Modeling through nonlinear flux limited spreading

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D-V neural patterning

Dorsoventral **spinal cord patterning** of the chick embryo

In *Drosophila*, Hh plays the same role than Shh in Vertebrates.

(Gilbert)
Models of signal propagation and transduction

How do morphogen gradients form and propagate?

- Diffusion equation (Fick’s law) is frequently used to describe morphogen propagation and formation of concentration gradient

\[ u_t = \nu \Delta x u \]

(Fick (1855), Brown (1828), Einstein (1905),...)

- randomness
- small particles
Models of signal propagation and transduction

How do morphogen gradients form and propagate?

- **Diffusion equation (Fick’s law)** is frequently used to describe morphogen propagation and formation of concentration gradient.

How is the signal interpreted by the responding cells?

- **Law of mass action** to describe rates of change in protein concentrations and gene codifications.

Reaction-diffusion equations

\[ u_t = \nu \Delta_x u + f(u(t, x), ...) \]

(Turing, 1953, Meinhard, Wolpert, 1969, Lander, 2002, ...
Modeling Shh by linear diffusion

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

(Saha and Schaffer, Development, 2006)
Modeling Shh by linear diffusion

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Modeling Shh by linear diffusion

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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.
  - (J. Briscoe et al., Nature, 2007)
Alternative description of the transport mechanism

- Substituting Fick’s law by the Cattaneo law gives
  \[ \tau u_{tt} + u_t = \nu \Delta u \]

  In 1992, M.B. Rubin showed that Cattaneo’s model of hyperbolic heat conduction violates the second law of thermodynamics.
Substituting Fick’s law by the Cattaneo law gives

$$\tau u_{tt} + u_t = \nu \Delta u$$

Changing the classical diffusion term by a power law diffusion of porous medium type

$$u_t = \nu \nabla \cdot (u^m \nabla u)$$

(Murray, 2002, Vázquez 2007)
Alternative description of the transport mechanism

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  (Murray, 2002, Vázquez 2007)

- Ph. Rosenau (1992), from the observation that the speed of sound is the highest admissible free velocity in a medium, derived
  \[ u_t = \nabla \cdot (Vu) \quad \text{s.t.} \quad |V| \leq c \]
Alternative description of the transport mechanism

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\[ u_t = \nu \nabla \cdot \left( \frac{|u| \nabla u}{\sqrt{|u|^2 + \frac{\nu^2}{c^2} |\nabla u|^2}} \right) \quad \xrightarrow{c \to \infty} \quad \nu \Delta u \quad \text{(RHE)} \]
Alternative description: flux limited operators

Different operators can be deduced by considering optimal mass transportation, kinetic derivations, porous versions, ...

1D examples:

\[ u_t = \nu \left( \frac{|u|^m u_x}{\sqrt{|u|^2 + \frac{\nu^2}{c^2} |u_x|^2}} \right)_x \quad m \geq 1 \quad \text{(PRHE)} \]

\[ u_t = \nu \left( \frac{|u|(u^m)_x}{\sqrt{1 + \frac{\nu^2}{c^2} |(u^m)_x|^2}} \right)_x \quad m \geq 1 \quad \text{(FLPME)} \]

The mathematical properties of this equation and related models have been analyzed thoroughly. Well-posedness (especially uniqueness) is properly dealt with in the framework of entropy solutions (Andreu, Caselles, Mazón, Moll, Calvo,... See references in Calvo et al., EMS Surv. Math. Sci, 2015)
Qualitative behavior of flux limited solutions

Regularity

<table>
<thead>
<tr>
<th>Model</th>
<th>RHE</th>
<th>FLPME</th>
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</thead>
<tbody>
<tr>
<td>Support growth</td>
<td>$c$</td>
<td>$c$</td>
</tr>
<tr>
<td>Discontinuities</td>
<td>$[0, \infty)$</td>
<td>$[0, T]$</td>
</tr>
<tr>
<td>Smootherness ($u &gt; 0$)</td>
<td>$[0, \infty)$</td>
<td>$[0, T]$</td>
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Figure 1. Numerical evolution of a stepwise initial condition by the relativistic equation (1.5) in A), and the flux-saturated porous media equation (2.9) with $mD_2$ in B). In both examples we have taken $\nu = D_1$ and $t_{2} \in [0, 0.9]$. The time step between different profiles is 0.05 for the three first profiles and 0.2 for the rest in order to capture the different velocities. Note the instantaneous regularization at the interior jumps although this is not the case at the boundary. We remark the persistence of the discontinuous jumps at the boundary in A), which disappear in B). It is interesting to observe that velocity of support is constant in A) against the fact that it decreases in B).

