The study of differentation of mesenchymal stromal cells

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Contents

1 Introduction

The differentiation of MSC's is a complex process. Up to now, the full process and all its influences is not yet known.
The reason to study the behaviour of MSC's, is because they have promising features in tissue engineering. With its mobility and differentiation properties, these cells could be able to repair tissue in various parts of the body.

In biological cell experiments, it is a challenge to reproduce the exact same experiment every time. Aside from this challenge, these experiments are time and money consuming. An indication on the costs can be found by looking at cell-selling sites, which can go up to 1000+ euros (depending on size).
Then there are also the ethical restrictions which must be satisfied. Some experiments might be harder to perform, due to social pressure or anxieties. Take for example genetic modification, cloning or even stem cell research.

A way to avoid these downsides of biological experiments, is by making a (mathematical) model of the desired process. By doing so, the mentioned problems are solved. But one has to give in on realistic results, since (mathematical) models are a mere approximation of reality.
An ideal solution is to combine both ways of doing an experiment. Hence, use biological experiments to preserve the realism and the mathematical experiments to increase the knowledge on the underlying mechanisms that are investigated.

In this report we will focus on the construction of a mathematical model. This model will simulate the differentiation process of a set of cells.
These cells will start off as MSC's and have the possibility to differentiate into two phenotypes: fat cells and muscle cells.
The idea behind this choice of cell specialisations is to be able to interpret this model as a model about the forming of obesity.

Numerous research projects have already been completed to understand the driving factors behind obesity. Some examples of these factors are age, genetic predisposition, medication, eating behaviour, etc. These factors can help people deal with obesity on a practical level. For example by eating more healthy, getting sufficient exercise, etc.
But our interest lies in the way obesity forms on a *cellular-level*.

1.1 Goal definition

Depending on the interpretation of the subject, we can define various problem definitions. For example, we can say that our goal is to model the process of obesity.
Another example could be to model the change in cell composition due to chemical and mechanical influences. Or our goal could be to implement a set of equations as efficient as possible, where efficiency is based on the computation time.
From these examples it is apparent that we need to start from the 'right' interpretation. Not too abstract, because then the interpretation of the numbers is lost. But not too concrete either, because then the underlying mechanisms will seem to be forgotten.

In this we report we choose a cell-based perspective. Hence we use the (known) properties of the various cells to set up a model, while keeping in mind that we wish to model the process of obesity formation.
If we would put it in one sentence, we would ask our selves:

> We wish to model the differentiation process of MSC's and the behaviour of myocytes and adipocytes. Such that we can eventually relate this process to a real life situation.

1.2 Report structure

In the first part of this paper we will treat the biological background of the problem. Subsequently, several mathematical models are discussed that concerns cell differentiation or cell migration.
Then a novel model approach is introduced, which will be the main focus of this report. This model has already been implemented as far as possible, hence some results will follow from this approach.
At last, some future research directions will be discussed.

2 Biology background

In this section we will analyse the biological background of our problem. Since we restricted the amount of phenotypes of the MSC, we will analyse the following cell types: The *MSC's*, the *myoctes* and the *adipocytes*.

2.1 The MSC

The MSC, otherwise known as the mesenchymal stromal cell, is isolated from bone marrow, adipose, and other tissue sources [1]. Stem cells, in general, were discovered around the 1950's. The first stem cells were found in the bone marrow, where two types were identified.
The first type got the name *hematopoietic stem cell*, which are able to differentiate to all kind of blood types. The second type, which was found a few years after the discovery of the hematopoietic stem cell, was called the *bone marrow stromal cell*. The bone marrow stromal cell is also called the mesenchymal stromal cell.
Since the discovery of the MSC a lot of research has been conducted to find the defining properties. Although there is no precise definition of the MSC in terms of markers, they do posses promising features. In this section we will discuss three of these properties.

The first property is its multipotency. In studies on *in vitro* differentiation of MSC's have shown that the following phenotypes can be produced:
bone, cartilage, tendon, muscle, adipose tissue, and hematopoietic-supporting stroma. This characteristic of MSC's can be very beneficial for clinical tissue regeneration.

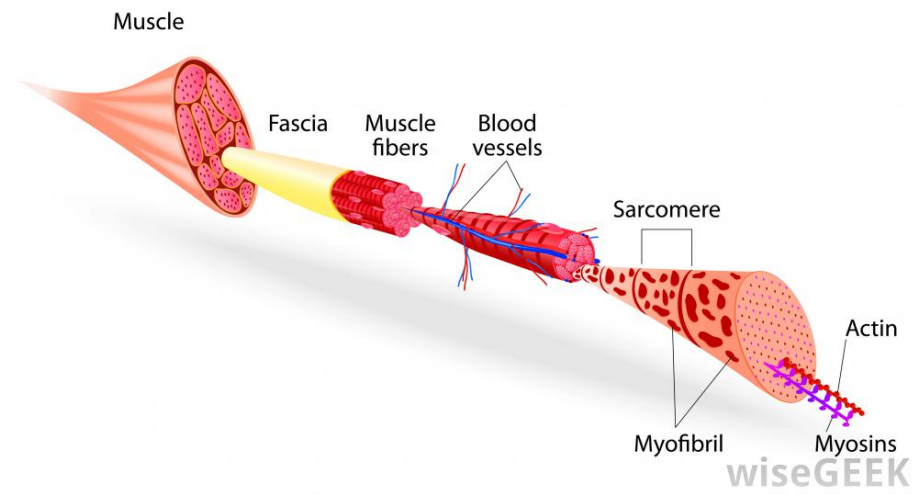
Then there is also the self-renewal property. And another important property of the MSC is that, when transplanted systemically, they are able to migrate to sites of injury in animals. This suggests that MSC's possess migratory capacity. But the mechanisms that are concerned with self-renewal and migration are not well understood and remain an active area of investigation [2].

2.1.1 Myoblast - Myocyte

The family of myocytes can be devided into three groups:

- *cardiac* myocytes, can be found in the heart region;
- *smooth* myocytes, can be found in regions around other organs;
- *skeletal* myocytes, can be found attached to the skeleton.

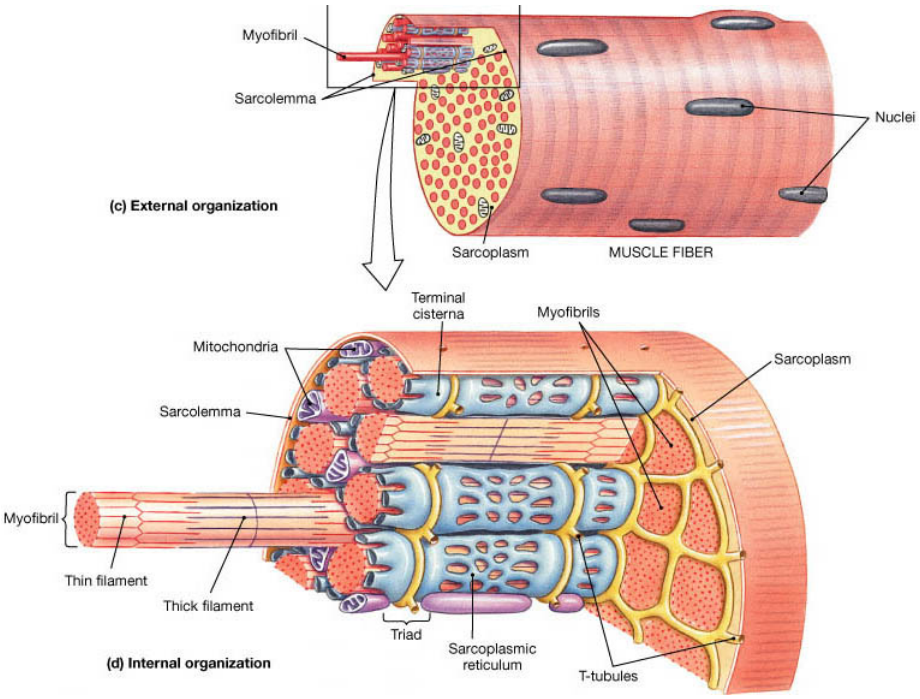
The structure of a skeletal myocyte can be seen in the following picture



These skeletal muslce cells, as can be seen from the picture, are long cylindrical myocytes. They are referred to as fibers, or myofibers.
A myofiber is made by fusing many myoblasts. Because of this, myofibers are polyplod cells, which means that it contains multiple ovoid nuclei. This characteristic distinguishes skeletal muscle cells from cardiac muscle cells, which usually have one centrally-located nucleus.

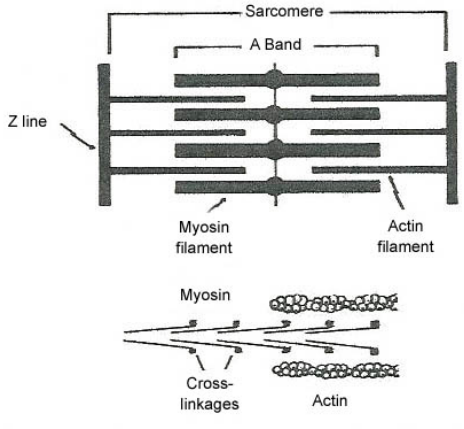
Myoblasts are bipolar, spindle-shaped cells. In the maturation process, myoblasts will start to line up to form myofibers. This process of lining up is very important. It can only occur if the free end of the myoblast at one end of the line attaches itself to an appropriate point at one end of the future muscle and if the free end of the myoblast at the other end of the line attaches itself to the other end of the future muscle. This process makes sure that these connected myoblasts lay in line with the long axis of the (future) muscle.

If bad connections are made (say both ends of the line of myoblasts attach to the same end of the muscle) - then the line of myoblasts degenerates. Thus, a developing muscle contains many degenerating myoblasts which have failed to develop appropriate connections. Only if the line of myoblasts is properly attached at both ends can the myoblasts contract, stretch their membranes, and take up amino acids for further protein synthesis. [10]



When a myofiber has been formed, it will last (in most cases) for the entire life time of the animal. But at this point the myofiber is unable to proliferate. If a myofiber is damaged, the only way to repair itself is by the use of satellite cells. Typically, myofibers can vary in length from a few milimeter to a couple of decimeters. The diameter ranges from 10-100μm. [11]

A mature myofiber consists of many myofibrils. These myofibrils consists of many departments, called sarcomeres. Inside these sarcomeres the contraction takes place. This is caused by the movement of myosin- and actin-myofilaments, this causes the sarcomeres to shorten [12]:



Solely by the change of length on this level is a muscle able to contract and exert forces. This characteristic behaviour of a muscle cell is thus of utmost importance for the modeling of a muscle cell.

