

# 生物の形づくりと 計算科学

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生体構造医学講座 形態形成機構学教室

# 発生生物学



Langman's Medical Embryology

# *Developmental Biology*

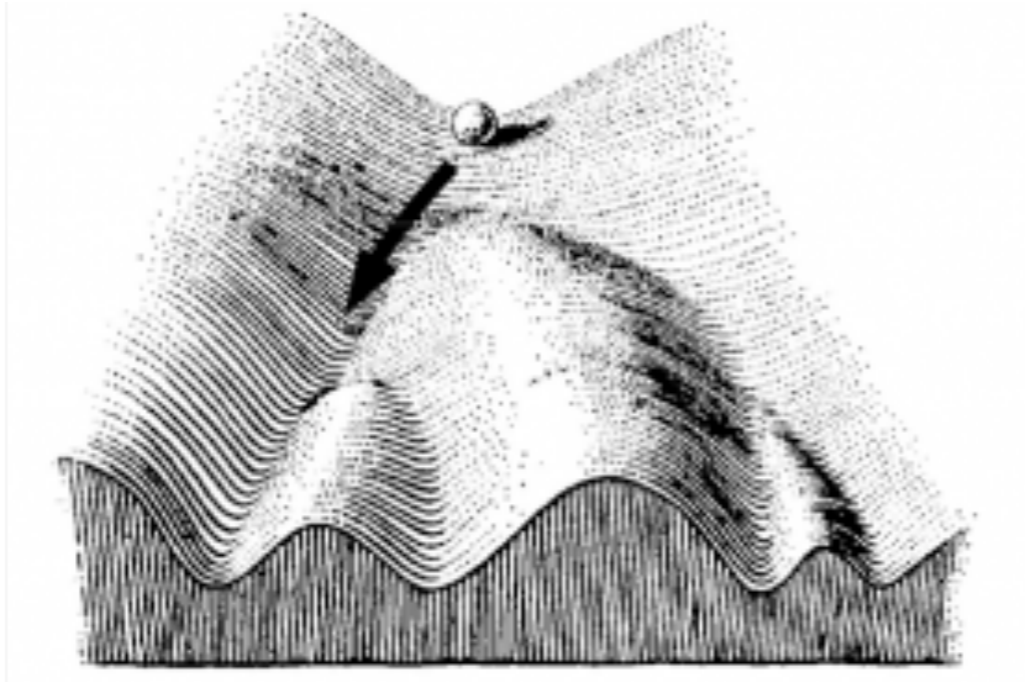
FOR  
DUMMIES®

# 発生生物学の2つの

## 大テーマ

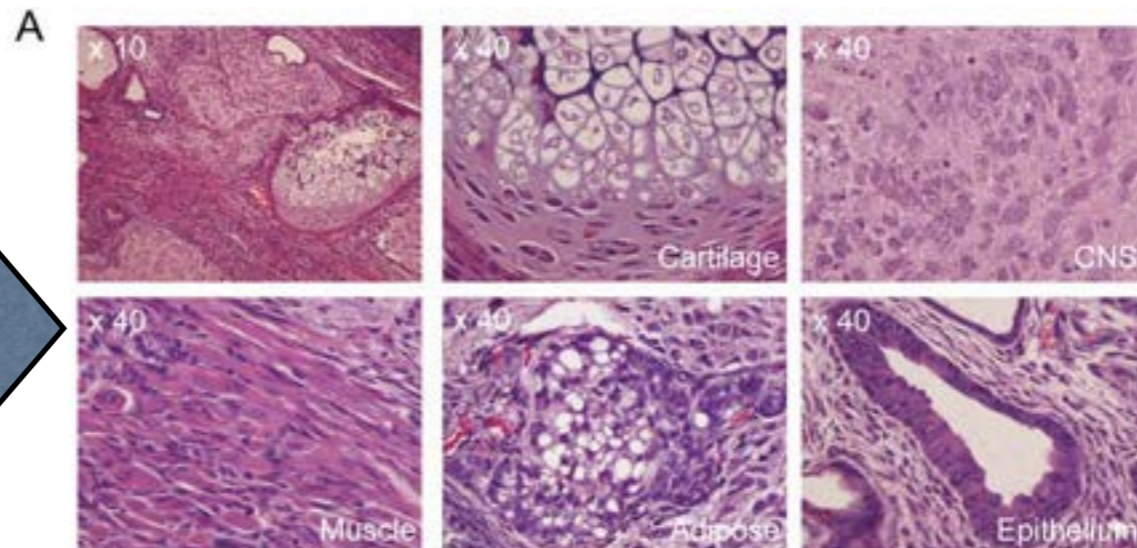
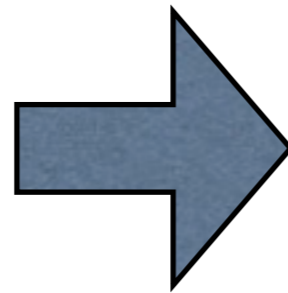
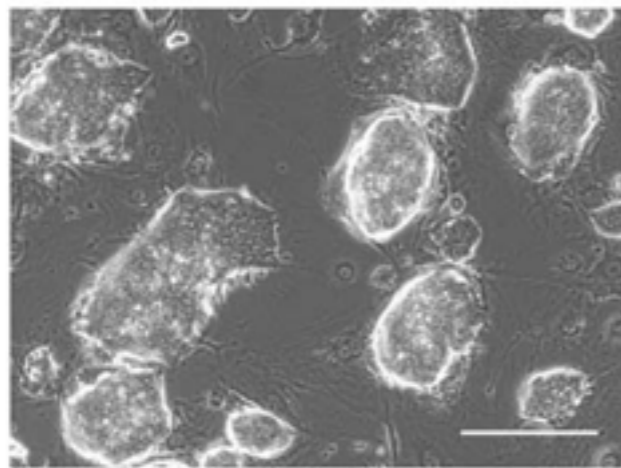
- 分化 (Differentiation)
- 形態形成 (Morphogenesis)

# 分化



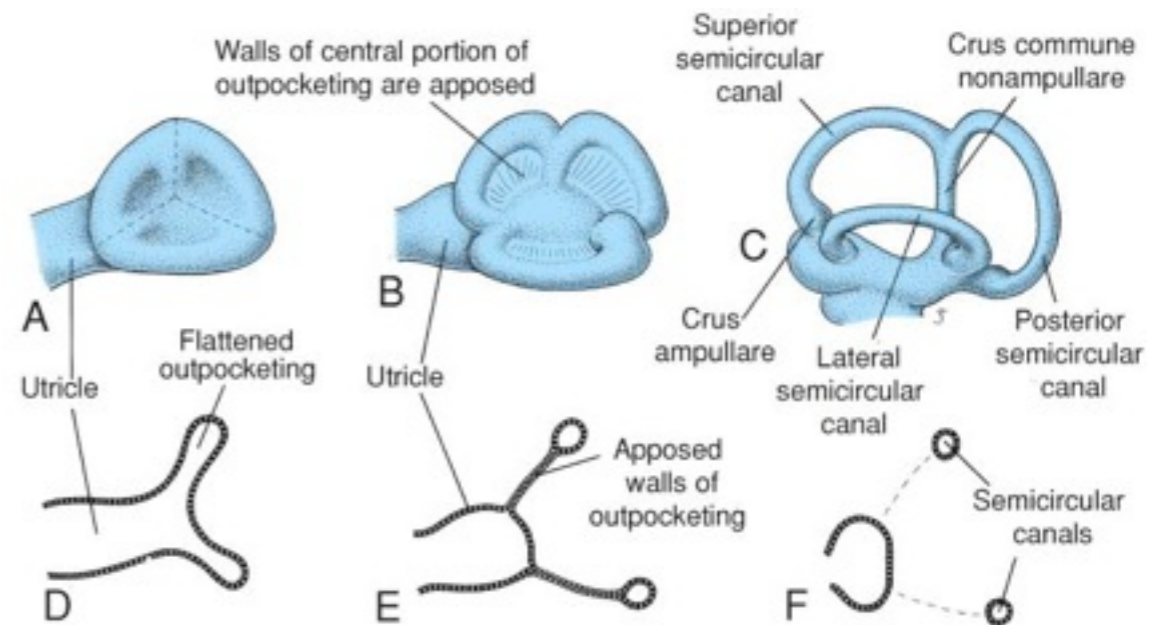
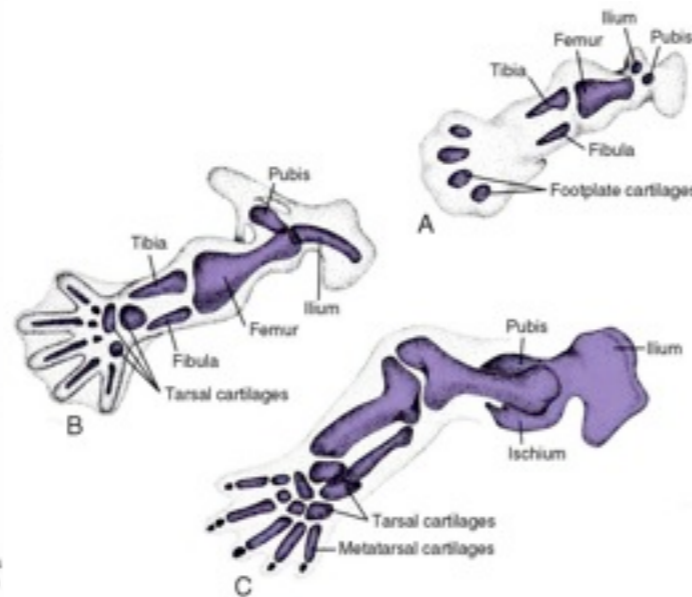
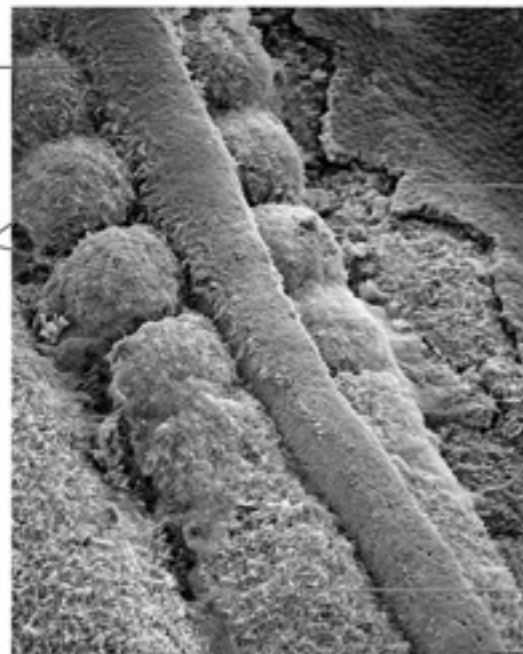
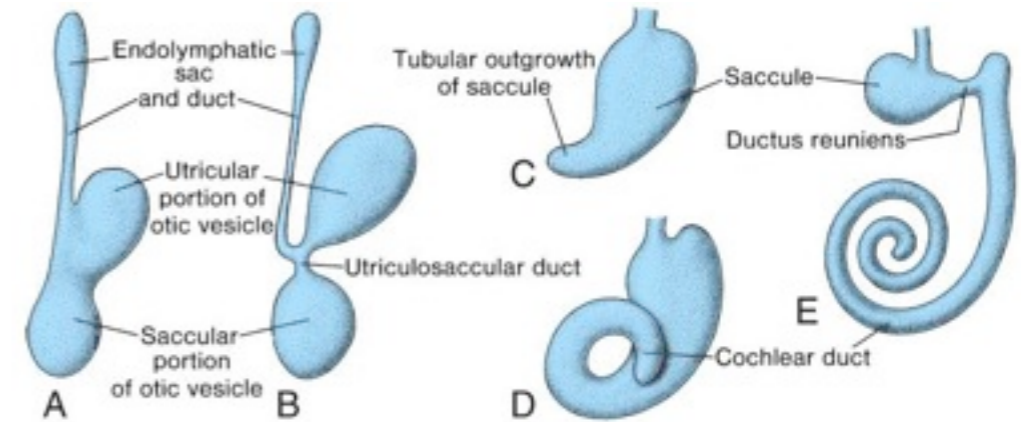
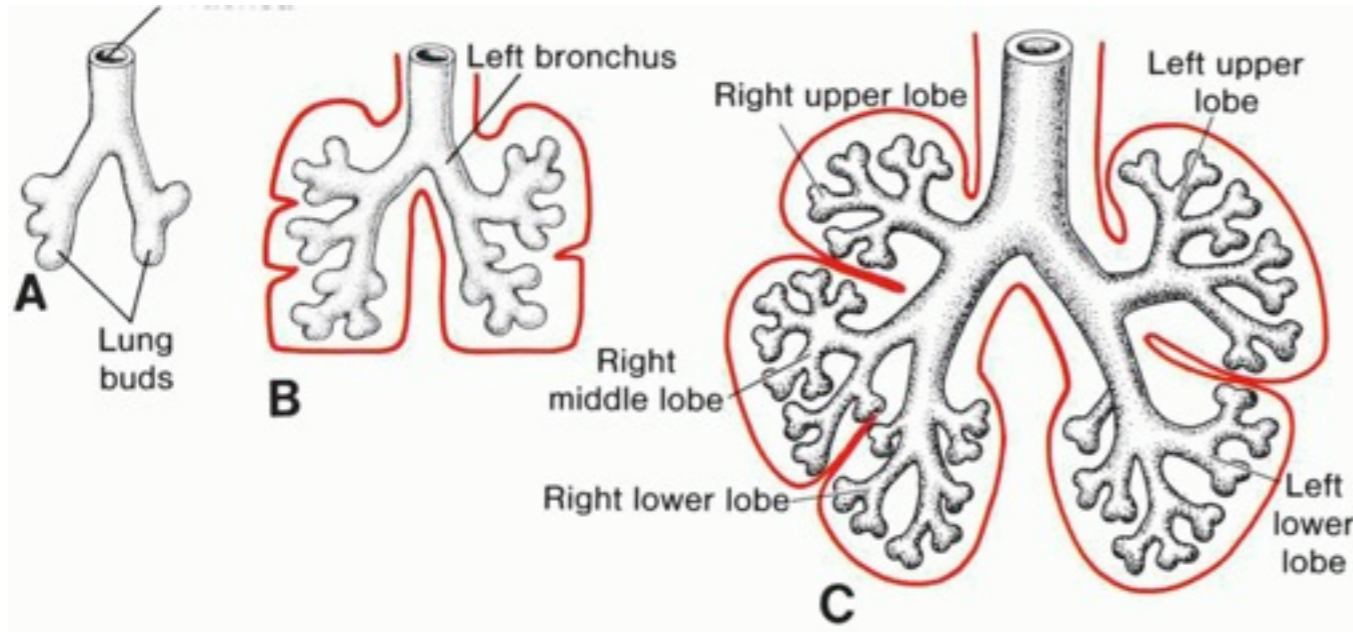
Epigenetic landscape  
(Waddington)

iPS



一種類の細胞から体のすべての組織を作れる

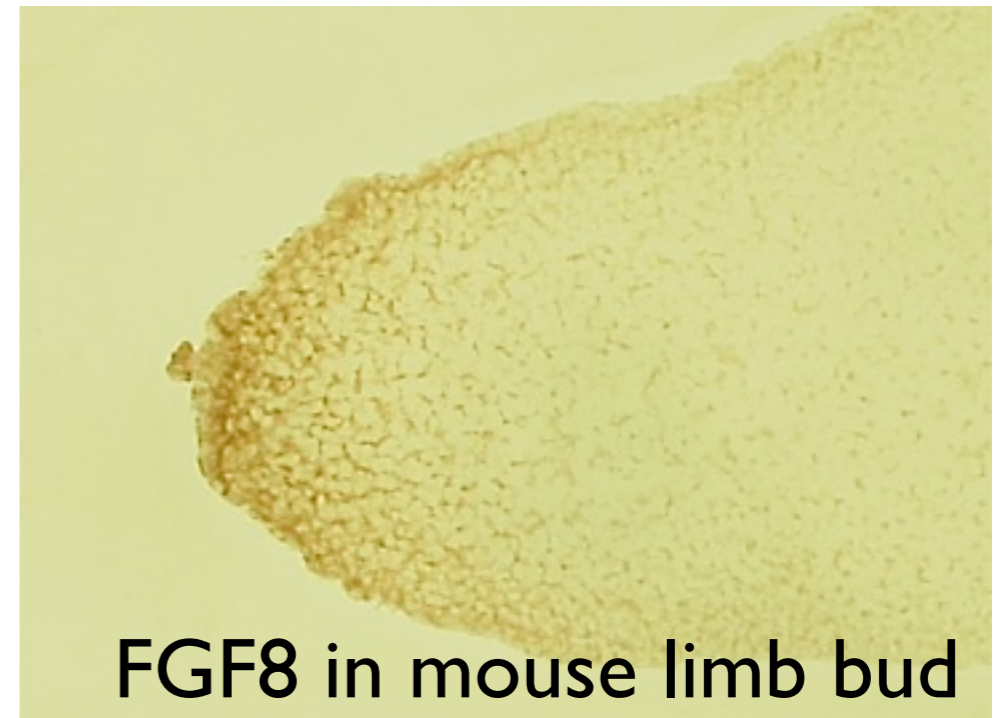
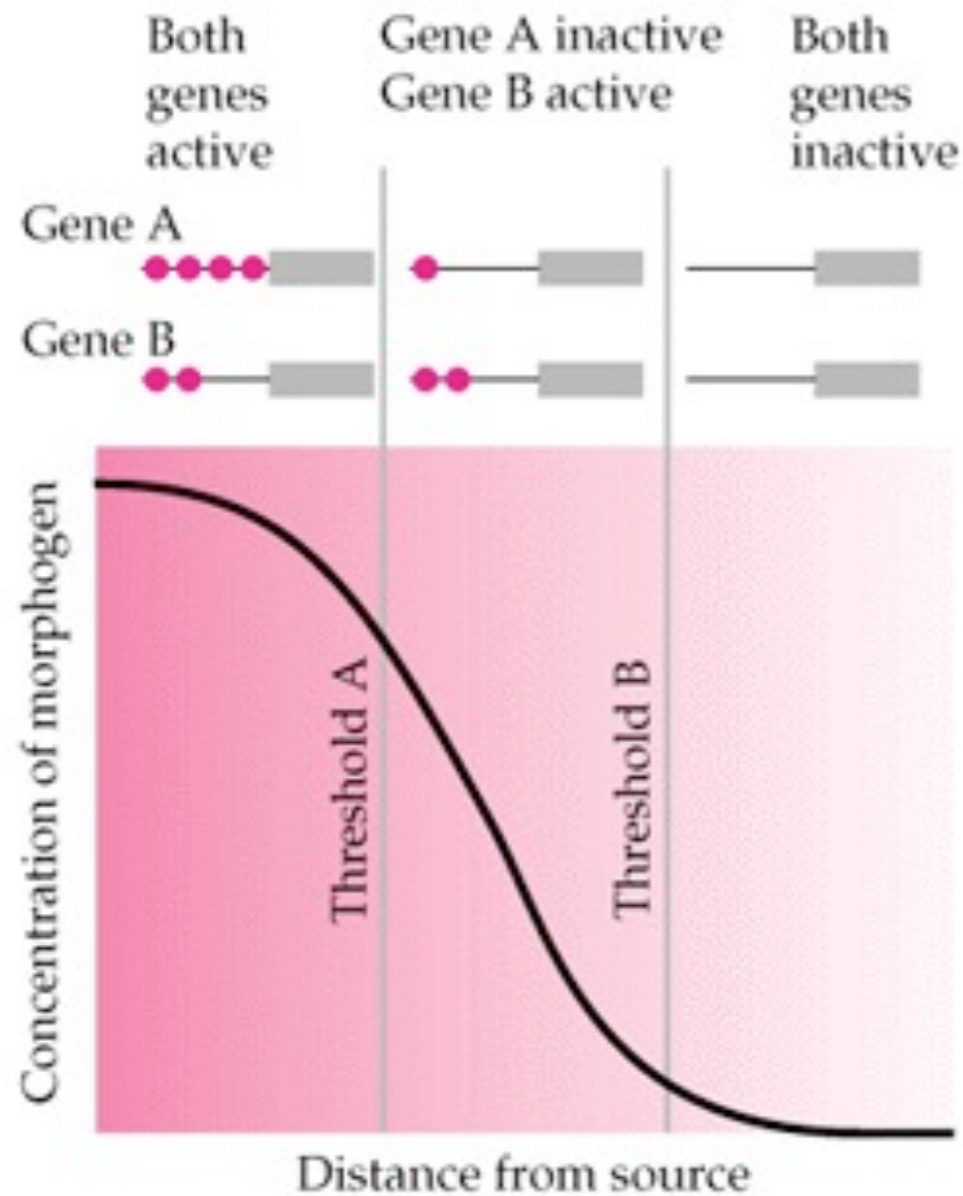
# 形態形成



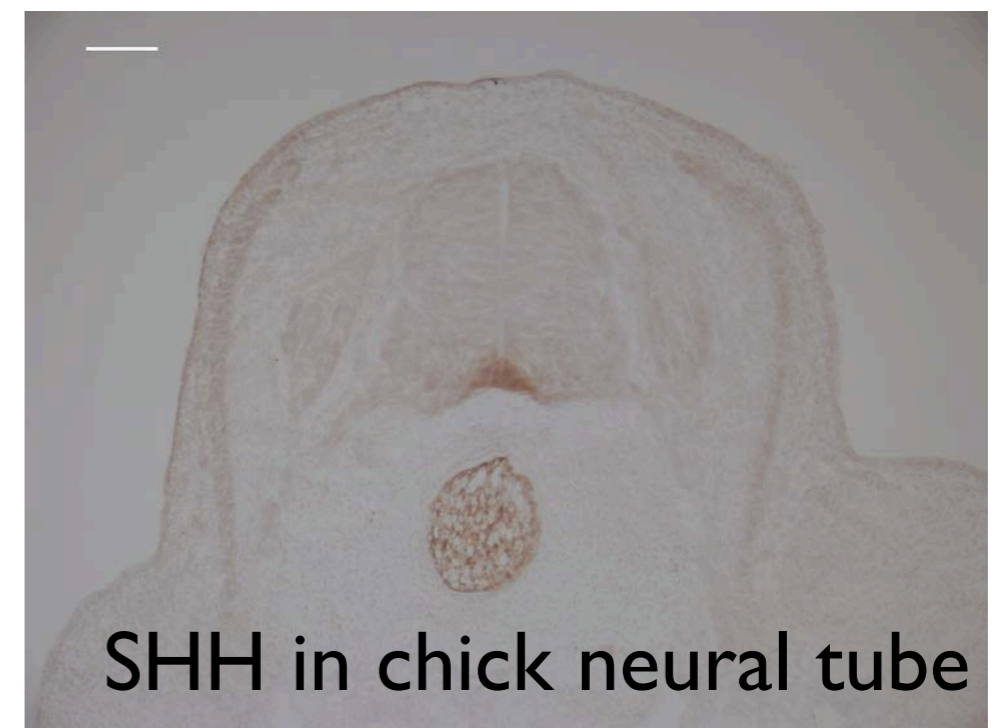
# 形態形成のしくみ

- モルフォゲン
- 細胞増殖—細胞死
- 細胞運動
- 細胞接着

# Morphogen gradient



FGF8 in mouse limb bud



SHH in chick neural tube

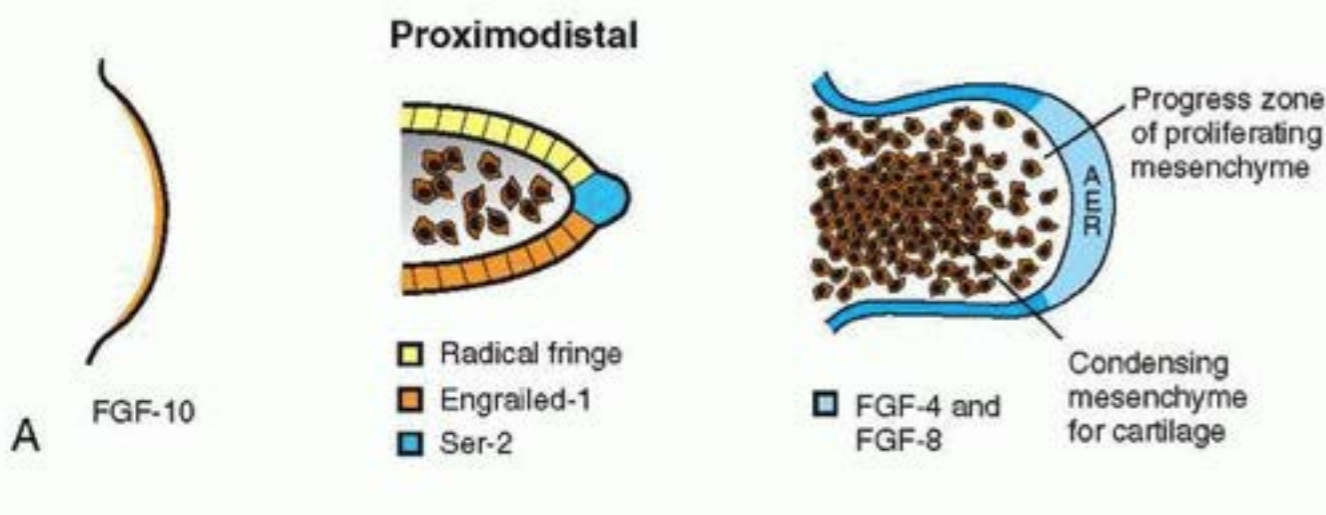
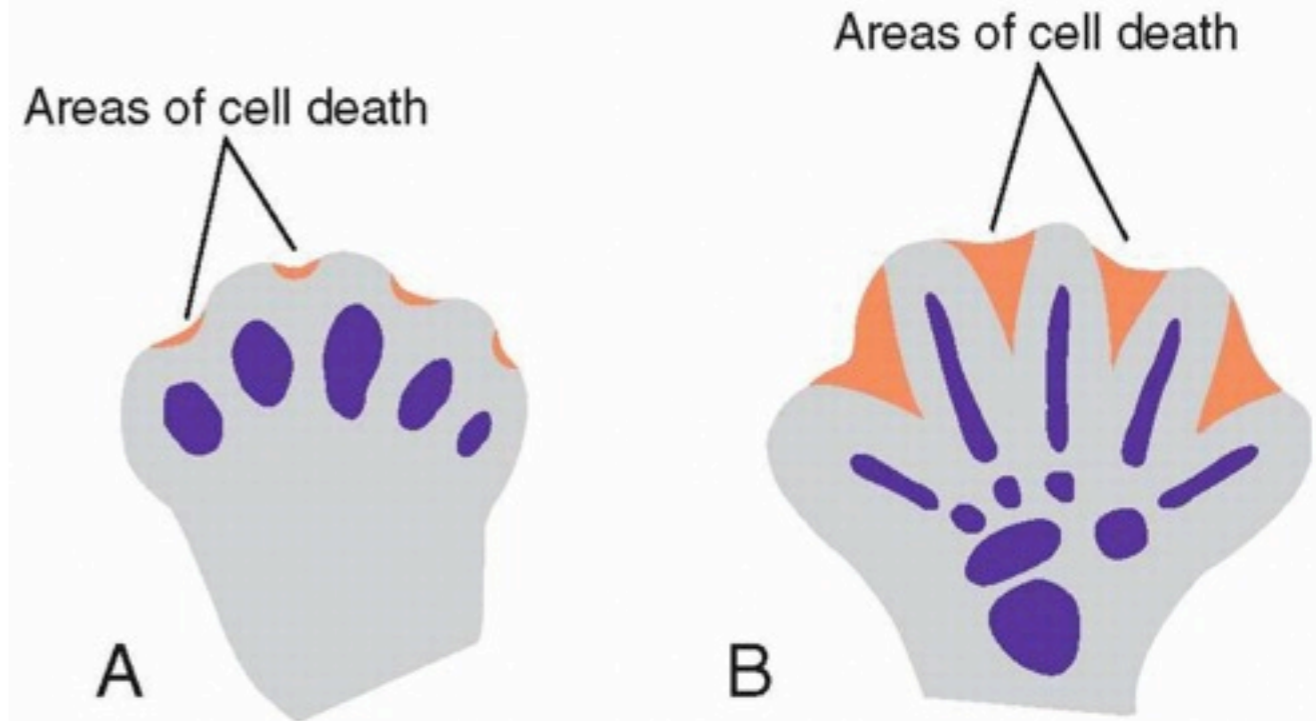
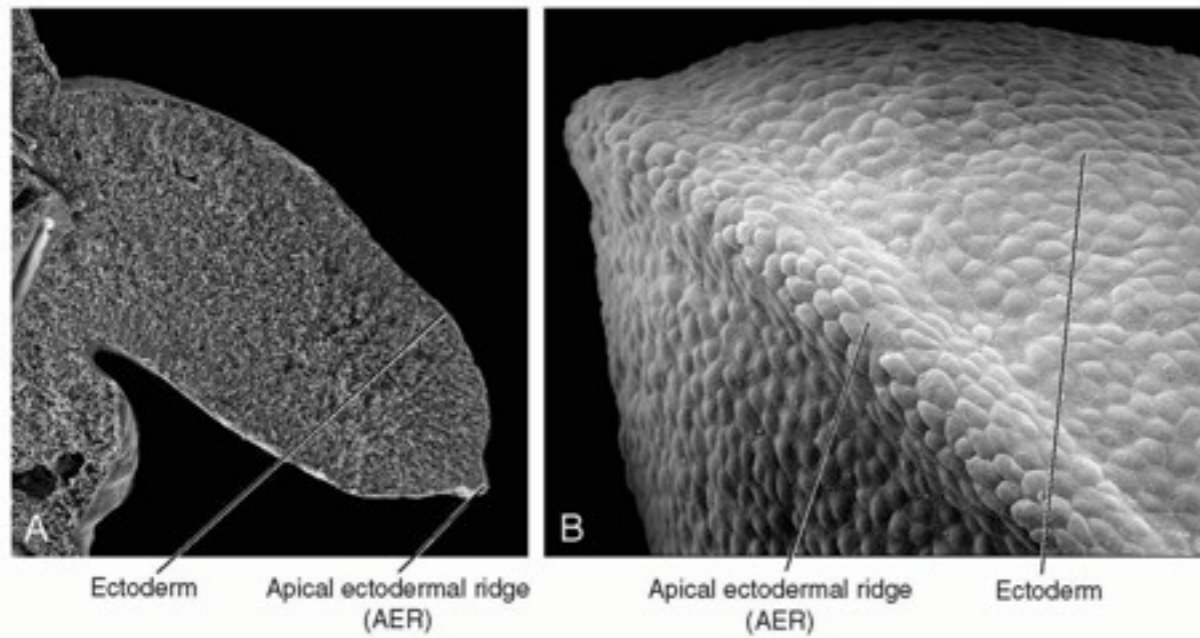
Gilbert "Developmental Biology"



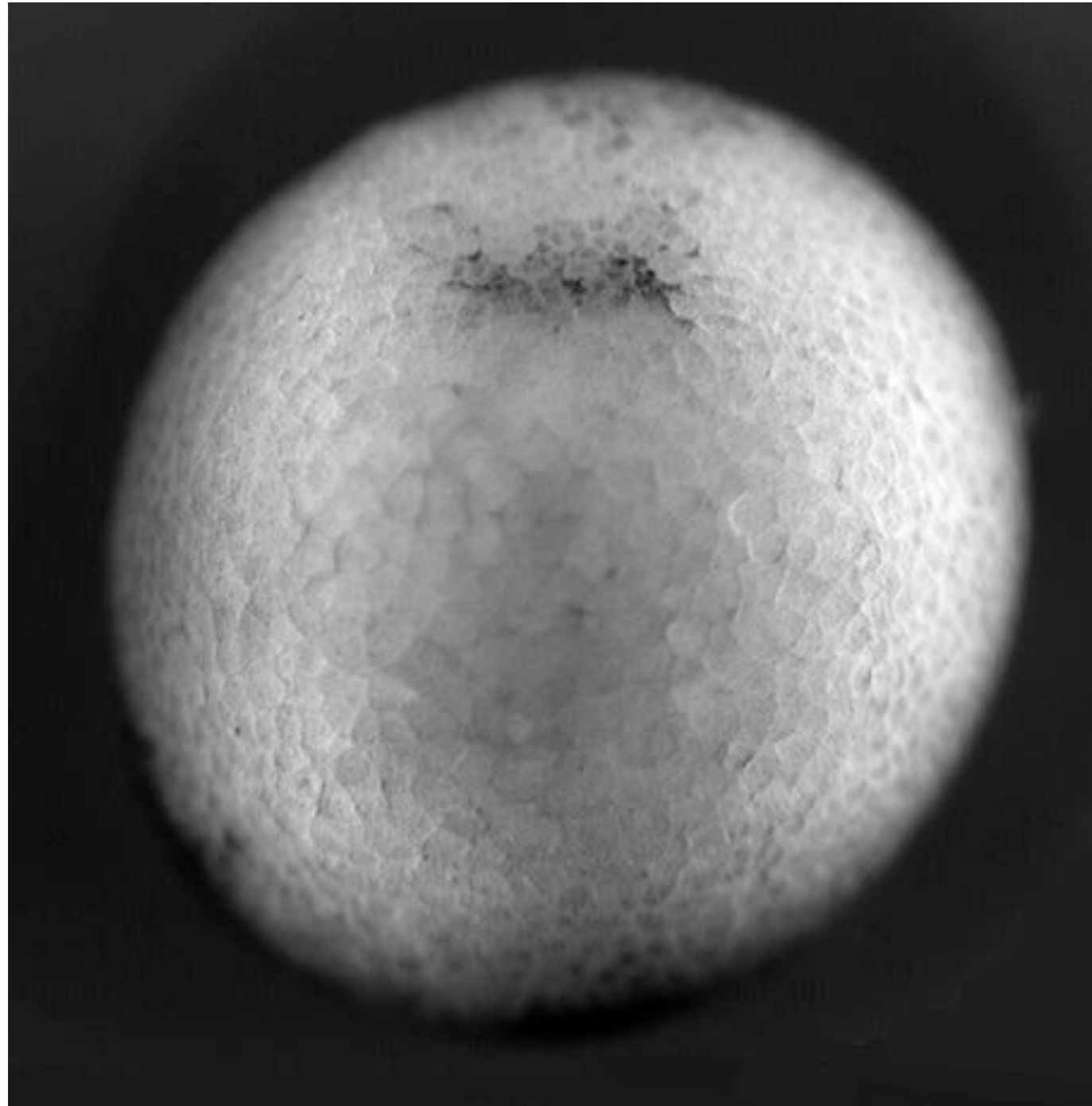
# 「発生4種の神器」

- FGF (Fibroblast growth factor)
- BMP (Bone Morphogenetic Protein)
- Shh (Sonic Hedgehog)
- Wnt

