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Self-synchronization of the integrate-and-fire pacemaker model with continuous couplings

M.U. Akhmet *

Department of Mathematics, Middle East Technical University, 06531 Ankara, Turkey

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ABSTRACT

The integrate-and-fire cardiac pacemaker model of the pulse coupled oscillators was introduced by C. Peskin. Due to the function of the pacemaker, two famous synchronization conjectures for identical and not identical oscillators were formulated. There are still many issues related to the nature and types of couplings. The couplings may be impulsive, continuous, delayed or advanced, and oscillators may be locally or globally connected. Consequently, it is reasonable to consider various ways of synchronization, if one wants the biological and mathematical analyses to interact productively. We investigate the integrate-and-fire model in both cases – one with identical, and another with not quite identical oscillators. A combination of continuous and pulse couplings that sustain the firing in unison is carefully constructed. Moreover, we obtain conditions on the parameters of continuous couplings that make possible a rigorous mathematical investigation of the problem. The technique developed for differential equations with discontinuities at non-fixed moments and a special continuous map lies on the basis of the analysis. This is the first analytically derived synchronization result for a model with continuous couplings. Illustrative examples are provided.

1. Introduction

The cells that create rhythmical impulses for the contraction of the cardiac muscle, and control the heart rate, are called pacemaker cells. Peskin developed a model of an encoding neuron [1] for a population of identical pulse-coupled oscillators [2]. The synchronization of the system, viewed as firing in unison, was proved for two [2] and more than two [3] identical oscillators. In fact, Peskin proposes a model, which is a hybrid of continuous and discrete equations, that admits synchrony. The suggestion was so attractive that it has been used not only for cardiac models, but also, for example, for coupled neurons [4]. The paper [3] has been the most stimulating and intensive analysis of the problem [5–17]. In [18,19], we propose a method of investigation of pulse-coupled integrate-and-fire biological oscillators of the general type. It is effective if they are not quite identical. Thus, the second conjecture of Peskin [2] was proven in [18].

Now, we extend this method and these results to the model with continuous couplings. Sufficient conditions for synchronization are found. The present research utilizes results and proposals from [1,2,8,20–39]. The mathematical problems connected to synchrony emerge in numerous applications—not only in a model of heart beat [1,2], but also in models of firefly flashing [21,26], insulin-secreting cells of the pancreas [40], neural networks [29,32,41,40,42,43], etc. There is still much uncertainty with respect to the types of coupling in population (these may be impulsive, continuous, delayed, advanced, regular or random) [3,6,7,20–22,26–28,30,32,39], and with respect to the structural complexity of networks—connections may be local or global, with various quantitative characteristics and geometrical configurations [22,36,37]. It is

* Tel.: +90 312 210 5355; fax: +90 312 210 2972.
E-mail address: marat@metu.edu.tr.

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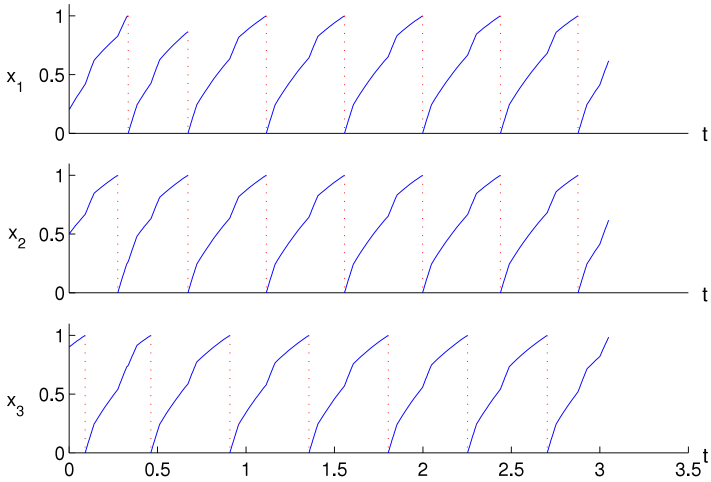

Fig. 1. The intervals where oscillators satisfy Eqs. (1.2) and (1.3) are depicted.

clear that the larger the diversity of mathematical models, the more opportunities to tackle the biological issues. Hopfield remarks in [41] that "… the measured synaptic currents do not rise as a step but increase smoothly from zero …", and authors of [3] recognize that "The pulse coupling (1.2) is a simplification of biological reality". Consequently, it is reasonable to include the continuous interaction of oscillators in investigation. In our paper a combination of continuous and pulse couplings that sustain the firing in unison is carefully constructed. We investigate the integrate-and-fire model for both cases—with identical and not quite identical oscillators. Moreover, we find conditions on the parameters of continuous couplings that make possible a rigorous mathematical investigation of the problem. The analysis is based on a technique developed for differential equations with discontinuities at non-fixed moments [44–54], and a special continuous map.

Let us consider, first, n identical oscillators, which are characterized by voltage state variables $x_1, x_2, \ldots, x_n$ with values in $[0, 1]$. The following assumptions describe the model and its coupling style.

(A1). If $x_j(t) = 1$, then the oscillator fires, and there exists a positive number ϵ such that

$$x_i(t+) = 0, \quad \text{if } x_i(t) \geq 1 - \epsilon \tag{1.1}$$

for all $i \neq j$.

Fix a positive τ. If $t = s$ is a firing moment of x_j, then the interval $[s, s + \tau]$ is said to be the e^j-interval or e-interval for all x_i, $i \neq j$. We say that an oscillator $x_i(t)$, $i = 1, 2, \ldots, n$, *is continuously excited* if t is in an e^j-interval, $i \neq j$, and $x_i(t) < 1$.

(A2). When $x_i(t)$, $i = 1, 2, \ldots, n$, is not continuously excited, then

$$x_i' = S - \gamma x_i. \tag{1.2}$$

Otherwise, there exists a positive real number η such that

$$x_i' = (S + \eta) - \gamma x_i. \tag{1.3}$$

(A3). Positive constants S, γ, η and ϵ satisfy the following inequalities:

(i) $\gamma < S$;
(ii) $e^{\gamma\tau} - 1 < \frac{\epsilon\gamma}{S-\gamma+\eta}$.

