A Phase Field Model for Stem Cell Differentiation

Gabriele Witterstein
Technische Universität München, Zentrum für Mathematik,
Boltzmannstr. 3, D - 85747 Garching bei München,
E-Mail: gw@ma.tum.de, Phone: +49-89 28916832, Fax:+49-89 28916809

SUMMARY

Our aim is to develop a two-dimensional model describing the dynamics of stem cell differentiation. Here we regard the differentiation process as phase change of the biological material. The resulting phase field model is coupled with the description of liquid flows representing the motility of cytoplasma. We show that in the process of phase change an additional stress force acts on the liquid particle. Under the assumption of this additional force we can demonstrate that for the process of chemical induced differentiation the second law of thermodynamics is fulfilled. The entropy inequality ensures, that the proposed model is consistent with the thermodynamics.

KEY WORDS:
Modeling biomaterials, Allen-Cahn equation, Compressible viscous fluids.

1. MOTIVATION

Stem cells are primal unspecialized cells. They retain the ability to differentiate into other cell types as response to appropriate signals from the adjacent environment. Here applies, different components of the extracellular environment can cause the development into various cell lineages. Together with the characteristic of self-renewal, stem cells act as repair system for the body, replenishing other cells as long as the organism is alive. Therefore, stem cells promise a renewable source of human tissue for research, pharmaceutical testing, and cell-based therapies. Here we want to restrict our investigations on a special class of somatic stem cells, extracted from the periodontium of wisdom teeth. That is the dental follicle of the tooth. Previous in-vivo and in-vitro experiments have shown, these cells are pluripotent and highly proliferative. To a purified extract of stem cells a mineralisation supplement is added in order to initiate a directed differentiation. Hereby, the mineralisation factors diffuse and trigger odontoblast-like cell differentiation.

Internally, the directed differentiation is the result from many successive cascades of signaling pathways. They include an immense number of small components, not all identified yet. But on the large scale it is seen, during the formation of odontoblasts, the cytoplasma produce two key components which are brought outside the cells. The first is Collagen Type I and the second Calcium-Hydroxylapatit crystals which are incorporated in the Collagen. The assembly and bonding of these two components sets up the new material
phase between the cells. In progressive time this material phase grows and solidifies. At the end, this process results in living bone material.

The left part of Figure 1 illustrates undifferentiated stem cells. After a differentiation process of 30 days it is seen on the right part of Figure 1 the straightened formation of bone nodules.

2. MODELING

We regard the gradual changeover from undifferentiated stem cells to living bone as a phase change in biological material. Hereby the cluster of stem cells will be considered as fluid, mostly come from the cytoplasma, with an averaged viscosity including the existence of cell membranes, nuclei etc. With progressive time, in this fluid will be incorporated solid elements. Further, we assume that the process is independent of the temperature $T$.

2.1. DYNAMICS OF MASS

Let $\Omega \subset \mathbb{R}^2$ a bounded domain with $C^2$-boundary. We assume that the cytoplasma phase arises with a mass density $\rho_1$ and the bone phase with the mass density $\rho_2$. Both, $\rho_1$ and $\rho_2$, works in a velocity field $v : (0,T) \times \Omega \to \mathbb{R}^2$. In this process, no new cytoplasma is generated, but a very small part is lost. This small part we neglect. Further, the mass of the bone phase, which doesn’t exist at the beginning, is produced out from the chemical reaction of the cytoplasma phase with the mineralisation supplement. $\rho_3$ denotes the mass density of the mineralisation supplement. Then the conservation law yields

$$\rho_1|_t + \text{div} (\rho_1 v) = -\kappa + \lambda \quad \text{and} \quad \rho_2|_t + \text{div} (\rho_2 v) = +\kappa. \quad (1)$$

Hereby, the term $\lambda = \lambda(\rho_1,\rho_3) > 0$ representing the additional mass production, is an arbitrary, non-negative function depending only on the cytoplasma concentration and the mineralisation supplement. The reaction term $\kappa$ arise how far the phase change develops.

It is further assumed that $\rho_3$ is not influenced from the given velocity field $v$. Then it holds following equation for $\rho_3$

$$\rho_3|_t + \text{div} (q_{\rho_3}) = -\lambda.$$

The flux $q_{\rho_3}$ has’nt to be specified. For example, it could be $q_{\rho_3} = -\nabla \rho_3$.

This setting is illustrated in Figure 2. Here, the petri dish forms a closed system. In this closed system the added mass of both, stem cells and mineralisation supplement, equals the mass of the outcoming bone material. That means, the total mass $\tilde{\rho} := \rho + \rho_3$ is conserved. It holds

$$\tilde{\rho}|_t + \text{div} (\rho v - q_{\rho_3}) = 0.$$

But in contrary, stem cells are living material, however the supplement isn’t it. We don’t regard the material alteration as a pure chemical reaction of two initial components, as it is common in anorganic material models. In this biological model, we only account the changing of the living material. Therefore, in this setting, we suppose that the mass density of the whole living material $\rho := \rho_1 + \rho_2$ is growing. That means, we have a mass production which is greater than zero.

$$\rho|_t + \text{div} (\rho v) = \lambda > 0. \quad (1*)$$

This is a appropriate modeling, because on the one hand the process exhausts the mineralisation supplement and on the other hand stem cells lost their capability to differentiate
which we can express by the choice of \( \lambda \).