# 細胞增殖—細胞死

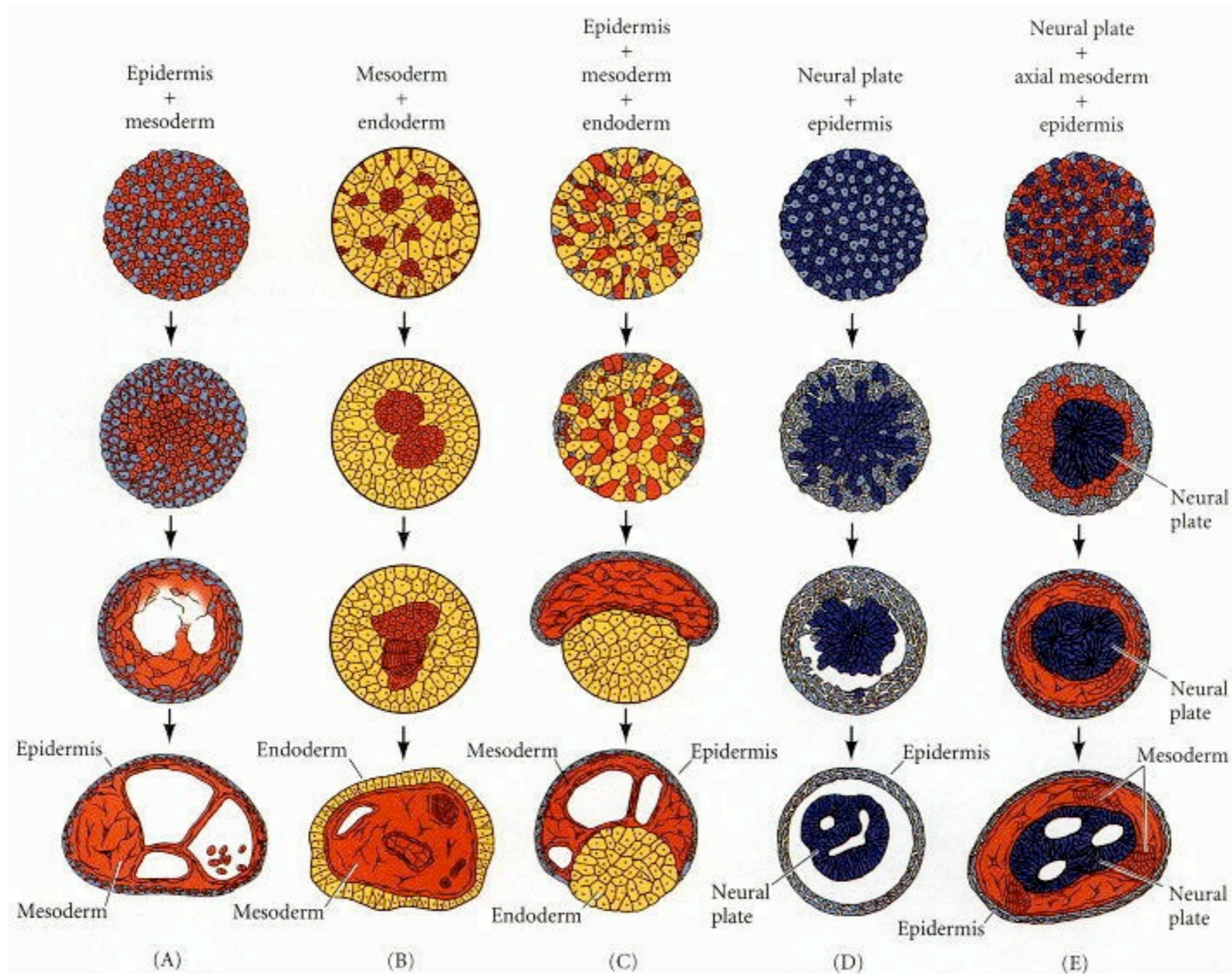


# 細胞運動



- 原腸陷入
- 神經管形成

# 細胞接着—細胞選別



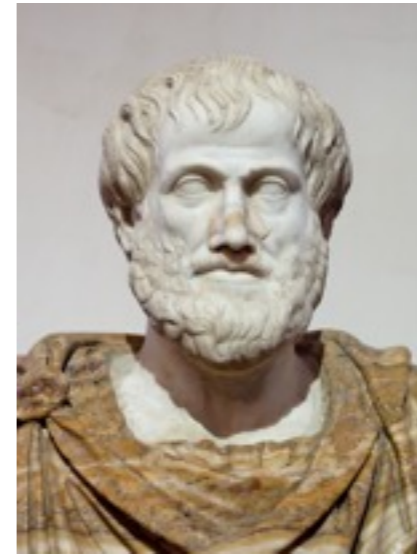
Gilbert "Developmental Biology"

# 発生生物学の歴史

- 記載
- 進化との関連
- 実験発生生物学
- 分子生物学

# 記載

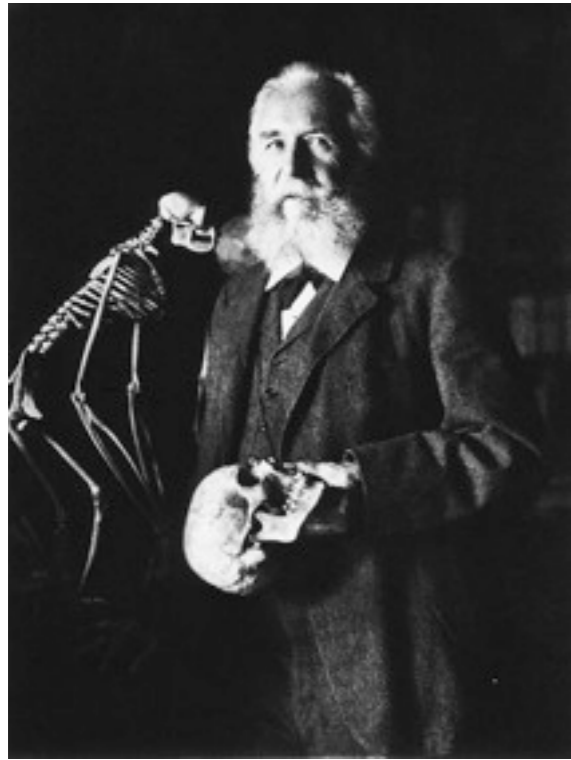
アリストテレス  
(384-322 B.C.)  
「動物誌」



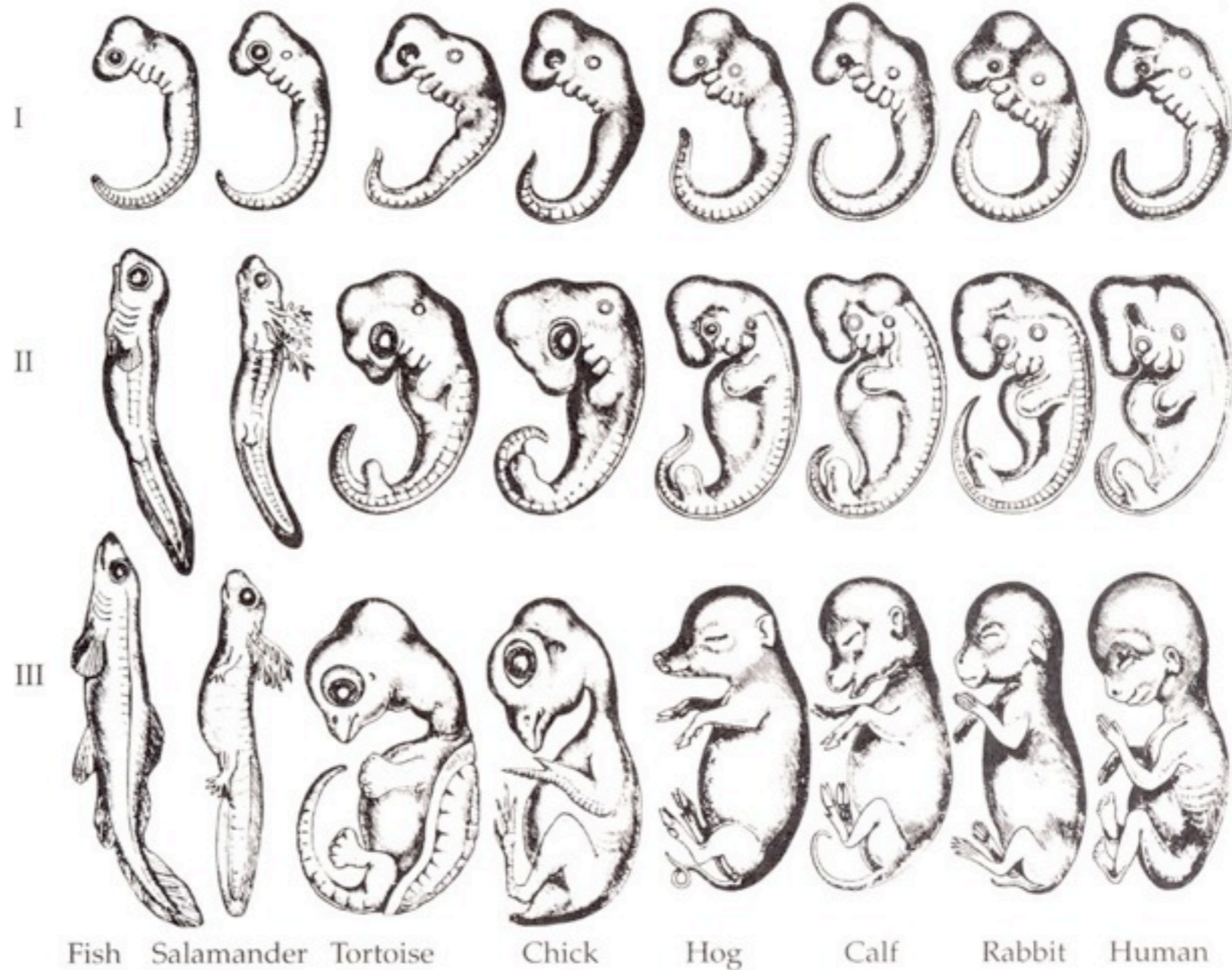
レオナルド・ダビンチ  
"Views of a Fetus in the  
Womb"  
1510-1512



# 進化との関連

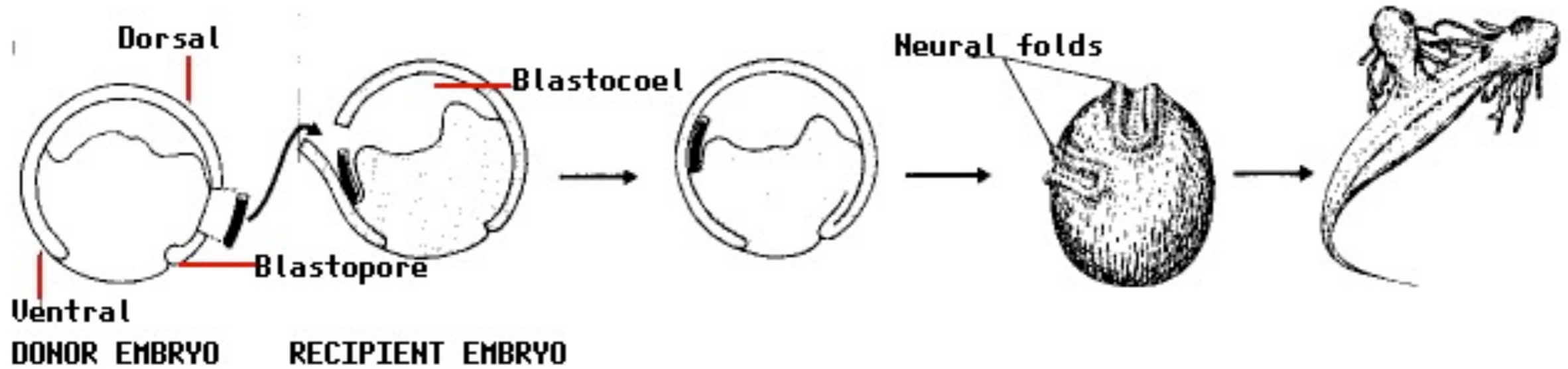


Ernst Haeckel  
(1834-1919)



反復説 > ベーアの法則

# 実験発生生物学



シュペーマン(1869-1941)



マンゴールド(1898-1924)



# 発生遺伝学



Eric Wieschaus  
Nobel Prize, 1995

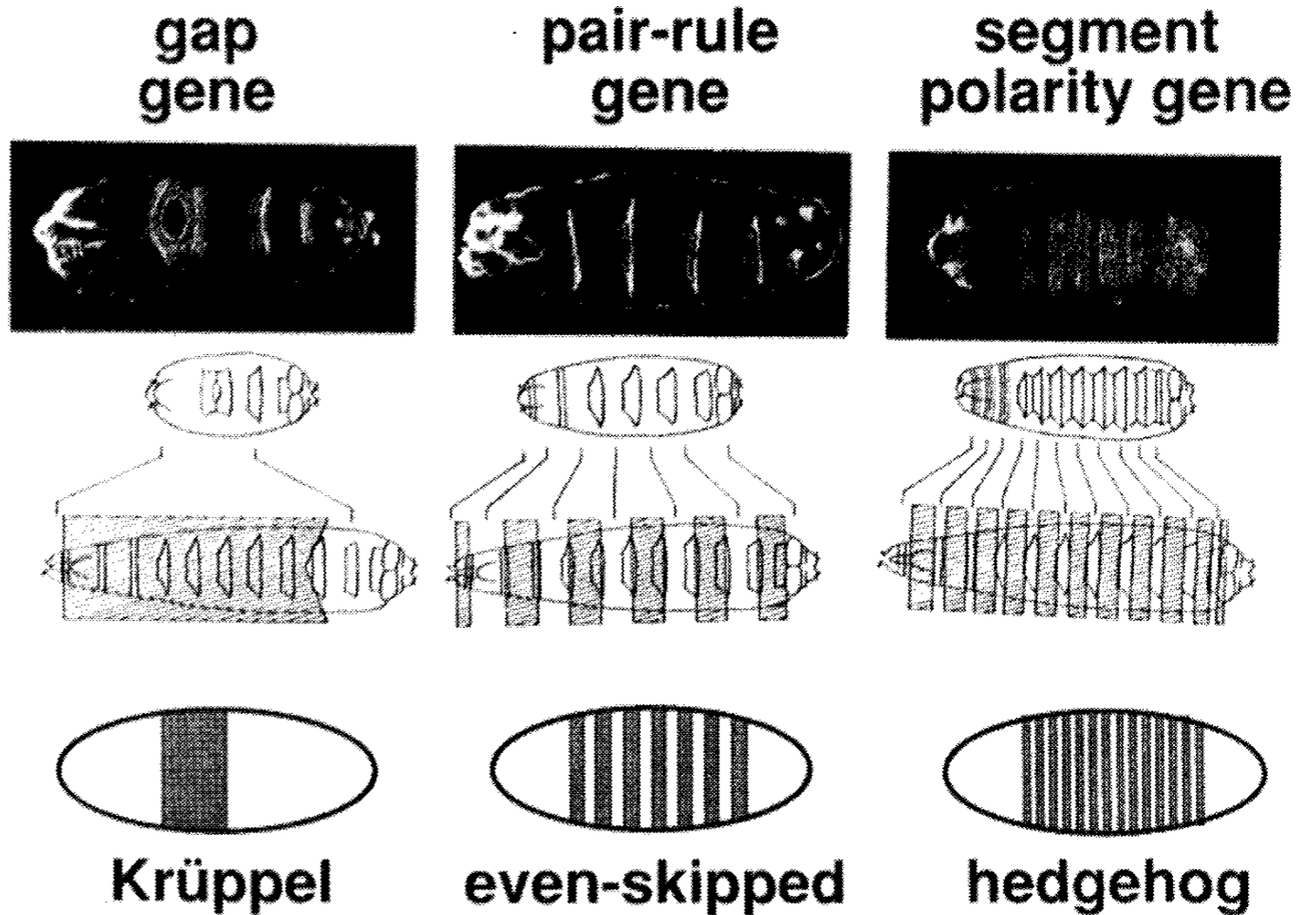
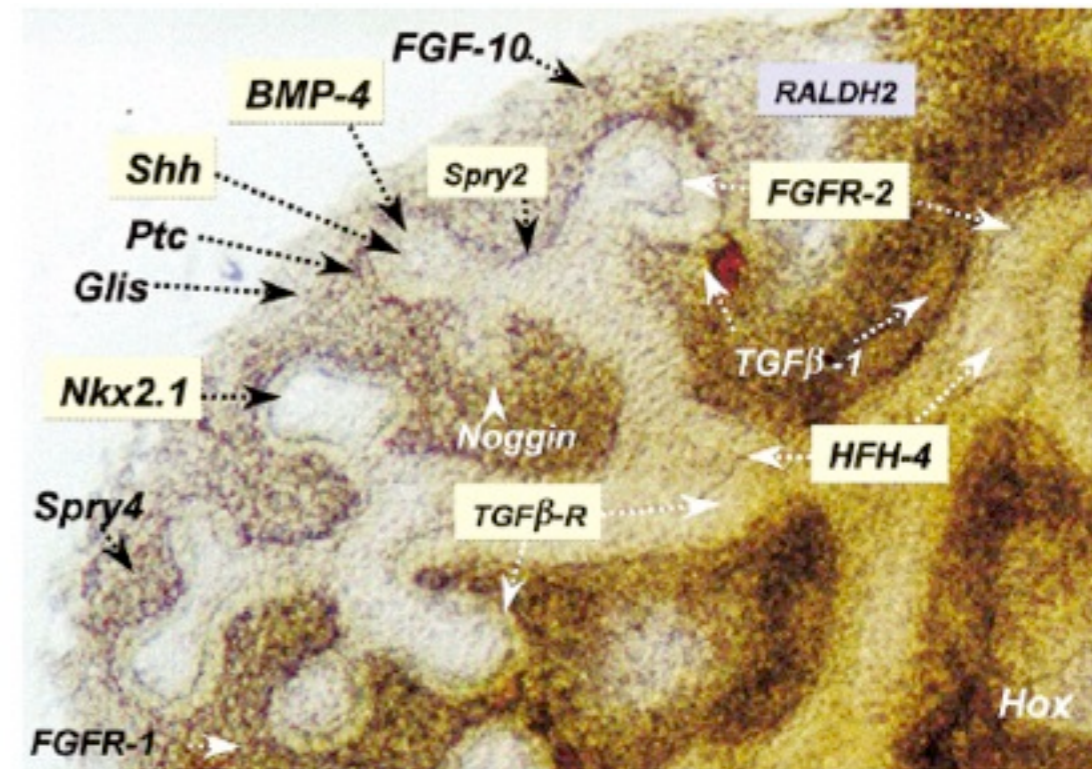
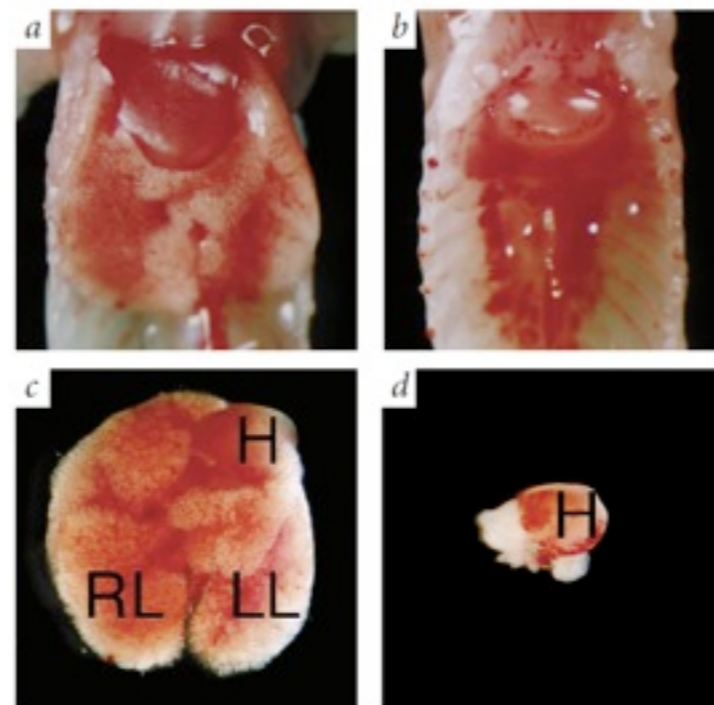
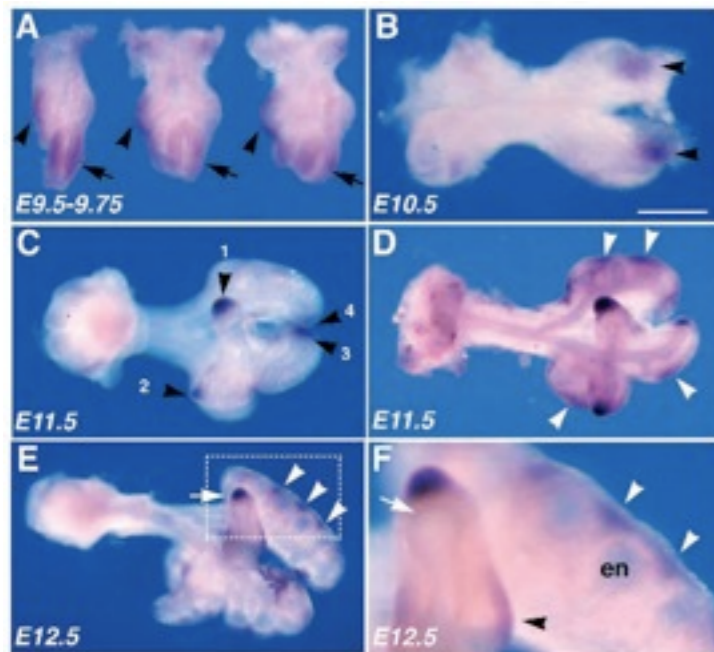


Figure 2. *Phenotypes of Mutations affecting segmental pattern.* The size and spacing of the pattern deletions in mutant embryos at the end of development allows extrapolation back to requirements for gene activities at blastoderm stage. Segmentation genes can be grouped into three classes: mutations in gap genes show large contiguous deletions in the pattern, mutations in pair-rule genes show pattern deletions spaced at double segment intervals, and mutations in segment polarity genes cause pattern deletions in each segment. One example is shown for each class.

# "Developmental Biology"



## FGF10

Development 124,  
4867-4878 (1997)

## FGF10 KO

Nat Gen. 21, 138- (1999)

## Review

Dev Dyn 219:121-130 (2000)

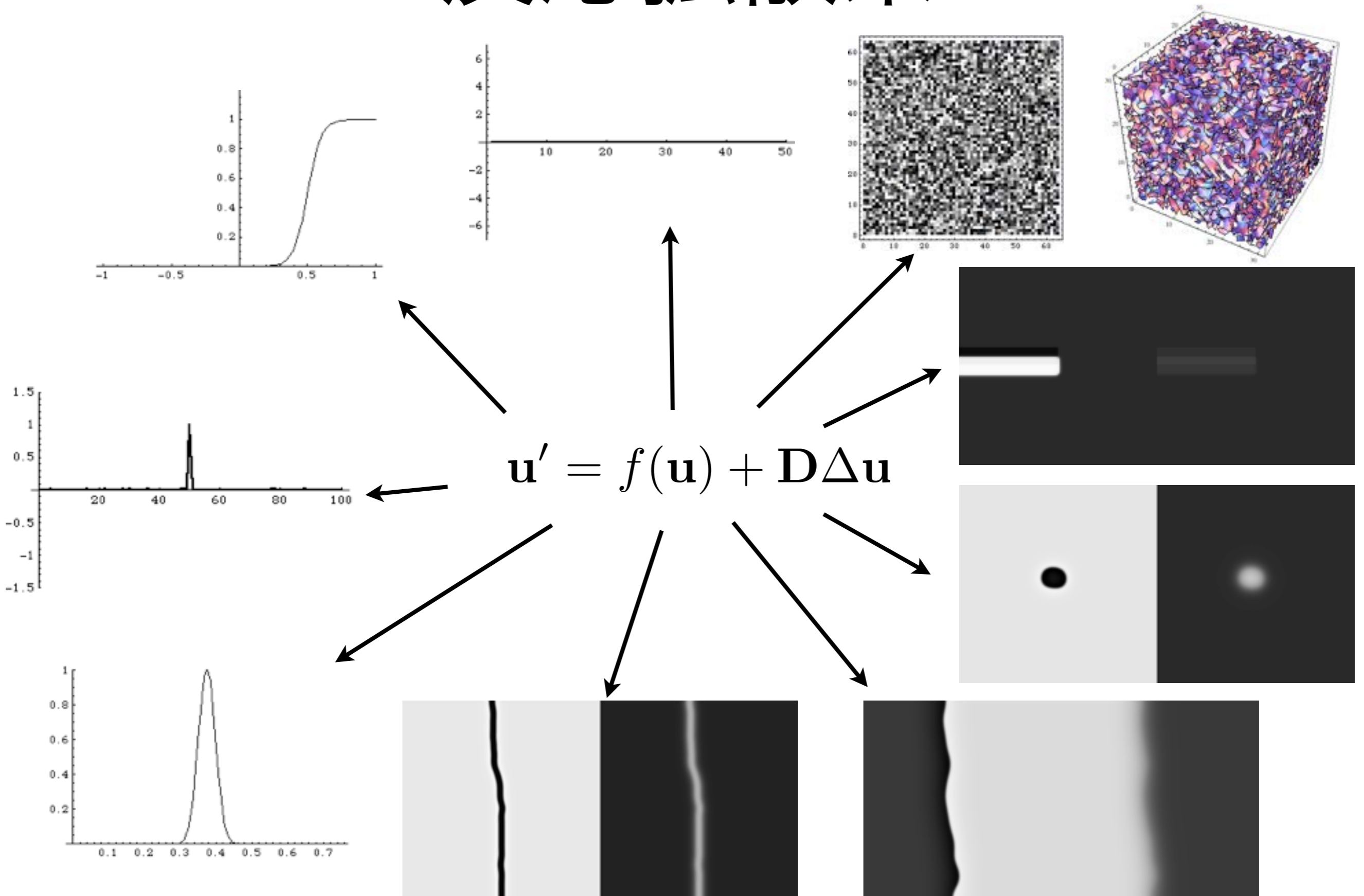
# 情報爆発

Table 1. Examples of mutations in mouse giving a reported lung and/or tracheal phenotype

Gene symbol	Gene name	Expression pattern	Phenotype	Reference
<b>Signalling molecule</b>				
<i>Egfr</i>	Epidermal growth factor receptor	Epithelium and mesenchyme	Impaired branching and deficient alveolization	Miettinen et al. (1997)
<i>Fgf18</i>	Fibroblast growth factor 18	Mesenchyme	Deficient alveolization	Usui et al. (2004)
<i>Fgf9</i>	Fibroblast growth factor 9	Epithelium and pleura	Impaired branching, reduced mesenchyme	Colvin et al. (2001)
<i>Grem1</i>	Gremlin 1	Epithelium and mesenchyme	Deficient alveolization	Michos et al. (2004)
<i>Hip1</i>	Huntingtin-interacting protein 1	Mesenchyme	Impaired branching	Chuang et al. (2003)
<i>Shh</i>	Sonic hedgehog	Epithelium	Impaired branching, tracheoesophageal fistula	Litingtung et al. (1998)
<i>Tgfb3</i>	Transforming growth factor, $\beta$ 3	Epithelium and pleura	Impaired branching	Kaartinen et al. (1995)
<i>Wnt7b</i>	Wingless-related MMTV integration site 7B	Epithelium	Vascular defect, reduced mesenchyme	Shu et al. (2002)
<i>Catnbn1</i>	$\beta$ -Catenin	Epithelium	Impaired branching, proximal/distal specification	Mucenski et al. (2003)
<i>Ltbp4</i>	Latent transforming growth factor $\beta$ binding protein 4	Not reported	Pulmonary emphysema	Sterner-Kock et al. (2002)
<i>Wnt5a</i>	Wingless-related MMTV integration site 5A	Mesenchyme and epithelium	Increased branching, tracheal defect	Li et al. (2002)
<i>Fgf10</i>	Fibroblast growth factor 10	Mesenchyme	Lung agenesis	Sekine et al. (1999)
<i>Fgfr2b</i>	Fibroblast growth factor receptor 2b	Epithelium	Lung agenesis	De Moerlooze et al. (2000)
<i>Fgf8</i>	Fibroblast growth factor 8	Not reported	Right pulmonary isomerism	Fischer et al. (2002)
<i>Acvr2b</i>	Activin receptor IIB	Not reported	Right pulmonary isomerism	Oh and Li (1997)
<i>Nodal</i>	Nodal	Not reported	Right pulmonary isomerism	Lowe et al. (2001)
<i>Lefty1</i>	Left right determination factor 1	Not reported	Left pulmonary isomerism	Meno et al. (1998)
<i>Traf4</i>	Tnf receptor associated factor 4	Not reported	Tracheal defect	Shiels et al. (2000)
<i>Fgfr3/Fgfr4</i>	Fibroblast growth factor receptor 3/4	Epithelium and mesenchyme	Deficient alveolization	Weinstein et al. (1998)
<i>Nog</i>	Noggin	Mesenchyme	Lobation defect	Weaver et al. (2003)
<b>Transcription factor</b>				
<i>Cebpa</i>	CCAAT/enhancer binding protein (C/EBP), $\alpha$	Epithelium	Hyperproliferation of type II cells	Sugahara et al. (2001)
<i>Foxa1/Foxa2</i>	Forkhead box A1/A2	Epithelium	Impaired branching, reduced smooth muscle	Wan et al. (2005)
<i>Foxf1a</i>	Forkhead box F1a	Mesenchyme	Impaired branching, lobation defect	Lim et al. (2002)
<i>Hoxa5</i>	Homeobox A5	Mesenchyme	Impaired branching, tracheal defect	Aubin et al. (1997)
<i>Klf2</i>	Kruppel-like factor 2 (lung)	Not reported	Impaired sacculation	Wani et al. (1999)
<i>Mycn</i>	Neuroblastoma myc-related oncogene 1	Epithelium	Impaired branching	Moens et al. (1992)
<i>Trp63</i>	Transformation-related protein 63	Epithelium	Tracheobronchial defect	Daniely et al. (2004)
<i>Titf1</i>	Thyroid transcription factor 1	Epithelium	Loss of distal lung fate, impaired branching, tracheoesophageal fistula	Kimura et al. (1996)
<i>Nfib</i>	Nuclear factor I/B	Epithelium and mesenchyme	Sacculation defect	Steele-Perkins et al. (2005)
<i>Sox11</i>	SRY-box-containing gene 11	Epithelium	Hypoplastic lung	Sock et al. (2004)
<i>Tcf21</i>	Transcription factor 21 (Pod1)	Mesenchyme	Impaired branching	Quaggin et al. (1999)
<i>Rarb/Rara</i>	Retinoic acid receptor $\alpha/\beta$	Epithelium and mesenchyme	Left lung agenesis and right lung hypoplasia	Mendelsohn et al. (1994)
<i>Pitx2</i>	Paired-like homeodomain transcription factor 2	Mesenchyme	Right pulmonary isomerism	Lin et al. (1999)
<i>Foxj1</i>	Forkhead box J1	Epithelium	Left-right asymmetry, loss of ciliated cells	Brody et al. (2000)
<i>Gata6</i>	GATA-binding protein 6	Epithelium	Impaired sacculation	Yang et al. (2002)
<i>Gli2/Gli3</i>	GLI-Kruppel family member GLI2/GLI3	Mesenchyme	Lung agenesis	Motoyama et al. (1998)
<i>Ascl1</i>	Achaete-scute complex homolog-like 1	Neuroendocrine cells	Loss of neuroendocrine cells	Ito et al. (2000)
<b>Others</b>				
<i>Eln</i>	Elastin	Mesenchyme	Deficient alveolization	Wendel et al. (2000)
<i>Lmnb1</i>	Lamin B1	Epithelium and mesenchyme	Deficient alveolization	Vergnes et al. (2004)
<i>Lama5</i>	Laminin $\alpha$ 5	Epithelium and pleura	Defective lobation	Nguyen et al. (2002)
<i>Pcaf</i>	p300/CBP-associated factor	Epithelium and mesenchyme	Defective proximal and distal epithelial cell differentiation	Shikama et al. (2003)
<i>Adam17</i>	A disintegrin and metallopeptidase domain 17	Epithelium	Impaired epithelial differentiation, impaired branching	Zhao et al. (2001)
<i>Crh</i>	Corticotropin releasing hormone	Epithelium	Defective epithelial and mesenchymal maturation	Peschon et al. (1998)
<i>Pthlh</i>	Parathyroid hormone-like peptide	Epithelium	Deficient alveolization	Muglia et al. (1999)
<i>Itga3</i>	Integrin $\alpha$ 3	Epithelium	Impaired branching	Rubin et al. (2004)
<i>Cutl1</i>	Cut-like 1	Epithelium	Impaired epithelial differentiation	Kreidberg et al. (1996)
				Ellis et al. (2001)

この情報の山から  
現象を理解できるのか？

# 反応拡散系

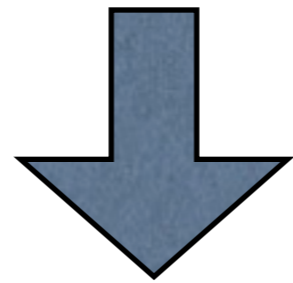


# 計算科学との関連

- 基礎方程式の不在 > 現象論的モデル
- 方程式が非線形 > (普通) 解析解が存在しない > 数値計算の必要性
- どのクラスのモデルが適切か? Computational -  
Mathematical

