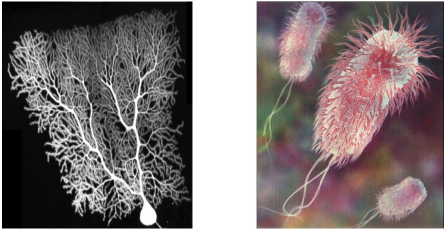
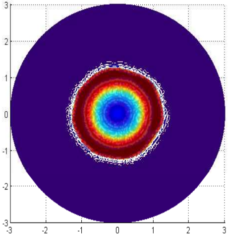
Some equations from mathematical biology

Benoît Perthame





Equations of physics

- The status of physics his written in the names of equations
- What are the fundamental principle of biology ?

Equations of physics

- The status of physics his written in the names of equations
- What are the fundamental principle of biology ?
- Is mathematics the good language for life sciences ?

Equations of physics

- The status of physics his written in the names of equations
- What are the fundamental principle of biology ?
- “Science is a differential equation” (Alan Turing)

Equations of physics

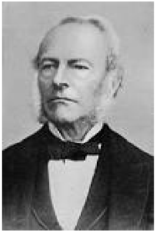
- The status of physics his written in the names of equations
- Newton's fundamental principle of dynamics

$$\begin{cases} \frac{d}{dt}X(t) = V(t) \\ \frac{d}{dt}V(t) = F\big(X(t), V(t)\big) \end{cases}$$

Equations of physics

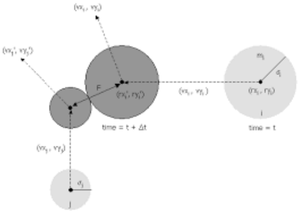
- The status of physics his written in the names of equations
- Fluid flows (Navier-Stokes eq., 1823-1845)

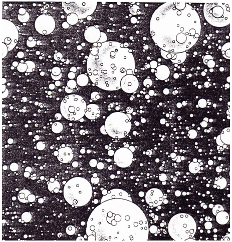
$$\begin{cases} \frac{\partial}{\partial t} u + u.\nabla u + \nabla p = \nu \Delta u, \\ \operatorname{div} u = 0 \end{cases}$$



Equations of physics

L. Boltzmann - A gas is the result of collisions between molecules (1872)





$f(x,\xi,t)$ = density of molecules with velocity $\xi \in V = \mathbb{R}^3$

$$\underbrace{\frac{\partial}{\partial t} f(x,\xi,t) + \xi.\nabla_x f}_{\text{Transport with velocity } \xi} = \underbrace{Q(f,f)}_{\text{Binary collisions}}$$

Equations of physics

PARTICLE SCALE

$$\begin{cases} \frac{d}{dt} X_i(t) = V_i(t), \qquad 1 \le i \le N, \\ \frac{d}{dt} V_i(t) = F\big(X(t), V(t)\big) \end{cases}$$

KINETIC/DILUTE GAS $N \to \infty$

$$\underbrace{\frac{\partial}{\partial t} f(x,\xi,t) + \xi.\nabla_x f}_{\text{Transport with velocity } \xi} = \frac{1}{\kappa} \underbrace{Q(f,f)}_{\text{Binary collisions}}$$

MACROSCOPIC/FLUID $\kappa \to 0$

$$\begin{cases} \frac{\partial}{\partial t} u + u.\nabla u + \nabla p = \nu \Delta u, \\ \mathrm{div}\, u = 0 \end{cases}$$

Equations of physics

- The status of physics his written in the names of equations

$$-\Delta u = f \qquad \text{(Laplace/Poisson)}$$

$$\frac{\partial^2 u}{\partial t^2} - \Delta u = 0 = \Box u \qquad \text{(D'Alembert)}$$

$$\frac{\partial u}{\partial t} - \Delta u = 0 \qquad \text{(Fourier)}$$

$$\begin{cases} \mathrm{div} E = 0, & \mathrm{curl}\ E = -\frac{\partial B}{\partial t} \\ \mathrm{div} B = 0, & \mathrm{curl}\ B = -\frac{1}{c^2}\frac{\partial E}{\partial t} \end{cases} \qquad \text{(Maxwell)}$$

