Derivation and Approximation of Hyperbolic Models for Chemotaxis

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Ph. Laurencot, **B. Perthame** (*Model derivation*)

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Outline of the talk:

- **How do cells move?**
- **Modelling chemotaxis**
  - **Macroscopic models : parabolic models, hyperbolic models**
  - **Mesoscopic or kinetic models: an intermediate approach between micro and macro models.**
- **Kinetic equations to make the link between the different models:**
  - **Cattaneo system for chemotaxis**
  - **Nonlinear hyperbolic model.**
- **Overview of the well-balanced algorithm**
- **Simulation of hyperbolic models**
- **Conclusions and perspectives**

How do cells move?

Nearly all cells are endowed with devices allowing them to move.
From E. Coli (bacteria)...

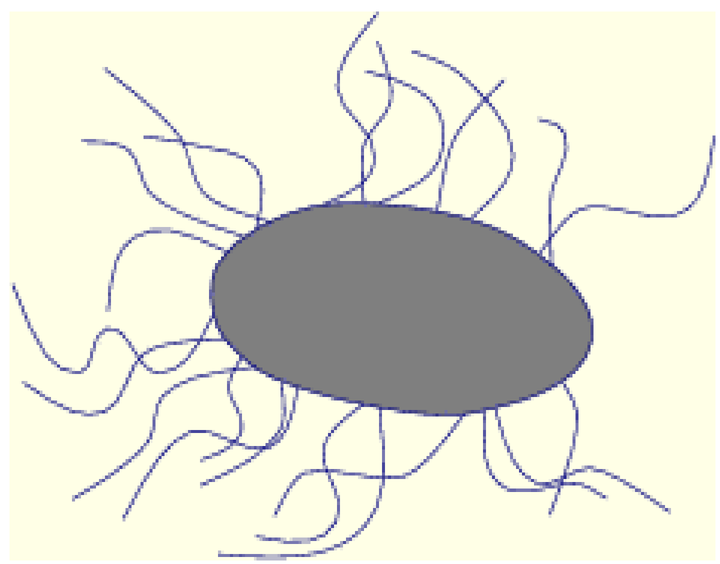


Figure 1: A representation of bacterium Escherichia Coli.

How do cells move?

the Dictyostelium Discoideum (amoeboid cells)

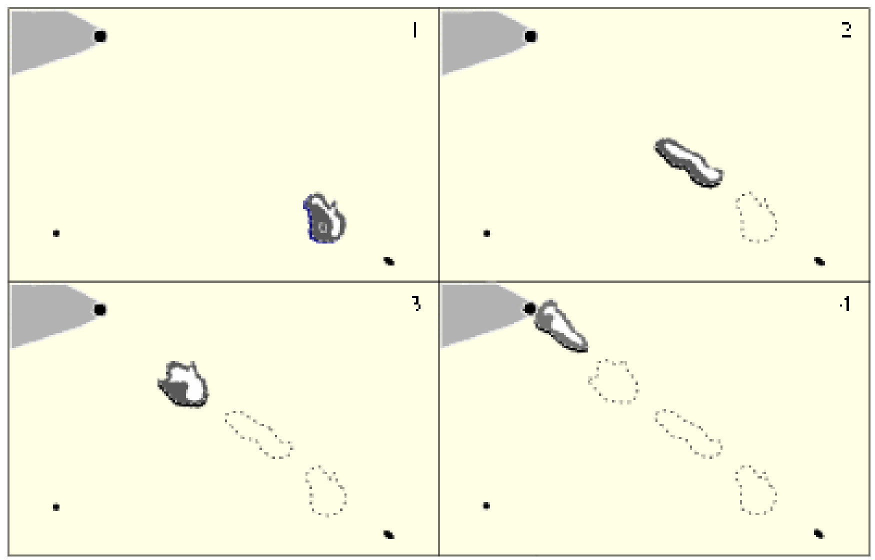
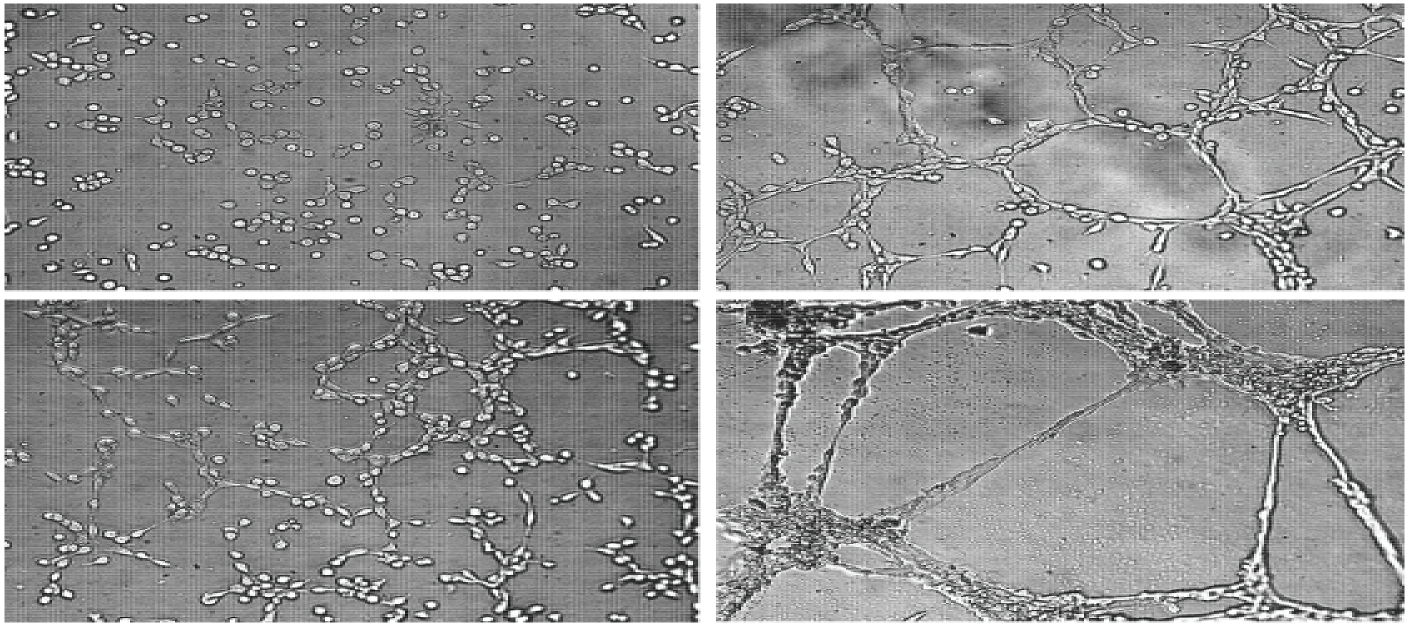
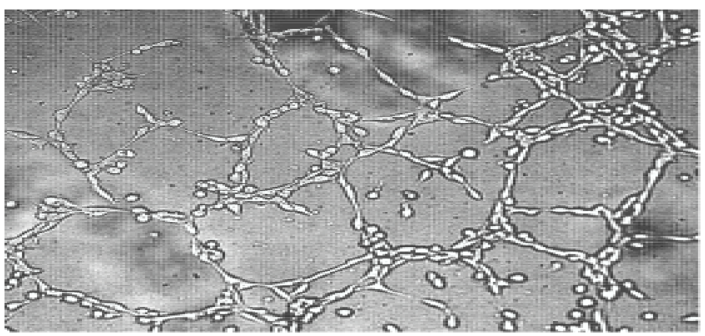


Figure 2: Motion of Dictyostelium in reaction to a chemoattractant emitted at a certain point (upper left corner).





HBMEC SUR MATRIGEL
T=0 ,2H,4H,6H,20H

Introduction

In the simple situation where we only consider cells and a chemical substance (the chemo-attractant), a model for the space and time evolution of the density $n = n(t, x)$ of cells and the chemical concentration $c = c(t, x)$ at time t and position $x \in \Omega \subset \mathbb{R}^d$ has been introduced by Patlak and Keller & Segel and reads

$$\frac{\partial n}{\partial t} - \mathrm{div}(\nabla n - \chi n \nabla c) = 0,$$

coupled with the chemoattractant equation for c

$$\frac{\partial c}{\partial t} - \Delta c = g(n, c).$$

Chemotaxis : mathematical theory for $d = 2$

(i) **for** $\|n_0\|_{L^1}$ **small enough** (8π)**, then there exist weak solutions.**

(ii) **these weak solutions propagate** L^p **regularity.**

(iii) **for** $(\int |x|^2 n_0)$ **is finite, then there is blow-up**[a] **time** T^*

(iv) $(d = 2)$ **with radial symmetry**[b] $n(t) \to 8\,\pi\delta_0(x) + R$**.**

(v) $(d > 2)$ **various (stable or unstable) radial blow-up profiles.**

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[a] Herrero,Medina and Velazquez; Nonlinearity (1997), Dolbeault-Perthame; CRAS (2004)

[b] Nagai; Adv. Math. Appl. Sci. (1995)

Kinetic framework

We start from the transport equation for the distribution function $f = f(t, x, v)$[a]

$$\frac{\partial f}{\partial t} + \frac{1}{\varepsilon} v \cdot \nabla_x f = \frac{1}{\varepsilon^2} \mathcal{T}(c, f).$$

The density of cells n **is given by**

$$n(t, x) = \int_V f(t, x, v) dv.$$

and we assume herein that the turning operator is of the form

$$\mathcal{T}(c, f) = \mathcal{T}_0(f) + \varepsilon \mathcal{T}_1(c, f).$$

It is possible to derive rigorously the PKS model: large time[b]**.**

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[a] Othmer, Dunbar & Alt, JMB (1988), A. Stevens SIAM JAM

[b] Hillen & Othmer SIAM JAM (2000); Chalub *et al.* (Monast.)