実験: ~100 変数

理論: 1-3 変数



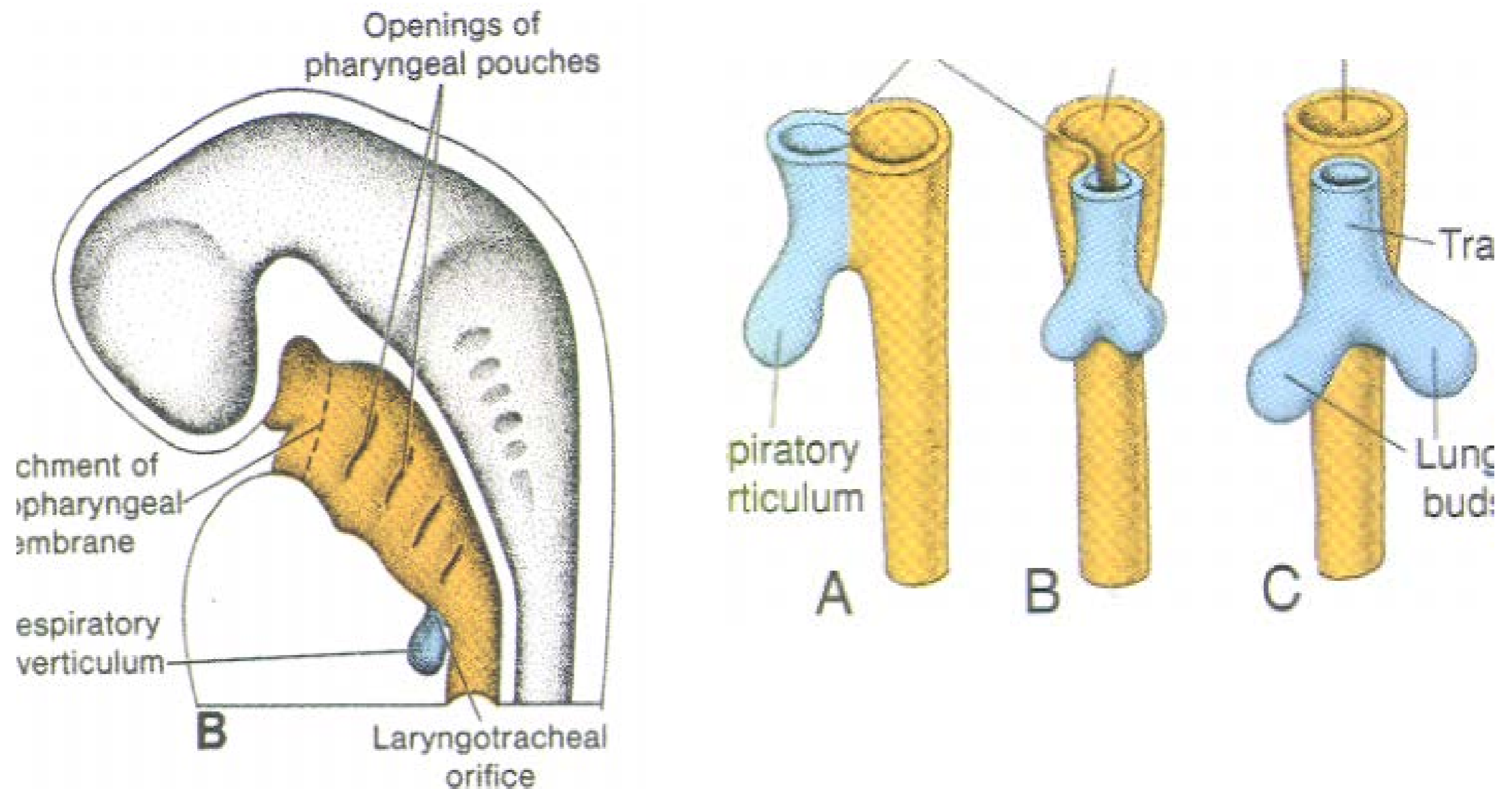
どう対応をつける？

例 1 :

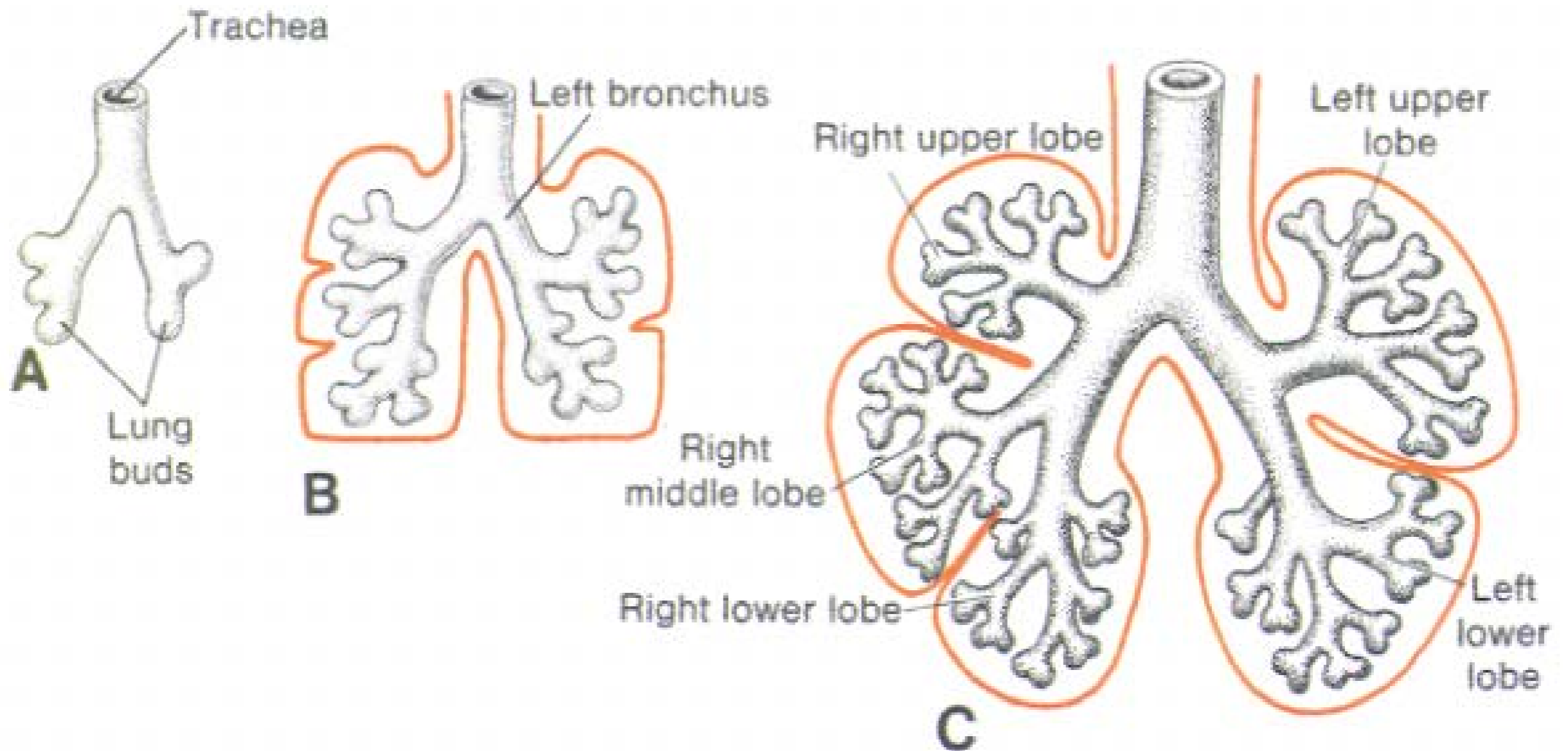
肺の枝分かれ形成



# ヒト肺の枝分かれ形成



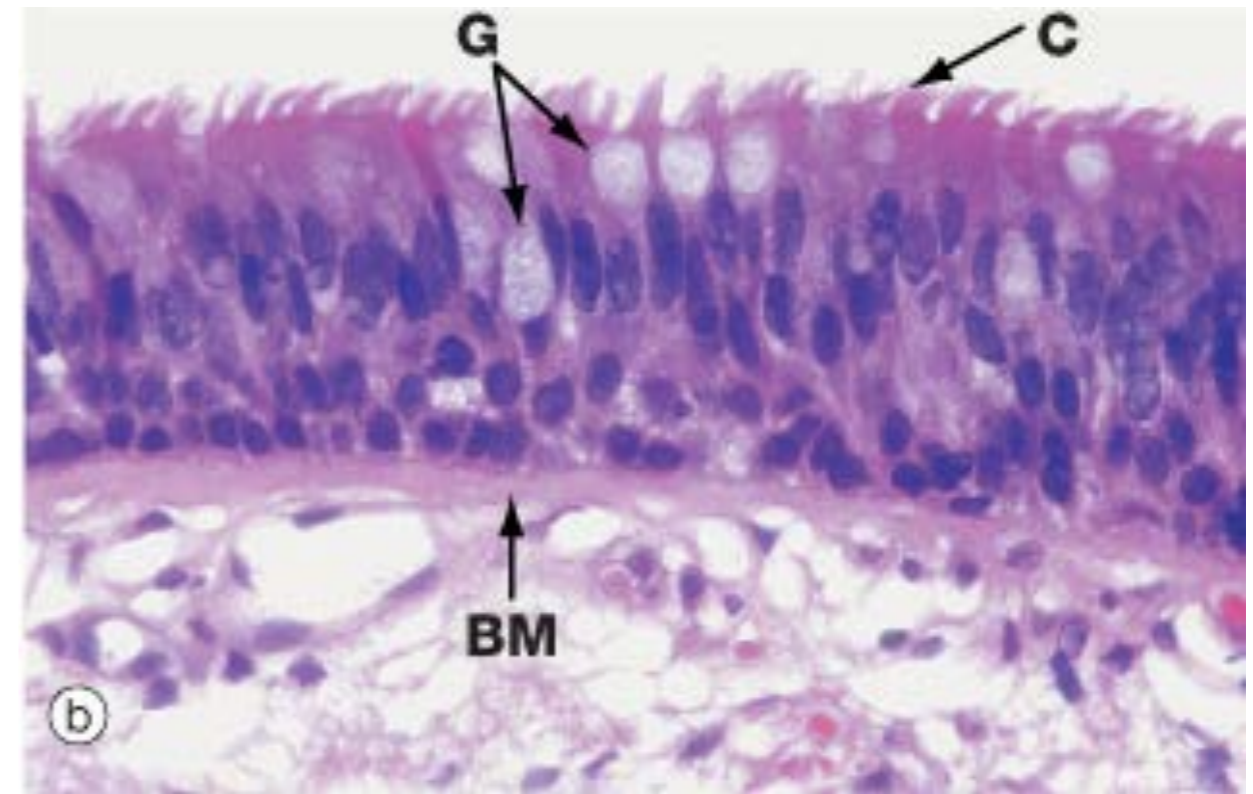
# ヒト肺の枝分かれ形成



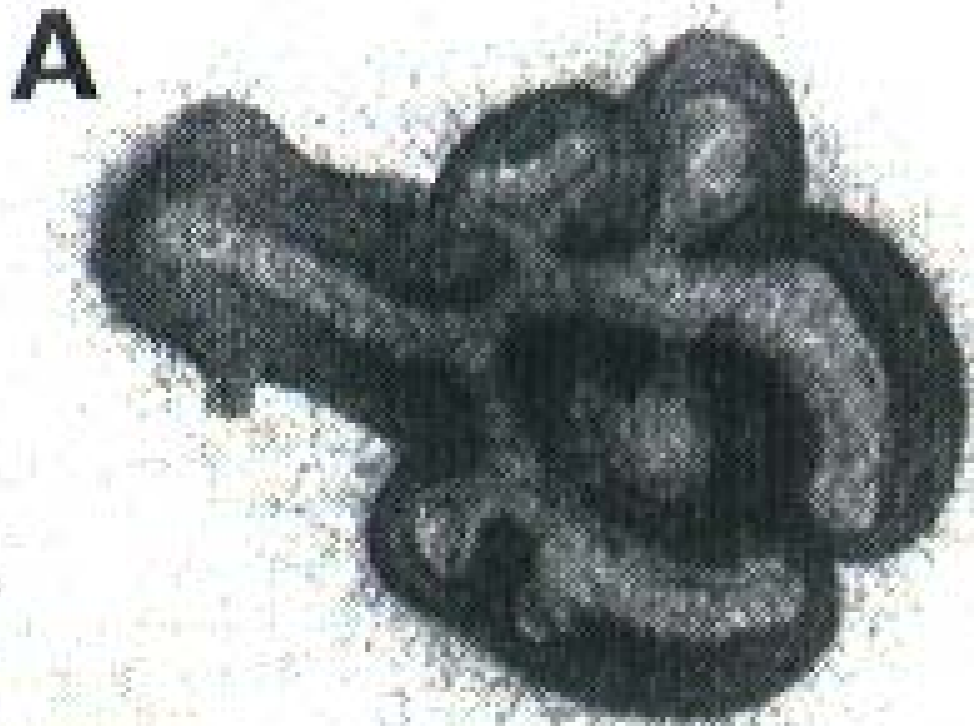
Langman's medical embryology

# 組織の種類

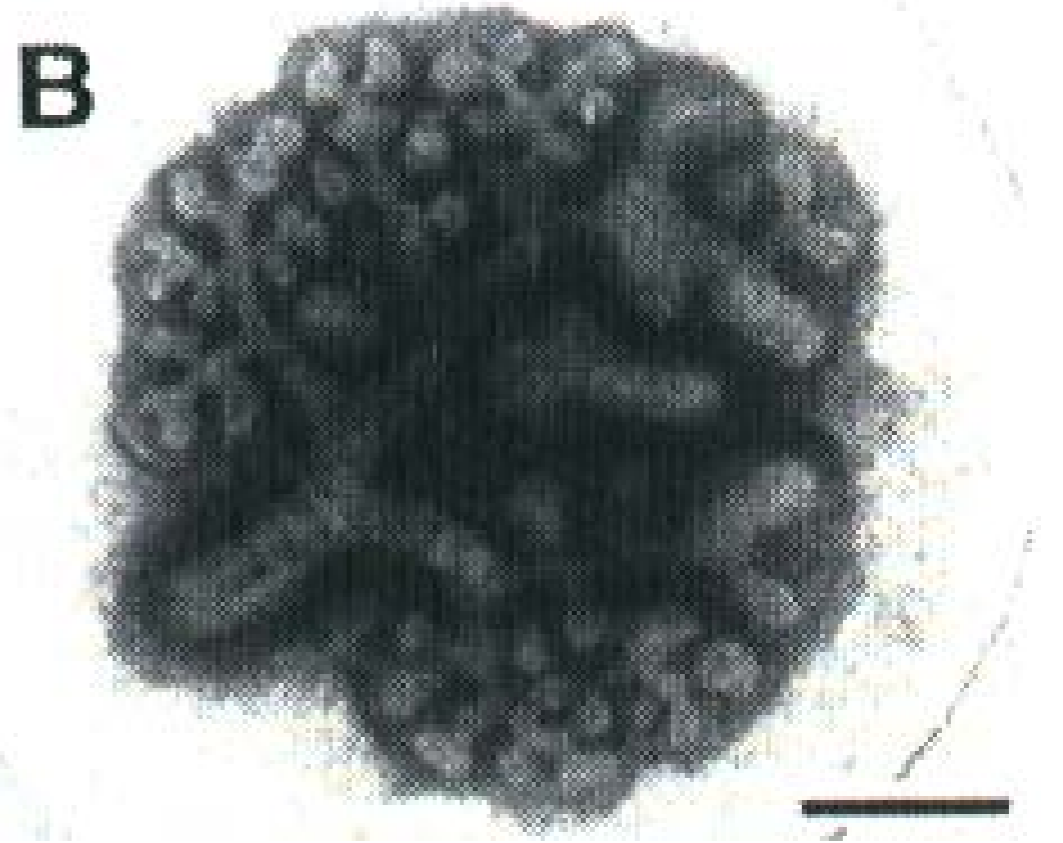
- Epithelium - interface
- Mesenchyme -inside



# 器官培養系



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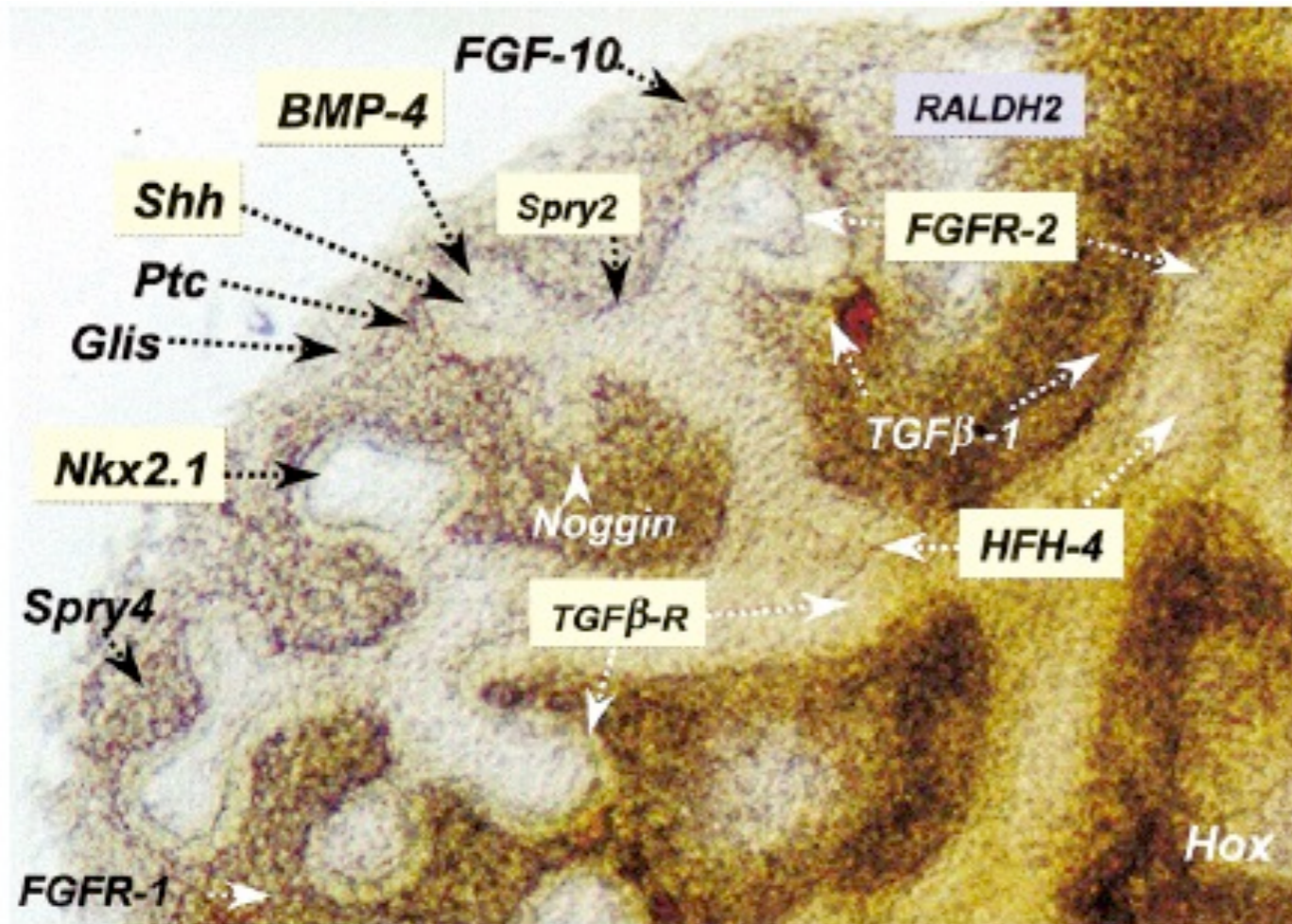


48 h

# 器官培養系



# 肺発生に関わる遺伝子



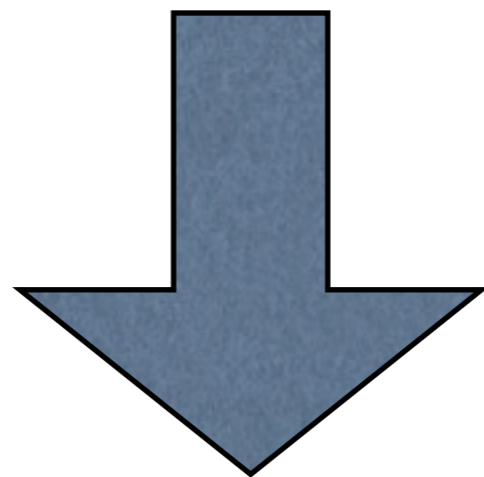
Dev Dyn 219:121-130 (2000)

Table 1. Examples of mutations in mouse giving a reported lung and/or tracheal phenotype

Gene symbol	Gene name	Expression pattern	Phenotype	Reference
<b>Signaling molecule</b>				
<i>Egfr</i>	Epidermal growth factor receptor	Epithelium and mesenchyme	Impaired branching and deficient alveolization	Miettinen et al. (1997)
<i>Fgf18</i> <i>Fgf9</i>	Fibroblast growth factor 18 Fibroblast growth factor 9	Mesenchyme Epithelium and pleura	Deficient alveolization Impaired branching, reduced mesenchyme	Usui et al. (2004) Colvin et al. (2001)
<i>Grem1</i>	Gremlin 1	Epithelium and mesenchyme	Deficient alveolization	Michos et al. (2004)
<i>Hip1</i> <i>Shh</i>	Huntingtin-interacting protein 1 Sonic hedgehog	Mesenchyme Epithelium	Impaired branching Impaired branching, tracheoesophageal fistula	Chuang et al. (2003) Litingtung et al. (1998)
<i>Tgfb3</i> <i>Wnt7b</i>	Transforming growth factor, $\beta$ 3 Wingless-related MMTV integration site 7B	Epithelium and pleura Epithelium	Impaired branching Vascular defect, reduced mesenchyme	Kaartinen et al. (1995) Shu et al. (2002)
<i>Catnbl</i>	$\beta$ -Catenin	Epithelium	Impaired branching, proximal/distal specification	Mucenski et al. (2003)
<i>Ltbp4</i>	Latent transforming growth factor $\beta$ binding protein 4	Not reported	Pulmonary emphysema	Stermer-Kock et al. (2002)
<i>Wnt5a</i>	Wingless-related MMTV integration site 5A	Mesenchyme and epithelium	Increased branching, tracheal defect	Li et al. (2002)
<i>Fgf10</i> <i>Fgfr2b</i> <i>Fgf8</i> <i>Acvr2b</i> <i>Nodal</i> <i>Lefty1</i> <i>Traf4</i> <i>Fgfr3/Fgfr4</i>	Fibroblast growth factor 10 Fibroblast growth factor receptor 2b Fibroblast growth factor 8 Activin receptor IIB Nodal Left right determination factor 1 Tnf receptor associated factor 4 Fibroblast growth factor receptor 3/4	Mesenchyme Epithelium Not reported Not reported Not reported Not reported Not reported Epithelium and mesenchyme	Lung agenesis Lung agenesis Right pulmonary isomerism Right pulmonary isomerism Right pulmonary isomerism Left pulmonary isomerism Tracheal defect Deficient alveolization	Sekine et al. (1999) De Moerlooze et al. (2000) Fischer et al. (2002) Oh and Li (1997) Lowe et al. (2001) Meno et al. (1998) Shiels et al. (2000) Weinstein et al. (1998)
<i>Nog</i>	Noggin	Mesenchyme	Lobation defect	Weaver et al. (2003)
<b>Transcription factor</b>				
<i>Cebpa</i>	CCAAT/enhancer binding protein (C/EBP), $\alpha$	Epithelium	Hyperproliferation of type II cells	Sugahara et al. (2001)
<i>Foxa1/Foxa2</i>	Forkhead box A1/A2	Epithelium	Impaired branching, reduced smooth muscle	Wan et al. (2005)
<i>Foxf1a</i> <i>Hoxa5</i> <i>Klf2</i> <i>Mycn</i>	Forkhead box F1a Homeobox A5 Kruppel-like factor 2 (lung) Neuroblastoma myc-related oncogene 1	Mesenchyme Mesenchyme Not reported Epithelium	Impaired branching, lobation defect Impaired branching, tracheal defect Impaired sacculcation Impaired branching	Lim et al. (2002) Aubin et al. (1997) Wani et al. (1999) Moens et al. (1992)
<i>Trp63</i> <i>Ttf1</i>	Transformation-related protein 63 Thyroid transcription factor 1	Epithelium Epithelium	Tracheobronchial defect Loss of distal lung fate, impaired branching, tracheoesophageal fistula	Daniely et al. (2004) Kimura et al. (1996)
<i>Nfib</i>	Nuclear factor I/B	Epithelium and mesenchyme	Sacculcation defect	Steele-Perkins et al. (2005)
<i>Sox11</i> <i>Tcf21</i> <i>Rarb/Rara</i>	SRY-box-containing gene 11 Transcription factor Z1 (Pod1) Retinoic acid receptor $\alpha/\beta$	Epithelium Mesenchyme Epithelium and mesenchyme	Hypoplastic lung Impaired branching Left lung agenesis and right lung hypoplasia	Sock et al. (2004) Quaggin et al. (1999) Mendelsohn et al. (1994)
<i>Pitx2</i>	Paired-like homeodomain transcription factor 2	Mesenchyme	Right pulmonary isomerism	Lin et al. (1999)
<i>Foxj1</i>	Forkhead box J1	Epithelium	Left-right asymmetry, loss of ciliated cells	Brody et al. (2000)
<i>Gata6</i> <i>Gliz/Gli3</i>	GATA-binding protein 6 GLI-Kruppel family member GLI2/GLI3	Epithelium Mesenchyme	Impaired sacculcation Lung agenesis	Yang et al. (2002) Motoyama et al. (1998)
<i>Ascl1</i>	Achaete-scute complex homolog-like 1	Neuroendocrine cells	Loss of neuroendocrine cells	Ito et al. (2000)
<b>Others</b>				
<i>Eln</i> <i>Lmnbl</i>	Elastin Lamin B1	Mesenchyme Epithelium and mesenchyme	Deficient alveolization Deficient alveolization	Wendel et al. (2000) Vergnes et al. (2004)
<i>Lama5</i> <i>Pcaf</i>	Laminin $\alpha$ 5 p300/CBP-associated factor	Epithelium and pleura Epithelium and mesenchyme	Defective lobation Defective proximal and distal epithelial cell differentiation	Nguyen et al. (2002) Shikama et al. (2003)
<i>Adam17</i>	A disintegrin and metallopeptidase domain 17	Mesenchyme	Impaired epithelial differentiation, impaired branching	Zhao et al. (2001) Peschon et al. (1998)
<i>Crh</i>	Corticotropin releasing hormone	Epithelium	Defective epithelial and mesenchymal maturation	Muglia et al. (1999)
<i>Pthlh</i>	Parathyroid hormone-like peptide	Epithelium	Deficient alveolization	Rubin et al. (2004)
<i>Itga3</i> <i>Cutl1</i>	Integrin $\alpha$ 3 Cut-like 1	Epithelium Epithelium	Impaired branching Impaired epithelial differentiation	Kreidberg et al. (1996) Ellis et al. (2001)

Development 133, 1611- (2006)

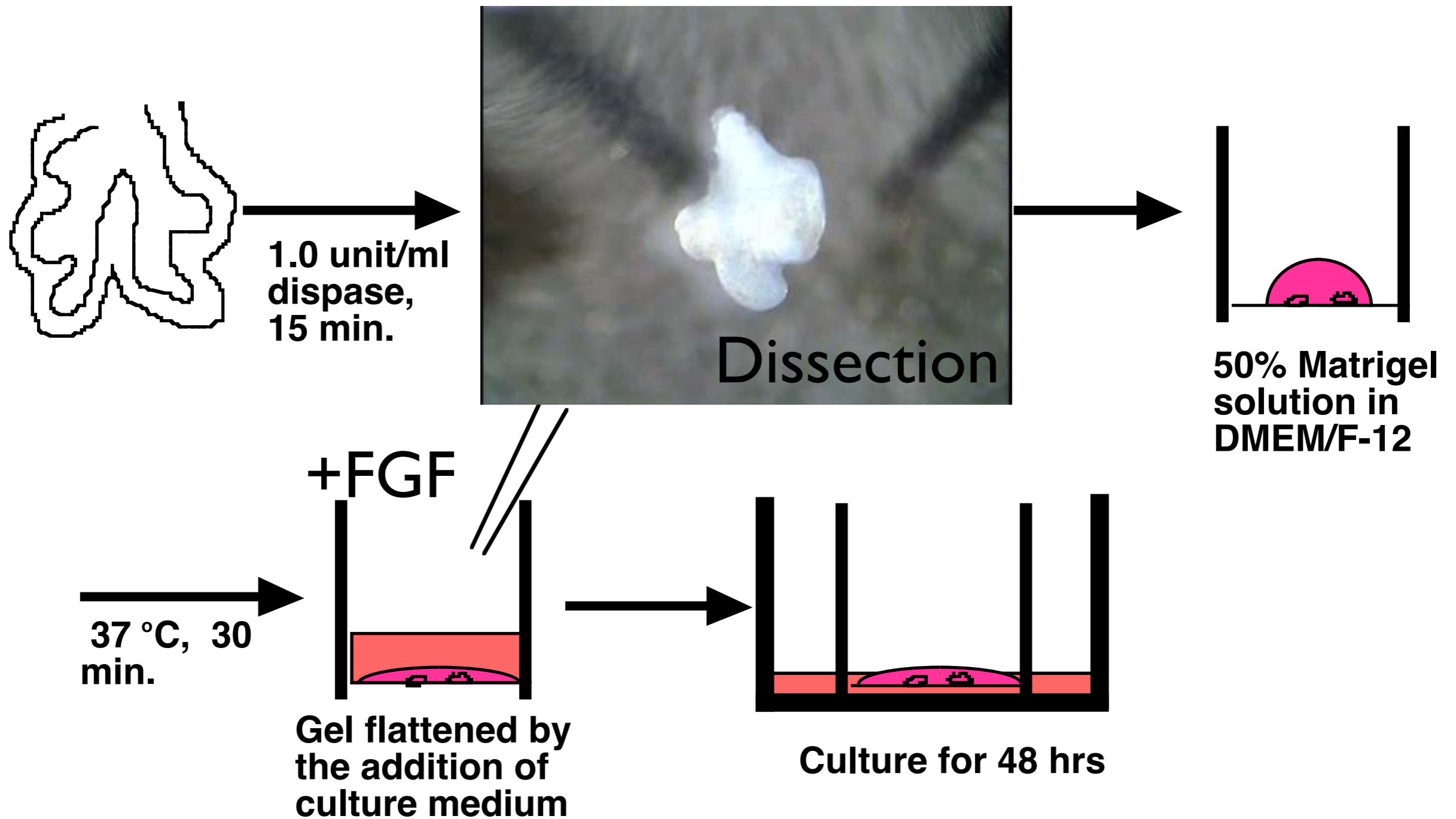
複雑すぎる



最も単純な実験系から

始める

# 上皮の単離培養



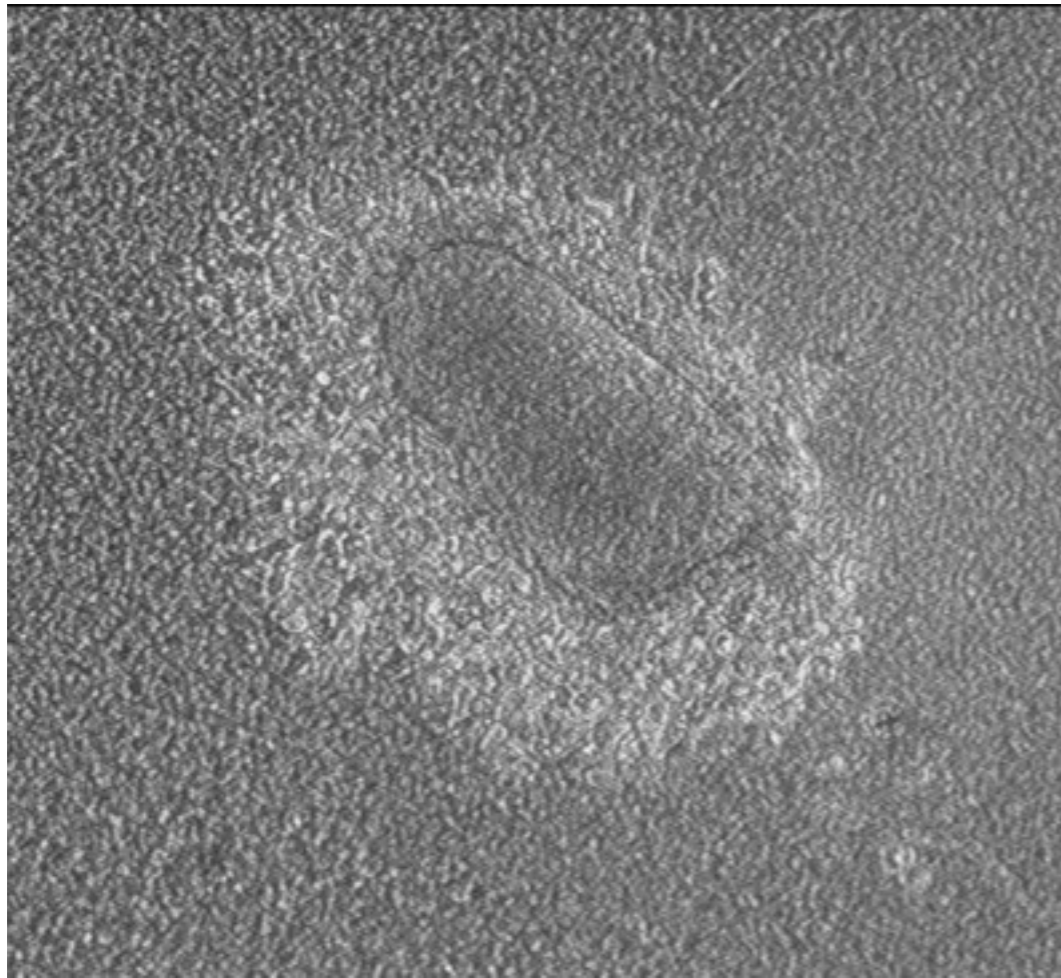
Ito & Nogawa, Development 121(4) 1015-22 (1995)



