Agent-based modelling of the behavior of stem cells in a 3D-printed bio-device to be used in regenerative medicine

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Abstract

A novel treatment proposed for patients who have suffered a myocardial infarction is based on the design and construction of a 3D-printed bio-device where mesenchymal stem cells (MSC), along with other cell types, are cultivated for being later implanted in the patient's myocardium.

It is very important to understand the behavior of the bio-device, which can be affected by different variables. In line with this goal, we present, herein, our contribution to the development of a computational model of the behavior of the MSC and other cell types used in the 3D-printed scaffold.

First, we explored the use of a model based on ordinary differential equations and concluded that it was limited regarding the possibilities to take into account additional characteristics of the cellular microenvironment, we opted for an Agent-Based modeling approach. The model considers some basic MSC's characteristics and their interactions with the microenvironment. Until now, our results have shown that the emergent behavior of the cells in the model agrees with other cellular modeling results and observations of preliminary experiments. Further simulations will be performed to analyze the effect of parameters in the results and will be validated with in-vitro observations.

Overview

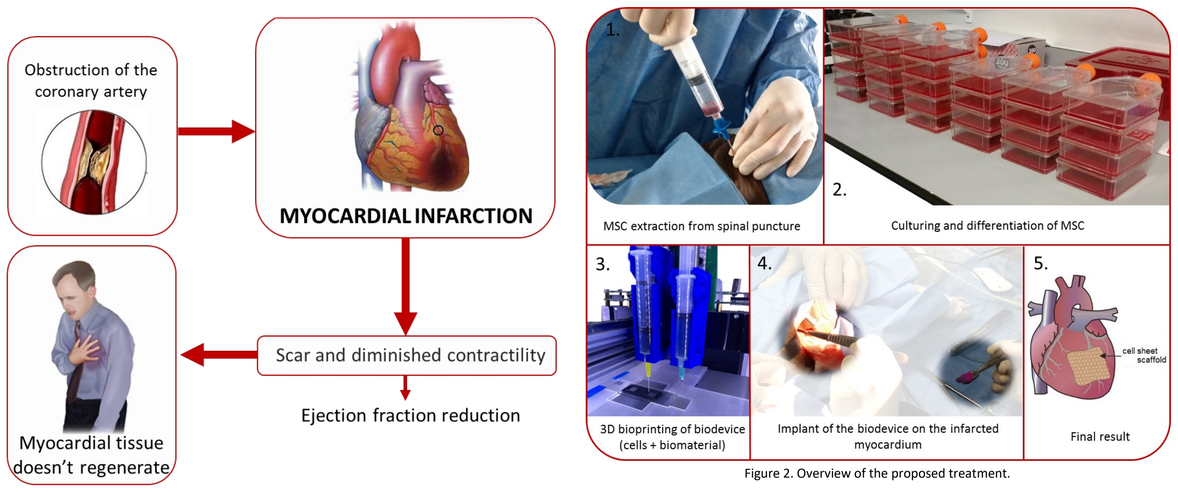


Figure 1. Overview of the myocardial infarction.

Figure 2. Overview of the proposed treatment.

Data acquisition

We designed an experiment to acquire data in order to observe and analyze some dynamics in scaled bio-devices along time

1. Determine relevant and measurable data we could obtain.

- **Cellular viability** → % of healthy cells along time (Tripan blue staining)
- **Cellular migration** → movement of cells along time (Fluorescence microscopy)

2. Determine factors that might affect the data.

- **Cell concentration** → amount of cells in the bio-device
- **Distribution** → 3D-printed pattern

3. Choose a significant number of samples for observation.

- **Viability assay** → 3 different concentrations, 20 samples of each concentration.
- **Migration assay** → 2 different distributions, 8 samples of each distribution.
  - Each assay has a duplicate for validation, for a total of 152 samples.

4. 3D-print the scaled bio-devices.

