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Qualitative Analysis of Somitogenesis Models

Petrov V.[1*], Wierling C.[2], Maschke-Dutz E.[2], Herwig R.[2]

[1]Institute of Mechanics and Biomechanics
Bulgarian Academy of Sciences
4, Acad. G. Bonchev Str., 1113 Sofia, Bulgaria
E-mail: valko@ibmb.bas.bg

[2]Max-Planck Institute of Molecular Genetics
Ihnestr.73, D-14195 Berlin, Germany

[*]Corresponding author

Summary: Although recently the properties of a single somite cell oscillator have been intensively investigated, the system-level nature of the segmentation clock remains largely unknown. To elaborate qualitatively this question, we examine the possibility to transform a well-known time delay somite cell oscillator to dynamical system of differential equations allowing qualitative analysis.

Keywords: Somitogenesis, Synchronization, Difusion Reaction Modelling.

1. INTRODUCTION

As it can be seen from the literature [1], the mechanism of “cell to cell” interaction is *coupling-like*, instead of free Brownian motion. This study addresses the molecular mechanism of the somitogenesis in the context of reaction-diffusion modelling firstly proposed in [2], but not related to gene expression factors being unknown in that time. In the earlier paper [3], such named “clock and wave-front” model has been proposed to explain segmentation. Later modifications of this approach are related with some contradictions noted in paper [4]. For example, in the models [5, 6] it is assumed that clock and FGF-8 wave-front are independent, but in another paper [7] it is shown not to be the case. In accordance with this understanding, recently two mathematical works devoted on clock and wave-front mechanism for somite formation have been published [8, 9]. We are inspired from the valuable mathematical approach accepted in [8, 9] to elaborate more concrete model of type “clock and wave-front”, where all variables involved have a sense of concrete molecular concentrations of the somite cell oscillator. For this purpose, besides some results of paper [1], we take also into account numerical data from paper [10] as well as the basic time delay model of somite oscillator from [11].

2. TRANSFORMING A TIME DELAY SOMITE CELL OSCILLATOR TO SIMPLE ORDINARY DIFFERENTIAL EQUATION

We consider the system of two time delay differential equations, taken from Lewis paper [11] and presenting a somite cell oscillator:

$$\begin{aligned} \frac{dp}{dt} &= a.m(t-T_p)-b.p \\ \frac{dm}{dt} &= f\left[p(t-T_m)\right]-c.m \end{aligned} \qquad (2.1)$$

where the protein molecular concentration p and mRNA molecular concentration m are unknown functions of a time t, f is a known function, a, b, c are constant parameters and T_p, T_m are constant time delays. Following [11], the brief qualitative description of this oscillator consists in the assertion that it presents a simple negative feedback loop with a timing delay. In paper [11] as well as in paper [10], it is shown numerically the existence of self-oscillatory solutions of (2.1) and other solutions asymptotically converging to selfoscillations. In accordance with the well-known trajectory classification [13], that means the corresponding phase trajectories $(p(t), m(t))$ of all these solutions are a simple and regular plane curve. (It is known from the differential geometry that simple curve is not self-intersected and regular one has no steady state point on itself). In the authors paper [14] it is proved a general theorem for existence of dynamical system having solution in the form of a given simple and regular curve. For our purposes here, a two-dimensional formulation of the theorem can be used in the following form:

Theorem *Let* $p(t)$ *and* $m(t)$ *be real-valued analytic functions, defined on interval* (t_1, t_N)*, such that for* $\forall\, t \in (t_1, t_N)$ *the curve* $\vec{c}(t) = \left(p(t), m(t)\right)$ *is simple and regular. Then there exist real-valued analytic functions* $F\left(p, m\right)$ *and* $G(p,m)$*, such that* $\vec{c}(t)$ *is a solution of the system*

$$\frac{dp}{dt} = F(p,m)$$
$$\frac{dm}{dt} = G(p,m) \qquad (2.2)$$

If the system (2.2) has self-oscillatory behaviour [11, 10], it can be transformed in the form

$$\frac{dx}{dt} = \omega y$$
$$\frac{dy}{dt} = e\omega f(y) - \omega x \qquad (2.3)$$

by substituting appropriate changes of variables $(p,m) \to (x,y)$ [15].