$$i\frac{\partial u}{\partial t} - \Delta u = 0 \qquad \text{(Schrödinger)}$$

Names of PDE of physics

Euler   Lagrange   Liouville   Boussinesq

Hamilton-Jacobi   Bellman   Kirchhoff

Allen-Cahn   Cahn-Hilliard   Vlasov   Landau

Ginzburg-Landau   Gross-Pitaevski   Helmholtz

Thomas-Fermi   Einstein   Hartree-Fock

Dirac   Airy   Kolmogorov   Fokker-Planck

Monge-Ampère   Korteweg de Vries   Camassa-Holme

Maxwell-Stefan   Kuramoto-Shivashinsky   Choquard

Burgers   Lorentz   Saint-Venant   Benjamin-Ono

KPP   KPZ   Zhakarov   Born-Infeld

Equations of physics

And in biology ?

Lotka-Volterra

And in biology ?

$$\begin{cases} \frac{dS(t)}{dt} = aS(t) - bS(t)P(t), \\ \frac{dP(t)}{dt} = -cP(t) + bS(t)P(t), \end{cases} \qquad \textbf{(Lotka-Volterra)}$$

Became a generic name for a class of equations in **ecology**

Lotka-Volterra

- $x =$ phenotypical trait (size, type of nutrient,...)
- $n(x,t) =$ number of individuals of type x
- $S(t) =$ environment (nutrient)

Lotka-Volterra

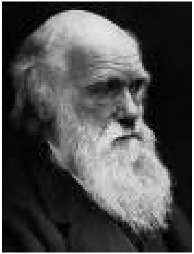
- x = phenotypical trait (size, type of nutrient,...)
- $n(x,t)$ = number of individuals of type x
- $S(t)$ = environment (nutrient)

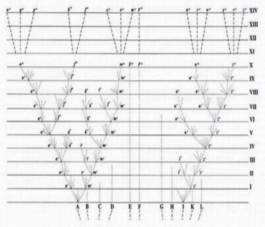
$$\frac{\overbrace{\partial n(x,t)}^{\text{change in number}}}{\partial t} = \underbrace{R(x,S(t))}_{\text{growth/death rate}}\; n(x,t) + \mu \overbrace{\int b(y,S(t))M(y\to x)n(y,t)dy}^{\text{mutations}}$$

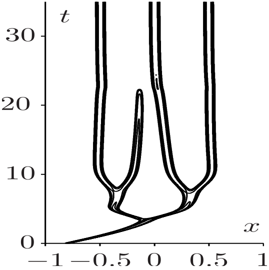
$$S(t) = S([n(t)] \qquad S(t) = \frac{S_0}{1+\int n(x,t)dx}$$

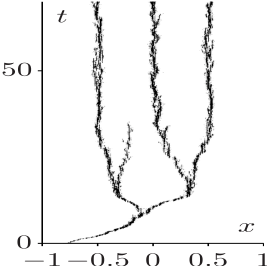
This expresses selection by competition with finite resources

Lotka-Volterra







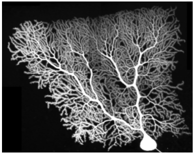


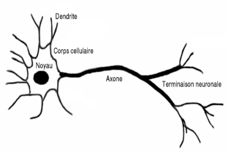
There is a small parameter for mutations

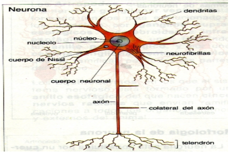
Neuroscience

The electrically active cells are described by

- **action potential** $v(t)$
- **ionic chanels** $g_i(t)$







Neuroscience

The electrically active cells are described by

- **action potential** $v(t)$
- **ionic chanels** $g_i(t)$

- Hodgkin-Huxley
- Morris-Lecar
- Mitchell-Schaeffer
- FitzHugh-Nagumo

$$\begin{cases} \frac{dv(t)}{dt} = \sum_i g_i(t)\big(V_i - v(t)\big) + I(t) \\ \frac{dg_i(t)}{dt} = \frac{G_i(v(t)) - g_i(t)}{\tau_i}, \end{cases}$$

