Zakład Mechaniki i Fizyki Płynów
IPPT PAN

Modelling cell aggregation in Vasculogenesis

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Presentation schedule

- Literature
- Phenomenological description – chemotaxis and mechanical interaction
- Models introduction and stability results
- Boundedness and blow-up
- Computer simulations
- Final remarks

Main Literature

1. D. Ambrosi, A. Gamba, E. Giraudo, G. Serini, L. Preziosi and F. Bussolino. Burgers' dynamics governs the early stages of vascular network assembly, *EMBO J. Biol*. 22, 1771-1779 (2003).
2. D. Manoussaki, S. R. Lubkin, R. B. Vernon and J. D. Murray. A mechanical model for the formation of vascular networks in vitro, *Acta Biotheoretica* 44, 271-282 (1996).
3. J. D. Murray, **Mathematical biology**, Springer, Berlin, 1993.
4. R. Kowalczyk, A. Gamba and L. Preziosi, On the stability of homogeneous solutions to some aggregation models, *Discrete and Continuous Dynamical Systems Series B*, Volume 4, Number 1, February 2004;
5. R. Kowalczyk, Preventing Blow-up in a Chemotaxis Model, *J. Math. Anal. Appl. 305* (2005) 566-588.

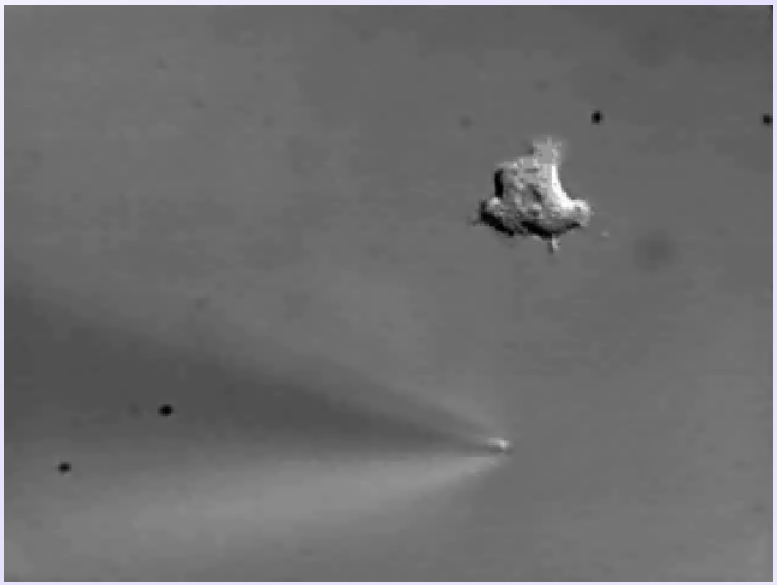
Phenomenological Description

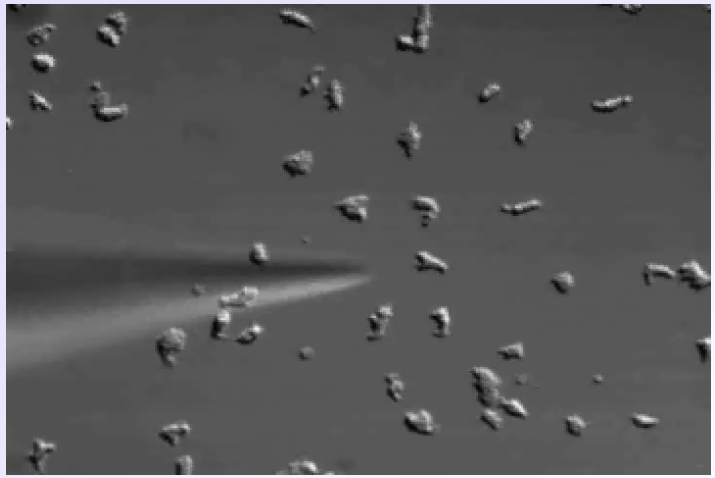
Some of the factors which affect the movement of cells (see *Murray*) :

- Convection
- Diffusion
- Contact inhibition
- Chemotaxis
- Mechanical interaction

Chemotaxis

Chemotaxis of *Dictyostelium* cells to a micropipette emitting the chemoattractant cAMP. The time frame of the movie is approximately 20 minutes. Images were taken every 6 seconds (S. Lee, Firtel lab.)





