Modeling through nonlinear flux limited spreading

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Luis Santaló school: Mathematics of planet Earth
15-19 July 2013

Outline

First session:

- Biological motivation: Propagation of tumors, Morphogenesis
- Mathematical motivation: Cattaneo, Porous media, Optimal transportation
- Going back to biological models

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Second session:

- Pattern formation: PDE's *vs* Dynamical Systems

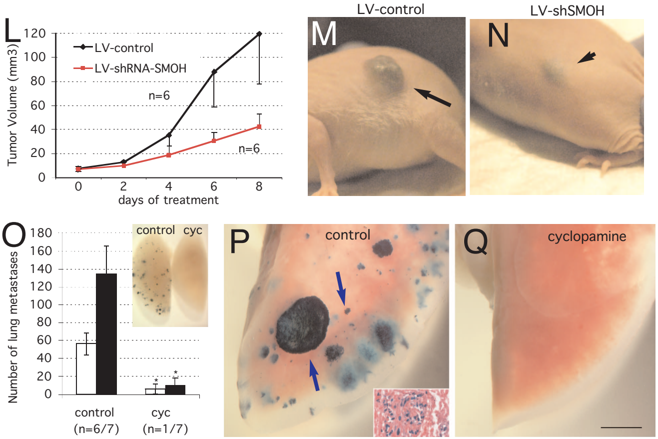
Colaborators

This talks are based on some works in collaboration with:

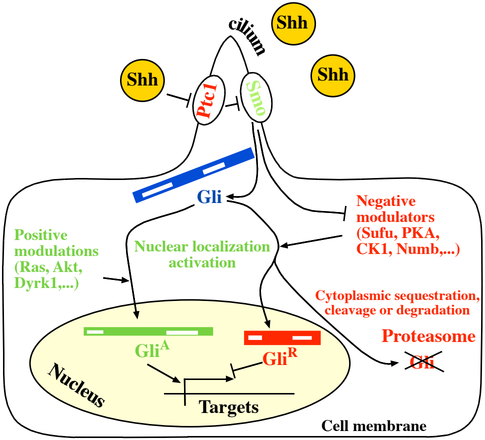
- U. Granada: J. Campos, P. Guerrero (CRM $\rightarrow$ UCL), J. Soler, M. Verbeni
- U. Pompeu Fabra: V. Caselles, J. Calvo (UGR $\rightarrow$ UPF)
- Centro de Biología Molecular, CSIC: I. Guerrero, E. Mollica
- Médecine Génétique et Développement, U. Geneve: A. Ruiz i Altaba
- Neurosciences, U. Geneve: A. Carleton

Signaling proteins (Shh) $\longleftrightarrow$ change in cell behavior (GLI code)

A. Ruiz i Altaba, PNAS 2007



Naive scheme of the Shh signaling pathway



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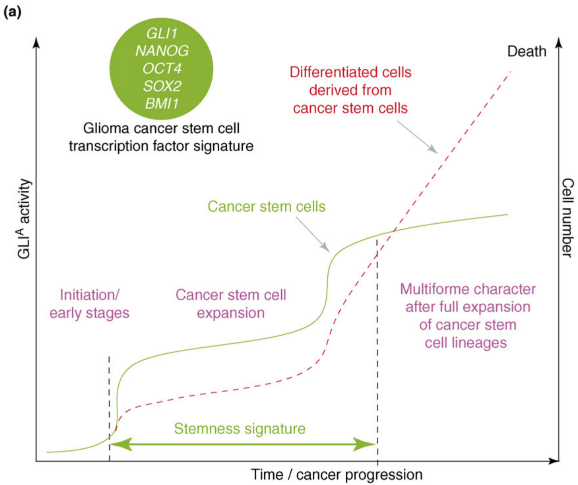
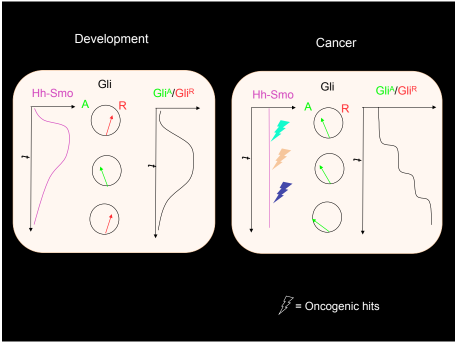


Shh signaling pathway



- Implicated in development of many tissues and organs (skin, lungs, brain, bone and blood).
- Shh has an important role via GLI regulation in tumor formation: deregulation of Shh pathway leads to various tumors (skin, prostate, brain, colon).

