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Author: David Vegge	……………………………………… (signature of author)

Faculty supervisor: Steinar Evje

External supervisors: Helmer André Friis and Ingunn Westvik Jolma at the International Research Institute of Stavanger

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A Study of a Mathematical Model for Cancer Cell Growth in a Gel

David Vegge

University of Stavanger

Faculty of Science and Technology

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Abstract

In this thesis, a mathematical model describing gel contraction is derived and studied. The mathematical model describes the process where cells are compressing the gel, and the model is therefore used to study the cell traction forces, in for example cancer cells. In order for the cells to leave the primary tumor and invade through the tissue and extracellular matrix towards other parts of the body, they need to extract forces(Mierke, Rösel, Fabry, & Brábek, 2008). These forces are studied using the mathematical model, which is derived in this thesis. The main equations used when deriving the mathematical model are the mass balance equations for the gel and cells, together with the momentum balance equation. In order to solve the mass balance equation, equations describing the force exerted by the cells on the gel and an equation describing the evolution of cell-produced chemicals are included, together with several initial and boundary conditions. The different equations needed in the numerical simulations are then converted into a new coordinate system to make the computations easier, before the equations are discretized.

The mathematical models include seven different parameters which were investigated. During the numerical simulations, the parameters were altered to see how they affected the cell traction forces. The results were that the contact inhibition parameter, bulk viscosity, proportionality constant for the chemical flux out of the gel and decay rate of the cell-produced chemicals should be high, while the isothermal compressibility, the parameter describing cell traction (τ_0) and preferred density should be low in order to obtain low cancer cell traction forces.

The numerical results were compared with experimental data from ((Moon & Tranquillo, 1993), (Raymond & Thompson, 1990)). It was seen that both the numerical results from the mathematical model and the experimental results gave very similar shapes of the graphs representing gel radius over time (which is a measure of the cell traction forces), together with similar end values of the gel radius as well. It was therefore concluded that the mathematical model is representing the cell traction forces in a satisfactory manner, and can therefore be used in further investigations of cancer cell traction forces in the future.

Towards the end of the thesis, cancer metastases was investigated. It was then seen from an experimental paper (Fenner et al., 2014) that an increased stiffness of the collagen gel decreased the possibility of cancer metastases. A high stiffness corresponds to a low isothermal compressibility, which can be accomplished by for instance decreasing the temperature in the collagen gel or increasing the pressure (*Table 1-42 Isothermal compressibility of liquids @ONLINE*, n.d.).

The relationship between the cancer cell traction forces and metastases were also investigated, using different papers (e.g. (Kraning-Rush, Califano, & Reinhart-King, 2012), (Indra et al., 2011)). The logical conclusion would be that an increase of the cancer cell traction forces would increase the degree of metastases, since the cell traction forces are needed in order for the cancer cells to move from the primary tumor to other parts of the body. This is also what is the most common conclusion, and what can be concluded from the results in (Kraning-Rush et al., 2012). However, the results from (Indra et al., 2011) give the opposite conclusion, which means that the relationship between cancer cell traction forces and cancer metastases might not be as straightforward as one might think. Future experiments should therefore be conducted on the relationship between the size of cancer cell traction forces and cancer metastases.

# Contents

Contents

1 Introduction

Mechanical interactions between cells and the extracellular matrix are to be studied with regards to tumor cells. Mechanical interactions bewteen cells and the extracellular matrix is also important in many other biological processes including such as in wound healing and the structures pattern in limb buds in the embryo. (Green, Bassom, & Friedman, 2013) The mathematical model derived and used in this thesis could therefore also be used when studying wound healing and the pattern of structures. The mathematical model is useful as a first step when making more complicated models when investigating interactions happening during for example tissue development and regeneration. (Green et al., 2013)

90% of all cancer deaths today are due to metastases, which is cancer cells spreading to other parts of the body. (Christofori, 2006)In order for the cancer cells to be metastatic, there are several steps they must go through. First, they need to leave the primary tumor and invade through the tissue and extracellular matrix. Then they are transported to different sites by entering a near blood and lymph vessel. (Mierke et al., 2008) There are some uncertainty regarding the next steps, but in order for the cancer cells to leave the primary tumor and invade the tissue and extracellular matrix, the tumor cells must exert forces (Mierke et al., 2008), and these traction forces will be studied more closely in this thesis, by first deriving and later using a mathematical model.

The extracellular matrix in the model, and in other experiments, corresponds to a gel with cells seeded within. The gel consists of components forming parts of the extracellular matrix, and collagen is often used since collagen is a major component in the extracellular matrix. (Green et al., 2013) The cells will compact the gel until it reaches a steady state after some days, depending on different parameter values. These parameters will be investigated to see how they affect the radius of the collagen gel, and therefore also the cell traction forces. The mathematical model is used in order to obtain a better understanding of the tumor cell-exerted traction forces, because the decrease in gel radius over time gives a measurement of the cell-exerted forces.

Below is a figure (which is taken from (Stevenson et al., 2010)) showing the gel seeded with cells, where the dark blue area represents the area of influence, which will be described later. The contraction of the collagen gel from the start of the numerical simulations towards the end can be clearly seen. As will be shown later, the cell density will initially be slightly greater towards the center of the collagen gel when using the mathematical model, but the figure gives an understanding of how the collagen gel seeded with cells can look like.

Figure 1: Gel seeded with cells (Stevenson et al., 2010)
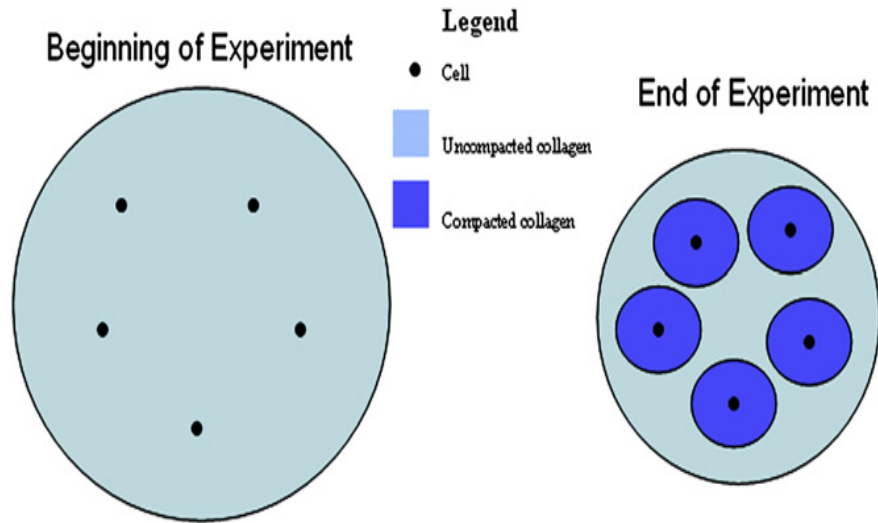
In this thesis,the mathematical model will first be derived, where the most important parts are the mass balance equations for the cells and gel, and the momentum balance equation between the cells and the gel. The model is then converted into another coordinate system in order to make the numerical computations easier. The numerical results are then displayed, and the effects from the parameters will be shown by changing these in the mathematical model. The published experimental data ((Moon & Tranquillo, 1993), (Raymond & Thompson, 1990)) will then be used to compare with the results from the numerical computations in this thesis to see how the cell traction forces with its parameters will affect how the cancer cells spread through the body.

The main objectives in this thesis are therefore:

- Derive the mathematical model

- Examine how the different parameters affect the tumor radius and cell traction forces

- Investigate how the results can be used to decrease the death rate from cancer

In the thesis, there are a number of important letters which represents different parameters. These letters are listed in the table below, with a short explenation of each parameter.

Table 1: Parameter Description

Character	Description
ρ	Collagen gel density
n	Cell density
$\boldsymbol{u}$	Velocity vector of the gel boundary
t	Time
$\boldsymbol{\sigma}$	Stress tensor of the gel
P	Pressure
F	Force per unit volume exerted by the cells
λ	Contact inhibition parameter
τ_0	A measure of cell traction
β	Isothermal compressibility of the gel
κ	Bulk viscosity of the gel
α_1	Decay rate of the cell-produced chemicals
γ	Proportionality constant of the chemical flux at gel boundary
ρ_c	Preferred density parameter
D	Diffusion coefficient of the cells
μ	Dynamic viscosity of the gel
α_2	Production rate of the cell-produced chemicals

2 The mathematical model

In this thesis, forces exerted by cells are to be studied. The cells are seeded within a gel which occupies a region $\Omega^*(t)$, and the density of cells are denoted by $n(\boldsymbol{x})$, while the density of the extracellular matrix is denoted by $\rho(\boldsymbol{x})$. The velocity of the extracellular matrix is given the symbol $\boldsymbol{u}(\boldsymbol{x},t)$ where $\boldsymbol{x}$ is referring to the position within the gel and t is referring to time. The cells can produce chemicals, where the chemical concentration is denoted $c(\boldsymbol{x},t)$, which might affect the forces exerted by the cells as will be seen later. Collagen production or degradation by the cells are here assumed negligible, and cell proliferation and cell death are ignored (Green et al., 2013)

In order to study the forces exerted by the cells, five governing equations must be derived. Two mass balance equations must also be derived, one for the collagen and one for the cells. Then a momentum balance equations for the forces exerted by the cells and gel will be derived. Then an equation relating pressure and density will be derived, before an equation describing the evolution of the chemical concentration produced by the cells will be derived. The two mass balance equations will now be derived.

2.1 Deriving the Mass Balance Equation for the Collagen Gel

Since the production and degradation by the cells are assumed negligible in this derivation, the expression for the final mass can be expressed as:

$$\text{Final mass} = \text{Original mass} + \text{mass inflow} - \text{mass outflow}$$

The derivation needed in order to find the expression for the conservation of mass for the collagen gel is shown in Appendix A, and the result is shown here:

$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \boldsymbol{u}) = 0 \tag{1}$$

2.2 Deriving the Mass Balance Equation for the Cells

During the derivation of the mass balance equation for the cells, cell proliferation and cell deaths were ignored. The mass balance for the cell does also have to take into account the diffusion, so the mass balance expression for the cells will have the following form, where the velocity vector $\boldsymbol{u}$ is the same for both the collagen gel and the cells:

$$\frac{\partial n}{\partial t} + \nabla \cdot (n\boldsymbol{u}) = \text{Diffusion term} \tag{2}$$

where n in this context refers to the density of the cells. The diffusion term on the right side of the equation needs to be derived, and this is done in Appendix B. The derivation gave an expression for the conservation of mass for the cells as shown below:

$$\frac{\partial n}{\partial t} + \nabla \cdot (n\boldsymbol{u}) = D^* \nabla^2 n \tag{3}$$

2.3 The momentum balance equation

The momentum balance equation is then to be derived, by first deriving the general force balance expression, before inserting the expression for the stresses for the gel and introducing the Laplacian. Then these things are used together to get the momentum balance equation.

2.3.1 The general force balance

The momentum balance equations between the gel and cells is an important part of the model, and the derivation for the general expression is shown in Appendix C. The compaction of the gel is slow, and it is therefore assumed that the inertial effects can be neglected. (Green et al., 2013) The equation derived in Appendix C is:

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$$\nabla \cdot \begin{bmatrix} \sigma_x & \tau_{yx} & \tau_{zx} \\ \tau_{xy} & \sigma_y & \tau_{zy} \\ \tau_{xz} & \tau_{yz} & \sigma_z \end{bmatrix} + \boldsymbol{F} = 0, \tag{4}$$

which is equivalent to writing:

$$\nabla \cdot \boldsymbol{\sigma} + \boldsymbol{F} = 0, \tag{5}$$

where σ is the stress tensor of the gel and F is the force per unit volume exerted by the cells on the gel.

The next step in deriving the momentum balance equation is then to get the expression for σ_{ij}, before deriving the divergence of $\boldsymbol{\sigma}$, $\nabla \cdot \boldsymbol{\sigma}$, which will then give the desired expression for the momentum balance equation.

2.3.2 The expression for the stresses for the gel

Previous experiments have tested how well the collagen gel could be treated as an upper-convected Maxwell (UCM) fluid, which can be used in a viscoelastic model. ((Knapp et al., 1997), (Green et al., 2013)) For a UCM-fluid, the relative importance of elastic and viscous effects can be measured by calculating the Deborah number, D_e:

$$D_e = \frac{\mu^*}{G^* T^*}$$

where G and μ represent the shear modulus and shear viscosity, respectively, while T is the time-scale of gel compaction. The experiments gave a value of the Deborah number approximately around 0.1-0.01 (Green et al., 2013), meaning that the elastic effects are so small that they can be neglected, and the result is that the gel can be approximated as a compressible Stokes fluid with the following expression for the stress (Green et al., 2013):

$$\sigma_{ij} = -P\delta_{ij} + 2\mu^* \epsilon_{ij} + \left(\kappa^* - \frac{2}{3}\mu^* \right) \epsilon_{kk}\delta_{ij}, \tag{6}$$

where P is included because it is the effective stress which is of interest, and not just the total stress. μ^* and κ^* represents the dynamic viscosity and bulk viscosity. ϵ_{ij} represents the rate of strain tensor:

$$\epsilon_{ij} = \frac{1}{2} \left(\frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i} \right),$$

where the subscripts i and j can be any of the three number 1, 2 or 3, which represents the x, y and z-direction, respectively.(*Course 12.800 Fluid Dynamics of the Atmosphere and Ocean, Chapter 3 @ONLINE*, 2006) ϵ_{kk} represents the rate of volume expansion:

$$\epsilon_{kk} = \nabla \cdot \boldsymbol{u} = \frac{\partial u_i}{\partial x} + \frac{\partial u_j}{\partial y} + \frac{\partial u_k}{\partial z}$$

The Kronecker's delta is defined as (Fjaer, Horsrud, Raaen, Risnes, & Holt, 1992)

$$\delta_{ij} = \begin{cases} 1, & \text{if } i = j, \\ 0, & \text{if } i \neq j, \end{cases}$$

so that the first and third term to the right side of equation (6) will be zero for shear stresses. By substituting the expression for the rate of strain tensor, ϵ_{ij} into the expression for the stress, σ_{ij}, it is shown in Appendix D that the result is:

$$-\nabla P + \left[\mu^*\left(\frac{\partial^2 u_i}{\partial x^2} + \frac{\partial^2 u_i}{\partial y^2} + \frac{\partial^2 u_i}{\partial z^2}\right) + (\lambda^* + \mu^*)\left(\frac{\partial^2 u_i}{\partial x^2} + \frac{\partial^2 u_j}{\partial y\partial x} + \frac{\partial^2 u_k}{\partial z\partial x}\right) + F_x\right]\hat{i}$$

$$+ \left[\mu^*\left(\frac{\partial^2 u_j}{\partial x^2} + \frac{\partial^2 u_j}{\partial y^2} + \frac{\partial^2 u_j}{\partial z^2}\right) + (\lambda^* + \mu^*)\left(\frac{\partial^2 u_i}{\partial x\partial y} + \frac{\partial^2 u_j}{\partial y^2} + \frac{\partial^2 u_k}{\partial z\partial y}\right) + F_y\right]\hat{j}$$

$$+ \left[\mu^*\left(\frac{\partial^2 u_k}{\partial x^2} + \frac{\partial^2 u_k}{\partial y^2} + \frac{\partial^2 u_k}{\partial z^2}\right) + (\lambda^* + \mu^*)\left(\frac{\partial^2 u_i}{\partial x\partial z} + \frac{\partial^2 u_j}{\partial y\partial z} + \frac{\partial^2 u_k}{\partial z^2}\right) + F_z\right]\hat{k} = 0 \quad (7)$$

These expressions can be simplified by introducing some identities, namely the Laplacian operator, the gradient and the divergence, which is done in the following.

2.3.3 The vector Laplacian

In Appendix E, it is shown that the vector Laplacian, $\nabla^2\boldsymbol{A}$ can be written as

$$\nabla^2\boldsymbol{A} = \nabla(\nabla \cdot \boldsymbol{A}) - \nabla \times (\nabla \times \boldsymbol{A}), \quad (8)$$

which will give a more compact expression for the momentum balance equation shown below.

2.3.4 Momentum balance equation

The momentum balance equation can then be derived using the results from above. By taking the Laplacian of $\boldsymbol{u}$, the result is:

$$\nabla^2\boldsymbol{u} = \nabla^2(u_i)\hat{i} + \nabla^2(u_j)\hat{j} + \nabla^2(u_k)\hat{k}$$
$$= \left(\frac{\partial^2 u_i}{\partial x^2} + \frac{\partial^2 u_i}{\partial y^2} + \frac{\partial^2 u_i}{\partial z^2}\right)\hat{i} + \left(\frac{\partial^2 u_j}{\partial x^2} + \frac{\partial^2 u_j}{\partial y^2} + \frac{\partial^2 u_j}{\partial z^2}\right)\hat{j} + \left(\frac{\partial^2 u_k}{\partial x^2} + \frac{\partial^2 u_k}{\partial y^2} + \frac{\partial^2 u_k}{\partial z^2}\right)\hat{k}$$

Then the gradient of the divergence of $\boldsymbol{u}$ will be utilized. (Adams & Essex, 2010) This can be written as:

$$\nabla(\nabla \cdot \boldsymbol{u}) = \nabla\left[\frac{\partial u_i}{\partial x} + \frac{\partial u_j}{\partial y} + \frac{\partial u_k}{\partial z}\right]$$

$$= \left[\frac{\partial^2 u_i}{\partial x^2} + \frac{\partial^2 u_j}{\partial x\partial y} + \frac{\partial^2 u_k}{\partial x\partial z}\right]\hat{i} + \left[\frac{\partial^2 u_i}{\partial y\partial x} + \frac{\partial^2 u_j}{\partial y^2} + \frac{\partial^2 u_k}{\partial z\partial x}\right]\hat{j} + \left[\frac{\partial^2 u_i}{\partial z\partial x} + \frac{\partial^2 u_j}{\partial z\partial y} + \frac{\partial^2 u_k}{\partial z^2}\right]\hat{k}$$

$\nabla^2\boldsymbol{u}$ is then multiplied with μ and $\nabla(\nabla \cdot \boldsymbol{u})$ is multiplied with $\lambda + \mu$, and then the equations are added together to give the following:

$$\mu^* \cdot \nabla^2\boldsymbol{u} + (\lambda + \mu^*) \cdot \nabla(\nabla \cdot \boldsymbol{u}) \quad (9)$$

$$= \mu^* \cdot \left(\frac{\partial^2 u_i}{\partial x^2} + \frac{\partial^2 u_i}{\partial y^2} + \frac{\partial^2 u_i}{\partial z^2}\right)\hat{i} + \mu^* \cdot \left(\frac{\partial^2 u_j}{\partial x^2} + \frac{\partial^2 u_j}{\partial y^2} + \frac{\partial^2 u_j}{\partial z^2}\right)\hat{j} + \mu^* \cdot \left(\frac{\partial^2 u_k}{\partial x^2} + \frac{\partial^2 u_k}{\partial y^2} + \frac{\partial^2 u_k}{\partial z^2}\right)\hat{k}$$

$$+ (\lambda^* + \mu^*) \cdot \left[\frac{\partial^2 u_x}{\partial x^2} + \frac{\partial^2 u_y}{\partial x\partial y} + \frac{\partial^2 u_k}{\partial x\partial z}\right]\hat{i} + (\lambda^* + \mu^*) \cdot \left[\frac{\partial^2 u_x}{\partial y\partial x} + \frac{\partial^2 u_y}{\partial y^2} + \frac{\partial^2 u_k}{\partial z\partial x}\right]\hat{j} + (\lambda^* + \mu^*) \cdot \left[\frac{\partial^2 u_x}{\partial z\partial x} + \frac{\partial^2 u_y}{\partial z\partial y} + \frac{\partial^2 u_k}{\partial z^2}\right]\hat{k}$$

which can be rewritten in a more compact form as:

$$\left[\mu^* \cdot \left(\frac{\partial^2 u_i}{\partial x^2} + \frac{\partial^2 u_i}{\partial y^2} + \frac{\partial^2 u_i}{\partial z^2}\right) + (\lambda^* + \mu^*)\left(\cdot\frac{\partial^2 u_i}{\partial x^2} + \frac{\partial^2 u_j}{\partial x\partial y} + \frac{\partial^2 u_k}{\partial x\partial z}\right)\right]\hat{i}$$

$$+ \left[\mu^* \cdot \left(\frac{\partial^2 u_j}{\partial x^2} + \frac{\partial^2 u_j}{\partial y^2} + \frac{\partial^2 u_j}{\partial z^2}\right) + (\lambda^* + \mu^*) \cdot \left(\frac{\partial^2 u_i}{\partial y\partial x} + \frac{\partial^2 u_j}{\partial y^2} + \frac{\partial^2 u_k}{\partial z\partial x}\right)\right]\hat{j}$$

$$+ \left[\mu^* \cdot \left(\frac{\partial^2 u_k}{\partial x^2} + \frac{\partial^2 u_k}{\partial y^2} + \frac{\partial^2 u_k}{\partial z^2}\right) + (\lambda^* + \mu^*) \cdot \left(\frac{\partial^2 u_i}{\partial z\partial x} + \frac{\partial^2 u_j}{\partial z\partial y} + \frac{\partial^2 u_k}{\partial z^2}\right)\right]\hat{k}$$

The only difference between this equation and equation (7) is now $-\nabla P$, $\boldsymbol{F}$ and the zero on the right side of the equation. This means that equation (5) can be written in a compact form including the expression for the stress tensor by adding expression (9) with $-\nabla P$ and $\boldsymbol{F}$, and then setting this equal to the zero-vector as follows:

$$-\nabla P + \mu^* \nabla^2 \boldsymbol{u} + (\lambda^* + \mu^*) \nabla(\nabla \cdot \boldsymbol{u}) + \boldsymbol{F} = \boldsymbol{0}$$

which can be rearranged as follows by substituting for λ^* to give the momentum balance equation:

$$- \nabla P + \mu^* \nabla^2 \boldsymbol{u} + \left(\kappa^* + \frac{\mu^*}{3}\right) \nabla(\nabla \cdot \boldsymbol{u}) + \boldsymbol{F} = \boldsymbol{0} \tag{10}$$

2.4   Force function

The force exerted by the cells is assumed to be the sum of forces exerted by the cells at point x' to points x within the sphere of influence. The strength of each force is dependent on the distance between x' and x, where a smaller distance would indicate a stronger force. The forces are also dependent on the cell density, collagen gel density and chemical concentration at the cell position x'. A general expression for the force exerted by the cells can then be written as:

$$\boldsymbol{F} = \int_V \boldsymbol{K}\left(\boldsymbol{x} - \boldsymbol{x'}\right) \mathcal{F}\left(n(\boldsymbol{x'}), \rho(\boldsymbol{x'}), c(\boldsymbol{x'})\right) dx', \tag{11}$$

where $\boldsymbol{K}\left(\boldsymbol{x} - \boldsymbol{x'}\right)$ is the force per volume exerted from the cells at x' to the gel at x. $\mathcal{F}$ is also included, since the magnitude of the force depends on the cell density, gel density and the chemical concentration at the position of the exerted force, x'.

Taylor expansion is used when expressing a point $\boldsymbol{x'}$ within the sphere of influence of $\boldsymbol{x}$. Taylor expansion in one dimension, by considering $f(x)$ around $x = x_0 + \delta$, can be written as:

$$f(x) = f(x_0) + \delta f'(x_0) + \frac{1}{2}\delta^2 f''(x_0) + ...$$

In two dimensions, around $x = x_0 + h$ and $y = y_0 + k$, this becomes:

$$f(x,y) = f(x_0,y_0) + f_x(x_0,y_0)\Delta x + f_y(x_0,y_0)\Delta y + \frac{1}{2}\left[f_{xx}(x_0,y_0)\Delta x^2 + 2f_{xy}(x_0,y_0)\Delta x \Delta y + f_{yy}(x_0,y_0)\Delta y^2\right] + ..$$

which, by including $x = x_0 + h$ and $y = y_0 + k$, gives the rewritten expression:

$$f(x,y) = f(x_0,y_0) + \left(h\frac{\partial f}{\partial x} + k\frac{\partial f}{\partial y}\right) + \frac{1}{2}\left(h^2\frac{\partial^2 f}{\partial x^2} + 2hk\frac{\partial^2 f}{\partial x \partial y} + k^2\frac{\partial^2 f}{\partial y^2}\right) + ...$$

The expansion to three dimensions, where $x = x_0 + \delta x_0$, $y = y_0 + \delta y_0$ and $z = z_0 + \delta z_0$, is:

$$f(x,y,z) = f(x_0,y_0,z_0) + \delta\left(x_0\frac{\partial f}{\partial x} + y_0\frac{\partial f}{\partial y} + z_0\frac{\partial f}{\partial z}\right) + ...$$

This can be rewritten by introducing the gradient operator, and that $\boldsymbol{x'} = x, y, z$ and $\boldsymbol{x} = x_0, y_0, z_0$:

$$f(\boldsymbol{x'}) = f(\boldsymbol{x}) + \delta\left(\boldsymbol{x} \cdot \nabla\right) f + ...$$

which is evaluated around $\boldsymbol{x}$, and can therefore be further rewritten as:

$$f(\boldsymbol{x'}) = f(\boldsymbol{x}) + \delta\left(\boldsymbol{x} \cdot \nabla\right) f|_{\boldsymbol{x}} + ...$$

A general version of equation (11) can be written as

$$\boldsymbol{F} = \int_V \boldsymbol{K}\left(\boldsymbol{x} - \boldsymbol{x'}\right) \mathcal{F}(\boldsymbol{x'})d\boldsymbol{x'}.$$

This is a vector, and therefore has three components. The first component can be written as

$$F_1 = \int_V K_1\left(\boldsymbol{x} - \boldsymbol{x}'\right)\mathcal{F}(\boldsymbol{x}')d\boldsymbol{x}',$$

where 1 refers to component 1. The function $\boldsymbol{K}\left(\boldsymbol{x} - \boldsymbol{x}'\right)$ is assumed to be an odd function of its argument, and it is assumed that it can have the expression

$$K\left(\boldsymbol{x} - \boldsymbol{x}'\right) = f\left(|\boldsymbol{x} - \boldsymbol{x}'|\right)\left(\boldsymbol{x} - \boldsymbol{x}'\right)$$

The first component can therefore be written as:

$$K_1 = f(\delta|\boldsymbol{x_1}|)(-\delta x_{11}),$$

where x_{11} represents the first component of $\boldsymbol{x_1}$. This leads to a rewritten form of F_1:

$$F_1 = \int f(\delta|\boldsymbol{x_1'}|)(-\delta x_{11})(\boldsymbol{x}')d\boldsymbol{x}'$$

By using the Taylor expansion, where $x = x_{11} + \delta x_{11}$, $y = x_{12} + \delta x_{12}$ and $z = x_{13} + \delta x_{13}$, the expression for $\mathcal{F}$ becomes:

$$\mathcal{F}(x,y,z) = \mathcal{F}(x_{11},x_{12},x_{13}) + \delta\left(x_{11}\frac{\partial\mathcal{F}}{\partial x} + x_{12}\frac{\partial\mathcal{F}}{\partial y} + x_{13}\frac{\partial\mathcal{F}}{\partial z}\right) + ...$$

where the non-local component of $\mathcal{F}$ is the second term to the right of the equality sign, which can also be written in a more compact form as $\delta\left(x_1 \cdot \nabla\right)\mathcal{F}$, which again is the same as writing

$$\delta(x_1 \cdot \nabla)\mathcal{F} = \delta\sum_{j=1}^{3} x_{1j}\frac{\partial\mathcal{F}}{\partial x_j}$$

Since this is the non-local component of $\mathcal{F}$, this is inserted into the general expression for F_1 further up (since F_1 is a global force function at the moment) together with the expression for K_1. This gives:

$$F_1 = -\int f(\delta|\boldsymbol{x_1}|)\delta x_{11}\delta^3\sum_{j=1}^{3} x_{1j}\frac{\partial\mathcal{F}}{\partial x_j}\bigg|_{\boldsymbol{x}} d^3 x_1$$

By including all three components, this becomes:

$$F_i = -\delta^5\int_V f(\delta|\boldsymbol{x_1}|)\sum_{i=1}^{3} x_{1i}\sum_{j=1}^{3} x_{1j}\frac{\partial\mathcal{F}}{\partial x_j}\bigg|_{\boldsymbol{x}} d^3 x_1$$

The equations are considered inside a region Ω, but when considering cells very close to the boundary of the region Ω, problems arise because then the whole sphere of influence is not inside this region. The distance between the cells lying inside the region Ω (x) and the boundary of the region must therefore always be greater than the radius of the sphere of influence δ. This must therefore be fulfilled for the following equations to be valid.

Since the function f only depends on an absolute value of $\boldsymbol{x_1} \cdot \delta$, the value of f will be the same both for x_{1i} and the negative version $-x_{1i}$. When lying inside the region $\omega(x)$ with a distance greater than δ to the boundary and $i \neq j$, it follows that the integrand of the expression

$$\mathcal{I}_{ij} = \int_{S_1} -f(\delta|\boldsymbol{x_1}|)\sum_{i=1}^{3} x_{1i}\sum_{j=1}^{3} x_{1j}d^3 x_1$$

is an isotropic integral with an odd-valued integrand in terms of x_{1i} (the same is true for x_{1j}), and the integration will therefore give zero as a result.

Due to the isotropic integral above, which is included in the expression for F_i, the force tensor $\boldsymbol{F}(\boldsymbol{x})$ can be written as an integral times the gradient of $\mathcal{F}$ to give:

$$F(x) = K_1 \nabla \mathcal{F},$$

which is a local force function, because it is only valid when lying inside the region $\omega(x)$ with a distance smaller than δ to the boundary of the region. K_1 in Cartesian coordinates is:

$$\delta^5 \int_{S_1} -f(\delta|\boldsymbol{x}_1|) \sum_{i=1}^{3} x_{1i} \sum_{j=1}^{3} x_{1j} d^3 x_1$$

K_1 should rather be written in spherical coordinates. The gel is assumed to remain spherical through the whole compation process so that the dependence on the polar and azimuthal angles can be neglected. $\boldsymbol{F}(\boldsymbol{x})$ therefore only depends on r and so should therefore also K_1 do. Angle integration is therefore performed explicitly to give $\frac{4\pi}{3}$, while x_{1i} and x_{1j} gives one r each while the Jacobian give r^2 which in total results in r^4. The expression for K_1 depending only on r can therefore be written as:

$$K_1 = -\frac{4\pi}{3} \int_0^1 f(\delta r_1) r_1^4 dr_1$$

The cell stress tensor in (Moon & Tranquillo, 1993) has the expression

$$\boldsymbol{\sigma} = \frac{\tau_0 \rho n}{1 + \lambda n^2} \boldsymbol{I},$$

where $\boldsymbol{I}$ is the unit tensor. By taking the divergence of this, the expression becomes essentially the same as the expression for $\boldsymbol{F}$ derived above, only with different parameters. Including the parameters from (Moon & Tranquillo, 1993) in the expression for $\boldsymbol{F}$ gives the final expression for the local force function $\boldsymbol{F}$

$$\boldsymbol{F} = \tau_0 \nabla \left(\frac{\rho n}{1 + \lambda n^2} \right) \tag{12}$$

2.5 The relationship between the gel density and pressure

A relationship between gel density and pressure is desired. The density at a given pressure can be written as a reference density minus this reference density times the relative change in volume between the reference pressure and the given pressure for which the new density value is to be calculated at. This can be written in the form of an equation by assuming isothermal flow an low pressure (Georgiou & Crochet, 1994):

$$\rho = \rho_0 - \rho_0 \frac{1}{V_0} \left(\frac{\partial V}{\partial p} \right)_{P_0, T} (p - p_0)$$

This can be written in a more compact form by introducing the isothermal compressibility(Georgiou & Crochet, 1994):

$$\rho = \rho_0 + \rho_0 \beta^* (p - p_0) = \rho_0 \left[1 + \beta^*(p - p_0) \right], \quad \text{where } \beta^* = -\frac{1}{V_0} \left(\frac{\partial V}{\partial p} \right)_{P_0, T}.$$

V_0 and ρ_0 is the volume and density at reference pressire P_0, and T is temperature. In order to further simplify this expression, the gage pressure is used instead of absolute pressure to obtain:

$$\rho = \rho_0 (1 + \beta^* p)$$

By also assuming no cell exerted forces, the gel density at reference pressure is constant since the temperature is also constant, and given the symbol ρ_i. This gives the final simplified relationship between density and pressure for the gel to be:

$$\rho = \rho_i \left(1 + \beta^* p \right) \tag{13}$$

2.6 The evolution of the cell-produced chemicals

An equation describing the change of chemical concentration is also needed. The chemicals are produced by the cells, but they are also assumed to be subject to the processes of diffusion and decaying. Diffusion is the most rapid one of the three processes mentioned, a due to this a quasi-steady state can be assumed for the production and decaying of the chemicals, and the equation therefore does not contain any time-derivatives of the rates. The diffusion is expressed in the same manner as in equation (3), only replacing the density with the chemical concentration. The diffusion rate of the chemicals is denoted by D_c, the decay rate is denoted by α_1 and the production rate is denoted by α_2. The expression for the chemical concentration can then be expressed as:

$$D_c \nabla^2 c - \alpha_1 c + \alpha_2 n = 0 \tag{14}$$

where c denotes the chemical concentration(Green et al., 2013). The cell density n is computed in another equation, and can then be inserted into the other equation afterwards to update equation (12) above for new time-steps.