2.1.2 Lipoblast - Adipocyte

Adipocytes, which means *fat cell*, orginates from lipo*blasts*. This transition process is called adipogenesis.

From *in vitro* studies, the intermediate stages of adipogenesis are defined. From [19] we have the following table that summerizes adipogenesis.

Stage of adipogenesis	**Characteristics**
Mesenchymal precursor	Proliferation Ability to differentiate into multiple lineages
Committed preadipocyte	Proliferation Commitment to differentiation along adipocyte lineage Fibroblast-like morphology
Growth-arrested preadipocyte	Lack of proliferation due to contact inhibition
Mitotic clonal expansion	Re-entry into the cell cycle induced by hormonal stimulation Several rounds of cell divisions (i.e. mitotic clonal expansion) Induction of C/EBPb and C/EBPd expression and activity
Terminal differentiation	Cell-cycle arrest Induction of PPARg and C/EBPa expression Transcriptional activation of adipocyte genes (lipid and carbohydrate metabolism genes, adipokines)
Mature adipocyte	High expression of adipocyte genes Transcriptionally active PPARg, C/EBPa and C/EBPb Signet-ring morphology: large lipid droplet occupies majority of cell volume aThese distinctions are based primarily on in vitro studies.

This table is shown just for the sake of completeness. In the novel model approach, we will not deal with this detailed description of adipogenesis.
Since the main function of a fat cell is to store energy, we will treat such a cell as a simple circle that can increase in size. If needed, a model can also be proposed to simulate the shrinkage of fat cells, because the subject used or needed more energy. Hence, any internal reaction in the fat cell will be neglected.

The formation of fat cells is a crucial part of obesity. According to [17], there are two types of obesity. One is characterized by a *hypertrophy* of fat cells and is of moderate degree. This type of obesity is associated with metabolic disturbances. Increased fat cell size might not be a primary factor in this form.

The other form is called *hyperplastic* obesity. This is characterized by an increased number of fat cells and is associated with much more severe obesity, particularly since fat cell size is often increased also in these obese patients.

The contents of a fat cell is mostly filled with triglycerides, which are esters derived from glycerol and three fatty acids. From [17], we have gathered some data on the fat cell size of obese patients. From these data, we find that the mean of the diameter of abdominal fat cell size of 37 obese patients is approximately $126.8\mu m$.

There are other studies that investigate the fat cell size. For example [18], but the results here are given in x μg lipid/cell. Since we are interested in the diameter of a fat cell, we cannot use these results.
From [17] we also found that the amount of fat cells will not increase after a certain (mature) body age. This gives that obesity is mainly caused by a fixed high number of fat cells in the early ages, which then can expand to cause the increase in body weight.

2.1.3 Cytokine

The cytokine production of a cell is important in the signaling to other cells. These cytokines are a broad and loose category of small proteins (5-20 kDa).

These proteins are released by cells and affect the behaviour of other cells and sometimes the released by the cell itself.
In general cytokines are regulators of the immune system, but can also be seen as a communication substance. Since they are closely related to hormones, which are all about internal communication.

The amount of cytokine or the way they are produced is explained in [16]. However, this is done in great molecular-biological detail, which is not convenient. Hence, there is no information on what amount or what way (pulsing or constant) the cytokine is secreted.

We can subdivide the broad group of cytokines in the following classification

- chemokines - their ability is to induce directed chemotaxis in nearby responsive cells. They are **chemo**tactic cyto**kines**.

  The major role of chemokines is to act as a chemoattractant to guide the migration of cells. Cells that are attracted by chemokines follow a signal of increasing chemokine concetration towards the source of the chemokine.

  The role of this attraction can be classified in two ways: homeostatic chemokines and inflammatory chemokines. The former kind the cells are regulated to let internal conditions remain stable and relatively constant (think of temperature). The latter makes sure that the leukocytes (white blood cells) are attracted to the site of inflammation, to secure the threat.

- interferons - (IFNs) used to trigger the protective defenses of the immune system that help eradicate pathogens. They can interfere with viral replication by protecting cells from virus infection. They can also active immune cells. Certain symptoms of infections, such as fever, muscle plain and flu-like symptoms are also caused by the production of IFNs and other cytokines.

- interleukins (ILs) - expressed by leukocytes (white blood cells). Also involved in the immume system. They promote the development and differentation of T and B lymphocytes and hematopoietic cells.

- lymphokines - produced by a type of immune cell known as lymphocyte. They are protein mediators typically produced by T cells to direct the immune system response by signalling between its cells.

- tumour necrosis factor (TNF) - this kind can signal cells to deactivate (cell death, apoptosis).

Generally, cytokines do not include hormones or growth factors (despite some terminolgic overlap).

Cytokine concentrations are of the order picomolar (pico $\equiv 10^{-12}$) and hormones are more in the order of nanomolar (nano $\equiv 10^{-9}$). However, the concentration of cytokines can increase a 1,000-fold during trauma or infection. The widespread distribution of cellular sources for cytokines may be a feature that differentiates them from hormones.

What is interesting to know, is the type of cytokine the adipose tissue generates. These are called adipokines, or adipocytokines and given below:

- Leptin
- Adiponectin
- Apelin
- Chemerin
- Interleukin-6 (IL-6)
- Monocyte chemotactic protein-1 (MCP-1)
- Plasminogen Activator inhibitor-1 (PAI-1)
- Retinol Binding protein 4 (RBP-4)
- Tumor Necrosis Factor alpha (TNFα)
- Visfatin

In addition, Interleukin 8 (IL-8), Interleukin 10 (IL-10), Interferon gamma (IFN-γ) and inducible protein 10 (IP-10) have been shown to be associated with excessive body weight.

As of 2008, the current terminology refers to a cytokine as an immunomodulating agent. However, conflicting data exists about what is termed a cytokine and what is termed a hormone. More research is needed in this area defining cytokines and hormones.
Under current terminology, adiponectin, leptin and resistin are not cytokines as they do not act on the immune system. They can be put into the list of adipose-derived hormones.

In addition to Adipokines, we also have Myokines. The cytokines which are produced, expressed and released by muscle fibers and exert either autocrine, paracrine or endocrine effects. Of particular interest is the fact that contractile activity plays a role in regulating the expression of these cytokines in skeletal muscle.

Myokines are involved in exercise-associated metabolic changes, as well as in the metabolic changes following training adaptation

The interaction between exercise and the immune system proveded a unique opportunity to evaluate the role of underlying endocrine and cytokine mechanisms.
The list of cytokines that fall under the myokines are given by:

- Myostatin - the first myokine to be identified. Regulates muscle growth. Both aerobic exercise and strength training in humans and animals attenuate myostatis expression. Myostatin inactivation seems to potentiate the benefical effects of endurance exercise on metabolism. This cytokine is involved with muscle hypertrohpy and myogenesis
- Interleukin 6 (IL-6) - the first myokine to be found secreted into the blood stream in response to muscle contractions. It appears consistently in the literature that IL-6 produced locally by different cell types, has a positive impact on hte proliferative capacity of muscle stem cells. This cytokine is involved with muscle hypertrohpy and myogenesis, and also in AMPK-mediated fat oxidation.
- LIF - This cytokine is involved with muscle hypertrohpy and myogenesis
- IL-7 - This cytokine is involved with muscle hypertrohpy and myogenesis
- BDNF - involved in AMPK-mediated fat oxidation. Full name is Brain-derived neurotrophic factor. Besides secretetion of hte chemicla in the skeletal muscle, it also secretes more in the brain. BDNF plays a key role in regulating survival, growith and maintenance of neurons and BDNF has a bearing on learning and memory.
- IGF-1, FGF2, FSTL-1 - which improves the endothelial function of the vascular sytem
- PGC - 1α-dependent myokine irisin, which drives brown-fat-like develpoment
- IL-15 - appears to play a significant role in the reduction of visceral (intra-abdominal or interstilitial) fat
- Decorin
- Irisin

Of particular interest is the fact that differing muscle fiber types (slow twitch oxidative, intermediate and fast twitch fibers) release differing clusters of myokines during contraction. This implies that variation of exercise types, particularly aerobic training/endurance training and muscle contraction against resistance (strength training) may offer differing myokine-induced benefits
(**Add references**)

3 Classic Models for cell populations and differentiation

There are many different models in the world of biomathematical modelling. It is an important task to learn from previous models.

The first section deals with several cell based migration and maturation models. These models are not all focused on the growth of adipose tissue, but most of them are concerned with mesenchymal stem cells. They just treat a different phenotype.

The second section deals with discrete models. These models are mostly lattice based.

Some models use partial differential equations to solve mass-balance problems, they get cell densities as a result. Opposed to other models, who use discrete entities. The difference here lies in the amount of detail the modeller wants.
In continuum models, it is easier to compute a (physical) larger domain than with a discrete model. Since then one needs to model all the discrete cells and how they move, which costs a lot of computational power.

3.1 Conventional Continuum Scale model

In [21], a continuum scale model is proposed. The idea here is to set up a mass-balance equation for each cell type, where cell proliferation, differentiation and death is included.
The solution of these mass-balance equations produces a distribution function of the cell densities over the domain.

A useful addition in this model is that cell proliferation is modelled by a mother cell dividing into two daughter cells.
Furthermore, there is no sign of using cell movement in this model. However, this model is validated with some experimental data.

In [22] a continuous based model is chosen to model the behaviour of T cell differentiation. The reasoning behind choosing the continuous model comes from the following:

> For example, the earth is treated as a particle in celestial mechanics, since there is no difference among its constituents as far as their mechanical properties are concerned. However, when it comes to geology the earth is usually, continuously, modeled since its geological constituents are quite different. From this perspective, we concluded that to study T cell differentiation as a continuous model is preferable.

The governing equations in this model GuanYu Wang are derived by the analysis of an infinitesimal element of the flow (of thymocytes). Thymocytes are hematopoietic progenitor cells present in the thymus [23].

In [24] we see a model not for the differentiation rate, but for the cell migration. In this model a strain-energy-density approach has been used to model the movement of cells. With this approach cell contact forces and haptotaxis are included.
An application of this kind of model can be found in the wound-healing section. The model for the movement of cells, especially the contact forces, is very interesting.