Intercellular communication: Hedgehog

Shh-Gli in vertebrates $\longleftrightarrow$ Hh-Ci in Drosophila

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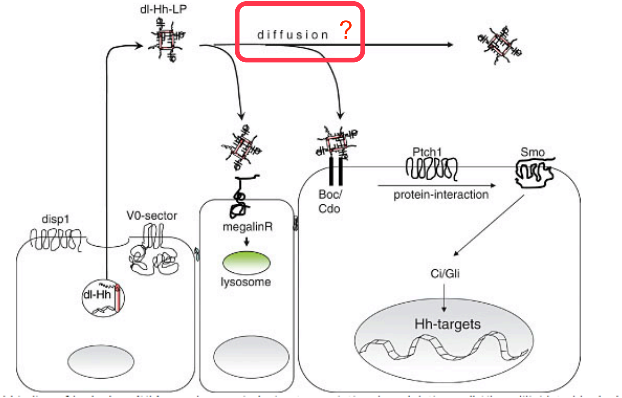
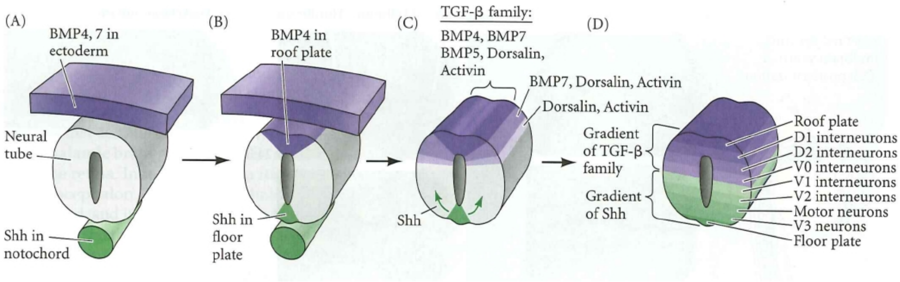


Different space and time scales

D-V neural patterning

The neural tube is polarized along the anteroposterior and dorsoventral axis.

Dorsoventral spinal cord patterning of the chick embryo



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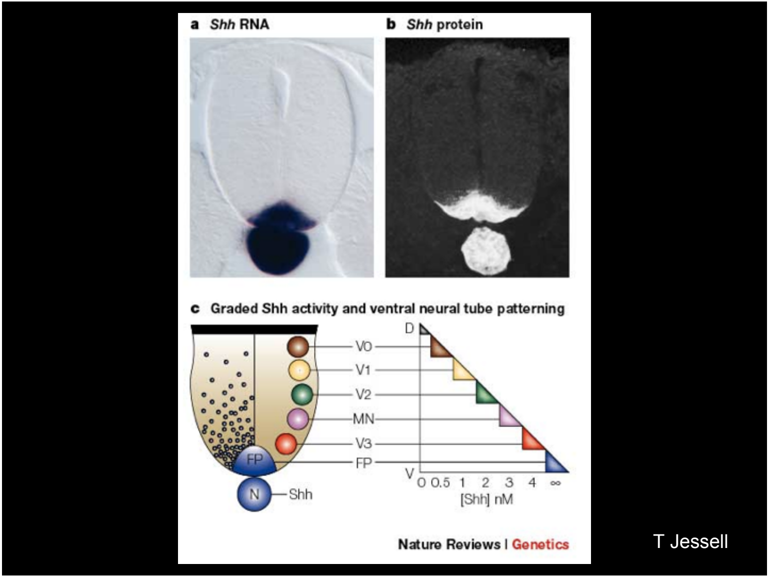

Models of signal propagation and transduction

- How do morphogen gradients form and propagate? By diffusion?
- How is the signal interpreted by the responding cells?

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Reaction-diffusion equations: basic ingredients

- Diffusion equation to describe morphogen propagation and formation of concentration gradient
- Law of mass action to describe rates of change in protein concentrations and gene codifications.

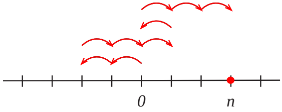
(Turing, Meinhard, Wolpert, Lander, Lai, Schaffer, ...)

Models of signal propagation and transduction

Brownian motion / Fick's second law (or a coupled system of them)

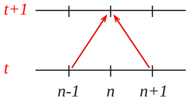
$$\frac{\partial u}{\partial t} = \nu \frac{\partial^2 u}{\partial x^2} + f(t, x, u(t,x), \dots)$$

Single particle moving in a lattice
transition probability 1/2

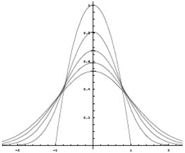


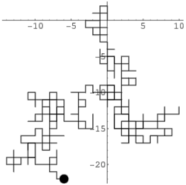
$p_n(t)$ = propability of having a particle in the node n at time t

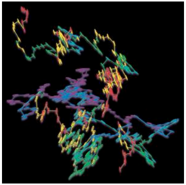
Equation satisfied by the probability distribution $\{p_n(t)\}$



$p_n(t+1) = (1/2)p_{n-1}(t) + (1/2)p_{n+1}(t)$







Model by Saha and Schaffer

(Saha and Schaffer, 2006 (Development) and 2004)

- Main purpose: to understand the dynamics of morphogen gradient formation and interpretation.
- The model studies D-V patterning in the chick embryo spinal cord, beginning when Shh is first secreted by the floor plate.
- The model focus on the ventral-most binary cell fate (V3 interneurons).

Modeling morphogenetic responses

- Transport of the Shh signal: Fick's law: linear diffusion.

$$\frac{\partial[\text{Shh}]}{\partial t} = \nu\,\Delta_x[\text{Shh}] + k_{off}[\text{Ptc1Shh}_{mem}] - k_{on}[\text{Shh}][\text{Ptc1}_{mem}](t,x)$$

