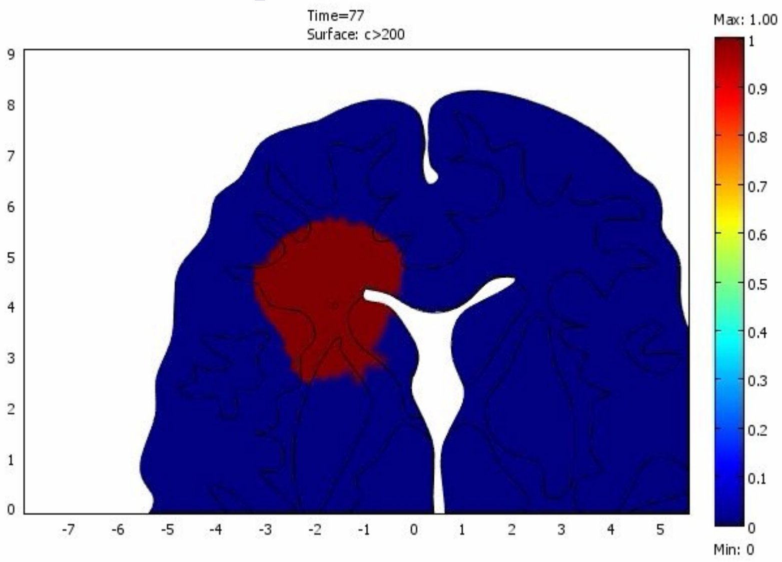
POLITECNICO DI TORINO

Growth of a glioblastoma

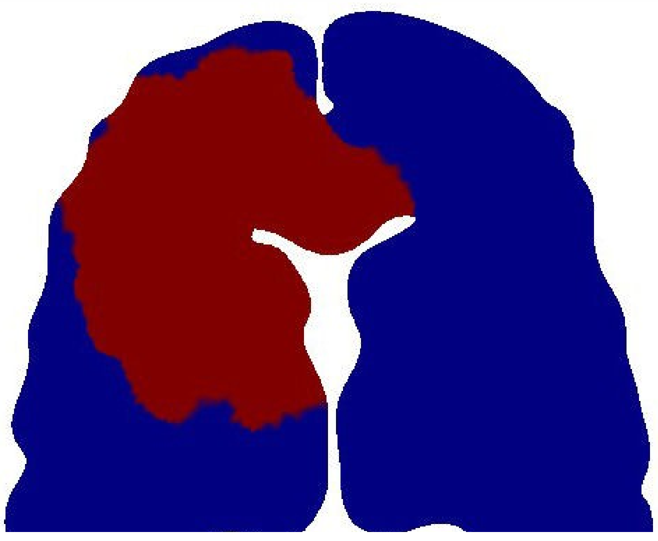


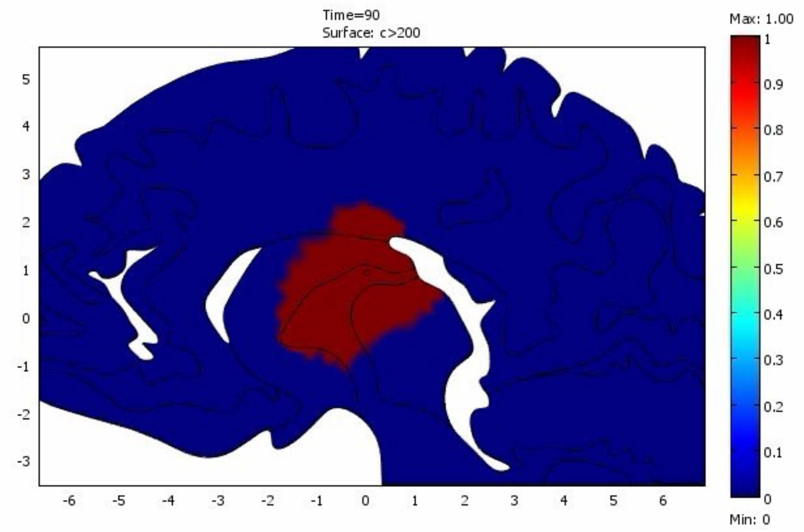
rate of change of tumor cell population

= diffusion (motility) of tumor cells

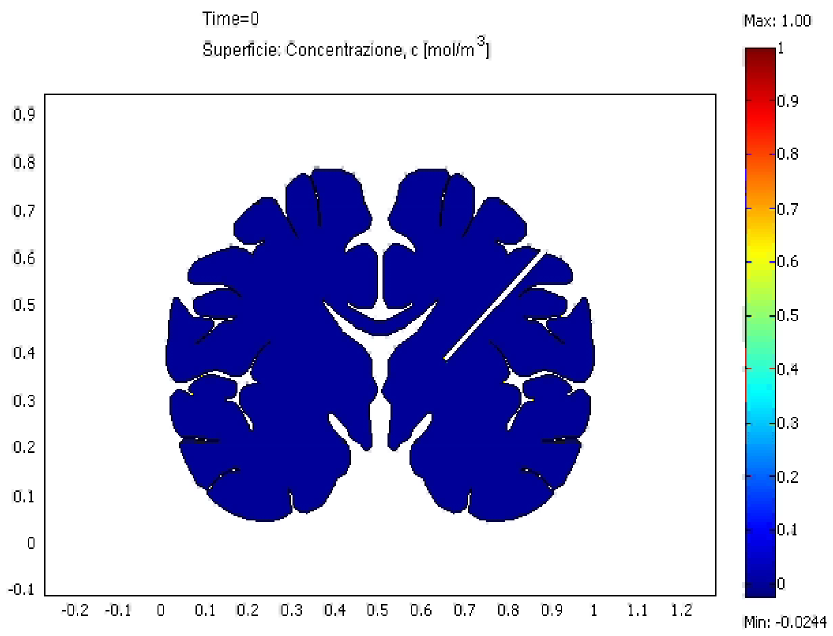
+ net proliferation of tumor cells

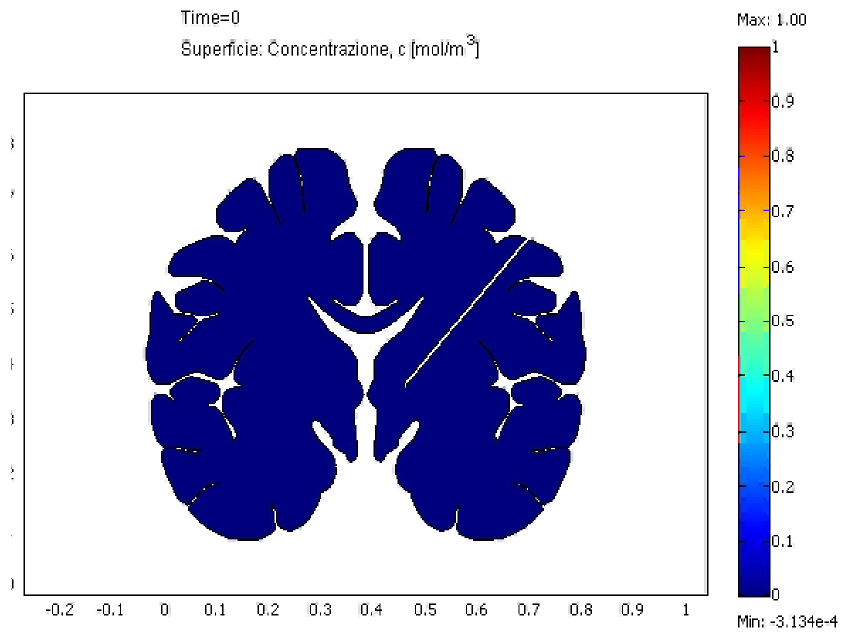
$$\frac{\partial c}{\partial t} = \nabla \cdot (D \nabla c) + \rho c$$



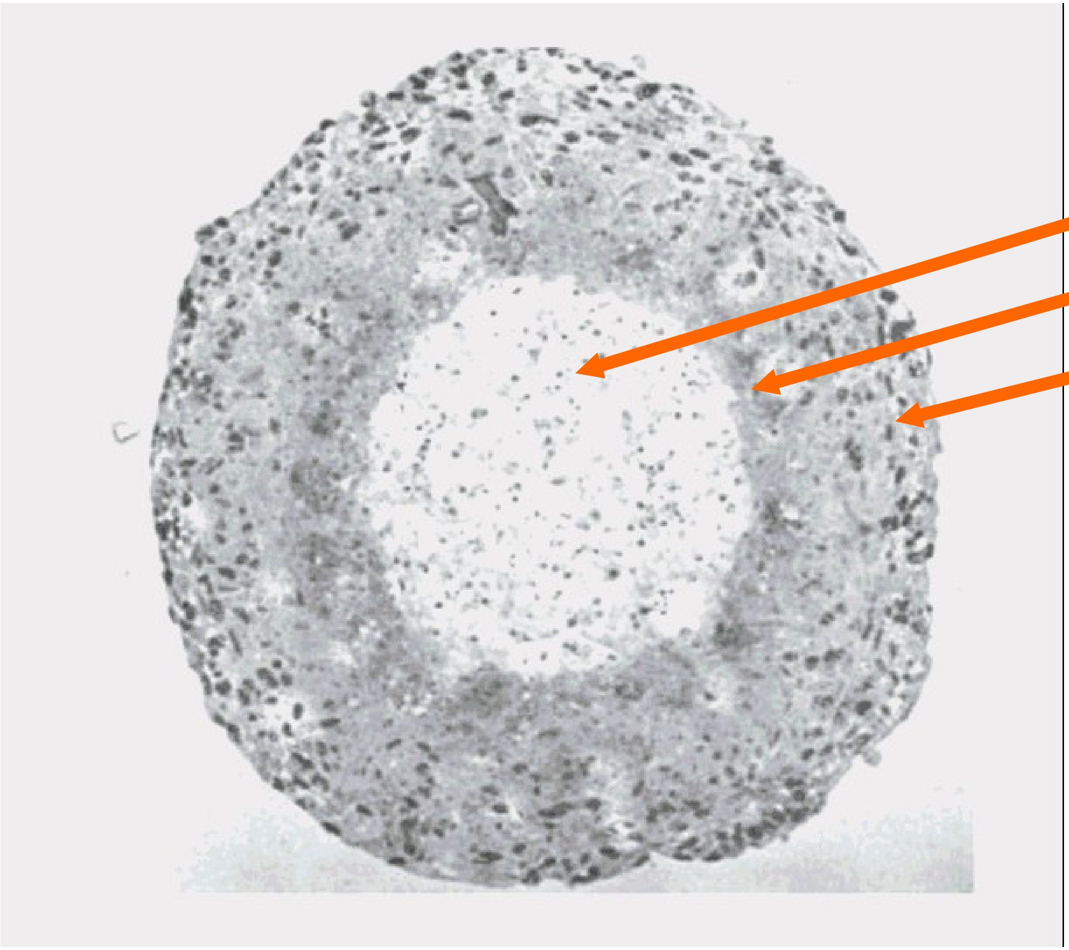


Convection-enhanced delivery





Multicellular spheroids



- ~ 10^6 cells
- Maximum diameter ~ 2 mm
- Necrotic core
- Quiescent region
- Periferic proliferation
- **“Nutrient” diffusion limit**