Run and tumble process:

We assume that cells move, stop and suddenly change their directions.

$\mathcal{T}(c, f)$ **describes this change of direction:**

$$\mathcal{T}(c, f) = \int_V K(v, v', c)\, f(v')\, dv' - \int_V K(v', v, c)\, dv'\, f(v),$$

where $K(v, v', c)$ **is the rate of change of direction.**

Now, we consider the following scaling:

$$\frac{\partial f}{\partial t} + v \cdot \nabla_x f = \frac{1}{\varepsilon} \mathcal{T}(c, f).$$

Assumptions on the turning operators

- The turning operators $\mathcal{T}_0$ and $\mathcal{T}_1$ preserve the local mass

$$\int_V \mathcal{T}_0(f)\,dv = \int_V \mathcal{T}_1(c,f)\,dv = 0,$$

for any $c \geq 0$.

- In addition, $\mathcal{T}_0$ conserves the population flux, that is,

$$\int_V \mathcal{T}_0(f)\,v\,dv = 0.$$

- For all $n \in [0,+\infty)$ and $u \in \mathbb{R}^d$, there exists a unique function $F_{n,u} \in L^1(V;(1+|v|)dv)$ such that

$$\mathcal{T}_0(F_{n,u}) = 0\,, \quad \int_V F_{n,u}(v)\,dv = n, \quad \int_V F_{n,u}(v)\,v\,dv = n\,u.$$

Hydrodynamic limits

Let f be a solution to the kinetic equation and set

$$n(t,x) = \int_V f(t,x,v)dv, \qquad n(t,x)\,u(t,x) = \int_V f(t,x,v)\,v dv.$$

We introduce f_1 such that

$$\varepsilon\, f_1(t,x,v) = f(t,x,v) - F_{n(t,x),u(t,x)}(v),$$

We integrate the KE over $v \in V$ and use the conservation of mass

$$\frac{\partial n}{\partial t} + \mathbf{div}(n\;u) = 0.$$

Owing to the conservation of momentum by the turning operator $\mathcal{T}_0$

$$\frac{\partial (nu)}{\partial t} + \mathbf{div}\left(\int_V v \otimes v\, F_{n,u}(v)\, dv \right) = \int_V \mathcal{T}_1(c, F_{n,u})\, v dv + O(\varepsilon).$$

Next, we compute

$$\int_V v \otimes v \, F_{n,u} \, dv = \int_V (v-u) \otimes (v-u) \, F_{n,u} \, dv + n \, u \otimes u, = P + n \, u \otimes u$$

where the pressure tensor is given by

$$P(t,x) = \int_V (v - u(t,x)) \otimes (v - u(t,x)) \, F_{n(t,x),u(t,x)} \, dv.$$

Then,

$$\begin{cases} \dfrac{\partial n}{\partial t} + \mathbf{div}(n \, u) = 0, \\ \\ \dfrac{\partial (nu)}{\partial t} + \mathbf{div}(n \, u \otimes u + P) = \displaystyle\int_V (v-u) \, \mathcal{T}_1(c, F_{n,u}) \, dv, \end{cases}$$

Cells are interacting together locally

Then, the turning operator $\mathcal{T}_0$ is like a BGK operator

$$\mathcal{T}_0(f)(v) = \lambda \left(\frac{n}{\vartheta(n)} F\left(\frac{v-u}{\vartheta^{1/2}(n)} \right) - f(v) \right).$$

where

$$\int_V F(v)\,dv = 1, \quad \int_V v\,F(v)\,dv = 0.$$

$$\Rightarrow P = n \int_V (v-u) \otimes (v-u) F\left(\frac{v-u}{\vartheta^{1/2}(n)} \right) dv = n\vartheta(n)\ p,$$

Moreover, let $\mathcal{T}_1$ be such that

$$\mathcal{T}_1(c,f) = \int_V K_1(v,v',\nabla c)\,f(v')\,dv' - \int_V K_1(v',v,\nabla c)\,dv'\,f(v).$$

Nonlinear Hyperbolic Model

From these assumptions on $\mathcal{T}_1$, we get the following nonlinear model

$$\begin{cases} \dfrac{\partial n}{\partial t} + \mathbf{div}(n\, u) = 0, \\ \\ \dfrac{\partial (nu)}{\partial t} + \mathbf{div}(n\, u \otimes u + n\vartheta(n) p) = -\sigma\, n\, u + n\, \vartheta^{3/2}(n)\ \chi' \nabla c, \end{cases}$$

coupled with the concentration equation for c.

- **already obtained by Serini & *al*[a]:**

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[a] Serini et al. EMBO J. (2003)

What about entropy inequality?

For the PKS model $\frac{\partial \tilde{\eta}}{\partial t} + \mathrm{div}\, \tilde{G} \leq 0$, where

$$\tilde{\eta} = n(\log\, n - 1 - c) + \frac{c^2}{2} + \frac{(\nabla c)^2}{2},$$

$$\tilde{G} = (n\, \nabla c - \nabla\, n)\, (\log n - c) - (n - c + \Delta c)\, \nabla c,$$

For the hyperbolic model when $\chi(c) = c$

$$\frac{\partial \eta}{\partial t} + \mathrm{div}\, G = -\sigma n u^2 - \left(\frac{\partial c}{\partial t}\right)^2 \leq 0,$$

$$\eta = n(\log\, n - 1) + \frac{1}{2}\, n\, u^2 - nc + \frac{1}{2}\left(c^2 + \left(\frac{\partial c}{\partial x}\right)^2\right),$$

$$G = n\, u\, (\log n + \frac{1}{2}\, u^2) - nu\, c - \frac{\partial c}{\partial t}\, \frac{\partial c}{\partial x}.$$

Cells are not interacting: Cattaneo model

Since cells are not interacting, the turning operator is linear

$$\mathcal{T}_0(f)(t,x,v) = \int_V \left(T_0(v,v')f(t,x,v') - T_0(v',v)f(t,x,v)\right) dv'.$$

with $V = S^1$

$$T_0(v,v') = (1 + C_0 v \cdot v')$$

The steady state is a linear combination of $1, v_1, ..., v_d$

$$F_{n,u}(v) = \left(n + C_1 n \sum_{i=1}^{d} v_i \, u_i\right),$$

$$\begin{cases} \dfrac{\partial n}{\partial t} + \mathbf{div}(n\, u) = 0, \\ \\ \dfrac{\partial (nu)}{\partial t} + \nabla n = -\sigma n\, u + n\, \nabla c \end{cases}$$

- **another model (Hillen and Othmer[a]) can be also obtained using a similar technique.**
- **linear with respect to $(n, n\, u)$**

[a] Othmer-Dunbar Alt JMB (1988); Hillen M3AS (2002))

Numerical Methods

Write the discrete version of the system in the following form

$$\Delta x_i \frac{d}{dt} U_i(t) + F_{i+1/2} - F_{i-1/2} = \Delta x_i \, S_i \qquad (1)$$

where Δx_i denotes the mesh size $\Delta x_i = x_{i+1/2} - x_{i-1/2}$, and the cell-average vector of discrete unknowns is

$$U_i(t) = \begin{pmatrix} n_i(t) \\ n_i(t)\, u_i(t) \end{pmatrix},$$

and S_i is a "smart" approximation of the source.

A first order well-balanced scheme

For a first order scheme, we get

$$F_{i+1/2} = \mathcal{F}(U_i(t), U_{i+1}(t)),$$

and you want to preserve $\log(n_i) - \chi(c_i) = c^{te}, \quad u_i = 0$. **Then replace**[a] $F_{i+1/2}$ **by**

$$F_{i+1/2} = \mathcal{F}(U^-_{i+1/2}, U^+_{i+1/2}),$$

The source term is discretized as ($\sigma = 0$.)

$$S_i = \frac{1}{\Delta x_i} \begin{pmatrix} 0 \\ n^-_{i+1/2} - n^+_{i-1/2} \end{pmatrix}.$$

This ansatz is motivated by the balancing requirement. Indeed, when steady state holds $\nabla n = n\,\chi'(c)\,\nabla c = n\,e^{-\chi(c)}\nabla(e^{\chi(c)})$.

[a] Audusse et al. SISC (2004), Bouchut Birkauser (2004), Gosse CNR report (2000)

A first order well-balanced scheme

To ensure steady state conservation (with zero population flux), we must choose

$$n^-_{i+1/2} = n^+_{i+1/2}, \quad u_i = 0.$$

From this observation, we take

$$n^-_{i+1/2} = n_i \, e^{\chi_{i+1/2} - \chi(c_i)}$$

and

$$n^+_{i+1/2} = n_{i+1} \, e^{\chi_{i+1/2} - \chi(c_{i+1})}.$$

Here we could choose for instance

$$\chi_{i+1/2} = \max\left(\chi(c_i), \chi(c_{i+1})\right).$$

Theorem: consistency and well-balancing

Consider a numerical flux $\mathcal{F}$ for the homogeneous problem, which preserves nonnegativity of $n_i(t)$. Then, the scheme with periodic boundary conditions satisfies the following

(i) preserves the nonnegativity of $n_i(t)$

(ii) preserves the steady state: $\log(n_i) - \chi(c_i) = c^{te}$

(iii) is consistent with the Hyperbolic system with a source term.

