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Abstract

We investigate stability of the solution of the equations proposed in [Moreo, 2008], which model peri-implant osseointegration process. For certain parameter values, the solution has a 'wave-like' profile, which appears in the distribution of osteogenic cells, osteoblasts, growth factor and bone matrix. That is in contradiction with experimental observations.

In our study we investigate the conditions, under which such profile appears in the solution. Those conditions are determined in terms of model parameters, by means of linear stability analysis, carried out at one of the homogeneous steady-state solutions of the simplified system. The analysis is validated with finite element simulations. The simulations show, that stability of the homogeneous steady-state could determine the behavior of the solution of the whole system, when certain initial conditions are considered.

1 Introduction

A number of models were proposed so far for the process of bone formation. It is reported by many researchers, that mechanical stimulation is an important factor, which influences bone formation. For example, [Vandamme et al., 2007a–d] investigated peri-implant bone ingrowth under well controlled mechanical loading of the interface tissue, and reported that relative implant-interface tissue micromotions qualitatively and quantitatively altered the osseointegration process. The mechanoregulatory models for bone formation were defined, for instance, in [Andreykiv, 2006], [Carter et al., 1998], [Claes and Hiegele, 1999], [Doblaré et al. (2005)], [Prendergast et al., 1997].

Another biological model for peri-implant osseointegration was proposed in [Moreo, 2008]. It allows to simulate osseointegration under low-medium loading regime taking into account implant surface microtopography. The author did not introduce explicitly the dependence of cell and tissue processes on mechanical stimulus, and outlined the incorporation of differentiation laws in terms of mechanical variables as one of the future lines of research. The results presented in [Moreo, 2008] were in agreement with experiments. They predicted that bone formation can occur through contact osteogenesis and distance osteogenesis.

Though, we found that the system of equations, proposed in [Moreo, 2008], is characterized by appearance of a 'wave-like' profile in the solution for a certain range of parameters. That feature has not been noticed before, since for the geometry and parameter values used in the simulations, a 'wave-like' profile does not become apparent. Though its presence is obvious, if a larger domain is considered. That could be observed in Figure 1, where several plots of the numerical solutions of the model equations, obtained for various 1D domains in axisymmetric coordinates, are shown.

The conditions, under which a 'wave-like' profile appears, are studied. Such a 'wave-like' profile in the solution for cell densities and growth factor concentrations is not realistic. In some cases it also leads to a 'wave-like' distribution of bone matrix inside the peri-implant region. That is in contradiction with experimental observations, which evidence that bone forms by deposition on

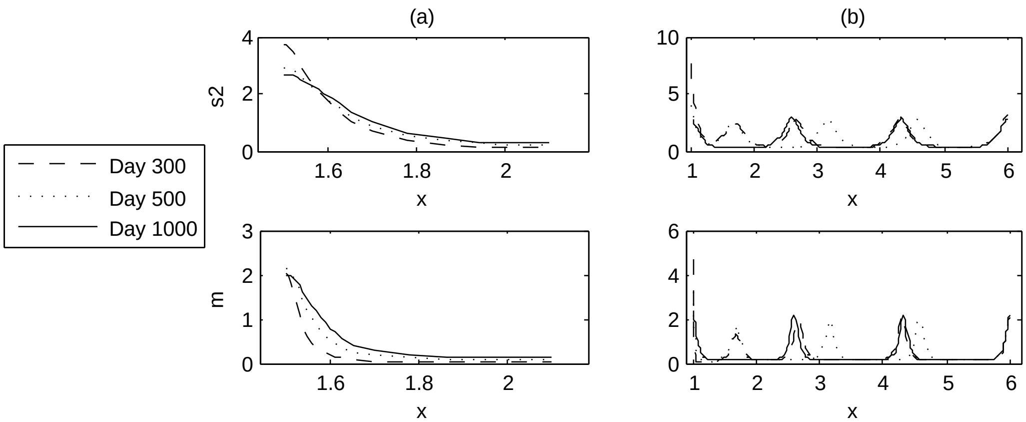


Figure 1: Osteogenic cell m and growth factor 2 s_2 distributions at different time moments, obtained for domain length (a) $L = 0.6\,mm$, (b) $L = 5\,mm$.

the preexisting bone matrix, and no isolated bone regions appear. Thus, it is desirable to avoid such a profile in the solution of the original model by [Moreo, 2008], and to take in account the stability properties of the system of equations when introducing mechanical variables in it.

The proposed approach is to study the linear stability of homogeneous steady-states of the system. As the full system of equations is large and extremely complicated for analytic derivations, an equivalent simplified system with similar properties will be defined.

The phenomenon of a 'wave-like' profile in the solution could be related to the appearance of bacterial patterns in liquid medium, described mathematically by similar partial differential equations. Those pattern analysis could be found in [Myerscough and Murray, 1992], [Tyson, 1999], [Miyata, 2006].

In section 2 the system of equations proposed in [Moreo, 2008] is reviewed. The linear stability analysis of the system is carried out in section 3. In section 4 analysis is validated with a sequence of numerical simulations. Finally, in section 5 some conclusions are drawn.

2 Biological model

The original model proposed in [Moreo, 2008] consists of the eight equations, defined for eight variables, representing densities of platelets c, osteogenic cells m, osteoblasts b, concentrations of two generic growth factor types s_1 and s_2, and volume fractions of fibrin network v_{fn}, woven bone v_w, and lamellar bone v_l. The above notations are introduced for non-dimensional cell densities and growth factor concentrations, i.e. for those, related to some characteristic values. If $\hat{f}$ and f_c are notations of a dimensional variable and of its characteristic value, then a non-dimensional variable f is defined as $f = \hat{f}/f_c$, $f = c, m, b, s_1, s_2$. The following characteristic values are proposed: $c_c = 10^8\ platelets/ml$, $m_c = 10^6\ cells/ml$, $b_c = 10^6\ cells/ml$, $s_{1_c} = 100\ ng/ml$, $s_{2_c} = 100\ ng/ml$. The model equations are:

$$\frac{\partial c}{\partial t} = \nabla \cdot [D_c \nabla c - H_c c \nabla p] - A_c c, \tag{2.1}$$

$$\begin{aligned}\frac{\partial m}{\partial t} =& \nabla \cdot [D_m \nabla m - m(B_{m1} \nabla s_1 + B_{m2} \nabla s_2)] + \\ &+ \Big(\alpha_{m0} + \frac{\alpha_m s_1}{\beta_m + s_1} + \frac{\alpha_m s_2}{\beta_m + s_2}\Big) m(1-m) - (\alpha_{p0} + \frac{\alpha_{mb} s_1}{\beta_{mb} + s_1}) m - A_m m,\end{aligned} \tag{2.2}$$

$$\frac{\partial b}{\partial t} = (\alpha_{p0} + \frac{\alpha_{mb} s_1}{\beta_{mb} + s_1}) m - A_b b, \tag{2.3}$$

$$\frac{\partial s_1}{\partial t} = \nabla \cdot [D_{s1} \nabla s_1] + \Big(\frac{\alpha_{c1} p}{\beta_{c1} + p} + \frac{\alpha_{c2} s_1}{\beta_{c2} + s_1}\Big) c - A_{s1} s_1, \tag{2.4}$$

$$\frac{\partial s_2}{\partial t} = \nabla \cdot [D_{s2} \nabla s_2] + \frac{\alpha_{m2} s_2}{\beta_{m2} + s_2} m + \frac{\alpha_{b2} s_2}{\beta_{b2} + s_2} b - A_{s2} s_2, \tag{2.5}$$

$$\frac{\partial v_{fn}}{\partial t} = -\frac{\alpha_w s_2}{\beta_w + s_2} b v_{fn} (1 - v_w), \tag{2.6}$$

$$\frac{\partial v_w}{\partial t} = \frac{\alpha_w s_2}{\beta_w + s_2} b v_{fn} (1 - v_w) - \gamma v_w (1 - v_l), \tag{2.7}$$

$$\frac{\partial v_l}{\partial t} = \gamma v_w (1 - v_l). \tag{2.8}$$

Initial and boundary conditions will be given later in the text.

In equations (2.1) and (2.4) p denotes the concentration of adsorbed proteins, which is a predefined function of the distance from the implant surface. According to [Moreo, 2008] the following parameters values are proposed:

$$\begin{aligned}
&D_c = 1.365 \cdot 10^{-2}\, mm^2/day, \quad A_c = 0.067\, day^{-1}, \quad H_c = 0.333\, mm^4/(day \cdot mg),\\
&D_m = 0.133\, mm^2/day, \quad B_{m1} = 0.667\, mm^2/day, \quad B_{m2} = 0.167\, mm^2/day,\\
&\alpha_{m0} = 0.25\, day^{-1}, \quad \alpha_m = 0.25\, day^{-1}, \quad A_m = 2 \cdot 10^{-3}\, day^{-1}, \quad \beta_m = 0.1,\\
&\beta_{mb} = 0.1, \quad A_b = 6.67 \cdot 10^{-3}\, day^{-1}, \quad D_{s1} = 0.3\, mm^2/day, \quad D_{s2} = 0.1\, mm^2/day,\\
&A_{s1} = 10\, day^{-1}, \quad A_{s2} = 10\, day^{-1}, \quad \alpha_{c1} = 66.7\, day^{-1}, \quad \alpha_{c2} = 10\, day^{-1}\\
&\alpha_{m2} = 25\, day^{-1}, \quad \alpha_{b2} = 25\, day^{-1}, \quad \beta_{c1} = 0.1, \quad \beta_{c2} = 0.1, \quad \beta_{m2} = 0.1,\\
&\beta_{b2} = 0.1, \quad \alpha_w = 0.1\, day^{-1}, \quad \beta_w = 0.1, \quad \gamma = 0.01\, day^{-1}.
\end{aligned} \tag{2.9}$$

Remark 2.1 *In [Moreo, 2008] originally, the differentiation term in equations* (2.2) *and* (2.3) *was given in the form* $\frac{\alpha_{mb} s_1}{\beta_{mb} + s_1} m$*. And here we introduced parameter* α_{p0}*, assuming that differentiation could take place, when the growth factor 1 concentration* s_1 *is zero [García-Aznar, 2009].*

Therefore, according to [Moreo, 2008]:

$$\alpha_{mb} = 0.5\ day^{-1}, \quad \alpha_{p0} = 0\ day^{-1}, \tag{2.10}$$

and our proposal is:

$$\alpha_{mb} = \frac{2}{3} \cdot 0.5\ day^{-1}, \quad \alpha_{p0} = \frac{1}{3} \cdot 0.5\ day^{-1}. \tag{2.11}$$

3 Stability analysis

3.1 The simplified biological model

Our present aim is to study the conditions characterizing wave-like profile appearance. Simulations, performed for the full system, show that the wave-like profile can appear in the solution for densities of osteogenic cells m and osteoblasts b, for growth factor 2 concentration s_2, and for volume fractions of fibrin network v_{fn}, woven bone v_w and lamellar bone v_l. Equations for variables m, b and s_2 (2.2), (2.5), (2.3) are coupled and can be solved, after the solution for c and s_1 is obtained from the equations (2.1) and (2.4). Equations for variables v_{fn}, v_w and v_l (2.6), (2.7), (2.8) contain only reaction terms in their right part. The wave-like profile in the solution for these variables appears due to the wave-like profile in the solution for osteoblasts and growth factor 2.

Therefore we will study the phenomenon of the wave-like profile in the solution for variables m, b and s_2. Solution for m, b and s_2 is provided by the system of equations (2.1)–(2.5).

We assume, that the profile appearance could be related to the stability of the homogeneous steady-state solutions of the system. System (2.1)–(2.5) has no homogeneous steady-state solutions for variables c and s_1, if protein concentration is not homogeneous in the problem domain: $p(\mathbf{x}) \neq const$. Therefore we reduce this system to three equations, eliminating unknown functions c and s_1.

The equations for platelets c and growth factor 1 s_1 (2.1) and (2.4), could be solved separately of other equations. That means, that platelet density $c(x,t)$ and growth factor 1 concentration $s_1(x,t)$ evolution does not depend on the evolution of other biological and chemical species involved in the model. Equation (2.1) contains a term, corresponding to the death of platelets, but it does not contain a term, corresponding to the production of platelets. Therefore, the total amount of platelets decays to zero with time. The production of growth factor 1 s_1 is proportional to platelets concentration, and thus the production of s_1 also decays with time, while death rate A_{s1} is constant in time. It can be proved, that the integrals of platelet density and growth factor 1 concentration over the problem domain tend to zero with time, when zero flux on the boundaries is considered. If negative values in the solution for $c(x,t)$ and $s_1(x,t)$ are avoided (otherwise the solution becomes biologically irrelevant), then it follows, that these functions tend to zero almost everywhere in the problem domain. Numerical simulations confirm (Figure 2), that for a large time t the solution $s_1(x,t)$ is very close to zero.

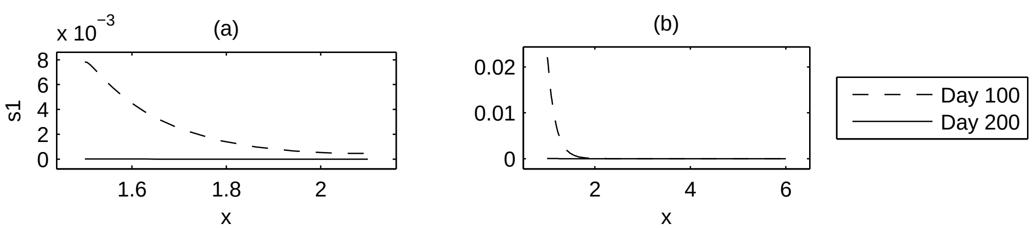


Figure 2: Growth factor 1 $s1$ distribution at different time moments, taken from the solutions of the full system (2.1)–(2.8) for domain length (a) $L = 0.6\,mm$, (b) $L = 5\,mm$.

The stability analysis deals with the asymptotic behavior of the system, that is with the behavior of the solution for long time periods. Therefore, we derive the simplified system from equations (2.2), (2.5) and (2.3), assuming $s_1(x,t) \equiv 0$, which gives

$$\frac{\partial m}{\partial t} = \nabla \cdot [D_m \nabla m - B_{m2} m \nabla s_2)] + + \left(\alpha_{m0} + \frac{\alpha_m s_2}{\beta_m + s_2}\right) m(1-m) - (\alpha_{p0} + A_m)m - A_m m, \tag{3.1}$$

$$\frac{\partial s_2}{\partial t} = \nabla \cdot [D_{s2} \nabla s_2] + \frac{\alpha_{m2} s_2}{\beta_{m2} + s_2}(m+b) - A_{s2} s_2, \tag{3.2}$$

$$\frac{\partial b}{\partial t} = \alpha_{p0} m - A_b b. \tag{3.3}$$

Remark 3.1 *Deriving* (3.2) *we assumed, that* $\alpha_{b2} = \alpha_{m2}$ *and* $\beta_{b2} = \beta_{m2}$. *In* (2.9) *the identical values for parameters* α_{b2} *and* α_{m2}, *and for parameters* β_{b2} *and* β_{m2} *were specified.*

[Moreo, 2008] investigated the linear stability of the homogeneous steady-states of the system, which is similar to system (3.1)–(3.3), against purely temporal perturbations. In this paper we will study the system stability against arbitrary perturbations (also non-homogeneous perturbations).