The equations which has been shown is to be solved inside the gel, which has a domain denoted by $\Omega^*(t)$. Boundary conditions are needed in order to solve the equations, and they are stated below:

$$\Omega^*|_{t=0} = \Omega_0^*, \quad \rho|_{t=0} = \rho_0^*(x), \quad n|_{t=0} = n_0^*(\boldsymbol{x}) \tag{15}$$

$$\hat{\boldsymbol{n}} \cdot (n\boldsymbol{u} - D\nabla n) = 0, \quad \boldsymbol{\sigma} \cdot \hat{\boldsymbol{n}} = 0, \quad \boldsymbol{u} \cdot \hat{\boldsymbol{n}} = V \quad \text{on } \Gamma^*(t) \tag{16}$$

$\Gamma^*(t)$ is the gel boundary defined as $\Gamma^*(t) = \partial\Omega^*(t)$, while $\hat{n}$ and $V*$ are respectively the unit outward normal to and the normal velocity of the gel boundary. In order to impose condition for the flux of the concentration, it is assumed that there exists a a large well of growth medium in which the gel resides, but the culture medium does not contain any of the chemical to be studied. Therefore, the flux of the chemical out of the gel is proportional to the chemical concentration at the gel boundary, and this proportionality is expressed using the proportionality constant γ^*. (Green et al., 2013)The flux condition for the chemical can then be expressed as:

$$-D_c^* \hat{\boldsymbol{n}} \cdot \nabla c = \gamma^* c \quad \text{on} \quad \Gamma^*(t), \tag{17}$$

where the negative sign on the left side of the equation is due studying the flux out of the gel, and that flux is defined positive when influx.

2.7 Non-dimensionalization

In order to generalize the equations above, the variables are non-dimensionalized. This is done in following, where the thildes are representing the non-dimensional variables:

$$t = T^* \cdot \widetilde{t}, \quad \boldsymbol{x} = R_0 \widetilde{\boldsymbol{x}} \quad \rho = \rho_i \widetilde{\rho}, \quad n = n_i \widetilde{n}, \quad \boldsymbol{u} = \frac{R_0}{T^*} \widetilde{\boldsymbol{u}},$$

$$\boldsymbol{\sigma} = \frac{\mu^*}{T^*} \widetilde{\boldsymbol{\sigma}}, \quad P = \frac{\mu^*}{T^*} \widetilde{P}, \quad \boldsymbol{F} = \frac{\mu^*}{T^* R_0} \widetilde{\boldsymbol{F}}, \quad c = \frac{\alpha_2^* n_i R_0^2}{D_c} \widetilde{c}$$

T is a typical time-length for the compaction, R_0 is a typical length of the gel, while n_i and ρ_i are the average initial densities. The different steps showing the derivation from the dimensional form of the five governing equations to the non-dimensional form are shown in Appendix F, and the results are shown below. The equations which were non-dimensionalized were the initial- and boundary conditions together with the following five equations:

$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \boldsymbol{u}) = 0$$

$$\frac{\partial n}{\partial t} + \nabla \cdot (n\boldsymbol{u}) = D^* \nabla^2 n$$

$$-\nabla P + \mu^* \nabla^2 \boldsymbol{u} + \left(\kappa^* + \frac{\mu^*}{3} \right) \nabla(\nabla \cdot \boldsymbol{u}) + \boldsymbol{F} = \boldsymbol{0}$$

$$D_c \nabla^2 c - \alpha_1 c + \alpha_2 n = 0$$

$$\rho = \rho_i \left(1 + \beta^* p \right)$$

As shown in Appendix F, the non-dimensional versions are of the initial-and boundary conditions are:

$$\Omega(t)|_{t=0} = \Omega_0, \qquad \rho|_{t=0} = \rho_0(\boldsymbol{x}), \qquad n|_{t=0} = n_0(\boldsymbol{x})$$

$$\hat{\boldsymbol{n}} \cdot \left(n\boldsymbol{u} - P_e^{-1} \nabla n \right) = 0$$

$$\boldsymbol{\sigma} \cdot \hat{\boldsymbol{n}} = V$$

$$\boldsymbol{u} \cdot \hat{\boldsymbol{n}} = V$$

$$\hat{\boldsymbol{n}} \cdot \nabla c = -\gamma c$$

where ω_0, ρ_0 and n_0 are the non-dimensional counterparts of ω_0^*, ρ_0^* and n_0^*, while V is the non-dimensional normal velocity of $\Gamma(t)$.

The non-dimensional versions of the five governing equations, whose dimensional versions were shown earlier, are shown below together with the force function:

$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \boldsymbol{u}) = 0$$

$$\frac{\partial n}{\partial t} + \nabla \cdot (n\boldsymbol{u}) = P_e^{-1} \frac{\partial^2}{\partial x^2} n$$

$$-\nabla P + \nabla^2 \boldsymbol{u} + \left(\kappa + \frac{1}{3} \right) \cdot \nabla(\nabla \cdot \boldsymbol{u}) + \boldsymbol{F} = 0$$

$$\nabla^2 c - \alpha_1^* c + n = 0$$

$$\boldsymbol{F} = \tau_0 \nabla \left(\frac{\rho n}{1 + \lambda n^2} \right)$$

$$\rho = 1 + \beta p$$

These equations will be converted to other coordinate systems, and later discretized before implementing them on the computer in order to investigate how the different parameters are effecting the cell exerted forces and to compare with experimental data to see if the experimental data and numerical model gives good agreement.

2.8 Spherical coordinates

The Cartesian versions of the equations derived earlier will now be converted to spherical coordinates, which is a useful step before implementing the equations on the computer later. But first, some mathematical operators should be converted to spherical coordinates, which is shown in Appendix G, with only the results shown here. The gel is assumed to stay spherical through the whole compaction process, and the parameters will therefore not be dependent on the polar and azimuthal angles. The velocity and the cell-induced forces are assumed to be zero, except in the radial direction, and in mathematical terms this can be written as

$$\boldsymbol{u} = u(r,t)\hat{\boldsymbol{r}}, \qquad \boldsymbol{F} = F_r \hat{\boldsymbol{r}}$$

Due to this, the inverse Péclet number (which is defined in Appendix F) is small, and can be neglected. As stated above, the dependence on the polar and azimuthal angles can be neglected, which will simplify the derivation for the spherical versions of the equations. The expressions for the gradient and divergence in spherical coordinates is shown in Appendix G together witht the derivation of the vector Laplacian and scalar Laplacian, and the results are shown below:
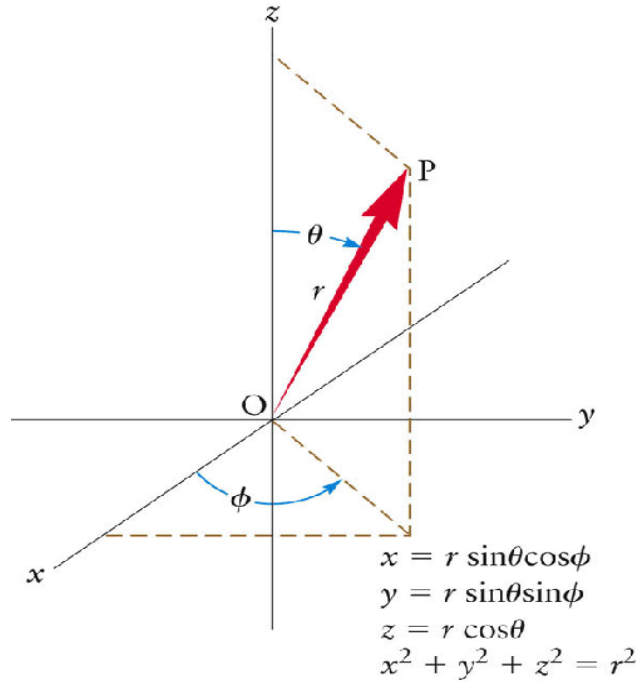
$$\nabla f(r) = \frac{\partial f}{\partial r}\hat{r}$$

$$\nabla \cdot \boldsymbol{F} = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 F_r\right)$$

$$\nabla^2(\boldsymbol{u}) = -\frac{2u}{r^2} + \frac{2}{r}\frac{\partial u}{\partial r} + \frac{\partial^2 u}{\partial r^2} = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial u}{\partial r}\right) - \frac{2u}{r^2}$$

$$\nabla^2 u = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial u}{\partial r}\right)$$

The relationship between the vector Laplacian,$\nabla^2\boldsymbol{u}$, and scalar Laplacian,$\nabla^2 u$, can then be written as:

$$\nabla^2(\boldsymbol{u}) = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial u}{\partial r}\right) - \frac{2u}{r^2} = \nabla^2 u - \frac{2u}{r^2}$$

A figure showing the spherical coordinate system is shown below, and is taken from (Tuckerman, 2011)

Figure 2: Spherical coordinate system (Tuckerman, 2011)

$$x = r\,\sin\theta\cos\phi$$
$$y = r\,\sin\theta\sin\phi$$
$$z = r\,\cos\theta$$
$$x^2 + y^2 + z^2 = r^2$$

The equations needed in the computations in order to study the forces exerted by the cells must be transformed to spherical coordinates, which is to be done in the following.

2.8.1 Mass balance equations

The first equations to be converted into spherical coordinates are the mass balance equations. Since the Péclet number was negligible, the right side of the cell mass balance equation becomes zero. This means that

both expressions become the same, only that the gel density is considered in the first, while the cell density in the second. The expressions are the same, so the the conversion into spherical coordinates is shown for the gel density, but is the same for the density of the cells. The gel density is chosen, and the left side of the equation is shown below (the right side of the equation is zero):

$$\frac{\partial \rho}{\partial t} + \nabla(\rho \boldsymbol{u})$$

The first step is to rewrite the divergence of the product of ρ and $\boldsymbol{u}$ in Cartesian coordinates:

$$\nabla \cdot (\rho \boldsymbol{u}) = \frac{\partial}{\partial x}(\rho u_1) + \frac{\partial}{\partial y}(\rho u_2) + \frac{\partial}{\partial z}(\rho u_3) = \rho \frac{\partial u_1}{\partial x} + u_1 \frac{\partial \rho}{\partial y} + \rho \frac{\partial u_2}{\partial y} + u_3 \frac{\partial \rho}{\partial z} + \rho \frac{\partial u_3}{\partial z},$$

which can be rewritten in a more compact form as

$$\nabla \cdot (\rho \boldsymbol{u}) = \rho \left(\frac{\partial u_1}{\partial x} + \frac{\partial u_2}{\partial y} + \frac{\partial u_3}{\partial z} \right) + \boldsymbol{u} \cdot \left(\frac{\partial \rho}{\partial x} + \frac{\partial \rho}{\partial y} + \frac{\partial \rho}{\partial z} \right).$$

This can be simplified to:

$$\nabla \cdot (\rho \boldsymbol{u}) = \rho \left(\nabla \cdot \boldsymbol{u} \right) + \boldsymbol{u} \left(\nabla \rho \right)$$

Then, the expressions for divergence and gradient for spherical coordinates showed further up are utilized:

$$\nabla \cdot (\rho \boldsymbol{u}) = \rho \left(\nabla \cdot \boldsymbol{u} \right) + \boldsymbol{u} \left(\nabla \rho \right) = \frac{\partial \rho}{\partial r} \hat{r} \cdot u \cdot \hat{r} + \rho \left(\frac{1}{r^2} \frac{\partial}{\partial r}(r^2 u) \right),$$

which is equivalent to writing

$$\nabla \cdot (\rho \boldsymbol{u}) = \frac{\partial \rho}{\partial r} u + \frac{\rho}{r^2} \frac{\partial}{\partial r}(r^2 u) = \frac{\partial \rho}{\partial r} u + \frac{\rho}{r^2} \left(2 \cdot r \cdot u + r^2 \frac{\partial u}{\partial r} \right).$$

This gives:

$$\nabla \cdot (\rho \boldsymbol{u}) = \frac{\partial \rho}{\partial r} u + \frac{2 \rho u}{r} + \rho \frac{\partial u}{\partial r}$$

which can be rewritten as the following to get a more compact expression:

$$\nabla \cdot (\rho \boldsymbol{u}) = \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \rho u \right)$$

This expression can then be inserted into the mass balance equation for the gel:

$$\frac{\partial \rho}{\partial t} + \nabla(\rho \boldsymbol{u}) = \frac{\partial \rho}{\partial t} + \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \rho u \right) \tag{18}$$

Since the expression for mass balance for the cells is the same, this can also be written in spherical coordinates as:

$$\frac{\partial n}{\partial t} + \nabla(n \boldsymbol{u}) = \frac{\partial n}{\partial t} + \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 n u \right) \tag{19}$$

2.8.2 Momentum balance equation

The next expression which will be converted from Cartesian coordinates to spherical coordinates is the force balance between the gel and cells. The expression in Cartesian coordinates was written earlier but repeated here:

$$-\nabla P + \nabla^2 \boldsymbol{u} + \left(\kappa^* + \frac{1}{3} \right) \cdot \nabla (\nabla \cdot \boldsymbol{u}) + \boldsymbol{F} = 0$$

This can be converted to spherical coordinates by using the expressions for the gradient, divergence and Laplacian for spherical coordinates shown earlier. Since all the terms are in the radial direction, the unit vector in r-direction is dropped, and the result for the force balance is:

$$\frac{\partial P}{\partial r} + \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial u}{\partial r}\right) - \frac{2u}{r^2} + \left(\kappa + \frac{1}{3}\right)\frac{\partial}{\partial r}\left(\frac{1}{r^2}\frac{\partial}{\partial r}(r^2 u)\right) = 0,$$

which is equivalent to writing

$$\frac{\partial P}{\partial r} + \nabla^2\boldsymbol{u} + \left(\kappa + \frac{1}{3}\right)\frac{\partial}{\partial r}\left(\frac{1}{r^2}\frac{\partial}{\partial r}(r^2 u)\right) = 0. \tag{20}$$

It is shown that $\nabla^2\boldsymbol{u} = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial u}{\partial r}\right) - \frac{2u}{r^2}$ in Appendix G.

2.8.3 Evolution of the chemicals

The equation describing the evolution of the chemical concentration is converted to spherical coordinates using the expression for the Laplacian further up:

$$\nabla^2 c - \alpha_1 + n = \frac{1}{r^2}\left(\frac{\partial}{\partial r}(r^2\frac{\partial c}{\partial r})\right) - \alpha_1 c + n$$

This is equivalent to writing:

$$\nabla^2 c - \alpha_1 + n = \frac{2}{r}\frac{\partial c}{\partial r} + \frac{\partial^2 c}{\partial r^2} - \alpha_1 + n = 0 \tag{21}$$

2.8.4 Summary of the expressions in the spherical coordinates

The five governing equations and the force function written in spherical coordinates is summarized below:

$$\frac{\partial \rho}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}(r^2\rho u) = 0$$

$$\frac{\partial n}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}(r^2 n u) = 0$$

$$-\frac{\partial P}{\partial r} + \nabla^2\boldsymbol{u} + \left(\kappa + \frac{1}{3}\right)\frac{\partial}{\partial r}\left(\frac{1}{r^2}\frac{\partial}{\partial r}(r^2 u)\right) + F_r = 0$$

$$\frac{\partial^2 c}{\partial r^2} + \frac{2}{r}\frac{\partial c}{\partial r} - \alpha_1 c D + n = 0$$

$$\boldsymbol{F} = \tau_0\frac{\partial}{\partial r}\left(\frac{\rho n}{1 + \lambda n^2}\right)$$

$$\rho = 1 + \beta P$$

The change in the gel radius with respect with time is equal to the gel velocity at the gel boundary, which in mathematical terms becomes:

$$\frac{dR}{dt} = u(R(t), t) \tag{22}$$

2.8.5 Initial and boundary conditions

The initial conditions are treated first. The gel density is assumed to be uniform and equal to 1 initially, while the initial cell density is slightly higher near the center of the gel. The cell density varies slightly, because if both of the densities were uniform, equilibrium would already have been established, and the cell forces could not have been studied. The mathematical versions of the three initial conditions are stated below:

$$\rho(r,0) = 0, \qquad R(0) = 0, \qquad n(r,0) = n_i(r) \tag{23}$$

Then to the boundary conditions: The first boundary condition is zero movement of the gel at the gel center, and the second boundary condition is that there is zero stress at the gel boundary, which can be expressed in mathematical terms as:

$$u = 0, \quad \text{at} \quad r = 0. \tag{24}$$

It is also assumed that at $r = R(t)$ there is no stress, meaning that the stress boundary condition in spherical coordinates becomes:

$$-P + 2\epsilon_{ij} + \left(\kappa - \frac{2}{3}\right)\epsilon_{kk} = 0 \tag{25}$$

where the expressions for ϵ_{ij} and ϵ_{kk} in spherical coordinates is $\epsilon_{ij} = \frac{\partial u}{\partial r}$ and $\epsilon_{kk} = \frac{1}{r^2}\frac{\partial}{\partial r}(r^2 u)$ (using the expressions for divergence shown earlier), which gives rise to the following boundary condition for the stresses:

$$-P + 2\frac{\partial u}{\partial r} + \left(\kappa - \frac{2}{3}\right)\frac{1}{r^2}\frac{\partial}{\partial r}(r^2 u) = 0, \quad \text{at} \quad r = R(t). \tag{26}$$

The third boundary condition is that the chemical flux is zero at $r =$ due to symmetry, and in mathematical terms this becomes:

$$\frac{\partial c}{\partial r} = 0, \quad \text{at} \quad r = 0. \tag{27}$$

At $r = R(t)$, the boundary condition is different:

$$\frac{\partial c}{\partial r} = -\gamma c, \quad \text{at} \quad r = R(t). \tag{28}$$

2.9   The compressibility and bulk viscosity of the gel from experiments

The gel compressibility and the bulk viscosity can be determined from laboratory experiments when no cells are present in the gel. A known radial stress is applied on the gel, and the measured results are used to get the values for the gel compressibility and bulk viscosity. (Green et al., 2013) This is useful when inserted into the mathematical model, because two of the parameters are then known values, and then only the other five parameters can then be changed.

In Appendix H, it were shown that the expressions for the bulk viscosity, κ, and the gel compressibility, β, used when measuring them during experiments are:

$$\kappa = \frac{\sum(t)}{\dot{R}(0)} \tag{29}$$

The bulk viscosity depends on the externally applied stress at time t and the measured initial rate change of the radius, R. Both of these parameters can be measured in the laboratory, and the value of the bulk viscosity can then be inserted into the mathematical model. In order to derive the expression for β, it is assumed that $\beta \sum(t)$ is less than one.
The expression for the isothermal compressibility of the gel is:

$$\beta = \frac{1 - R_{t\to\infty}^{-3}}{\sum(t)} \tag{30}$$

where $R_{t\to\infty}$ is the steady state value of the radius, R. The isothermal compressibility of the gel therefore depends on the steady state value of the radius and the externally applied stress. The externally applied stress is known, since it is the stress applied, and the steady state value of the radius can be measured in the same experiment. The isothermal compressibility of the gel can therefore also be determined from laboratory experiments and together with the bulk viscosity be inserted into the mathematical model to learn more about the fluid in question when both κ and β are known values.

2.10   New coordinates (ζ, τ)

The spherical coordinates used so far have been (r, t), but this will now be converted to the coordinates (ζ, τ). The spherical coordinates could have been used when implementing the equations on the computer, but in order to further simplify the implementations, the new coordinate system is introduced. The equations including such as mass balance and force balance which were derived for the spherical coordinates further up will therefore now be converted to the coordinate system (ζ, τ). The same method used to convert the equations from Cartesian to spherical coordinates will be used, but it will here be utilized from the beginning that the polar and azimuthal angles can be neglected in order to simplify the derivation. First the relationship between r and ζ is shown (Green et al., 2013), before moving on to the derivation:

$$r = R(t)\zeta \tag{31}$$

This expression is then inserted into the expressions for x, y and z:

$$x = R(t)\zeta \cos(\phi)\sin(\theta)$$

$$y = R(t)\zeta \sin(\theta)\sin(\phi)$$

$$z = R(t)\zeta \cos(\theta)$$

The partial derivatives can then be written as:

$$\frac{\partial}{\partial x} = \frac{\partial \zeta}{\partial x}\frac{\partial}{\partial \zeta} + \frac{\partial \theta}{\partial x}\frac{\partial}{\partial \theta} + \frac{\partial \phi}{\partial x}\frac{\partial}{\partial \phi}$$

$$\frac{\partial}{\partial y} = \frac{\partial \zeta}{\partial y}\frac{\partial}{\partial \zeta} + \frac{\partial \theta}{\partial y}\frac{\partial}{\partial \theta} + \frac{\partial \phi}{\partial y}\frac{\partial}{\partial \phi}$$

$$\frac{\partial}{\partial z} = \frac{\partial \zeta}{\partial z}\frac{\partial}{\partial \zeta} + \frac{\partial \theta}{\partial z}\frac{\partial}{\partial \theta} + \frac{\partial \phi}{\partial z}\frac{\partial}{\partial \phi}$$

The partial derivatives on the right side of the equations must then be calculated:

$$\frac{\partial \zeta}{\partial x} = \frac{x}{\zeta R(t)R(t)} = \frac{\zeta R(t)\cos(\phi)\sin(\theta)}{\zeta R(t)R(t)} = \frac{\cos(\phi)\sin(\theta)}{R(t)}$$

$$\frac{\partial \zeta}{\partial y} = \frac{y}{\zeta R(t)R(t)} = \frac{\zeta R(t)\sin(\theta)\sin(\phi)}{\zeta R(t)R(t)} = \frac{\sin(\theta)\sin(\phi)}{R(t)}$$

$$\frac{\partial \zeta}{\partial z} = \frac{z}{\zeta R(t)R(t)} = \frac{\zeta R(t)\cos(\theta)}{\zeta R(t)R(t)} = \frac{\cos(\theta)}{R(t)}$$

The expression for the partial derivative of angle θ with respect to x, y and z is:

$$\frac{\partial \theta}{\partial x} = \frac{xz}{\sqrt{\frac{x^2+y^2}{x^2+y^2+z^2}}\,(x^2+y^2+z^2)^{\frac{3}{2}}} = \frac{\cos(\theta)\cos(\phi)}{R(t)\zeta}, \qquad \frac{\partial \theta}{\partial y} = \frac{\cos(\theta)\sin(\phi)}{R(t)\zeta}, \qquad \frac{\partial \phi}{\partial z} = -R(t)\zeta\sin(\theta)$$

The partial derivatives of the angle ϕ with respect to x, y and z is:

$$\frac{\partial \phi}{\partial x} = -\frac{\sin(\theta)}{R(t)\zeta\sin(\theta)}, \qquad \frac{\partial \phi}{\partial y} = \frac{\cos(\phi)}{R(t)\zeta\sin(\theta)}, \qquad \frac{\partial \theta}{\partial z} = -\frac{\sin(\phi)}{R(t)\zeta}$$

Inserting the partial derivatives into the expressions for $\frac{\partial}{\partial x}$, $\frac{\partial}{\partial y}$ and $\frac{\partial}{\partial z}$:

$$\frac{\partial}{\partial x} = \frac{\cos(\phi)\sin(\theta)}{R(t)}\frac{\partial}{\partial \zeta} + \frac{\cos(\theta)\cos(\phi)}{R(t)\zeta}\frac{\partial}{\partial \theta} - \frac{\sin(\phi)}{R(t)\zeta\sin(\theta)}\frac{\partial}{\partial \phi}$$

$$\frac{\partial}{\partial y} = \frac{\sin(\phi)\sin(\theta)}{R(t)}\frac{\partial}{\partial \zeta} + \frac{\cos(\theta)\sin(\phi)}{R(t)\zeta}\frac{\partial}{\partial \theta} + \frac{\cos(\phi)}{R(t)\zeta\sin(\theta)}\frac{\partial}{\partial \phi}$$

$$\frac{\partial}{\partial z} = \frac{\cos(\theta)}{R(t)}\frac{\partial}{\partial \zeta} - \frac{\sin(\theta)}{R(t)\zeta}\frac{\partial}{\partial \phi}$$

Since it is the Laplacian operator which is of interest, the second derivatives must be calculated. This is done in Appendix I, but the results are used here: By summing the expressions for $\frac{\partial^2}{\partial x^2}$, $\frac{\partial^2}{\partial y^2}$ and $\frac{\partial^2}{\partial z^2}$ and using factorization gives that $\frac{\partial}{\partial \zeta}$ and $\frac{\partial^2}{\partial \zeta^2}$ can be written as:

$$\frac{\partial}{\partial \zeta}\left[\frac{\sin^2(\phi)}{R^2\zeta} + \frac{\cos^2(\phi)\cos^2(\theta)}{R^2\zeta} + \frac{\sin^2(\phi)}{R^2\zeta} + \frac{\cos^2(\phi)}{R^2\zeta} + \frac{\sin^2(\phi)\cos^2(\theta)}{R^2\zeta}\right]$$

$$= \frac{\partial}{\partial \zeta}\frac{1}{R^2\zeta}\left[1 + \sin^2(\theta) + \cos^2(\theta)\left(\cos^2(\phi) + \sin^2(\phi)\right)\right] = \frac{2}{R^2\zeta}\frac{\partial}{\partial \zeta},$$

and:

$$\frac{\partial^2}{\partial \zeta^2}\left[\frac{\cos^2(\phi)}{R^2} + \frac{\cos^2(\phi)\sin^2(\theta)}{R^2} + \frac{\sin^2(\theta)\sin^2(\phi)}{R^2}\right].$$

$$\frac{\partial^2}{\partial \zeta^2}\frac{1}{R^2}\left[\cos^2(\phi) + \sin^2(\theta)\left(\cos^2(\phi) + \sin^2(\phi)\right)\right] = \frac{1}{R^2}\frac{\partial^2}{\partial \zeta^2}$$

Since both the polar and azimuthal angles can be neglected, the expression for the Laplacian operator becomes:

$$\nabla^2 = \frac{2}{R^2\zeta}\frac{\partial}{\partial \zeta} + \frac{1}{R^2}\frac{\partial^2}{\partial \zeta^2}$$

which gives the scalar Laplacian operator of u to be:

$$\nabla^2 u = \frac{2}{R^2\zeta}\frac{\partial u}{\partial \zeta} + \frac{1}{R^2}\frac{\partial^2 u}{\partial \zeta^2}$$

The divergence of $\boldsymbol{u}$ in the coordinate system (ζ, τ) is:

$$\nabla \cdot \boldsymbol{u} = \frac{1}{r^2} \frac{\partial}{\partial r} (r^2 u) = \frac{1}{R^2 \zeta^2} \frac{1}{R} \frac{\partial}{\partial \zeta} \left(R^2 \zeta^2 u \right) = \frac{1}{R \zeta^2} \frac{\partial}{\partial \zeta} \left(\zeta^2 u \right),$$

which gives that

$$\nabla(\nabla \cdot \boldsymbol{u}) = \frac{\partial}{\partial \zeta} \left(\frac{1}{R^2 \zeta^2} \frac{\partial}{\partial \zeta} \left(\zeta^2 u \right) \right)$$

$$= \frac{1}{R^2} \left(-\frac{2}{\zeta^3} \frac{\partial}{\partial \zeta} (\zeta^2 u) + \frac{1}{\zeta^2} \frac{\partial^2}{\partial \zeta^2} (\zeta^2 u) \right) = \frac{1}{R^2} \left(-\frac{2}{\zeta^3} (2\zeta u + \zeta^2 \frac{\partial u}{\partial \zeta}) + \frac{1}{\zeta^2} \frac{\partial}{\partial \zeta} (2\zeta u + \zeta^2 \frac{\partial u}{\partial \zeta}) \right)$$

$$= -\frac{4u}{R^2 \zeta^2} - \frac{2}{R^2 \zeta} \frac{\partial u}{\partial \zeta} + \frac{1}{R^2 \zeta^2} \left(2u + 2\zeta \frac{\partial u}{\partial \zeta} + 2\zeta \frac{\partial u}{\partial \zeta} + \zeta^2 \frac{\partial^2 u}{\partial \zeta^2} \right) = -\frac{4u}{R^2 \zeta^2} - \frac{2}{R^2 \zeta} \frac{\partial u}{\partial \zeta} + \frac{2u}{R^2 \zeta^2} + \frac{2}{R^2 \zeta} \frac{\partial u}{\partial \zeta} + \frac{2}{R^2 \zeta} \frac{\partial u}{\partial \zeta} + \frac{1}{R^2} \frac{\partial^2 u}{\partial \zeta^2}$$

As shown further up for the spherical coordinates, the vector Laplacian, $\nabla^2(\boldsymbol{u})$, can be written equal to the gradient of the divergence of $\boldsymbol{u}$ because the polar and azimuthal angles are neglected. This is also the case for the new coordinate system, which gives:

$$\nabla^2(\boldsymbol{u}) = \nabla(\nabla \cdot \boldsymbol{u}) = -\frac{2u}{R^2 \zeta^2} + \frac{2}{R^2 \zeta} \frac{\partial u}{\partial \zeta} + \frac{1}{R^2} \frac{\partial^2 u}{\partial \zeta^2} = -\frac{2u}{R^2 \zeta^2} + \nabla^2 u, \tag{32}$$

where $\nabla^2(u)$ represents the scalar Laplacian.