5. Culture scaled bio-devices in a heart-like in-vitro environment and observe periodically to obtain the data.

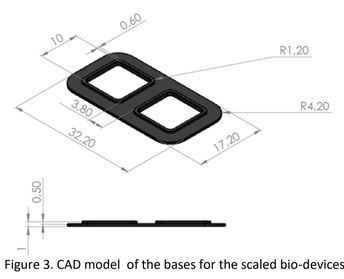


Figure 3. CAD model of the bases for the scaled bio-devices.

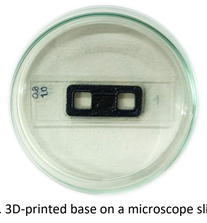


Figure 4. 3D-printed base on a microscope slide.

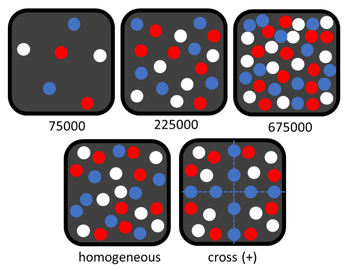


Figure 5. Types of experiments to be observed.

Model characterization

Define the outputs of the model according to the inputs, which need to be comparable to the data that would be obtained from the experiment's observations.

- Amount of living and dead cells of each type after a specific time.
- Position of the cells after a specific time.

Implementation of an ODE modelling approach

After documentating various ODE based models for stem cell growth and proliferation[1][2][3] the "*Hyperbolastic model H3*"[4] was chosen for implementation.

$$\frac{dP(t)}{dt} = \left(L - P(t)\right)\left(\delta\gamma t^{\gamma-1} + \frac{\theta}{\sqrt{1+\theta^2 t^2}}\right)$$

Accurate description of the self-limited growth thar occurs in some biological systems.

Parameters:

- L → Carrying capacity
- δ→ Intrinsinc biological growth rate
- θ→ Variation of growth rate over time
- ϒ→ Allometric constant

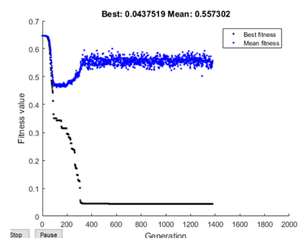


Figure 6. Genetic Algoritghm implemmentation

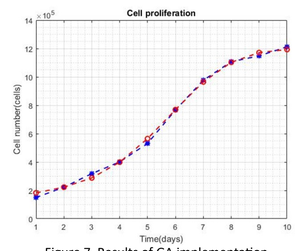


Figure 7. Results of GA implementation.

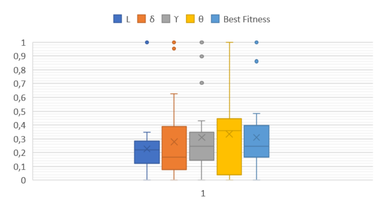


Figure 8. Analysis of GA results.

This approach is discarded because it wouldn't represent the cell's behavior through the whole treatment as it doesn't allow considering the cellular microenvironment's effects.

Agent Based Modelling approach[5]

With ABM we could add features easily to allow the model to consider characteristics and processes of the cellular microenvironment. The main characteristics of the model are:

- Including the 3 different cell types and their interactions between each other and the environment, including blood vessels and scar tissues.
- Modelling the processes of apoptosis, differentiation, proliferation and inflammation[6].
- Possibility of variying initial conditions to compare resulting behaviors.

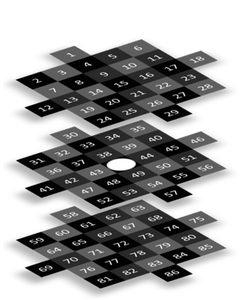


Figure 9. Neighborhood of a MSC.

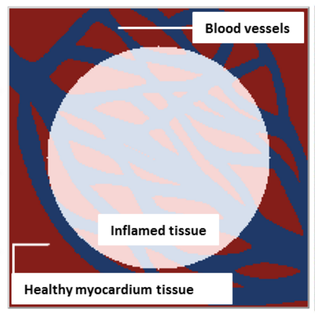


Figure 10. Microenvironment of the cells.