Homogeneous steady-state solutions $z' = (m', s', b')$ of equation system (3.1)–(3.3) are derived from the algebraic system:

$$\begin{aligned}
&\Big(\alpha_{m0} + \frac{\alpha_m s_2'}{\beta_m + s_2'}\Big) m'(1-m') - (\alpha_{p0} + A_m) m' = 0, \\
&\frac{\alpha_{m2} s_2'}{\beta_{m2} + s_2'}(m' + b') - A_{s2} s_2' = 0, \\
&\alpha_{p0} m' - A_b b' = 0.
\end{aligned} \tag{3.4}$$

The above system has 4 solutions. Two of them are denoted by [Moreo, 2008] as:

- "Chronic non healing state": $z_t = (0,0,0)$
- "Low density state": $z_0 = (m_0, 0, b_0)$

where

$$m_0 = 1 - \frac{\alpha_{p0} + A_m}{\alpha_{m0}}, \quad b_0 = \frac{\alpha_{p0}}{A_b} m_0. \tag{3.5}$$

Two other homogeneous steady-states are denoted as $z_- = (m_-, s_{2-}, b_-)$ and $z_+ = (m_+, s_{2+}, b_+)$. Then the values s_{2-} and s_{2+} are determined as

$$s_{2\pm} = \frac{-a_1 \pm \sqrt{a_1^2 - 4a_2 a_0}}{2a_2}, \tag{3.6}$$

where

$$\begin{cases}
a_2 = A_{s_2}\left(1 + \dfrac{\alpha_m}{\alpha_{m0}}\right), \\
a_1 = \left(1 + \dfrac{\alpha_m}{\alpha_{m0}}\right)(\beta_{m2} A_{s_2} - \chi m_0) + \dfrac{\alpha_m}{\alpha_{m0}} \chi (m_0 - 1) + \beta_m A_{s_2}, \\
a_0 = \beta_m (\beta_{m2} A_{s_2} - \chi m_0),
\end{cases} \tag{3.7}$$

$$\chi = \alpha_{m2}\left(1 + \alpha_{p0}/A_b\right), \tag{3.8}$$

and m_0 is from (3.5). The important restriction should be imposed, that $s_{2\pm} \neq -\beta_m$ and $s_{2\pm} \neq -\beta_{m2}$. Then $m_\pm, b_\pm$ is defined as:

$$m_\pm = \frac{A_b A_{s2}(s_{2\pm} + \beta_{m2})}{\alpha_{m2}(A_b + \alpha_{p0})} = \frac{A_{s2}(s_{2\pm} + \beta_{m2})}{\chi}, \quad b_\pm = \frac{\alpha_{p0}}{A_b} m_\pm. \tag{3.9}$$

We mention here, that for the existence of real $s_{2\pm}$ the necessary condition is:

$$a_1^2 - 4a_2 a_0 \geq 0 \tag{3.10}$$

That necessary condition could be written in term of model parameter as:

$$\begin{aligned}
a_1^2 - 4a_2 a_0 = &\left(\chi\left(m_0 + \frac{\alpha_m}{\alpha_{m0}}\right) - A_{s2}\left(\beta_m + \beta_{m2}\left(1 + \frac{\alpha_m}{\alpha_{m0}}\right)\right)\right)^2 - \\
&- 4A_{s2}\beta_m\left(1 + \frac{\alpha_m}{\alpha_{m0}}\right)(\beta_{m2} A_{s2} - \chi m_0) = \\
&= \left(\chi\left(m_0 + \frac{\alpha_m}{\alpha_{m0}}\right) - \xi\right)^2 + \chi\left(m_0 + \frac{\alpha_m}{\alpha_{m0}}\right)\eta - \eta\left(\beta_{m2} A_{s2} + \chi \frac{\alpha_m}{\alpha_{m0}}\right) = \\
&= \left(\chi\left(m_0 + \frac{\alpha_m}{\alpha_{m0}}\right)\right)^2 + \chi\left(m_0 + \frac{\alpha_m}{\alpha_{m0}}\right)(\eta - 2\xi) + \xi^2 - \eta\left(\beta_{m2} A_{s2} + \chi \frac{\alpha_m}{\alpha_{m0}}\right) \geq 0
\end{aligned}$$

where

$$\xi = A_{s2}\left(\beta_m + \beta_{m2}\left(1 + \frac{\alpha_m}{\alpha_{m0}}\right)\right), \quad \eta = 4A_{s2}\beta_m\left(1 + \frac{\alpha_m}{\alpha_{m0}}\right) \tag{3.11}$$

From the above relation it is derived, that (3.10) is equivalent to:

$$\left[\begin{array}{l} \chi\left(m_0+\frac{\alpha_m}{\alpha_{m0}}\right) \geq -A_{s2}\beta_m\frac{\alpha_m}{\alpha_{m0}} + \sqrt{\eta\frac{\alpha_m}{\alpha_{m0}}\chi}, \\ \chi\left(m_0+\frac{\alpha_m}{\alpha_{m0}}\right) \leq -A_{s2}\beta_m\frac{\alpha_m}{\alpha_{m0}} - \sqrt{\eta\frac{\alpha_m}{\alpha_{m0}}\chi}. \end{array}\right. \tag{3.12}$$

The sign of $s_{2\pm}$ depends on the sign of coefficients a_1 and a_0 (coefficient a_2 is greater than zero, which follows from its definition). Both roots will be positive if $a_1 < 0$ and $a_0 > 0$ and if (3.10) holds.

For parameter values (2.9), (2.10) the homogeneous steady-state solutions have values: $(m_0, b_0) \approx (0.9920, 0)$, $(m_-, s_{2-}, b_-) \approx (0.0201, -0.0498, 0)$, $(m_+, s_{2+}, b_+) \approx (0.9959, 2.3898, 0)$; and for parameter values (2.9), (2.11): $(m_0, b_0) \approx (0.3253, 8.1293)$, $(m_-, s_{2-}, b_-) \approx (0.0012, -0.0245, 0.0290)$, $(m_+, s_{2+}, b_+) \approx (0.6623, 42.9271, 16.5486)$.

Remark 3.2 *For the chosen parameter values growth factor 2 concentration s_{2-} is negative, which is unphysical. It is desirable to avoid such a negative concentration of growth factor 2 in the solution of the problem* (3.1)–(3.3)*. Calculations showed, that for the chosen parameter set* (2.9), (2.10) *and* (2.9), (2.11) *homogeneous steady-state z_- is unstable against temporal perturbations. In simulations we were able to avoid negative values in the solution for s_2, by choosing sufficiently small time step and mesh size and starting with positive initial values for concentrations of cells and growth factor.*

3.2 Non-homogeneous perturbations

Further we propose an approach, to study the stability of homogeneous steady-state solutions of the system (3.1)–(3.3) in 1D domain against non-homogeneous spatial perturbations. Suppose that non-homogeneous perturbations $m_p(x,t)$, $s_{2p}(x,t)$ and $b_p(x,t)$ are imposed on the homogeneous steady-state solution (m', s_2', b'). Then the solution is given in the form:

$$\begin{cases} m(x,t) = m' + \varepsilon m_p(x,t), \\ s_2(x,t) = s_2' + \varepsilon s_{2p}(x,t), \\ b(x,t) = b' + \varepsilon b_p(x,t) \end{cases} \tag{3.13}$$

where $|\varepsilon| \ll 1$. Then we substitute (3.13) into (3.1)–(3.3), and linearize with respect to small ε:

$$\begin{cases} \dfrac{\partial m_p}{\partial t} = D_m\nabla^2 m_p - m'B_{m2}\nabla^2 s_{2p} + \Big[\Big(\alpha_{m0} + \dfrac{\alpha_m s_2'}{\beta_m + s_2'}\Big)(1-2m') - \\ \qquad - (\alpha_{p0} + A_m)\Big]m_p + \dfrac{\alpha_m\beta_m}{(\beta_m + s_2')^2}m'(1-m')s_{2p}, \\ \dfrac{\partial s_{2p}}{\partial t} = D_{s2}\nabla^2 s_{2p} + \dfrac{\alpha_{m2}s_2'}{\beta_{m2}+s_2'}(m_p + b_p) + \Big[\dfrac{\alpha_{m2}\beta_{m2}}{(\beta_{m2}+s_2')^2}(m'+b') - A_{s2}\Big]s_{2p}, \\ \dfrac{\partial b_p}{\partial t} = \alpha_{p0}m_p - A_b b_p \end{cases} \tag{3.14}$$

Let us denote the problem domain as $[x_0, x_0 + L]$. Assume, that on the boundaries the flux of cells and growth factor is zero. Then we consider perturbations of the form:

$$\begin{cases} m_p(x,t) = C_0^m(t) + \displaystyle\sum_{n=1}^{\infty} C_n^m(t)\phi_n(x), \\ s_{2p}(x,t) = C_0^{s2}(t) + \displaystyle\sum_{n=1}^{\infty} C_n^{s2}(t)\phi_n(x), \\ b_p(x,t) = C_0^b(t) + \displaystyle\sum_{n=1}^{\infty} C_n^b(t)\phi_n(x) \end{cases} \tag{3.15}$$

Functions $C_0^m(t)$, $C_0^{s2}(t)$, $C_0^b(t)$ represent purely temporal perturbations. Functions $\phi_n(x)$ satisfy equation $\nabla^2\phi_n(x) = -k_n^2\phi_n(x)$ and considered boundary conditions, i.e. zero flux on the boundaries: $\nabla\phi_n(x_0) = \nabla\phi_n(x_0+L) = \mathbf{0}$.

When Cartesian coordinates are considered, then $\phi_n(x)$ is given as $\phi_n^C(x) = \cos(k_n(x-x_0))$, where $k_n = \frac{\pi n}{L}$, $n = 1, 2, \ldots$. In this case k_n is a wavenumber.

In the case of axisymmetric coordinates functions $\phi_n(x)$ have the form $\phi_n^a(x) = Y_0'(k_n x_0)J_0(k_n x) - J_0'(k_n x_0)Y_0(k_n x)$, where $J_0(k_n x)$ and $Y_0(k_n x)$ are Bessel functions, $k_n = \frac{w_n}{x_0+L}$ and w_n, $n = 1, 2, \ldots$ are positive real zeros of the function $\Phi(w) = -Y_0'(k_n x_0)J_1(w) + J_0'(k_n x_0)Y_1(w)$. Functions $\phi_n^a(x)$, $n = 1, 2, \ldots$ are not periodic. They could be roughly described as "waves" with variable in space wavelength and magnitude. For simplicity, k_n will be referred to as 'wavenumber', also when it is introduced in functions $\phi_n^a(x)$.

Remark 3.3 *Perturbation modes $\phi_n(x)$, $n = 1, 2, \ldots$ by their definition have positive wavenumbers $k_n > 0$. For the sake of generality, further we will consider purely temporal perturbations as perturbations of mode $n = 0$ with zero wavenumber $k_0 = 0$. We also define $\phi_0(x) \equiv 1$.*

Substituting (3.15) into (3.14), we get:

$$\mathbf{C}_n'(t) = \mathbf{A}_{k_n}\mathbf{C}_n(t), \quad n = 0, 1, \ldots \tag{3.16}$$

where

$$\mathbf{C}_n(t) = \begin{bmatrix} C_n^m(t) \\ C_n^{s2}(t) \\ C_n^b(t) \end{bmatrix}, \quad n = 0, 1, \ldots, \tag{3.17}$$

$$\mathbf{A}_{k_n} = \begin{pmatrix} \left(\alpha_{m0} + \dfrac{\alpha_m s_2'}{\beta_m + s_2'}\right)(1-2m') - (\alpha_{p0} + A_m) - k_n^2 D_m & \dfrac{\alpha_m\beta_m}{(\beta_m + s_2')^2}m'(1-m') + k_n^2 B_{m2}m' & 0 \\ \dfrac{\alpha_{m2}s_2'}{\beta_{m2} + s_2'} & \dfrac{\alpha_{m2}\beta_{m2}}{(\beta_{m2} + s_2')^2}\left(1 + \dfrac{\alpha_{p0}}{A_b}\right)m' - A_{s2} - k_n^2 D_{s2} & \dfrac{\alpha_{m2}s_2'}{\beta_{m2} + s_2'} \\ \alpha_{p0} & 0 & -A_b \end{pmatrix}. \tag{3.18}$$

Then from (3.16):

$$\mathbf{C}_n(t) = e^{\mathbf{A}_{k_n}t}\mathbf{C}_n^0, \quad n = 0, 1, \ldots \tag{3.19}$$

where $\mathbf{C}_n^0$ define the perturbations imposed on the homogeneous steady-state solution of the system initially at time $t = 0$:

$$\begin{bmatrix} m_p(x,0) \\ s_{2p}(x,0) \\ b_p(x,0) \end{bmatrix} = \sum_{n=0}^{\infty}\mathbf{C}_n^0\phi_n(x).$$

Thus the solution of (3.14) is written as:

$$\begin{bmatrix} m_p(x,t) \\ s_{2p}(x,t) \\ b_p(x,t) \end{bmatrix} = \sum_{n=0}^{\infty} e^{\mathbf{A}_{k_n}t}\mathbf{C}_n^0\phi_n(x). \tag{3.20}$$

The magnitude of perturbations $\|\mathbf{C}_n(t)\| = \|e^{\mathbf{A}_{k_n}t}\mathbf{C}_n^0\|$ of mode n, will grow in time, when at least one of the eigenvalues of matrix $\mathbf{A}_{k_n}$ is a positive real number or a complex number with a positive real part. And $\|\mathbf{C}_n(t)\|$ will converge to zero, if all the eigenvalues of $\mathbf{A}_{k_n}$ are real negative, or complex numbers with the real part less than zero. When matrix $\mathbf{A}_{k_n}$ has precisely one zero eigenvalue, and other eigenvalues are real negative of complex with negative real part, then small perturbations remain small for infinite time period.

It is not complicated to find expressions for the eigenvalues of $\mathbf{A}_{k_n}$, evaluated at the steady-states z_t and z_0. For the homogeneous steady-state $z_t = (0, 0, 0)$ eigenvalues of $\mathbf{A}_{k_n}$ are:

$$\begin{aligned} \lambda_{1t}(k_n^2) &= \alpha_{m0} m_0 - k_n^2 D_m > 0, \ \text{ if } \ 0 \leq k_n^2 < \frac{\alpha_{m0} m_0}{D_m}, \\ \lambda_{2t}(k_n^2) &= -A_{s2} - k_n^2 D_{s2} < 0, \quad \lambda_{3t}(k_n^2) = -A_b < 0, \end{aligned} \tag{3.21}$$

Therefore, if m_0 is positive, steady-state z_t is unstable against purely temporal perturbations and perturbations with small wavenumber $0 < k_n < \sqrt{\frac{\alpha_{m0} m_0}{D_m}}$. The first eigenvalue $\lambda_{1t}(k_n^2)$ takes the largest positive value for wavenumber k_0, i.e. for the purely temporal perturbation mode.