We call the collection of n oscillators $x_1, x_2, \ldots, x_n$, *the integrate-and-fire model of continuously coupled identical biological oscillators*, if conditions (A1)–(A3) hold.

One should emphasize that the coupling is all-to-all, and exciting strengths are not additive. The model of the present paper admits two types of coupling: the *continuous* one, which is described by (A2); the *impulsive* coupling given by (A1). In the first case the motion of oscillators remains continuous, if they are not near the threshold. Nevertheless, the rate of oscillators jumps to response. Otherwise, by assumption (A1) oscillators are coupled impulsively.

This assumption is natural, since firing provokes other oscillators instantaneously, if they are near thresholds, and are therefore in the state ready to fire. From the proofs of this paper it will be seen that the constant η in (A2) can be replaced with a function defined on the real axis, continuous and non-zero on e-intervals. That is why it is reasonable to say that oscillators are *continuously* coupled. To illustrate the last remark, let us provide the following simulation. Consider three oscillators: x_1, x_2 and x_3 with initial values 0.2, 0.5 and 0.9 respectively. They satisfy (1.2) and (1.3) with $S = 2, b = 2, \eta = 2.1, \tau = 0.05, \epsilon = 0.15$. The motion of these oscillators is seen in Fig. 1.

It is clear that to couple oscillators continuously, one has to deviate the right-hand-side of differential equations. We do that by adding the positive term η to the first coefficient, S. The positive number τ is the duration of excitation. Biologically this choice of perturbation is reasonable, since the coefficient S is considered in the literature [1,2] as the external stimulus for oscillators. The self-synchronization is firing in unison as a result of the weak interaction of oscillators. From this point of view, the smallness of either or both of parameters η and τ, which is required, according to the results of our paper, is natural.

Couplings $\alpha^2(t-t_0)e^{\alpha(t-t_0)}$, where t_0 is the firing moment, were used in paper [55] to find that with "fast enough excitatory coupling both the fully synchronized and the asynchronous state are unstable. In this case individual units fire quasi-periodically even though the network as a whole shows a periodic firing pattern". The results of our paper are different from those of [55]. Firing in unison is achieved, and this synchrony is stable. The difference can be explained with the smallness of α functions near the firing moments. Clustering phenomenon has been also investigated for an interesting model of cell cycle dynamics in paper [56]. We plan to adapt our method of analysis to the model in [56] and discuss the clustering and periodicity phenomena of integrate-and-fire models in [57].

Since the dynamics of systems considered in the present paper are discontinuous, we strongly believe that they can be investigated with the methods developed for differential equations with variable moments of discontinuity [44] in the future. Controllability, phase locking, frequency locking, synchrony, almost periodic solutions and even chaos can be considered in this theory.

2. The model of two identical oscillators

Start the investigation with the simplest model of two identical oscillators. That is, assume that $n = 2$ in the description of the last section.

Let $[s, s+\tau]$ be e-interval for $x_i(s)$. Then, one can easily find that

$$x_i(t) = x_i(s)e^{-\gamma(t-s)} + \int_s^t e^{-\gamma(t-u)}(S+\eta)du, \tag{2.4}$$

for $t > s$.

Set $\kappa = \frac{S}{\gamma} > 1$. By integrating in (2.4), we have that

$$x_i(s+\tau) = x_i(s)e^{-\gamma\tau} + \left(\kappa + \frac{\eta}{\gamma}\right)(1-e^{-\gamma\tau}).$$

From (A3)(ii), it follows, that $x_i(t) < 1$ for all $t \in [s, s+\tau]$. That is, x_i does not fire in the e-interval, if $x_i(s) < 1-\epsilon$. Consequently, the domain of any oscillator contains only disjoint e-intervals.

Denote by t_1, t_2, t_3 three successive firing moments of the system such that x_1 fires at t_1 and t_3, the oscillator x_2 fires at t_2, and the oscillators are not synchronized until t_3. We have that $0 < x_2(t_1) < 1-\epsilon$, and $x_2(t_1+\tau) < 1$. From $x_2(t_2) = 1$ or $\left[x_2(t_1)e^{-\gamma\tau} + \left(\kappa + \frac{\eta}{\gamma}\right)(1-e^{-\gamma\tau})\right]e^{-\gamma(t_2-t_1-\tau)} + \kappa[1-e^{-\gamma(t_2-t_1-\tau)}] = 1$, it follows that

$$e^{-\gamma(t_2-t_1)} = \frac{\kappa-1}{\kappa - x_2(t_1) - \eta_1} \tag{2.5}$$

where $\eta_1 = \frac{\eta}{\gamma}(e^{\gamma\tau}-1)$.

Apply (2.5) in

$$x_1(t_2) = \int_{t_1}^{t_2} e^{-\gamma(t-u)}S du = \kappa[1-e^{-\gamma(t_2-t_1)}]$$

to obtain $x_1(t_2) = L_C(x_2(t_1))$, where

$$L_C(v) = \kappa\frac{1-v-\eta_1}{\kappa-v-\eta_1} \tag{2.6}$$

is a map defined for $0 < v < 1-\eta_1$. Similarly, by using the identity of oscillators, one can find that $x_2(t_3) = L_C(x_1(t_2))$. That is, the map L_C evaluates the sequence of coordinates of the model interchanging at firing moments. Its derivatives satisfy

$$L_C'(v) = \kappa\frac{1-\kappa}{(\kappa-(v+\eta_1))^2} < 0,$$

and

$$L_C''(v) = 2\kappa\frac{1-\kappa}{(\kappa-(v+\eta_1))^3} < 0$$

in $(0, 1-\eta_1)$. There is a fixed point of L_C, and it is equal to $v^* = \left(\kappa - \frac{\eta_1}{2}\right) - \sqrt{\kappa^2 - \kappa + \frac{\eta_1^2}{4}}$.