In [26], this model is concerned with the differentiation of MSC. Here it is assumed that these differentiate only in three phenotypes: osteo-, fibroblasts and chondrocytes.
Another aspect that characterizes this modelling approach is the following quote

> "*The most important innovating assumption of the current approach is that cells are supposed to gain the properties of another cell type gradually, in the course of time, until a complete differentiation of MSCs takes place. Therefore, a certain finite time of differentiation can be related to each MSC*"

This differentiation time is then dependent on the environment of the cell. Thus it depends on the amount of chemical and mechanical stimulus.

Note however that in this situation the MSC differentiates only permanent when the cell is "matured". The maturation process of a cell is tracked by an n-dimensional unit vector, where n stands for the amount of phenotypes. Each cell has the ability to traverse an axis of the n-dimensional plane, but can only stay on the axis itself.
Thus, if a cell is growing towards phenotype 1, but then gains more stimulus for phenotype 2. It has to 'grow back' to its original state, zero, before being able to continue to grow to phenotype 2.
When a cell reaches a maturity of one at a certain axis, it is "matured" and will stay this phenotype permanently.

The rate at which this differentiation happens is modelled by a vector $\underline{u}$, which depends on the chemical, mechanical, random input parameters and on the maturity of the cells.

The paper first describes a mathematical model to simulate the differentiation of MSC cells. Later on, a specific case is dealt with: the differentiation of MSC's into osteoblasts and fibroblasts. The goal here is to simulate the growth of bone tissue and to compare it with several experimental data.
The formation of cartilage (chondrocytes) is neglected, because there is no data of this formation in the experiments.

In [25] a stem-cell model is also treated. Opposed to the model of Prokharau [26], the maturity path of a cell is a one-way direction. This model is again a continuous based model and will be used as a tool to investigate the mathematical assumptions with practical experiments/thoughts.

In [27] we see a model for obesity. This is modelled in a different way than all the other models. Instead of choosing a cell-based model, here a balance equation has been established between types of humans.
There is a **n**ormal-sized class $N(t)$, an overweight class, $S(t)$ and an **o**bese class $O(t)$. The relation between these three types is defined by a mass-balance DE, with several external factors like lifestyle and social pressure.

Although this model is not cell based, it is nice to see a different approach in modeling obesity, on a more practical level. This model has been used to model the obesity epidemic in the region of Valencia, Spain.

The, mathematically, simple model is given by the following set of equations

$$N'(t) = \mu N_0 - \mu N(t) - \beta N(t)(S(t) + O(t)) + \rho S(t) \tag{1}$$

$$S'(t) = \mu S_0 + \beta N(t)(S(t) + O(t)) - (\mu + \gamma s + \rho)S(t) + \epsilon O(t) \tag{2}$$

$$O'(t) = \mu O_0 + \gamma s S(t) - (\mu + \epsilon)O(t) \tag{3}$$

$$N(t) + S(t) + O(t) = 1 \tag{4}$$

The interpretation of the parameters is as follows:

- ϵ, the rate at which an obese adult with a healthy lifestyle becomes an overweight individual.
- μ, average stay time in the system of 24- to 65-year-old adults.
- ρ, the rate at which an overweight individual moves to the normal-weight subpopulation.
- β, transmission rate because of social pressure to adopt an unhealthy lifestyle (TV, friends, family, job and so on).
- γS, the rate at which an overweight 24- to 65-year-old adult becomes an obese individual because of unhealthy lifestyle.
- N_0, proportion of normal weight coming from the 23 years age group.
- S_0, proportion of overweight coming from the 23 years age group.
- O_0, proportion of obese coming from the 23 years age group.

The next challenge is to find the right values for these parameters. The paper also deals with that and shows some analytic stability situations. At last, some numerical simulation are run and a conclusion is drawn for this specific case.

3.2 Conventional discrete cell based models

In discrete models, one chooses to work on a lattice. A grid of size $n \times n$, on which cells will live as discrete entities.
Discrete models can be seen as a more intuitive (or less complex) way of looking at the world.

In [28], the behaviour of tumor cell growth is modelled. In this model it is assumed that at each time step all the cells have a chance of dying/surviving, migrating and to proliferate. Also there is a quiescence state of a cell, in which the cell is idle.
From this, relatively, simple model results were obtained concerning the population growth over time.

Other discrete models that have been reviewed are the cellular Potts model and methods like the Lattice Boltzmann Method. But the main focus in our research lays on the continuous models. This is because our novel model, which we will discuss in the following section, is mainly driven by partial differential equations.

4 A novel model approach for cell differentiation

The model approach we will use here is based on a combination between a discrete and continuous model. The goal here is to model the differentiation behaviour of mesenchymal stem cells.
This differentiation process is characterised by the following equation:

$$\frac{dm_j}{dt} = U(t, \underline{x}(t), \underline{\psi}(t), \underline{m}(t)), \quad j = 1, \ldots, C$$

$$m_j(0) = Q_j, \; Q_j \sim \mathrm{U}(0, 1)$$

This equation simulates the maturation rate of every cell $j \in [1, C]$, where C is the total amount of cells. The rate $U(t, \sim)$ shows how fast cell j is heading towards maturity.
Starting from a random maturity level $\mathrm{U}(0, 1)$, the cell then grows in time towards a more mature state. Once it reaches a level of $m_j(t) = 1$, the rate is set to zero and we have obtained a mature cell.
During this process, a cell has a certain direction in which it grows, since it can either become a myocyte or a adipocyte. The mechanics behind this process is also given by the maturation speed. Or, since it now also has a direction, the maturation velocity.

This way of modeling the maturity of a cell corresponds to the method used in Vermolen (2010) [24].

The function $U(t, \sim)$ represents the rate of maturation. This function combines the influence of the chemical and mechanical stimuli the cells produce, which again influence all the cells in their way to adulthood. The exact formulation of this function will be given in the sections to come.

During this process of becoming a mature cell, all kind of characteristics about the cell change. Its length, width, the amount of force it exerts on the extra cellular matrix and more. These are all influenced by the level of maturity. In doing so, we wish to simulate the effect that a cell gradually gains the characteristics of the phenotype it is heading to.

4.1 Cell behaviour

The cells we will model do not truly represent their physical behaviour. In this section we make a summary of our assumptions on cell behaviour:

- The simulation starts with a population of cells with a random distributed maturity rate and maturation direction;
- Each cell that tends to a myocyte will produce a force that is exerted from the boundary of the cell;
- Cells that tend toward an adipocyte also exert a force in the same way, but only after their radius has reached a fixed activation radius.
- Every cell will produce their type of cytokine into the domain, which scales with their maturity rate;
- The movement of cells is influenced by four factors: randomness, mechanical strain energy, bounce force from other cells and the gradient of cytokine production;
- The radius of adipocytes increases in the maturation process, keeping it a circle;
- The length of myocytes increase in the maturation process, the width is kept fixed making it an ellipse;
- While a cell has not reached its mature state, it is still considered a MSC.
- While a cell has not reached its mature state, it can always change its tendency toward another phenotype. For this change to happen, the maturity level first must reach zero before it can grow to another phenotype.
- (Future work:) the orientation of myocytes changes in time, its goal is to allign itself to another myocyte
- (Future work:) all non-matured cells can proliferate and die.

The exact details will be explained in the sections to come by the use of formula's.

4.2 The aging speed

The aging speed, or in other words, the rate of change of the maturity is given by:

$$U = U(t, \underline{x}(t), \underline{\psi}(t), \underline{m}(t)) = \frac{1}{2}(U_c(\psi_1, \psi_2) + U_m(\psi^M))$$

where U_c is the contribution to the aging speed by chemical influences and U_m is a similar result of the mechanical model.
In the following sections we will discuss in great detail how these variables are defined and calculated.

4.2.1 The Chemical model

The chemical contribution function is defined as:

$$U_c(\psi_1, \psi_2) = U_{max} \tanh\left(\frac{\psi_1 - \psi_2}{\xi}\right)$$

where U_{max} is the maximal differentiation speed, ξ is a scaling parameter and we have that

$$\psi_1(t, \underline{x}(t)) = \max_{i=1,\dots,p} \{c_i\}, \quad \psi_2(t, \underline{x}(t)) = \max_{i=1,\dots,p\setminus\psi_1} \{c_i\}$$

Where $c_k, k = 1, \dots, p$ is the concentration of the cytokine of phenotype k. As said before, in this model we will restrict ourselves to two phenotypes: Myocyte and Adipocytes. The former will be indexed by $k = 1$ and the latter by $k = 2$. The direction in which a certain cell will grow is given by which phenotype has the biggest cytokine concetration at that point.
By taking the `tanh` of the difference we get a more gradual change. This change can then be further influenced by the scaling parameter ξ.

We assume that every cell produces some kind of cytokine, which spreads across the domain according to the advection-diffusion model:

$$\begin{cases} \frac{\partial c_k}{\partial t} + \nabla \cdot (\underline{v} c_k) - D_k \Delta c_k & = \sum_{j=1}^{C \cdot L} \gamma_k(m_j) \delta(\underline{x} - \underline{x}_j(t)) & \underline{x} \in \Omega \\ c_k(0, \underline{x}) & = 0, & \underline{x} \in \Omega \\ D_k \frac{\partial c_k}{\partial n} + \kappa c_k & = 0, & \underline{x} \in \partial\Omega \end{cases}$$

Where $\underline{v}$ is the velocity of change in the domain in [units], D_k the diffusion coefficients [units], $\gamma_k(m_j)$ a scaling function and $\delta(x)$ the Dirac delta function.

The domain Ω is a simple square, with dimensions $l_0 \times l_0$ and the boundary condition applies to the whole (outside) boundary. On the boundary we have a parameter κ:

$$\frac{\partial c_k}{\partial n} = -\frac{\kappa}{D_k} c_k, \ \underline{x} \in \partial\Omega$$

This parameter influences the cytokine flux at the boundary.

In the source function we find the function γ_k. This function is defined to increase the cytokine production when a cell reaches a more mature state:

$$\gamma_A(m_j) = \begin{cases} -\gamma_A^0 m_j, & m_j \in [-1, 0) \\ 0, & m_j \in [0, 1] \end{cases} \qquad \gamma_M(m_j) = \begin{cases} 0, & m_j \in [-1, 0] \\ \gamma_M^0 m_j, & m_j \in (0, 1] \end{cases}$$

At this moment it is defined linearly, with a factor γ_k^0. This choice can be changed if arguments can be found to avoid a linear relation.

