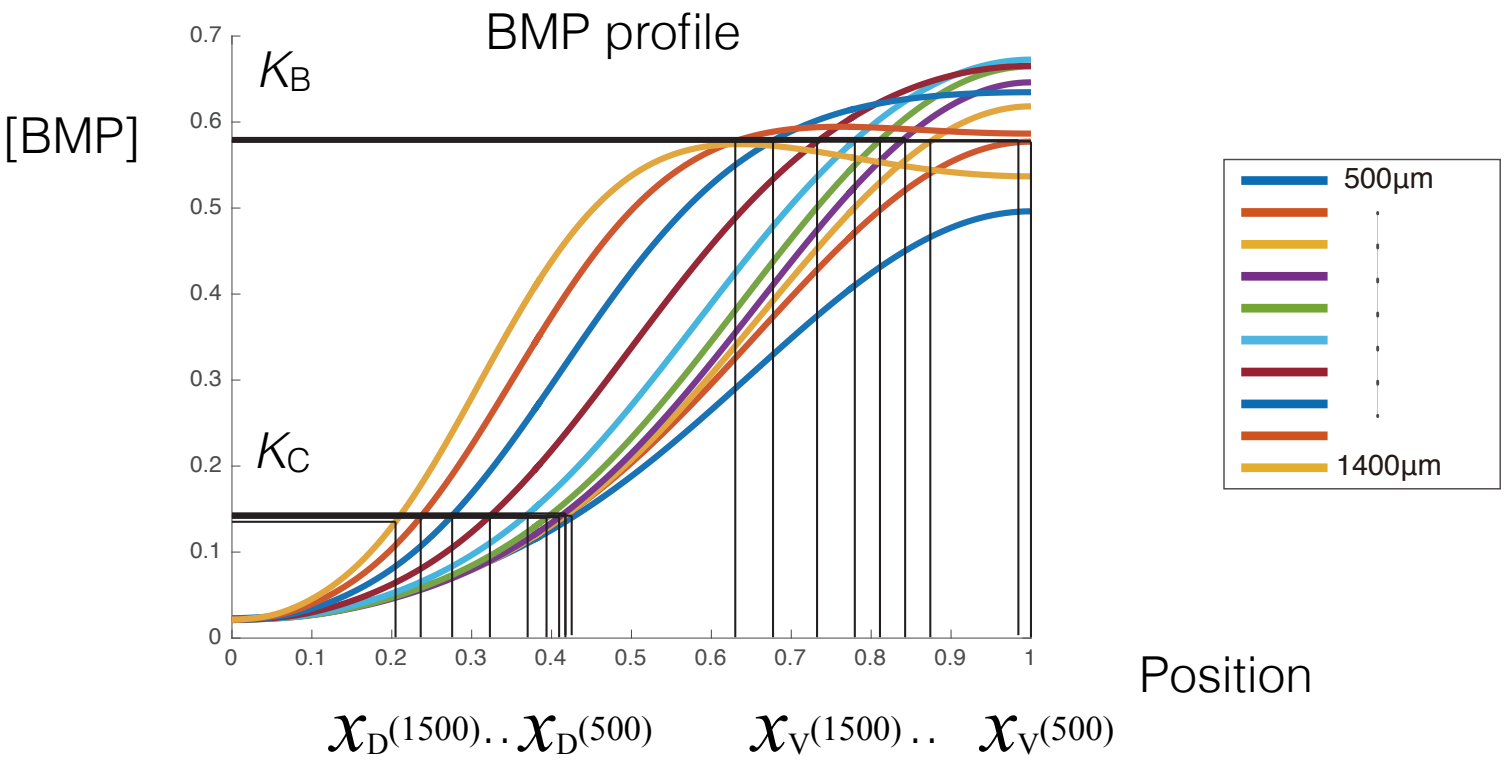
$D_C, D_B, D_A, D_S, D_{CB}, D_{CA}$ ..... (5) Diffusion

