Modeling an angiogenesis treatment after a myocardial infarction

- using the discontinuous Galerkin method -

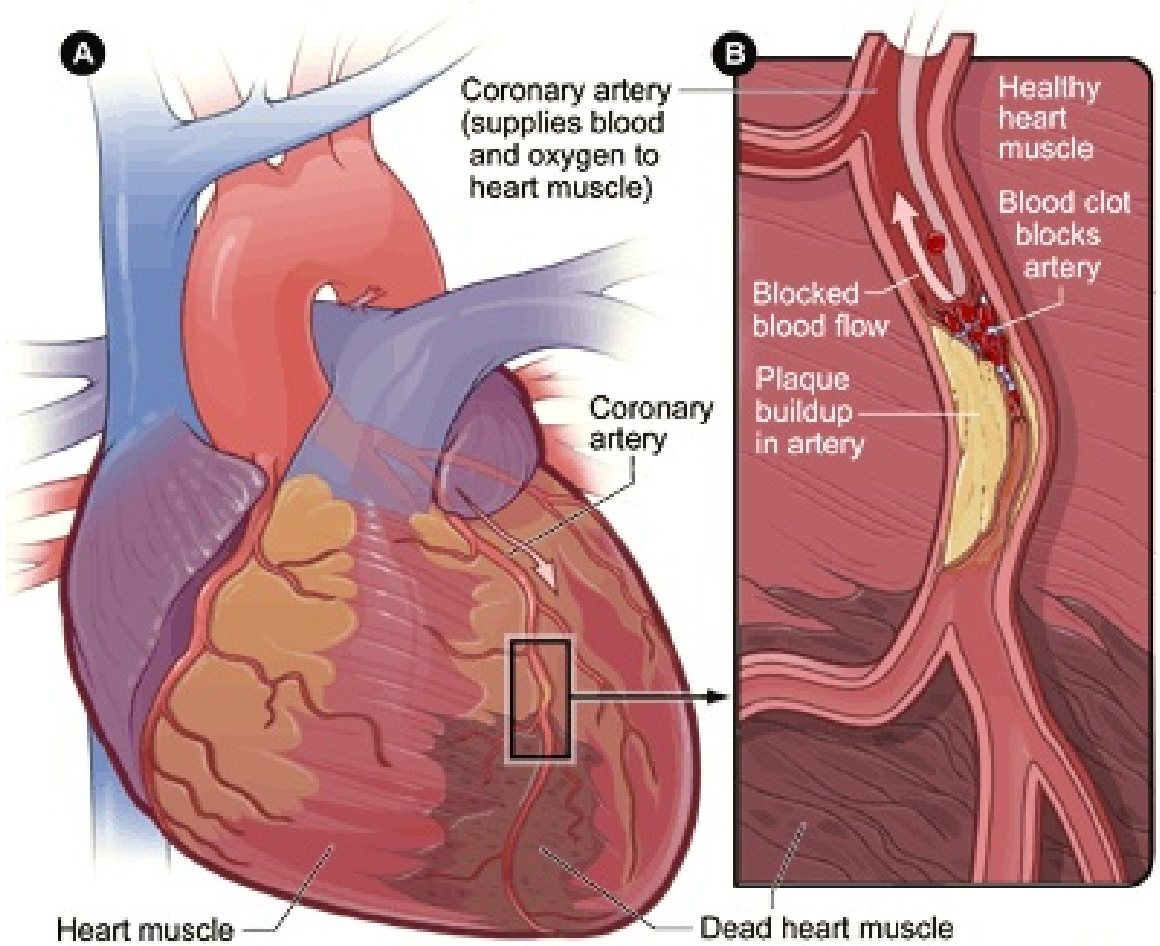
Linda Crapts

September 27, 2012

Outline

Next section

Biological background
Heart attack



Biological background
Stem cell treatment

In order to avoid the formation of scar tissue on the wound:

- Stem cells are injected which secrete, among others, the growth factor TG$-\beta$, which enhances angiogenesis:
  - endothelial cells are provoked to move towards the wound (chemotaxis);
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- After the enhanced angiogenesis, vessels have been formed in the damaged part of the heart.

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Question

How many stem cells should be injected when aiming at avoiding the formation of scar tissue?

Next section

Mathematical model

We observed two models:

- A model based on the work of Byrne et al;
- And a model based on the work of Maggelakis.

We choose to work with the *first* model since it is biologically the most extensive and mathematically the bigger challenge.

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Variables

- $m(\mathbf{x}, t)$: number of stem cells;
- $c(\mathbf{x}, t)$: concentration TG$-\beta$;
- $n(\mathbf{x}, t)$: capillary tip density;
- $\rho(\mathbf{x}, t)$: vessel density.

Mathematical model

Number of stem cells

$$\frac{\partial m}{\partial t} = -\beta_1 m,$$

- $m(\mathbf{x}, 0) = \begin{cases} m_0, & \mathbf{x} \in \Omega_w, \\ 0, & \mathbf{x} \in \Omega \backslash \Omega_w. \end{cases}$

Concentration TG$-\beta$ (attractor)

$$\frac{\partial c}{\partial t} - \underbrace{D_1 \nabla \cdot (\nabla c)}_{\text{random walk}} + \lambda c = \alpha m,$$

- $c(\mathbf{x}, 0) = 0,$
- $\frac{\partial c}{\partial n}\Big|_{\Gamma} = 0.$

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Mathematical model

Capillary tip density

$$\frac{\partial n}{\partial t} + \underbrace{\chi_1 \nabla \cdot (n \nabla c)}_{\text{chemotaxis}} - D_2 \nabla \cdot (\nabla n) = \underbrace{\alpha_0 \rho c + \alpha_1 H(c - \hat{c}) n c - \beta_2 n \rho}_{\text{bifurcations and anastomosis}}$$

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Vessel density

$$\frac{\partial \rho}{\partial t} - \epsilon \nabla \cdot (\nabla \rho) + \gamma(\rho - \rho_{eq}) = \underbrace{(\mu_1 \nabla n - \chi_2 n \nabla c)}_{\text{snail trail}} \cdot \frac{\mathbf{x}}{||\mathbf{x}||},$$

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- $\rho|_\Gamma = \rho_{eq}$

