OBSERVATIONS AND MODELING OF UNUSUAL PATTERNS IN HUMAN HEART RATE VARIABILITY*

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Dedicated to Professor Andrzej Fuliński on the occasion of his 70th birthday

We investigate nonlinear instabilities in human heart rate variability. We focus on phenomena with characteristic, easily recognizable features which are well known in physics. In the past we were able to show two groups of evidence. The first was an ever expanding roster of such cases of heart rate variability pathology which exhibit type I intermittency. This phenomenon occurs in those dynamical systems which have come close to a saddle-node bifurcation. The second were observations of homoclinic orbits and the gluing bifurcation in measured heart rate variability. We present here two cases of 24-hour recordings of human heart rate which exhibit special, regular patterns. We show that period-1, period-2 orbits and homoclinic orbits may be found in return maps formed using this data. Using a pair of coupled modified van der Pol–Duffing oscillators, we are able to model the behavior of the sino-atrial node and of the atrio-ventricular node (elements of the conduction system of the heart) in such a way as to obtain orbits similar to those measured during the sino-atrial block in a human.

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1. Introduction

Human heart rate is not a constant. There is an obvious need to change the frequency of the heartbeats as a response to exercise, emotions or sleep. However, even in brain-death heart rate fluctuations persist [1] which shows that the source of the variability in heart rate is situated outside the central nervous system. Considerable attention is focused on heart rate variability both in medical literature [2] as well as in physics [3,4] because of applications to medical diagnostics. Standard signal analysis in the time domain and in the frequency domain [5,6] have made an important contribution to both the understanding of the physiology of heart rate variability and as diagnostic tools. However, it is well known that these methods often fail to distinguish between a high risk of cardiac death and a healthy heart rhythm. There is now a large literature on the use of non-linear methods for the analysis of heart rate variability (see *e.g.* [7–10]). The deterministic origin of heart rate variability is still disputed and there is also a large literature on statistical methods of analysis of this phenomenon [11–14].

Most of the research carried out on both sides of the argument requires the use of some statistic (*e.g.* entropy, fractal dimension or scaling exponent) to assess the nature of heart rate variability. One of the reasons for this is that the main part of such research is aimed at obtaining a diagnostic tool for the assessment of the risk of sudden cardiac death and so a discriminating measure to be used by the physicians is required. The general problem with such an approach is that the data analyzed is in general non-stationary and very often contains noise. And then the question remains how well the technique of choice used in the given research can handle such data — even when some sort of windowing techniques or some way of standardizing the conditions of measurement (*e.g.* the supine position) be used. Of course, a great effort has been made to alleviate these problems but none of the techniques used truly avoids the limiting effect of non-stationarity or noise completely. Thus, the arguments of both approaches are somewhat weakened.

Some years ago, out of the steady stream of patients at the Holter lab of the Institute of Cardiology we began selecting recordings of 24-hour heart rate variability (time series of RR intervals *i.e.* time intervals between heart beats [2, 16]) which had outstanding features. The preselection method at this level is completely subjective. We were looking for tachograms on which one could observe: (almost) instantaneous changes of standard deviation, box like envelopes of the tachogram or features resembling oscillations found in physics of deterministic, non-linear systems. We focused on patients with arrhythmia of various kinds (especially sustained atrial fibrillation) but also on patients with apparently normal sinus rhythm and various kinds of heart block. In a number of the recordings,

we were able to identify type I intermittency [16–19]. We showed that the characteristic U-shaped laminar phase distribution is obtained in recordings of patients with different kinds of pathology — with arrhythmia but also with a dominating sinus rhythm. Using simple models [17,18] we found that the departures from the simple U-shaped distribution of textbooks [20, 21] are due in some cases to dichotomous noise (the additional tail extending towards large laminar phase values) or — in others — due to dichotomous parameter change. The results indicate that, when type I intermittency is found, the system that controls heart rate variability remains close to the saddle-node bifurcation. We argue that, because arrhythmia causes a change in the instantaneous blood pressure and heart rate [22], these small perturbations effectively change the control parameter of the system resulting in the effects documented in [16–18]. Although these results seem to be a strong indication of the importance of deterministic processes in the origin of heart rate variability, they are burdened by the same weakness as the other research quoted above. Namely, they require statistical analysis of the laminar phase distribution and certainly that in a nonstationary and noisy system is always difficult.