J_c .....(6) Chordin production at dorsal end

L .....(7) embryo size

- パラメータの数 >> 変数の数

異なるサイズに対する
モルフォゲン濃度勾配の数値計算

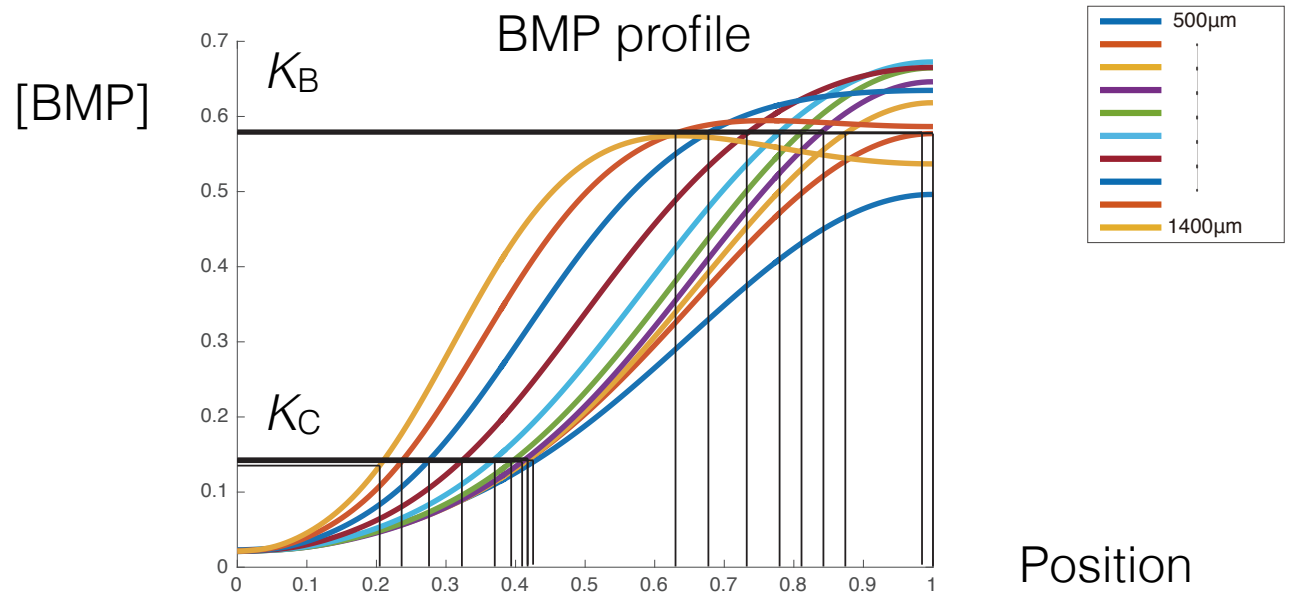


- [BMP] = K_C, 背領域の境界, x_D
- [BMP] = K_B, 腹領域の境界, x_V

$$b = \{x_D(1500), \ldots, x_D(500), x_V(1500), \ldots, x_V(500)\}$$

実験結果を説明するパラメータの推定

simulation

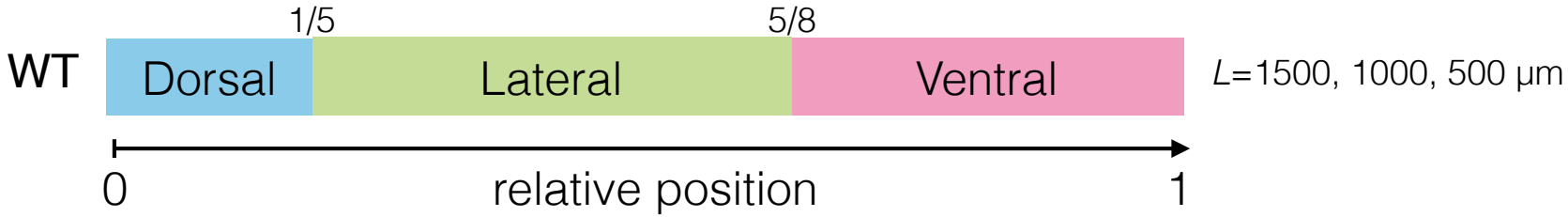


$$b = \{x_{D(1500)}, \ldots, x_{D(500)}, x_{V(1500)}, \ldots, x_{V(500)}\}$$

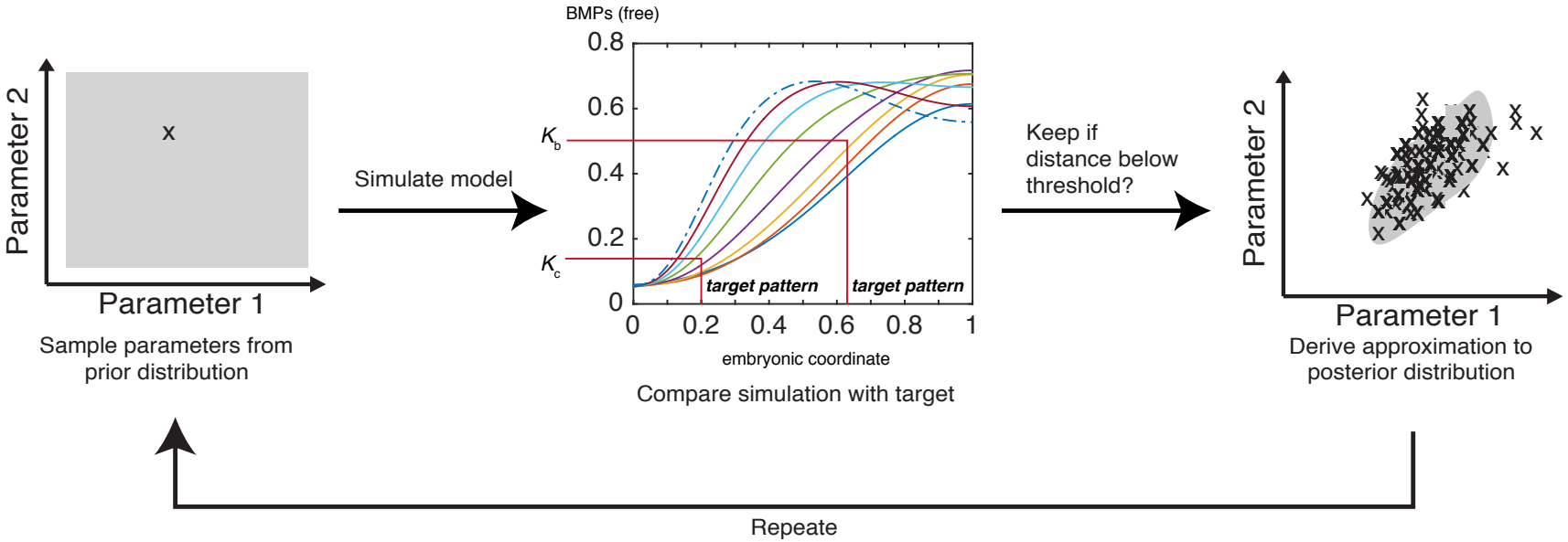
$$\downarrow$$

$$b^* = \{x_{D(1500)}=1/5,\ \ldots,\ x_{D(500)}=1/5,\ x_{V(1500)}=5/8, \ldots, x_{V(500)}=5/8\}$$

observation

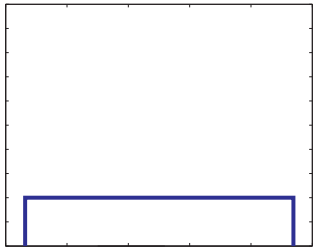


近似ベイズ法を用いたパラメータ推定



Liepe, Juliane, Liepe, Juliane, Paul Kirk, Paul Kirk, Sarah Filippi, Sarah Filippi, Tina Toni, Chris P Barnes & Michael P H Stumpf “A framework for parameter estimation and model selection from experimental data in systems biology using approximate Bayesian computation”. Nat Protoc 9, 439–456 (2014).

