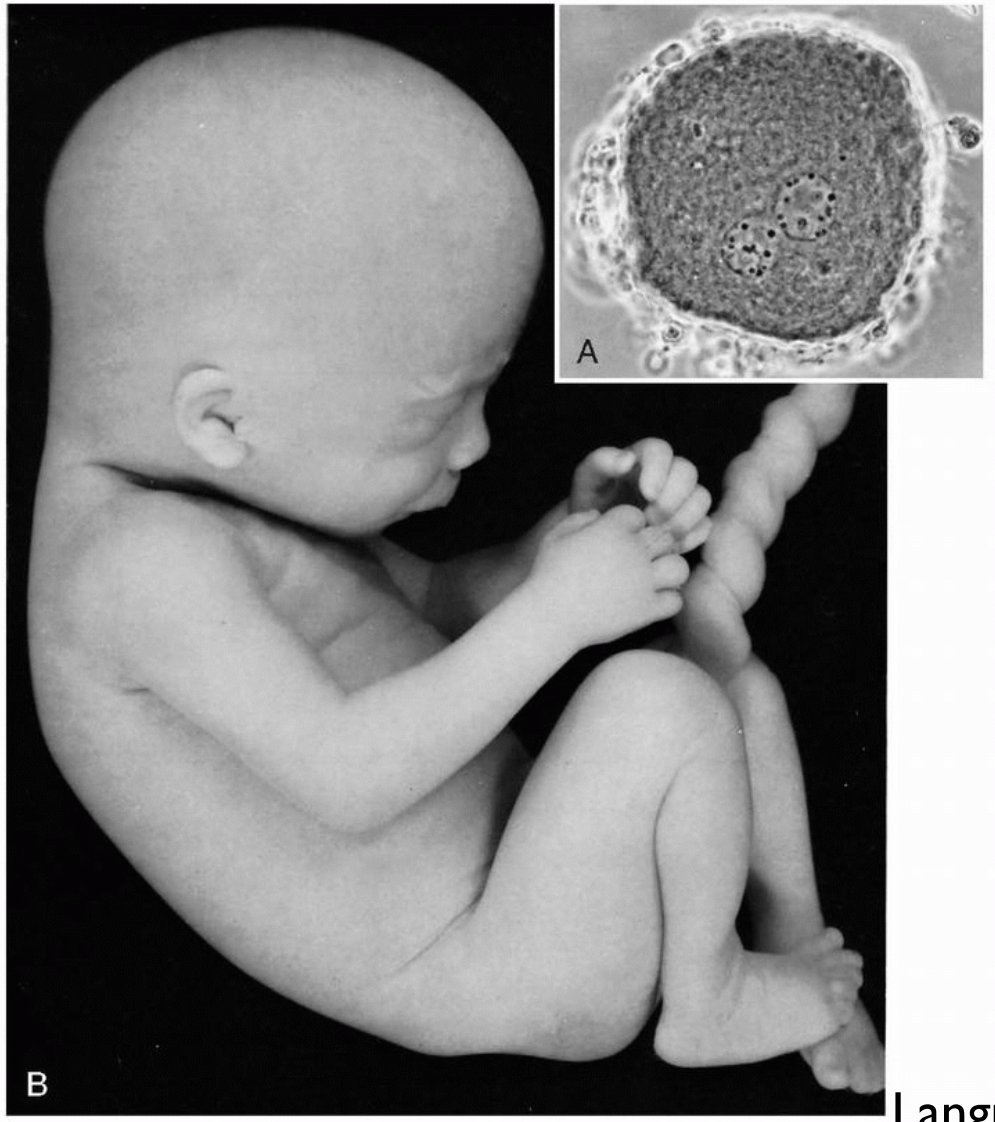
定量生物学の会 第七回年会

生物のかたちづくりのモデリングの歴史：単純と複雑の循環

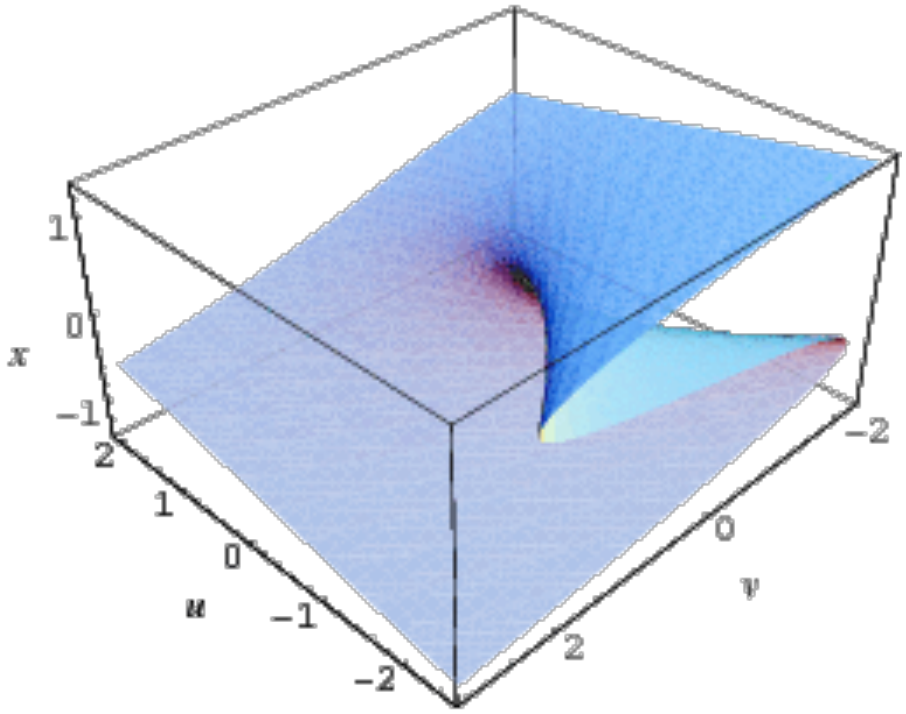
三浦　岳
九州大学大学院医学研究院

Basic question:
生物の形づくりを理解したい



Langman's Medical Embryology

カタストロフ理論

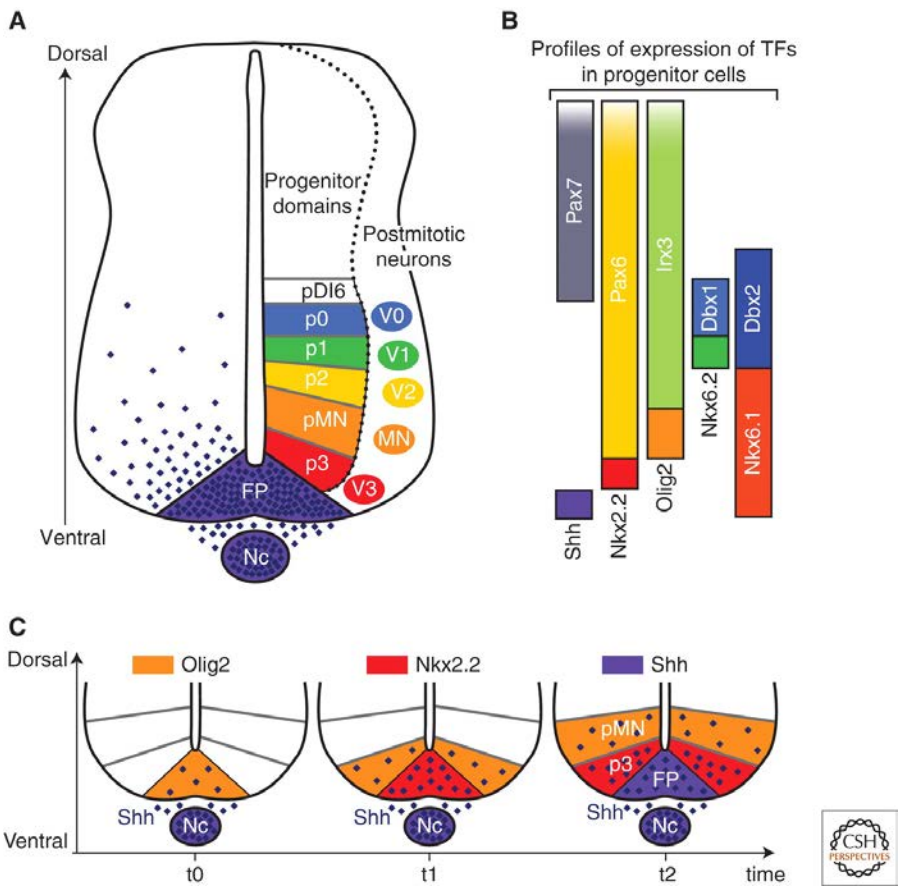


Cusp

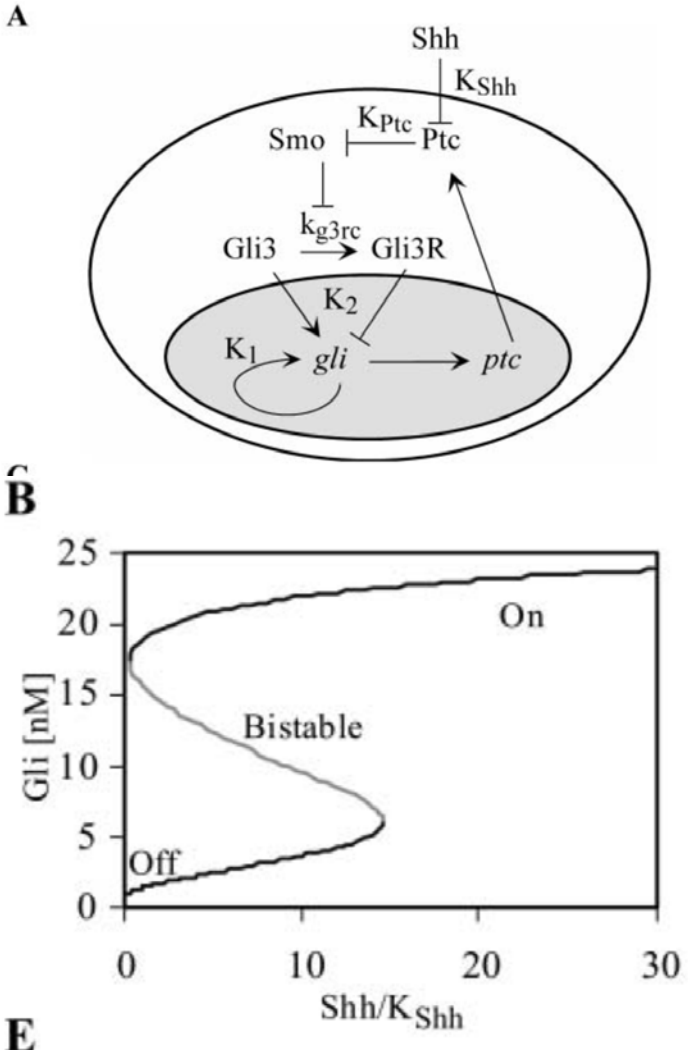
消滅

カタストロフィー理論：フランスの数学者トム（René Thom）は，1960年代に，純粋な数学形式論としてカタストロフィー理論を発展させた。しかし，トムと他の研究者は「それは，イモ虫から蝶への変態や文明の崩壊などに至るまで，突然に起こる不連続性をすべて説明できる」と主張し始め，その結果，1970年代の後半までには，カタストロフィー理論は，興奮のるつぼを経て自滅してしまった。「トムの仕事は，すべてのものに対して何の新しい情報ももたらさない」とある批評家は結論した。

Shh gradientと神経管の分化

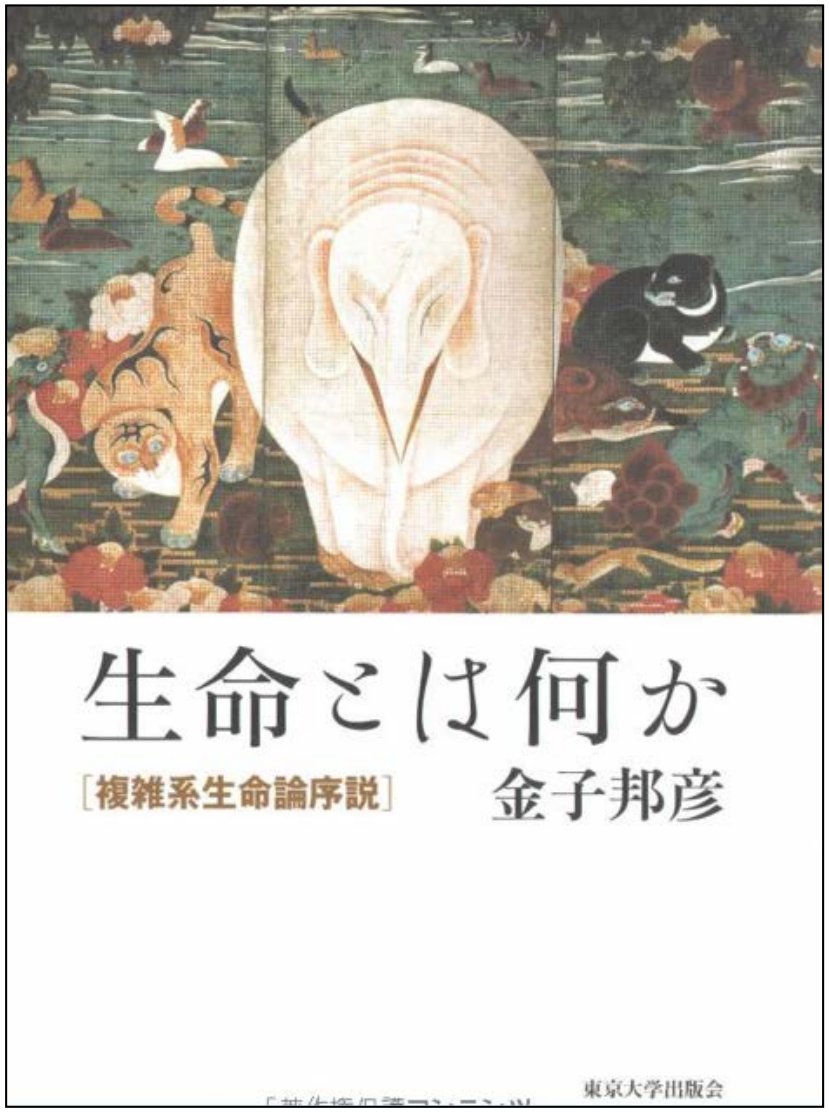


Ribes V , and Briscoe J Cold Spring Harb Perspect Biol 2009;1:a002014



Biophysical Journal Volume 86 May 2004 2748–2757

複雑系：生命を複雑なまま捉える



- 大自由度系
- 90年代にブーム
- 数値計算＋big story

形に弱い

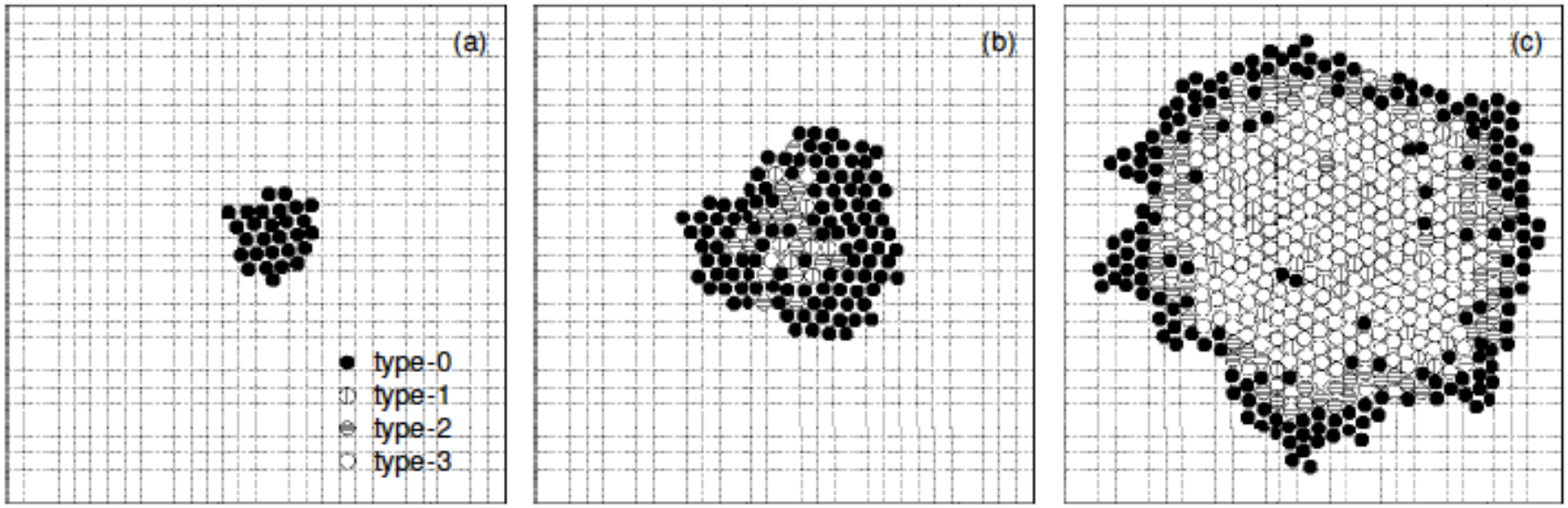
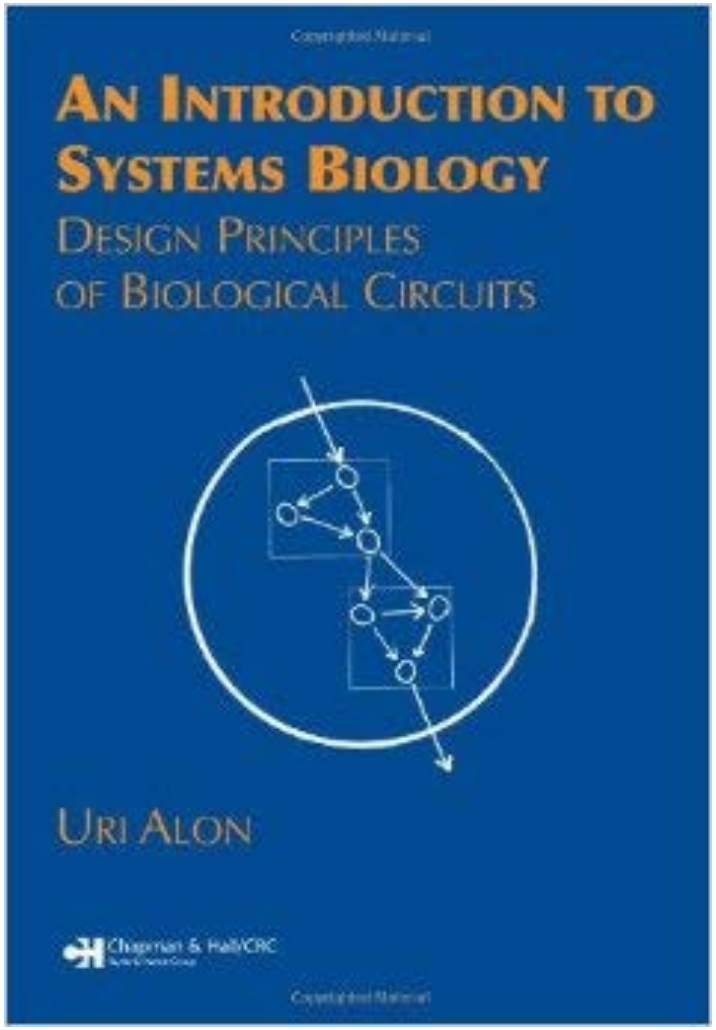