### 2.2. EVOLUTION OF THE PHASE FRACTION

We define the fraction of the phases 1, 2 with

\[
\Phi := \Phi := \frac{\rho_1}{\rho} \quad \text{and} \quad \Phi := \frac{\rho_2}{\rho}.
\]

\( \Phi = \Phi_1 \) represents the cytoplasm phase, and \( \Phi_2 = (1 - \Phi) \) the bone material phase. \( \Phi_2 = 0 \) means that no bone phase exists. Then it valids \( \Phi_1 = 1 \). On each point we have cytoplasm. \( \Phi_1 = \Phi_2 = \frac{1}{2} \) indicates an intermediate state in the changeover. It holds \( \Phi_1 + \Phi_2 = 1 \).

Now, we determine the interrelation between the phase parameter \( \Phi \), the mass production \( \lambda \) and the reaction term \( \kappa \). With the equations (1), (1\( ^* \)) we calculate

\[
+ \kappa = (\Phi_2 \rho) + \text{div}(\Phi_2 \rho v) = \rho(\Phi_2 + \nabla \Phi_2 \cdot v) + \Phi_2(\rho + \text{div}(\rho v)) = \rho D_s \Phi_2 + \Phi_2 \lambda
\]
and

\[
- \kappa + \lambda = (\Phi_1 \rho) + \text{div}(\Phi_1 \rho v) = \rho(\Phi_1 + \nabla \Phi_1 \cdot v) + \Phi_1(\rho + \text{div}(\rho v)) = \rho D_s \Phi_1 + \Phi_1 \lambda.
\]

These two equations are equivalent. For \( \Phi \) it holds

\[
\rho D_s \Phi = - \kappa - (\Phi - 1) \lambda.
\]

Hereby denotes \( D_s \Phi := \Phi_t + \nabla \Phi \cdot v \) the substantial derivative in a non-inert system.

### 2.3. IMPULS CONSERVATION

In general, we assume that both material types, cytoplasm and bone, have a special motility. Now we develop the conservation of impuls under the condition that a part of the phase will become solid. From this solid phase acts a surface tension on each density particle. This special force have to be covered in the model if we apply Newtons law. We are mainly interested on the change of the biological material. We observe therefore the impuls conservation only for the open system consisting of \( \rho_1 \) and \( \rho_2 \). The existence of the layer \( \rho_3 \) could cause a certain dissipative term, but this may be neglected because we only treat the relativ velocity to the dish bottom and the ceiling forming out from the mineralisation supplement.

Then the conservation of impuls yields

\[
(\rho v)_t + \text{div} (\rho v \otimes v + \Pi) = f_e + \lambda v.
\]  

(2\( ^* \))

\( f_e \) is the external force acting on a test volume. Here, in a first step, we assume that no external force appears, i.e. \( f_e = 0 \). Due to the mass production, an impuls source \( \lambda v \) arises. Further, an additional force evokes by the change from liquid to solid and operates on the surface of a test volume. Therefore, it has to be incorporated a further summand in the flux-Term. We set

\[
g(\Phi) := \delta^2 \nabla \Phi \otimes \nabla \Phi.
\]

\( \Pi := (\Pi_{kl})_{k=1,2} := (\Pi_{kl})_{k,l=1,2} \), denotes the usual stress tensor containing the pressure und the viscosity coefficients. Then \( \Pi \) is given by

\[
\Pi = + p I - \tau + g(\Phi)
\]

and

\[
\tau(\rho) = \mu_1(\rho) \text{div} v I + \mu_2(\rho) (\frac{\partial}{\partial x_i} v_j + \frac{\partial}{\partial x_j} v_i)_{ij}.
\]
In this process, the temperature plays no role, but the compressibility of the fluids. The pressure \( p = p(\rho, T) \) is a given function depending in general on \( \rho \) and \( T \). Here \( p = \bar{p}(\rho) \) reflects a certain compressibility of the fluids.

Altogether, equation \((2\ast)\) describes the homogenized motility of the stems cells. At the beginning, both represents fluids and we regard the mean value about this fluids.

## 3. TOTAL FREE ENERGY OF THE SYSTEM

We introduce a free energy density \( f(t,x) \) without a kinetic term \( f_{\text{kin}} = \frac{1}{2}|v|^2 \rho \) for the open system with

\[
f = f(\rho, \Phi, \nabla \rho, \nabla \Phi) = f(\rho, \Phi, \nabla \Phi).
\]

The first tuple \((\rho, \Phi)\) is equivalent to the dependence of \((\rho_1, \rho_2)\).

Then the total free energy for a time point is

\[
\mathcal{E}(\rho, \Phi, \nabla \rho, \nabla \Phi)(t) \equiv \mathcal{E}(t) := \int_{\Omega} \left[ f(\rho(t,x), \Phi(t,x), \nabla \Phi(t,x)) \right] \, dx.
\]

Here, we make the ansatz

\[
f(\rho, \Phi, \nabla \Phi) := W_0(\Phi) + A(\Phi) + B(\rho, \Phi) + C(\nabla \Phi) + D(\rho).
\]

Hereby,

\[
D(\rho) := E \ln(1/\rho) - cp_1(T)\rho,
\]

where \( E := \sup_{x \in (0,1)} |\ln(x/2)(1-x)| + \sup_{x \in [0,1]} |(1-2x)(1-x)| > 0 \) is a constant.

### 3.1. COMPONENTS OF THE FREE ENERGY

**Phase separation.** \(W_0\) stands for the well-known logarithmic free energy function. \(W_0\) is choosed in such a manner that it potentially induce phase separation.

\[
W_0(\Phi) := c_1[\Phi \ln \Phi + (1-\Phi) \ln(1-\Phi)].
\]

Here, we concentrate on a two-phase version. Then, it constitutes a convex function, even \(\Phi \ln \Phi + (1-\Phi) \ln(1-\Phi)\), representing a mixing measure.