Chemotaxis

2-D experiment with Human Endothelial Cells (ECs) from bone marrow (see *Ambrosi*):

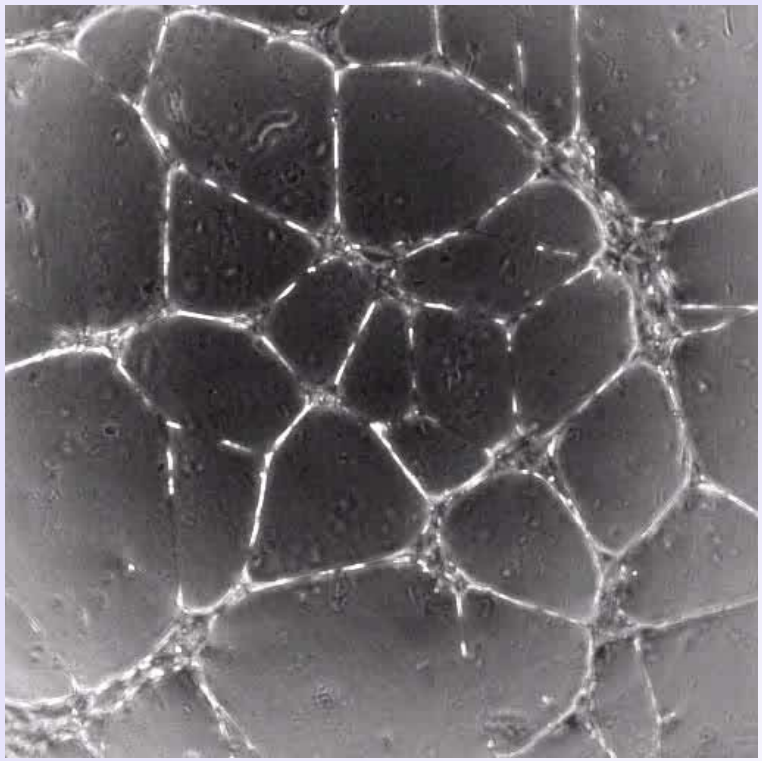
1. (3-6 hours) ECs randomly seeded on the Matrigel surface (the extracellular matrix) start moving in different directions, interact and adhere with their neighbors, and eventually form a continuous multicellular network

2. (6-9hours) The network undergoes a slight deformation

3. Individual cells fold up to form capillary-like tubes along the lines of the previously formed bidimensional network

Chemotaxis

Types of capillary-like network formed by plating different number of cells n_0 in a Petri dish covered with a substratum favoring the growth of a vascular-type network (movie provided by F. Bussolino and G. Serini from IRCC - Institute for Cancer Research & Treatment)



Persistance and Chemotaxis Model (PaCh)

$$\begin{cases} \dfrac{\partial n}{\partial t} + \nabla \cdot (n\mathbf{v}) = 0\,, \\ \dfrac{\partial \mathbf{v}}{\partial t} + \mathbf{v} \cdot \nabla \mathbf{v} = \mu \nabla c - \beta \mathbf{v} + \gamma \nabla^2 \mathbf{v} - \nabla g(n)\,, \\ \cancel{\dfrac{\partial c}{\partial t}} = D\nabla^2 c + an - \tau^{-1} c\,. \end{cases}$$

n - density distribution of ECs,

$\mathbf{v}$ - velocity of ECs,

c - density of soluble molecules.