Another interesting result that we obtained analyzing the selected recordings are homoclinic orbits [15] associated with hyperbolic saddles. We soon found that such orbits occur not only in cases in which arrhythmia dominates the heart rhythm but also in patients who have sinus rhythm. This is an interesting observation because we are interested in the location of the instability (*i.e.* the hyperbolic saddle). In the case of arrhythmia, as mentioned above, the perturbation due to it causes a reaction of the autonomous nervous system due to baroreceptors. The system in which the instability occurs may be then somewhere outside the heart itself. This system is spatially extended and has built in time delays making it difficult to study, especially through clinical data. However, when the homoclinic orbits occur in sinus rhythm then there is a possibility that the instability occurs within the heart itself. Good candidates within the heart are the natural pacemakers: the SA node and the AV node as well as the His–Purkinje system [2]. We pursue this line of reasoning in the present paper.

The purpose of this paper is to study low dimensional structure in phase space of heart rate variability which exhibited unusual patterns in the tachograms: the heart rate changes in these recordings in an exceptionally regular although not necessarily periodic way. These recordings were taken from 24-hour recordings of ECG in patients with two different kinds of heart block. A heart block is a medical condition, in which the pulses originating at the sinus node may be blocked at different locations along the conductive system of the heart. This choice of data considerably narrows down the field of possible locations for the instability observed. We first

examine the return maps formed of consecutive RR intervals of the cases of heart block. We also present a new model of coupled nonlinear oscillators which is partially able to reproduce the properties of the return maps observed in the clinical data. The oscillators in this model were designed so as to reproduce the physiological properties (shape of pulse, refraction period and modes of frequency change) of the natural pacemakers of the heart much more accurately than the models published so far.

2. Medical data

Heart rate variability is measured as a time series of time intervals between successive contraction of the ventricles of the heart (RR intervals of the full ECG). For the two patients discussed below, heart rate variability data was extracted from 24-hour Holter device ECG recordings using the 563 Del Mar Avionics system at the Institute of Cardiology (Warszawa, Poland). All data were checked by a qualified cardiologist: normal beats were detected, artifacts were deleted and arrhythmias were recognized but not filtered out. The data was sampled at 256 Hz which is typical for modern Holter devices and introduces an error of approximately 4 ms into the detection of the R-peak in the ECG. In the recordings analyzed below such a sampling frequency allowed to recognize the R-peak of the ECG trace adequately.

The patient LTK had a sino-atrial block of a variable degree. In this condition the principal pacemaker, the SA node, oscillates with its normal frequency moderated by the autonomous nervous system. But the action potential of the SA node is not (or not perfectly) conducted to the atria and then to the AV node and to the ventricles. Note that the R-peaks always coincide with the contraction of the ventricles.

The patient ZNKW had atrio-ventricular block of second degree. In this condition, the frequency of the activity of the sinus node is within the normal range. Thus, all the pulses should be conducted to the AV node but they are not. When such an AV block occurs we can observe escape heart beats. These originate from the pacemakers situated below the localization of the block. The rate of such escape beats is much lower than the sinus node frequency. For pacemakers located in (or close to) the AV node, it is around 50 beats/min. If the pacemaker is located in the His–Purkinje system, the frequency of the escape beats may be about 40–30 beats/min.

3. Homoclinic chaos in heart block

In Ref. [15], homoclinic orbits in heart rate variability were initially found in patients with various types of arrhythmia. However, in the same paper such orbits were also obtained when sinus rhythm was dominant and ectopic

beats (arrhythmia) were either rare or none at all. In one category of patients with sinus heart rhythm the character of the tachograms may be especially ordered. These are patients with different types of a condition called heart block.

An example of a fragment of such an especially regular tachogram recorded between 8:28 and 8:41 am is seen in Fig. 1(a) for the patient LTK, the patient with the sino-atrial block. Contrary to what one normally expects from sinus rhythm, the data points are seen to aggregate mostly in narrow strips around 800 ms and 1600 ms. If we form the first return map of the data in Fig. 1(a), we obtain Fig. 1(b). It can be seen that this image is complex and not completely symmetric with respect to the diagonal.