**Phase interaction.** We consider here the quadratic term

\[
A(\Phi) := c_2 \Phi (1-\Phi)
\]

standing for the interaction of the two phases, if no self interaction occurs. Here \(c_1 < c_2\) containing the absolute and critical temperature, respectively. Only on that positions where cytoplasma exist, bone material can be produced.

This both first terms are choosed in a way, so that \(W_0 + A\) has two distinct local minimas on the set \(\mathcal{G} := \{(\Phi_1, \Phi_2) \in \mathbb{R}^2 : \Phi_1 + \Phi_2 = 1, 0 \leq \Phi_i \leq 1\}\). In this setting, we obtain the classical obstacle potential, that is to minimize.

Because all, we can write this as

\[
W_0(w) + A(w) = c_1 \frac{1}{2}[(1 + w) \ln(\frac{1+w}{2}) + (1 - w) \ln(\frac{1-w}{2})] + c_2 \frac{1}{2}(1 - w^2)
\]

with \(w := \Phi_2 - \Phi_1\). \(W_0 + A\) has exact two distinct local minima, namely in the pure phases \(\Phi_1 = 0\) and \(\Phi_1 = 1\).
Chemical induction.  

\[ B(\rho, \Phi) = \Phi c_p(1) \rho + (1 - \Phi) c_p(2) \rho \]  

\( c_p(1) = c_p(2) = 0 \) the minima are situated in the pure phases, i.e. \( \Phi = 0 \) and \( \Phi = 1 \).

The only way to indicate which phase is preferred will be done by the last summand in equation (\( \ast \)). It characterizes the deviation from the thermodynamical equilibrium. \( c_p(1,2) \) stands for the chemical potentialities of the phases. \( c_p(1) \) denotes the possibility of phase 1 to transform in phase 2. And \( c_p(2) \) denotes the possibility of phase 2 to transform in phase 1. (\( \ast \)) is equivalent to

\[ B(\rho, w) = \frac{1}{2}(1 - w) c_p(1) \rho + \frac{1}{2}(1 + w) c_p(2) \rho. \]

In our case the direction of phase change promotes the transformation of cytoplasm to bone material. In the rigorous manner, we can set \( c_p(2) = 0 \) and \( c_p(1) > 0 \). If we set \( c_p(1) > 0 \), then phase 2 is preferred. In the time evolution most of the stem cells will differentiate.

Geometry. Here is incorporated the geometry of the considered domain. We regard the isotropic case. Therefore, we set

\[ C(\nabla \Phi) := \frac{\delta^2}{2} |\nabla \Phi|^2. \]

\( \delta \) determines the thickness of the transition layer between the pure phases.

3.2. DERIVATION OF THE GOVERNING EQUATION FOR THE PHASE CHANGE DYNAMICS

Now, we regard the dynamics of the phase parameter \( \Phi : (0, T) \times \Omega \to [0, 1] \) in the velocity field \( v \). First, we want to achieve the variational derivation of \( E \). We calculate

\[ \frac{\delta E}{\delta \Phi}(\psi) := \frac{d}{d\epsilon} E(\rho, \Phi + \epsilon \psi, \nabla \Phi + \epsilon \nabla \psi)_{\epsilon=0}. \]

Then, if \( \Phi + \epsilon \psi \in \mathcal{G} \)

\[ \begin{align*}
\frac{d}{d\epsilon} E(\rho, \Phi + \epsilon \psi, \nabla \Phi + \epsilon \nabla \psi)_{\epsilon=0} &= \left[ \int_{\Omega} \frac{d}{d\epsilon} f(\rho, \Phi + \epsilon \psi, \nabla \Phi + \epsilon \nabla \psi) \, dx \right]_{\epsilon=0} \\
&= \int_{\Omega} \left( f_{\Phi} \psi + f_{\nabla \Psi} \cdot \nabla \psi \right) \, dx \\
&= \int_{\Omega} \left[ f_{\Phi} - \text{div}(f_{\nabla \Psi}) \right] \, dx + \int_{\partial \Omega} f_{\nabla \Psi} \cdot \vec{n} \, \text{d} \sigma.
\end{align*} \]

Then, it holds

\[ \frac{\delta E}{\delta \Phi} = f_{\Phi} - \text{div}(f_{\nabla \Psi}). \]

With the definition of \( f \) we calculate

\[ \frac{\delta E}{\delta \Phi} = W_{\Phi} + A_{\Phi} + B_{\Phi} - \text{div}(C_{\nabla \Phi}) \]

\[ = c_1 \ln \left( \frac{\Phi}{1 - \Phi} \right) + c_2(1 - 2\Phi) + \left[ c_p(1)(T) - c_p(2)(T) \right] \rho - \delta^2 \Delta \Phi. \]

Now, we make following ansatz for the evolution of \( \Phi \):

\[ \kappa = \rho \frac{\delta E}{\delta \Phi}. \]
Then from equation (2) we have following evolution equation for $\Phi$:

$$ (\mathbf{\Phi}_t + \mathbf{v} \cdot \nabla \mathbf{\Phi}) = - W_0 |\mathbf{\Phi} - A| \mathbf{\Phi} - \frac{\lambda}{\rho}. \quad (3^*) $$

with

$$ W_0 |\mathbf{\Phi} = c_1 \ln \left( \frac{\Phi}{1 - \Phi} \right) \quad \text{and} \quad A |\mathbf{\Phi} = c_2 (1 - 2 \Phi). $$

The evolution is mainly forced by the free energy of the homogeneous problem. That means, the development of the phase parameter $\Phi$ in equation (3*) is caused by the minima of the $W_0 + A + B$ function and the definition of the mass production $\lambda$.