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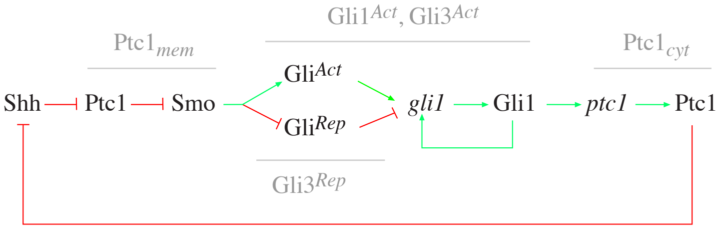
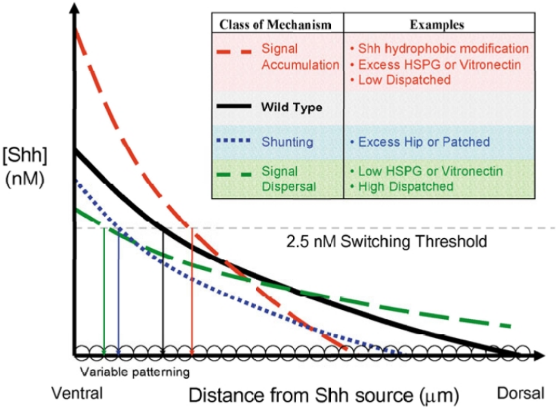


Shh propagation along the neural tube

Movie time

(K. Saha and D.V. Schaffer, 2006)

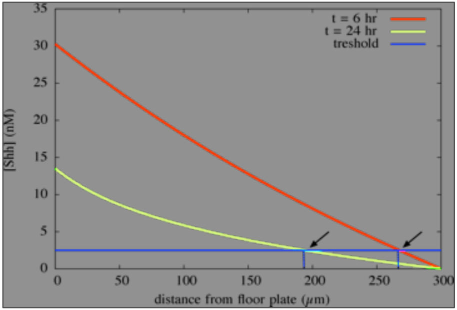
How to reduce diffusivity



(K. Saha and D.V. Schaffer, 2006)

An arbitrary (non dynamic) threshold had to be introduced in order for the model to yield a wave front radically distinct from the instantaneous gradient implied by linear diffusion.

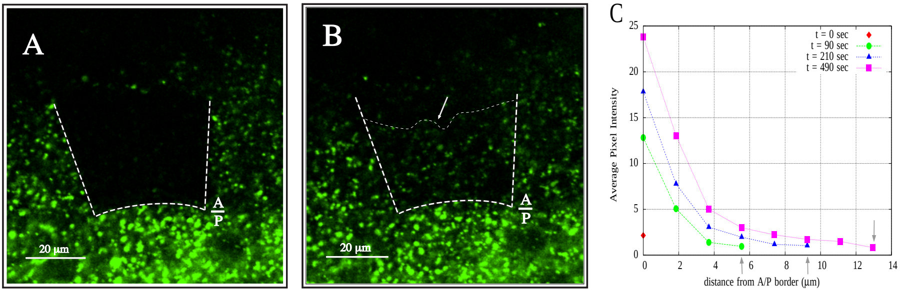
Insoluble (!) problems for linear diffusion:



- Instant spreading derived from Brownian motion
- No real wave fronts (retrograde fronts?)
- No time to respond. Linear diffusion prevents the activity of activators or repressors, avoiding morphogenetic responses.

Finite speed of propagation

Isabel Guerrero's Lab



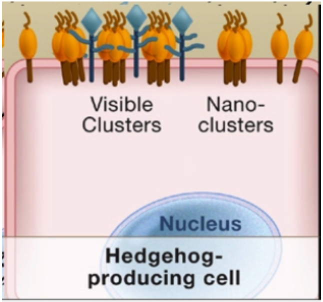
Corroborated by other experiments (Su, Briscoe, Chamberlain,...)

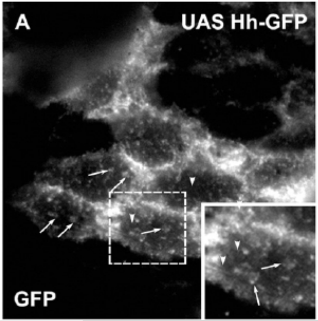
⟶ making in question linear diffusion.

Going back to the biology

Nanoscale Hh organization (Vyas et al., 2008)

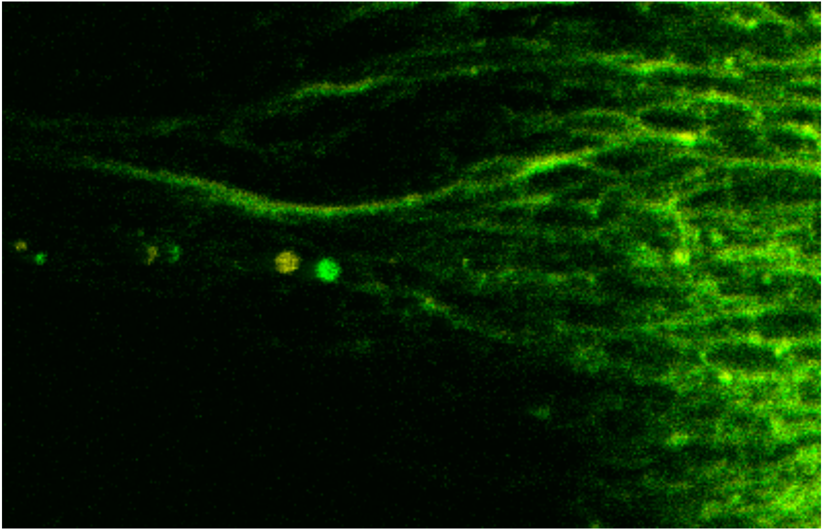
- Hh forms visible aggregates ($\sim$ 100 nm) composed by Hh oligomers, HSPG ... and the dimension of these aggregates is large with respect to the dimension of the cells.
- The ratio of these scales violates the Brownian foundation that assumes that particles are small with respect to the size of the space they are occupying.