(iv) there is a discrete entropy property.

Flux Splitting Scheme

To approximate the flux function, we use a flux splitting scheme

$$F(U_l, U_r) = F^+(U_l) + F^-(U_r), \quad \text{and } F(U,U) = F(U)$$

In most applications the simple Lax-Friedrichs flux splitting

$$F^{\pm}_{LF}(U) = \frac{1}{2}(F(U) \pm \alpha\, U), \qquad \alpha = \max_{m,U} |\lambda_m(U)|,$$

Local characteristic Lax-Friedrichs flux splitting and get a k-th order approximation of the flux $\hat{F}_{i+1/2}$ via a WENO reconstruction.

$$\hat{F}_{i+1/2} = \hat{F}^+_{i+1/2} + \hat{F}^-_{i+1/2},$$

where

$$\hat{F}^+_{i+1/2} = R_{i+1/2} \left(R^{-1}_{i+1/2} \left(F(U) + \alpha\, U \right) \right)_{i,r}.$$

Steady state preserving scheme

We perform a well-balanced reconstruction not of the density n but of the numerical fluxes $\hat{F}^{\pm}_{i+1/2}$

$$F^{+}_{i+1/2} = \hat{F}^{+}_{i+1/2} \frac{(e^{\chi(c)})_{i+1/2}}{(e^{\chi(c)})_{i,r}}, \quad F^{-}_{i+1/2} = \hat{F}^{-}_{i+1/2} \frac{(e^{\chi(c)})_{i+1/2}}{(e^{\chi(c)})_{i+1,l}},$$

with

$$(e^{\chi(c)})_{i+1/2} = \max\left((e^{\chi(c)})_{i,r}, (e^{\chi(c)})_{i+1,l}\right)$$

and $(e^{\chi(c)})_{i,r}$ is a right hand side k-th order approximation of $e^{\chi(c)}$ on the interval $(x_{i-1/2}, x_{i+1/2})$.

The source term is approximated as

$$S_i = \frac{1}{\Delta x} n_i \, e^{-\chi(c_i)} \left((e^{\chi(c)})_{i+1/2} - (e^{\chi(c)})_{i-1/2}\right).$$

WENO reconstruction properties

1. **The scheme is proven to be uniformly fifth order accurate including at smooth extrema, and this is verified numerically.**

2. **Near discontinuities the scheme behaves very similarly to an ENO scheme, namely the solution has a sharp and non-oscillatory discontinuity transition.**

3. **The numerical flux has the same smoothness dependency on its arguments as that of the physical flux $F(U)$. This helps in a convergence analysis for smooth solutions and in steady state convergence.**

4. **The approximation is self similar. That is, when fully discrete with Runge-Kutta methods, the scheme is invariant when the spatial and time variables are scaled by the same factor.**

What about for high order schemes?

THEOREM. **Consider the Lax-Friedrich flux splitting scheme $\mathcal{F}$ coupled with the k-th order ENO or WENO reconstruction for the homogeneous problem. Then, this scheme with periodic boundary conditions**

(i) preserves the steady state for the ENO reconstruction :

$$\log(n_i) - \chi(c_i) = c^{te},$$

whereas it preserves steady state up to tε for the WENO reconstruction.

(ii) is k-th order accurate with the system Hyperbolic system with source term.

Numerical simulations

- **Justification of the Well Balanced Algorithm in 1d.**
- **Illustration of chemosensitive movement.**
- **Network formation of Endothelial cells and early stage of blood vessel formation.**

Tests 1: one dimensional model

Number of points	Finite Volume		Well-balanced Finite Volume	
	L^1 error	order	L^1 error	order
50	1.21E-04		7.90E-05	
100	5.86E-06	4.37	3.69E-06	4.42
200	4.00E-07	3.87	2.22E-07	4.05
400	2.00E-08	4.32	1.27E-08	4.13

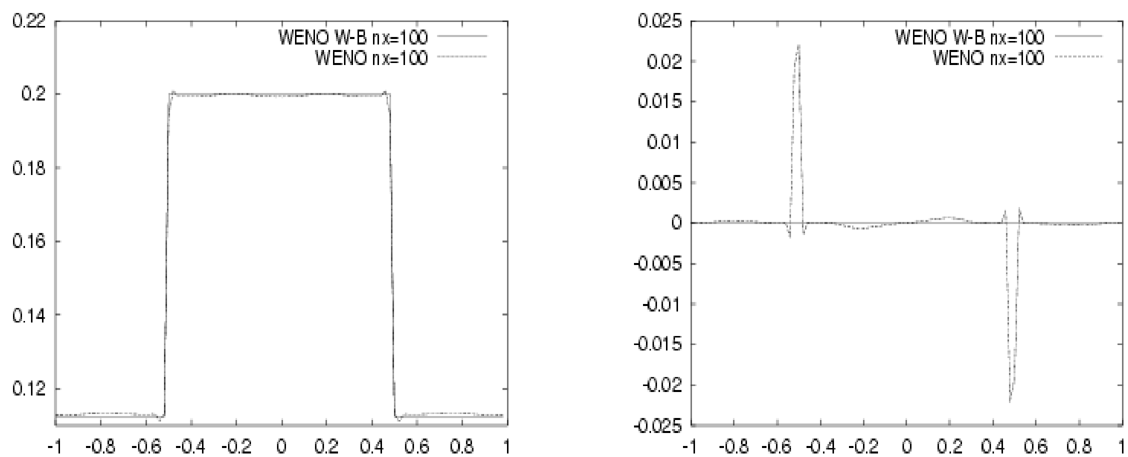
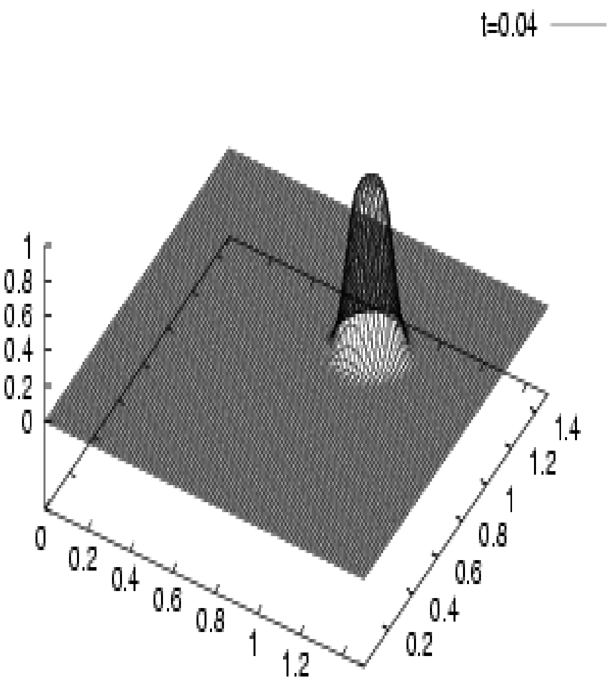