Spheroid from V-79 Chinese hamster lung cells
Folkman & Hochberg, Exp Med. 138:745-753 (73)

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Nutrient diffusion in spheroids

$$\begin{cases} \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial u}{\partial r}\right) - \alpha u = 0 \\ \frac{\partial u}{\partial r}(r=0) = 0 \\ u(r=R) = u_0 \end{cases}$$

$$\frac{\partial^2 u}{\partial r^2} + \frac{1}{r}\frac{\partial u}{\partial r} - \alpha u = 0$$

$$u = \frac{A}{r}\operatorname{senh}\frac{r}{d} + \frac{B}{r}\cosh\frac{r}{d}$$

$$u = u_0\frac{R}{r}\frac{\operatorname{senh}\frac{r}{d}}{\operatorname{senh}\frac{R}{d}}$$

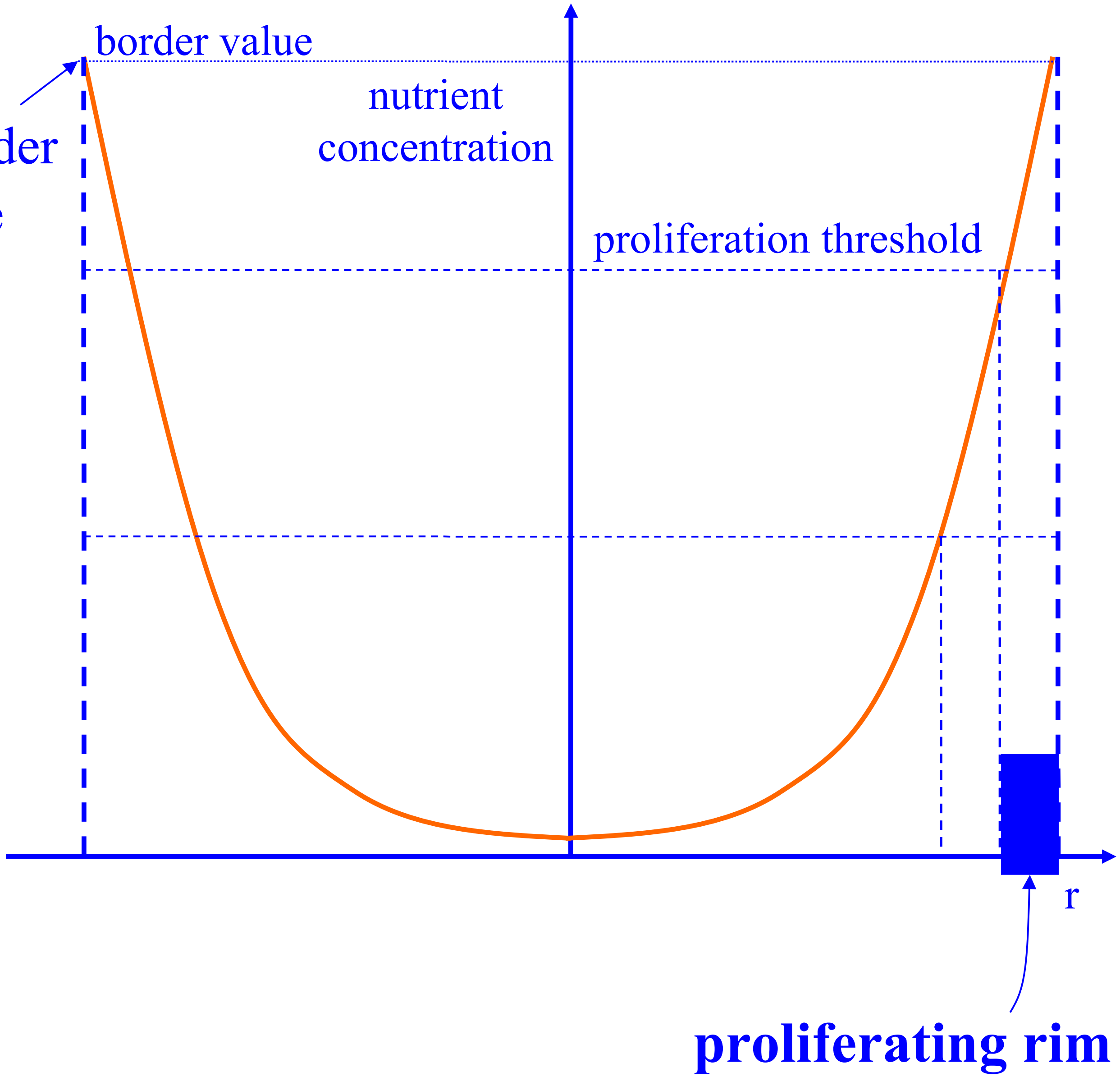
Nutrient diffusion in spheroids

nutrient diffuses in the tumour through its border and is consumed inside

$$\begin{cases} \dfrac{D}{r^2}\dfrac{\partial}{\partial r}\left(r^2\dfrac{\partial\sigma}{\partial r}\right) - \delta\sigma = 0 \\ \sigma(r=R) = \bar{\sigma} \\ \dfrac{\partial\sigma}{\partial r}(r=0) = 0 \end{cases}$$

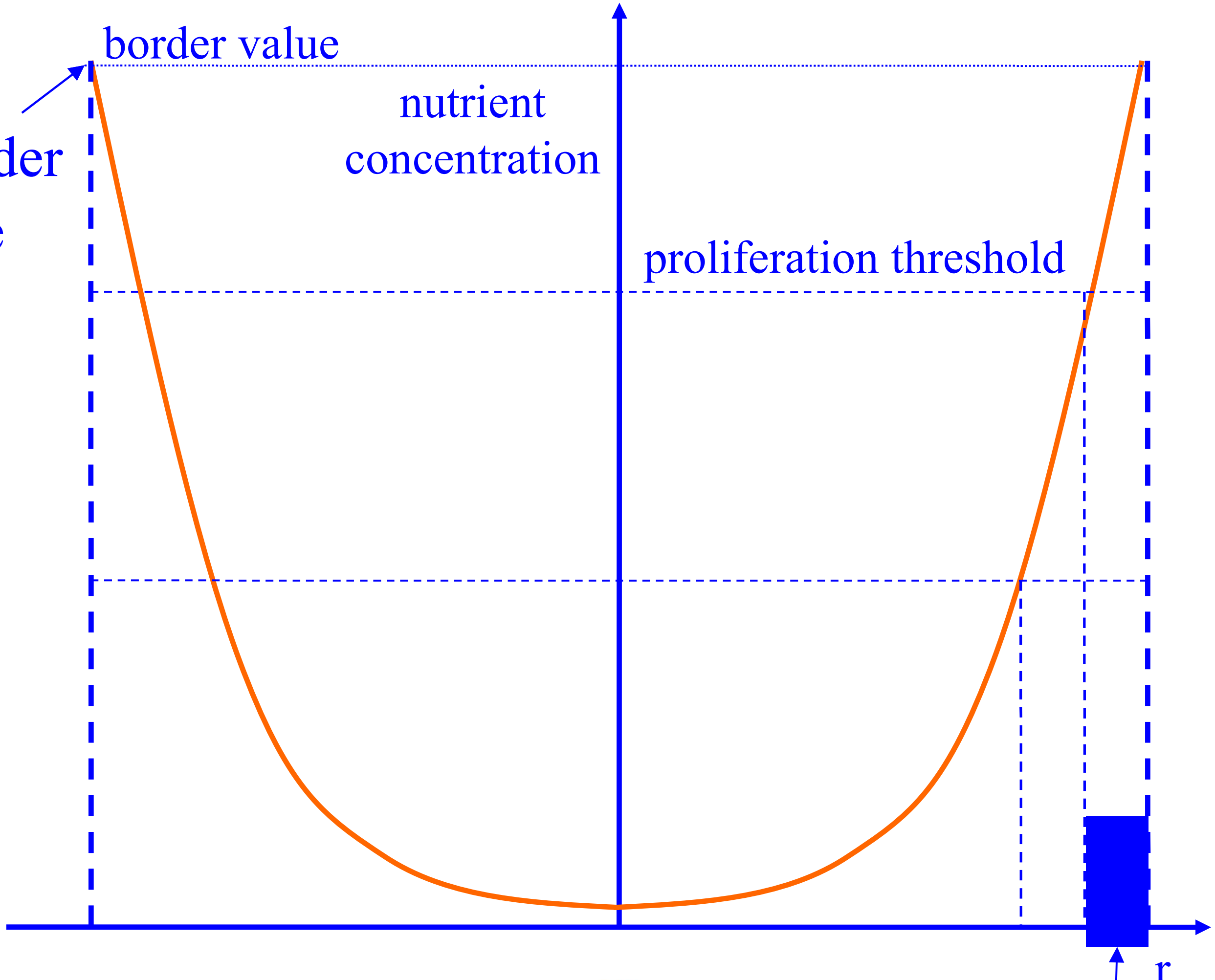
$$\sigma = \bar{\sigma}\frac{R\sinh\dfrac{r}{d}}{r\sinh\dfrac{R}{d}},$$