In fact, we will display a number of simulations not just here but rather throughout the text. We focus in this section (Figures 1, 2 and 3) in both pure flux-saturated equations and some porous media variants; later on we will show some simulations where coupling with a reaction term or even with a system of ODE's is featured. Regardless of these characteristics, the setup used for those numerical simulations that are presented in the document is always the same. The numerical solution considers a spatial discretization of the flux-saturated transport equation by using a fifth-order finite difference WENO (Weighted Essentially Non-Oscillatory) scheme [92] with Lax–Friedrichs flux splitting [84]. For the time evolution we use a fourth order Runge–Kutta method, which also allows to deal with possible delay phenomena. A spatial grid between 1000 and 2000 points with an appropriate CFL condition is considered.

The previous procedure is but one among a number of different possibilities. There are in the literature different numerical approaches to flux-saturated equations, among which we mention [20, 129, 52, 50, 57, 67, 68, 102, 122].

4. Mathematical preliminaries: The bounded variation scenario

In this section we introduce a number of tools that are needed to set up the well-posedness framework in [11, 12] and some of its extensions. As pointed out in the introduction and in the previous numerical examples, in general we may not expect solutions of flux-saturated equations to be more regular than $u \in BV([0, T])$. This makes operations like integration by parts already involved. But in fact this may be even worse. First, there is no particular reason why $u_t$ should even be a Radon measure, which creates a number of
Qualitative behavior of flux limited solutions

Waiting time

<table>
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<tr>
<td>Support growth</td>
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<td>( c )</td>
</tr>
<tr>
<td>Waiting time</td>
<td>( m &gt; 1 )</td>
<td>( m &gt; 1 )</td>
</tr>
<tr>
<td>Smoothness</td>
<td>!!!</td>
<td>!!!</td>
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</tbody>
</table>

Figure 2. Numerical evolution of an initial condition given by a continuous polynomial spline. Plot A) depicts the evolution by (2.11), while plot B) shows the evolution by (2.9). In both cases \( m \) and \( \delta \). The time step between successive profiles is 0.48. In both cases we find a waiting time for support spreading which is longer for the case of (2.9). Note that the cusp is regularized in both cases but a discontinuity occurs in the derivative of the solution when sliding through the initial profile. The result is a continuous profile for (2.9), which reduces its velocity, and the emergence of a jump discontinuity in the case of (2.11), which is a moving front in which the velocity of propagation depend on the parameters of the system via a Rankine–Hugoniot-type condition. Therefore, in both cases there is a smoothing process but, simultaneously, another one of singularization emerges either in the derivative in B) or as a jump in A).

Technical issues (we will treat this in more detail in Section 10.2). And second, the degeneracy of the equation may spoil the previous spatial regularity on the zeroth level set. Then it will be mandatory to avoid this set when dealing with certain delicate technical issues related with well-posedness. This motivates the introduction of a specific set of truncation functions that will be essential in order to construct the functional framework in which well-posedness can be proved. Another set of specific truncation functions will be required for the sole purpose of showing uniqueness, as the extremely low regularity of solutions requires to use Kruzkov's doubling variables methodology. This proof uses very complicated combinations of terms involving functions with extremely low regularity. A very specific functional calculus needs to be defined in order to make sense of the previous. In particular, lower semicontinuity results for energy functionals in this degenerate framework will be needed.
Traveling waves in reaction-diffusion models

At the continuous level, diffusion equations coupled to reaction terms are able to display wave-like phenomena. For instance, the FKPP model

\[ u_t = \nu u_{xx} + ku(1 - u). \]

displays classical traveling waves \( u(t, x) = u(x - \sigma t) \) for wavespeeds \( \sigma \geq 2\sqrt{k\nu} \).

(Fisher; Kolmogoroff, Petrovsky, Piscounoff, 1937)
Are flux-limited models able to reproduce patterns?

