

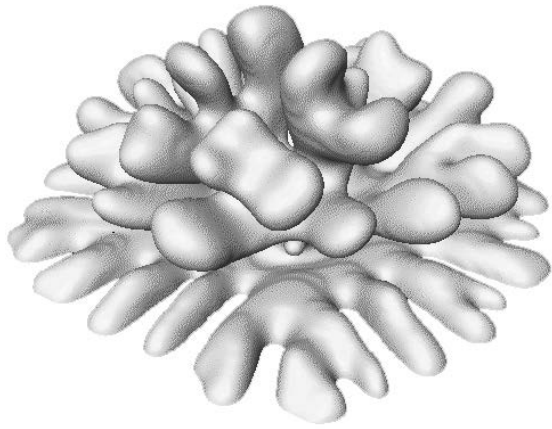
肺の枝分れの三次元モデルと 頭蓋骨縫合線のパターン形成の 数理モデル

三浦 岳

九州大学大学院医学研究院

生体制御学講座 系統解剖学部門

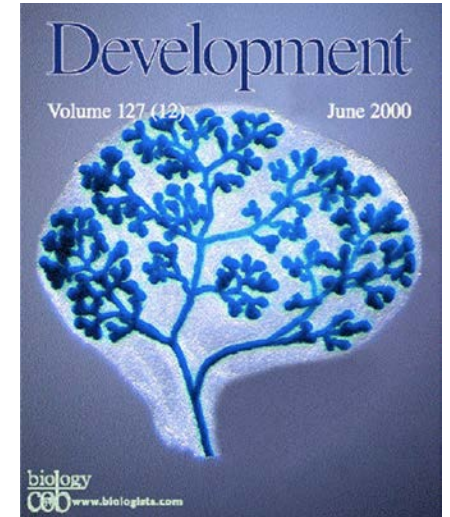
枝分れ構造形成



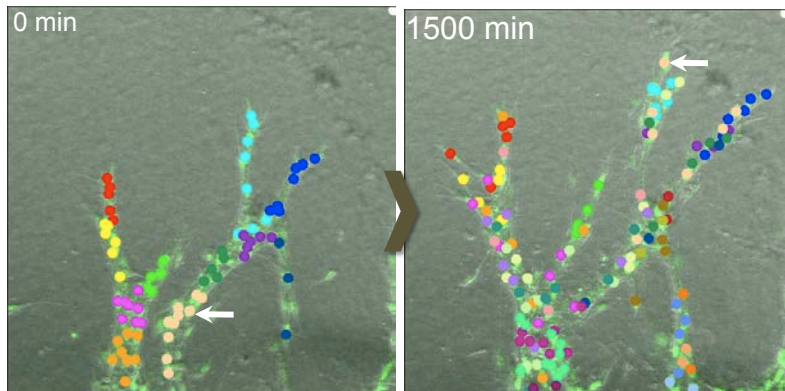
結晶



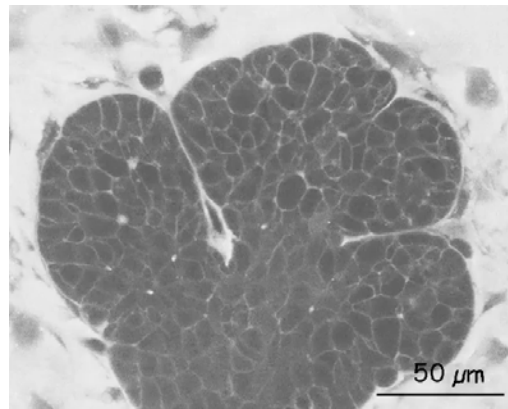
肺



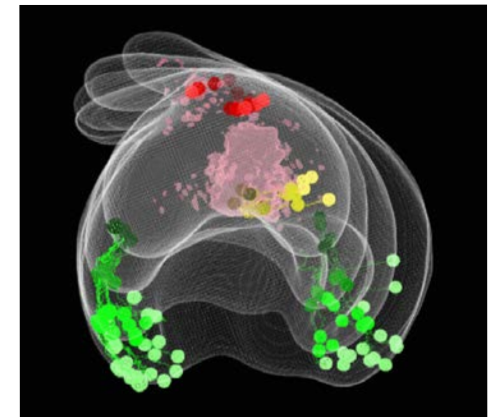
涙腺



血管

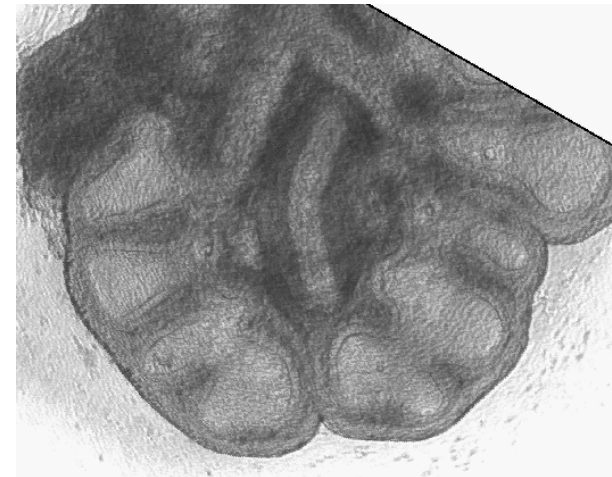
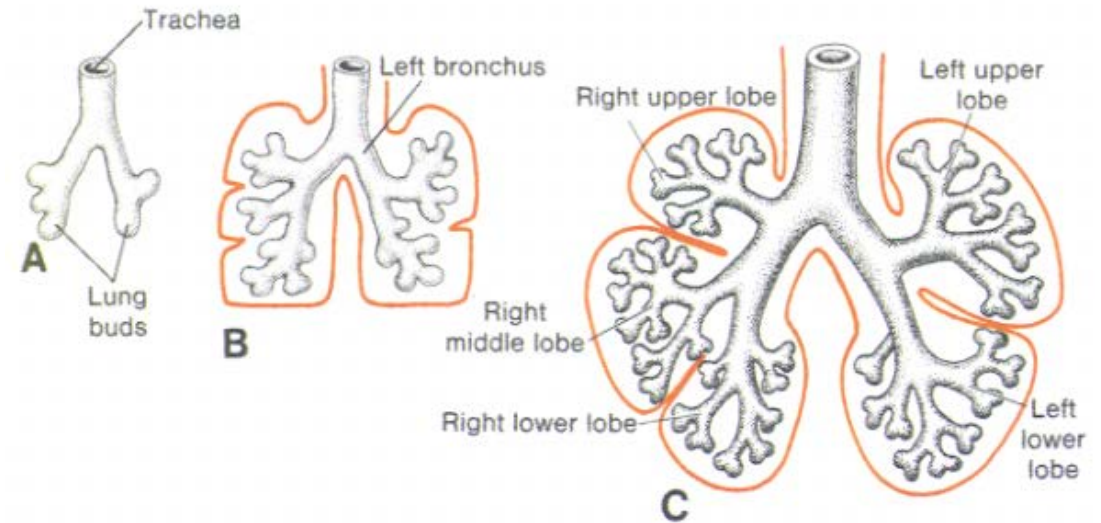
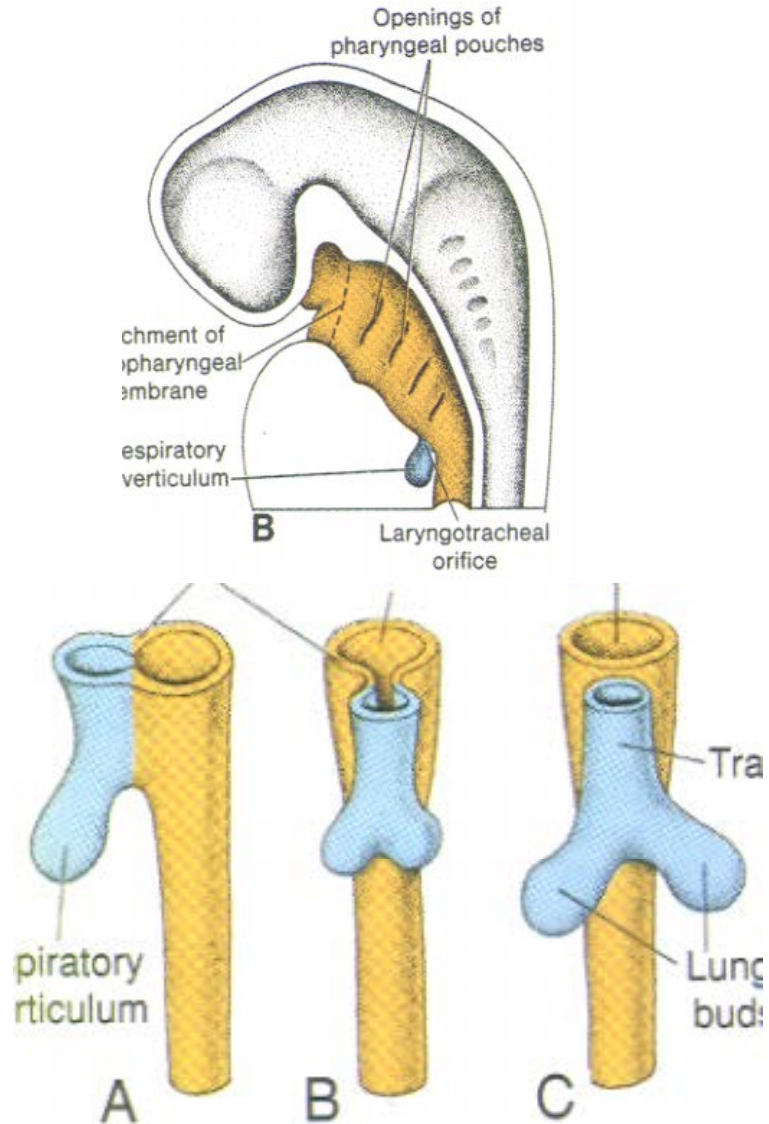


