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Numerical Simulations of Dynamics Behaviour of the Action Potential of the Human Heart's Conduction System

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Additional information is available at the end of the chapter

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Abstract

A proposed model consisting of two coupled van der Pol models is considered as a description of the heart action potential. A system of ordinary differential equations is used to recreate pathological behaviour in the conducting system of the heart such as Wolff-Parkinson-White (WPW) syndrome and the most common tachycardia: atrioventricular nodal reentrant tachycardia (AVNRT). Part of the population has abnormal accessory pathways: fast and slow. These pathways in the atrioventricular node (AV node) are anatomical and functional excipients of supraventricular tachycardia. However, the appearance of two pathways in the AV node may be an excipient of arrhythmia—the WPW syndrome. The difference in the conduction time between these pathways is the most important factor. This is the reason to introduce three types of couplings and delay to our system in order to reproduce different types of the AVNRT. In our research, the result of introducing the feedback loops and couplings entails the creation of waves which can correspond to the re-entry waves which occur in the AVNRT. Our main aim is to study solutions of the equations of the system and to take into consideration the influence of feedback and delays which occur in the pathological modes. The proposed models made it possible to reproduce the most important physiological properties of the discussed pathologies. Since the model is phenomenological, the results are accurate as far as a simple model can describe the potential found in one of the more complex oscillators found in biology.

Keywords: van der Pol model, ordinary differential equations, delay, feedback, couplings, action potential, WPW syndrome, AVNRT, numerical analysis

1. Introduction

In this chapter, the research on the electrical conduction system of the human heart is concerned. The parts of this system are pacemaker centres made of special cells similar to embryonic cells which form the following concentrations: sino-atrial node (SA), atrioventricular node (AV) and His-Purkinje system [1]. The key elements of the conduction system considered include SA node and AV node. Modelling the formation and conduction of electrical impulses in the heart is one of the most developed areas of mathematical biology. For years, the most popular models of action potentials which occur in the heart have included the Hodgkin-Huxley model and the Purkinje cells model. These models, even though very effective, are not very suitable for studying the dynamics of the system, which is described in view of high dimensionality of the phase space and very broad spatial parameters. In this chapter, we propose ordinary differential system which is based on the van der Pol models and which makes it possible to reconstruct pathological behaviours in the system of the heart, such as the WPW syndrome and different types of AVNRT. The motivation for writing this chapter was that there is a problem with making the appropriate diagnosis and therefore with treating the disease effectively. This kind of problem is observed mainly in different types of AVNRT. The reasons of those problems are not fully known and the mechanisms of these pathologies are not fully understood. Also, the symptoms are often mistakenly taken for other heart diseases. It should be emphasized that the clinical pictures of these disease are also non-specific. In the past few years, we understood that the structure of the AV node has a multi-level architecture in which there may be many pathways (slow and fast) at different locations in the AV node [2, 3]. This helped to recognize many types of AVNRT, which previously were understood as one, although the mechanisms of action were different. In literature, there are no mathematical models that would specifically model the various types of AVNRT. There were attempts to model AVNRT only as a single pathology having the slow and fast pathways [4, 5]. Part of the population has abnormal accessory pathways: fast and slow, cf. [1, 6]. The pathways in the AV node are anatomical and functional contributions of the most popular supraventricular tachycardia, which is a re-entry tachycardia from the AV node. The atrioventricular nodal re-entrant tachycardia is caused by re-entries. A condition for AVNRT to occur is that two electric pathways occur in and around the AV node (for example, slow and fast pathways). This gives way to the occurrence of re-entry. We can distinguish five different forms of the AVNRT (typical: slow/fast, atypical: fast/slow and other forms: slow/slow, more than two re-entries waves, one fast pathway with depolarization of slow pathway) [7, 8, 9]. This depends on the multi-level architecture of the AV node. The AVNRT circuit involves larger areas including atrioventricular junction, adjacent atrial structures and in particular so-called atrial inputs including at least antero-superior and postero-inferior entries, and sometimes also the left atrial entry. Based on the van der Pol equation, we study the influence of feedback which occurs in the normal heart action mode as well as in pathological modes. Particularly, it is important to introduce the time delay into this feedback. Delay values used in our research correspond to those which occur in the electrical conduction system, for example, in the case of an accessory conducting pathway, so-called Wolff-

Parkinson-White syndrome. In the conduction system of the heart, the only correct electrical conduction pathway between atria and ventricles is the bundle of His. Part of the population has abnormal accessory pathways through which electrical pulses are directly conducted from atria to ventricles. The extra electrical pathway is presented at birth and is fairly rare. The WPW syndrome is detected in about 4 out of every 100000 people. People of all ages, including infants, can experience the symptoms related to the WPW syndrome. Additional path conducts electrical impulses to the ventricles in the case of WPW. This conduction takes place without proper synchronization. Usually, this extra conduction pathway does not cause serious disturbances. Sometimes, however, there is a reflection of the electrical impulse, and it returns to the atria after each heartbeat. This causes the coupling in which each atrial contraction is followed by chambers contraction and then atrial contraction again. The heart rate can reach about 200 beats per minute when the normal rhythm at rest is about 72 beats per minute.

As already mentioned, synchronization is very important for a correctly functioning heart in the sense of cardiovascular conduction. The impact of different types of couplings related to the pathologies which are presented in this research and how do they affect the synchronization of the two oscillators will be discussed in this chapter. The analysis of synchronization of various modifications of the van der Pol model has been considered in many works. For example, paper [10] presents synchronization areas near the main parametric resonance and transition conditions from regular to chaotic motion. In paper [11], authors analyse the phenomenon of complete synchronization in a network of four coupled oscillators. Reference [12] considered mechanisms of various bifurcation phenomena occurring in Bonhoffer van der Pol neurons coupled with a time delay through the characteristics of synaptic transmissions. The phenomenon of synchronization in van der Pol oscillators coupled by a time-varying resistor is researched in ref. [13]. However, in these papers there are no examples of application of this model for recreating a pathological behaviour of the electrical-conduction system of the human heart, and therefore the considered ranges of parameters are wider than those which can be used in medical applications. The van der Pol oscillator provides rich dynamical behaviour [14] and also synchronization phenomena. In order to better understand the mechanisms that cause these arrhythmias in paper are proposed models of AVNRT and WPW syndrome.

2. Modelling techniques

The van der Pol model was used in this research because it is a two-dimensional model with small number of parameters and it is a relaxation oscillator. The van der Pol equation is often used to describe an action potential occurring in the heart. The model with a delay and often with a term including a coupling coefficient has been a topic of many articles, e.g. [15–17]. However, in these articles there are no exact examples of application of this model for recreating a pathological behaviour of the electrical conduction system of the human heart such as the AVNRT and the WPW, and therefore the range of parameters considered by them is wider than that which can be used in medical applications. Below, the author will present

one of the most important existing mathematical models of the action potential. Basing on the knowledge of van der Pol model given below will be carried out construction of the proposed models.