Size of the aggregates

Isabel Guerrero's Lab



Exposure time

Drawbacks of the model

- Transport modeled with diffusion equation: unphysical spreading out of morphogen to all the neural tube soon after secretion.
- The concentration of Shh received by the cells and the time of exposure are of similar relevance

(H.C. Park, J. Shin, B. Appel, *Spatial and temporal regulation of ventral spinal cord precursor specification by Hedgehog signaling*. Development, 2004)

(J. Briscoe et al., *Interpretation of the sonic hedgehog morphogen gradient by a temporal adaptation mechanism*. Nature, 2007)

Problems in linear-diffusion-based models

1. The morphogen signal is received instantaneously and accumulates from the beginning and continuously. The necessity of an arbitrary threshold.
2. Aggregates do not behave as very small particles in large spaces, thus denying one of the assumptions of the brownian motion.
3. There are privileged ways of propagation.
4. Patterning action of morphogens is a dynamic process: responding cells are not inert.
5. Time is needed for the active interplay between morphogens and cellular response.

⟶ To reevaluate the very basis of the Turing-Wolpert modeling of morphogenetic action.

Alternative description of the transport mechanism

The controversy about the applicability of linear diffusion (Brownian mechanism of motion) was already pointed out in the pioneer work of Einstein over a century ago (1906). He discussed the possibility of considering the variance linear in time, which implies linear diffusion and infinite speed of propagation, which Einstein noted as impossible from the physical point of view. Einstein explicitly commented:

> *... the mean velocity of change of the observable (...) becomes infinitely great for an infinitely small interval of time; which is evidently impossible ...*

Alternative description of the transport mechanism

$\longrightarrow$ Models based on linear diffusion are in question in Biology

- Substituting the Fick law by the Cattaneo law gives

$$\tau \frac{\partial^2 u}{\partial t^2} + \frac{\partial u}{\partial t} - \nu \frac{\partial^2 u}{\partial x^2} = \text{reactions.}$$

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- Changing the classical diffusion term $\nu \Delta u$ by a power law diffusion of porous medium type $\nu \mathrm{div}(u^m \nabla u)$.

Alternative description of the transport mechanism

Ph. Rosenau (1992), from the observation that the speed of sound is the highest admissible free velocity in a medium, derived

$$\frac{\partial u}{\partial t} = \nu \frac{\partial}{\partial x}\left(\frac{|u| \frac{\partial u}{\partial x}}{\sqrt{|u|^2 + \frac{\nu^2}{c^2} \left| \frac{\partial u}{\partial x} \right|^2}} \right)$$

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  - From kinetic theory of multicellular growing system

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  - Y. Brenier (2000) obtained this equation by means of an optimal mass transport theory as a gradient flow of the Boltzmann entropy for the metrics corresponding to the cost function

$$k(z) = \begin{cases} c^2\left(1 - \sqrt{1 - \frac{|z|^2}{c^2}}\right), & \text{if } |z| \le c, \\ +\infty, & \text{if } |z| > c \end{cases}$$

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(ANDREU, CASELLES, MAZÓN, MOLL, PUEL, MCCANN, CALVO, SOLER.. 2004-12)

Modification of the Model. Transport by Diffusion?

- Alternative description of the transport mechanism to solve the problem of infinite speed of propagation of the linear diffusion theory.

- How should the flux be modified? Transport kinetic equations

$$\frac{\partial u}{\partial t} = \nu \Delta u = \nu div(\nabla u) = \nu div((\nabla \ln u) u) = \nu div(v\, u)$$

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From a microscopic point of view the particles are moving with velocity v, determined by the entropy of the system $S(u) = u \ln u$ and the concentration u ($\sim$ chemical potential):

$$v = \nabla \left(\frac{S(u)}{u} \right)$$

Modification of the Fokker–Plack model

new microscopic velocity depending on the relative entropy

$$\tilde{v} = \frac{\nabla(S(u)/u)}{\sqrt{1 + \frac{\nu^2}{c^2}\left[\nabla(S(u)/u)\right]^2}} \,.$$

which gives

$$\frac{\partial u}{\partial t} = \nu \, \mathrm{div} \left(\frac{u \, \nabla u}{\sqrt{u^2 + \frac{\nu^2}{c^2}|\nabla u|^2}} \right)$$

Flux-limited porous media

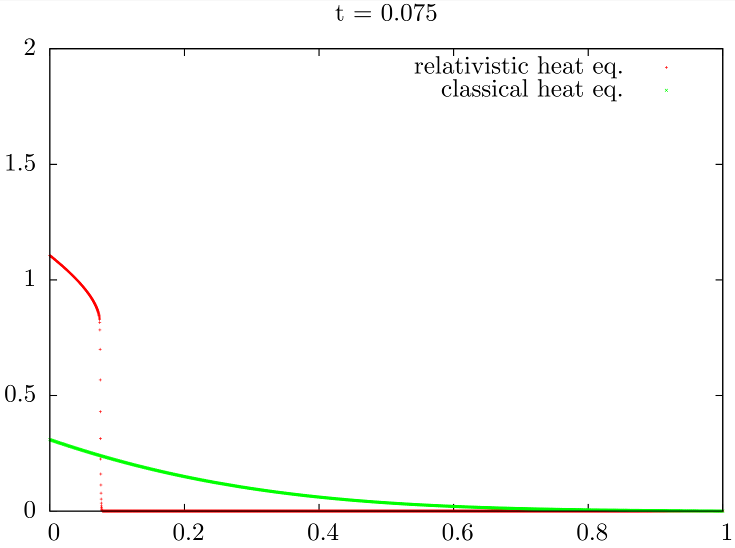
But there are other possibilities

$$\frac{\partial u}{\partial t} = \nu \, \mathrm{div} \left(\frac{u^m \, \nabla u}{\sqrt{u^2 + \frac{\nu^2}{c^2} |\nabla u|^2}} \right)$$