Figure 3: Accuracy test for well-balanced steady state resolution: cell density $n(t,x)$ (left) and population flux $n(t,x)\ u(t,x)$ (right) at time $T = 20$. Solid lines: WENO scheme with the well-balanced reconstruction; dotted lines: WENO schemes with a centered approximation of the source term.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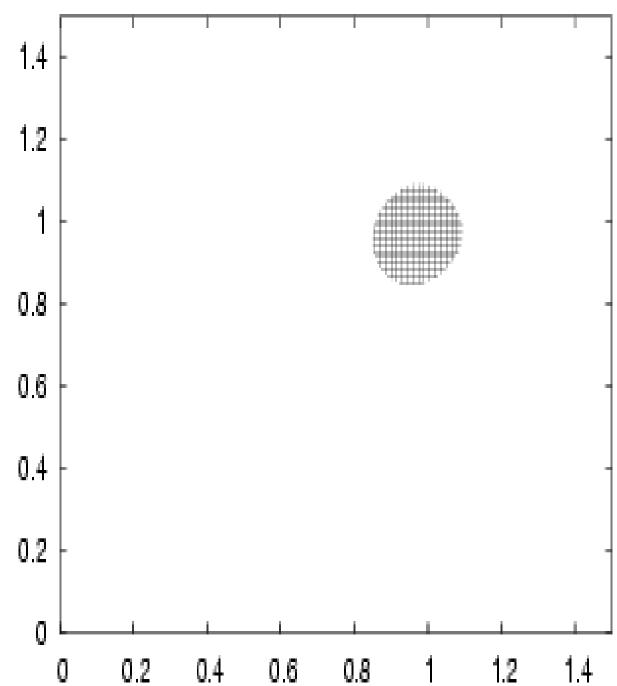
0.4
0.2
0
0
0.2
0.4
0.6
0.8
1
1.2
0.2
0.4
0.6
0.8
1
1.2
1.4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0.8
0.6
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0.2
0
0
0.2
0.4
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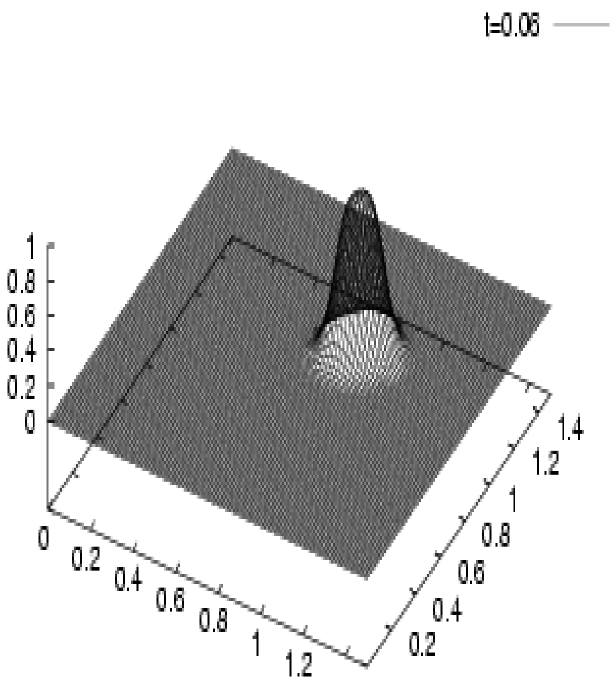
0.8
1
1.2
1.4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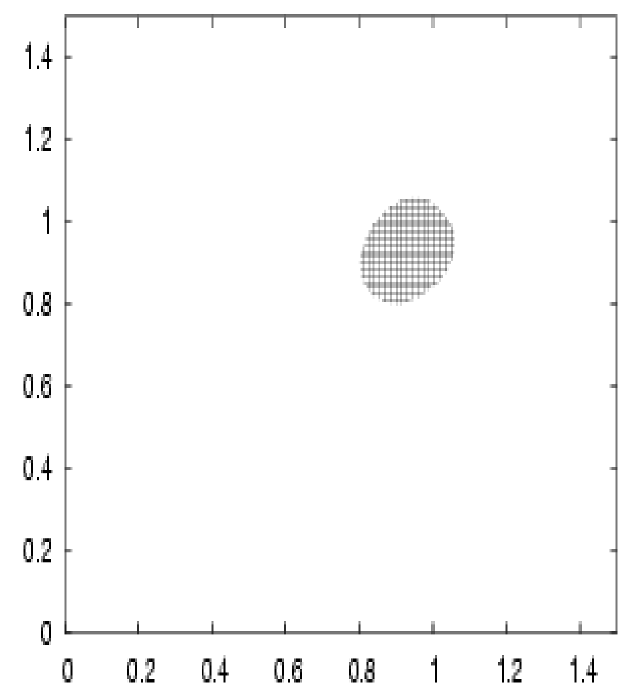
0.8
1
1.2
1.4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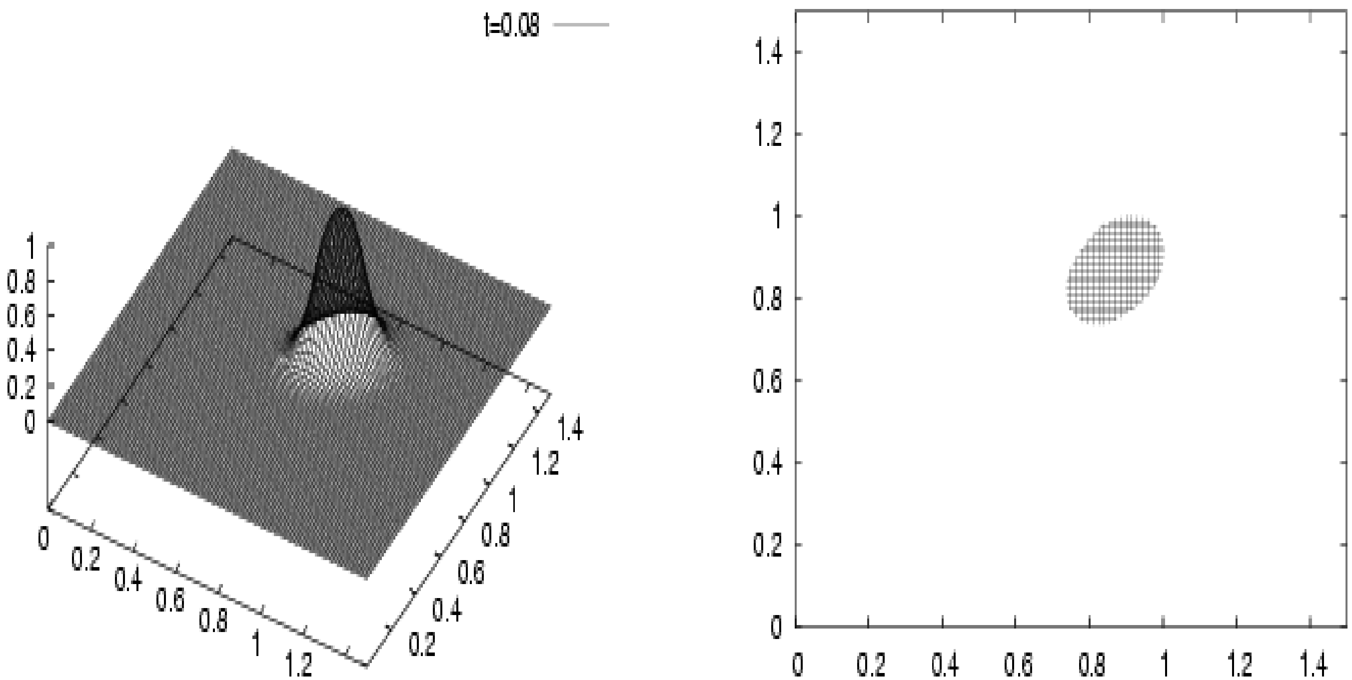
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0.6
0.8
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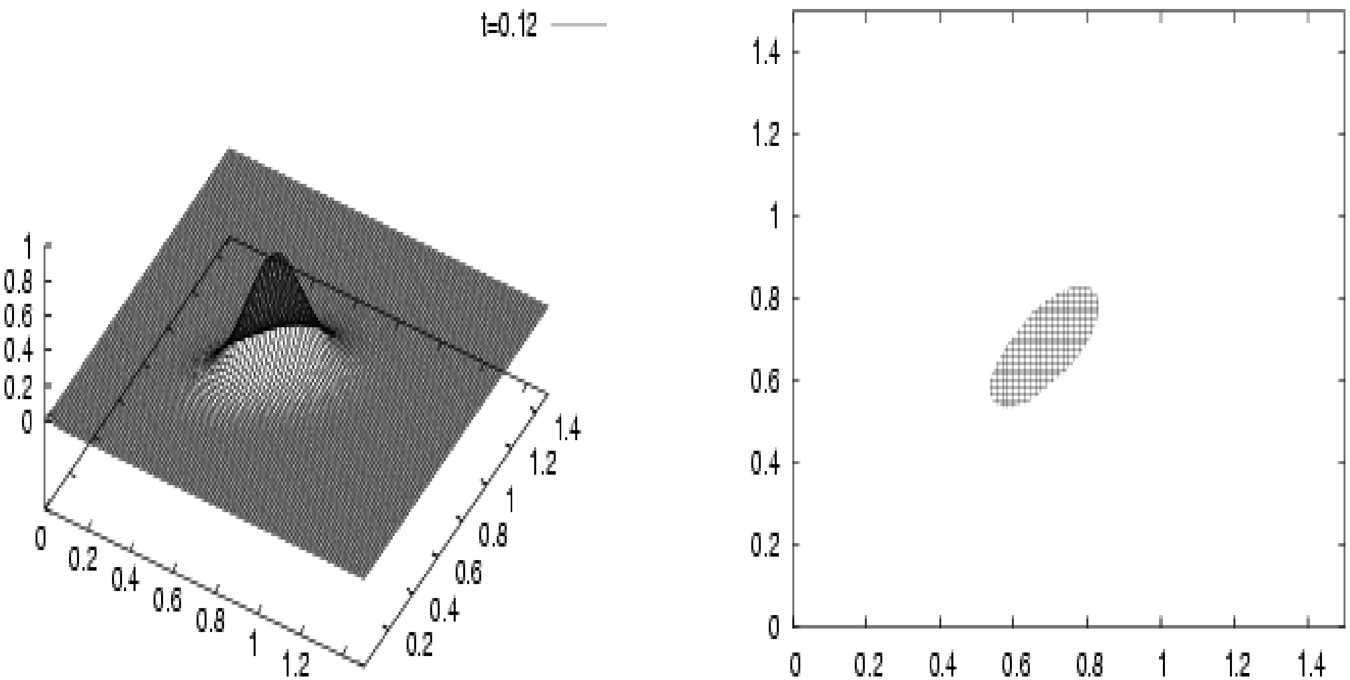
1.2
1.4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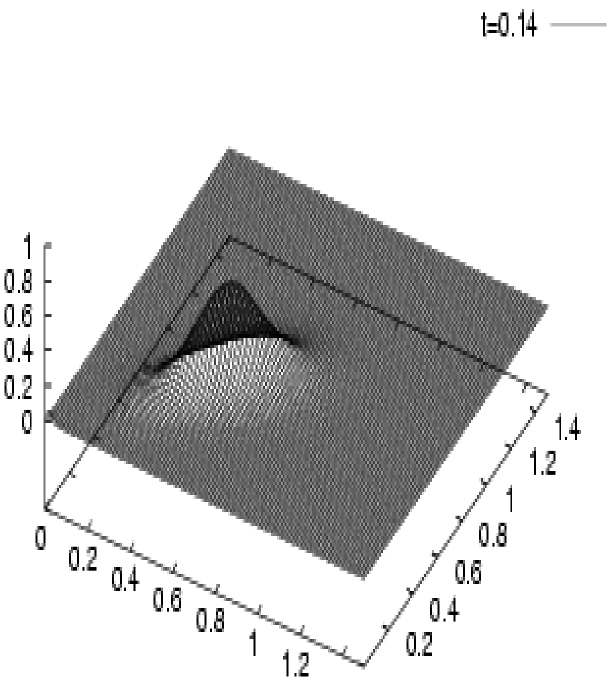
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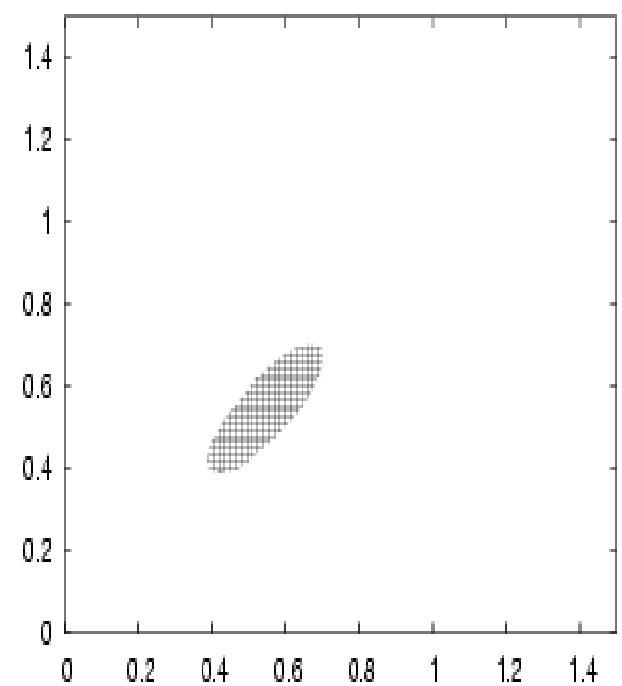
1.4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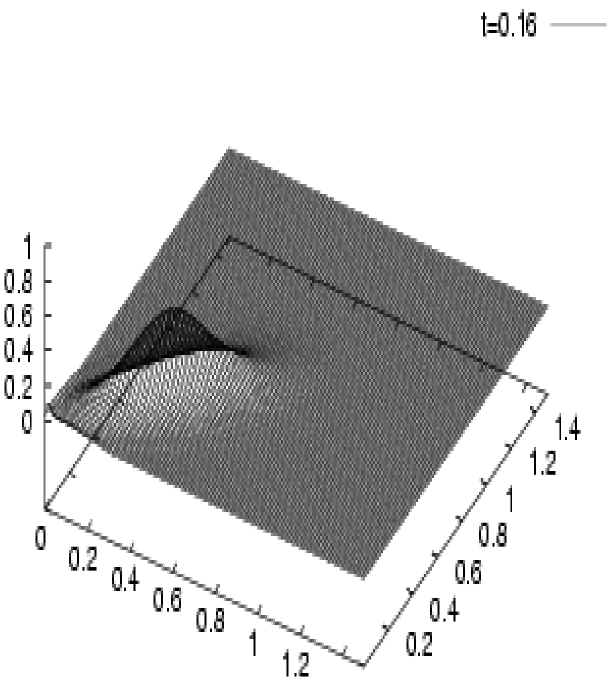
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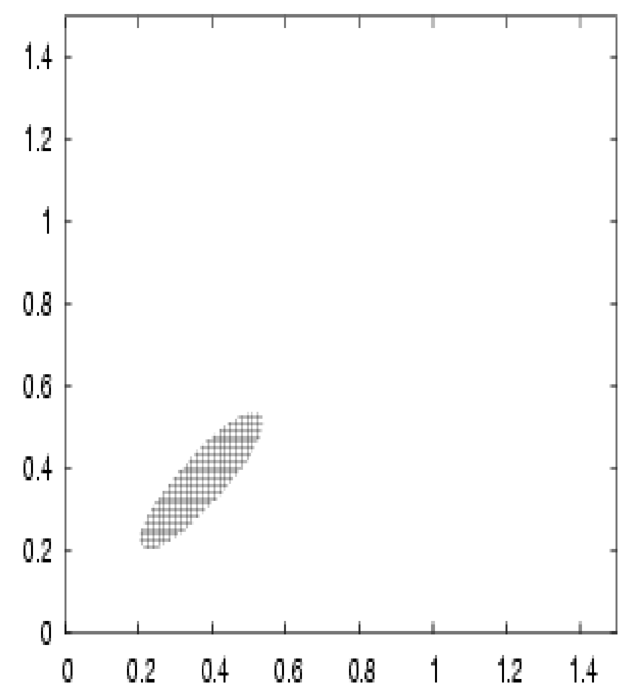
1.4