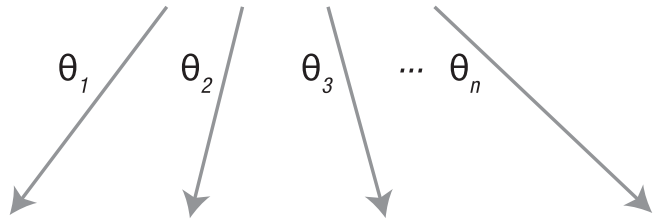
Approximate Bayesian computation (ABC) with sequential Monte Carlo (SMC) method



$P_0(\theta)$

prior distribution of model parameters θ

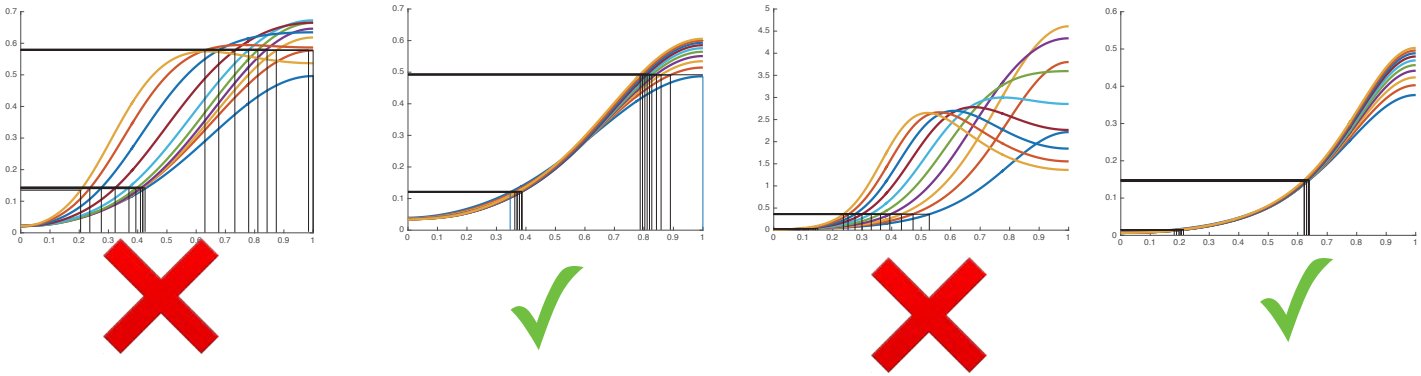
1. pick a parameter value from the prior distribution $P_{n-1}(\theta)$



2. perform simulation

3. compute D, V positions

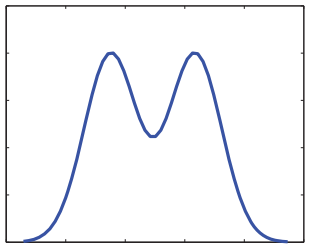
$$b = \{x_D^{(1500)}, \ldots, x_D^{(500)}, x_V^{(1500)}, \ldots, x_V^{(500)}\}$$



4. compute *error* from target, $\rho(b, b^*)$

5. accept ✓ parameter θ that errors $\rho(b, b^*) < \varepsilon$

6. Approximate the posterior distribution $P_n(\theta)$.



$P_n(\theta)$

Posterior distribution of model parameters θ

Use $P_n(\theta)$ as the prior distribution for the next iteration. Repeat this procedure until the error ρ are sufficiently small