Mathematical model

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Mathematical model

Question

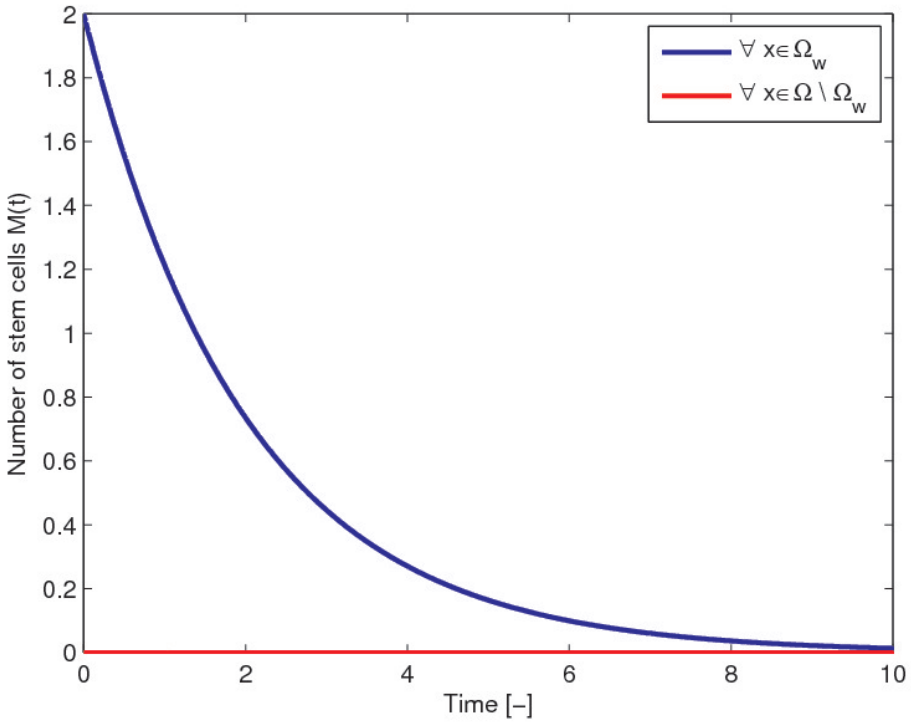
Which numerical technique should be used?

Next section

Analytical solutions
Number of stem cells

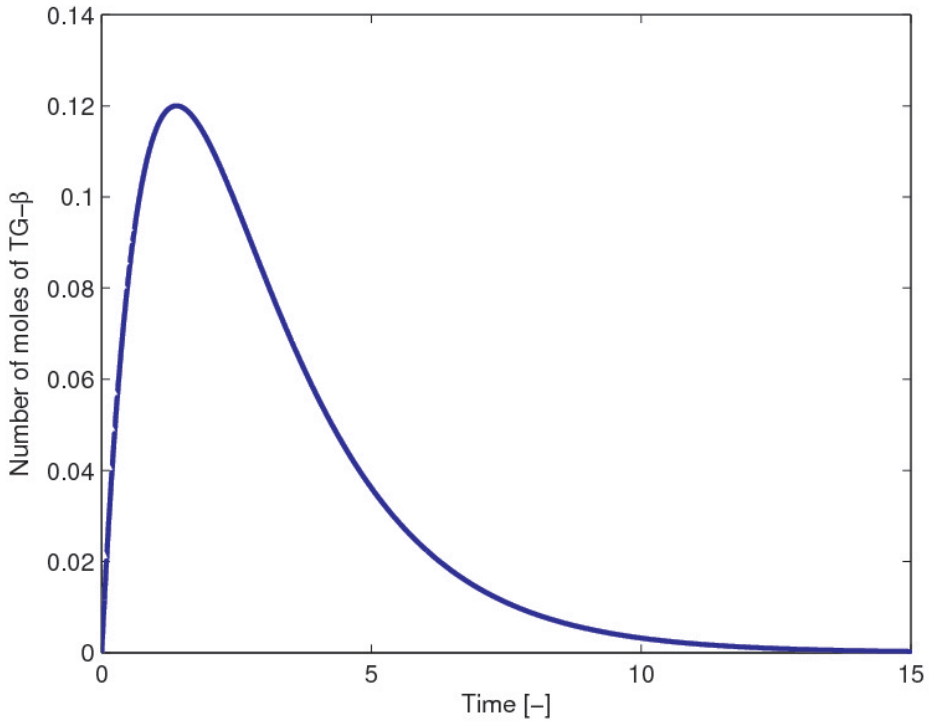
The number of stem cells decreases exponentially:

$$m(\mathbf{x}, t) = \begin{cases} m_0 e^{-\beta_1 t} & \mathbf{x} \in \Omega_w, \\ 0 & \mathbf{x} \in \Omega \backslash \Omega_w. \end{cases}$$



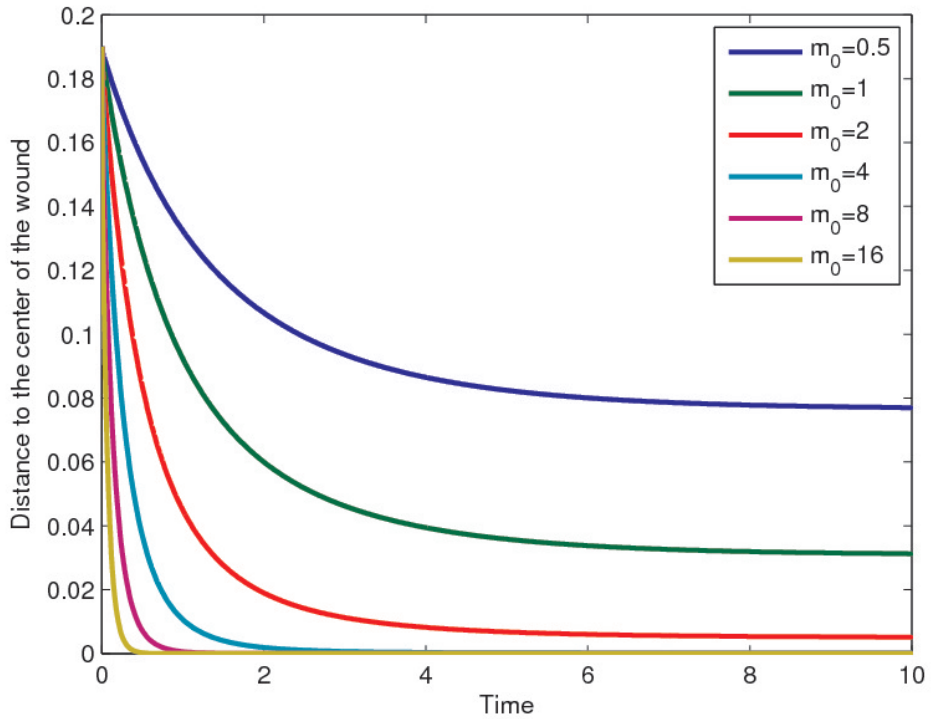
Analytical solutions
Number of TG$-\beta$

The number of TG$-\beta$ is determined by $\bar{c}(t) = \int_\Omega c(\mathbf{x}, t)\, d\Omega$.



Analytical solutions
Characteristics of the capillary tip density

The only parameter not fixed by biology, is the number of injected stem cells m_0.



Speed of the characteristics:
$\frac{dx}{dt} = \chi 1 \frac{\partial c}{\partial x}$.

Boundary wound: $\delta = 0.2$.

