Journal of Mechanics in Medicine and Biology
Vol. 9, No. 3 (2009) 259–272

World Scientific
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ONE-DIMENSIONAL MODEL OF SOMITIC CELLS POLARIZATION IN A BISTABILITY WINDOW OF EMBRYONIC MESODERM

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Received 17 November 2008
Accepted 6 March 2009

The considerations are based on the understanding that somitic cells polarization in bistability window of embryonic (pre-somitic) mesoderm is a dynamical process. It occurs in the form of a polarization wavefront of somite cells spread in anterior–posterior direction of the embryonic mesoderm. It is assumed that a macroscopic cell polarization has a bistable behavior corresponding to the molecular mechanism of bistability window formation. Moreover this type of polarization is supposed to be transmittable to the other cells by contact interaction. At the end, a volume of polarized cells is taken, which is able to create mechanical tension in the volume of nonpolarized neighbor cells and to inhibit their polarization. On this basis we explore the leading aspect of somitogenesis robustness by considering a simple wavefront model of polarization and analyzing its propagation in terms of the standard methods of qualitative theory of differential equations. The obtained theoretical results are interpreted in the context of their possible experimental verification.

1. Introduction

It is known that the somite formation correlates with cycles of cell-autonomous gene expression, which spread from the tail bud to the rostral presomitic mesoderm (PSM) border with a periodicity equal to that of the somitogenesis.[1] Real-time imaging of *Hes 1* expression suggests that a given cell moving from the tail bud undergoes around five oscillations before reaching the forming somite. The mechanism by which the PSM oscillations are converted into a spatial pattern remains unknown, inspite of some hints provided by theoretical models. One explanation is that the PSM gradients affect a biochemical parameter of the segmentation clock by which the oscillation period tends towards infinitive in the most rostral PSM.[2]

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Another one is that a permanent record, e.g. a covalent protein modification, is made when the PSM cells exit the tail bud, and the actual somite formation depends on the time needed to interpret this record.[3] A third proposition is that the oscillation arrest is defined after a given number of oscillations, e.g. through the accumulation of some molecule.[4,5]

The general impression from all the models cited above and other similar models (see Ref. 6; Baker *et al.*, 2003; Petrov *et al.*, 2007) is that they are mathematical formalisms of somite biochemical specifications but not somite physical formation.[7] The last paper shows as an exception the mathematical model of Schnell *et al.*[8] attempting to describe the bulk movement of somitic cells to form a somite. We would also mention here a paper of Beloussov,[9] presenting exception in this sense. Segmentation mechanism of somitogenesis is a result of axial stretch (chemotaxis) action. Together with surface tension (adhesion) it can account for post-gene-expression stage in converting temporal into spatial patterns of somitogenesis. It means the gene expression oscillations govern on time the axial stretching and surface compression of PSM. On the other hand the variable mechanical factors (stretching, compression and viscosity) determine the morphological changes in the time allotted for somite formation. In addition Beloussov argues the idea that somitogenesis is a *robust* process based upon the mechanical relationship between a long-range tension forces stretching the axial mesoderm and short-range forces of presomite cell cohesion. In the literature the terms *robust* and *structurally stable* have one and the same sense.[10] It is of interest therefore to analyze the stability in terms of both Lyapunov's definition and structural one and to interpret it in the context of somitogenesis robustness.

In an earlier paper of Beloussov,[11] it is suggested that the organization of the axial structures is established and maintained by tensile fields created by uniformly *polarized* cells. Following Belintsev *et al.*,[12,13] we consider somatic cells polarization exists in a form of morphologically polarized and nonpolarized cells distributed in somite pre-pattern of embryonic mesoderm. Both polarized and nonpolarized states should be considered as stable ones by analogy with the sharp developmental thresholds defined through bistability by antagonistic gradients of retinoic acid (RA) and fibroblast growth factor (FGF) signaling.[14] Moreover cell polarization can be transmitted by contact from a given somite cell to its neighbor. At the end a mutual relationship between cross polarization and axial elastic tension of the mesoderm is introduced. That is why we call this model as elasto-polarization model. In this paper we show that, as a result of interaction of elastic forces, spontaneous and contact polarization, a traveling front of somatic cells polarization, propagates through the bistability window of mesoderm layer. The specificity of this propagating wavefront is discussed in terms of stability and robustness analysis.