Remark 3.4 *If we consider negative m_0, then 'chronic non-healing state' z_t will become stable against perturbations with any wavenumber. Further the homogeneous steady-state solution z_0 will contain unphysical negative concentration for osteogenic cells. Inequality $m_0 = 1 - \frac{\alpha_{p0} + A_m}{\alpha_{m0}} < 0$ implies, that differentiation and death of osteogenic cell dominate over their production. Therefore, this situation is not relevant for the considered model of bone formation, and further $m_0 > 0$ is assumed a priori.*

For the homogeneous steady-state solution $z_0 = (m_0, 0, b_0)$ matrix $\mathbf{A}_{k_n}$ eigenvalues are:

$$\begin{aligned} \lambda_{10}(k_n^2) = -\alpha_{m0} m_0 - k_n^2 D_m < 0, \quad \lambda_{20}(k_n^2) = \frac{\alpha_{m2}}{\beta_{m2}} m_0 (1 + \frac{\alpha_{p0}}{A_b}) - A_{s2} - k_n^2 D_{s2}, \\ \lambda_{30}(k_n^2) = -A_b < 0. \end{aligned} \tag{3.22}$$

When expression $\frac{\alpha_{m2}}{\beta_{m2}} m_0 (1 + \frac{\alpha_{p0}}{A_b}) - A_{s2}$ takes positive value, which is true for the considered parameter values (2.9), (2.10) and (2.11), then the steady-state z_0 is unstable against perturbations with wavenumbers $k_n^2 < \left(\frac{\alpha_{m2}}{\beta_{m2}} m_0 (1 + \frac{\alpha_{p0}}{A_b}) - A_{s2} \right) / D_{s2}$. The largest eigenvalue λ_{20} corresponds to zero wavenumber k_0, i.e. to the purely temporal mode of perturbation.

The eigenvalues of matrix $\mathbf{A}_{k_n}$ defined at points z_- and z_+ could not be found in such a trivial manner, as for steady-states z_t and z_0. They are obtained from the characteristic equation, which is a non-trivial cubic algebraic equation. Therefore, instead of analyzing the expressions for the eigenvalues, which are extremely complicated in this case, we propose another approach to study the stability of the considered system of equations.

Remark 3.5 *For the chosen parameter values* (2.9), (2.10) *and* (2.9), (2.11) *s_{2-} is negative, hence homogeneous steady-state z_- is biologically irrelevant in that cases. Further we will analyze only the stability of homogeneous steady-state solution z_+ and not of z_-. The stability analysis, being introduced for z_+, is not valid for the homogeneous steady-state z_-, when it contains the negative value of growth factor concentration. Calculations also show, that for parameter values* (2.9), (2.10) *and* (2.11), *homogeneous steady-state z_- is unstable against at least purely temporal perturbations.*

3.3 Stability of the system of two equations

To simplify the stability analysis, we reduce system (3.1)–(3.3) to a system of two equations. For this reduced system we assume, that $b(x, t) = \frac{\alpha_{p0}}{A_b} m(x, t)$ instead of equation (3.3). Later in the text we will demonstrate, that stability properties of this reduced system are similar to those of the system (3.1)–(3.3). We define:

$$\begin{cases} \dfrac{\partial m}{\partial t} = \nabla \cdot [D_m \nabla m - B_{m2} m \nabla s_2)] + \\ \qquad + \Big(\alpha_{m0} + \dfrac{\alpha_m s_2}{\beta_m + s_2} \Big) m(1 - m) - (\alpha_{p0} + A_m) m, \\ \dfrac{\partial s_2}{\partial t} = \nabla \cdot [D_{s2} \nabla s_2] + \dfrac{\alpha_{m2} s_2}{\beta_{m2} + s_2} (1 + \dfrac{\alpha_{p0}}{A_b}) m - A_{s2} s_2 \end{cases} \tag{3.23}$$

This system has the homogeneous steady-states analogous to those of the system (3.1)–(3.3). They are: $\tilde{z}_t = (0,0)$, $\tilde{z}_0 = (m_0, 0)$, $\tilde{z}_+ = (m_+, s_{2+})$, $\tilde{z}_- = (m_-, s_{2-})$. Linearizing the system near point (m', s'_2), with $m(x,t) = m' + \varepsilon m_p(x,t)$ and $s_2(x,t) = s'_2 + \varepsilon s_{2p}(x,t)$, we get:

$$\begin{cases} \dfrac{\partial m_p}{\partial t} = D_m \nabla^2 m_p - m' B_{m2} \nabla^2 s_{2p} + \Big[\Big(\alpha_{m0} + \dfrac{\alpha_m s'_2}{\beta_m + s'_2}\Big)(1-2m') - \\ \qquad - (\alpha_{p0} + A_m)\Big] m_p + \dfrac{\alpha_m \beta_m}{(\beta_m + s'_2)^2} m'(1-m') s_{2p}, \\ \dfrac{\partial s_{2p}}{\partial t} = D_{s2} \nabla^2 s_{2p} + \dfrac{\alpha_{m2} s'_2}{\beta_{m2} + s'_2}(1 + \dfrac{\alpha_{p0}}{A_b}) m_p + \Big[\dfrac{\alpha_{m2}\beta_{m2}}{(\beta_{m2} + s'_2)^2}(1 + \dfrac{\alpha_{p0}}{A_b}) m' - A_{s2}\Big] s_{2p} \end{cases} \tag{3.24}$$

Considering the solution in the form

$$\begin{cases} m_p(x,t) = \sum_{n=0}^{\infty} C_n^m(t)\phi_n(x), \\ s_{2p}(x,t) = \sum_{n=0}^{\infty} C_n^{s2}(t)\phi_n(x) \end{cases}$$

and substituting it in (3.24), for each $n = 0, 1, \ldots$ we derive:

$$\begin{bmatrix} \dfrac{dC_n^m(t)}{dt} \\ \dfrac{dC_n^{s2}(t)}{dt} \end{bmatrix} = \widetilde{\mathbf{A}}_{k_n} \begin{bmatrix} C_n^m(t) \\ C_n^{s2}(t) \end{bmatrix}$$

where

$$\widetilde{\mathbf{A}}_{k_n} = \begin{pmatrix} \Big(\alpha_{m0} + \dfrac{\alpha_m s'_2}{\beta_m + s'_2}\Big)(1-2m') - (\alpha_{p0} + A_m) - k_n^2 D_m & \dfrac{\alpha_m \beta_m}{(\beta_m + s'_2)^2} m'(1-m') + k_n^2 B_{m2} m' \\ \dfrac{\alpha_{m2} s'_2}{\beta_{m2} + s'_2}(1 + \dfrac{\alpha_{p0}}{A_b}) & \dfrac{\alpha_{m2}\beta_{m2}}{(\beta_{m2} + s'_2)^2}(1 + \dfrac{\alpha_{p0}}{A_b}) m' - A_{s2} - k_n^2 D_{s2} \end{pmatrix}.$$

First we investigate the stability properties of the system (3.24) and then determine, how they are related to the stability properties of the system of three equations (3.14). Since $s_{2+} \neq -\beta_{m2}$, then from (3.9) $m_+ \neq 0$. Therefore, matrix $\widetilde{\mathbf{A}}_{k_n}$, evaluated at point (m_+, s_{2+}), can be simplified. From (3.4) we get:

$$\Big(\alpha_{m0} + \frac{\alpha_m s_{2+}}{\beta_m + s_{2+}}\Big)(1 - m_+) - (\alpha_{p0} + A_m) = 0. \tag{3.25}$$

Then:

$$\begin{aligned} \widetilde{\mathbf{A}}_{k_n(1,1)}(m_+, s_{2+}) &= \Big(\alpha_{m0} + \tfrac{\alpha_m s_{2+}}{\beta_m + s_{2+}}\Big)(1-2m_+) - (\alpha_{p0} + A_m) - k_n^2 D_m = \\ &= 2\Big(\Big(\alpha_{m0} + \tfrac{\alpha_m s_{2+}}{\beta_m + s_{2+}}\Big)(1-m_+) - (\alpha_{p0} + A_m)\Big) - \\ &- \Big(\Big(\alpha_{m0} + \tfrac{\alpha_m s_{2+}}{\beta_m + s_{2+}}\Big) - (\alpha_{p0} + A_m)\Big) - k_n^2 D_m = \\ &= -\alpha_{m0} m_0 - \tfrac{\alpha_m s_{2+}}{\beta_m + s_{2+}} - k_n^2 D_m, \end{aligned}$$

$$\widetilde{\mathbf{A}}_{k_n(2,1)}(m_+, s_{2+}) = \frac{\alpha_{m2}s_{2+}}{\beta_{m2}+s_{2+}}(1+\frac{\alpha_{p0}}{A_b}) = \chi\frac{s_{2+}}{\beta_{m2}+s_{2+}},$$

where χ is defined in (3.8). Considering (3.9), we derive

$$\begin{aligned}\widetilde{\mathbf{A}}_{k_n(1,2)}(m_+, s_{2+}) =& \frac{\alpha_m\beta_m}{(\beta_m+s_{2+})^2}m_+(1-m_+) + k_n^2 B_{m2}m_+ = \\ =& \frac{A_{s2}\alpha_m\beta_m}{\chi(\beta_m+s_{2+})}\frac{\beta_{m2}+s_{2+}}{\beta_m+s_{2+}}(1-m_+) + k_n^2 B_{m2}m_+.\end{aligned}$$

Everywhere in the calculations, presented in [Moreo, 2008] and in this paper, the same values are used for parameters β_m and β_{m2}. So both notations β_m and β_{m2} is used, though $\beta_{m2} = \beta_m$ is supposed below. Then

$$\widetilde{\mathbf{A}}_{k_n(1,2)}(m_+, s_{2+}) = \frac{A_{s2}\alpha_m\beta_m}{\chi(\beta_m+s_{2+})}(1-m_+) + k_n^2 B_{m2}m_+,$$

$$\widetilde{\mathbf{A}}_{k_n(2,2)}(m_+, s_{2+}) = \frac{\alpha_{m2}\beta_{m2}}{(\beta_{m2}+s_{2+})^2}(1+\frac{\alpha_{p0}}{A_b})m_+ - A_{s2} - k_n^2 D_{s2} =$$

$$= A_{s2}(\frac{\beta_{m2}}{\beta_{m2}+s_{2+}} - 1) - k_n^2 D_{s2} = -A_{s2}\frac{s_{2+}}{\beta_{m2}+s_{2+}} - k_n^2 D_{s2}.$$

Therefore, we end up with

$$\widetilde{\mathbf{A}}_{k_n}(m_+, s_{2+}) = \begin{pmatrix} -\alpha_{m0}m_0 - \frac{\alpha_m s_{2+}}{\beta_m+s_{2+}} - k_n^2 D_m & \frac{A_{s2}\alpha_m\beta_m}{\chi(\beta_m+s_{2+})}(1-m_+) + k_n^2 B_{m2}m_+ \\ \chi\frac{s_{2+}}{\beta_{m2}+s_{2+}} & -A_{s2}\frac{s_{2+}}{\beta_{m2}+s_{2+}} - k_n^2 D_{s2} \end{pmatrix}.$$

Then the characteristic equation for matrix $\widetilde{\mathbf{A}}_{k_n}$, evaluated at point (m_+, s_{2+}), is given as:

$$\lambda^2(k_n^2) + b(k_n^2)\lambda(k_n^2) + c(k_n^2) = 0, \tag{3.26}$$

where

$$\begin{aligned} b(k_n^2) =& -(\widetilde{\mathbf{A}}_{k_n(1,1)}(m_+, s_{2+}) + \widetilde{\mathbf{A}}_{k_n(2,2)}(m_+, s_{2+})) = \\ =& k_n^2 D_m + \alpha_{m0}m_0 + \frac{\alpha_m s_{2+}}{\beta_m+s_{2+}} + k_n^2 D_{s2} + A_{s2}\frac{s_{2+}}{\beta_{m2}+s_{2+}} = \\ =& k_n^2(D_m + D_{s2}) + \alpha_{m0}m_0 + (\alpha_m + A_{s2})\frac{s_{2+}}{\beta_m+s_{2+}},\end{aligned}$$

$$\begin{aligned} c(k_n^2) =& \widetilde{\mathbf{A}}_{k_n(1,1)}(m_+, s_{2+})\widetilde{\mathbf{A}}_{k_n(2,2)}(m_+, s_{2+}) - \widetilde{\mathbf{A}}_{k_n(1,2)}(m_+, s_{2+})\widetilde{\mathbf{A}}_{k_n(2,1)}(m_+, s_{2+}) = \\ =& \left(k_n^2 D_m + \alpha_{m0}m_0 + \frac{\alpha_m s_{2+}}{\beta_m+s_{2+}}\right)\left(k_n^2 D_{s2} + A_{s2}\frac{s_{2+}}{\beta_{m2}+s_{2+}}\right) - \\ -& \left(k_n^2 B_{m2}m_+ + \frac{A_{s2}\alpha_m\beta_m}{\chi(\beta_m+s_{2+})}(1-m_+)\right)\chi\frac{s_{2+}}{\beta_{m2}+s_{2+}}.\end{aligned}$$

From equation (3.26) the eigenvalues of $\widetilde{\mathbf{A}}_{k_n}(m_+, s_{2+})$ are determined as:

$$\lambda_{1,2}(k_n^2) = -\frac{b(k_n^2)}{2} \pm \frac{1}{2}\sqrt{b^2(k_n^2) - 4c(k_n^2)}. \tag{3.27}$$

We mention that, if

$$\begin{cases} s_{2+} > 0, \\ m_0 > 0 \end{cases} \quad\Rightarrow\quad b(k_n^2) > 0. \tag{3.28}$$

Thus, we can formulate the lemma.