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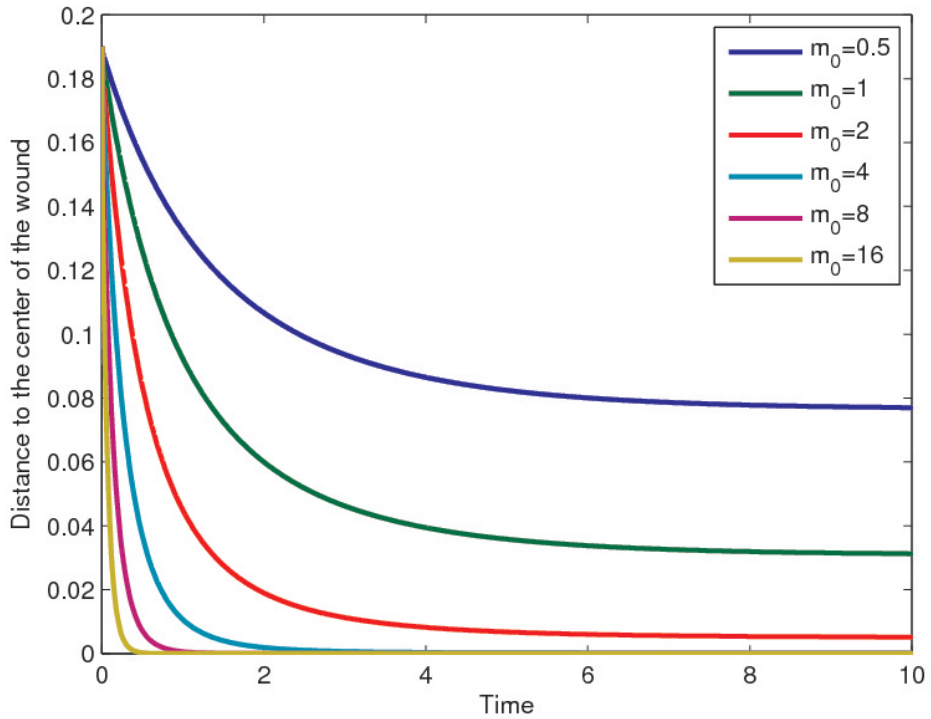

Speed of the characteristics: $\frac{dx}{dt} = \chi 1 \frac{\partial c}{\partial x}$.

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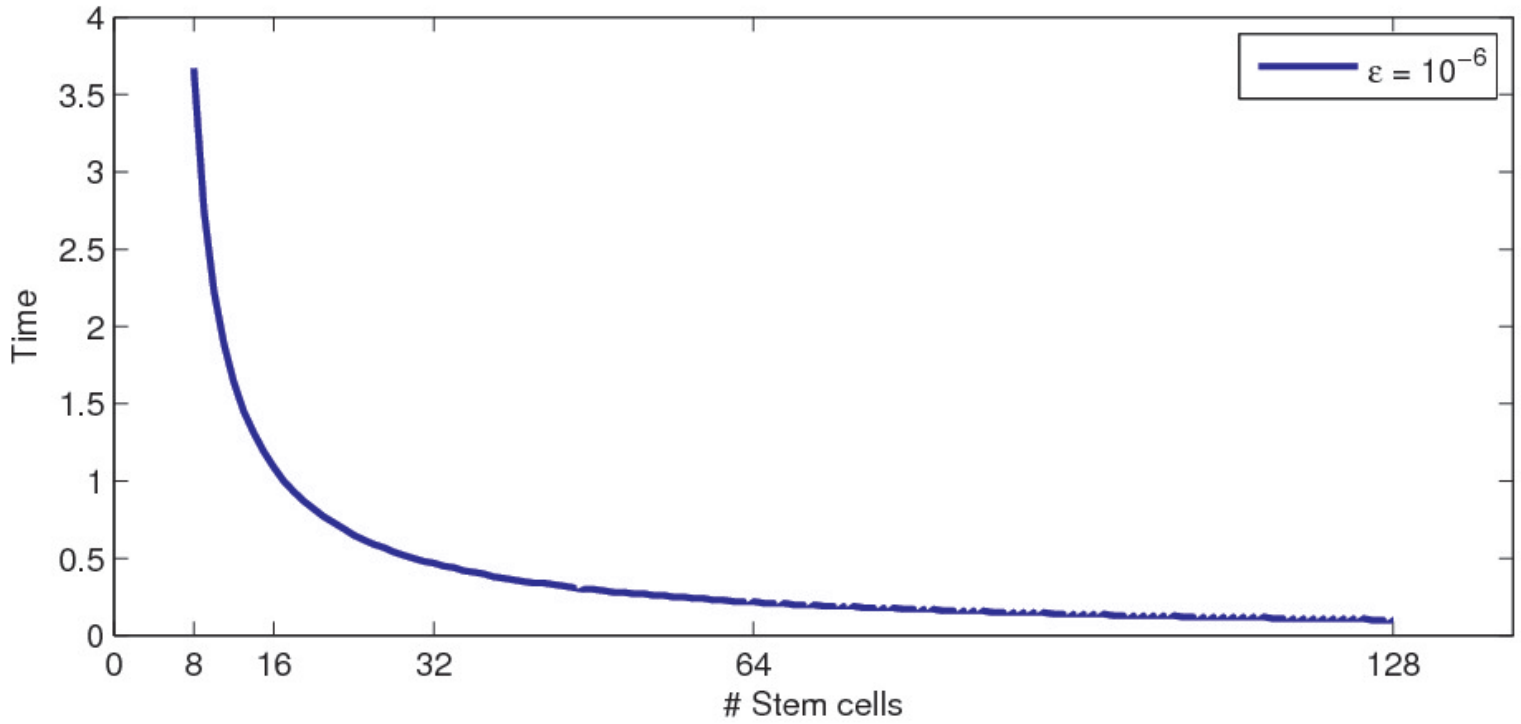
Number of stem cells is not always enough for the characteristics to converge to the center of the wound!

Analytical solutions
Characteristics of the capillary tip density

The wound will have sufficient blood supply if there exists a time $\tilde{t}$ such that, $\tilde{t} = \text{argmin}_{t \in (0,T]} \{t \in (0, T] : |x(t)| < \epsilon\}$.



Next section

Numerical methods
Mesh Péclet number

mesh Péclet number

$$Pe_m = \frac{v\Delta x}{D},$$

where v is the absolute speed and D the diffusion coefficient.

If Pe_m is relatively large, the problem is dominated by convection and the hyperbolicity of the problem increases.

The equation for the capillary tip density was

$$\frac{\partial n}{\partial t} + \chi_1 \nabla \cdot (n \nabla c) - D_2 \nabla \cdot (\nabla n) = \alpha_0 \rho c + \alpha_1 H(c - \hat{c}) nc - \beta_2 n\rho,$$

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- We succesfully implemented the finite element method for simulating the model with certain parameters;
- The chemotaxis term was suspected to have more influence than we used for these simulations;
- Therefore, we increased the chemotaxis coefficient χ_1, which increased the mesh Péclet number $Pe_m = \frac{|\chi_1 \nabla c| \Delta x}{D_2}$;
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Numerical methods
DG vs FEM

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complicated geometries	yes	yes
global solution	discontinuous	continuous
smoothness	local	global
jumps possible	yes	no

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Numerical methods
The discontinuous Galerkin method

For a one-dimensional problem:

- Partition the domain into N elements;
- Each element is denoted by $e_j = [x_{j-1/2}, x_{j+1/2}]$, for $1 \leq j \leq N$, with element size Δx;
- The solution in element e_j is approximated by

$$u_h(x,t) = \sum_{l=0}^{K} \hat{u}_j^l(t)\varphi_j^l(x),$$

  which is a linear combination of polynomials of order $l = 0$ up to $l = K$;
- High accuracy can be otbained.