The mass balance equations for the collagen gel and cells in new Coordinates

The mass balance equations for the gel and cells will now be converted to the new coordinate system with (ζ, τ):

The first term of the mass balance equations:

$$\frac{\partial \rho}{\partial t} = \frac{\partial \rho}{\partial \tau} + \frac{\partial \rho}{\partial \zeta} \frac{\partial \zeta}{\partial R} \frac{\partial R}{\partial \tau}$$

where the expression for $\frac{\partial \zeta}{\partial R}$ is calculated as:

$$\zeta = \frac{r}{R} \quad \text{which gives the partial derivative} \quad \frac{\partial \zeta}{\partial R} = -\frac{r}{R^2} = -\frac{R\zeta}{R^2} = -\frac{\zeta}{R}.$$

This is then inserted into the expression for $\frac{\partial \rho}{\partial t}$ to get:

$$\frac{\partial \rho}{\partial t} = \frac{\partial \rho}{\partial \tau} - \frac{\zeta}{R} \dot{R} \frac{\partial \rho}{\partial \zeta}$$

The second term of the mass balance equations:

$$\frac{1}{r^2} \frac{\partial}{\partial r} (r^2 \rho u) = \frac{1}{R^2 \zeta^2} \frac{\partial}{\partial \zeta} \frac{\partial \zeta}{\partial r} \left(R^2 \zeta^2 \rho u \right),$$

where

$$\frac{\partial \zeta}{\partial r} = \frac{1}{R}.$$

This is then inserted to give:

$$\frac{1}{r^2} \frac{\partial}{\partial r} (r^2 \rho u) = \frac{1}{R^3 \zeta^2} \frac{\partial}{\partial \zeta} \left(R^2 \zeta^2 \rho u \right) = \frac{1}{R \zeta^2} \frac{\partial}{\partial \zeta} \left(\zeta^2 \rho u \right)$$

which means that the mass balance equations for the gel and cells in the coordinates (ζ, τ) become:

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$$\frac{\partial \rho}{\partial \tau} - \zeta \frac{\dot{R}}{R} \frac{\partial \rho}{\partial \zeta} + \frac{1}{R\zeta^2} \frac{\partial}{\partial \zeta} (\zeta^2 \rho u) = 0$$

$$\frac{\partial n}{\partial \tau} - \zeta \frac{\dot{R}}{R} \frac{\partial n}{\partial \zeta} + \frac{1}{R\zeta^2} \frac{\partial}{\partial \zeta} (\zeta^2 n u) = 0$$

The momentum balance equation in the new coordinates (ζ, τ)

Then the force balance between the gel and cells is also going to be converted into the new coordinate system:

The first term of the momentum balance equation:

$$-\frac{\partial P}{\partial r} = -\frac{1}{R} \frac{1}{\beta} \frac{\partial \rho}{\partial \zeta} = -\frac{1}{R\beta} \frac{\partial \rho}{\partial \zeta}$$

The second and third term of the momentum balance equation were converted further up as:

$$\nabla^2(\boldsymbol{u}) = \nabla(\nabla \cdot \boldsymbol{u}) = -\frac{2u}{R^2\zeta^2} + \frac{2}{R^2\zeta} \frac{\partial u}{\partial \zeta} + \frac{1}{R^2} \frac{\partial^2 u}{\partial \zeta^2} = -\frac{2u}{R^2\zeta^2} + \nabla^2 u$$

The fourth term of the momentum balance equation:

$$\frac{\partial}{\partial r} \left(\frac{1}{r^2} \frac{\partial}{\partial r} (r^2 u) \right)$$

where

$$\frac{\partial}{\partial r} = \frac{\partial}{\partial \zeta} \frac{\partial \zeta}{\partial r} = \frac{1}{R} \frac{\partial}{\partial \zeta}$$

This is then inserted into the fourth term of the momentum balance equation to give:

$$\frac{\partial}{\partial r} \left(\frac{1}{r^2} \frac{\partial}{\partial r} (r^2 u) \right) = \frac{1}{R} \frac{\partial}{\partial \zeta} \left(\frac{1}{R^2\zeta^2} \frac{1}{R} \frac{\partial}{\partial \zeta} (R^2\zeta^2 u) \right) = \frac{1}{R^2} \frac{\partial}{\partial \zeta} \left(\frac{\partial}{\partial \zeta} (\zeta^2 u) \right)$$

This means that the momentum balance equation in the coordinates (ζ, τ) can be written as:

$$-\frac{1}{R\beta} \frac{\partial \rho}{\partial \zeta} - \frac{2u}{R^2\zeta^2} + \nabla^2 u + \frac{1}{R^2} \left(\kappa + \frac{1}{3} \right) \frac{\partial}{\partial \zeta} \left(\frac{\partial}{\partial \zeta} (\zeta^2 u) \right) + F_r = 0$$

And by multiplying the above equation with R:

$$-\frac{1}{\beta} \frac{\partial \rho}{\partial \zeta} - \frac{2u}{R\zeta^2} + R\nabla^2 u + \frac{1}{R} \left(\kappa + \frac{1}{3} \right) \frac{\partial}{\partial \zeta} \left(\frac{\partial}{\partial \zeta} (\zeta^2 u) \right) + RF_r = 0 \qquad (33)$$

Equation describing chemical evolution in new coordinates

Then, moving on to the equation describing the chemical evolution:

$$\frac{\partial^2 c}{\partial r^2} + \frac{2}{r} \frac{\partial c}{\partial r} - \alpha_1 c + n = 0$$

Using again that $\frac{\partial}{\partial r} = \frac{1}{R} \frac{\partial}{\partial \zeta}$ to get the expression for the chemical evolution in the coordinates (ζ, τ):

$$\frac{1}{R^2} \frac{\partial^2 c}{\partial \zeta^2} + \frac{2}{R^2\zeta} \frac{\partial c}{\partial \zeta} - \alpha_1 + n = 0 \qquad (34)$$

Change of gel radius at outher boundary in new coordinates

The expression for the change of gel radius at outher boundary in the coordinate system (ζ, τ) can be written as the velocity of the gel at the boundary, at $\zeta = 1$:

$$\frac{dR}{d\tau} = \dot{R} = u|_{\zeta=1} \tag{35}$$

Initial conditions in new coordinates

By using that $\frac{\partial}{\partial r} = \frac{1}{R}\frac{\partial}{\partial \zeta}$ and that $\rho = 1 + \beta P$, the initial conditions in the coordinate system (ζ, τ) become:

$$\rho(\zeta, 0) = 0, \text{ and } n(\zeta, 0) = n_i(\zeta). \tag{36}$$

Boundary conditions in the new coordinates (ζ, τ)

Then, by still using that $\frac{\partial}{\partial r} = \frac{1}{R}\frac{\partial}{\partial \zeta}$, the boundary conditions converted to the new coordinate system become:

$$u(0, \tau) = 0 \tag{37}$$

$$-\left(\frac{\rho - 1}{\beta}\right) + \frac{1}{R}\left(\kappa - \frac{2}{3}\right)\left(\frac{1}{\zeta^2}\frac{\partial}{\partial \zeta}(\zeta^2 u)\right) + \frac{2}{R}\frac{\partial u}{\partial \zeta} = 0, \quad \text{at } \zeta = 1. \tag{38}$$

$$\frac{\partial c}{\partial \zeta} = 0 \text{ at } \zeta = 0, \qquad \frac{\partial c}{\partial \zeta} = -R\gamma c \text{ at } \zeta = 1. \tag{39}$$

The two partial differential equations describing the mass balance for the gel and cells, the momentum balance equation, the partial differential equation describing the evolution of the cell-produced chemicals together with the boundary and initial conditions are summarized below:

$$\frac{\partial \rho}{\partial \tau} - \zeta\frac{\dot{R}}{R}\frac{\partial \rho}{\partial \zeta} + \frac{1}{R\zeta^2}\frac{\partial}{\partial \zeta}(\zeta^2 \rho u) = 0$$

$$\frac{\partial n}{\partial \tau} - \zeta\frac{\dot{R}}{R}\frac{\partial n}{\partial \zeta} + \frac{1}{R\zeta^2}\frac{\partial}{\partial \zeta}(\zeta^2 n u) = 0$$

$$-\frac{1}{\beta}\frac{\partial \rho}{\partial \zeta} - \frac{2u}{R\zeta^2} + R\nabla^2 u + \frac{1}{R}\left(\kappa + \frac{1}{3}\right)\frac{\partial}{\partial \zeta}\left(\frac{\partial}{\partial \zeta}(\zeta^2 u)\right) + RF_r = 0$$

$$\frac{1}{R^2}\frac{\partial^2 c}{\partial \zeta^2} + \frac{2}{R^2\zeta}\frac{\partial c}{\partial \zeta} - \alpha_1 + n = 0$$

$$\frac{dR}{d\tau} = \dot{R} = u|_{\zeta=1}$$

$$u(0, \tau) = 0$$

$$-\left(\frac{\rho - 1}{\beta}\right) + \frac{1}{R}\left(\kappa - \frac{2}{3}\right)\left(\frac{1}{\zeta^2}\frac{\partial}{\partial \zeta}(\zeta^2 u)\right) + \frac{2}{R}\frac{\partial u}{\partial \zeta} = 0, \quad \text{at } \zeta = 1.$$

$$\frac{\partial c}{\partial \zeta} = 0 \text{ at } \zeta = 0, \qquad \frac{\partial c}{\partial \zeta} = -R\gamma c \text{ at } \zeta = 1.$$

$$\rho(\zeta, 0) = 0, \text{ and } n(\zeta, 0) = n_i(\zeta)$$

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2.11 Different types of contractions

The gel density is initially uniformly distributed, while there are slightly more cells near the center of the sphere compared to the rest of the sphere in order to describe gel compaction. If both the cell- and gel densities were uniform, there would be no net forces, and there would already be an equilibrium and therefore no gel compaction to study. A cosine function is therefore used to express the the initial cell densities, since the cosine function has its maximum value at the center of the sphere:

$$n_i = 1 + \frac{1}{100} \cos\left(\frac{\pi r}{2}\right)$$

which in the ζ coordinate system becomes:

$$n_i = 1 + \frac{1}{100} \cos\left(\frac{\pi R \zeta}{2}\right) \tag{40}$$

2.11.1 Mechanical Driven Contraction

Mechanical driven contraction means that the force exerted on the gel by the cells is assumed not to be dependent on the chemical produced by the cells, but only on the cell- and gel densities. Two different types of mechanical driven contraction will be investigated here.
The first force function has the following expression (Green et al., 2013):

$$F_r = \tau_0 \frac{\partial}{\partial r}\left(\frac{n\rho}{1 + \lambda n^2}\right) \tag{41}$$

where τ_0 and λ are positive constants. By using that $\frac{\partial}{\partial r} = \frac{1}{R}\frac{\partial}{\partial \zeta}$, this is converted to the new coordinate system as:

$$F_\zeta = \frac{\tau_0}{R} \frac{\partial}{\partial \zeta}\left(\frac{n\rho}{1 + \lambda n^2}\right) \tag{42}$$

The force exerted by the cells is increasing with increasing gel densities, and decreasing with overcrowding, where overcrowding means that the cell density becomes so high that the cells are interacting in such a way that the cell exerted forces decreases. (Green et al., 2013) This can be seen from $1 + \lambda n^2$ in the denominator. It were also suggested in (Green et al., 2013) that $1 + \lambda n^2$ in

$$F_r = \tau_0 \frac{\partial}{\partial r}\left(\frac{n\rho}{1 + \lambda n^2}\right),$$

should be replaced by $1 + \lambda \rho^2$ instead due to two reasons:

- The cells are often spread too much for cell overcrowding to have an effect (Barocas, Moon, Tranquillo, et al., 1995)

- As can be seen from the experimental values from figure 5 taken from (Moon & Tranquillo, 1993), an increase in cell density should increase the gel compaction.

The mechanical force function for the cells which does not include the preferred extracellular matrix density then becomes:

$$F_r = \tau_0 \frac{\partial}{\partial r}\left(\frac{n\rho}{1 + \lambda \rho^2}\right),$$

and in the new coordinate system:

$$F_\zeta = \frac{\tau_0}{R} \frac{\partial}{\partial \zeta}\left(\frac{n\rho}{1 + \lambda \rho^2}\right) \tag{43}$$

By using ρ in the denominator instead of n as earlier gives a very similar result, but it is more biologically correct to express it like this.

The next type of mechanical driven contraction force function takes into account that cells have a certain maximum density for which it will continue to compact the gel. The reason for this is that the gel compacts because the cell traction forces initially are greater than the elastic forces which the gel can resist without compacting. When the gel is compacted, the elastic modulus (which describes the ratio between stress and strain (Fjaer et al., 1992)) of the gel increases. This means that the cells must exert a greater force in order to compact the gel a specific percent, relative to when the gel was less compacted. The density of the gel will therefore after some time reach an equilibrium. A preferred density parameter is therefore included in the force function, where the preferred density parameter represents the maximum gel density inside the sphere of influence of the cell where the cell continue to compact the gel, and the force expression can then be written as:

$$F_r = \tau_0 \frac{\partial}{\partial r} \left(n\rho(\rho_c - \rho) \right),$$

where ρ_c is the preferred density parameter. (Green et al., 2013) In the new coordinate system, this equation becomes:

$$F_\zeta = \frac{\tau_0}{R} \frac{\partial}{\partial \zeta} \left(n\rho(\rho_c - \rho) \right), \tag{44}$$

2.11.2 Chemically Driven Contraction

As mentioned earlier, chemicals are produced by the cells. These chemicals can affect the traction forces from the cells. Two different expressions for the force function F_r will be investigated further below.

In the first expression, it is assumed that F_r is proportional to the product $n\rho c$ as seen below(Green et al., 2013):

$$F_r = \tau_0 \frac{\partial}{\partial r} \left(n\rho c \right),$$

which in the new coordinate system becomes:

$$F_\zeta = \frac{\tau_0}{R} \frac{\partial}{\partial \zeta} \left(n\rho c \right). \tag{45}$$

The other expression for F_r is including both the effect caused by the chemical c, and the preferred density parameter as follows(Green et al., 2013):

$$F_r = \tau_0 \frac{\partial}{\partial r} \left(n\rho c(\rho_c - \rho) \right)$$

This is also converted into the new coordinate system, and the equation becomes:

$$F_\zeta = \frac{\tau_0}{R} \frac{\partial}{\partial \zeta} \left(n\rho c(\rho_c - \rho) \right) \tag{46}$$

These force functions will later be used when discretizing the mathematical model when investigating the role of the different parameters, and when the mathematical model is compared to experimental data.

2.12 Discretization

The mathematical model is now to be discretized in one dimension. The equation describing the momentum balance equation has the expression

$$-\frac{1}{\beta} \frac{\partial \rho}{\partial \zeta} - \frac{2u}{R\zeta^2} + R\nabla^2 u + \frac{1}{R} \left(\kappa + \frac{1}{3} \right) \frac{\partial}{\partial \zeta} \left(\frac{\partial}{\partial \zeta} (\zeta^2 u) \right) + RF_r = 0$$

Since this is now to be discretized in one dimension, the expression from equation (30), which can be rewritten as $\frac{2}{R^2\zeta} \frac{\partial u}{\partial \zeta} + \frac{1}{R^2} \frac{\partial^2 u}{\partial \zeta^2} = \nabla^2 u$. This is substituted into the equation above to give the equation

$$-\frac{1}{\beta}\frac{\partial \rho}{\partial \zeta} + \frac{1}{R\zeta^2}\frac{\partial}{\partial \zeta}\left(\zeta^2\frac{\partial u}{\partial \zeta}\right) - \frac{2u}{R\zeta^2} + \frac{1}{R}\left(\kappa + \frac{1}{3}\right)\frac{\partial}{\partial \zeta}\left(\frac{1}{\zeta^2}\frac{\partial}{\partial \zeta}(\zeta^2 u)\right) + RF_r = 0,$$

which will be used during the one dimensional discretization of the mathematical model below.

The equations which will be shown how to discretized below, are:

$$\frac{\partial \rho}{\partial \tau} - \zeta\frac{\dot{R}}{R}\frac{\partial \rho}{\zeta} + \frac{1}{R\zeta^2}\frac{\partial}{\partial \zeta}\left(\zeta^2\rho u\right) = 0 \tag{47}$$

$$F_\zeta = \frac{\tau_0}{R}\frac{\partial}{\partial \zeta}\left(\frac{n\rho}{1+\lambda n^2}\right) \tag{48}$$

$$-\frac{1}{\beta}\frac{\partial \rho}{\partial \zeta} + \frac{1}{R\zeta^2}\frac{\partial}{\partial \zeta}\left(\zeta^2\frac{\partial u}{\partial \zeta}\right) - \frac{2u}{R\zeta^2} + \frac{1}{R}\left(\kappa + \frac{1}{3}\right)\frac{\partial}{\partial \zeta}\left(\frac{1}{\zeta^2}\frac{\partial}{\partial \zeta}(\zeta^2 u)\right) + RF_r = 0 \tag{49}$$

$$\frac{1}{R^2}\frac{\partial^2 c}{\partial \zeta^2} + \frac{2}{R^2\zeta}\frac{\partial c}{\partial \zeta} - \alpha_1 c + n = 0, \tag{50}$$

where the gel density and the cell density is defined at the cell centers, while the velocity is defined at the cell boundaries.

The initial conditions and boundary conditions which is used are:

$$\rho(\zeta,0) = 1 \tag{51}$$

$$n(\zeta,0) = n_i(\zeta) \tag{52}$$

$$u(0,\tau) = 0 \tag{53}$$

$$-\left(\frac{\rho - 1}{\beta}\right) + \frac{1}{R}\left(\kappa - \frac{2}{3}\right)\left(\frac{1}{\zeta^2}\frac{\partial}{\partial \zeta}(\zeta^2 u)\right) + \frac{2}{R}\frac{\partial u}{\partial \zeta} = 0 \tag{54}$$

$$\frac{\partial c}{\partial \zeta} = 0 \quad \text{at} \ \zeta = 0 \tag{55}$$

$$\frac{\partial c}{\partial \zeta} = -R\gamma c \quad \text{at} \ \zeta = 1 \tag{56}$$

For each new time interval, the new gel radius must be updated. This is accomplished using the following equation:

$$\frac{dR}{d\tau} = \dot{R} = u|_{\zeta=1} \tag{57}$$

The different cell blocks are represented by i, where an integer value for i means the center of the cell, while fraction value for i means at the cell boundary. The distance between each cell center is denoted by $\Delta\zeta$. The first cell block is $i = 1$, while the last cell block is represented by N, while the different time steps are represented by n, so that the next time step is written as $n + 1$. Below is a figure showing the spatial domain:

Figure 3: Figure showing the total discretization domain from i=1:N
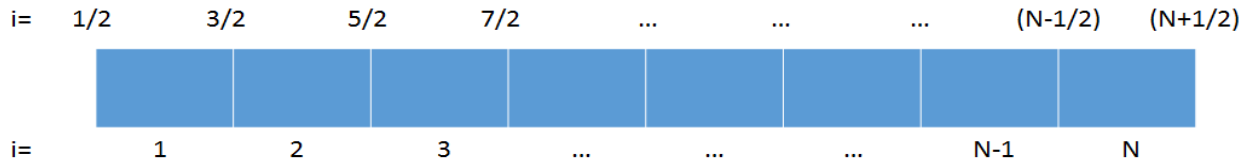
There are five steps during the numerical simulations, and they are written below:

- First, the momentum balance equation is solved with respect to the velocity u, using the boundary conditions (53) and (54).

- Then, the values for u is inserted into the mass balance equation for the gel and for the cells. The initial conditions used in order to solve for ρ and n are equations (51) and (52). The mass balance equation for the gel is equation (47), but the cells have an equivalent expression, only replacing the gel density ρ with the cell density n.

- The equation describing the chemical evolution (equation (50)) is then solved using the values for the cell density n from the previous step, together with the boundary conditions (55) and (56).

- The force function (48) is then updated using the values for the gel density and cell density, ρ and n. If another force function is used than (48), the same procedure is followed, only change equation (48) to the desired force function.

- The last step is to use equation (57), which describes the rate at which the gel radius is changing, in order to update the gel radius, before starting at the first step again for the next time step.

2.12.1 Mass balance equation

The mass balance equation for the gel is then to be discretized. The equation is first repeated together with the boundary conditions which are used during the numerical computation:

$$\frac{\partial \rho}{\partial \tau} - \zeta \frac{\dot{R}}{R} \frac{\partial \rho}{\zeta} + \frac{1}{R\zeta^2} \frac{\partial}{\partial \zeta} \left(\zeta^2 \rho u \right) = 0$$

$$\rho(\zeta, 0) = 1$$
$$n(\zeta, 0) = n_i(\zeta)$$

The discretized version of this equation is written first, before it is shown how it was discretized:

$$\rho_i^{n+1} = \rho_i^n + \frac{\Delta \tau}{\Delta \zeta} \left(F_{II} - F_I \right) - b_{\rho,i} \frac{\Delta \tau}{\Delta \zeta} \left(E_{II} - E_I \right),$$

where F_{II}, F_I, E_{II} and E_I is defined further down in the discretization.

Substitution is used in order to simplify mass balance equation during the discretization and the implementation on the computer later:

$$\frac{\partial \rho}{\partial \zeta} - a_\rho \frac{\partial \rho}{\zeta} + b_\rho \frac{\partial}{\partial \zeta} \left(\zeta^2 \rho u \right) = 0,$$

where $a_\rho = \zeta \frac{\dot{R}}{R}$ and $b_\rho = \frac{1}{R\zeta^2}$. Term two and three are discretized by subtracting the flux going out of cell i to the right with the flux coming in to cell i from the left, and dividing this by $\Delta \zeta$.

The second term in the mass balance equation is discretized as follows:

$$F_{II} = a_{\rho,i} \rho_{i+\frac{1}{2}} = a_{\rho,i} \left(\frac{\rho_{i+1} + \rho_i}{2} \right) - \frac{|a_{\rho,i}|}{2} \left(\rho_{i+1} - \rho_i \right)$$

$$F_I = a_{\rho,i} \rho_{i-\frac{1}{2}} = a_{\rho,i} \left(\frac{\rho_i + \rho_{i-1}}{2} \right) - \frac{|a_{\rho,i}|}{2} \left(\rho_i - \rho_{i-1} \right)$$

This gives the discretization of the second term to be:

$$a_\rho \frac{\partial \rho}{\partial \zeta} = \frac{F_{II} - F_I}{\Delta \zeta}$$

The third term in the mass balance equation is also discretized using the fluxes:

$$E_{II} = \left(\zeta^2 \rho u\right)_{i+\frac{1}{2}} = \left(\zeta^2 u\right)_{i+\frac{1}{2}} \left(\frac{\rho_{i+1} + \rho_i}{2}\right) - \frac{\left(\zeta^2 |u|\right)_{i+\frac{1}{2}}}{2} \left(\rho_{i+1} - \rho_i\right)$$

$$E_I = \left(\zeta^2 \rho u\right)_{i-\frac{1}{2}} = \left(\zeta^2 u\right)_{i-\frac{1}{2}} \left(\frac{\rho_i + \rho_{i-1}}{2}\right) - \frac{\left(\zeta^2 |u|\right)_{i-\frac{1}{2}}}{2} \left(\rho_i - \rho_{i-1}\right)$$

By subtracting the fluxes, $E_{II} - E_I$ before dividing by the spatial distance between the cells, $\Delta\zeta$, gives:

$$b_\rho \frac{\partial}{\partial\zeta} \left(\zeta^2 \rho u\right) = b_\rho \frac{E_{II} - E_I}{\Delta\zeta}$$

The first term is discretized as:

$$\frac{\partial\rho}{\partial\tau} = \frac{\rho_i^{n+1} - \rho_i^n}{\Delta\tau}$$

These discretized terms are then inserted into the momentum balance equation to give:

$$\frac{\partial\rho}{\partial\tau} - \zeta\frac{\dot{R}}{R}\frac{\partial\rho}{\zeta} + \frac{1}{R\zeta^2}\frac{\partial}{\partial\zeta}\left(\zeta^2 \rho u\right) \approx \frac{\rho_i^{n+1} - \rho_i^n}{\Delta\tau} - \left(\frac{F_{II} - F_I}{\Delta\zeta}\right) + b_\rho \left(\frac{E_{II} - E_I}{\Delta\zeta}\right) = 0$$

$$\implies \rho_i^{n+1} = \rho_i^n + \frac{\Delta\tau}{\Delta\zeta}\left(F_{II} - F_I\right) - b_{\rho,i}\frac{\Delta\tau}{\Delta\zeta}\left(E_{II} - E_I\right)$$

The mass balance equation for the cells is discretized the exact same way, only replacing ρ with n.

2.12.2 Boundary condition for the momentum balance equation

Equation (54), which is the boundary condition needed when solving the momentum balance equation, is repeated below:

$$-\left(\frac{\rho - 1}{\beta}\right) + \frac{1}{R}\left(\kappa - \frac{2}{3}\right)\left(\frac{1}{\zeta^2}\frac{\partial}{\partial\zeta}(\zeta^2 u)\right) + \frac{2}{R}\frac{\partial u}{\partial\zeta} = 0,$$

at $\zeta = 1$, meaning cell block N.
This is the boundary condition for the velocity at the outer boundary of the gel, so it gives an expression for $u_{N+\frac{1}{2}}$, which will be used together with boundary condition (53) when solving equation (49) numerically. The discretized expression is first written, before it is shown how the equation was discretized:

$$u_{N+\frac{1}{2}} = G - u_{N-\frac{1}{2}} \cdot H,$$

where

$$G = \frac{\rho_N - 1}{\beta \cdot (b + 2a - a\zeta_N^2)} \quad \text{and} \quad H = \frac{\left[-a\zeta_N^2 - b\right]}{\left[b + 2a - a\zeta_N^2\right]}.$$

This equation was discretized as follows:

$$-\frac{\rho_N^n - 1}{\beta} + \frac{a}{\zeta_{N+\frac{1}{2}}^2 \Delta\zeta}\left[(u\zeta^2)_{N+1} - (u\zeta^2)_N\right] + \frac{b}{\Delta\zeta}\left[u_{N+1} - u_n\right] = 0$$

$$-\frac{\rho_N^n - 1}{\beta} + \frac{a}{\zeta_{N+\frac{1}{2}}^2 \Delta\zeta}\left[\frac{(u\zeta^2)_{N+\frac{1}{2}} - (u\zeta^2)_N}{\frac{1}{2}}\right] + \frac{b}{\Delta\zeta}\left[\frac{u_{N+\frac{1}{2}} - u_N}{\frac{1}{2}}\right] = 0$$

Putting $u_{N+\frac{1}{2}}$ and u_N outside of the parenthesis gives:

$$u_{N+\frac{1}{2}} \left[\frac{2a\zeta_{N+\frac{1}{2}}^2}{\zeta_{N+\frac{1}{2}}\Delta\zeta} + \frac{2b}{\Delta\zeta} \right] + u_N \left[-\frac{2a\zeta_N^2}{\zeta_{N+\frac{1}{2}}\Delta\zeta} \right] = \left(\frac{\rho_N - 1}{\beta} \right)$$

Using that $\zeta_{N+\frac{1}{2}} = 1$, gives the expression:

$$u_{N+\frac{1}{2}} \left[\frac{2a + 2b}{\Delta\zeta} \right] + \left(\frac{u_{N+\frac{1}{2}} + u_{N-\frac{1}{2}}}{2} \right) \left[-\frac{2a\zeta_N^2}{\Delta\zeta} - \frac{2b}{\Delta\zeta} \right] = \frac{\rho_N - 1}{\beta}$$

$$u_{N+\frac{1}{2}} \left[\frac{b + 2a}{\Delta\zeta} - \frac{a\zeta_N^2}{\Delta\zeta} \right] + u_{N-\frac{1}{2}} \left[-\frac{a\zeta_N^2}{\Delta\zeta} - \frac{b}{\Delta\zeta} \right] = \frac{\rho_N - 1}{\beta}$$

which gives the final expression for $u_{N+\frac{1}{2}}$:

$$u_{N+\frac{1}{2}} = \frac{\rho_N - 1}{\beta \cdot \left(\frac{b+2a}{\Delta\zeta} - \frac{a\zeta_N^2}{\Delta\zeta} \right)} - u_{N-\frac{1}{2}} \frac{\left[-\frac{a\zeta_N^2}{\Delta\zeta} - \frac{b}{\Delta\zeta} \right]}{\left[\frac{b+2a}{\Delta\zeta} - \frac{a\zeta_N^2}{\Delta\zeta} \right]}$$

$$u_{N+\frac{1}{2}} = \frac{\rho_N - 1}{\beta \cdot (b + 2a - a\zeta_N^2)} - u_{N-\frac{1}{2}} \frac{\left[-a\zeta_N^2 - b \right]}{\left[b + 2a - a\zeta_N^2 \right]}$$

This expression for the boundary velocity is used below when finalizing the discretization of equation (54), and therefore some substitution is made in order to make the below discretization more lucid:

$$u_{N+\frac{1}{2}} = G - u_{N-\frac{1}{2}} \cdot H,$$

where

$$G = \frac{\rho_N - 1}{\beta \cdot (b + 2a - a\zeta_N^2)} \quad \text{and} \quad H = \frac{\left[-a\zeta_N^2 - b \right]}{\left[b + 2a - a\zeta_N^2 \right]}.$$

2.12.3 Force function

The force function F_ζ for mechanical driven compaction on the form of equation (48) is one of several force functions which can be used during the implementation on the computer, but the discretization for the other force functions has the same procedure are equation (48). The force function is needed when when solving the momentum balance equation on the computer, and it will shown how the force function on the form as equation (48) is discretized below, first repeating the equation:

$$F_\zeta = \frac{\tau_0}{R} \frac{\partial}{\partial\zeta} \left(\frac{n\rho}{1 + \lambda n^2} \right),$$

and will be discretized below. Discretized, this force function from the cells is:

$$F_\zeta \approx \frac{\tau_0}{R\Delta\zeta} \left[\left(\frac{n\rho}{1 + \lambda n^2} \right)_{i+1} - \left(\frac{n\rho}{1 + \lambda n^2} \right)_i \right]$$

The discretization of the other force functions, is accomplished using the same method as was used in the force function above.

2.12.4   Momentum balance equation

The momentum balance equation will then be discretized. The discretized version of the force function shown above will be used when implementing the momentum balance equation on the computer, together with the boundary condition (53) and (54). The momentum balance equation (equation (49)) is repeated below:

$$-\frac{1}{\beta}\frac{\partial \rho}{\partial \zeta} + \frac{1}{R\zeta^2}\frac{\partial}{\partial \zeta}\left(\zeta^2\frac{\partial u}{\partial \zeta}\right) - \frac{2u}{R\zeta^2} + \frac{1}{R}\left(\kappa + \frac{1}{3}\right)\frac{\partial}{\partial \zeta}\left(\frac{1}{\zeta^2}\frac{\partial}{\partial \zeta}(\zeta^2 u)\right) + RF_r = 0,$$

This will be solved using the implicit method, which gives a matrix structure as follows (it will be shown how to get this matrix structure below):

$$
\begin{bmatrix}
B_{i=1} & C_{i=1} & 0 \\
A_{i=2} & B_{i=2} & C_{i=2} \\
0 & A_{i=3} & B_{i=3} - H \cdot C_{i=3}
\end{bmatrix}
\cdot
\begin{bmatrix}
u_{\frac{3}{2}} \\
u_{\frac{5}{2}} \\
u_{\frac{7}{2}}
\end{bmatrix}
=
\begin{bmatrix}
\frac{a_{i=1}}{\Delta\zeta}\left(\rho_2^n - \rho_1^n\right) - RF_{r,i=1} \\
\frac{a_{i=2}}{\Delta\zeta}\left(\rho_3^n - \rho_2^n\right) - RF_{r,i=2} \\
\frac{a_{i=3}}{\Delta\zeta}\left(\rho_4^n - \rho_3^n\right) - RF_{r,i=3} - G \cdot C
\end{bmatrix}
$$

In order to simplify the momentum balance equation), some substitution is made as a first step in showing how the to get the matrix structure shown above:

$$a = \frac{1}{\beta}, \quad b = \frac{1}{R\zeta^2}, \quad c = \frac{2}{R\zeta^2} \quad \text{and} \quad d = \frac{1}{R}\left(\kappa + \frac{1}{3}\right)$$

This gives the following simplified expression for the momentum balance equation:

$$-a\frac{\partial \rho}{\partial \zeta} + b\frac{\partial}{\partial \zeta}\left(\zeta^2\frac{\partial u}{\partial \zeta}\right) - cu + d\frac{\partial}{\partial \zeta}\left(\frac{1}{\zeta^2}\frac{\partial}{\partial \zeta}(\zeta^2 u)\right) + RF_r = 0$$

The fourth term in the equation above is discretized as follows (not including $d = \frac{1}{R}\left(\kappa + \frac{1}{3}\right)$):

$$\frac{\partial}{\partial \zeta}\left(\frac{1}{\zeta^2}\frac{\partial}{\partial \zeta}(\zeta^2 u)\right) = \frac{\partial}{\partial \zeta}(f_i) \approx \frac{f_{i+1} - f_i}{\Delta\zeta},$$

where $f = \frac{1}{\zeta^2}\frac{\partial}{\partial \zeta}(\zeta^2 u)$.

The expressions for f_{i+1} and f_i are discretized as follows:

$$f_i = \frac{1}{\zeta_i^2}\left(\frac{(\zeta^2 u)_{i+\frac{1}{2}} - (\zeta^2 u)_{i-\frac{1}{2}}}{\Delta\zeta}\right)$$

$$f_{i+1} = \frac{1}{\zeta_{i+1}^2}\left(\frac{(\zeta^2 u)_{i+\frac{3}{2}} - (\zeta^2 u)_{i+\frac{1}{2}}}{\Delta\zeta}\right)$$

Subtracting f_{i+1} with f_i and dividing with $\Delta\zeta$ gives the expression for the discretized fourth term (not including $d = \frac{1}{R}\left(\kappa + \frac{1}{3}\right)$):

$$\frac{f_{i+1} - f_i}{\Delta\zeta} = \frac{1}{\zeta_{i+1}^2}\left(\frac{(\zeta^2 u)_{i+\frac{3}{2}} - (\zeta^2 u)_{i+\frac{1}{2}}}{\Delta\zeta^2}\right) - \frac{1}{\zeta_i^2}\left(\frac{(\zeta^2 u)_{i+\frac{1}{2}} - (\zeta^2 u)_{i-\frac{1}{2}}}{\Delta\zeta^2}\right)$$

The second term (not including $b = \frac{1}{R\zeta^2}$) is discretized as shown below:

$$\frac{\partial}{\partial \zeta}\left(\zeta^2\frac{\partial u}{\partial \zeta}\right) = \frac{\partial}{\partial \zeta}(k_i) \approx \frac{k_{i+1} - k_i}{\Delta\zeta},$$

where $k = \zeta^2\frac{\partial u}{\partial \zeta}$.