Figure 5. Development of a cell cluster on a two-dimensional grid. Each mark corresponds to a particular cell type determined by differing internal dynamics. The grid indicates the unit of discretization on the diffusive chemicals $C^{(\ell)}(x, y, t)$.

Artificial Life 4: 79–93 (1998)

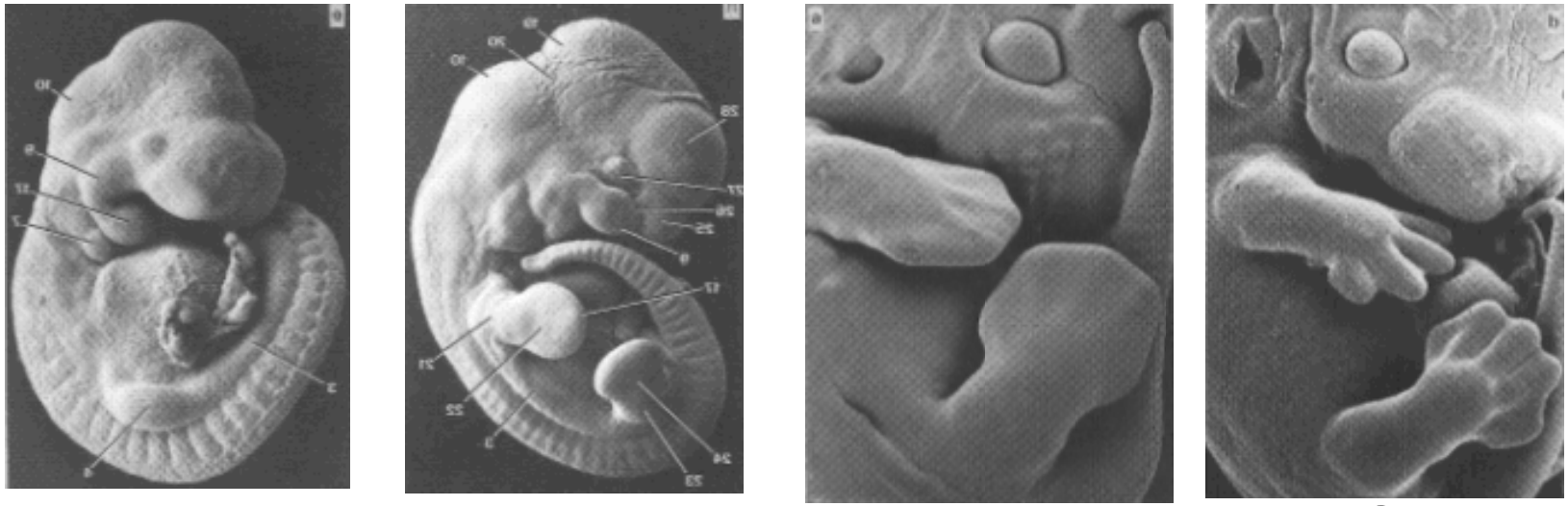
単純な扱いに戻る



- 要素に分割
  （Network motif），
  線形化＞解析
- 普通に活用 (FFLなど)

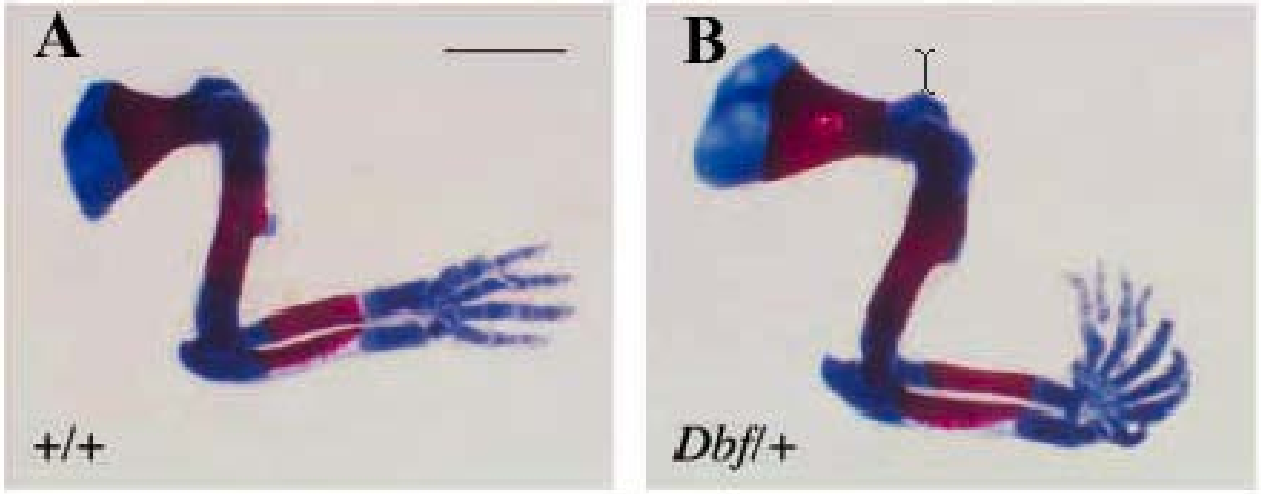
- Turing instability
- Fractal Geometry
- 粒子多体系

肢芽の周期的パターン形成



E9.5　E11.5　E12　E13.5

Atlas of Mouse Development

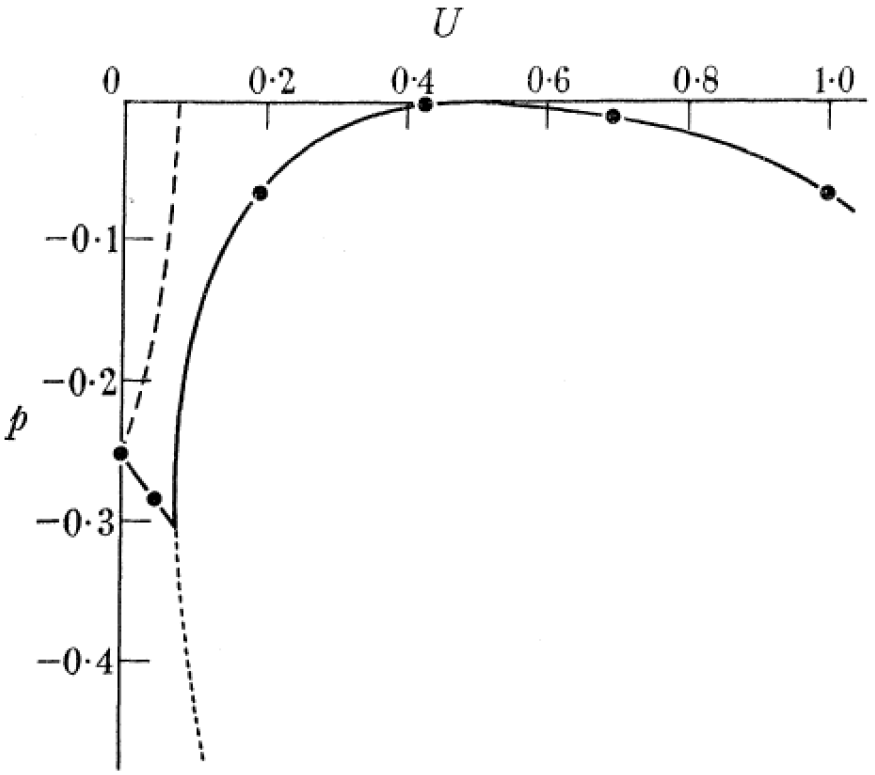


Development 125, 351-357 (1998)

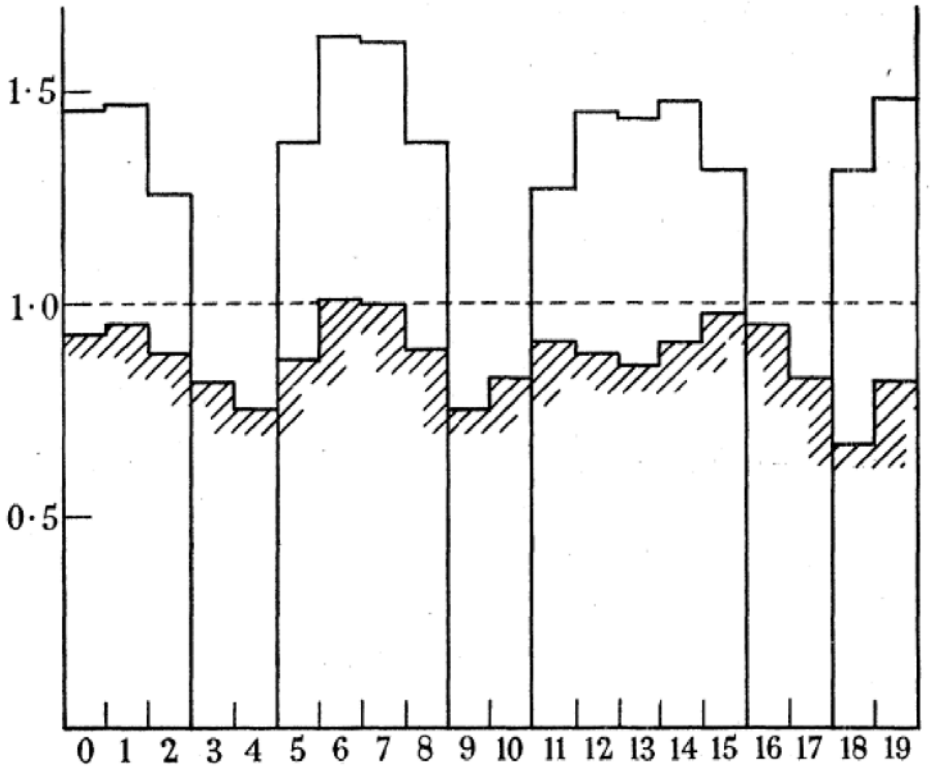
Turing instability (1952)

$$\left.\begin{aligned}\frac{\mathrm{d}x_r}{\mathrm{d}t} &= ax_r + by_r + \mu(x_{r+1} - 2x_r + x_{r-1}),\\ \frac{\mathrm{d}y_r}{\mathrm{d}t} &= cx_r + dy_r + \nu(y_{r+1} - 2y_r + y_{r-1}).\end{aligned}\right\}$$

$$\left.\begin{aligned}X_r &= h + \sum_{s=1}^{N} (A_s\, \mathrm{e}^{p_s t} + B_s\, \mathrm{e}^{p'_s t}) \exp\left[\frac{2\pi i r s}{N}\right],\\ Y_r &= k + \sum_{s=1}^{N} (C_s\, \mathrm{e}^{p_s t} + D_s\, \mathrm{e}^{p'_s t}) \exp\left[\frac{2\pi i r s}{N}\right].\end{aligned}\right\}$$



線形



Gierer-Meinhardt系

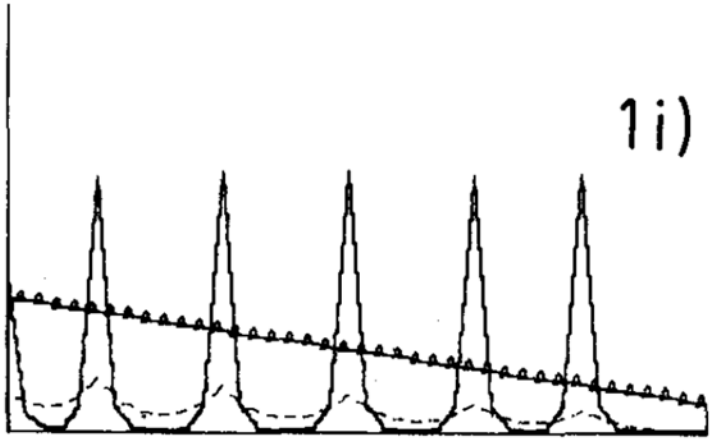
Kybernetik 12, 30—39 (1972)

A Theory of Biological Pattern Formation

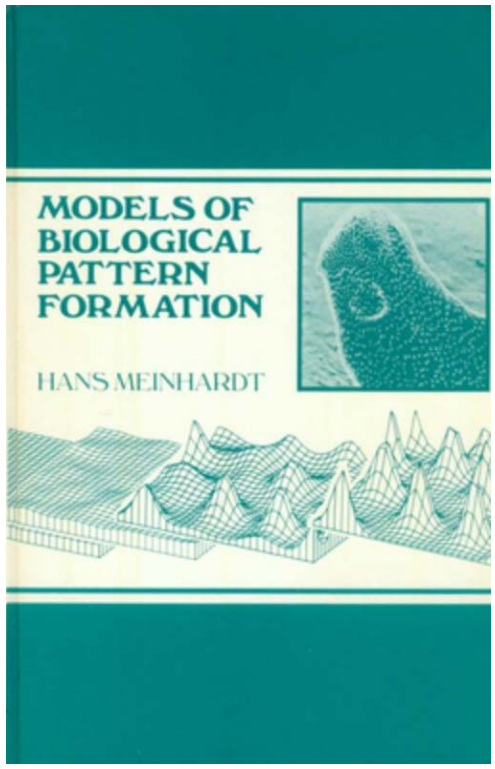
A. Gierer and H. Meinhardt
Max-Planck-Institut für Virusforschung, Tübingen, Germany

$$\frac{\partial a}{\partial t} = \varrho_0 \varrho + c\varrho \frac{a^r}{h^s} - \mu a + D_a \frac{\partial^2 a}{\partial x^2},$$

$$\frac{\partial h}{\partial t} = c' \varrho' \frac{a^t}{h^u} - \nu h + D_h \frac{\partial^2 h}{\partial x^2}.$$



- Activator-inhibitor
- Local positive feedback - global lateral inhibition



パターンの正確性

J. theor. Biol. (1974) **45**, 501–531

How well does Turing's Theory of Morphogenesis work?