Neuroscience

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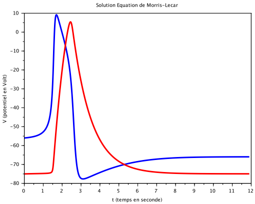

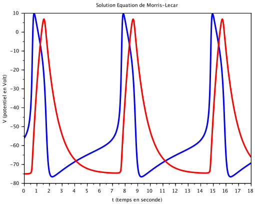

spike↑ ↑Hyperpolarisation

Leaky Integrate and Fire (linear)

The Leaky Integrate & Fire model is simpler

$$dv(t) = \big(- v(t) + I(t)\big) dt + \sigma dW(t), \qquad v(t) < V_{\mathrm{Firing}}$$

$$v(t_-) = V_{\mathrm{Firing}} \quad \Longrightarrow \quad v(t_+) = V_{\mathrm{Reset}}$$

$$0 < V_R < V_F$$

- $I(t)$ input current
- Noise or not

- Much simpler that Hodgkin-Huxley/Morris-Lecar models
- The idea was introduced by L. Lapicque (1907)

A short break

Brother of Charles Lapicque



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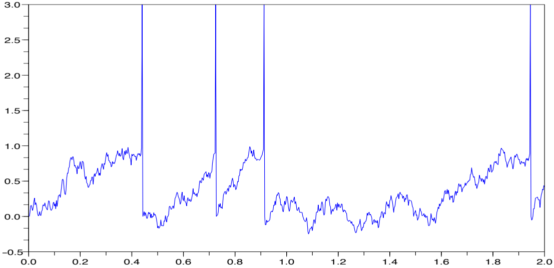
Leaky Integrate and Fire (linear)



Solution to the LIF model

- N. Brunel and V. Hakim, R. Brette, W. Gerstner and W. Kistler, Omurtag, Knight and Sirovich, Cai and Tao...
- Fit to measurements
- Use more realistic dynamics in place of $-\mathbf{v}$

Leaky Integrate and Fire (linear)

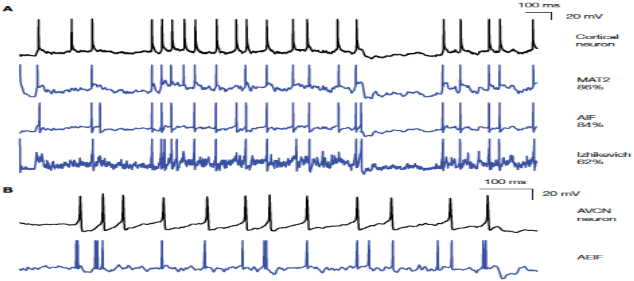


FIGURE 4 | Fitting spiking models to electrophysiological recordings. (A) The response of a cortical pyramidal cell to a fluctuating current (from the INCF competition) is fitted to various models: MAT (Kobayashi et al., 2009), adaptive integrate-and-fire, and Izhikevich (2003). Performance on the training data is indicated on the right as the gamma factor (close to the proportion of predicted spikes), relative to the intrinsic gamma factor of the neuron (i.e., proportion of common spikes between two trials). Note that the voltage units for the models are irrelevant (only spike trains are fitted). **(B)** The response of an anteroventral cochlear nucleus neuron (brain slice made from a P12 mouse, see Methods in Magnusson et al., 2008) to the same fluctuating current is fitted to an adaptive exponential integrate-and-fire [Brette and Gerstner, 2005; note that the responses do not correspond to the same portion of the current as in **(A)**]. The cell was electrophysiologically characterized as a stellate cell (Fujino and Oertel, 2001). The performance was $\Gamma = 0.39$ in this case (trial-to-trial variability was not available for this recording).