The expressions for k_{i+1} and k_i are discretized below:

$$k_i = \zeta_i^2 \left(\frac{u_{i+\frac{1}{2}} - u_{i-\frac{1}{2}}}{\Delta\zeta} \right)$$

$$k_{i+1} = \zeta_{i+1}^2 \left(\frac{u_{i+\frac{3}{2}} - u_{i+\frac{1}{2}}}{\Delta\zeta} \right)$$

The expression for k_{i+1} is then subtracted with k_i, before dividing the whole expression with $\Delta\zeta$ to give:

$$\frac{k_{i+1} - k_i}{\Delta\zeta} = \zeta_{i+1}^2 \left(\frac{u_{i+\frac{3}{2}} - u_{i+\frac{1}{2}}}{\Delta\zeta^2} \right) - \zeta_i^2 \left(\frac{u_{i+\frac{1}{2}} - u_{i-\frac{1}{2}}}{\Delta\zeta^2} \right)$$

These discretized expressions are then inserted into equation (49) to give:

$$-\frac{a}{\Delta\zeta} \left(\rho_{i+1}^n - \rho_i^n \right) + b \left[\zeta_{i+1}^2 \left(\frac{u_{i+\frac{3}{2}} - u_{i+\frac{1}{2}}}{\Delta\zeta^2} \right) - \zeta_i^2 \left(\frac{u_{i+\frac{1}{2}} - u_{i-\frac{1}{2}}}{\Delta\zeta^2} \right) \right] - c \cdot u_{i+\frac{1}{2}}$$

$$+d \left[\frac{1}{\zeta_{i+1}^2} \left(\frac{(\zeta^2 u)_{i+\frac{3}{2}} - (\zeta^2 u)_{i+\frac{1}{2}}}{\Delta\zeta^2} \right) - \frac{1}{\zeta_i^2} \left(\frac{(\zeta^2 u)_{i+\frac{1}{2}} - (\zeta^2 u)_{i-\frac{1}{2}}}{\Delta\zeta^2} \right) \right] + RF_r = 0$$

This can be rewritten further in order to later using a matrix structure:

$$u_{i+\frac{1}{2}} \left[-\frac{b\zeta_{i+1}^2}{\Delta\zeta^2} - \frac{b\zeta_i^2}{\Delta\zeta^2} - c - \frac{\zeta_{i+\frac{1}{2}}^2 d}{\zeta_{i+1}^2 \Delta\zeta^2} - \frac{d\zeta_{i+\frac{1}{2}}}{\zeta_i^2 \Delta\zeta^2} \right] + u_{i+\frac{3}{2}} \left[\frac{b\zeta_{i+1}^2}{\Delta\zeta^2} + \frac{d\zeta_{i+\frac{3}{2}}^2}{\zeta_{i+1}^2 \Delta\zeta^2} \right]$$

$$+u_{i-\frac{1}{2}} \left[\frac{b\zeta_i^2}{\Delta\zeta^2} + \frac{d\zeta_{i-\frac{1}{2}}}{\zeta_i^2 \Delta\zeta^2} \right] = \frac{a}{\Delta\zeta} \left(\rho_{i+1}^n - \rho_i^n \right) - RF_r$$

where the parenthesis can be substituted in order to further simplify the expression:

$$u_{i+\frac{1}{2}} \cdot B + u_{i+\frac{3}{2}} \cdot C + u_{i-\frac{1}{2}} \cdot A = \frac{a}{\Delta\zeta} \left(\rho_{i+1}^n - \rho_i^n \right) - RF_r$$

where

$$A = \left[\frac{b\zeta_i^2}{\Delta\zeta^2} + \frac{d\zeta_{i-\frac{1}{2}}}{\zeta_i^2 \Delta\zeta^2} \right], \quad B = \left[-\frac{b\zeta_{i+1}^2}{\Delta\zeta^2} - \frac{b\zeta_i^2}{\Delta\zeta^2} - c - \frac{\zeta_{i+\frac{1}{2}}^2 d}{\zeta_{i+1}^2 \Delta\zeta^2} - \frac{d\zeta_{i+\frac{1}{2}}}{\zeta_i^2 \Delta\zeta^2} \right] \text{ and } C = \left[\frac{b\zeta_{i+1}^2}{\Delta\zeta^2} + \frac{d\zeta_{i+\frac{3}{2}}^2}{\zeta_{i+1}^2 \Delta\zeta^2} \right].$$

This expression will then be rewritten in matrix form, and in order to show how this is done, the entire spatial domain is split into four parts. When i is an integer, it refers to the cell center, while otherwise it refers to cell boundary.

Figure 4: Spatial domain split into four grid blocks
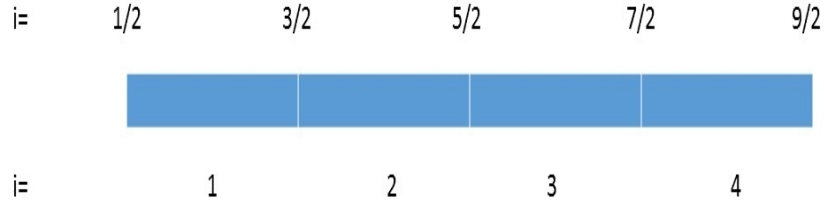
$$i = 1: \qquad A \cdot u_{\frac{1}{2}} + u_{\frac{3}{2}} \cdot B + u_{\frac{5}{2}} \cdot C = \frac{a}{\Delta \zeta} \left(\rho_2^n - \rho_1^n \right) - RF_{r,i=1},$$

which, by using that $u_{\frac{1}{2}} = 0$, can be written as

$$i = 1: \qquad u_{\frac{3}{2}} \cdot B + u_{\frac{5}{2}} \cdot C = \frac{a}{\Delta \zeta} \left(\rho_2^n - \rho_1^n \right) - RF_{r,i=1}.$$

$$i = 2: \qquad u_{\frac{3}{2}} \cdot A + u_{\frac{5}{2}} \cdot B + u_{\frac{7}{2}} \cdot C = \frac{a}{\Delta \zeta} \left(\rho_3^n - \rho_2^n \right) - RF_{r,i=2}$$

$$i = 3: \qquad u_{\frac{5}{2}} \cdot A + u_{\frac{7}{2}} \cdot B + u_{N+\frac{1}{1}} \cdot C = \frac{a}{\Delta \zeta} \left(\rho_4^n - \rho_3^n \right) - RF_{r,i=3},$$

which, by inserting the expression for $u_{N+\frac{1}{2}}$, gives for cell number three ($i = 3$):

$$u_{\frac{5}{2}} \cdot A + u_{\frac{7}{2}} \cdot B + \left(G - u_{\frac{7}{2}} \cdot H \right) \cdot C = \frac{a}{\Delta \zeta} \left(\rho_4^n - \rho_3^n \right) - RF_{r,i=3}.$$

By moving all expressions which do not contain a velocity term over to the right side of the equality sign, gives for cell number three ($i = 3$):

$$i = 3 \qquad u_{\frac{5}{2}} \cdot A + u_{\frac{7}{2}} \left(B - H \cdot C \right) = \frac{a}{\Delta \zeta} \left(\rho_4^n - \rho_3^n \right) - RF_r (i = 3) - G \cdot C$$

The matrix structure then becomes:

$$\begin{bmatrix} B_{i=1} & C_{i=1} & 0 \\ A_{i=2} & B_{i=2} & C_{i=2} \\ 0 & A_{i=3} & B_{i=3} - H \cdot C_{i=3} \end{bmatrix} \cdot \begin{bmatrix} u_{\frac{3}{2}} \\ u_{\frac{5}{2}} \\ u_{\frac{7}{2}} \end{bmatrix} = \begin{bmatrix} \frac{a_{i=1}}{\Delta \zeta} \left(\rho_2^n - \rho_1^n \right) - RF_{r,i=1} \\ \frac{a_{i=2}}{\Delta \zeta} \left(\rho_3^n - \rho_2^n \right) - RF_{r,i=2} \\ \frac{a_{i=3}}{\Delta \zeta} \left(\rho_4^n - \rho_3^n \right) - RF_{r,i=3} - G \cdot C \end{bmatrix} \qquad (58)$$

The value for $u_{\frac{1}{2}}$ equals zero, and the expression for $u_{\frac{9}{2}} = G - u_{\frac{7}{2}} \cdot H$.

2.12.5 Cell-produced chemical evolution

The equation describing the evolution (equation (50)) of the chemicals is then to be discretized. The equation is first repeated, together with the two boundary conditions:

$$\frac{1}{R^2} \frac{\partial^2 c}{\partial \zeta^2} + \frac{2}{R^2 \zeta} \frac{\partial c}{\partial \zeta} - \alpha_1 c + n = 0$$

The boundary conditions which is used for the equation describing the chemical evolution is:

$$\frac{\partial c}{\partial \zeta} = 0 \quad \text{at} \ \zeta = 0,$$

and

$$\frac{\partial c}{\partial \zeta} = -R \gamma c \quad \text{at} \ \zeta = 1.$$

In order to solve equation (50), the implicit method is used, and the result is:

$$\begin{bmatrix} B_{c,i=2} & D_{c,i=2} & 0 \\ A_{c,i=3} & B_{c,i=3} & D_{c,i=3} \\ 0 & A_{c,i=4} & B_{c,i=4} \end{bmatrix} \cdot \begin{bmatrix} c_2 \\ c_3 \\ c_4 \end{bmatrix} = \begin{bmatrix} -n_2 - \frac{n_1}{\alpha_1} A_{c,i=2} \\ -n_3 \\ -n_4 - \frac{n_N}{b_c R \gamma + \alpha_1} D_{c,i=4} \end{bmatrix}$$

Below, it will be shown how to get this matrix structure for equation (50). In order to simplify the deduction of the matrix structure, the equation describing the chemical evolution can be rewritten as

$$a_c \frac{\partial^2 c}{\partial \zeta^2} + b_c \frac{\partial c}{\partial \zeta} - \alpha_1 c + n = 0,$$

where $a_c = \frac{1}{R^2}$ and $b_c = \frac{2}{R^2 \zeta}$.

The discretization is then shown below:

$$\frac{a_c}{\Delta \zeta^2} \left(c_{i+1} - 2c_i + c_{i-1} \right) + \frac{b_c}{\Delta \zeta} \left(c_{i+\frac{1}{2}} - c_{i-\frac{1}{2}} \right) - \alpha_1 c_i + n_i = 0$$

$$\frac{a_c}{\Delta \zeta^2} \left(c_{i+1} - 2c_i + c_{i-1} \right) + \frac{b_c}{2\Delta \zeta} \left(c_{i+1} + c_i - c_i - c_{i-1} \right) - \alpha_1 c_i + n_i = 0$$

For cell $i = 2 : N - 1$, the expression is:

$$c_{i+1} \left(\frac{a_c}{\Delta \zeta^2} + \frac{b_c}{2\Delta \zeta} \right) + c_i \left(-\frac{2a_c}{\Delta \zeta^2} - \alpha_1 \right) + c_{i-1} \left(\frac{a_c}{\Delta \zeta^2} - \frac{b_c}{2\Delta \zeta} \right) = -n_i$$

where the expressions inside the parenthesis are substituted as capital letters in order to make the implementation easier when using the implicit scheme:

$$c_{i+1} D_c + c_i B_c + c_{i-1} A_c = -n_i$$

where $D_c = \frac{a_c}{\Delta \zeta^2} + \frac{b_c}{2\Delta \zeta}$, $B_c = -\frac{2a_c}{\Delta \zeta^2} - \alpha_1$ and $A_c = \frac{a_c}{\Delta \zeta^2} - \frac{b_c}{2\Delta \zeta}$.
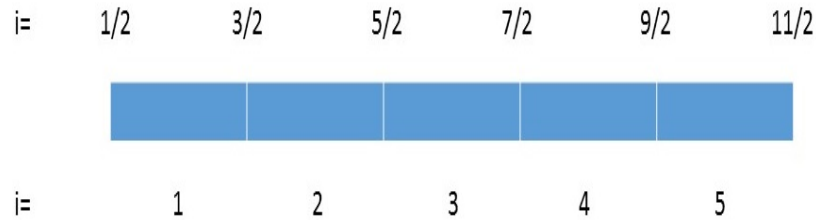
The expressions for c_1 and c_N are calculated using the following boundary conditions:

$$\text{At } \zeta = 0 \quad : \quad \frac{\partial c}{\partial \zeta} = 0$$

$$\implies c_1 = \frac{n_1}{\alpha_1}$$

$$\text{At } \zeta = 1 \quad : \quad \frac{\partial c}{\partial \zeta} = -R\gamma c \implies -b_c R\gamma c_N - \alpha_1 c_N = -n_N$$

$$\implies c_N = \frac{n_N}{b_c R\gamma + \alpha_1}$$

Five grid cells are now used to display how the implicit scheme becomes:

Figure 5: Spatial domain split into five grid blocks

$$i = 1 \quad \implies c_1 = \frac{n_1}{\alpha_1}$$

$$i = 2 \quad \implies c_1 A_{c,i=2} + c_2 B_{c,i=2} + c_3 D_{c,i=2} = -n_2$$

$$i = 3 \quad \Longrightarrow c_2 A_{c,i=3} + c_3 B_{c,i=3} + c_4 D_{c,i=3} = -n_3$$

$$i = 4 \quad \Longrightarrow c_3 A_{c,i=4} + c_4 B_{c,i=4} + c_5 D_{c,i=4} = -n_4$$

$$i = 5 = N \quad \Longrightarrow c_N = \frac{n_N}{b_c R \gamma + \alpha_1}$$

In matrix form, this becomes:

$$
\begin{bmatrix}
B_{c,i=2} & D_{c,i=2} & 0 \\
A_{c,i=3} & B_{c,i=3} & D_{c,i=3} \\
0 & A_{c,i=4} & B_{c,i=4}
\end{bmatrix}
\cdot
\begin{bmatrix}
c_2 \\
c_3 \\
c_4
\end{bmatrix}
=
\begin{bmatrix}
-n_2 - \frac{n_1}{\alpha_1} A_{c,i=2} \\
-n_3 \\
-n_4 - \frac{n_N}{b_c R \gamma + \alpha_1} D_{c,i=4}
\end{bmatrix}
\tag{59}
$$

3 Results

Numerical simulations is now performed using the mathematical model which was discretized above. The different parameters are first changed, in order to see how they affect the cell traction forces, before the numerical results are compared to experimental data in order to see if there is good agreement between the mathematical model and the experimental data.

3.1 Changing the parameters

The seven different parameters which is used in the mathematical model is then to be investigated further. Six of the seven parameters are kept constant, while the last parameter is given three different values to see how this parameter is affecting the gel radius, and therefore also the cell exerted traction forces. The first parameter to have three different values is the contact inhibition parameter, as shown below.

3.1.1 Contact inhibition parameter

The traction force exerted from the cells, F_r, increases with increasing cell densities, but when the cell densities become sufficiently large (overcrowding) the traction force from the cells will start to decrease due to cell contact inhibition. λ, which is the contact inhibition parameter, is a measure of how the neighboring cells are reducing the traction force. (Murray, 2003) Since the cells are often well spaced when compacted, the cell density is often not sufficiently large for significant cell contact inhibition to occur. (Barocas et al., 1995)

From figure 8, it can be seen that an increase in λ, meaning that the effect from overcrowding increases, causes the final gel radius to be higher compared to a lower contact inhibition parameter λ. It can also be seen from the figure that an increase in λ from $\lambda = 0.08$ to $\lambda = 0.3$ also delays the decrease in the gel radius and the slope where R decreases for a higher λ value. The reason that the gel radius will decrease more for lower contact inhibition parameters, is because the effect of contact inhibition will then be lower and therefore the cell traction force will be greater, causing the gel radius to decrease more.

From figure 9, it can be seen that a lower λ-value will give a higher ρ-value closer to the center of the gel, but a lower λ-value will also cause the gel density to start decreasing closer to the gel center compared to a higher contact inhibition parameter.

An interesting thing which can be seen figure 10 is that the density goes up to about $\rho = 8$ at the gel cancer before it starts to decrease at later times. This might be due to overcrowding of the cells, which causes the cell traction forces to decrease, and therefore the gel density decreases due to the elastic forces from the gel.

3.1.2 A measure of the cell traction

τ_0 is a measure of the cell traction (Moon & Tranquillo, 1993) As can be seen from figure 11, an increase in the cell traction parameter τ_0 causes the gel radius to decrease at an earlier time, increases the gel radius decreasing slope and the gel radius is reduced to a lower final value. This is because by increasing τ_0, the cell traction force increases and therefore the gel radius will decrease faster and also to a lower final value.

3.1.3 Isothermal compressibility

β represents the isothermal compressibility of the gel (Green et al., 2013), and an increase in β should therefore cause the gel to be more compressed at final time, meaning a higher final gel density, and also a lower final gel radius. From figure 12, it can be seen that a higher isothermal compressibility gives a more rapid decrease in the gel radius and the gel radius also decreases down to a lower value compared to higher isothermal compressibility.

From figure 13, it can be seen that ρ is highest near the gel center for higher isothermal gel compressibility, but starts to decrease closer to the center of the gel compared to lower β-values. It can also here be seen the effect from overcrowding, which is most significant for higher β-values.

3.1.4 Bulk viscosity

κ represents the bulk viscosity of the gel. (Green et al., 2013) While shear viscosity describes the resistance to deformation, bulk viscosity describes the resistance a fluid (the gel) has in changing its volume (Denicol, 2016)

From figure 14, it can be seen that the final radius will be the same for all κ-values, but a larger bulk viscosity will cause the gel radius to decrease at a slower rate so that it takes more time to reach the same final gel radius. This is because a higher bulk viscosity means that the resistance to a volume change increases, and therefore it should take more time to get to the same final gel radius.

Equation (46) is used for γ, ρ_c and α_1. This is because equation (46) also takes into account for the chemicals produced by the cells, which will affect the traction force the cells are exerting on th egel. It also takes into account for the preferred cell density ρ_c. The next parameter to be studied is α_1.

3.1.5 Decay rate of the cell-produced chemicals

As noted earlier, α_1 is the rate at which the chemicals are decaying, so a higher α_1 would mean more chemical decay. From figure 15, it can be seen that an increase in α_1, chemical decay, will cause the gel radius to decrease to take more time and also cause the final gel radius to be slightly higher compared to a situation with less chemical decay. Around the gel center, the chemical concentration will be much higher for a lower α_1, which is due to less chemical decay. The chemicals are therefore causing a more rapid decrease in radius and a slightly lower radius at final time.

3.1.6 Proportionality constant of the chemical flux out of the boundary

The chemical can flow out of the gel, and this flux of chemicals out of the gel is proportional to the chemical concentration at the boundary. The proportionality constant describing this relationship is γ. From figure 16, it can be seen that only small γ-values will give changes in the gel radius. A small γ-value gives a more rapid decrease in R, and R also becomes slightly smaller in the end for a small γ. By decreasing the γ-value, less chemicals would be leaving the gel, and there would therefore be more chemicals contributing to higher cell traction forces, and the gel radius would therefore decrease to a lower value compared to a higher γ-value.

3.1.7 Preferred density parameter

As mentioned earlier, there is a certain maximum gel density, ρ_c, for which the cells will no longer compact the gel at any higher gel densities. A higher ρ_c should therefore lead to a lower gel density, which can also

be seen from figure 17. From the graph, it can also be seen that a higher ρ_c makes the gel radius to start decreasing at an earlier time compared to higher ρ_c-values.

3.1.8 Summary of the results

From figure 18 and 19, it can be seen that a low γ-value and α_1-value would lead to a higher chemical concentration. This is because a lower γ means a lower chemical flux out of the gel boundary, and a lower α_1 means a lower decay rate, which again leads to higher cell traction forces.

As seen in the above discussion, high λ, κ, γ and α_1-values, and low β, τ_0 and ρ_c-values would give lower cell traction forces. This is also summarized in table 2 below, where it is shown what parameter values which contributed to high cell traction forces, and what parameter values which gave low cell traction forces. Approximately 90% of cancer deaths comes from cancer metastases(Christofori, 2006), and it would therefore be important to know the effect the cell traction forces has on cancer metastases. As will be shown below some experimental data shows that an increase in cancer cell traction forces also increases the probability of getting cancer metastases, while some experiments gives the opposite conclusion. This will be discussed further later, but first the numerical results will be compared to experimental data.

Table 2: Cell traction force.

Cell traction force	λ	β	κ	τ_0	γ	ρ_c	α_1
High	0.03	5	1	6	0.1	6	0.1
Low	3	0.5	10	2	100	2	10

3.2 Comparing the numerical results with experimental data

The experiments which was used to get the results in figure 6 (from reference (Moon & Tranquillo, 1993)) used a spherical collagen gel, which was also assumed in the mathematical model. When comparing the numerical results with those in figure 6, the results give the same shape, where the gel radius first decreases slowly, before changing rapidly, and then slowing down before reaching steady state.

Figure 10, which used the force function from equation (42) (mechanical driven contraction) has the same shape as the figure 6 below, which is taken from reference (Moon & Tranquillo, 1993). The human skin fibroblast cells, which is what has been used in (Moon & Tranquillo, 1993), is therefore not significantly affected by the chemicals produced by the cells, because that would give a shape of the graph more equal the figures which used equation (46) (chemical driven contraction) as the force function (figure 14-16).

In the experiments conducted to get figure 7 below (from reference (Raymond & Thompson, 1990)), collagen discs are used instead of collagen spheres, which means that the results cannot be directly compared, but the shape of the graphs can be compared to give an indication whether the cells studied in (Raymond & Thompson, 1990) is mechanically driven contracted or chemically driven contracted.

As seen from figure 7 below, it can be clearly seen that the graph, which shows contraction of the gel over time, is much smoother and with a much less steep slope (but the slope starts earlier). This shape is similar to that of chemically driven contraction as figures 14-16, using equation (46) as force function, meaning that pigment epithelial cells (which was studied in reference (Raymond & Thompson, 1990)) is best explained by chemically driven contraction.

As can be seen from figure 10, it starts to decrease slightly before that of figure 6, which is from the experimental results. The slopes from the two figure are very similar and goes down to similar final values.

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This is important, because it describes the cell traction forces, and if they were not similar, the mathematical model would not describe the cell traction forces well. Since the mathematical model does give a very similar shape as the experimental results shown in figure 6, the mathematical model gives a good description of the cell traction forces, and can be further used in the future when studying cancer cell traction forces to learn more about the behavior of the cancer cells.

Figure 6: Graph showing how the radius changes with time, for different initial cell concentrations. The figure is taken from (Moon & Tranquillo, 1993)
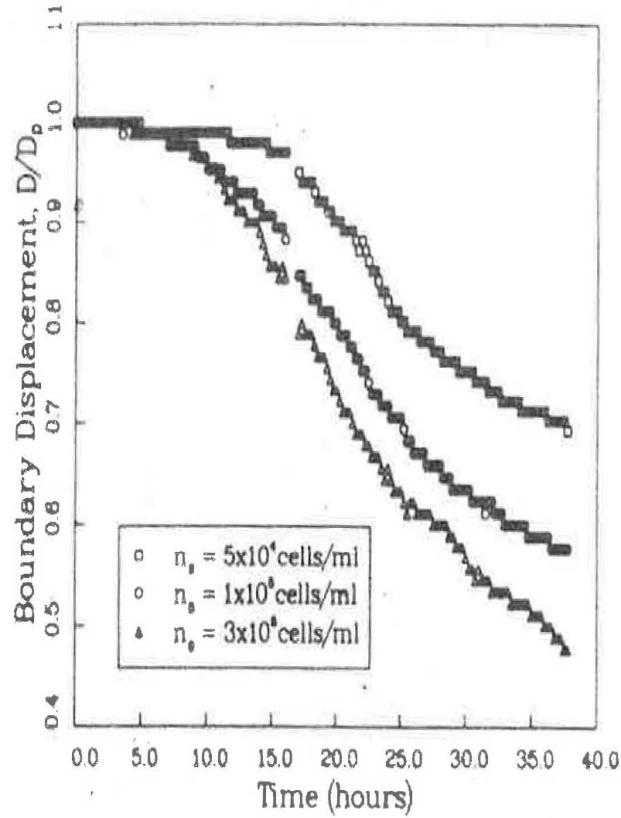
Figure 7: Graph showing how the gel area (and therefore also the gel radius) changes with time. The figure is taken from (Raymond & Thompson, 1990)
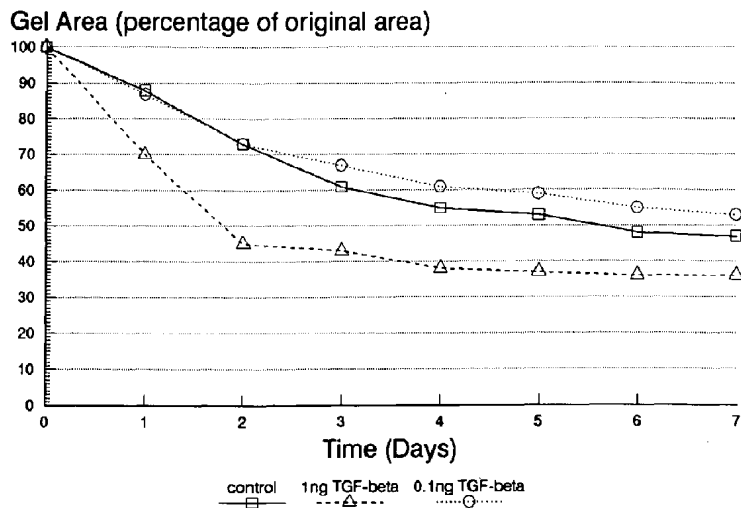

Fig. 5. Contraction versus time: the contraction of collagen gels by RPE cells treated with TGF-beta. TGF-beta at 0.1 ng/ml had no effect on contraction of the collagen gel. TGF-beta at 1 ng/ml enhanced the rate and degree of collagen gel contraction.

3.3 Comparing the numerical results from this thesis with those from another paper

The numerical results using the discretization in section 2.12 gave slightly different results compared to those in (Green et al., 2013), which used the same mathematical model. By comparing figure 3 from (Green et al., 2013) with figure 10 from this thesis, it can be seen that the shape of the graphs is very similar, and the gel radius also starts to decrease at the same time. The final gel radius however, is slightly different. This difference in final gel radius, is therefore probably due to different discretization methods used. The discretization method which has been used for figure 2 and onwards in (Green et al., 2013), has not been shown, and can therefore not be verified.

3.4 Can the mathematical model be further simplified?

The proportionality constant of the chemical flux out of the gel boundary, γ, and the bulk viscosity of the gel, κ, don't have a large impact on the final gel radius, but they have a small impact. These two parameters had the smallest impact on the final gel radius, and therefore also on the cell traction forces. It could therefore be considered to simplify the model by neglecting these two parameters, but since they actually has a small, but not insignificant, effect it is recommended to include them as well. The model should therefore not be further simplified.

4 Relating the cell traction forces to cancer metastases

Using the mathematical model, the cell traction forces exerted by the cancer cells have been investigated, and it has been seen how the different parameters are affecting the cell traction forces. Cancer metastases will be investigated below, to see what parameters are affecting this, and also of what affect the cancer cell traction forces has on this. First cancer metastases will be described in general, and then the effects from the stiffness of the collagen gel and bulk modulus on cancer metastases will be described, before the relationship with cancer cell traction forces will be described.

4.1 Cancer metastases

Localized tumors, meaning tumors which haven't spread to other parts of the body, can be treated with surgery and/or with radiation. Metastatic cancer is a much more complicated and dangerous case, because

it means that the cancer has detached itself from the primary (original) tumor and spread to other parts of the body. (*Understanding Advanced Cancer, Metastatic Cancer, and Bone Metastasis@ONLINE*, 2016)

Metastasis means that the cells from the primary tumor travel to other parts of the body where it can damage important organs. Metastases in most solid tumors demands that the cells exert a force in order to detach from the primary tumor and to travel to tissues and organs in other parts of the body. (Kraning-Rush et al., 2012)

It is an important objective to find prognostic biomarkers for metastatic cancer, so that those with higher probability for having metastatic cancer would get a more aggressive treatment, and the other patients would receive a lighter treatment (since it is easier to cure localized cancer). It would also be important to see if there is something which can be done to avoid the cancer cells to be metastatic.

4.2 Stiffness on the Collagen Gel

Experiments (Fenner et al., 2014) have been done to test if the stiffness of the tumors would be a prognostic biomarker in breast cancer, in order to increase the decision-making quality for the cancer treatment of such patients. Stiffness is defined as (Baumgart, 2000):

$$Stiffness = \frac{stress}{strain},$$

and the compliance is the inverse of stiffness (Tarantola, 2006) so that:

$$Compliance = \frac{1}{Stiffness} = \frac{strain}{stress}$$

The experiments were performed on mice. Mouse breast cancer were implanted in laboratory mice. Excised mammary tumors were then compressed using a piston in order to determine the stiffness. The tests showed that the mammary tumors with the highest compliance (least stiffness) had a markedly higher degree of metastases than those with lower compliance. (Fenner et al., 2014)The compliance of tumors can therefore be used to identify patients with higher risk of metatheses, and therefore also as a prognostic biomaker in breast cancer, although there should be several other prognostic biomakers as well in order to increase the quality of the decision making process when planning the best treatment for the patient.

4.3 Bulk Modulus

Collagen is the primary component in the extracellular matrix in breast cancer, and the bulk compression of these tumors is therefore heavily dependent on the amount of collagen. The laboratory tests from (Fenner et al., 2014) showed that there exists a direct correlation between high collagen amount and high bulk modulus, and that there is a clear inverse relationship between bulk modulus and metastases. This means that a higher collagen content in the extracellular matrix should indicate lower metastases. However, there are other studies showing that the amount of collagen in breast tissue did not change the probability of death (Indra et al., 2011), and the effect of the extracellular matrix content is therefore uncertain due to this different results. The changes in the content of the extracellular matrix is therefore just one of several extracellular parameters which is impacting the probability of metastases.

The relationship between stiffness, bulk modulus and isothermal compressibility will then be discussed.The bulk modulus is a measure of the compressibility of the fluid, and is defined as(*Properties of fluids@ONLINE*, n.d.):

$$K = -V\frac{dP}{dV},$$

where K is the symbol of the bulk modulus.
The isothermal compressibility is defined as(Celli, 1997):

$$\beta = -\frac{1}{V}\left(\frac{\partial V}{\partial P}\right)_T$$

As can be seen from these two definitions, the bulk modulus is the inverse of the isothermal compressibility. A high isothermal compressibility would therefore indicate a low ratio of the relative change in volume over change in pressure, which again leads to a low stress to strain ratio. Since the stiffness was defined as the stress to strain ratio (Baumgart, 2000), it follows that a high isothermal compressibility therefore leads to a low stiffness. A high isothermal compressibility therefore means a low bulk modulus and low stiffness. The opposite is also true; A low isothermal compressibility, means a high bulk modulus and a high stiffness.

Therefore a low bulk modulus would also mean a high compliance, which should indicate a higher occurens of metastases. This was also verified by the experiments (Fenner et al., 2014), showing that there was a clear inverse relationship between the bulk modulus and cases with metastasis.

Below is shown three examples of how to obtain a low isothermal compressibility, but since a low isothermal compressibility also means a high stiffness and bulk modulus, they are also examples of how one might obtain a high stiffness and bulk modulus (which decreases the probability of cancer metastases):

- Increase pressure would decrease the isothermal compressibility, β (*Table 1-42 Isothermal compressibility of liquids @ONLINE*, n.d.)

- Decrease the temperature in the collagen gel would decrease the isothermal compressibility, β (because at a lower temperature, the atoms will move less, and it will be easier to compress the collagen gel)

- Increase density of the collagen gel would decrease the isothermal compressibility , β (because atoms gets closer and therefore stronger repelling forces occur)

4.4 Relationship between Cell Traction Forces and metastases

Several different experiments have been conducted on the relationship between cell traction forces and metastases, and reported in other papers such as ((Kraning-Rush et al., 2012), (Indra et al., 2011)). The logical results would be that higher cell traction forces would lead to a higher degree of cancer metastases, because the cancer cells must exert forces in order to leave the primary tumor and invade the surrounding tissue. This is also what most experimental results shows (like (Kraning-Rush et al., 2012)), but there is an experiment showing opposite results also (Indra et al., 2011). Reasons for the different results is uncertain, but might be due to differences in the cell and tissue structures, and differences in the extracellular matrix, or due to different experimental system used during the experiments.