JONATHAN BARD† AND IAN LAUDER

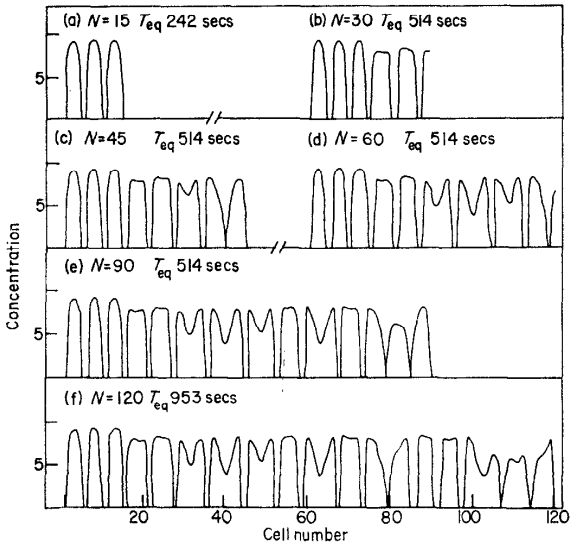
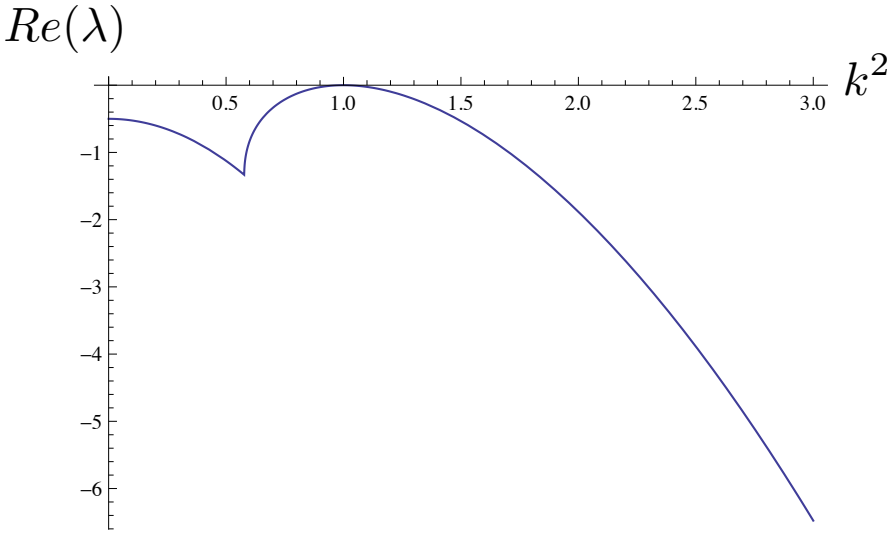
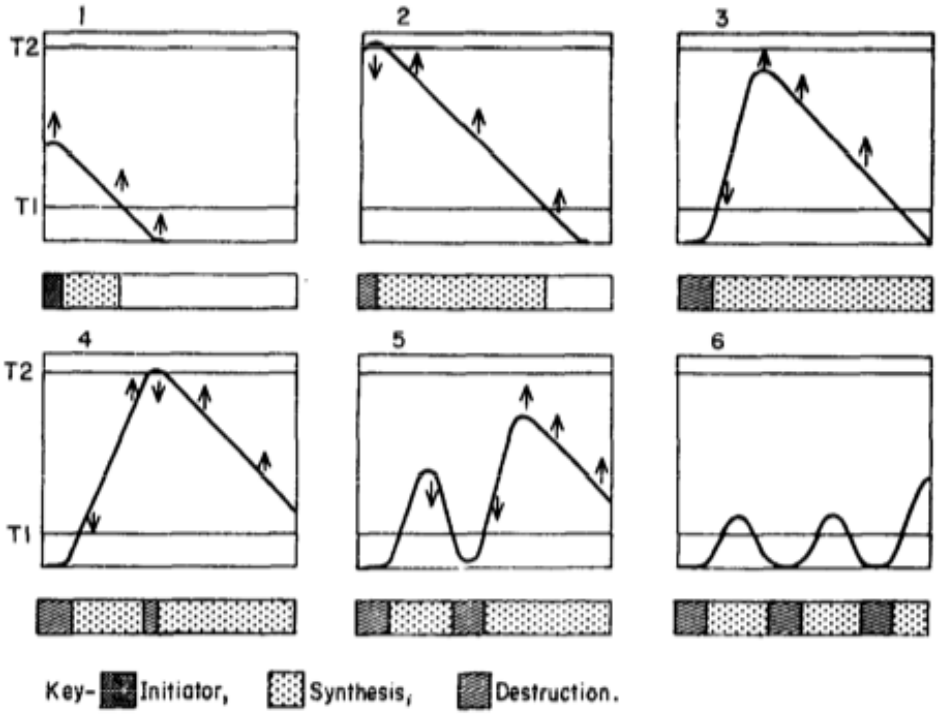


FIG. 4. Turing patterns: the effect of increasing the number of cells in the line. In this and subsequent figures, only the Y morphogen concentration is shown ($S_p = 1{\cdot}0$; $I = 84643$; $S = 0{\cdot}25$).



Ede model



$$[\text{Inactive}] \xrightarrow{[M]>T1} [\text{Synthetic}] \xrightarrow{[M]>T2} [\text{Destructive}]$$

- Iterative specification

J. theor. Biol. (1975) **52,** 199–217

Newman-Frisch model

SCIENCE, VOL. 205, 17 AUGUST 1979

Dynamics of Skeletal Pattern Formation in Developing Chick Limb

Stuart A. Newman and H. L. Frisch

$$\frac{\partial C}{\partial t} = D\nabla^2 C + R(C)$$

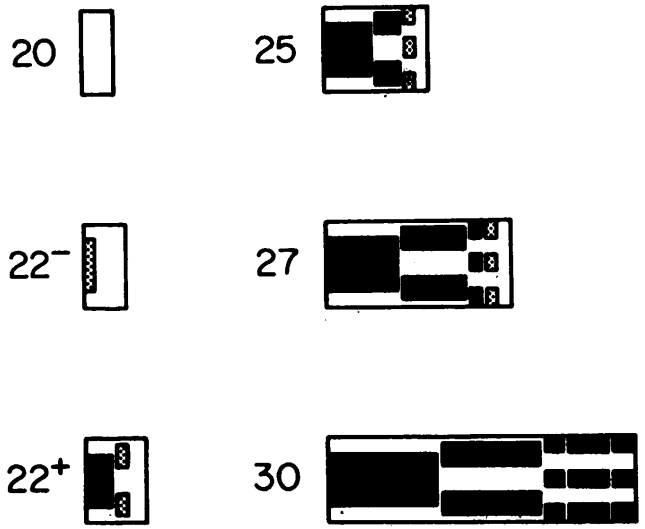


Fig. 6. Patterns of chondrogenesis predicted by the model described in the text at successive stages of development. Elongation of "skeletal elements" is based on empirical measurements (*8*, *10*). Solid black represents cartilage or precartilage condensation; stippling represents hypothetical distribution of substance M in competent tissue preceding overt chondrogenesis. Hamburger-Hamilton stages (*33*) to which the model stages correspond are indicated by numbers.

批判

J. theor. Biol. (1986) **121**, 505–508

On the Newman–Frisch Model of Limb Chondrogenesis

H. G. Othmer†

Dept of Mathematics, University of Utah, Salt Lake City, Utah 84112, *U.S.A.*

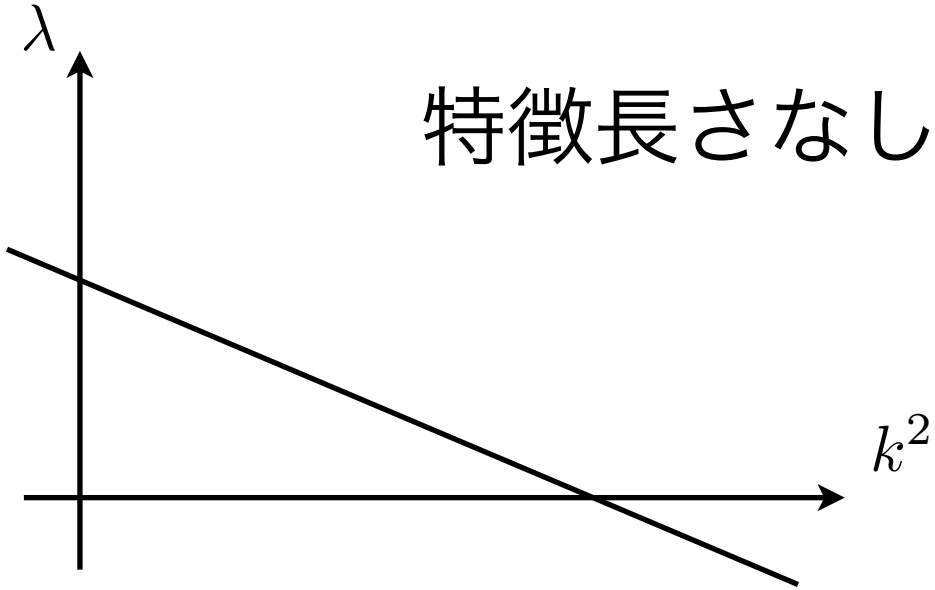
(*Received* 1 *February* 1986)

I変数では安定な構造ができない

$$u' = au + d\Delta u$$

$$u = u_0 e^{\lambda t} sinkx$$

$$\lambda = a - k^2 d$$



特徴長さなし

修正

J. theor. Biol. (1988) **134,** 183–197

On the Stationary State Analysis of Reaction-Diffusion Mechanisms for Biological Pattern Formation

STUART A. NEWMAN,

Department of Anatomy, New York Medical College, Valhalla, New York 10595, *U.S.A.*

H. L. FRISCH

Department of Chemistry, State University of New York at Albany, Albany, New York 12222, *U.S.A.*

AND

J. K. PERCUS

Courant Institute of Mathematical Sciences and Department of Physics, New York University, New York 10012, *U.S.A.*

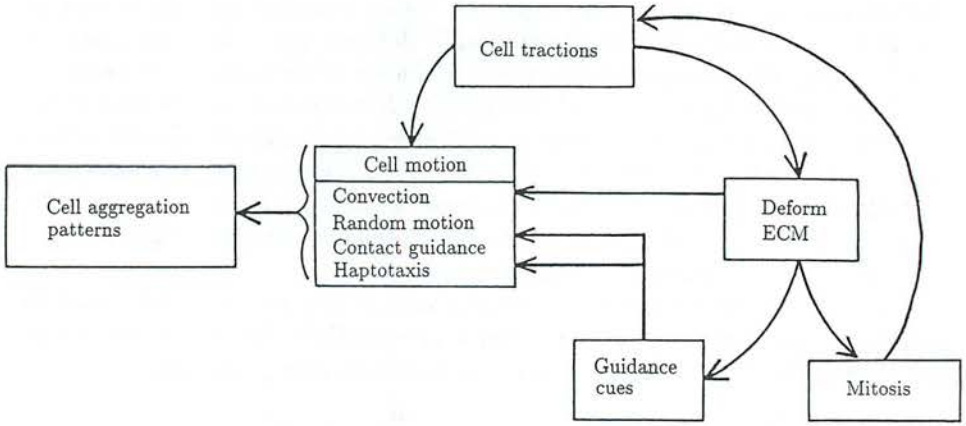
(*Received* 20 *October* 1987, *and in revised form* 25 *March* 1988)

$$\frac{\partial C}{\partial t} = R(C, I) + D\nabla^2 C$$

$$\frac{\partial I}{\partial t} = F(C - \gamma I).$$

- ２変数モデルへ
- 以後実験的検証

Mechanochemical model



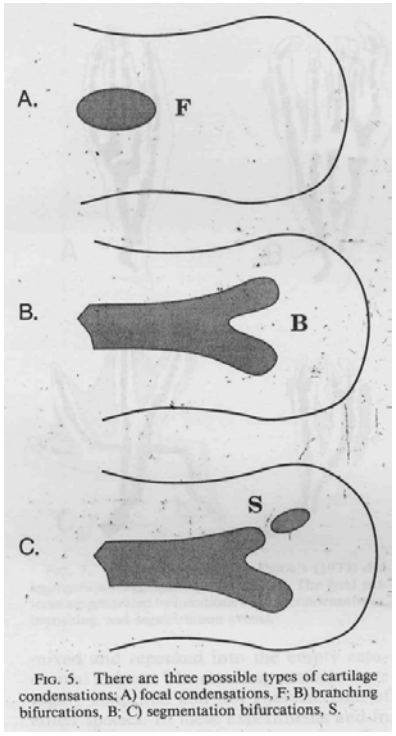
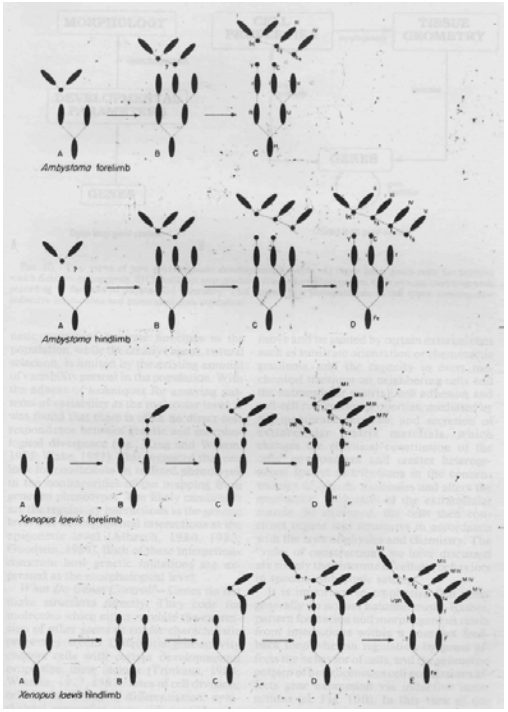


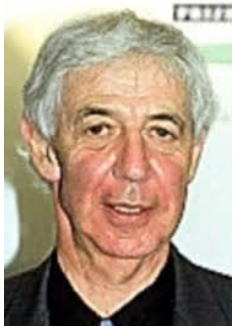
FIG. 5. There are three possible types of cartilage condensations; A) focal condensations, F; B) branching bifurcations, B; C) segmentation bifurcations, S.



Evolution, 42(5), 1988, 862–884

J. Murray
"Mathematical Biology"

Chemotaxis部分しか使っていない



実験により否定？

Development 109, 961–966 (1990)
Printed in Great Britain © The Company of Biologists Limited 1990

Double anterior chick limb buds and models for cartilage rudiment specification

LEWIS WOLPERT and AMATA HORNBRUCH

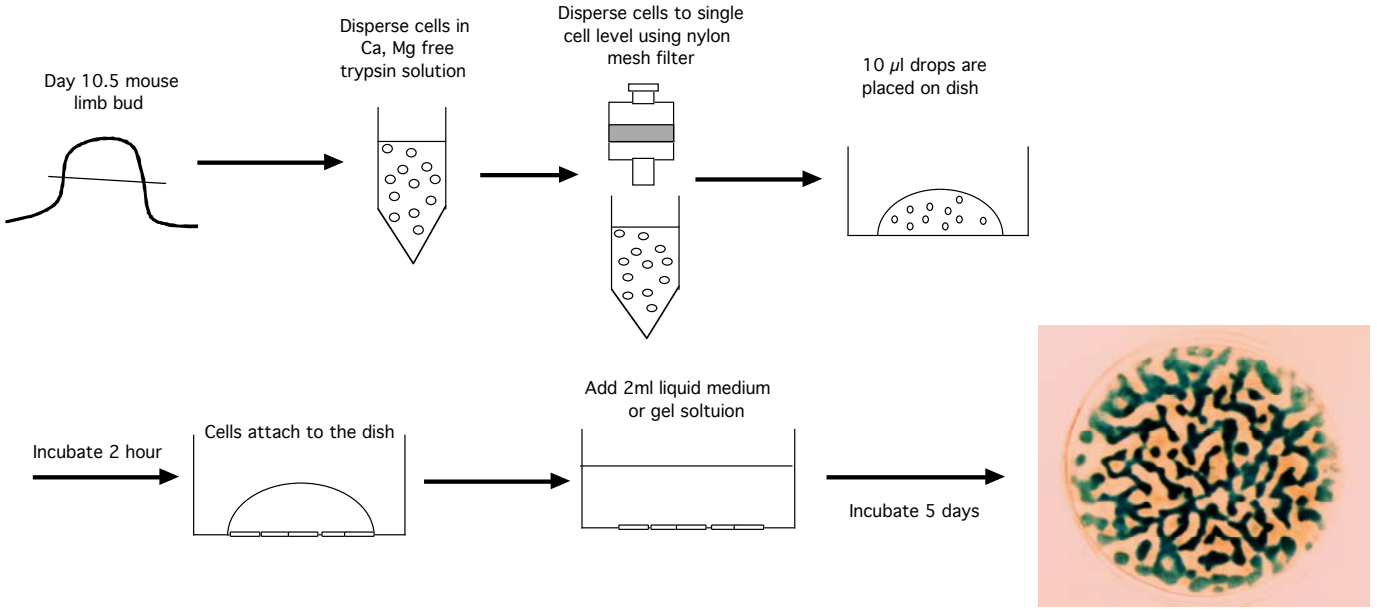
Department of Anatomy and Developmental Biology, University College and Middlesex School of Medicine, Windeyer Building, Cleveland Street, London, W1P 6DB, UK

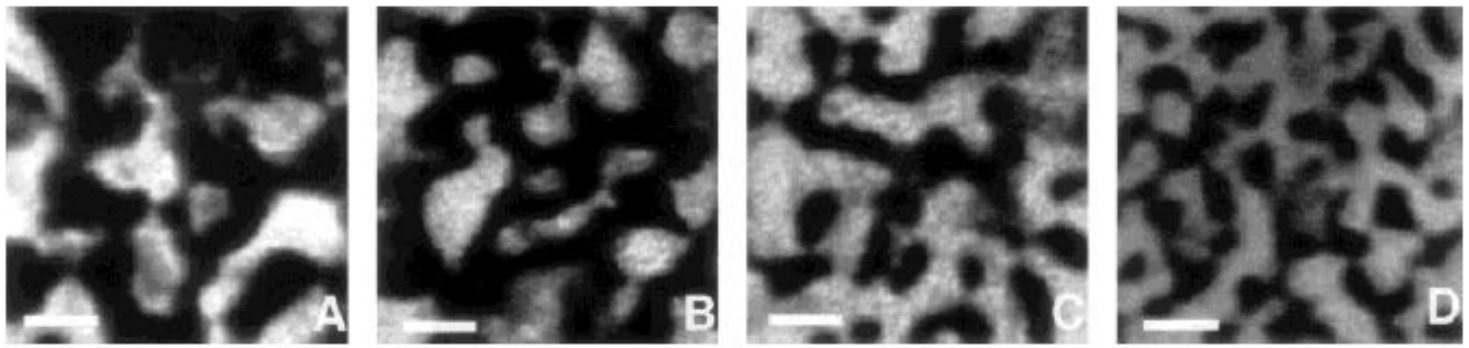
Summary

Most models for the specification of the skeletal elements in the developing limb bud are based on a chemical specification well before overt cartilage differentiation. By contrast, a physico-mechanical model proposes that the process of condensation – an early feature of cartilage differentiation – is itself the basis for patterning the elements. The models thus make quite different predictions as to when the rudiments are specified. Double anterior limb buds have been constructed at stages earlier than condensation, with the expectation that, if specification of the humerus occurs before cartilage condensation, then limbs containing two humeri should develop, since the presumptive humerus lies largely in the anterior region. The development of anterior and posterior parts, on their own, was in general, consistent with the fate map; both developed a humerus that was thinner than normal. Double anterior limbs developed two humeri in 28 % of cases and a much thicker humerus in 39 %. These results strongly support models based on an early specification of limb rudiments and cannot be accounted for by the physical model. Double anterior limbs in which the two parts were from different stages, developed such that a digit 3 could lie adjacent to the radius, giving further striking evidence for early specification and local autonomy of development.