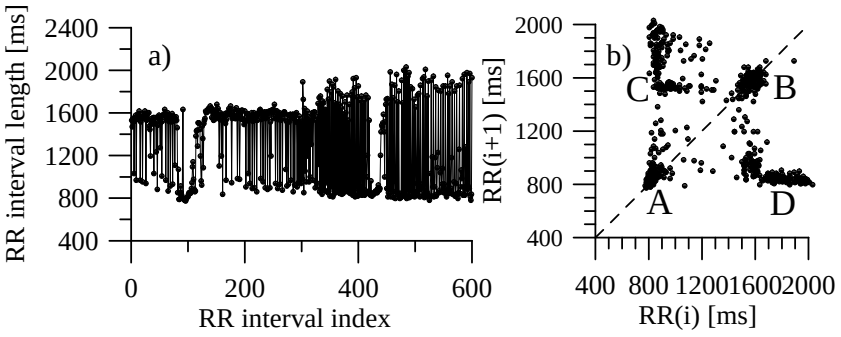

Fig. 1. Tachogram of the data measured for patient LTK. The 600 RR intervals shown represent approximately 12 minutes of real time (part (a)). Part (b): the first return map formed of the data.

Analyzing Fig. 1(b) in greater detail, we find that between interval index 84 and 110 the variability is extremely low and the return map has the form of a somewhat noisy fixed point (marked A in Fig. 2(a)). Within the same period of the time, two departures from stability of this point occurred resulting in homoclinic loops visible in Fig. 2(a). Apart from these loops, however, the variability of the RR intervals is extremely low — only 30 ms. As can be ascertained from the morphology of the full ECG trace, in this part of the data there was normal sinus rhythm *i.e.* all pulses originating at the SA node were conducted to the ventricles (we may formally denote this as **1:1 conduction**).

In the next part of this data set, a drift begins from the fixed point A to a new fixed point B situated at approximately 1600 ms (Fig. 2(b)) at which the trajectory resides from interval index 127 to 151. From the morphology of the ECG trace, we find that this fixed point is an example of a **2:1** sino-atrial block. The standard deviation of the fixed point B within the period of its stability in Fig. 2(b) is only 26 ms.

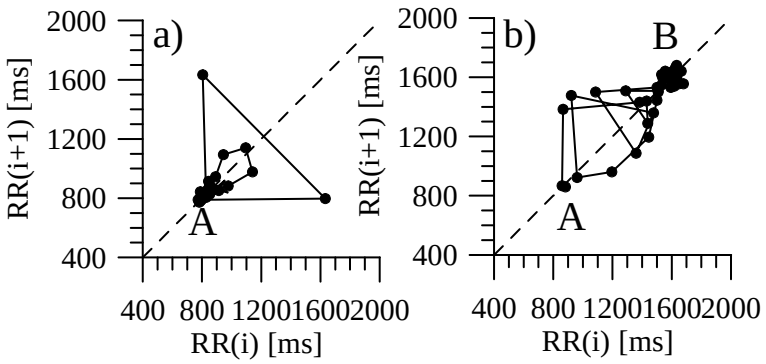

Fig. 2. Patient LTK: 1:1 conduction from interval index 84 to 110 (part (a)) and the drift on a spiral to the 2:1 conduction until interval index 152 (part (b)).

At interval index 152 an instability of the fixed point occurs taking the form of a homoclinic orbit seen in Fig. 3 and lasts until index 313. The unstable direction forms the downward leg of the triangle seen in this figure.

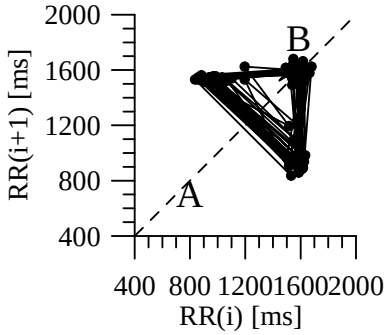

Fig. 3. Patient LTK: Repeated sequence of 3:2 (motion along the downwards pointing diagonal) and 2:1 conduction (point B). The motion is always clockwise and lasts from index 152 to 314 in Fig. 1(a).

Beginning at interval index 314 to 416 a noisy period 2 orbit was found — a manifestation of the **3:2 conduction** in which 2 out of 3 action potentials originating in the SA node are conducted to the atria, then to the AV node and the ventricles. Fig. 4(a) depicts the return map associated with this sequence. Fig. 4(b) depicts the second iterate of this map showing that this is a period-2 orbit. It can be seen that, as the period-2 orbit looses stability several times in Fig. 4(a), it passes next to fixed points A (normal sinus rhythm — 1:1 conduction without a block) and B (sino-atrial block — a 2:1 conduction). Note that — from the medical point of view — such passages

close to point A are episodes of a less advanced form of the sino-atrial block *i.e.* a 4:3 conduction. We see also that Fig. 3 depicts an orbit formed as a sequence of 2:1 and 3:2 conductions.