The mathematical scheme of the above described mechanism is already developed in the papers of Belintsev *et al.*[12,13] Nevertheless, we realize as necessary some specification of the analysis, in view of the fact that the concrete process of somite formation is not considered there.

It is known that at cellular level the somitogenesis is accompanied with the same forms of mechanical activity of the cells as during the polarization in epithelial tissues.[9] Nonsegmented mesoderm presents a bushy cell mass, essential part of which is occupied by intercellular elements. The same tissue, involved in somites, is essentially different. It distinguishes by denser and more extended intercellular contacts, resembling to polarized cells of embryonic epithelial tissues. In papers of Belintsev *et al.*,[12,13] the universal event in morphogenesis, i.e. the formation of domains of morphologically polarized cells in the initially homogeneous epithelial sheets can be obtained as self-organization effect of elasto-polarization model. When considering PSM we can interpret this event as somite formation.

2. Determining the Bistability Window of Embryonic Mesoderm where Somitic Cells Polarization Occurs

In the paper of Goldbeter *et al.*,[14] a remarkable scheme (Fig. 1) is shown. It presents dependence between the *stable* steady state values M_G of *fgf8* mRNA concentration in PSM and the positions x along PSM of the lower and upper limits of the region of RA and FGF bistability.

From the graphs of this figure it is seen that, the position of such named bistability window can be parametrically moved from left to right, when the concentration M_G of *fgf8* mRNA tends to zero by low values. The kinetic explanation of this dependence consists in the consideration that bistability window moves at the expense of decreasing the effect of FGF inhibition on segmentation clock rest.[14] However for fixed value of M_G the window does not move and we can consider it as constant prepattern (with fixed boundaries), where a somatic cells polarization occurs.

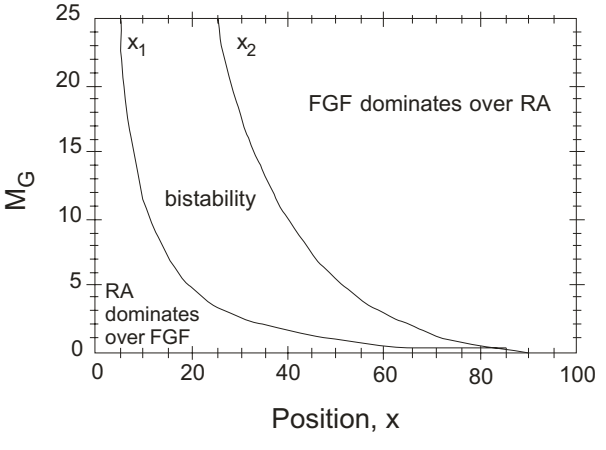

Fig. 1. Relationship between *fgf8* concentration and bistability domain position.

As it is shown by Goldbeter *et al.*,[14] in order to prove the existence of bistability window in the PSM of the embryo, we have to consider the establishment of thresholds along morphogen gradients. It is mathematically proven that mutual inhibitory gradients generate sharp morphogen thresholds in the PSM. For this purpose it is demonstrated that the antagonistic gradients of RA and FGF along PSM may lead to the coexistence of two stable states. Bistability results from the mutual inhibition of RA and FGF and provides a molecular mechanism for the "all-or-none" transitions assumed both in the specific clock and wavefront model of somitogenesis[15] and more general cell polarization model of morphogenesis.[12,13]

In order to specify the model of Belintsev *et al.*[12,13] for the case of somatic cells polarization, it is necessary to accentuate the circumstance that the *molecular mechanism* for "all-or-none" transition, established by Goldbeter *et al.*,[14] is in evident correspondence with the well-known capacity of an individual cell for *morphological polarization* considered as a bistable "all-or-none" transition of a cell from a nonpolarized to a polarized state. In this way we consider the cell polarization in the bistability window of PSM as an apico-basal elongation (i.e. macroscopic deformation), connected with the above-mentioned molecular mechanism.