Reference (Kraning-Rush et al., 2012) concluded that higher cancer cell traction forces would lead to more cancer metastases. In order to avoid this, low cell traction forces are therefore needed. In order to get low cell traction forces, high α_1, γ and λ -values and low a τ_0 value would be necessary. In order to accomplish this, one opportunity is to inject chemicals which will decrease the production of the chemicals produced by the cells (which contributes to higher F_r-values), and increase the decay rate of the chemicals, α_1. One could also inject something which increases the proportionality constant of the flux of chemicals out of the gel (γ). A decrease in the collagen density would also contribute to lower cell traction forces. (Kraning-Rush et al., 2012) Since the relationship between cell traction forces and metastases is uncertain, this should be studied more extensively in the future.

5   Conclusion

Compliance of a tumor strongly affects the degree of cancer metastases (Fenner et al., 2014), and metastases is responsible for approximately 90% of all cancer deaths in today's society.(Christofori, 2006) Compliance of the tumor can be used as a prognostic biomarker in order to increase the decision making quality of the treatment of each cancer patient, but the compliance of a tumor can also be altered. A stiffer tumor decreases the probability of metastases (Fenner et al., 2014), and a decrease in the compliance of the tumor can be accomplished by for example decreasing the temperature and increasing the pressure (*Table 1-42 Isothermal compressibility of liquids @ONLINE*, n.d.). An increase in the density of collagen might also accomplish this.

The mathematical model describing cell traction forces was compared to experimental data ((Moon & Tranquillo, 1993), (Raymond & Thompson, 1990)), and it was shown that the model gave very similar rate of the gel radius over time, and similar final values (at least for the two lowest initial cell densities). From this, it can be concluded that the mathematical model describes the cell traction forces (which is what causes the change in gel radius) well, and can therefore be used further when investigating cell traction forces in order to get a better understanding of the effect it has on cancer cell metastases.

The cancer cell traction forces in the mathematical model depends on different parameters, where seven different parameters were investigated to see how they affect the cancer cell traction forces. The numerical results from using the mathematical model showed that in order to have low cell traction forces, the parameters isothermal compressibility, bulk viscosity, the proportionality constant for the flux out of the gel boundary and the decay rate of the chemicals must be high, while the contact inhibition parameter, the measure of cell traction force (τ_0) and the preferred density parameter must be low. This can be accomplished by for instance decreasing the temperature in the tumor or injecting some chemicals into the tumor which will increase the decay rate of the cell-produced chemicals and also decrease the production of the cell-produced chemicals.

The logical conclusion is that an increase in cell traction forces would increase the degree of cancer metastases, and this is also what the experiments in (Kraning-Rush et al., 2012) showed. There is however, an experiment giving the opposite result (Indra et al., 2011), so there is no certain relationship between cancer cell traction forces and cancer metastases, and there should therefore be conducted more experiments to learn more about this relationship. Some reasons for the opposite results might come from different experimental system used in the experiments, differences in the cell and tissue structures or differences in the extracellular matrix.

6   Future Work

The mathematical model gave good results compared to the experimental data ((Moon & Tranquillo, 1993), (Raymond & Thompson, 1990)), but more could have been included in the model to make it more biologically correct. Below is mentioned several examples of things which can be included in the model in the future:

- Taking into account that the gel velocity and cell velocity can be different by introducing a two phase model

- Include the effects from fluids leaving the gel

- The elastic modulus and viscosity has an effect on the collagen density, and therefore introduce a relationship between these (Green et al., 2013)

- A three dimensional model instead of one dimensional which was implemented in this theses

Some experimental results show that cell traction forces gives rise to more metastases (Kraning-Rush et al., 2012), while another experiment gives the opposite conclusion (Indra et al., 2011). More experiments should therefore be conducted to understand the reason for the different results, and to obtain a better understanding on the relationship between the magnitude of the cell traction forces and the degree of cancer cell metastases.

Appendix for the figures from the numerical experiments

The numerical results from using the mathematical model derived in this thesis are shown in the figures below. Six of the seven parameters are kept constant for each figure, while one of the parameters are given three different values to see how the cell traction forces responds to the different values.

Figure 8: R vs t for λ. Equation (42) used as the force function.
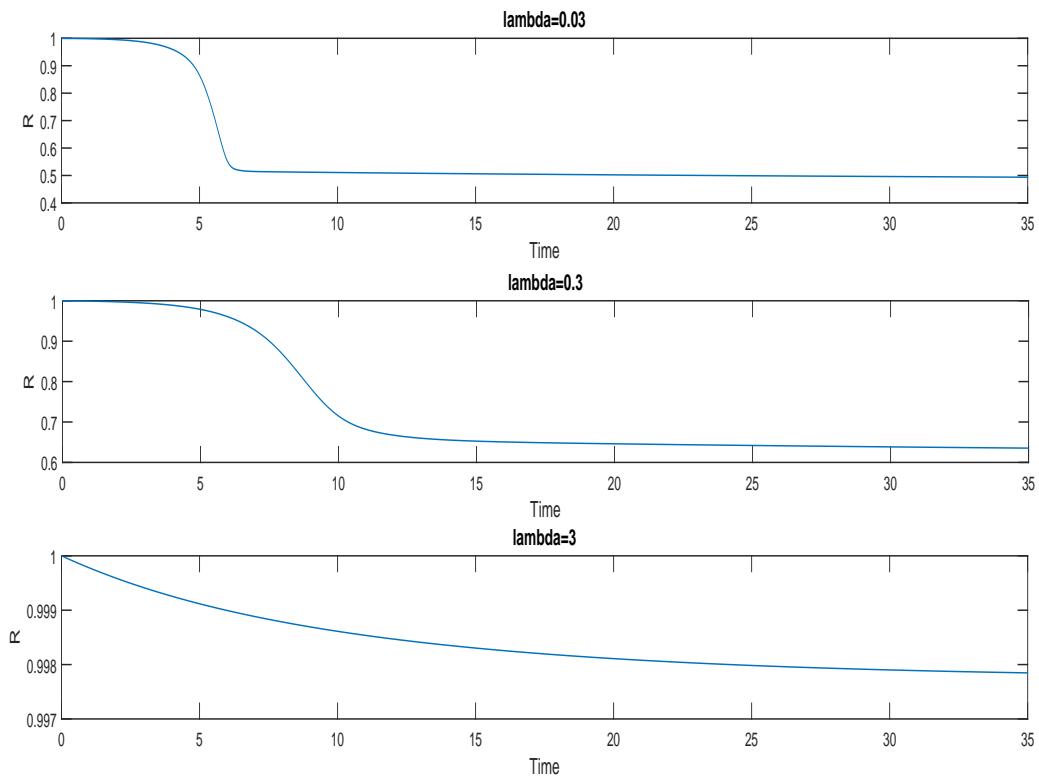
Parameter values used in the figure: $\beta = 1$, $\kappa = 5$ and $\tau_0 = 4$.

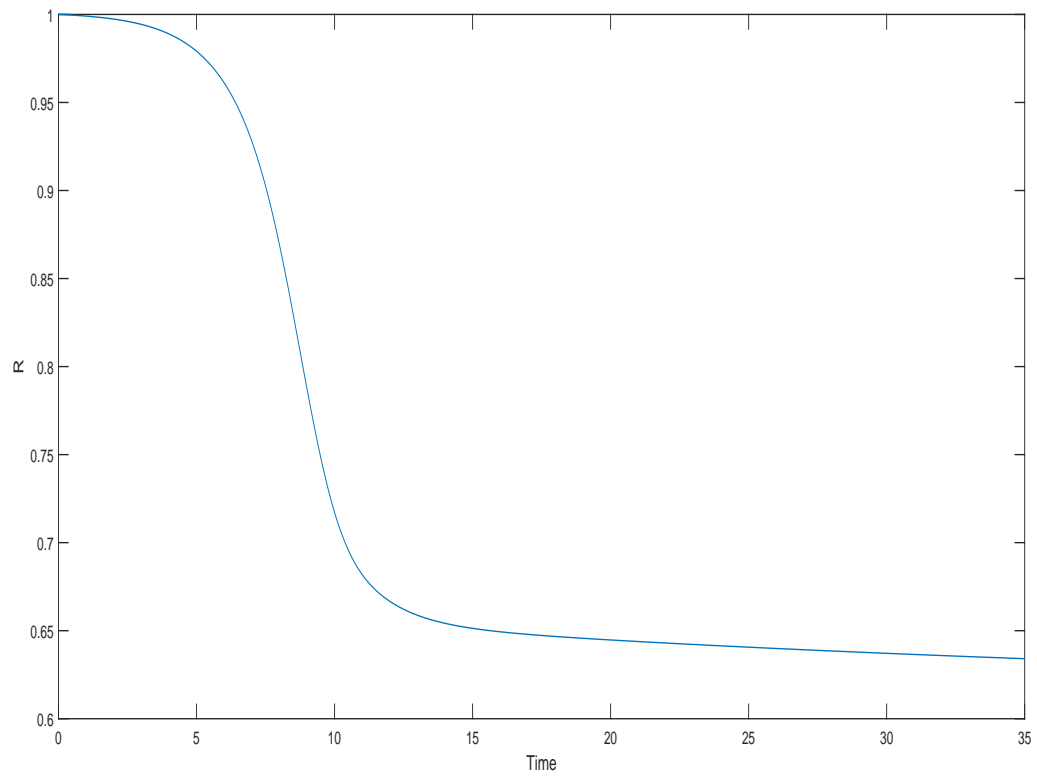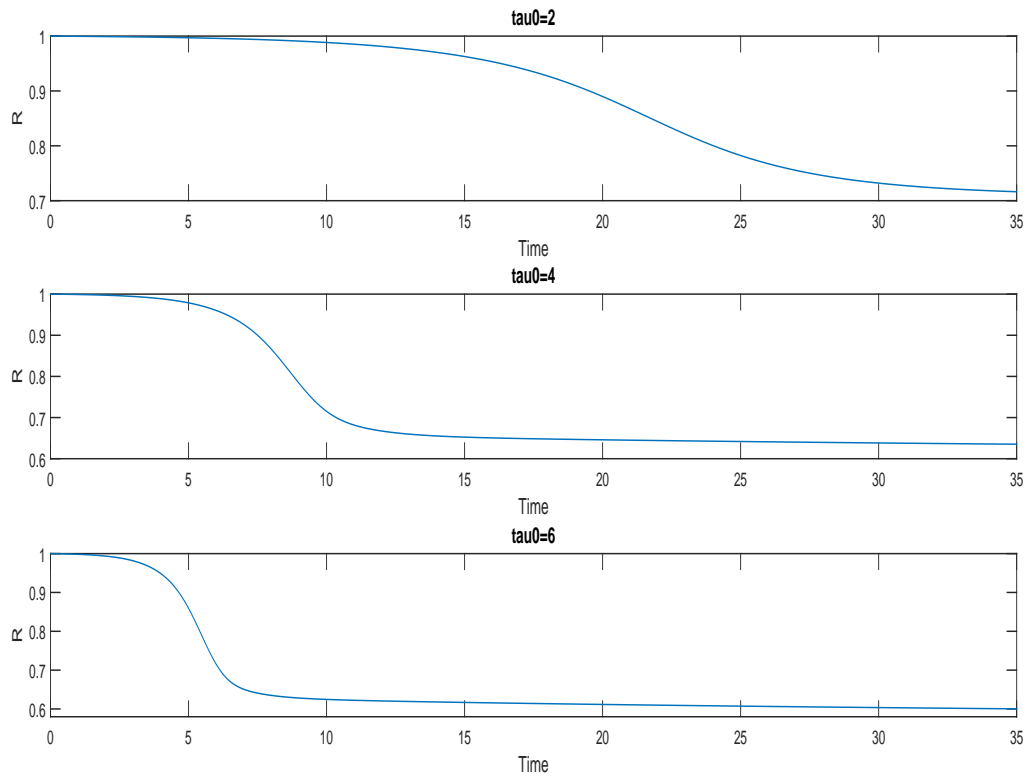Figure 9: ρ vs r for λ.Equation (42) used as the force function.
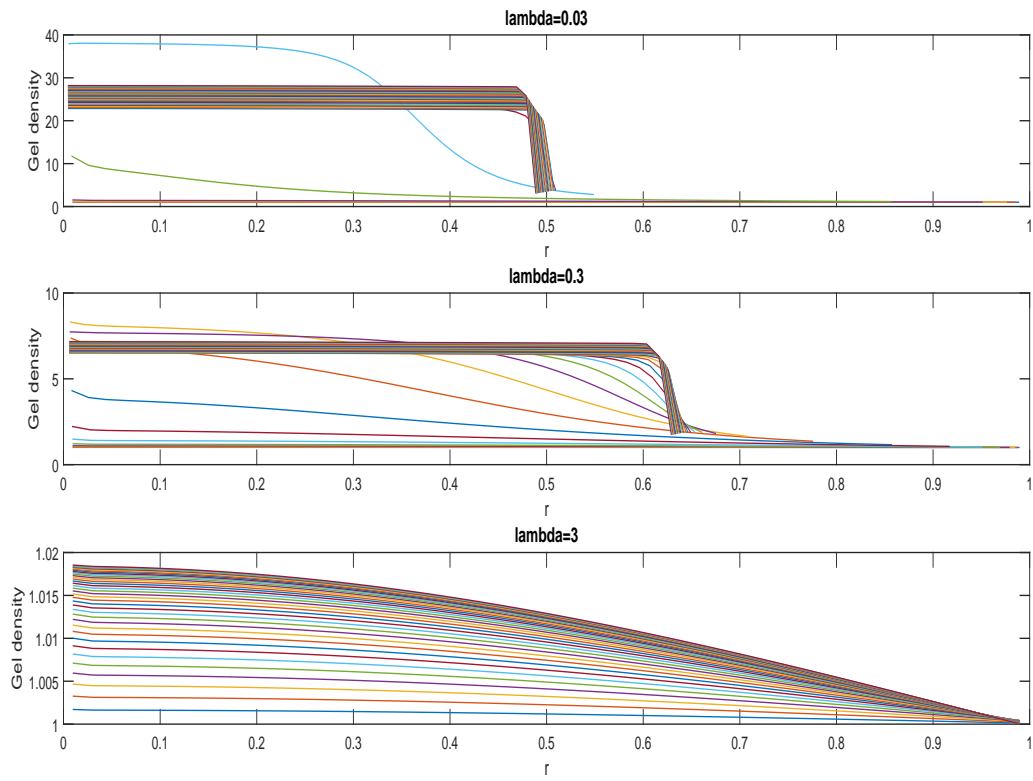
Parameter values used in the figure:$\beta = 1$, $\kappa = 5$ and $\tau_0 = 4$.

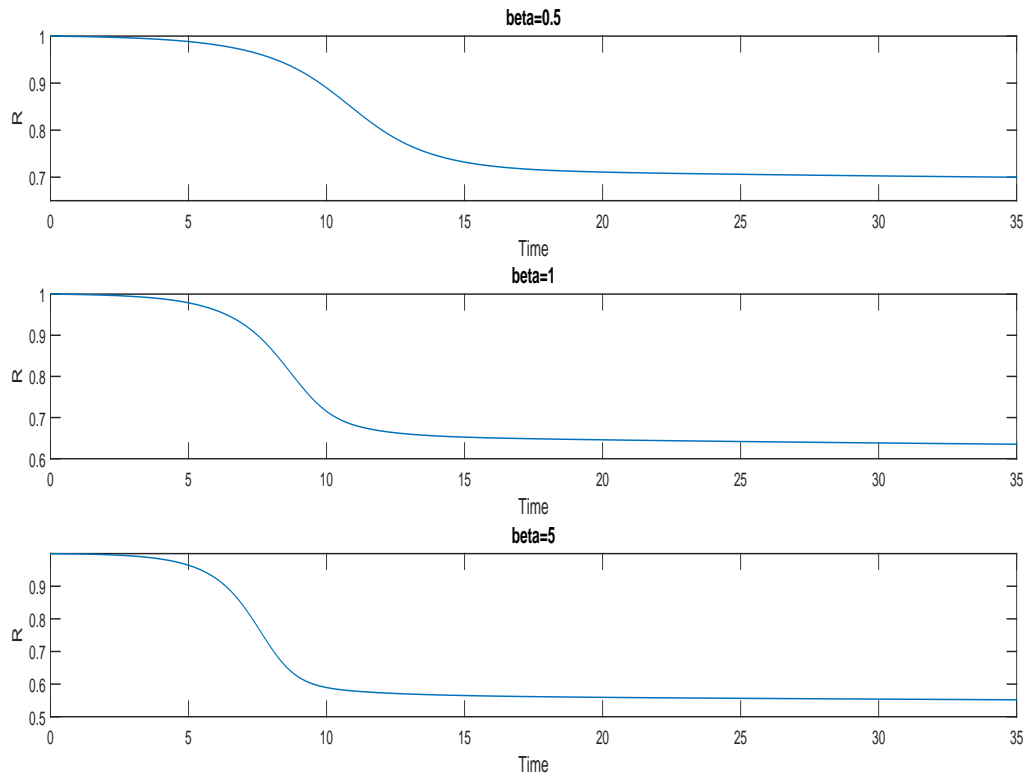Figure 10: ρ vs r .Equation (42) used as the force function.

Parameter values used in the figure:$\beta = 1$, $\kappa = 5$, $\tau_0 = 4$ and $\lambda = 0.3$.

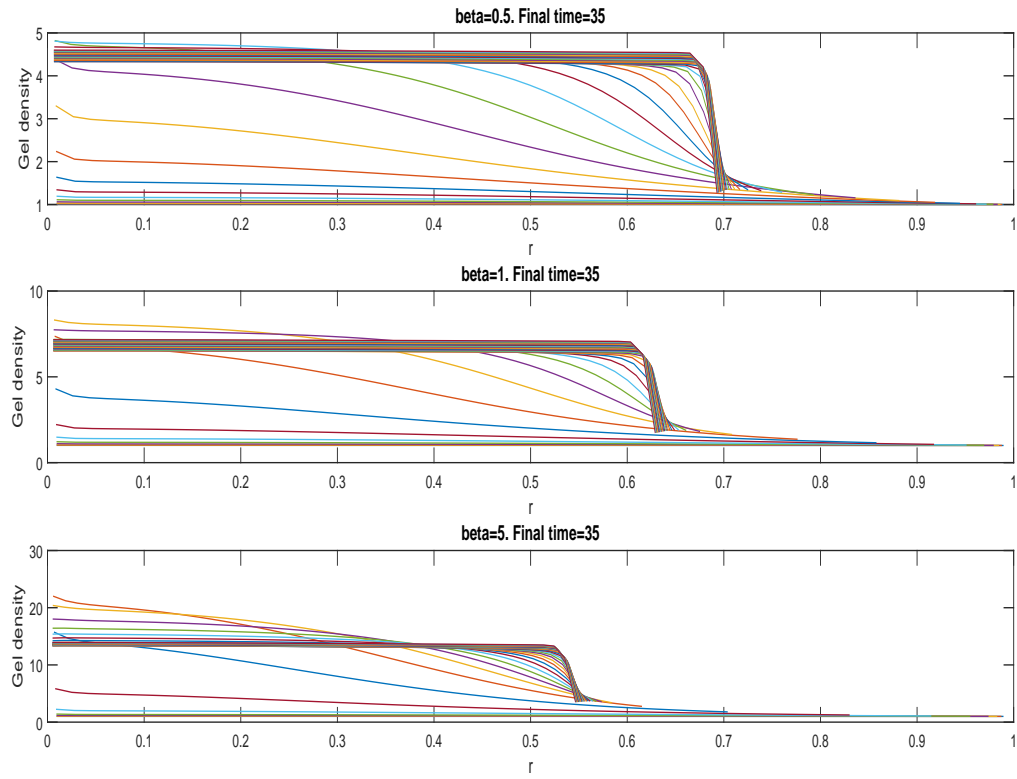Figure 11: R vs t for τ_0. Equation (42) used as the force function.

Parameter values used in the figure:$\beta = 1$, $\kappa = 5$ and $\lambda = 0.3$.

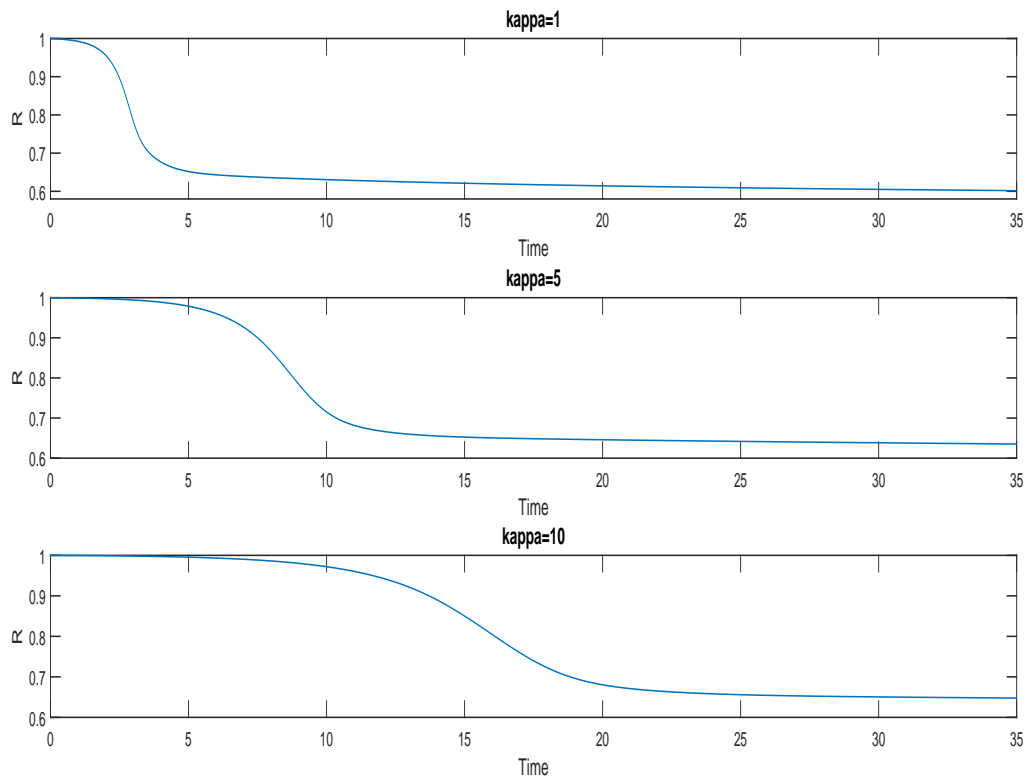Figure 12: R vs t for β. Equation (42) used as the force function.

Parameter values used in the figure:$\kappa = 5$, $\tau_0 = 4$ and $\lambda = 0.3$.

Figure 13: ρ vs r for β. Equation (42) used as the force function.
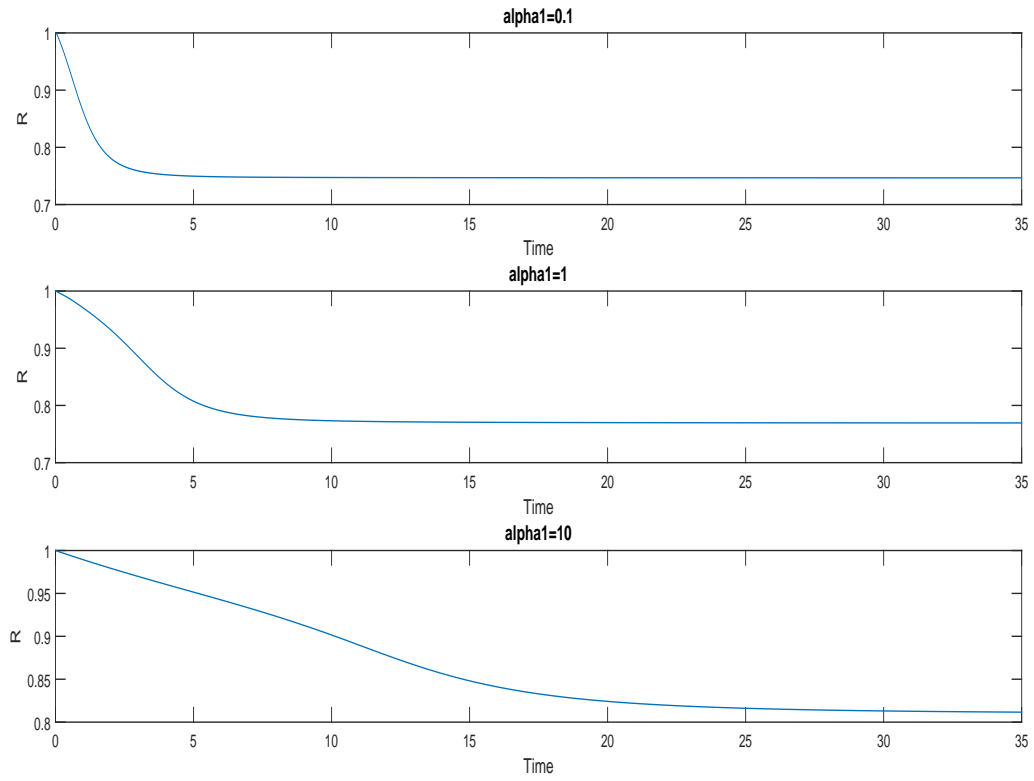

Parameter values used in the figure:$\kappa = 5$, $\tau_0 = 4$ and $\lambda = 0.3$.

Figure 14: R vs t for κ. Equation (42) used as the force function.

Parameter values used in the figure:$\beta = 1$, $\tau_0 = 4$ and $\lambda = 0.3$.

Figure 15: R vs t forr α_1. Equation (46) used as the force function.

Parameter values used in the figure:$\beta = 1$, $\kappa = 5$, $\tau_0 = 4$, $\lambda = 0.3$, $\gamma = 20$ and $\rho_c = 4$

Figure 16: R vs t for γ. Equation (46) used as the force function.
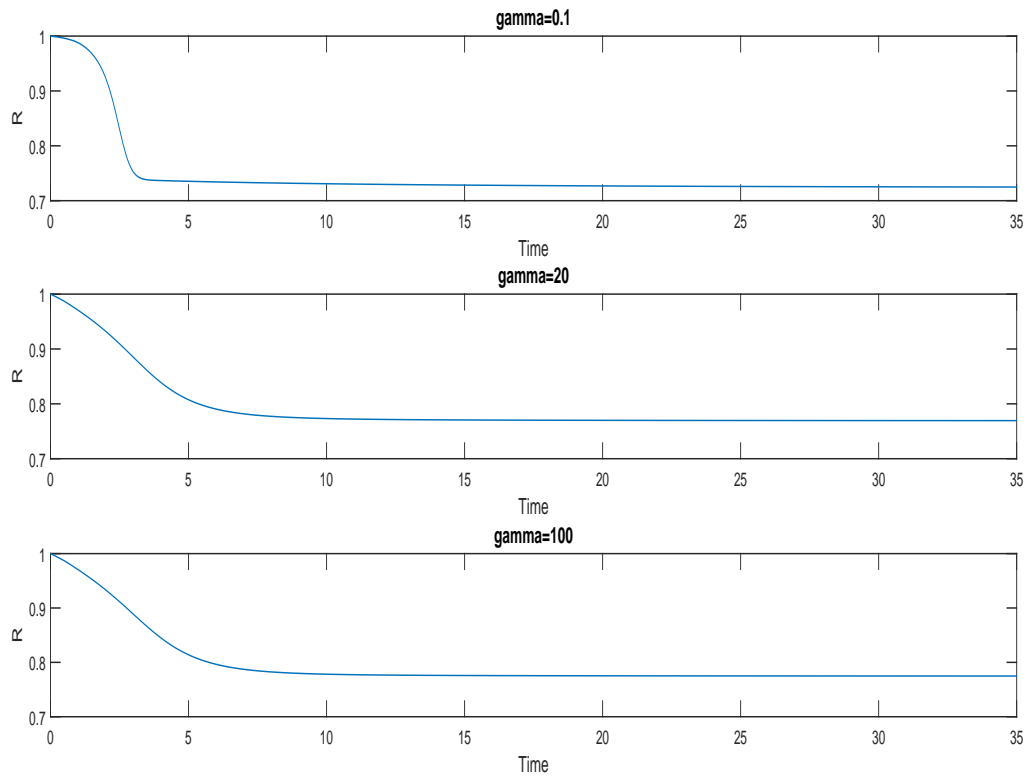
Parameter values used in the figure: $\beta = 1$, $\kappa = 5$, $\tau_0 = 4$, $\lambda = 0.3$, $\alpha_1 = 1$ and $\rho_c = 4$

Figure 17: R vs t for ρ_c. Equation (46) used as the force function.

Parameter values used in the figure:$\beta = 1$, $\kappa = 5$, $\tau_0 = 4$, $\lambda = 0.3$, $\gamma = 20$ and $\alpha_1 = 1$.

Figure 18: c vs r for γ .Equation (46) used as the force function.

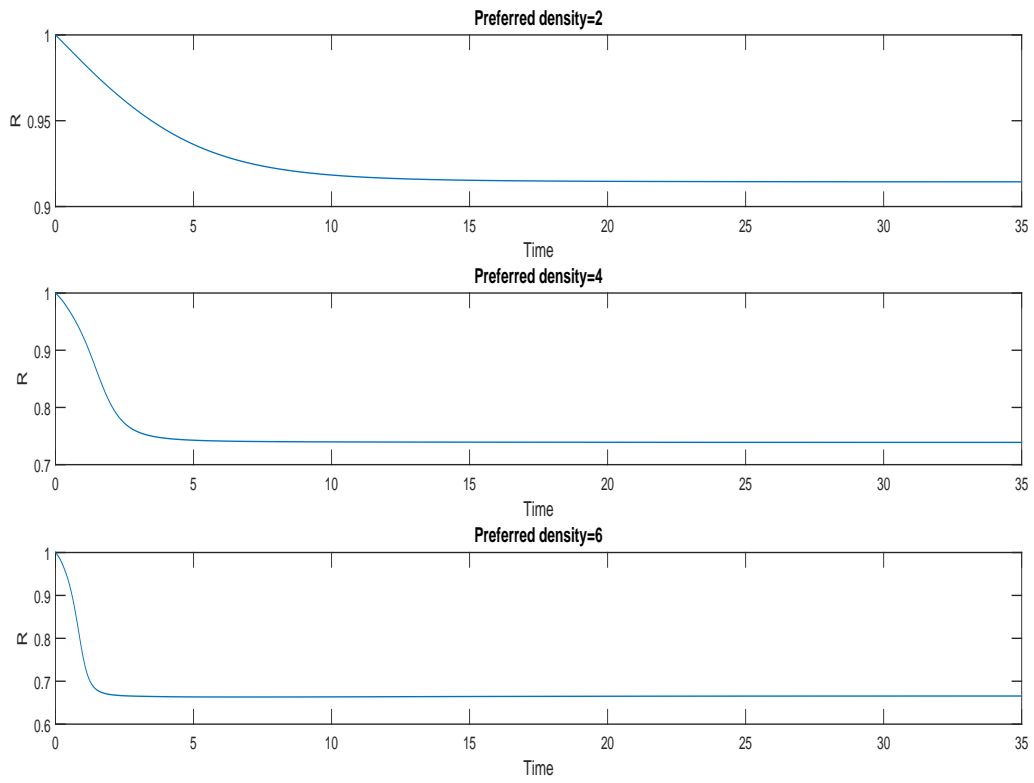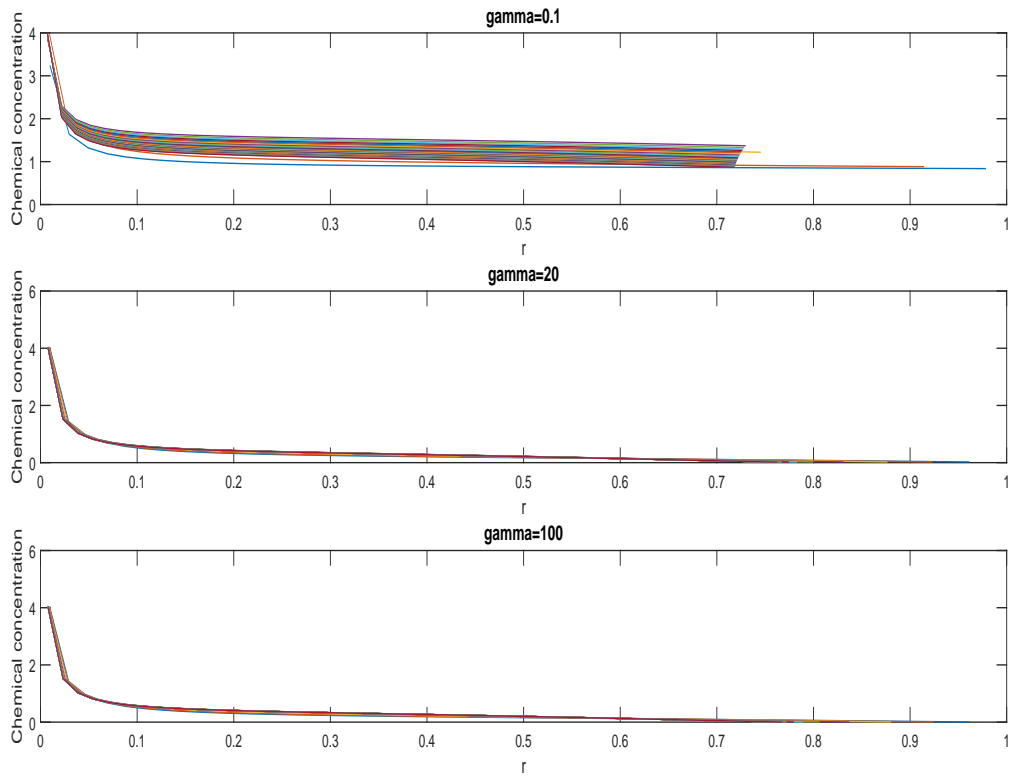Parameter values used in the figure:$\beta = 1$, $\kappa = 5$, $\tau_0 = 4$, $\lambda = 0.3$, $\alpha_1 = 1$ and $\rho_c = 4$

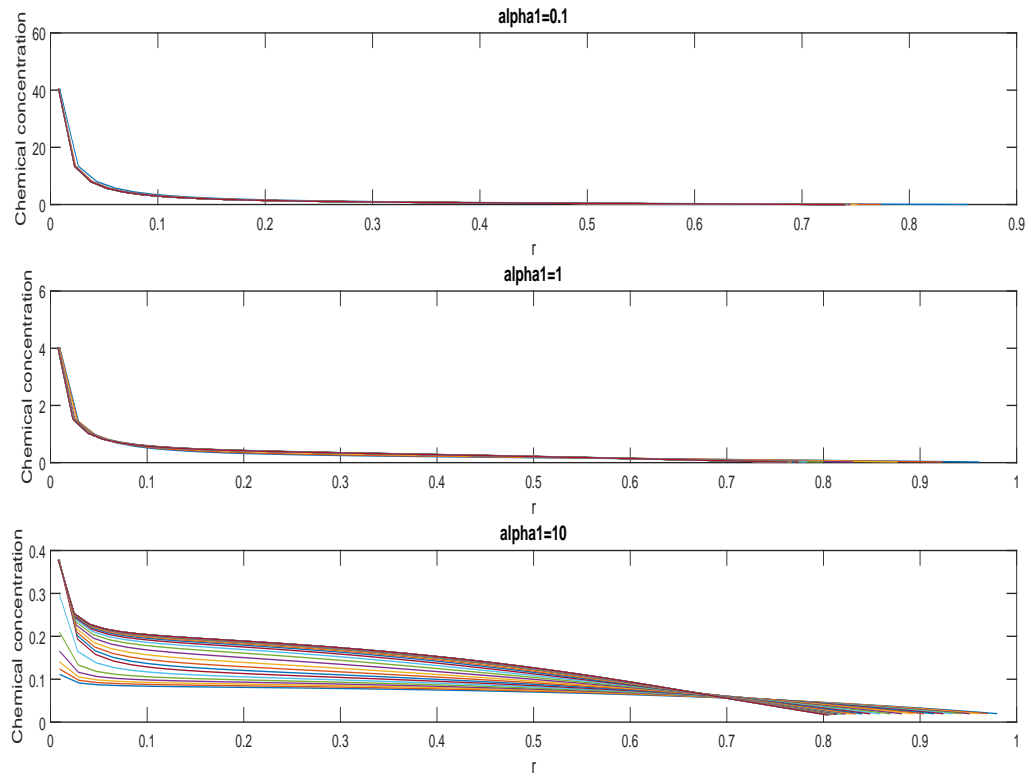Figure 19: c vs r for α_1 . Equation (46) used as the force function.