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Numerical methods
The discontinuous Galerkin method

- In order to do this we scale each element $e_j = [x_{j-1/2}, x_{j+1/2}]$ to the reference element $[-1, 1]$;
- For the polynomials we use the Legendre polynomials which are defined on the local element $[-1, 1]$.

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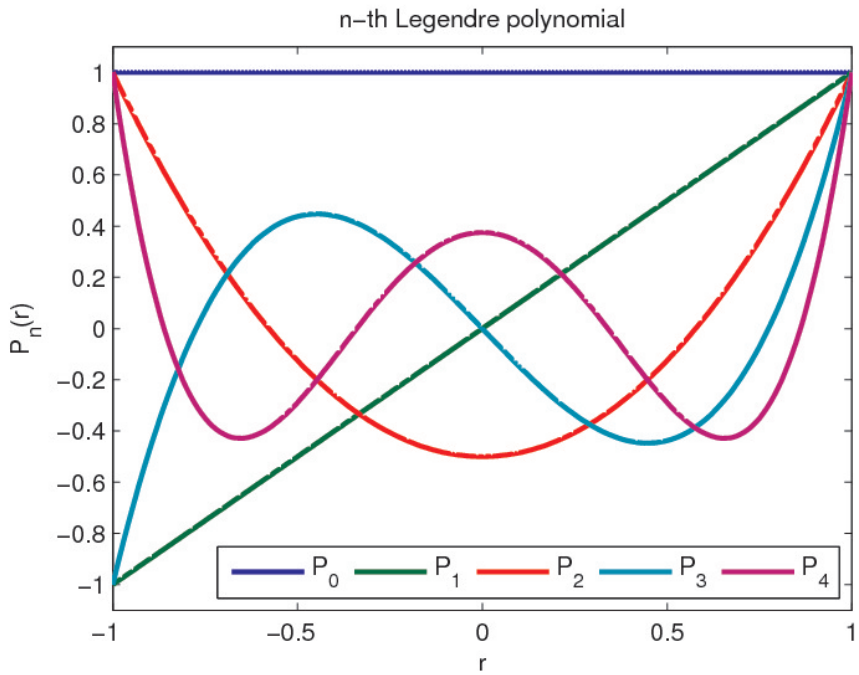

Numerical methods
The discontinuous Galerkin method

We need to determine the coefficients corresponding to the polynomials for all elements and for all time steps in order to determine the solution

$$u_h(x,t) = \sum_{l=0}^{K} \hat{u}_j^l(t)\varphi_j^l(x),$$

which is, after scaling the element,

$$u_h(x,t) = \sum_{l=0}^{K} \hat{u}_j^l(t)P_l(r).$$

Numerical methods
The discontinuous Galerkin method

The coefficients $\hat{u}_j^l(t)$ are determined by deriving the weak formulation and numerically solving equations of matrix-vector products.

For a higher dimensional model the discontinuous Galerkin method works in a similar way.

Limiting

If there is no diffusion and a discontinuity stays a discontinuity, as in the advection equation, a limiter should be used in order to prevent wiggles.

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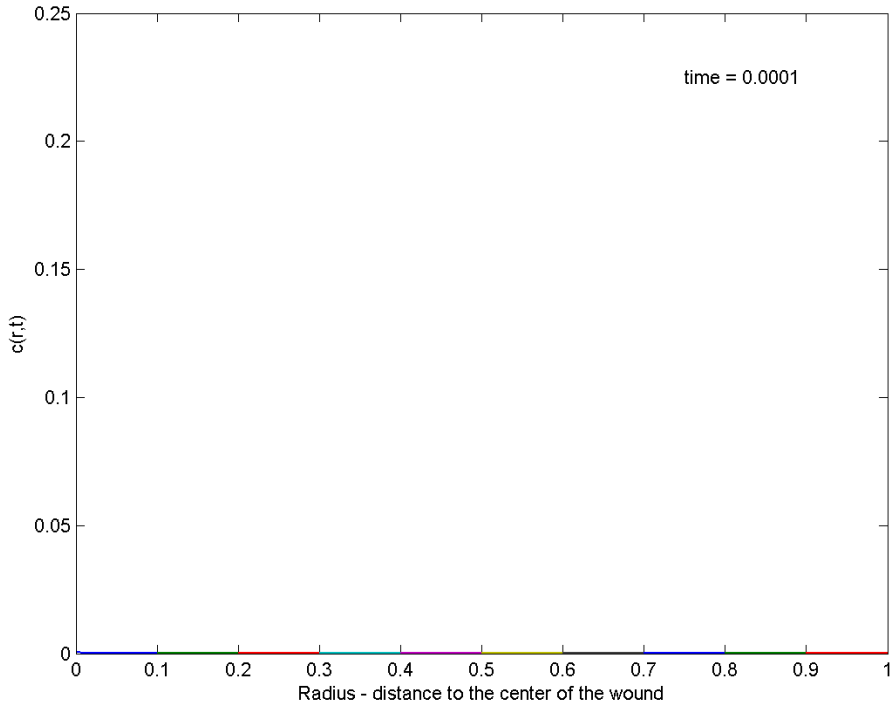
Next section

Next subsection

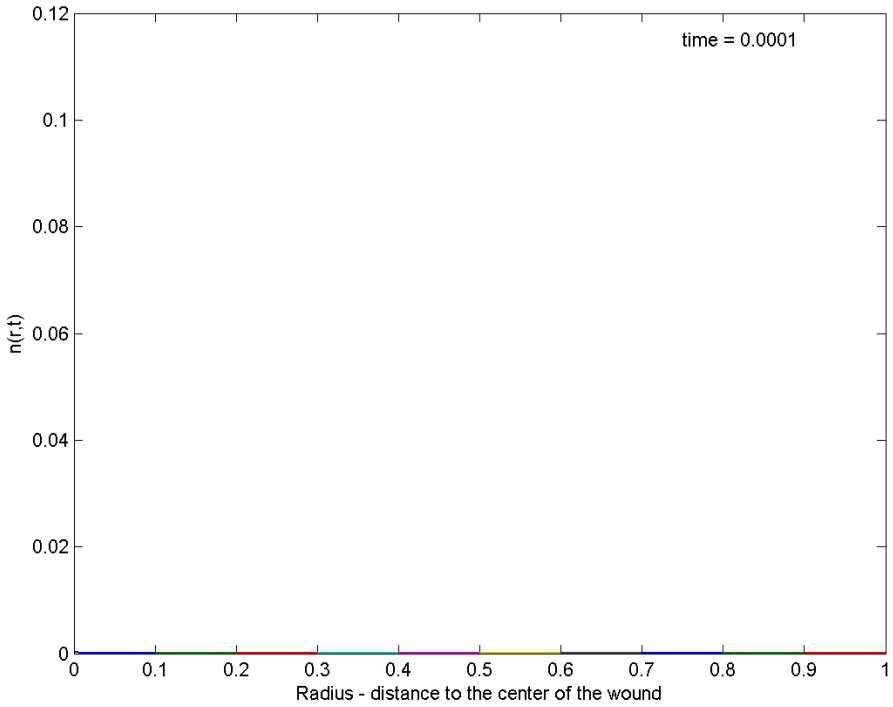
Simulations
DG - circular wound

Two-dimensional model rewritten into polar coordinates.
The concentration TG$-\beta$, $c(r,t)$:



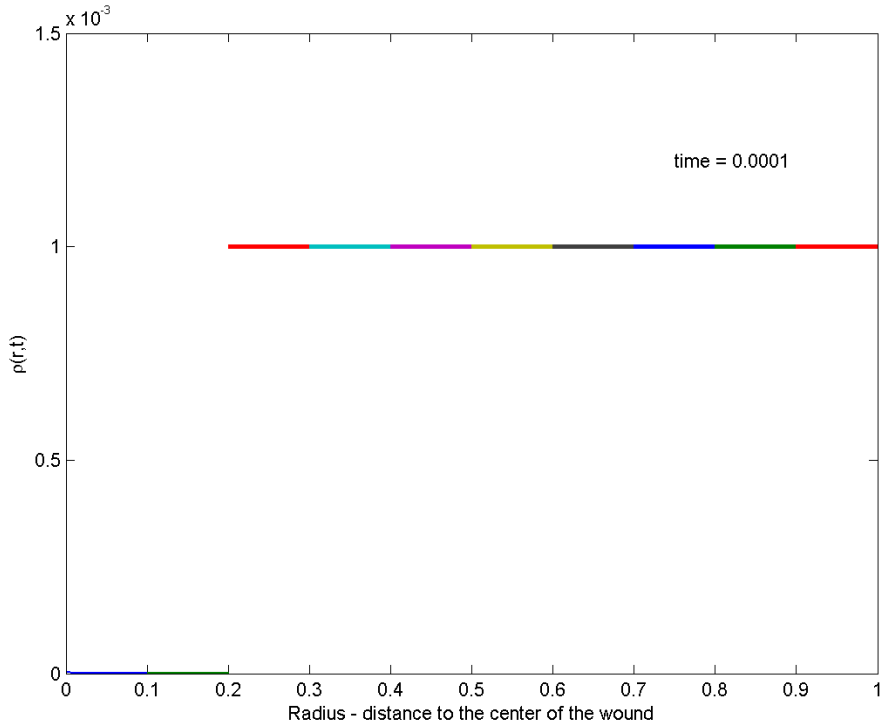
Simulations
DG - circular wound

The capillary tip density, $n(r, t)$:



Simulations
DG - circular wound

The vessel density, $\rho(r, t)$, with discontinuous initial condition:



Simulations
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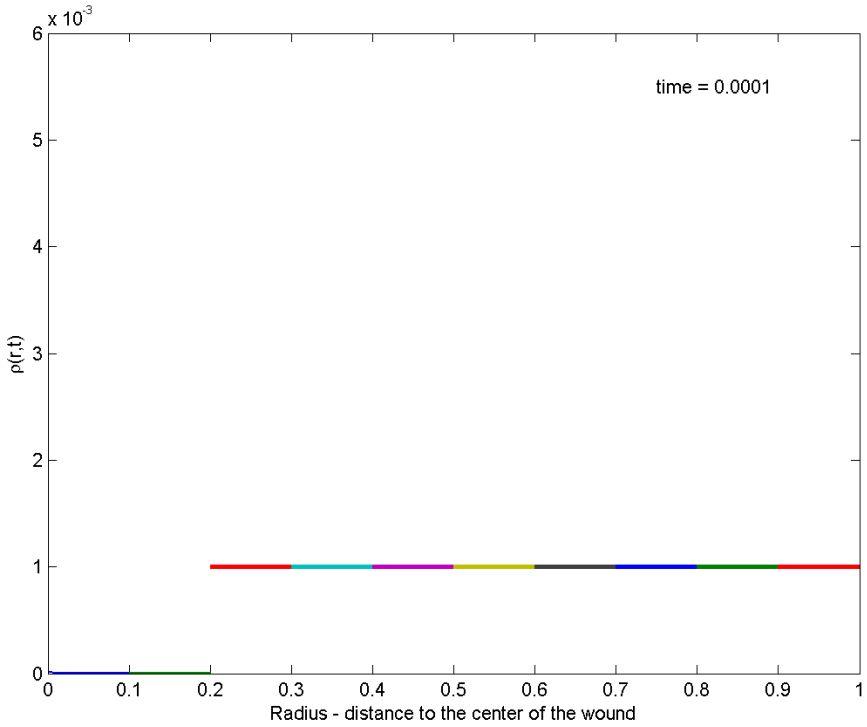