From C. Rossant et al, Frontiers in Neuroscience (2011)

Noisy LIF networks

It is now possible to write a system of N interacting neurons,

- For $1 \leq j \leq N$
- with t_j^k the spiking times : $v_j(t_j^{k-}) = V_F$
- $v_j(t_j^{k+}) = V_R$

$$\frac{d}{dt} v_i(t) = -v_i(t) + \underbrace{\frac{\beta}{N} \sum_{j=1}^{N} \sum_{k} \delta(t - t_j^k)}_{\text{current generated by spikes}} + \sigma dW_i(t), \qquad v_i(t) < V_F$$

Noisy LIF networks

See Delarue, Inglis, Rubenthaler, Tanre, Tallay, Locherbach, Lucon :

For assemblies, the **mean field limit** yields a current $I = bN(t)$

$$\begin{cases} \frac{\partial n(v,t)}{\partial t} + \frac{\partial}{\partial v}\left[\left(-v + bN(t)\right) n(v,t)\right] - a\big(N(t)\big)\frac{\partial^2 n(v,t)}{\partial v^2} = N(t)\,\delta_{V_R}(v), \\ \hfill v \leq V_F, \\ n(V_F,t) = 0, \qquad n(-\infty,t) = 0, \\ N(t) := -a\big(N(t)\big)\frac{\partial}{\partial v} n(V_F,t) \geq 0, \qquad \text{flux of firing neurons at } V_F \end{cases}$$

Constitutive laws

- $b =$ connectivity
- $b > 0$ excitatory neurones
- $b < 0$ inhibitory neurones
- $a(N) = a_0 + a_1 N$

Noisy LIF networks (blow-up)

Theorem (M. Cáceres, J. Carrillo, BP) [excitatory, blow-up]
Assume $a \geq a_0 > 0$ and $b > 0$. Then the solution blows-up in finite time in the two cases

- the initial data is concentrated enough around $v = V_F$ (depending on b)
- initial data is given, b is large enough

Surprisingly

- Noise does not help
- value of b does not count

Noisy LIF with refractory state

Proof. For $\mu = 2\max(\frac{1}{b}, \frac{V_F}{a_0})$, define

$$\phi(v) = e^{\mu v}, \qquad M_\mu(t) := \int_{-\infty}^{V_F} \phi(v) n(v,t).$$

For smooth solutions, we prove that $M_\mu(t)$ becomes larger than $e^{\mu V_F}$

$$\frac{dM_\mu}{dt} = \mu \int_{-\infty}^{V_F} (bN(t) - v + \mu a)\phi(v)p(v,t) - N(t)\phi(V_F) + \frac{N(t)}{\tau}\phi(V_R)$$

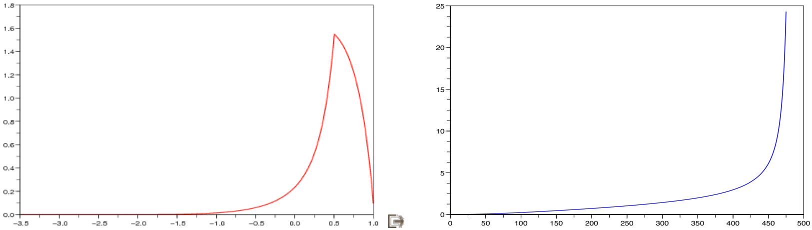
$$\geq N(t)\underbrace{\left[b\mu M_\mu(t) - \phi(V_F)\right]}_{\searrow} + \mu\underbrace{\left[\mu a_0 - V_F\right]}_{\geq \mu V_F > 0} M_\mu(t)$$

> 0 is needed only initially

OK for b large enough or $M_\mu(0)$ large enough

To go further : the difficulty : no relation between M_μ and N

Noisy LIF networks (blow-up)



Excitatory integrate and fire model. Blow-up case. Left $p(v, t)$, Right : N(t)

Noisy LIF networks (blow-up)

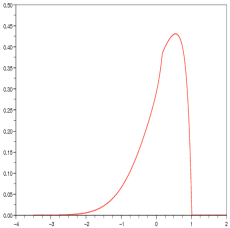
Possible interpretation

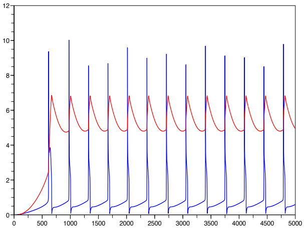
- $N(t) \to \rho\delta(t - t_{\mathrm{BU}})$ and $t_{\mathrm{BU}} > 0$,
- partial synchronization