Key words: cartilage, chick, limb, model, specification.

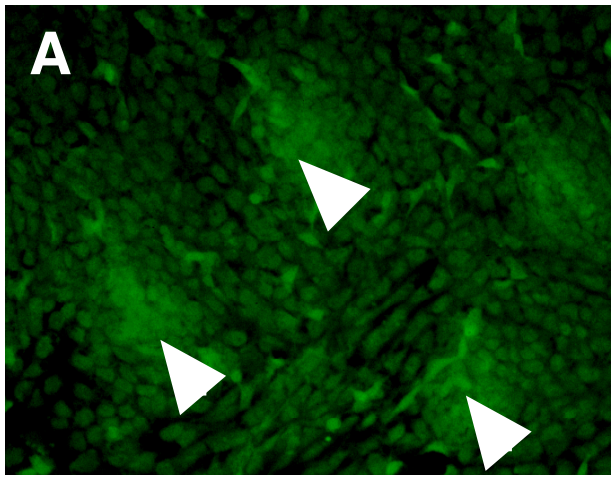
周辺環境の固さと パターンの特徴長さ

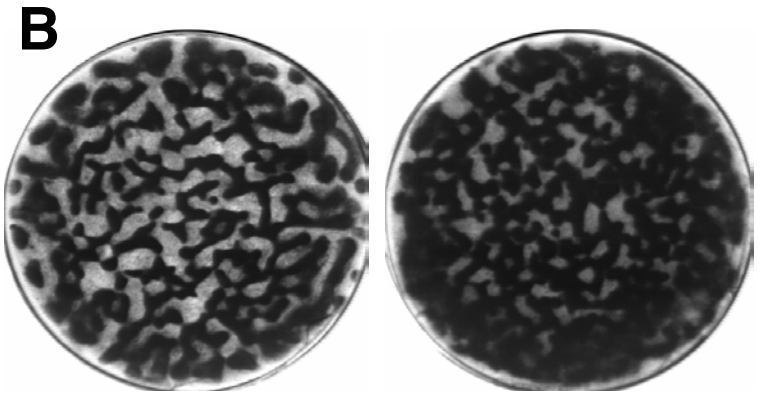


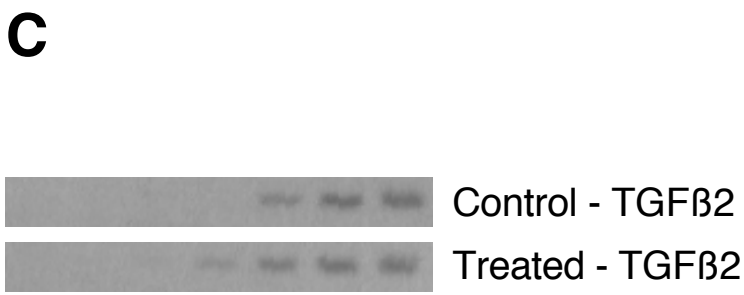


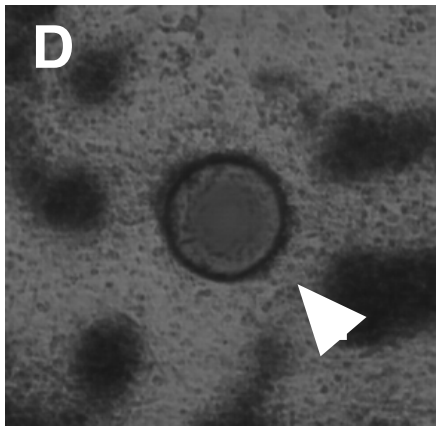
Miura & Shiota, 2000

TGFb2 as an activator









Miura & Shiota, Dev Dyn 217: 241- (2000)

J. Sharpe

2010 発生生物学会（京都）

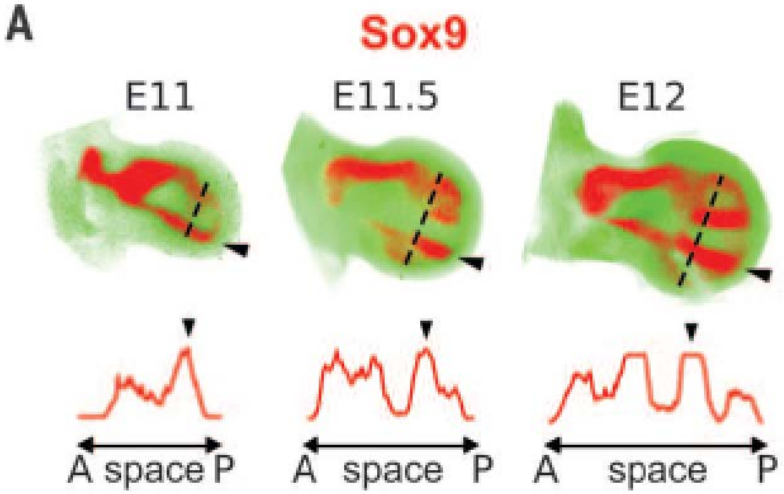
MODELING DIGITS

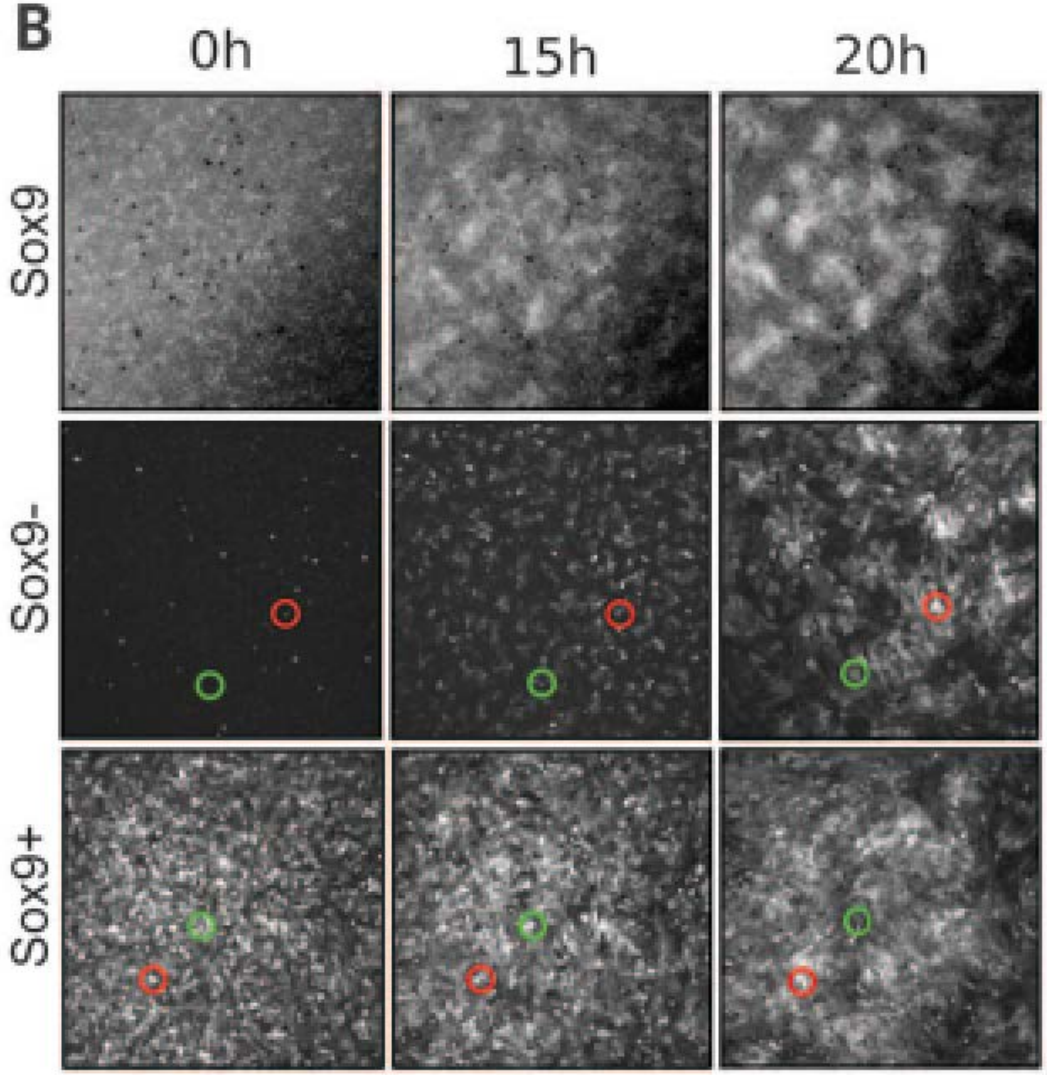
Digit patterning is controlled by a Bmp-Sox9-Wnt Turing network modulated by morphogen gradients

J. Raspopovic,[1*] L. Marcon,[1*] L. Russo,[1] J. Sharpe[1,2]†

During limb development, digits emerge from the undifferentiated mesenchymal tissue that constitutes the limb bud. It has been proposed that this process is controlled by a self-organizing Turing mechanism, whereby diffusible molecules interact to produce a periodic pattern of digital and interdigital fates. However, the identities of the molecules remain unknown. By combining experiments and modeling, we reveal evidence that a Turing network implemented by Bmp, Sox9, and Wnt drives digit specification. We develop a realistic two-dimensional simulation of digit patterning and show that this network, when modulated by morphogen gradients, recapitulates the expression patterns of *Sox9* in the wild type and in perturbation experiments. Our systems biology approach reveals how a combination of growth, morphogen gradients, and a self-organizing Turing network can achieve robust and reproducible pattern formation.

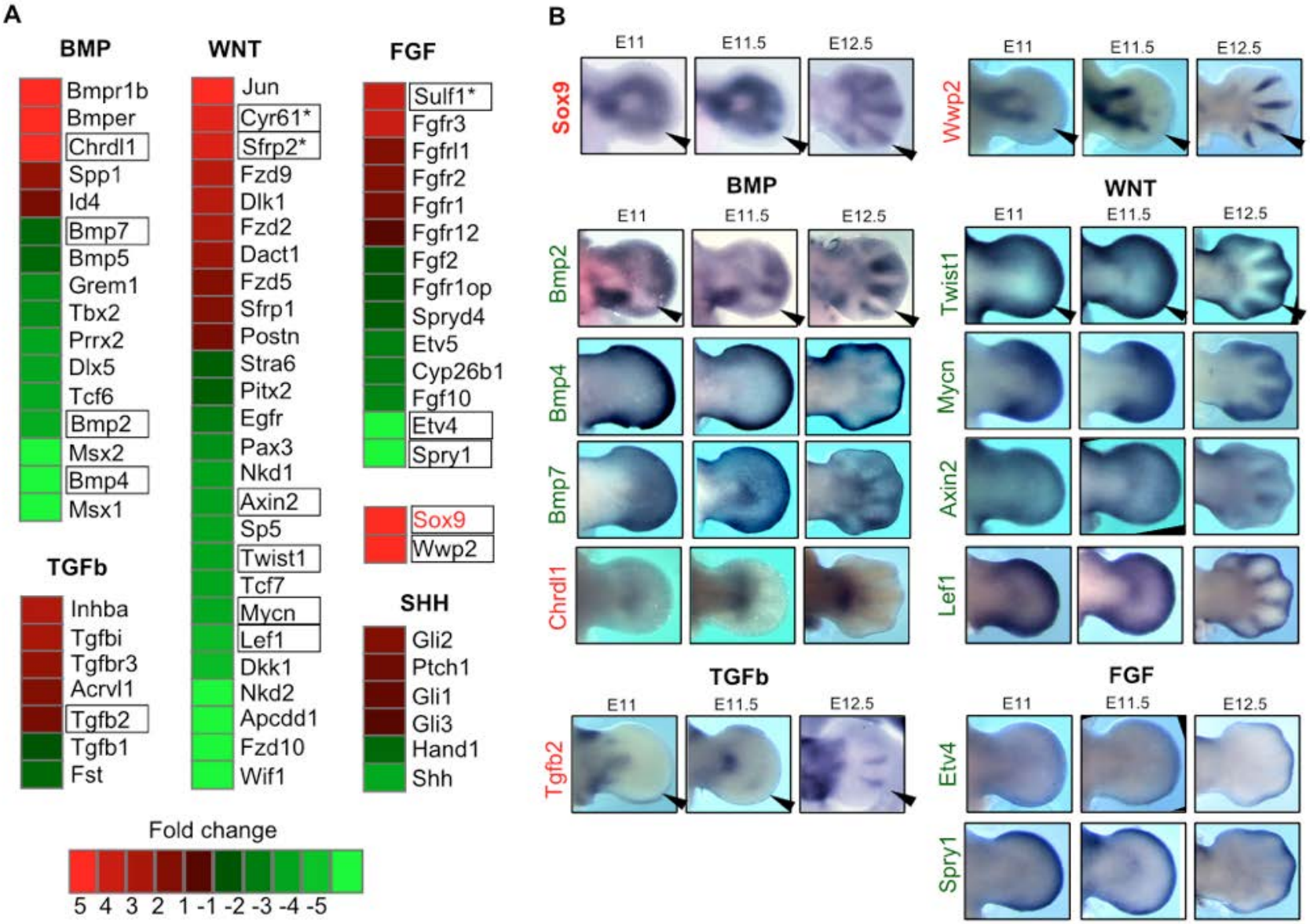
自発的パターン形成





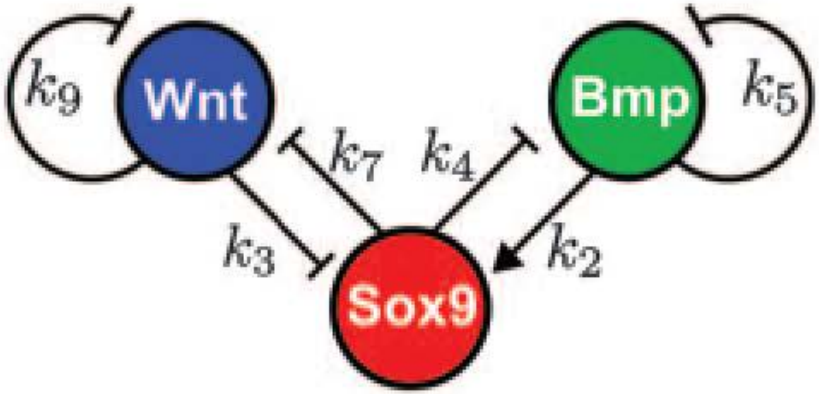
- Sox9(+)細胞のみを分離して培養してもパターンができる
- Sox9(-) 細胞との遺伝子発現の差をスクリーニング