Lemma 3.3.1 *Suppose, that for the chosen parameter values m_0 defined in* (3.5) *is positive, $\beta_m = \beta_{m2}$ and that there exists a real positive s_{2+} defined in* (3.6)*. Then the nature of eigenvalues of matrix $\widetilde{\mathbf{A}}_{k_n}(m_+, s_{2+})$ is determined by the sign of $c(k_n^2)$:*

- *if $c(k_n^2) < 0$, then one of eigenvalues is positive and the other is negative,*
- *if $c(k_n^2) = 0$, then matrix $\widetilde{\mathbf{A}}_{k_n}(m_+, s_{2+})$ has one zero eigenvalue and one negative.*
- *if $c(k_n^2) > 0$ then both eigenvalues are either negative, or complex with negative real part.*

Thus, the wavenumbers which lead to growing perturbations are determined by inequality $c(k_n^2) < 0$. We can write $c(k_n^2)$ is the form:

$$c(k_n^2) = \gamma_2 k_n^4 + \gamma_1 k_n^2 + \gamma_0, \tag{3.29}$$

where

$$\gamma_2 = D_m D_{s2}, \tag{3.30}$$

$$\gamma_1 = (D_m A_{s2} + D_{s2}\alpha_m - \chi m_+ B_{m2}) \frac{s_{2+}}{\beta_{m2} + s_{2+}} + D_{s2}\alpha_{m0} m_0, \tag{3.31}$$

$$\gamma_0 = A_{s2} \frac{s_{2+}}{\beta_{m2} + s_{2+}} \left(\alpha_{m0} m_0 + \alpha_m \frac{s_{2+}}{\beta_m + s_{2+}} (2 - m_+) + \alpha_m (m_+ - 1) \right). \tag{3.32}$$

Lemma 3.3.2 *Suppose, that for the chosen parameter values m_0 defined in* (3.5) *is positive, and that $\beta_{m2} = \beta_m$. Then if there exists a real positive s_{2+} defined in* (3.6)*, then γ_0 defined in* (3.32) *is non-negative.*

Proof. Since $s_{2+} > 0$, then it is necessary to prove, that

$$\alpha_{m0} m_0 + \alpha_m \frac{s_{2+}}{\beta_m + s_{2+}} (2 - m_+) + \alpha_m (m_+ - 1) \geq 0.$$

Using (3.25) and (3.5), we simplify the previous inequality:

$$\begin{aligned}
&\alpha_{m0} m_0 + \alpha_m \frac{s_{2+}}{\beta_m + s_{2+}} (2 - m_+) + \alpha_m (m_+ - 1) = \\
&= \left(\alpha_{m0} m_0 + \alpha_m \frac{s_{2+}}{\beta_m + s_{2+}} (1 - m_+) - \alpha_{m0} m_+ \right) + \alpha_m \frac{s_{2+}}{\beta_m + s_{2+}} + \alpha_{m0} m_+ + \alpha_m (m_+ - 1) = \\
&= m_+ (\alpha_{m0} + \alpha_m) + \alpha_m \left(\frac{s_{2+}}{\beta_m + s_{2+}} - 1 \right) \geq 0.
\end{aligned}$$

That is equivalent to $m_+(\alpha_{m0} + \alpha_m) \geq \left(\frac{\alpha_m \beta_m}{\beta_m + s_{2+}} \right)$. Considering (3.9), this transforms to

$$(\beta_m + s_{2+})^2 \geq \frac{\alpha_m \beta_m \chi}{A_{s2}(\alpha_{m0} + \alpha_m)}, \tag{3.33}$$

where χ is defined in (3.8). First, we show, that inequality (3.33) holds. From equation (3.6) and assumption $\beta_{m2} = \beta_m$ it follows, that

$$\begin{aligned}
s_{2+} + \beta_m &= \frac{-a_1 + \sqrt{a_1^2 - 4a_2 a_0}}{2a_2} + \beta_m \geq -\frac{a_1}{2a_2} + \beta_m = \\
&= -\frac{(\alpha_{m0} + \alpha_m)(\beta_m A_{s_2} - \chi m_0) + \alpha_m \chi (m_0 - 1) + \alpha_{m0} \beta_m A_{s_2} - 2\beta_m A_{s2}(\alpha_{m0} + \alpha_m)}{2A_{s2}(\alpha_{m0} + \alpha_m)} = \\
&= \frac{\alpha_m \beta_m A_{s2} + \chi(\alpha_m + \alpha_{m0} m_0)}{2A_{s2}(\alpha_{m0} + \alpha_m)},
\end{aligned} \tag{3.34}$$

where a_2, a_1, a_0 are defined in (3.7). Since $\chi = \alpha_{m2}\left(1 + \alpha_{p0}/A_b\right) > 0$ and m_0 is supposed to be positive, then from (3.12) we get:

$$\chi\left(m_0 + \frac{\alpha_m}{\alpha_{m0}}\right) \geq -A_{s2}\beta_m\frac{\alpha_m}{\alpha_{m0}} + \sqrt{\eta\frac{\alpha_m}{\alpha_{m0}}\chi}. \tag{3.35}$$

where η is defined in (3.11). Thus from (3.34) and (3.35) we get:

$$\beta_m + s_{2+} \geq \frac{\alpha_m\beta_m A_{s2} + \chi(\alpha_m + \alpha_{m0}m_0)}{2A_{s2}(\alpha_{m0} + \alpha_m)} \geq$$

$$\frac{\alpha_m\beta_m A_{s2} - \alpha_m\beta_m A_{s2} + \sqrt{\eta\alpha_m\alpha_{m0}\chi}}{2A_{s2}(\alpha_{m0} + \alpha_m)} = \frac{\sqrt{\eta\alpha_m\alpha_{m0}\chi}}{2A_{s2}(\alpha_{m0} + \alpha_m)} = \sqrt{\frac{\alpha_m\beta_m\chi}{A_{s2}(\alpha_{m0} + \alpha_m)}}$$

Thus inequality (3.33) holds, and consequently $\gamma_0 \geq 0$. $\square$

Remark 3.6 *From the proof of Lemma 3.3.2 it follows, that $\gamma_0 = 0$, if and only if $a_1^2 - 4a_2a_0 = 0$ which is equivalent for $m_0 > 0$ to*

$$\chi\left(m_0 + \frac{\alpha_m}{\alpha_{m0}}\right) = -A_{s2}\beta_m\frac{\alpha_m}{\alpha_{m0}} + \sqrt{\eta\frac{\alpha_m}{\alpha_{m0}}\chi}. \tag{3.36}$$

where η is defined in (3.11). *In this case two steady-states z_- and z_+ coincide, since $s_{2-} = s_{2+} = -\frac{a_1}{2a_0}$.*

Remark 3.7 *We mention here, that under assumptions of Lemma 3.3.2, $c(0) = \gamma_0 \geq 0$. Then from Lemma 3.3.1 we deduce, that for zero wavenumber k_0, matrix $\widetilde{\mathbf{A}}_{k_n}(m_+, s_{2+})$ has either one zero eigenvalue and one negative, or two negative eigenvalues, or two complex eigenvalues with negative real part. This means, that the steady-state (m_+, s_{2+}) of the system* (3.23) *is stable against the purely temporal perturbations.*

Since $k_n \in [0, \infty)$, then $c(k_n^2)$, given in (3.29) could be considered as a real function of a real non-negative argument. It is a quadratic polynomial. The interval, where $c(k_n^2) < 0$, is defined by the roots of the polynomial. If this polynomial has no roots among non-negative real numbers, then for $\forall k_n \in [0, \infty)$, $c(k_n^2) > 0$, since γ_2 defined (3.30) is positive. Thus, it is necessary to find the conditions, when polynomial defined in (3.29) has at least one non-negative real root. The general formula for the roots of the polynomial is:

$$\kappa_{1,2}^2 = \frac{-\gamma_1 \pm \sqrt{\gamma_1^2 - 4\gamma_2\gamma_0}}{2\gamma_2}. \tag{3.37}$$

The discriminant of the polynomial is:

$$\mathscr{D}_\gamma = \gamma_1^2 - 4\gamma_0\gamma_2. \tag{3.38}$$

Since $\gamma_2 > 0$ and $\gamma_0 \geq 0$ under the conditions of Lemma 3.3.2, the polynomial $c(k_n^2)$ has either two real roots of the same sign as $-\gamma_1$, which are different when $\mathscr{D}_\gamma > 0$, and coincident when $\mathscr{D}_\gamma = 0$; or two complex roots, when $\mathscr{D}_\gamma < 0$. In other words, the following cases are possible:

Theorem 3.3.1 *Suppose, that for the chosen parameter values m_0 defined in* (3.5) *is positive, $\beta_m = \beta_{m2}$ and that there exists a real positive s_{2+} defined in* (3.6). *Let $\lambda_1(k_n^2)$ and $\lambda_2(k_n^2)$ be the eigenvalues of matrix $\widetilde{\mathbf{A}}_{k_n}(m_+, s_{2+})$ defined in* (3.27)*; $c(k_n^2)$ be defined in* (3.29), *discriminant $\mathscr{D}_\gamma$ be defined in* (3.38) *and parameter γ_1 be defined in* (3.31). *Then:*

1. *If $\mathscr{D}_\gamma > 0$, and*

   (a) *if $\gamma_1 < 0$, then $\exists \kappa_1^2, \kappa_2^2 \in \mathbb{R}$ defined by expression* (3.37), *such that $0 \leq \kappa_1^2 < \kappa_2^2$ and:*

- *for* $k_n^2 \in (\kappa_1^2, \kappa_2^2)$*:* $c(k_n^2) < 0$*, and consequently* $\lambda_1(k_n^2) < 0$ *and* $\lambda_2(k_n^2) > 0$*;*

- *for* $k_n^2 = \{\kappa_1^2; \kappa_2^2\}$*:* $c(k_n^2) = 0$*, and* $\lambda_1(k_n^2) < 0$ *and* $\lambda_2(k_n^2) = 0$*;*

- *for* $k_n^2 \in [0, \infty)/[\kappa_1^2, \kappa_2^2]$*:* $c(k_n^2) > 0$*, and* $\lambda_1(k_n^2)$*,* $\lambda_2(k_n^2)$ *are either real and negative, or complex with negative real part;*

(b) *if* $\gamma_1 > 0$*, then:*

i. *if* $\gamma_0 > 0$*, then for* $\forall k_n^2 \in [0, \infty)$*:* $c(k_n^2) > 0$ *and* $\lambda_1(k_n^2)$*,* $\lambda_2(k_n^2)$ *are either real and negative, or complex with negative real part;*

ii. *if* $\gamma_0 = 0$*, then*
- *for* $\forall k_n^2 \in (0, \infty)$ $c(k_n^2) > 0$ *and* $\lambda_1(k_n^2)$*,* $\lambda_2(k_n^2)$ *are either real and negative, or complex with negative real part;*

- $c(0) = 0$ *and* $\lambda_1(0) < 0$ *and* $\lambda_2(0) = 0$*.*

2. *If* $\mathscr{D}_\gamma = 0$*, and*

(a) *if* $\gamma_1 \leq 0$*, then* $\exists \kappa_1^2 = \kappa_2^2 = -\frac{\gamma_1}{2\gamma_2} \geq 0$ *, such that*

- $c(\kappa_1^2) = 0$*, and* $\lambda_1(\kappa_1^2) < 0$ *and* $\lambda_2(\kappa_1^2) = 0$*;*

- *for* $k_n^2 \in [0, \infty)/\{\kappa_1^2\}$*:* $c(k_n^2) > 0$ *and* $\lambda_1(k_n^2)$*,* $\lambda_2(k_n^2)$ *are either real and negative, or complex with negative real part;*

(b) *if* $\gamma_1 > 0$*, then for* $\forall k_n^2 \in [0, \infty)$*:* $c(k_n^2) > 0$ *and* $\lambda_1(k_n^2)$*,* $\lambda_2(k_n^2)$ *are either real and negative, or complex with negative real part;*

3. *if* $\mathscr{D}_\gamma < 0$*, then for* $\forall k_n^2 \in [0, \infty)$ $c(k_n^2) > 0$ *and* $\lambda_1(k_n^2)$*,* $\lambda_2(k_n^2)$ *are either real and negative, or complex with negative real part.*

Parameters γ_1 and $\mathscr{D}_\gamma$, could be written in terms of model parameters as

$$\gamma_1 = (D_m A_{s2} + D_{s2}\alpha_m - \chi m_+ B_{m2})\frac{s_{2+}}{\beta_{m2} + s_{2+}} + D_{s2}\alpha_{m0}m_0, \tag{3.39}$$

$$\begin{aligned} \mathscr{D}_\gamma = &\left((D_m A_{s2} + D_{s2}\alpha_m - \chi m_+ B_{m2})\frac{s_{2+}}{\beta_{m2} + s_{2+}} + D_{s2}\alpha_{m0}m_0\right)^2 - \\ &- 4D_m D_{s2} A_{s2}\frac{s_{2+}}{\beta_{m2} + s_{2+}}\left(\alpha_{m0}m_0 + \alpha_m\frac{s_{2+}}{\beta_{m2} + s_{2+}}(2 - m_+) + \alpha_m(m_+ - 1)\right). \end{aligned} \tag{3.40}$$

In Theorem 3.3.1 we have stated the correspondence between the wavenumber and the signs of eigenvalues of matrix $\widetilde{\mathbf{A}}_{k_n}(m_+, s_{2+})$ for different cases, defined by the conditions on model parameters $\mathscr{D}_\gamma$ and γ_1.

3.4 Correspondence between the systems of two and three equations

Further we will determine the relations between the eigenvalues of matrices $\widetilde{\mathbf{A}}_{k_n}(m_+, s_{2+})$ and $\mathbf{A}_{k_n}(m_+, s_{2+}, b_+)$. Let us define matrix $\mathbf{M}_{k_n}$:

$$\mathbf{M}_{k_n} = \begin{bmatrix} \mathbf{A}_{k_n(1,1)} - \lambda & \mathbf{A}_{k_n(1,2)} \\ \mathbf{A}_{k_n(2,1)} & \mathbf{A}_{k_n(2,2)} - \lambda \end{bmatrix}.$$

From the definition of $\mathbf{A}_{k_n}$ we have: $\mathbf{A}_{k_n(2,3)} = \mathbf{A}_{k_n(2,1)}$. Then

$$\mathbf{A}_{k_n} - \lambda\mathbf{I} = \begin{bmatrix} \mathbf{A}_{k_n(1,1)} - \lambda & \mathbf{A}_{k_n(1,2)} & 0 \\ \mathbf{A}_{k_n(2,1)} & \mathbf{A}_{k_n(2,2)} - \lambda & \mathbf{A}_{k_n(2,1)} \\ \alpha_{p0} & 0 & -A_b - \lambda \end{bmatrix} =$$

$$= \begin{bmatrix} \begin{bmatrix} & \mathbf{M}_{k_n} & \end{bmatrix} & \begin{matrix} 0 \\ \mathbf{A}_{k_n(2,1)} \end{matrix} \\ \begin{matrix} \alpha_{p0} & 0 \end{matrix} & -A_b - \lambda \end{bmatrix}.$$

The determinant of this matrix is the characteristic polynomial of $\mathbf{A}_{k_n}$:

$$det\left(\mathbf{A}_{k_n} - \lambda\mathbf{I}\right) = \big(-A_b - \lambda\big)det(\mathbf{M}_{k_n}) + \alpha_{p0}\mathbf{A}_{k_n(1,2)}\mathbf{A}_{k_n(2,1)}. \tag{3.41}$$

From the definition of matrices $\widetilde{\mathbf{A}}_{k_n}$ and $\mathbf{A}_{k_n}$, it follows that $\widetilde{\mathbf{A}}_{k_n(2,1)} = \left(1 + \frac{\alpha_{p0}}{A_b}\right)\mathbf{A}_{k_n(2,1)}$, $\widetilde{\mathbf{A}}_{k_n(1,1)} = \mathbf{A}_{k_n(1,1)}$, $\widetilde{\mathbf{A}}_{k_n(1,2)} = \mathbf{A}_{k_n(1,2)}$, $\widetilde{\mathbf{A}}_{k_n(2,2)} = \mathbf{A}_{k_n(2,2)}$. Therefore, the determinant of matrix $\widetilde{\mathbf{A}}_{k_n} - \lambda\mathbf{I}$ and characteristic polynomial of matrix $\widetilde{\mathbf{A}}_{k_n}$ is

$$det\left(\widetilde{\mathbf{A}}_{k_n} - \lambda\mathbf{I}\right) = det\left(\begin{bmatrix} \mathbf{A}_{k_n(1,1)} - \lambda & \mathbf{A}_{k_n(1,2)} \\ \mathbf{A}_{k_n(2,1)} + \frac{\alpha_{p0}}{A_b}\mathbf{A}_{k_n(2,1)} & \mathbf{A}_{k_n(2,2)} - \lambda \end{bmatrix}\right) = \tag{3.42}$$

$$= det(\mathbf{M}_{k_n}) - \frac{\alpha_{p0}}{A_b}\mathbf{A}_{k_n(1,2)}\mathbf{A}_{k_n(2,1)}.$$

From (3.41) and (3.42) we derive:

$$det\left(\mathbf{A}_{k_n} - \lambda\mathbf{I}\right) = \big(-A_b - \lambda\big)det\left(\widetilde{\mathbf{A}}_{k_n} - \lambda\mathbf{I}\right) - \lambda\frac{\alpha_{p0}}{A_b}\mathbf{A}_{k_n(1,2)}\mathbf{A}_{k_n(2,1)}. \tag{3.43}$$