2.1. Van der Pol model

Since every node is a self-exciting pacemaker, it can be described using the van der Pol oscillator which is the relaxation oscillator. It was first introduced by van der Pol and van der Mark as a model in the electronic circuit theory in 1927, [19]:

$$\ddot{x} + a(x^2 - 1)\dot{x} + x = 0 \quad (1)$$

where

$$f(x) = 0.5a(x^2 - 1) \quad (2)$$

$f(x)$ is a damping coefficient, which is negative for $|x| < 1$ and positive for $|x| > 1$. Nevertheless, the van der Pol model requires some changes to be introduced in order to reproduce features of heart's action potential. In paper [20], Postnov substituted a linear term by a non-linear cubic force called the Duffing term

$$\ddot{x} + a(x^2 - \mu)\dot{x} + \frac{x(x+d)(x+2d)}{d^2} = 0 \quad (3)$$

where a, μ, d are positive control parameters.

In this way, he introduced modifications which allowed maintaining the required structure of the phase space. Such model can be applied to model either SA or AV node. The main property of a modified relaxation oscillator is the mutual interaction of a limit cycle which is presented around an unstable focus with a saddle and a stable node. This allows reproducing correctly the refraction period and non-linear phase sensitivity of an action potential of node cells.

A solution of Eq. (3) in time presents the action potential whereas a solution in velocity makes it possible to obtain very important phase portrait. We can easily see that the main qualitative difference between Eqs. (1) and (3) is the appearance of two additional steady states, $x_2 = -d$ and $x_3 = -2d$. As before, $x_1 = 0$ is an unstable node or a focus surrounded by a stable unique limit cycle, $x_2 = -d$ is a saddle and $x_3 = -2d$ forms a focus or a node and can be either stable or unstable, depending on the sign of $4d^2 - \mu$. In the case considered by Postnov [20], the first steady state is an unstable focus, the third one is a stable node. In the considered model (5), the problem is the adjustment of the position of stationary states in the phase space. In order to reproduce behaviour of the heart, a new parameter e is added. For better regulation of the frequency, the

$e \cdot d$ factor is substituted with an independent coefficient f corresponding to harmonic oscillator's frequency, [20]. We present the final version of the model in its two variable first-order form that reads [20]:

$$\begin{aligned}\dot{x} &= y, \\ \dot{y} &= -a(x^2 - 1)y - fx(x + d)(x + e)\end{aligned}\quad (4)$$

The system that we use as a reference one is given in following form:

$$\begin{aligned}\dot{x}_1 &= y_1 \\ \dot{y}_1 &= -a_1(x_1^2 - 1)y_1 - f_1x_1(x_1 + d_1)(x_1 + e_1) \\ \dot{x}_2 &= y_2 \\ \dot{y}_2 &= -a_2(x_2^2 - 1)y_2 - f_2x_2(x_2 + d_2)(x_2 + e_2)\end{aligned}\quad (5)$$

where $a_1=a_2=5$; $f_1=f_2=3$; $d_1=d_2=3$; $e_1=7$; $e_2=4.5$ are control parameters. In the next part of this paper, a modified van der Pol system with delayed feedback and couplings describes various pathologies observed in heart action, for example, WPW syndrome and different types of AVNRT pathology.

3. Construction and analysis of proposed models

In this section we turn to constructing new models for specific pathologies we would like to describe. All the models we propose below consist of two modified van der Pol models. The system with delayed feedback describes various pathologies observed in the heart action, e.g. WPW syndrome and different types of AVNRT.

A numerical model was created using Dynamics Solver and a program which was written in C++. The explicit Runge-Kutta formula with a variable integration step was used. Results were confirmed and plots were made with Matlab standard dde23 solver.

For the single node model (Eq. (4)) of an electrical conduction system with no feedback, a periodic potential and the corresponding limit cycle (with a transient state) are obtained like in **Figures 1** and **2**. Potential period equals 1.4.

The reference parameters have values which are given below:

$$a_1 = a_2 = 5, d_1 = d_2 = 3, e_1 = 7, e_2 = 4.5, f_1 = f_2 = 3. \quad (6)$$

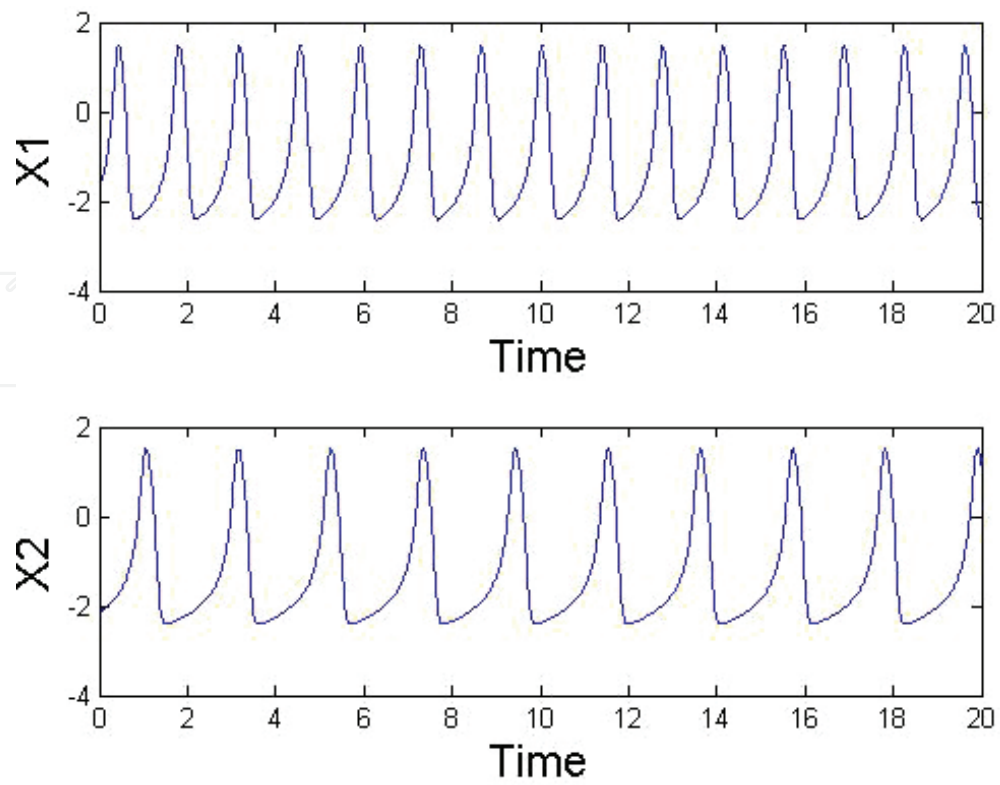


Figure 1. Time series for reference model without feedback and delay, see Eq. (5).