$$d = \sqrt{\frac{D}{\delta}} = \sqrt{D\tau}$$



Nutrient diffusion in spheroids

nutrient diffuses in the tumour through its border and is consumed inside



$$\sigma = \bar{\sigma} \frac{R \sinh \frac{r}{d}}{r \sinh \frac{R}{d}} ,$$

$$d = \sqrt{\frac{D}{\delta}} = \sqrt{D\tau}$$

For $R >> d$

$$\sigma_p = \bar{\sigma} \frac{R \sinh \frac{R - \Delta_p}{d}}{(R - \Delta_p) \sinh \frac{R}{d}} \approx \bar{\sigma} e^{-\Delta_p / d} \quad \Rightarrow \quad \Delta_p \approx \ln \frac{\bar{\sigma}}{\sigma_p} d$$

proliferating rim

Nutrient diffusion in spheroids

nutrient diffuses in the tumour through its border and is consumed inside

$$\sigma = \bar{\sigma} \frac{R \sinh \frac{r}{d}}{r \sinh \frac{R}{d}},$$

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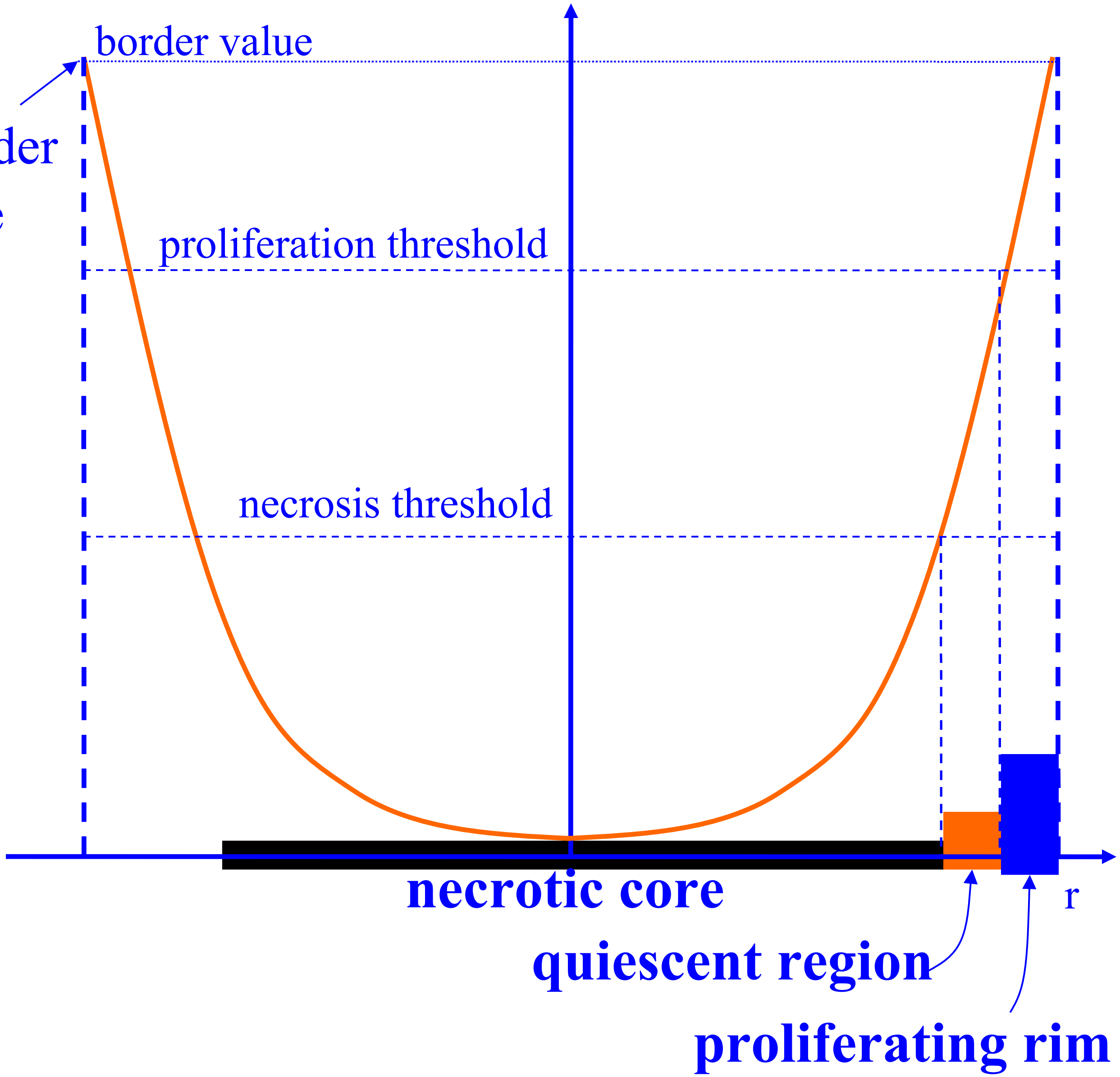
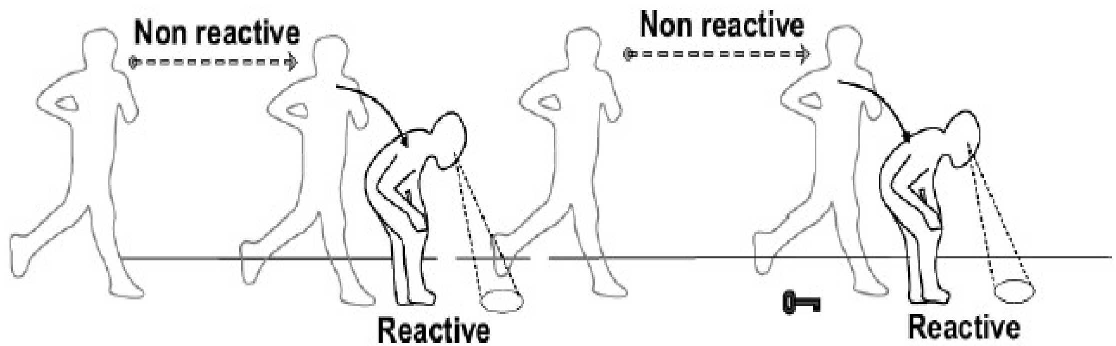
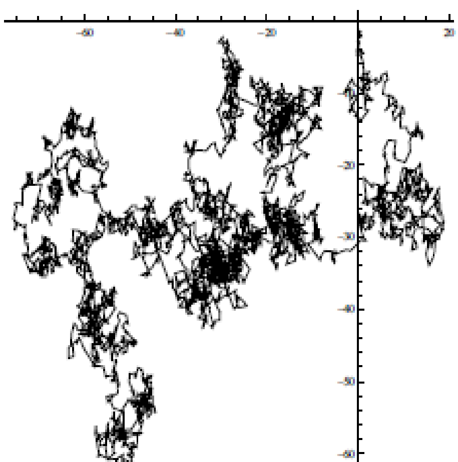
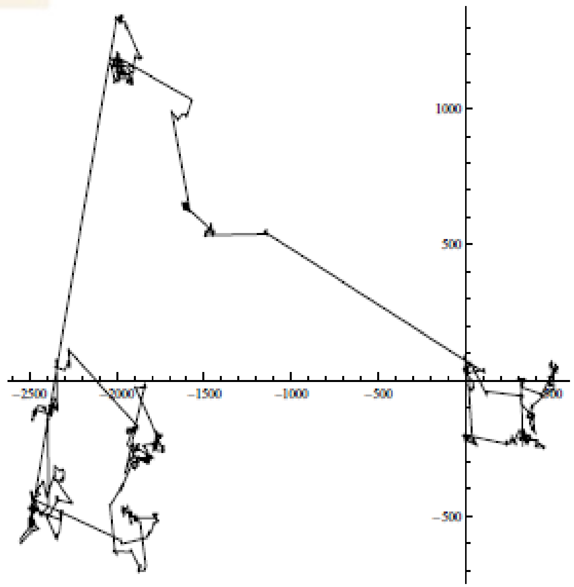
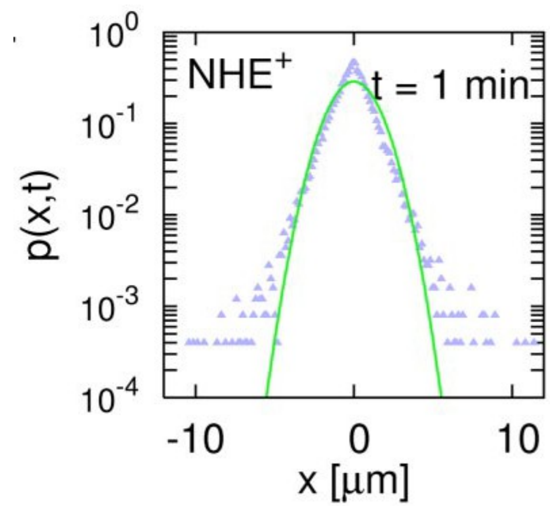