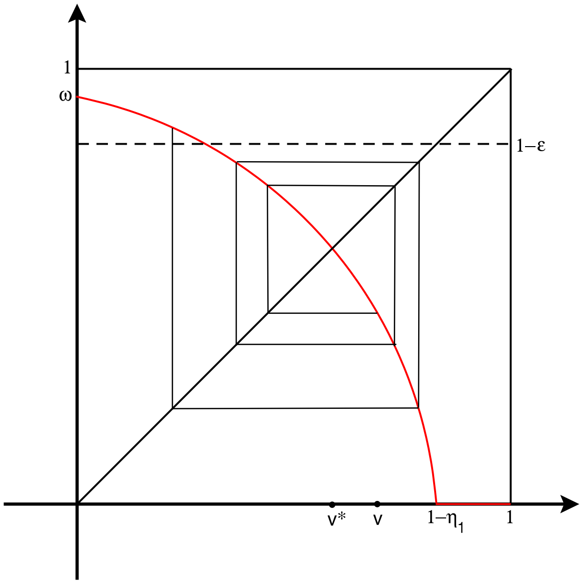

Fig. 2. A sketch of the map L_C, in red, and a stabilized trajectory. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Moreover, we have that

$$L_C'(v^*) = \kappa \frac{1-\kappa}{\left(\sqrt{\kappa^2 - \kappa + \frac{\eta_1^2}{4}} - \frac{\eta_1}{2}\right)^2} < -1. \tag{2.7}$$

That is, v^* is a repeller.

Next, we extend the map on [0, 1] in the following way. Set $L_C(0) = \omega$, where $\omega = \kappa\frac{1-\eta_1}{\kappa-\eta_1}$. It is easy to check that $1-\epsilon < \omega < 1$. Moreover, we define $L_C(v) = 0$, if $1-\eta_1 \le v \le 1$. On the basis of the analysis above, one finds that this newly introduced map is continuous and monotonic, and [0, 1] is an invariant set. Hence, $L_C(v)$ is very appropriate for iteration analysis. The graph of the function $w = L_C(v)$ is seen in Fig. 2. Let us show how synchronization can be investigated by analyzing iterations of L_C. Fix $t_1 \ge 0$, a firing moment, $x_1(t_1) = 1, x_1(t_1+) = 0$. While the couple x_1, x_2 does not synchronize, there exists a sequence of moments $t_1 < t_2 < t_3 < \cdots$ such that x_1 fires at t_i with odd i and x_2—at t_i with even i. Set $u_i = x_1(t_i)$, if i is even, and $u_i = x_2(t_i)$, if i is odd. Then $u_{i+1} = L_C(u_i), i \ge 1$. The pair synchronizes if and only if there exists $j \ge 1$ such that $x_1(t) \ne x_2(t)$, if $t \le t_j$, and $x_1(t) = x_2(t)$, for $t > t_j$. In particular, both oscillators have to fire at t_j. That is, inequalities $1-\epsilon \le u_j < 1$ hold, which is possible if $0 \le u_{j-1} \le L^{-1}(1-\epsilon)$. We have that $L_C(0) = \omega$ satisfies this condition.

If $1-\epsilon \le x_2(t_1) \le 1$, then we have that t_1 is a common firing moment of both x_1 and x_2, and it is the synchronization moment. Moreover, $1-\epsilon < L_C^2(x_2(t_1)) = \eta < 1$. That is, the map L_C brings us to synchrony, with one step of delay. If $\eta_1 > \epsilon$, then $1-\eta_1 < 1-\epsilon$, and one can easily see that the couple synchronizes in one iteration. That is, the map brings to synchronization with the same number of iterations. Summarizing, if there exists an integer $k \ge 0$ such that $1-\epsilon \le L_C^k(v) \le 1$, then a motion $(x_1(t), x_2(t))$ with $x_1(t_1+) = v, x_2(t_1+) = 0$, synchronizes. Conversely, if a motion $(x_1(t), x_2(t))$ synchronizes, then one can find a firing moment, t_1, such that $x_1(t_1+) = v, v \in [0, 1], x_2(t_1+) = 0$, and a number k such that $1-\epsilon \le L_C^k(v) \le 1$. Thus, it is verified that the constructed map is in full correspondence with the synchronization goal.

Analyzing maps $L_C^k, k \ge 0$, one can easily obtain that they all have only one non-zero fixed point v^*, and $|[L_C^k(v^*)]'| > 1$. Consequently, there is no k-periodic motion, $k > 1$, of the map, and a motion stabilizes, if its initial point $v \ne v^*$ (see Fig. 2).

Our next goal is to locate, for each non-negative integer k, the set of initial points such that their motions synchronize in precisely k iterations of the map. In the sequel, denote by S_k the region in [0, 1], where points v are synchronized after precisely k-iterations of L_C. Let $a_0 = L_C^{-1}(\eta) = 0, a_{k+1} = L_C^{-1}(a_k), k = 0, 1, 2, \ldots$. The points are pictured in Fig. 3. One can see that $S_0 = [1-\epsilon, 1], S_1 = [a_0, a_2]$ and $S_k = (a_{k-1}, a_{k+1}]$, if $k \ge 3$ is an odd positive integer, and $S_k = [a_{k+1}, a_{k-1})$, if $k \ge 2$ is an even positive integer. We have that $a_k \to v^*$ as $k \to \infty$. We shall call $S_k, k \ge 0$, as the rate intervals.

From the discussion above it follows that there is no finite time in which *all points* of the unit square synchronize. The closer v is to the equilibrium v^*, the later is the moment of synchronization.

Denote by $T = \frac{1}{\gamma}\ln\frac{\kappa}{\kappa-1}$ the natural period of oscillators, that is, the period of motion without couplings, and denote by $\tilde{T}$ the time needed for solution $u(t, 0, v^*)$ of the equation $u' = S - \gamma u$, to achieve threshold. Since both oscillators fire

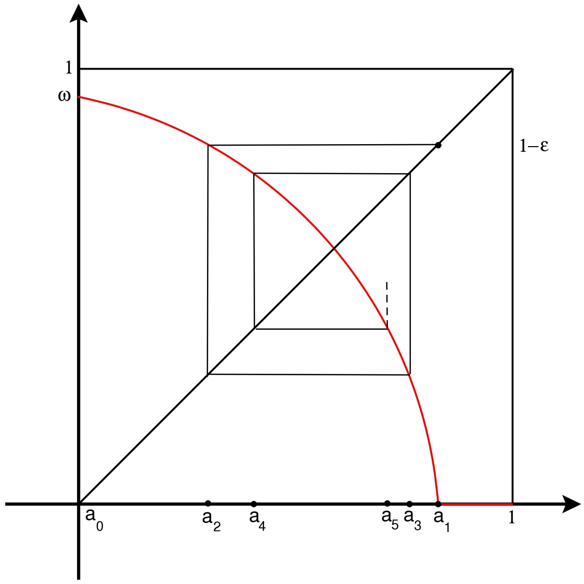

Fig. 3. The points $a_0 = L_C^{-1}(\eta) = 0$, $a_{k+1} = L_C^{-1}(a_k)$, $k = 0, 1, 2, \ldots$.

within an interval of length T and the distance between two firing moments of an oscillator is not less than $\tilde{T}$, the following assertion is valid.