Parameter values used in the figure:$\beta = 1$, $\kappa = 5$, $\tau_0 = 4$, $\lambda = 0.3$, $\gamma = 20$ and $\rho_c = 4$

Appendices for the mathematical derivations

A   Mass balance for the collagen gell

The expression for the conservation of mass for the collagen is here to be derived. Due to the assumption that there is no production or degradation by the cells, the expression for the final mass of the collagen gel can be expressed as:

$$\text{Final mass} = \text{Original mass} + \text{mass inflow} - \text{mass outflow}$$

By integrating the densities over the whole control volume and dividing by the time-interval, the mass rate within the control volume can be calculated:
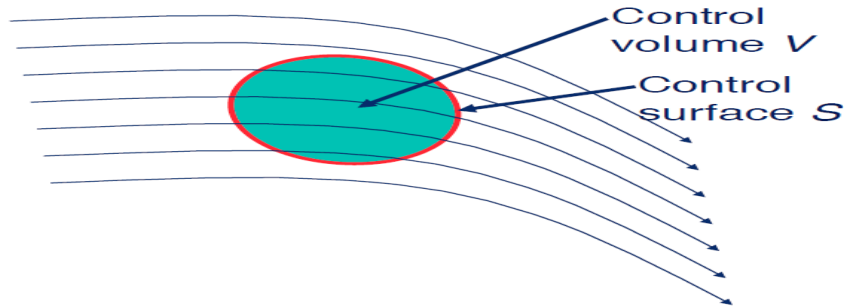
$$\dot{m} = \frac{\partial}{\partial t} \int_{CV} \rho dV$$

The flux of mass can also be written as a surface integral, using a control surface, where the negative sign is because flux of mass is defined positive when influx, while the surface integral gives the flux out:

$$\dot{m} = - \oint_S \rho \mathbf{u}\hat{\mathbf{n}} dS$$

A figure (taken from (*Navier Stokes - Lecture 4@ONLINE*, 2011)) showing the relationship between a control volume and a control surface is shown below, where the blue lines are representing stream lines of the fluids:

Figure 20: Relationship between control volume and control surface (*Navier Stokes - Lecture 4@ONLINE*, 2011)

Both the expressions above represents flux of mass, so they must be equal:

$$\frac{\partial}{\partial t} \int_{CV} \rho dV = - \oint_S \rho \mathbf{u}\hat{\mathbf{n}} dS \tag{60}$$

The divergence theorem (Adams & Essex, 2010) is then used to convert the surface integral to a volume integral. The divergence theorem states that:

$$\oint_S \rho \mathbf{u}\hat{\mathbf{n}} dS = \int_V \nabla \cdot (\rho \boldsymbol{u}) dV$$

The divergence theorem is therefore used to convert the right side of equation (60) to a volume integral:

$$- \oint_S \rho \mathbf{u}\hat{\mathbf{n}} dS = - \int_V \nabla(\rho \boldsymbol{u}) dV$$

By substituting this into equation (60), the result is:

$$\frac{\partial}{\partial t} \int_{CV} \rho dV = -\int_{V} \nabla \cdot (\rho \boldsymbol{u}) dV$$

In order to simplify the equation above, an assumption that both the density and its derivative with respect to time in the fixed control volume is continuous, and it is then used that the derivatives outside of the integral above can be taken inside of the integral (Conrad, n.d.). The expression is then simplified to :

$$\int_{V} \frac{\partial \rho}{\partial t} dV + \int_{V} \nabla \cdot (\rho \boldsymbol{u}) dV = 0$$

which can be further simplified to:

$$\int_{V} [\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \boldsymbol{u})] dV = 0$$

From the above equation, it is clear that the expression inside the brackets has to be zero in order for the equality to hold for all control volumes. So, the result for conservation of mass of collagen gel is:

$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \boldsymbol{u}) = 0$$

B   Mass balance for the cells

The mass balance equation for the cells will be derived below, where cell proliferation and cell deaths are ignored. The expression is equal to that of the collagen gel, but the mass balance for the cells also has a diffusion term, which is to be derived.

$$\frac{\partial n}{\partial t} + \nabla \cdot (n\boldsymbol{u}) = \text{Diffusion term} \tag{61}$$

where n in this context refers to the density of the cells. This diffusion term will be derived below.

The figure (taken from (*Introduction cell systems biology, diffusion, fick's law@ONLINE*, 2009)) showing the set up in the derivation is shown to make the derivation easier to understand, where the red dots are representing the cells and the arrows the direction they are heading:

Figure 21: Figure used in the derivation (*Introduction cell systems biology, diffusion, fick's law@ONLINE*, 2009)
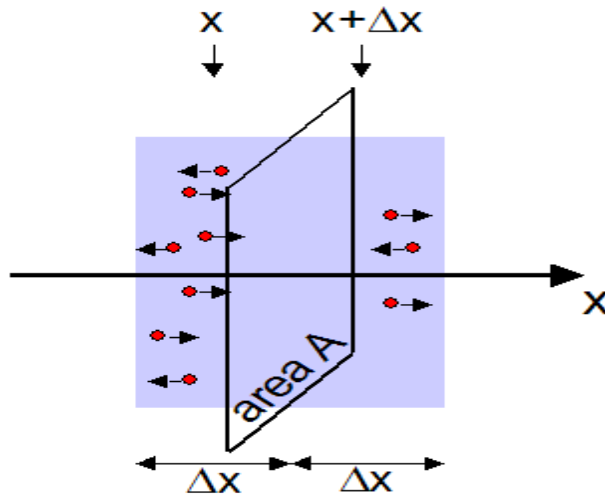
Consider a cross-sectional area A with cell moving through at random motion. Due to the random motion of the cells, the probability that the cell mass moving to from a position x to the left of the cross-sectional area to $x + \Delta x$ can be set to a value P. The cell mass rate traveling from x to $x + \Delta x$ is denoted by $\dot{m}$, and expressed as:

$$\dot{m} = \frac{P[m(x) - m(x + \Delta x)]}{\Delta t} = -\frac{P[m(x + \Delta x) - m(x)]}{\Delta t} \tag{62}$$

where m represents mass at the different positions. This expression can also be written in terms of density instead of mass as follows:

$$\dot{m} = \frac{P[n(x + \Delta x)A\Delta x - n(x)A\Delta x]}{\Delta t}$$

where n represents density and Δx is the width between the two x-positions. Then, by looking at the density gradient with respect to x-position:

$$\frac{\Delta n}{\Delta x} = \frac{n(x + \Delta x) - n(x)}{(x + \Delta x) - x} = \frac{n(x + \Delta x) - n(x)}{\Delta x},$$

and when Δx becomes infinitely small:

$$\frac{dn}{dx} = \frac{n(x + dx) - n(x)}{dx} = \frac{m(x + dx) - m(x)}{dx^2 A}$$

The equation above is used to get an expression for the change of mass between the two positions:

$$m(x + dx) - m(x) = \frac{dn}{dx}dx^2 A$$

This expression for m is then substituted into equation (53) above to get:

$$\dot{m} = \frac{PA}{dt}\frac{dn}{dx}dx^2 = -A \cdot D\frac{dn}{dx}, \tag{63}$$

where the diffusion coefficient D is assumed constant, and have the expression $D = \frac{P}{dt}dx^2$.

Then, consider cell mass traveling through a small control volume CV during a small time-interval Δt. The control-volume has a cross-sectional area A and a depth Δx (when considering the x-direction), where the x-position at the left boundary of CV is denoted by x, while the right boundary of CV is denoted by $x + \Delta x$. By assuming no cell proliferation or death and utilizing equation (62) above, the final diffusion term will be the result. The first step is to use that the change of cell mass inside the control volume during the small time-interval Δt can be written in several ways, where two of them will be used here:

The first method: This method considers the difference in mass rates between the two x-positions, multiplied by the time-interval:

$$[\dot{m}(x) - \dot{m}(x + \Delta x)]\Delta t$$

The second method: This method considers the change in density in the control volume during the time-interval Δt, and multiplies this with the volume of CV:

$$[n(t + \Delta t) - n(t)]A\Delta x$$

Since the two expressions above represents the same, because mass $m = nA\Delta x$, they can be written in the same equation as:

$$[\dot{m}(x) - \dot{m}(x + \Delta x)]\Delta t = [n(t + \Delta t) - n(t)]A\Delta x$$

Then by letting Δx and Δt approach zero, and rearranging the equation above:

$$\frac{\partial n}{\partial t} = -\frac{1}{A}\frac{\partial \dot{m}}{\partial x} \tag{64}$$

The derivative of equation (63) above is then calculated for further use:

$$\dot{m} = \frac{PA}{dt}\frac{dn}{dx}dx^2 = -A \cdot D^*\frac{dn}{dx}$$

$$\implies \frac{\partial \dot{m}}{\partial x} = -A \cdot D^*\frac{\partial^2 n}{\partial x^2}$$

This expression is then inserted into equation (64) to get:

$$\frac{\partial n}{\partial t} = \left(-\frac{1}{A}\right) \cdot \left(-A \cdot D^*\frac{\partial^2 n}{\partial x^2}\right) = D^*\frac{\partial^2 n}{\partial x^2}$$

This derivation is done by only considering the x-direction, but the same procedure holds for the y-direction and z-direction as well. So, by also including the y- and z-directions, the total diffusion term becomes:

$$\frac{\partial n}{\partial t} = D^*\left[\frac{\partial^2 n}{\partial x^2} + \frac{\partial^2 n}{\partial y^2} + \frac{\partial^2 n}{\partial z^2}\right] = D^*\nabla^2 n$$

This expression for the total diffusion is then inserted into equation (61) to get the total conservation of mass equation for the cells:

$$\frac{\partial n}{\partial t} + \nabla \cdot (n\boldsymbol{u}) = D^*\nabla^2 n$$

C   General force balance

In this section, the general force balance equation between the gel and the cells is derived. The inertial effects are neglected, due to the slow compaction of the gel.

The figure shown below (taken from (Fjaer et al., 1992)) is only in two dimensions, but gives an understanding of how the force balance will look like also in three dimensions:

Figure 22: Two dimensional stresses (Fjaer et al., 1992)
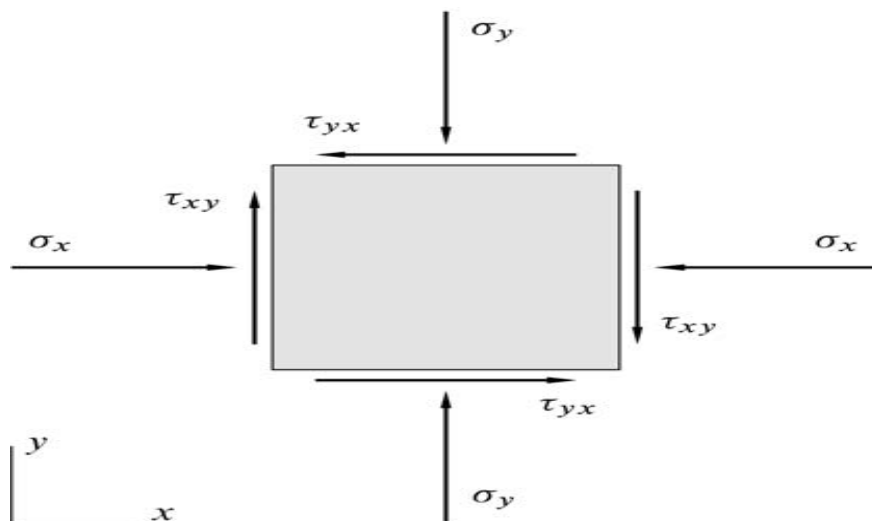
The force balance in the x-direction can be written as:

$$[(\sigma_x + \frac{\partial \sigma_x}{\partial x}dx) - \sigma_x]dydz + [(\tau_{yx} + \frac{\partial \tau_{yx}}{\partial y}dy) - \tau_{yx}]dxdz + [(\tau_{zx} + \frac{\partial \tau_{zx}}{\partial z}dz) - \tau_{zx}]dxdy + f_x = 0$$

In the y-direction:

$$[(\sigma_y + \frac{\partial \sigma_y}{\partial y}dy) - \sigma_y]dxdz + [(\tau_{zy} + \frac{\partial \tau_{zy}}{\partial z}dz) - \tau_{zy}]dxdy + [(\tau_{xy} + \frac{\partial \tau_{xy}}{\partial x}dx) - \tau_{xy}]dydz + f_y = 0$$

In the z-direction:

$$[(\sigma_z + \frac{\partial \sigma_z}{\partial z}dz) - \sigma_z]dxdy + [(\tau_{xz} + \frac{\partial \tau_{xz}}{\partial x}dx) - \tau_{xz}]dydz + [(\tau_{yz} + \frac{\partial \tau_{yz}}{\partial y}dy) - \tau_{yz}]dxdz + f_z = 0$$

where f represents the force per unit volume exerted on the gel by the cells, while the stresses are from the gel. σ and τ represents the normal and shear stress components, respectively. Then, by dividing the three equations above with $dxdydz$ the result is:

$$\frac{\partial \sigma_x}{\partial x} + \frac{\partial \tau_{yx}}{\partial y} + \frac{\partial \tau_{zx}}{\partial z} + F_x = 0$$

$$\frac{\partial \sigma_y}{\partial y} + \frac{\partial \tau_{xy}}{\partial x} + \frac{\partial \tau_{zy}}{\partial z} + F_y = 0$$

$$\frac{\partial \sigma_z}{\partial z} + \frac{\partial \tau_{xz}}{\partial x} + \frac{\partial \tau_{yz}}{\partial y} + F_z = 0$$

where $F = \frac{f}{dxdydz}$.

This can also be written in another form by introducing the divergence of the stresses, and the general expression for the force balance between the cells and the gel can then be written as

$$\nabla \cdot \begin{bmatrix} \sigma_x & \tau_{yx} & \tau_{zx} \\ \tau_{xy} & \sigma_y & \tau_{zy} \\ \tau_{xz} & \tau_{yz} & \sigma_z \end{bmatrix} + \boldsymbol{F} = 0$$

because the divergence of a tensor gives a vector, and not a scalar as the divergence of a vector (first order tensor) would have given. (*Tensor Calculus I@ONLINE*, n.d.) Or in a more compact form:

$$\nabla \cdot \boldsymbol{\sigma} + \boldsymbol{F} = 0$$

D   Expression for the stresses for the gel

By substituting the expression for the stress from equation (2.4 i heftet) into equation (2.3 i heftet) and using that $\lambda^* = \kappa^* - \frac{2}{3}\mu^*$, the following expressions are obtained:

$$\left[\frac{\partial}{\partial x}\left(-P + 2\mu^*\epsilon_{ii} + \lambda^*\epsilon_{kk}\right) + \frac{\partial}{\partial y}\left(2\mu^*\epsilon_{ji}\right) + \frac{\partial}{\partial z}\left(\mu^*\epsilon_{ki}\right) + F_x\right]\hat{i} +$$

$$\left[\frac{\partial}{\partial x}\left(2\mu^*\epsilon_{ij}\right) + \frac{\partial}{\partial y}\left(-P + 2\mu^*\epsilon_{jj} + \lambda^*\epsilon_{kk}\right) + \frac{\partial}{\partial z}\left(2\mu^*\epsilon_{kj}\right) + F_y\right]\hat{j} +$$

$$\left[\frac{\partial}{\partial x}\left(2\mu^*\epsilon_{ik}\right) + \frac{\partial}{\partial y}\left(2\mu^*\epsilon_{jk}\right) + \frac{\partial}{\partial z}\left(-P + 2\mu^*\epsilon_{kk} + \lambda^*\epsilon_{kk}\right) + F_z\right]\hat{k} = 0$$

The expressions for the rate of strain tensor and rate of volume expansion are then substituted into equation (15) above to get:

$$\left[\frac{\partial}{\partial x}\left(-P+2\mu^*\left(\frac{\partial u_i}{\partial x}\right)+\lambda^*\left(\frac{\partial u_i}{\partial x}+\frac{\partial u_j}{\partial y}+\frac{\partial u_k}{\partial z}\right)\right)+\frac{\partial}{\partial y}\mu^*\left(\frac{\partial u_j}{\partial x}+\frac{\partial u_i}{\partial y}\right)+\frac{\partial}{\partial z}\mu^*\left(\frac{\partial u_k}{\partial x}+\frac{\partial u_i}{\partial z}\right)+F_x\right]\hat{i}+$$

$$\left[\frac{\partial}{\partial x}\mu^*\left(\frac{\partial u_i}{\partial y}+\frac{\partial u_j}{\partial x}\right)+\frac{\partial}{\partial y}\left(-P+2\mu^*\frac{\partial u_j}{\partial y}+\lambda^*\left(\frac{\partial u_i}{\partial x}+\frac{\partial u_j}{\partial y}+\frac{\partial u_k}{\partial z}\right)\right)+\frac{\partial}{\partial z}\mu^*\left(\frac{\partial u_k}{\partial y}+\frac{\partial u_j}{\partial z}\right)+F_y\right]\hat{j}+$$

$$\left[\frac{\partial}{\partial x}\mu^*\left(\frac{\partial u_i}{\partial z}+\frac{\partial u_k}{\partial x}\right)+\frac{\partial}{\partial y}\mu^*\left(\frac{\partial u_j}{\partial z}+\frac{\partial u_k}{\partial y}\right)+\frac{\partial}{\partial z}\left(-P+2\mu^*\frac{\partial u_k}{\partial z}+\lambda^*\left(\frac{\partial u_i}{\partial x}+\frac{\partial u_j}{\partial y}+\frac{\partial u_k}{\partial z}\right)\right)+F_z\right]\hat{k}=0$$

Then, by including the partial derivatives inside of the parentheses:

$$-\frac{\partial P}{\partial x}\hat{i}-\frac{\partial P}{\partial y}\hat{j}-\frac{\partial P}{\partial z}\hat{k}$$

$$+\left[\left(2\mu^*\frac{\partial^2 u_i}{\partial x^2}\right)+\lambda^*\left(\frac{\partial^2 u_i}{\partial x^2}+\frac{\partial^2 u_j}{\partial y\partial x}+\frac{\partial^2 u_k}{\partial z\partial x}\right)+\mu^*\left(\frac{\partial^2 u_j}{\partial x\partial y}+\frac{\partial^2 u_i}{\partial y^2}\right)+\mu^*\left(\frac{\partial^2 u_k}{\partial x\partial z}+\frac{\partial^2 u_i}{\partial z^2}\right)+F_x\right]\hat{i}$$

$$+\left[\mu^*\left(\frac{\partial^2 u_i}{\partial y\partial x}+\frac{\partial^2 u_j}{\partial x^2}\right)+\left(2\mu^*\frac{\partial^2 u_j}{\partial y^2}+\lambda^*\left(\frac{\partial^2 u_i}{\partial x\partial y}+\frac{\partial^2 u_j}{\partial y^2}+\frac{\partial^2 u_k}{\partial z\partial y}\right)\right)+\mu^*\left(\frac{\partial^2 u_k}{\partial y\partial z}+\frac{\partial^2 u_j}{\partial z^2}\right)+F_y\right]\hat{j}$$

$$+\left[\mu^*\left(\frac{\partial^2 u_i}{\partial z\partial x}+\frac{\partial^2 u_k}{\partial x^2}\right)+\mu^*\left(\frac{\partial^2 u_j}{\partial z\partial y}+\frac{\partial^2 u_k}{\partial y^2}\right)+2\mu^*\frac{\partial^2 u_k}{\partial z^2}+\lambda^*\left(\frac{\partial^2 u_i}{\partial x\partial z}+\frac{\partial^2 u_j}{\partial y\partial z}+\frac{\partial^2 u_k}{\partial z^2}\right)+F_z\right]\hat{k}=0$$

The expression for the pressure can be written as the gradient of the pressure to simplify the expression above:

$$-\nabla P+\left[\left(2\mu^*\frac{\partial^2 u_i}{\partial x^2}\right)+\lambda^*\left(\frac{\partial^2 u_i}{\partial x^2}+\frac{\partial^2 u_j}{\partial y\partial x}+\frac{\partial^2 u_k}{\partial z\partial x}\right)+\mu^*\left(\frac{\partial^2 u_j}{\partial x\partial y}+\frac{\partial^2 u_i}{\partial y^2}\right)+\mu^*\left(\frac{\partial^2 u_k}{\partial x\partial z}+\frac{\partial^2 u_i}{\partial z^2}\right)+F_x\right]\hat{i}$$

$$+\left[\mu^*\left(\frac{\partial^2 u_i}{\partial y\partial x}+\frac{\partial^2 u_j}{\partial x^2}\right)+\left(2\mu^*\frac{\partial^2 u_j}{\partial y^2}+\lambda^*\left(\frac{\partial^2 u_i}{\partial x\partial y}+\frac{\partial^2 u_j}{\partial y^2}+\frac{\partial^2 u_k}{\partial z\partial y}\right)\right)+\mu^*\left(\frac{\partial^2 u_k}{\partial y\partial z}+\frac{\partial^2 u_j}{\partial z^2}\right)+F_y\right]\hat{j}$$

$$+\left[\mu^*\left(\frac{\partial^2 u_i}{\partial z\partial x}+\frac{\partial^2 u_k}{\partial x^2}\right)+\mu^*\left(\frac{\partial^2 u_j}{\partial z\partial y}+\frac{\partial^2 u_k}{\partial y^2}\right)+2\mu^*\frac{\partial^2 u_k}{\partial z^2}+\lambda^*\left(\frac{\partial^2 u_i}{\partial x\partial z}+\frac{\partial^2 u_j}{\partial y\partial z}+\frac{\partial^2 u_k}{\partial z^2}\right)+F_z\right]\hat{k}=0$$

It will then be assumed that the partial derivatives above are continuous, which means that the partial derivatives are symmetric. This will be used to rewrite expressions further down to make the expressions more compact (Feldman, 2004):

$$-\nabla P+\left[\mu^*\left(\frac{\partial^2 u_i}{\partial x^2}+\frac{\partial^2 u_i}{\partial y^2}+\frac{\partial^2 u_i}{\partial z^2}\right)+(\lambda^*+\mu^*)\left(\frac{\partial^2 u_i}{\partial x^2}+\frac{\partial^2 u_j}{\partial y\partial x}+\frac{\partial^2 u_k}{\partial z\partial x}\right)+F_x\right]\hat{i}$$

$$+\left[\mu^*\left(\frac{\partial^2 u_j}{\partial x^2}+\frac{\partial^2 u_j}{\partial y^2}+\frac{\partial^2 u_j}{\partial z^2}\right)+(\lambda^*+\mu^*)\left(\frac{\partial^2 u_i}{\partial x\partial y}+\frac{\partial^2 u_j}{\partial y^2}+\frac{\partial^2 u_k}{\partial z\partial y}\right)+F_y\right]\hat{j}$$

$$+\left[\mu^*\left(\frac{\partial^2 u_k}{\partial x^2}+\frac{\partial^2 u_k}{\partial y^2}+\frac{\partial^2 u_k}{\partial z^2}\right)+(\lambda^*+\mu^*)\left(\frac{\partial^2 u_i}{\partial x\partial z}+\frac{\partial^2 u_j}{\partial y\partial z}+\frac{\partial^2 u_k}{\partial z^2}\right)+F_z\right]\hat{k}=0$$

E   Vector Laplacian

The expression for the vector Laplacian operator includes the gradient of the divergence of the vector and the the cross product of the cross product of the vector. This will be showed below.

The first step is therefore to find an expression for $\nabla\times(\nabla\times\boldsymbol{A})$: In order to simplify the derivation, let $\boldsymbol{B}=\nabla\times\boldsymbol{A}$:

$$\boldsymbol{B} = \begin{vmatrix} \hat{i} & \hat{j} & \hat{k} \\[4pt] A_x & A_y & A_z \\[4pt] \frac{\partial}{\partial x} & \frac{\partial}{\partial y} & \frac{\partial}{\partial x} \end{vmatrix}$$

$$\implies \boldsymbol{B} = \hat{i}\left(\frac{\partial A_y}{\partial z} - \frac{\partial A_z}{\partial y}\right) - \hat{j}\left(\frac{\partial A_x}{\partial z} - \frac{\partial A_z}{\partial x}\right) + \hat{k}\left(\frac{\partial A_x}{\partial z} - \frac{\partial A_y}{\partial x}\right)$$

So:

$$\nabla \times \boldsymbol{B} = \begin{vmatrix} \hat{i} & \hat{j} & \hat{k} \\[6pt] \left(\frac{\partial A_y}{\partial z} - \frac{\partial A_z}{\partial y}\right) & \left(\frac{\partial A_x}{\partial z} - \frac{\partial A_z}{\partial x}\right) & \left(\frac{\partial A_x}{\partial z} - \frac{\partial A_y}{\partial x}\right) \\[6pt] \frac{\partial}{\partial x} & \frac{\partial}{\partial y} & \frac{\partial}{\partial x} \end{vmatrix}$$

$$= \hat{i}\left[-\frac{\partial}{\partial z}\left(\frac{\partial A_x}{\partial z} - \frac{\partial A_z}{\partial x}\right) - \frac{\partial}{\partial z}\left(\frac{\partial A_x}{\partial z} - \frac{\partial A_y}{\partial x}\right)\right] - \hat{j}\left[\frac{\partial}{\partial z}\left(\frac{\partial A_y}{\partial z} - \frac{\partial A_z}{\partial y}\right) - \frac{\partial}{\partial x}\left(\frac{\partial A_x}{\partial z} - \frac{\partial A_y}{\partial x}\right)\right]$$

$$+ \hat{k}\left[\frac{\partial}{\partial y}\left(\frac{\partial A_y}{\partial z} - \frac{\partial A_z}{\partial y}\right) + \frac{\partial}{\partial x}\left(\frac{\partial A_x}{\partial z} - \frac{\partial A_y}{\partial x}\right)\right]$$

$$= \hat{i}\left(-\frac{\partial^2 A_x}{\partial z^2} + \frac{\partial^2 A_z}{\partial z\partial x} - \frac{\partial^2 A_x}{\partial y\partial z} + \frac{\partial^2 A_y}{\partial z\partial x}\right) + \hat{j}\left(-\frac{\partial^2 A_y}{\partial z^2} + \frac{\partial^2 A_z}{\partial z\partial y} + \frac{\partial^2 A_x}{\partial x\partial z} - \frac{\partial^2 A_y}{\partial x^2}\right)$$

$$+ \hat{k}\left(\frac{\partial^2 A_y}{\partial y\partial z} - \frac{\partial^2 A_z}{\partial y^2} + \frac{\partial^2 A_x}{\partial x\partial z} - \frac{\partial^2 A_z}{\partial x^2}\right)$$

The divergence of $\boldsymbol{A}$ in Cartesian coordinates is defined as (Adams & Essex, 2010):

$$\nabla \cdot \boldsymbol{A} = \frac{\partial A_x}{\partial x} + \frac{\partial A_y}{\partial y} + \frac{\partial A_z}{\partial z},$$

which means that:

$$\nabla(\nabla \cdot \boldsymbol{A}) = \frac{\partial}{\partial x}\left(\frac{\partial A_x}{\partial x} + \frac{\partial A_y}{\partial y} + \frac{\partial A_z}{\partial z}\right)\hat{i} + \frac{\partial}{\partial y}\left(\frac{\partial A_x}{\partial x} + \frac{\partial A_y}{\partial y} + \frac{\partial A_z}{\partial z}\right)\hat{j} + \frac{\partial}{\partial x}\left(\frac{\partial A_x}{\partial x} + \frac{\partial A_y}{\partial y} + \frac{\partial A_z}{\partial z}\right)\hat{k}$$

Then, by subtracting $\nabla \times (\nabla \times \boldsymbol{A})$ with $\nabla(\nabla \cdot \boldsymbol{A})$:

$$\nabla \times (\nabla \times \boldsymbol{A}) - \nabla(\nabla \cdot \boldsymbol{A}) = -\hat{i}\left[\frac{\partial^2 A_x}{\partial x^2} + \frac{\partial^2 A_x}{\partial y^2} + \frac{\partial^2 A_x}{\partial z^2}\right] - \hat{j}\left[\frac{\partial^2 A_y}{\partial x^2} + \frac{\partial^2 A_y}{\partial y^2} + \frac{\partial^2 A_y}{\partial z^2}\right] - \hat{k}\left[\frac{\partial^2 A_z}{\partial x^2} + \frac{\partial^2 A_z}{\partial y^2} + \frac{\partial^2 A_z}{\partial z^2}\right]$$

which is also equal to the negative value of the Laplacian operator of $\boldsymbol{A}$ so that:

$$\nabla \times (\nabla \times \boldsymbol{A}) - \nabla(\nabla \cdot \boldsymbol{A}) = -\nabla^2 \boldsymbol{A}$$

This means that the expression for the vector laplacian is:

$$\nabla^2 \boldsymbol{A} = \nabla(\nabla \cdot \boldsymbol{A}) - \nabla \times (\nabla \times \boldsymbol{A})$$

F Non-dimensionalization

The non-dimensionalization of the initial- and boundary conditions together with the five governing equations are derived below. The tildes are representing the non-dimensional variables:

$$t = T^* \cdot \widetilde{t}, \quad \boldsymbol{x} = R_0 \widetilde{\boldsymbol{x}} \quad \rho = \rho_i \widetilde{\rho}, \quad n = n_i \widetilde{n}, \quad \boldsymbol{u} = \frac{R_0}{T^*} \widetilde{\boldsymbol{u}},$$

$$\boldsymbol{\sigma} = \frac{\mu^*}{T^*} \widetilde{\boldsymbol{\sigma}}, \quad P = \frac{\mu^*}{T^*} \widetilde{P}, \quad \boldsymbol{F} = \frac{\mu^*}{T^* R_0} \widetilde{\boldsymbol{F}}, \quad c = \frac{\alpha_2^* n_i R_0^2}{D_c} \widetilde{c}$$

T is a typical time-length for the compaction, R_0 is a typical length of the gel, while n_i and ρ_i are the average initial densities.