唾液腺

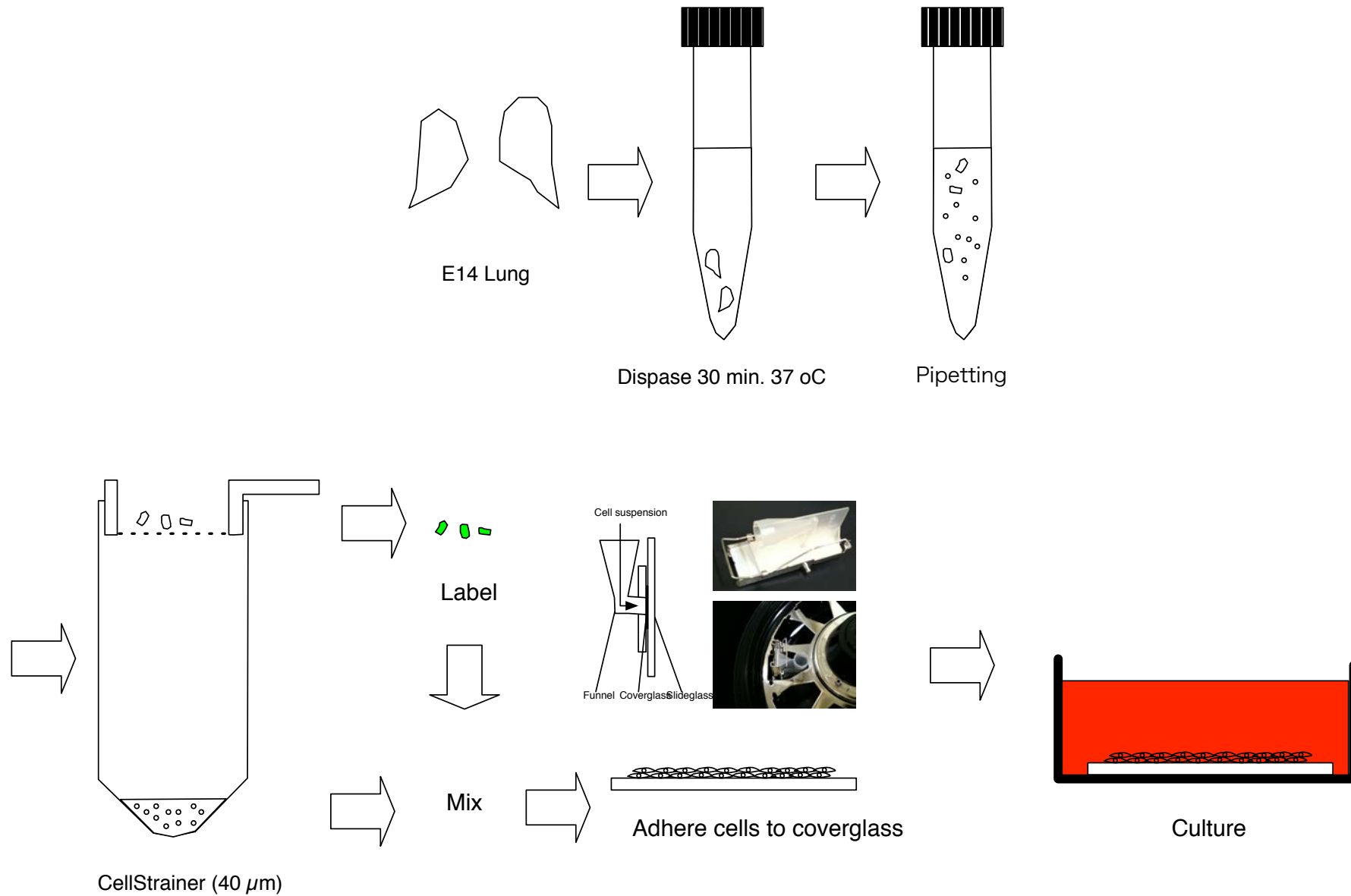


歯牙

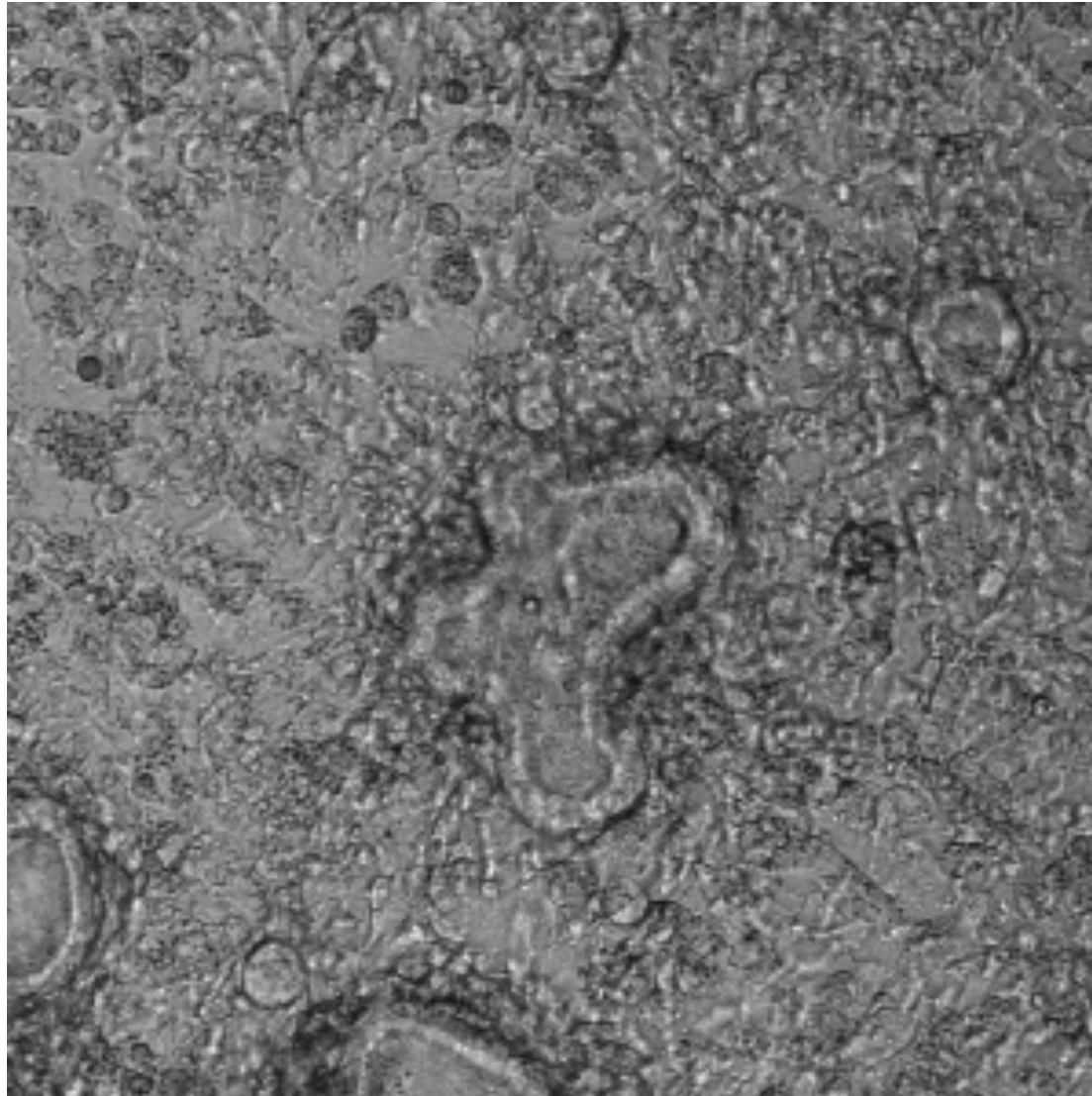
例：肺の枝分れ



再構成培養法



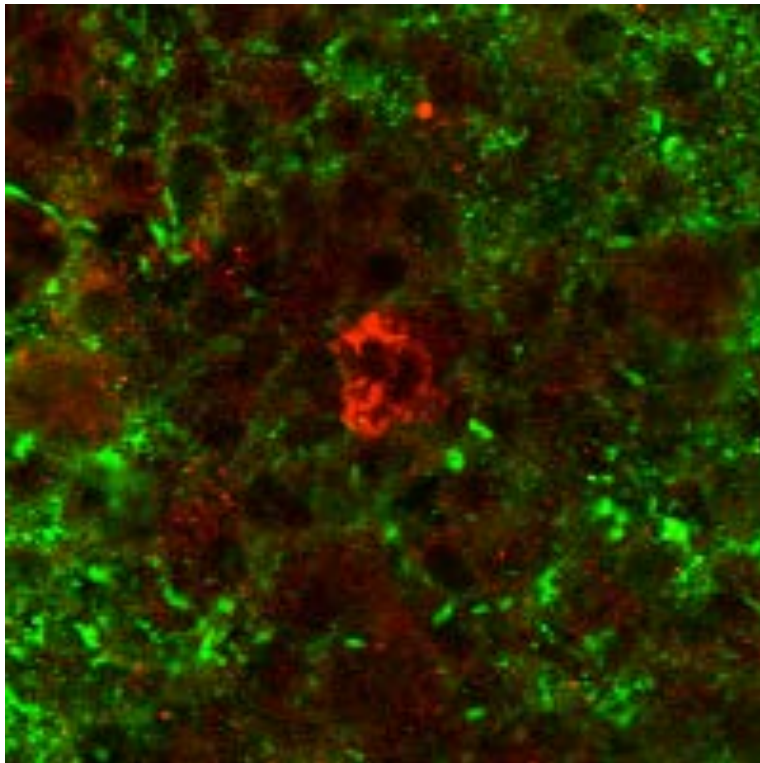
例：肺の枝分れ



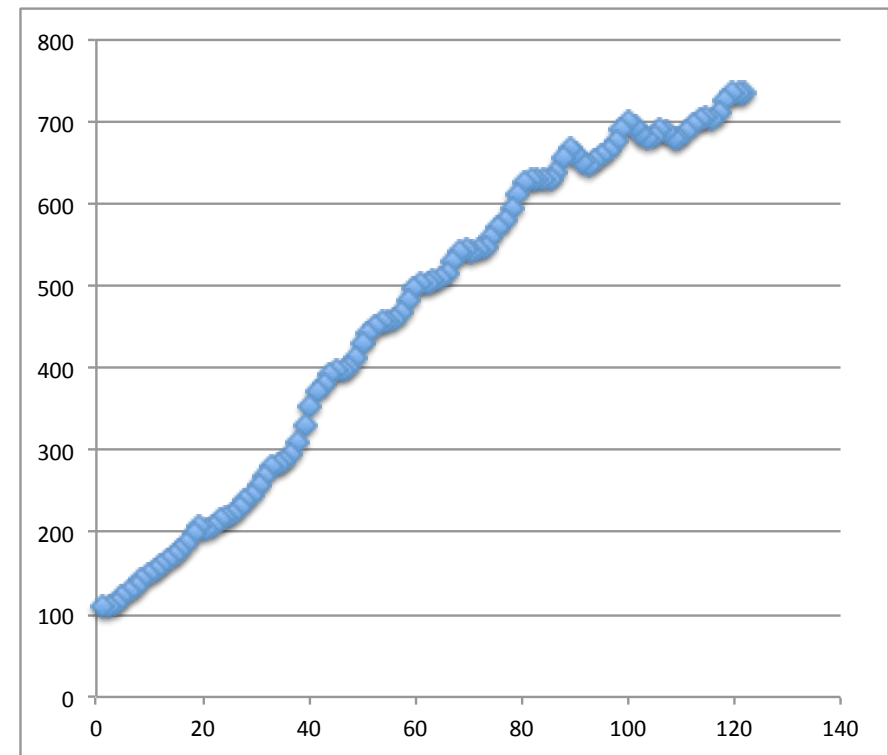
- 24-36 hrs

単一の上皮細胞のFGF10発現への影響

FGF10

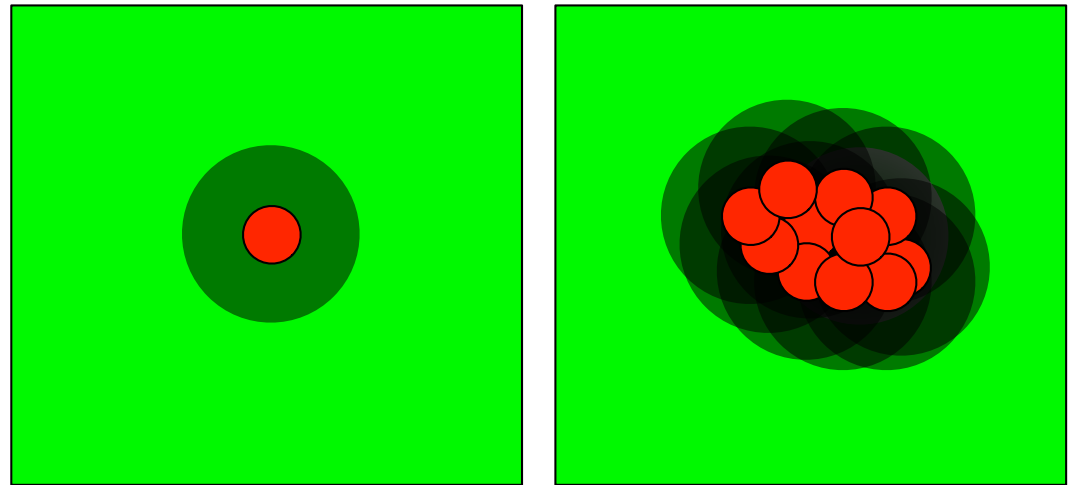
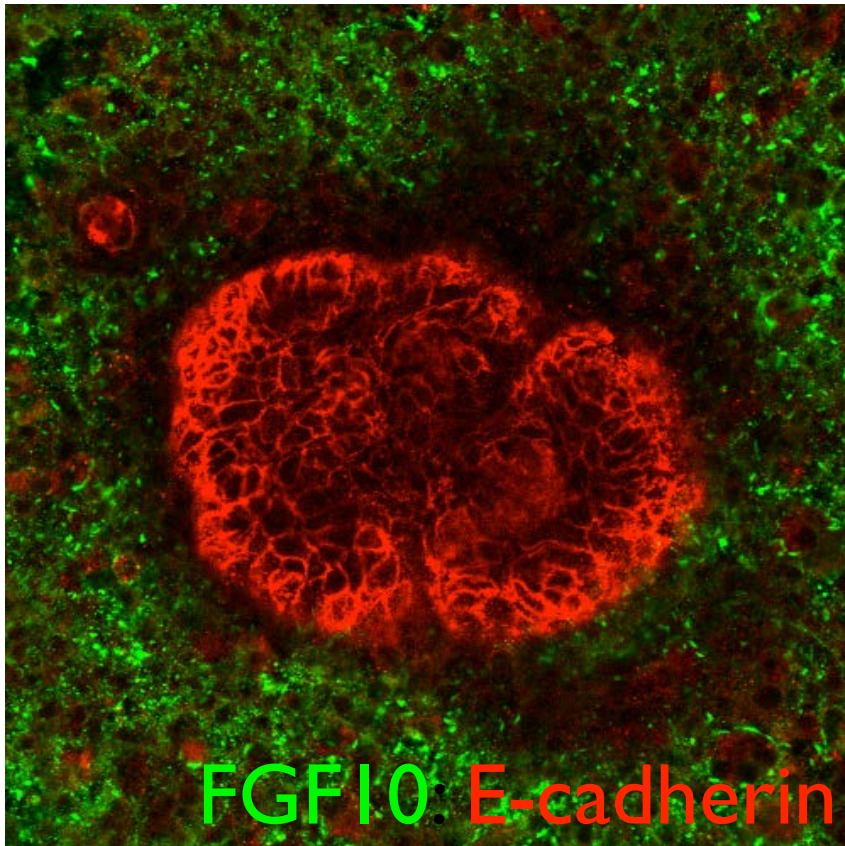