Theorem 2.1. *Assume that $t_1 \geq 0$ is a firing moment, $x_1(t_1) = 1$, $x_1(t_1+) = 0$. If $x_2(t_1) \in S_m$ for some natural number m, then the couple x_1, x_2 of continuously coupled identical biological oscillators synchronizes within the time interval $\left[t_0 + \frac{m}{2}\tilde{T}, t_0 + Tm\right]$.*

3. Synchronization of an ensemble of identical oscillators

Consider the integrate-and-fire model of continuously coupled identical biological oscillators $x_1, x_2, \ldots, x_n$. We intend to apply the map L_C defined in the last section to this model. Let us start with the synchronization of a pair of oscillators in the multi-oscillatory ensemble, and prove that the synchrony occurs for this couple, if the parameters are close to zero. Next, we prove the phenomenon for the whole model. Fix two of the oscillators, let us say x_l and x_r.

Lemma 3.1. *If $t_0 \geq 0$ is a firing moment, $x_l(t_0) = 1, x_l(t_0+) = 0$. If parameter η (or/and τ) is sufficiently small, then the couple x_l, x_r synchronizes within the time interval $[t_0, t_0 + T]$ if $x_r(t_0) \notin [a_0, a_1)$ and within the time interval $\left[t_0 + \frac{m-1}{2}\tilde{T}, t_0 + (m+1)T\right]$, if $x_r(t_0) \in S_m$, $m \geq 1$.*

Proof. While the pair does not synchronize, there exists a sequence of firing moments, t_i, such that $0 \leq t_0 < t_1 < \cdots$, the oscillator x_l fires at t_i with even i, and x_r fires at t_i with odd i. For the sake of brevity let $u_i = x_l(t_i)$, $i = 2j+1, j \geq 0$, $u_i = x_r(t_i)$, $i = 2j, j \geq 0$.

Let us fix an even i. There are k, $k \leq n-2$ distinct firing moments of the motion $x(t)$ on the interval (t_i, t_{i+1}). Denote by $t_i < \theta_1 < \theta_2 < \cdots < \theta_k < t_{i+1}$, the moments of firing, when at least one of the coordinates of $x(t)$ fires. We assume, without loss of generality, that the length of intervals $(t_i, \theta_1), (\theta_1, \theta_2), \ldots, (\theta_k, t_{i+1})$ is more than τ. Other cases can be considered similarly.

We have that

$$
\begin{aligned}
x_r(t_i + \tau) &= x_r(t_i)\mathrm{e}^{-\gamma\tau} + \left(\kappa + \frac{\eta}{\gamma}\right)(1 - \mathrm{e}^{-\gamma\tau}),\\
x_r(\theta_1) &= x_r(t_i + \tau)\mathrm{e}^{-\gamma(\theta_1 - t_i - \tau)} + \kappa(1 - \mathrm{e}^{-\gamma(\theta_1 - t_i - \tau)}),\\
x_r(\theta_1 + \tau) &= x_r(\theta_1)\mathrm{e}^{-\gamma\tau} + \left(\kappa + \frac{\eta}{\gamma}\right)(1 - \mathrm{e}^{-\gamma\tau}),\\
x_r(\theta_2) &= x_r(\theta_1 + \tau)\mathrm{e}^{-\gamma(\theta_2 - \theta_1 - \tau)} + \kappa(1 - \mathrm{e}^{-\gamma(\theta_2 - \theta_1 - \tau)}),\\
&\ldots\\
x_r(\theta_j) &= x_r(\theta_{j-1} + \tau)\mathrm{e}^{-\gamma(\theta_j - \theta_{j-1} - \tau)} + \kappa(1 - \mathrm{e}^{-\gamma(\theta_j - \theta_{j-1} - \tau)}),
\end{aligned}
$$

$$x_r(\theta_j+\tau) = x_r(\theta_j)\mathrm{e}^{-\gamma\tau} + \left(\kappa + \frac{\eta}{\gamma}\right)(1-\mathrm{e}^{-\gamma\tau}),$$
$$\ldots$$
$$x_r(t_{i+1}) = x_r(\theta_k+\tau)\mathrm{e}^{-\gamma(t_{i+1}-\theta_k-\tau)} + \kappa(1-\mathrm{e}^{-\gamma(t_{i+1}-\theta_k-\tau)}). \tag{3.8}$$

The moment t_{i+1} satisfies

$$1-\epsilon \le x_r(t_{i+1}) \le 1. \tag{3.9}$$

We also have that

$$x_l(\theta_1) = \kappa(1-\mathrm{e}^{-\gamma(\theta_1-t_i)}),$$
$$x_l(\theta_1+\tau) = x_l(\theta_1)\mathrm{e}^{-\gamma\tau} + \left(\kappa + \frac{\eta}{\gamma}\right)(1-\mathrm{e}^{-\gamma\tau}),$$
$$\ldots$$
$$x_l(\theta_k+\tau) = x_l(\theta_k)\mathrm{e}^{-\gamma\tau} + \left(\kappa + \frac{\eta}{\gamma}\right)(1-\mathrm{e}^{-\gamma\tau}),$$
$$x_l(t_{i+1}) = x_l(\theta_k)\mathrm{e}^{-\gamma(t_{i+1}-\theta_k-\tau)} + \kappa(1-\mathrm{e}^{-\gamma(t_{i+1}-\theta_k-\tau)}). \tag{3.10}$$