The dimensional variables above are then used in the equations below:

The mass balance equation for the cells are first to be non-dimensionalized, and the dimensional version is repeated below:

$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \boldsymbol{u}) = 0$$

Since it is a one dimensional case, the following simplifications can be done during the non-dimensionalization:

$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \boldsymbol{u}) = \frac{\partial \rho}{\partial t} + \frac{\partial}{\partial x} (\rho \boldsymbol{u})$$

This can be rewritten as

$$\frac{1}{T^*} \frac{\partial (\rho_i \widetilde{\rho})}{\partial \widetilde{t}} + \frac{1}{R_0} \frac{\partial}{\partial \widetilde{x}} \left(\rho_i \widetilde{\rho} \frac{R_0}{T^*} \widetilde{\boldsymbol{u}} \right) = \frac{\rho_i}{T^*} \frac{\partial \widetilde{\rho}}{\partial \widetilde{t}} + \frac{\rho_i}{T^*} \frac{\partial}{\partial \widetilde{x}} (\widetilde{\rho} \widetilde{\boldsymbol{u}}) = 0.$$

This can then be simplified to:

$$\frac{\partial \widetilde{\rho}}{\partial \widetilde{t}} + \frac{\partial}{\partial \widetilde{x}} (\widetilde{\rho} \widetilde{\boldsymbol{u}}) = \frac{\partial \widetilde{\rho}}{\partial \widetilde{t}} + \nabla \cdot (\widetilde{\rho} \widetilde{\boldsymbol{u}})$$

The non-dimensional version of the mass balance for the cells is therefore:

$$\frac{\partial \widetilde{\rho}}{\partial \widetilde{t}} + \nabla \cdot (\widetilde{\rho} \widetilde{\boldsymbol{u}}) = 0$$

The non-dimensionalization of the mass balance for the gel is shown below:

$$\frac{\partial n}{\partial t} + \nabla \cdot (n \boldsymbol{u}) = D \nabla^2 n,$$

which can be rewritten as

$$\frac{1}{T^*} \frac{\partial (n_i \widetilde{n})}{\partial \widetilde{t}} + \frac{1}{R_0} \frac{\partial}{\partial \widetilde{x}} \left(n_i \widetilde{n} \frac{R_0}{T^*} \widetilde{\boldsymbol{u}} \right) = D \frac{1}{R_0^2} \frac{\partial^2}{\partial \widetilde{x}^2} (n_i \widetilde{n}).$$

This equation can be simplified to

$$\frac{n_i}{T^*} \frac{\partial \widetilde{n}}{\partial \widetilde{t}} + \frac{n_i}{T^*} \frac{\partial}{\partial \widetilde{x}} (\widetilde{n} \widetilde{\boldsymbol{u}}) = D \frac{n_i}{R_0^2} \frac{\partial^2}{\partial \widetilde{x}^2} \widetilde{n}.$$

Then, by introducing the Péclet number, P_e, the equation becomes:

$$\frac{\partial \widetilde{n}}{\partial \widetilde{t}} + \frac{\partial}{\partial \widetilde{x}} (\widetilde{n} \widetilde{\boldsymbol{u}}) = D \frac{T^*}{R_0^2} \frac{\partial^2}{\partial \widetilde{x}^2} \widetilde{n} = P_e^{-1} \frac{\partial^2}{\partial \widetilde{x}^2} \widetilde{n},$$

where $P_e = \frac{R_0^2}{DT^*}$.

The mass balance equation for the gel in non-dimensional form can therefore be written as:

$$\frac{\partial \widetilde{n}}{\partial \widetilde{t}} + \nabla \cdot (\widetilde{n}\boldsymbol{u}) = P_e^{-1} \frac{\partial^2}{\partial \widetilde{x}^2} \widetilde{n}$$

The non-dimensionalization of the momentum balance equation is done in the following, first repeating the dimensional version:

$$-\nabla P + \mu^* \nabla^2 \boldsymbol{u} + \left(\kappa^* + \frac{\mu^*}{3}\right) \cdot \nabla(\nabla \cdot \boldsymbol{u}) + \boldsymbol{F} = 0$$

Inserting the non-dimensional versions of the parameters gives:

$$-\frac{1}{R_0} \frac{\partial}{\partial \widetilde{x}} \left(\frac{\mu^*}{T^*}\widetilde{P}\right) + \frac{1}{R_0^2} \frac{\partial^2}{\partial \widetilde{x}^2} \left(\frac{R_0\mu^*}{T^*}\widetilde{\boldsymbol{u}}\right) + \left(\kappa^* + \frac{1}{3}\right) \frac{\mu^*}{R_0^2} \frac{\partial^2}{\partial \widetilde{x}^2} \left(\frac{R_0}{T^*}\widetilde{\boldsymbol{u}}\right) + \frac{\mu^*}{T^*R_0}\widetilde{\boldsymbol{F}} = 0,$$

which can be rewritten as:

$$-\frac{\mu^*}{R_0T^*} \frac{\partial}{\partial \widetilde{x}} \widetilde{P} + \frac{\mu^*}{R_0T^*} \frac{\partial^2}{\partial \widetilde{x}^2} \widetilde{\boldsymbol{u}} + \left(\kappa^* + \frac{1}{3}\right) \frac{\mu^*}{R_0T^*} \frac{\partial^2}{\partial \widetilde{x}^2} \widetilde{\boldsymbol{u}} + \frac{\mu^*}{T^*R_0}\widetilde{\boldsymbol{F}} = 0.$$

Multiplying with $R_0 T^*$ gives:

$$-\mu^* \frac{\partial}{\partial \widetilde{x}} \widetilde{P} + \mu^* \frac{\partial^2}{\partial \widetilde{x}^2} \widetilde{\boldsymbol{u}} + \left(\kappa^* + \frac{1}{3}\right) \mu^* \frac{\partial^2}{\partial \widetilde{x}^2} \widetilde{\boldsymbol{u}} + \mu^*\widetilde{\boldsymbol{F}} = 0$$

The two terms involving $\frac{\partial^2}{\partial \widetilde{x}^2}$ are then factorized as one term:

$$-\mu^* \frac{\partial}{\partial \widetilde{x}} \widetilde{P} + \left(\mu^* + \kappa^* + \frac{\mu^*}{3}\right) \frac{\partial^2}{\partial \widetilde{x}^2} \widetilde{\boldsymbol{u}} + \mu^*\widetilde{\boldsymbol{F}} = 0,$$

which can be rewritten as

$$-\mu^* \frac{\partial}{\partial \widetilde{x}} \widetilde{P} + \left(\frac{4}{3}\mu^* + \mu^*\frac{\kappa^*}{\mu^*}\right) \frac{\partial^2}{\partial \widetilde{x}^2} \widetilde{\boldsymbol{u}} + \mu^*\widetilde{\boldsymbol{F}} = 0.$$

This expression can be further simplified to:

$$-\mu^* \frac{\partial}{\partial \widetilde{x}} \widetilde{P} + \frac{\partial^2}{\partial \widetilde{x}^2} \widetilde{\boldsymbol{u}} + \left(\frac{1}{3} + \kappa\right) \frac{\partial^2}{\partial \widetilde{x}^2} \widetilde{\boldsymbol{u}} + \mu^*\widetilde{\boldsymbol{F}} = 0,$$

where $\kappa = \frac{\kappa^*}{\mu^*}$.

The non-dimensional version of the momentum balance equation can therefore be written as:

$$-\nabla \widetilde{P} + \nabla^2 \widetilde{\boldsymbol{u}} + \left(\kappa + \frac{1}{3}\right) \cdot \nabla(\nabla \cdot \widetilde{\boldsymbol{u}}) + \widetilde{\boldsymbol{F}} = 0$$

The equation showing the relationship between the gel density and pressure is then non-dimensionalized as shown below, starting with repeating the equation:

$$\rho = \rho_i \left(1 + \beta^* p\right)$$

Inserting the non-dimensional version of the parameters:

$$\rho_i \widetilde{\rho} = \rho_i \left(1 + \beta^* \frac{\mu}{T}\widetilde{p}\right)$$

The non-dimensionalized version can then be written as:

$$\widetilde{\rho} = 1 + \beta \widetilde{p}$$

where $\beta = \beta^* \frac{\mu}{T}$

The equation showing the evolution of the cell-produced chemicals is then to be non-dimensionalized:

$$D_c^* \nabla^2 c - \alpha_1^* c + \alpha_2^* n = 0$$

The non-dimensional versions of the parameters are then inserted for the dimensional parameters to give:

$$D_c^* \frac{1}{R_0^2} \frac{\partial^2}{\partial \widetilde{x}^2} \left(\frac{\alpha_2^* n_i R_0^2}{D_c^*} \widetilde{c} \right) - \alpha_1^* \frac{\alpha_2^* n_i R_0^2}{D_c^*} \widetilde{c} + \alpha_2^* n_i \hat{n} = 0,$$

which can be simplified to

$$\alpha_2^* n_i \frac{\partial^2}{\partial \widetilde{x}^2} \widetilde{c} - \alpha_1^* \frac{\alpha_2^* n_i R_0^2}{D_c^*} \widetilde{c} + \alpha_2^* n_i \hat{n} = 0.$$

Then, by dividing by $\alpha_2^* n_i$ gives

$$\frac{\partial^2}{\partial \widetilde{x}^2} \widetilde{c} - \alpha_1^* \frac{R_0^2}{D_c^*} \widetilde{c} + \widetilde{n} = 0$$

This can be simplified by introducing α_1:

$$\frac{\partial^2}{\partial \widetilde{x}^2} \widetilde{c} - \alpha_1 \widetilde{c} + \widetilde{n} = 0,$$

where $\alpha_1 = \alpha_1^* \frac{R_0^2}{D_c^*}$.

The non-dimensional version of the equation describing the cell-produced chemical evolution can therefore be written as:

$$\nabla^2 \widetilde{c} - \alpha_1^* \widetilde{c} + \widetilde{n} = 0$$

Then, to sum up the last five non-dimensionalized equations, they are rewritten below without the tildes, and the expression for the force function is also included:

$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \boldsymbol{u}) = 0$$

$$\frac{\partial n}{\partial t} + \nabla \cdot (n \boldsymbol{u}) = P_e^{-1} \frac{\partial^2}{\partial x^2} n$$

$$-\nabla P + \nabla^2 \boldsymbol{u} + \left(\kappa + \frac{1}{3} \right) \cdot \nabla (\nabla \cdot \boldsymbol{u}) + \boldsymbol{F} = 0$$

$$\nabla^2 c - \alpha_1^* c + n = 0$$

$$\boldsymbol{F} = \tau_0 \nabla \left(\frac{\rho n}{1 + \lambda n^2} \right)$$

$$\rho = 1 + \beta p$$

The equation for the effective stresses for the gel is to then be non-dimensionalized. The equation is first repeated, before non-dimensionalizing it:

$$\sigma_{ij} = -P \delta_{ij} + 2\mu^* \epsilon_{ij} + \left(\kappa^* - \frac{2}{3} \mu^* \right) \epsilon_{kk} \delta_{ij}$$

Introducing the non-dimensional parameter expressions gives

$$\frac{\mu^*}{T^*} \widetilde{\sigma}_{ij} = -\frac{\mu^*}{T^*} \widetilde{P} \delta_{ij} + 2\mu^* \widetilde{\epsilon}_{ij} + \left(\kappa^* - \frac{2}{3} \mu^* \right) \widetilde{\epsilon}_{kk} \frac{R_0}{T^* R_0} \delta_{ij},$$

where $\widetilde{\sigma}_{ij}$ and $\widetilde{\epsilon}_{kk}$ are the rescaled versions of the stress tensor rate. The non-dimensional version of equation (6) therefore becomes:

$$\widetilde{\sigma}_{ij} = -\widetilde{P}\delta_{ij} + 2\widetilde{\epsilon}_{ij} + \left(\kappa^* - \frac{2}{3}\right)\widetilde{\epsilon}_{kk}\delta_{ij},$$

The non-dimensional versions of the initial conditions and the boundary conditions are then to be shown:

$$\Omega(t)|_{t=0} = \Omega_0, \qquad \rho|_{t=0} = \rho_0(\boldsymbol{x}), \qquad n|_{t=0} = n_0(\boldsymbol{x})$$

The boundary condition

$$\hat{\boldsymbol{n}} \cdot (n\boldsymbol{u} - D\nabla n) = 0,$$

is non-dimensionalized as follows:

$$\hat{\boldsymbol{n}} \cdot (n\boldsymbol{u} - D\nabla n) = 0.$$

By introducing the non-dimensional versions of the parameter gives:

$$\hat{\boldsymbol{n}}\left(n_i\widetilde{n}\frac{R_0}{T^*}\widetilde{\boldsymbol{u}} - D_c\frac{1}{R_0}\frac{\partial}{\partial\widetilde{x}}(n_i\widetilde{n})\right) = 0$$

Then, dividing by $n_i\frac{R_0}{T^*}$ gives:

$$\hat{\boldsymbol{n}}\left(\widetilde{n}\widetilde{\boldsymbol{u}} - D_c\frac{T^*}{R_0^2}\frac{\partial}{\partial\widetilde{x}}\widetilde{n}\right) = 0$$

Introducing the Péclet number, P_e, gives:

$$\hat{\boldsymbol{n}}\left(\widetilde{n}\widetilde{\boldsymbol{u}} - P_e^{-1}\frac{\partial}{\partial\widetilde{x}}\widetilde{n}\right) = 0,$$

where $P_e = \frac{R_0^2}{D_c T^*}$. The dimensional version of the first part of equation (2.12 a) therefore becomes:

$$\hat{\boldsymbol{n}}\left(\widetilde{n}\widetilde{\boldsymbol{u}} - P_e^{-1}\nabla\widetilde{n}\right) = 0$$

The boundary condition

$$\boldsymbol{\sigma} \cdot \hat{\boldsymbol{n}} = 0,$$

is non-dimensionalized as:

$$\hat{\boldsymbol{\sigma}}\frac{\mu^*}{T^*} \cdot n_i\hat{\boldsymbol{n}} = 0.$$

Multiplying this with $\frac{T^*}{\mu^*}$ gives the dimensionless version of the equation to become:

$$\hat{\boldsymbol{\sigma}} \cdot \hat{\boldsymbol{n}} = 0$$

The boundary condition

$$\boldsymbol{u} \cdot \hat{\boldsymbol{n}} = V,$$

is non-dimensionalized as:

$$\widetilde{\boldsymbol{u}}\frac{R_0}{T^*} \cdot n_i\hat{\boldsymbol{n}} = V.$$

Multiplying this with $\frac{T^*}{R_0 n_i}$ and introducing V^* gives the dimensional version of the equation:

$$\widetilde{\boldsymbol{u}} \cdot \hat{\boldsymbol{n}} = V^*,$$

where $V^* = V\frac{T^*}{R_0}$. The last equation to be non-dimensionalized is:

$$-D_c^* \hat{\boldsymbol{n}} \cdot \nabla c = \gamma^* c, \quad \text{on} \quad \Gamma^*(t).$$

Introducing the non-dimensional parameters:

$$-D_c^* \hat{\boldsymbol{n}} \frac{1}{R_0} \frac{\partial}{\partial \widetilde{x}} \left(\frac{\alpha_2^* n_i R_0^2}{D_c^*} \widetilde{c} \right) = \gamma^* \frac{\alpha_2^* n_i R_0^2}{D_c^*} \widetilde{c}$$

This can be rewritten as:

$$\hat{\boldsymbol{n}} \alpha_2^* n_i R_0 \frac{\partial}{\partial \widetilde{x}} \widetilde{c} = -\gamma^* \frac{\alpha_2^* n_i R_0^2}{D_c^*} \widetilde{c}$$

Further simplifications, and introducing the parameter γ gives:

$$\hat{\boldsymbol{n}} \frac{\partial}{\partial \widetilde{x}} \widetilde{c} = -\gamma^* \frac{R_0}{D_c^*} \widetilde{c} = -\gamma \widetilde{c},$$

where $\gamma = \gamma^* \frac{R_0}{D_c^*}$.

The dimensionless version of

$$-D_c^* \hat{\boldsymbol{n}} \cdot \nabla c = \gamma^* c, \quad \text{on} \quad \Gamma^*(t).$$

is therefore:

$$\hat{\boldsymbol{n}} \nabla \widetilde{c} = -\gamma \widetilde{c}.$$

The dimensionless boundary conditions and initial conditions are repeated below, skipping the tildes, but they are still dimensionless:

$$\Omega(t)|_{t=0} = \Omega_0, \quad \rho|_{t=0} = \rho_0(\boldsymbol{x}), \quad n|_{t=0} = n_0(\boldsymbol{x})$$
$$\hat{\boldsymbol{n}} \cdot \left(n\boldsymbol{u} - P_e^{-1} \nabla n \right) = 0$$
$$\boldsymbol{\sigma} \cdot \hat{\boldsymbol{n}} = V$$
$$\boldsymbol{u} \cdot \hat{\boldsymbol{n}} = V$$
$$\hat{\boldsymbol{n}} \cdot \nabla c = -\gamma c$$

ω_0, ρ_0 and n_0 are the non-dimensional counterparts of ω_0^*, ρ_0^* and n_0^*, while V is the non-dimensional normal velocity of $\Gamma(t)$.

The other non-dimensionalized equations and the force function are also repeated below:

$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \boldsymbol{u}) = 0$$
$$\frac{\partial n}{\partial t} + \nabla \cdot (n\boldsymbol{u}) = P_e^{-1} \frac{\partial^2}{\partial x^2} n$$
$$-\nabla P + \nabla^2 \boldsymbol{u} + \left(\kappa + \frac{1}{3} \right) \cdot \nabla(\nabla \cdot \boldsymbol{u}) + \boldsymbol{F} = 0$$
$$\nabla^2 c - \alpha_1^* c + n = 0$$

$$\boldsymbol{F} = \tau_0 \nabla \left(\frac{\rho n}{1 + \lambda n^2} \right)$$
$$\rho = 1 + \beta p$$

G   Gradient, divergence, scalar Laplacian and vector Laplacian in spherical coordinates

The expression for the gradient and the divergence in spherical coordinates are shown below together with the derivation of the spherical coordinate versions of the vector Laplacian and the scalar Laplacian. The assumption that the collagen gel remains spherical through the whole compaction is important to keep in mind, because from this assumption it follows that none of the operators which is to be derived below (or in this whole theses) depends on the polar or azimuthal angles. (Green et al., 2013) This will simplify the derivation. A figure (taken from (Tuckerman, 2011)) showing the spherical coordinates is shown first, before the definition of the gradient:

Figure 23: Spherical coordinate system (Tuckerman, 2011)

$$x = r\,\sin\theta\cos\phi$$
$$y = r\,\sin\theta\sin\phi$$
$$z = r\,\cos\theta$$
$$x^2 + y^2 + z^2 = r^2$$
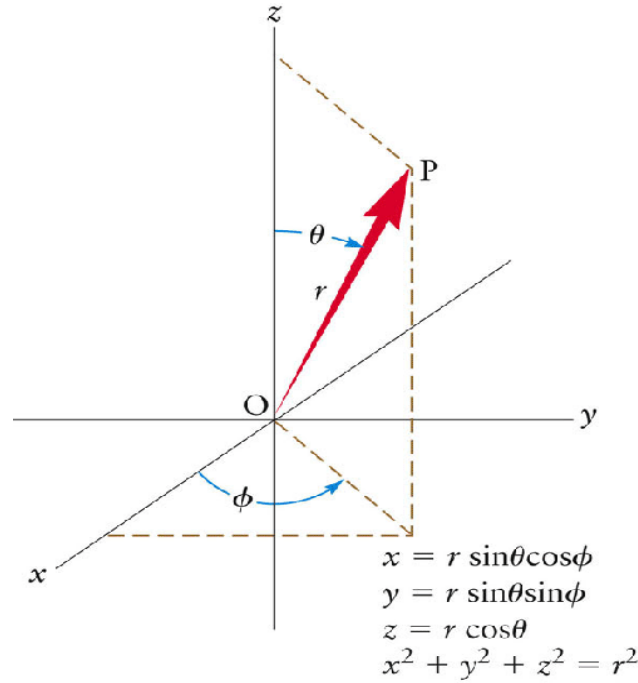
Gradient

The gradient in Cartesian coordinates (Adams & Essex, 2010):

$$\nabla f(x,y,z) = \frac{\partial f}{\partial x}\hat{i} + \frac{\partial f}{\partial y}\hat{j} + \frac{\partial f}{\partial z}\hat{k}$$

The gradient in spherical coordinates (Adams & Essex, 2010):

$$\nabla f(r,\phi,\theta) = \frac{\partial f}{\partial r}\hat{r} + \frac{1}{r}\frac{\partial f}{\partial \phi}\hat{\phi} + \frac{1}{r\sin(\phi)}\frac{\partial f}{\partial \theta}\hat{\theta}$$

which due to neglecting the azimuthal and polar angles is simplified to:

$$\nabla f(r) = \frac{\partial f}{\partial r}\hat{r}$$

Divergence

The divergence in Cartesian coordinates (Adams & Essex, 2010):

$$\nabla \cdot \boldsymbol{F}(x,y,z) = \frac{\partial F_1}{\partial x} + \frac{\partial F_2}{\partial y} + \frac{\partial F_3}{\partial z}$$

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where $\boldsymbol{F} = F_1 \hat{i} + F_2 \hat{j} + F_3 \hat{k}$.

The divergence in spherical coordinates(Adams & Essex, 2010):

$$\nabla \cdot \boldsymbol{F} = \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 F_r \right) + \frac{1}{r \sin(\theta)} \frac{\partial (F_\theta \sin(\theta))}{\partial \theta} + \frac{1}{r \sin(\theta)} \frac{\partial F_\phi}{\partial \phi}$$

where $\boldsymbol{F} = F_r \hat{r} + F_\theta \hat{\theta} + F_\phi \hat{\phi}$. This can be simplified to only the first term to the right of the equality sign due to neglection of azimuthal and polar angles as follows:

$$\nabla \cdot \boldsymbol{F} = \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 F_r \right)$$

The Laplacian in spherical coordinates

The expression for the vector Laplacian for spherical coordinates is now going to be derived. As for the Cartesian coordinates, the expression is also:

$$\nabla^2 \boldsymbol{A} = \nabla(\nabla \cdot \boldsymbol{A}) - \nabla \times (\nabla \times \boldsymbol{A})$$

It will now be shown that the cross-product becomes zero because of the neglection of polar and azimuthal angles: $\boldsymbol{B}$ will also here be defined as $\nabla \times \boldsymbol{A}$, and then one can calculate $\nabla \times (\nabla \times \boldsymbol{A})$ as follows, where $\boldsymbol{C} = \nabla \times B$:

$$\boldsymbol{C} = \begin{vmatrix} \hat{r} & r\hat{\theta} & r\sin(\theta)\hat{\phi} \\ \frac{\partial}{\partial r} & \frac{\partial}{\partial \theta} & \frac{\partial}{\partial \phi} \\ B_r & rB_\theta & r\sin(\theta)B_\phi \end{vmatrix} \cdot \frac{1}{r^2 \sin(\theta)} = 0$$

because all the terms will be dependent on either the polar angle or the azimuthal angle, or both. This means that the vector Laplacian in the case considering here equals the gradient of the divergence of the vector $\boldsymbol{u}$:

$$\nabla^2(\boldsymbol{u}) = \nabla(\nabla \cdot \boldsymbol{u}) = \nabla \left(\frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 u_r \right) \right) = \frac{\partial}{\partial r} \left(\frac{1}{r^2} \frac{\partial (r^2 u)}{\partial r} \right)$$

$$= -\frac{2}{r^3} \left(2ru + r^2 \frac{\partial u}{\partial r} \right) + \frac{1}{r^2} \frac{\partial}{\partial r} \left(2ru + r^2 \frac{\partial u}{\partial r} \right)$$

$$= -\frac{4u}{r^2} - \frac{2}{r} \frac{\partial u}{\partial r} + \frac{1}{r^2} \left(2u + 2r \frac{\partial u}{\partial r} + 2r \frac{\partial u}{\partial r} + r^2 \frac{\partial^2 u}{\partial r^2} \right) = -\frac{4u}{r^2} + \frac{2u}{r^2} - \frac{2}{r} \frac{\partial u}{\partial r} + \frac{2}{r} \frac{\partial u}{\partial r} + \frac{2}{r} \frac{\partial u}{\partial r} + \frac{\partial^2 u}{\partial r^2}$$

This then gives the expression for the vector Laplacian of $\boldsymbol{u}$ to be:

$$\nabla^2(\boldsymbol{u}) = -\frac{2u}{r^2} + \frac{2}{r} \frac{\partial u}{\partial r} + \frac{\partial^2 u}{\partial r^2}$$

In order to simplify the expression above, the scalar Laplacian in spherical coordinates should be derived: First, the definition of the new spherical coordinates (Tuckerman, 2011):

$$x = r \cos(\phi) \sin(\theta)$$

$$y = r \sin(\theta) \sin(\phi)$$

$$z = r \cos(\theta)$$

The expression for θ and ϕ can be visually seen from a figure above to be:

$$\cos(\theta) = \frac{z}{\sqrt{x^2 + y^2 + z^2}}, \qquad \sin(\theta) = \frac{\sqrt{x^2 + y^2}}{\sqrt{x^2 + y^2 + z^2}}, \qquad \theta = \cos^{-1}\left(\frac{z}{\sqrt{x^2 + y^2 + z^2}}\right).$$

$$\cos(\phi) = \frac{x}{\sqrt{x^2 + y^2}}, \qquad \sin(\phi) = \frac{y}{\sqrt{x^2 + y^2}}, \qquad \phi = \cos^{-1}\left(\frac{x}{\sqrt{x^2 + y^2}}\right).$$

The Laplacian operator in Cartesian coordinates (Adams & Essex, 2010) will first be briefly looked at in order to use this as a starting point in the derivation for spherical coordinates:

$$\nabla^2 F = \frac{\partial^2 F}{\partial x^2} + \frac{\partial^2 F}{\partial y^2} + \frac{\partial^2 F}{\partial z^2}$$

From $x = r\cos(\phi)\sin(\theta)$, the following partial derivative expressions for F can be written:

$$\frac{\partial F}{\partial x} = \frac{\partial F}{\partial r}\frac{\partial r}{\partial x} + \frac{\partial F}{\partial \theta}\frac{\partial \theta}{\partial x} + \frac{\partial F}{\partial \phi}\frac{\partial \phi}{\partial x}$$

$$\frac{\partial F}{\partial y} = \frac{\partial F}{\partial r}\frac{\partial r}{\partial y} + \frac{\partial F}{\partial \theta}\frac{\partial \theta}{\partial y} + \frac{\partial F}{\partial \phi}\frac{\partial \phi}{\partial y}$$

$$\frac{\partial F}{\partial z} = \frac{\partial F}{\partial r}\frac{\partial r}{\partial z} + \frac{\partial F}{\partial \theta}\frac{\partial \theta}{\partial z} + \frac{\partial F}{\partial \phi}\frac{\partial \phi}{\partial z}$$

which, by removing F is written as:

$$\frac{\partial}{\partial x} = \frac{\partial r}{\partial x}\frac{\partial}{\partial r} + \frac{\partial \theta}{\partial x}\frac{\partial}{\partial \theta} + \frac{\partial \phi}{\partial x}\frac{\partial}{\partial \phi}$$

$$\frac{\partial}{\partial y} = \frac{\partial r}{\partial y}\frac{\partial}{\partial r} + \frac{\partial \theta}{\partial y}\frac{\partial}{\partial \theta} + \frac{\partial \phi}{\partial y}\frac{\partial}{\partial \phi}$$

$$\frac{\partial}{\partial z} = \frac{\partial r}{\partial z}\frac{\partial}{\partial r} + \frac{\partial \theta}{\partial z}\frac{\partial}{\partial \theta} + \frac{\partial \phi}{\partial z}\frac{\partial}{\partial \phi}$$

Then the partial derivatives of r should be calculated:

$$\frac{\partial r}{\partial x} = \frac{1}{2}\left(x^2 + y^2 + z^2\right)^{-\frac{1}{2}} \cdot 2x = x \cdot \left(x^2 + y^2 + z^2\right)^{-\frac{1}{2}} = \frac{x}{r} = \cos(\phi)\sin(\theta)$$

$$\frac{\partial r}{\partial y} = \frac{1}{2}\left(x^2 + y^2 + z^2\right)^{-\frac{1}{2}} \cdot 2y = y \cdot \left(x^2 + y^2 + z^2\right)^{-\frac{1}{2}} = \frac{y}{r} = \sin(\theta)\sin(\phi)$$

$$\frac{\partial r}{\partial z} = \frac{1}{2}\left(x^2 + y^2 + z^2\right)^{-\frac{1}{2}} \cdot 2z = z \cdot \left(x^2 + y^2 + z^2\right)^{-\frac{1}{2}} = \frac{z}{r} = \cos(\theta)$$

where the expressions for x, y, z and r was used to get the final results to the utter right end in the three equations above. The next step is to calculate the partial derivatives of θ and ϕ:

$$\frac{\partial \theta}{\partial x} = \frac{xz}{\sqrt{\frac{x^2+y^2}{x^2+y^2+z^2}}\left(x^2 + y^2 + z^2\right)^{\frac{3}{2}}} = \frac{z\cos(\phi)r}{r^3} = \frac{\cos(\phi)\cos(\theta)}{r}$$

By using the same method as above, the partial derivatives of θ with respect to y and z can also be calculated:

$$\frac{\partial \theta}{\partial y} = \frac{\cos(\theta)\sin(\phi)}{r}$$

$$\frac{\partial \theta}{\partial z} = -\frac{\sin(\theta)}{r}$$

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ϕ is independent on z- values, so the partial derivative of ϕ is only with respect to x and y, which is shown below:

$$\frac{\partial \phi}{\partial x} = \frac{\partial}{\partial x}\left[cos^{-1}\left(\frac{x}{\sqrt{x^2+y^2}}\right)\right] = -\frac{\sqrt{\frac{y^2}{x^2+y^2}}}{\sqrt{x^2+y^2}} = -\frac{\sin(\phi)}{r\sin(\theta)}$$

$$\frac{\partial \phi}{\partial y} = \frac{\cos(\phi)}{r\sin(\theta)}$$

These partial derivatives are then inserted into the expressions for $\frac{\partial}{\partial x}$, $\frac{\partial}{\partial y}$ and $\frac{\partial}{\partial z}$ from the previous page:

$$\frac{\partial}{\partial x} = \sin(\theta)\cos(\phi)\frac{\partial}{\partial r} + \frac{\cos(\theta)\cos(\phi)}{r}\frac{\partial}{\partial \theta} - \frac{\sin(\phi)}{r\sin(\theta)}\frac{\partial}{\partial \phi}$$

$$\frac{\partial}{\partial y} = \sin(\theta)\sin(\phi)\frac{\partial}{\partial r} + \frac{\cos(\theta)\sin(\phi)}{r}\frac{\partial}{\partial \theta} + \frac{\cos(\phi)}{r\sin(\theta)}\frac{\partial}{\partial \phi}$$

$$\frac{\partial}{\partial z} = \cos(\theta)\frac{\partial}{\partial r} - \frac{\sin(\theta)}{r}\frac{\partial}{\partial \theta}$$

Since it is the second derivatives which are needed, the partial derivatives of the three equations right above are also calculated:

$$\frac{\partial^2}{\partial x^2} = \left[\sin(\theta)\cos(\phi)\frac{\partial}{\partial r} + \frac{\cos(\theta)\cos(\phi)}{r}\frac{\partial}{\partial \theta} - \frac{\sin(\phi)}{r\sin(\theta)}\frac{\partial}{\partial \phi}\right]\left[\sin(\theta)\cos(\phi)\frac{\partial}{\partial r} + \frac{\cos(\theta)\cos(\phi)}{r}\frac{\partial}{\partial \theta} - \frac{\sin(\phi)}{r\sin(\theta)}\frac{\partial}{\partial \phi}\right]$$