$$\frac{\partial u}{\partial t} = \frac{m+1}{m} \mathrm{div} \left(\frac{u \nabla u^m}{\sqrt{1 + \left(\frac{m+1}{mc}\right)^2 |\nabla u^m|^2}} \right)$$

(F. Andreu. V. Caselles, J. Mazon, M. Verbeni, J.Soler., *SIAM J. Math. Anal 2012*)

Numerical comparison



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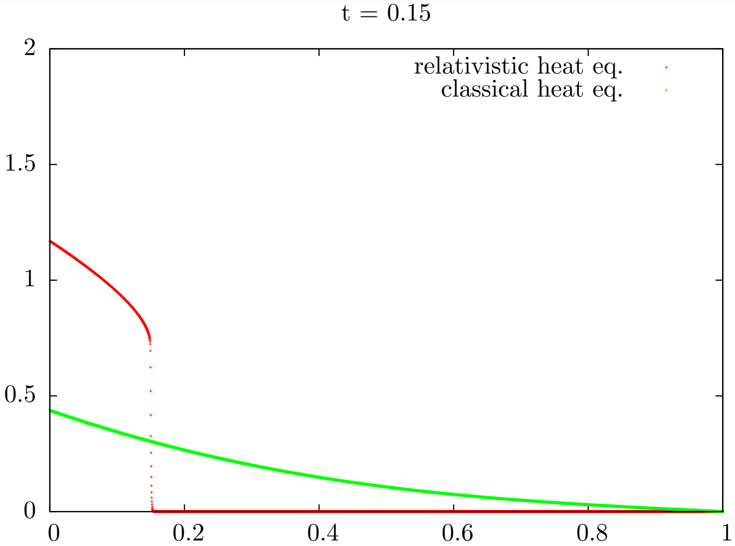

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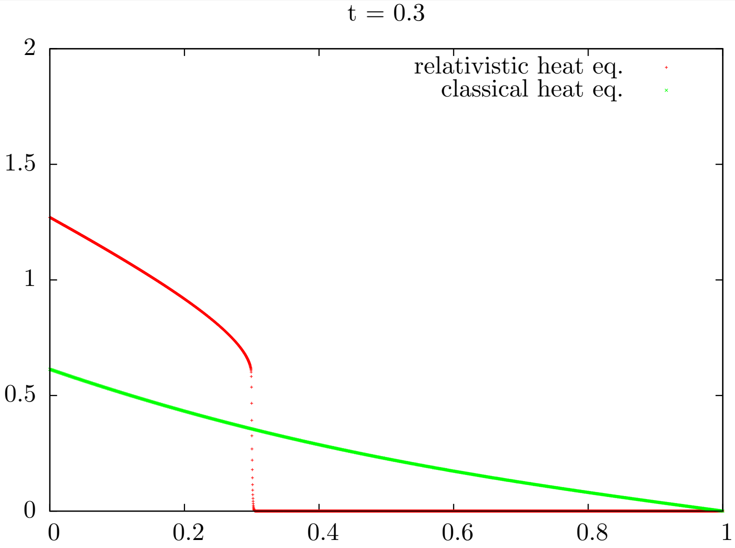

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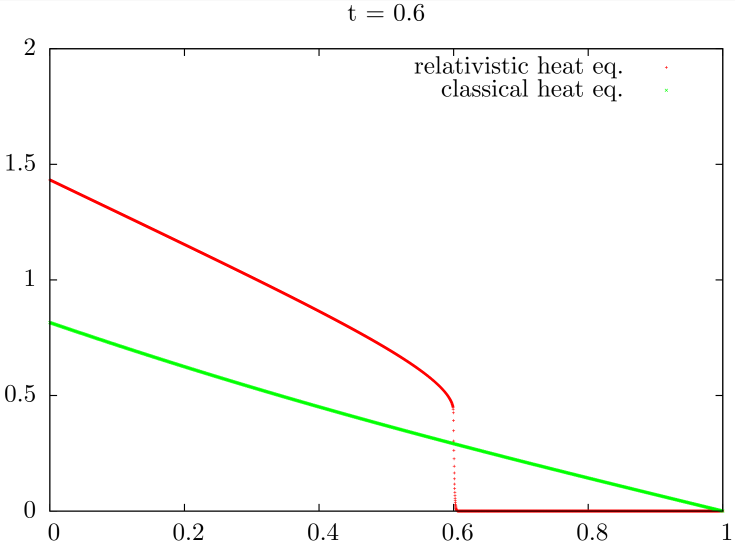