FGF10: E-cadherin



Distance from center (um)

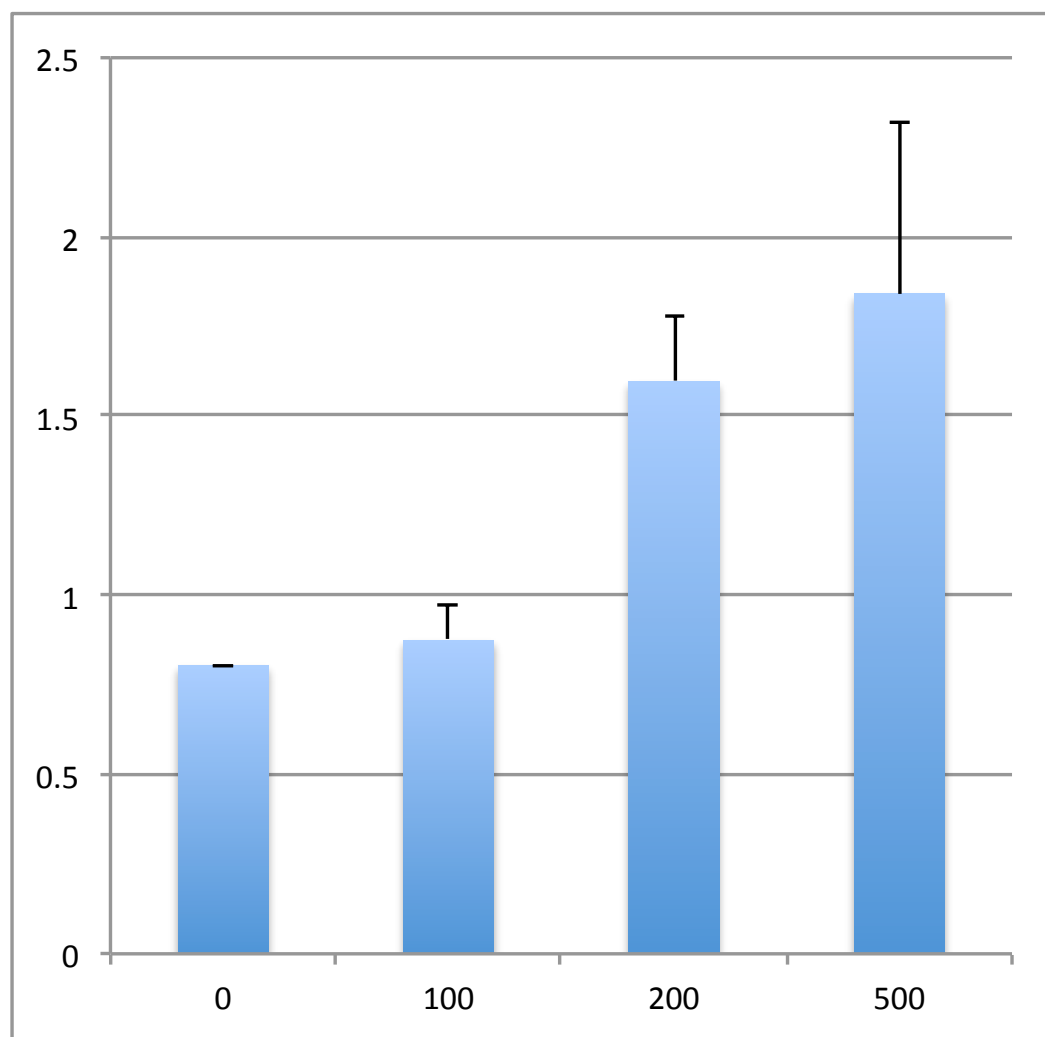
細胞集団の場合：個々の細胞の効果の総和



個々の細胞の効果の総和
> 畳み込み積分

FGF10 による肺上皮の成長

Relative
area



0-24hrs

ng/ml

遺伝子発現の変化よりかなり遅い

界面方程式と

畳み込み積分による実装

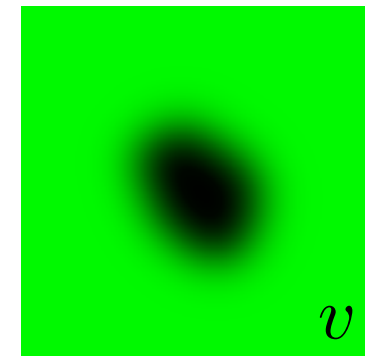
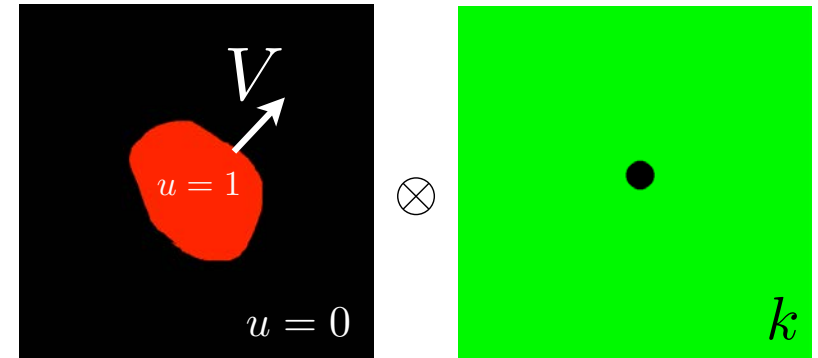
- 上皮 > 間葉：個々の上皮細胞は周辺のFGF産生を抑制する
- 間葉 > 上皮：上皮組織はFGFがあると成長する

支配方程式

成長速度 FGFの効果 表面張力

$$\begin{aligned} V &= f(v) - \sigma \kappa \\ v &= k \otimes u \end{aligned}$$

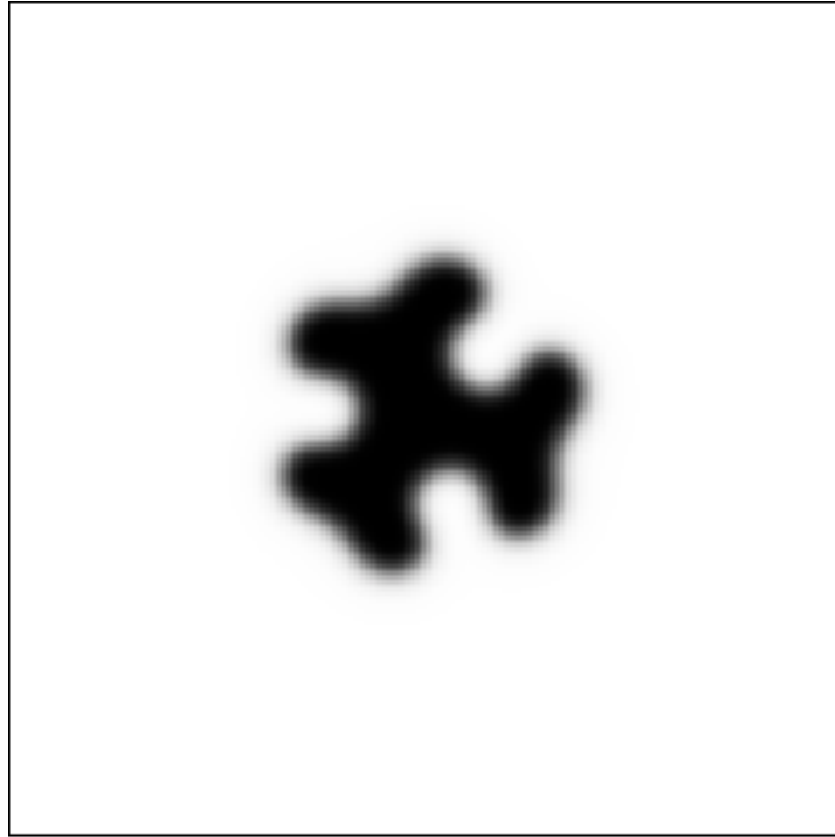
FGF分布 単一細胞の 上皮の分布
効果



\otimes :畳み込み積分

$$k(x, y) = \begin{cases} 1/(\pi r_0^2) & (x^2 + y^2 \leq r_0) \\ 0 & (x^2 + y^2 > r_0) \end{cases}$$

数值計算 (2次元)

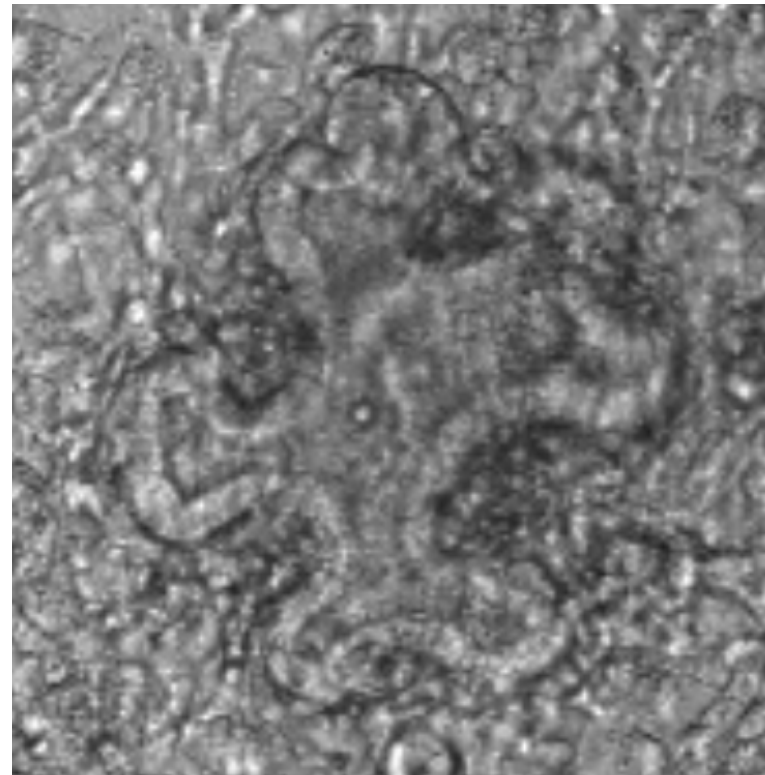
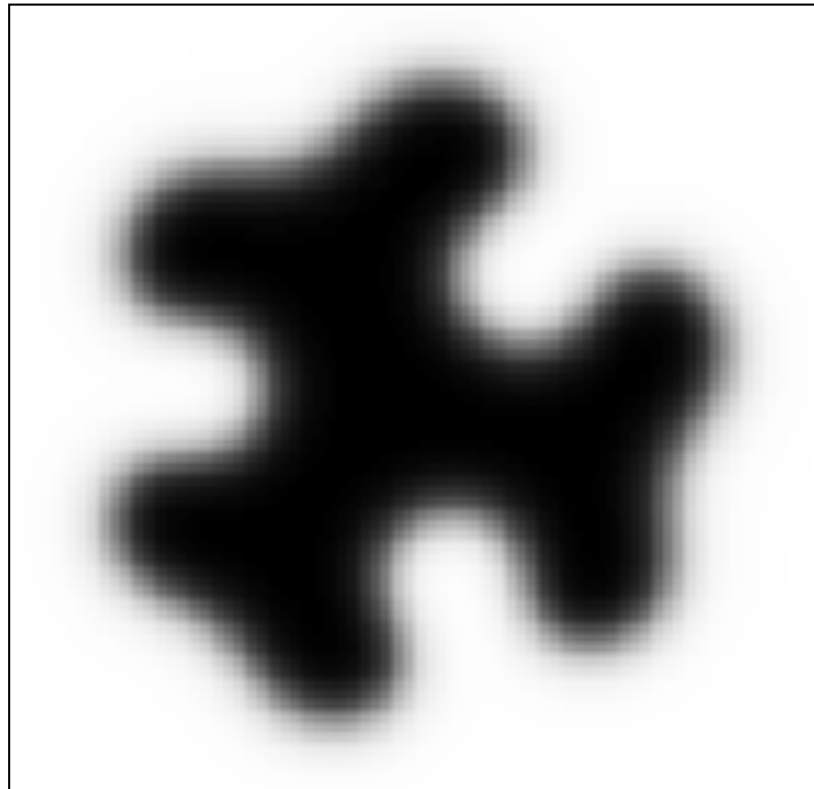