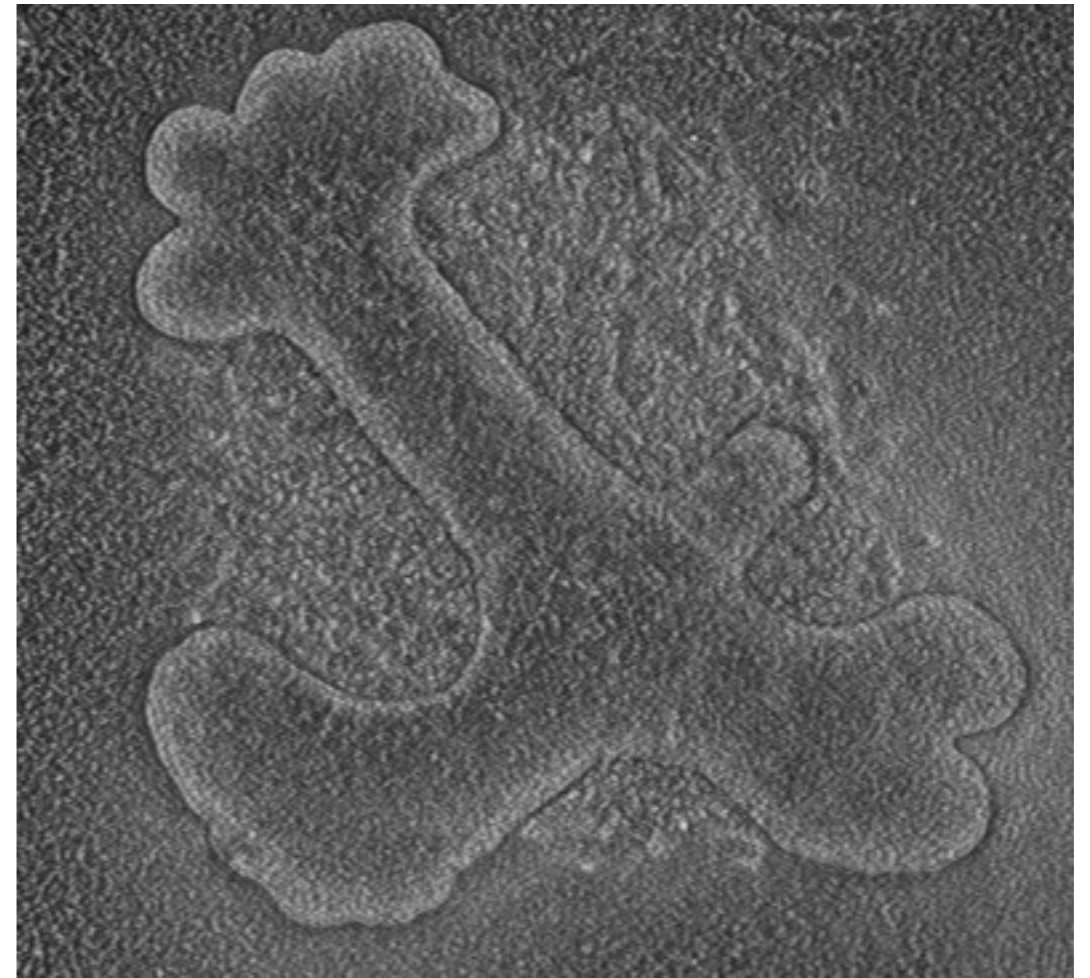
# 上皮の単離培養



# FGFがないと枝分かれが起きない



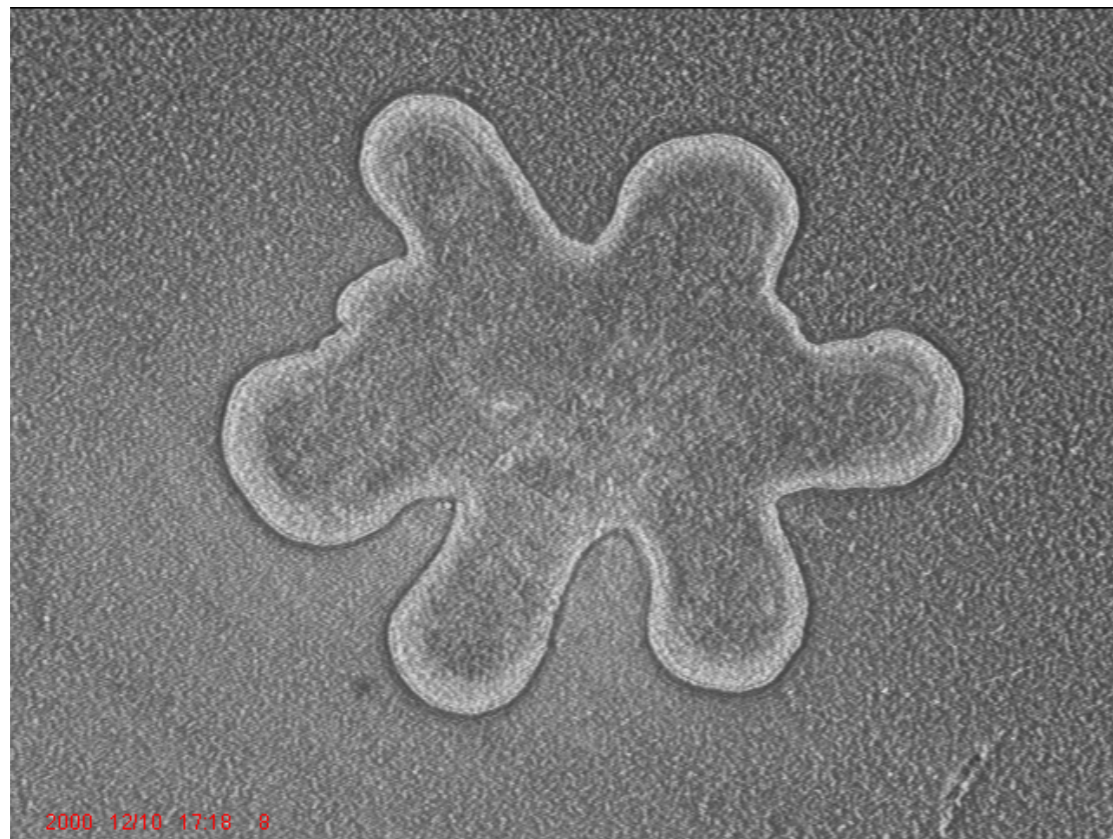
10 ng/ml FGF1



100 ng/ml FGF1

Development 121(4) 1015-22 (1995)

# 細胞外基質の分解によって 嚢胞状の形態になる

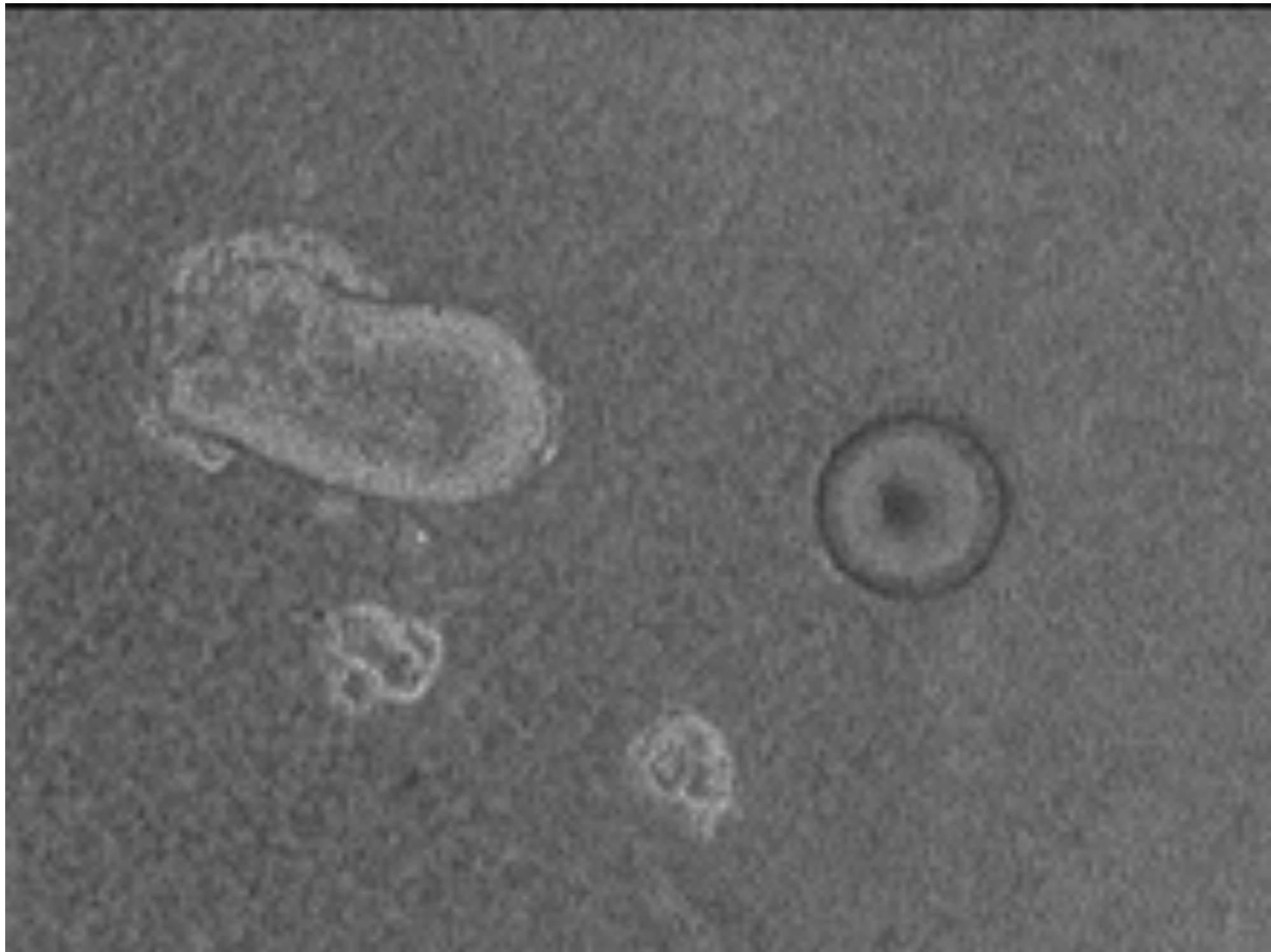


Control



2 µg/ml collagenase I

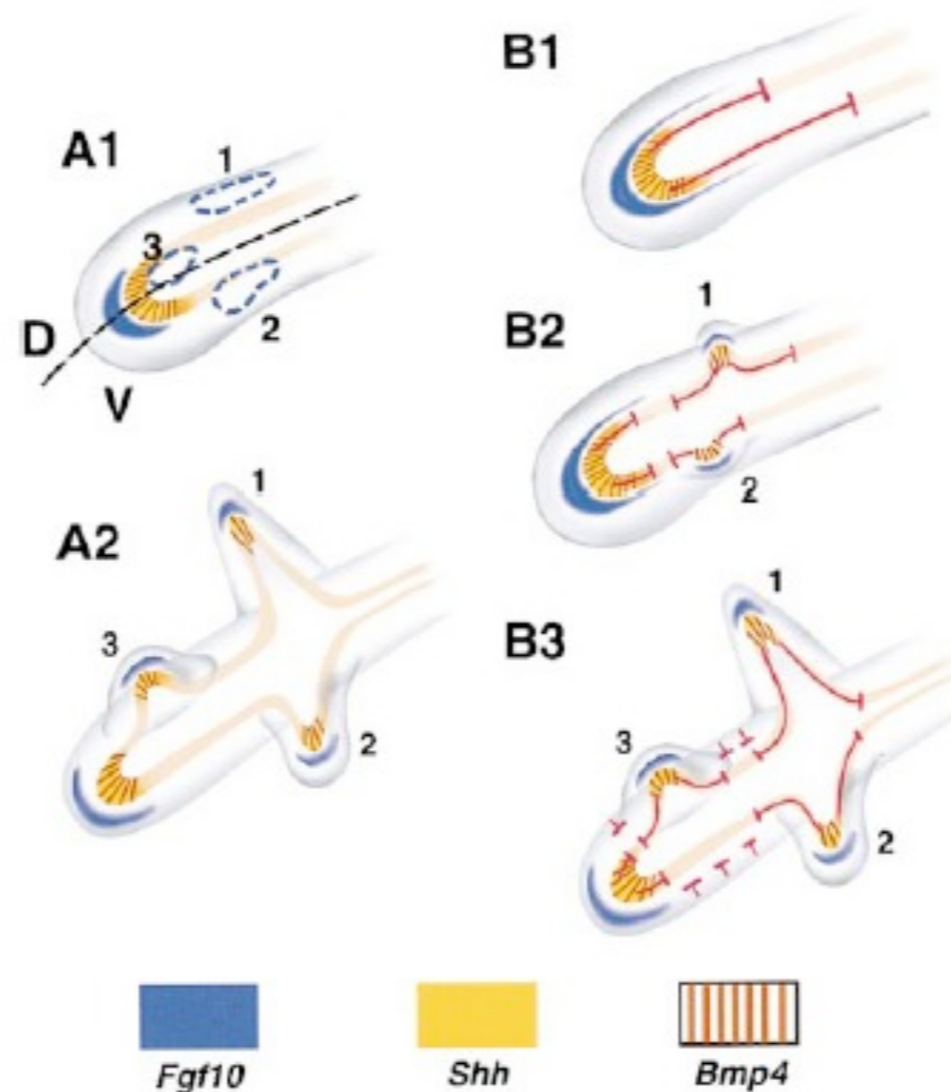
# 肺の上皮はFGFのある方に成長する



Development 124(23) 4867-78 (1997)

# 枝分れパターンは最初から

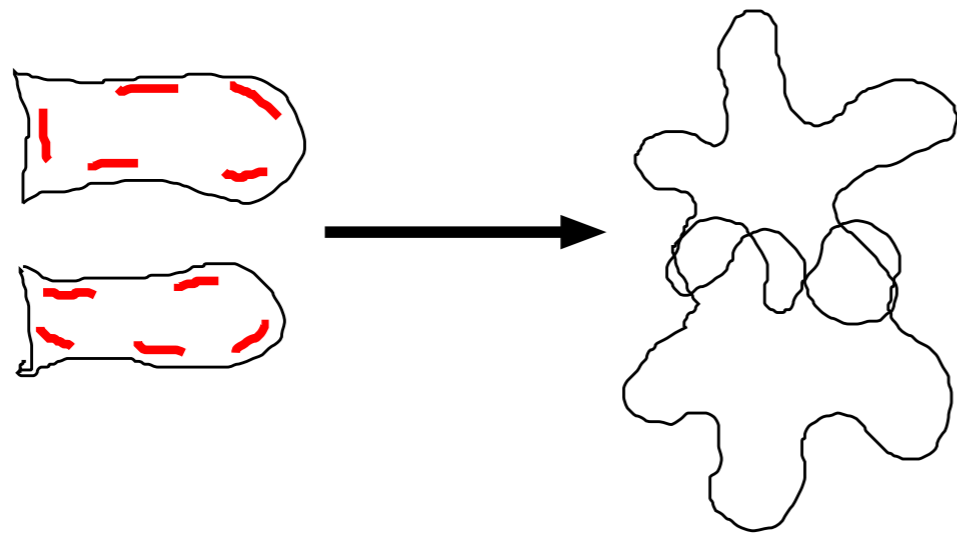
## 決まっているのか？



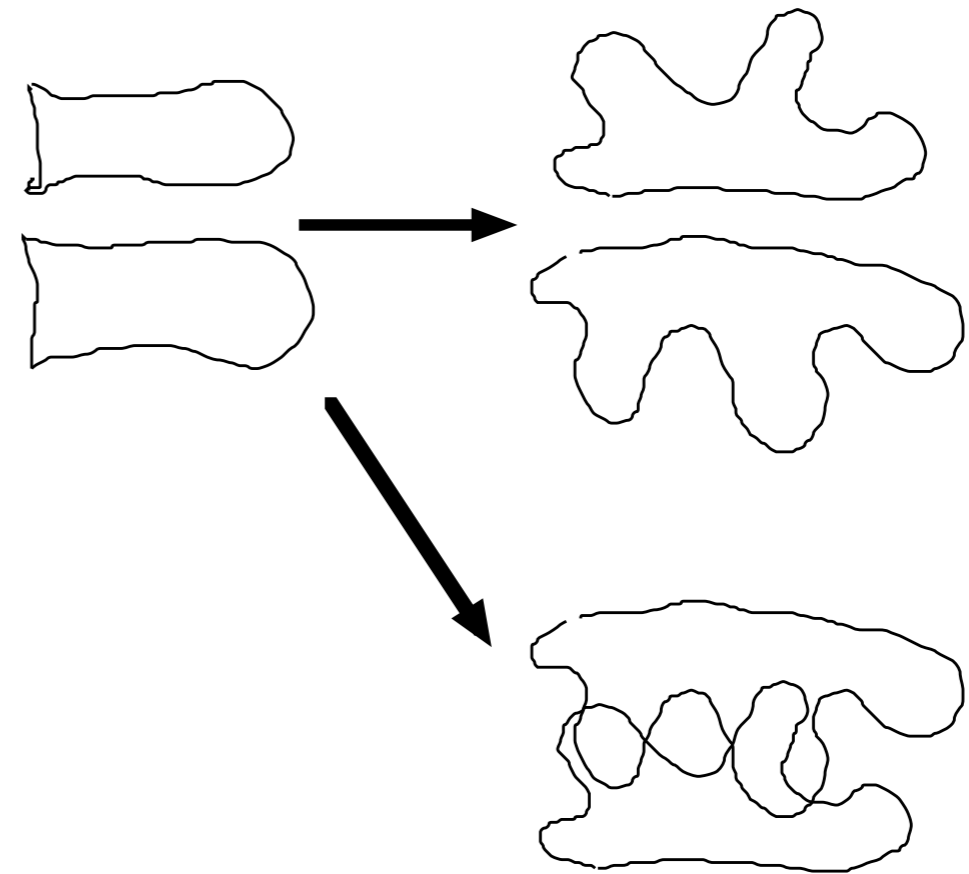
Cell 96, 225-233 (1999)

# 枝分れパターンは最初から

## 決まっているのか？

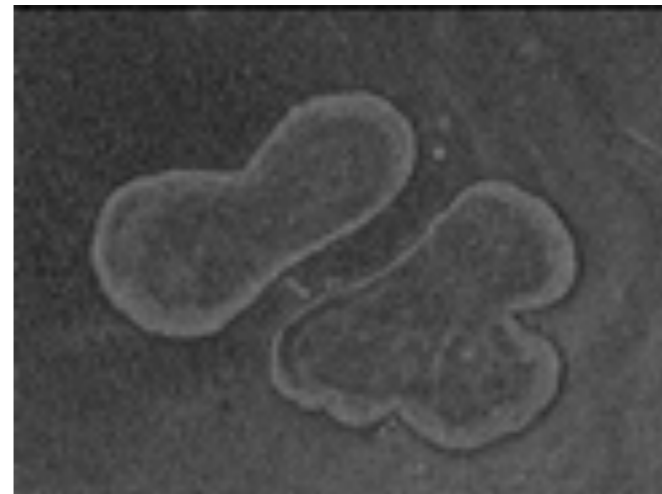
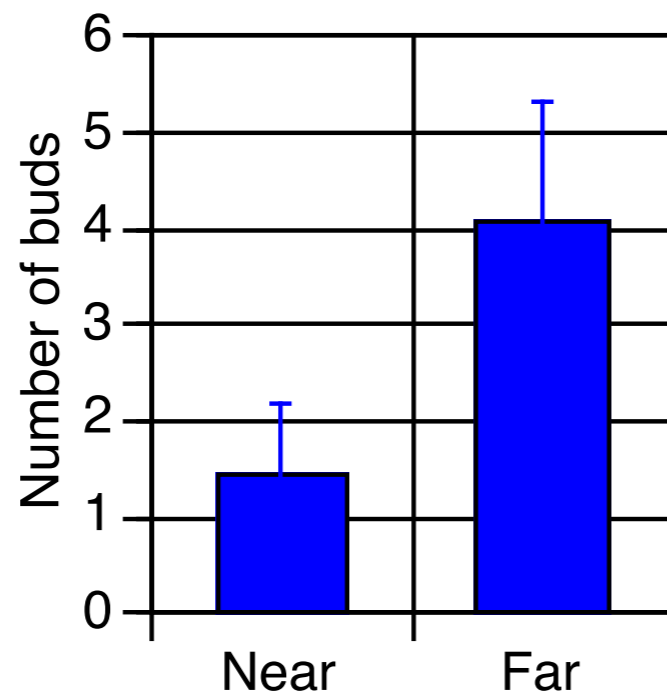
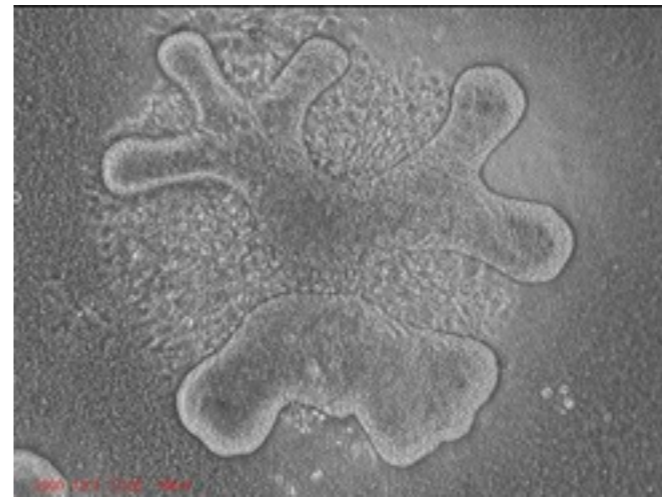
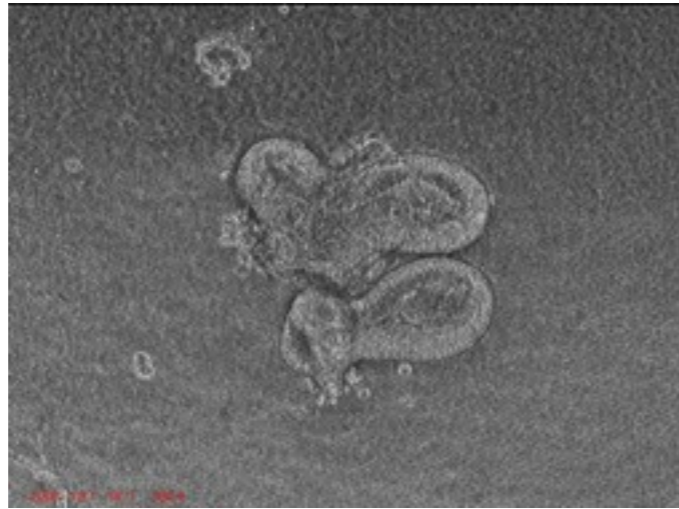


A. predetermined



B: dynamically determined

# 遮蔽效果



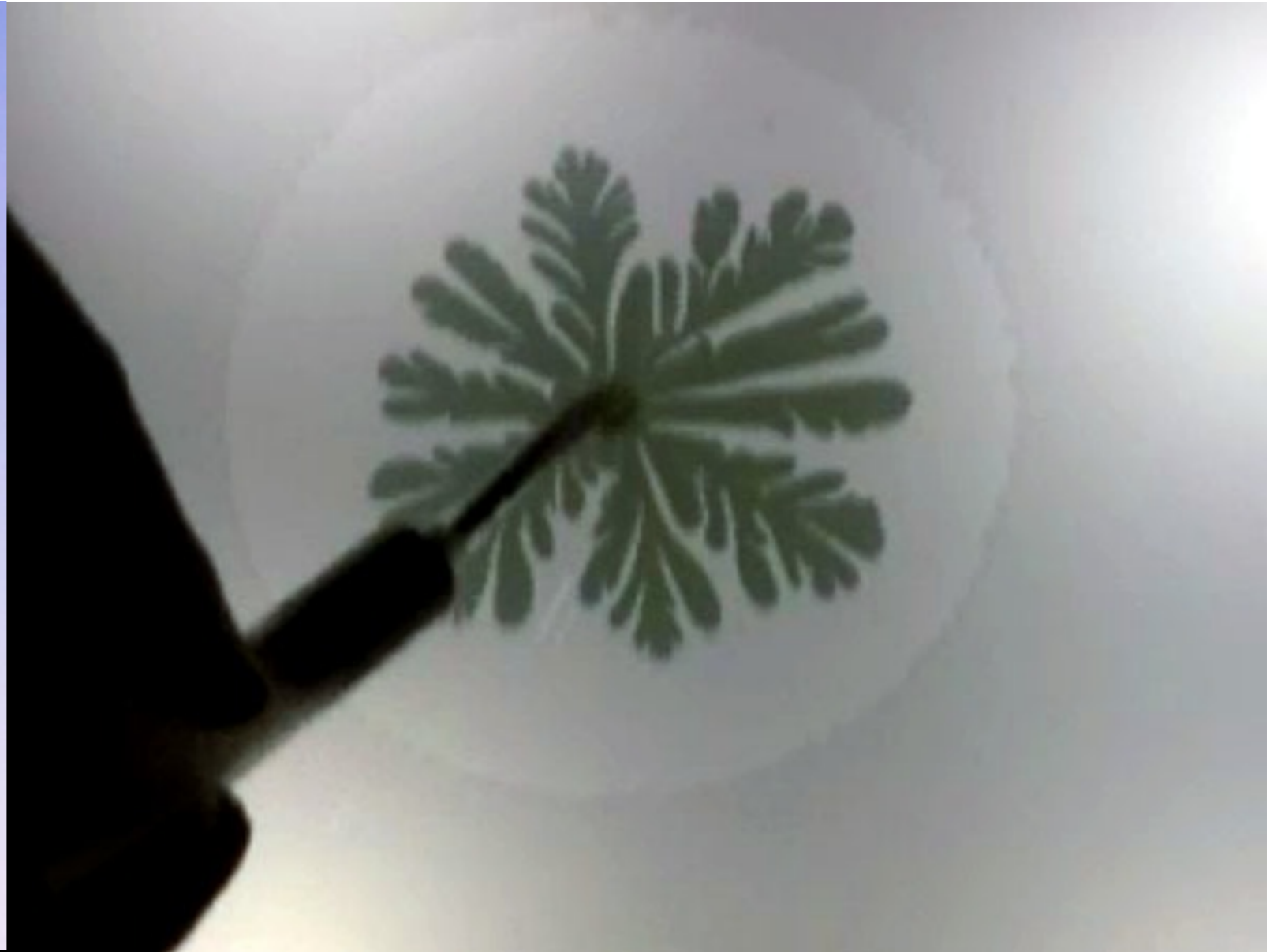
枝分れのできる原理は？



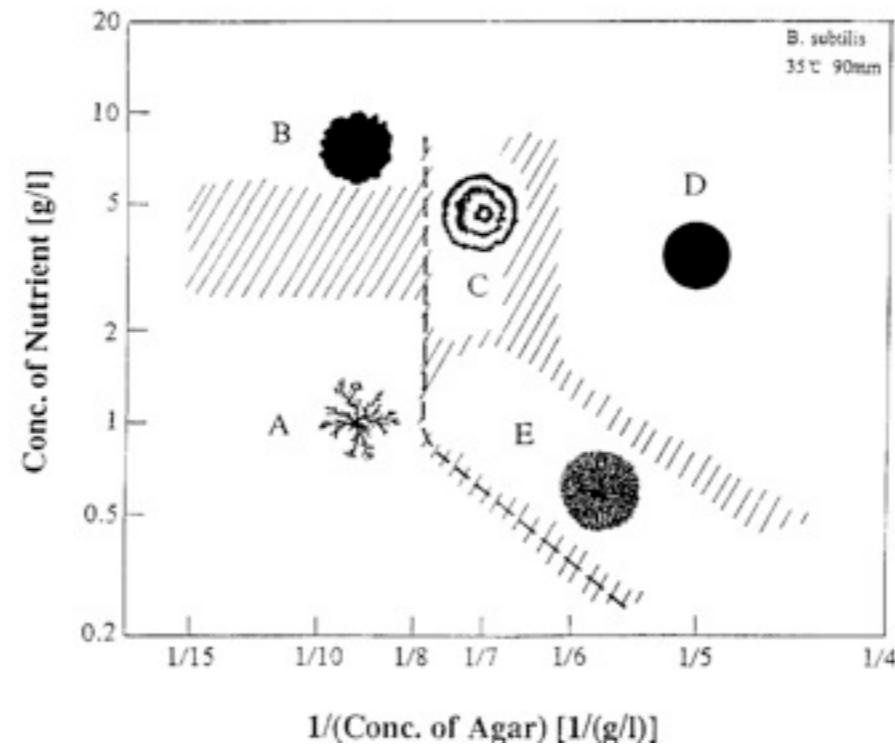
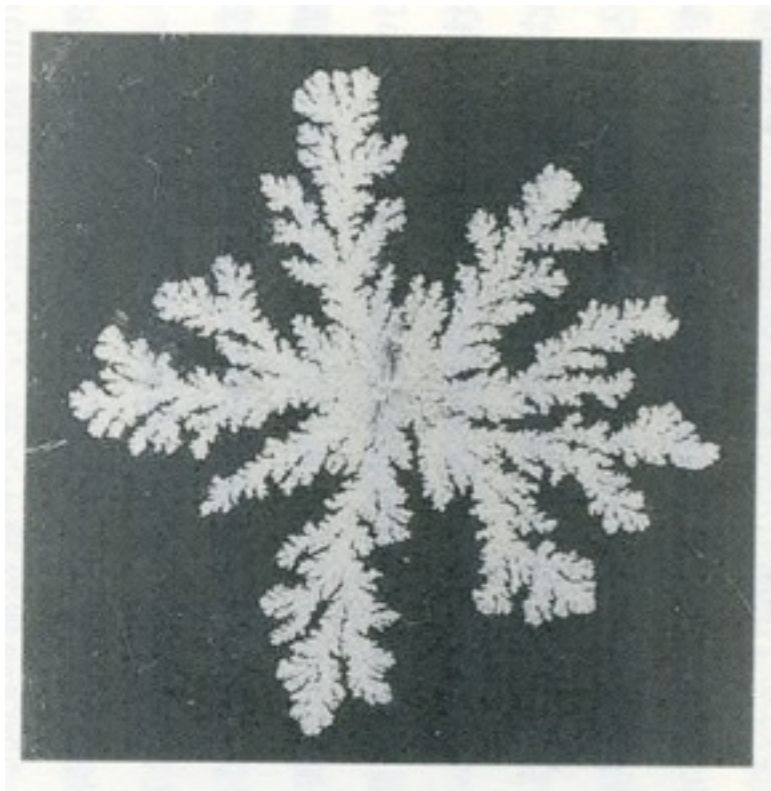
別の系に学ぶ



# 無生物で 枝分れを起こす系



# バクテリアコロニーの パターン形成



松下貢先生  
(中大)

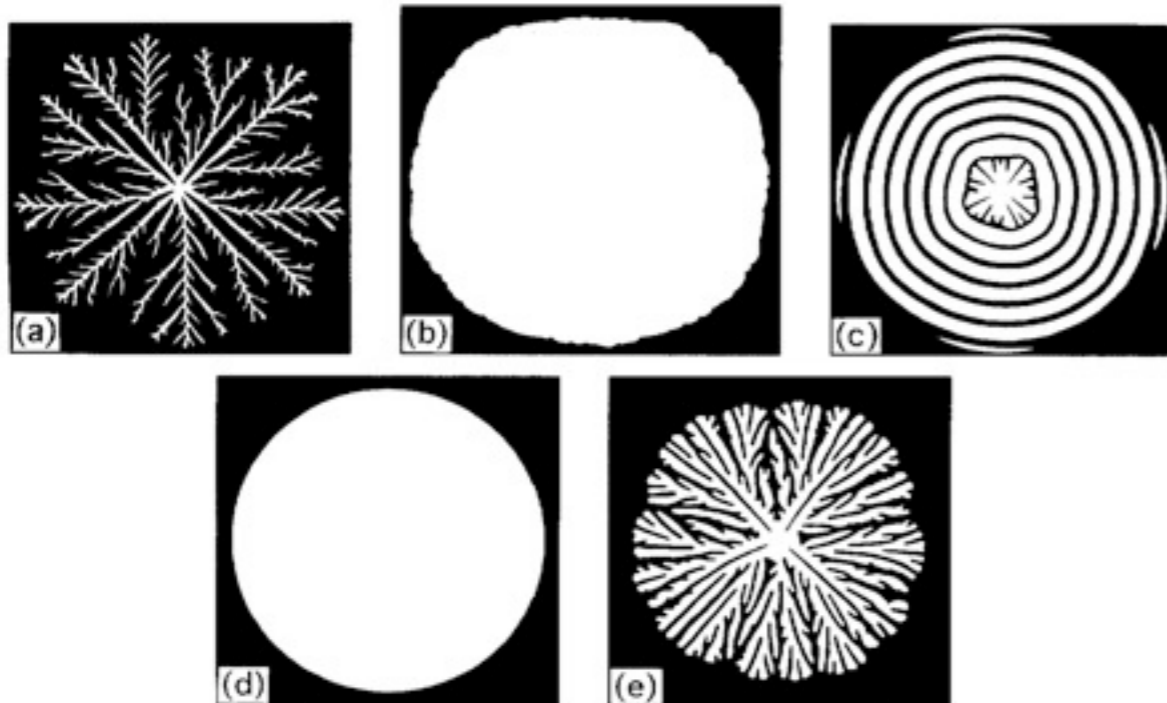
低栄養下でバクテリアのコロニーが  
様々なパターンをつくる

# 三村モデル

$$\frac{\partial b}{\partial t} = \nabla(d(b, n)\nabla b) + \varepsilon g(n)b - a(b, n)b,$$

$$\frac{\partial s}{\partial t} = a(b, n)b,$$

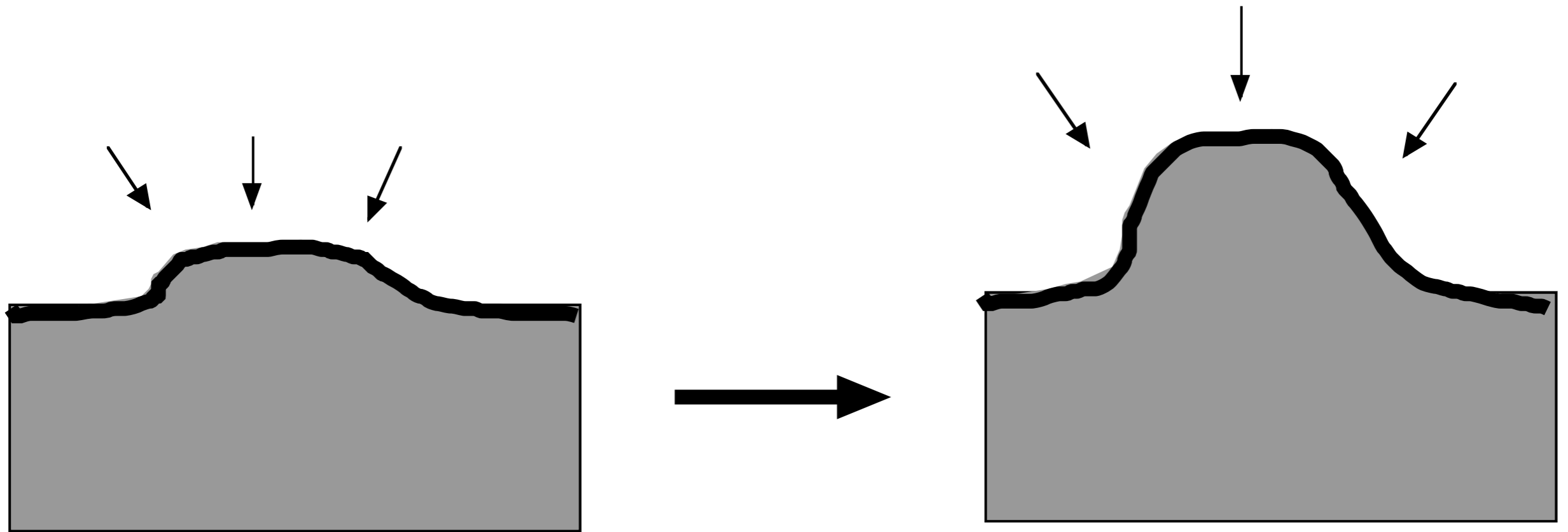
$$\frac{\partial n}{\partial t} = \nabla^2 n - g(n)b.$$