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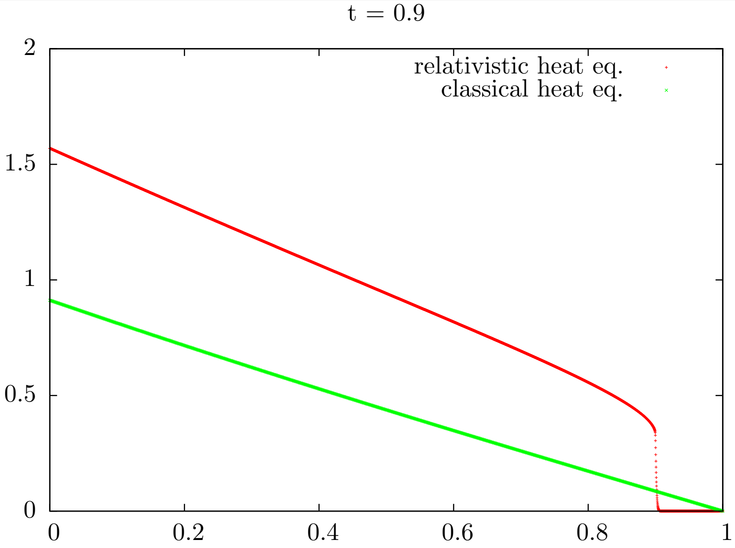

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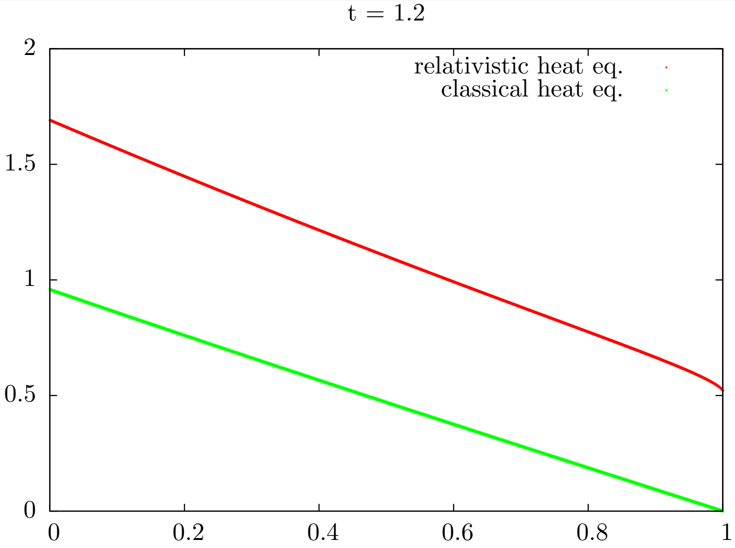

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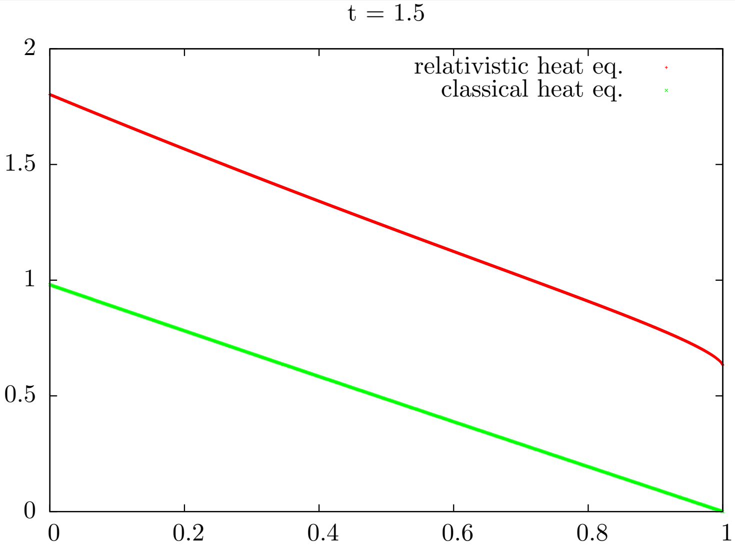
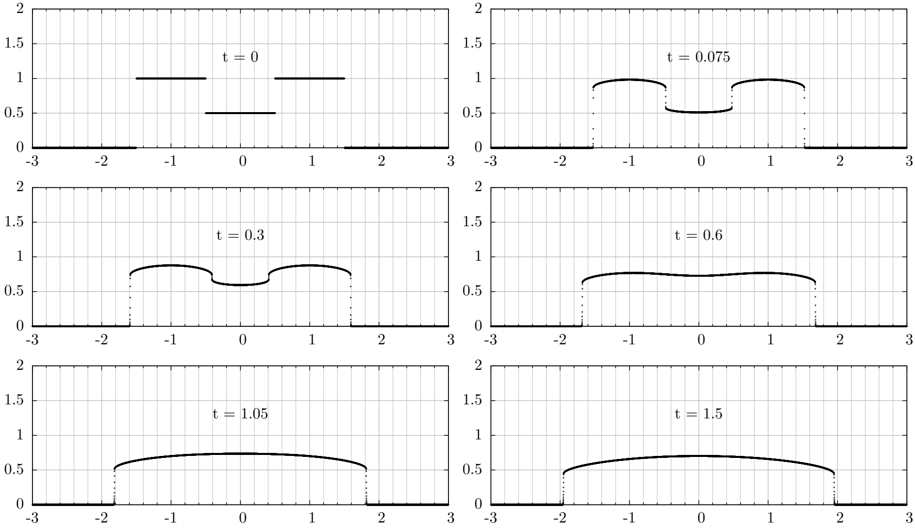
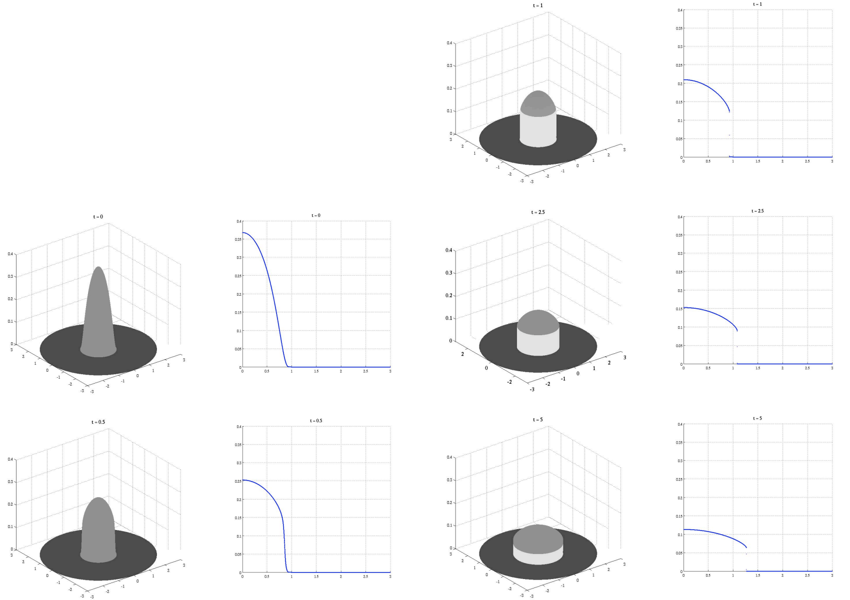