$$u' = u(1 - u)(u - 1/2 + (1/2 - v)) + d_u \Delta u$$

$$v = k \otimes u$$

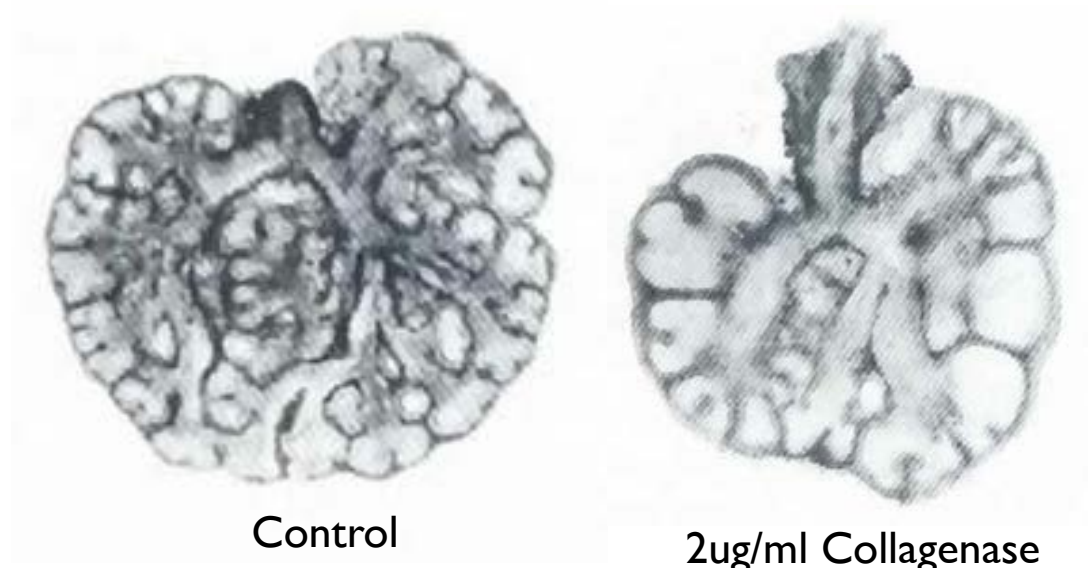
$$k(x, y) = \begin{cases} 1/(\pi r_0^2) & (x^2 + y^2 \leq r_0) \\ 0 & (x^2 + y^2 > r_0) \end{cases}$$

実験データとの比較



ECM degradation

> fast FGF diffusion > cyst



Int. J. Dev. Biol
35: 453-461 (1991)

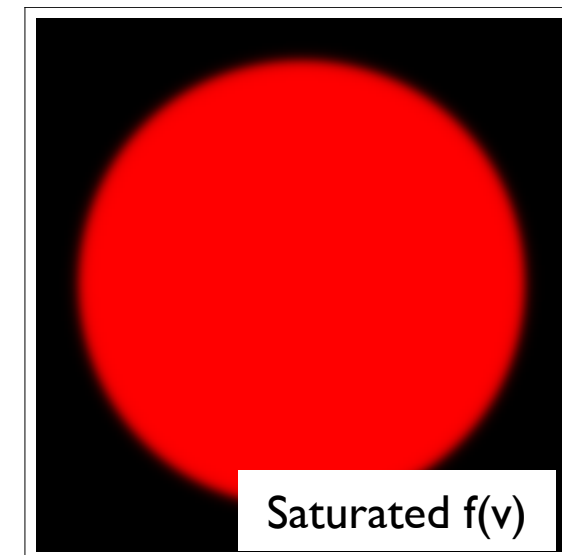
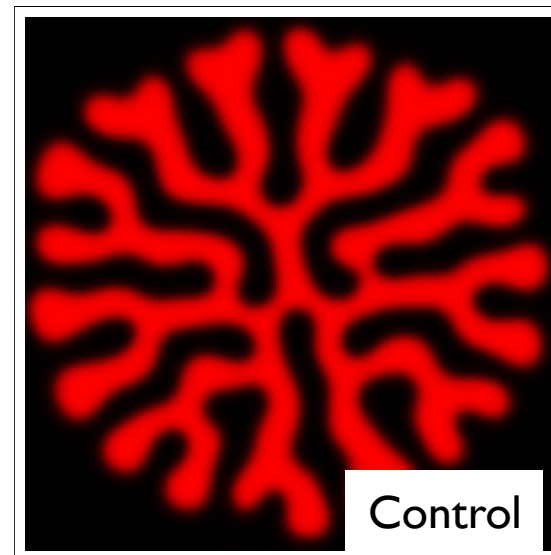
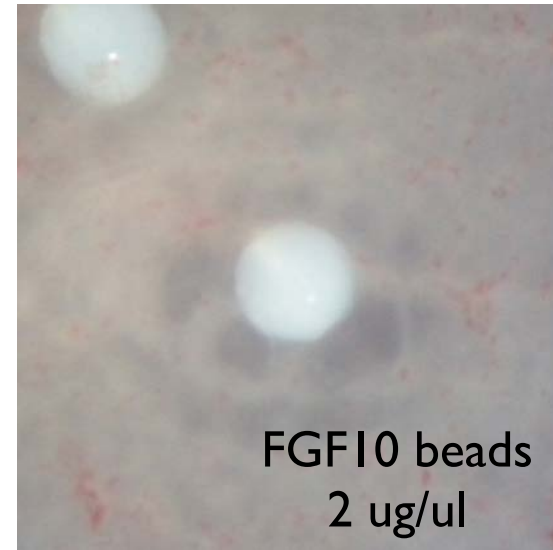


