MODELS OF CARDIOVASCULAR SYSTEM CONTROL IN HORSES

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Abstract: Shortening of RR intervals is often associated with prolonging QT intervals in dynamic studies of the cardiovascular activity in horses. This behaviour is typical, but not the only one in equine heart. We designed several original mathematical models describing all types of relationships RR/QT. The model structures were based on principles of the heart activity control by both the vegetative neural branches. The obtained simulation results showed that the most important parameter for explaining various types of RR/QT relationships in the dynamic experiment is balance between activities of neural branches in the heart.

Introduction

Cardiovascular system in horses is specific in various ways. In our project we analyze the dynamic changes of the electrical part of myocardium as a tool for exposing the system control mechanisms of a heart activity. Generally accepted image is based on two contradictory control subsystems – activities of the sympathetic (stimulating) and parasympathetic (inhibiting) neural branches. Both the branches have their nerve ends leading to atria (near sinus node) and ventricles.

Because of practical difficulties with direct measuring of the neural activities, we have used two indirect indicators determined by balance between the activities of neural branches. We supposed that two mutually independent control mechanisms can be fully described by two indicators – RR intervals that can serve as an indirect indicator of the balance between both the neural branches in heart atria, and QT intervals as mediators of the neural balance in ventricles.

There is a lot of published studies in human cardiology intent on the relationship between RR and QT intervals, mostly obtained from a static experiment without dynamic changes in heart rate. That is probably why cardiologists accepted the direct linear relationship between RR and QT intervals, e.g. shortening of RR intervals is associated with shortening of QT intervals.

Despite of the clear correlation in human ECG signal the relationship RR/QT in equine ECG is different. We have made experiments with the external stimulation of the equine heart, then classified equine ECG signals (35 records) and divided them into four classes:

a. 30% of records had similar relationship RR/QT with human ECG (Figure 8a),
b. 33% of records represented inverse relationship between RR and QT intervals – QT intervals were clearly prolonged during shortening of RR intervals (Figure 8b),
c. 22% of records combined both the previous classes (Figure 9),
d. 15% of records had either no or non-identifiable change in QT intervals.

We believe that various reactions of heart ventricles (QT intervals) could help us to understand more detail structure of heart control.

Materials and Methods

The basic structure of the cardiovascular system used in all our models is depicted in Figure 1. The basic structure of a real cardiovascular system is closed-loop – with a feedback control. Our model structure without the feedback represents compromise between simplicity and validity of the model.

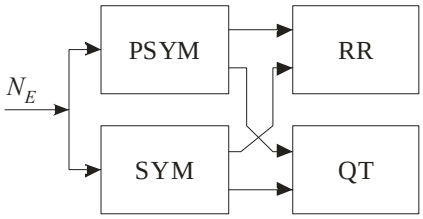

Figure 1: Principle structure of the cardiovascular system control

Our open-loop system is controlled by empirically described input signal

$$N_E = \begin{cases} A.\left[\sin\left(\frac{2\pi}{T}(t-t_1)-\frac{\pi}{2}\right)+1\right], \\ \quad \text{if } t_1 \le t \le t_1+T \\ \\ 0, \quad \text{otherwise,} \end{cases} \qquad (5)$$

where T is a duration of the input impulse and t_1 represents its lag after some reference starting point (see also Figure 2).

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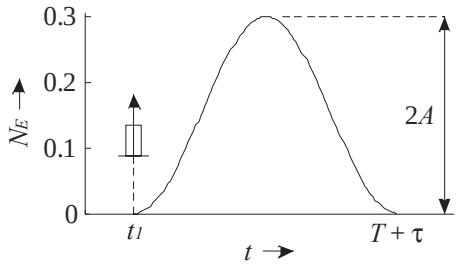

Figure 2: Input signal N_E

As it follows from our previous studies [3] we used the formula

$$RR(t) = RR_{SAU} - k_{SR} N_S(t) + k_{PR} N_P(t) \qquad (1)$$

for generating sequences of RR intervals. RR_{SAU} is a basic heart period of the sine node not influenced by the nervous system. $N_S(t)$ and $N_P(t)$ represent sympathetic and parasympathetic activity levels. k_{SR}, k_{PR} are gain factors that express levels of influence of each neural branch upon the duration of RR intervals. Similarly,

$$QT(t) = QT_0 - k_{SQ} N_S(t - \tau_{SQ}) + \\ + k_{PQ} N_P(t - \tau_{PQ}) \qquad (2)$$

describes an equation generating QT intervals where τ_{SQ} and τ_{PQ} are delays in sympathetic and parasympathetic neural branches in heart ventricles and k_{SQ}, k_{PQ} are gain factors, similar to those in the eq. (1). QT_0 is a basic length of QT interval at neural ventricular blockade. Both the delays are associated with the finite velocity of spreading the nervous stimulation.

The aim of extending the described model was to find the internal structure of the subsystems SYM and PSYM (see Figure 3), their mutual relationship and influence on the heart activity control. The models for simulating both static and dynamic properties of the mentioned types of nerve fibres have structures depicted in Figure 3, as published in [1].