The last three formulas determine the relation $u_{i+1} = K_i(u_i)$. A similar one can be found if i is odd. Evaluations in (3.8) and (3.10) bring us to expressions

$$x_r(t_{i+1}) = x_r(t_i)\mathrm{e}^{-\gamma(t_{i+1}-t_i)} + \kappa(1-\mathrm{e}^{-\gamma(t_{i+1}-t_i)}) + \frac{\eta}{\gamma}(1-\mathrm{e}^{-\gamma\tau})\left(\mathrm{e}^{-\gamma(t_{i+1}-t_i-\tau)} + \sum_{j=1}^{k}\mathrm{e}^{-\gamma(t_{i+1}-\theta_j-\tau)}\right) \tag{3.11}$$

and

$$x_l(t_{i+1}) = \kappa(1-\mathrm{e}^{-\gamma(t_{i+1}-t_i)}) + \frac{\eta}{\gamma}\mathrm{e}^{-\gamma(t_{i+1}-\theta_k-\tau)}(1-\mathrm{e}^{-\gamma\tau})\sum_{j=1}^{k}\mathrm{e}^{-\gamma(\theta_k-\theta_j)}. \tag{3.12}$$

Recall map L_C defined in the last section. We have

$$\phi(t_i+\tau) = x_r(t_i)\mathrm{e}^{-\gamma\tau} + \left(\kappa + \frac{\eta}{\gamma}\right)(1-\mathrm{e}^{-\gamma\tau}),$$
$$\phi(\bar{t}_{i+1}) = \phi(t_i+\tau)\mathrm{e}^{-\gamma(\bar{t}_{i+1}-t_i-\tau)} + \kappa(1-\mathrm{e}^{-\gamma(\bar{t}_{i+1}-t_i-\tau)}),$$

or

$$\phi(\bar{t}_{i+1}) = x_t(t_i)\mathrm{e}^{-\gamma(\bar{t}_{i+1}-t_i)} + \kappa(1-\mathrm{e}^{-\gamma(\bar{t}_{i+1}-t_i)}) + \frac{\eta}{\gamma}\mathrm{e}^{-\gamma(\bar{t}_{i+1}-t_i-\tau)}(1-\mathrm{e}^{-\gamma\tau}), \tag{3.13}$$

where $\bar{t}_{i+1}$ satisfies

$$\phi(\bar{t}_{i+1}) = 1, \tag{3.14}$$

and

$$\psi(\bar{t}_{i+1}) = \kappa(1-\mathrm{e}^{-\gamma(\bar{t}_{i+1}-t_i)}), \tag{3.15}$$

to evaluate $L_C(u_i) = \psi(\bar{t}_{i+1})$.

We assume, without loss of generality, that $\bar{t}_{i+1} \le t_{i+1}$. Then one can find that

$$x_r(\bar{t}_{i+1}) - \phi(\bar{t}_{i+1}) = x_r(\bar{t}_{i+1}) - 1 = \Phi(\eta,\gamma,\tau), \tag{3.16}$$

where

$$\Phi(\eta,\gamma,\tau) = \frac{\eta}{\gamma}(1-\mathrm{e}^{-\gamma\tau})\sum_{j=1}^{k}\mathrm{e}^{-\gamma(\bar{t}_{i+1}-\theta_j-\tau)},$$

and the last expression tends to zero as $\eta \to 0$. Next, by applying (3.9) and (3.16) we have that

$$t_{i+1} - \bar{t}_{i+1} \le \frac{|\Phi(\eta,\gamma,\tau)|}{S+\eta-\gamma}.$$

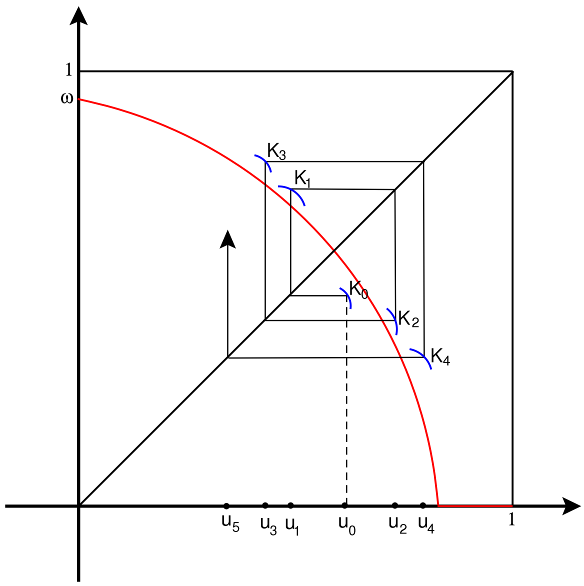

Fig. 4. The dynamics of the couple (x_l, x_r).

Now, consider

$$K_i(u_i) - L_C(u_i, \epsilon) = x_l(t_{i+1}) - \psi(\bar{t}_{i+1}) = \frac{\eta}{\gamma} \mathrm{e}^{-\gamma(t_{i+1}-\theta_k-\tau)}(1-\mathrm{e}^{-\gamma\tau}) \sum_{j=1}^{k} \mathrm{e}^{-\gamma(\theta_k-\theta_j)} + \kappa(\mathrm{e}^{-\gamma(\bar{t}_{i+1}-t_i)} - \mathrm{e}^{-\gamma(t_{i+1}-t_i)})$$

to see that $K_i(u_i) - L_C(u_i, \epsilon)$ can be made arbitrarily small if η is sufficiently small. This convergence is uniform with respect to u_0. We can also vary the number of points θ_i between 0 and $n-1$, as well as the distance between them. The convergence is indifferent with respect to these variations. Remember that the exciting strengths are not additive. Consider now the sequence $L_C^i(u_0, \epsilon)$. We have that $1-\epsilon \le L_C^m(u_0, \epsilon) \le 1$. Now, since L_C is a continuous function, we can discuss recurrently inequalities

$$|u_i - L_C^i(u_0, \epsilon)| \le |K_{i-1}(u_{i-1}) - L_C^i(u_{i-1}, \epsilon)| + |L_C^i(u_{i-1}, \epsilon) - L_C(L_C^{i-1}(u_0, \epsilon))|, \quad i = 1, 2, \ldots,$$

to conclude that either $1-\epsilon \le u_m \le 1$ or $1-\epsilon \le u_{m+1} \le 1$, if the parameters are sufficiently small. Both of these inequalities confirm synchronization. In Fig. 4 one can see the sequence of maps K_i, and the synchronizing sequence u_i is constructed. In the figure we show not only u_i, but also the graphs of functions $w = K_i(u)$, $u_{i+1} = K_i(u_i)$, in the neighborhood of u_i, to give a better geometrical visualization of the convergence.