Beyond random walk









Brownian motion

⇩

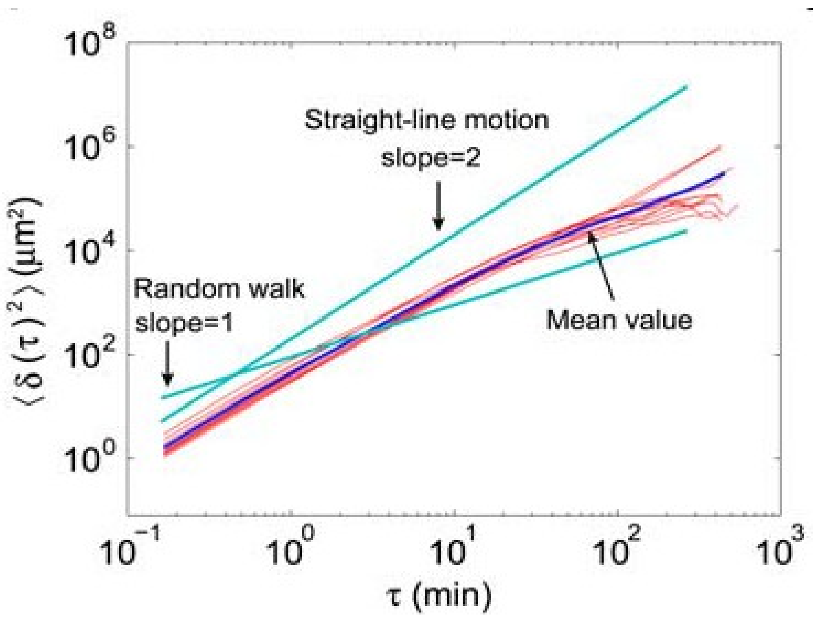
Diffusion

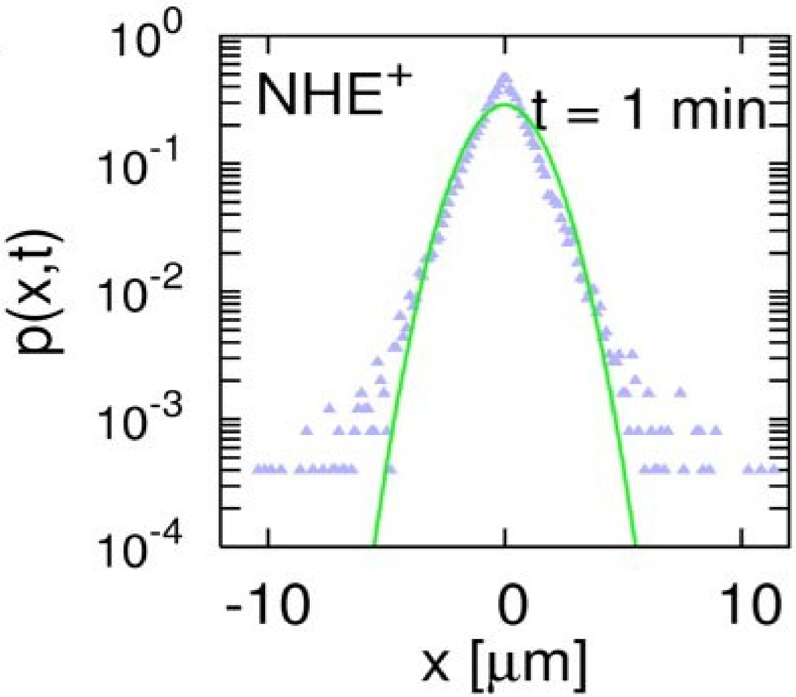
Levi flights (or Levi walks)

⇩

Anomalous diffusion (super-diffusion)

Levy flights

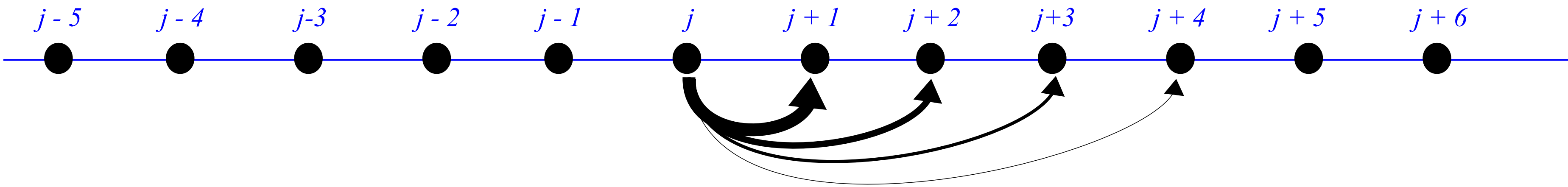




Brownian motion ⇩ Diffusion

Levi flights (or Levi walks) ⇩ Anomalous diffusion (super-diffusion)

Random walk



$$\widetilde{p}_{j\to k} = \Delta t \frac{C(\beta)}{|(k-j)\Delta x|^{\beta}} D$$

$$\frac{du_j}{dt} = D \sum_{k>j} C(\beta) \frac{u_{j-k} - 2u_j + u_{j+k}}{|(k-j)\Delta x|^{\beta}} \longrightarrow \frac{\partial u}{\partial t} = D(-\nabla)^{\alpha/2} u \qquad \beta = n + \alpha$$

$$C_{\alpha,n} P.V. \int_{R^n} \frac{u(\mathbf{x}+\mathbf{y}) - u(\mathbf{x})}{|\mathbf{y}|^{n+\alpha}} d\mathbf{y}$$

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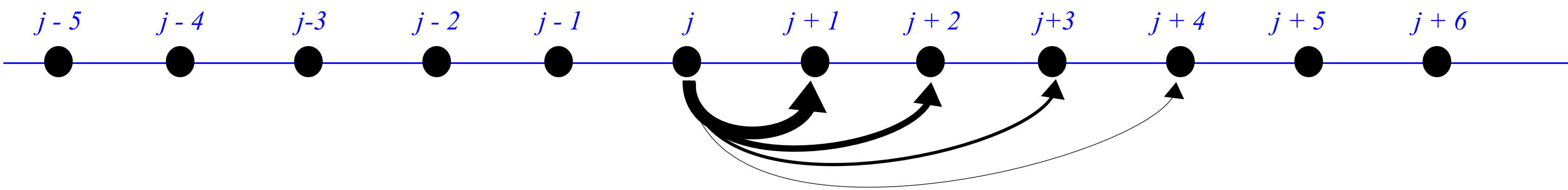
Random walk



$$\widetilde{p}_{j\to k} = \Delta t \frac{C(\beta)}{|(k-j)\Delta x|^{\beta}} D \qquad \beta = n + \alpha$$

$$u(x,t+\tau) - u(x,t) = \sum_{k\in\mathbb{Z}^n} \mathcal{K}(k)\big(u(x+hk,t) - u(x,t)\big)$$

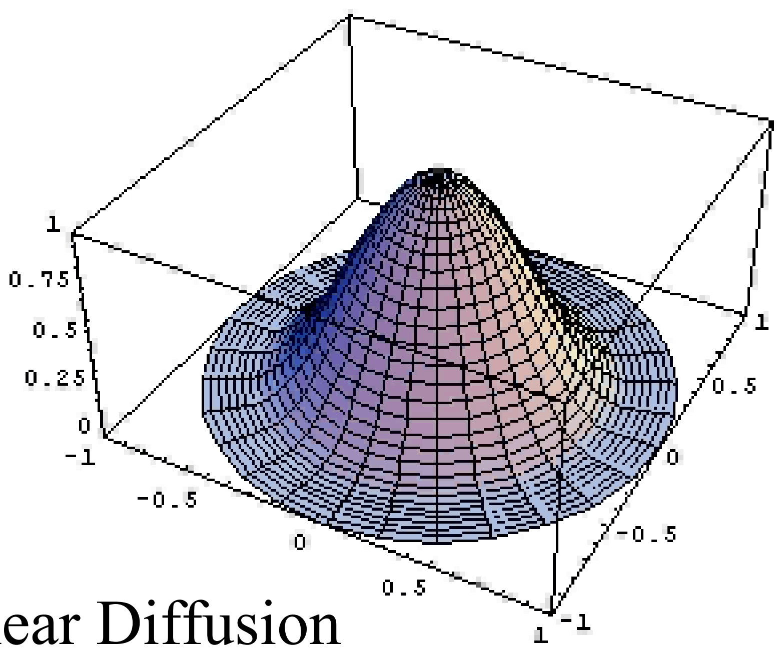
$$\mathcal{K}(k) = |y|^{-(n+\alpha)} \qquad \alpha \in (0,2)$$

$$\partial_t u(x,t) = \int_{\mathbb{R}^n} \frac{u(x+y,t) - u(x,t)}{|y|^{n+\alpha}}\, dy = (-\Delta)^{\alpha/2} u$$

Degenerate diffusion equation

$$\frac{\partial u}{\partial t} + \nabla \cdot (u\mathbf{v}) = \cancelto{0}{\nabla \cdot (D\nabla u)}$$

If $\mathbf{v} = -K\nabla u$ $\Rightarrow$ $$\frac{\partial u}{\partial t} = \nabla \cdot (K u \nabla u)$$



Linear Diffusion

Degenerate diffusion

with aggregation

with ill-posed region

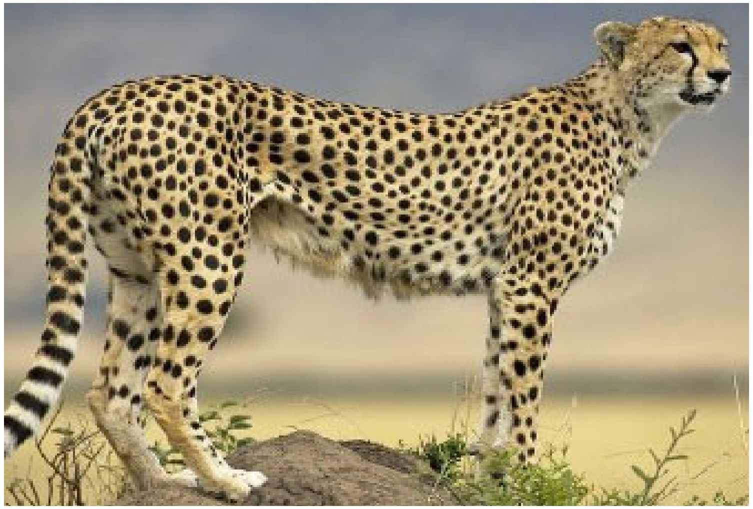
Pattern formation

How do patterns emerge in biology?

POLITECNICO DI TORINO

Pattern formation

How do patterns emerge in biology?