### 3.3 INTERNAL ENERGY CONSERVATION

Only for the sake of completeness, we give here the evolution equation for the internal energy. Such equation is only interesting in the case of a temperature changeable process. Here, in our process, the temperature plays no role, but the compressibility of the fluids.

For the total internal energy $e := \epsilon + e_{\text{kin}}$ in the open system with the energy production $|\mathbf{v}|^2 \lambda$ induced by the mass production $\lambda$, we have:

$$ e_t + \text{div}(e \mathbf{v} + \Pi^T \mathbf{v}) = |\mathbf{v}|^2 \lambda. \quad (4^*) $$

### 4. THERMODYNAMIC LAWS

Here we regard the whole system in the petri dish. That is a closed system.

We denote with $F$ the specific Helmholtz free energy, with $G$ the specific Gibbs free energy and with $S$ the specific entropy. In analogy, it is $f$ the Helmholtz free energy regarding above and holding $F = f / \rho$. $\eta = S / \rho$ stands for the entropy density. Further, $\theta$ stands for the absolute temperature and it holds $\theta = T$. $V = 1 / \rho$ denotes the specific volume.

**Lemma 1** It is valid

$$ G = f |\rho. $$

And equivalent to the Gibbs equality, the entropy and the pressure can be expressed by

$$ \rho f |\rho - f = p_f \quad \text{and} \quad - f |\theta = \eta. $$

**Proof.** It holds

$$ dF = \left( \frac{f(\rho, \theta)}{\rho} \right) d\rho + \left( \frac{f(\rho, \theta)}{\rho} \right) d\theta 
= \left( \frac{f |\rho}{\rho} - \frac{f}{\rho^2} \right) d\rho + \left( \frac{f |\theta}{\rho} \right) d\theta. \quad (4) $$

Further, $F = E - TS$. Then for the total differential it is valid

$$ dF = dE - TdS - SdT. $$

With the Gibbs equality $dE - TdS + p_f dV = 0$, it follows $dE - TdS = - p_f dV$. Then

$$ dF = - p_f dV - SdT
= - p_f \left( - \frac{1}{\rho^2} \right) d\rho - \frac{\eta}{\rho} d\theta. $$
As both by comparison we get
\[
\left( f \frac{\rho}{\rho} - f \right) d\rho + \left( \frac{f \theta}{\rho} \right) d\theta = p_f \int \frac{1}{\rho^2} d\rho - \frac{\eta}{\rho} d\theta.
\]
From that we get
\[
\rho f_{\rho} - f = p_f \quad \text{and} \quad - f_{\theta} = \eta.
\]
For the Gibbs free energy we have
\[
G = E - TS + p_f V = e - \theta \frac{\eta}{\rho} + \frac{p_f}{\rho} = \frac{1}{\rho} (f + p_f) = \frac{1}{\rho} \rho f_{\rho} = f_{\rho}.
\]

5. ENTROPY INEQUALITY

The equations, that we regard, are
\[
\begin{align*}
\rho_t + \text{div}(\rho v) &= \lambda > 0 \quad (1*) \\
(\rho v)_t + \text{div}(\rho v \otimes v + \Pi) &= v \lambda \quad (2*) \\
(\Phi_t + v \cdot \nabla \Phi) &= -W_{0\Phi} - A_{\Phi} - \left[ cp_1(T) - cp_2(T) \right] \rho + \delta^2 \Delta \Phi - \left( \Phi - 1 \right) \frac{\lambda}{\rho} \quad (3*) \\
e_t + \text{div}(ev + \Pi^T v) &= |v|^2 \lambda \quad (4*)
\end{align*}
\]
with the initial values \((\rho, \rho v, \Phi, e)(0) = (\rho_0, \rho_0 v_0, \Phi_0, e_0)\) and boundary values \(\Phi = C_\Phi\) on \(\partial \Omega\).

The first step of the mathematical analysis was to corroborate the usefulness of the proposed model. We show in our work that this model fulfills the first and second law of thermodynamics. This hints a certain correctness in a physical sense.

Assumptions.

1. Each of the two phases fulfills the first and second law of thermodynamics, especially the second law.

2. The flux of the total free energy \(q_f\) is equal the flux of the total internal energy \(q_e\). That means, \(q_f = q_e\).

3. The volume density at each point is constant. Here we choose 1. The specific volume is \(V = \frac{1}{\rho}\). Then we have \(\int_{\Omega} 1 dx = \int_{\Omega} \tilde{\rho} V dx = |\Omega|\).

4. The volume fraction for phase 1 is denoted by \(\chi_1\), for phase 2 and phase 3 by \(\chi_2\) and \(\chi_3\), respectively. Then \(\chi_1 + \chi_2 = 1 - \chi_3\).

5. Analogous, we define the specific volume fractions, \(V_i = \frac{\chi_i}{\tilde{\rho}_i}\). It is \(\rho_1 V_1 + \rho_2 V_2 + \rho_3 V_3 = 1\). Further
\[
\Phi_1 V_1 + \Phi_2 V_2 = V \tilde{\rho} \left( \frac{1}{\rho} \rho_3 V_3 \right) = \frac{1}{\rho} (1 - \rho_3 V_3).
\]

Let \(\eta_1(t, x)\) be the entropy density of phase 1, and \(\eta_2(t, x)\) the entropy density of phase 2. Then \(\eta(t, x) := \eta_1(t, x) + \eta_2(t, x)\) is the total entropy density. Further, the total entropy for the time point \(t\) is
\[
\eta(t) := \int_{\Omega} \eta_1(t, x) + \eta_2(t, x) dx.
\]
Theorem 2 It is $\lambda = A \rho$, where $A \in \mathbb{R}, A > 0$. Then the equations (1*)–(4*) fulfills the second law of thermodynamics.