三村昌泰先生 (明大)

Mimura et al., Physica A 249, 517- (1998)

“突起の部分が早くのびる”



# 対応が薄々見える

- FGF = 栄養
- 肺の上皮細胞=バクテリアの細胞密度

# FGF欠乏モデル

- 細胞密度  $c(x, y, t)$
- FGF 濃度  $n(x, y, t)$
- 細胞はFGFを消費して成長する
- FGF はゲルの中を拡散する
- 細胞は一定の細胞密度を保つように動く

# 定式化 (離散モデル)

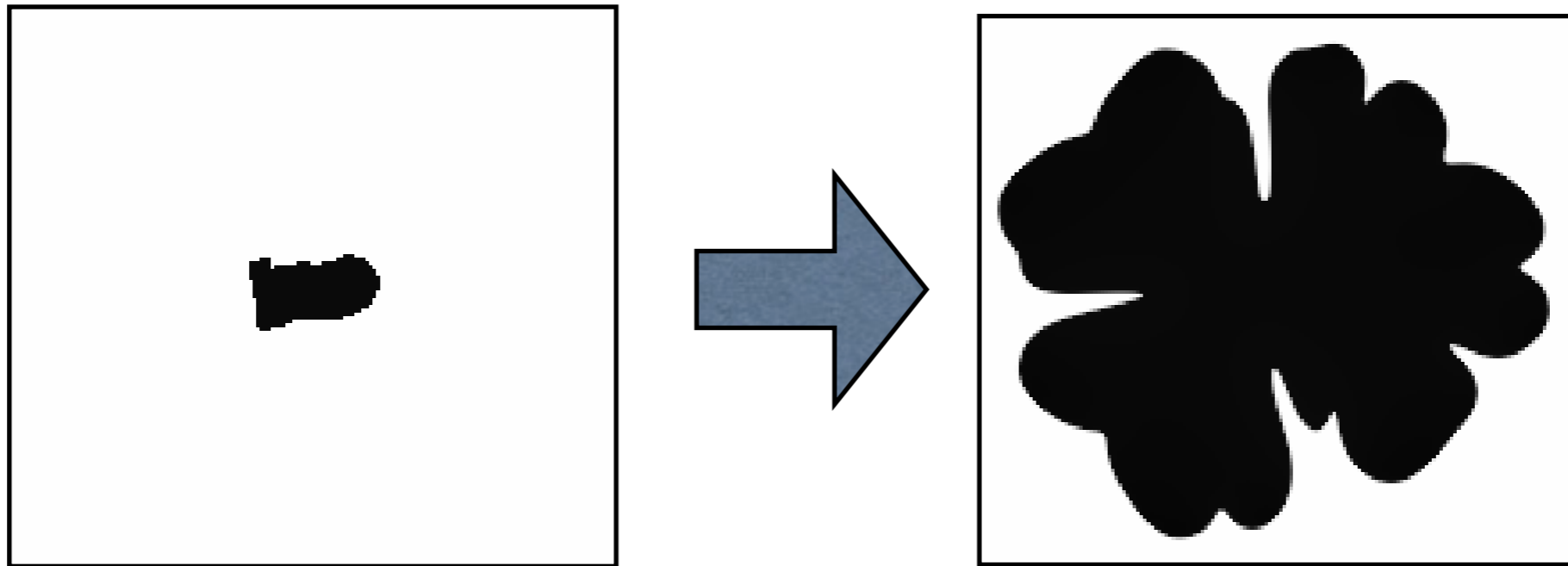
$$\begin{aligned}c(x, y, t + 1) - c(x, y, t) &= pf(c(x, y, t), n(x, y, t)) + d_1 J(c) \\n(x, y, t + 1) - n(x, y, t) &= -f(c(x, y, t), n(x, y, t)) + d_2 \Delta(c)\end{aligned}$$

$$\begin{aligned}\Delta(n) &= n(x + 1, y, t) + n(x - 1, y, t) \\&+ n(x, y + 1, t) + n(x, y - 1, t) \\&- 4n(x, y, t)\end{aligned}$$

$$J(c) = \Delta(\Phi(c - c_0))$$

$$\Phi(x) = \begin{cases} 0 & (x < 0) \\ x & (x \geq 0) \end{cases}$$

# 数值計算



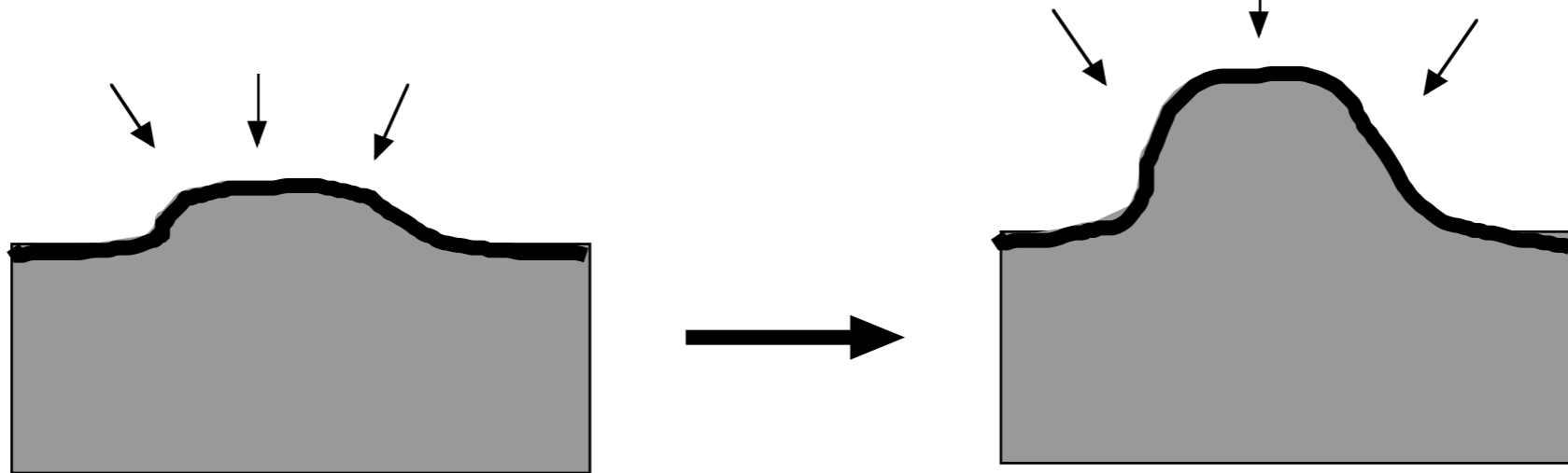
$$f(c, n) = \frac{5cn}{1 + 3n}, p = 1.0$$

$$d_1 = 4.0, d_2 = 1.7$$

$$n_0 = 0.5, c_0 = 1.0$$



# 直感的説明



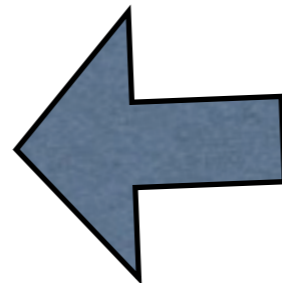
Slight protrusion



Growth



Higher FGF  
concentration

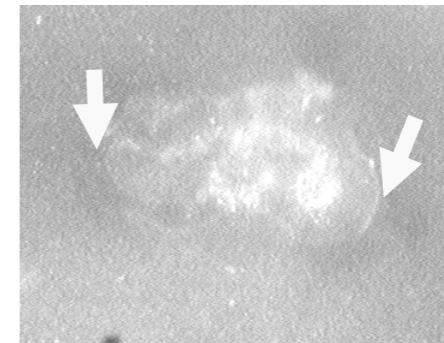


# FGFは消費されているか？

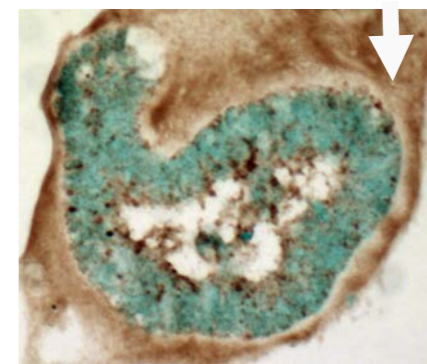
FGF distribution in  
numerical simulation



Cy3-labeled FGFI



FGFI immunohistochemistry



# 遮蔽効果の抑制

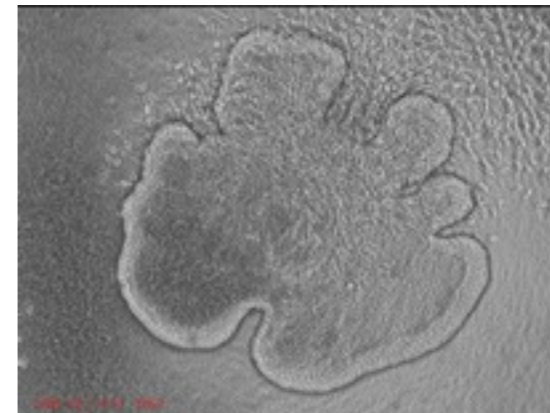
Simulation

Experiment

Low FGF

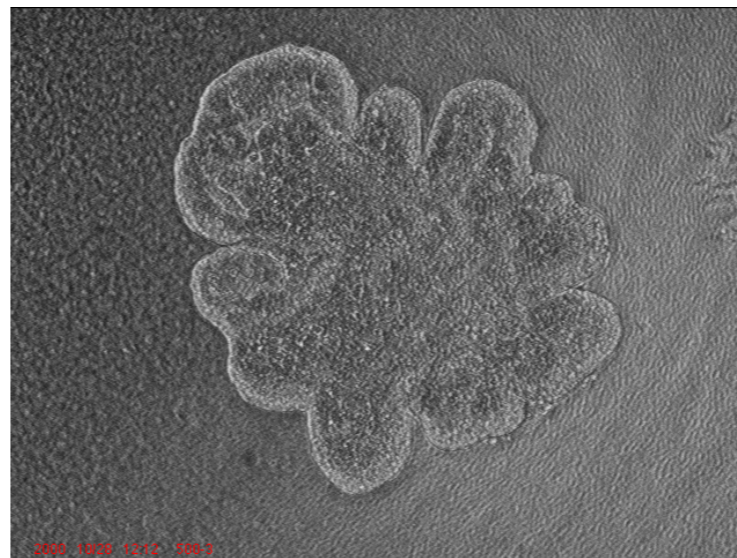


High FGF

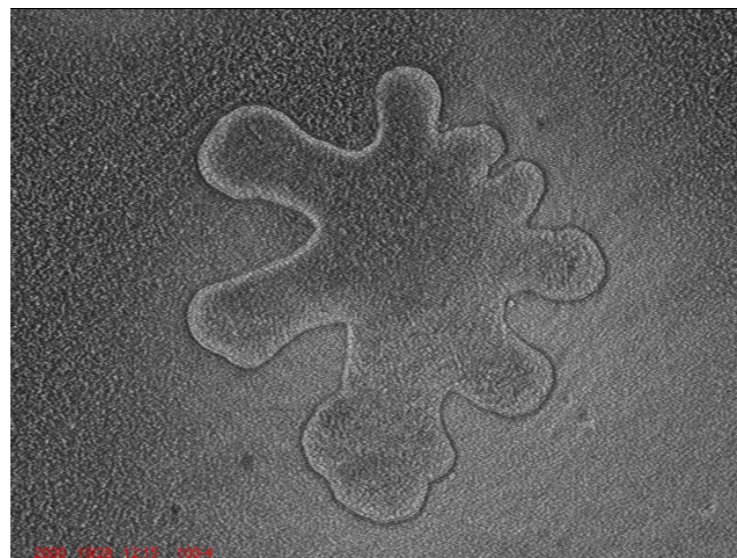


# FGFの濃度変化による 形態変化

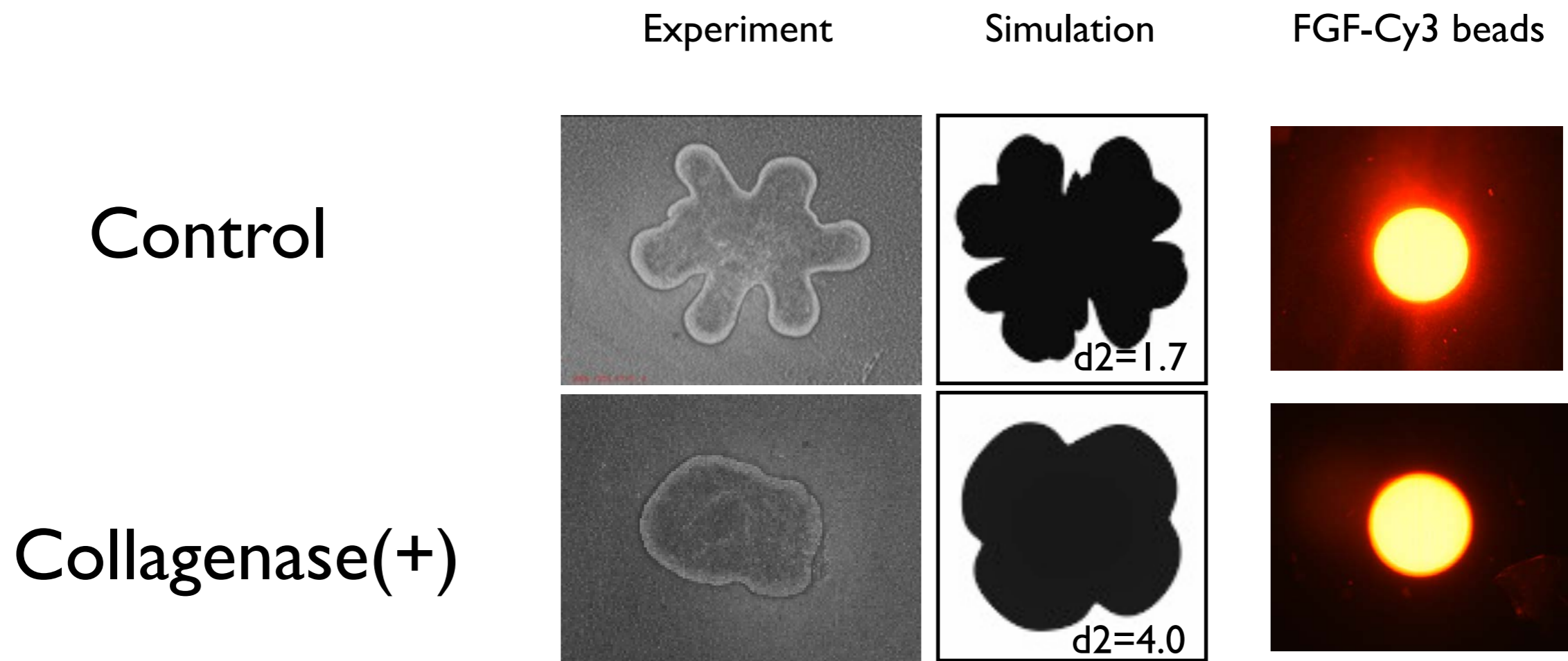
500 ng/ml FGF1



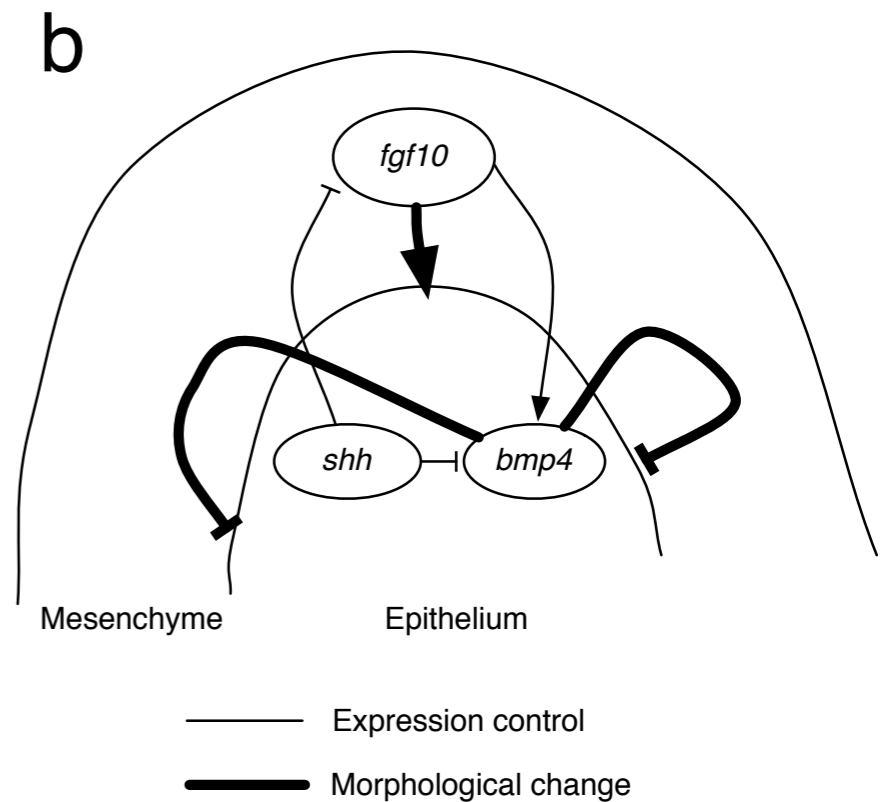
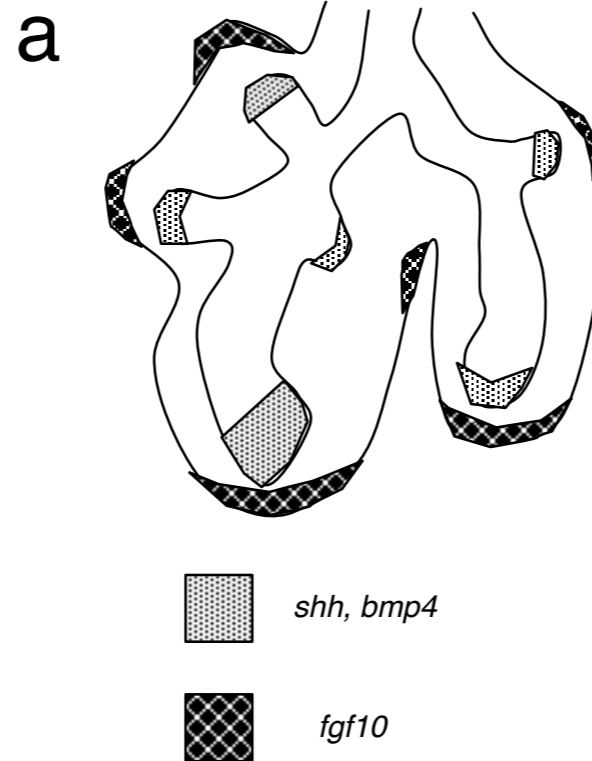
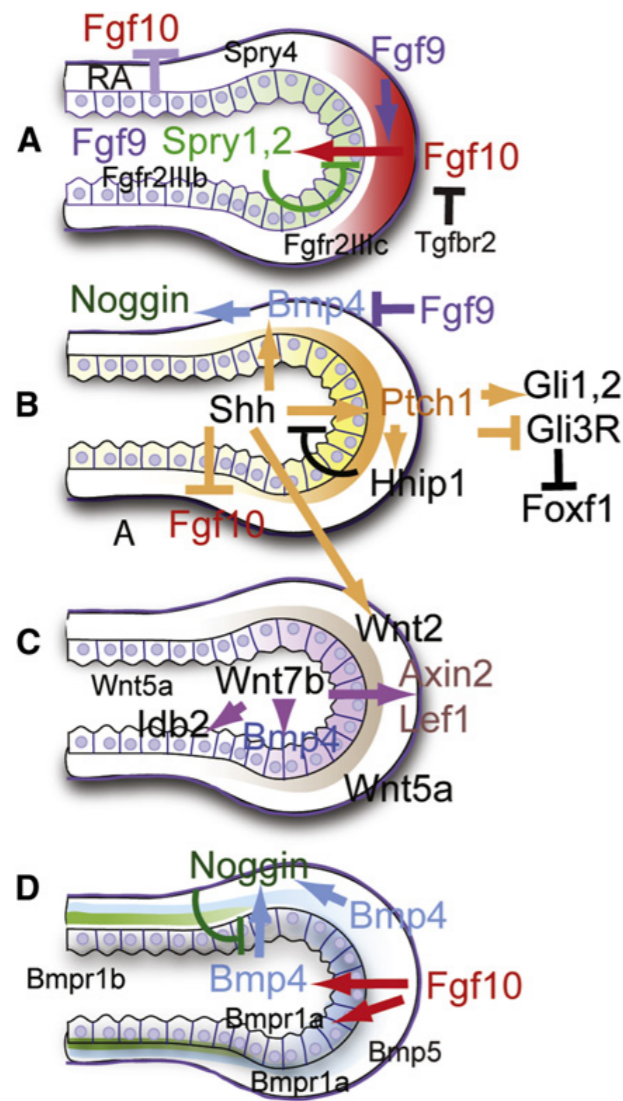
100 ng/ml FGF1



# 細胞外基質の分解と 嚢胞構造形成



# 生体内のメカニズムは まだよくわかっていない



Dev Cell 18, 8- (2010)

Curr Top Dev Biol, 81, 291-301 (2008)

# まとめ1

- 培養肺上皮の枝分かれ構造形成は反応拡散系を用いたモデルで理解できる
- 実際の分子がモデルに入っていると実験的検証ができる
- 生体内の、上皮間葉間相互作用による枝分かれ形成のメカニズムはまだよくわかっていない

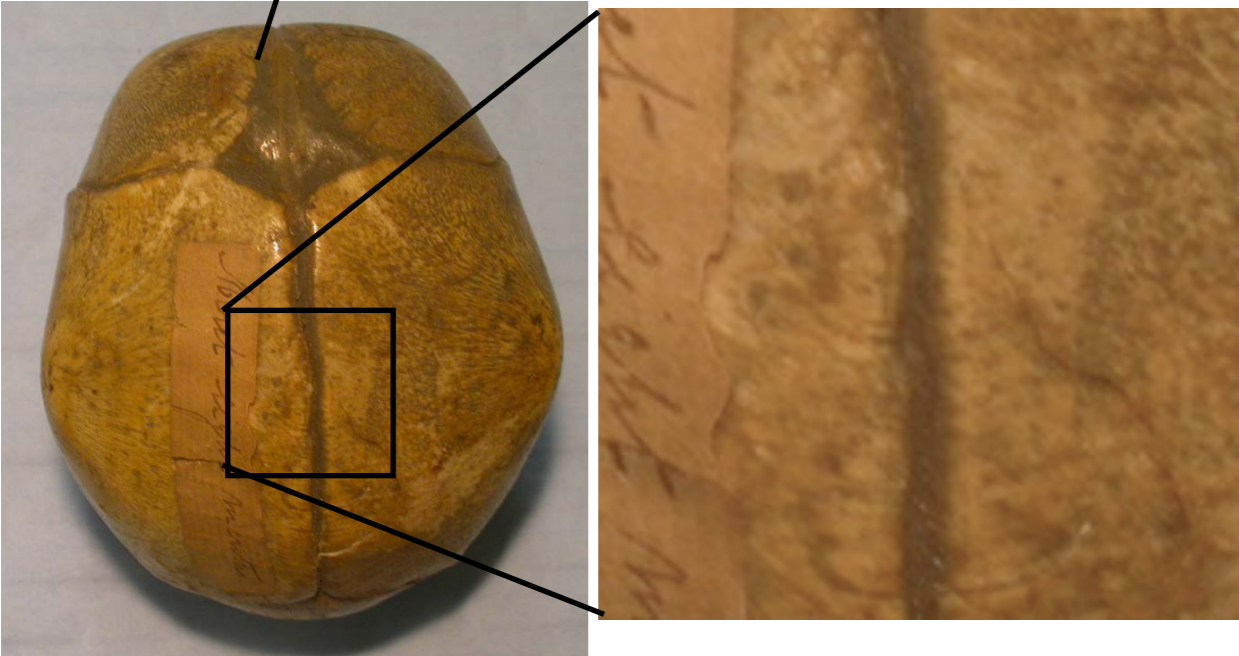
例 2 :