Then we denote the characteristic polynomials of matrices $\widetilde{\mathbf{A}}_{k_n}$ and $\mathbf{A}_{k_n}$, which are evaluated at the steady-states (m_+, s_{2+}) and (m_+, s_{2+}, b_+) respectively, as cubic polynomial $P_3(\lambda)$ and quadratic polynomial $P_2(\lambda)$ with regard to λ: $P_3(\lambda) = det(\mathbf{A}_{k_n}(m_+, s_{2+}, b_+) - \lambda\mathbf{I})$, $P_2(\lambda) = det(\widetilde{\mathbf{A}}_{k_n}(m_+, s_{2+}, b_+) - \lambda\mathbf{I})$. Equation (3.43) could be written as:

$$P_3(\lambda) = \big(-A_b - \lambda\big)P_2(\lambda) - C(k_n^2)\lambda, \tag{3.44}$$

where

$$C(k_n^2) = \frac{\alpha_{p0}}{A_b}\mathbf{A}_{k_n(1,2)}(m_+, s_{2+}, b_+)\mathbf{A}_{k_n(2,1)}(m_+, s_{2+}, b_+) = \\ = \frac{\alpha_{p0}}{A_b}\frac{\alpha_{m2}s_{2+}}{\beta_{m2} + s_{2+}}\left(\frac{\alpha_m\beta_m}{(\beta_m + s_{2+})^2}m_+(1 - m_+) + k_n^2 B_{m2}m_+\right). \tag{3.45}$$

If $s_{2+} > 0$, it follows from (3.9) that $m_+ > 0$, and from (3.25) that $m_+ = 1 - \frac{\alpha_{p0} + A_m}{\alpha_{m0} + \frac{\alpha_m s_{2+}}{\beta_m + s_{2+}}} < 1$. Thus,

$$s_{2+} > 0 \;\Rightarrow\; 0 < m_+ < 1 \;\Rightarrow\; C(k_n^2) > 0, \; \forall k_n^2 \in [0, \infty). \tag{3.46}$$

Lemma 3.4.1 *Suppose, that for the chosen parameter values m_0 defined in (3.5) is positive, and that there exists a real positive s_{2+} defined in (3.6). If the matrix $\widetilde{\mathbf{A}}_{k_n}(m_+, s_{2+})$ has one real negative eigenvalue $\tilde{\lambda}_1 < 0$ and one real positive eigenvalue $\tilde{\lambda}_2 > 0$, then $\mathbf{A}_{k_n}(m_+, s_{2+}, b_+)$ has one real positive eigenvalue and either two real negative eigenvalues, or two complex conjugated eigenvalues with negative real part.*

Proof. From the assumption of the lemma and from (3.46) it follows, that $C(k_n^2) > 0$. Let $\widetilde{\mathbf{A}}_{k_n}(m_+, s_{2+})$ have one real negative eigenvalue $\tilde{\lambda}_1 < 0$ and one real positive eigenvalue $\tilde{\lambda}_2 > 0$. The characteristic polynomial can be written as $P_2(\lambda) = (\lambda - \tilde{\lambda}_1)(\lambda - \tilde{\lambda}_2)$. Then

$$\begin{aligned} P_3(\lambda) &= \big(- A_b - \lambda\big)(\lambda - \tilde{\lambda}_1)(\lambda - \tilde{\lambda}_2) - C(k_n^2)\lambda = \\ &= -\lambda^3 + (\tilde{\lambda}_1 + \tilde{\lambda}_2 - A_b)\lambda^2 + (-\tilde{\lambda}_1\tilde{\lambda}_2 + A_b(\tilde{\lambda}_1 + \tilde{\lambda}_2) - C(k_n^2))\lambda - A_b\tilde{\lambda}_1\tilde{\lambda}_2. \end{aligned} \tag{3.47}$$

From (3.47) we get:

$$P_3(0) = -\tilde{\lambda}_1\tilde{\lambda}_2 A_b > 0 \quad \text{and} \quad P_3(\tilde{\lambda}_2) = -\tilde{\lambda}_2 C(k_n^2) < 0. \tag{3.48}$$

Since $P_3(\lambda)$ is continuous, it follows from (3.48), that polynomial $P_3(\lambda)$ has at least one real positive root λ_1 on the interval $(0, \tilde{\lambda}_2)$.

The other two eigenvalues λ_2 and λ_3 of $\mathbf{A}_{k_n}(m_+, s_{2+}, b_+)$ could be real (negative or positive) or complex conjugated numbers (as the coefficients of the polynomial are real). We can write:

$$P_3(\lambda) = -\lambda^3 + (\lambda_1 + \lambda_2 + \lambda_3)\lambda^2 - (\lambda_1\lambda_2 + \lambda_1\lambda_3 + \lambda_2\lambda_3)\lambda + \lambda_1\lambda_2\lambda_3 \tag{3.49}$$

As the coefficients at the second degree of λ in two expressions for $P_3(\lambda)$ from (3.47) and (3.49) should be equal, we have $\lambda_2 + \lambda_3 = \tilde{\lambda}_1 + \tilde{\lambda}_2 - A_b - \lambda_1$. From (3.27) it is derived:

$$\lambda_2 + \lambda_3 = -b(k_n^2) - A_b - \lambda_1 < 0 \tag{3.50}$$

The above inequality holds, since it was mentioned in (3.28), that $b(k_n^2) > 0$, if $m_0 > 0$ and $s_+ > 0$. Thus, if two other eigenvalues are real, then from (3.50) it follows, that at least one of them is negative. Let us suppose $\lambda_2 < 0$. Then

$$\lim_{\lambda \to -\infty} P_3(\lambda) = \infty$$

and $P_3(0) = -\tilde{\lambda}_1\tilde{\lambda}_2 A_b > 0$. That means that on the interval $(-\infty, 0)$ polynomial $P_3(\lambda)$ does not change its sign, or changes it twice. Since $P_3(\lambda)$ is continuous, it follows from $\lambda_2 < 0$ that λ_3 also is negative. In the case, when λ_2 and λ_3 are complex conjugated, their real part is $\lambda_{re} = (\lambda_2 + \lambda_3)/2 < 0$. □

Lemma 3.4.2 *Suppose, that for the chosen parameter values there exists a real positive s_{2+} defined in* (3.6)*. If $\widetilde{\mathbf{A}}_{k_n}(m_+, s_{2+})$ has one zero eigenvalue and one real negative eigenvalue, then $\mathbf{A}_{k_n}(m_+, s_{2+}, b_+)$ has one zero eigenvalue and either two real negative eigenvalues, or two complex conjugated eigenvalues with negative real part.*

Proof. From the assumption of the lemma and from (3.46) it follows, that $C(k_n^2) > 0$. Let $\widetilde{\mathbf{A}}_{k_n}(m_+, s_{2+})$ have one zero eigenvalue and one real negative eigenvalue, $\tilde{\lambda}_1 < \tilde{\lambda}_2 = 0$. Then characteristic polynomial $P_2(\lambda)$ has the form $P_2(\lambda) = \lambda(\lambda - \tilde{\lambda}_1)$. Then

$$\begin{aligned} P_3(\lambda) &= \big(- A_b - \lambda\big)\lambda(\lambda - \tilde{\lambda}_1) - C(k_n^2)\lambda = \\ &= -\lambda(\lambda^2 + (A_b - \tilde{\lambda}_1)\lambda + (C(k_n^2) - \tilde{\lambda}_1 A_b)). \end{aligned} \tag{3.51}$$

And eigenvalues of $\mathbf{A}_{k_n}(m_+, s_{2+}, b_+)$ are following:

$$\lambda_1 = 0, \quad \lambda_{2,3} = \frac{-A_b + \tilde{\lambda}_1 \pm \sqrt{(A_b - \tilde{\lambda}_1)^2 - 4(C(k_n^2) - \tilde{\lambda}_1 A_b)}}{2}. \tag{3.52}$$

Since $C(k_n^2) - \tilde{\lambda}_1 A_b > 0$ and $A_b - \tilde{\lambda}_1 > 0$, then from (3.52) it follows, that eigenvalues $\lambda_{2,3}$ are either real and negative (possible coincident), or complex with negative real part. □

Lemma 3.4.3 *Suppose, that for the chosen parameter values there exists a real positive s_{2+} defined in* (3.6)*. If $\widetilde{\mathbf{A}}_{k_n}(m_+, s_{2+})$ has two real negative eigenvalues, then $\mathbf{A}_{k_n}(m_+, s_{2+}, b_+)$ has either three real negative eigenvalues, or one real negative eigenvalue, and two complex eigenvalues with negative real part.*

Proof. From the assumption of the lemma and from (3.46) it follows, that $C(k_n^2) > 0$. Let $\widetilde{\mathbf{A}}_{k_n}(m_+, s_{2+})$ have two real negative eigenvalues $\tilde{\lambda}_1 \le \tilde{\lambda}_2 < 0$. Then the characteristic polynomial $P_2(\lambda)$ has the form $P_2(\lambda) = (\lambda - \tilde{\lambda}_1)(\lambda - \tilde{\lambda}_2)$. Then

$$\begin{aligned} P_3(\lambda) &= \big(-A_b - \lambda\big)(\lambda - \tilde{\lambda}_1)(\lambda - \tilde{\lambda}_2) - C(k_n^2)\lambda = \\ &= -\lambda^3 + (\tilde{\lambda}_1 + \tilde{\lambda}_2 - A_b)\lambda^2 + (-\tilde{\lambda}_1\tilde{\lambda}_2 + A_b(\tilde{\lambda}_1 + \tilde{\lambda}_2) - C(k_n^2))\lambda - A_b\tilde{\lambda}_1\tilde{\lambda}_2. \end{aligned} \tag{3.53}$$

From (3.53) we get:

$$P_3(-A_b) = C(k_n^2)A_b > 0 \quad \text{and} \quad P_3(0) = -\tilde{\lambda}_1\tilde{\lambda}_2 A_b < 0. \tag{3.54}$$

Since $P_3(\lambda)$ is continuous, it follows from (3.54), that polynomial $P_3(\lambda)$ has at least one root on the interval $(-A_b, 0)$. Thus we can suppose, that $-A_b < \lambda_1 < 0$. From (3.53) it follows, that for $\lambda \ge 0$ polynomial $P_3(\lambda)$ only takes values less than zero. That means, that $P_3(\lambda)$ has no non-negative real roots $P_3(\lambda)$. Thus, if two other eigenvalues of $\mathbf{A}_{k_n}(m_+, s_{2+}, b_+)$ are real, they are also negative. Though it is possible, that polynomial $P_3(\lambda)$ has two complex conjugated roots. Let us denote them as $\lambda_{2,3} = \lambda_{re} \pm i\lambda_{im}$. Then:

$$\begin{aligned} P_3(\lambda) &= -(\lambda - \lambda_1)(\lambda^2 - 2\lambda_{re}\lambda + \lambda_{re}^2 + \lambda_{im}^2) = \\ &= -\lambda^3 + (\lambda_1 + 2\lambda_{re})\lambda^2 - (2\lambda_1\lambda_{re} + \lambda_{re}^2 + \lambda_{im}^2)\lambda + \lambda_1(\lambda_{re}^2 + \lambda_{im}^2). \end{aligned} \tag{3.55}$$

As the coefficients at the second degree of λ in two expressions for $P_3(\lambda)$ (3.53) and (3.55) should be equal, we derive: $2\lambda_{re} = \tilde{\lambda}_1 + \tilde{\lambda}_2 - A_b - \lambda_1$. As $\tilde{\lambda}_1 \le \tilde{\lambda}_2 < 0$ and $-A_b - \lambda_1 < 0$, we get that $\lambda_{re} < 0$. That is, if two eigenvalues of $\mathbf{A}_{k_n}(m_+, s_{2+}, b_+)$ are complex, then their real part is less than zero. □

Lemma 3.4.4 *Suppose, that for the chosen parameter values there exists a real positive s_{2+} defined in* (3.6)*. If $\widetilde{\mathbf{A}}_{k_n}(m_+, s_{2+})$ has two complex conjugated eigenvalues with negative real part, then $\mathbf{A}_{k_n}(m_+, s_{2+}, b_+)$ has either three real negative eigenvalues, or one real negative eigenvalue, and two complex eigenvalues with negative real part.*

Proof. From the assumption of the lemma and from (3.46) it follows, that $C(k_n^2) > 0$. Let $\widetilde{\mathbf{A}}_{k_n}(m_+, s_{2+})$ have the complex conjugated eigenvalues with negative real part $\tilde{\lambda}_{1,2} = \tilde{\lambda}_{re} \pm i\tilde{\lambda}_{im}$, $\tilde{\lambda}_{re} < 0$. Then characteristic polynomial $P_2(\lambda)$ takes positive values for $\forall\lambda \in \mathbb{R}$ and has the form $P_2(\lambda) = (\lambda^2 - 2\tilde{\lambda}_{re}\lambda + \tilde{\lambda}_{re}^2 + \tilde{\lambda}_{im}^2)$. Then

$$\begin{aligned} P_3(\lambda) &= \big(-A_b - \lambda\big)(\lambda^2 - 2\tilde{\lambda}_{re}\lambda + \tilde{\lambda}_{re}^2 + \tilde{\lambda}_{im}^2) - C(k_n^2)\lambda = \\ &= -\lambda^3 + (2\tilde{\lambda}_{re} - A_b)\lambda^2 + (-\tilde{\lambda}_{re}^2 - \tilde{\lambda}_{im}^2 + 2A_b\tilde{\lambda}_{re} - C(k_n^2))\lambda - A_b(\tilde{\lambda}_{re}^2 + \tilde{\lambda}_{im}^2). \end{aligned} \tag{3.56}$$

From (3.56) we get:

$$P_3(-A_b) = C(k_n^2)A_b > 0 \quad \text{and} \quad P_3(0) = -A_b(\tilde{\lambda}_{re}^2 + \tilde{\lambda}_{im}^2) < 0. \tag{3.57}$$

Since $P_3(\lambda)$ is continuous, it follows from (3.57), that polynomial $P_3(\lambda)$ has at least one root on the interval $(-A_b, 0)$. Thus we can suppose $-A_b < \lambda_1 < 0$.

From (3.56) it follows, that for $\lambda \ge 0$ polynomial $P_3(\lambda)$ takes values less than zero. That means, that $P_3(\lambda)$ has no non-negative real roots $P_3(\lambda)$. Therefore, if two other roots of $P_3(\lambda)$ are real, they are also negative.