候補となる遺伝子のスクリーニング



- TGFb2は下流だった…

モデル

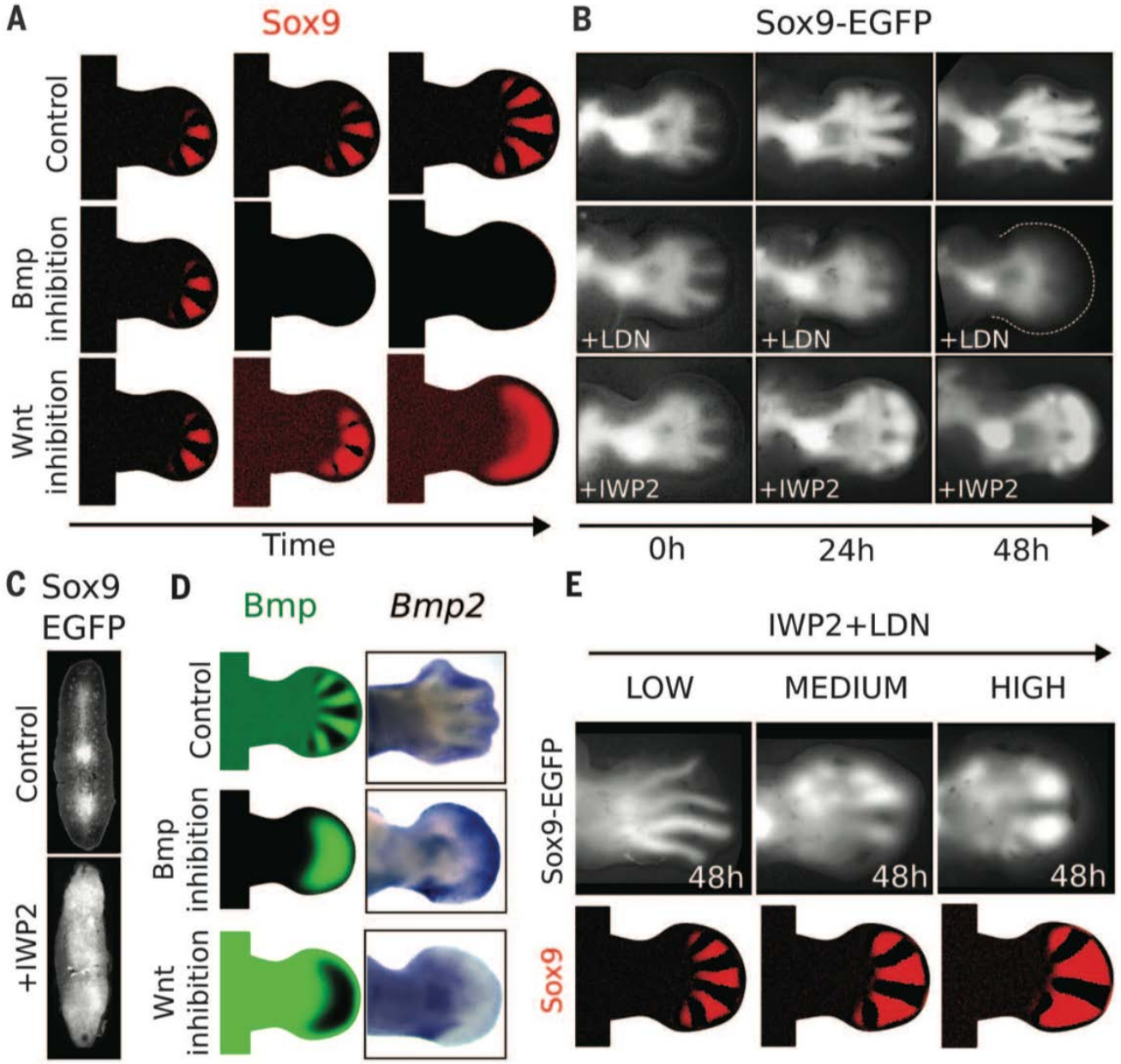


$$\frac{\partial sox9}{\partial t} = \alpha_{sox9} + k_2 bmp - k_3 wnt - sox9^3$$

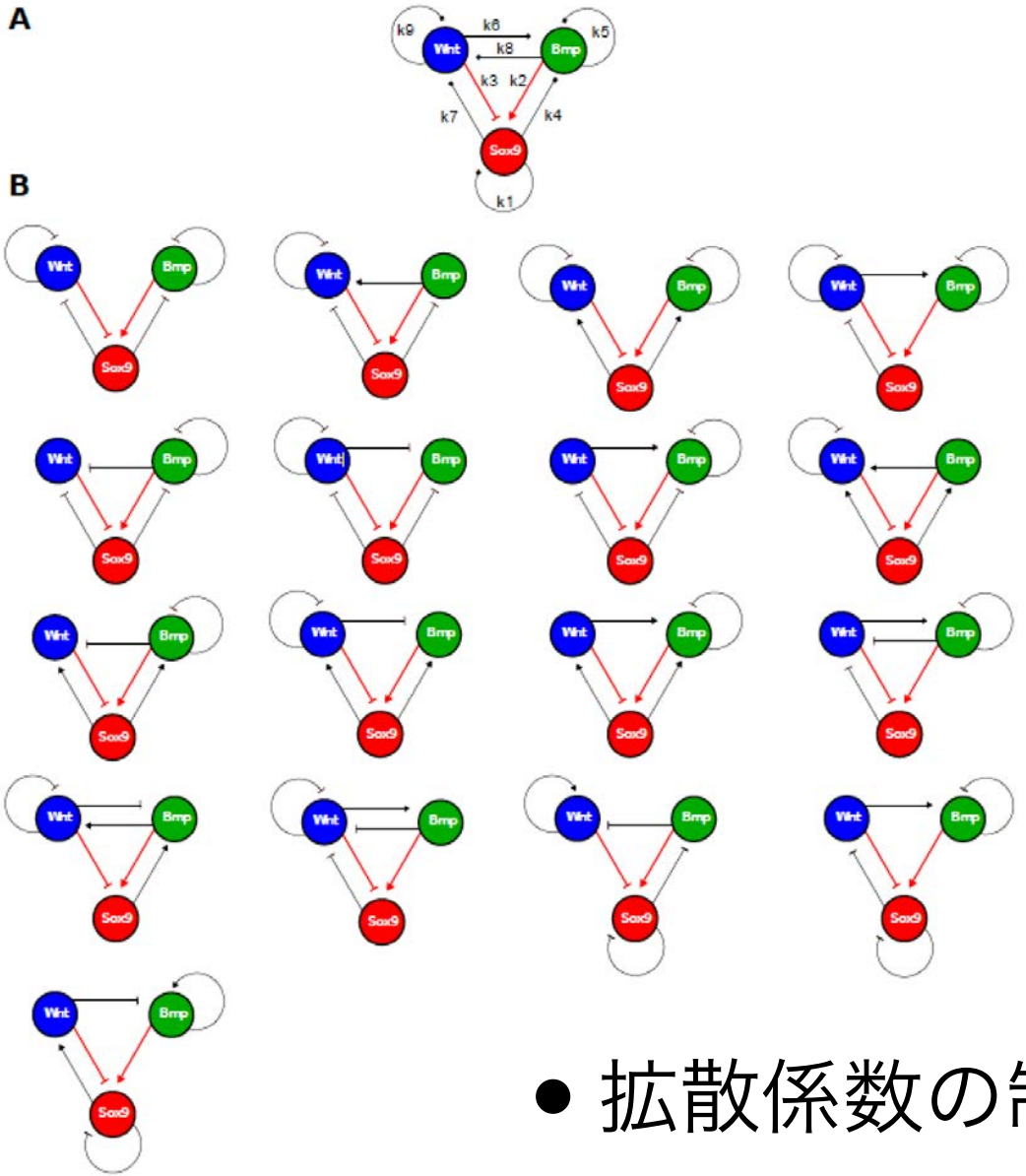
$$\frac{\partial bmp}{\partial t} = \alpha_{bmp} - k_4 sox9 - k_5 bmp + d_b \nabla^2 bmp$$

$$\frac{\partial wnt}{\partial t} = \alpha_{wnt} - k_7 sox9 - k_9 wnt + d_w \nabla^2 wnt$$

実験的なperturbation



3変数のTuring系の全探索

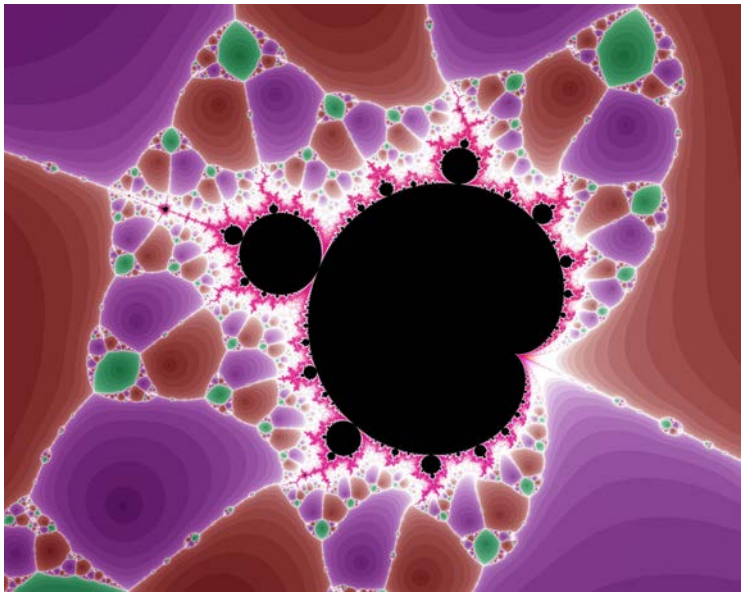


- 拡散係数の制約なし

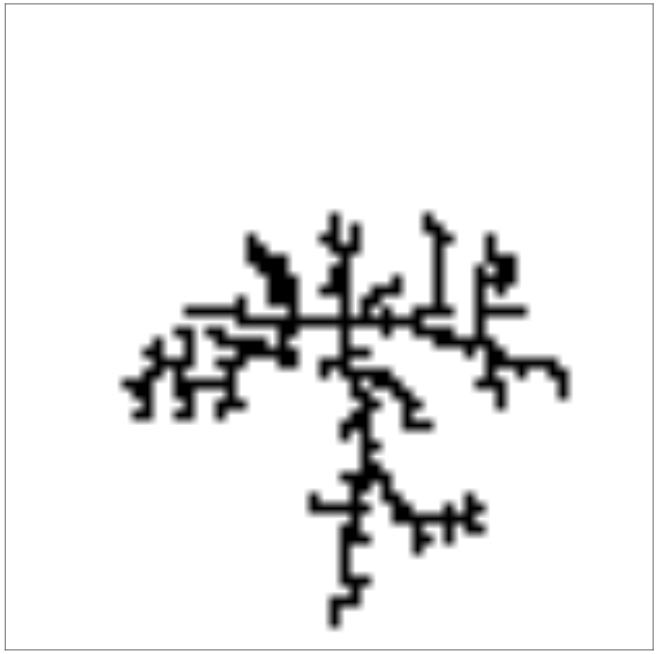
Still open problem

- 「三浦さん、あんな論文なんで通ったんですか！」（匿名S）
- Wnt側の証拠が弱い（mRNAの空間分布が一様＋そもそも軟骨分化ではあまりmajorなプレイヤーではない）
- 拡散係数の差は計測できるのでは？

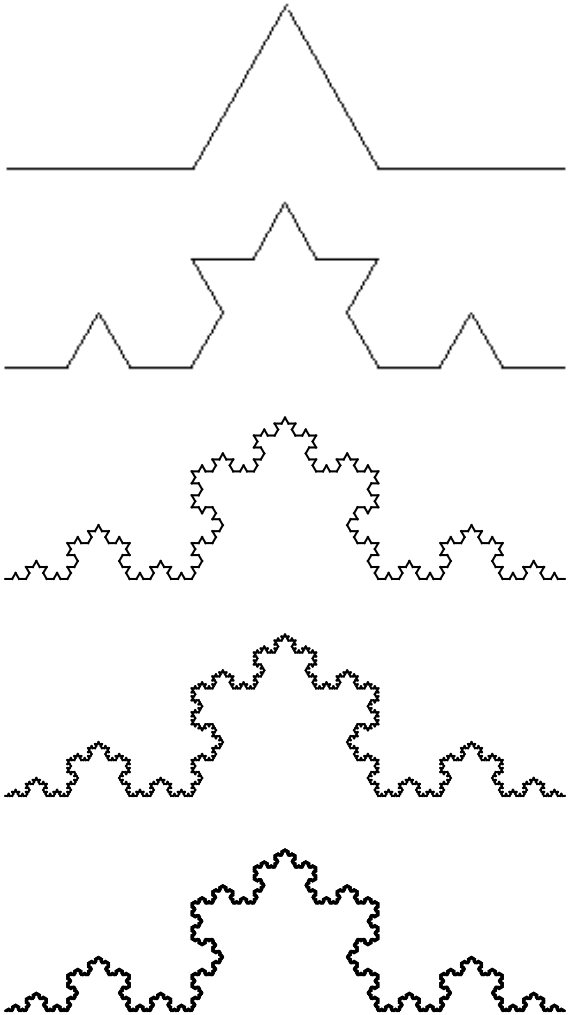
Fractal geometry



Mandelbrot set

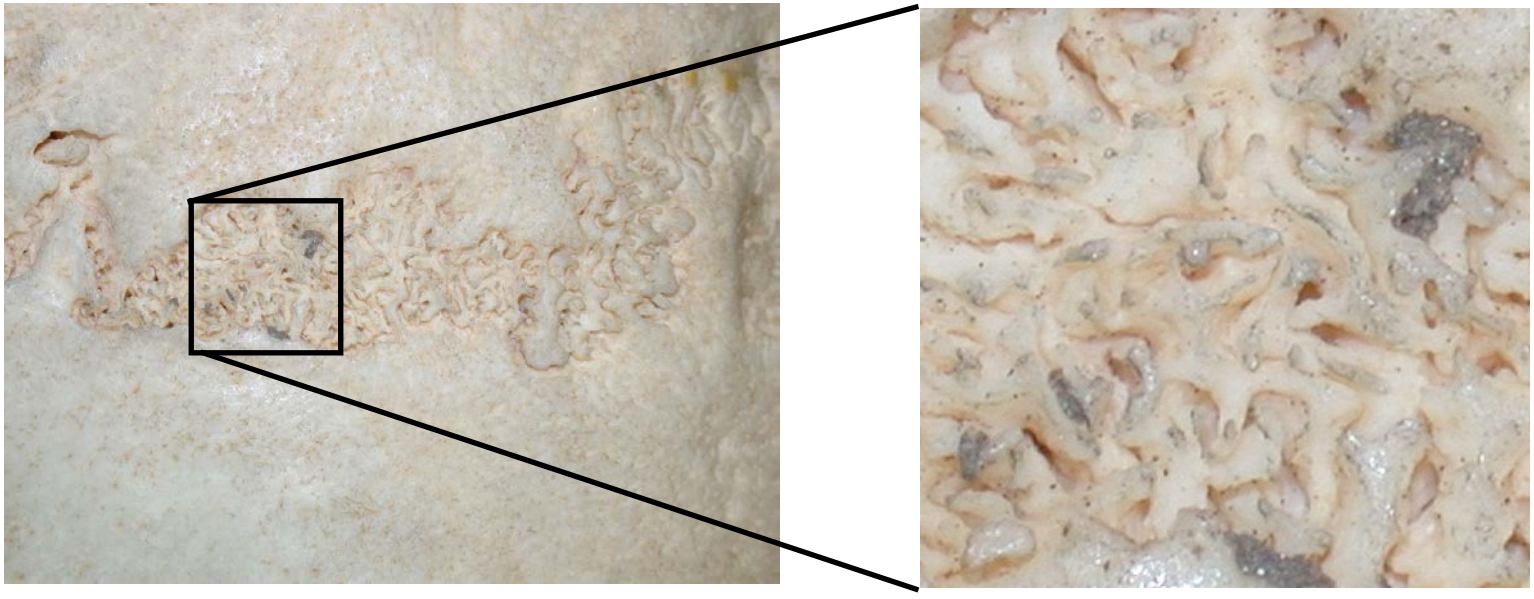


DLA



Koch curve

縫合線とフラクタル



Okajimas Folia Anat. Jpn., 64(1): 39–46, May 1987

Are There Any Regularities in Cranial Sutures ?