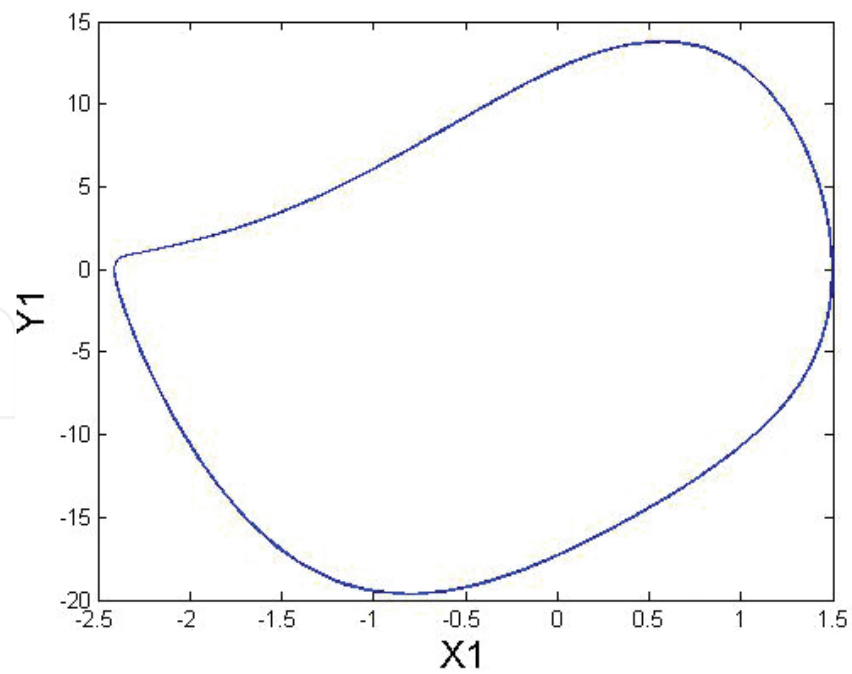


Figure 2. Phase portrait for reference model without feedback and delay, see first part of Eq. (5).

The addition of coupling (especially feedback with delay) to the x_1 term allows modelling the re-entry wave which causes the exceptional situation when AV node is the master for SA node. Such situation takes place in case of WPW syndrome, this situation is presented by the following equations:

$$\begin{aligned}\dot{x}_1 &= y_1 + k(x_1(t-\tau) - x_1) \\ \dot{y}_1 &= -a_1(x_1^2 - 1)y_1 - f_1x_1(x_1 + d_1)(x_1 + e_1)\end{aligned}$$

Parameters have the following values: $k=2$, $\tau=0.25$ and other parameters are the same as in the reference system. In the time series of the modified model with feedback, there is a 'delayed impulse'. The result of introducing feedback to the system is the creation of a wave similar to the initial wave—action potential, but delayed. It can be assumed that such a feedback can be treated as an external, periodic excitation of the wave. In **Figure 3** we can observe a kind of tachycardia which is a typical symptom of the Wolff-Parkinson-White syndrome. The period of oscillations is about 0.9 whereas the reference period of physiological action potential is 1.4.

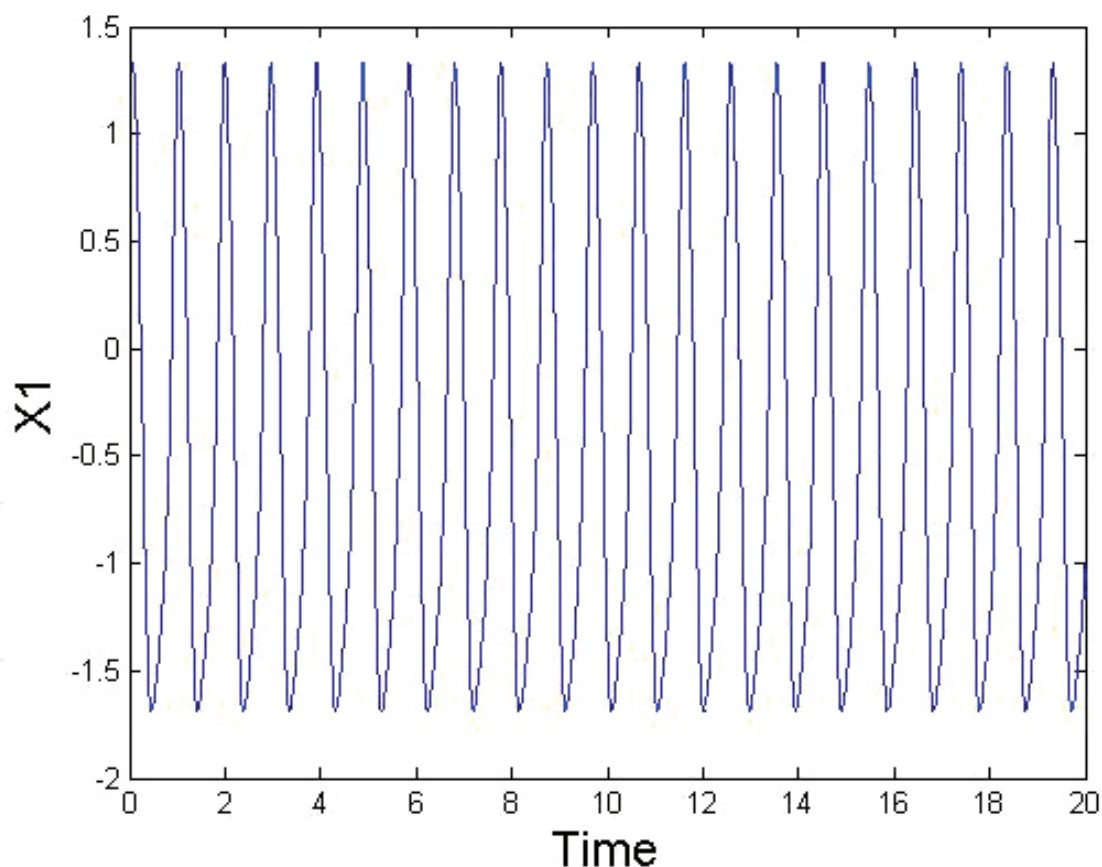


Figure 3. Dynamics of action potential during WPW syndrome.

Now we consider the AVNRT pathology. We would like to propose a mechanism which reproduces the dynamics of action potential occurring at the phenomenon of AVNRT. In this

case, we have a coexistent conduction by two or more pathways: slow and fast. In this model, we assume that the fast pathway is described by the first van der Pol model, but the slow pathway is treated as an action potential in other characteristic, so we use the second model of van der Pol to describe the pathway.

Next, we focus on such a type of AVNRT in which only one fast pathway with depolarization of slow pathway occurs. The conduction is only out of the fast pathway, because descending depolarization of slow pathway prevents conduction. To describe that situation, we add only one unidirectional coupling to our model. This coupling does not change the main rhythm x_1 (see **Figure 4**). In this case, the model could be written in the following form:

$$\begin{cases} \dot{x}_1 = y_1 \\ \dot{y}_1 = a_1(x_1^2 - 1)y_1 - f_1x_1(x_1 + d_1)(x_1 + e_1) \\ \dot{x}_2 = y_2 + kx_1 \\ \dot{y}_2 = a_2(x_2^2 - 1)y_2 - f_2x_2(x_2 + d_2)(x_2 + e_2) \end{cases} \quad (7)$$

where k is the coupled coefficient, τ is the delay and other parameters are fixed as $a=5$, $f=3$, $d=3$, $e=7$.