Control



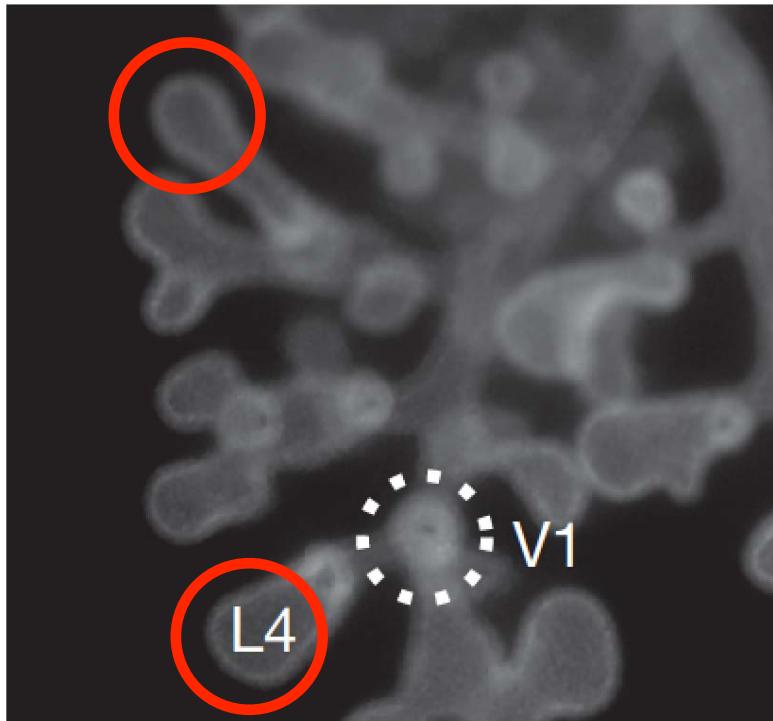
Kernel diameter x100

Saturating FGF concentration results in cyst



Tip dilatation

Experiment



Metzger 2008

Simulation

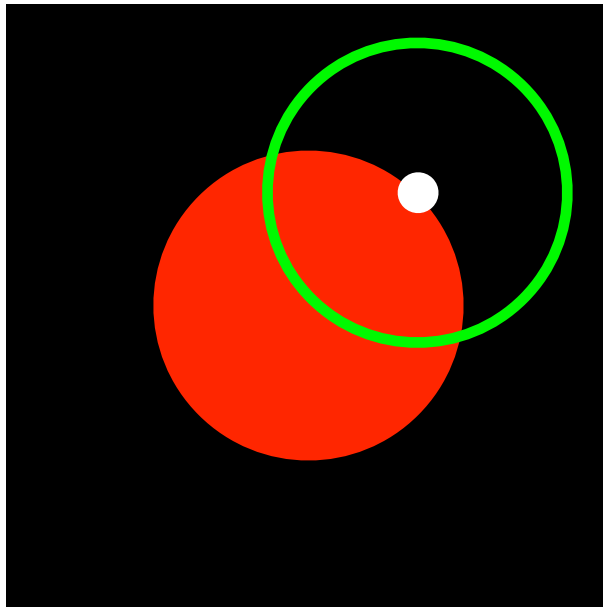


Tip

Stalk

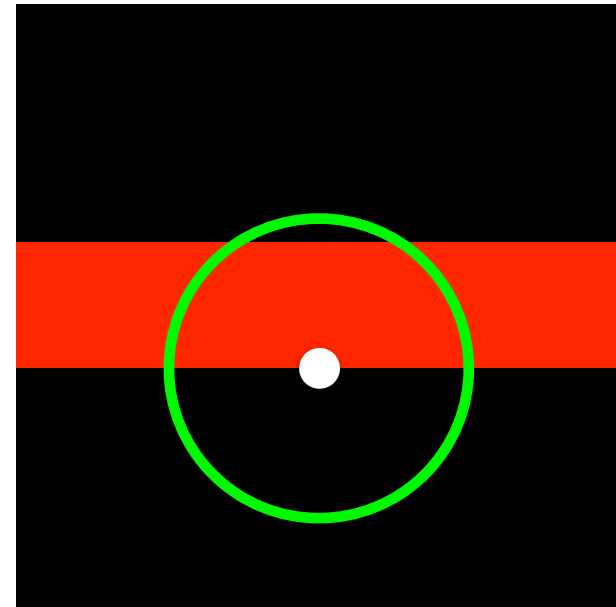
Tip & Stalk shape as quasi-steady state

Tip diameter

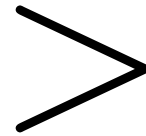


Bulk effect ($f(v)$)
balanced by
surface tension

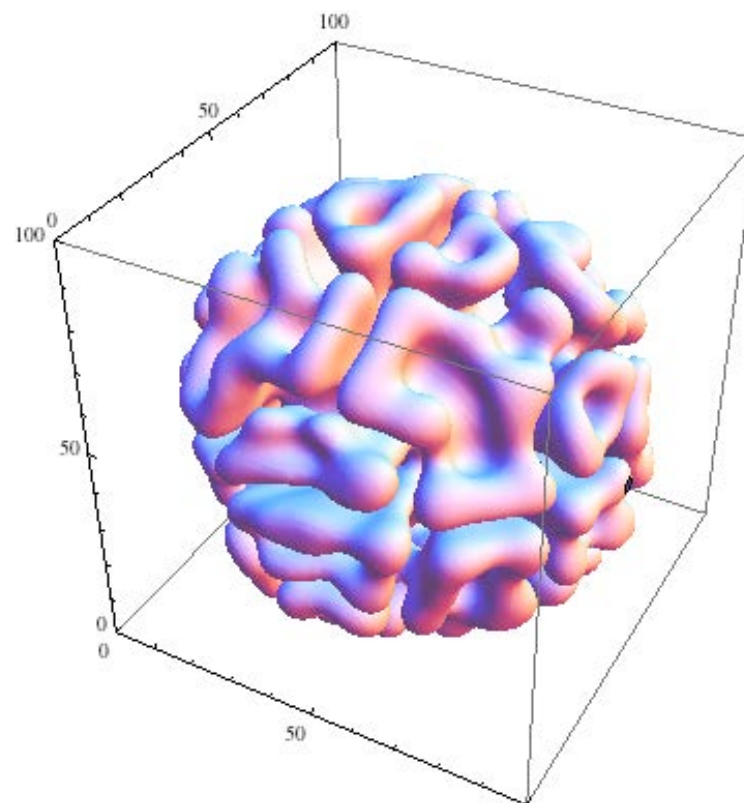
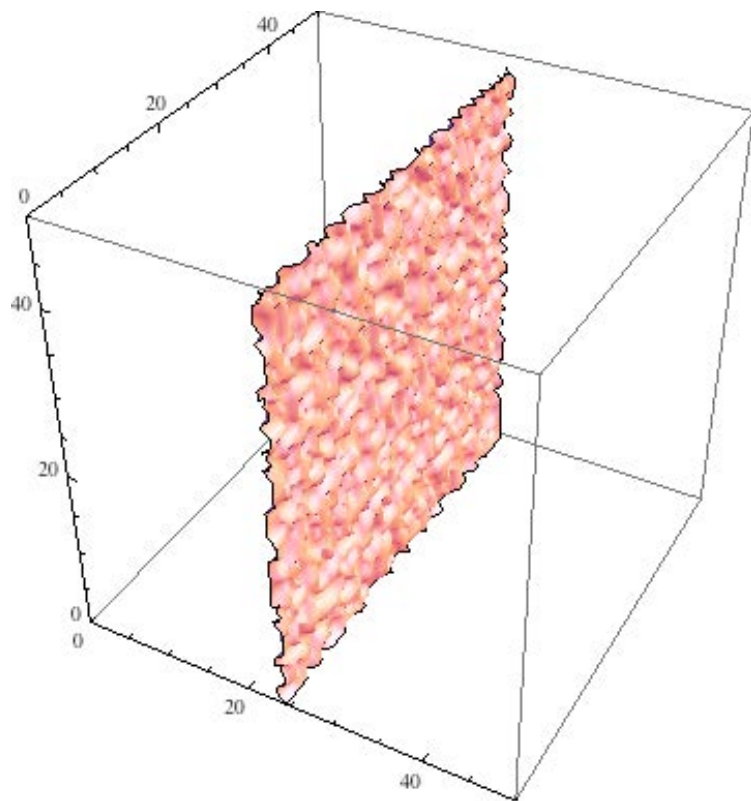
Stalk thickness



Bulk effect ($f(v)$)
balanced by
another interface



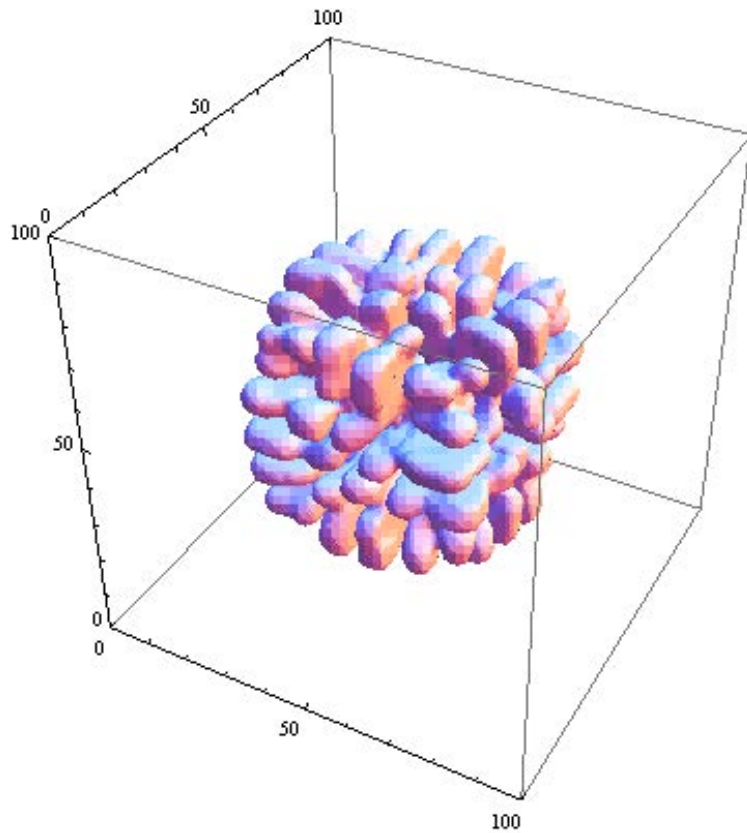
肺の枝分れの3次元の数値計算



not branch > Reverse symmetry?
f(v)を

村川さん

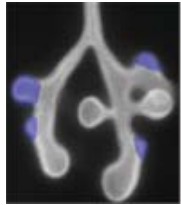
「 $\varepsilon = 0.1$ にしたら出ました」



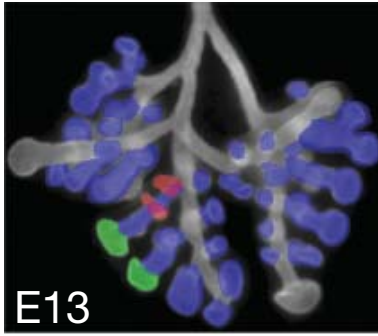
- 先端二分岐ではない $> \varepsilon$ 調節
- Grid効果が出る $> dx, dt$ も小さめに
- ノイズ入れる？

境界形状と分枝パターン

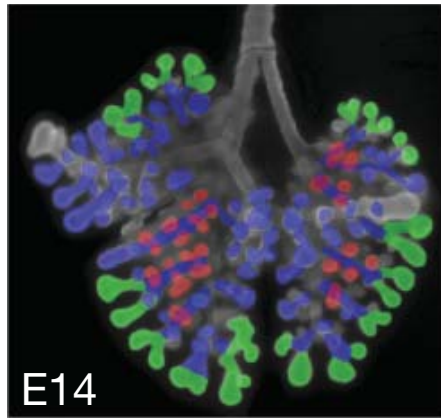
a



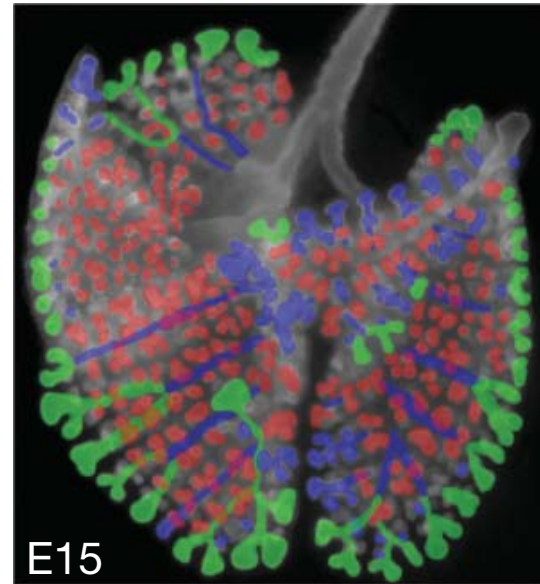
E12



E13



E14



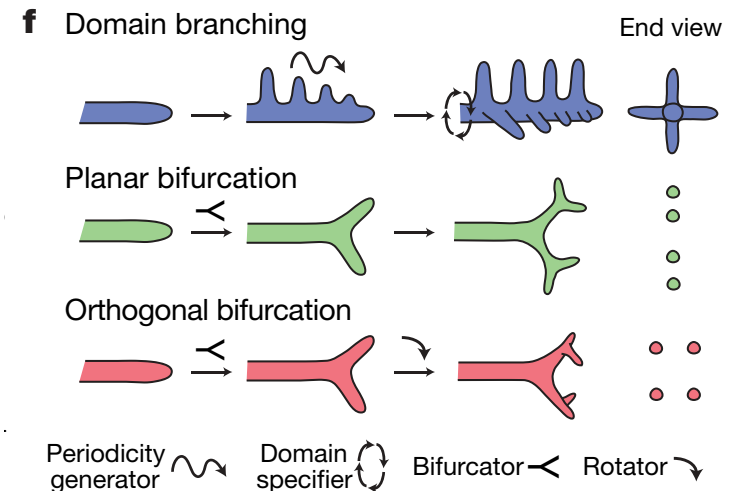
E15

Domain
branching
(scaffolds)

Planar
bifurcation
(edges)

Orthogonal
bifurcation
(surfaces/interior)

Metzger, R. J., et al. (2008). *Nature*,
453(7196), 745–750.



依頼 1 :