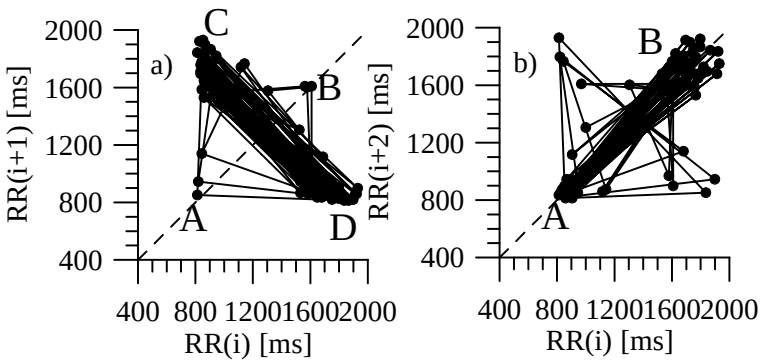

Fig. 4. Patient LTK: Stable period 2 orbit *i.e.* 3:2 conduction. Note the part of the trajectory along the diagonal is now longer than in Fig. 3. The state lasted from index 314 to 416 in Fig. 1(a).

Finally, after a short period of 1:1 conduction between index 416 and 450, a long lasting homoclinic orbit is formed consisting of the period-2 orbit and the unstable and stable directions leading to fixed point A (Fig. 5 — several transient departures from stability of the homoclinic orbit are visible in the figure). The trajectory now moves clockwise along the homoclinic orbit each time there are two passages along the diagonal (3:2 conduction) followed by a passage close to point A (a transient 4:3 conduction). Next the pattern repeats itself. This orbit lasts from index 450 to 530.

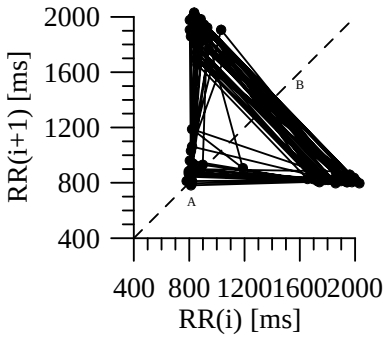

Fig. 5. Patient LTK: A complex state consisting of repeated sequences of two passages along the diagonal and a single pass close to point A. From index 416 to 530 in Fig. 1(a).

Summarizing the first analyzed data set, we see that the natural sinus rhythm and the sino-atrial block form a sequence of numbers 1:1, 2:1, 3:2 and (occasionally) 4:3 — a branch of the Stern–Brocot binary tree [23]. In effect the heart rhythm can be seen moving along a fragment of a devil's staircase [24]. It is intriguing that the Stern–Brocot numbers observed are ordered in the time just as they are situated on such a staircase and that the mode-locking ratios obtained by us are located on a single branch of the Stern–Brocot tree. Numbers belonging to another branch of the same tree (*e.g.* 2:1, 3:1 and 4:1) were also found in heart rhythm during stable atrial flutter resulting in an atrioventricular block by Castellanos *et al.* [25] and similar ratios in conduction — in preparations of Purkinje fibers by Chialvo *et al.* [26].

Similar results were obtained for patient ZNKW who had an atrio-ventricular block of varying advancement. In this paper we analyze two data sets from this patient. The first data set is shown in Fig. 6(a). The data form the return map depicted in Fig. 6(b) which again has a marked lack of symmetry. However, also in this case, a fixed point is visible (marked A Fig. 6(b)). The group of points marked B shows some dispersion because it is in fact a mixture of two kinds heart beats: the 2:1 atrio-ventricular block (the lower part of the group) occurring during certain periods of the time and the AV node escape beats — during other periods (the upper part of the group). The trajectory is found to pass from the homoclinic orbit of the fixed point to that of the group B.