3. Bistable Equation for Propagating Polarization WaveFront

The experimental observations of somitogenesis suggest the most natural assumption that somitic cells polarization wavefront looks like a moving plateau. If we use w to denote the wavefront variable of polarization, then in front of the wave, w is fixed at some low value, and behind the wave, w is fixed at higher value. A schematic diagram of such a wavefront is presented in Fig. 2. Such a wave is called *traveling front*.[16]

The observations show that the whole layer of somitic cells can be divided along the axis into three parts. The first one is a layer behind the traveling front, where the polarization has a higher steady state value. The second is a layer of traveling front of polarization drop value. The third is a layer in front of the drop, where the polarization has lower steady state value. The fact that relatively synchronous regions of two steady states are realized, means these states are stable, as otherwise they would not appear. So if we consider a somitic cells polarization as synchronous

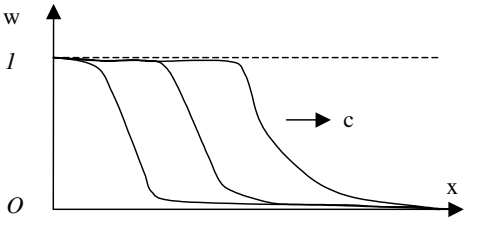

Fig. 2. Traveling wavefront of somatic cells polarization.

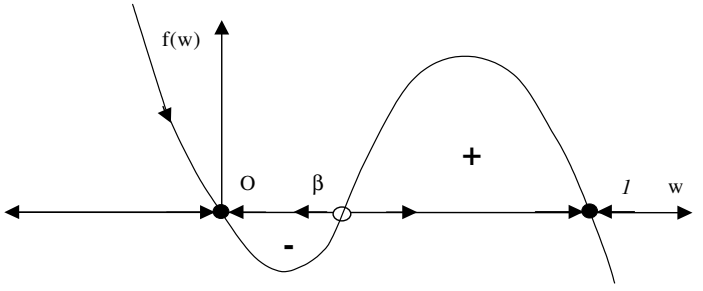

Fig. 3. Graphical presentation of steady state points of (1).

process, i.e. without diffusion, the corresponding dynamical system of ordinary differential equation should have two stable steady state solutions. We call such a system *bistable equation.*

One of the most well-known forms of a bistable equation is

$$\frac{dw}{dt} = -\alpha w(w-1)(w-\beta), \tag{1}$$

where $0 < \alpha, 0 < \beta \ll 1$. This equation can be applied to describe the polarization of a single somitic cell with number i between its neighbors numbered $i-1$ and $i+1$. The right hand side of (1) describes qualitatively the dynamical function of intracellular system for regulating polarization. In Fig. 3, the well-known "**И**-shaped" curve of the right side of (1) is presented. The points $w_0 = 0$ and $w_2 = 1$ correspond to two stable steady state values of polarization — lower and higher ones. The intermediate point $w_0 = \beta$ presents the unstable steady state. The type of the steady states, w_0, w_1, and w_2, follows directly from the signs of function $f(w) = -\alpha w(w-1)(w-\beta)$ as shown in Fig. 3.