This function is then multiplied by the Dirac delta function, in the point $(\underline{x} - \underline{x}_j)$. From the summation we see that the index j runs from $1, \ldots, C \cdot L$.
Where C stands for the amount of cells and where L is the amount of nodes to approximate the boundary of a cell. Hence, we assume that the cytokine is sourced from the boundary of the cell. The more nodes used, the better we approximate this boundary condition of a cell.

(Future work:) in the appendix a small study can be found of the effect on the solution by using different cell-cytokine-sourcing options. (More on this later)

The chemical model is mainly driven by the secretation of cytokine of the cells. An addition option we could add is to simulate an injection of a certain cytokine, to boost the differentiation to a certain cell type.

4.2.2 The Mechanical model

The mechanical contribution function is defined as:

$$U_m(\psi_3) = U_{max} \tanh\left(\frac{\psi_3 - \tilde{\psi}}{\eta}\right)$$

where U_{max} represents the maximal differentiation speed [units] and $\tilde{\psi}$ can be seen as a treshhold function. When ψ_3 exceeds the value of $\tilde{\psi}$ the mechanical stimulus will be positive, hence we get more myocytes.
An interesting research subject would be to find an analytical representation of the definition of $\tilde{\psi}$, such that the force behaviour of both cell types can be discriminated.
The value of $\psi_3(\phi)$ is derived from the mechanical stresses caused by the cells:

$$\psi_3(\phi) = \int_{(t-\tau)+}^{t} w(s) \left(\frac{d\phi}{ds}\right)^2 ds$$

where ϕ is the octahedral shear strain, $w(s)$ is a weight-function and τ is a parameter that represents how much impact the change in the octahedral shear strain has on the environment.
The octahedral shear strain is given by the principle strains:

$$\phi = \frac{1}{3}\sqrt{(\varepsilon_1 - \varepsilon_2)^2 + (\varepsilon_1 - \varepsilon_3)^2 + (\varepsilon_2 - \varepsilon_3)^2}.$$

These principle strains are the eigenvalues of the strain tensor. This tensor is calculated from the mechanical balance equation, also known as the Navier-Cauchy equation.

$$\begin{cases} \nabla \cdot \underline{\underline{\sigma}} + \underline{F}_A + \underline{F}_M & = 0, \quad \underline{x} \in \Omega \\ \underline{\underline{\sigma}} \cdot \underline{u} + K\underline{u} & = 0, \quad \underline{x} \in \partial\Omega \end{cases}$$

where $\underline{u}$ is the displacement vector, $\underline{F}_k$ are vector forces produced by the cells, $\underline{n}$ is the outward normal and $\underline{\underline{\sigma}}$ is the mechanical stress.

In this model we assume that the displacements that occur are small. Also we assume that we are working with the infinitesimal strain theory, since we are working on a microscopic scale. In mathematical language this means that we assume that

$$\|\underline{u}\| << 1, \text{ and }, \|\|\nabla \underline{u}\| << 1.$$

Which results in the following approximation of the strain tensor:

$$\underline{\underline{\varepsilon}} = \frac{1}{2}(\nabla \underline{u} + (\nabla \underline{u})^T)$$

Where we have that

$$\nabla \underline{u} = \begin{bmatrix} \frac{\partial}{\partial x} \\ \frac{\partial}{\partial y} \\ \frac{\partial}{\partial z} \end{bmatrix} [u\ v\ w] = \begin{bmatrix} u_x & v_x & w_x \\ u_y & v_y & w_y \\ u_z & v_z & w_z \end{bmatrix}$$

Thus, the strain and displacement relation tells us that

$$\underline{\underline{\varepsilon}} = \begin{bmatrix} u_x & \frac{1}{2}(u_y + v_x) & \frac{1}{2}(w_x + u_z) \\ \frac{1}{2}(u_y + v_x) & v_y & \frac{1}{2}(w_y + v_z) \\ \frac{1}{2}(w_x + u_z) & \frac{1}{2}(w_y + v_z) & w_z \end{bmatrix}$$

By Hooke's law, we have the following relation between stress and strain:

$$E \begin{bmatrix} \varepsilon_{11} \\ \varepsilon_{22} \\ \varepsilon_{33} \\ \varepsilon_{12} \\ \varepsilon_{23} \\ \varepsilon_{13} \end{bmatrix} = \begin{bmatrix} 1 & -\nu & -\nu & 0 & 0 & 0 \\ -\nu & 1 & -\nu & 0 & 0 & 0 \\ -\nu & -\nu & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1+\nu & 0 & 0 \\ 0 & 0 & 0 & 0 & 1+\nu & 0 \\ 0 & 0 & 0 & 0 & 0 & 1+\nu \end{bmatrix} \begin{bmatrix} \sigma_{11} \\ \sigma_{22} \\ \sigma_{33} \\ \sigma_{12} \\ \sigma_{23} \\ \sigma_{13} \end{bmatrix}$$

Now we take the inverse of this matrix and get

$$\begin{bmatrix} \sigma_{11} \\ \sigma_{22} \\ \sigma_{33} \\ \sigma_{12} \\ \sigma_{23} \\ \sigma_{13} \end{bmatrix} = \frac{E}{(1+\nu)(1-2\nu)} \begin{bmatrix} 1-\nu & \nu & \nu & 0 & 0 & 0 \\ \nu & 1-\nu & \nu & 0 & 0 & 0 \\ \nu & \nu & 1-\nu & 0 & 0 & 0 \\ 0 & 0 & 0 & 1-2\nu & 0 & 0 \\ 0 & 0 & 0 & 0 & 1-2\nu & 0 \\ 0 & 0 & 0 & 0 & 0 & 1-2\nu \end{bmatrix} \begin{bmatrix} \varepsilon_{11} \\ \varepsilon_{22} \\ \varepsilon_{33} \\ \varepsilon_{12} \\ \varepsilon_{23} \\ \varepsilon_{13} \end{bmatrix}$$

Substituting this back into matrix form and using the strain-displacement relation, we get:

$$\underline{\underline{\sigma}} = \frac{E}{(1+\nu)(1-2\nu)} \begin{bmatrix} u_x(1-\nu) + v_y\nu + w_z\nu & \frac{1}{2}(1-2\nu)(u_y + v_x) & \frac{1}{2}(1-2\nu)(w_x + u_z) \\ \frac{1}{2}(1-2\nu)(u_y + v_x) & u_x\nu + v_y(1-\nu) + w_z\nu & \frac{1}{2}(1-2\nu)(w_y + v_z) \\ \frac{1}{2}(1-2\nu)(w_x + u_z) & \frac{1}{2}(1-2\nu)(w_y + v_z) & u_x\nu + v_y\nu + w_z(1-\nu) \end{bmatrix}$$

Now we are able to solve the problem and get the amount of displacement of hte domain caused by the external forces.

The force vector

The force vector plays an important role in this model. Just like the source function in the chemical model, is the force vector the driving force behind the mechanical model.
Besides the importance of this vector, it is also very complicated to get a realistic formulation. Because the biology behind it is so complex, we are required to simplify the behaviour.

This simplification means that we neglect the internal molecular reaction that cause force exertion on the extra cellular matrix (ECM). Hence, we will only look at the resulting behaviour of a cell. This concludes that fat cells push against the ECM when growing in size. In addition, muscle cells also pull on the ECM.

We assume that the boundary of a cell exerts a certain amount of force on the ECM. The direction in which this happens, is the normal direction on the cell. The total force a cell produces is then equal to the sum of all the small contributions of the force on the boundary.
By these assumptions, we came up with a force vector. We start with an example of a myocyte force vector, the adipocyte force vector is defined in an analogous way.

$$\underline{F}_M(t, \underline{x}(t)) = \sum_{j=1}^{C} \underline{F}_j^M(t, \underline{x}(t))$$

Hence, the force vectorfield is the summation of all the individual cells.
The next step is to define $\underline{F}_j^M$, the force that *one* cell produces. As stated before, we assume that the boundary exerts the force on the ECM in the normal direction of the cell. This constitutes the following vector:

$$F_j^M(t, \underline{x}(t)) = \int_{\partial\Omega_j} P(t, m_j)\underline{n}(\underline{x}')\delta(\underline{x} - \underline{x}')d\Gamma'$$

where $\underline{x}'$ is a node on the boundary. From a computational point of view it is easier to approximate this integral by a (discrete) summation

$$F_j^M(t, \underline{x}(t)) = \sum_{e=1}^{L} P(t, m_j)\underline{n}(\underline{x}_e)\delta(\underline{x} - \underline{x}_e)\Delta\Gamma_e$$

Just like with the sourcing of the chemical model, the force is produced on these L discrete points on the boundary of the cell in the (outward)normal direction of this point.

The function $P(t, m_j)$ present the amount of force produced. This is given by

$$P(t, m_j) = \begin{cases} 0 & m_j \in [-1, 0] \\ P_0 m_j \cos(\omega t) & m_j \in (0, 1] \end{cases}$$

where P_0 is the force produced by the cell and $\omega = \frac{2\pi}{T}$, is the frequency at which forces contract. Here T is the period of the muscle contraction.

Because our cell shapes are either circles or ellipses, we can analytically calculate the normal directions.
The equation for an ellipse is given by $f(x, y) = \frac{x^2}{a^2} + \frac{y^2}{b^2} = 1$ where $a, b \in \mathbb{R}_{>0}$. We will have a circle when $a = b$. The outward normal is defined by

$$\underline{n} = \begin{bmatrix} \frac{\partial f}{\partial x} \\ \frac{\partial f}{\partial x} \end{bmatrix} = \begin{bmatrix} 2\frac{x}{a^2} \\ 2\frac{y}{b^2} \end{bmatrix}$$

Then there is also the Dirac delta function, which simplifies the calculation when we use the Finite Element Method to solve this problem. More on this later.
The definition of $\Delta\Gamma_e$ is the length between two consecutive points on the boundary. Because we are also dealing with ellipses, the calculations for $\Delta\Gamma_e$ are done rather brutal.
We divide the length between two consecutive boundary points in 1000 sub intervals. The length $\Delta\Gamma_e$ is then approximated by the summation over these 1000 smaller distances. The length of these sub intervals are calculated using the Pythagoras' theorem.

The force evaluation of adipocytes is defined in an analogous way. Instead of a function $P(t, m_j)$, we have a function called $Q(R)$:

$$Q(R) = \begin{cases} 0 & 0 \leq R \leq R_A \\ \alpha(R - R_A) & R_A < R \end{cases}$$

Here R is the radius of cell j and R_A is the *activation* radius. If this cell becomes larger than this value R_A, it starts pushing its surroundings.
The coefficient α is similar to P_0, it shows how much force the fat cells exert.