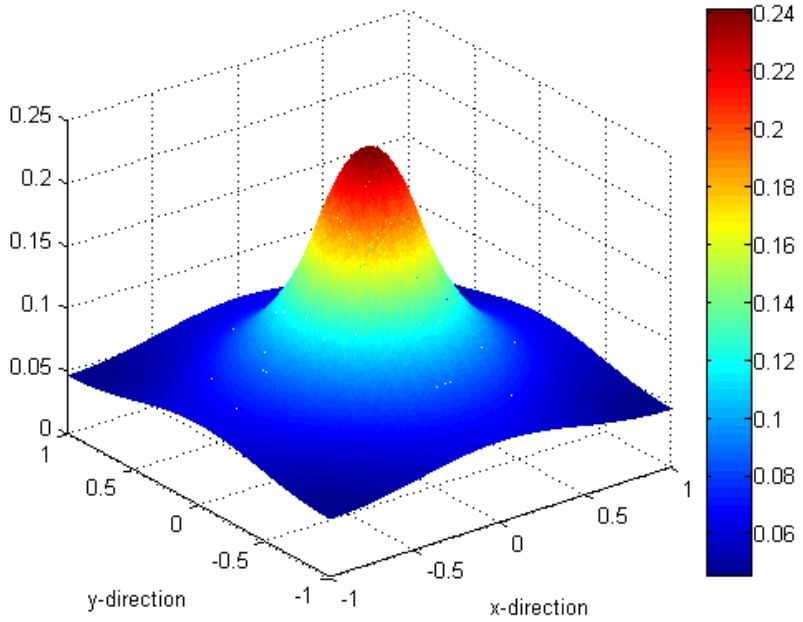
Next subsection

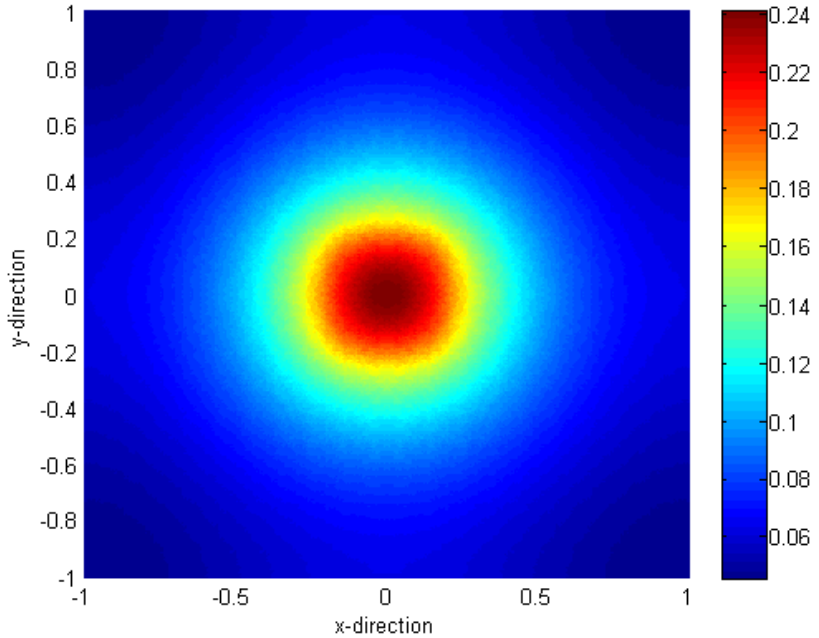
Simulations
DG - rectangular wound

Simulations for a rectangular wound, using:

- rectangular elements e_{ij},
- relatively low order of polynomials.

The concentration TG$-\beta$, $c(\mathbf{x}, t)$, at $t = 0.5$:





Simulations
DG - rectangular wound

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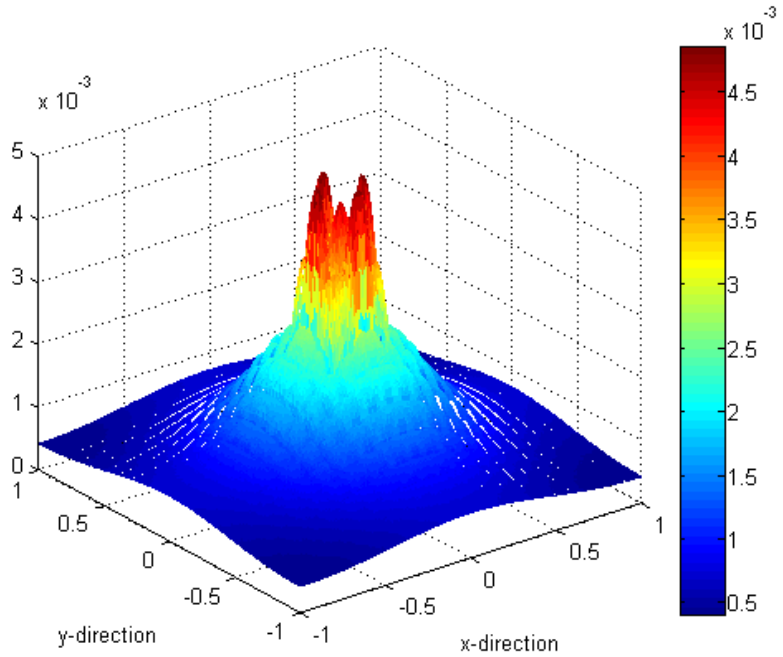