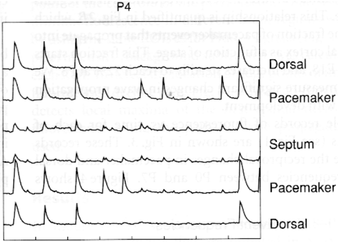
Simplified models : Kuramoto, Carillo-Ha-Kang, Dumont-Henry, Giacomin, Pakdaman

Huygens

Spontaneous activity (regularized)







Left : Excitatory integrate & fire with refractory state and random firing threshold

Right : Conhaim et al (2011) J. of physiology 589(10) 2529-2541.

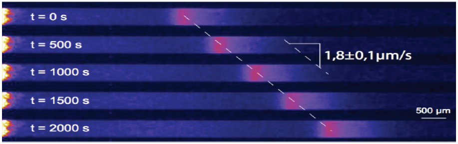
Bacterial motion

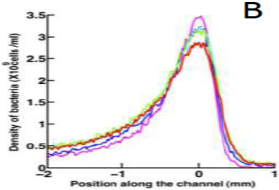
Paradigm for collective organisation

Left :Courtesy S. Seror, B. Holland (Paris-Sud),

Right : Numerical simulation of a mathematical model

Bacterial motion



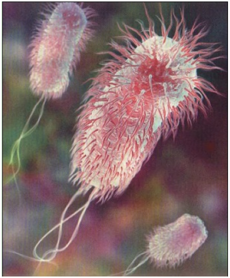


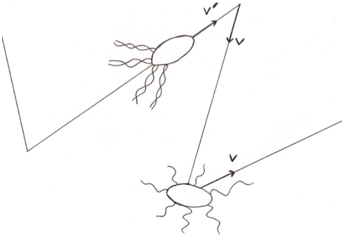
- Adler's famous experiment for *E. Coli* (1966) - chemotactic
- Explain this pattern ; its asymmetry (experiments Curie institute)

- How can a model of chemotaxis (Keller-Segel) generate robust trvaeling pulses ?

Bacterial motion

E. Coli is known to move by run and tumble Alt, Dunbar, Othmer, Stevens, Hillen, Schmeiser...





A beautiful example of multiscale motion

Bacterial motion

- $f(t, x, \xi)$ population density of cells moving with velocity ξ
- $c(t, x)$ the chemoattractant concentration

$$\frac{\partial}{\partial t} f(t, x, \xi) + \underbrace{\xi \cdot \nabla_x f}_{\textbf{run}} = \underbrace{\mathcal{K}[c, S] f}_{\textbf{tumble}},$$

$$\mathcal{K}[c, S]f = \int_B K(c, S; \xi, \xi') f(\xi') d\xi' - \int_B K(c, S; \xi', \xi) d\xi' \; f,$$

$$-\Delta c = n(x, t) := \int f(t, x, \xi) d\xi$$

- Typical is pathwise sensing

$$K(c; \xi, \xi') = K\big(\partial_t c + \xi' . \nabla_x c)\big)$$

Bacterial motion

Multiscale analysis based on the stiffness

Define the small parameter ε

$$K(c;\xi,\xi') = \mathbf{K}_\varepsilon\Big(\underbrace{\frac{\partial c}{\partial t} + \xi'.\nabla c}_{D_t c}\Big)$$

$$\begin{cases} \frac{\partial}{\partial t} f_\varepsilon(t,x,\xi) + \frac{\xi \cdot \nabla_x f_\varepsilon}{\varepsilon} = \frac{\mathcal{K}[c_\varepsilon, f_\varepsilon]}{\varepsilon^2}, \\ -\Delta c_\varepsilon(t,x) = n_\varepsilon(t,x) := \int f_\varepsilon(t,x,\xi) d\xi. \end{cases}$$