The radius of a (fat) cell also changes in time, this is defined by the following formula

$$R(m) = \begin{cases} R_0 + (R_0 - R_\infty)m, & m \in [-1, 0] \\ R_0, & m \in (0, 1] \end{cases}$$

Here R_0 is the initial radius and R_∞ is the maximum radius.
The length of a (muscle) cell also changes in time, this is defined by the following formula

$$L(m) = \begin{cases} L_0 + (L_0 - L_\infty)m, & m \in (0, 1] \\ L_0, & m \in [-1, 0] \end{cases}$$

Here L_0 is the initial length and L_∞ is the maximum length.

4.3 Cell Movement

The last subject we will treat for this model is the cell movement. This continuous behaviour of the cells is given by the following equation

$$d\underline{x}_j(t) = \sigma(m_j)d\mathbf{W}(t) + \underline{v}_p(t,\underline{x})dt + 4\Big[\,\mu_M m_j(1-m_j)H(m_j)\nabla c_M$$

$$-\mu_a m_j(1+m_j)H(-m_j)\nabla c_A\,\Big]\,dt$$

where we have that $\sigma(m_j) = \sigma_0(m_j+1)(1-m_j), \sigma_0 = \sqrt{2D_k}$, $H(s)$ is the heaviside function.

This definition of the standard deviation in the random walk make sure that as a cell becomes mature, its random movement will be reduced.
The function $\underline{v}_p$ makes sure that when a cell collides, they bounce off of each other.
The last term is used to stimulate movement towards high concentration of cytokine for its corresponds cell type.

In order to solve this Stochastic Differential Equation (SDE) we use the Euler-Maruyama method. This is a generalization of the well known Euler methods for time differentiation.
When we use this method, we get the following updating formula:

$$\underline{x}_j^{n+1}(t) = \underline{x}_j^n(t) + \sigma(m_j)\Delta\mathbf{W}(t) + \underline{v}_p(t,\underline{x})\Delta t + 4\Big[\,\mu_M m_j(1-m_j)H(m_j)\nabla c_M$$

$$-\mu_a m_j(1+m_j)H(-m_j)\nabla c_A\,\Big]\,\Delta t$$

Here n stands for the nth timestep.

5 Numerical implementation 2D-model

The numerical model has been implemented in a rough way. As will be stated in the Future Work section, there are still parts to improve, but the main mechanisms work.
Because of that we can present some preliminary results. These will probably not act as we expect, yet, but that will be a matter of time.

5.1 Test case: influence of cytokine

In this section we will show some simulation results concerning the 'convergence' of the maturity. We will try to modify the cytokine secretion is such a way that we end up with only myocytes, adipocytes or a decent mix between these two.

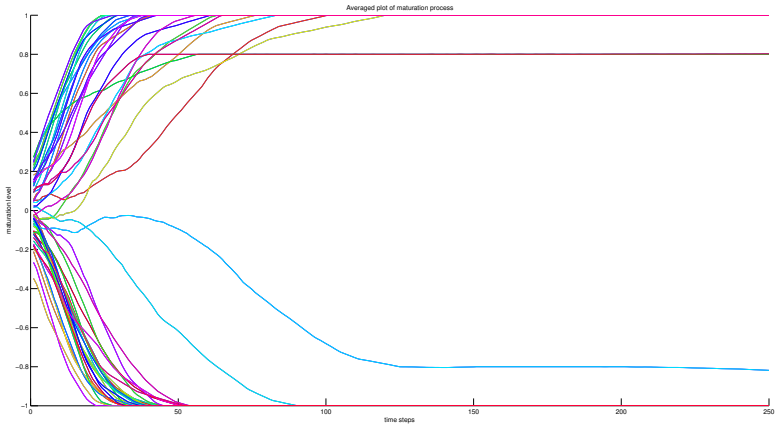
During these tests we have the following parameter set

- $E = 16 \cdot 10^{-3}$
- $\nu = 0.3$
- $\tilde{\psi} = \frac{1}{5}\mathrm{N}(0,1), U_{max} = 0.1, \xi = 0.05, \eta = 10$
- $K = 10$, $\kappa = 0.1$
- $\alpha = P_0 = 1 \cdot 10^{-3}$
- $T = 10, \omega = 2\pi$
- $D_A = D_M = 1 \cdot 10^{-3}, \mu_M = \mu_M = 9 \cdot 10^{-3}$

Where we let the following variables vary: $\gamma_M, \gamma_A \in \{1 \cdot 10^{-3}, 1 \cdot 10^{-2}\}$. To test what the influence is of the change in the cytokine parameter, we run our simulation 50 times with ten cells. The starting maturity of these are chosen at random. The simulation stops after 250 time steps.

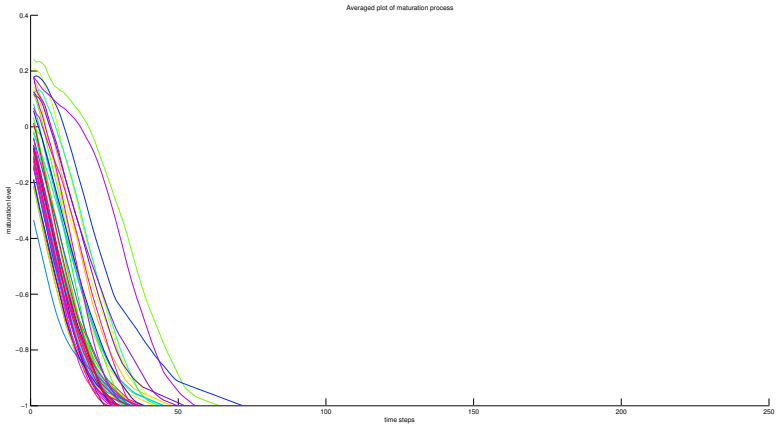
When we present the results below, note that one line is the mean of the behaviour of ten cells during one simulation.

In the first case we choose $\gamma_M = 1 \cdot 10^{-2}, \gamma_A = 1 \cdot 10^{-2}$. Then we get the following results



On the x-axis we have the amount of time steps and on the vertical axis the level of maturity, ranging between -1 and 1.
The graph shows an (almost) even distribution of myocytes and adipocytes. Which is what we would expect when both cytokine source functions have the same value.

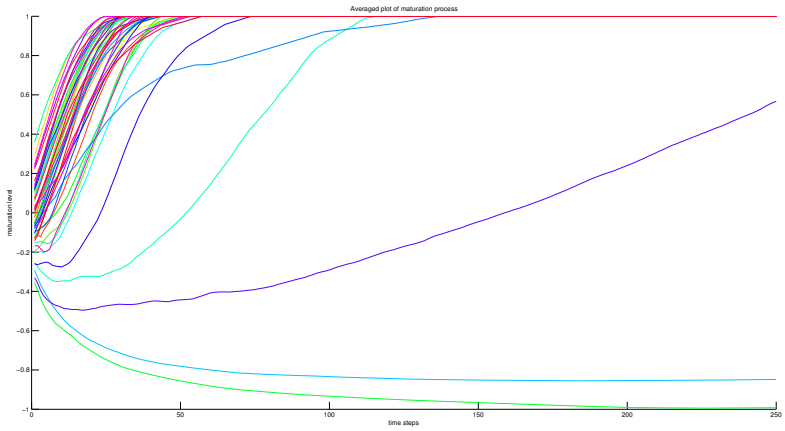
In the second case we choose $\gamma_M = 1 \cdot 10^{-3}, \gamma_A = 1 \cdot 10^{-2}$. Then we get the following results



On the x-axis we have the amount of time steps and on the vertical axis the level of maturity, ranging between -1 and 1.

We would expect that when the cytokine production of adipocytes is dominating, the end distribution will laso result in more adipocytes. From the plot it can be seen that this is indeed the case.

In the last case we choose $\gamma_M = 1 \cdot 10^{-2}, \gamma_A = 1 \cdot 10^{-3}$. Then we get the following results



On the x-axis we have the amount of time steps and on the vertical axis the level of maturity, ranging between -1 and 1.

We get an analogous result as in the previous case. We end up with more myocytes when we increase the cytokine production of these cells.

Conclusion:

These small experiments are just some toy cases to get used to the (preliminary) model. It is nice to see that the model behaves as we would expect. This gives some motivation that the model is working correctly.

6 Future work

The proposed model is far for complete. The ideas for behaviour implementation is the start. In the future, we wish to add the following

- Add cell proliferation and death in the model. This effect should also affect the chemical model, not only in-/decrease the number of cells.
- Add a model for myocyte rotation, cell size in- and decrease.
- Reconsider if we want to model myocytes or maybe myoblasts that can fuse together.
- If necessary, and when there is enough time, simulate the model in 3D.
- Investigate what the influence is of the cytokine source function implementation. What if we would source the cytokine only from the center of the cell, what if we would do it from every node on the cell, what if we would fix the position and make a boundary condition that produces cytokine.
- Find a definition for the weight function $w(s)$ to calculate ψ_3.
- Assign units to the parameters and give logical feedback to the chosen values.

7 Appendix

Notation

- $\underline{x}$ - a vector
- $\underline{\underline{x}}$ - a tensor
- $f_{x,y,z}$ - derivative of $f(x,y,z)$ towards x, y or z
- x^i - ith index of vector $\underline{x}$

Variables

- t - time
- $\underline{x}(t)$ - position vector at time t
- i, j, k - index variable
- $m_j(t)$ - maturity rate of jth cell at time t
- $\underline{\psi}(\underline{x}(t), t)$ - collection vector of chem/mechanical stimuli
  - $\psi^1(\underline{x}(t), t) = c_M(\underline{x}(t), t)$
  - $\psi^2(\underline{x}(t), t) = c_A(\underline{x}(t), t)$
  - $\psi^3(t, \phi(t))$
- $U(t, \underline{x}(t), \underline{\psi}(t))$ - aging speed
- $c_k(\underline{x}(t), t)$ - cytokine concentration at position $\underline{x}$ and time t.
- $\gamma_k(m_j)$ - source function for the amount of cytokine secreted by cell j.
- $U_c(\psi^1, \psi^2)$ - contribution to aging speed by chemical stuff
- $U_m(\psi^3)$ - contribution to aging speed by mechanical stuff
- $\underline{\underline{\sigma}}$ - stress tensor
- $\underline{\underline{\varepsilon}}$ - strain tensor
- ε_i - principle strain
- $\phi(\varepsilon_1, \varepsilon_2, \varepsilon_3)$ - octahedral shear strain
- $\underline{F_k}(\underline{x}(t), t)$ - force due to cell type k

Parameters

We have the following parameters:

- D_k - cytokine diffusion of cell type k
- γ_k^0 - scaling parameter in cytokine secretation of cell type k
- κ - present in the boundary condition of the cytokine problems
- U_{max} - maximum differentiation speed
- ξ - slope of the transition between two phenotypes
- $\tilde{\psi}$ - point of transition that the mechanical stimulus changes its phenotype direction
- η - slope of transition between two phenotypes?
- τ - represents the length of the time-interval that has an impact on the octahedral shear strain
- $w(s)$ - weight function (of time)
- K - present in the boundary condition of the mechanical problem

Abbreviations

- MSC - Mesenchymal stem cell
- FEM - Finite Element Method

7.1 The Finite Element Method

In this paper we will use the Finite Element Method (FEM) to solve the differential equations we have. In order to understand the preparation work in order to use the method, we give a(n) (small) introduction.