Though it is possible, that polynomial $P_3(\lambda)$ has two complex conjugated roots. We denote them as $\lambda_{2,3} = \lambda_{re} \pm i\lambda_{im}$. Then:

$$\begin{aligned} P_3(\lambda) &= -(\lambda-\lambda_1)(\lambda^2 - 2\lambda_{re}\lambda + \lambda_{re}^2 + \lambda_{im}^2) = \\ &= -\lambda^3 + (\lambda_1 + 2\lambda_{re})\lambda^2 - (2\lambda_1\lambda_{re} + \lambda_{re}^2 + \lambda_{im}^2)\lambda + \lambda_1(\lambda_{re}^2 + \lambda_{im}^2). \end{aligned} \tag{3.58}$$

As the coefficients of λ^2 in two expressions for $P_3(\lambda)$ (3.56) and (3.58) should be equal, we derive: $2\lambda_{re} = 2\tilde{\lambda}_{re} - A_b - \lambda_1$. As $\tilde{\lambda}_{re} < 0$ and $-A_b - \lambda_1 < 0$, we get that $\lambda_{re} < 0$. That is, if two eigenvalues of $\mathbf{A}_{k_n}(m_+, s_{2+}, b_+)$ are complex, then their real part is less than zero. □

3.5 Stability of the system of three equations

From Remark 3.7 and Lemmas 3.4.2, 3.4.3 and 3.4.4 we deduce:

Remark 3.8 *Suppose, that for the chosen parameter values, m_0 defined in (3.5) is positive, $\beta_m = \beta_{m2}$ and there exists a real positive s_{2+}. Then for zero wavenumber k_0, matrix $\mathbf{A}_{k_n}$ evaluated at the steady-state $z_+ = (m_+, s_{2+}, b_+)$ has either*

- *two negative eigenvalues and one zero eigenvalue; or*
- *three real negative eigenvalues; or*
- *one real non-posistive eigenvalue, and two complex eigenvalues with negative real part.*

That means that the steady-state solution $z_+ = (m_+, s_{2+}, b_+)$ of the system (3.1)–(3.3) is stable against purely temporal perturbations.

Using Lemma 3.4.1 – 3.4.4, we can reformulate Theorem 3.3.1 for the system of three equations (3.14).

Theorem 3.5.1 *Suppose, that for the chosen parameter values m_0 defined in (3.5) is positive, $\beta_m = \beta_{m2}$ and there exists a real positive s_{2+} defined in (3.6). Let matrix $\mathbf{A}_{k_n}$ be defined in (3.18) and evaluated at the steady-state $z_+ = (m_+, s_{2+}, b_+)$, parameter γ_1 be defined in (3.39) and discriminant $\mathscr{D}_\gamma$ be defined in (3.40). Then:*

1. *If $\mathscr{D}_\gamma > 0$, and*
   (a) *if $\gamma_1 < 0$, then $\exists \kappa_1^2, \kappa_2^2 \in \mathbb{R}$ defined by expression (3.37), such that $0 \le \kappa_1^2 < \kappa_2^2$ and:*
      - *for $k_n^2 \in (\kappa_1^2, \kappa_2^2)$ matrix $\mathbf{A}_{k_n}$ has one real positive eigenvalue and either two real negative eigenvalues, or two complex conjugated eigenvalues with negative real part;*
      - *for $k_n^2 = \{\kappa_1^2; \kappa_2^2\}$ matrix $\mathbf{A}_{k_n}$ has one zero eigenvalue and either two real negative eigenvalues, or two complex conjugated eigenvalues with negative real part;*
      - *for $k_n^2 \in [0, \infty)/[\kappa_1^2, \kappa_2^2]$ matrix $\mathbf{A}_{k_n}$ has either three real negative eigenvalues, or one real negative eigenvalue, and two complex eigenvalues with negative real part;*

   (b) *if $\gamma_1 > 0$, then:*
      i. *if $\gamma_0 > 0$, then for $\forall k_n^2 \in [0, \infty)$, matrix $\mathbf{A}_{k_n}$ has either three real negative eigenvalues, or one real negative eigenvalue, and two complex eigenvalues with negative real part;*
      ii. *if $\gamma_0 = 0$, then*

- *for* $\forall k_n^2 \in (0,\infty)$ *matrix* $\mathbf{A}_{k_n}$ *has either three real negative eigenvalues, or one real negative eigenvalue, and two complex eigenvalues with negative real part;*

- *for* $k_n^2 = 0$ *matrix* $\mathbf{A}_{k_n}$ *has one zero eigenvalue and either two real negative eigenvalues, or two complex conjugated eigenvalues with negative real part;*

2. *If* $\mathscr{D}_\gamma = 0$, *and*

   (a) *if* $\gamma_1 \le 0$, *then* $\exists \kappa_1^2 = \kappa_2^2 = -\frac{\gamma_1}{2\gamma_2} \ge 0$, *such that*

   - *for* $k_n^2 = \kappa_1^2$ *matrix* $\mathbf{A}_{k_n}$ *has one zero eigenvalue and either two real negative eigenvalues, or two complex conjugated eigenvalues with negative real part;*

   - *for* $k_n^2 \in [0,\infty)/\{\kappa_1^2\}$ *matrix* $\mathbf{A}_{k_n}$ *has either three real negative eigenvalues, or one real negative eigenvalue, and two complex eigenvalues with negative real part;*

   (b) *if* $\gamma_1 > 0$, *then for* $\forall k_n^2 \in [0,\infty)$ *matrix* $\mathbf{A}_{k_n}$ *has either three real negative eigenvalues, or one real negative eigenvalue, and two complex eigenvalues with negative real part;*

3. *if* $\mathscr{D}_\gamma < 0$, *then for* $\forall k_n^2 \in [0,\infty)$, *and matrix* $\mathbf{A}_{k_n}$ *has either three real negative eigenvalues, or one real negative eigenvalue, and two complex eigenvalues with negative real part.*

Corollary 3.5.1 *Suppose that the conditions of Theorem 3.5.1 hold. Then if* $\mathscr{D}_\gamma$ *defined in* (3.40) *is positive and* γ_1 *defined in* (3.39) *is negative, then* $\exists \kappa_1^2, \kappa_2^2 \in \mathbb{R}$ *defined by expression* (3.37)*, such that the magnitude of perturbation modes with wavenumbers* $k_n^2 \in (\kappa_1^2, \kappa_2^2)$ *grow monotonically after a certain period of time. Otherwise, i.e. when* $\mathscr{D}_\gamma \le 0$ *or when* $\gamma_1 \ge 0$, *then initially small perturbations remain small during any period of time, or even disappear when* $t \to \infty$.

4 Numerical results

The predictions from the linear stability analysis are validated against a sequence of numerical simulations. For the chosen parameter value sets (2.9), (2.10) and (2.9), (2.11), the inequalities $\mathscr{D}_\gamma > 0$ and $\gamma_1 < 0$ hold. They are most sensitive against parameters B_{m2} and D_m. Using (3.38), (3.30), (3.31) and (3.32) we derive:

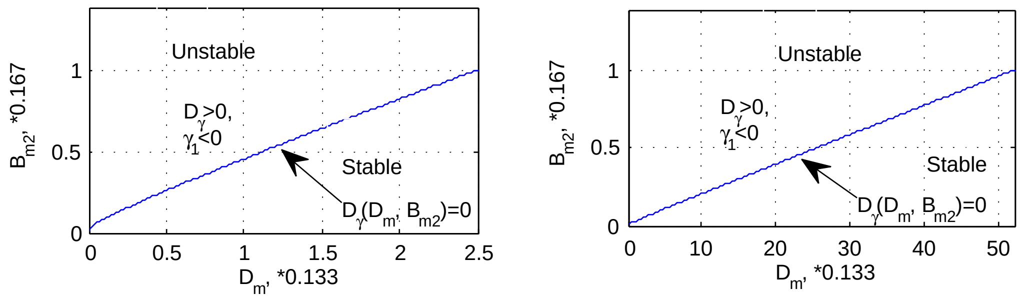
$$\begin{cases} \gamma_1 < 0, \\ \mathscr{D}_\gamma = \gamma_1^2 - 4\gamma_0\gamma_2 > 0 \end{cases} \Leftrightarrow \ \gamma_1 < -2\sqrt{\gamma_2\gamma_0} \ \Leftrightarrow,$$

$$\begin{aligned} B_{m2} > \frac{D_m A_{s2}}{\chi m_+} + D_{s2}\left(\frac{\alpha_m}{\chi m_+} + \frac{\alpha_{m0} m_0}{A_{s2} s_{2+}}\right) + \\ + 2\sqrt{\frac{D_m D_{s2}}{A_{s2} s_{2+}(\beta_{m2} + s_{2+})}}\left(\alpha_{m0} m_0 + \frac{\alpha_m s_{2+}}{\beta_m + s_{2+}}(2 - m_+) + \alpha_m(m_+ - 1)\right). \end{aligned} \tag{4.1}$$

The region in the first quadrant of plane (D_m, B_{m2}), defined by inequality (4.1), is shown in Figure 3.

If we fix the values of all parameters, except B_{m2}, then the right part of inequality (4.1) could be denoted as the ultimate value B_{m2}^{lim}, such that for $B_{m2} \le B_{m2}^{lim}$ small perturbations near (m_+, s_{2+}, b_+) are predicted not to grow with time. For $B_{m2} > B_{m2}^{lim}$ small perturbations of mode $\phi_n(x)$ will grow, if $\kappa_1 < k_n < \kappa_2$. We mention here, that when $B_{m2} \to B_{m2}^{lim} + 0$, then $\kappa_1 \to \kappa_2$. That means, that if B_{m2} is close to ultimate value B_{m2}^{lim}, then the interval (κ_1, κ_2) is small, and it could happen, that no wavenumber k_n lies inside this interval. In this case perturbations near the homogeneous steady-state will not grow, in spite of the fact, that condition (4.1) holds.

From (3.21) and (3.22) it follows, that parameter B_{m2} does not influence the stability of the steady-states $z_t = (0,0,0)$ and $z_0 = (m_0, 0, b_0)$. The stability of the steady-state $z_- =$



(a) (b)

Figure 3: Plot of the region, where $\gamma_1 < 0$ and $\mathscr{D}_\gamma > 0$ in the first quadrant of plane (D_m, B_{m2}). The rest of parameters are initialized: (a) as in (2.9), (2.10), and (b) as in (2.9), (2.11).

(m_-, s_{2-}, b_-) against purely temporal perturbations is determined from the eigenvalues of matrix $A_{k_0}(m_-, s_{2-}, b_-)$ (3.18). As $k_0 = 0$, then this matrix does not depend on parameter B_{m2}. For the considered parameter values (2.9), (2.10) and (2.11), and for any B_{m2}, z_- is unstable against purely temporal perturbations. Therefore, varying B_{m2}, we can change the stability of the steady-state z_+, while the stability of the steady-states z_t, z_0 and z_- remains unchanged. Since for parameter values (2.9), (2.10) and (2.11) (B_{m2} can be arbitrary), homogeneous steady-states z_t, z_0 and z_- are unstable, the solution will not converge to these steady-states.

For the cases when the model parameters are initialized as in (2.9), (2.10) and (2.9), (2.11), the ultimate values are $B_{m2}^{lim} \approx 0.4571 * 0.167\, mm^2/day$ and $B_{m2}^{lim} \approx 0.02481 * 0.167\, mm^2/day$.

First, the parameter values (2.9), (2.10) are considered. When the problem domain is a 1D interval $x \in [1, 6]$ in Cartesian coordinates, the wavenumbers are determined as $k_n = \pi n/5\, mm^{-1}$, $n = 0, 1, 2, \ldots$. Then for $B_{m2} = 0.4572 * 0.167\, mm^2/day$, which is larger than the ultimate value, still no wavenumber lies inside $(\kappa_1, \kappa_2) = (\approx 4.2805 mm^{-1}, \approx 4.3838 mm^{-1})$. Though, for $B_{m2} = 0.4573 * 0.167\, mm^2/day$, $k_7 \approx 4.3982 mm^{-1} \in (\kappa_1, \kappa_2) = (\approx 4.2322 mm^{-1}, \approx 4.4339 mm^{-1})$. When the parameter values (2.9), (2.11) are chosen, then for $B_{m2} = 0.0249 * 0.167\, mm^2/day$, $k_6 \approx 3.7699 mm^{-1} \in (\kappa_1, \kappa_2) = (\approx 3.6417 mm^{-1}, \approx 4.324 mm^{-1})$.

In Figure 4, 5 the results of numerical simulations are shown. The solutions were obtained with use of finite element method. Zero flux of m, $s2$ on the boundaries was specified as the boundary conditions. Initial conditions were taken in the form of small random perturbations near the homogeneous steady-state solution (m_+, s_{2+}, b_+). To introduce the perturbations in the initial solution during simulations, the corresponding steady-state value plus a small random number were assigned to every degree of freedom at time $t = 0$. From Figure 4, 5 it follows, that for values B_{m2} less than the ultimate value, the numerical solution tends to the homogeneous steady-state solution (m_+, s_{2+}, b_+) with time. And when parameter B_{m2} is larger than B_{m2}^{lim} and such, that $\exists k_n \in (\kappa_1, \kappa_2)$, then there is no convergence to the homogeneous solution, and a wave-like profile occurs in the solution. However, when B_{m2} is larger than B_{m2}^{lim}, though such that still no wave number lies inside (κ_1, κ_2), then the numerical solutions again converge to the homogeneous steady-state (m_+, s_{2+}, b_+). Thus, the predictions of the linear stability analysis are fully confirmed by the numerical simulations.

The introduced linear stability analysis allows to assess the stability of the considered homogeneous steady-state solution. From its stability it can be concluded, whether or not small perturbations grow with time. Though, what could be said, when the perturbations are not small? The only thing, that can be asserted, is that if the homogeneous steady-state solution is not stable, then the solution of the problem will never converge to that steady-state solution, unless the initial conditions are identical to the steady-state solution. Though, when the steady-state solution is stable, it is still unknown, how large initial perturbations behave, whether they disappear or prevail, or even grow.