- 皺ではなく枝分かれを三次元で安定して出すための条件は？
- Metzgerの提唱した3パターンを境界形状のみで実現できる？

頭蓋骨の縫合線のパターン形成

前頭縫合

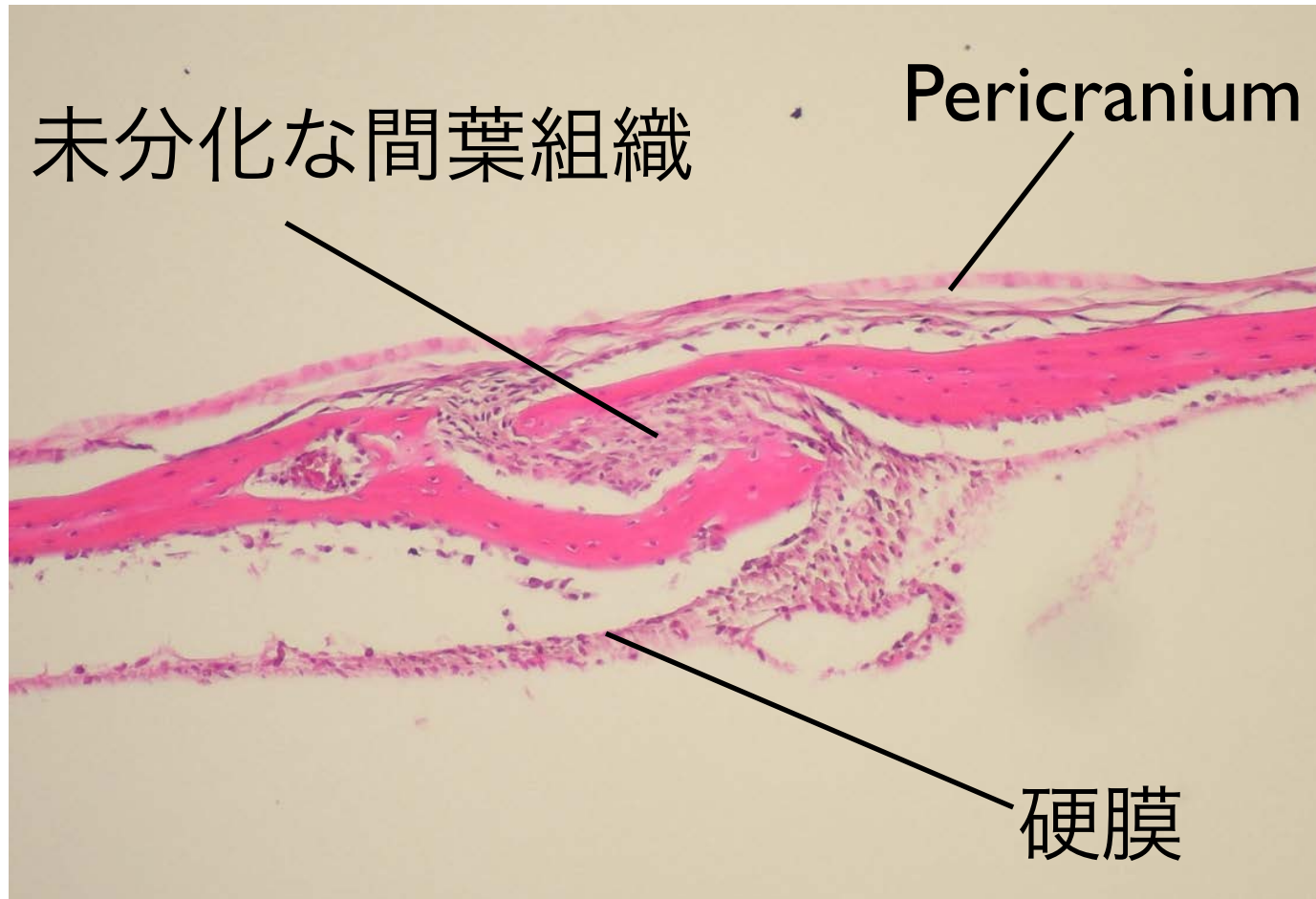


新生児



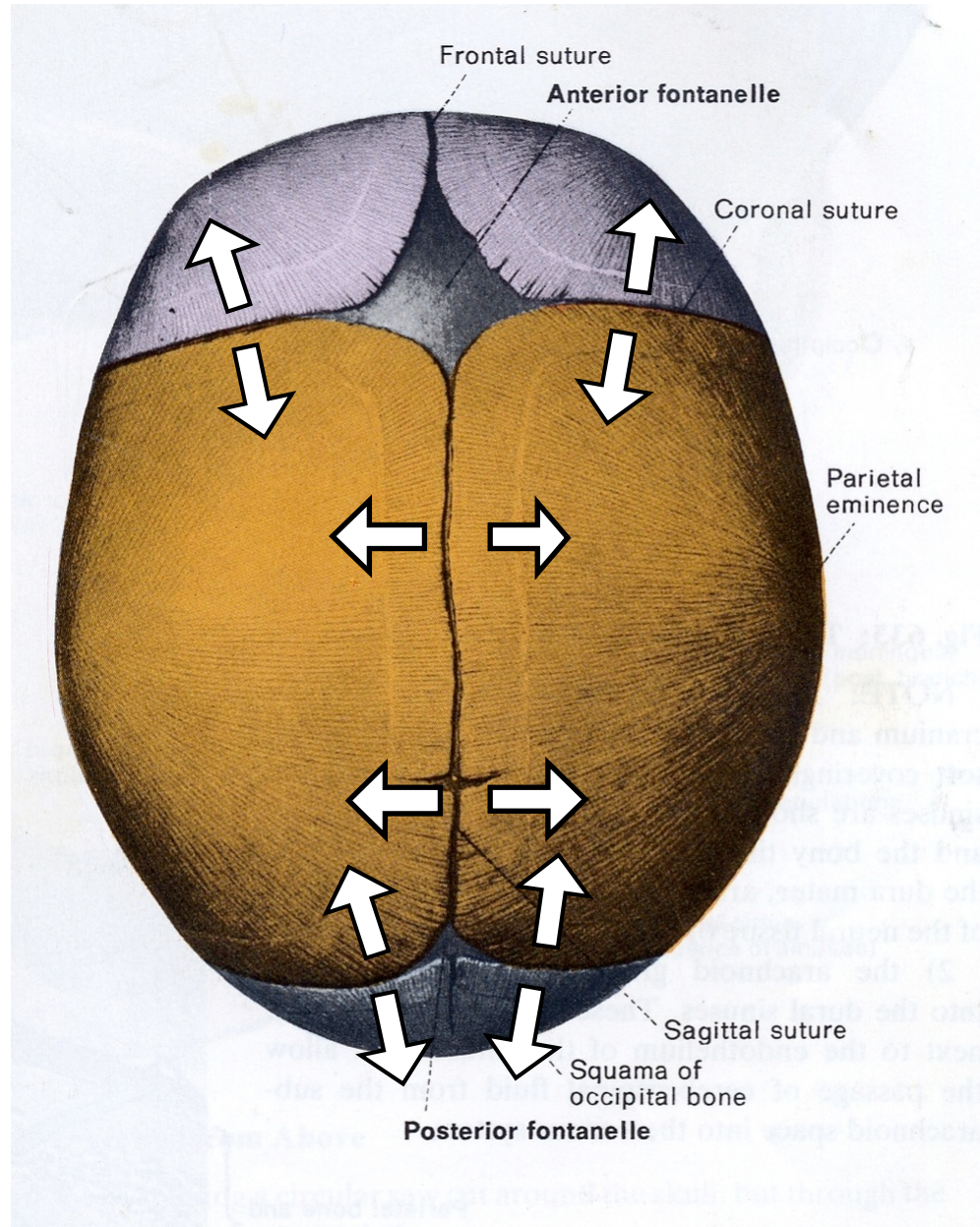
成人

組織

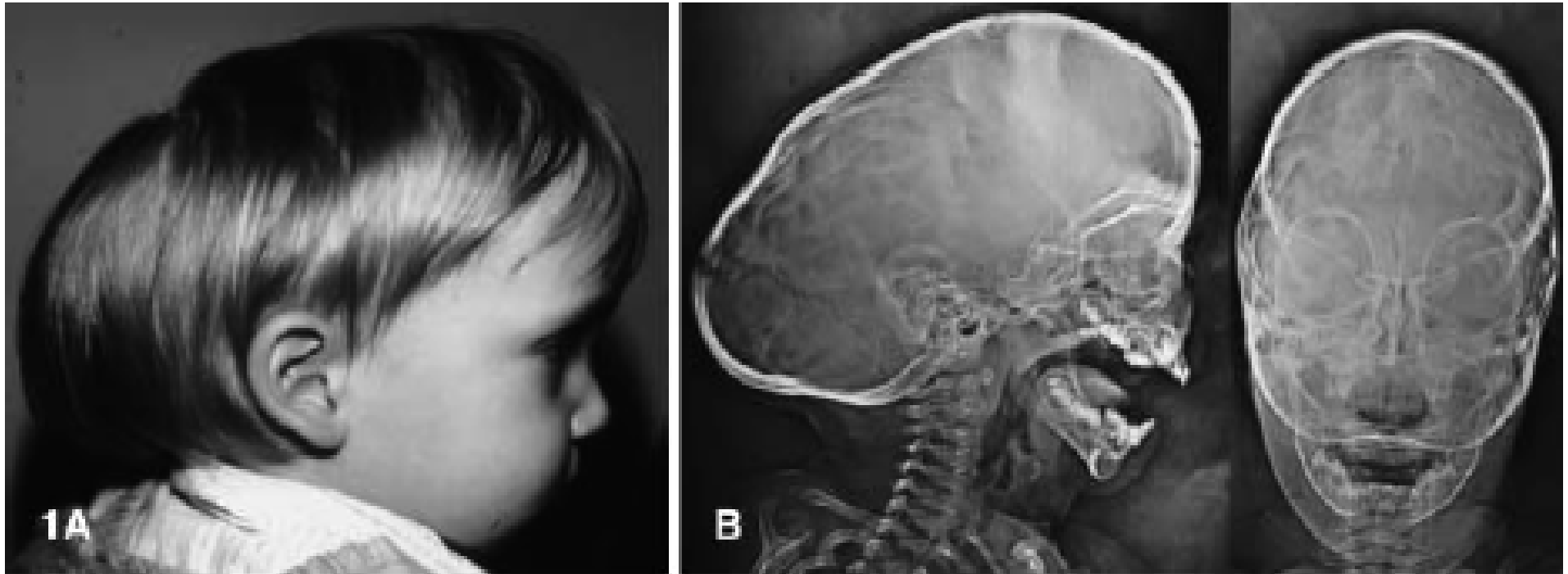


3週齡マウス矢状縫合

機能：頭蓋骨の成長

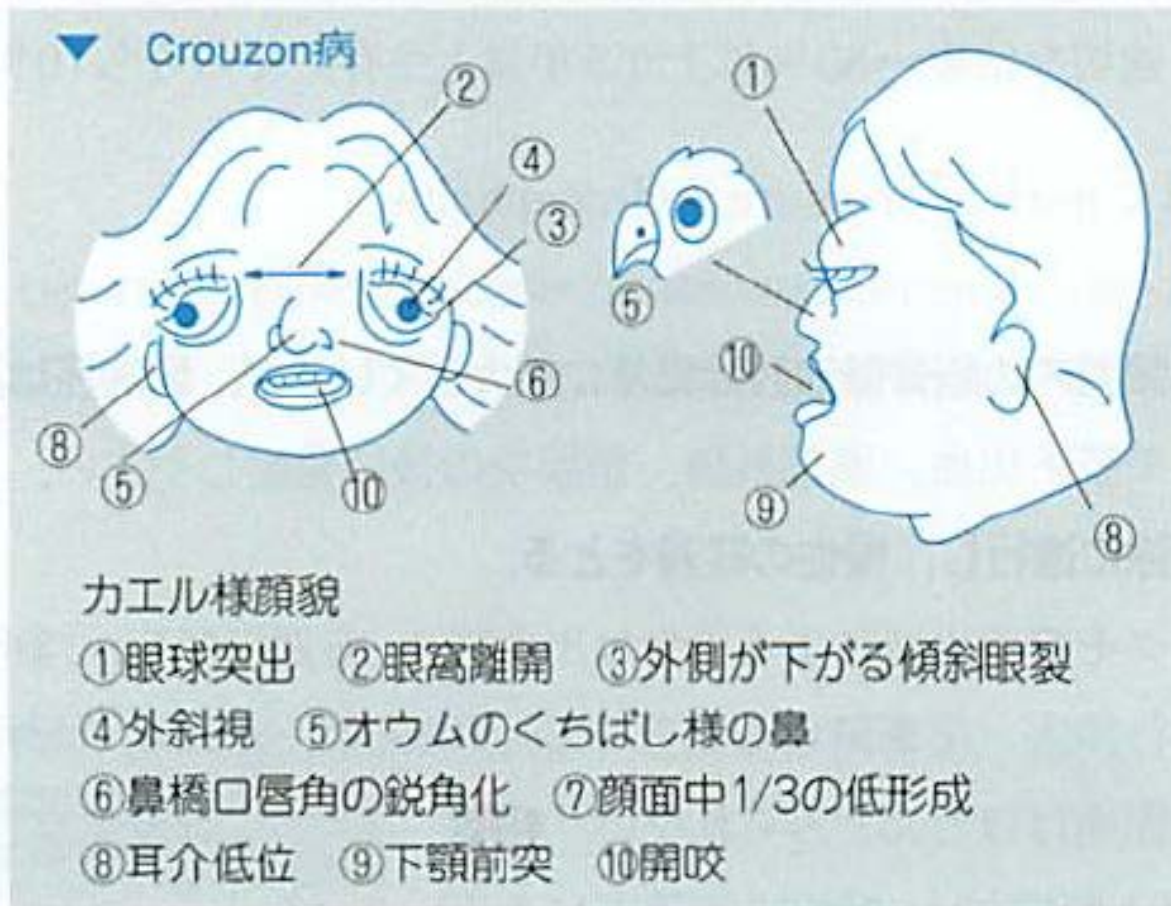
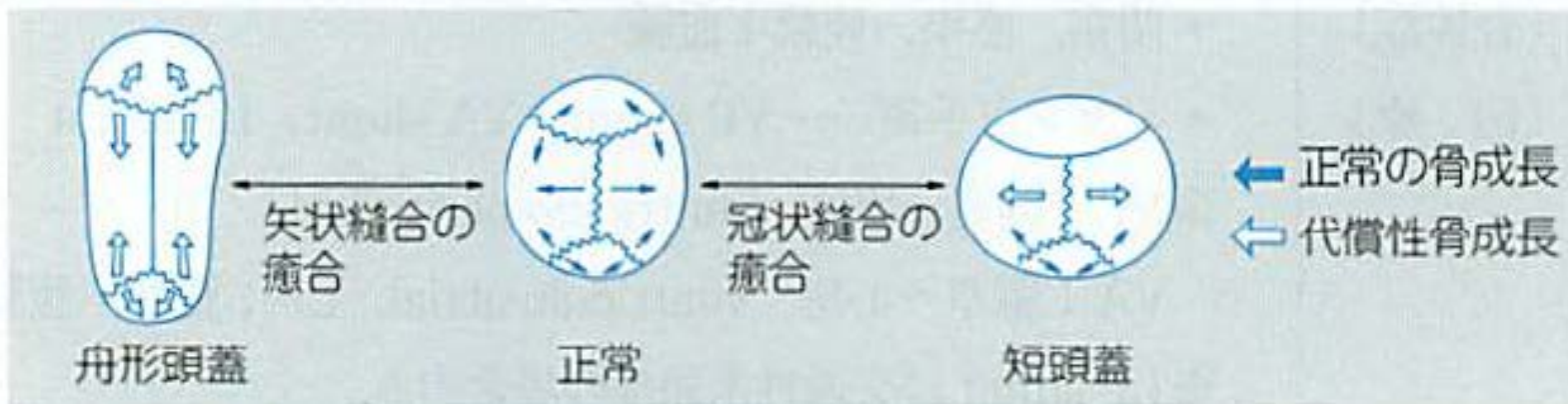