We expect to get front-like traveling waves when we couple such a non-linear diffusion \((m \geq 1)\) to a Fisher–Kolmogorov reaction term:

\[
    u_t = \nu v_0 \left( \frac{(u/v_0)^m u_x}{\sqrt{|u|^2 + \frac{\nu^2}{c^2}|u_x|^2}} \right)_x + ku(1 - u/v_0)
\]

Several other models are embodied as limiting cases.
Catalog of solutions, case $m = 1$

(Campos, Guerrero, Sánchez, Soler, Ann. IHP 2013)
Traveling waves

Catalog of solutions, case $m > 1$

A) $u, \xi_1$

B) $u, \xi_1$

C) $u, \xi_1$

D) $u, \xi_1$

Figure 1: Travelling wave profiles for 2:
A) $\sigma > \sigma_{\text{smooth}}$, B) $\sigma = \sigma_{\text{smooth}}$, C) $\sigma \in (\sigma_{\text{ent}}, \sigma_{\text{smooth}})$, D) $\sigma = \sigma_{\text{ent}}$. Vertical dotted lines show singular tangent points. These profiles are in correspondence with the orbits depicted in Fig. 2B). Thus they encode processes in which the propagation of information (whatever it may be) takes place at finite speeds – see discussions elsewhere [ ].

The natural context where studying discontinuous solutions to flux–limited porous media equations is the $\text{BV}$–theory as it has been analyzed in [7, 17, 18] which provides a suitable functional $L^1$–framework that allows to treat such singular objects by means of the concept of entropy solutions.

2 Entropy solutions

Our purpose in this section is to state existence and uniqueness of entropy solutions of the reaction-diffusion equation (2). Moreover, we also give a geometric interpretation of the entropy conditions on the jump set of the solutions. Equation (2) belongs to the more general class of flux limited diffusion equations for which the correct concept of solution, permitting to prove existence and uniqueness results, is the notion of entropy solution [4, 17]. This class of equations with $F = 0$ has been studied in a series of papers [3, 4, 6, 17, 18, 7] and for the so-called relativistic heat equation ($m = 1$ in (2)) with a Fisher–Kolmogorov type reaction term in [5]. The notion of entropy solution is described in terms of a set of inequalities of Kruzhkov's type [31]. As proved in [18] when $F = 0$, they can be characterized more geometrically on the jump set of the solution by saying that the graph of the function is vertical at those points. Our purpose is to extend these results to the case of (2) and a reaction term of Fisher–Kolmogorov type. This will be fundamental to construct discontinuous traveling waves that are entropy solutions of (2).

Our first purpose is to give a brief review of the concept of entropy solution (Calvo, Campos, Caselles, Sánchez, Soler, to appear Invent. Math.)
The traveling wave ansatz

We want solutions connecting the constant states one and zero having a constant shape:

\[ u(t, x) = u(\tau) = u(x - \sigma t), \quad \sigma > 0. \]

The profiles we are seeking are non-negative functions \( u(\tau) \) defined on \( -\infty, \tau_\infty ] \) for some \( \tau_\infty \in ] -\infty, +\infty \] , such that

\[ \lim_{\tau \to -\infty} u(\tau) = 1 \quad \text{and} \quad u'(\tau) < 0. \]

Remark:
\( \tau_\infty = \infty \) and \( \lim_{\tau \to \infty} u(\tau) = 0 \) are posteriorly deduced.
Existence FKPP: reduction to a planar system

The traveling profile must solve the following equation:

\[ \nu (u')' + \sigma u' + ku(1 - u) = 0. \]

Setting

\[ r(\tau) = -\nu u'(\tau), \]

the second order ODE is equivalent to a first order planar dynamical system:

\[
\begin{cases}
  u' = -\frac{1}{\nu} r, \\
  r' = -\frac{\sigma}{\nu} r + ku(1 - u).
\end{cases}
\]
Traveling waves

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Furthermore, \( \lim_{\tau \to -\infty} u(\tau) = 1 \) and \( r > 0 \) by hypothesis.
Existence: linear analysis around equilibria points

There exist only two equilibria points,

\((1, 0)\), saddle node.

Eigenvalues: \(\lambda_{\pm} = \frac{-\sigma \pm \sqrt{\sigma^2 + 4k\sigma}}{2\nu}\)

Eigenvectors: \(\approx (-\frac{1}{\nu\lambda_{\pm}}, 1)\)

\((0, 0)\), (im)-proper iff \(\sigma \geq 2\sqrt{k\nu}\)

Eigenvalues: \(\lambda_{\pm} = \frac{-\sigma \pm \sqrt{\sigma^2 - 4k\sigma}}{2\nu}\)

The condition \(\lim_{\tau \to -\infty} u(\tau) = 1\) implies that the traveling wave profile is determined by the unstable variable.
The existence of an heteroclinic solution joining the fixed points is consequence of the existence of a positive invariant region for the planar flux.
Case $m>1$, Orbits for the singular dynamical system

A) Normalized direction field of the flux related to (29) for $\sigma = c = 1$, $m = 2$, $f(u) = u(1-u)$ and $\epsilon = 4/3$. Different types of arrows were used to stress the fact that the actual flux is singular at the boundaries $r = 1$ and $u = 0$.