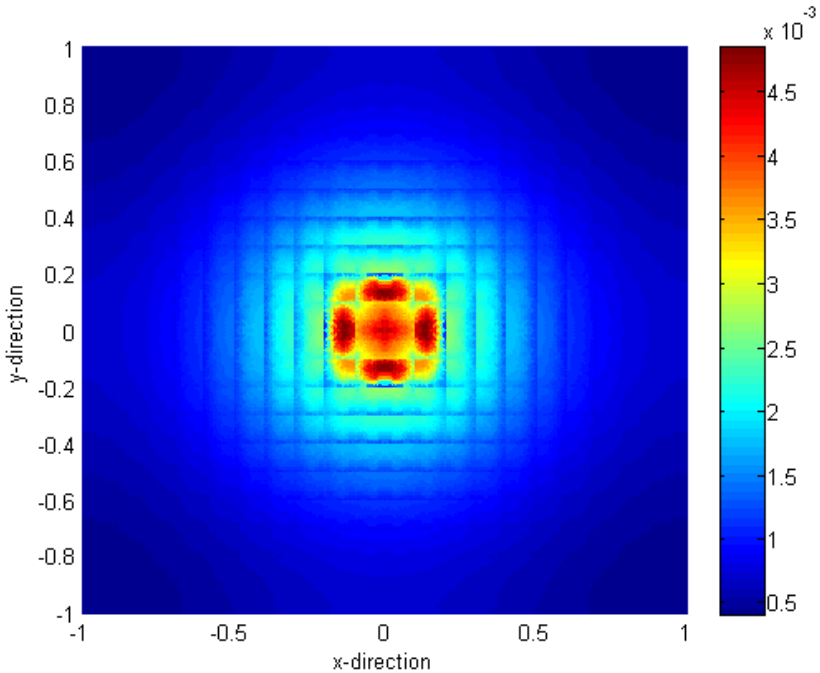

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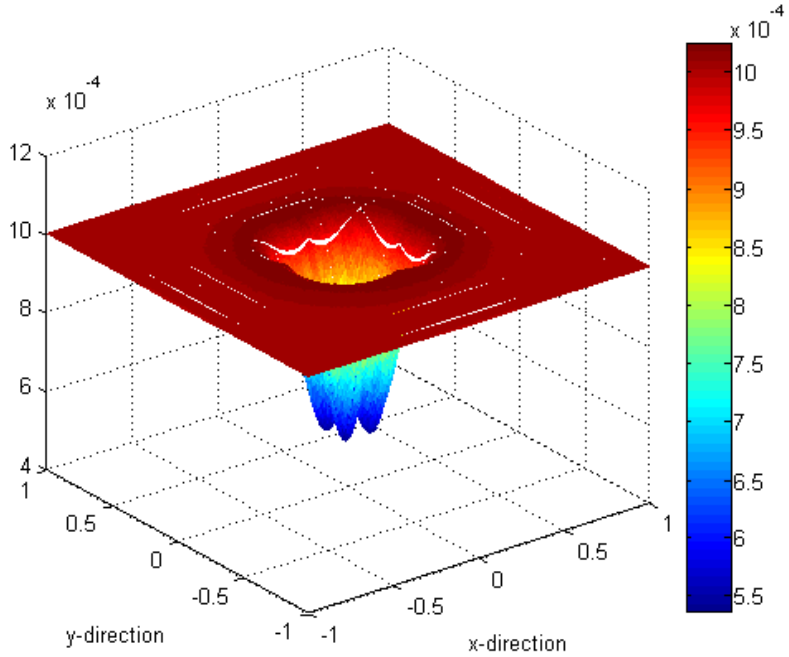
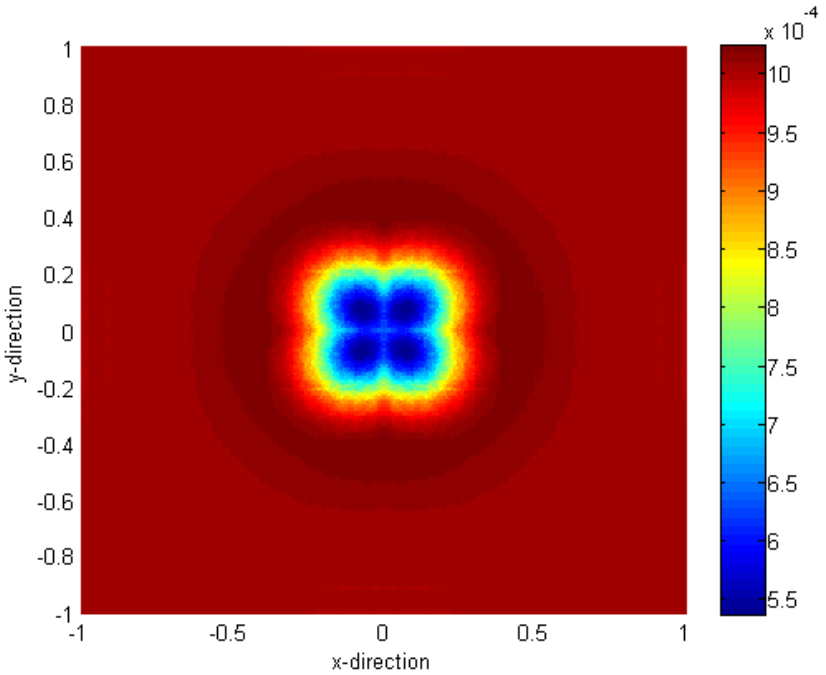
DG - rectangular wound

The vessel density, $\rho(\mathbf{x}, t)$, at $t = 0.5$:





Next section

Influence of the shape of the wound
The shapes

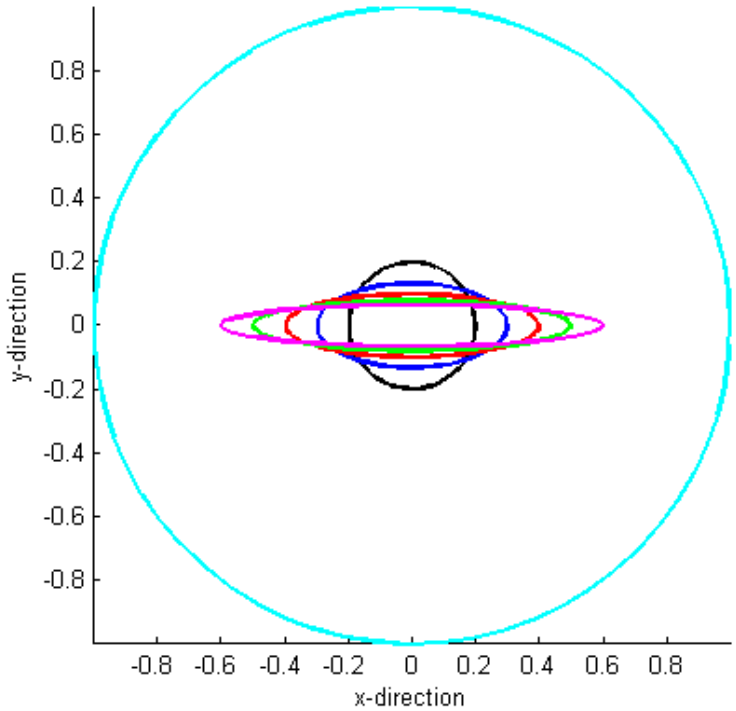
Question

What is the influence of the shape of the wound?

Compare simulations with:

- Wounds of different shapes;
- Wounds with the same area;
- The same parameter values.

We used the finite element method.



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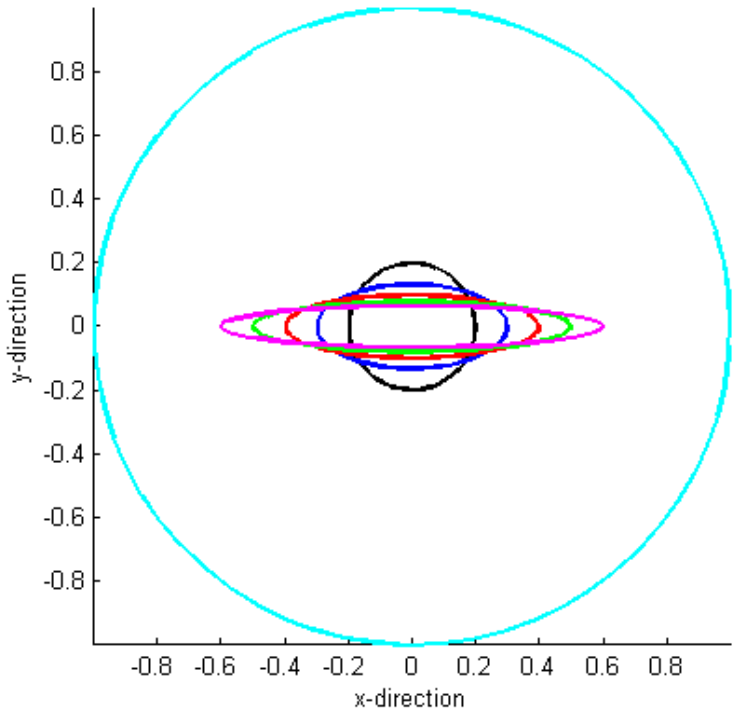