The corresponding *variation* equations centered at the steady state values w_0, w_1, and w_2 have the forms

$$\frac{d\omega}{dt} = -\alpha\beta \cdot \omega, \quad \text{for } w_0 = 0 \text{ (stable)}, \tag{2}$$

$$\frac{d\omega}{dt} = \alpha\beta(1-\beta) \cdot \omega, \quad \text{for } w_1 = \beta \text{ (unstable)}, \tag{3}$$

$$\frac{d\omega}{dt} = -\alpha(1-\beta) \cdot \omega, \quad \text{for } w_2 = 1 \text{ (stable)}, \tag{4}$$

here the variation ω is an infinitesimal virtual deviation of the polarization variable w from the corresponding steady state value.

4. Bistable Equation with a Diffusion Term

We assume the contact polarization between neighbor cells of PSM is realized by the diffusion law of intracellular interactions from the higher to lower polarizations.

In one-dimensional case when the diffusion of interactions occurs along axial coordinate, the differential equation by accounting the diffusive term can be written in the form

$$\frac{\partial w}{\partial t} = f(w) + Q(x), \tag{5}$$

where the function $Q(x)$ defines dependence of the *cross* polarization w on the axial coordinate x, and the nonlinear function $f(w) = -\alpha w(w-1)(w-\beta)$ in the right-hand side of (5) corresponds to a "point" model, i.e. the synchronous process considered in the previous section. The spatial distribution in the cell layer is presented by polarization–diffusion process of interaction between cells.

Let us assume that the solution of (5) has the form

$$w = w(t, x). \tag{6}$$

In order to find in explicit form the function $Q(x)$ we consider the *competent* part of PSM as having the form of long narrow tube with a length L and cross section S (Fig. 4). *Competent* means capability of PSM cells to be determined as polarized ones. Certainly, when somitogenesis finishes, cells at the end of PSM are not competent, because they remain nonpolarized.

In the tube we separate an elementary volume ΔV with limiting coordinates x and $x + \Delta x$. Thus we have $\Delta V = S\Delta x$. The *quantity* ΔM_x of the polarization moving through the tube section with coordinate x is proportional to the gradient of polarization $\frac{\Delta w}{\Delta x}$ in direction x and to the time interval $[t, t + \Delta t]$ when the interactive diffusion occurs

$$\Delta M_x = -D\frac{\Delta w(x,t)}{\Delta x} S\Delta t, \tag{7}$$

where D is a diffusion coefficient, defined by the *ability* of cells to transmit polarization by contacting each the other.

Through the other limit of the volume with coordinate $x + \Delta x$, in the opposite direction and during the same time interval it diffuses a mass

$$\Delta M_{x+\Delta x} = D\frac{\Delta w(x+\Delta x,t)}{\Delta x} S\Delta t. \tag{8}$$

In this way, the total variation of polarization in the elementary volume ΔV at the expend of diffusion is

$$\Delta M = \Delta M_{x+\Delta x} + \Delta M_x = \frac{DS\Delta t}{\Delta x}[-\Delta w(x,t) + \Delta w(x+\Delta x,t)], \tag{9}$$

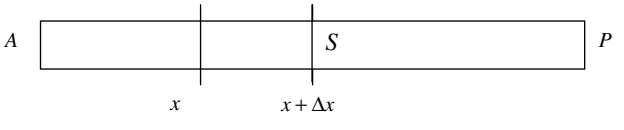

Fig. 4. Scheme of spatial volume in PSM (A — anterior of PSM, P — posterior of PSM).

and the variation of polarization w is presented by

$$\Delta c_i = \frac{\Delta M}{\Delta V} = \frac{\Delta M}{S\Delta x} = \frac{D\Delta t}{\Delta x}\left[\frac{\Delta w(x+\Delta x,t)}{\Delta x} - \frac{\Delta w(x,t)}{\Delta x}\right]. \tag{10}$$