頭蓋骨早期癒合症

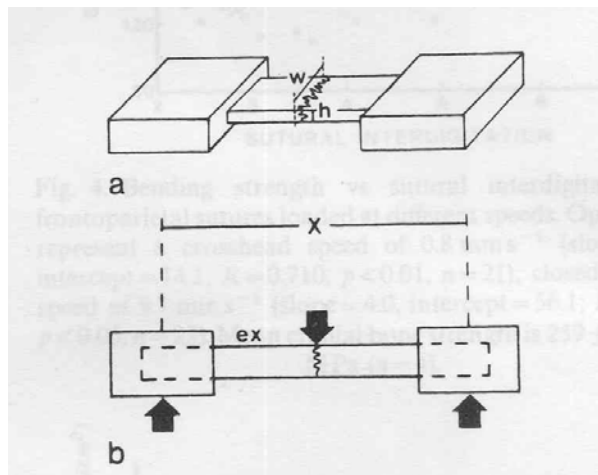
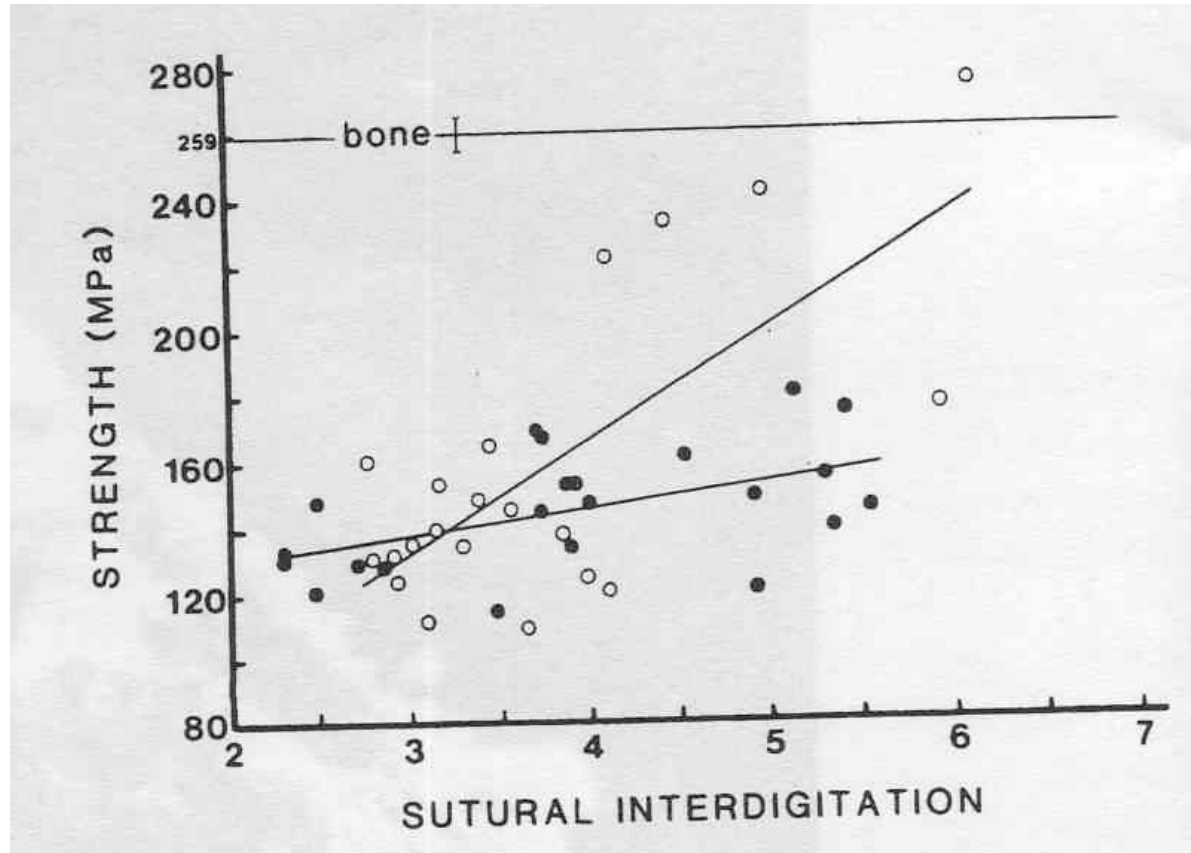
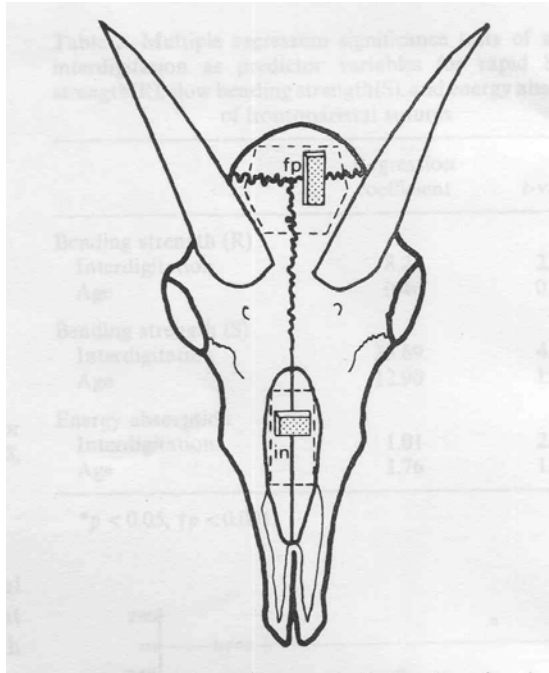


Crouzon syndrome - FGFR GOF mutation

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

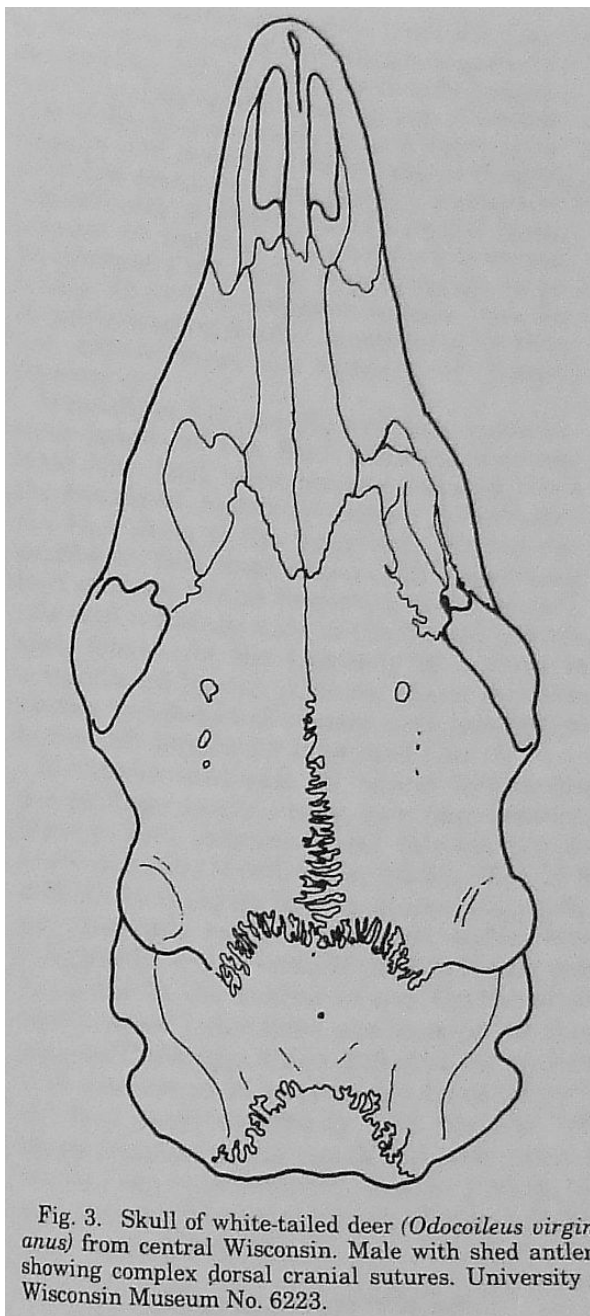


Fig. 3. Skull of white-tailed deer (*Odocoileus virginianus*) from central Wisconsin. Male with shed antler showing complex dorsal cranial sutures. University Wisconsin Museum No. 6223.

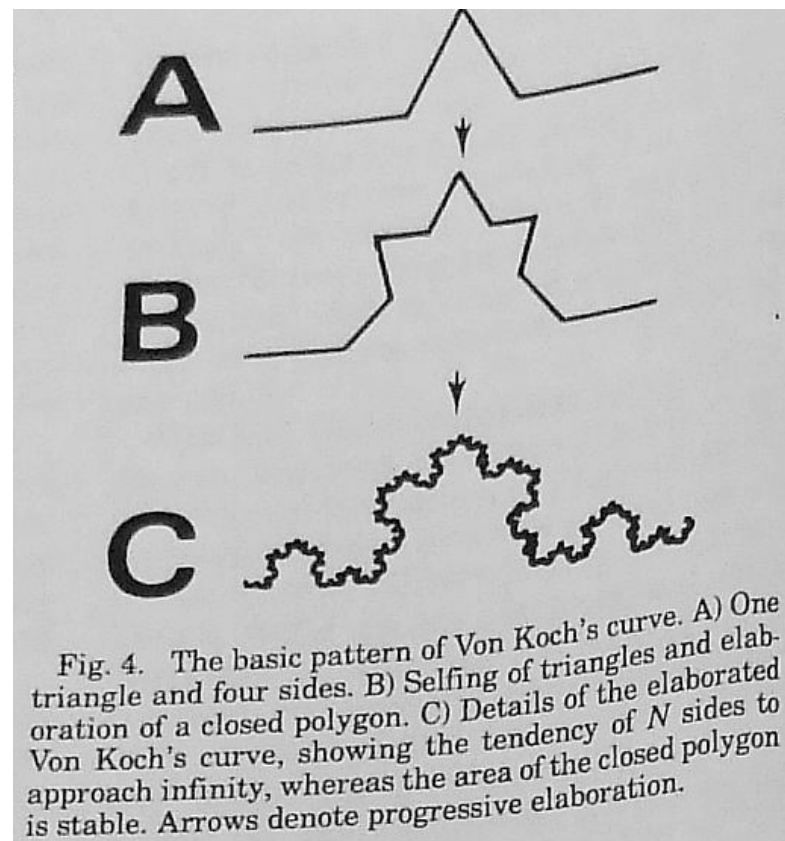


Fig. 4. The basic pattern of Von Koch's curve. A) One triangle and four sides. B) Selfing of triangles and elaboration of a closed polygon. C) Details of the elaborated Von Koch's curve, showing the tendency of N sides to approach infinity, whereas the area of the closed polygon is stable. Arrows denote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

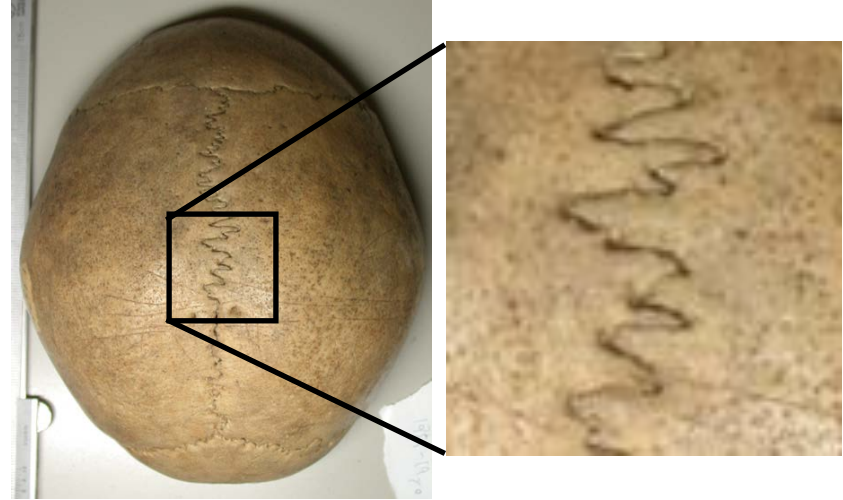
J. Morphol. 185. 285- (1985)