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1
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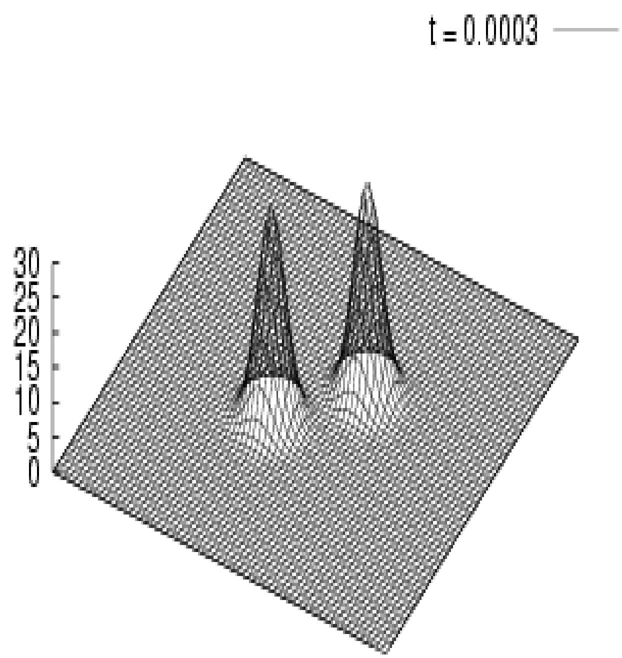
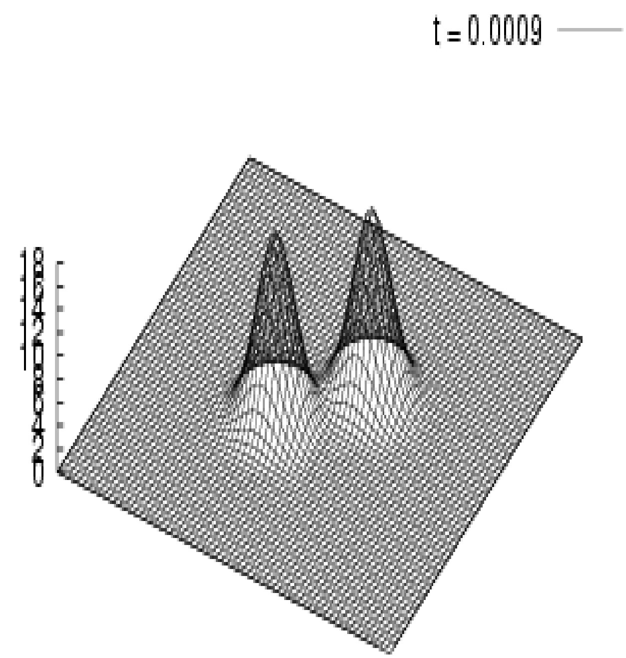
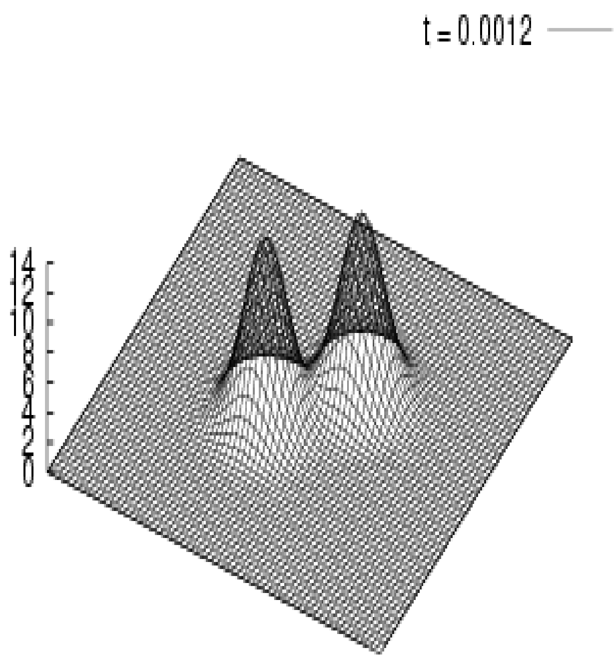
1.4