By limit transition to $\Delta x \to 0$ we obtain

$$\Delta w = D\Delta t \frac{\partial^2 w(x,t)}{\partial x^2}. \tag{11}$$

By definition, in the absence of cell polarization in correspondence with (1) we have $Q = \lim \frac{\Delta w}{\Delta t}$, when the limit transition $\Delta t \to 0$ takes place. Thus, at the same transition we can write

$$Q = D\frac{\partial^2 w(x,t)}{\partial x^2}, \tag{12}$$

where the quantities Q have the same physical meaning as in Eq. (5). Therefore, the distributed system (5) in case of one-dimensional diffusion has the form

$$\frac{\partial w}{\partial t} = f(w) + D\frac{\partial^2 w(x,t)}{\partial x^2}, \tag{13}$$

where the nonlinear function $f(w) = -\alpha w(w-1)(w-\beta)$ corresponds as before to the point (synchronous) model and $D\frac{\partial^2 w(x,t)}{\partial x^2}$ corresponds to the diffusion transport between the neighbor cells volumes.

5. Polarization–Diffusion Model with Elastic Tension

Following Belintsev *et al.*,[12] we take into account the inhibition of the elastic tension generated by the polarization on its propagation. By analogy with the well-known activator–inhibitor interaction in the biochemical kinetics we just add a term proportional to elastic tension with negative sign to the right-hand side of (13). As a result we obtain

$$\frac{\partial w}{\partial t} = -\alpha w(w-1)(w-\beta) + D\frac{\partial^2 w(x,t)}{\partial x^2} - \kappa\sigma, \tag{14}$$

where σ is an *axial* elastic tension and κ is a coefficient of proportionality. When $\sigma > 0$, we say it is an axial *stretch* tension. For $\sigma < 0$ it is an axial *compression.* We use also the terms *positive* cross polarization when $w > 0$ and *negative* one for $w < 0$ (Fig. 5).

As we already mentioned, the axial stretch tension σ not only inhibits the positive cross polarization w, but also depends on the polarization. The corresponding dependence is given by the equilibrium condition

$$\varepsilon\frac{\partial w}{\partial x} + \frac{\partial \sigma}{\partial x} = 0. \tag{15}$$

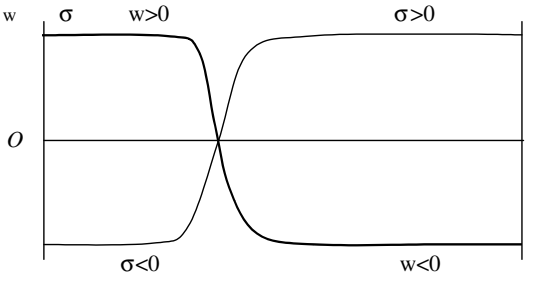

Fig. 5. Graphical presentation of polarization w and tension σ.

We call ε in (15) a phenomenological coefficient of proportionality. To complete the consideration we also need to introduce the well-known Hook's law in the form

$$\sigma = E\frac{\partial u}{\partial x}, \tag{16}$$

where u is an axial displacement as a result of the deformation.

Equations (14) and (15) present a system of nonlinear partial differential equations for the unknown functions $w(t,x)$ and $\sigma(t,x)$ with partial derivatives. In order to analyze qualitatively these equations, it is necessary to fix some boundary conditions for the unknown *cross* polarization w at the tube ends $x = 0$ and $x = L$, i.e.

$$\left.\frac{\partial w}{\partial x}\right|_{x=0,L} = 0, \quad u(0) = u(L). \tag{17}$$

Further we integrate Eq. (15) by taking into account (16) and (17). We substitute the obtained result for σ in (14) and as a result the following governing equation of polarization wavefront can be written:

$$\frac{\partial w}{\partial t} = -\alpha w(w-1)(w-\beta) + D\frac{\partial^2 w(x,t)}{\partial x^2} - \kappa\varepsilon(w-\bar{w}), \tag{18}$$

where

$$\bar{w} = \frac{1}{L}\int_0^L w(t,x)dx = \bar{w}(t)$$

is an average (with respect to x) value of w, depending only on t.