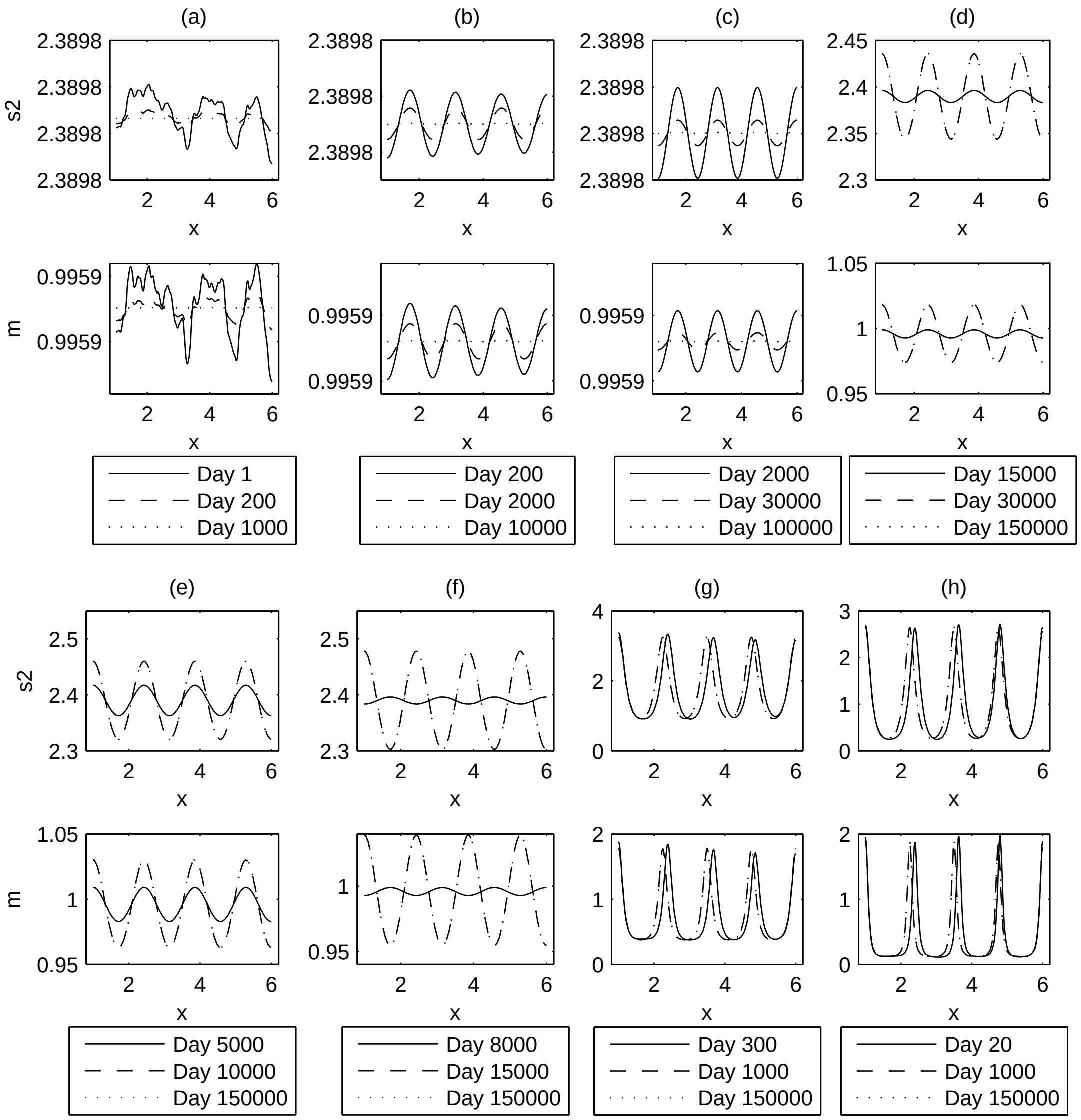


Figure 4: Solution of equations (3.1)–(3.3) in Cartesian coordinates at different time moments. Small random initial perturbations near the homogeneous steady-state solution (m_+, s_{2+}, b_+) are considered. Zero fluxes of m, $s2$, b on the boundaries are taken as the boundary conditions. Parameter B_{m2} takes different values: $B_{m2} = k \cdot 0.167\ mm^2/day$, (a) $k = 0.3$, (b) $k = 0.4571$, (c) $k = 0.4572$, (d) $k = 0.4573$, (e) $k = 0.4574$, (f) $k = 0.4575$, (g) $k = 0.6$, (h) $k = 1$. The rest of parameters are initialized as in (2.9), (2.10).

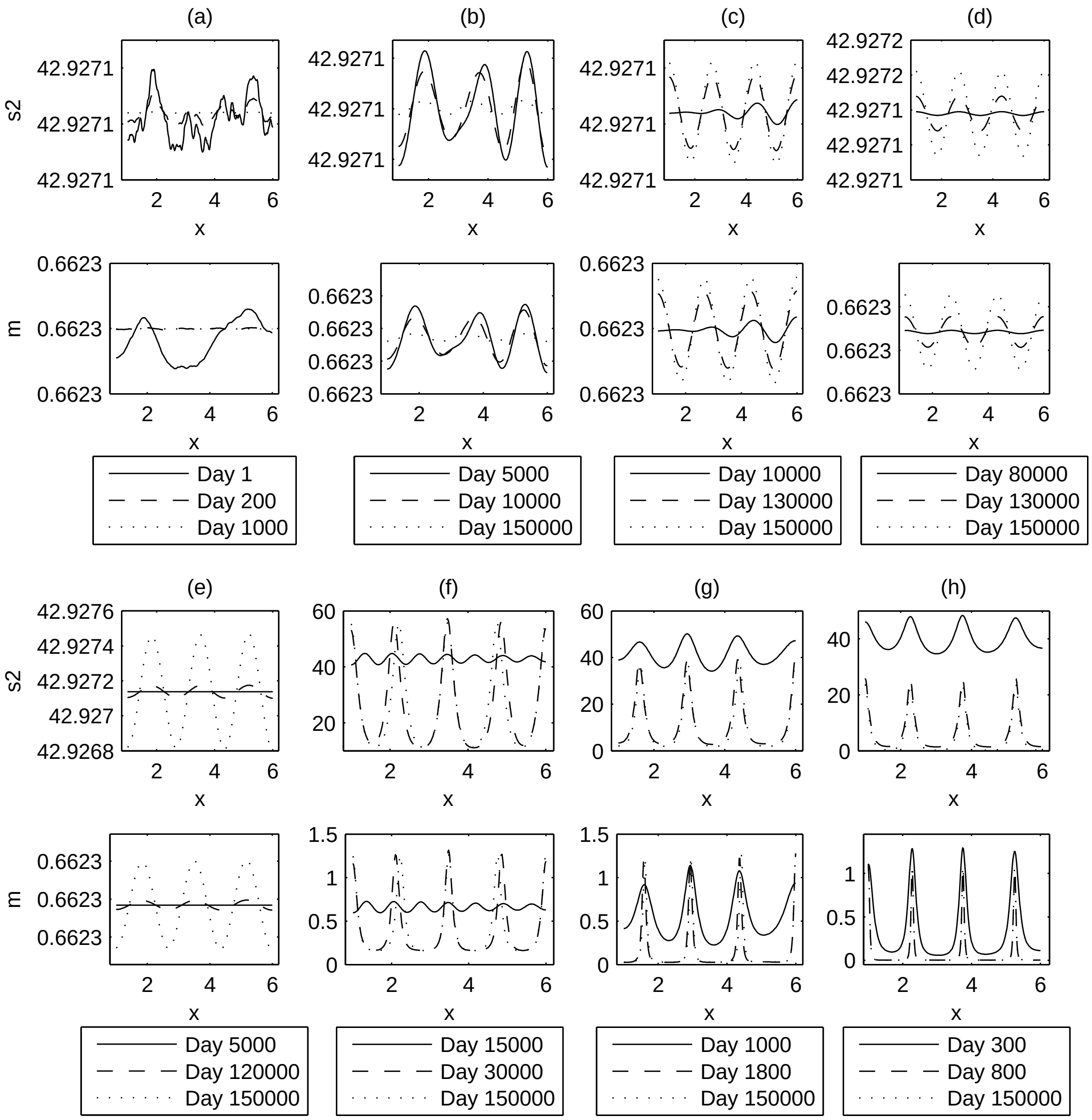


Figure 5: Solution of equations (3.1)–(3.3) in Cartesian coordinates at different time moments. Small random initial perturbations near the homogeneous steady-state solution (m_+, s_{2+}, b_+) are considered. Zero fluxes of m, $s2$, b on the boundaries are taken as the boundary conditions. Parameter B_{m2} takes different values: $B_{m2} = k \cdot 0.167\ mm^2/day$, (a) $k = 0.01$, (b) $k = 0.0248$, (c) $k = 0.0249$, (d) $k = 0.0250$, (e) $k = 0.0251$, (f) $k = 0.04$, (g) $k = 0.09$, (h) $k = 0.2$. The rest of parameters are initialized as in (2.9), (2.11).

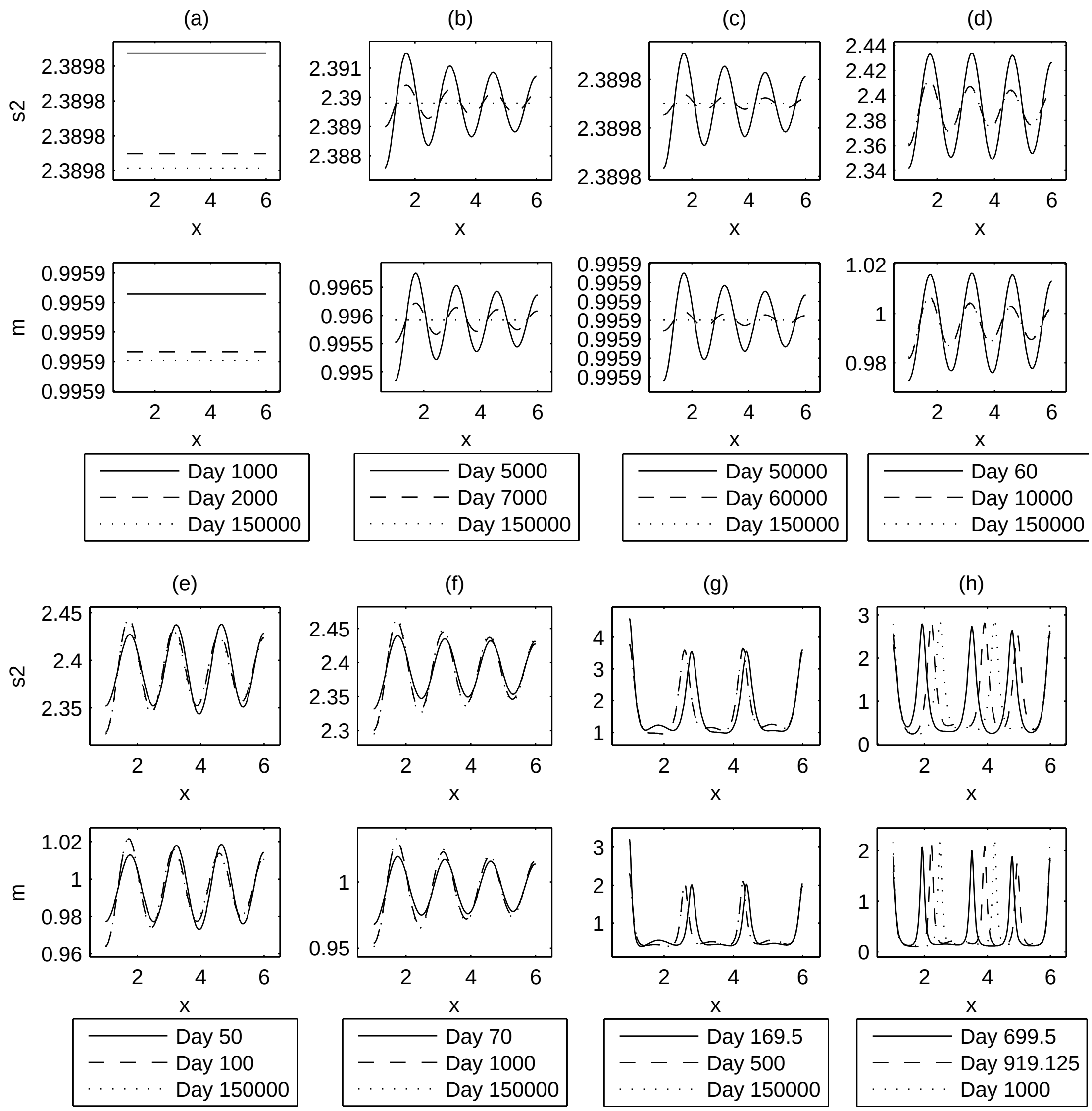


Figure 6: Solution of equations (3.1)–(3.3) in axisymmetric coordinates at different time moments. Initial and boundary conditions are as proposed in [Moreo, 2008]. Parameter B_{m2} takes different values: $B_{m2} = k \cdot 0.167\ mm^2/day$, (a) $k = 0.3$, (b) $k = 0.4571$, (c) $k = 0.4572$, (d) $k = 0.4573$, (e) $k = 0.4574$, (f) $k = 0.4575$, (g) $k = 0.6$, (h) $k = 1$. The rest of parameters are initialized as in (2.9), (2.10).

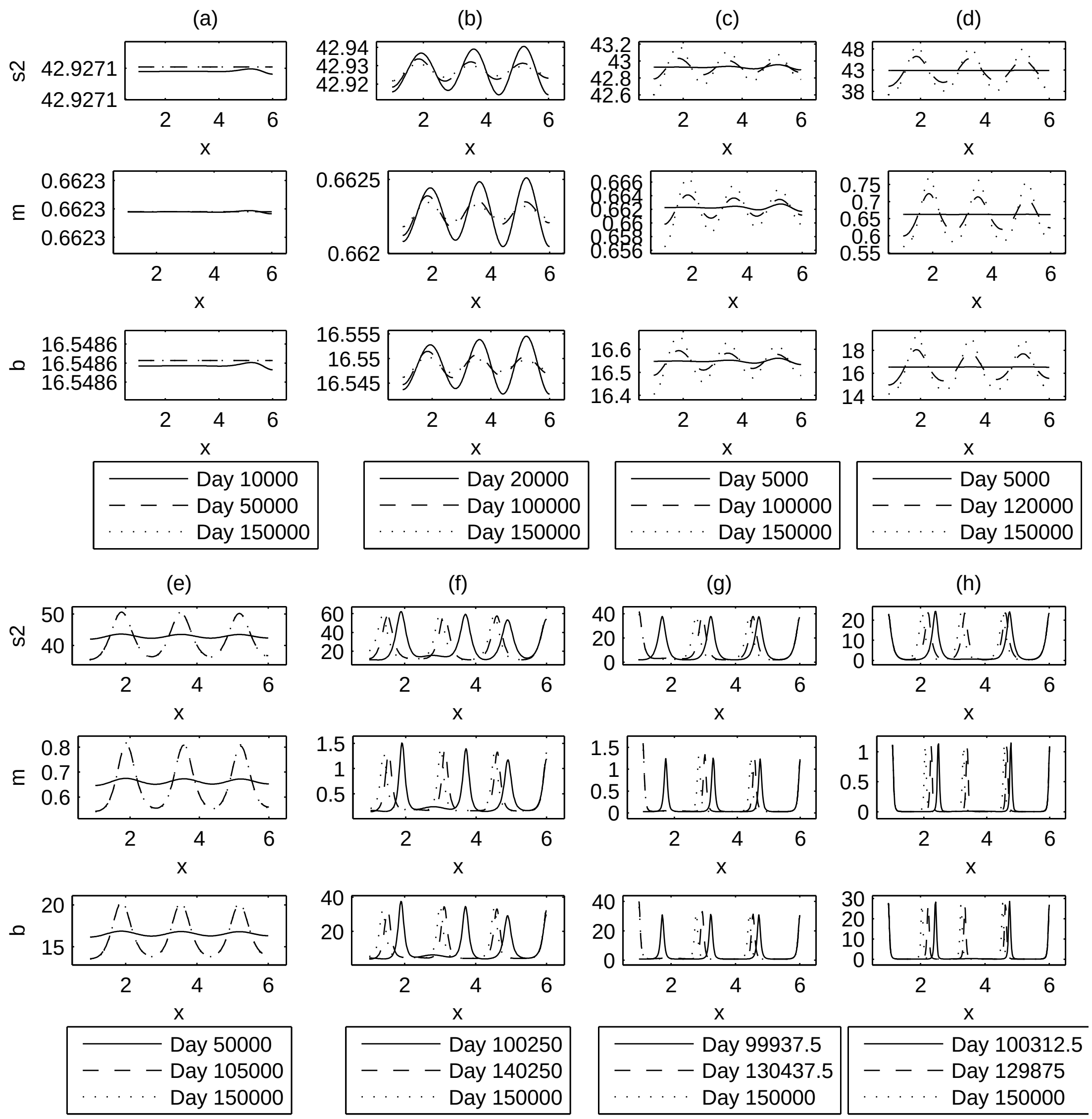


Figure 7: Solution of equations (3.1)–(3.3) in Cartesian coordinates at different time moments. Initial and boundary conditions are as proposed in [Moreo, 2008]. Parameter B_{m2} takes different values: $B_{m2} = k \cdot 0.167\ mm^2/day$, (a) $k = 0.01$, (b) $k = 0.0248$, (c) $k = 0.0249$, (d) $k = 0.0250$, (e) $k = 0.0251$, (f) $k = 0.04$, (g) $k = 0.09$, (h) $k = 0.2$. The rest of parameters are initialized as in (2.9), (2.11).