Pattern formation

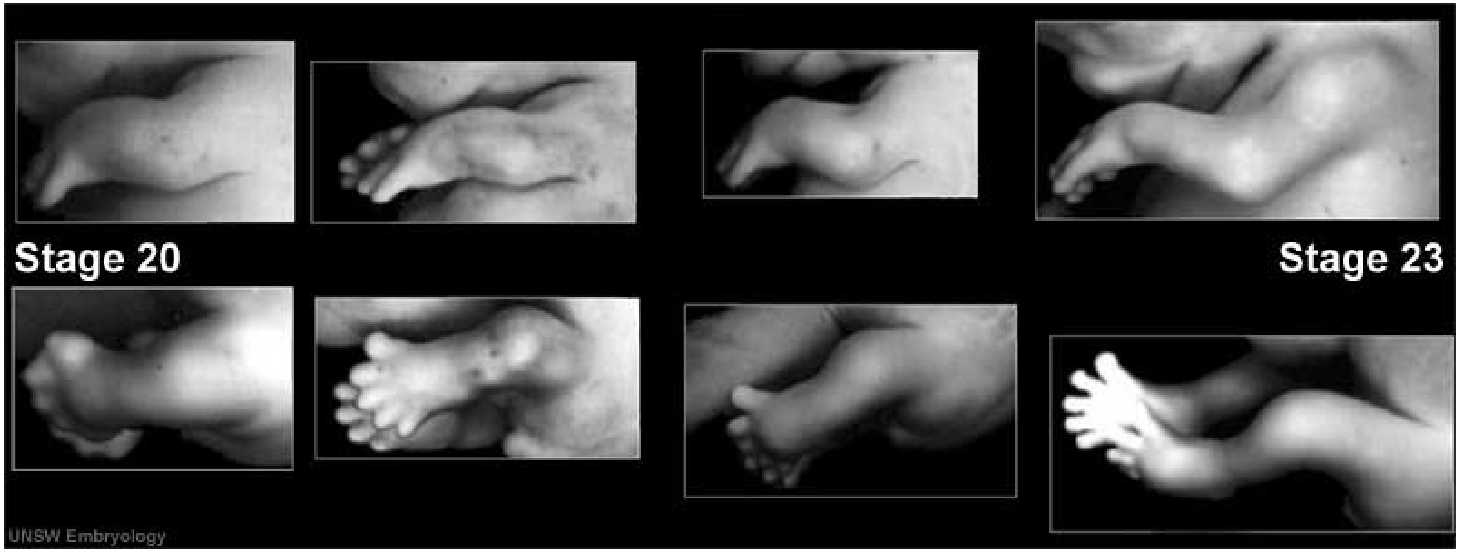
How do patterns emerge in biology?

Pattern formation

How do patterns emerge in biology?

Embriogenesis

How do patterns emerge in biology?



Embriogenesis

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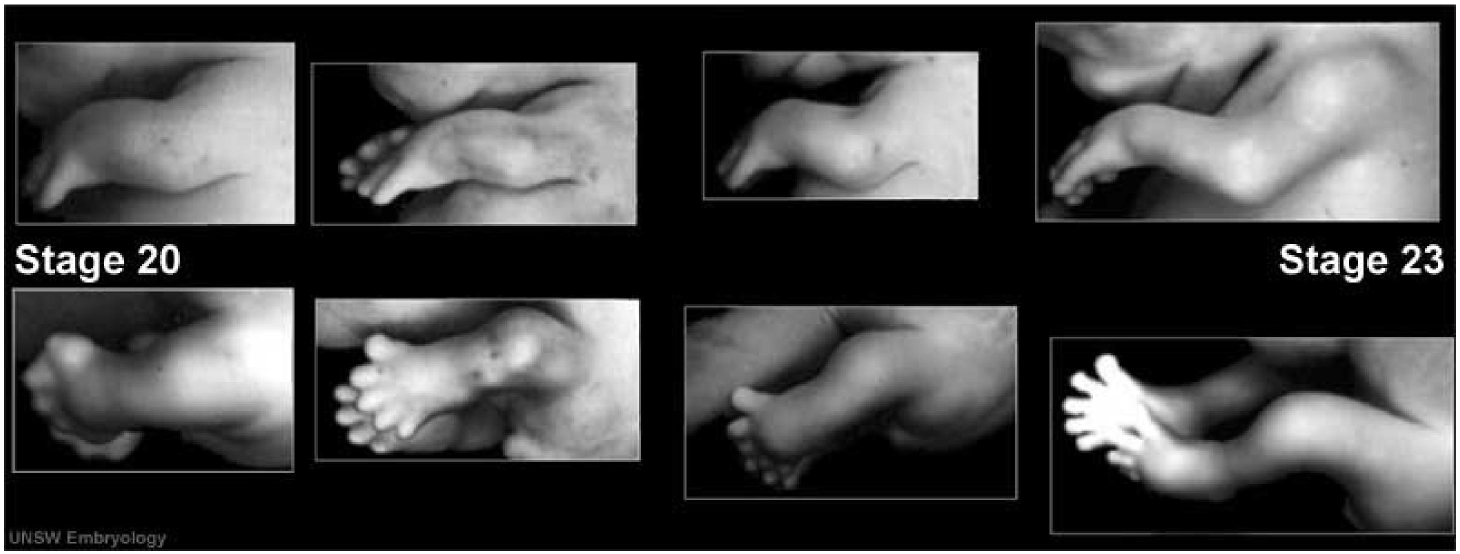
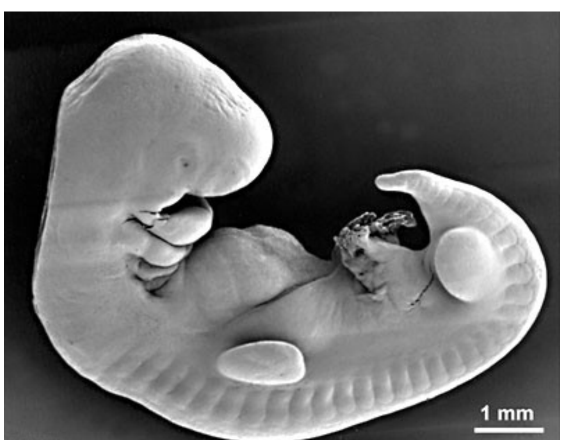
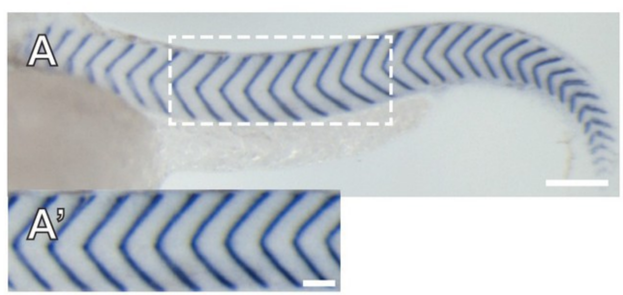
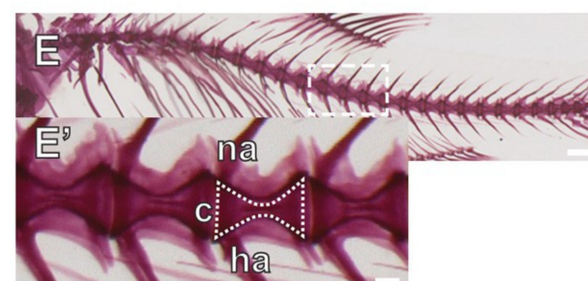
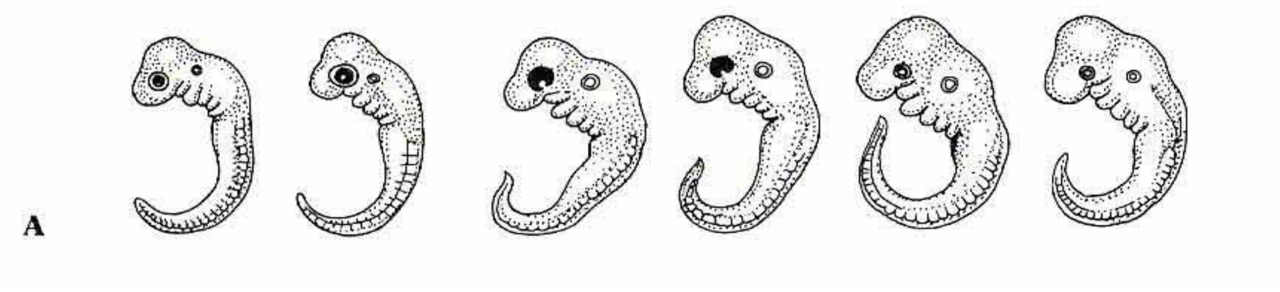