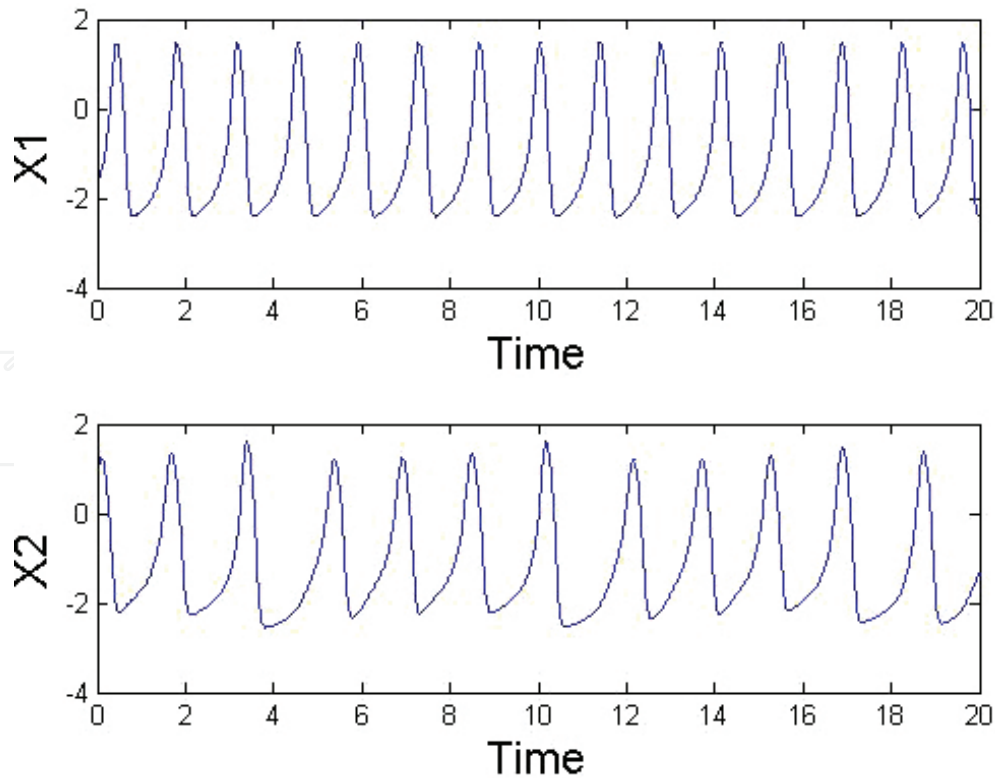


Figure 4. Time series for fast type of AVNRT.

Now, we consider a situation where the difference in the refractive state of both pathways leads to an excitation of one of them causing the re-entry wave [20]. In **Figure 5**, the result for a typical AVNRT (fast/slow) is presented. This type of AVNRT is described by the following system:

$$\begin{cases} \dot{x}_1 = y_1 - k(x_1(t-\tau) - x_1) \\ \dot{y}_1 = a_1(x_1^2 - 1)y_1 - f_1x_1(x_1 + d_1)(x_1 + e_1) \\ \dot{x}_2 = y_2 \\ \dot{y}_2 = a_2(x_2^2 - 1)y_2 - f_2x_2(x_2 + d_2)(x_2 + e_2) \end{cases} \quad (8)$$

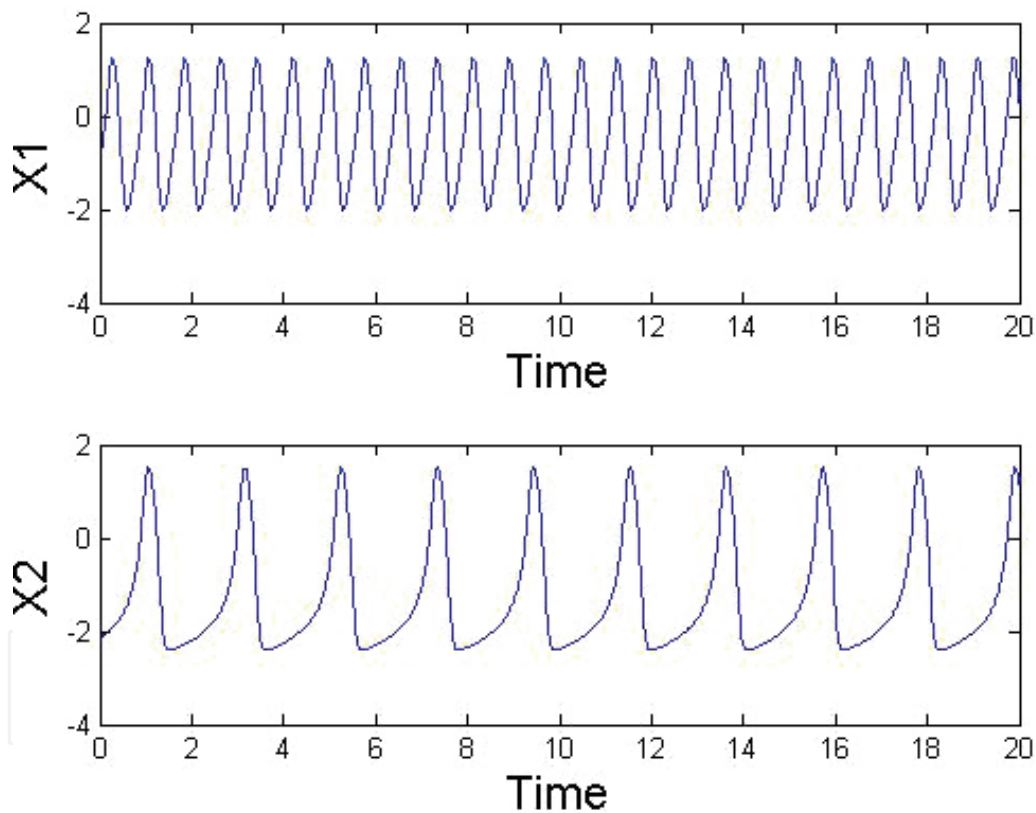


Figure 5. Dynamics of action potential for a typical AVNRT, given in Eq. (8).

The mechanism of the typical AVNRT is similar to this which is observed in the WPW syndrome. Also, we have a feedback with delay in the first part of the given model.

The atypical AVNRT (slow/fast type of AVNRT) is described in the following way:

$$\begin{cases} \dot{x}_1 = y_1 - k_1(x_2(t-\tau) - x_1) \\ \dot{y}_1 = a_1(x_1^2 - 1)y_1 - f_1x_1(x_1 + d_1)(x_1 + e_1) \\ \dot{x}_2 = y_2 - k_2(x_1 - x_2(t-\tau)) \\ \dot{y}_2 = a_2(x_2^2 - 1)y_2 - f_2x_2(x_2 + d_2)(x_2 + e_2) \end{cases} \quad (9)$$

In both of those types of AVNRT (fast/slow and slow/fast) we obtain regular fast rhythm, which is a typical behaviour for this kind of pathology (during this type of tachycardia, the rhythm of the heart is about 35% more frequent than normal rhythm, which is in accordance with our results).

The last case is for the situation where there are two re-entry waves but both go through slow pathways (slow/slow type of AVNRT), which we reflect by the following system of equations:

$$\begin{cases} \dot{x}_1 = y_1 - k_1(x_2(t-\tau) - x_1) \\ \dot{y}_1 = a_1(x_1^2 - 1)y_1 - f_1x_1(x_1 + d_1)(x_1 + e_1) \\ \dot{x}_2 = y_2 - k_2(x_1 - x_2(t-\tau_1)) - k_3(x_1 - x_2(t-\tau_2)) \\ \dot{y}_2 = a_2(x_2^2 - 1)y_2 - f_2x_2(x_2 + d_2)(x_2 + e_2) \end{cases} \quad (10)$$

In this variant, we also observe shortening (like in **Figure 5**) of the period of oscillations. In this pathology, the presence of more than two conduction paths is possible which is associated with more re-entry waves. Increasing the number of feedbacks modelling re-entry waves of slow pathways causes a progressive shortening of the period of oscillation, while the rhythm remains regular. The conclusion is that a regular excitation may evoke a regular answer.