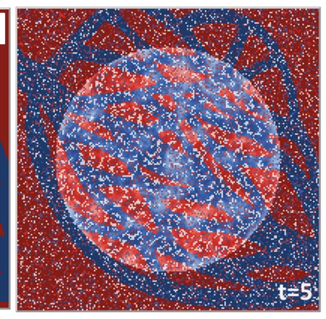


Figure 11. Inflammation reduction thanks to MSC presence.

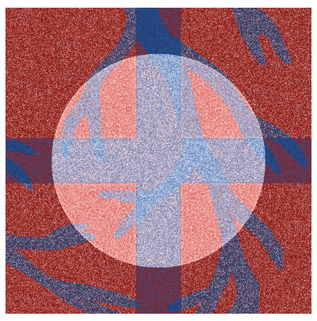


Figure 12. Simulation of 'cross' distribution.

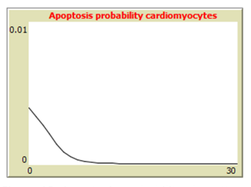


Figure 13. Apoptosis probability along time.

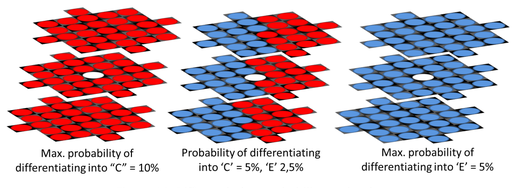


Figure 14. Differentiation probability evaluation.

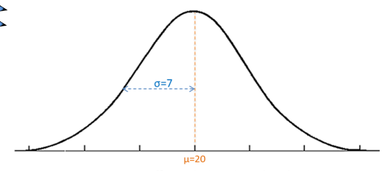


Figure 15. Differentiation time distribution.

Main results

12 simulations were run using a server via SSH connection. The initial number of cells and distribution were varied randomly in each simulation to compare the results.

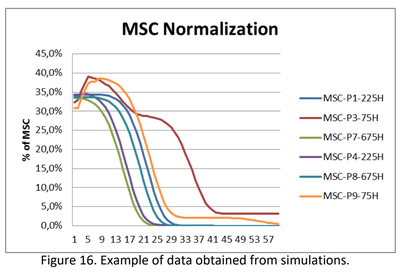
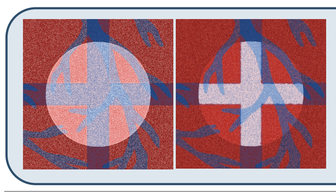


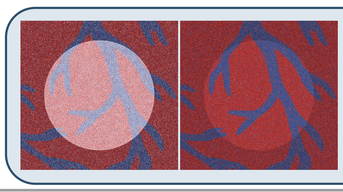
Figure 16. Example of data obtained from simulations.

- MSC have a longer proliferation period when there are less of them, after that their population decays due to differentiation ('C' and 'E' population grows).
- With 'cross' distribution the inflammation is less reduced, avoiding growth of the 'E' population.
- Inflammation reduces faster when there are more MSC.



Initial → 225000 - 'cross'
Final
- 0% MSC - 66% C - 27% E

Proliferation
- 0.35% MSC - 0% E



Initial → 225000 - 'homog'
Final
- 0% MSC - 57% C - 42% E

Proliferation
- 0.02% MSC - 29.09% E

Conclusions and future work

- An ABM approach allows the addition of features during the modelling process, which is not so easy when working with an ODE model.
- Resulting growth-curves resemble a self-regulated growth curve and differentiation, agreeing with previous cell-growth models.
- The 'cross' distribution didn't show any advantage over the 'homogeneous' one.

Future work:

- Results obtained with the simulation of the 'cross' distribution lead to consider that new distribution patterns should be considered for simulation.
- The model can be implemented in a 3D environment to simulate other signals coming from the heart.

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