B) Numerical solutions to type I (solid), II (dashed) and III (dotted) orbits of (29) for several values of $\epsilon$. The lowest type II and III orbits are those corresponding to $\sigma = \epsilon_{\text{smooth}}$. The uppermost type II orbit corresponds to $\sigma = \epsilon_{\text{ent}}$. The intermediate type II orbit and the uppermost type III orbit correspond to a value $\sigma = \epsilon_{2}$ ($\epsilon_{\text{ent}}, \epsilon_{\text{smooth}}$) and are related by the jump law (25).
Traveling waves

Characterizing the entropy solution

Distributional solutions to our model having a jump discontinuity must satisfy the Rankine-Hugoniot jump condition:

\[ \nu = \frac{F(u)^+ - F(u)^-}{u^+ - u^-} \]

- \( \nu \) velocity at which the jump discontinuity moves
- \( u^\pm \) values of the solution at both sides of the discontinuity
- \( F(u)^\pm \) values of the flux at both sides of the discontinuity
Characterizing the entropy solution

Distributional solutions to our model having a jump discontinuity must satisfy the Rankine-Hugoniot jump condition:

\[ v = \frac{\mathcal{F}(u)^+ - \mathcal{F}(u)^-}{u^+ - u^-} \]

In our particular situation, this reduces to

\[ v = c \left( \frac{(u^+)^m - (u^-)^m}{u^+ - u^-} \right) \]
Traveling waves

Characterizing the entropy solution

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Entopic solutions must satisfy

- Rankine-Hugoniot jump condition
- They must have infinite slopes at both sides of the possible discontinuities (except if \( u^+ = 0 \))
Singular traveling waves viewed as attractors

Spontaneous singularization and convergence towards traveling waves, which constitute super-solutions for the time-dependent problem.
Modeling morphogenetic responses

- Transport of the Shh signal: introduction of flux limiter

\[
\frac{\partial [\text{Shh}]}{\partial t} = \nu \frac{\partial_x [\text{Shh}]}{\sqrt{[\text{Shh}]^2 + \frac{\nu^2}{c^2} (\partial_x [\text{Shh}])^2}} \\
+ k_{\text{off}}[\text{Ptc1Shh}_{\text{mem}}] - k_{\text{on}}[\text{Shh}][\text{Ptc1}_{\text{mem}}](t, x)
\]

Modeling morphogenetic responses

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+ k_{\text{off}}[\text{Ptc1Shh}_{\text{mem}}] - k_{\text{on}}[\text{Shh}][\text{Ptc1}_{\text{mem}}](t, x)
\]
Modeling morphogenetic responses

\[ \frac{\partial [\text{Ptc1Shh}_{\text{mem}}]}{\partial t} = k_{\text{on}}[\text{Shh}][\text{Ptc1}_{\text{mem}}] - k_{\text{off}}[\text{Ptc1Shh}_{\text{mem}}] + k_{\text{Out}}[\text{Ptc1Shh}_{\text{cyt}}] - k_{\text{In}}[\text{Ptc1Shh}_{\text{mem}}] \]

\[ \frac{\partial [\text{Ptc1Shh}_{\text{cyt}}]}{\partial t} = k_{\text{In}}[\text{Ptc1Shh}_{\text{mem}}] - k_{\text{Out}}[\text{Ptc1Shh}_{\text{cyt}}] - k_{\text{Cdeg}}[\text{Ptc1Shh}_{\text{cyt}}]. \]

\[ \frac{\partial [\text{Ptc1}_{\text{mem}}]}{\partial t} = k_{\text{off}}[\text{Ptc1Shh}_{\text{mem}}] - k_{\text{on}}[\text{Shh}][\text{Ptc1}_{\text{mem}}] + k_{\text{cyt}}[\text{Ptc1}_{\text{cyt}}]. \]