Bacterial motion

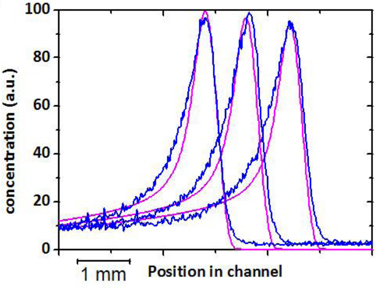
Multiscale analysis based on sensing stiffness

Theorem (Diffusion limit)

As ε vanishes, $f_\varepsilon \to n(x,t)\mathbb{1}_{\{v\in V\}}$ and

$$\begin{cases} \frac{\partial}{\partial t} n(t,x) - \Delta n(t,x) + \mathrm{div}(nU) = 0 \\ -\Delta c(t,x) = n(t,x) \\ U = \phi(|\nabla c|)\, \nabla c \end{cases}$$

Flux Limited Keller-Segel system



Bacterial motion

POPULATION SCALE

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KINETIC/INDIVIDUAL SCALE

$$\frac{\partial}{\partial t} f_\varepsilon(t,x,\xi) + \frac{\xi \cdot \nabla_x f_\varepsilon}{\varepsilon} = \frac{\mathcal{K}[c_\varepsilon, f_\varepsilon]}{\varepsilon^2},$$

Bacterial motion

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KINETIC/INDIVIDUAL SCALE

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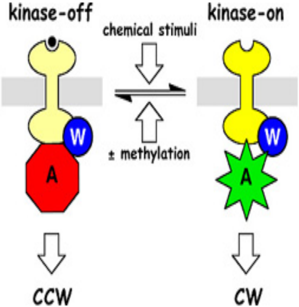
MOLECULAR SCALE

$$\frac{\partial}{\partial t} f_\varepsilon(t,x,\xi,y) + \xi \cdot \nabla_x f_\varepsilon + \frac{1}{\varepsilon} \mathrm{div}_y [R_\varepsilon f_\varepsilon] = \Lambda_\varepsilon(y) \int [f_\varepsilon(\xi') - f_\varepsilon(\xi)] d\xi'$$

Biochemical pathways

Can one explain the tumbling rate

$$K(c;\xi,\xi') = \mathbf{K}\left(\frac{\partial c}{\partial t} + \xi'.\nabla c\right)?$$



Extracellular medium

——membrane——

Cytosol

Biochemical pathways

Can one explain the tumbling rate $\mathbf{K}\big(\frac{\partial c}{\partial t} \; + \xi'.\nabla c\big)$?

Departing from

$$\frac{\partial}{\partial t} f_\varepsilon(t,x,\xi,y) + \xi \cdot \nabla_x f_\varepsilon + \frac{1}{\varepsilon}\mathrm{div}_y[R_\varepsilon f_\varepsilon] = \Lambda_\varepsilon(y) \int [f_\varepsilon(\xi') - f_\varepsilon(\xi)]d\xi'$$

Theorem As $\varepsilon \to 0$, the limit is

$$f_\varepsilon(t,x,\xi,y) \to \bar{f}(t,x,\xi)\delta(y = Y(c))$$

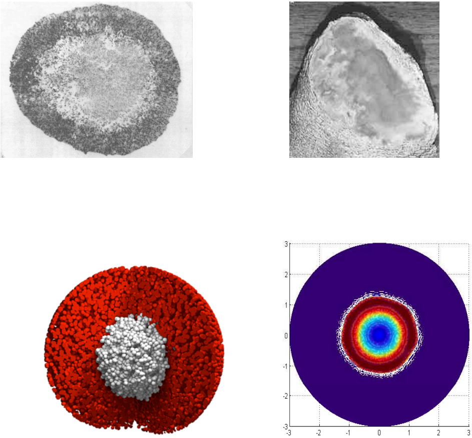
and

$$\tfrac{\partial}{\partial t}\bar{f}(t,x,\xi) + \xi \cdot \nabla_x \bar{f} =$$

$$= \int \left[\mathbf{K}\Big(\frac{\partial c}{\partial t} \; + \xi'.\nabla c\Big)\bar{f}(\xi') - \mathbf{K}\Big(\frac{\partial c}{\partial t} \; + \xi.\nabla c\Big)\bar{f}(\xi) \right] d\xi'$$