In most cases, there is a problem that needs to be solved. This problem consist of a (differential) equation with initial and boundary conditions.
The first step towards the finite element method is to derive the weak form. (See comment on why the weak form).
This formulation is obtained by multiplying the differential equation by a test function $\phi \in \mathfrak{H}^1$ (thus from the Sobolev space) and then integrating this over the whole domain Ω.
In most cases, this new formulation allows us to simplify the equation. Either by using Gauss'/Green's theorem, or by using the boundary conditions.

The next step consists of approximating the (unknown) functions by basis functions. In general this is done by

$$f(x) = \sum_{j=1}^{N} f_j \phi_j(x)$$

where f_j are the unknown coefficients (to be solved for) and ϕ_j are the basis functions of the problem. The test function $\phi(x)$ is immediately approximated by $\phi_i(x)$. The reason for this can be found in [20, p.123-124].

Note however that the approximation in these N points corresponds to the discretization of the domain in N points. Hence, at every node i we have a different basis function.

The definition of these basis functions is given by

- $\phi_i(\underline{x})$ is linear per sub-domain. $i = 1, \ldots, N$
- $\phi_i(\underline{x}_j) = \delta_{ij}$. $i, j = 1, \ldots, N$

where $\underline{x}_j$ is the coordinate of the j^{th} node.

The sub-domain that we are talking about in this definitions comes from the discretization of the domain, also called the meshing process. Here we scattered the domain with points and defined sub-domains with these points.
These sub-domains can be lines (1D), triangles (2D), rectangles (2D), quadrilaterals (2D), tetrahedrons (3D) and so on.

Therefore, the basis function $\phi_i(x)$ depends on what kind of sub-domain we choose. Here are some examples:

lines, for the 1D case

$$\phi_i(\underline{x}) = a_0^i + a_1^i x$$

triangles, for the 2D case

$$\phi_i(\underline{x}) = a_0^i + a_1^i x + a_2^i y$$

tetrahedrons, for the 3D case

$$\phi_i(\underline{x}) = a_0^i + a_1^i x + a_2^i y + a_3^i z$$

The coefficients used here, a_k^i, will be discussed later in this section.

The next step is to approximate the integral $\int_\Omega$ by $\sum_{e=1}^{M} \int_{\Omega_e}$, which we got because of the weak formulation.. Here $e = 1, \ldots, M$ represents all the elements (sub-domains) we have defined.

This step really shows why the FEM is such a powerful method. By this approximation we can locally (independent of neighbouring elements) discretize the problem. All the information we gather from such an element-wise operation is put into an element matrix/vector.
What we end up with is an equation where we integrate products/derivatives of the basis functions. Because of the choice of the simple basis functions, these integrals are not hard to compute. In most cases we can calculate them before hand by using Holand and Bell's theorem.
In the end, we need to assemble all these element matrices/vectors and use the boundary conditions to be able to solve the problem.

It is possible that in the obtained weak form, we are left with a boundary integral. While we are approximating the integrals, we need to separate the domain- and boundary-integrals. This prevents us from using a confusing matrix notation while treating every element separately.

Thus, at each element we will get an element matrix (from the differential equations), possibly a boundary element matrix (from the boundary integral) and possibly an element vector (from the external force).
To give an example, such a construction could look like:

$$\begin{bmatrix} \mathbf{S}_{11} & \mathbf{S}_{12} & \mathbf{S}_{13} \\ \mathbf{S}_{21} & \mathbf{S}_{22} & \mathbf{S}_{23} \\ \mathbf{S}_{31} & \mathbf{S}_{32} & \mathbf{S}_{33} \end{bmatrix} \begin{bmatrix} \mathbf{u}_1 \\ \mathbf{u}_2 \\ \mathbf{u}_3 \end{bmatrix} = \begin{bmatrix} \mathbf{f}_1 \\ \mathbf{f}_2 \\ \mathbf{f}_3 \end{bmatrix}$$

where $\mathbf{S}_{ij} = \int_{\Omega_e} \nabla\phi_i \nabla\phi_j d\Omega, \mathbf{f}_i = \int_{\Omega_e} f(\underline{x})\phi_i(\underline{x}) d\Omega$ and $\mathbf{u}_i$ represent the local nodes. These local nodes have a certain relationship with the global nodes $u_i, i = 1, \ldots, N$. This relation is very important in the assembly process.
When the assembly is done we are left with a typical structure:

$$M\underline{f} + B\underline{f} = \underline{v}$$

where the vector $\underline{f}$ contains all the coefficients $f_j, j = 1, \ldots, N$
In the following sections we will derive this for the mechanical/chemical model.

The last thing we will concern ourselves with, are the coefficients of the basis functions. The solution to this can be found by using the definition of the basis functions. By using the basis functions that define a tetrahedron, we see that we must be able to solve the following system

$$\begin{bmatrix} 1 & \mathbf{x}_1 & \mathbf{y}_1 & \mathbf{z}_1 \\ 1 & \mathbf{x}_2 & \mathbf{y}_2 & \mathbf{z}_2 \\ 1 & \mathbf{x}_3 & \mathbf{y}_3 & \mathbf{z}_3 \\ 1 & \mathbf{x}_4 & \mathbf{y}_4 & \mathbf{z}_4 \end{bmatrix} \begin{bmatrix} a_0^1 & a_0^2 & a_0^3 & a_0^4 \\ a_1^1 & a_1^2 & a_1^3 & a_1^4 \\ a_2^1 & a_2^2 & a_2^3 & a_2^4 \\ a_3^1 & a_3^2 & a_3^3 & a_3^4 \end{bmatrix} = \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}$$

This only happens when we have that the position determinant Δ does not vanish:

$$\Delta = \begin{vmatrix} 1 & \mathbf{x}_1 & \mathbf{y}_1 & \mathbf{z}_1 \\ 1 & \mathbf{x}_2 & \mathbf{y}_2 & \mathbf{z}_2 \\ 1 & \mathbf{x}_3 & \mathbf{y}_3 & \mathbf{z}_3 \\ 1 & \mathbf{x}_4 & \mathbf{y}_4 & \mathbf{z}_4 \end{vmatrix} \neq 0$$

What we see is that $|\Delta|$ represents twice the volume of the tetrahedron. This variable will be used in the definition of the coefficients.

By taking the inverse of the position matrix, we get a solution for the coefficient matrix:

$$\begin{bmatrix} a_0^1 & a_0^2 & a_0^3 & a_0^4 \\ a_1^1 & a_1^2 & a_1^3 & a_1^4 \\ a_2^1 & a_2^2 & a_2^3 & a_2^4 \\ a_3^1 & a_3^2 & a_3^3 & a_3^4 \end{bmatrix} = \begin{bmatrix} 1 & \mathbf{x}_1 & \mathbf{y}_1 & \mathbf{z}_1 \\ 1 & \mathbf{x}_2 & \mathbf{y}_2 & \mathbf{z}_2 \\ 1 & \mathbf{x}_3 & \mathbf{y}_3 & \mathbf{z}_3 \\ 1 & \mathbf{x}_4 & \mathbf{y}_4 & \mathbf{z}_4 \end{bmatrix}^{-1} \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix} = \begin{bmatrix} 1 & \mathbf{x}_1 & \mathbf{y}_1 & \mathbf{z}_1 \\ 1 & \mathbf{x}_2 & \mathbf{y}_2 & \mathbf{z}_2 \\ 1 & \mathbf{x}_3 & \mathbf{y}_3 & \mathbf{z}_3 \\ 1 & \mathbf{x}_4 & \mathbf{y}_4 & \mathbf{z}_4 \end{bmatrix}^{-1}$$

After evaluation we see that $a_0^i = 1 - a_1^i - a_2^i - a_3^i$. By defining the following operator

$$A(f_{\{i,j,k\}}, g_{\{i,j,k\}}) = \begin{vmatrix} 1 & 1 & 1 \\ f_i & f_j & f_k \\ g_i & g_j & g_k \end{vmatrix}$$

we can define the coefficients as:

$$a_1^1 = A(\mathbf{y}_{\{2,3,4\}}, \mathbf{z}_{\{2,3,4\}}), a_1^2 = A(\mathbf{y}_{\{1,3,4\}}, \mathbf{z}_{\{1,3,4\}}), a_1^3 = A(\mathbf{y}_{\{1,2,4\}}, \mathbf{z}_{\{1,2,4\}}), a_1^4 = A(\mathbf{y}_{\{1,2,3\}}, \mathbf{z}_{\{1,2,3\}})$$

$$a_2^1 = A(\mathbf{x}_{\{2,3,4\}}, \mathbf{z}_{\{2,3,4\}}), a_2^2 = A(\mathbf{x}_{\{1,3,4\}}, \mathbf{z}_{\{1,3,4\}}), a_2^3 = A(\mathbf{x}_{\{1,2,4\}}, \mathbf{z}_{\{1,2,4\}}), a_2^4 = A(\mathbf{x}_{\{1,2,3\}}, \mathbf{z}_{\{1,2,3\}})$$

$$a_3^1 = A(\mathbf{x}_{\{2,3,4\}}, \mathbf{y}_{\{2,3,4\}}), a_3^2 = A(\mathbf{x}_{\{1,3,4\}}, \mathbf{y}_{\{1,3,4\}}), a_3^3 = A(\mathbf{x}_{\{1,2,4\}}, \mathbf{y}_{\{1,2,4\}}), a_3^4 = A(\mathbf{x}_{\{1,2,3\}}, \mathbf{y}_{\{1,2,3\}})$$

7.1.1 Derivation (weak) formulation mechanical model

The mechanical problem was characterised by the following equations

$$\begin{cases} E_\nu \nabla \cdot \underline{\underline{\sigma}}^1 = -f^1, & \underline{x} \in \Omega \\ E_\nu \nabla \cdot \underline{\underline{\sigma}}^2 = -f^2, & \underline{x} \in \Omega \\ E_\nu \nabla \cdot \underline{\underline{\sigma}}^3 = -f^3, & \underline{x} \in \Omega \\ \underline{\underline{\sigma}} \cdot \underline{n} + K\underline{u} = 0, & \underline{x} \in \partial\Omega \end{cases}$$

where $E_\nu = \frac{E}{(1+\nu)(1-2\nu)}$ and $\underline{f}$ is the force contribution of the cells. The value K represents a spring-like boundary, thus the resistance the boundary will put up against the internal forces.