モデルと数値計算

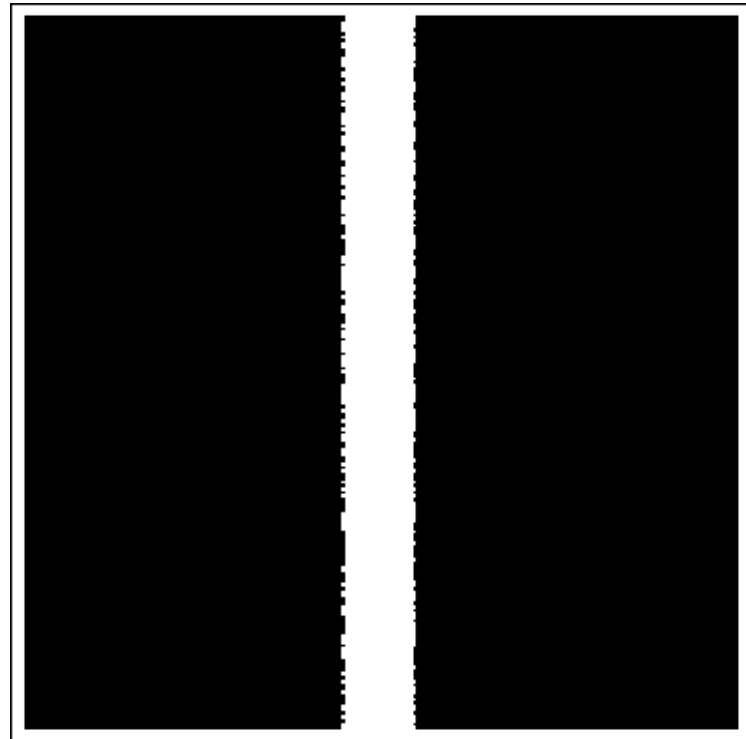
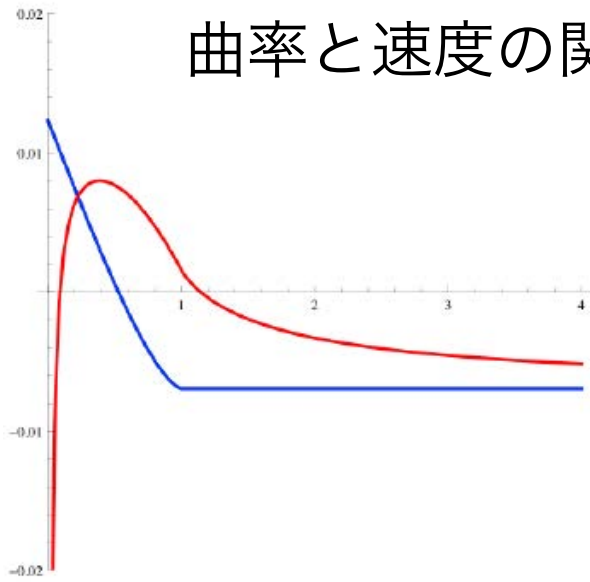
骨成長速度 FGFの効果 表面張力

$$\begin{aligned} \dot{V} &= f(v) - \sigma \kappa \\ v &= k \otimes u \end{aligned}$$

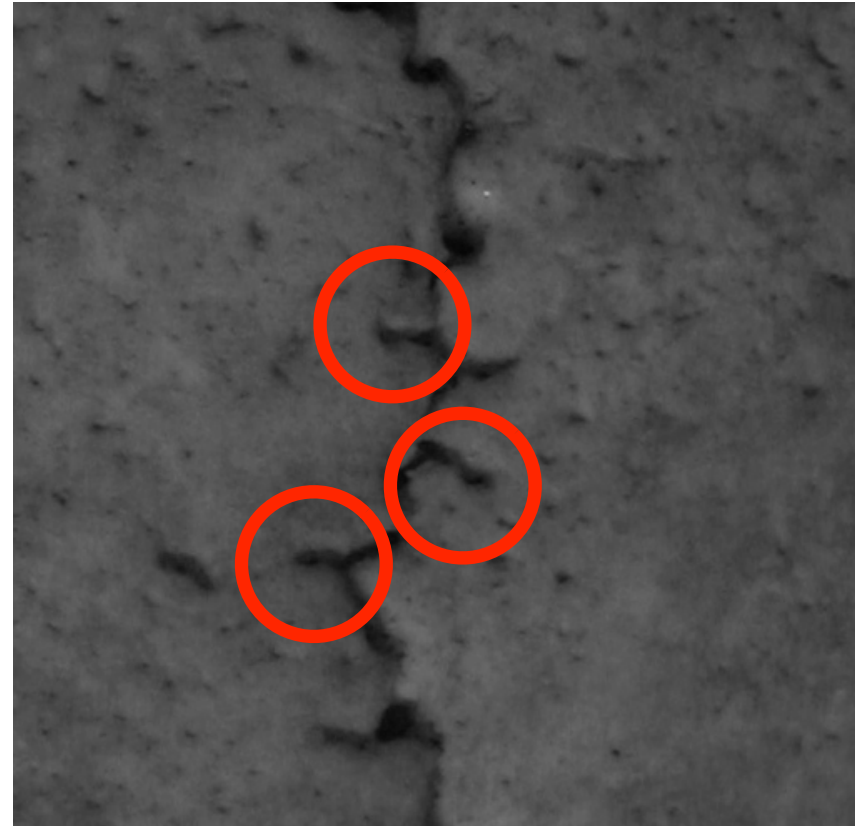
FGF分布 単一細胞の効果 間葉分布



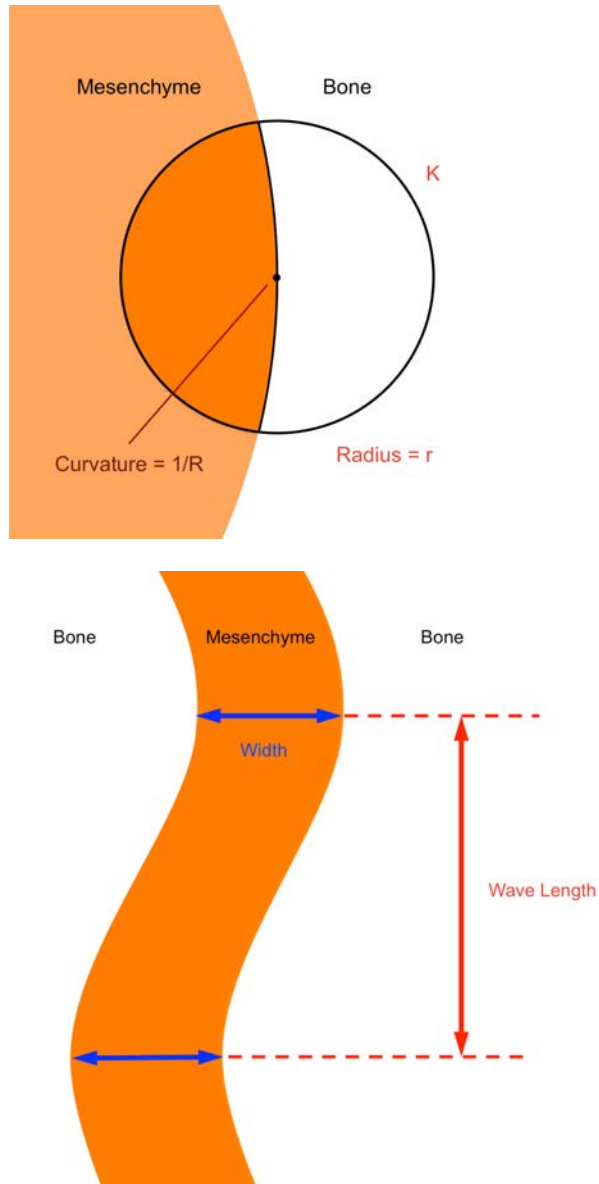
曲率と速度の関係



出芽パターン

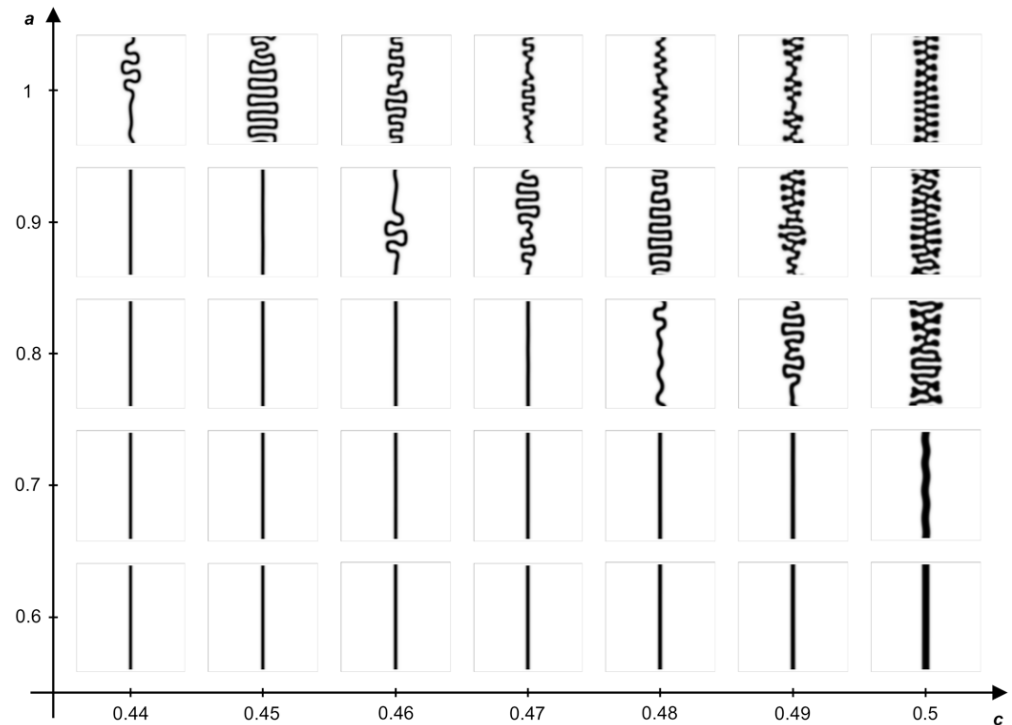


数理解析

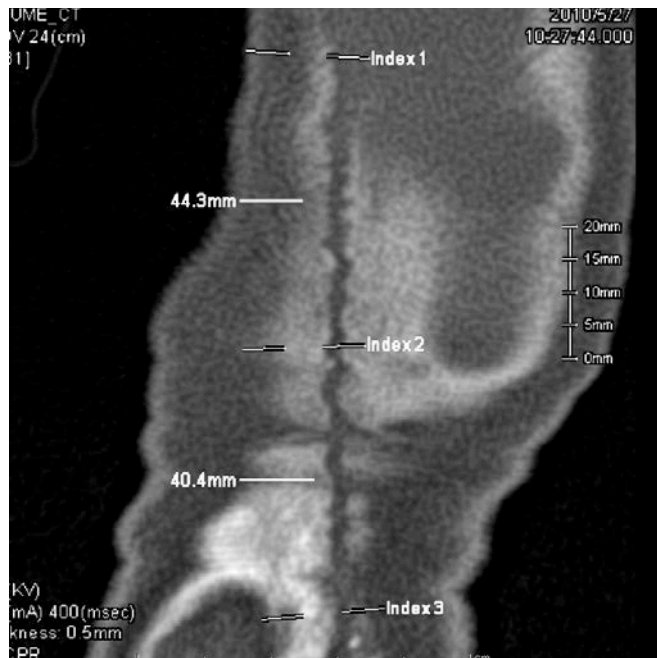


$$V = f(v) - \sigma \kappa$$

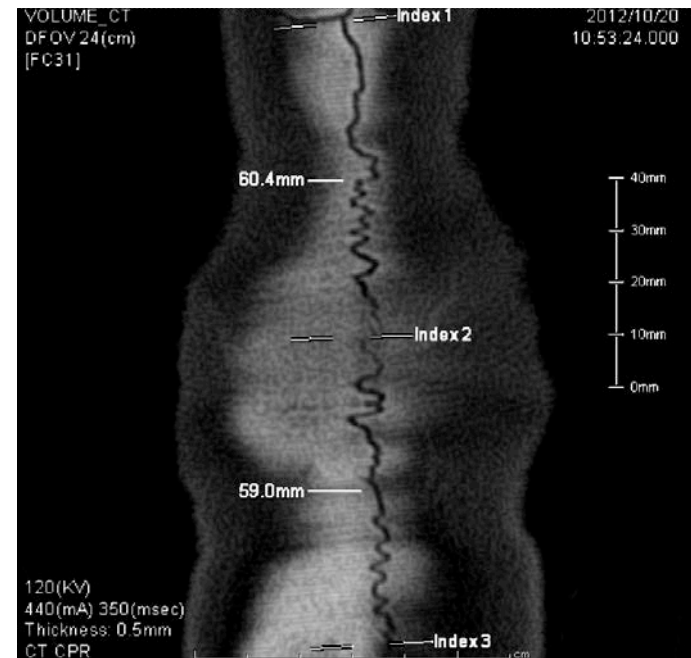
$$v = k \otimes u$$



実測データ:大阪医大



3m



32m

- 頭蓋骨縫合線早期癒合症の診断に必要

依頼 2

- 「出芽」パターンの生じる条件
- 実測データからモデル（関数＋カーネル）を推定できる？