(CALVO, MAZÓN, SOLER & VERBENI, M3AS 2011)

Relativistic heat equation



Flux-limited porous media



Modeling morphogenetic responses

- Transport of the Shh signal: introduction of flux limiter

$$\frac{\partial[\mathrm{Shh}]}{\partial t} = \nu\,\partial_x \frac{[\mathrm{Shh}]\partial_x[\mathrm{Shh}]}{\sqrt{[\mathrm{Shh}]^2 + \frac{\nu^2}{c^2}(\partial_x[\mathrm{Shh}])^2}}$$

$$+ k_{off}[\mathrm{Ptc1Shh}_{mem}] - k_{on}[\mathrm{Shh}][\mathrm{Ptc1}_{mem}](t,x)$$

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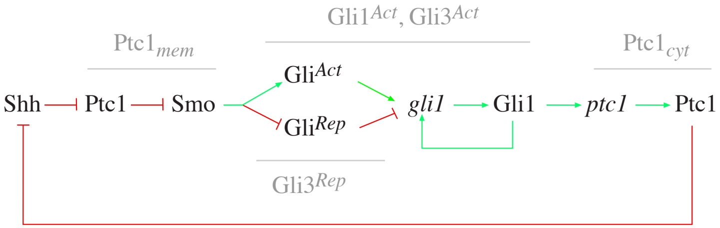


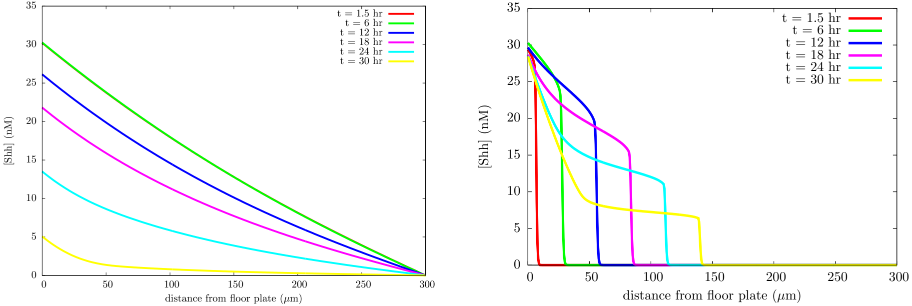
Modeling morphogenetic responses

$$
\begin{aligned}
\frac{\partial[\text{Ptc1Shh}_{mem}]}{\partial t} &= k_{on}[\text{Shh}][\text{Ptc1}_{mem}] - k_{off}[\text{Ptc1Shh}_{mem}] + k_{Cout}[\text{Ptc1Shh}_{cyt}] - k_{Cin}[\text{Ptc1Shh}_{mem}] \\
\frac{\partial[\text{Ptc1Shh}_{cyt}]}{\partial t} &= k_{Cin}[\text{Ptc1Shh}_{mem}] - k_{Cout}[\text{Ptc1Shh}_{cyt}] - k_{Cdeg}[\text{Ptc1Shh}_{cyt}]. \\
\frac{\partial[\text{Ptc1}_{mem}]}{\partial t} &= k_{off}[\text{Ptc1Shh}_{mem}] - k_{on}[\text{Shh}][\text{Ptc1}_{mem}] + k_{cyt}[\text{Ptc1}_{cyt}], \\
\frac{\partial[\text{Ptc1}_{cyt}]}{\partial t} &= -k_{cyt}[\text{Ptc1}_{cyt}] + k_P P_{tr}\left([\text{Gli1}^{Act}](t-\tau), [\text{Gli3}^{Act}](t), [\text{Gli3}^{Rep}(t)]\right)\Phi_{Ptc} \\
\frac{\partial[\text{Gli1}^{Act}]}{\partial t} &= -k_{deg}[\text{Gli1}^{Act}] + k_G P_{tr}\left([\text{Gli1}^{Act}](t-\tau), [\text{Gli3}^{Act}](t), [\text{Gli3}^{Rep}(t)]\right)\Phi_{Ptc} \\
\frac{\partial[\text{Gli3}^{Act}]}{\partial t} &= \frac{\gamma_{g3}}{1+R_{Ptc}} - [\text{Gli3}^{Act}]\frac{k_{g3r}}{1+R_{Ptc}} - k_{deg}[\text{Gli3}^{Act}] \\
\frac{\partial[\text{Gli3}^{Rep}]}{\partial t} &= [\text{Gli3}^{Act}]\frac{k_{g3r}}{1+R_{Ptc}} - k_{deg}[\text{Gli3}^{Rep}].
\end{aligned}
$$