We will now use the finite element method as discussed in the previous chapter. Most comment will be left out. We will work out one of the three equations and let Ω be a 3D domain.
The weak form is given by

$$\begin{cases} E_\nu \int_\Omega \nabla \cdot \underline{\underline{\sigma}}^1 \phi \; d\Omega = -\int_\Omega f^1 \phi \; d\Omega, & \underline{x} \in \Omega \\ \\ \underline{\underline{\sigma}} \cdot \underline{n} + K\underline{u} = 0, & \underline{x} \in \partial\Omega \end{cases}$$

Using Green's Theorem:

$$\begin{cases} -\int_\Omega \underline{\underline{\sigma}}^1 \nabla \cdot \phi \; d\Omega + \oint_\Gamma (\underline{\underline{\sigma}}^1 \cdot \underline{n})\phi \; d\Gamma = -\frac{1}{E_\nu} \int_\Omega f^1 \cdot \phi d\Omega \\ \underline{\underline{\sigma}} \cdot \underline{n} + K\underline{u} = 0, \quad \underline{x} \in \partial\Omega \end{cases}$$

Now we recognize that the boundary condition can be used in the boundary integral. Observe that $\underline{\underline{\sigma}} \cdot \underline{n} = -K\underline{u} \Rightarrow \underline{\underline{\sigma}}^1 \cdot \underline{n} = -Ku$. Where u is the displacement in the x-direction.
Thus we get

$$-\int_\Omega \underline{\underline{\sigma}}^1 \cdot \nabla \phi \; d\Omega - K \oint_\Gamma u \cdot \phi \; d\Gamma = -\frac{1}{E_\nu} \int_\Omega f^1 \cdot \phi d\Omega$$

$$\int_\Omega \underline{\underline{\sigma}}^1 \cdot \nabla \phi \; d\Omega + K \oint_\Gamma u \cdot \phi \; d\Gamma = \frac{1}{E_\nu} \int_\Omega f^1 \cdot \phi d\Omega$$

Approximate the domain integral

$$\sum_{e=1}^{M} \int_{\Omega_e} \underline{\underline{\sigma}}^1 \cdot \nabla \phi \; d\Omega_e + K \oint_\Gamma u \cdot \phi \; d\Gamma = \sum_{e=1}^{M} \frac{1}{E_\nu} \int_{\Omega_e} f^1 \cdot \phi d\Omega_e$$

Expand the solutions in a serie of basis functions, an example:

$$u(\underline{x}) = \sum_{j=1}^{N} u_j \phi_j(\underline{x}), \frac{\partial u(\underline{x})}{\partial x} = \sum_{j=1}^{N} u_j \frac{\partial \phi(\underline{x})}{\partial x}$$

We now focus on one tetrahedron

$$\int_{\Omega_e} \underline{\sigma}^1 \cdot \nabla\phi \; d\Omega_e + K \oint_{\Gamma} u \cdot \phi \; d\Gamma = \frac{1}{E_\nu} \int_{\Omega_e} f^1 \cdot \phi \; d\Omega_e$$

In the pages to come we will write the domain- and boundary integrals separately. This is done because the element matrix of a boundary element is one dimensionless than the element matrix of a sub-domain. Using the definition for $\underline{\sigma}^1$ and the divergence operator, we get:

$$\int_{\Omega_e} \begin{bmatrix} (1-\nu)u_x + \nu v_y + v w_z \\ \frac{1}{2}(1-2\nu)(u_y + v_x) \\ \frac{1}{2}(1-2\nu)(w_x + u_z) \end{bmatrix} \cdot \begin{bmatrix} \frac{\partial \phi_i}{\partial x} \\ \frac{\partial \phi_i}{\partial y} \\ \frac{\partial \phi_i}{\partial z} \end{bmatrix} \; d\Omega_e = \frac{1}{E_\nu} \int_{\Omega_e} f^1 \cdot \phi_i \; d\Omega_e, i = 1,2,3,4$$

$$K \oint_{\Gamma} u \cdot \phi_i \; d\Gamma_k, i = 1,2,3$$

Expanding this formula and using the approximation for $u(\underline{x}), v(\underline{x})$ and $w(\underline{x})$:

$$\int_{\Omega_k} \sum_{j=1}^{4} u_j \left[(1-\nu) a_1^j a_1^i + \frac{1}{2}(1-2\nu)(a_2^j a_2^i + a_3^j a_3^i) \right] + \sum_{j=1}^{4} v_j \left[\nu a_2^j a_1^i + \frac{1}{2}(1-2\nu) a_1^j a_2^i \right] +$$

$$\sum_{j=1}^{4} w_j \left[\nu a_3^j a_1^i + \frac{1}{2}(1-2\nu) a_1^j a_3^i \right] d\Omega_k = \frac{1}{E_\nu} \int_{\Omega_k} f^1 \cdot \phi_i \; d\Omega_k, i = 1,2,3,4$$

These coefficients inside the integral are already determined by the shape of the sub-domain. Hence, since we have that $\frac{\Delta}{n!} = \int_{\Omega_k} d\Omega, n \in \mathbb{N}$, we can calculate these integrals.
For the boundary integral, we will use Holand-Bell's theorem to obtain

$$K \sum_{j=1}^{3} u_j \oint_{\Gamma_k} \phi_j \cdot \phi_i \; d\Gamma_k = K \frac{\Delta}{24} \begin{bmatrix} 2 & 1 & 1 \\ 1 & 2 & 1 \\ 1 & 1 & 2 \end{bmatrix} \begin{bmatrix} \mathbf{u}_1 \\ \mathbf{u}_2 \\ \mathbf{u}_3 \end{bmatrix}$$

The force vector is a different story. Remember that

$$\underline{F}_M(t, \mathbf{x}, \underline{m}) = \sum_{J=1}^{C} \underline{F}_J^M(t, \mathbf{x}, m_J) = \sum_{J=1}^{C} \left(\sum_{I=1}^{L} P(t, m_J) \mathbf{n}(\mathbf{x}_I) \delta(\mathbf{x} - \mathbf{x}_I) \Delta\Gamma \right)$$

The variable $\mathbf{x}_I$ is the position of the I^{th} boundary-cell node and $\mathbf{n}(\mathbf{x}_I)$ is the normal vector at that point.
If we look at a specific direction, for example the x-direction, we get:

$$f^1 = \sum_{J=1}^{C} \left(\sum_{I=1}^{L} (P(t, m_J) + Q(t, m_J)) n_I^1 \delta(x - x_I) \Delta\Gamma \right)$$

Thus our external force vector is equal to:

$$\frac{1}{E_\nu}\int_{\Omega_k} f^1\phi_i\, d\Omega_k = \frac{1}{E_\nu}\sum_{J=1}^{C}\left(\sum_{I=1}^{L}(P(t,m_J)+Q(t,m_J))n_I^1\Delta\Gamma\int_{\Omega_k}\delta(x-x_I)\phi_i\, d\Omega_k\right)$$

In the case that x_I lies in the domain of Ω_k, the Dirac delta function takes on the following value

$$\frac{1}{E_\nu}\int_{\Omega_k} f^1\phi_i\, d\Omega_k = \frac{1}{E_\nu}\sum_{J=1}^{C}\left(\sum_{I=1}^{L}(P(t,m_J)+Q(t,m_J))n_I^1\Delta\Gamma\phi_i(x_I)\right)$$

In summary, for one element we find the following equations:

$$M_1^{\Omega_e}\mathbf{u}+M_2^{\Omega_e}\mathbf{v}+M_3^{\Omega_e}\mathbf{w}=\mathbf{f}^{1,\Omega_e}$$

with the following contribution to the boundary contribution

$$B^{\Omega_e}\mathbf{u}$$

For completeness, we will also give the end result for the other two equations. For the second problem:

$$\begin{cases} E_\nu\nabla\cdot\underline{\sigma}^2=-f^2, & \underline{x}\in\Omega \\ \underline{\underline{\sigma}}\cdot\underline{n}+K\underline{u}=0, & \underline{x}\in\partial\Omega \end{cases}$$

we get

$$\int_{\Omega_k}\sum_{j=1}^{4}u_j\left[\nu a_1^j a_2^i+\frac{1}{2}(1-2\nu)a_2^j a_1^i\right]+\sum_{j=1}^{4}v_j\left[(1-\nu)a_2^j a_2^i+\frac{1}{2}(1-2\nu)(a_1^j a_1^i+a_3^j a_3^i)\right]+$$

$$\sum_{j=1}^{4}w_j\left[\nu a_3^j a_2^i+\frac{1}{2}(1-2\nu)a_2^j a_3^i\right]d\Omega_k=\frac{1}{E_\nu}\int_{\Omega_k}f^2\cdot\phi_i\, d\Omega_k, i=1,2,3,4$$

$$K\sum_{j=1}^{3}v_j\oint_{\Gamma_k}\phi_j\cdot\phi_i\, d\Gamma_k=K\frac{\Delta}{24}\begin{bmatrix}2&1&1\\1&2&1\\1&1&2\end{bmatrix}\begin{bmatrix}\mathbf{v}_1\\\mathbf{v}_2\\\mathbf{v}_3\end{bmatrix}$$