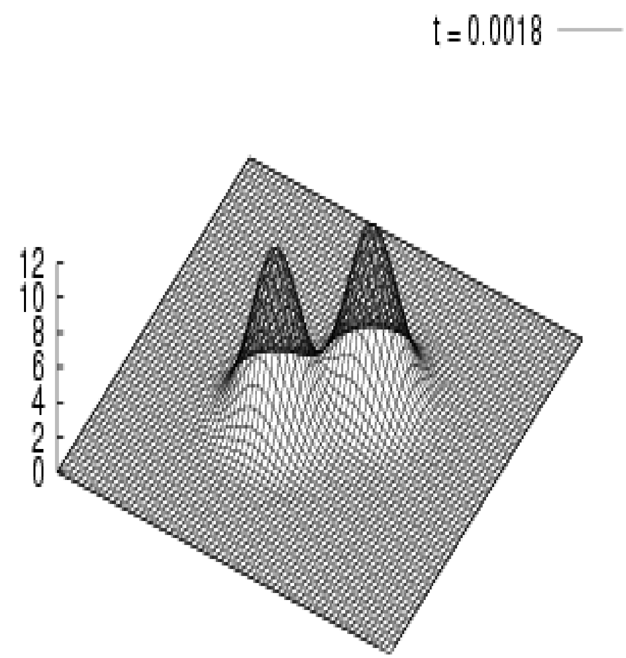
Simulation of the PKS model



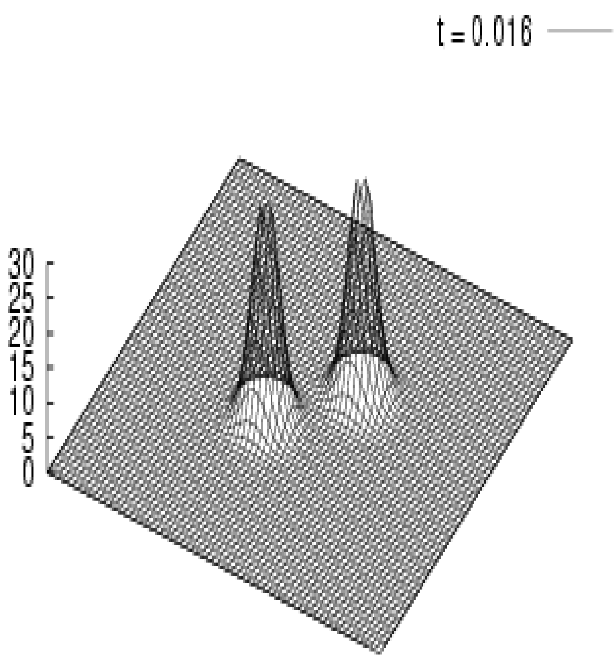


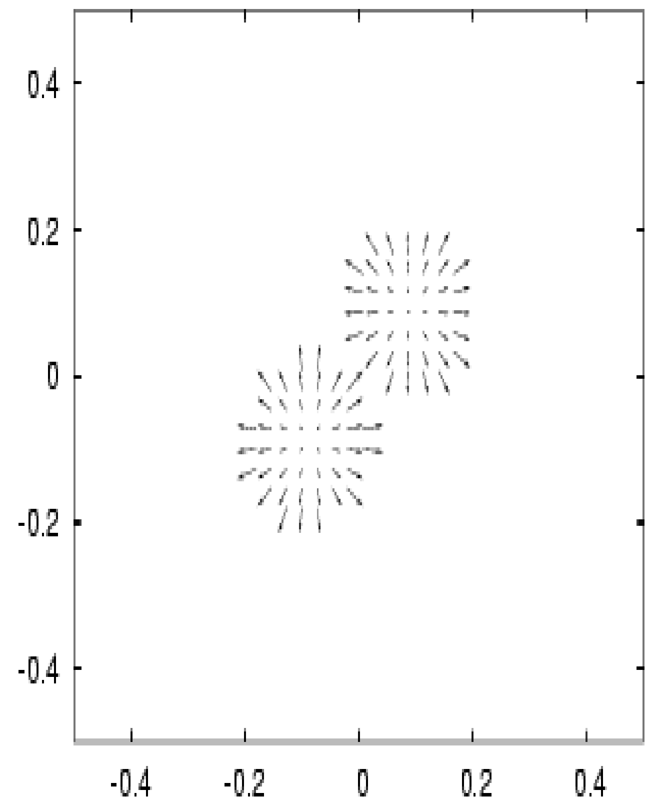
Simulation of the PKS model



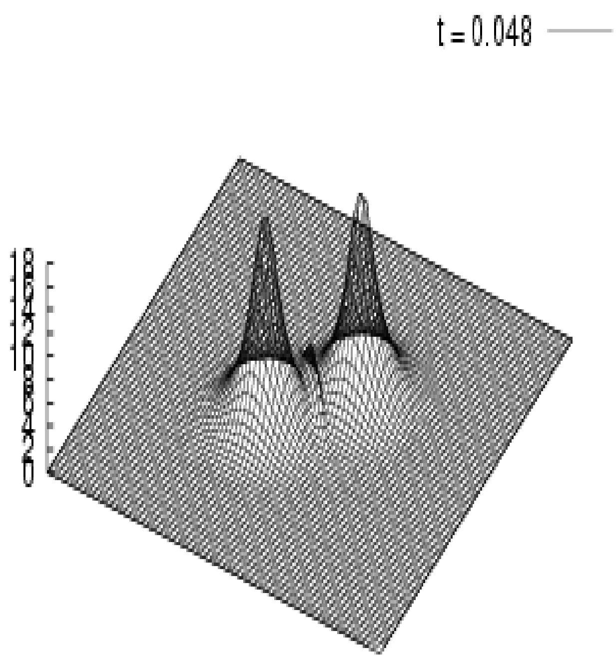


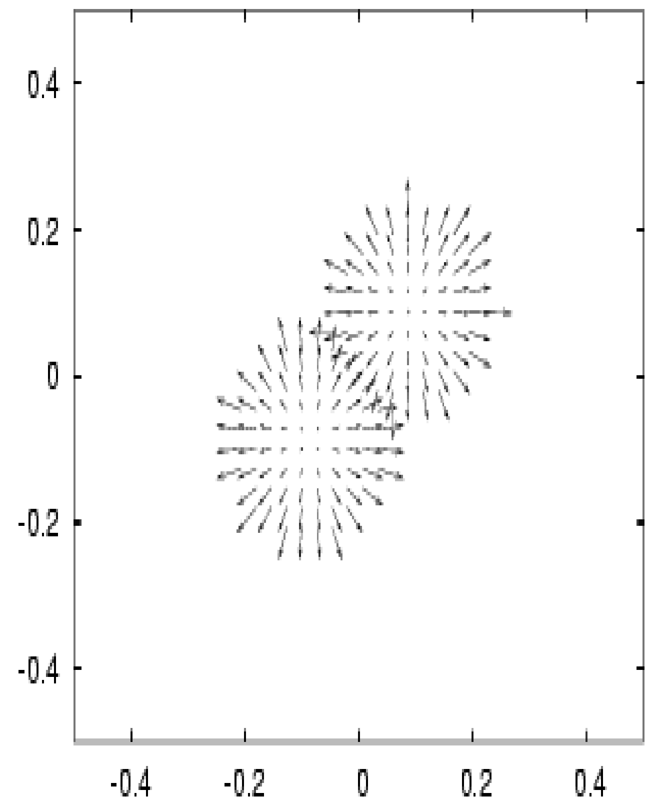
Simulation of the hyperbolic model



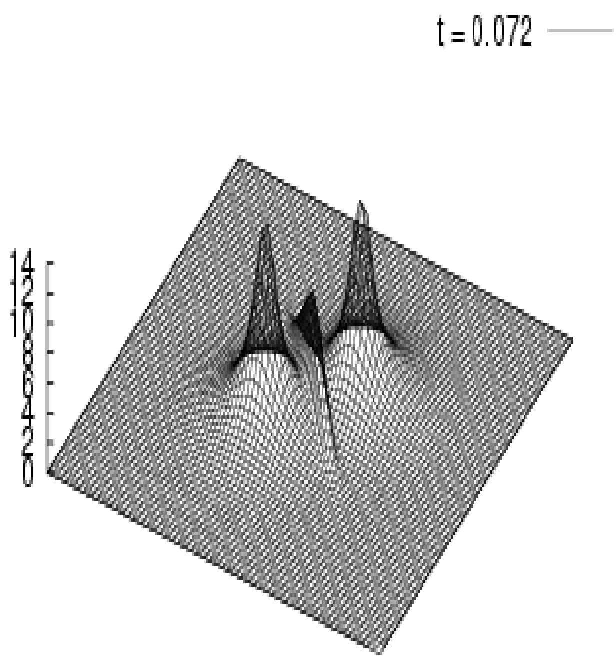


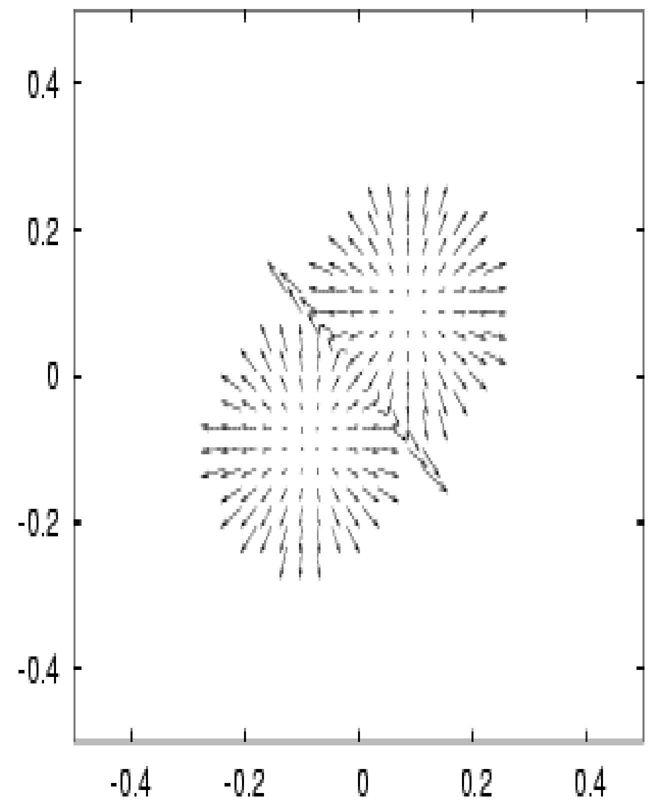
Simulation of the hyperbolic model