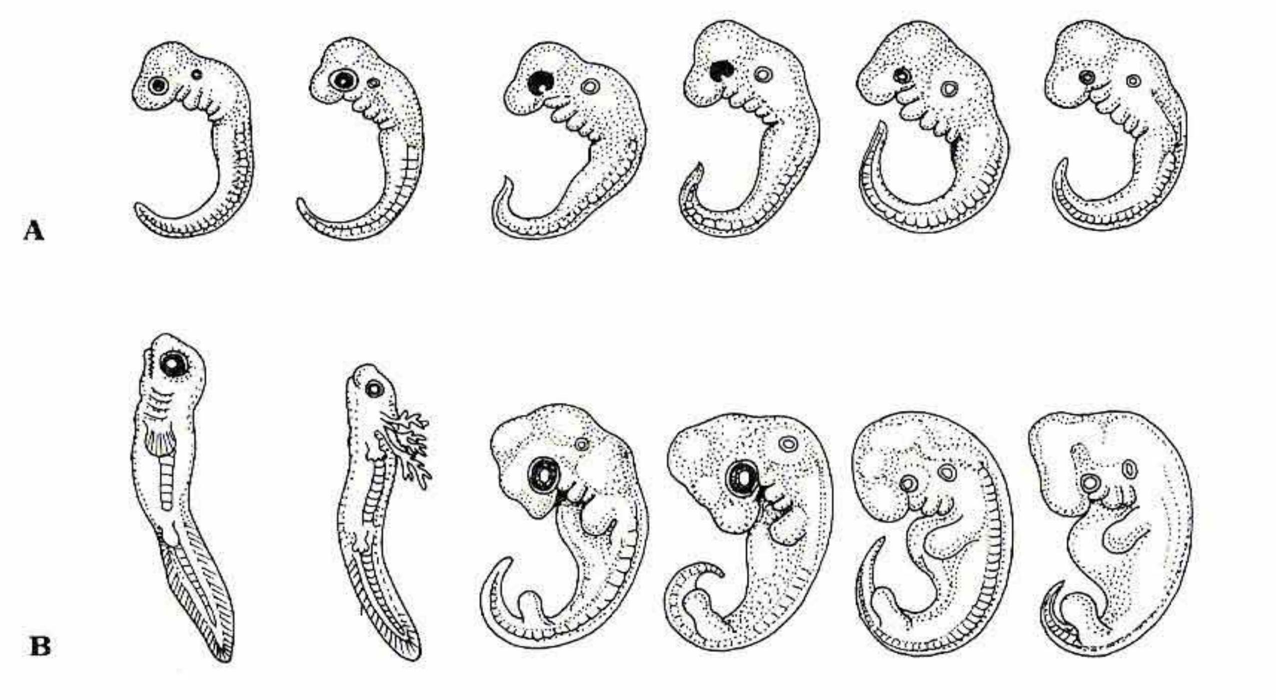




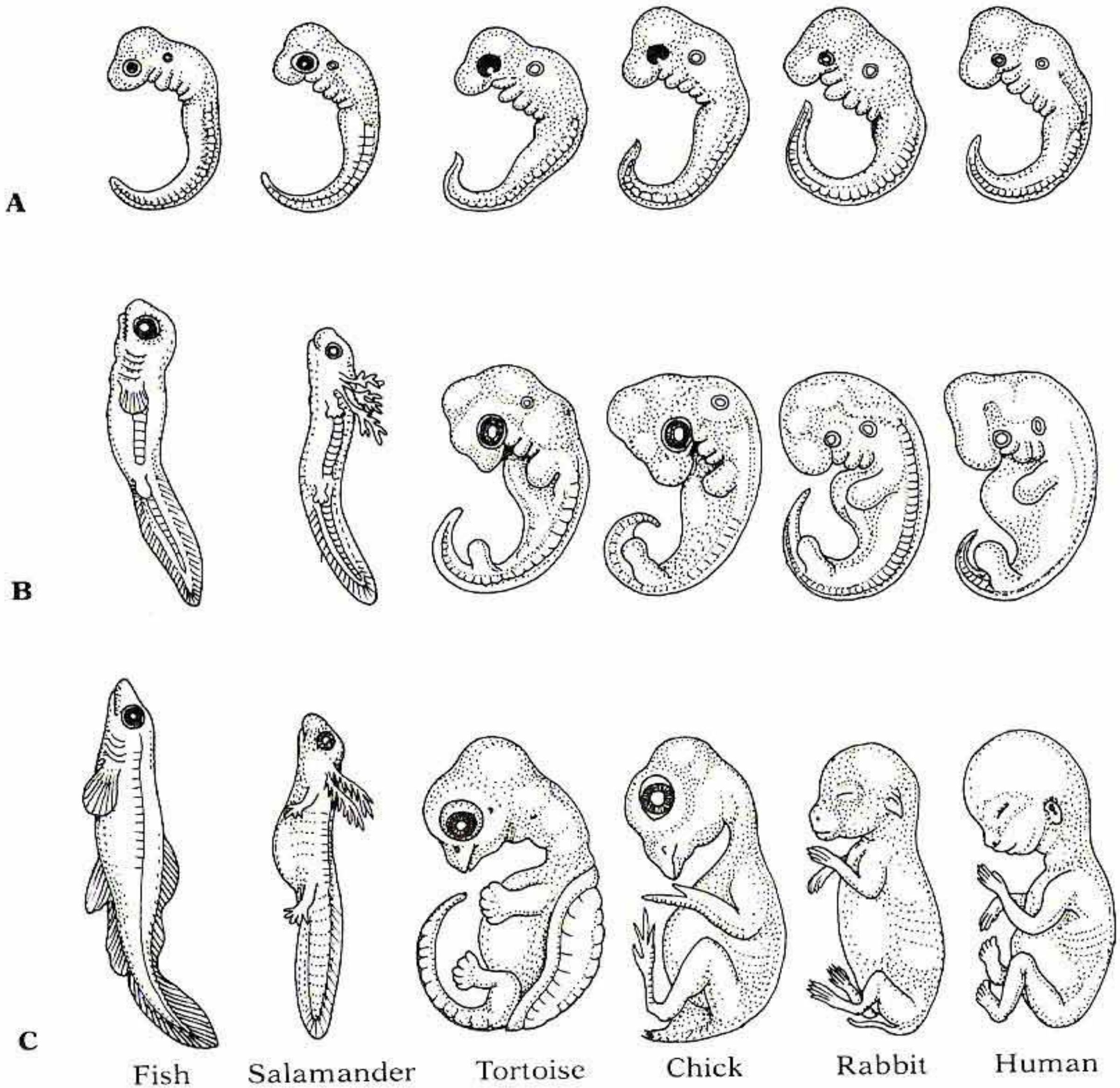
Embriogenesis



Embriogenesis



Embriogenesis

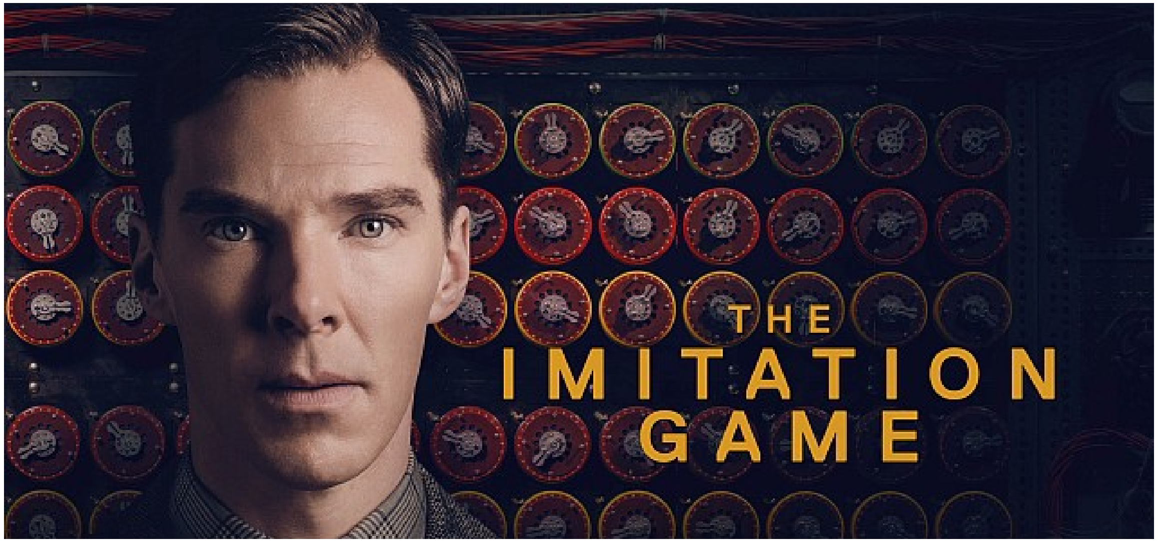


Alan Turing (1912-1954)

Pioneer mathematician in

- Computer science
- Cryptography
- Biology

Alan Turing (1912-1954)



Pioneer mathematician in

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Turing instability

THE CHEMICAL BASIS OF MORPHOGENESIS

By A. M. TURING, F.R.S. *University of Manchester*

(*Received* 9 *November* 1951—*Revised* 15 *March* 1952)

Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences, 237, No. 641. (Aug. 14, 1952), pp. 37-72.

Diffusion driven (Turing) instability:

incorporation of diffusion within an otherwise stable dynamical system induces an instability which drives spatial organization

Turing instability

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Diffusion driven (Turing) instability:

incorporation of diffusion within an otherwise stable dynamical system induces an instability which drives spatial o

$$\mathbf{u}(\mathbf{x}, t)_t = D\nabla^2\mathbf{u}(\mathbf{x}, t) + \mathbf{f}(\mathbf{u}(\mathbf{x}, t))$$

- $\mathbf{u} = (u_1, u_2, .., u_n)$ respresents the chemical concentrations.
- D is the $n \times n$ nonnegative diagonal matrix for chemical diffusion coefficients.
- $\mathbf{f}(\mathbf{u}(\mathbf{x}, t), t)$ defines the chemical reactions.