After examining the influence of excitation with modified van der Pol oscillator wave, we have analysed behaviour of the modified van der Pol oscillator with feedback excited with a single rectangular pulse. In this way, two excitations co-exist in the system—the wave brought by the oscillator's feedback and the one from the external pulse. The pulse is defined by a step function H for the amplitude $A=4$ and the length of pulse $L=0.05$ and it is applied to the oscillator with $k=1$ and $T=1$. The function H is defined as:

$$H_{A,L}(t) = \begin{cases} A, & 0 < t < L \\ 0, & \text{otherwise} \end{cases}$$

Influence of the pulse is treated as an appearance of the accessory current in the system. For this reason, this pulse is introduced to the equation describing the potential change (the x variable):

$$\begin{aligned}\dot{x} &= y(t) + k(x(t-T) - x(t)) + H_{A,L}(t - t_p), \\ \dot{y} &= -a(x^2(t) - 1)y(t) - fx(t)(x(t) + d)(x(t) + e)\end{aligned}$$

where t_p denotes the moment in time when the pulse starts.

The influence of the pulse, which results in the period length change, depends on in which phase of oscillations it is applied. As mentioned before, the excitation influences the system having the regular behaviour.

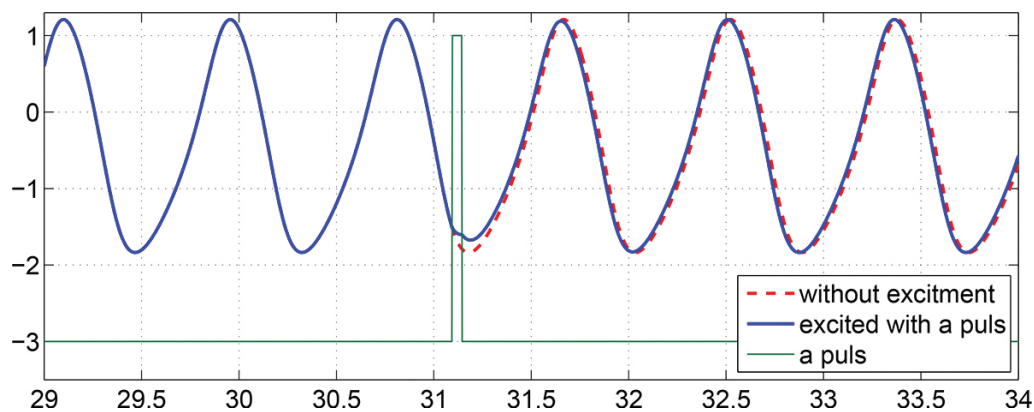


Figure 6. Numerical solution of the system with feedback ($k=1$, $T=0.5$), excited with the rectangular pulse.

Numerical solution of the system with feedback ($k=1$, $T=0.5$), excited with the rectangular pulse is presented in **Figure 6**. Red colour presents modified van der Pol model with feedback, whereas blue one shows the modified van der Pol model with feedback, which is additionally excited with the rectangular pulse. In this case application of the external pulse does not influence oscillator's period length, oscillations are stable. There are phase ranges for which oscillations are sensitive to a disturbance. Phase response curves for modified van der Pol system without feedback and for two cases with feedback ($k=1$, $T=1$ and $k=1$, $T=0.5$) which are excited with the rectangular pulse ($A=4$, $L=0.05$) are shown in **Figure 7**. A phase response curve is a graphic presentation of the influence of excitation for oscillation phases of modified van der Pol system. Its shape depends on in which phase of oscillation the excitation is exerted. This curve describes the dependence between the change of length of one cycle of oscillation and the excitation phase φ . For example, the application of the excitation in a moment when the system abides in the refraction state does not change the behaviour of the system.

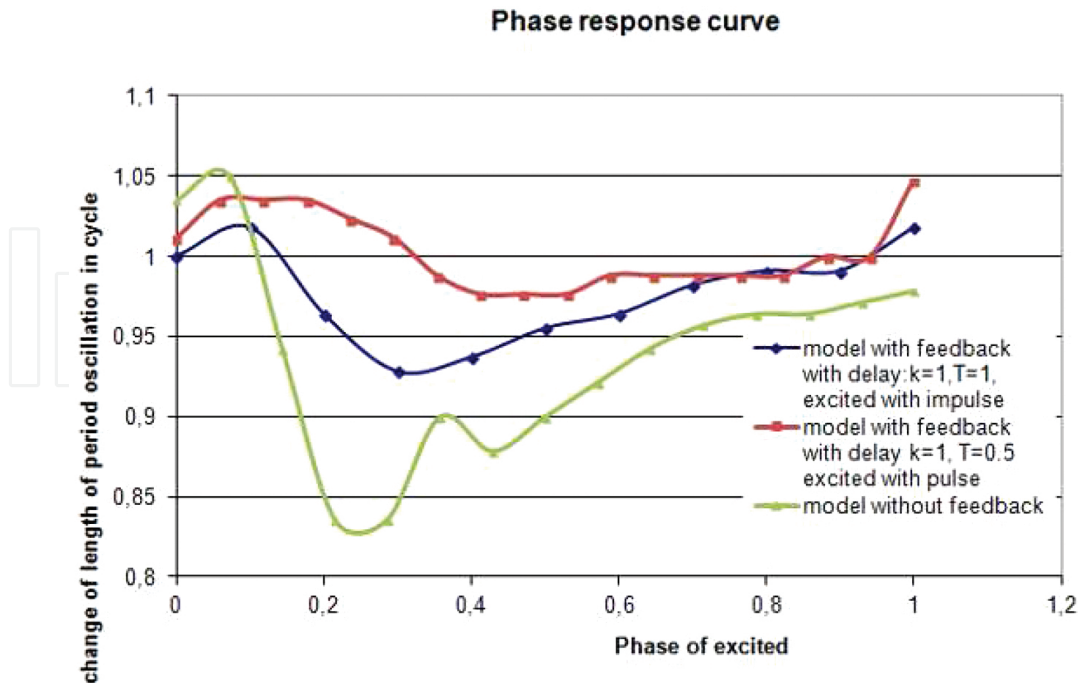


Figure 7. Phase response curves for models with rectangular pulse.

The system is phase-sensitive, and that, depending on the phase, excitation may change the potential period length. Models with feedback are much less phase-sensitive, **Figure 7**. The feedback strongly modifies the properties of the modified van der Pol model.

The human heart rhythm with feedback about AV node is low-variable. The results of this study were consulted with the medical doctor from the Institute of Cardiology in Anin near Warsaw, who confirmed that the very stable heart rhythm is typical for patients with AV nodal re-entrant tachycardia.