μ – the measure of the strength of cell response,

β – drag coefficient,

γ – viscosity coefficient,

D – diffusion coefficient of chemical factors,

a – rate of release,

τ – characteristic degradation time of soluble mediators,

$g(n)$ – the cell pressure.

We assume that the pressure function is a convex C^1 function, such that $g(n) = 0$ for $n_0 < n_S$ and $g(n)$ increases to infinity as n_0 goes to $n_M > n_S$.

Mechanical interaction with ECM

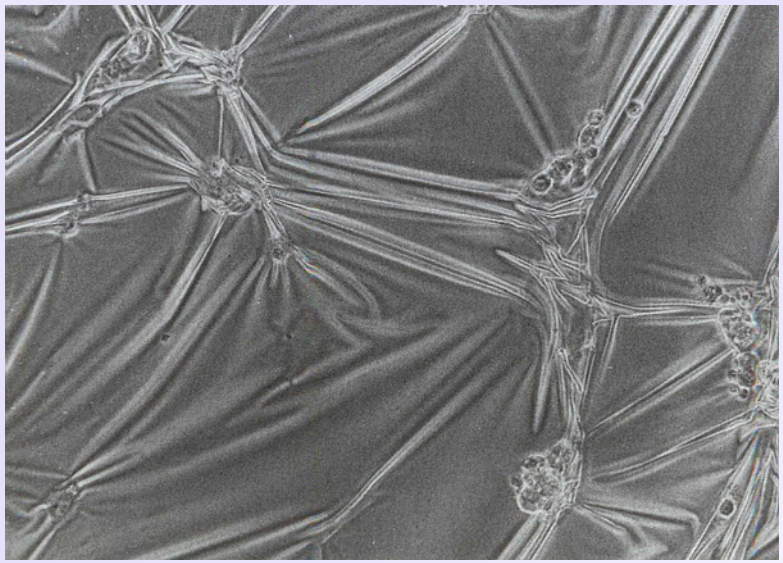
The formation of pattern (Bovine Aortic Endothelial Cells) takes about 24 hours.

1. Cells adhere to the matrix, start pulling in it and form aggregates;
2. The matrix accumulates underneath the cells;
3. The matrix condenses along the tension lines and forms lines of aligned matrix fibers;
4. Cells elongate parallel to the fibers and start moving along them;
5. The matrix lines filled with the cells form the chords, which join the aggregates and define the polygons that cover the entire dish;

The ECM properties influence the formation of stuctures (thickness, stiffness)

Mechanical interaction with ECM

Mesenchymal cells on an elastic substratum. The strong tractions generated deform the substratum and create compression and tension wrinkles (photo by A. K. Harris, see [Murray]).



Mechanical Model (Mech)

$$\begin{cases} \dfrac{\partial \rho}{\partial t} + \nabla \cdot (\rho \mathbf{v}) = 0\,, \\ \dfrac{\partial n}{\partial t} + \nabla \cdot (n\mathbf{v}) = D\nabla^2 n\,, \\ \dfrac{s}{h(\rho)}\mathbf{v} = \nabla \cdot \mathbf{T} + f'(n)\nabla n\,, \\ \Lambda \dfrac{\partial \mathbf{T}}{\partial t} + \mathbf{T} = \dfrac{E}{1+\nu}\left[\mu_1 \dfrac{\partial \epsilon}{\partial t} + \mu_2 \dfrac{\partial \theta}{\partial t}\mathbf{I} + \epsilon + \dfrac{\nu}{1-2\nu}\theta \mathbf{I}\right]. \end{cases}$$

ρ – ECM density,
$\mathbf{v}$ – ECM velocity,
n – density of EC,
$\mathbf{T}$ – stress tensor.