頭蓋骨縫合線形成

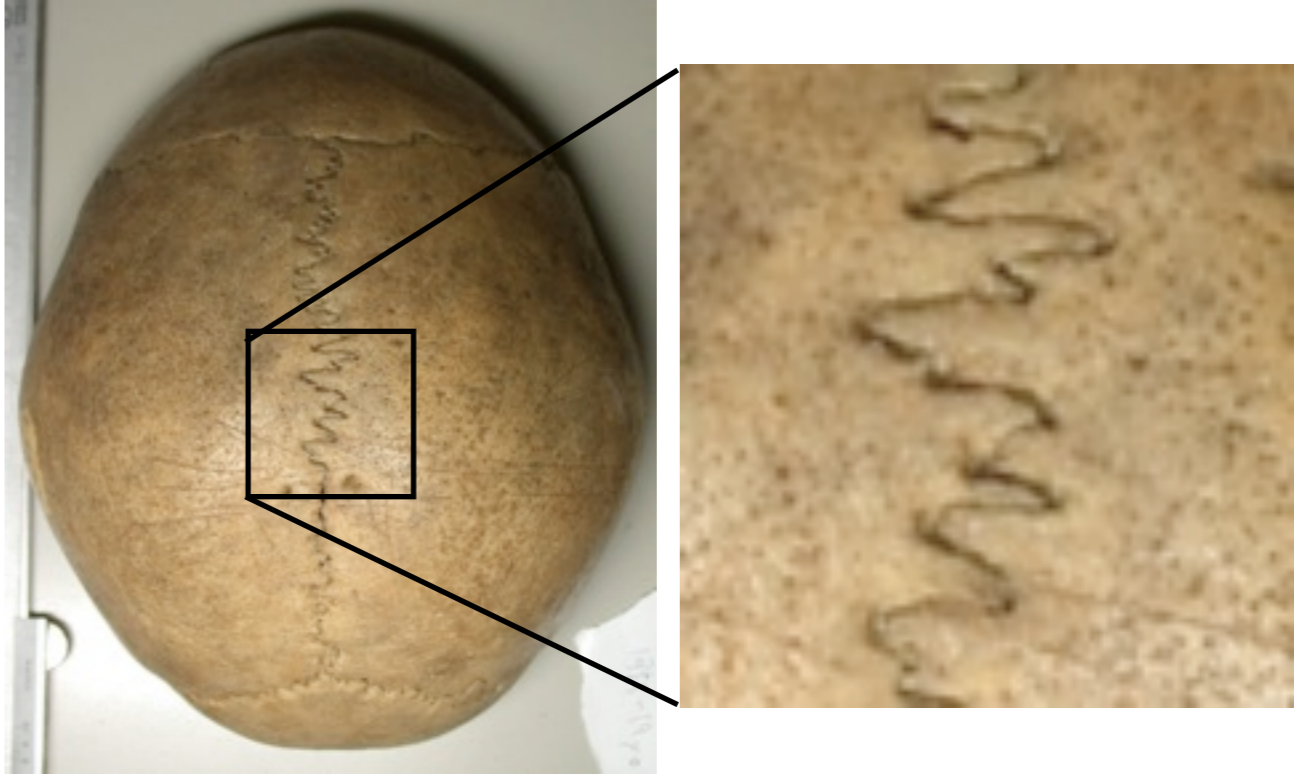


# 頭蓋骨の縫合線のパターン形成

前頭縫合

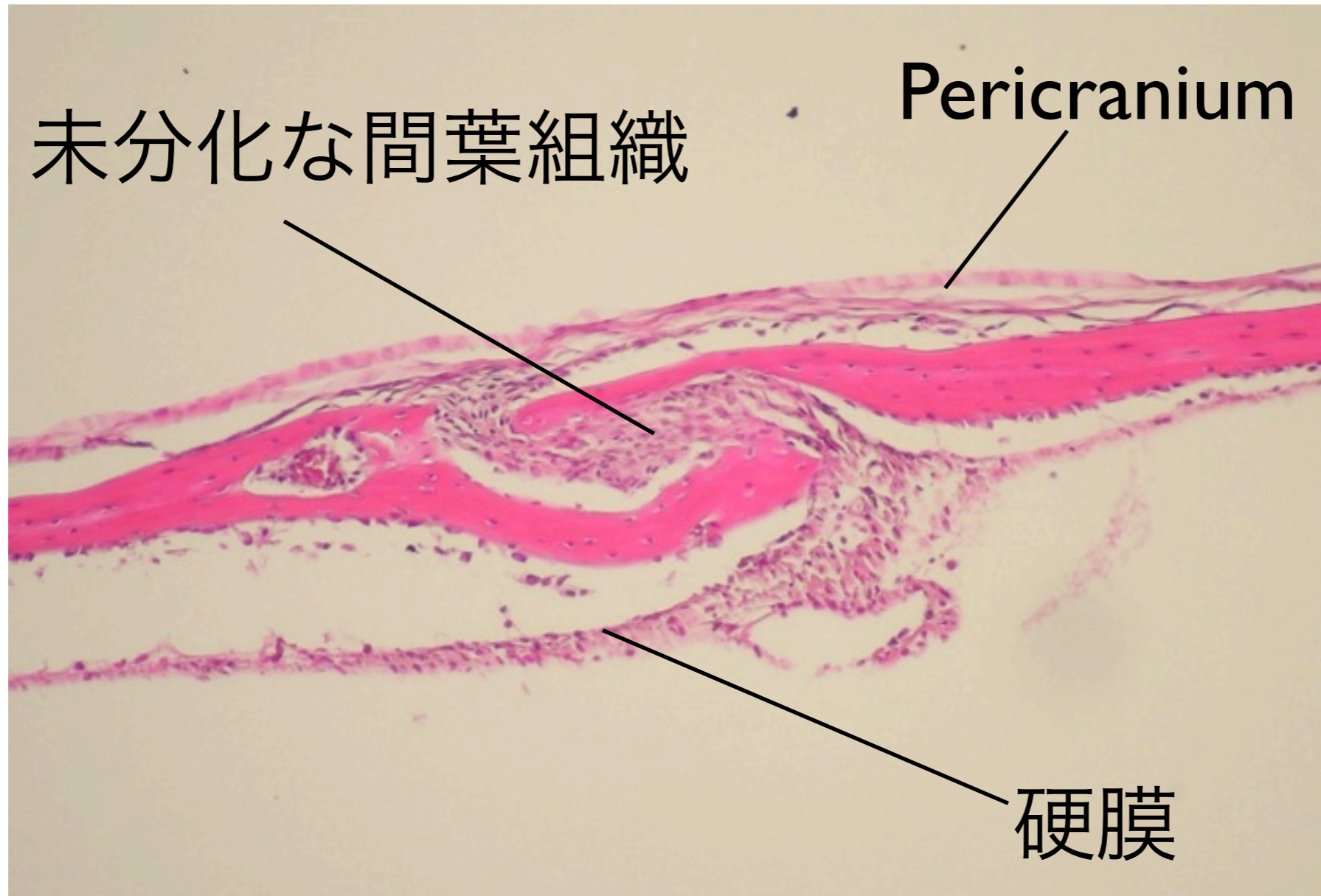


新生児



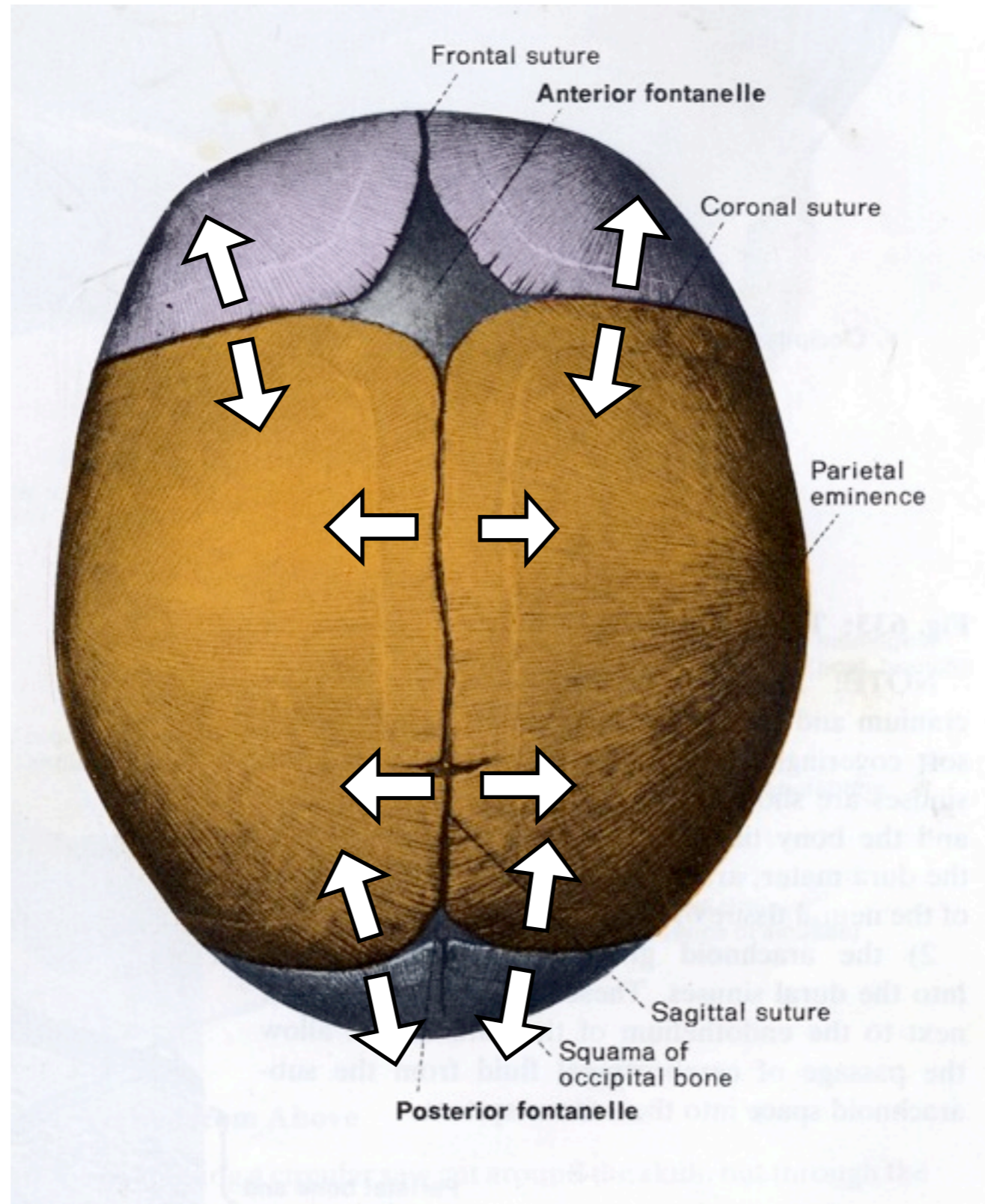
成人

# 組織

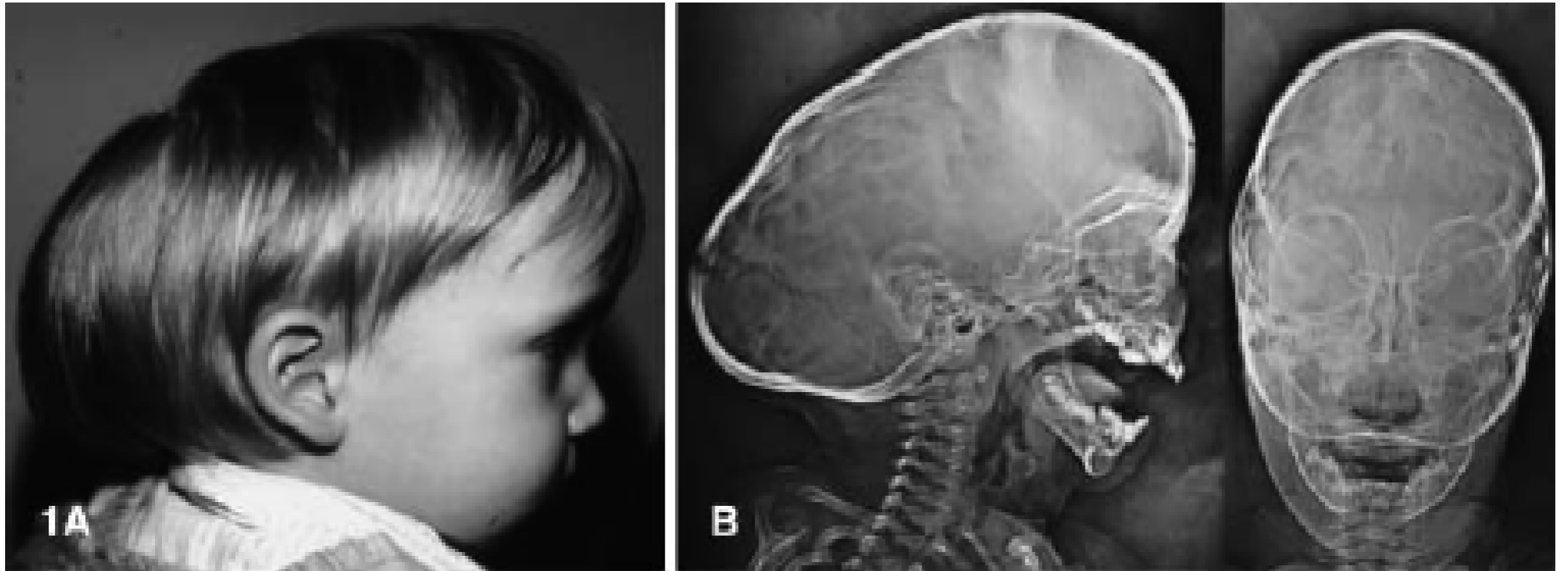


3週齡マウス矢状縫合

# 機能：頭蓋骨の成長



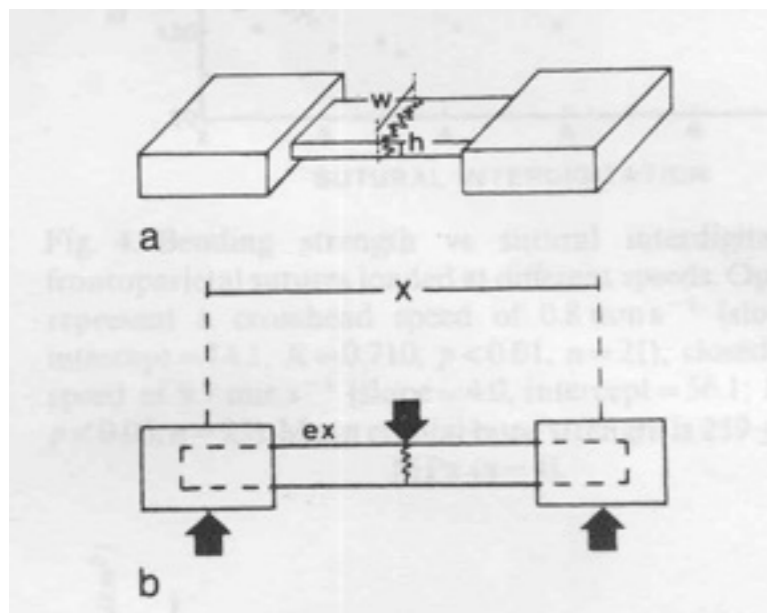
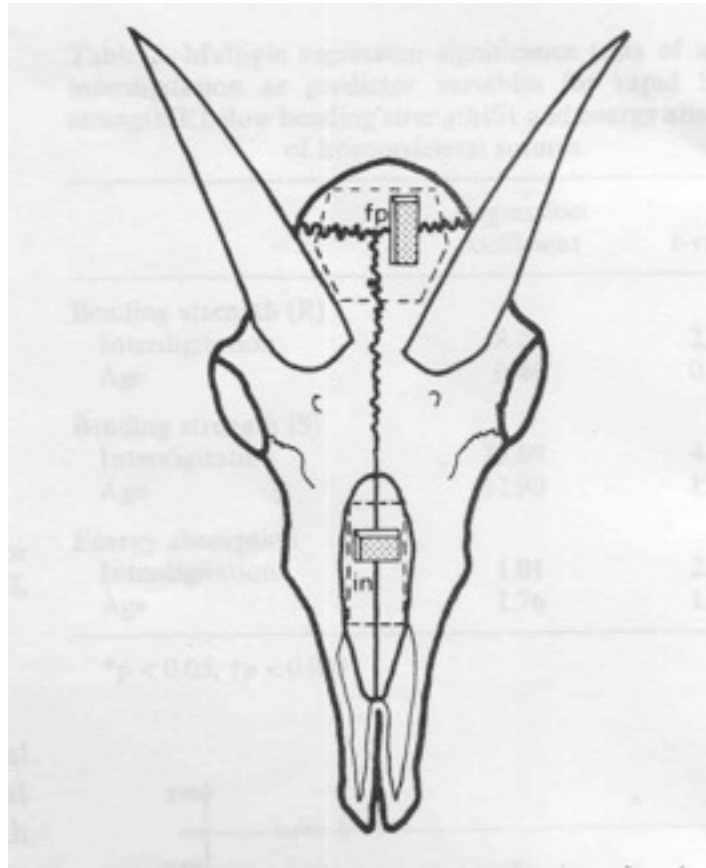
# 頭蓋骨早期癒合症



Crouzon syndrome - FGFR GOF mutation

Child's Nerv Syst (2000) 16:645–658

# 湾曲の機能：縫合線の強度



J Biomechanics 23(4) 313-321  
(1990)

# フラクタル構造

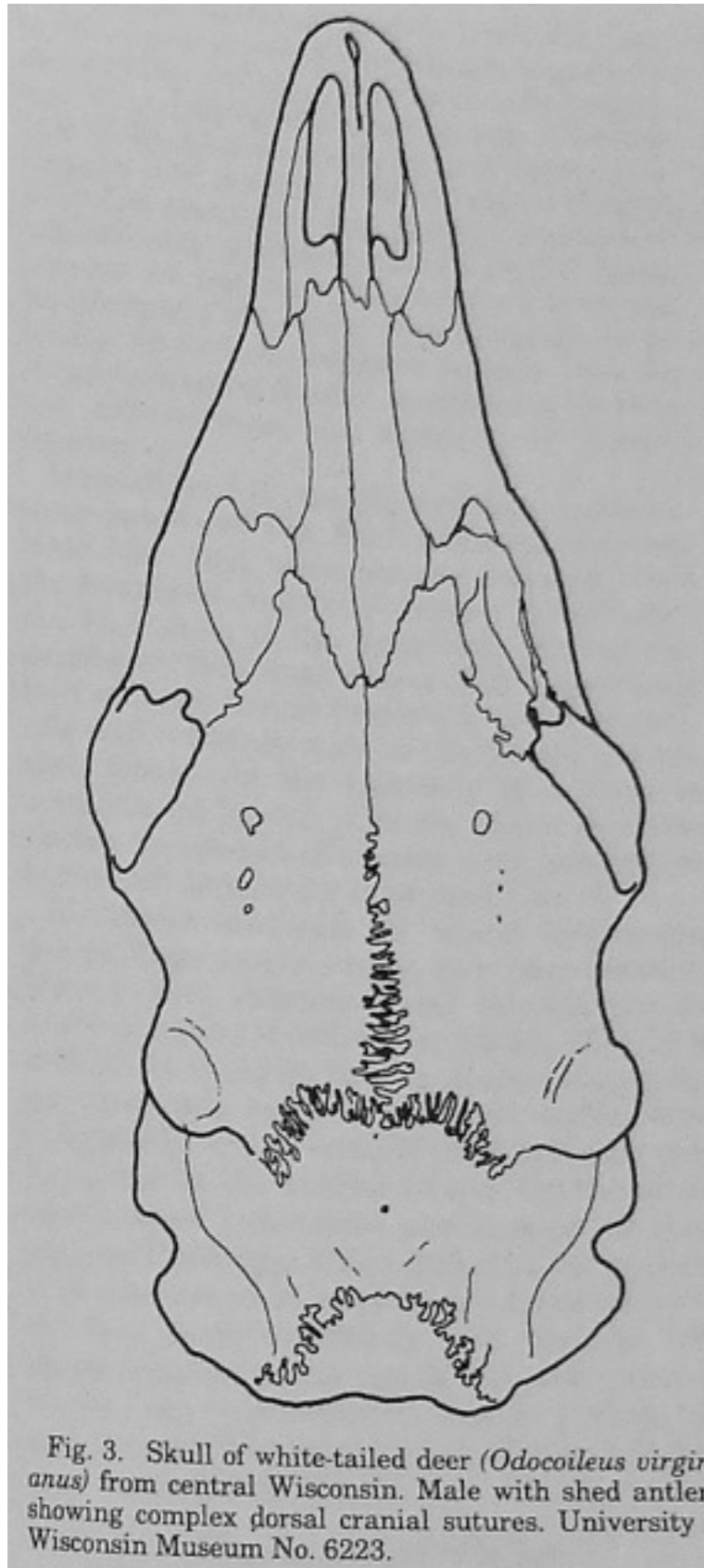


Fig. 3. Skull of white-tailed deer (*Odocoileus virginianus*) from central Wisconsin. Male with shed antler showing complex dorsal cranial sutures. University Wisconsin Museum No. 6223.

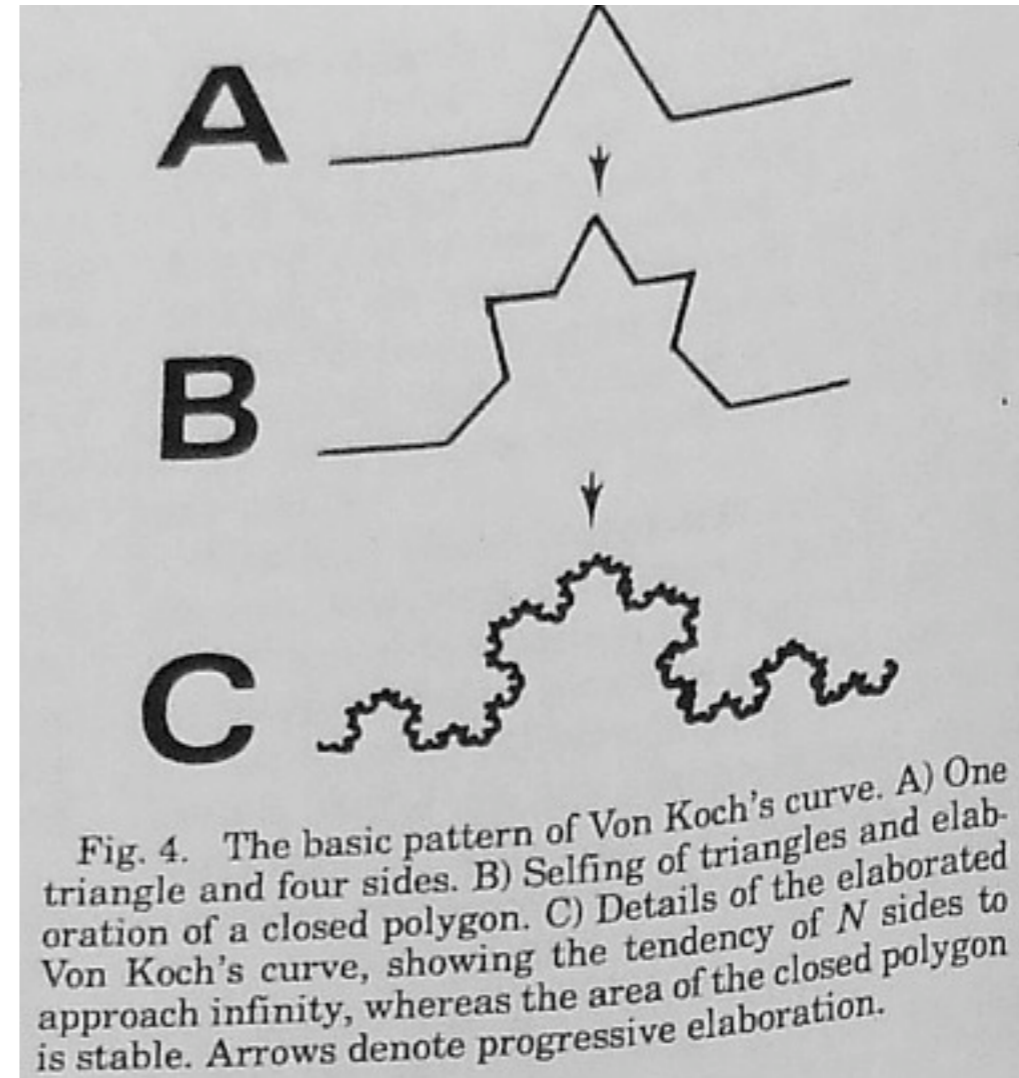
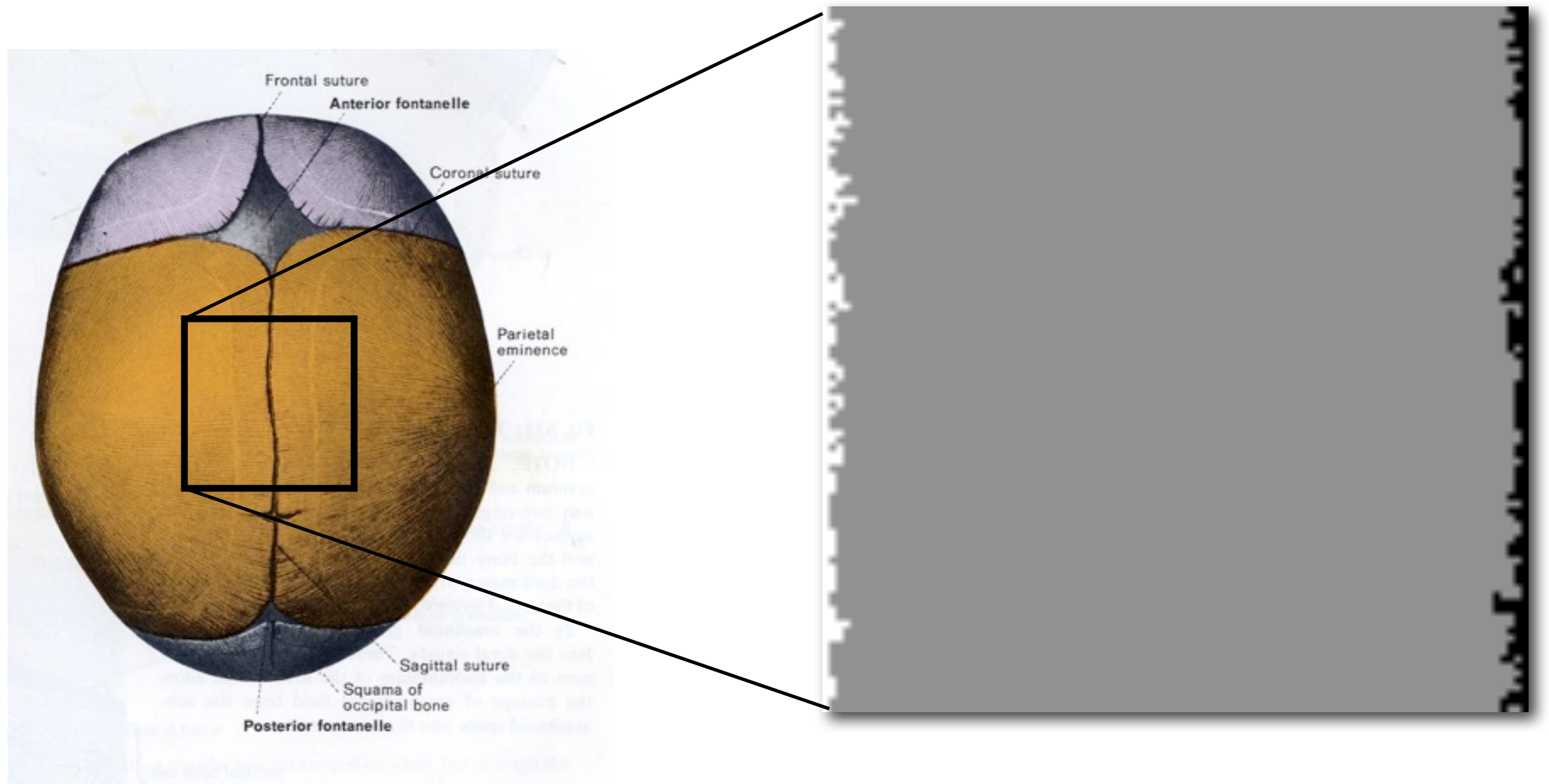


Fig. 4. The basic pattern of Von Koch's curve. A) One triangle and four sides. B) Selfing of triangles and elaboration of a closed polygon. C) Details of the elaborated Von Koch's curve, showing the tendency of  $N$  sides to approach infinity, whereas the area of the closed polygon is stable. Arrows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

J. Morphol. 185. 285- (1985)

# Eden 衝突モデル



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

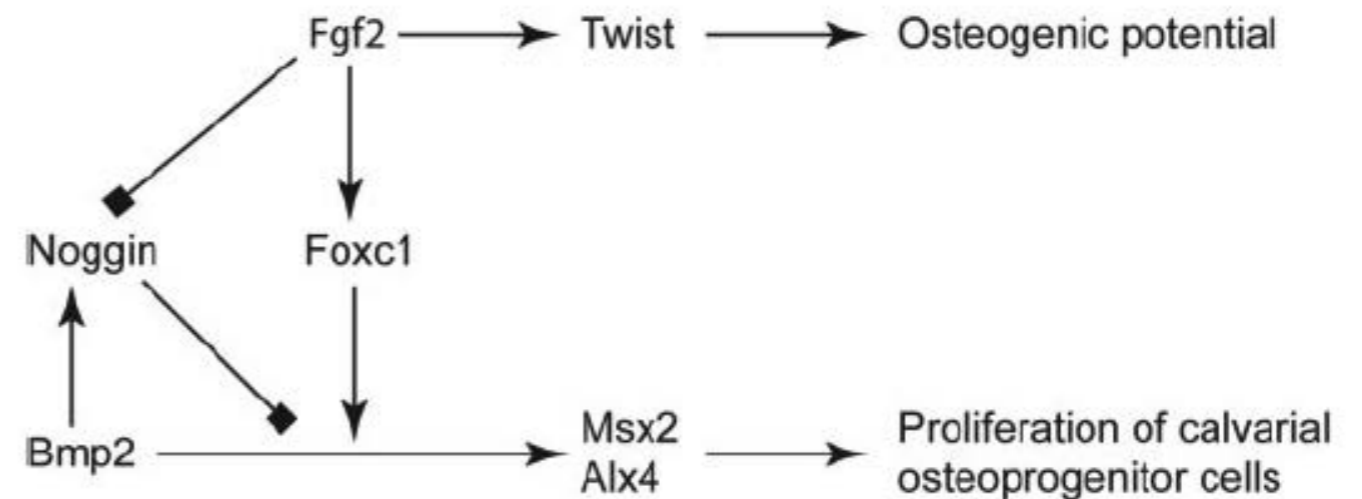
# 基本的な問題

- 未分化な間葉組織が一定幅で維持されているのはなぜか？
- 縫合線組織が湾曲するのはなぜか？



# 関わっている分子

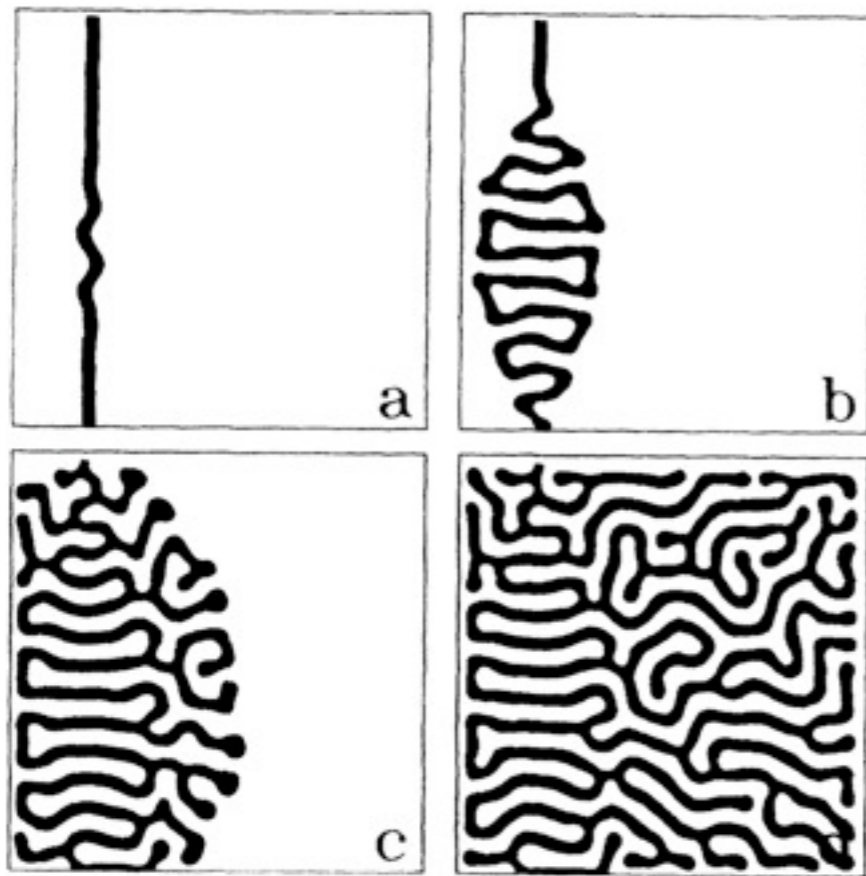
- FGF2, FGF18, FGFR1-4
- BMP4, Noggin, TGF beta 1,2,3
- Osteopontin, Osterix
- Twist, Msx2, Alx4, Runx2, Foxc1



**Fig. 4.** Fibroblast growth factor (Fgf) and bone morphogenetic protein (Bmp) signalling are integrated through the transcription factor Foxc1, and this integration regulates proliferation of osteoprogenitor cells in calvarial mesenchyme independently of Noggin and Twist.

Dev Dyn 233:847-852, 2005

# 似てるけど対応が わからない系



$$u_t = u - u^3 - v + \nabla^2 u,$$

$$v_t = \epsilon(u - a_1 v - a_0) + \delta \nabla^2 v,$$

FIG. 3. The development of a labyrinthine pattern from a single stripe in the Ising front regime. The light and dark regions correspond to the down and up states, respectively. (a), (b), (c), and (d) pertain to times  $t = 100, 950, 1900,$  and  $5000$ . Parameters used:  $a_0 = -0.1, a_1 = 2, \epsilon = 0.05, \delta = 4$ .

PRL 72(15) 2494- (1994)

# モデル化戦略

- モノが多すぎる > どう  
単純化するか？

# 分類

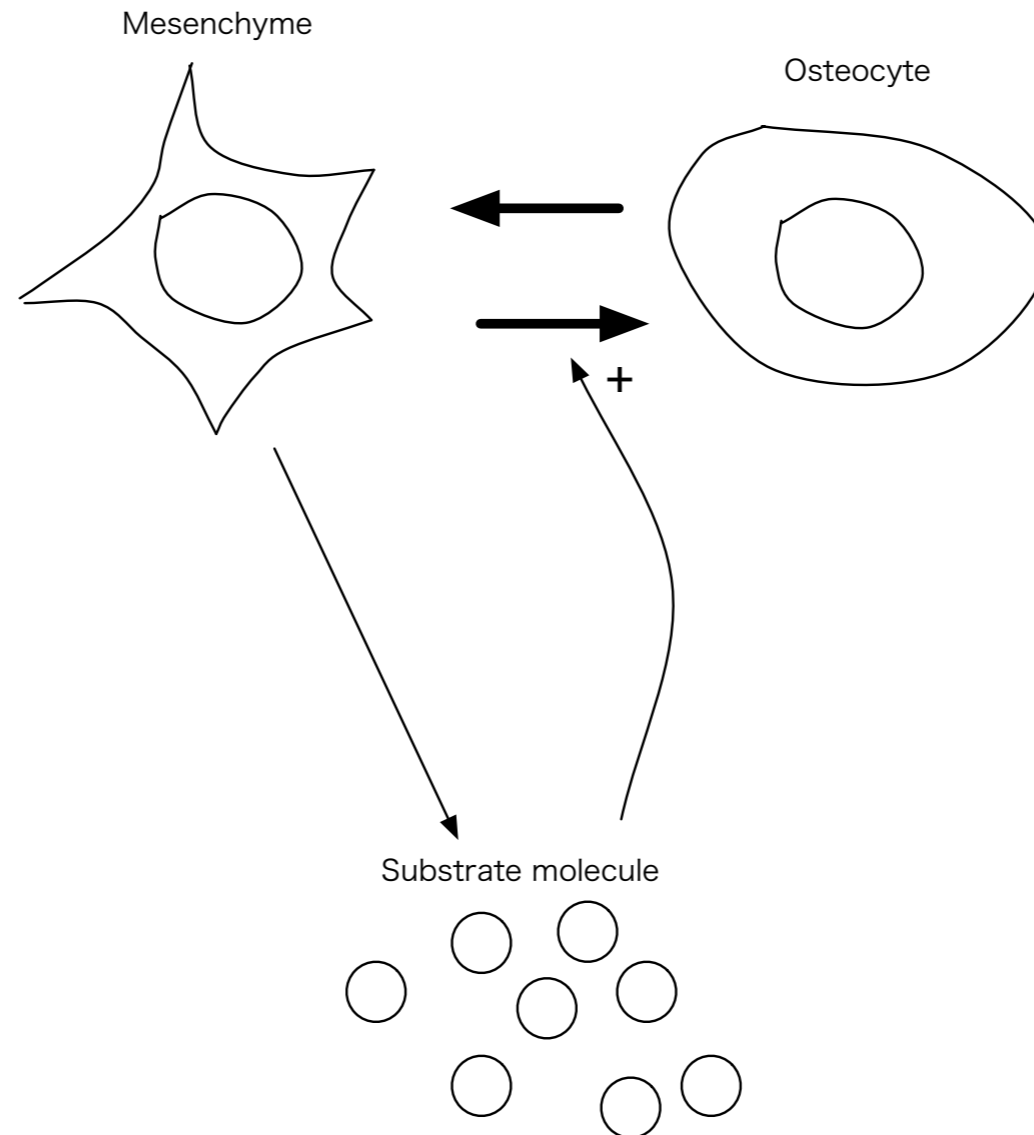
Differentiation Localization	Promote	Inhibit
Bone	Runx2, Osterix	-
Mesenchyme	FGF2, FGF18, BMP4	Noggin, Twist

- Stabilizing factors
- Substrate molecules

Differentiation Localization	Promote	Inhibit
Bone	Runx2, Osterix	-
Mesenchyme	FGF2, FGF18, BMP4	Noggin, Twist