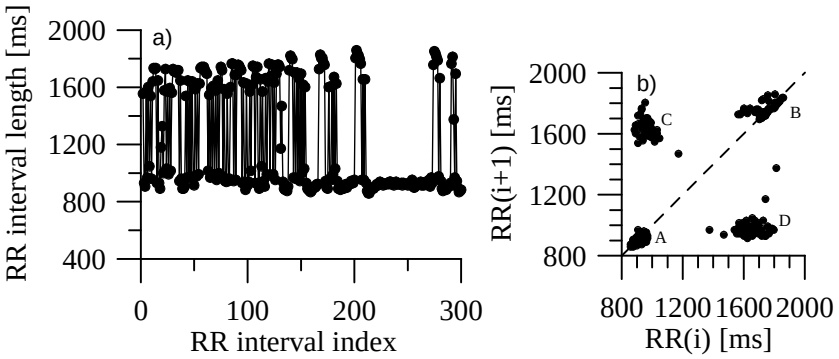

Fig. 6. Part (a): patient ZNKW: Tachogram of the first data set analyzed for this patient (approximately 6 min. of real time). Part (b): the return map of the data in part (a).

From the dynamical point of view the most interesting difference to the previous case discussed is that, now, the homoclinic connections are so close to each other that a switch occurs every certain number of rotations around the homoclinic orbit. An example of such a switch is marked by the large arrow in Fig. 7. In this figure — which spans the indices 176 to 202 in Fig. 6 — the trajectory was initially moving clockwise around the homoclinic orbit of fixed point A. At the switch point marked in Fig. 7, the trajectory began to move along the homoclinic orbit of fixed point B — also in a clockwise manner. Thus, at that moment the trajectory had reversed its direction abruptly. Such changes of direction of movement occurred in the data set of Fig. 6 several times.

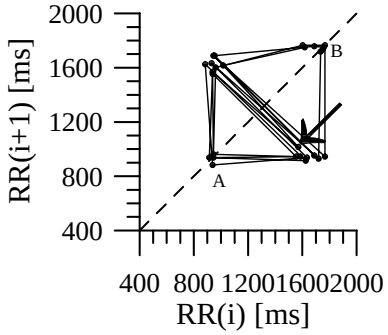

Fig. 7. Return map of a fragment of the data in Fig. 6(a) (index 176 to 202) showing the switch (arrow) from homoclinic orbit of point A to the homoclinic orbit of point B.

In another part of the heart rate variability recorded for the patient ZNKW and depicted in Fig. 8(a) the escape beats were found to be an unstable fixed point — the saddle point in homoclinic chaos. The return

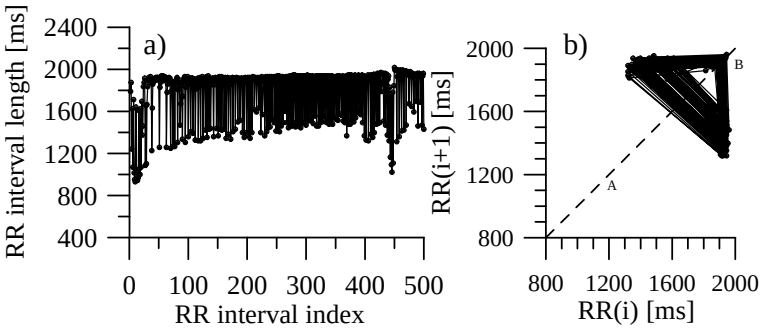

Fig. 8. Part (a): patient ZNKW — Tachogram of the second data set analyzed (approximately 15 min. of real time). Part (b): return map of data in part (a).

map for this case is shown in Fig. 8(b) and covers indices from 100 to 420 in Fig. 8(a). It can be seen that the hypotenuses moves along the diagonal remaining perpendicular to it. Thus, the shape of the trajectory remains constant while its length changes with each homoclinic loop — a feature typical for homoclinic chaos.

4. Model

The cardiac conducting system can be treated as a network of self excitatory elements: the SA node (the primary pacemaker), the AV node and the His–Purkinje system. Since these elements exhibit oscillatory behavior, they can be modeled as nonlinear oscillators [27]. This approach is not suitable for the investigation of the cardiac conducting system at a cellular level but allows an analysis of heartbeat dynamics by investigating interactions between its elements.