Since each of the iterations of the map L_C happens within an interval of length not more than T, and the distance between two firing moments of an oscillator is not smaller than $\tilde{T}$, we obtain that the couple x_l, x_r is synchronized no earlier than $t = t_0 + \frac{m-1}{2}\tilde{T}$, and no later than $t = t_0 + (m+1)T$.

Thus, one can conclude that if a couple of oscillators is synchronized at some moment of time then, since the oscillators are identical, it persistently continues to fire in unison.

The lemma is proved. □

Let us apply the last lemma to the entire ensemble.

Theorem 3.1. *Let $t_0 \ge 0$ be a firing moment such that $x_j(t_0) = 1$, $x_j(t_0+) = 0$. If parameter η is sufficiently small, then the motion $x(t)$ of the system synchronizes within the time interval $[t_0, t_0+T]$, if $x_i(t_0) \notin [a_0, a_1)$, $i \ne j$, and within the time interval $\left[t_0 + \frac{\max_{i\ne j} k_i - 1}{2}\tilde{T}, t_0 + (\max_{i\ne j} k_i + 1)T\right]$, if there exist $x_s(t_0) \in [a_0, a_1)$ for some $s \ne j$ and $x_i(t_0) \in S_{k_i}$, $i \ne j$.*

Proof. Apply the last lemma to each pair (x_j, x_i), $i \ne j$ to obtain that it synchronizes within the time interval. The theorem is proved. □

On the basis of the last proof and the analysis of formulas (3.13)–(3.15) with (3.11), (3.9) and (3.12), one can conclude that the following assertion, which can be useful in applications and theory, is valid.

Theorem 3.2. *Assume that $t_0 \ge 0$ is a firing moment, $x_j(t_0) = 1$, $x_j(t_0+) = 0$. The motion $x(t)$ of the integrate-and-fire model of identical continuously coupled biological oscillators synchronizes within the time interval $[t_0, t_0+T]$, if $x_i(t_0+) \notin [a_0, a_1)$, $i \ne j$, and within the time interval $\left[t_0 + \frac{\max_{i\ne j} k_i - 1}{2}\tilde{T}, t_0 + (\max_{i\ne j} k_i + 1)T\right]$, if there exist $x_s(t_0) \in [a_0, a_1)$ for some $s \ne j$ and $x_i(t_0) \in S_{k_i}$, $i \ne j$, and if the delay τ is sufficiently small.*

4. Non-identical oscillators

Let us describe a more general system of oscillators such that the synchronization is still true.

Consider a system of n non-identical oscillators x_i, $i = 1, 2, \ldots, n$, whose values are in $[0, 1 + \xi_i]$. We assume that the following conditions are valid:

(B1). If several oscillators x_{i_m}, $m = 1, 2, \ldots, k$, fire at a moment $t = s$, such that $x_{i_m}(s) = 1 + \xi_{i_m}$, and $x_{i_m}(s+) = 0$, then all other oscillators x_{i_p}, $p = k + 1, k + 1, \ldots, n$, exhibit the following behavior near the moment of firing:

- If $x_{i_p}(s) + \epsilon + \epsilon_{i_p} \geq 1 + \xi_{i_p}$, then $x_{i_p}(s+) = 0$.
- Otherwise,

$$x'_{i_p} = \left(S + s_{i_p} + \eta + \sum_{m=1}^{k} s_{i_p i_m}(t - \theta_{i_p i_m}(t))\right) - (\gamma + \gamma_{i_p})x_{i_p}, \tag{4.17}$$

for all $t \in [s, s + \tau + \tau_{i_p}]$ that belong to the same continuity interval of x_{i_p} as s. Functions s_{ij} are piecewise continuous and $\theta_{i_p i_m}(t) > 0$ are bounded delays. There exist positive constants η_{ij} such that $|s_{ij}(t)| < \eta_{ij}$ for all i, j.

If x_j fires at a moment $t = s$, we name the interval $[s, s + \tau]$ as an e^j-interval. An oscillator x_i *is excited* at a moment t, if the moment belongs to an e^j-interval with $j \neq i$, or $x_i(t) = 1 + \xi_i$.

(B2). When i-th oscillator is not excited

$$x'_i = (S + s_i) - (\gamma + \gamma_i)x_i. \tag{4.18}$$

In (B1) and (B2) constants $S, \gamma, \epsilon, \eta$ are the same as in (A1)–(A4), parameters $s_i, \gamma_i, \xi_i, \eta_{ij}, \tau_{i,j}, i, j = 1, 2, \ldots, n$, are fixed real numbers. Additionally we require that

(B3). $\tau + \tau_{i_p} > 0$, $\eta - \sum_{s=1}^{k} \eta_{i_p i_s} > 0$, for all possible k, i_p and i_s.

We shall call the system of n oscillators with conditions (B1)–(B3), (A3) *the integrate-and-fire model of continuously coupled non-identical biological oscillators*.