By

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Department of Anatomy, University of Tokyo
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縫合線とフラクタル

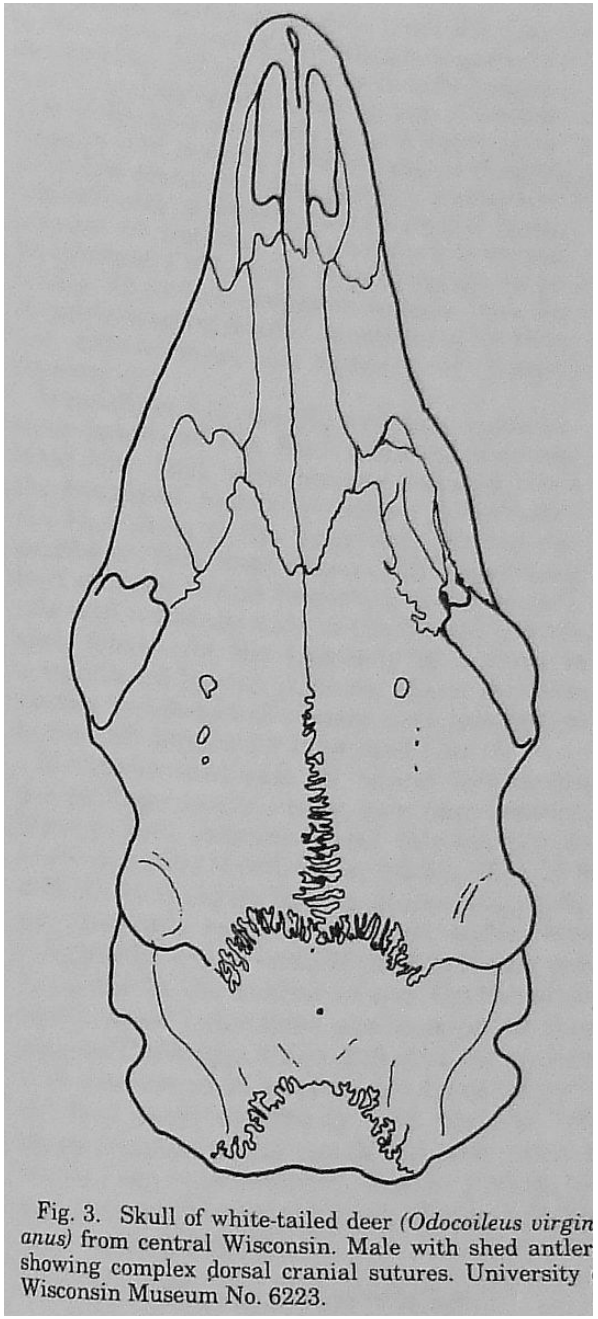


Fig. 3. Skull of white-tailed deer *(Odocoileus virgin anus)* from central Wisconsin. Male with shed antler showing complex dorsal cranial sutures. University Wisconsin Museum No. 6223.

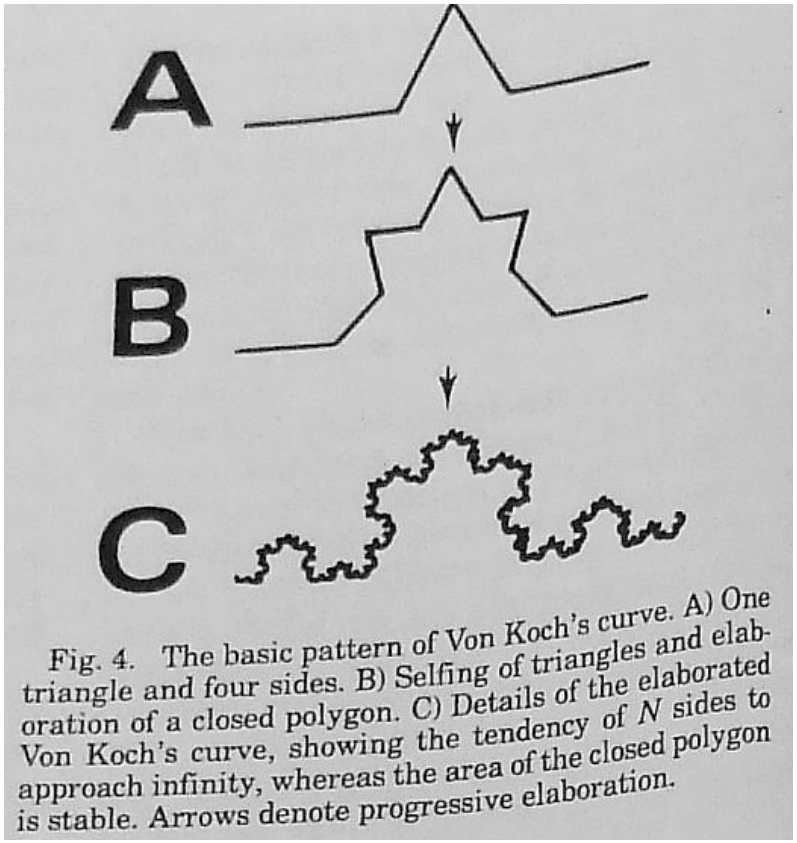
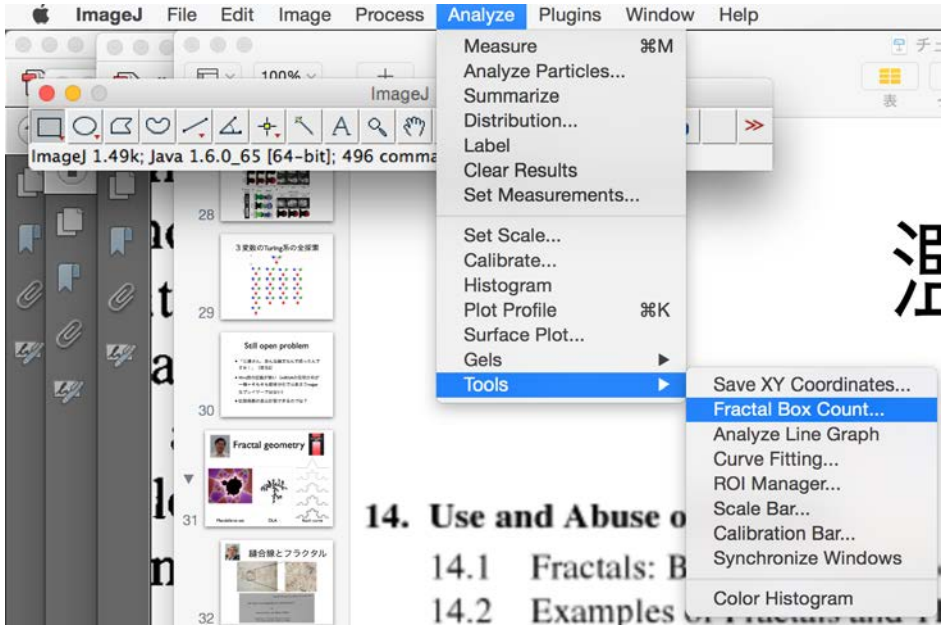


Fig. 4. The basic pattern of Von Koch's curve. A) One triangle and four sides. B) Selfing of triangles and elaboration of a closed polygon. C) Details of the elaborated Von Koch's curve, showing the tendency of N sides to approach infinity, whereas the area of the closed polygon is stable. Arrows denote progressive elaboration.

J. Morphol. 185. 285- (1985)

濫用



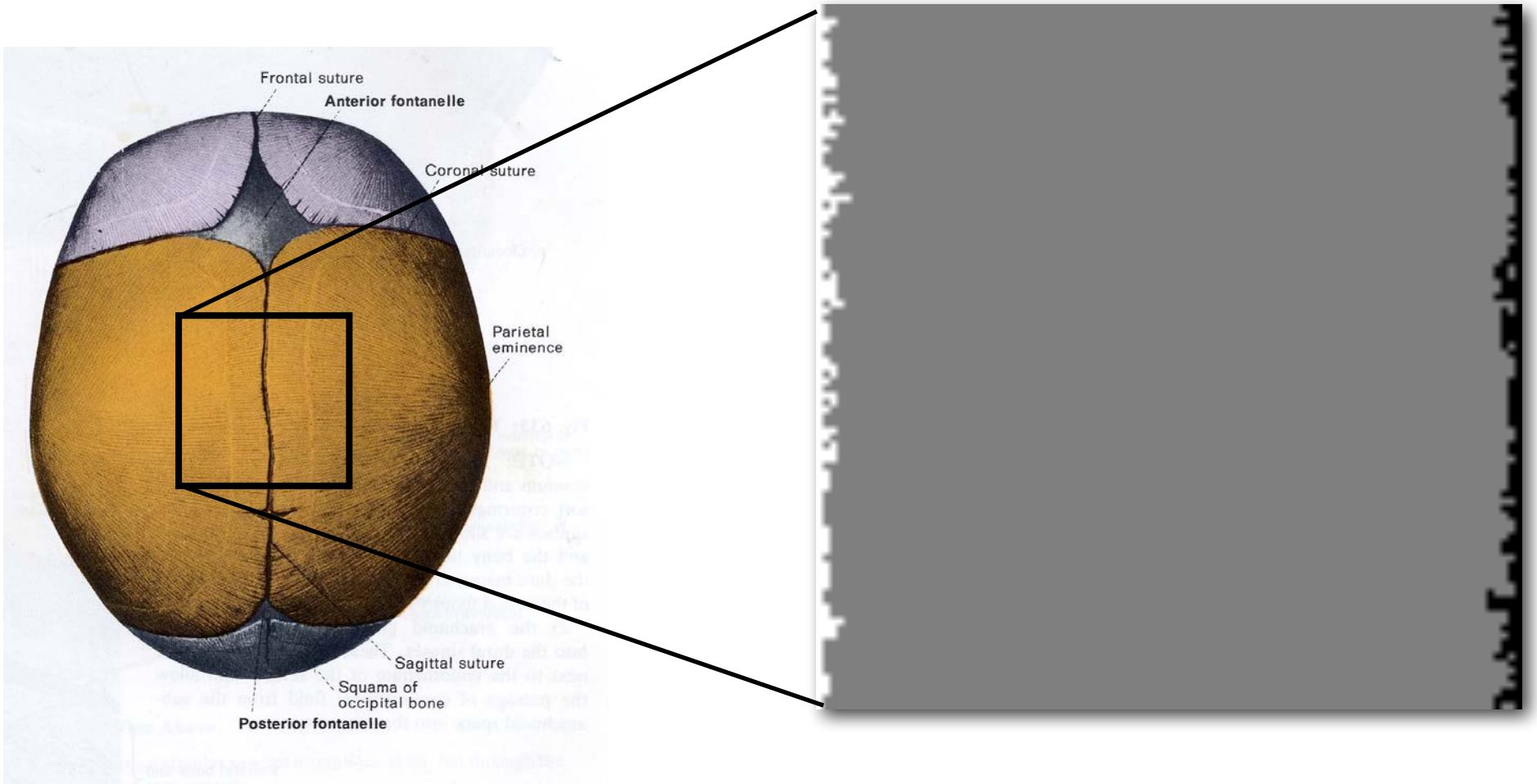
- Box count で計測が簡単にできる＞測って「フラクタルです」と主張するだけの論文量産

14. Use and Abuse of Fractals **484**

14.1 Fractals: Basic Concepts and Biological Relevance 484
14.2 Examples of Fractals and Their Generation 487
14.3 Fractal Dimension: Concepts and Methods of Calculation 490
14.4 Fractals or Space-Filling? 496

Murray Mathematical Biology, 2nd ed.

Eden 衝突モデル

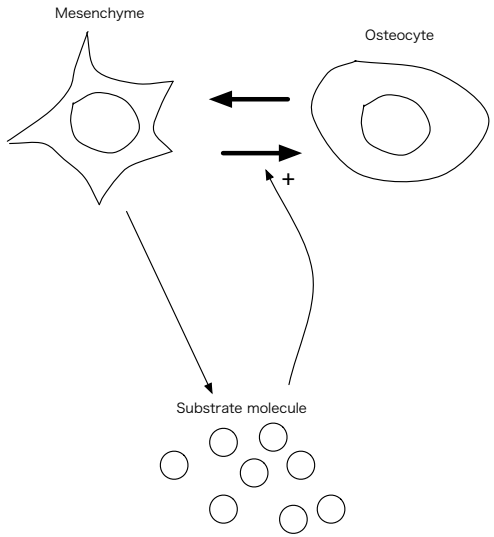


Prof S. Miyajima, FORMA 19, 197-205 (2004)

反応拡散＋時間依存パラメータ

u: 組織の分化度

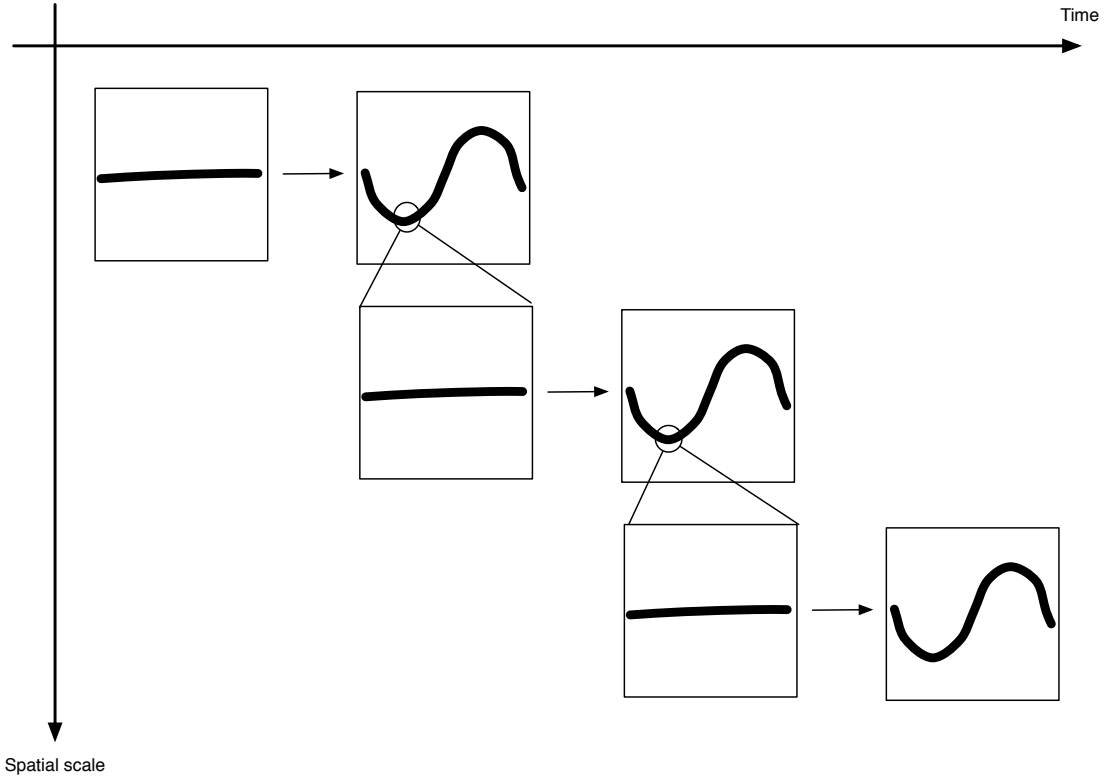
v: 基質因子



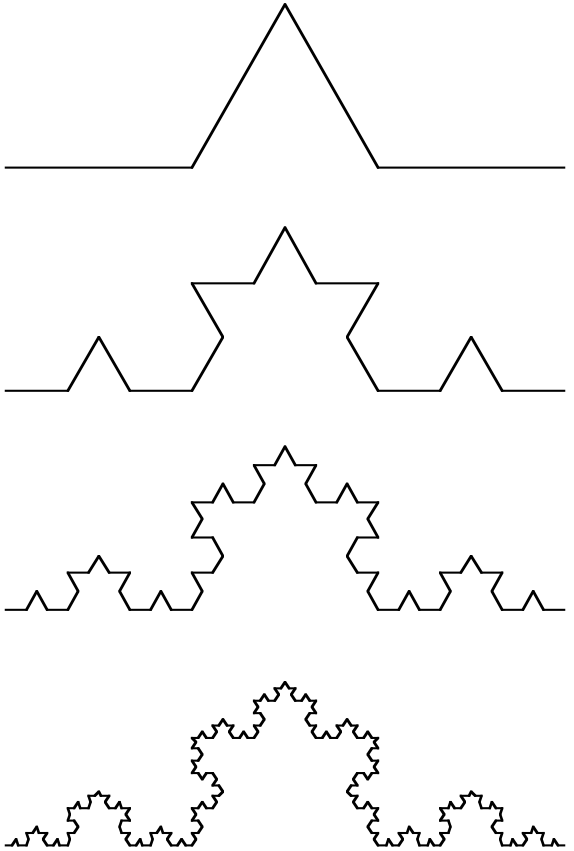
$$
\begin{aligned}
u' &= u - u^3 + a_1 v + a_0 + h(t)\Delta u \\
v' &= \epsilon(-u - v) + h(t)\delta\Delta v
\end{aligned}
$$