Turing instability

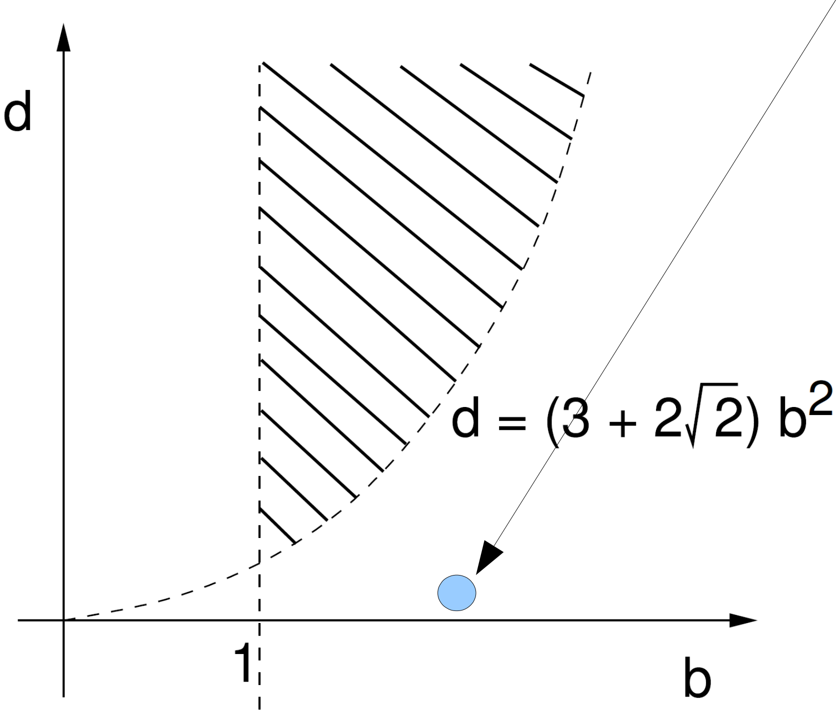
$$\begin{cases} \dfrac{\partial u}{\partial t} = D_u \dfrac{\partial^2 u}{\partial x^2} + f(u,v) \\ \\ \dfrac{\partial v}{\partial t} = D_v \dfrac{\partial^2 v}{\partial x^2} + g(u,v) \end{cases}$$

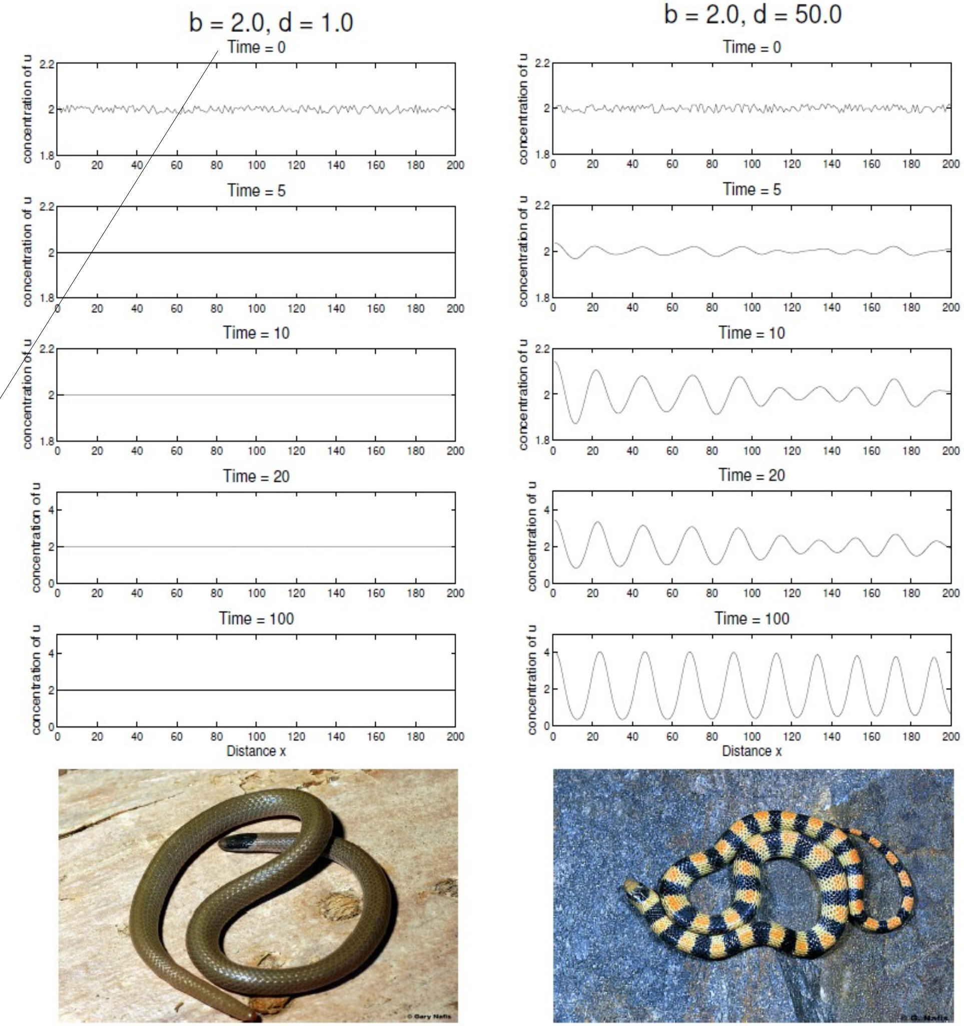
$D_v > D_u$ → **the inhibitor must diffuse faster than the activator.**

Over short ranges the activator dominates leading to increase in *u*
Over longer ranges inhibition dominates leading to a suppression of *u*

Example

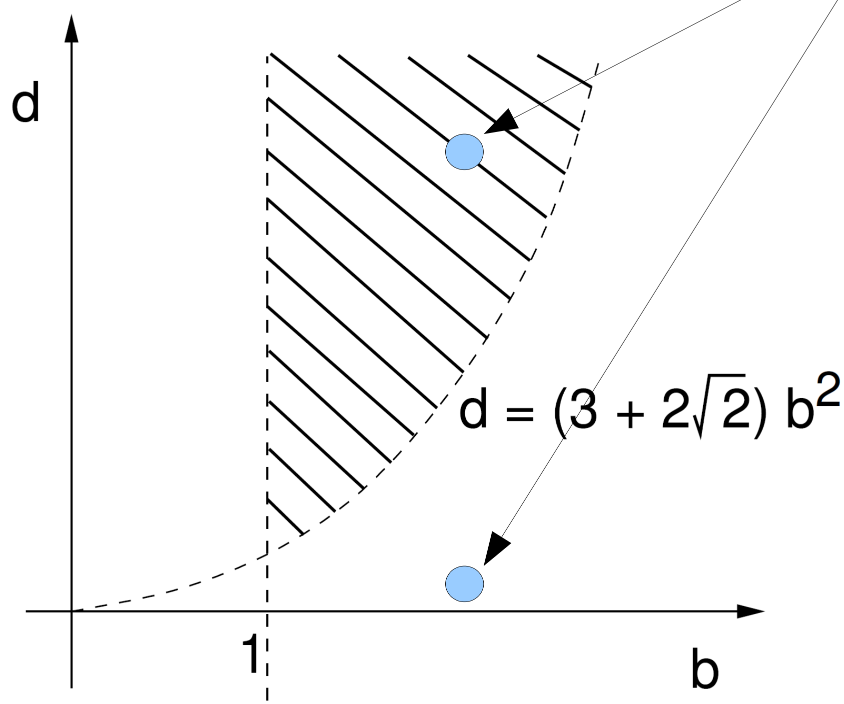
$$
\begin{aligned}
u_t &= u_{xx} + u^2 v - u \\
v_t &= d v_{xx} + b - u^2 v
\end{aligned}
$$