One of the most important features of oscillators is synchronization. The behaviour of cardiac pacemaker cells resembles those relaxation oscillators. A characteristic property of relaxation oscillators is that they may be synchronized by an external signal, if the latter has a periodicity similar to spontaneous frequency of the oscillator [14]. We investigate a phenomenological model for the heartbeat which consists of two coupled van der Pol oscillators. The coupling between these oscillator (action potential) can be either unidirectional or bidirectional, with or without feedback. Below, we present our model with possible couplings and feedbacks and try to analyse all of them for behaviour of given system and its synchronization.

$$\begin{cases} \dot{x}_1 = y_1 - k_1(x_2(t-\tau) - x_1) \\ \dot{y}_1 = a_1(x_1^2 - 1)y_1 - f_1x_1(x_1 + d_1)(x_1 + e_1) + s_1(x_2 - x_1) \\ \dot{x}_2 = y_2 - k_2(x_1 - x_2(t-\tau)) \\ \dot{y}_2 = a_2(x_2^2 - 1)y_2 - f_2x_2(x_2 + d_2)(x_2 + e_2) + s_2(x_1 - x_2) \end{cases} \quad (11)$$

If we consider physiological coupling between nodes, then the s_2 coupling is introduced to our system. It means that the SA node directs AV node. For small value of s_2 (in **Figure 8**, $s_2=1$, $k_1=0$, $s_1=0$, $k_2=0$) the result is similar to ref. [1], **Figure 8**.

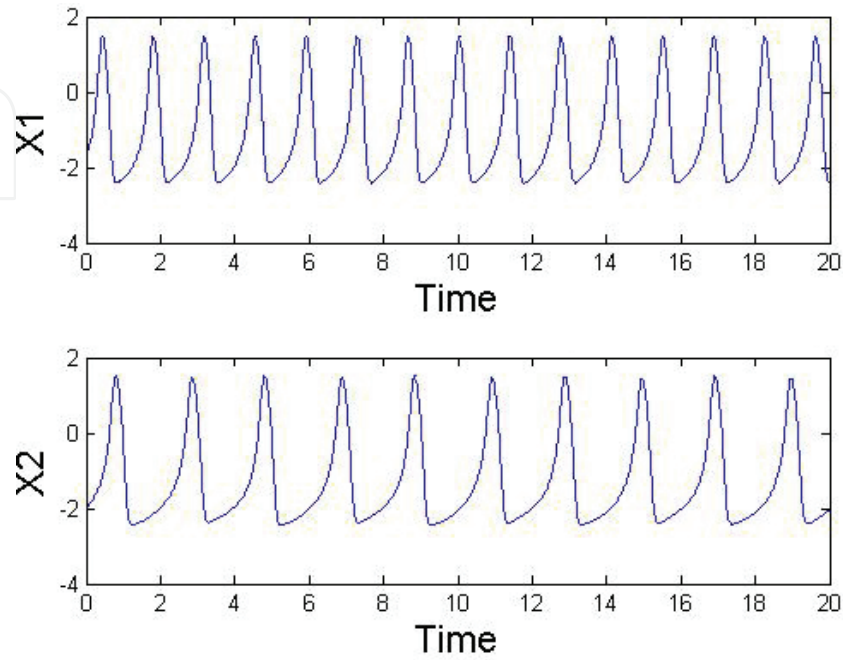


Figure 8. Time series: physiological coupling between nodes, the parameters are given in Eq. (9).

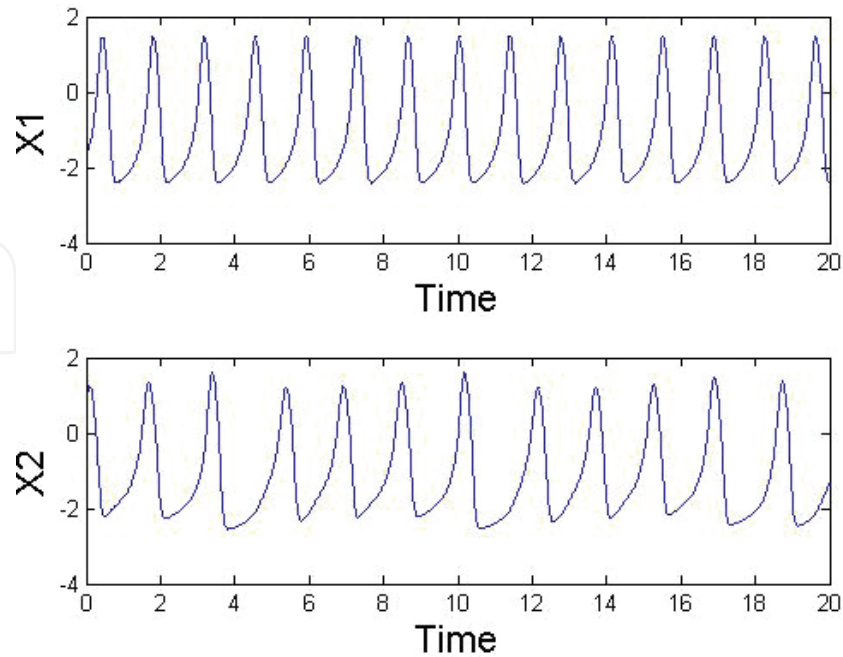


Figure 9. Time series: physiological coupling for $s_2=5$.

But for bigger value (e.g. 10 or 100), parts of amplitudes are synchronized in-phase with x_1 and aperiodic behaviour appears, which is presented in **Figures 9 and 10**.

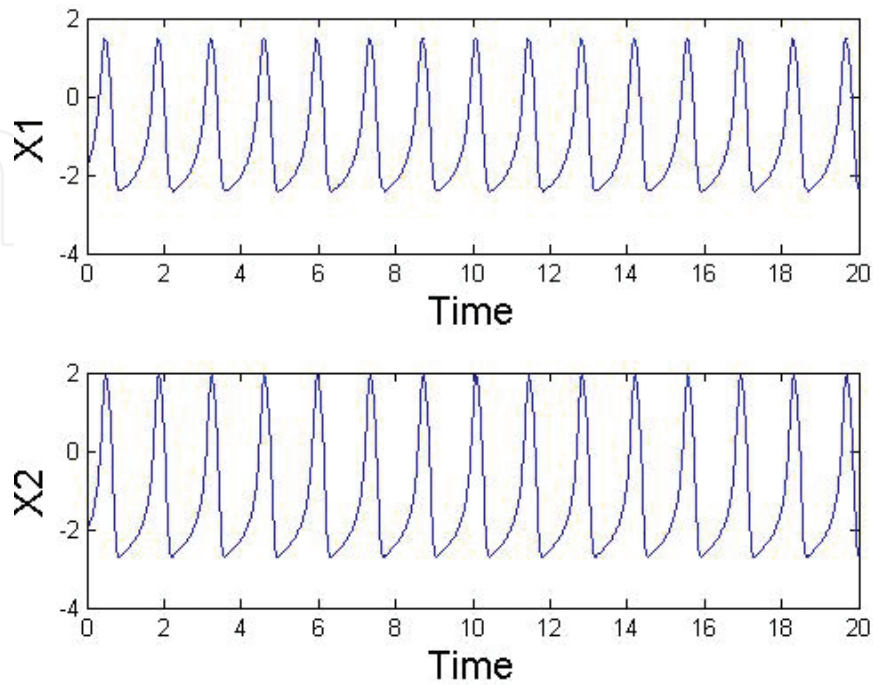


Figure 10. Time series: physiological coupling for $s_2=100$.