D – diffusion coefficient of ECs,
s – drag coefficient,
$h(\rho)$ – thickness function for ECM,

Λ – relaxation time,
E, ν – Young's modulus and Poisson ratio,
μ_1, μ_2 – shear and bulk retardation times,
ε, θ – strain and dilation,

$f(n)$ – traction function,

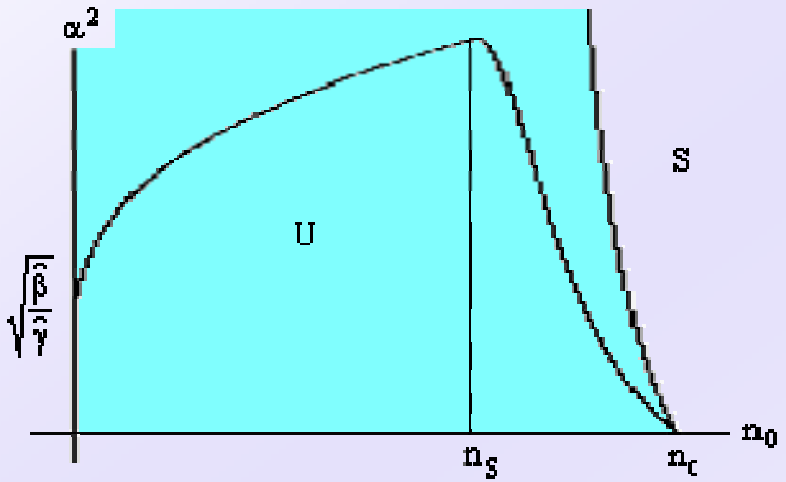
$$f(n) = \tau \frac{n}{1 + an^2}.$$

Here: τ is the traction parameter
a is the crowding parameter

Liner stability results

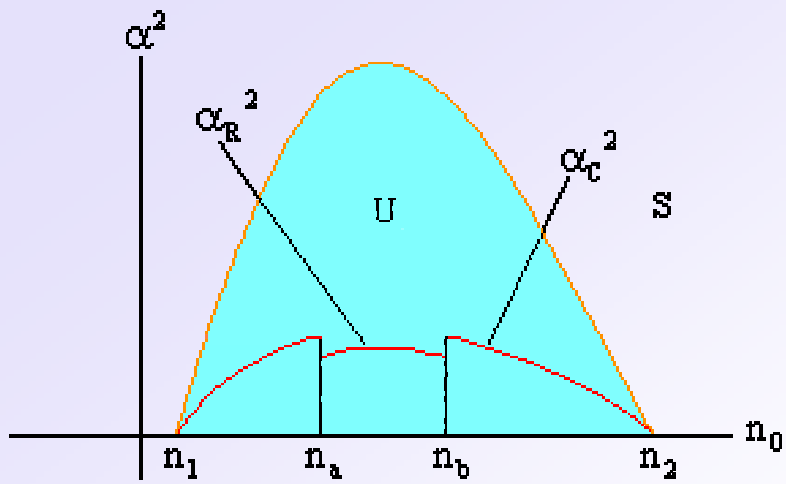
PaCh Model

$$(n, \mathbf{v}, c) = (n_0, \mathbf{0}, a\tau n_0)$$



Mech Model

$$(\rho, n, \mathbf{u}, \mathbf{T}) = (\rho_0, n_0, \mathbf{0}, \mathbf{0})$$



Here: n_C is such that $g'(n_C) = \mu a \tau$.

α^2 - wave number.

Aggregation Model

1. We neglect the persistence in the momentum equation,

2. The diffusion of chemicals is much faster that the pattern formation.

$$\frac{\partial n}{\partial t} + \nabla \cdot (n\mathbf{v}) = 0,$$

$$\frac{\partial \mathbf{v}}{\partial t} + \mathbf{v} \cdot \nabla \mathbf{v} = \mu \nabla c - \beta \mathbf{v} - \nabla g(n),$$

$$\frac{\partial c}{\partial t} = D\nabla^2 c + an - \tau^{-1} c.$$

The aggregation model follows:

$$\begin{cases} \dfrac{\partial n}{\partial t} = \nabla \cdot \big(nh'(n)\nabla n \; - \; \chi n \nabla c\big), \\ 0 = \nabla^2 c + \alpha\, n - \gamma\, c, \\ \nabla n \cdot \mathbf{N} = \nabla c \cdot \mathbf{N} = 0 \quad \text{in} \quad [0,T) \times \partial\Omega, \\ n(0,\mathbf{x}) = n_0(\mathbf{x}) \quad \text{in} \quad \Omega, \end{cases}$$

where:

$$\chi = \tfrac{\mu}{\beta},\; h(n) = \tfrac{1}{\beta} g(n);$$
$$n_0(\mathbf{x}) \geq 0;$$

Aggregation Model

Simple properties:

- The solution (*n,c*) is nonnegative;
- The mass of cells is conserved, i.e.

$$\frac{\gamma}{\alpha}||c(t)||_{L^1(\Omega)} = ||n(t)||_{L^1(\Omega)} = ||n_0||_{L^1(\Omega)} \stackrel{\text{def}}{=} 2\pi\theta;$$

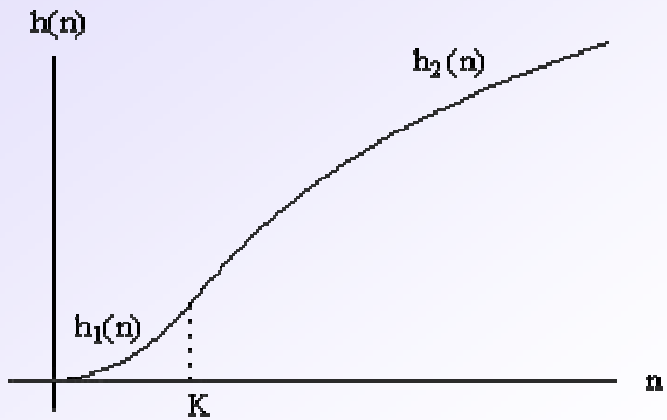
- A finite time blow-up of a radially symmetric solution is possible if $h'(n) \geq 0$ for all $n > 0$ and

$$\int_0^n \Big(uh'(u) - M \Big)\, du \leq 0, \quad M < \frac{\alpha\chi\theta}{4}.$$

e.g.

$$h(n) = \begin{cases} h_1(n) & \text{if } n \leq K, \\ h_1(K) + h_2(n) & \text{if } n > K. \end{cases}$$

$$h_1(n) = \frac{a}{2K^2} n^2, \quad K > 0$$
$$h_2(n) = a \log \frac{n}{K}, \quad a < \frac{\alpha\chi\theta}{4}.$$



Aggregation Model

Theorem 1.
Let Ω be an open, bounded domain in $\mathbf{R}^2$ with $C^{1,1}$ boundary.
Assume that there exists $N > 0$, such that

$$nh'(n) \geq \frac{9\pi}{2} C_\Omega \alpha \chi \theta + \delta \quad \forall n \geq N$$

for some arbitrarily small $\delta > 0$ and C_Ω being a constant depending on Ω.
Then for any finite T the solution to Aggregation Model is uniformly bounded in $[0,T]$.

Examples:

- $h(n)$ should grow sufficiently fast, e.g. $h'(n) \geq \epsilon$ for some $\varepsilon > 0$ and $n \geq N$.
- $h(n)$ can be a concave function, e.g. $h(n) = C_1 n^\delta + C_2$ for $0 < \delta < 1$ and $n \geq N$.

Aggregation Model

Theorem 2.
Let Ω be an open, bounded domain in $\mathbf{R}^d$ $(d \geq 2)$ with $C^{1,1}$ boundary.

- Assume that there exists $\varepsilon > 0$ and $n_\varepsilon > 0$, such that $nh'(n) \geq \varepsilon$ for all $n \geq n_\varepsilon$
- Assume also that

$$h(n) \geq p\eta n^{p-1}$$

for some $p > d$, $\eta > 0$ and every $n \geq n_\varepsilon$.