Aspects of living tissues

Models used for tumor growth



Aspects of living tissues

Simplest model is mechanical only :

$n(x,t) =$ population density of tumor cells at location x, time t,

$v(x,t) =$ cell velocity at location x and time t,

$p(x,t) =$ pressure in the tissue,

$$\overbrace{\frac{\partial n}{\partial t}}^{\text{Change in number of cells}} = \underbrace{-\mathrm{div}\big(nv\big)}_{\text{movement of cells}} + \mathit{division} - \mathit{death}$$

Darcy's law for friction (with ECM) dominated flow

$$v = -\nabla p(x,t),$$

Constitutive law (compressible fluid)

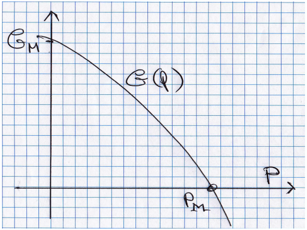
$$p(x,t) \equiv \Pi(n) := n^{\gamma}, \quad \gamma > 1$$

Aspects of living tissues

The compressible mechanical model

$$\begin{cases} \frac{\partial}{\partial t} n + \mathrm{div}\big(nv\big) = nG\big(p(x,t)\big), \qquad x \in \mathbb{R}^d, \; t \geq 0, \\ \\ v = -\nabla p(x,t), \qquad p(x,t) \equiv \Pi(n) := n^\gamma, \quad \gamma > 0. \end{cases}$$

Byrne, Drasdo, Chaplain, Joanny-Prost-Jülicher...etc 'homeostatic pressure'



Aspects of living tissues

The compressible mechanical model

$$\begin{cases} \frac{\partial}{\partial t} n + \mathrm{div}\big(nv\big) = nG\big(p(x,t)\big), \qquad x \in \mathbb{R}^d,\ t \geq 0, \\ v = -\nabla p(x,t), \qquad p(x,t) \equiv \Pi(n) := n^\gamma, \quad \gamma > 0. \end{cases}$$

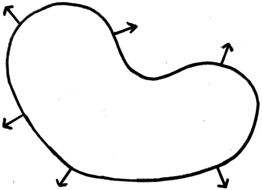
Specific properties

- $\frac{\partial}{\partial t} n(t=0) \geq 0 \ \Rightarrow\ \frac{\partial}{\partial t} n(t) \geq 0 \quad \forall t > 0$
- $\frac{\partial}{\partial t} n(t=0) \geq -\frac{C}{t} e^{-\gamma c_G t}$

Aspects of living tissues

Spatial domain $\Omega(t)$

$v(x,t) = -\nabla p(x,t)$



Compute the pressure as

$$\begin{cases} -\Delta p = G(p) & x \in \Omega(t), \\ p = 0 & \text{on } \partial\Omega(t). \end{cases}$$

Surface tension may be included (κ = mean curvature)

$$p(x,t) = \eta\kappa(x,t), \qquad \text{on } \partial\Omega(t)$$

Aspects of living tissues

$$\begin{cases} \frac{\partial}{\partial t} n_\gamma + \operatorname{div}\big(n_\gamma v_\gamma\big) = n_\gamma G\big(p_\gamma(x,t)\big), \qquad x \in \mathbb{R}^d \\ v_\gamma = -\nabla p_\gamma(x,t), \qquad p_\gamma(x,t) \equiv \Pi(n_\gamma) := n^\gamma, \end{cases}$$

Theorem (Hele-Shaw limit) : As $\gamma \to \infty$

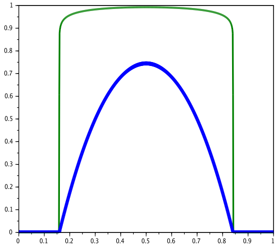
$$n_\gamma \to n_\infty \leq 1, \qquad p_\gamma \to p_\infty \leq p_M$$