Theorem 4.1. *Let $t_0 \geq 0$ be a firing moment such that $x_j(t_0) = 1, x_j(t_0+) = 0$. If parameters $s_i, \gamma_i, \zeta_i, \eta_{ij}, \tau_{ij}$ and η (or/and τ) are sufficiently small, then the motion $x(t)$ of the integrate-and-fire model of continuously coupled non-identical biological oscillators synchronizes within the time interval $[t_0, t_0 + T]$, if $x_i(t_0) \notin [a_0, a_1), i \neq j$, and within the time interval $\left[t_0 + \frac{\max_{i\neq j} k_i - 1}{2}\tilde{T}, t_0 + (\max_{i\neq j} k_i + 1)T\right]$, if there exist $x_s(t_0) \in [a_0, a_1)$ for some $s \neq j$ and $x_i(t_0) \in S_{k_i}, i \neq j$.*

We decided to omit the proof of the last theorem, since it is very similar to that of Theorem 3.1 with slight changes caused by newly introduced parameters. Still, one point in the proof deserves special attention. If two oscillators x_l and x_r are non-identical and fire simultaneously at a moment $t = \theta$, how will they retain the state of firing in unison, despite being different? To find the required conditions, let us denote by $\tau, \tau > \theta$ a moment when one of them, let us say x_l, fires. We have that $x_l(\theta+) = x_r(\theta+) = 0$. This time it is not necessary to have $x_l(t) = x_r(t), \theta \leq t \leq \tau$. It is clear that to satisfy $x_l(\tau+) = x_r(\tau+) = 0$, we need $x_r(\tau) + \epsilon + \epsilon_r \geq 1 + \xi_r$. By applying formulas similar to (3.8) and (3.9), this time with $t_i = \theta, t_{i+1} = \tau, x_r(\theta) = 0$, one can easily obtain that the inequality is correct if the parameters are sufficiently small. Thus, one can conclude that if a couple of oscillators is synchronized at some moment of time then it persistently continues to fire in unison.

Remark 4.1. We do not impose any restriction on the delay functions $\theta_{i_p i_m}(t)$ in (4.17), except that they are bounded functions. Oscillators with delayed excitatory interaction, without leakage, and their applications are discussed in [7]. Similarly to the way it is done for pulse-coupled models in [18], all results can be extended to systems, when the coupling is not all-to-all, and general types of thresholds and differential equations are considered. Parameter η is chosen as the main one to establish synchronization. It is obvious that the choice of the control can be varied, for example, by choosing τ, or both of them, instead.

5. Simulations

To illustrate the theory, consider a system of oscillators, $x_1, x_2, \ldots, x_{100}$, with random start values in $[0, 1]$. Choose, also randomly, numbers $\xi_i, \alpha_i, \beta_i, i = 1, 2, \ldots, 100$, from the interval $[0, 1]$. Assume that if $x_j(s) = 1 + 0.005\xi_j$ at some moment $t = s$, then the oscillator fires, $x_j(s+) = 0$, and other oscillators $x_i, i \neq j$, change their behavior near the firing moment in the following way: if $x_i(s) + 0.03 \geq 1 + \xi_i$, then $x_i(s+) = 0$; otherwise,

$$x'_i = (13 + 0.01\alpha_i) - (2 + 0.01\beta_i)x_i, \tag{5.19}$$

for all $t \in [s, s + 0.01]$, till x_i fires.

If x_j fires at a moment $t = s$, then an oscillator x_i is excited at the moment t, if either the moment belongs to the interval $[s, s + 0.01]$ with $j \neq i$, or $x_i(t) = 1 + 0.005\xi_i$.

When $x_i, i = 1, 2, \ldots, n$, is not excited then

$$x'_i = (3 + 0.01\alpha_i) - (2 + 0.01\beta_i)x_i. \tag{5.20}$$

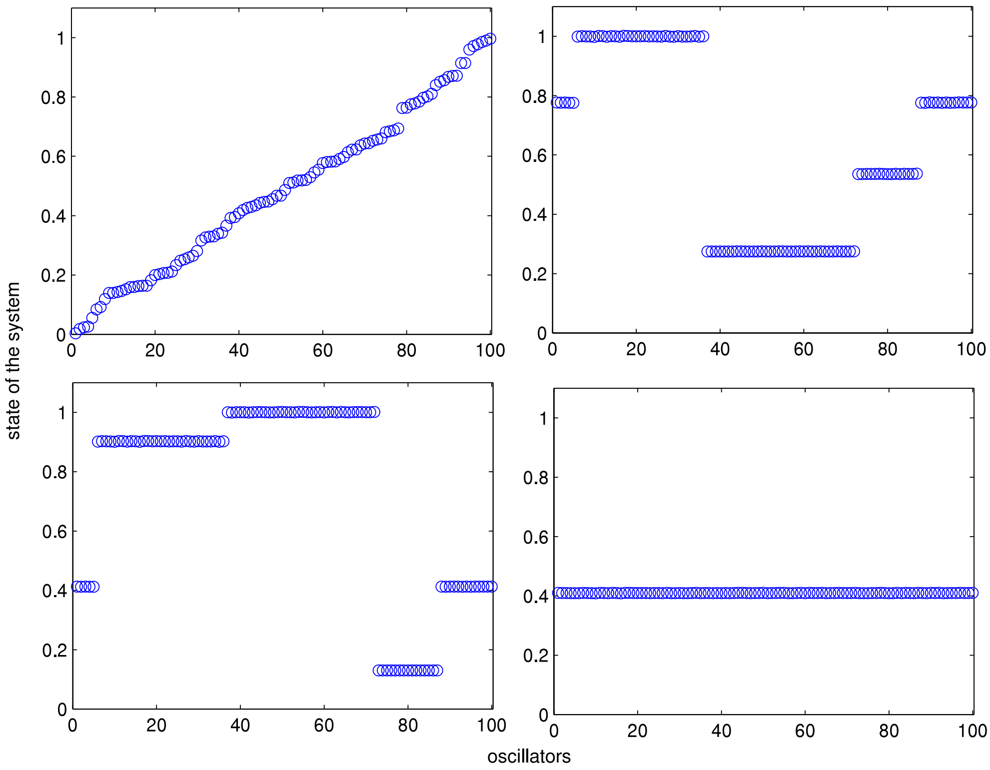

Fig. 5. The figure in the upper left corner depicts the initial positions, the one in the upper right corner depicts the situation just before the thirtieth jump, the one in the lower left corner – just before the sixtieth jump, and the final figure – before the ninetieth jump of the system. The flat sections of the graph are groups of synchronized oscillators.

In Fig. 5 one can see the result of the simulation, where the upper left figure corresponds to the initial states, the upper right one shows the situations just before the thirtieth jump, the lower left one – just before the sixtieth jump, and the final one – before the ninetieth jump of the system.

In the next simulation we provide a stroboscopic vision of synchronization process.