Further we extend our consideration by introducing a second equation for the average polarization validating for arbitrary values of time in the form

$$\frac{d\bar{w}}{dt} = \delta f(w,\bar{w}), \tag{19}$$

where $f(w,\bar{w})$ is unknown function, and δ is a small coefficient presenting the fact that the average polarization $\bar{w}$ is slow-varying with respect to the fast-varying w.

6. On the Robustness of Polarization Wavefront Propagation in PSM Bistability Window

In this section we apply the qualitative and computational theory of differential equations to the dynamical system

$$\frac{\partial w}{\partial t} = -\alpha w(w-1)(w-\beta) - \kappa\varepsilon(w-\bar{w}) + D\frac{\partial^2 w(x,t)}{\partial x^2}, \tag{20}$$

$$\frac{d\bar{w}}{dt} = \delta f(w,\bar{w}) = \delta(w-\bar{w}). \tag{21}$$

First of all we apply such named Quasi-steady-state-approximation (QSSA), Petrov *et al.*, 2007. The essence of QSSA claims that the character of the solution for (20) and (21) does not change when the small parameter δ converges to zero. Thus we can assume $\delta = 0$ in (21) and instead of differential equation to consider $\bar{w}$ is constant.

In this way the complete system of two equations (20) and (21) can be reduced to the degenerate system of one equation (21). Then the stationary values of the fast variable w depend only on the current values of the slow variable $\bar{w}$, but not on final stationary values. In this sense the variable $\bar{w}$ plays a role of *driver* of the *subordinated* variable w. The corresponding investigation of the dependence of Eq. (20) solution behavior on the parameter $\bar{w}$, i.e. such named structural stability analysis,[10] can be considered as a control analysis. Also in terms of QSSA, in the right-hand side of (21) we can replace w, by its zero solution from (20), when $\bar{w}$ is considered as a constant. Moreover the experimental observations suggest that for sufficiently large time, $\bar{w}$ evidently tends to the stable steady state value of w, taken at fixed x. The simplest approximation of similar tending dynamics can be described by the differential equation (21) with linear function $f(w,\bar{w}) = \delta(w-\bar{w})$ in its right-hand side. In this case at fixed x, the variable w approaches its steady state value very *fast* and then $\bar{w}$ (not depending of x) tends very *slow* to this value. If κ and ε are sufficiently small, in correspondence with QSSA the system (20) and (21) can be written in the form

$$\frac{\partial w}{\partial t} = -\alpha(w-w_0)(w-w_1)(w-w_2) + D\frac{\partial^2 w(x,t)}{\partial x^2}, \tag{22}$$

$$\frac{d\bar{w}}{dt} = \delta(w-\bar{w}), \tag{23}$$

where w_0, w_1, and w_2 are positive roots of the cubic polynomial

$$\varphi(w) = -\alpha w(w-1)(w-\beta) - \kappa\varepsilon(w-\bar{w}) \tag{24}$$

in the right-hand side of (20). If $\delta = 0$ we have zero approximation $\bar{w} = \text{const.}$ and polynomial (24) being a right-hand side of (20). Then the zero approximation for

w can be found as a traveling front solution of (22) at boundary conditions

$$\left.\frac{\partial w}{\partial x}\right|_{x=0,L} = 0. \tag{25}$$

That means we search for solution in the form $w(x,t) = w(x \pm ct) = w(\eta)$, where $\eta = x \pm ct$. In the new variables Eq. (22) takes the form

$$\frac{dw}{d\eta} = v, \tag{26}$$

$$D\frac{dv}{d\eta} = \pm cv + \alpha(w - w_0)(w - w_1)(w - w_2). \tag{27}$$

The boundary conditions (25) take the form

$$v(0) = v(L) = 0. \tag{28}$$

In this way (25)–(28) present an eigenvalue problem for the stationary traveling front.