The system (2.3) presents some approximation of (2.1) and should have some of their properties concerning self-oscillatory behaviour. That is why it is of interest to investigate the qualitative behaviour of (2.3). The variables $x(t)$ and $y(t)$ are considered as deviations from the steady state values $\overline{p}$ and $\overline{m}$ of (2.2). If the dimensionless parameter e is small the self-oscillations are quasi-harmonic and are small too (with respect to $\overline{p}$ and $\overline{m}$).

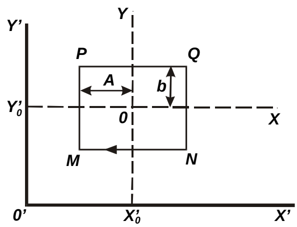

Fig. 1

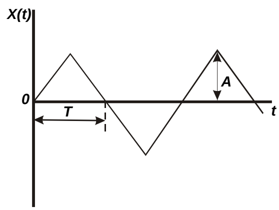

Fig. 2

The main isoclines of system (2.3) are: the isocline of vertical tangents and isocline of horizontal tangents. Their equations are

$y = 0$ and $x = e\,f(y)$.

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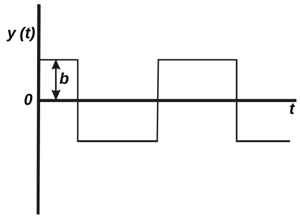

Fig. 3

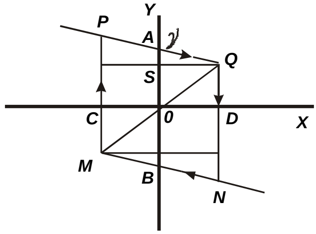

Fig. 4

In order to consider oscillatory behaviour of (2.3) we accept that the function $e\,f(y)$ has a form similar to that shown in Fig. 4 (the curve PQOMN). For $e > 0$ the steady state (0,0) presents an unstable focus. If $e \ll 1$, the system (2.3) has a limit cycle near to ellipse and $x(t)$ and $y(t)$ vary along harmonic law (i.e. quasi-harmonic oscillations). If $e \gg 1$, the limit cycle is near the rectangle MNQP. In a particular case, when PQ||CD||MN, the limit cycle is a rectangle. The corresponding dynamical system having rectangular solution is

$$y = \frac{dx}{dt} = \pm b\,, \tag{2.4}$$

where b is the magnitude of oscillations of $y(t)$. The magnitude of $x(t)$ is A (as it is shown in Fig. 1 and Fig. 2. The oscillations $x(t)$ are triangle (see Fig. 2) and those of $y(t)$ are rectangular (see Fig. 3). The sign *plus* is taken during the change of x from $x = -A$ to $x = +A$ along the top of the rectangle. The sign *minus* is taken along the bottom of rectangle. The half of the period T of the triangle oscillations is equal to the time of variable change from P to Q. Thus the frequency is

$$\Omega = \pi / T = \pi b / 2A\,.$$

For relaxant oscillations we can show that the system (2.3) is reducible to (2.4) in the following way: Let us introduce a new time t' and new coordinate z by substituting $t = e t'/\omega$ and $x = e z$ in (2.3). Then we obtain the system (2.3) in the form

$$\frac{dz}{dt} = y$$
$$\frac{1}{e^2}\frac{dy}{dt} = -z + f(y) \qquad (2.5)$$

where "prime" of t is missed. Following the well-known *Tichonov's* theorem of quasi-steady-state approximation [16], we can replace the second equation of (2.5) by the algebraic one

$$z = f(y). \qquad (2.6)$$

The function $f(y)$ can be replaced by segments of PQ and MN. Then (2.6) takes the form $z = (y \mp b)\, tg\, \gamma$. The sign *minus* can be taken during the movement along PQ, and the sign *plus* – along NM. The angle γ and $b = OS$ are shown in Fig. 4.

At the end, in order to receive the simple ordinary differential equation (2.4) presenting a rectangular limit cycle, we apply the transition $\gamma \to \pi/2$. Then PQMN tends to the rectangle, and $y \to \mp b$. By replacing these values in the first equation of (2.5) we obtain the equation (2.4).