In order to model the cardiac pacemaker, we decided to use relaxation (van der Pol) oscillators for two reasons. Firstly, the van der Pol oscillator adapts its intrinsic frequency to the frequency of the external driving signal, without changing its amplitude [28]. This is a very important feature because the main cardiac pacemaker — the SA node — is the element of the conducting system with the highest frequency to which all other pacemakers must adjust. This observation led van der Pol and van der Mark to the first model of the heart [29]. Secondly, FitzHugh [30] showed that a relation exists between an extended version of the van der Pol oscillator and the Hodgkin–Huxley equations which describe the generation of action potentials [31]. Since the work of van der Pol and van der Mark [29], other models involving relaxation oscillators ([32–34]) were published and focused mainly on the interaction between the AV and SA nodes. Although they provided many interesting results, these models were not able to reproduce some important features of real cardiac action potentials. In Ref. [35], we developed a modified van der Pol–Duffing oscillator which has a richer structure of the phase space than the original van der Pol. It is much more physiologically accurate than the other relaxation oscillators published so far. It thus can be used for the investigation of the dynamics of the heartbeat. In particular, it allows to change the frequency of the oscillations in all three ways that are found in the physiology of the heart: by a change of the depolarization time, of the threshold level or of the resting potential [35]. From the dynamical point of view, the model of Ref. [35] allows to control separately the positions in phase space of the saddle, the limit cycle and of the node.

In the model [35], the rescaling of the Duffing part of the equation was done in such a way that made changing the frequency of the oscillator in a wide range difficult. By getting rid of this rescaling term, we obtain the

equation

$$\frac{d^2x}{dt^2} + \alpha(x - v_1)(x - v_2)\frac{dx}{dt} + x(x + d)(x + e) = 0,\ d, e, \alpha > 0\,, \qquad (1)$$

where α is the damping constant and changes the shape of the pulse. This affects the refractory time — the part of the action potential during which the oscillator will not react to external stimulus. The parameters v_1 and v_2 must have opposite signs to preserve the required self-oscillatory properties of the system and together they control the resting potential. Parameter e controls the depolarization time. The saddle point is situated at $x = -d$ and the stable node at $x = -e$. Their locations are inexchangable — the node will always be on the left of the saddle point [35].

To model the different kinds of heart block that occur one needs to connect two oscillators described by Eq. (1). We assumed that there is only a unidirectional, diffusive coupling between the two oscillators representing the SA and the AV node, respectively. We thus assumed a master–slave system. Instead of assuming a diffusive coupling by means of *currents* (as was done by di Bernardo *et al.* [34]), in analogy to the Hudgkin–Huxley equations, we assumed that the diffusive coupling is mediated by the action potentials. Thus, in our model of the interacting SA and AV nodes, the driving equation remains in the form of Eq. (1) while the second equation — representing the AV node — takes the form

$$\frac{d^2x_2}{dt^2} + \alpha(x - v_1)(x - v_2)\frac{dx_2}{dt} + x_2(x_2 + d)(x_2 + e) + k_1x_1 - k_2x_2 = 0\,, \quad (2)$$

where x_1 is the potential of the SA node given by Eq. (1) and x_2 is the potential of the AV node. The introduction here of two coupling constants k_1 and k_2 allows to study asymmetry in the coupling. Since the coupling constants may be interpreted as conductances — by using two different coupling constants — we allow the action potential of the SA node to have a different effect at the AV node than that of the action potential of the latter. Note that the AV node is a complex, spatially extended structure [2] with at least two entry points accepting action potentials from the SA node and the atrium. Thus, it is not unusual to expect that a variety of medical conditions may result in the asymmetry assumed in our model.

Before we can compare the results of simulations with the measured data, the action potential computed in our model need to be changed into a series of interspike intervals (ISI). To do this we measured the time intervals between the crossing of the voltage level 0.5 mV in the positive direction. Fig. 9(a) depicts the interspike intervals obtained in this way as a function of interval index for the parameters of the model in Table I. The intervals

remain most of the time at a fixed value and only burst out at regular periods of the time to larger lengths (Fig. 9(a)). The dynamics of the intervals during the bursts, however, does not repeat exactly so that the first return map in Fig. 9(b) is obtained. There seems to be a certain resemblance to the orbits found for heart rate variability such as the one in Fig. 5. The results in Fig. 9(a) and (b) indicate quasi-periodicity rather than homoclinic chaos and this may be a good explanation why some many data points in Fig. 5 are seen above the diagonal along the upward leg of the triangle. The situation is different *e.g.* in Fig. 8(b) where a well defined (unstable) fixed point is seen at B.