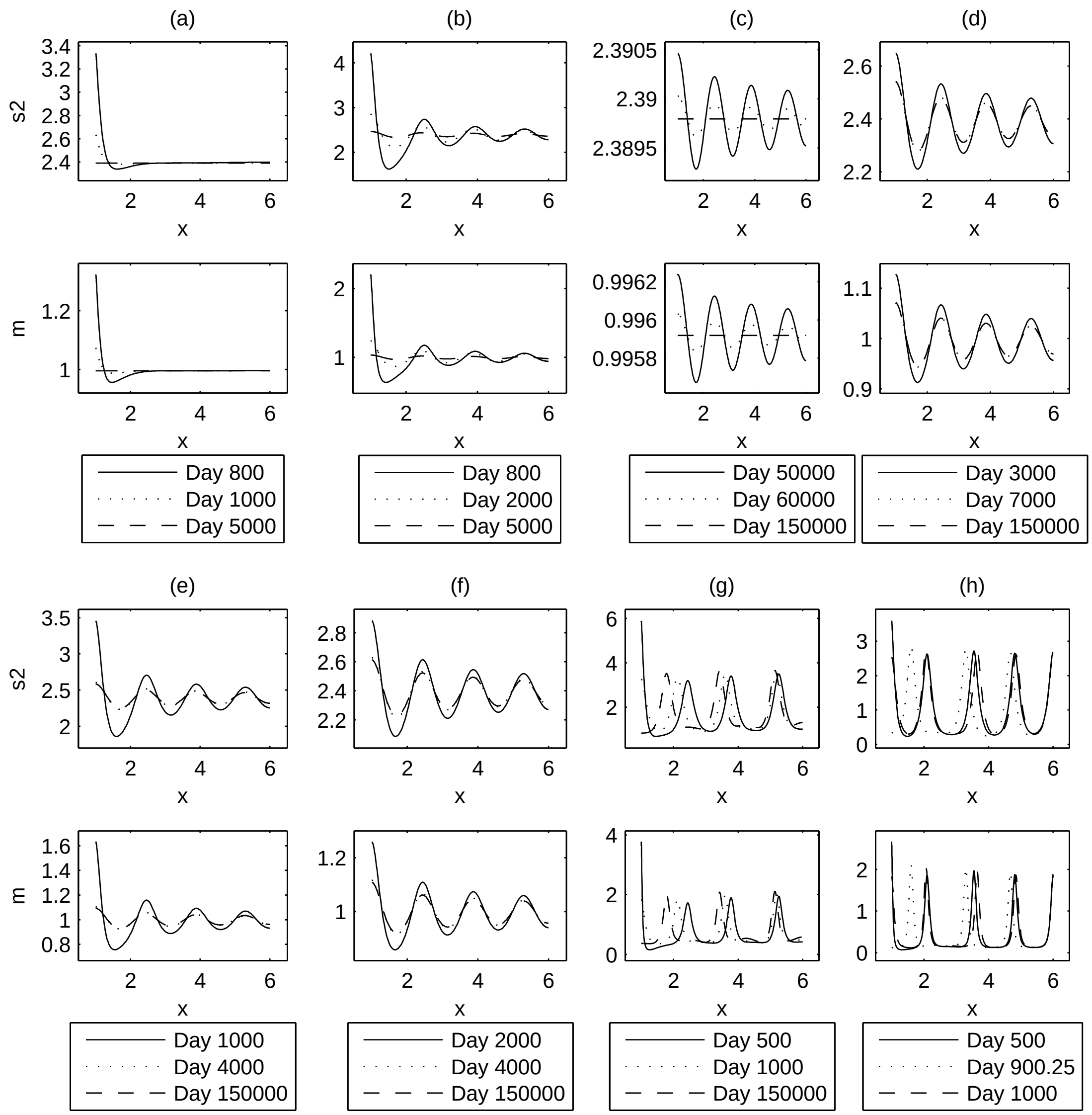


Figure 8: Solution of equations (2.1)–(2.8) in axisymmetric coordinates at different time moments. Initial and boundary conditions are as proposed in [Moreo, 2008]. Parameter B_{m2} takes different values: $B_{m2} = k \cdot 0.167\ mm^2/day$, (a) $k = 0.3$, (b) $k = 0.4571$, (c) $k = 0.4572$, (d) $k = 0.4573$, (e) $k = 0.4574$, (f) $k = 0.4575$, (g) $k = 0.6$, (h) $k = 1$. The rest of parameters are initialized as in (2.9), (2.10).

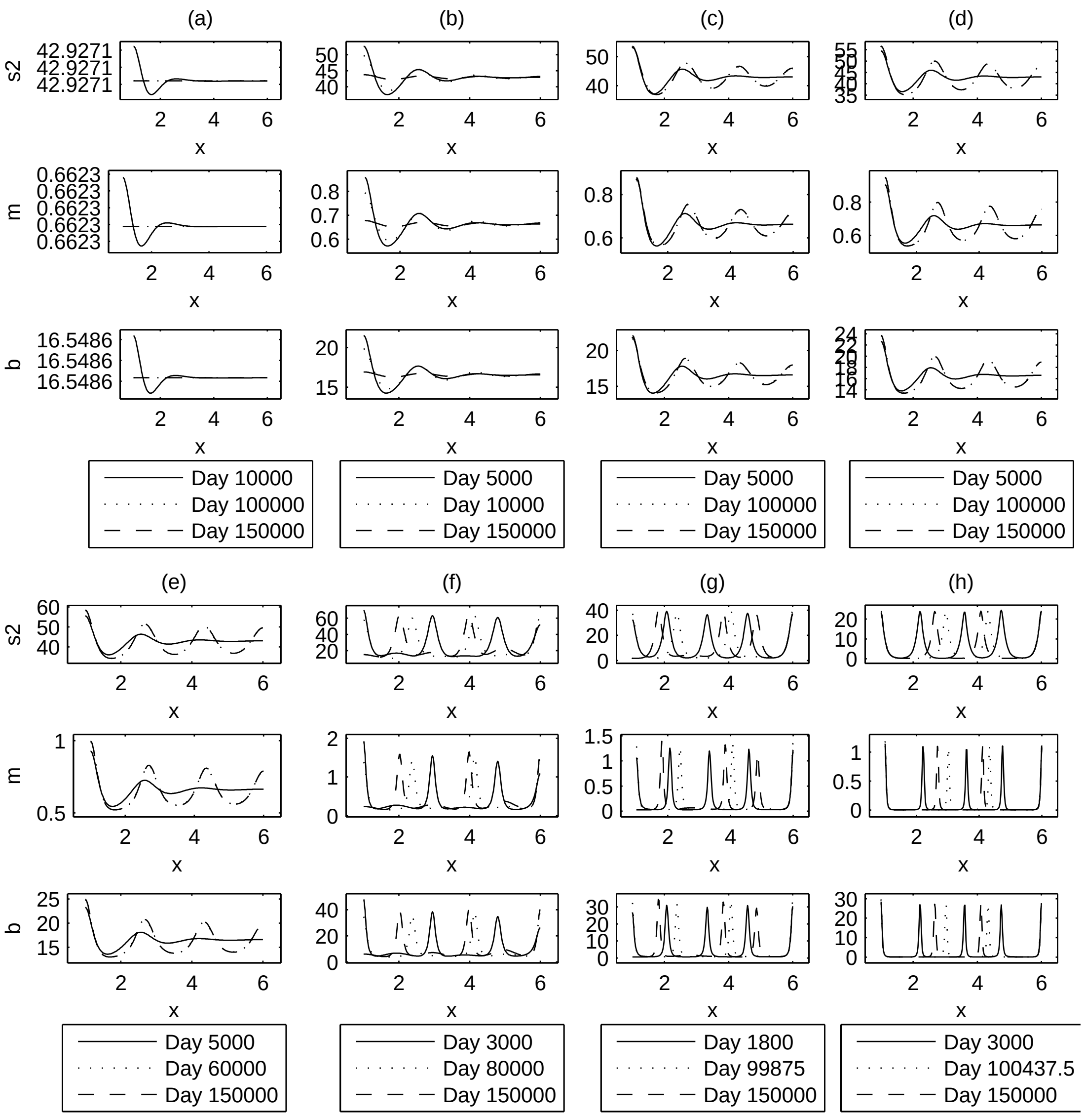


Figure 9: Solution of equations (2.1)–(2.8) in axisymmetric coordinates at different time moments. Initial and boundary conditions are as proposed in [Moreo, 2008]. Parameter B_{m2} takes different values: $B_{m2} = k \cdot 0.167\ mm^2/day$, (a) $k = 0.01$, (b) $k = 0.0248$, (c) $k = 0.0249$, (d) $k = 0.0250$, (e) $k = 0.0251$, (f) $k = 0.04$, (g) $k = 0.09$, (h) $k = 0.2$. The rest of parameters are initialized as in (2.9), (2.11).

In reality, we have to deal with large deviations from the steady-state. [Moreo, 2008] proposed the following initial and boundary conditions for the model, which resembles the bone formation process near a dental implant. Let $\mathbf{\Omega}$ be a problem domain with the boundary $\mathbf{\Gamma}$, and $\mathbf{\Gamma_b}$ is a part of boundary, corresponding to bone surface, and $\mathbf{n}$ is an outward unit normal. Then, according to [Moreo, 2008]:

$$\begin{cases} c(\mathbf{x},0) = 0.25, & m(\mathbf{x},0) = 0.001, \\ b(\mathbf{x},0) = 0.001, & s_1(\mathbf{x},0) = 0.01, \\ s_2(\mathbf{x},0) = 0.01, & v_{fn}(\mathbf{x},0) = 1, \\ v_w(\mathbf{x},0) = 0, & v_l(\mathbf{x},0) = 0, \end{cases} \quad \mathbf{x} \in \mathbf{\Omega}. \tag{4.2}$$

$$\begin{cases} (D_c \nabla c(\mathbf{x},t) - H_c c(\mathbf{x},t) \nabla p(\mathbf{x})) \cdot \mathbf{n} = 0, & \\ D_{s1} \nabla s_1(\mathbf{x},t) \cdot \mathbf{n} = 0, \quad D_{s2} \nabla s_2(\mathbf{x},t) \cdot \mathbf{n} = 0, & \mathbf{x} \in \mathbf{\Gamma},\ t \in (0,\infty) \\ m(\mathbf{x},t) = 0.2, & \mathbf{x} \in \mathbf{\Gamma_b},\ t \in (0,14]\ [days] \\ (D_m \nabla m(\mathbf{x},t) - m(\mathbf{x},t)(B_{m1} \nabla s_1(\mathbf{x},t) + & \mathbf{x} \in \mathbf{\Gamma} \backslash \mathbf{\Gamma_b},\ t \in (0,14]\ [days],\ \text{and} \\ \quad + B_{m2} \nabla s_2(\mathbf{x},t))) \cdot \mathbf{n} = 0, & \mathbf{x} \in \mathbf{\Gamma},\ t \in (14,\infty)\ [days]. \end{cases} \tag{4.3}$$

When adapted to the simplified system of three equations, initial and boundary conditions (4.2), (4.3) are rewritten as:

$$m(\mathbf{x},0) = 0.001, \quad b(\mathbf{x},0) = 0.001, \quad s_2(\mathbf{x},0) = 0.01, \qquad \mathbf{x} \in \mathbf{\Omega}. \tag{4.4}$$

$$\begin{cases} D_{s1} \nabla s_1(\mathbf{x},t) \cdot \mathbf{n} = 0, \quad D_{s2} \nabla s_2(\mathbf{x},t) \cdot \mathbf{n} = 0, & \mathbf{x} \in \mathbf{\Gamma},\ t \in (0,\infty) \\ m(\mathbf{x},t) = 0.2, & \mathbf{x} \in \mathbf{\Gamma_b},\ t \in (0,14]\ [days] \\ (D_m \nabla m(\mathbf{x},t) - m(\mathbf{x},t) B_{m2} \nabla s_2(\mathbf{x},t)) \cdot \mathbf{n} = 0, & \mathbf{x} \in \mathbf{\Gamma} \backslash \mathbf{\Gamma_b},\ t \in (0,14]\ [days],\ \text{and} \\ & \mathbf{x} \in \mathbf{\Gamma},\ t \in (14,\infty)\ [days]. \end{cases} \tag{4.5}$$

Initial conditions (4.4) are far from the small perturbations near the homogeneous steady-state (m_+, s_{2+}, b_+).

The simplified system (3.1)–(3.3), and the full system (2.1)–(2.8) were solved numerically for initial and boundary conditions (4.2), (4.3) and (4.4), (4.5) respectively, and for a number of parameter value sets. The solutions are plotted in Figure 6, 7, 8, 9. The numerical simulations show, that if parameter values are such, that the homogeneous steady-state (m_+, s_{2+}, b_+) is stable, then the numerical solutions of both systems for the unknowns $m(x,t)$, $s_2(x,t)$, $b(x,t)$ converge to this homogeneous state after a certain period of time. Though, if the homogeneous solution (m_+, s_{2+}, b_+) is not stable, then a wave-like profile develops in the solution for osteogenic cells and growth factor 2 and for parameter values (2.9), (2.11) also in the solution for osteoblasts. For some values of parameter B_{m2} that 'wave-like' profile is steady (e.g. Figure 6(e)). Though, when B_{m2} is much larger than the ultimate value, then the waves in the numerical solution are not steady, but moving (e.g. Figure 6(h)).

5 Conclusions

We have defined a simplified system of three equations, characterized by the appearance of the wave-like profile in the solution under the same conditions, as for the solution of the full system of eight equations. For the considered parameter values the simplified system has four homogeneous steady-state solutions. The stability conditions for one of the steady-states, denoted as $z_+ = (m_+, s_{2+}, b_+)$, are determined in terms of model parameters. By changing the value of the model parameter B_{m2}, it is possible to make the solution z_+ unstable or stable, while three other homogeneous steady-states z_t, z_0 and z_- remain unstable. The analytical predictions on the stability of steady-state z_+ for various parameter sets are confirmed by numerical simulations, when starting from small perturbations near the homogeneous steady-state solution.

If the initial perturbations are not small, then one can only conclude, that the homogeneous steady-state will never be reached, if it is not stable. That is confirmed by the numerical simulations, which evidence, that a wave-like profile appears in the solution, if all the homogeneous steady-states are unstable. The numerical simulations also show, that if the solution z_+ is stable and z_t, z_0, z_- are unstable, then numerical solutions for unknowns $m(x,t)$, $s_2(x,t)$, $b(x,t)$ of full and simplified systems converge to the homogeneous steady-state solution (m_+, s_{2+}, b_+) after a certain period of time, when starting with initial conditions proposed in [Moreo, 2008].

Therefore, the numerical simulations demonstrate, that if homogeneous steady-states z_t, z_0, z_- are unstable, then stability of the homogeneous steady-state z_+ could determine the behavior of the solution of the whole system, when specific initial conditions are considered. That makes it possible to assess the values of model parameters, for which biologically irrelevant solutions with a 'wave-like' profile can be obtained.

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