This result means that there is no qualitative difference (in sense of the theory of differential equations) between (2.3) and (2.4). Thus in all further considerations we can consider simple equations of type (2.4) instead of more complex systems (2.3) and to apply the obtained conclusions for (2.3) to systems of type (2.1) too. More in detail we will analyse the question for synchronisation of two and more oscillators of these types.

3. REACTION-DIFFUSION MODEL OF SPATIALLY DISTRIBUTED SOMITE CELL OSCILLATORS

To modelling clock and wave front mechanism of somitogenesis we need to construct reaction-diffusion dynamical system principally based on experimentally derived somite oscillator of type proposed in [11]. As it is shown in Section 2 of this paper similar oscillator is qualitatively equivalent to selfoscillatory system of type (2.3). That's why we model somitogenesis as a large number of coupled oscillators (i.e. somite cells) of type (2.3) are spatially distributed on the axis *r* with sufficiently large *density* (i.e. number of cells per unit length on *x*). We concretise the type of relaxant oscillators by using the well-known Van der Pol differential equations. In this way we conserve the qualitative equivalence [17] of our models and their applicability to somitogenesis process. It can be proven mathematically, that if we introduce a coupling term of type $ma^2(x_{i-1} - 2x_i + x_{i+1})$ in the first equation of every *i*-th oscillator of Van der Pol type, then after such named *continualization*, the system of large number spatially distributed oscillators can be presented in the following form

$$\begin{aligned} \frac{d\bar{x}}{dt} &= \xi\,\bar{y} + ma^2\frac{\partial^2\bar{x}}{\partial r^2} - \lambda_1, \\ \frac{d\bar{y}}{dt} &= e(1-\bar{y}^2) - \bar{x} + na^2\frac{\partial^2\bar{y}}{\partial r^2}, \end{aligned} \tag{3.1}$$

where $\bar{x} = \bar{x}(r,t)$ and $\bar{y} = \bar{y}(r,t)$ are protein and mRNA variables respectively, ξ is untunung (dissonance) between neighbour somite cells, m and n are coefficients of protein and mRNA diffusion-like coupling, e is a large parameter, λ_1 is activation parameter, a is average distance between two neighbour somite cells (oscillators), t is the time. In this section the system (3.1) will be investigated for possible inhomogeneous effects in the context of clock and wavefront mechanism of somitogenesis.

Let us firstly analyse parametrically the homogeneous solution of (3.1). For this purpose we make the following substitutions

$$\begin{aligned} \bar{x}(t,r) &= \alpha\, x(\omega t, \mu r) \\ \bar{y}(t,r) &= \beta\, y(\omega t, \mu r) \end{aligned}.$$

Then the system (3.1) takes the form

$$\begin{aligned} x_t &= (\beta\xi/\alpha\omega)y + (ma^2\mu^2/\omega)x_{rr} - \lambda_1/\alpha\omega\,, \\ y_t &= -(\alpha/\beta\omega)x + (na^2\mu^2/\omega)y_{rr} - (e_1/\omega)y(1-\beta^2y^2)\,, \end{aligned}$$

where x_t, y_t, x_{rr}, y_{rr} are corresponding derivatives with respect to t and r. Choosing

$$\beta = 1, \quad \omega = \xi^{1/2}, \quad e = e_1 / \xi^{1/2}, \quad c^2 = m/n,$$
$$\lambda = \lambda_1 / \xi, \quad \alpha = \xi^{1/2}, \quad \mu = \xi^{1/4} / an^{1/2},$$

as a result we obtain

$$x_t = y + c^2 x_{rr} - \lambda\,,$$
$$y_t = -x + y_{rr} + ey(1-y)^2. \qquad (3.2)$$

This system has an unique fixed point $\left[e\lambda(1-\lambda^2),\, \lambda\right]$.

In homogeneous case the parameters are identical in every point of the volume occupied by the somite cells. Then the model with distributed parameters (3.2) transforms to the model with concentrated parameters. That is possible in the following cases:

- At first, when the coefficients m and n are equal to zero, the neighbour cells do not interact and propagation of a wave-front does not occur.
- Secondly, when m is sufficiently large, the velocity c of wave-front is essentially larger than the velocity of diffusion between the cells. In this way a wave-front propagation can be observed. Evidently, this is the case we are interesting in.