In the phase plane v, w for the two-dimensional dynamical system (26) and (27) we obtain the qualitative picture (phase portrait) of possible phase trajectories (Fig. 6).

The fixed points 0, 1, and 2 correspond to the roots w_0, w_1, and w_2, respectively, of the function $\varphi(w)$. The separatrix going from saddle point 0 to saddle point 2 defines the form of traveling front and the stationary velocity c.

To find traveling front solutions we look for a solution of (26) and (27) that connects the fixed points 0 and 2 in the v, w phase plane. Such a trajectory connects two different steady states and is called a heteroclinic trajectory. In our case it is parametrized by η. The heteroclinic trajectory approaches the point 0 when $\eta \to -\infty$, and approaches 2 when $\eta \to +\infty$. The fixed points 0 and 2 are saddle ones. Our purpose is to define whether or not the velocity $c$can be chosen such that the trajectory leaving 0 for $\eta = -\infty$ can be made to connect with the saddle point 1 for $\eta = +\infty$.

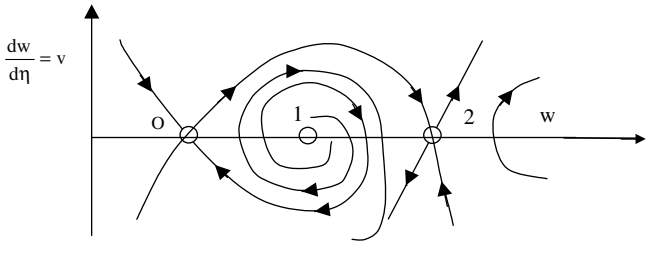

Fig. 6. Phase portrait of system (28) and (29).

As it is shown in the book of Keener and Sneyd,[16] a unique velocity c of traveling front propagation exists. The corresponding analytical expression for the velocity c has the form

$$c = \pm\sqrt{D\alpha/2}[w_0 + w_2 - 2w_1]. \tag{29}$$

The profile of the traveling front is defined by the formula

$$w(\eta) = \frac{w_0 + w_1}{2} - \frac{w_2 - w_0}{2}\ th\frac{\eta - \eta_0}{l_0}, \tag{30}$$

where $l_0 = \pm 2\sqrt{2/\alpha}\,(w_2 - w_0)$ and η_0 is an arbitrary constant defined by the initial conditions.

The qualitative analysis shows that, if a traveling wave solution exists, then the sign of $c$is the same as the sign of the area under the curve $\varphi(w)$ between the points 0 and 2. If this area is positive, then the traveling front propagates from the point 0 to 2, and the second point is called *dominant.* It is clear for sufficiently small β the fixed point 2 is dominant. Thus in our case the polarization front propagates from the point 0 to 2. In this way we can consider solved the problem of determining zero approximation ($\delta = 0$) of the polarization wavefront $w(x + ct)$.

The first approximation ($0 < \delta \ll 1$) can be qualitatively investigated by analogy with the above proposed phase analysis. For this purpose we transform the system (20) in the form

$$\begin{aligned}
\frac{dv}{d\eta} &= \frac{\alpha}{D}(w - w_0)(w - w_1)(w - w_2) + \frac{k\varepsilon}{D}\cdot\bar{w} + \frac{c}{D}\cdot v,\\
\frac{dw}{d\eta} &= v\ ,\\
\frac{d\bar{w}}{d\eta} &= \tfrac{\delta}{c}.(w - \bar{w})\ ,
\end{aligned} \tag{31}$$

by accepting the specific form of solution $w = w(\eta), \bar{w} = \bar{w}(\eta), v = v(\eta)$, and $\eta = x + ct$. It is easy to show that for small κ, ε, the system (31) has three unstable fixed points in the three-dimensional phase space. The projections of these points in the phase plane v, w are positioned near the fixed points of the two-dimensional system (26) and (27) presented in Fig. 6. The projections of the phase trajectories have similar behaviors as those in Fig. 6. So we can assert that the fixed point $(w_2, 0, w_2)$ being analogous to point 2 plays role of *dominant* saddle point. Thus in this case the traveling front also propagates from the saddle point $(w_0, 0, w_0)$ to the dominant one $(w_2, 0, w_2)$.