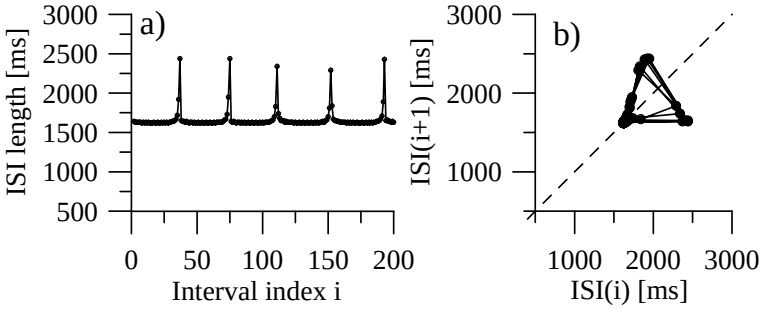

Fig. 9. Results of computation of interspike intervals ISI in the model (part (a)) and the corresponding return map (part (b)).

TABLE I

Model parameters. The colums denoted SA and AV refer to the master and the slave oscillator, respectively.

Parameters	SA	AV
α	3.0	3.0
v_1	−1.0	−1.0
v_2	1.0	1.0
d	3.0	3.0
e	12.0	7.0
k_1	0.5	
k_2	0.37	

Note that, usually, modeling of heart rate variability is a daunting task. One needs to take into account not only the internal dynamics of the natural pacemakers of the heart (the SA and AV nodes and the His–Purkinje system) but also the effect of the regulative systems moderating the heart rate. The most important of these is the autonomous nervous system but baroreceptor

and chemoreceptor loops also play a prominent role. Here, we attempted to model especially regular patterns in the heart rate associated with the special condition of a heart block. Thus, *we assumed* that these patterns are due to the properties of the dynamics of the electrical conduction system of the heart itself and that outside influence may be neglected. Moreover, in our simple model, we treated the His–Purkinje system as just a source of a more or less constant delay and so ignored it completely. We thus consider the action potential of our master oscillator to be the equivalent of the P-wave. We then apply the procedure described above to the action potential of the second (slave) oscillator to define the "RR interval" or ISI. Obviously, such a model would be unable to reconstruct the general dynamics of the heart rate. But for the patients with a heart block some of the results obtained by our model seem adequate.

A number of other complex behaviors have been noted in our model including complex chaotic and intermittent behavior. A search is currently on the way to identify homoclinic orbits among them and compare with the different examples observed in human heart rate variability. Given the large parameter space of the model this is not a short task.

5. Summary and conclusions

In our recent papers, we have documented examples of intermittency [16–18] and homoclinic orbits [15] in heart rate variability. The research presented there indicated the importance of nonlinear instabilities such as the saddle-node bifurcation or homoclinic chaos and the gluing bifurcation in the formation of heart rate variability. However, most of the data analyzed earlier by us referred to medical cases in which supraventricular arrhythmia (atrial fibrillation or atrial flutter) or ventricular arrhythmia was present. Thus there was reason to believe that the instabilities observed were due to the perturbing effect of arrhythmia on the sinus rhythm of the heart.

Here, we discussed two cases of heart rhythm in which supraventricular or ventricular arrhythmia is absent. The sinus rhythm in these cases is modified by the improper pulse propagation from the SA node through the conduction system of the heart. This results in a condition called a heart block of different kinds and advancement. We showed that fixed points, unstable periodic orbits and homoclinic chaos may be identified in the data and have physiological significance. In addition, the heart rhythms 1:1, 2:1, 3:2 and even 4:3 found adjacent in the time series are numbers from a single branch of the Stern–Brocot binary tree [23] and so these rhythms form a part of a devil's staircase.

The interpretation of our analysis was supplemented by a simple model consisting of two modified van der Pol oscillators in a master-slave config-

uration. The modifications serve to make the action potentials obtained to have the proper physiological properties (shape, refractory period and modes of frequency change [35]). If the two oscillators of the model are detuned properly (just like the SA and the AV node in the heart are) and if the diffusive coupling between them is asymmetric (which is very plausible in heart block) then a return map is obtained which bears some resemblance to that found in our data. However, the interspike intervals are much to regular so that a further improvement in the model as well as a detailed search of its parameter space are needed.

Our recently published papers, the research described in the current paper and the simple model presented all indicate that many features of human heart rate variability may be attributed to the instabilities due to the nonlinearity of the natural pacemakers of the heart — the SA and the AV nodes.

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