where

$$
\Phi_{Ptc} = \frac{[\text{Ptc1}_0]}{[\text{Ptc1}_0] + [\text{Ptc1}_{mem}]}, \qquad R_{Ptc} = \frac{[\text{Ptc1Shh}_{mem}]}{[\text{Ptc1}_{mem}]}
$$

Numerical experiments

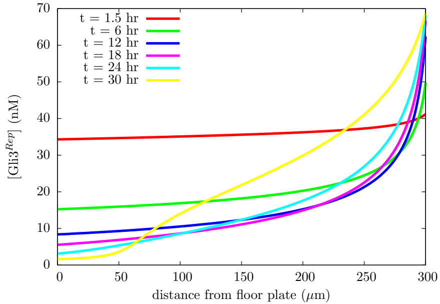


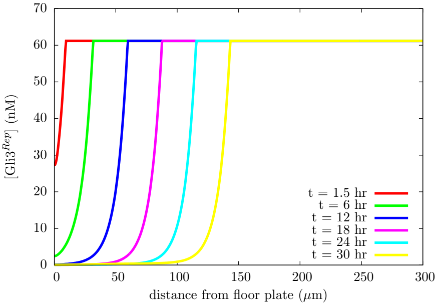
No instant spreading

Real wave fronts

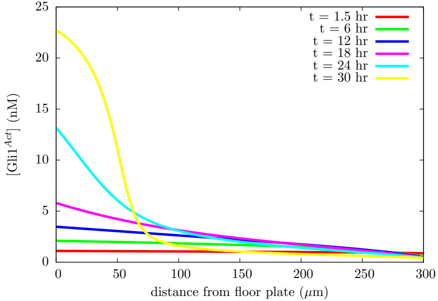
Time to respond

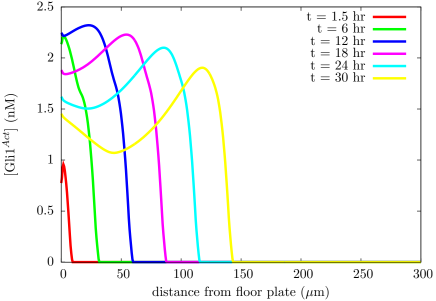
Numerical experiments





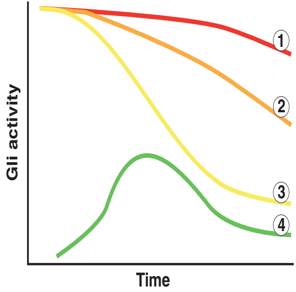
Numerical experiments



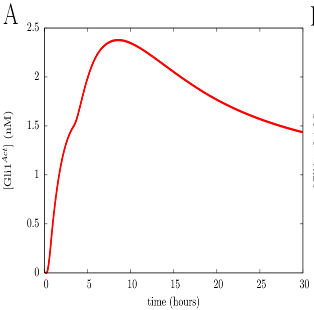


Numerical experiments: Desensitization

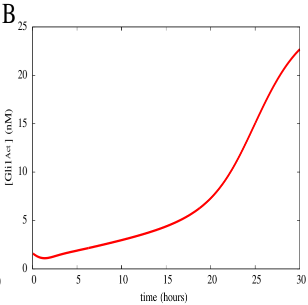
Briscoe experiments



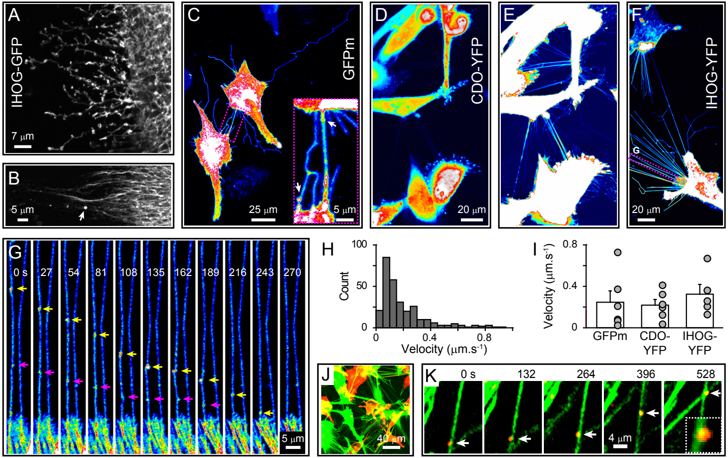
FLS



Linear diffusion



Cell extensions *vs* classical cell communication



Biological flux-limiters

(Verbeni, O. S., Mollica, Siegl-Cachedenier, Carleton, Guerrero, Ruiz i Altaba, Soler, appered in Physics of Life Reviews, 2013)