Then for any $T > 0$ the solution to Aggregation Model is uniformly bounded in $[0,T]$. Moreover, the constant M does not depend on T, i.e

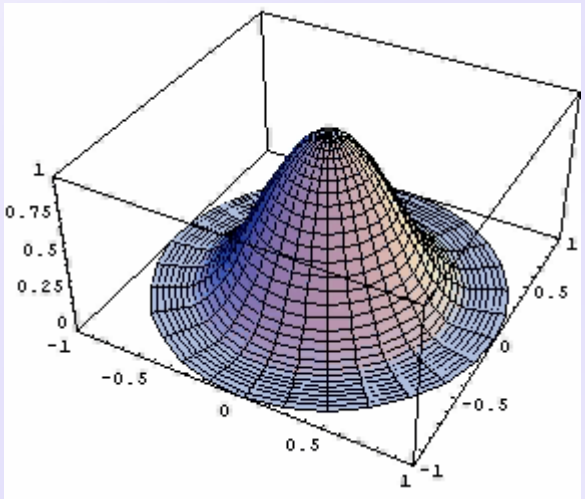
$$\exists_{0<M<+\infty} \quad \forall_{t \leq T} \quad ||n(t)||_{L^\infty} \leq M.$$

Computer Simulations

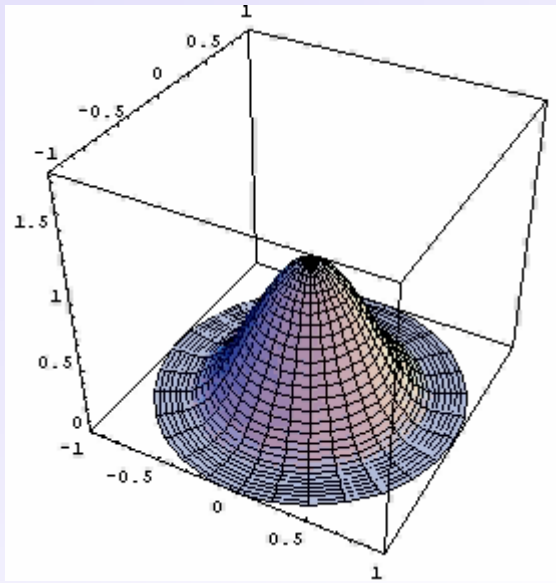
Consider $n(t,\mathbf{x}) = n(t,r)$, where $0 \le r \le R$. The initial function $n_0(r) = n_0(0,\mathbf{x})$ is a rescaled Cosine function, such that it has a compact support in $[0,R]$ and $n_0(0) = 1$.