The main conclusion we can derive from the above considerations is the following:

Despite the structural change of our model from the two-dimensional form (26) and (27) to the three-dimensional (31), the second saddle point with the higher value of polarization remains *dominant.* Moreover, the direction of traveling front

propagation conserves the same too, i.e. from anterior to posterior of the PSM. That means the model we constructed is *structurally stable* in sense analogous to the *robustness* property Beloussov[9] introduced. We can consider the leading process of polarization in somitogenesis, being *robust* could play role of a scaffold of large number of other properties specifying different kinds of somitogenesis. In this way our mathematical analysis supports the basic idea of Beloussov that somitogenesis is a robust process based upon the mechanical relationship between a long-range tension forces stretching the axial mesoderm and short-range forces of presomitic cell cohesion. Indeed, this relationship postulated as a basis of the wavefront polarization model, presented here, leads to the above shown structurally stable or robust behavior.

In accordance with somitogenesis robustness, the very dynamical process of the polarization front propagation is also stable in Lyapunov's sense, i.e. with respect to small disturbances of the initial conditions. As it is proved by Fife and McLeod,[17] the traveling wave solution of the bistable equation is stable in an asymptotic (i.e. very strong) way. Starting from arbitrary initial values lying between 0 and β in the limit $x \to -\infty$ and between β and 1 in the limit $x \to \infty$, the solution approaches infinitesimally near to some phase displacement of the traveling front solution when time tends to infinity.

However, there is an essential exception of both structural and dynamical stability of the model, which is of crucial importance for its validation. Aronson and Weinberger[18] proved that the initial value $w = \beta$ is a threshold point for the bistable equation. It means, if the initial values are sufficiently small, then the solution of the bistable equation approaches zero, when $t \to \infty$. But for initial values lying between 0 and 1, the solution approaches 1 for $t \to \infty$. In this case we say that the initial values are *super-threshold.* In the threshold point the model is structurally and dynamically unstable, or non-robust. This threshold type exception from the robustness assures essential qualitative validation of the model, in sense that sufficiently large initial polarization near the rostral end of the PSM is necessary in order to excite the propagation of a traveling front. For initial polarization smaller than β a traveling front does not appear, thus somitogenesis process does not start too.

7. Conclusion

We obtained realistic *qualitative* picture of polarization wavefront propagation in PSM window, in terms of dynamical model with distributed variables — functions of time and space coordinates, showing *robust* behavior. In order to confirm or reject *quantitatively* this robust model we could experimentally verify the relatively simple velocity formula

$$c = \pm\sqrt{D\alpha/2}[w_0 + w_2 - 2w_1], \tag{32}$$

where every parameter both in the right- and left-hand side of (32) could be in principle measured. In case of approximate validity of (32) we will be able to conclude that model "seems to be" realistic. Certainly other versions of the model, for example, with two space coordinates, would be of use to develop too. It depends on the results of experimental verification how this theory could be improved.

As it was noted in Sec. 2, the velocity should depend on the stable value M_0 of *fgf8* mRNA concentration in PSM. Looking at (32) it seems that the most appropriate candidate for depending on M_G is the dominant saddle point 2 with polarization value w_2. The dependence would be such that for large values of M_G, the dominant polarization value would be small and vice versa. Then, formula (32) would be in accordance with the dependence shown in Fig. 1, and taken from the bistability theory of RA and FGF concurrence in PSM, developed by Goldbeter *et al.*[14]

Acknowledgment

One of the authors (V. Petrov) expresses his gratitude to Deutsche Forschungs Gemeinschaft (DFG) for the financial support (TI315/6-1) during his work on this paper in Freiburg University (Germany).

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