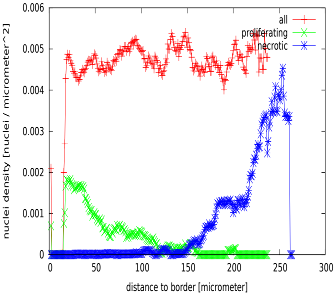
$$\begin{cases} \frac{\partial}{\partial t} n_\infty - \operatorname{div}\big(n_\infty \nabla p_\infty\big) = n_\infty G\big(p_\infty\big) \\ p_\infty = 0 \quad \text{for} \quad n_\infty(x,t) < 1 \\ p_\infty\big(\Delta p_\infty + G(p_\infty)\big) = 0 \end{cases}$$

Remarks

1. Unique solution to the equation on n_∞ (Oleinik, Crowley)
2. This is a weak formulation of the geometric problem
3. Benilan, Caffarelli-Friedman, Gil, Quiros, Vazquez...etc

Aspects of living tissues





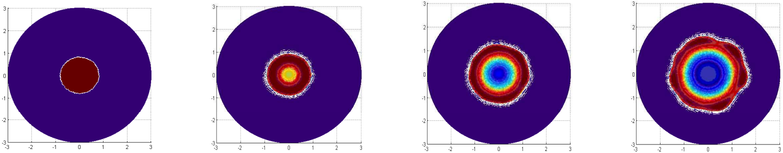
Left : The model solution

Right : Cell culture data in vitro at two different times.
From N. Jagiella PhD thesis, INRIA and UPMC (2012)

Model with nutrient

$$\begin{cases} \frac{\partial}{\partial t} n + \operatorname{div}(nv) = nG\big(p(x,t), \underbrace{c(x,t)}_{\text{nutrients}}\big), \\ v = -\nabla p, \qquad p = n^\gamma, \\ \frac{\partial}{\partial t} c - \Delta c + \underbrace{R(n) c = c_B}_{\text{nutrients consumption/release}} \end{cases}$$

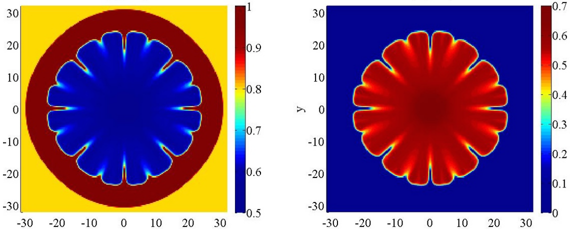
Open question. $p_\infty \big(\Delta p_\infty + G(p_\infty, c_\infty) \big) = 0$

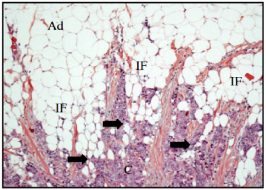


effect of nutrient consumption. Credit for pictures M. Tang, N. Vauchelet

Model with different cells

$$\begin{cases} \frac{\partial}{\partial t} n_P + \operatorname{div}\big(\mu_P n_P v\big) = n_P G\big(p(x,t)\big) - \alpha n_P, \\ \frac{\partial}{\partial t} n_H + \operatorname{div}\big(\mu_H n_H v\big) = 0, \\ v = -\nabla p, \qquad p = (n_P + n_H)^{\gamma} \end{cases}$$

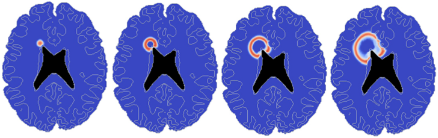




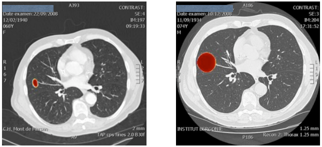
Credit for picture A. Lorz, T. Lorenzi (Saffman-Taylor instability ? growth is important)

Concrete applications

Image based predictions : include



- Active cells
- Nutrients and vasculature
- Quiescent, necrotic, healthy cells



Credit for pictures : INRIA team Monc (Bordeaux)

Conclusion

- 4 examples where Partial Differential Equations arise
- Many asymptotic problems
- There are concrete applications
- There are quantitative fit with experiments

- Unlike physics, parameters are not known (distributed)

Thanks to my co-authors

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A. Lorz, T. Lorenzi,

Thank you

THANK YOU