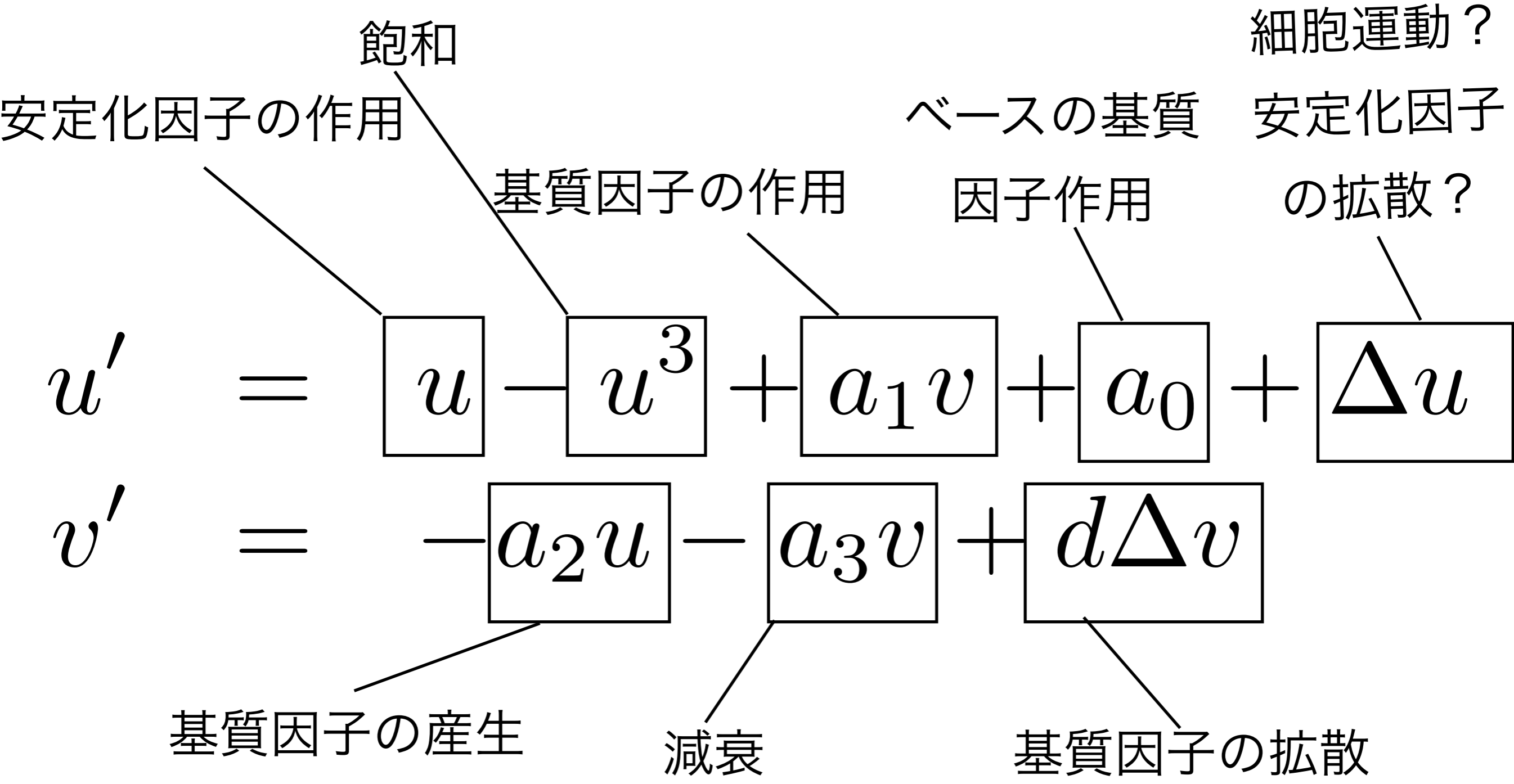
u: 組織の分化度

v: 基質因子

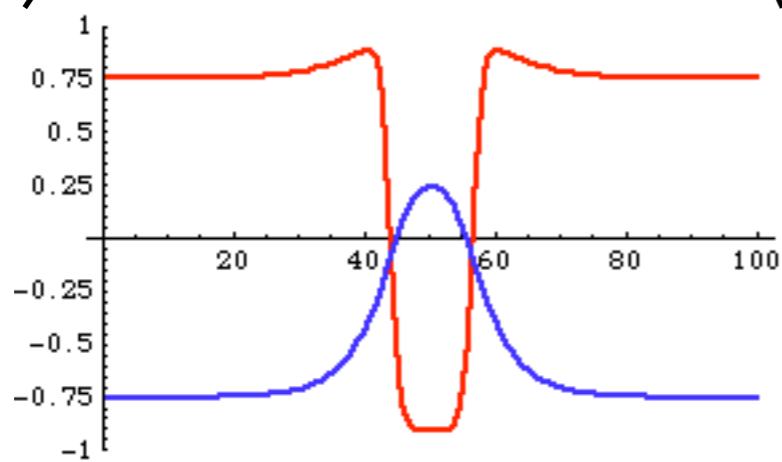
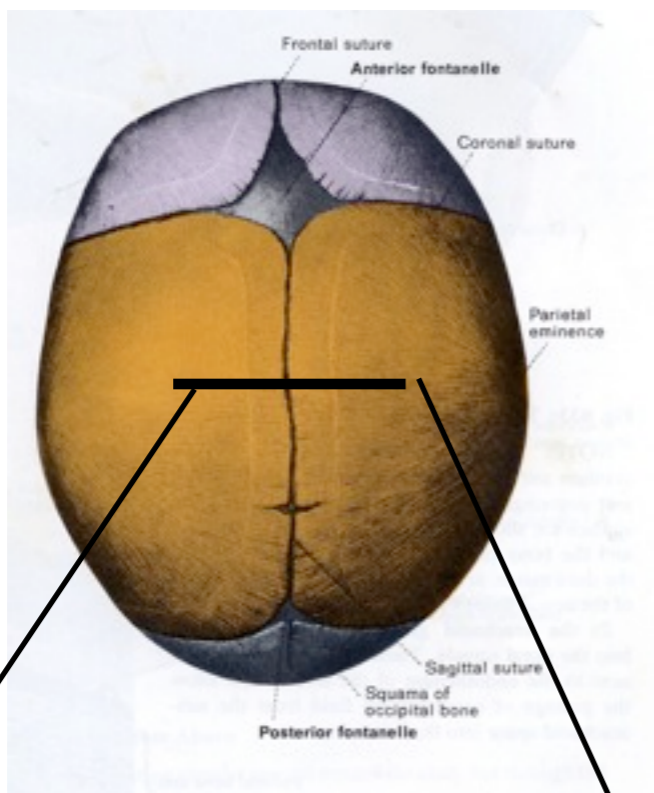


- 安定化因子の作用によって、組織には二つの安定な状態がある。一つは骨 (osteocyte,  $u > 0$ )、もう一つは未分化な間葉組織 (mesenchyme,  $u < 0$ ) である。
- 未分化な間葉組織は基質因子を分泌する
- 基質因子は骨分化を促進する

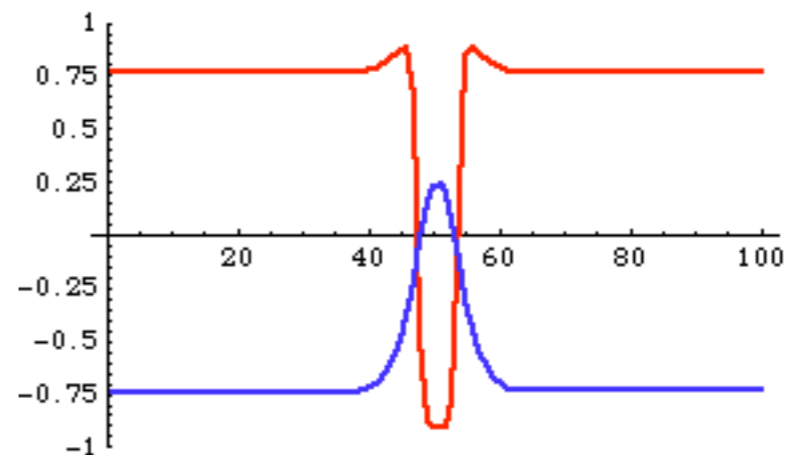
# 支配方程式



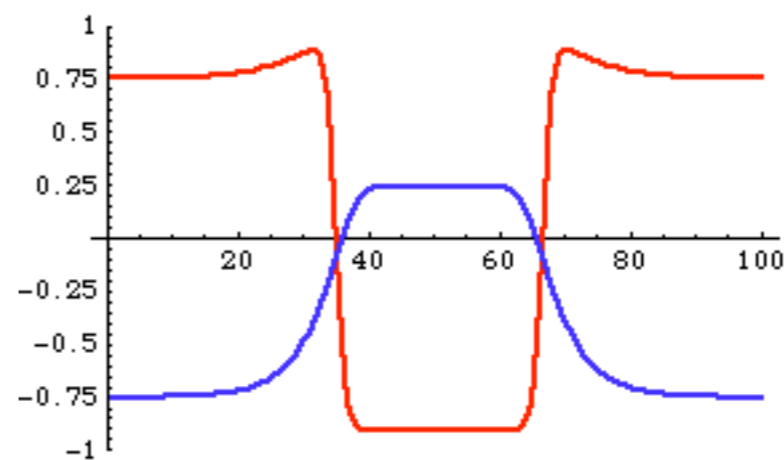
# 組織の幅の維持



定常解



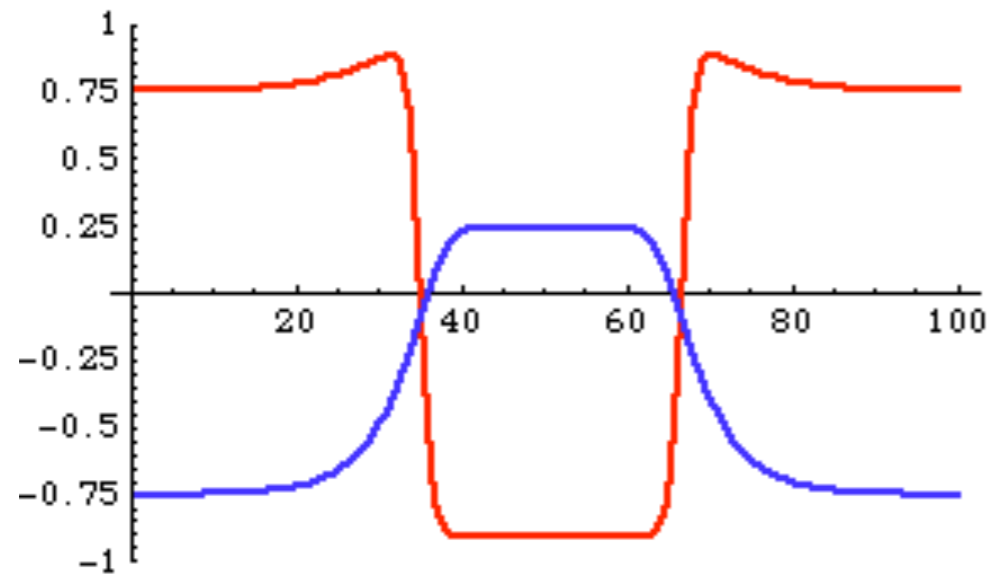
圧縮された場合



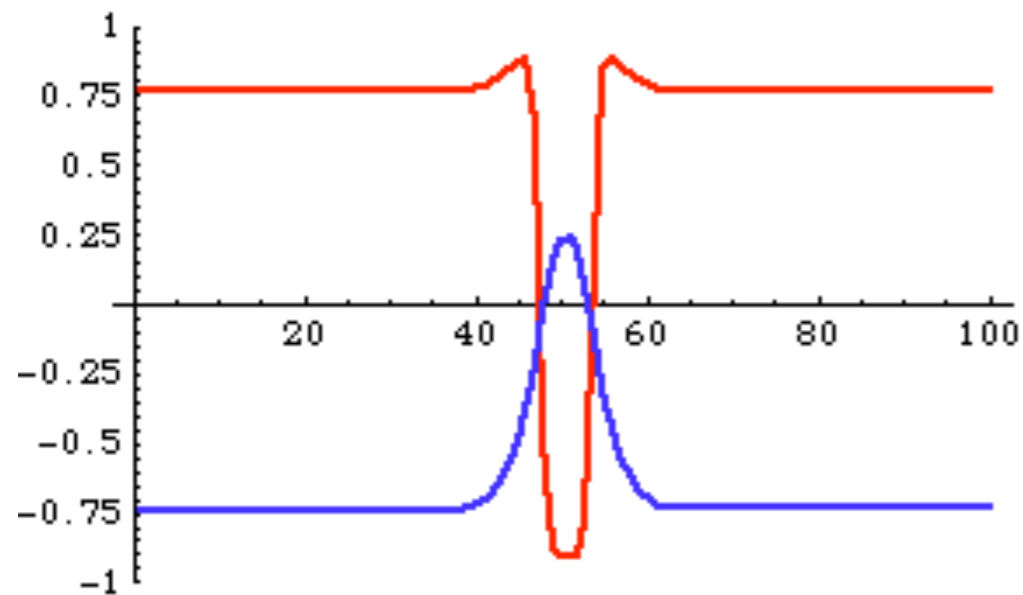
引き延ばされた場合



# なぜ一定間隔になるのか？

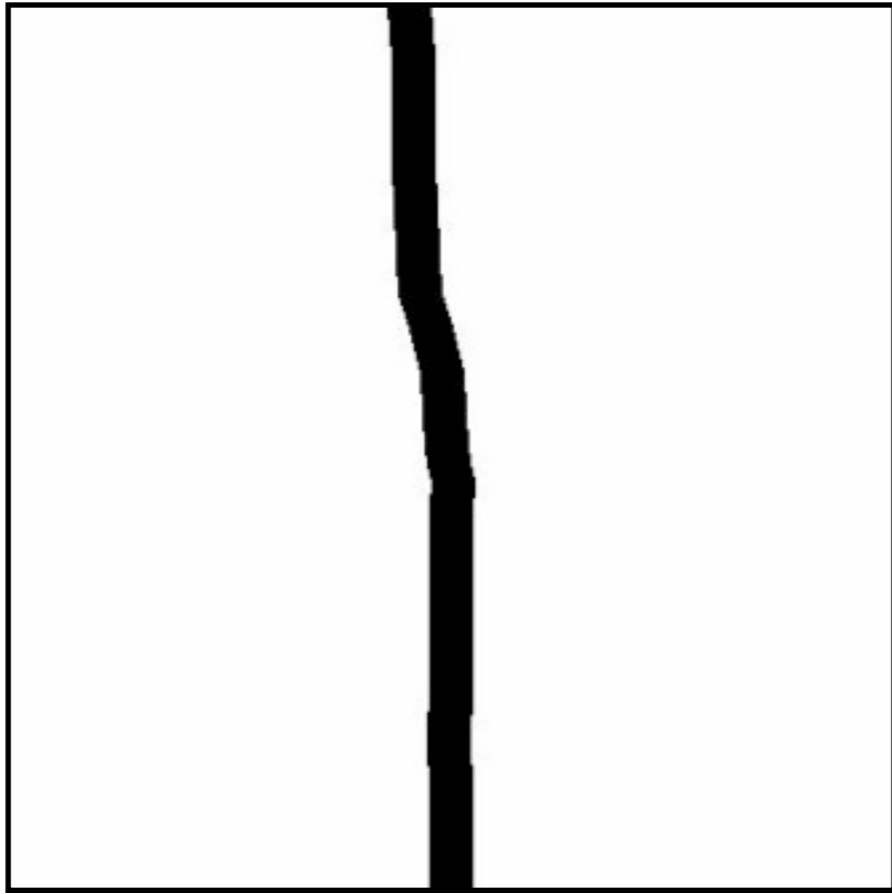


- 引き延ばされた場合：間の間葉組織が産生する基質因子が増加するので骨分化が進む

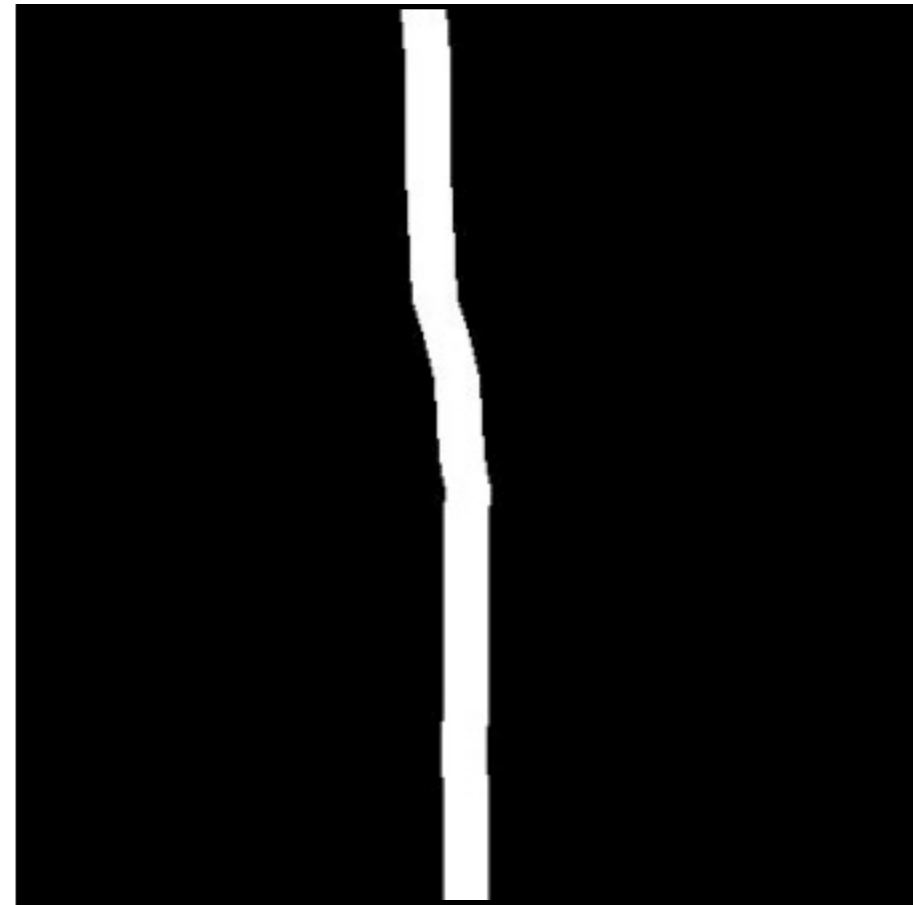


- 二つの界面が近づいた場合：間の間葉組織が減るために基質因子の産生が減って脱分化が起こる

# 縫合線の湾曲：初期状態



分化度



基質因子の濃度

(白い部分が高い値を表す)

- 未分化な間葉組織が細い線として存在する
- 基質因子が未分化な間葉で産生されている

# パターン形成



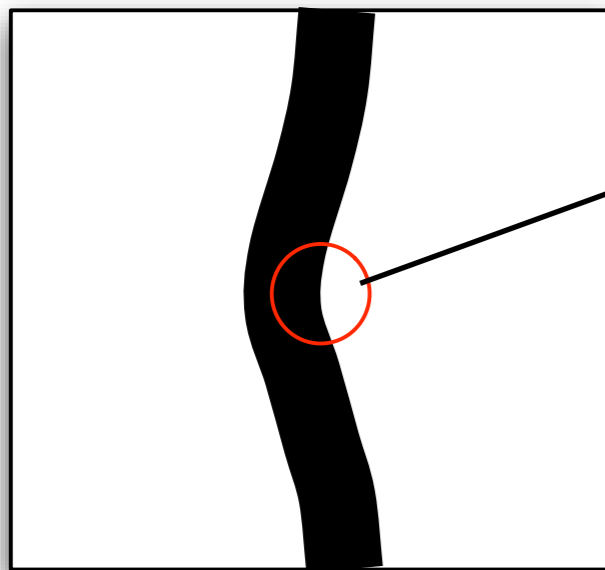
分化度

基質濃度

# なぜパターン形成が起こるのか？

- 組織が一定幅に保たれる+「突出部が早くのびる」傾向による界面の不安定化

周囲の未分化な間葉が多い >  
基質因子の濃度が高い > 分化  
が進む > さらに突出する

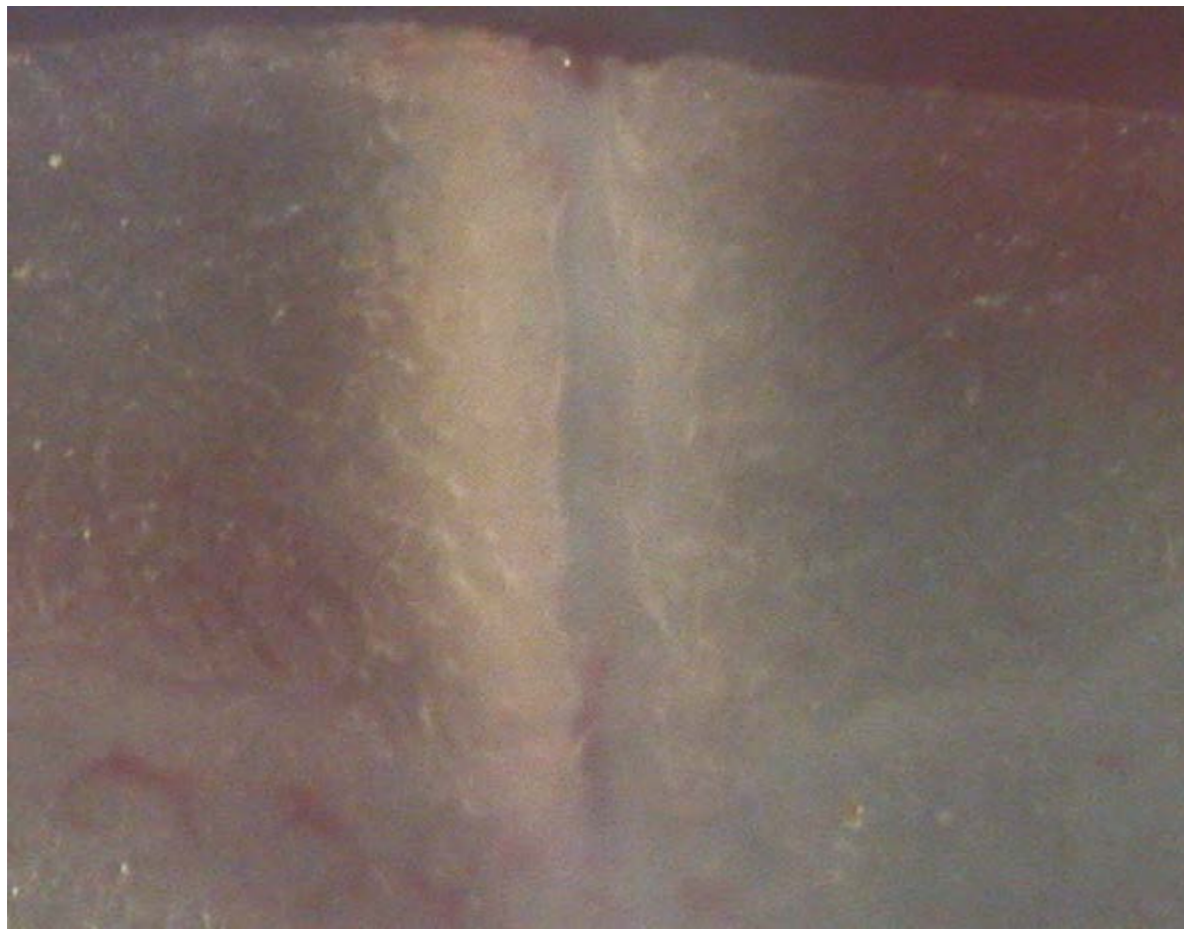


分化度

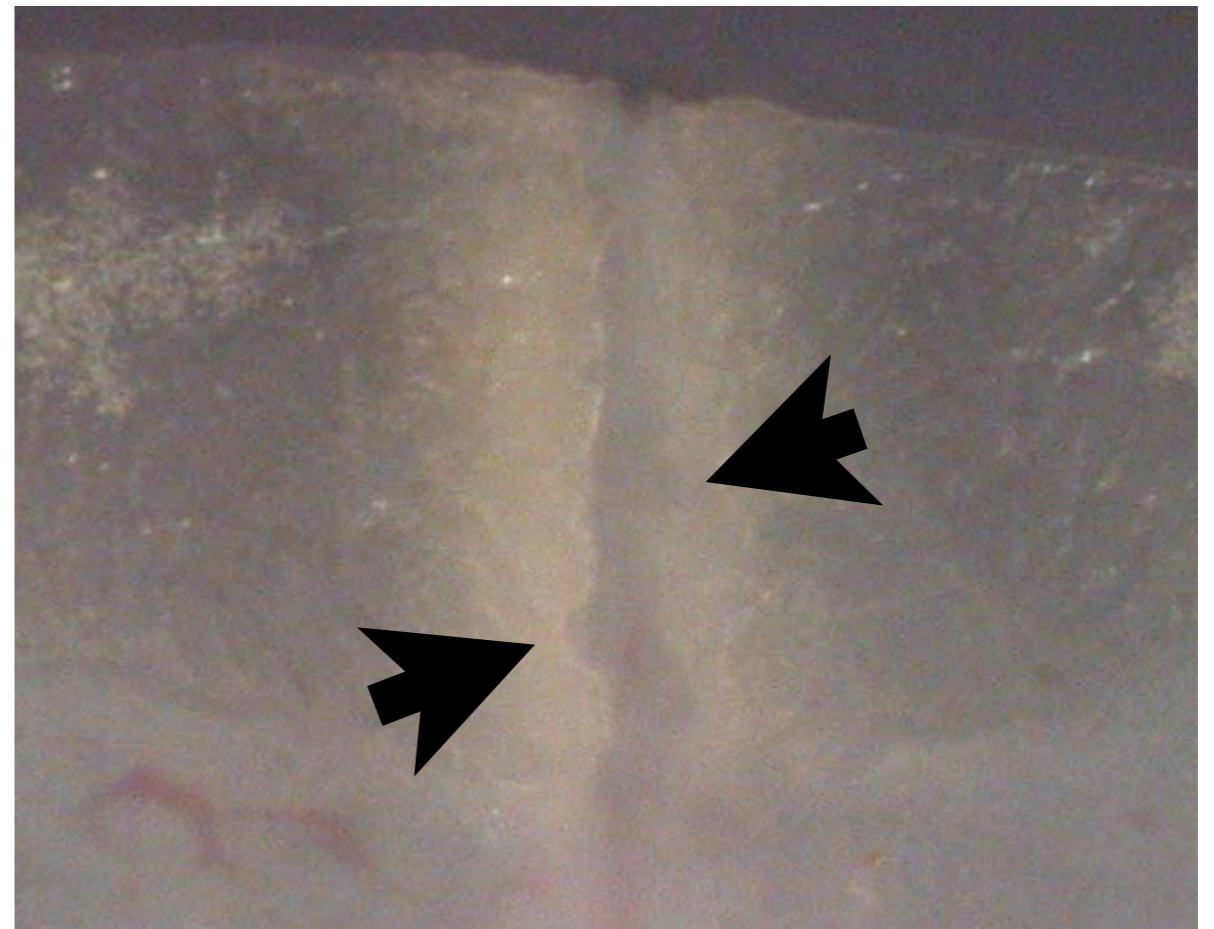
数理解析：

Physica D 34, 115- (1989)