In our situation we regard an open system. We have an extern energy inflow consisting in the mineralisation supplement. We have a no temperature, but a volume and pressure changeable process.

Proof. We have to show if for the whole domain the second law valid too. That means, it is to show

$$\eta_t + \text{div} (\eta \nu) \geq 0.$$  

We regard the specific entropy $S_1$ and $S_2$. Then $\eta_1 = \rho_1 S_1$ and $\eta_2 = \rho_2 S_2$. Then the total differential is

$$d\eta_i = d(\rho_i S_i) = S_i d\rho_i + \rho_i dS_i.$$  

(5)

The cytoplasm phase is subjected to be an irreversible process. Therefore, here holds the Gibbs inequality. The bone phase resides in the equilibrium state. Here holds the Gibbs equality. Then

$$dS_1 \geq \frac{1}{T} dE_1 + \frac{p_1}{T} dV_1 \quad \text{and} \quad dS_2 = \frac{1}{T} dE_2 + \frac{p_2}{T} dV_2.$$  

Here $E_1$ and $E_2$ denote the specific internal energies of the phases. $p_1, p_2$ is the physical pressure of the components. We assume and denote $p := p_1 \equiv p_2$.

Definition 3 The specific Helmholtz free energy $F_o$ of the open system is defined by

$$F_o := \Phi_1 F_1 + \Phi_2 F_2 = \Phi F_1 + (1 - \Phi) F_2,$$

where $F_1$ and $F_2$ the specific free energies, respectively. For the other values the setting is analog.

Then, from equation (5), with $\rho_i = \rho \Phi_i, e_i = \rho_i E_i$ and the chain rule we conclude

$$d\eta_i \geq S_i d\rho_i + \frac{\rho_i}{T} dE_i + \frac{\rho_i p}{T} dV_i$$

$$= \left( S_i - \frac{E_i}{T} \right) d\rho_i + \frac{1}{T} d(\rho_i E_i) + \frac{\rho_i p}{T} dV_i$$

$$= \frac{1}{T} F_i d\rho_i + \frac{1}{T} d e_i + \frac{\rho_i p}{T} dV_i$$

$$= \frac{1}{T} F_i d\rho_i + \frac{1}{T} d e_i + \frac{p}{T} d(\rho_i V_i) - \frac{p}{T} V_i d\rho_i$$

Then with $d\rho_i = d(\Phi_i \rho) = d(\Phi_i) \rho + \Phi_i d\rho$ observing that $d\Phi_1 = -d\Phi_2$. Further we have (see above) $\hat{\rho} V = \rho_1 V_1 + \rho_2 V_2 + \rho_3 V_3 \equiv \text{const}$. Then, we get

$$d\eta + \frac{1}{T} d\bar{\eta} = \sum_{i=1}^2 d\eta_i + \frac{1}{T} d\bar{\eta}$$

$$\geq - \frac{1}{T} \sum_{i=1}^2 F_i d\rho_i + \frac{1}{T} \sum_{i=1}^2 de_i + \frac{p}{T} d \left( \sum_{i=1}^3 \rho_i V_i \right) - \frac{p}{T} \sum_{i=1}^2 V_i d\rho_i - \frac{p}{T} V_3 d\rho_3$$

$$= - \frac{1}{T} \sum_{i=1}^2 \Phi_i F_i d\rho - \frac{\rho}{T} (F_1 - F_2) d\Phi + \frac{1}{T} d e - \frac{p}{T} \sum_{i=1}^2 \Phi_i V_i d\rho$$

(6)
where
\[ \eta(\Phi, \nabla \Phi) := W_0(\Phi) + A(\Phi) + \frac{\delta^2}{2} |\nabla \Phi|^2. \]

Lemma 4 For the internal energy we can the kinetic part neglect, that means \( \epsilon \) fulfills
\[ \epsilon_t + \text{div}(\epsilon v) + Dv \cdot (\Pi + g(\Phi)) \geq 0 \]

Proof. From \( e = \epsilon + \frac{\rho}{2} |v|^2 \) and the chain rule, we get
\[ \epsilon_t = \epsilon_t - v (\rho v)_t + \frac{1}{2} |v|^2 \rho_t \]

Then we use equation (1*), (2*) and (4*)
\[ \epsilon_t = \epsilon_t - v (\rho v)_t + \frac{1}{2} |v|^2 \rho_t \]

\[ = -\text{div}(\epsilon v + II^T v) + |v|^2 \lambda + v \text{div}(\rho v \otimes v + \Pi) - v \lambda v - \frac{1}{2} |v|^2 \text{div}(\rho v) + \frac{1}{2} |v|^2 \lambda \]

\[ = -\text{div}(\epsilon + \frac{1}{2} |v|^2 \rho) v + \sum_{i=1}^n v_i \Pi_v + \sum_{i=1}^n v_i \text{div}(\rho v_i v + \Pi_i) - \frac{1}{2} |v|^2 \text{div}(\rho v) + \frac{1}{2} |v|^2 \lambda \]

\[ = -\text{div}(\epsilon v) - Dv \cdot \Pi + \frac{1}{2} |v|^2 \lambda. \]

Notation: Here, \( Dv := (\nabla v_1, \ldots, \nabla v_n) \in \mathbb{R}^{n \times n} \). Hereby \( n = 2 \).