Miura et al., 2009

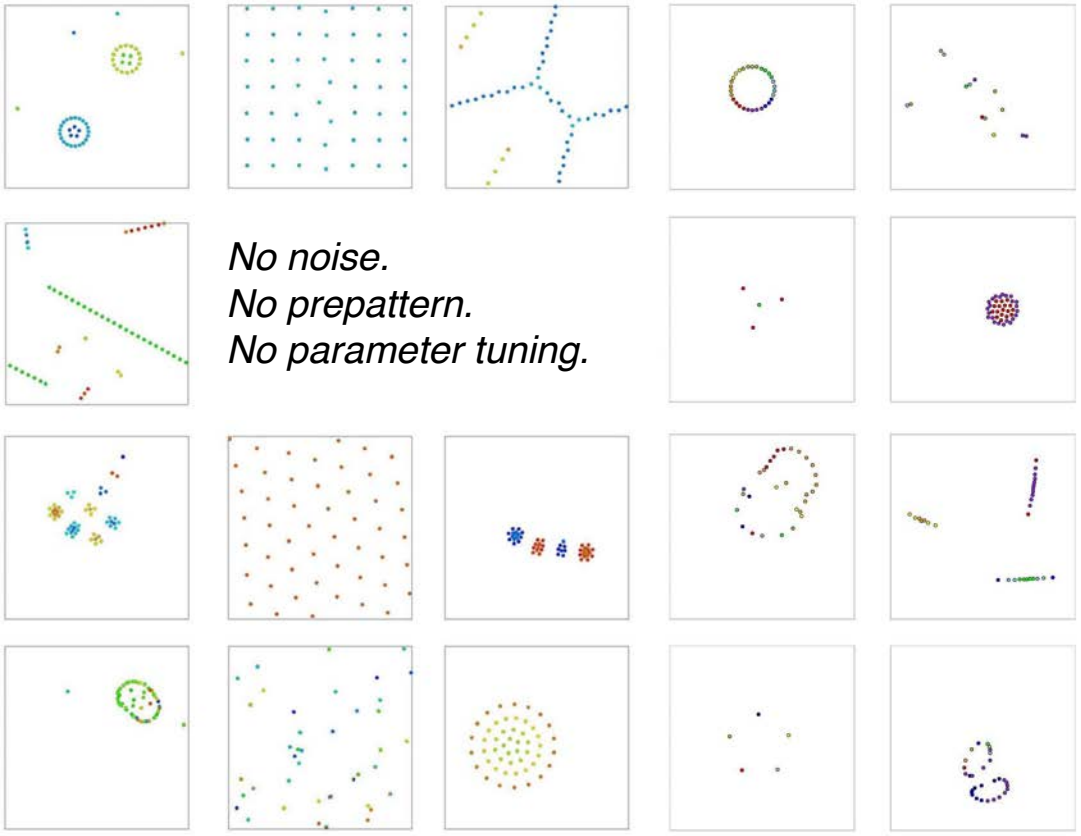
直感的説明



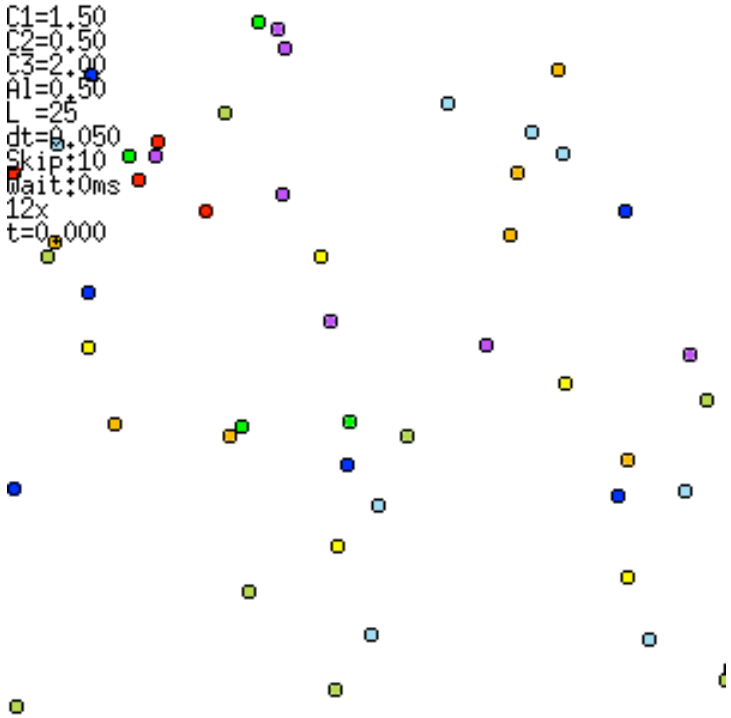
Koch 曲線



Swarm oscillators

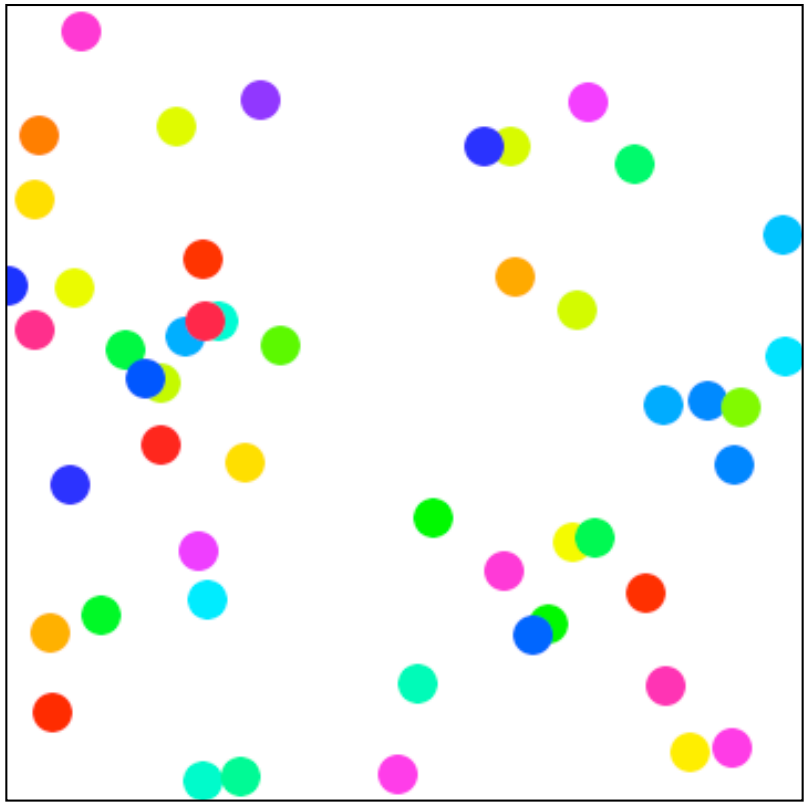


No noise.
No prepattern.
No parameter tuning.



PRL **99,** 134103 (2007)

Mathematicaで実装



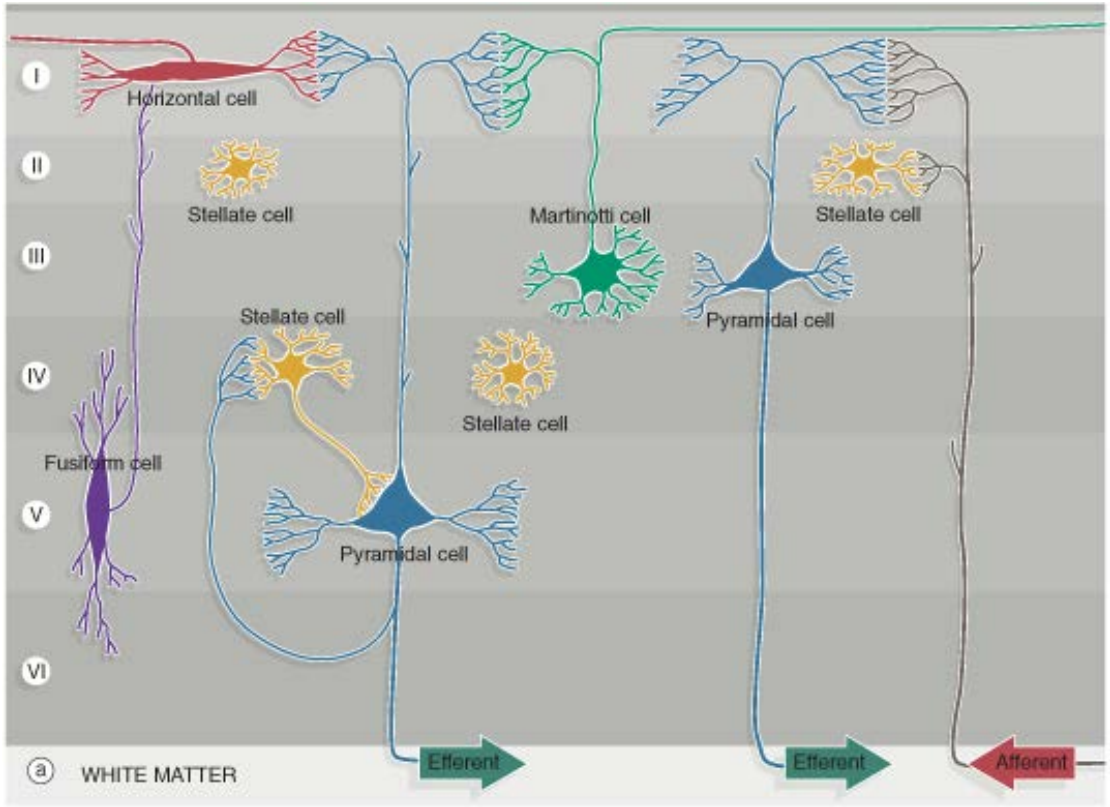
$$\dot{\psi}_i(t) = \sum_{j \neq i} e^{-|\boldsymbol{R}_{ji}|} \sin(\Psi_{ji} + \alpha|\boldsymbol{R}_{ji}| - c_1),$$

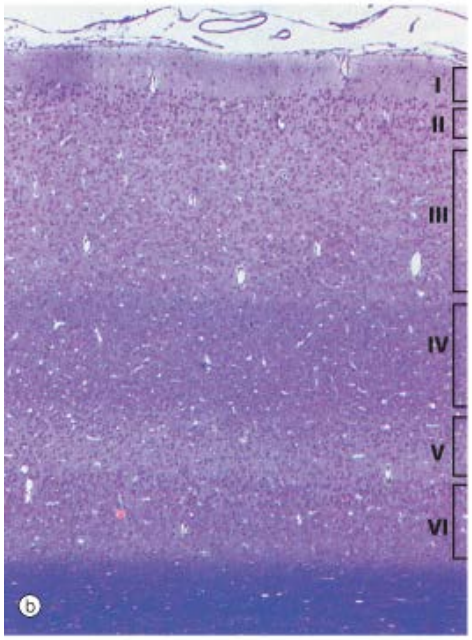
$$\dot{\boldsymbol{r}}_i(t) = c_3 \sum_{j \neq i} \hat{\boldsymbol{R}}_{ji} e^{-|\boldsymbol{R}_{ji}|} \sin(\Psi_{ji} + \alpha|\boldsymbol{R}_{ji}| - c_2),$$

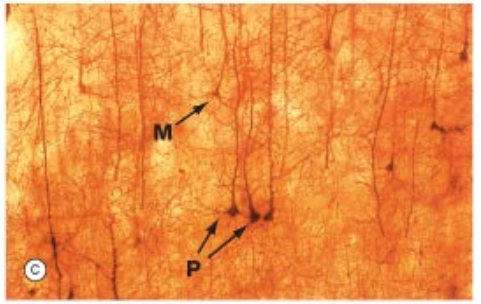
```
n = 50; L = 25; c1 = 1.5; c2 = 0.5; c3 = 2.0; α = 0.5; dt = 0.05;

ψ = Table[Random[Real, 2 Pi], {n}];
r = Table[{Random[Real, L], Random[Real, L]}, {n}];

dPsi[psi_, r_, i_] :=
  Sum[Exp[-Norm[r[[j]] - r[[i]]]]
     Sin[psi[[j]] - psi[[i]] + α Norm[r[[j]] - r[[i]]] - c1] , {j, 1, n}] -
   Sin[- c1];

dR[psi_, r_, i_] :=
  c3 Sum[ Normalize[r[[j]] - r[[i]]] Exp[-Norm[r[[j]] - r[[i]]]]
     Sin[psi[[j]] - psi[[i]] + α Norm[r[[j]] - r[[i]]] - c2] , {j, 1, n}];

oneStep[{ψ_, r_}] := {Mod[ψ + dt Table[dPsi[ψ, r, i], {i, 1, n}], 2 Pi],
  Mod[r + dt Table[dR[ψ, r, i], {i, 1, n}], L]}

result = NestList[oneStep, {ψ, r}, 5000]; // Timing

{620.421, Null}

showCells[{phi_, r_}] :=
  Show[
   Graphics[Table[{Hue[phi[[i]] / 2 Pi], PointSize[0.05], Point[r[[i]]]},
     {i, 1, n}]], PlotRange → {{0, L}, {0, L}}];

rg = Table[showCells[result[[i]]], {i, 1, 5000, 50}];

ListAnimate[rg]
```