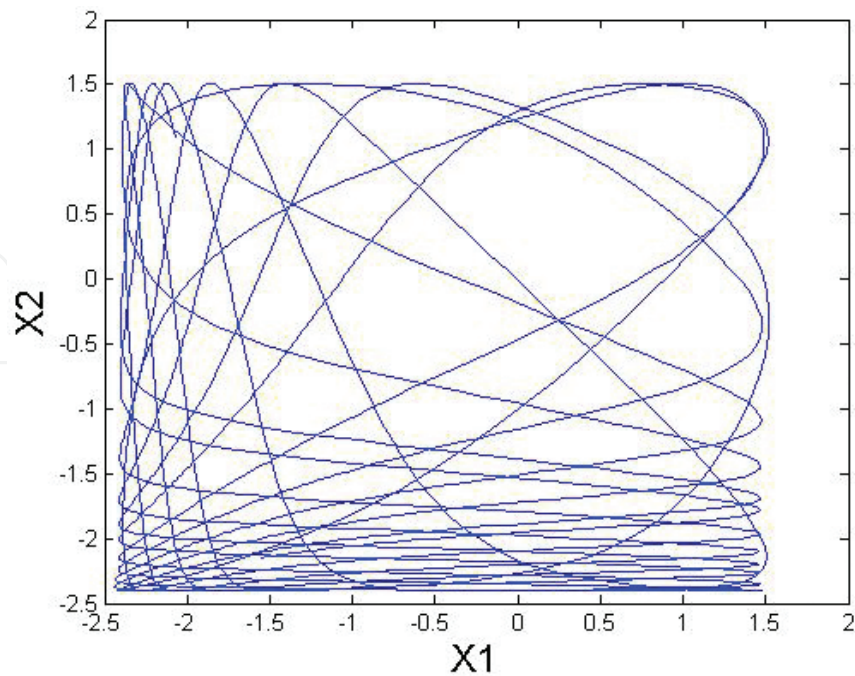


Figure 11. Projection of the phase space for $s_1=1$.

This causes the attempt of fitting the AV frequency to SA which slows down the heart rate.

We study here the synchronization properties of such an association with respect to the nature and intensity of coupling.

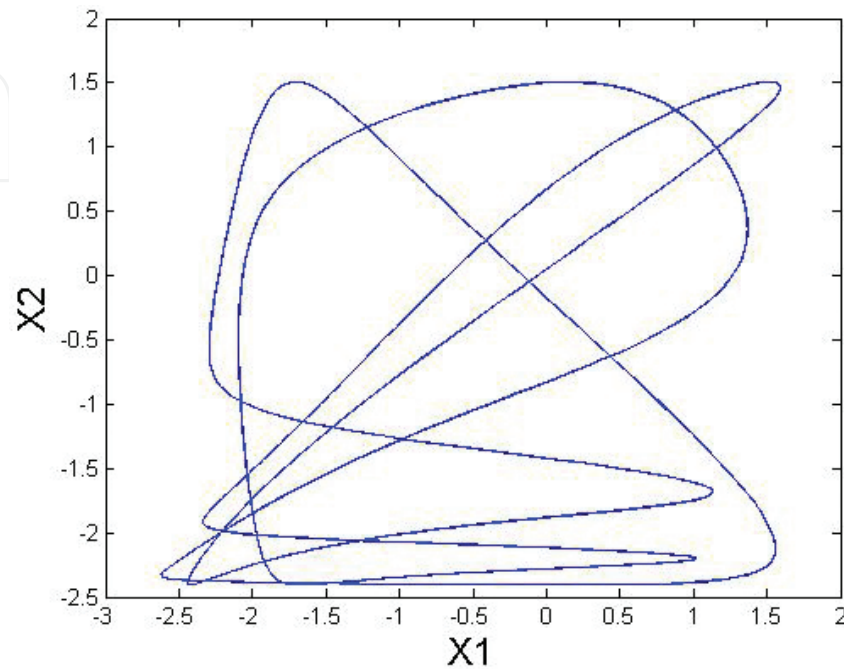


Figure 12. Projection of the phase space for $s1=10$.

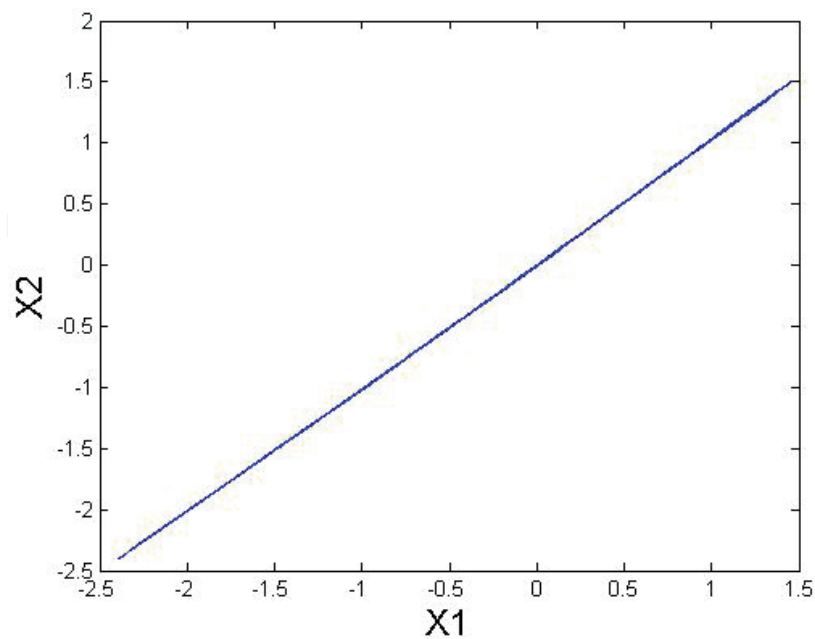


Figure 13. Projection of the phase space for $s1=1000$.

In **Figures 11–13**, we can observe an influence of unidirectional coupling for strength of synchronization of given oscillators (Eq. (11)). We must remember that complete synchronization of oscillators, characterized by $x_1(t)=x_2(t)$ and $y_1(t)=y_2(t)$, is unlikely to be observed in practice, due to the non-similarity of the coupled oscillators [21]. But oscillators, which are considered, are similar. In case when there is added unidirectional coupling to the system ($s_1 \neq 0$ or $s_2 \neq 0$), it is assumed that the coupling coefficient is a variable parameter in the analysed system. This parameter denotes the strength of the unidirectional coupling, all the remaining parameters being held constant. For small s_1 there is no synchronization, but for large s_1 there is complete synchronization, which is shown in **Figure 13**. Similar results are obtained for s_2 . When bidirectional coupling occurs in the system ($s_1 \neq 0$ and $s_2 \neq 0$), it can also obtain complete synchronization but there must be big asymmetry of value of coupling coefficients: $s_1 \ll s_2$ or $s_1 \gg s_2$.

Finally, the influence of the bidirectional coupling for behaviour of the model was studied. It would seem that the bidirectional coupling should operate so that when we enter it in relation 2:1 between oscillators, the rhythm of the fast pathway should be slowed down, while the rhythm of the fast pathway should accelerate.

In the model without feedback, periodic potential x_1 and x_2 are obtained, which is a dynamics of a physiological rhythm. But there is no synchronization for these parameters. When coupling coefficients are added to the system: $k_1 \neq 0$ and $k_2 \neq 0$, we obtain a set of projections of the phase space for different values of couplings, **Figures 14–16**.