Because the internal energy for the chemical reaction does not depend on \( v \), we have for \( v = 0 \) that the total differential \( de \) is equal to \( de \). Now we consider the equation as a relation in phase space and compare the \( \frac{dv}{dt} \)-terms separately to the \( \frac{d\Phi}{dt} \)-terms. Then we get after a space integration with an arbitrary test volume \( \Omega \):

\[ \int_{\Omega} T \eta_t \geq \int_{\Omega} \left[ -F_o \rho - \rho (F_1 - F_2) \Phi_t + \epsilon_t - p \left( \sum_{i=1}^2 \Phi_i \rho_i - \rho (V_1 - V_2) \Phi_t \right) \right], \]

With Lemma 4 we get
\[ \int_{\Omega} \epsilon_t = \int_{\Omega} -\text{div}(\epsilon v) - \int_{\Omega} Dv \cdot \Pi + \int_{\Omega} \frac{1}{2} |v|^2 \lambda \]

\[ = \int_{\partial \Omega} -\epsilon v \cdot \nu d\sigma - \int_{\Omega} Dv \cdot \Pi + \int_{\Omega} \frac{1}{2} |v|^2 \lambda \]
Further with (1*)

\[ \int_{\Omega} -F_o \rho_t = \int_{\Omega} F_o [\text{div}(\rho v) - \lambda] \]
\[ = -\int_{\Omega} \nabla(F_o) \rho v d\Omega + \int_{\partial \Omega} F_o \rho v \tilde{n} d\sigma - \int_{\Omega} F_o \lambda dx \]

For \( F_i \) holds the Gibbs inequality, that is \( dE_i - T dS_i + pdV_i \leq 0 \). Then with \( dF_i = dE_i - T dS_i \), it holds \( dF_i \leq -pdV_i \). By separation we get \( -\nabla F_i \geq p\nabla V_i \).

\[ \int_{\Omega} -F_o \rho_t = -\int_{\Omega} \nabla \left( \sum_{i=1}^{2} \Phi_i F_i \right) \rho v d\Omega + \int_{\partial \Omega} F_o \rho v \tilde{n} d\sigma - \int_{\Omega} F_o \lambda dx \]
\[ \geq \int_{\Omega} p \sum_{i=1}^{2} \nabla V_i \Phi_i \rho v d\Omega - \int_{\Omega} \sum_{i=1}^{2} F_i \nabla \Phi_i \rho v d\Omega + \int_{\partial \Omega} F_o \rho v \tilde{n} d\sigma \]
\[ - \int_{\Omega} F_o \lambda dx. \]

Further

\[ -\int_{\Omega} p \left( \sum_{i=1}^{2} \Phi_i V_i \right) \rho_t = \int_{\Omega} p \left( \sum_{i=1}^{2} \Phi_i V_i \right) [\text{div}(\rho v) - \lambda] \]
\[ = -\int_{\Omega} \nabla \left( \sum_{i=1}^{2} \Phi_i V_i \right) \rho v + \int_{\partial \Omega} pV_o \rho v \tilde{n} d\sigma - \int_{\Omega} pV_o \lambda dx \]
\[ = -\int_{\Omega} \nabla pV_o \rho v - \int_{\partial \Omega} p \sum_{i=1}^{2} \nabla \Phi_i V_i \rho v - \int_{\Omega} p \sum_{i=1}^{2} \Phi_i \nabla V_i \rho v \]
\[ + \int_{\partial \Omega} pV_o \rho v \tilde{n} d\sigma - \int_{\Omega} pV_o \lambda dx. \]

Sum it up

\[ \int_{\Omega} \nabla pV_o \rho v - \int_{\partial \Omega} \sum_{i=1}^{2} \nabla \Phi_i (F_i + pV_i) \rho v \]
\[ + \int_{\partial \Omega} (F_o \rho + pV_o \rho) v \tilde{n} d\sigma - \int_{\Omega} (F_o + pV_o) \lambda. \]

Further

\[ \int_{\Omega} \nabla pV_o \rho v - \int_{\partial \Omega} \sum_{i=1}^{2} \nabla \Phi_i G_i \rho v - \int_{\Omega} G_o \lambda + \int_{\Omega} \frac{1}{2} |v|^2 \lambda. \]

We have

\( Dv \cdot \Pi = \text{div} p_f + Dv \cdot (-\tau + g(\Phi)). \)

From Lemma 1 we have

\[ p_f = \rho f_{\rho} - f = \rho (\tilde{\eta} + B(\rho, \Phi) + D(\rho)|_\rho - (\tilde{\eta} + B(\rho, \Phi) + D(\rho)) \]
\[\begin{align*}
= \rho(B(\rho, \Phi) + D(\rho))|_\rho - (B(\rho, \Phi) + D(\rho)) - \tilde{\eta} \\
= p - \tilde{\eta}.
\end{align*}\]

Then it holds
\[
Dv \cdot \Pi = \text{div} p - \tilde{\eta} \text{div} v + Dv \cdot (-\tau + g(\Phi))
\]
and
\[
\text{div}(pv) = \nabla pv + p \text{div} v.
\]