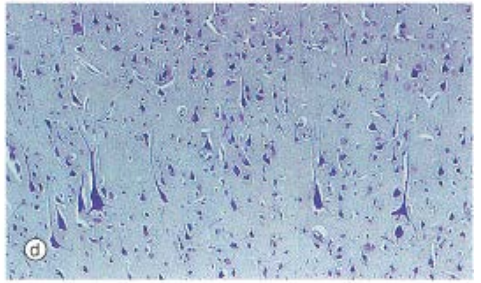
Norm[], Normalize[]で
コンパクトに表現

大脳皮質の層構造

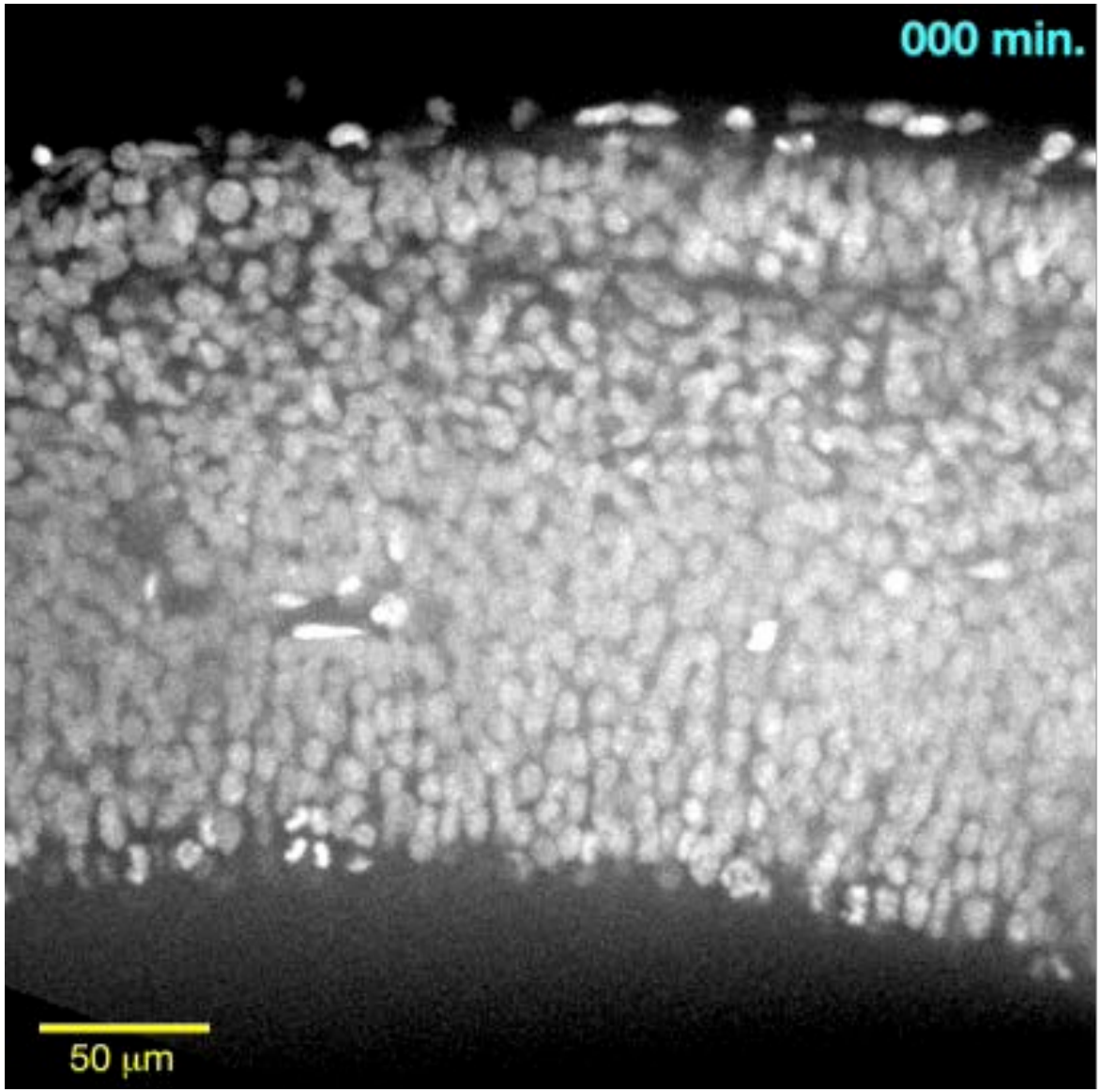








エレベーター運動



- 分化した Neuron
- エレベーター運動する細胞

宮田先生

似ている。

$$\psi_i \to z_i$$

分裂なしモデル

$$\phi_i' = c_1$$

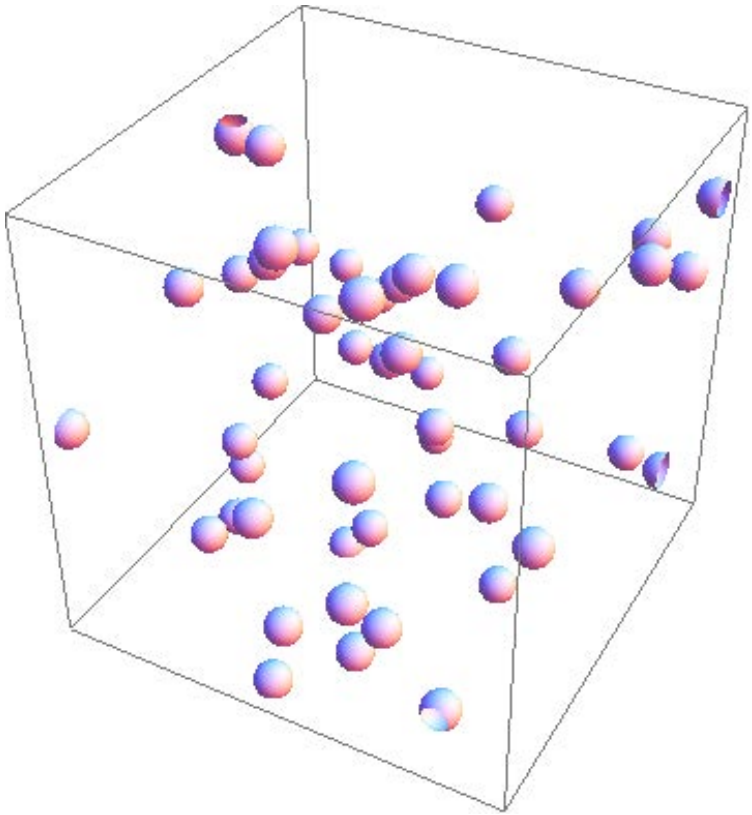
相互作用　　z方向の運動

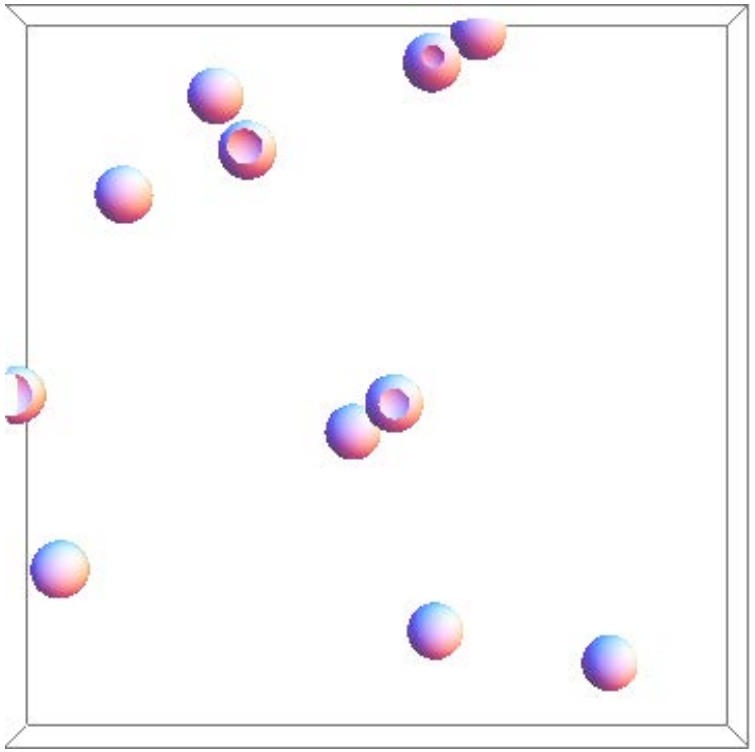
$$\vec{r_i}' = \boxed{\sum^{j} U(|\vec{r_j} - \vec{r_i}|)\frac{\vec{r_i}}{|\vec{r_i}|}} + \boxed{c_2(0, 0, z_i - \cos(\phi_i))}$$

$$U(r) = \begin{matrix} 0 & (r > 1) \\ -1 & (r \leq 1) \end{matrix}$$ Exclusion volume

- 細胞周期Φ　　Φはzの影響を受けない
- 座標 $r_i = (x_i, y_i, z_i)$

分裂なしモデル



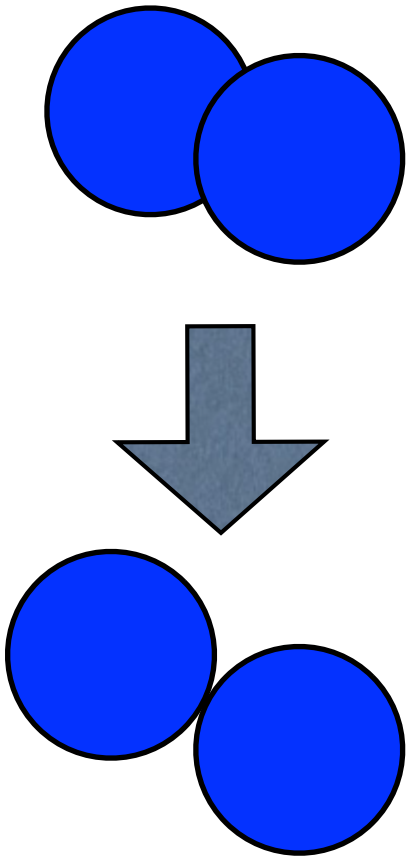


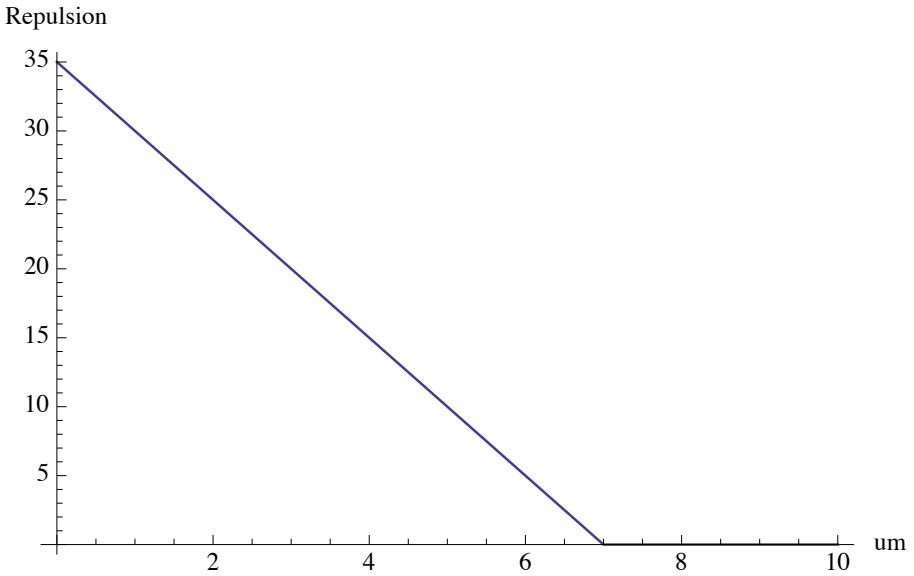
中間評価に活用したらしい

強化合宿（三浦研）

- Mathematicaのコーディング+モデルのプログラミング
- 1/7-11の４日間

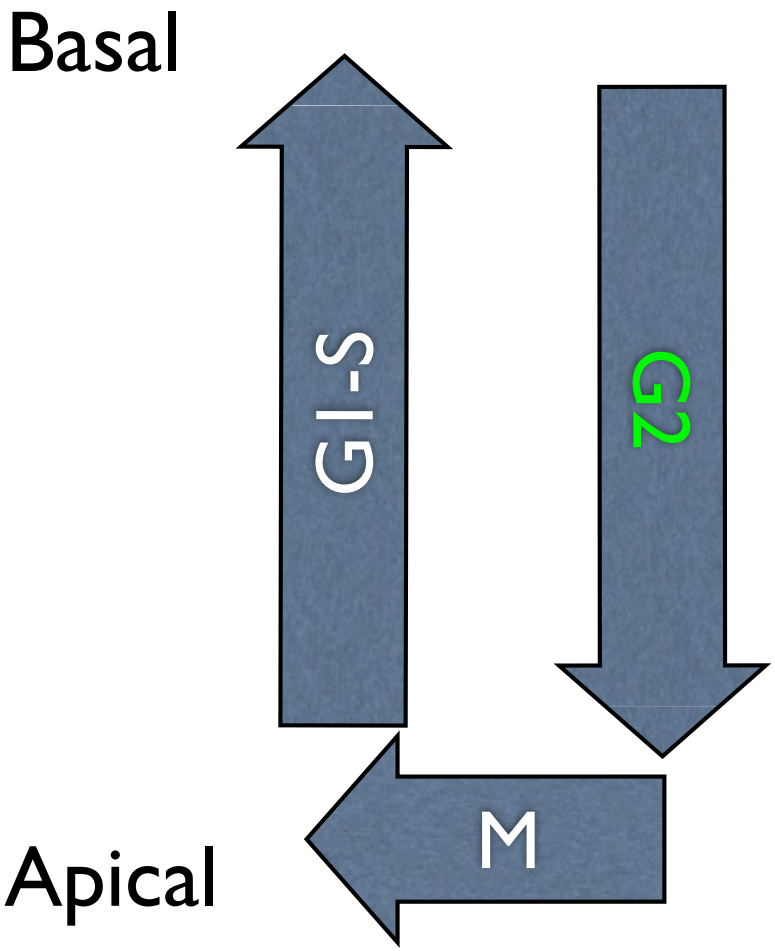
細胞間相互作用





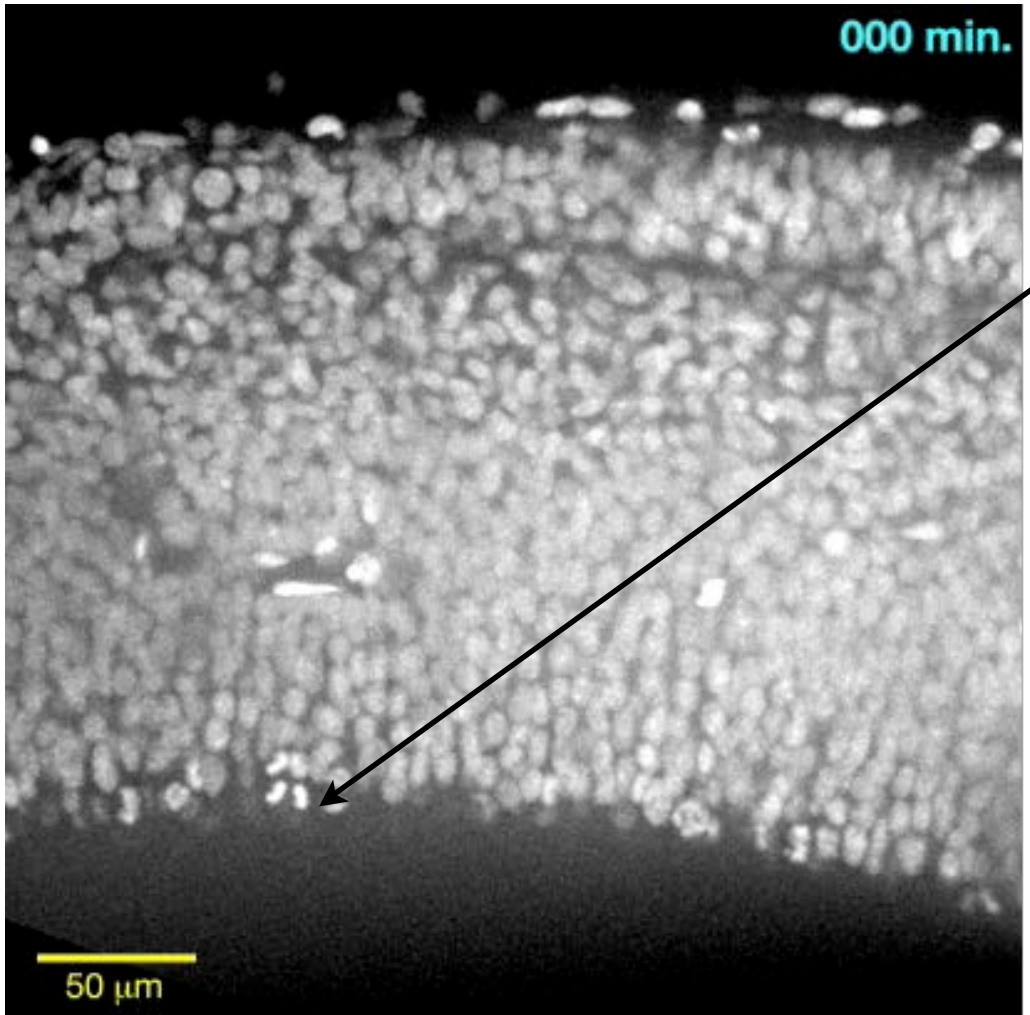
- ある程度ソフト＞LJPではなく線形関数
- 一定距離以上は0

周辺の混み合いによる位相（細胞周期）の変化



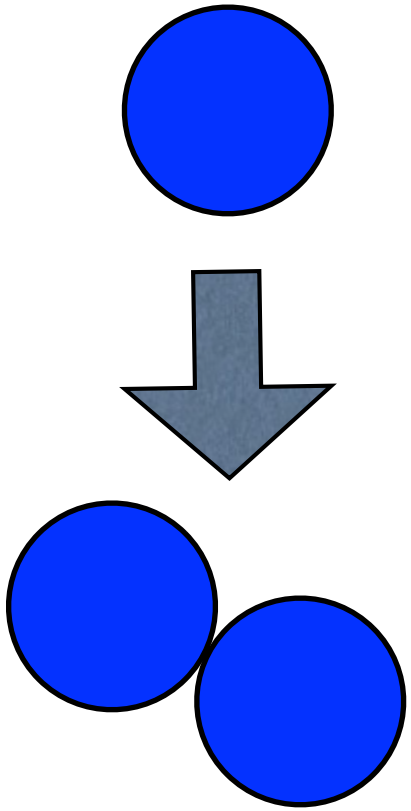
- いちばんApical側のみで細胞分裂が起こる（中心体の存在）
- G1:Apical面に達するまでは能動的に動く
- M: 1時間
- G2-S: 6時間。能動的な移動必要
- 細胞間相互作用で運動が遅れると周期がずれる

周辺の混み合いによる位相（細胞周期）の変化



- M期はApical面のみ！（中心体）
- Apical面が移動する：相対位置の変化？

細胞分裂

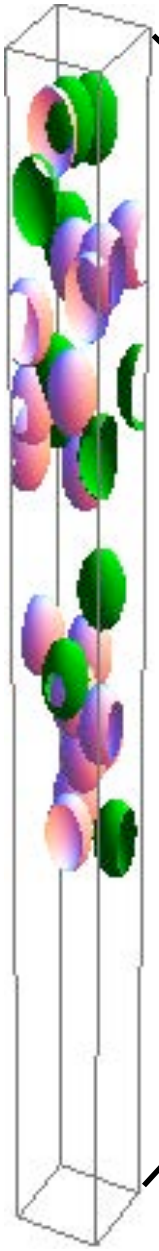


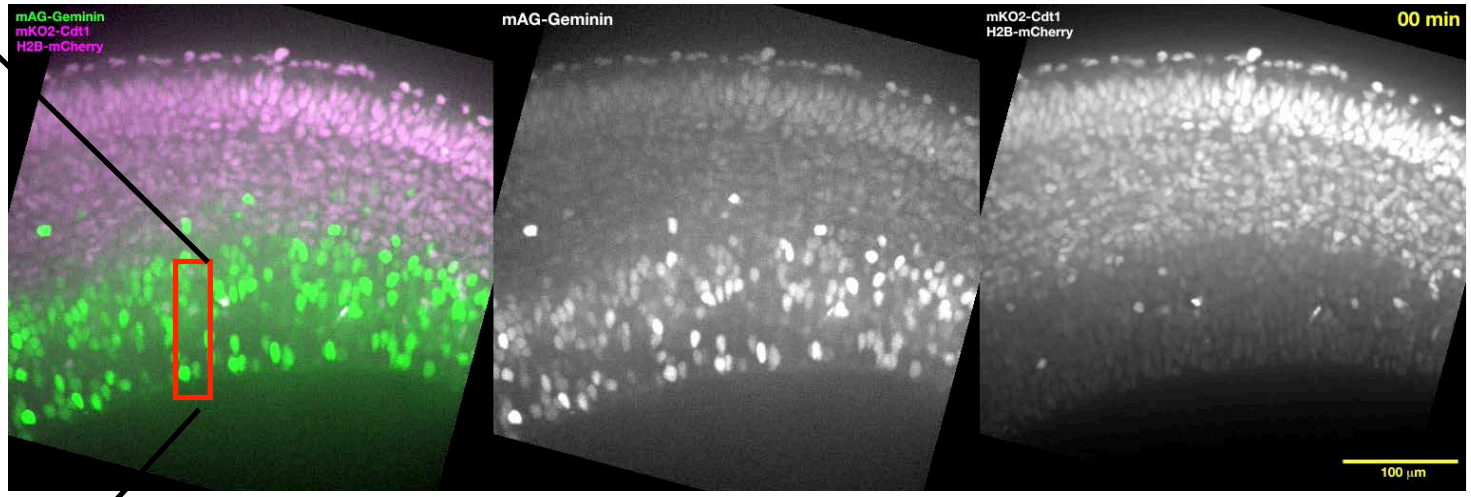
- Apical面のみで起こる
- 方向はランダム
- エレベーター運動する層の厚みは一定＞離脱する細胞を定義

細胞の最適位置

- Apical面、Basal面に到達したときは同じx, y座標に動く

数値計算とFucci





Geminin (G2 marker)

＞北大長山研にパス

1次元の連続モデルに落とせないか？