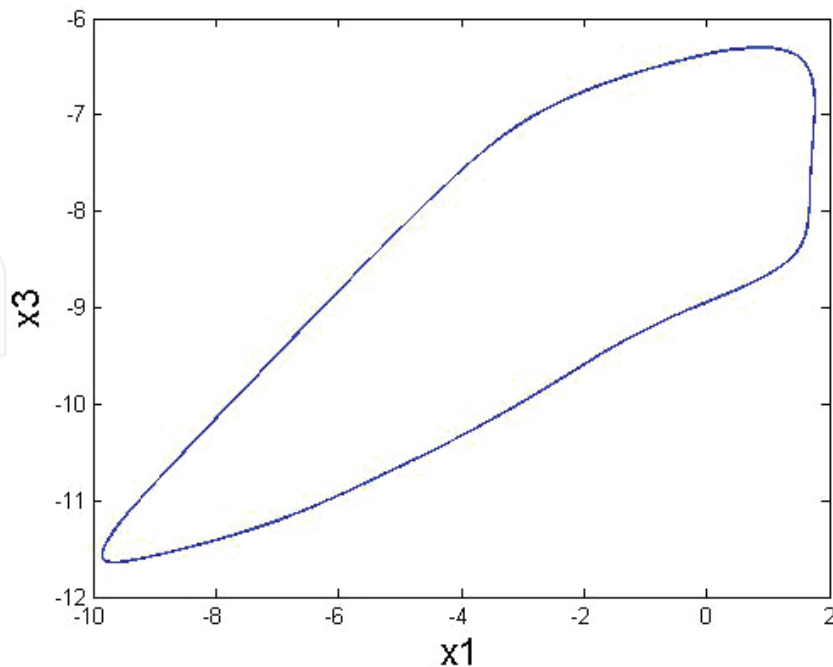


Figure 14. Projection of the phase space for $k_1=2$ and $k_2=1$.

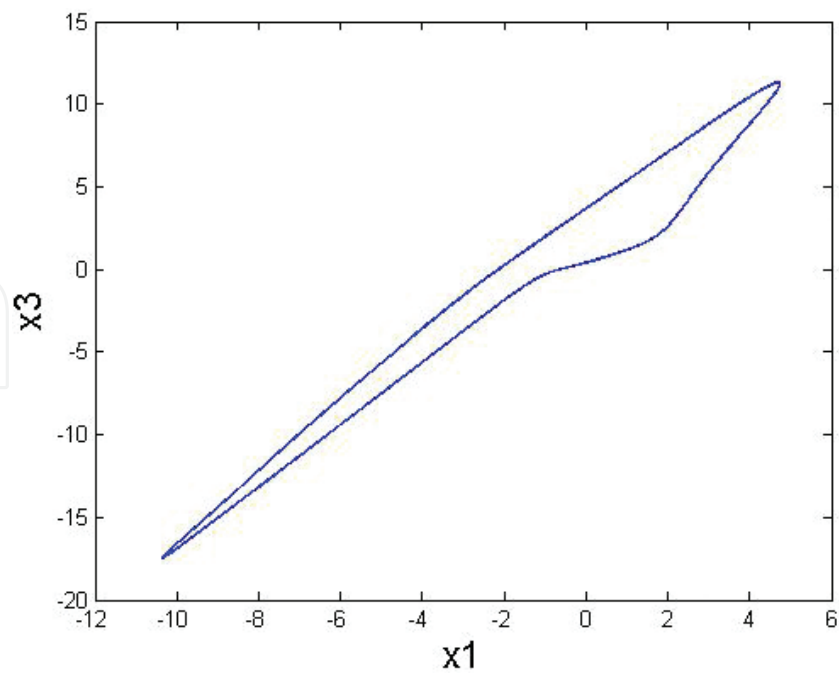


Figure 15. Projection of the phase space for $k_1=5$ and $k_2=10$.

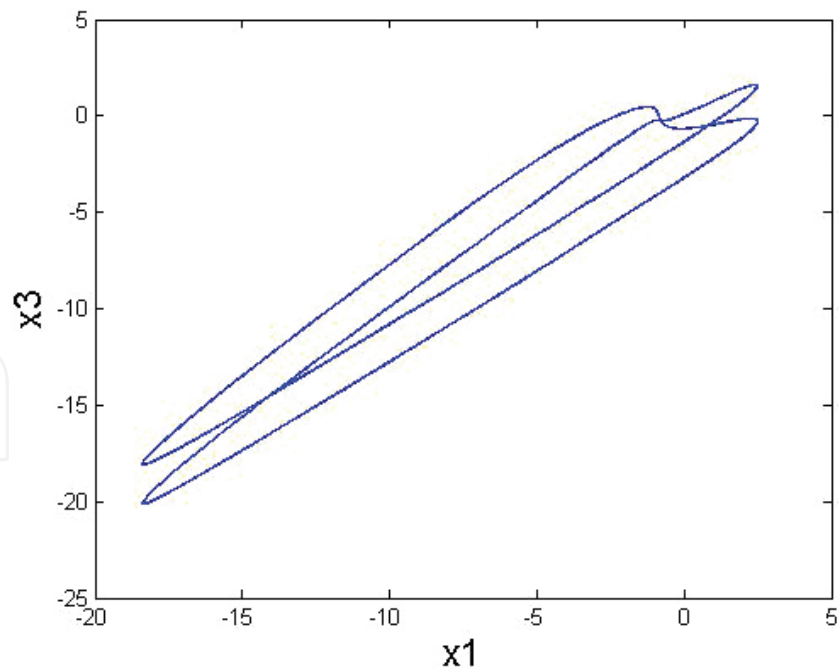


Figure 16. Projection of the phase space for $k_1=10$ and $k_2=10$.

However, with bigger values of k_1 , k_2 , a partial synchronization can be found in the system, **Figure 15**. Further increasing the value of the coefficients causes, however, the most significant

changes in the portrait of the phase space. We can observe partial synchronization, but this synchronization has asymmetric character, **Figure 16**.

We investigated the synchronization between oscillators themselves despite that the generation of cardiac dysrhythmias are associated with a lack of synchronization between autonomous pacemakers [22]. But we showed that we can obtain certain types of synchronization: phase synchronization, partial synchronization or lag synchronization. This depends on the strength of coupling coefficients. Corresponding large coefficient may cause synchronization, but often setpoints are not the values of the physiological range.

4. Conclusions

Main aim of the paper was to propose the system of differential equations describing the dynamics of action potential that accompanies the WPW syndrome and five different forms of AVNRT. In this work, by using the proposed models we were able to reproduce the most important physiological properties of the discussed pathologies. In literature, there are no mathematical models of AVNRT. By using one of the proposed models, we can try to add an equation which is responsible for modelling the pharmacological treatment of the pathologies of our interest. These type of models then can help to determine an optimal treatment. On the other hand, we should keep in mind that the proposed models are phenomenological, so the results are accurate as far as a simple model can describe the potential found in one of the more complex oscillators appearing in real biological phenomena. We can continue the validation of these models with the use of medical data. However, to collect the necessary data, only the invasive methods can be used, which constitutes an important difficulty.

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