背腹境界の分布の推移

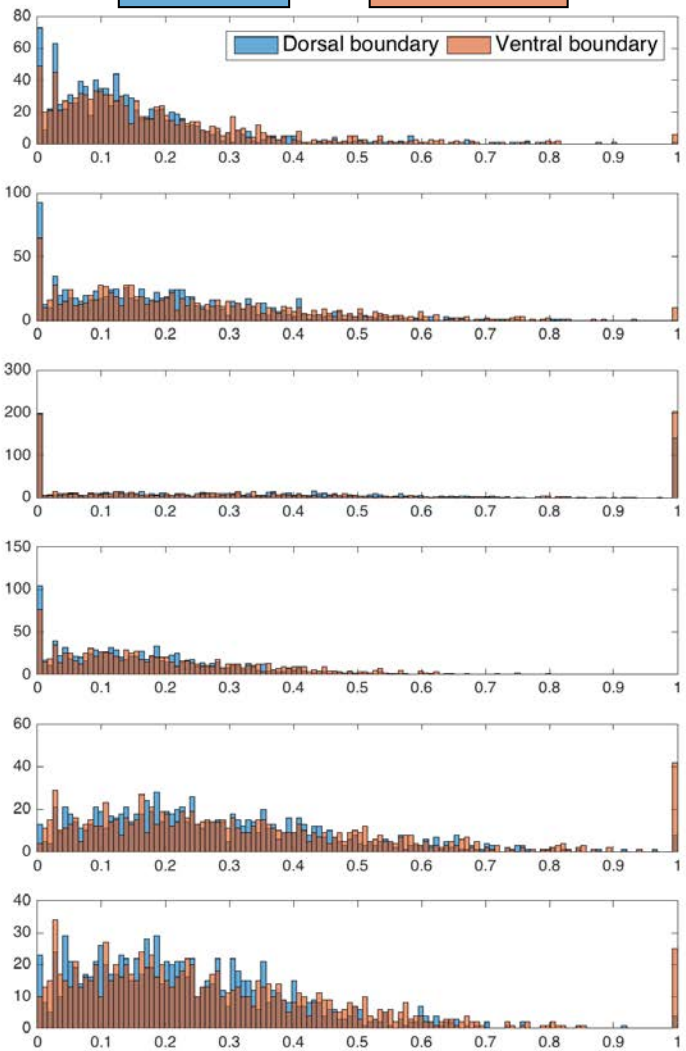
initial distribution

dorsal ventral

500μm

1000μm

1500μm



embryonic coordinate

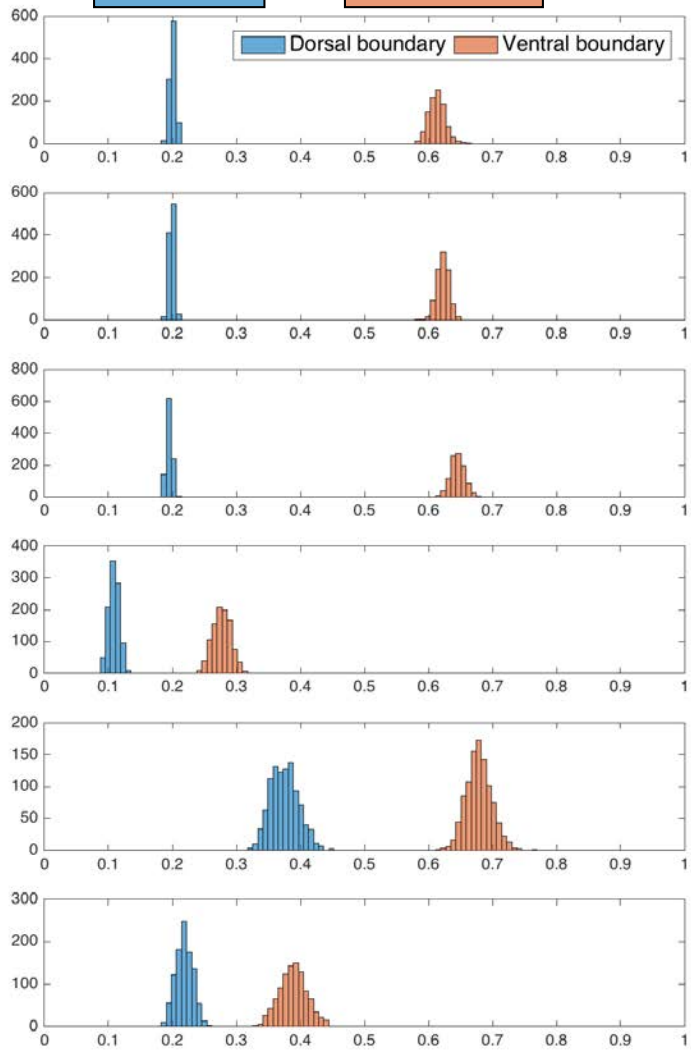
final distribution

dorsal ventral

500μm

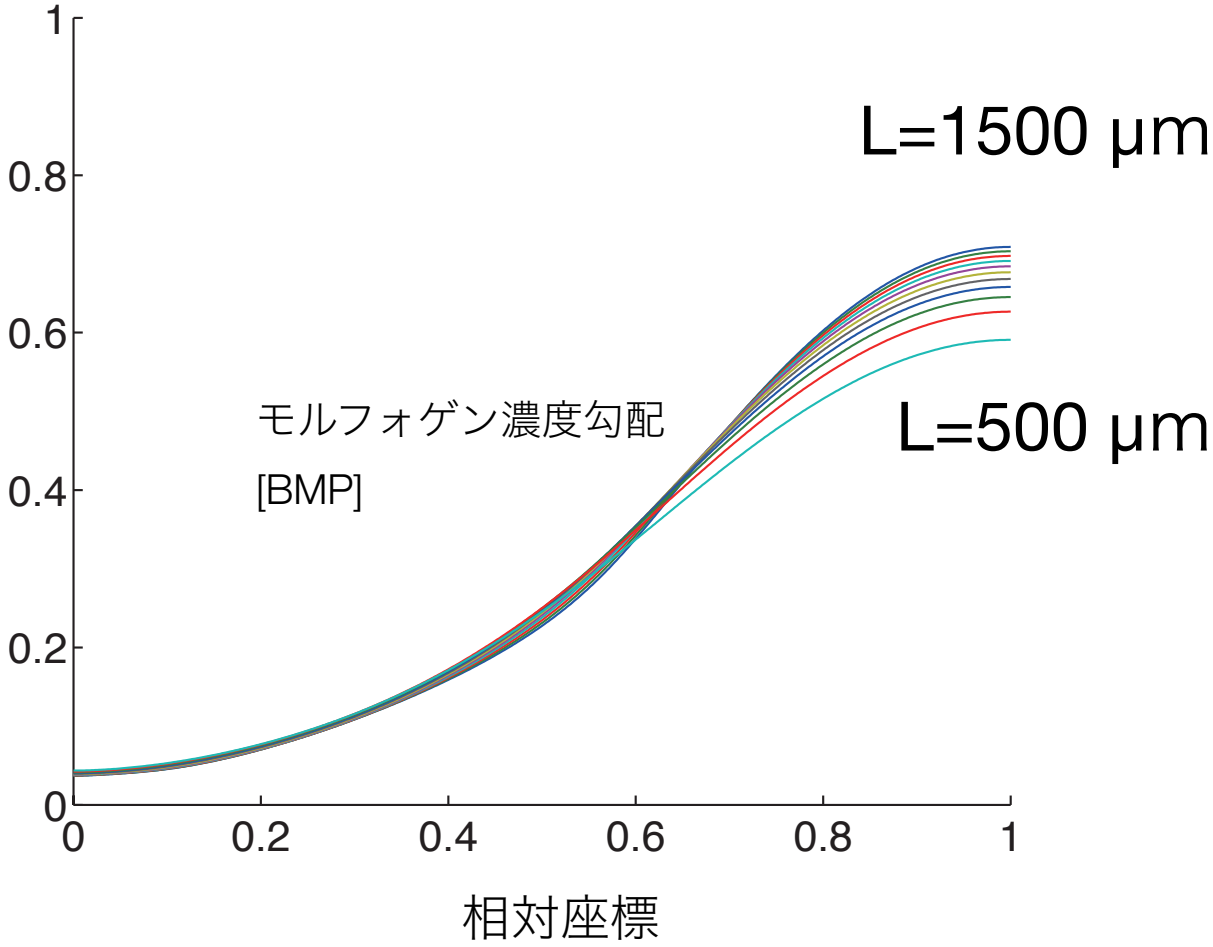
1000μm

1500μm

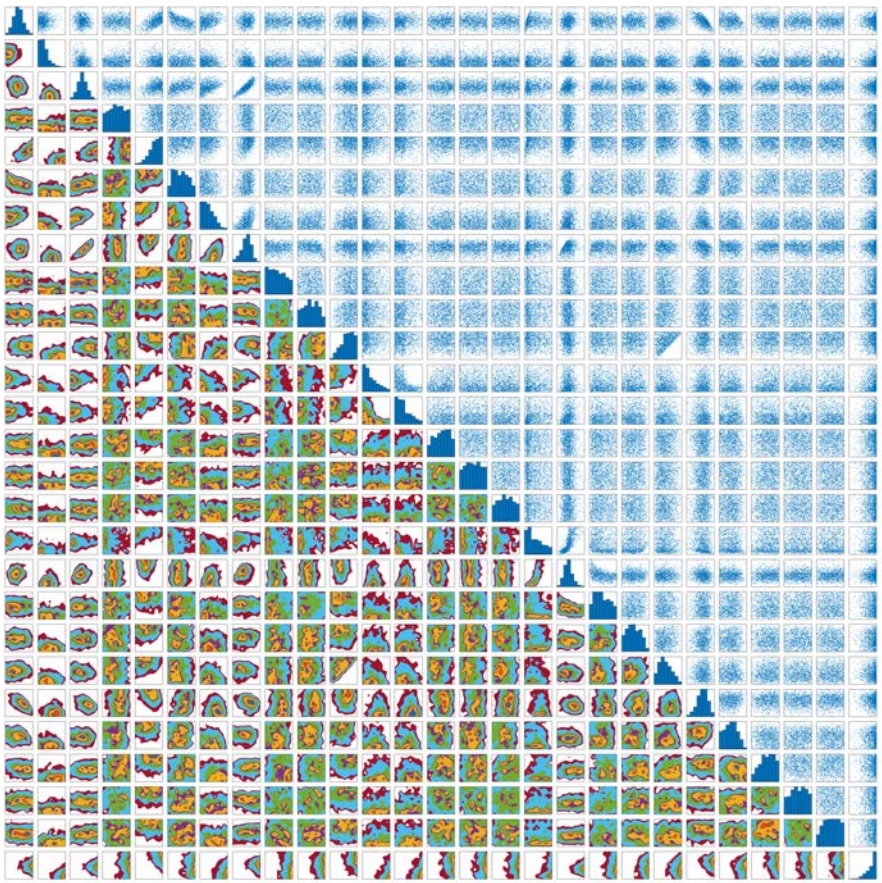


embryonic coordinate

モルフォゲン濃度勾配は同じ割合で変化する



データ駆動で本質を見抜く