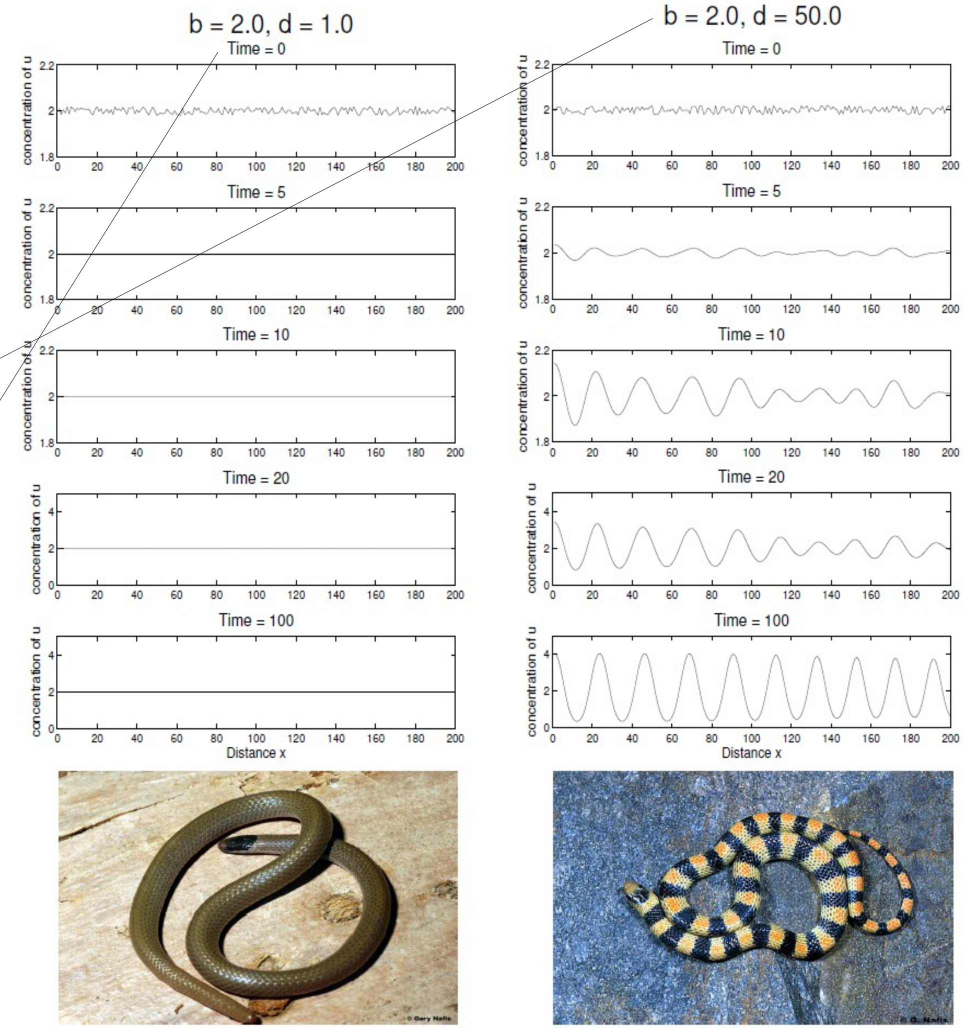




Example

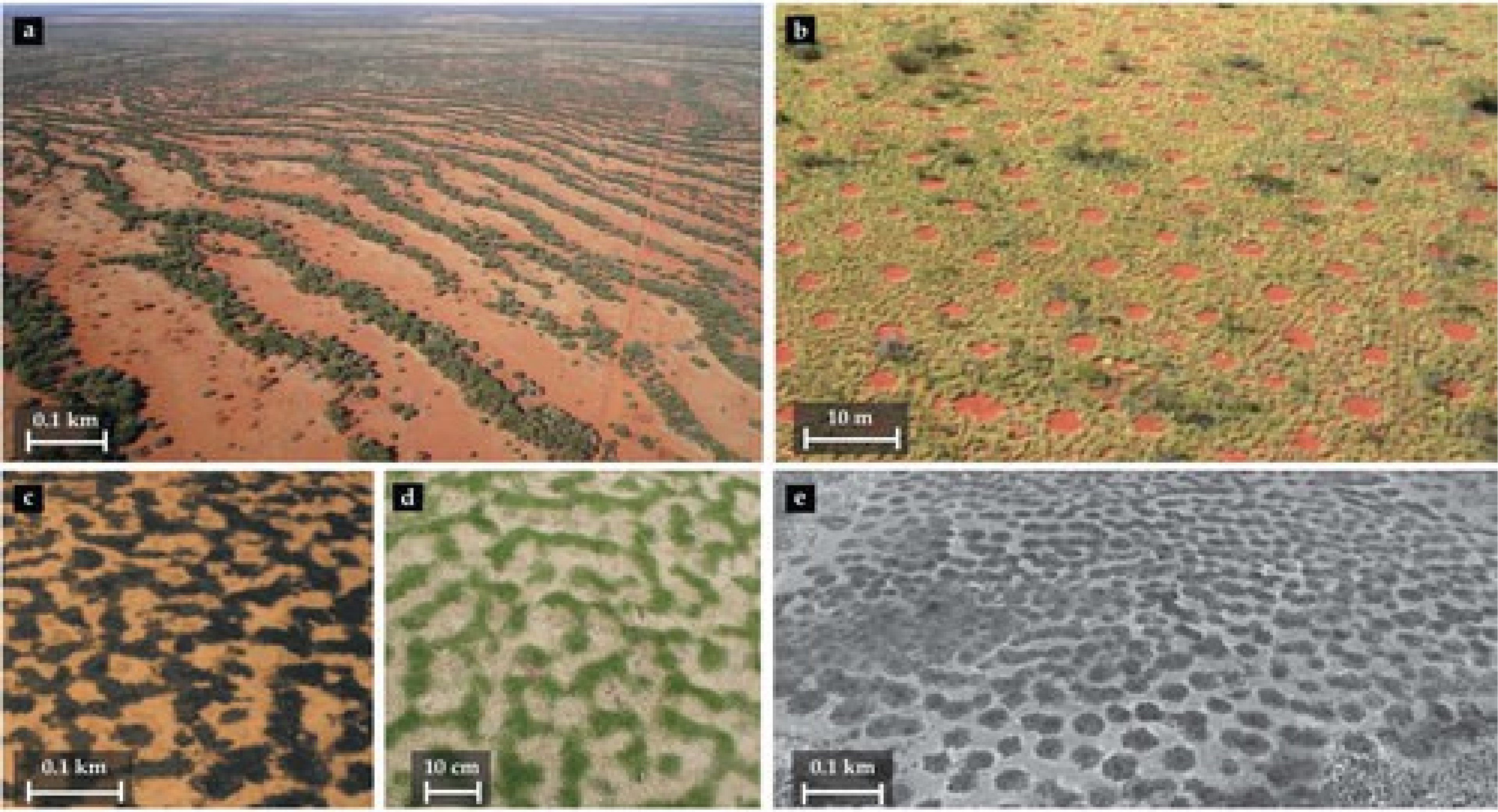
$$u_t = u_{xx} + u^2 v - u$$
$$v_t = d v_{xx} + b - u^2 v$$



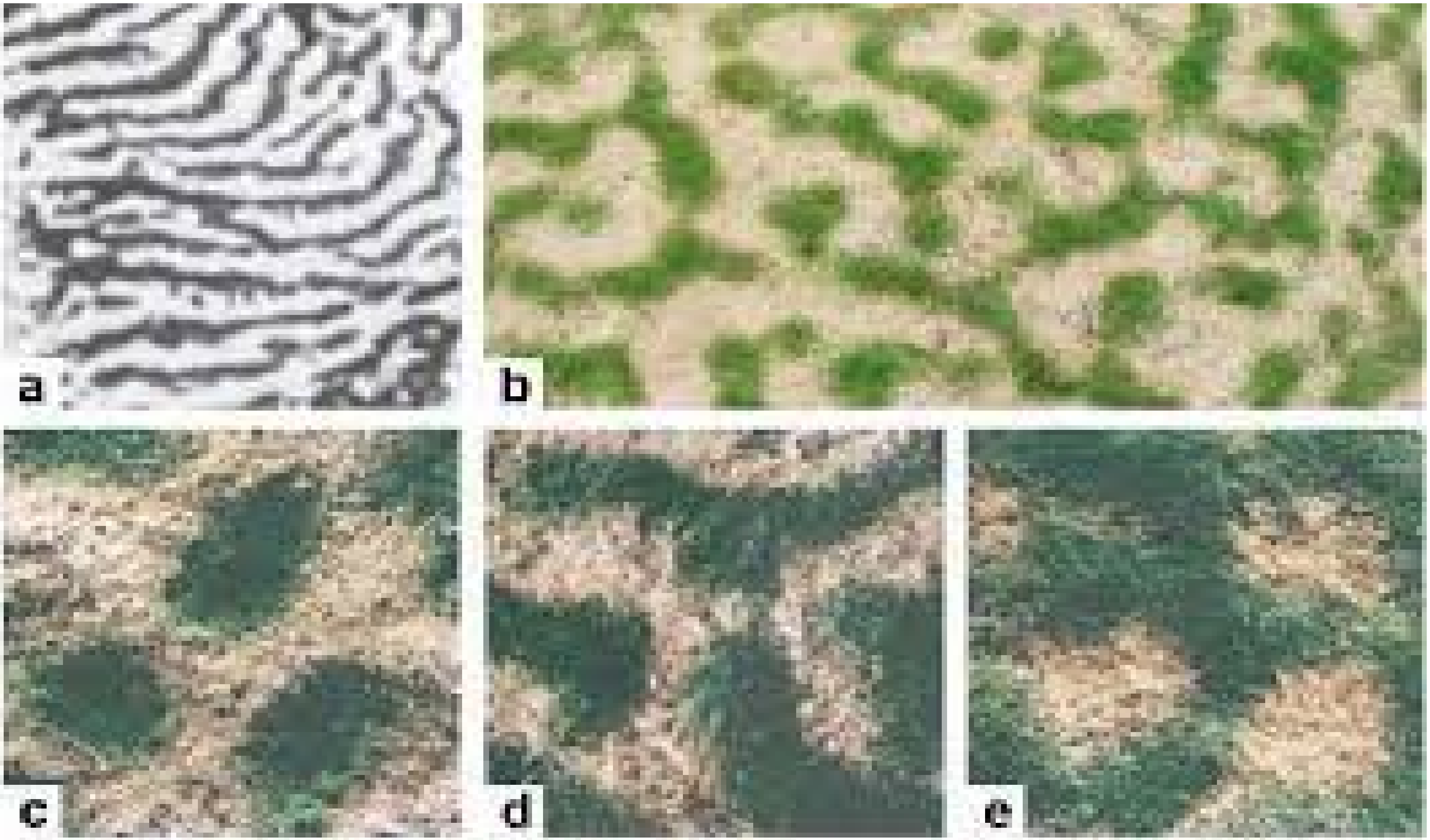


POLITECNICO DI TORINO

Vegetation patterns



Vegetation patterns

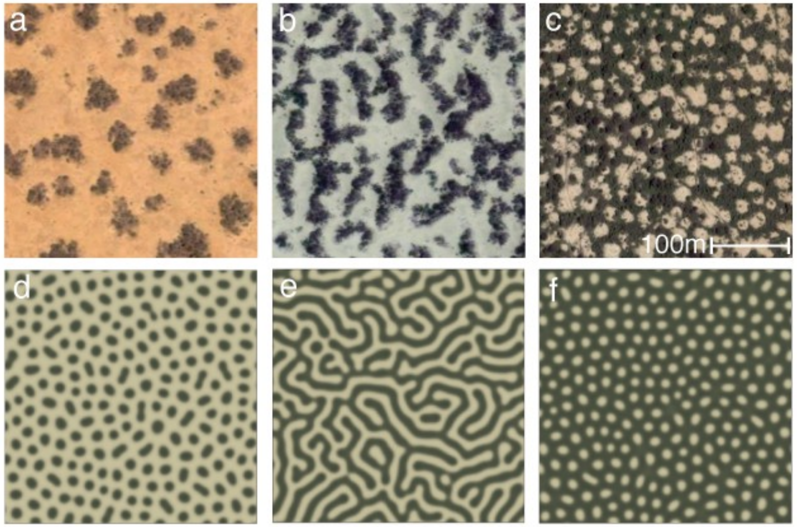


Vegetation patterns

$$\frac{\partial P(\boldsymbol{x},t)}{\partial t} = G_P(\boldsymbol{x},t)P(\boldsymbol{x},t)\left(1-\frac{P(\boldsymbol{x},t)}{K}\right) - m_P P(\boldsymbol{x},t) + D_P\nabla^2 P(\boldsymbol{x},t)$$

$$\frac{\partial W(\boldsymbol{x},t)}{\partial t} = \gamma\frac{P(\boldsymbol{x},t)+QW_0}{P(\boldsymbol{x},t)+Q}O(\boldsymbol{x},t) - N\left(1-\frac{R_{\mathrm{educ}}P(\boldsymbol{x},t)}{K}\right)W(\boldsymbol{x},t) - G_W(\boldsymbol{x},t)W(\boldsymbol{x},t) + D_W\nabla^2 W(\boldsymbol{x},t)$$

$$\frac{\partial O(\boldsymbol{x},t)}{\partial t} = R_{\mathrm{ainfall}} - \gamma\frac{P(\boldsymbol{x},t)+QW_0}{P(\boldsymbol{x},t)+Q}O(\boldsymbol{x},t) + D_O\nabla^2(O^2(\boldsymbol{x},t))$$



Namibian fairy circles