For the third problem

$$\begin{cases} E_\nu\nabla\cdot\underline{\sigma}^3=-f^3, & \underline{x}\in\Omega \\ \underline{\underline{\sigma}}\cdot\underline{n}+K\underline{u}=0, & \underline{x}\in\partial\Omega \end{cases}$$

we get

$$\int_{\Omega_k}\sum_{j=1}^{4}u_j\left[\nu a_1^j a_3^i+\frac{1}{2}(1-2\nu)a_3^j a_1^i\right]+\sum_{j=1}^{4}v_j\left[\nu a_2^j a_3^i+\frac{1}{2}(1-2\nu)a_3^j a_2^i\right]+$$

$$\sum_{j=1}^{4} w_j \left[(1-\nu) a_3^j a_3^i + \frac{1}{2}(1-2\nu)(a_1^j a_1^i + a_2^j a_2^i) \right] d\Omega_k = \frac{1}{E_\nu} \int_{\Omega_k} f^3 \cdot \phi_i \, d\Omega_k, i = 1,2,3,4$$

$$K \sum_{j=1}^{3} w_j \oint_{\Gamma_k} \phi_j \cdot \phi_i \; d\Gamma_k = K \frac{\Delta}{24} \begin{bmatrix} 2 & 1 & 1 \\ 1 & 2 & 1 \\ 1 & 1 & 2 \end{bmatrix} \begin{bmatrix} \mathbf{w}_1 \\ \mathbf{w}_2 \\ \mathbf{w}_3 \end{bmatrix}$$

7.1.2 Derivation (weak) formulation chemical model

The chemical model we have is given by the following differential equations

$$\frac{\partial c_k}{\partial t} + \nabla(\underline{v}c_k) - D_k \Delta c_k = \sum_{J=1}^{C} \gamma_k(m_j)\delta(\underline{x} - \underline{x}_j(t)) = S(\underline{x})$$

$$c_k(0, \underline{x}) = 0, \underline{x} \in \Omega$$

$$D_k \frac{\partial c_k}{\partial n} + \kappa c_k = 0, \underline{x} \in \partial\Omega$$

where $k = \{A, M\}$, which are the two type of cells we are dealing with. Note that $\underline{v} = \frac{d\underline{u}}{t}$. We follow the same procedure to get to the Finite Elment Method.

Multiplying by a test function $\phi \in \mathfrak{H}^1$ and integrating over the domain Ω:

$$\int_\Omega \frac{\partial c_k}{\partial t}\phi + \nabla(\underline{v}c_k)\phi - D_k \Delta c_k \phi \; d\Omega = \int_\Omega S(\underline{x})\phi \; d\Omega$$

Using Green's Theorem and the boundary condition to reduce the second order derivative to:

$$\int_\Omega \frac{\partial c_k}{\partial t}\phi + \nabla(\underline{v}c_k)\phi + D_k \nabla c_k \nabla\phi \; d\Omega + \kappa \oint_\Gamma c_k \phi \; d\Gamma = \int_\Omega S(\underline{x})\phi \; d\Omega$$

Expanding the gradient term:

$$\int_\Omega \frac{\partial c_k}{\partial t}\phi + \underline{v}\nabla c_k \phi + c_k \nabla \underline{v}\phi + D_k \nabla c_k \nabla\phi d\Omega + \kappa \oint_\Gamma c_k \phi d\Gamma = \int_\Omega S(\underline{x})\phi \; d\Omega$$

Intermezzo

Notice that the first two terms of the integral form a material derivative:

$$\int_\Omega \left(\frac{\partial c_k}{\partial t} + \underline{v}\nabla c_k \right) \phi d\Omega = \int_\Omega \left(\frac{\partial c_k}{\partial t} + \frac{\partial c_k}{\partial x}\frac{dx}{dt} + \frac{\partial c_k}{\partial y}\frac{dy}{dt} \right) \phi d\Omega = \int_\Omega \frac{Dc_k}{Dt}\phi d\Omega$$

We would like to have the test function also inside the material derivative operator. Hence we get:

$$\frac{Dc_k}{Dt}\phi = \frac{D(c_k\phi)}{Dt} - c_k \frac{D\phi}{Dt} = \frac{D(c_k\phi)}{Dt}$$

The last equality holds by Dziuk and Elliott (2007).

From the proof of the Reynolds Transport Theorem (material element section) (see wikipedia Reynolds transport theorem), we have the following property

$$\frac{d}{dt}\left(\int_{\Omega(t)} f(x,t) d\Omega \right) = \int_{\Omega(t)} \left(\frac{Df(x,t)}{Dt} + f(x,t)\nabla v(x,t) \right) d\Omega$$

Using this identity, we see that we have

$$\int_\Omega \left(\frac{\partial c_k}{\partial t} + \underline{v}\nabla c_k + c_k \nabla \underline{v} \right) \phi d\Omega = \int_\Omega \frac{D(c_k\phi)}{Dt} + c_k\phi\nabla\underline{v} d\Omega = \frac{d}{dt}\int_\Omega (c_k\phi) d\Omega$$

By this intermezzo we see that the equation turns to

$$\frac{d}{dt}\int_{\Omega(t)} c_k\phi d\Omega + D_k \int_{\Omega(t)} \nabla c_k \nabla\phi d\Omega + \kappa \oint_{\Gamma(t)} c_k\phi d\Gamma = \int_{\Omega(t)} S(\underline{x})\phi \; d\Omega$$

The next step is to approximate the domain integral by the sub-domains:

$$\frac{d}{dt}\sum_{e=1}^{M}\int_{\Omega_e(t)} c_k\phi d\Omega + D_k \sum_{e=1}^{M}\int_{\Omega_e(t)} \nabla c_k \nabla\phi d\Omega + \kappa \oint_{\Gamma(t)} c_k\phi d\Gamma = \sum_{e=1}^{M}\int_{\Omega_e(t)} S(\underline{x})\phi \, d\Omega$$

We approximate the unknown $c_k(\underline{x}, t)$ by

$$c_k(\underline{x}, t) = \sum_{j=1}^{4} c_{k,j}(t)\phi_j(\underline{x}), \quad \phi(\underline{x}) = \phi_i(\underline{x}), i = 1, 2, 3, 4$$

Then we pick out one element/sub-domain e and substitute this approximation:

$$\frac{d}{dt}\int_{\Omega_e(t)} \left(\sum_{j=1}^{4} c_{k,j}\phi_j \right) \phi_i \, d\Omega + D_k \int_{\Omega_e(t)} \nabla \left(\sum_{j=1}^{4} c_{k,j}\phi_j \right) \nabla\phi_i d\Omega = \int_{\Omega_e(t)} S(\underline{x})\phi_i d\Omega, i = 1, 2, 3, 4$$

$$\kappa \oint_{\Gamma(t)} \left(\sum_{j=1}^{4} c_{k,j}\phi_j \right) \phi_i d\Gamma, i = 1, 2, 3$$

$$\frac{d}{dt}\sum_{j=1}^{4} c_{k,j}\int_{\Omega(t)_e} \phi_j\phi_i \, d\Omega = \int_{\Omega(t)_e} S(\underline{x})\phi_i d\Omega - D_k \sum_{j=1}^{4} c_{k,j}\int_{\Omega(t)_e} \nabla\phi_j \nabla\phi_i d\Omega, i = 1, 2, 3, 4$$

$$\kappa \sum_{j=1}^{4} c_{k,j} \oint_{\Gamma(t)} \phi_j\phi_i d\Gamma, i = 1, 2, 3$$

Most integral can be calculated by using Holand-Bell, but the source-term integral will be dealt explicitly.

$$\int_{\Omega(t)_e} S(\underline{x})\phi_i d\Omega = \int_{\Omega(t)_e} \sum_{j=1}^{n_c} \gamma_k(m_j)\delta(\underline{x} - \underline{x}_j(t))\phi_i d\Omega =$$

$$= \sum_{j=1}^{n_c} \gamma_k(m_j) \int_{\Omega(t)_e} \delta(\underline{x} - \underline{x}_j(t))\phi_i d\Omega = \sum_{j=1}^{n_c} \gamma_k(m_j)\phi_i(\underline{x}_j(t))d\Omega$$

In one integral we will not use Holand-Bell to calculate its value. This integral is:

$$\sum_{j=1}^{4} c_{k,j} \int_{\Omega(t)_e} \phi_j \phi_i \ d\Omega$$

Instead, we will use Newton Cotes to process this integral. This approach uses that, for a general function $g(\underline{x})$, with the following integral over a sub-domain e:

$$\int_e g(\underline{x})d\Omega$$

We approximate the function by $g(\underline{x}) = \sum_{k=1}^{4} g(x_k)\phi_k(x)$. Substituting this into the desired integral, we get:

$$\int_e g(\underline{x})d\Omega = \int_e \sum_{k=1}^{4} g(x_k)\phi_k(x)d\Omega = \sum_{k=1}^{4} g(x_k) \int_e \phi_k(x)d\Omega = \frac{\Delta}{24} \sum_{k=1}^{4} g(x_k)$$

Using this approach to evaluate the integral, we get a element matrix of the form

$$T_e = \frac{|\Delta|}{24} \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix}$$

When we would use Holand bell, our element matrix would be

$$T_e = \frac{|\Delta|}{120} \begin{bmatrix} 2 & 1 & 1 & 1 \\ 1 & 2 & 1 & 1 \\ 1 & 1 & 2 & 1 \\ 1 & 1 & 1 & 2 \end{bmatrix}$$

Which would cause spurious errors in the calculations, leading to negative cytokine concentrations, which is something we do not want.

Using a matrix notation, we get for one element e the following abstract form

$$\frac{d}{dt}T\mathbf{c}_k = \underline{S} - C\mathbf{c}_k$$

$$B_C\mathbf{c}_k$$

After assembly, the following form is obtained:

$$\frac{d}{dt}T\underline{c}_k = \underline{S} - (C + B_C)\underline{c}_k$$

Using an Euler Backward scheme, we get

$$T^{n+1}\underline{c}_k^{n+1} - T^n\underline{c}_k^n = dt\underline{S}^{n+1} - dt(C^{n+1} + B_C^{n+1})\underline{c}_k^{n+1}$$

$$(T^{n+1} + dtC^{n+1} + dtB_C^{n+1})\underline{c}_k^{n+1} = T^n\underline{c}_k^n + dt\underline{S}^{n+1}$$

Because the distribution of non zero elements in M is similar to A and B, this method will not be that more expensive than an explicit method. In return, we do get the free choice of timestep as a huge bonus.
In a more abstract way, we can solve this problem by

$$\tilde{A}\underline{c}_k^{n+1} = \tilde{B}(\underline{c}_k, n)$$

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