$$\frac{\partial C}{\partial t} = V_C \frac{K_C^{h_C}}{K_C^{h_C} + (A+B)^{h_C}} - \lambda_C \frac{C}{1 + S/K_i + (C+BC+AC)/K_m} - kC \cdot B - kC \cdot A + D\Delta C$$

$$\frac{\partial B}{\partial t} = V_B \frac{(A+B)^{h_B}}{K_B^{h_B} + (A+B)^{h_B}} - \lambda_B B + \lambda_C \frac{BC}{1 + S/K_i + (C+BC+AC)/K_m} - kC \cdot B + D\Delta B$$

$$\frac{\partial A}{\partial t} = V_A \frac{K_A^{h_A}}{K_A^{h_A} + (A+B)^{h_A}} - \lambda_B A + \lambda_C \frac{AC}{1 + S/K_i + (C+BC+AC)/K_m} - kC \cdot A + D\Delta A$$

$$\frac{\partial S}{\partial t} = V_S \frac{(A+B)^{h_S}}{K_S^{h_S} + (A+B)^{h_S}} - \lambda_S S + D\Delta S$$

$$\frac{\partial BC}{\partial t} = -\lambda_C \frac{BC}{1 + S/K_i + (C+BC+AC)/K_m} + kC \cdot B + D\Delta BC$$

$$\frac{\partial AC}{\partial t} = -\lambda_C \frac{AC}{1 + S/K_i + (C+BC+AC)/K_m} + kC \cdot A + D\Delta AC$$

↓ データ駆動型の縮約

- スケーリング性の数理構造を、データ解析から抽出する