\[ \frac{\partial [\text{Ptc1}_{\text{cyt}}]}{\partial t} = -k_{\text{cyt}}[\text{Ptc1}_{\text{cyt}}] + k_{\text{P}} P_{\text{tr}} \left( [\text{Gli1}^{\text{Act}}](t - \tau), [\text{Gli3}^{\text{Act}}](t), [\text{Gli3}^{\text{Rep}}](t) \right) \Phi_{\text{Ptc}} \]

\[ \frac{\partial [\text{Gli1}^{\text{Act}}]}{\partial t} = -k_{\text{deg}}[\text{Gli1}^{\text{Act}}] + k_{G} P_{\text{tr}} \left( [\text{Gli1}^{\text{Act}}](t - \tau), [\text{Gli3}^{\text{Act}}](t), [\text{Gli3}^{\text{Rep}}](t) \right) \Phi_{\text{Ptc}} \]

\[ \frac{\partial [\text{Gli3}^{\text{Act}}]}{\partial t} = \frac{\gamma g 3}{1 + R_{\text{Ptc}}} - [\text{Gli3}^{\text{Act}}]k_{g3r} 1 + R_{\text{Ptc}} - k_{\text{deg}}[\text{Gli3}^{\text{Act}}] \]

\[ \frac{\partial [\text{Gli3}^{\text{Rep}}]}{\partial t} = [\text{Gli3}^{\text{Act}}]k_{g3r} 1 + R_{\text{Ptc}} - k_{\text{deg}}[\text{Gli3}^{\text{Rep}}]. \]

where

\[ \Phi_{\text{Ptc}} = \frac{[\text{Ptc1}_0]}{[\text{Ptc1}_0] + [\text{Ptc1}_{\text{mem}}]}, \quad R_{\text{Ptc}} = \frac{[\text{Ptc1Shh}_{\text{mem}}]}{[\text{Ptc1}_{\text{mem}}]} \]
Going back to biological models

Numerical experiments

No instant spreading
Real wave fronts
Time to respond
Going back to biological models

Numerical experiments

O. Sánchez et al. (UGR)
The repressive activities of neural tube GRN proteins might partly explain the temporal profiles of neural tube GRN genes. Members of each class of regulatory proteins are induced in the ventral neural tube in an order that corresponds to the class I proteins. Class II proteins, conversely, are sequentially induced in the ventral neural tube in an order that corresponds to the level and duration of Shh signaling in ventral neural tube patterning.

Together, the data suggest that the spatio-temporal pattern of gene expression during neural tube development (Fig. 2C, Fig. 6) is a consequence of both Gli activity and the duration of Shh exposure (time). The adaptation of cells to ongoing Shh signaling results in different concentrations of Shh necessary to sustain high levels of signal transduction increases with prior exposure to Shh signaling (Dessaud et al., 2007; Ericson et al., 1997). Thus, Shh genes are repressed is inversely related to their sensitivity to Shh signaling (Dessaud et al., 2007; Ericson et al., 1997). These temporal features of the neural tube GRN are consistent with the importance of cell-autonomous desensitization continues (t1), resulting in distinct temporal profiles of Gli activity in cells arrayed along the DV axis. In addition, the level of GliA declines (GliA, orange). This process is partially responsible for the distinction between Olig2 and Nkx2.2 induction. High levels of Gli activity induce Olig2 expression (cells 1-2, t2). If the levels of signaling in a cell decline prior to this time point, Olig2 expression is consolidated (cell 2, t3). The upregulation of Pax7 (cell 4, t4) as a result of the partial inhibition of the generation of GliR activity, are sufficient to repress Pax7 (cell 4, t5).

Olig2 and Nkx2.2 are expressed more ventrally in the neural tube but are progressively repressed in a ventral-to-dorsal manner. The order in which class I genes are repressed is inversely related to their sensitivity to Shh signaling (t1). As a result, the concentration of Shh necessary to sustain high levels of signal transduction increases with the duration of Shh signaling (Dessaud et al., 2007; Ericson et al., 1997). Thus, Shh genes are repressed is inversely related to their sensitivity to Shh signaling (Dessaud et al., 2007; Ericson et al., 1997).

Fig. 6. A 'temporal adaptation' model for interpreting graded Shh signaling.


J. Calvo, J. Campos, V. Caselles, O. S., J. Soler, Qualitative behaviour for flux-saturated mechanisms: traveling waves, waiting time and smoothing effects. To appear JEMS