# 骨端の退縮

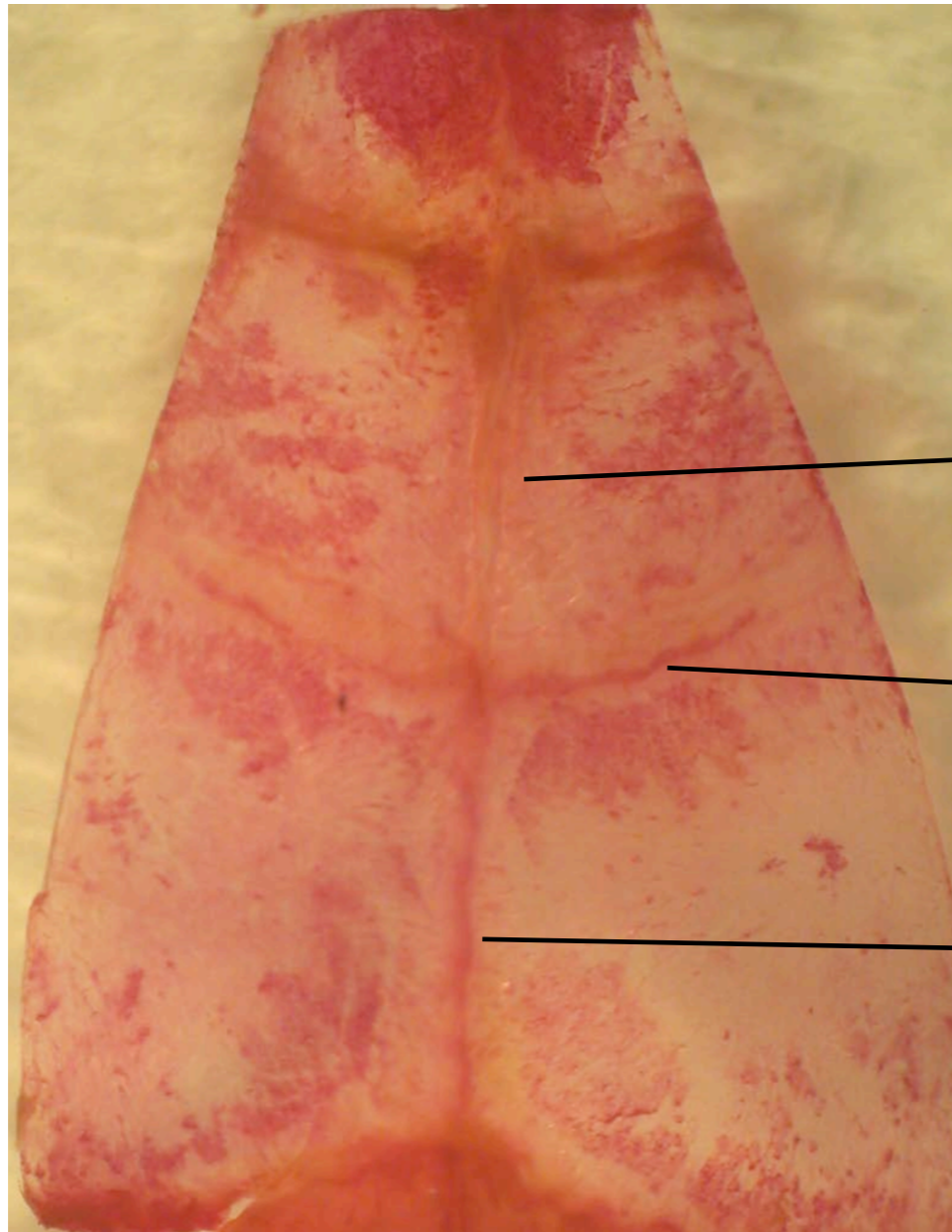


4 days



7 days

# 破骨細胞の活性



- 3W mouse skull  
TRAP stain

Posterior frontal suture

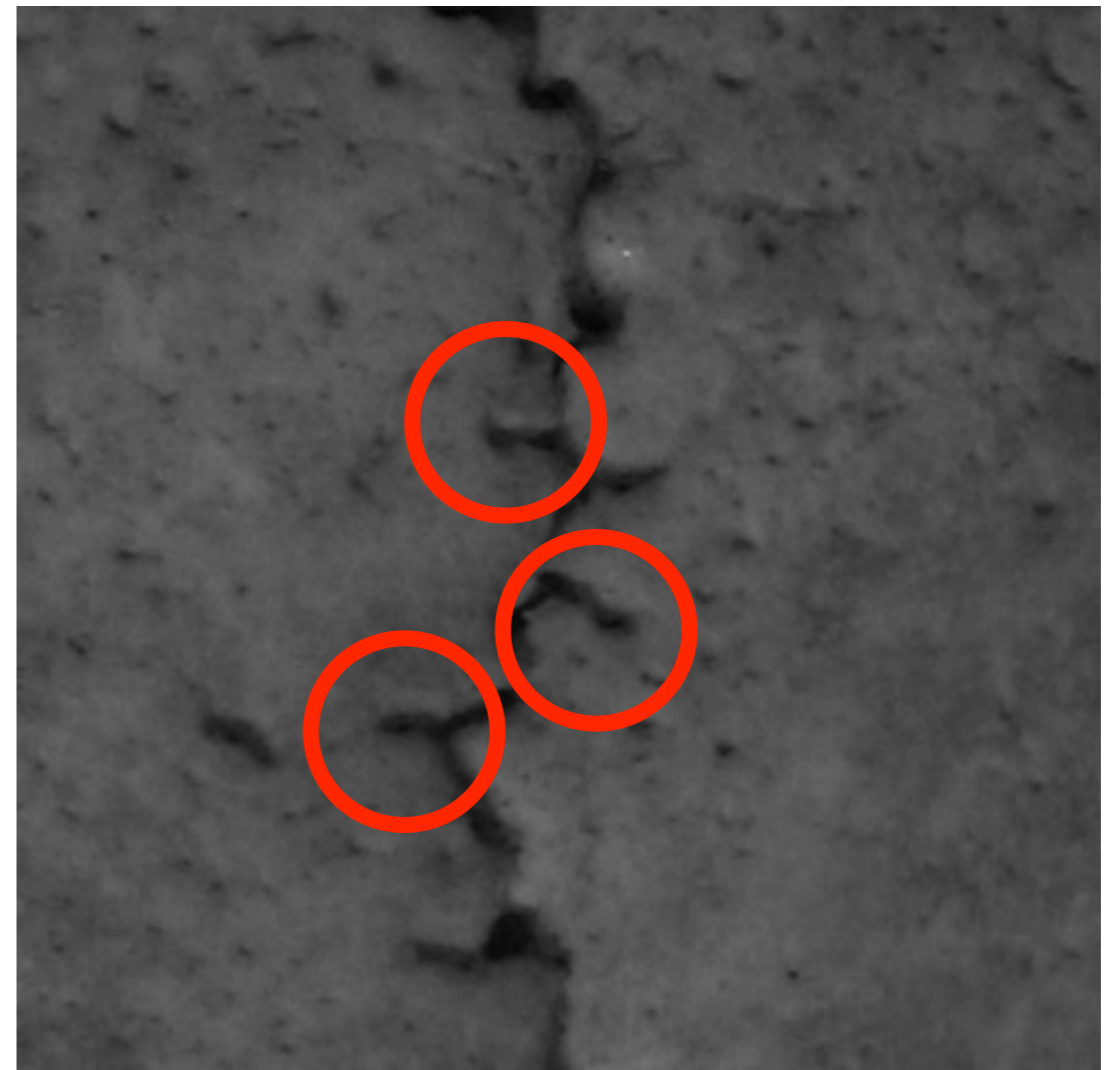
Coronal suture

Sagittal suture

# 「出芽」の存在

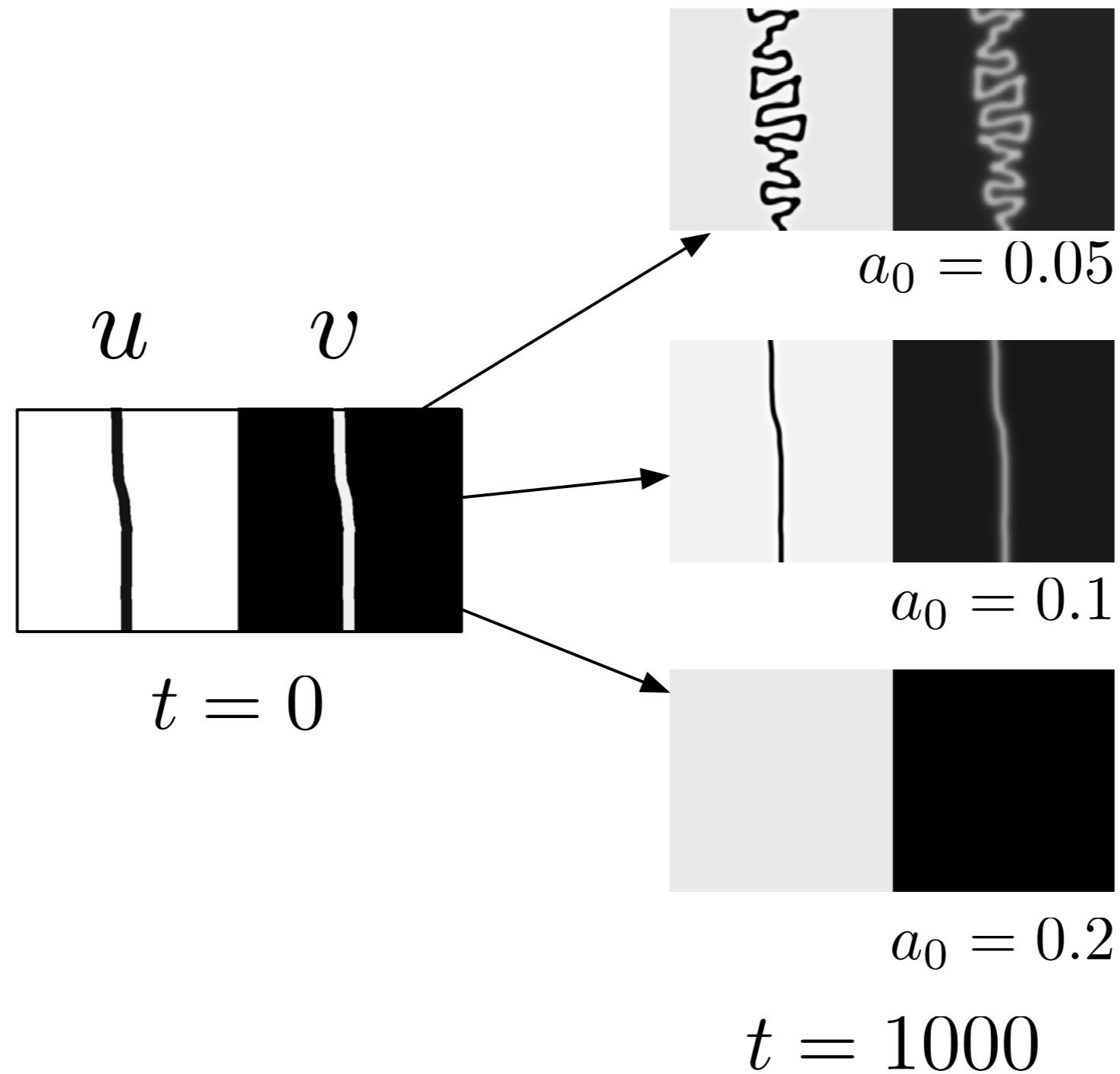


# 実際の標本での出芽



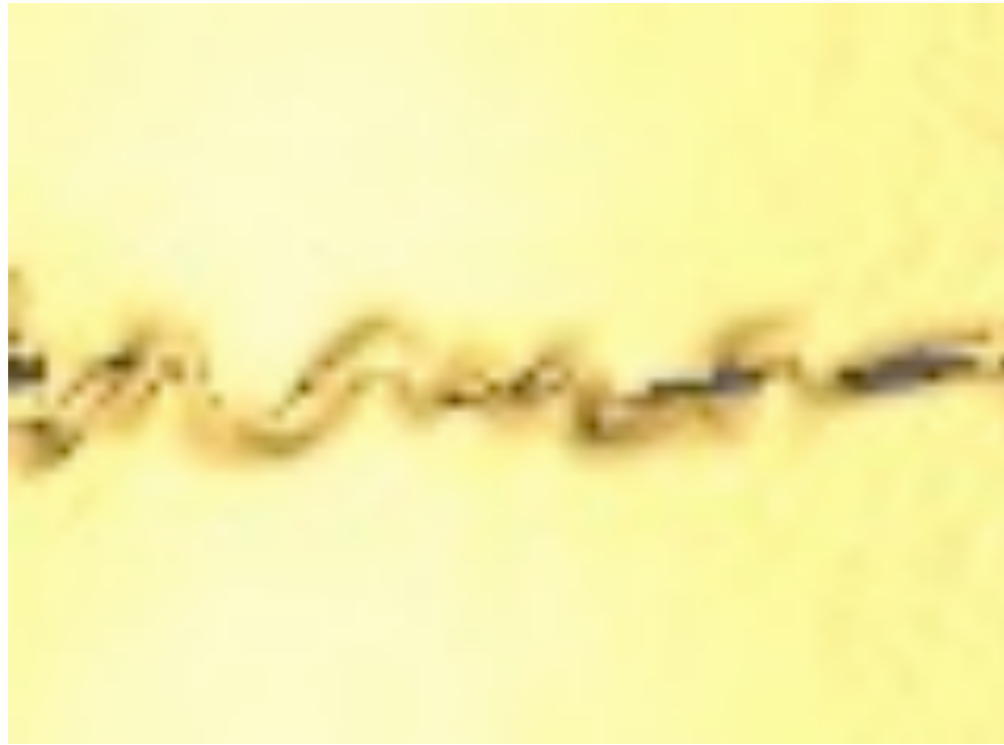


# $a_0$ によるパターンの変化

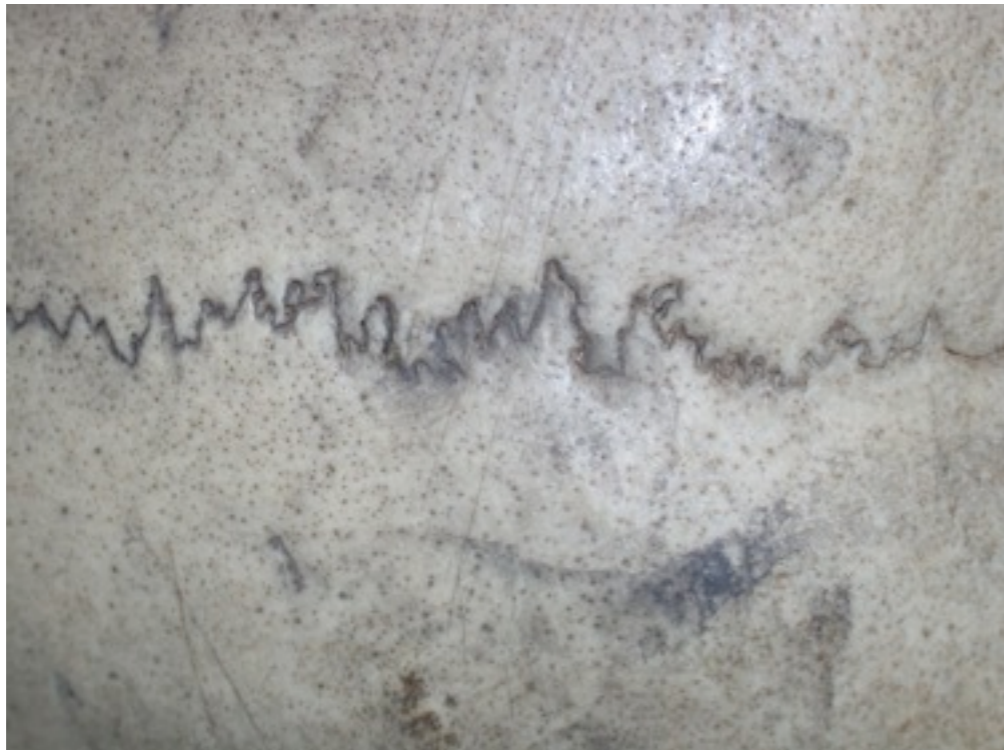


# 三次元構造

Mouse



Human

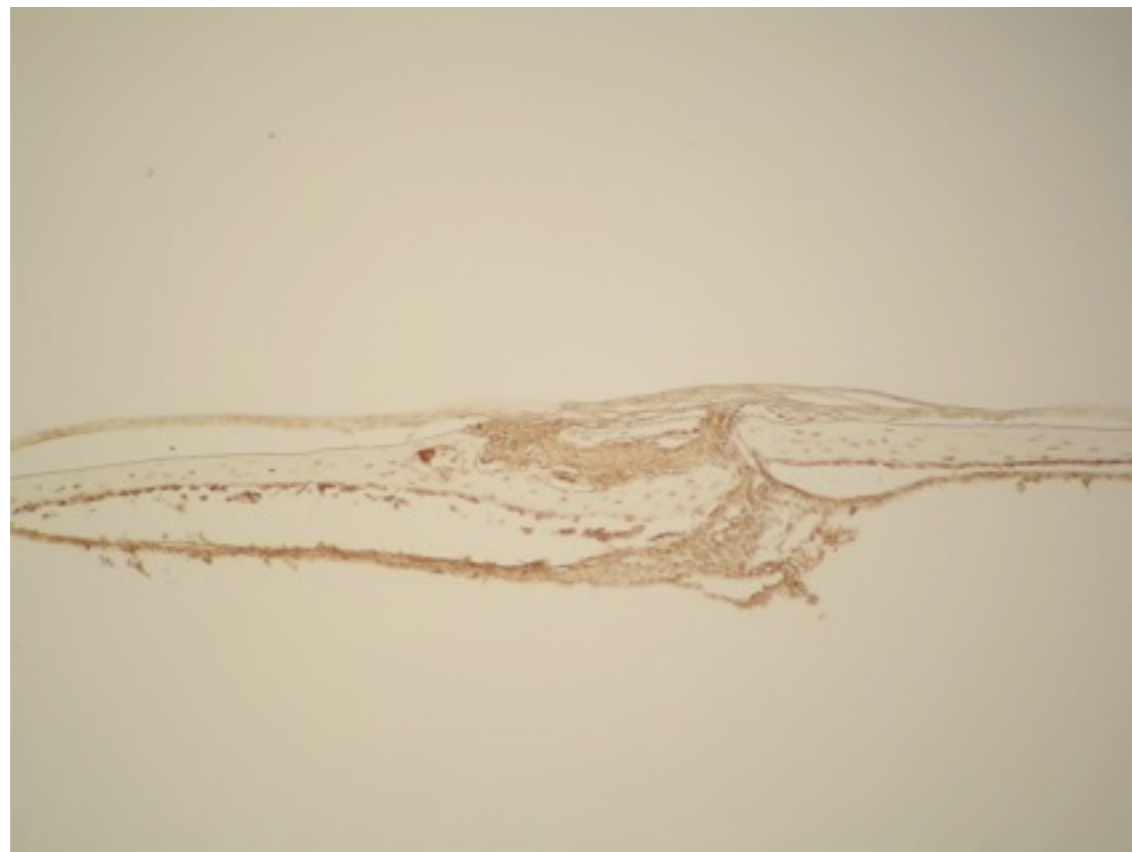


Superficial

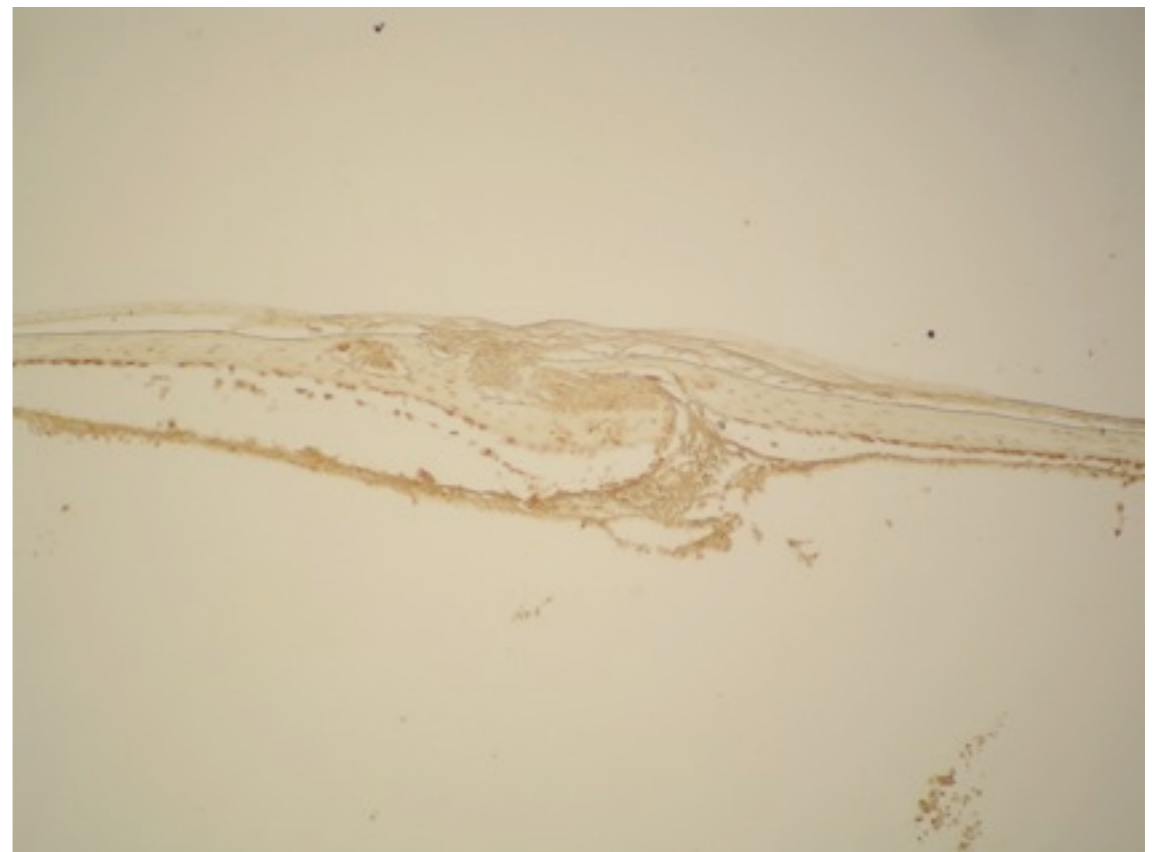
Deep

# 硬膜から分泌される基質因子

Surface



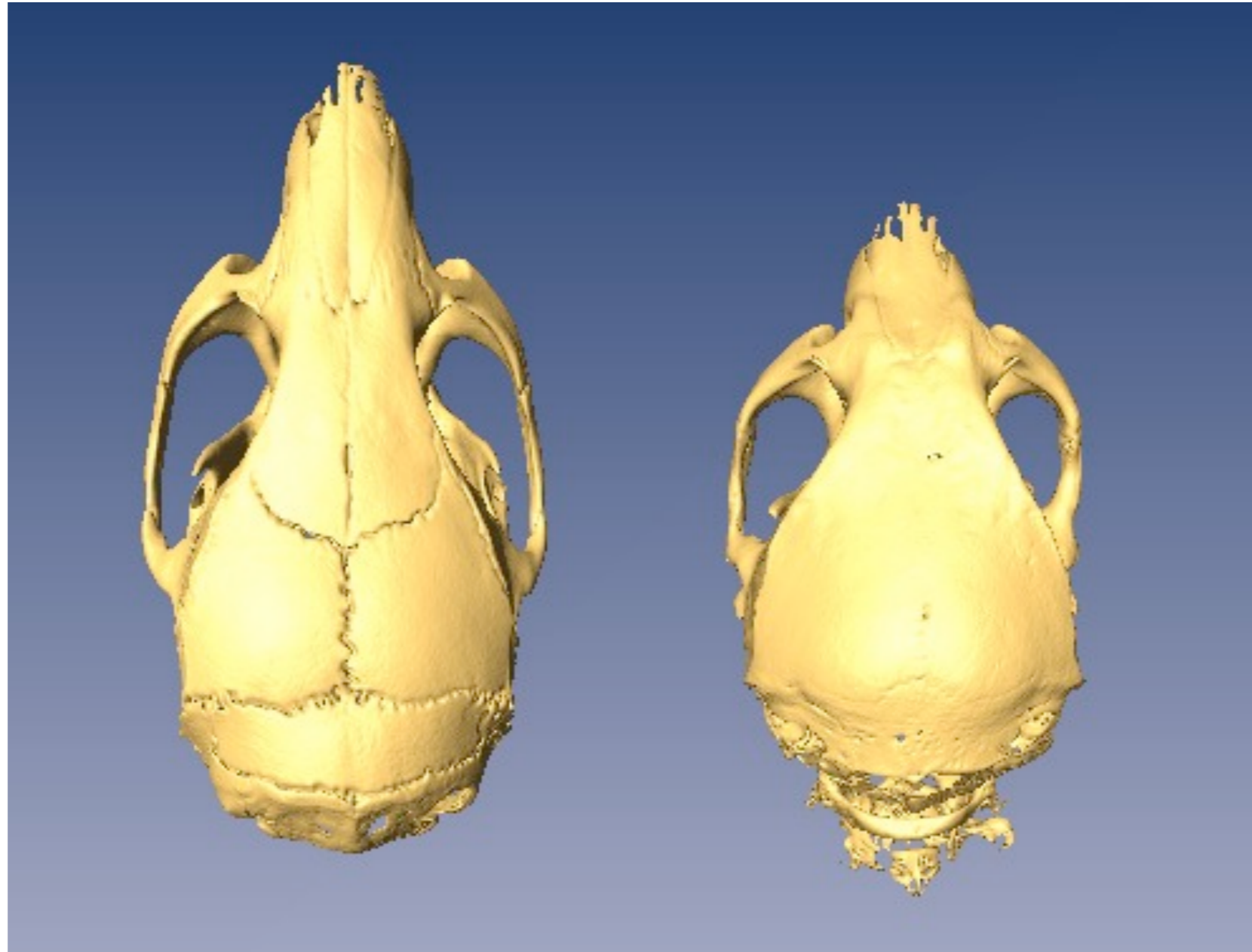
FGF2



FGF18

Deep

# 実験的に $a_0$ を増加させた場合



Wt

FGFR2c GOF Het

# 更に複雑な構造

Human lambda suture



入り組んでいてさらに一本線でできている

前述のモデルでは  
迷路パターンになってしまう



- 出芽が多すぎる...

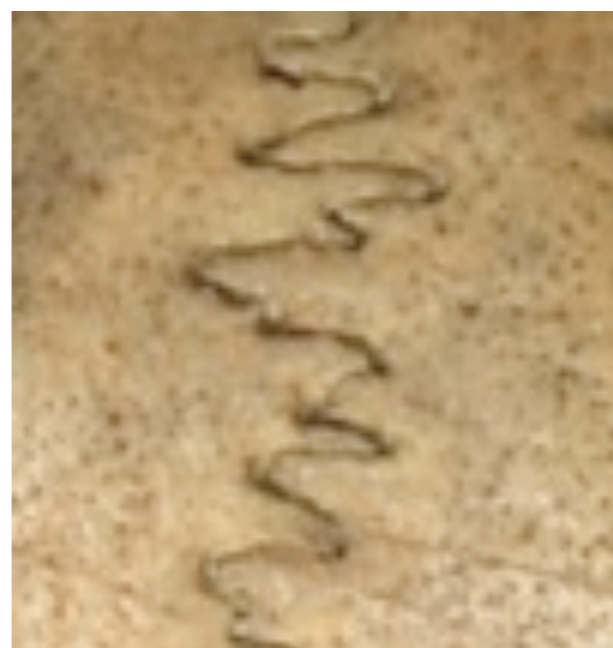
パターンを一本の線にするにはどうするか？

# 実際のパターン形成の観察

- 間葉組織の繊維化が進む  $\rightarrow$  拡散係数の変化？
- 年齢とともに縫合線の組織が細くなる



新生児



成人



# 時間依存パラメータ

$$u' = u - u^3 + a_1 v + a_0 + h(t) \Delta u$$

$$v' = \epsilon(-u - v) + h(t) \delta \Delta v$$

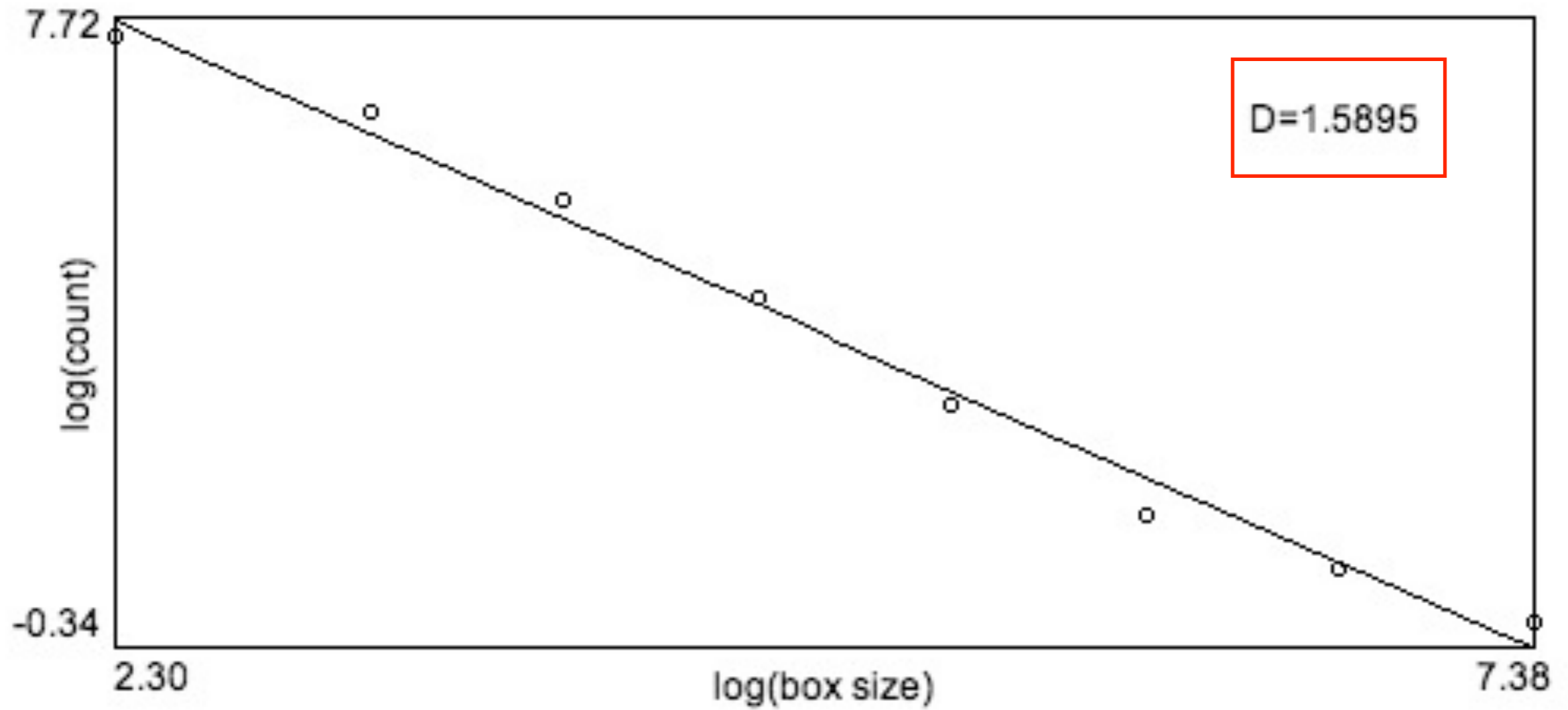
$h(t)$ : Exponential decreasing function with  $t$

# シミュレーション

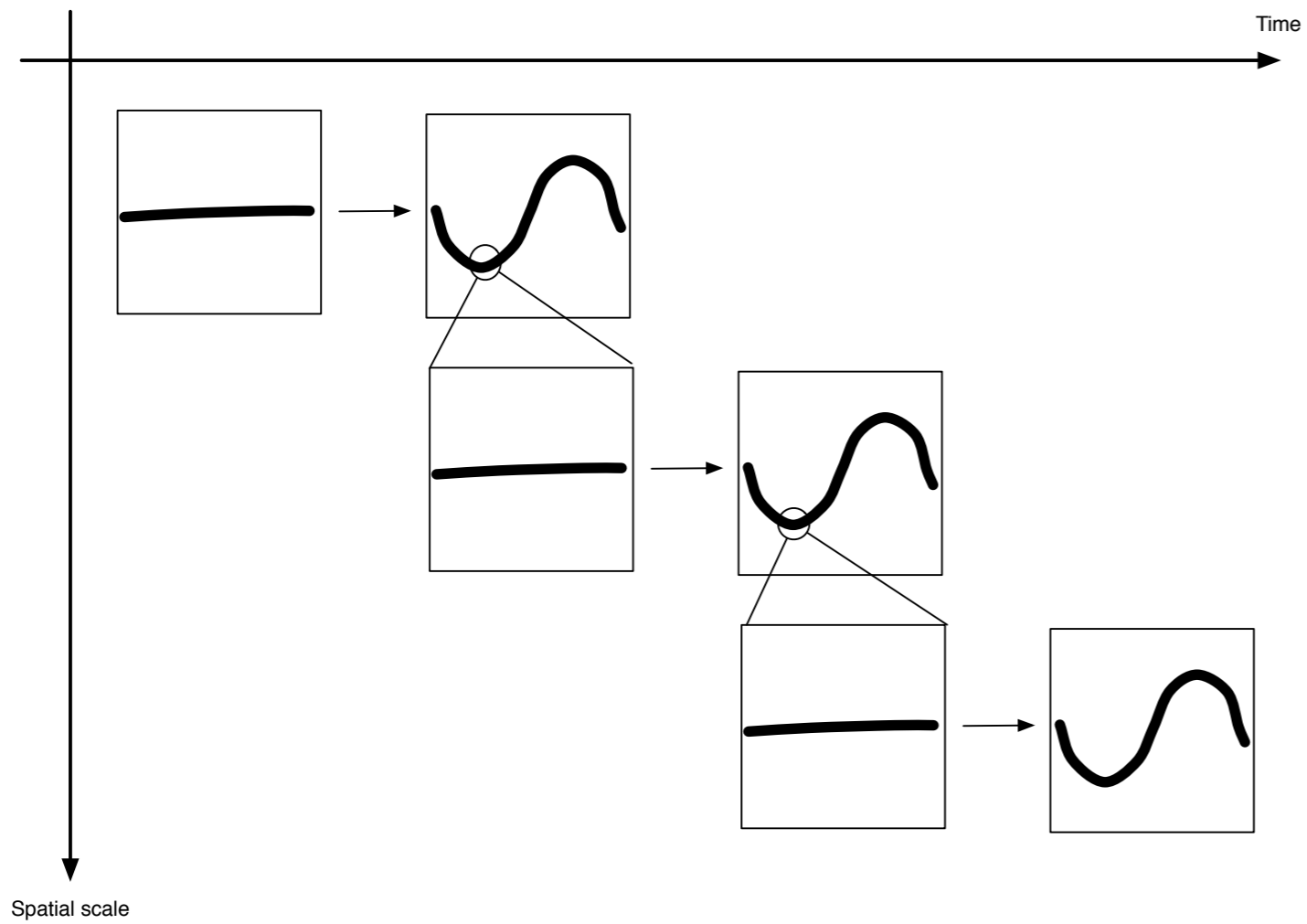


- 一本の線に出来る

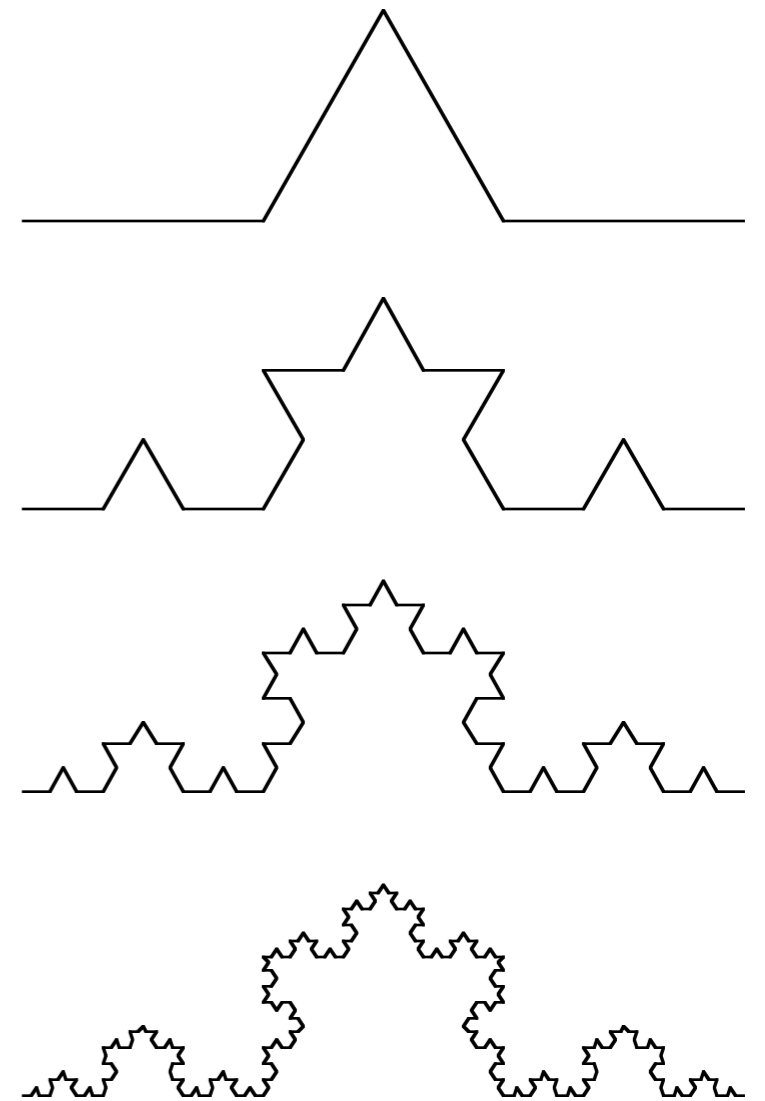
# フラクタル次元



# 直感的說明



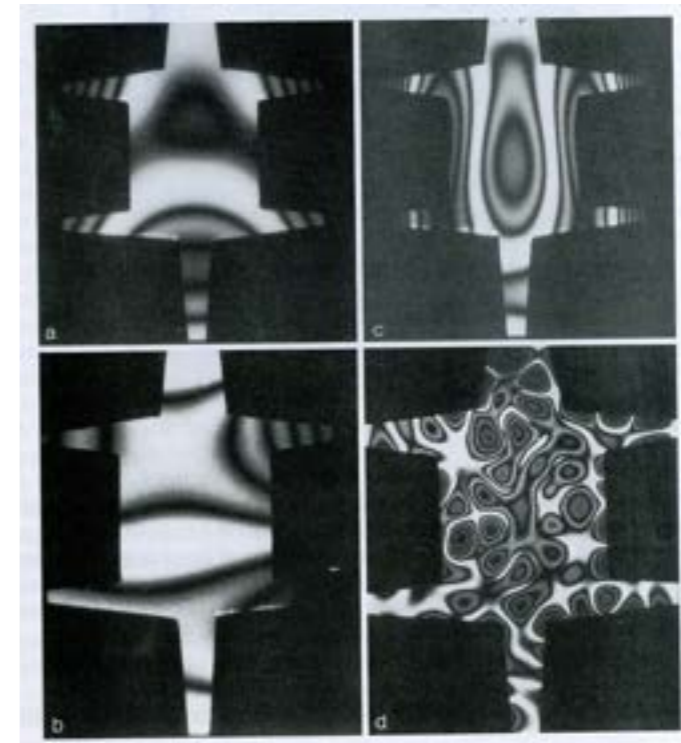
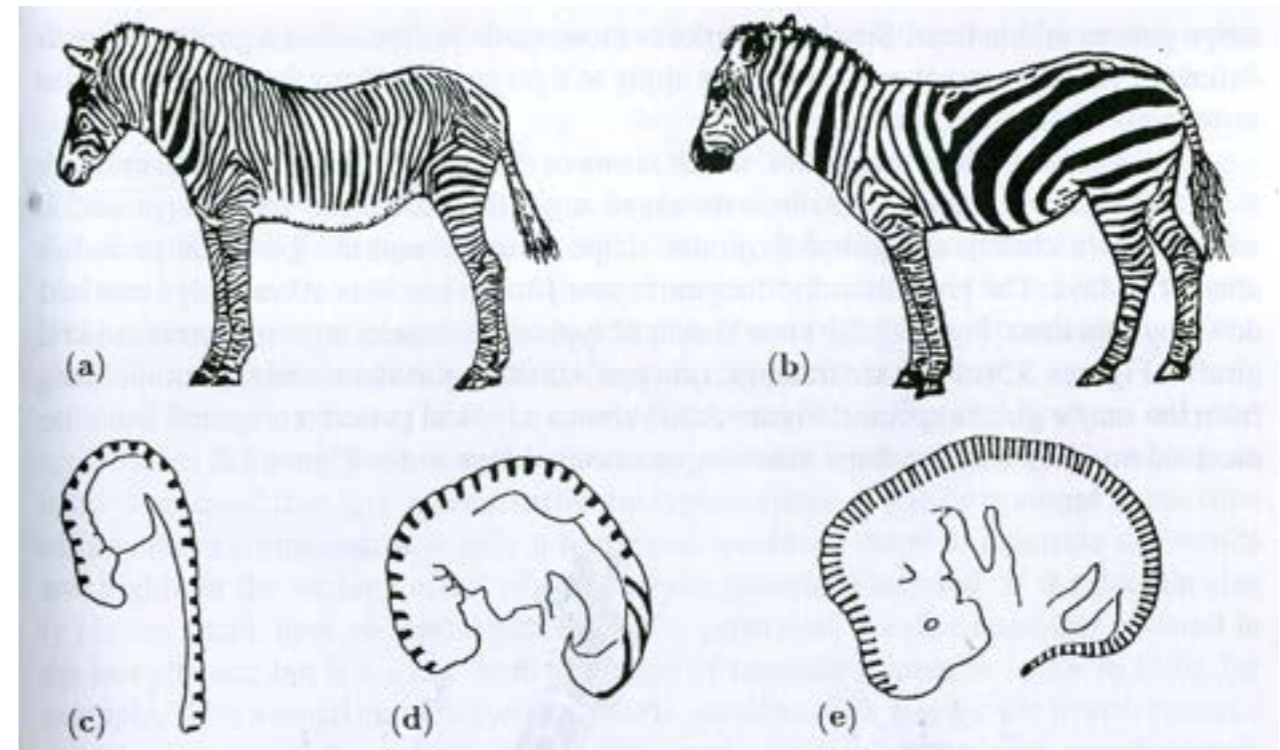
## Koch 曲線



# Summary II

- 頭蓋骨縫合線組織のパターン形成を2変数の反応拡散系で定式化した。
- 部位による形状の違いやFGFのシグナル入力による違い、フラクタル構造の形成等を説明できる

Coda.



J. Murray "Mathematical Biology"

**“Well, the stripes are easy but  
what about the horse part?”**

**F. Crick, 1972**



- 「パターン形成」 研究の限界
- 生物の形の定義 (Horse part)
- 形を作るやり方との関連

# レポート課題

- 自発的に枝分かれ構造が作られる系を一つ選び、それがどのようにできるか簡単に説明しなさい
- その他、講義の感想を自由に書いてください

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提出先：前回同様