From the definition, we have \(G_1 = F_1 + pV_1, \ G_2 = F_2 + pV_2\) and \(G_o = F_o + pV_o\). With Lemma 1 it is \(G_o = f|_\rho\). Further with \(F_o u - \epsilon = -T\eta\) and, because \(\Omega\) is a test domain situated in the open system, we have \(V_o u = 1\) over \(\Omega\). Then, we get
\[
\begin{align*}
\text{(1)} + \text{(5)} + \text{(4)} & \geq -\int_\Omega \text{div}(pv) - \int_\Omega Dv \cdot (-\tau + g(\Phi)) + \int_{\partial \Omega} (-T\eta - \tilde{\eta} + p)v \tilde{n} \, d\sigma \\
& \quad + \int_\Omega \tilde{\eta} \text{div} v - \int_\Omega \sum_{i=1}^2 \nabla \Phi_i G_i \cdot pv - \int_\Omega f|_\rho \lambda + \int_\Omega \frac{1}{2} |v|^2 \lambda \\
& = -\int_\Omega Dv \cdot (-\tau + g(\Phi)) - \int_{\partial \Omega} (T\eta + \tilde{\eta})v \tilde{n} \, d\sigma + \int_\Omega \tilde{\eta} \text{div} v \\
& \quad - \int_\Omega \sum_{i=1}^2 \nabla \Phi_i G_i \cdot pv - \int_\Omega f|_\rho \lambda + \int_\Omega \frac{1}{2} |v|^2 \lambda \\
& = -\int_\Omega Dv \cdot (-\tau + g(\Phi)) - \int_{\partial \Omega} (T\eta + \tilde{\eta})v \tilde{n} \, d\sigma + \int_\Omega \tilde{\eta} \text{div} v + \int_\Omega \frac{1}{2} |v|^2 \lambda \\
& \quad - \int_\Omega \rho(G_1 - G_2) \nabla \Phi \cdot v - \int_\Omega f|_\rho \lambda.
\end{align*}\]

Now, we regard \(\text{(2)} + \text{(5)}\)
\[
\begin{align*}
\text{(2)} + \text{(5)} & = -\int_\Omega \rho(F_1 - F_2) \Phi|_t - \int_\Omega \rho p(V_1 - V_2) \Phi|_t = -\int_\Omega \rho(G_1 - G_2) \Phi|_t.
\end{align*}\]

We have to treat \(\text{(7)} + \text{(8)}\)
\[
\begin{align*}
\text{(7)} + \text{(8)} & = -\int_\Omega \rho(G_1 - G_2)(\Phi|_t + \nabla \Phi \cdot v).
\end{align*}\]

After the setting above, it is on the domain \(\Omega\), \(G_o = f|_\rho = (c_1 - c_2)\Phi\) and \(f|_\rho = G_o|_\Phi = (\Phi_1 G_1 + \Phi_2 G_2)|_\Phi = G_1 - G_2\). Then
\[
G_1 - G_2 = c_1 - c_2.
\]

With equation (3*) we can write
\[
-\rho(G_1 - G_2) = D_\phi \Phi + W_0|_\Phi + A_\phi \Phi - \delta^2 \Delta \Phi - (1 - \Phi)^\lambda |_\rho.
\]

Then
\[
\begin{align*}
\text{(7)} + \text{(8)} & = \int_\Omega \left( (\Phi|_t + \nabla \Phi \cdot v) + W_0|_\Phi + A_\phi \Phi - \delta^2 \Delta \Phi - (1 - \Phi)^\lambda |_\rho \right)(\Phi|_t + \nabla \Phi \cdot v)
\end{align*}\]
Here we set
\[
\int_\Omega (D, \Phi)^2 + \int_\Omega \left( W_{0|\Phi} + A_{|\Phi} - \frac{\delta^2}{2} \Delta \Phi \right) \left( \Phi_{\mu} + \nabla \Phi \cdot v \right) - \int_\Omega (1 - \Phi) \frac{\lambda}{\rho} D_s \Phi.
\]

Regard on the one hand
\[
\nabla (W_0 + A + \frac{\delta^2}{2} |\nabla \Phi|^2) \cdot v = (W_{0|\Phi} + A_{|\Phi}) \nabla \Phi \cdot v + \left( \frac{\delta^2}{2} \nabla^2 \Phi \nabla \Phi \right) \cdot v,
\]
here denotes \( \nabla^2 \Phi \) the Hesse matrix of \( \Phi \). Further with the Gauss Theorem it follows
\[
\int_\Omega \delta^2 \nabla^2 \Phi \nabla \cdot v dx = \int_{\partial \Omega} \delta^2 \nabla \Phi \cdot (\nabla \Phi \cdot v) d\sigma - \int_\Omega \delta^2 \nabla \Phi \cdot \nabla \Phi dx
\]
\[
= \int_{\partial \Omega} \delta^2 \nabla \Phi \cdot v \nabla \Phi \cdot d\sigma
\]
\[
- \int_\Omega \delta^2 \nabla \Phi \cdot \nabla \Phi dx - \int_\Omega \delta^2 \nabla \Phi \cdot \nabla \Phi \nabla \Phi d\sigma.
\]

From that, we can directly conclude
\[
\int_\Omega \left( W_{0|\Phi} + A_{|\Phi} - \frac{\delta^2}{2} \Delta \Phi \right) \nabla \Phi \cdot v = \int_\Omega \nabla (W_0 + A + \frac{\delta^2}{2} |\nabla \Phi|^2 \cdot v) + \int_\Omega \delta^2 \nabla \Phi \nabla \Phi \nabla \Phi \nabla \Phi d\sigma
\]
\[
- \int_\Omega \delta^2 \nabla \Phi \cdot \nabla \Phi \nabla \Phi d\sigma.
\]

Here we set
\[
g(\Phi) := \delta^2 \nabla \Phi \nabla \Phi.
\]

Regard on the other hand
\[
(W_0 + A + \frac{\delta^2}{2} |\nabla \Phi|^2)_{|\mu} = (W_{0|\Phi} + A_{|\Phi}) \Phi_{\mu} + \frac{\delta^2}{2} \nabla \Phi \nabla \Phi_{|\mu}
\]
and
\[
\int_\Omega \delta^2 \nabla \Phi \nabla \Phi_{|\mu} d\sigma = \int_{\partial \Omega} \delta^2 \nabla \Phi \Phi_{|\mu} \cdot \tilde{n} d\sigma - \int_\Omega \delta^2 \nabla \Phi \Phi_{|\mu} d\sigma.
\]