To investigate the solutions of the system

$$\dot{x} = y - \lambda\,, \qquad (\dot{x} = \partial x / \partial t = dx / dt)$$
$$\dot{y} = -x + ey(1-y^2) \qquad (\dot{y} = \partial y / \partial t = dy / dt) \qquad (3.3)$$

we linearize it near the fixed point (steady state)

$$x = x' + ey(1-\lambda^2), \qquad y = y' + \lambda\,,$$

and obtain the fixed point is

(i) stable node for $e(1-3\lambda^2) < -2$;

(ii) stable focus for $-2 < e(1-3\lambda^2) < 0$;

(iii) unstable focus for $0 < e(1-3\lambda^2) < 2$;

(iv) unstable node for $2 < e(1-3\lambda^2)$.

The equilibrium state corresponding to the fixed point is unstable for $0 < \lambda < (1/3)^{1/2}$ and stable for $\lambda > (1/3)^{1/2}$. It can be shown that at transition of the parameter λ through the value $\lambda = (1/3)^{1/2}$ a stable limit cycle emerges (Andronov-Hopf bifurcation).

Now we are ready to analyse the wavefront solutions of the distributed model (3.2). After translating the steady state point $\left[e\lambda(1-\lambda^2), \lambda\right]$ at the origin (0,0) and for ($e > 0, \lambda > 0, c > 0$) we obtain the system

$$x_t = y + c^2 x_{rr} \quad y_t = -x + y_{rr} + e[y(1-3y^2) - 3\lambda y^2 - y^3] \tag{3.4}$$

By substituting $x = x(r-\omega t), y = y(r-\omega t)$ in the last system we obtain the following system of ordinary differential equations

$$c^2 x'' + \omega x' + y = 0, \quad y'' + \omega y' - x + ey(1-3\lambda^2 - 3\lambda y - y^2) = 0. \tag{3.5}$$

Further we apply the Hopf theorem to investigate the existence of periodic solution of (3.5) in a neighbourhood of the fixed point (0,0). By putting $\delta = e(1-3\lambda^2)$ the Routh-Hurwitz criteria for the characteristic equation of (3.5)

$$c^2\alpha^4 + \omega(1+c^2)\alpha^3 + (\omega^2 + c^2\delta)\alpha^2 + \omega\delta\alpha + 1 = 0 \tag{3.6}$$

takes the form

$$\omega > 0, \qquad \delta > \frac{2(1+c^2)}{\omega^2 + (\omega^4 + 4c^2)^{1/2}} \;\underline{\underline{\textit{denote}}}\; \Delta^2. \tag{3.7}$$

Let us now consider the case $\omega = 0$, i.e. we exclude the standing wavefronts. With a substitution $t \Leftrightarrow -t$ we can do $\omega > 0$. In this case the conditions (3.7) show, that the steady state is stable at $\delta > \Delta^2$ and unstable at $\delta < \Delta^2$. When $\delta = \Delta^2$, (3.6) has a couple conjugated roots

$$\alpha = \pm ik, \qquad k = \Delta/(1+c^2)^{1/2}.$$

The other two roots of (3.6) can be determined by the equation

$$c^2\alpha^2 + \omega(1+c^2)\alpha + 1/k^2 = 0.$$

These roots have a negative real part. If we put in (3.6) $\delta = \delta(\mu) = \Delta^2 - \mu$, and denote by $\alpha(\mu)$ the corresponding roots, then we have

$$\mathrm{Re}(d\alpha/d\mu)_{\mu=0} = \frac{\omega(\omega^2 + 2k^2c^4)}{2[\omega^2k^2(c^2+1)^2 + (\omega^2 + c^2k^2(c^2-1)^2]} > 0,$$

for the root with $\alpha(0) = ik$. Thus at the transition of δ through the critical value Δ^2 a limit cycle vanishes or emerges, i.e. a bifurcation takes place. To define what of two possibilities realizes, we calculate the first Lyapunov value L_1 for (3.5) at $\delta = \Delta^2$. In the case when $L_1 > 0$, the cycle is subcritical and unstable and for $L_1 < 0$ it is supercritical and stable.

The considerations in this section show that the transition from stable to unstable behaviour of the model (3.5) is possible for linear and nonlinear processes. That means the corresponding *wave-front* can be stable or unstable depending on the diffusive coefficients *m* and *n*.

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