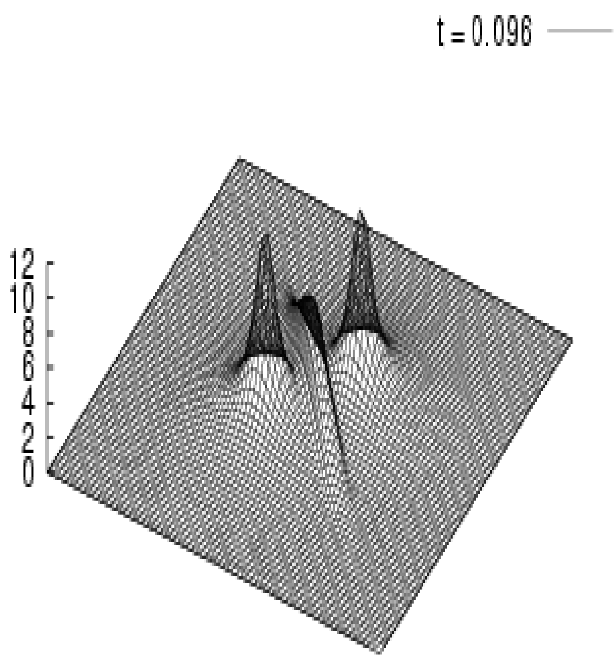


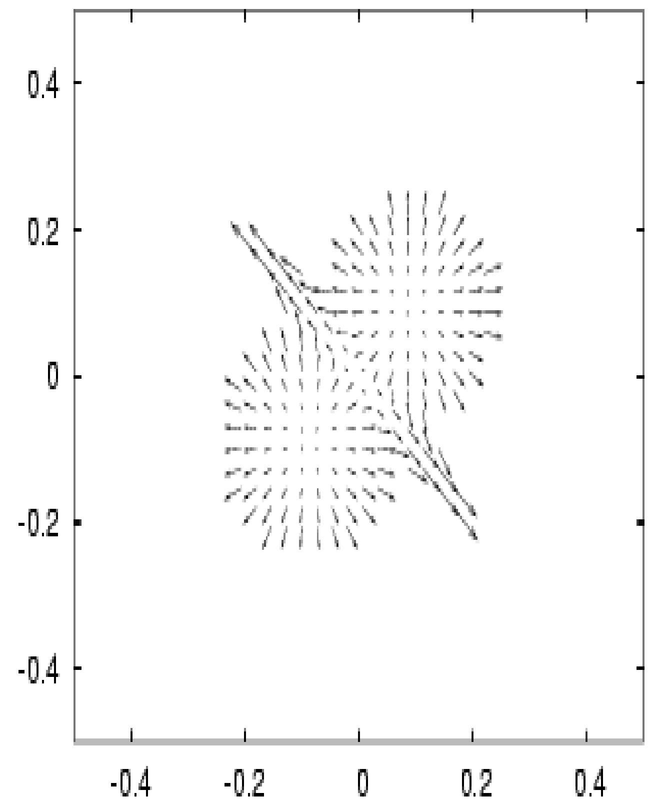
Simulation of the hyperbolic model



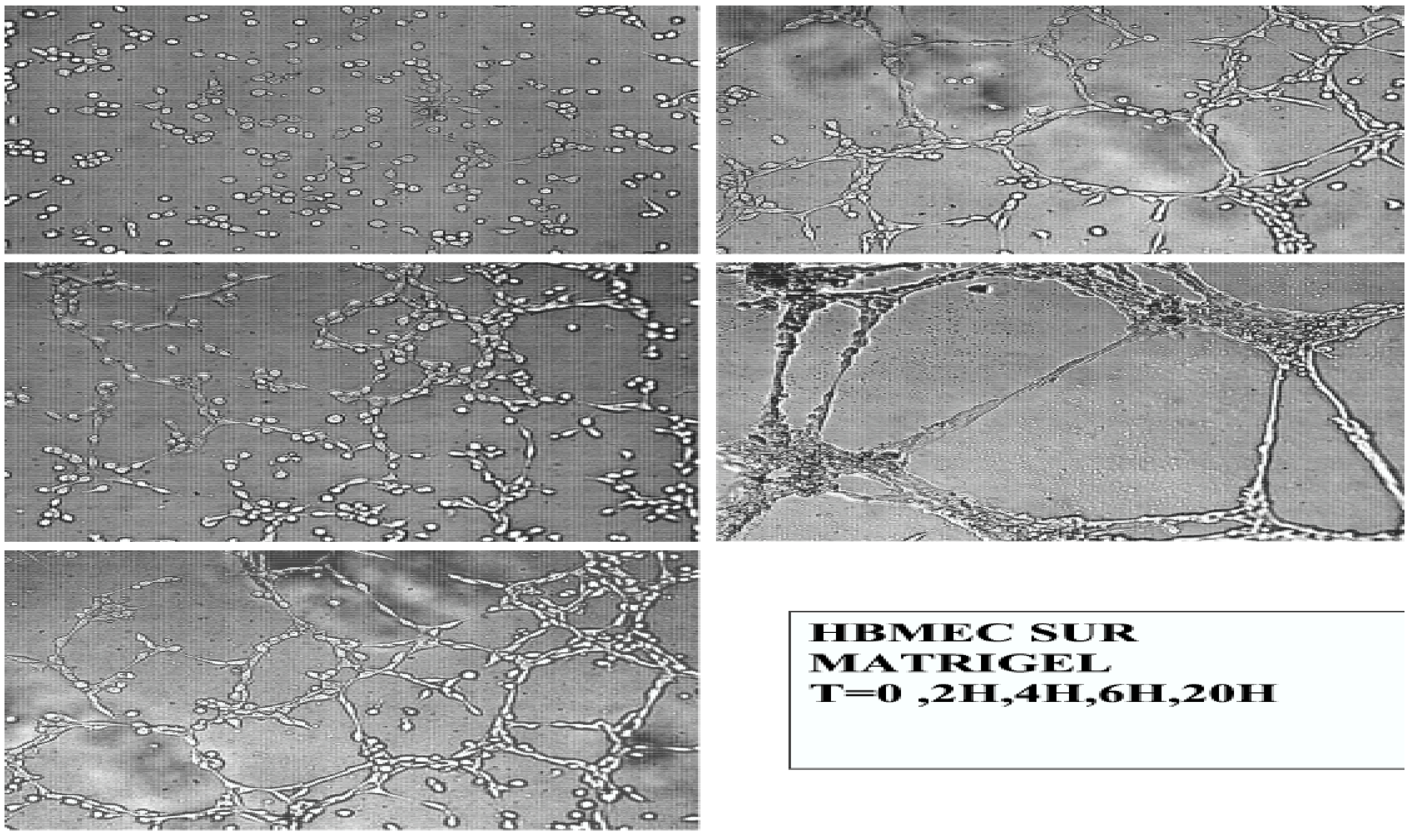


Simulation of the hyperbolic model

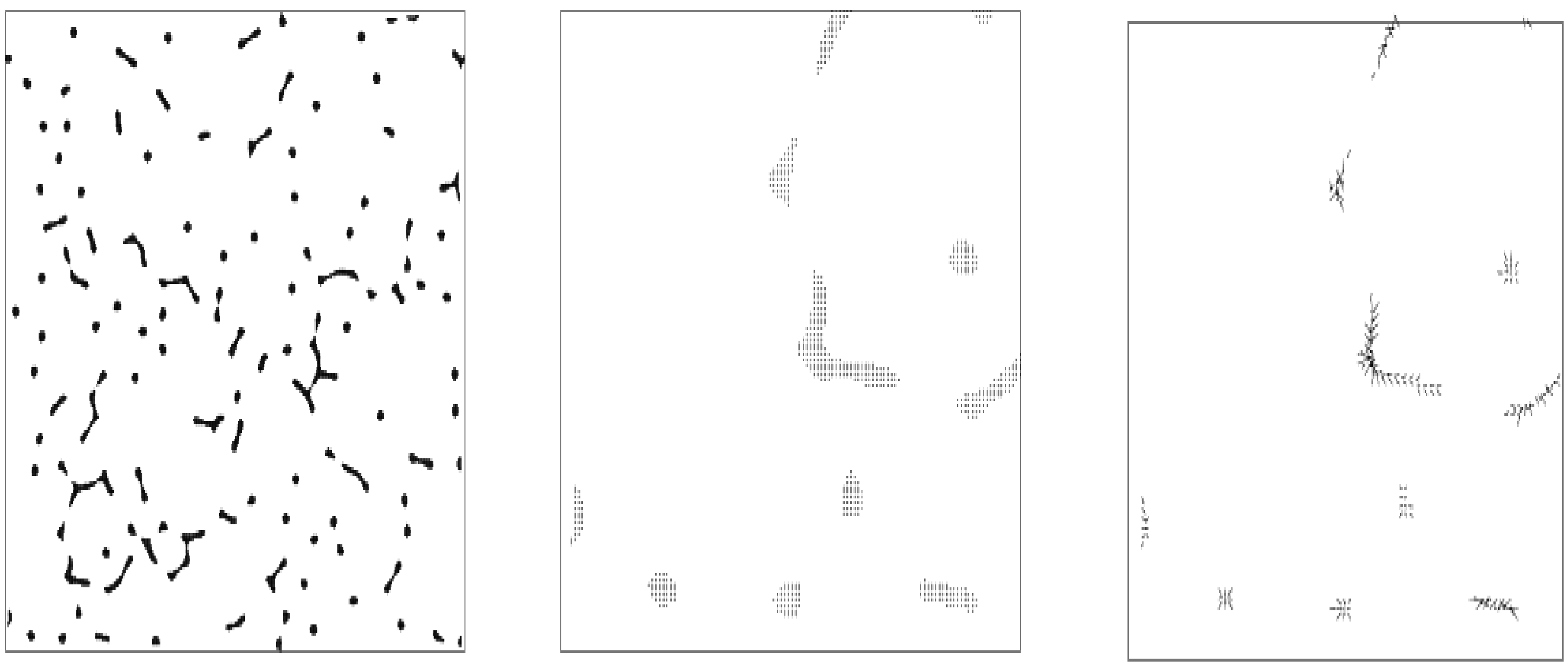


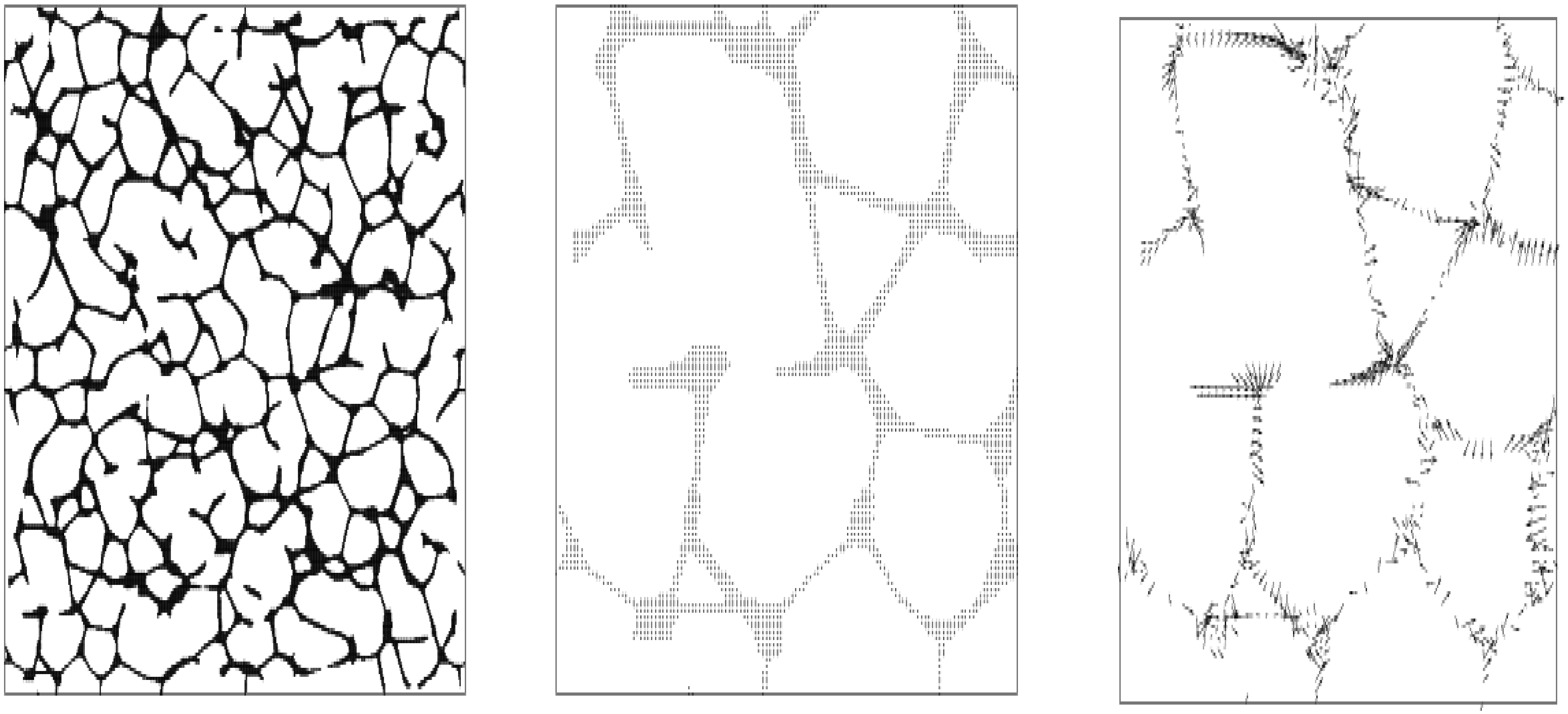


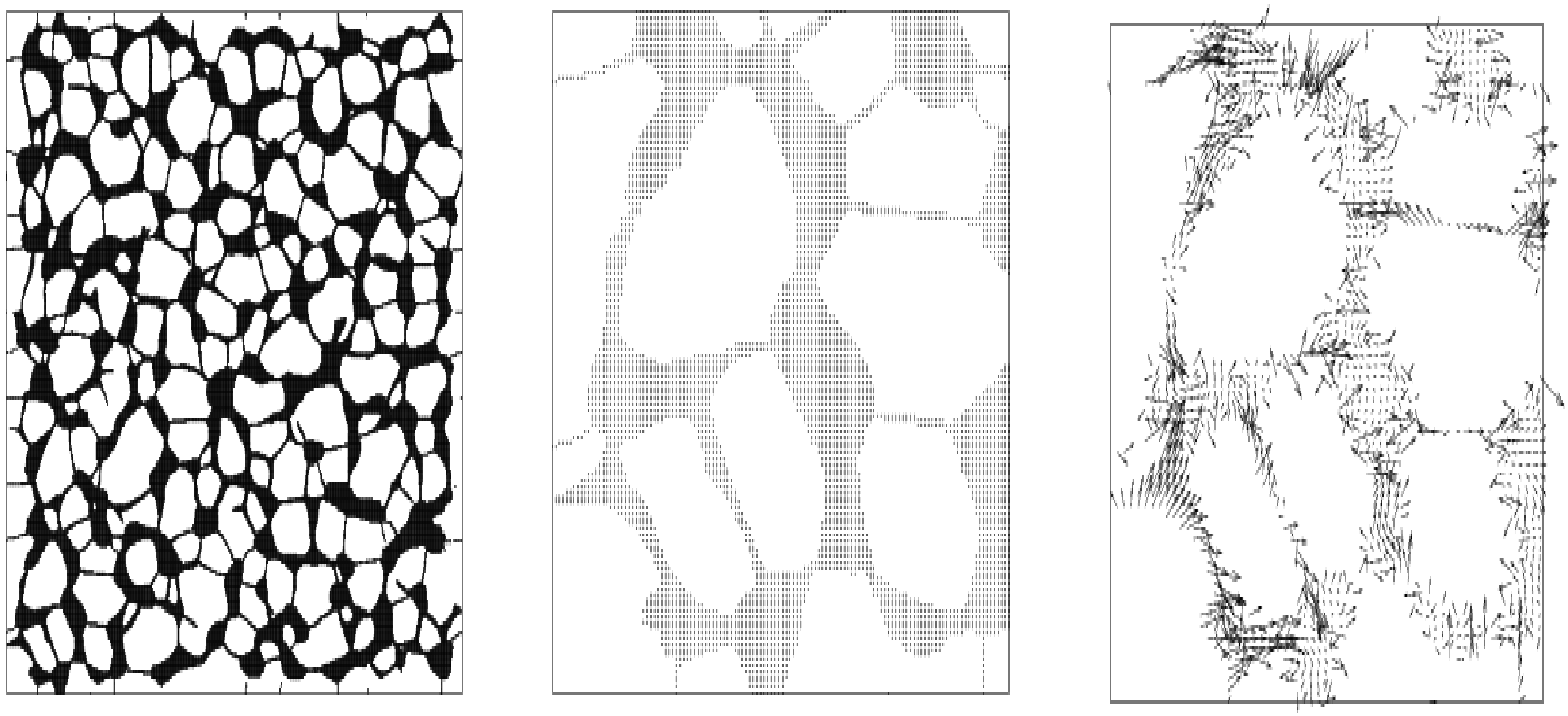
Network formation: early blood vessel formation



Network formation: early blood vessel formation







Conclusion and Discussion

- **nonlinear hyperbolic model arises when we consider interactions between cells.**
- **Blow-up of solution to the hyperbolic system: there is blow-up for Euler-Poisson.**
- **Play with the pressure to prevent blow-up $\equiv$ play with the diffusion on PKS**
- **the kinetic model does not blow-up!!**
- **Construct kinetic models describing cell interactions.**

Basic References

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