1. Keller-Segel Model

$$h(n) = \log n,$$
$$\chi = 1.$$



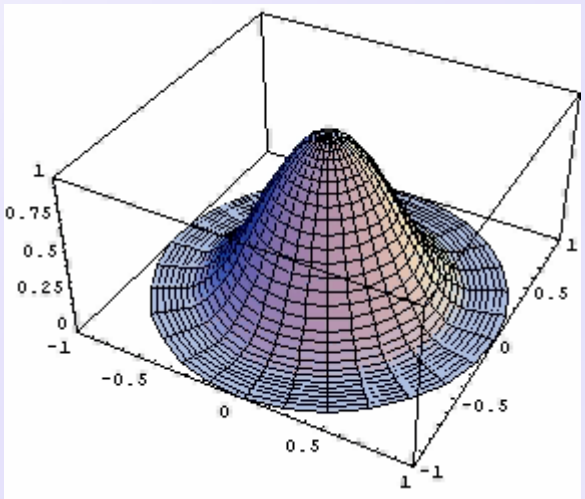
$$h(n) = \log n,$$
$$\chi = 45.$$



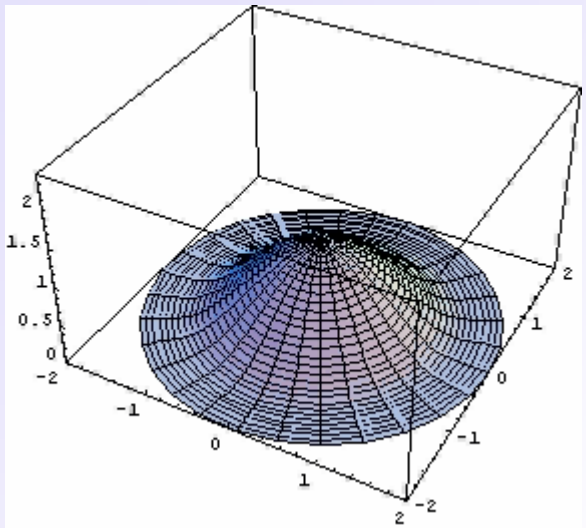
Computer Simulations

2. Porous medium.

$$h(n) = 2n,$$
$$\chi = 1,$$
$$R = 1.$$



$$h(n) = 2n,$$
$$\chi = 20,$$
$$R = 2.$$

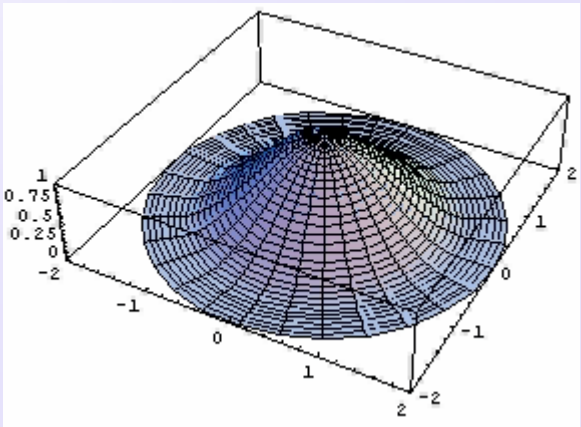


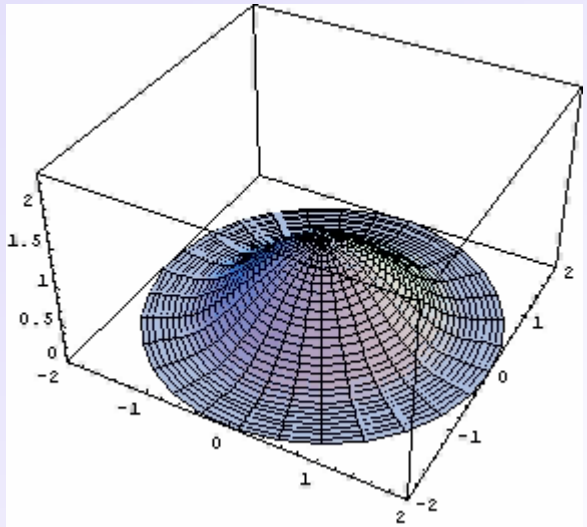
Computer Simulations

3. Convex function.

$$h(n) = \begin{cases} (n-0.5)^2 & for \;\; n > 0.5 \\ 0 & for \;\; n \leq 0.5 \end{cases}$$

$$h(n) = \begin{cases} (n-2)^2 & for \;\; n > 2 \\ 0 & for \;\; n \leq 2 \end{cases}$$





Final Remarks

PaCh Model succesfully describes the early, migration dominated stages of network formation observed in experiments performed with human ECs.

Mech Model describes a viscoelastic regime which is not accessible by PaCh Model, and which becomes relevant as soon as the early migration stage ends and the network structure is formed.

If the pressure function grows fast enough for large cell densities then no blow-up of solutions in a finite time is possible.

If the pressure function grows fast enough and takes large enough values for large cell densities then no blow-up of solutions in any time is possible.

If the pressure function grows not faster than a logarithm then the blow-up of solutions in a finite time can occur.

Thank You.