Modeling an angiogenesis treatment after a myocardial infarction - using the discontinuous Galerkin method -

Linda Crapts
September 27, 2012
Outline

1 Biological background
2 Mathematical model
3 Analytical solutions
4 Numerical methods
5 Simulations
   • Circular wound
   • Rectangular wound
6 Influence of the shape of the wound
7 Discussion, recommendations and conclusions
Next section

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7 Discussion, recommendations and conclusions
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−β, which enhances angiogenesis:
  - endothelial cells are provoked to move towards the wound (chemotaxis);
  - endothelial cells are provoked to divide.
- 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?
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2. Mathematical model

3. Analytical solutions

4. Numerical methods

5. Simulations
   - Circular wound
   - Rectangular wound

6. Influence of the shape of the wound

7. Discussion, recommendations and conclusions
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

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

Number of stem cells

\[
\frac{\partial m}{\partial t} = -\beta_1 m,
\]

\[
m(x, 0) = \begin{cases}
m_0, & x \in \Omega_w, \\
0, & x \in \Omega \setminus \Omega_w.
\end{cases}
\]

Concentration TG−β (attractor)

\[
\frac{\partial c}{\partial t} - D_1 \nabla \cdot (\nabla c) + \lambda c = \alpha m,
\]

\[
c(x, 0) = 0,
\]

\[
\frac{\partial c}{\partial n} |_{\Gamma} = 0.
\]
Mathematical model

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random walk

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\frac{\partial c}{\partial n} \big|_F = 0.
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Mathematical model

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Mathematical model

Capillary tip density

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

chemotaxis

\[
\begin{align*}
&n(x, 0) = 0, \\
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\end{align*}
\]

bifurcations and anastomosis

Vessel density

\[
\frac{\partial \rho}{\partial t} - \epsilon \nabla \cdot (\nabla \rho) + \gamma(\rho - \rho_{eq}) = \left(\mu_1 \nabla n - \chi_2 n \nabla c\right) \cdot \frac{x}{||x||},
\]

snail trail

\[
\rho(x, 0) = \begin{cases} 
\rho_0 & x \in \Omega_w \\
\rho_{eq} & x \in \Omega \setminus \Omega_w 
\end{cases}
\]

\[
\rho|_{\Gamma} = \rho_{eq}.
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Mathematical model

Capillary tip density
\[ \frac{\partial n}{\partial t} + \chi_1 \nabla \cdot (n \nabla c) - D_2 \nabla \cdot (\nabla n) = \alpha_0 \rho c + \alpha_1 H(c - \hat{c}) nc - \beta_2 n \rho \]

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Mathematical model

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- chemotaxis
- bifurcations and anastomosis

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\text{chemotaxis} \quad &\quad \text{bifurcations and anastomosis}
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Mathematical model

Question
Which numerical technique should be used?
Next section

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The number of stem cells decreases exponentially:

\[ m(x, t) = \begin{cases} 
    m_0 e^{-\beta_1 t} & x \in \Omega_w, \\
    0 & x \in \Omega \setminus \Omega_w.
\end{cases} \]
The number of TG$-\beta$ is determined by $\bar{c}(t) = \int_{\Omega} c(\mathbf{x}, t) \, d\Omega$. 

![Graph showing the number of moles of TG$-\beta$ over time.](image)
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: $\delta = 0.2$. 
Analytical solutions
Characteristics of the capillary tip density

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

Boundary wound: $\delta = 0.2$.

Number of stem cells is not always enough for the characteristics to converge to the center of the wound!
The wound will have sufficient blood supply if there exists a time $\tilde{t}$ such that, $\tilde{t} = \arg\min_{t \in (0, T]} \{ t \in (0, T] : |x(t)| < \epsilon \}$. 
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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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hence \( Pe_m = \frac{|\chi_1 \nabla c| \Delta x}{D_2} \).
Numerical methods

- We successfully 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 $\chi_1$, which increased the mesh Péclet number $Pe_m = \frac{\chi_1 \nabla c |\Delta x|}{D_2}$;
- The mesh Péclet number became too high, the hyperbolicity of the problem increased and the finite element method was not sufficient anymore;
- A different numerical method was needed.
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The discontinuous Galerkin method
**Numerical methods**

**DG vs FEM**

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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 $\Delta x$;
- 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 obtained.
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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 \([-1, 1]\).
Numerical methods
The discontinuous Galerkin method

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- For the polynomials we use the Legendre polynomials which are defined on the local element $[-1, 1]$. 
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

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

which is, after scaling the element,

\[ u_h(x, t) = \sum_{l=0}^{K} \hat{u}_j(t) P_l(r). \]
Numerical methods
The discontinuous Galerkin method

The coefficients $\hat{u}_j(t)$ 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.
Numerical methods
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Simulations
DG - circular wound

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

The vessel density, $\rho(r, t)$:
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Simulations for a rectangular wound, using:

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

The concentration $T_G - \beta$, $c(x, t)$, at $t = 0.5$:
Simulations
DG - rectangular wound

The capillary tip density, \( n(x, t) \), at \( t = 0.5 \):
Simulations
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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.
Influence of the shape of the wound
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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 \(\tau\), where the vessel density drops below \(\rho_{eq} + \epsilon\), with a small \(\epsilon\).
Influence of the shape of the wound
Shape Index

Shape Index (SI):

\[ SI(\Omega) = \frac{4\pi A(\Omega)}{l^2(\Omega)}, \]

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

Wound with \( SI(\Omega) = \pm 0.33 \) healed two times faster than a wound with \( SI(\Omega) = 1 \).
Influence of the shape of the wound

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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?
- The model is only applicable for a single wound.
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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.
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Discussion, recommendations and conclusions
Part 3/4

We successfully implemented the finite element (FEM) and the discontinuous Galerkin (DG) method for the one and two-dimensional problem.

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DG is very accurate and can handle hyperbolic problems, however the method, in particular in more dimensions, suffers from large computation time, which makes the method unattractive for now;

Note that we only implemented DG for circular and rectangular wounds.
Discussion, recommendations and conclusions
Part 4/4

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Thank you for your attention!

Questions?