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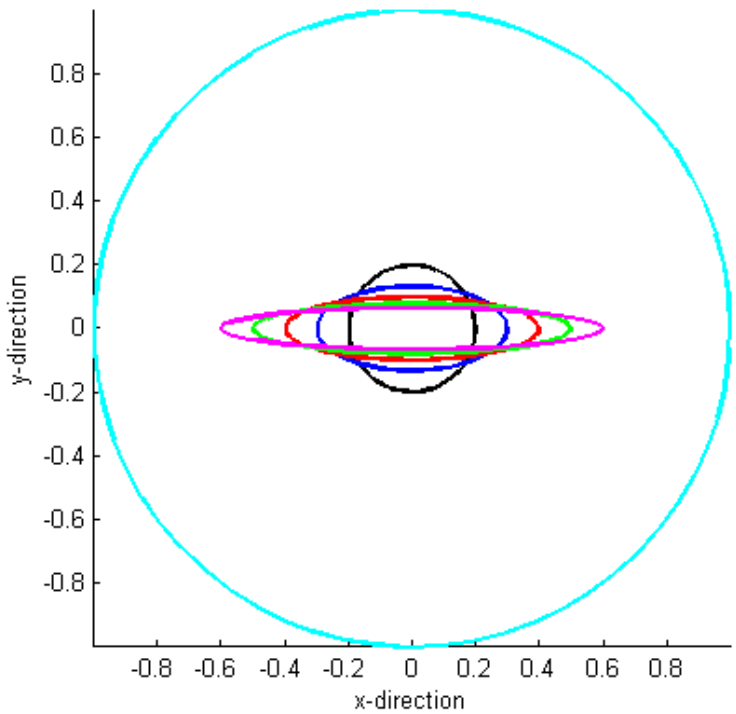
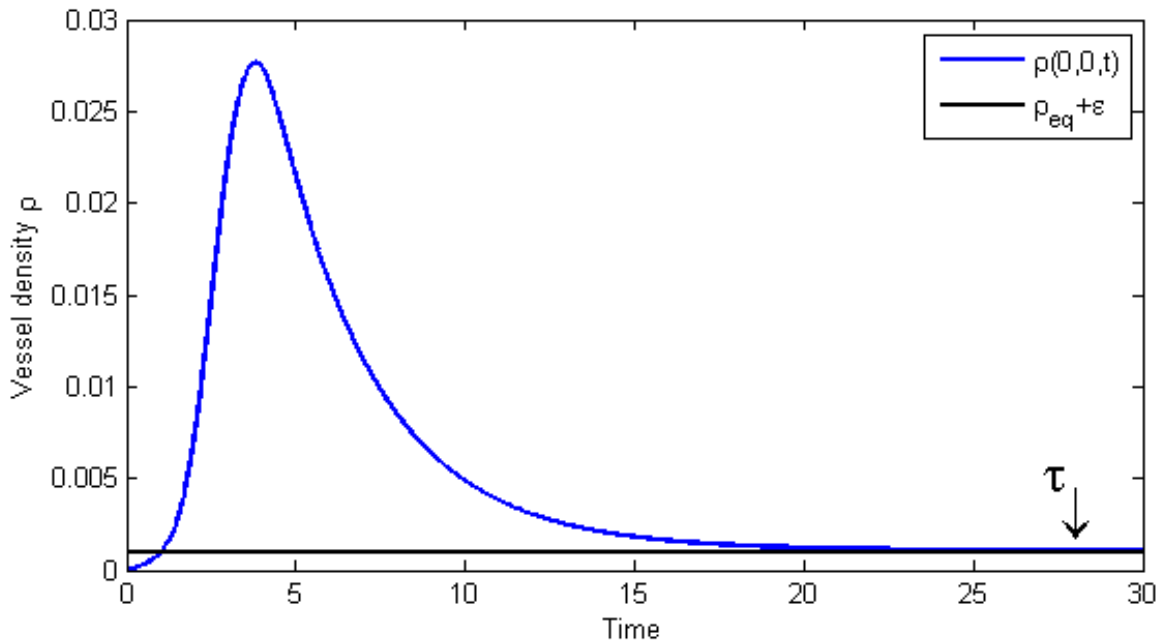


Influence of the shape of the wound
Vessel density in the center of the wound

We monitor the center of the wound $(0, 0)$ and determine the time τ, where the vessel density drops below $\rho_{eq} + \epsilon$, with a small ϵ.

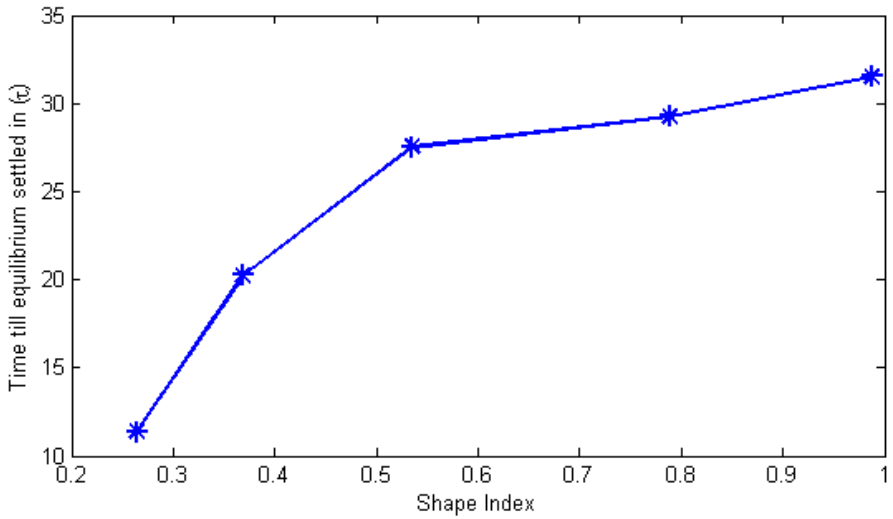


Influence of the shape of the wound
Shape Index

Shape Index (SI):

$$SI(\Omega) = \frac{4\pi A(\Omega)}{I^2(\Omega)},$$

where $SI(\Omega) = 1$ corresponds to a circle.



Wound with $SI(\Omega) = \pm 0.33$ healed *two* times faster than a wound with $SI(\Omega) = 1$.

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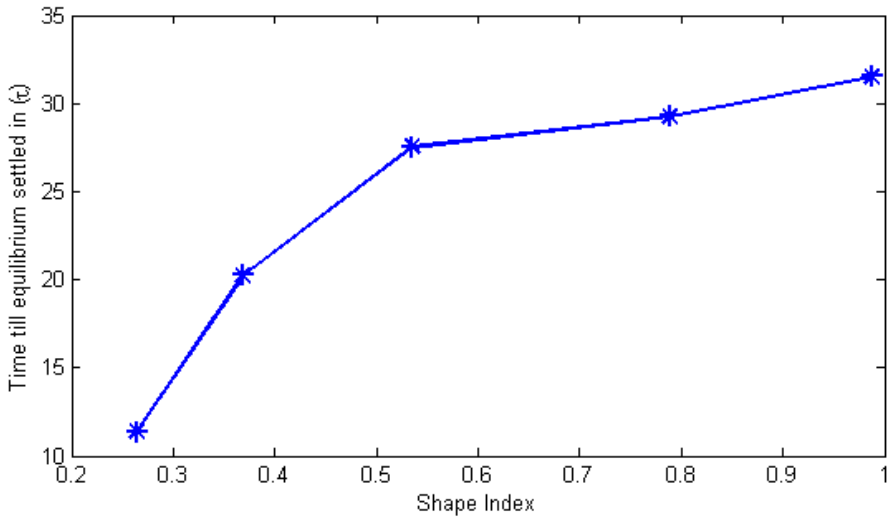

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Discussion, recommendations and conclusions
Part 1/4

We developed a model for angiogenesis under the injection of stem cells onto the damaged part of the heart after an infarction.

- Are the initial conditions a reflection of reality?
- Investigate realistic values for the parameters.
- What is the influence of multiple injections of stem cells instead of a single injection?
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We succesfully implemented the finite element (FEM) and the discontinuous Galerkin (DG) method for the one and two-dimensional problem.

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- Unfortunately, FEM was not sufficient anymore when we increased the hyperbolicity of the model;

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Thank you for your attention!

Questions?