Consider this time a system of fifty oscillators such that the non-excited equations are

$$x_i' = (3 + 0.1\alpha_i) - (2 + 0.1\beta_i)x_i, \tag{5.21}$$

and the excited ones are

$$x_i' = (4 + 0.1\alpha_i) - (2 + 0.1\beta_i)x_i. \tag{5.22}$$

Moreover, $\epsilon = 0.3$, $\tau = 0.05$, and the thresholds equations are $x_i(t) = 1 + 0.001\xi_i$. One can easily see that in this second simulation ϵ is larger than in the previous one. This condition provides a faster synchronization—in nine iterations of the map, that is, after seven firings of the model. All the snaps are shown in Fig. 6. The upper left diagram is the first snap, and the lower right one is the last snap. On the second diagram in the graph, one can see that the first horizontal cluster of synchronized oscillators is formed after the first firing. In the third diagram, we see that another cluster emerges. The following diagram depicts the formation of three clusters as completed. Next, these three synchronize in three consecutive firings. The last diagram shows that the synchronized oscillators are close to each other between firings as well.

6. Conclusion

The famous two conjectures of Peskin [2] were developed for further applications. One of important additional questions is: Do continuous or piece-wise continuous couplings synchronize the model? In the present paper, sufficient conditions for a positive answer are found. The method of investigation is based on a specially constructed map. One can remark that the systems investigated in this paper are, in fact, cooperative discontinuous systems [58–60] with monotone dynamics [61]. Consequently, by applying the methods of dynamical systems with discontinuities at variable moments [44] one can obtain more results concerning biological processes in the future. One should also emphasize that our results concern oscillators that are close to identical. This investigation is appropriate for homogeneous or close to homogeneous populations. If there is a large deviation from homogeneity, then we guess that even chaotic model behavior is possible. This requires additional investigation. Moreover, we think that for models with essentially non-identical oscillators one can prove results on a more general type of synchronization: phase and frequency locking, clustering, periodic, almost periodic and recurrent motions,

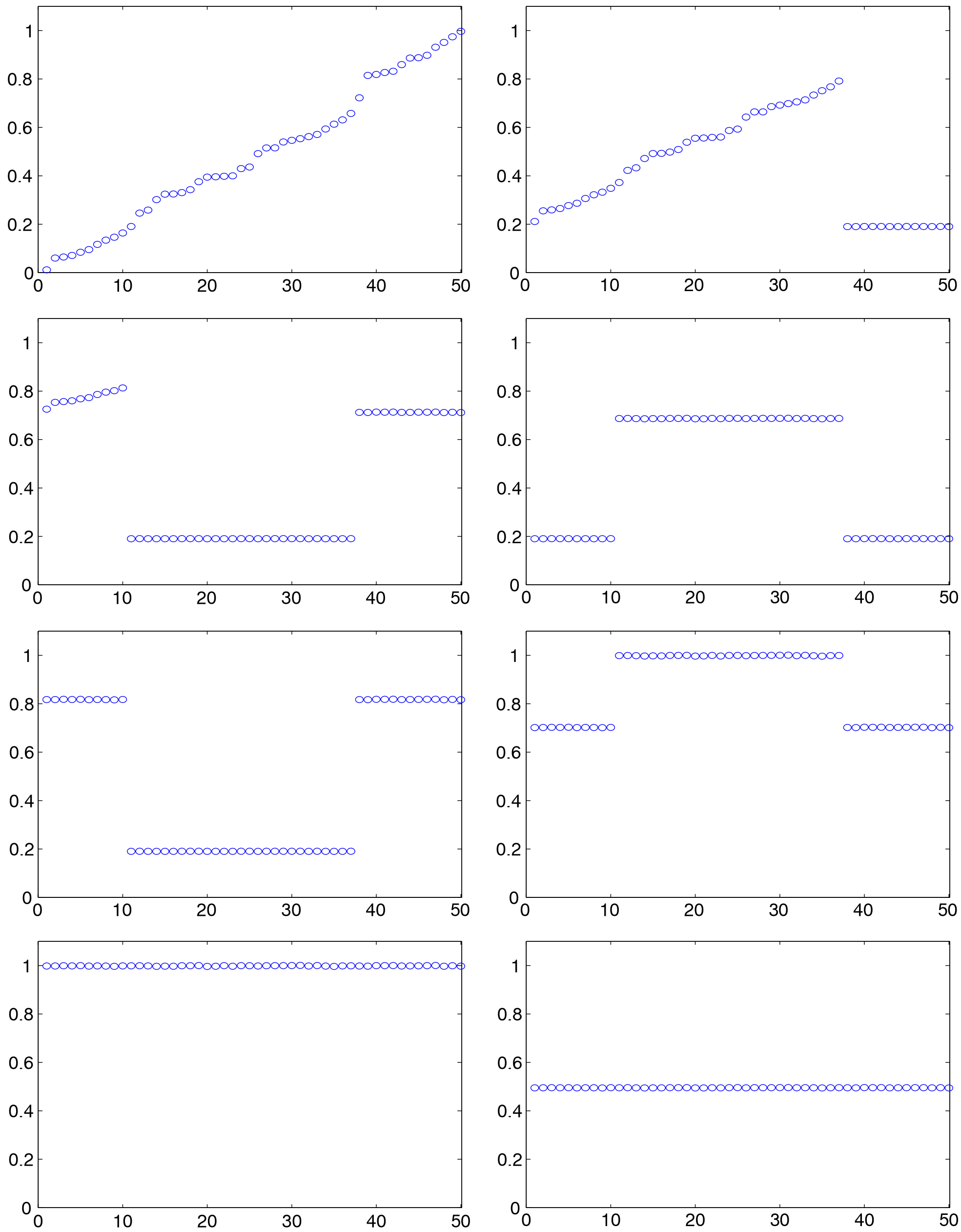

Fig. 6. The stroboscopic diagrams of fifty oscillators that have synchronized in seven consecutive firings.

motions with clustered coordinates, where clusters behave periodically, etc. For this inquiry, the theory of dynamical systems [18] with discontinuities at variable moments of time has to be developed more deeply, extending the methods of continuous dynamics of autonomous differential equations [62–67].

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