It is important to note that it is not a multiplication between the two large paranthesis, but like $[\frac{\partial}{\partial x}][\frac{\partial}{\partial x}]$ so that:

$$\frac{\partial^2}{\partial x^2} =$$

$$\left[\sin^2(\theta)\cos^2(\phi)\frac{\partial^2}{\partial r^2} - \frac{\sin(\theta)\cos(\theta)\cos^2(\phi)}{r^2}\frac{\partial}{\partial \theta} + \frac{\sin(\theta)\cos(\theta)\cos^2(\phi)}{r}\frac{\partial^2}{\partial r\partial \theta} + \frac{\cos(\phi)\sin(\phi)}{r^2}\frac{\partial}{\partial \phi} - \frac{\cos(\phi)\sin(\phi)}{r}\frac{\partial^2}{\partial r\partial \phi}\right]$$

$$+ \left[\frac{\cos^2(\theta)\cos^2(\phi)}{r}\frac{\partial}{\partial r} + \frac{\sin(\theta)\cos(\theta)\cos^2(\phi)}{r}\frac{\partial^2}{\partial \theta\partial r} - \frac{\sin(\theta)\cos(\theta)\cos^2(\phi)}{r^2}\frac{\partial}{\partial \theta} + \frac{\cos^2(\phi)\sin^2(\phi)}{r^2}\frac{\partial^2}{\partial \theta^2} + \frac{\cos^2(\theta)\cos(\phi)\sin(\phi)}{\sin^2(\theta)}\frac{\partial}{\partial \phi}\right.$$

$$+ \left[\frac{\sin^2(\phi)}{r}\frac{\partial}{\partial r} - \frac{\sin(\phi)\cos(\phi)}{r}\frac{\partial^2}{\partial \phi\partial r} + \frac{\sin^2(\phi)\cos(\theta)}{r^2\sin(\theta)}\frac{\partial}{\partial \theta} - \frac{\sin(\phi)\cos(\theta)\cos(\phi)}{\sin(\theta)r^2}\frac{\partial^2}{\partial \phi\partial \theta} + \frac{\sin(\phi)\cos(\phi)}{r^2 sin^2(\theta)}\frac{\partial}{\partial \phi} + \frac{\sin^2(\phi)}{r^2\sin^2(\theta)}\frac{\partial^2}{\partial \phi^2}\right]$$

Then over to $\frac{\partial^2}{\partial y^2}$:

$$\left[\sin(\theta)\sin(\phi)\frac{\partial}{\partial r} + \frac{1}{r}\cos(\theta)\sin(\phi)\frac{\partial}{\partial \theta} + \frac{1}{r}\frac{\cos(\phi)}{\sin(\theta)}\frac{\partial}{\partial \phi}\right]\left[\sin(\theta)\sin(\phi)\frac{\partial}{\partial r} + \frac{1}{r}\cos(\theta)\sin(\phi)\frac{\partial}{\partial \theta} + \frac{1}{r}\frac{\cos(\phi)}{\sin(\theta)}\frac{\partial}{\partial \phi}\right]$$

which gives:

$$\frac{\partial^2}{\partial y^2} =$$

$$= \left[-\frac{\sin(\theta)\cos(\theta)\sin^2(\phi)}{r^2}\frac{\partial}{\partial \theta} + \frac{\sin(\theta)\cos(\theta)\sin^2(\phi)}{r}\frac{\partial^2}{\partial r\partial \theta} + \sin^2(\theta)\sin^2(\phi)\frac{\partial^2}{\partial r^2} - \frac{\sin(\phi)\cos(\phi)}{r^2}\frac{\partial}{\partial \phi} + \frac{\sin(\phi)\cos(\phi)}{r}\frac{\partial^2}{\partial r\partial \phi}\right]$$

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$$+ \left[\frac{\cos^2(\theta)\sin^2(\phi)}{r} \frac{\partial}{\partial r} + \frac{\cos(\theta)\sin(\theta)\sin^2(\phi)}{r} \frac{\partial^2}{\partial\theta\partial r} - \frac{\cos(\theta)\sin(\theta)\sin^2(\phi)}{r^2} \frac{\partial}{\partial\theta} + \frac{\cos^2(\theta)\sin^2(\theta)}{r^2} \frac{\partial^2}{\partial\theta^2} - \frac{\cos^2(\theta)\cos(\phi)\sin(\phi)}{r^2\sin^2(\theta)} \frac{\partial}{\partial\phi} \right]$$

$$+ \left[\frac{\cos(\theta)\sin(\phi)\cos(\phi)}{r^2\sin(\theta)} \frac{\partial^2}{\partial\theta\partial\phi} \right]$$

$$+ \left[\frac{\cos^2(\phi)}{r} \frac{\partial}{\partial r} + \frac{\cos(\phi)\sin(\phi)}{r} \frac{\partial^2}{\partial\phi\partial r} + \frac{\cos^2(\phi)\cos(\theta)}{r^2\sin(\theta)} \frac{\partial}{\partial\theta} + \frac{\cos(\phi)\cos(\theta)\sin(\phi)}{r^2\sin(\theta)} \frac{\partial^2}{\partial\phi\partial\theta} - \frac{\cos(\phi)\sin(\phi)}{\sin^2(\theta)r^2} \frac{\partial}{\partial\phi} + \frac{\cos^2(\phi)}{r^2\sin^2(\theta)} \frac{\partial^2}{\partial\phi^2} \right]$$

The final second partial derivative to calculate is $\frac{\partial^2}{\partial z^2}$, which is done below:

$$\frac{\partial^2}{\partial z^2} = \left[\cos(\theta)\frac{\partial}{\partial r} - \frac{\sin(\theta)}{r}\frac{\partial}{\partial\theta} \right] \left[\cos(\theta)\frac{\partial}{\partial r} - \frac{\sin(\theta)}{r}\frac{\partial}{\partial\theta} \right]$$

$$= \cos^2(\theta)\frac{\partial^2}{\partial r^2} + \frac{\sin(\theta)\cos(\theta)}{r^2}\frac{\partial}{\partial\theta} - \frac{\cos(\theta)\sin(\theta)}{r}\frac{\partial^2}{\partial r\partial\theta} + \frac{\sin^2(\theta)}{r}\frac{\partial}{\partial r} - \frac{\sin(\theta)\cos(\theta)}{r}\frac{\partial^2}{\partial\theta\partial r} + \frac{\sin(\theta)\cos(\theta)}{r^2}\frac{\partial}{\partial\theta} + \frac{\sin^2(\theta)}{r^2}\frac{\partial^2}{\partial\theta^2}$$

Since the expressions for $\frac{\partial^2}{\partial x^2}$, $\frac{\partial^2}{\partial y^2}$ and $\frac{\partial^2}{\partial z^2}$ are to be summed in order to get the Laplacian operator, the different partial derivatives in the three expressions calculated above are factorized in order to simplify, because some of the terms will sum to zero. The expressions inside the paranthesis for $\frac{\partial^2}{\partial r\partial\theta}$, $\frac{\partial^2}{\partial\theta\partial\phi}$, $\frac{\partial^2}{\partial r\partial\phi}$ and $\frac{\partial}{\partial\phi}$ equals zero, so these terms will cancer out:

$$\frac{\partial^2}{\partial r\partial\theta} \left[-\frac{\cos(\theta)\sin(\theta)}{r} - \frac{\cos(\theta)\sin(\theta)}{r} + \frac{\cos(\theta)\sin(\theta)\cos^2(\phi)}{r} + \frac{\cos(\theta)\sin(\theta)\cos^2(\phi)}{r} + \frac{\sin(\theta)\cos(\theta)\sin^2(\phi)}{r} \right]$$

$$+ \frac{\partial^2}{\partial r\partial\theta} \left[\frac{\sin(\theta)\cos(\theta)\sin^2(\phi)}{r} \right] = 0$$

$$\frac{\partial^2}{\partial\theta\partial\phi} \left[-\frac{\cos(\theta)\cos(\phi)\sin(\phi)}{r^2\sin(\theta)} - \frac{\sin(\phi)\cos(\theta)\cos(\phi)}{r^2\sin(\theta)} + \frac{\sin(\phi)\cos(\theta)\cos(\phi)}{r^2\sin(\theta)} + \frac{\cos(\theta)\cos(\phi)\sin(\phi)}{r^2\sin(\theta)} \right] = 0$$

$$\frac{\partial^2}{\partial r\partial\phi} \left[-\frac{\cos(\phi)\sin(\phi)}{r^2} - \frac{\cos(\phi)\sin(\phi)}{r^2} + \frac{\cos(\phi)\sin(\phi)}{r^2} + \frac{\cos(\phi)\sin(\phi)}{r^2} \right] = 0$$

$$\frac{\partial}{\partial\phi} \left[\frac{\cos(\phi)\sin(\phi)}{r^2} + \frac{\cos^2(\theta)\cos(\phi)\sin(\phi)}{r^2\sin^2(\theta)} - \frac{\cos(\phi)\sin(\phi)}{r^2} + \frac{\sin(\phi)\cos(\phi)}{r^2\sin^2(\theta)} - \frac{\cos^2(\theta)\cos(\phi)\sin(\phi)}{r^2\sin^2(\theta)} - \frac{\sin(\phi)\cos(\phi)}{r^2\sin^2(\theta)} \right] = 0$$

The second partial derivative with respect with ϕ is shown below:

$$\frac{\partial^2}{\partial\phi^2} \left[\frac{\sin^2(\phi)}{r^2\sin^2(\theta)} + \frac{\cos^2(\phi)}{r^2\sin^2(\theta)} \right] = \frac{\partial^2}{\partial\phi^2} \left[\frac{1}{r^2\sin^2(\theta)} \right]$$

The expression for the partial derivative with respect with r is:

$$\frac{\partial}{\partial r} \left[\frac{\sin^2(\theta)}{r} + \frac{\cos^2(\theta)\cos^2(\phi)}{r} + \frac{\sin^2(\phi)}{r} + \frac{\cos^2(\theta)\sin^2(\phi)}{r} + \frac{\cos^2(\phi)}{r} \right]$$

$$= \frac{\partial}{\partial r} \left[\frac{1}{r}(\sin^2(\phi) + \cos^2(\phi)) + \frac{1}{r}\left(\cos^2(\theta)\sin^2(\phi) + \sin^2(\theta) + \cos^2(\theta)\cos^2(\phi)\right) \right]$$

$$= \frac{\partial}{\partial r} \left[\frac{1}{r} + \frac{1}{r} \cos^2(\theta) \left(\sin^2(\phi) + \cos^2(\phi) \right) + \frac{1}{r} \sin^2(\theta) \right] = \frac{\partial}{\partial r} \left(\frac{1}{r} + \frac{1}{r} \right) = \frac{2}{r} \frac{\partial}{\partial r}$$

The second partial derivative with respect with θ has the expression:

$$\frac{\partial^2}{\partial \theta^2} \left[\frac{\sin^2(\theta)}{r^2} + \frac{\cos^2(\theta) \cos^2(\phi)}{r^2} + \frac{\cos^2(\theta) \sin^2(\theta)}{r^2} \right] = \frac{1}{r^2} \left[\sin^2(\theta + \cos^2(\theta) \left(\cos^2(\phi) + \sin^2(\phi) \right) \right] \frac{\partial^2}{\partial \theta^2} = \frac{1}{r^2} \frac{\partial^2}{\partial \theta^2},$$

while the second partial derivative with respect with r is

$$\frac{\partial^2}{\partial r^2} \left[\cos^2(\theta) + \sin^2(\theta) \cos^2(\phi) + \sin^2(\theta) \sin^2(\phi) \right]$$

$$= \frac{\partial^2}{\partial r^2} \left[\cos^2(\theta) + \sin^2(\theta) \left(\cos^2(\phi) + \sin^2(\phi) \right) \right] = \frac{\partial^2}{\partial r^2}$$

The expression for the partial derivative with respect to θ is a bit more lengthy:

$$\frac{\partial}{\partial \theta} \left[\frac{\sin(\theta) \cos(\theta)}{r^2} + \frac{\sin(\theta) \cos(\theta)}{r^2} - \frac{\sin(\theta) \cos(\theta) \cos^2(\phi)}{r^2} + \frac{\sin^2(\phi) \cos(\theta)}{r^2 \sin(\theta)} - \frac{\sin(\theta) \cos(\theta) \sin^2(\phi)}{r^2} \right]$$

$$+ \frac{\partial}{\partial \theta} \left[-\frac{\cos(\theta) \sin(\theta) \sin^2(\phi)}{r^2} + \frac{\cos^2(\phi) \cos(\theta)}{r^2 \sin(\theta)} - \frac{\cos(\theta) \sin(\theta) \cos^2(\phi)}{r^2} \right]$$

$$= \frac{\partial}{\partial \theta} \frac{1}{r^2} \left[2 \sin(\theta) \cos(\theta) + \frac{\sin^2(\phi) \cos(\theta) + \cos^2(\phi) \cos(\theta)}{\sin(\theta)} - \sin(\theta) \cos(\theta) \left(\cos^2(\phi) + \sin^2(\phi) \right) \right]$$

$$+ \frac{\partial}{\partial \theta} \frac{1}{r^2} \left[-\cos(\theta) \sin(\theta) \left(\sin^2(\phi) + \cos^2(\phi) \right) \right] = \frac{\partial}{\partial \theta} \frac{1}{r^2} \left(\frac{\cos(\theta)}{\sin(\theta)} \right)$$

Then, the final expressions for $\frac{\partial^2}{\partial x^2}$, $\frac{\partial^2}{\partial y^2}$ and $\frac{\partial^2}{\partial z^2}$ have been greatly simplified, and by adding them together the scalar Laplacian in spherical coordinates is the result:

$$\nabla^2 = \frac{1}{r^2 \sin^2(\theta)} \frac{\partial^2}{\partial \phi^2} + \frac{2}{r} \frac{\partial}{\partial r} + \frac{1}{r^2} \frac{\partial^2}{\partial \theta^2} + \frac{\partial^2}{\partial r^2} + \frac{\cos(\theta)}{r^2 \sin(\theta)}$$

$$= \left(\frac{2}{r} + \frac{\partial}{\partial r} \right) \frac{\partial}{\partial r} + \left(\frac{\cos(\theta)}{r^2 \sin(\theta)} + \frac{1}{r^2} \frac{\partial}{\partial \theta} \right) \frac{\partial}{\partial \theta} + \frac{1}{r^2 \sin^2(\theta)} \frac{\partial^2}{\partial \phi^2}$$

which can be rewritten as follows to give the expression for the Laplacian operator in spherical coordinates:

$$\nabla^2 = \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial}{\partial r} \right) + \frac{1}{r^2 \sin(\theta)} \frac{\partial}{\partial \theta} \left(\sin(\theta) \frac{\partial}{\partial \theta} \right) + \frac{1}{r^2 \sin^2(\theta)} \frac{\partial^2}{\partial \phi^2}$$

Since both the polar angle and the azimuthal angle is neglected in the case which are studied in this thesis, the Laplacian operator for a scalar can be further simplified to :

$$\nabla^2 = \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial}{\partial r} \right)$$

This gives the expression for $\nabla^2 u$:

$$\nabla^2 u = \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial u}{\partial r} \right)$$

which can be inserted into the expression for the vector Laplacian to give the following when both the polar and azimuthal angles are neglected, where $\nabla^2(\boldsymbol{u})$ is the vector Laplacian and $\nabla^2 u$ is the scalar Laplacian:

$$\nabla^2(\boldsymbol{u}) = \frac{1}{r^2} \frac{\partial}{\partial r} \left(r^2 \frac{\partial u}{\partial r} \right) - \frac{2u}{r^2} = \nabla^2 u - \frac{2u}{r^2}$$

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H Expressions for the measured values of gel compressibility and bulk viscosity

The compressibility β and bulk viscosity κ of the gel can be determined from experiments when there are no cells present in the gel. The experiments use a known radial stress on the gel, and the expressions for the gel compressibility and bulk viscosity using this method is derived below. The radial stress is exerted on the sphere-surface of the cell-free gel. During the experiments, there are no cells present in the gel (n is zero), and no cell-exerted forces causes F_r to be zero as well. The chemicals are produced by the cells, but since there are no cells present, it follows that there will be no chemicals either, so $c = 0$. (Green et al., 2013) Since the forces are imposed on the gel sphere surface, the right side of equation

$$-P + 2\frac{\partial u}{\partial r} + \left(\kappa - \frac{2}{3}\right)\frac{1}{r^2}\frac{\partial}{\partial r}(r^2 u) = 0, \qquad \text{at} \qquad r = R(t).$$

is no longer zero, but equal to the externally exerted forces, and hence:

$$-P + 2\frac{\partial u}{\partial r} + \left(\kappa - \frac{2}{3}\right)\frac{1}{r^2}\frac{\partial}{\partial r}(r^2 u) = \sum(t), \quad \text{at} \quad r=R(t).$$

The form of the desired solution is:

$$\rho = \rho(t), \qquad P = P(t), \qquad u = A(t)r,$$

The expression for ρ can be derived using the spherical equation for mass balance of the gel:

$$\frac{\partial \rho(t)}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 \rho(t) A(t) r\right) = 0,$$

which is the same as writing

$$\frac{\partial \rho(t)}{\partial t} + \frac{1}{r^2}\rho(t)A(t)\frac{\partial}{\partial r}r^3 = 0.$$

By calculating the derivative of the second term in the expression above, the expression above becomes

$$\frac{1}{\rho(t)}\frac{\partial \rho(t)}{\partial t} = -3A(t)$$

Integrating with respect to t on both sides of the equation above gives the expression

$$ln|\rho| = -3A(t)t + c_1,$$

which is the same as writing:

$$\rho = e^{-3A(t)t+c_1} = e^{-3B(t)},$$

where $B(t) = A(t)t - \frac{1}{3}c_1 = A(t)t + c_2$. The expression for the pressure can then be found from from the equation describing the relationship between the gel density and pressure:

$$\rho = 1 + \beta P$$

$$P = \frac{\rho - 1}{\beta} = \frac{e^{-3B(t)} - 1}{\beta}$$

In order to simplify the expression for pressure, $e^{-B(t)}$ is given the symbol $\frac{1}{R(t)}$. The expression for pressure and velocity is then substituted into the equation for the boundary condition for the stresses:

$$-P + 2\frac{\partial u}{\partial r} + \left(\kappa - \frac{2}{3}\right)\frac{1}{r^2}\frac{\partial}{\partial r}(r^2 u) = \sum(t), \quad \text{at} \quad r=R(t).$$

By inserting for P and using that $u = A(t)r$ gives:

$$-\frac{R^3-1}{\beta} + 2\frac{\partial(A(t)r)}{\partial r} + \left(\kappa - \frac{2}{3}\right)\left(\frac{1}{r}\frac{\partial}{\partial r}\left(r^2A(t)r\right)\right) = \sum(t)$$

By calculating the derivatives in the expression above, the resulting expression is:

$$-\frac{R^3-1}{\beta} + \left(\kappa - \frac{2}{3}\right)\left(3r^2A(t)\right) + 2A(t) = \sum(t)$$

Then, by multiplying with $\frac{R}{3\kappa}$, the equation becomes:

$$\left(\frac{1-\sum\beta}{3\beta\kappa}\right)R(t) - \frac{1}{3R^2(t)\beta\kappa} + A(t)R(t) - \frac{2}{3}R(t)A(t) + \frac{2}{3}R(t)A(t) = 0$$

which is equivalent to writing

$$\left(\frac{1-\sum\beta}{3\beta\kappa}\right)R(t) - \frac{1}{3R^2(t)\beta\kappa} + A(t)R(t) = 0.$$

$A(t)R(t)$ can be rewritten as:

$$A(t)R(t) = A(t)e^{B(t)} = A(t)e^{A(t)t+c_1} = \frac{d(e^{A(t)t+c_1})}{dt} = \frac{dR(t)}{dt}$$

This is then inserted for $A(t)R(t)$ in the stress boundary condition:

$$\frac{dR(t)}{dt} + \left(\frac{1-\beta\sum(t)}{3\kappa\beta}\right)R(t) - \frac{1}{3\kappa\beta R^2(t)} = 0$$

The expression for R is then to be derived. In order to simplify the derivation, $\frac{1}{3\kappa\beta}$ is given the symbol a, while $\frac{1-\beta\sum(t)}{3\kappa\beta}$ is given the symbol b:

$$\frac{dR}{dt} - \frac{a}{R^2} + bR = 0,$$

which can be factorized as

$$\frac{dR}{dt} + \frac{1}{R^2}(bR^3 - a) = 0.$$

Multiplying the above equation with R^2 and dt, while dividing with $(bR^3 - a)$ gives:

$$\frac{R^2dR}{bR^3 - a} = -dt$$

By multiplying the above equation with -1 avoids the negative sign to the right of the equality sign:

$$\frac{R^2dR}{a - bR^3} = dt$$

Then, by using u-substitution in order to easier solve the differential equation above:

$$u = a - bR^3 \quad \text{which means that} \quad \frac{du}{dR} = -3bR^3.$$

The expression for du is then inserted into the differential equation to give:

$$-\frac{1}{3b}\left(\frac{du}{u}\right) = dt \quad \text{which can be rearranged as} - \frac{du}{u} = 3bdt.$$

This expression is then integrated as follows:

$$-\int \frac{du}{u} = 3b \int dt,$$

which gives

$$ln|u| = -3bt + c_1.$$

The equation is then solved with respect to u to give:

$$u = e^{-3bt} \cdot e^{c_1}$$

Substituting back for u gives:

$$a - bR^3 = e^{-3bt} \cdot e^{c_1}$$

Then, substituting back for a and b:

$$\frac{1}{3\kappa\beta} - \left(\frac{1 - \beta\sum(t)}{3\kappa\beta}\right) R^3 = e^{-3\left(\frac{1 - \beta\sum(t)}{3\kappa\beta}\right)t} e^{c_1}$$

By moving all of the above expression to the right side of the equation, except R^3 gives:

$$R^3 = \left(\frac{3\kappa\beta}{1 - \beta\sum(t)}\right) \left(\frac{1}{3\kappa\beta} - e^{\left(\frac{\beta\sum(t)-1}{\kappa\beta}\right)t} e^{c_1}\right)$$

Rearranging the equation above, and using that the constant e^{c_1} is the same as writing c_2 gives:

$$R^3 = \frac{1}{1 - \beta\sum(t)} \left(1 - 3\kappa\beta e^{\left(\frac{\beta\sum(t)-1}{\kappa\beta}\right)t} \cdot c_2\right)$$

Then, using the boundary condition $R(0) = 1$ gives the following expression for the constant c_2:

$$R(0) = \left[\frac{1}{1 - \beta\sum(t)} \left(1 - 3\kappa\beta e^0 \cdot c_2\right)\right]^{\frac{1}{3}} = 1,$$

which gives the expression for c_2 to be

$$c_2 = \frac{\sum(t)}{3\kappa}.$$

Then, inserting for c_2 in the expression for R:

$$R^3 = \frac{1 - e^{\frac{\left(\beta\sum(t)-1\right)t}{\kappa\beta}}}{1 - \beta\sum(t)}$$

Then, by knowing the value of the applied stress and measuring the change in radius $R(t)$ with time, both compressibility β and bulk viscosity κ can be calculated using the equations which will now be derived: In order to derive the expression for κ, time is set to approach zero, so that the initial rate of change of R becomes (using that $R(0) = 1$):

$$\frac{dR(0)}{dt} = \frac{\beta\sum(t)}{3\kappa\beta} + \frac{1}{3\kappa\beta} - \frac{1}{3\kappa\beta} = \frac{\beta\sum(t)}{3\kappa\beta} = \dot{R}$$

which then gives the expression for κ:

$$\kappa = \frac{\sum(t)}{\dot{R}(0)}$$

In order to derive the expression for β, it is assumed that $\beta\sum(t)$ is less than one. Then, using the expression for R^3 above when time goes to infinity:

$$R_{t\to\infty} = \left(\frac{1 - \beta \sum(t)e^{-\infty}}{1 - \beta \sum(t)}\right)^{\frac{1}{3}} = \left(1 - \beta \sum(t)\right)^{-\frac{1}{3}},$$

which gives the expression for the isothermal compressibility of the gel to be:

$$\beta = \frac{1 - R_{t\to\infty}^{-3}}{\sum(t)}$$

I Expressions for the second derivatives in the coordinates (ζ, τ)

$$\frac{\partial^2}{\partial x^2} = \left(\frac{\cos(\phi)\sin(\theta)}{R(t)}\frac{\partial}{\partial\zeta} + \frac{\cos(\theta)\cos(\phi)}{R(t)\zeta}\frac{\partial}{\partial\theta} - \frac{\sin(\phi)}{R(t)\zeta\sin(\theta)}\frac{\partial}{\partial\phi}\right)\left(\frac{\cos(\phi)\sin(\theta)}{R(t)}\frac{\partial}{\partial\zeta} + \frac{\cos(\theta)\cos(\phi)}{R(t)\zeta}\frac{\partial}{\partial\theta} - \frac{\sin(\phi)}{R(t)\zeta\sin(\theta)}\frac{\partial}{\partial\phi}\right)$$

$$= \left(\frac{\cos^2(\phi)\sin^2(\theta)}{R^2}\frac{\partial^2}{\partial\zeta^2} - \frac{\cos(\theta)\sin(\theta)\cos^2(\phi)}{R^2\zeta^2}\frac{\partial}{\partial\theta} + \frac{\sin(\theta)\cos(\theta)\cos^2(\phi)}{R\zeta}\frac{\partial^2}{\partial\zeta\partial\theta} + \frac{\cos(\phi)\sin(\phi)}{R^2\zeta^2}\frac{\partial}{\partial\phi} - \frac{\cos(\phi)\sin(\phi)}{R^2\zeta}\frac{\partial^2}{\partial\zeta\partial\phi}\right)$$

$$+ \left(\frac{\cos^2(\phi)\cos^2(\theta)}{R^2\zeta}\frac{\partial}{\partial\zeta} + \frac{\cos(\theta)\sin(\theta)\cos^2(\phi)}{R^2\zeta}\frac{\partial^2}{\partial\theta\partial\zeta} - \frac{\sin(\theta)\cos(\theta)\cos^2(\phi)}{R^2\zeta^2}\frac{\partial}{\partial\theta} + \frac{\cos^2(\phi)\cos^2(\theta)}{R^2\zeta^2}\frac{\partial^2}{\partial\theta^2}\right)$$

$$+ \left(\frac{\cos^2(\theta)\cos(\phi)\sin(\phi)}{R^2\zeta^2\sin^2(\theta)}\frac{\partial}{\partial\phi} - \frac{\cos(\theta)\cos(\phi)\sin(\phi)}{R^2\zeta^2\sin(\theta)}\frac{\partial^2}{\partial\theta\partial\phi}\right)$$

$$+ \left(\frac{\sin^2(\phi)}{R^2\zeta}\frac{\partial}{\partial\zeta} - \frac{\sin(\phi)\cos(\phi)}{R^2\zeta}\frac{\partial^2}{\partial\phi\partial\zeta} + \frac{\sin^2(\phi)\cos(\theta)}{R^2\zeta^2\sin(\theta)}\frac{\partial}{\partial\theta} - \frac{\sin(\phi)\cos(\phi)\cos(\theta)}{R^2\zeta^2\sin(\theta)}\frac{\partial^2}{\partial\phi\partial\theta} + \frac{\sin(\phi)\cos(\phi)}{R^2\zeta^2\sin^2(\theta)}\frac{\partial}{\partial\phi} + \frac{\sin^2(\phi)}{R^2\zeta^2\sin^2(\theta)}\frac{\partial^2}{\partial\theta^2}\right)$$

The second partial derivative with respect to y is:

$$\frac{\partial^2}{\partial y^2} = \left(\frac{\sin(\phi)\sin(\theta)}{R(t)}\frac{\partial}{\partial\zeta} + \frac{\cos(\theta)\sin(\phi)}{R(t)\zeta}\frac{\partial}{\partial\theta} + \frac{\cos(\phi)}{R(t)\zeta\sin(\theta)}\frac{\partial}{\partial\phi}\right)\left(\frac{\sin(\phi)\sin(\theta)}{R(t)}\frac{\partial}{\partial\zeta} + \frac{\cos(\theta)\sin(\phi)}{R(t)\zeta}\frac{\partial}{\partial\theta} + \frac{\cos(\phi)}{R(t)\zeta\sin(\theta)}\frac{\partial}{\partial\phi}\right)$$

$$= \left(\frac{\sin^2(\theta)\sin^2(\phi)}{R^2}\frac{\partial^2}{\partial\zeta^2} - \frac{\sin^2(\phi)\cos(\theta)\sin(\theta)}{R^2\zeta^2}\frac{\partial}{\partial\theta} + \frac{\sin^2(\phi)\cos(\theta)\sin(\theta)}{R^2\zeta}\frac{\partial^2}{\partial\zeta\partial\theta} - \frac{\sin(\phi)\cos(\phi)}{R^2\zeta^2}\frac{\partial}{\partial\phi} + \frac{\sin(\phi)\cos(\phi)}{R^2\zeta}\frac{\partial^2}{\partial\zeta\partial\phi}\right)$$

$$+ \left(\frac{\sin^2(\phi)\cos^2(\theta)}{R^2\zeta}\frac{\partial}{\partial\zeta} + \frac{\sin^2(\phi)\sin(\theta)\cos(\theta)}{R^2\zeta}\frac{\partial^2}{\partial\zeta\partial\theta} - \frac{\sin^2(\phi)\sin(\theta)\cos(\theta)}{R^2\zeta^2}\frac{\partial}{\partial\theta} + \frac{\sin^2(\phi)\cos^2(\theta)}{R^2\zeta^2}\frac{\partial^2}{\partial\theta^2}\right)$$

$$+ \left(-\frac{\cos^2(\theta)\cos(\phi)\sin(\phi)}{R^2\zeta^2\sin^2(\theta)}\frac{\partial}{\partial\phi} + \frac{\cos(\theta)\sin(\phi)\cos(\phi)}{R^2\zeta^2\sin(\theta)}\frac{\partial^2}{\partial\theta\partial\phi}\right)$$

$$+ \left(\frac{\cos^2(\phi)}{R^2\zeta}\frac{\partial}{\partial\zeta} + \frac{\cos(\phi)\sin(\phi)}{R^2\zeta}\frac{\partial^2}{\partial\zeta\partial\phi} + \frac{\cos^2(\phi)\cos(\theta)}{R^2\zeta^2\sin(\theta)}\frac{\partial}{\partial\theta} + \frac{\cos(\phi)\sin(\phi)}{R^2\zeta^2\sin(\theta)}\frac{\partial^2}{\partial\phi\partial\theta} - \frac{\cos(\phi)\sin(\phi)}{R^2\zeta^2\sin^2(\theta)}\frac{\partial}{\partial\phi} + \frac{\cos^2(\phi)}{R^2\zeta^2\sin^2(\theta)}\frac{\partial^2}{\partial\phi^2}\right)$$

The expression for the second partial derivative with respect to z is:

$$\frac{\partial^2}{\partial z^2} = \left(\frac{\cos(\phi)}{R(t)} \frac{\partial}{\partial \zeta} - \frac{\sin(\phi)}{R(t)\zeta} \frac{\partial}{\partial \phi} \right) \left(\frac{\cos(\phi)}{R(t)} \frac{\partial}{\partial \zeta} - \frac{\sin(\phi)}{R(t)\zeta} \frac{\partial}{\partial \phi} \right)$$

$$= \left(\frac{\cos^2(\phi)}{R^2} \frac{\partial^2}{\partial \zeta^2} + \frac{\cos(\phi)\sin(\phi)}{R^2\zeta^2} \frac{\partial}{\partial \phi} - \frac{\cos(\phi)\sin(\phi)}{R^2\zeta} \frac{\partial^2}{\partial \zeta \partial \phi} + \frac{\sin^2(\theta)}{R^2\zeta} \frac{\partial}{\partial \zeta} - \frac{\sin(\phi)\cos(\phi)}{R^2\zeta} \frac{\partial^2}{\partial \phi \partial \zeta} \right)$$

$$+ \left(\frac{\sin(\phi)\cos(\phi)}{R^2\zeta^2} \frac{\partial}{\partial \phi} + \frac{\sin^2(\phi)}{R^2\zeta^2} \frac{\partial^2}{\partial \phi^2} \right)$$

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