From the last two equations follow
\[
\int_\Omega \left( W_{0|\Phi} + A_{|\Phi} - \frac{\delta^2}{2} \Delta \Phi \right) \Phi_{|\mu} = \int_\Omega (W_0 + A + \frac{\delta^2}{2} |\nabla \Phi|^2)_{|\mu} - \int_\Omega \delta^2 \nabla \Phi \Phi_{|\mu} \cdot \tilde{n} d\sigma.
\]

With this, the 3-term can be transformed to
\[
\int_\Omega \left[ \nabla \Phi + \nabla \Phi \cdot v \right] + \int_\Omega \delta^2 \nabla \Phi \nabla \Phi \nabla \Phi \nabla \Phi d\sigma - \int_\Omega \delta^2 \nabla \Phi \Phi_{|\mu} \cdot \tilde{n} d\sigma.
\]

Using \( \Theta = -p(\rho_3 V_3) \geq 0 \) in equation (8), we can altogether infer
\[
\int_\Omega T_{\eta_{|\mu}} \geq + \int_\Omega D_v \cdot T - \int_\Omega (T_{\eta} + \tilde{\eta}) \nabla \Phi \nabla \Phi \cdot d\sigma + \int_\Omega \tilde{\eta} \nabla \Phi \cdot d\sigma + \int_\Omega \left[ \nabla \Phi + \nabla \Phi \cdot v \right] + \int_\Omega \left( D_s \Phi \right)^2 + \int_\Omega \frac{1}{2} |v|^2 \lambda - \int_\Omega f_{|\beta} \lambda - \int_\Omega \left( 1 - \Phi \right) \frac{\lambda}{\rho} D_s \Phi.
\]
\[ \int_{\Omega} T(\eta_t + \text{div}(\eta v)) \geq + \int_{\Omega} Dv \cdot \tau + \int_{\Omega} (D_\Phi)^2 - \int_{\Omega} f_{\rho} \lambda - \int_{\Omega} (1 - \Phi) \frac{\lambda}{\rho} D_\Phi. \]

Because
\[ (D_\Phi)^2 - (1 - \Phi) \frac{\lambda}{\rho} D_\Phi = \left( - \frac{\delta E}{\delta \Phi} \right)^2 - \frac{\delta E}{\delta \Phi} (1 - \Phi) \frac{\lambda}{\rho}, \]
we have
\[ \int_{\Omega} T(\eta_t + \text{div}(\eta v)) \geq + \int_{\Omega} Dv \cdot \tau - \int_{\Omega} f_{\rho} \lambda - \int_{\Omega} \frac{\delta E}{\delta \Phi} (1 - \Phi) \frac{\lambda}{\rho}. \] (9)

Finally, it is to show, that the last two summands on the right-hand side are greater than zero. Here, at the end of the proof, we exploit the setting \( \lambda = A\rho \). First, it is
\[ - \int_{\Omega} \frac{\delta E}{\delta \Phi} (1 - \Phi) \frac{\lambda}{\rho} = - c_1 A \int_{\Omega} \ln \left( \frac{\Phi}{1 - \Phi} \right) (1 - \Phi) - c_2 A \int_{\Omega} (1 - 2\Phi)(1 - \Phi) \]
\[ - A \int_{\Omega} \left[ cp_1(T) - cp_2(T) \right] \rho(1 - \Phi) + \delta^2 A \int_{\Omega} \Delta \Phi(1 - \Phi). \] (10)

The last summand is positiv
\[ \delta^2 A \int_{\Omega} \Delta \Phi(1 - \Phi) = - \delta^2 A \int_{\Omega} \text{div} \nabla (\Phi - 1)(\Phi - 1) \]
\[ = - \delta^2 A \int_{\Omega} \nabla \Phi \cdot \nabla (\Phi - 1) + \int_{\Omega} \frac{\partial E}{\partial \rho} \nabla (\Phi - 1)^2 \geq 0, \]
with the parabolic maximum principle it follows \( 0 \leq \Phi \leq 1 \). Then
\[ - c_2 A \int_{\Omega} (1 - 2\Phi)(1 - \Phi) \geq - c_2 AC |\Omega| \]
and
\[ - c_1 A \int_{\Omega} \ln \left( \frac{\Phi}{1 - \Phi} \right) (1 - \Phi) \geq - c_1 AC |\Omega|, \]
where \( C \) is a positiv, generic constant. We add the estimation of equation (10) with
\[ - \int_{\Omega} f_{\rho} \lambda \]
and obtain:
\[ - \int_{\Omega} f_{\rho} \lambda - \int_{\Omega} \frac{\delta E}{\delta \Phi} (1 - \Phi) \frac{\lambda}{\rho} \geq - \int_{\Omega} \left[ cp_1(T)\Phi + cp_2(T)(1 - \Phi) - E \frac{1}{\rho} - cp_1(T) \right] A\rho \]
\[ - AC |\Omega| - A \int_{\Omega} \left[ cp_1(T) - cp_2(T) \right] \rho(1 - \Phi) \]
\[ = - AC |\Omega| + AE |\Omega| \geq 0, \]
because \( E \) is in such a manner defined.

From the standard theory \( Dv \cdot \tau \geq 0 \) is valid. Then, we can inequality (9) further estimate
\[ \int_{\Omega} T(\eta_t + \text{div}(\eta v)) \geq 0. \]
\[ \square \]
References


Figures

Figure 1: Stem cell differentiation process

Figure 2: Closed and open system