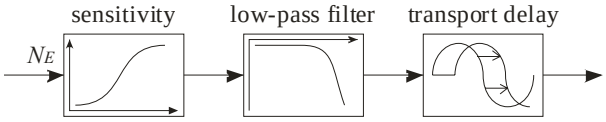

Figure 3: Basic structure of nervous fibres' model

The sensitivity of each neural branch is modelled with bottom-limited piecewise linear function (Figure 4)

$$N_{S,P} = \begin{cases} a_{S,P} N_E + b_{S,P} & \text{if } N_E > -\dfrac{b_{S,P}}{a_{S,P}} \\ 0 & \text{otherwise} \end{cases} \qquad (3)$$

where indexes "*S*" and "*P*" represent sympathetic and parasympathetic branch, $a_{S,P}$ is the sensitivity coefficient. Inertia of the nerves is modelled by the first-order low-pass filter described by the frequency response

$$F_X(\mathrm{j}\omega) = \frac{k}{\mathrm{j}\omega T_X + 1} \cdot \mathrm{e}^{-\mathrm{j}\omega\tau_X} \qquad (4)$$

where ω represents an angular frequency, T_X is a time constant of the filter, τ_X is a unit delay and k is a gain of filter. The inertia is associated with the limited delay in response of the cells to their excitation. Finally, the "time-delay" block τ_X represents a final velocity of spreading the excitation along nerves and through heart tissue.

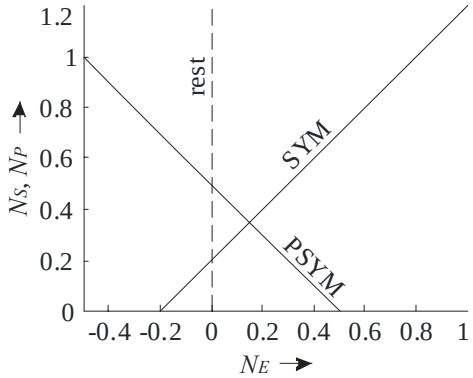

Figure 4: Sympathetic and/or parasympathetic sensitivities, N_S, N_P

Previous paragraphs describe basic elements implemented in all our models. We stated a hypothesis that the unusual behaviour of the electric part of the heart is caused by the unusual structure of nervous control mechanisms in equine organism.

To verify the hypothesis we have designed several model structures and make some simulation experiments (Figure 5, Figure 6, Figure 7).

The serial model (Figure 5) was based on knowledge of vegetative nervous system anatomy in the horse: Each branch has

a. a common part for control of artia and ventricles (PSYM and $PSYM_R$, respectively SYM and SYM_R in Figure 5),
b. separated part that depends on the common part and controls only ventricles ($PSYM_Q$ and SYM_Q in Figure 5).

Obvious dependences between structure of the RR block and that for QT intervals make the model difficult to analyze. That was the reason to modify its structure in order to RR and QT parts become mutually independent, see Figure 6. As we discuss below in this paper, properties of the serial and parallel model are similar in a specific range defined by our experimental conditions.

Another hypothesis is depicted in Figure 7: The unusual relationship RR/QT can be simulated by an additional control mechanism managed by direct RR-QT relationship. The hypothesis is based on physiological

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background of myocardium cells [2] where it is described an obvious dependency between frequency of impulses stimulating the cell and length of cell depolarisation.

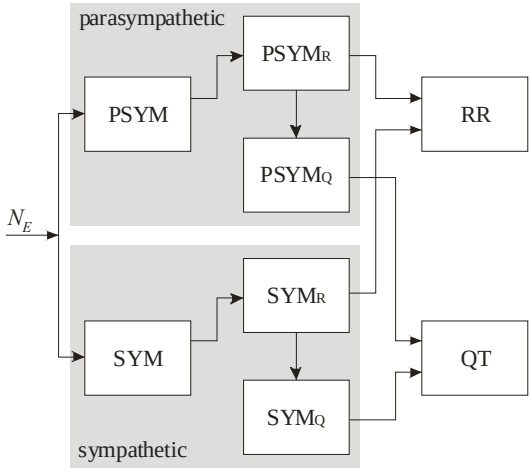

Figure 5: Serial model, [3]

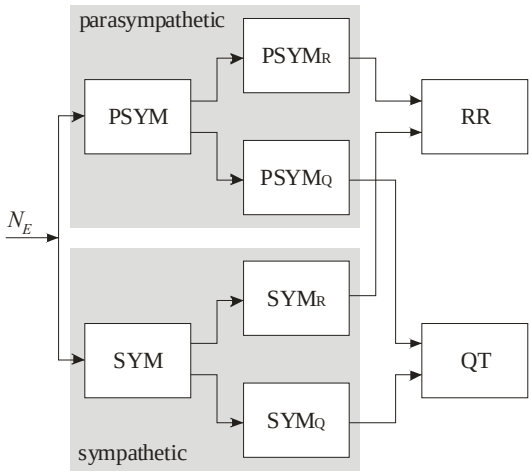

Figure 6: Parallel model, [3]

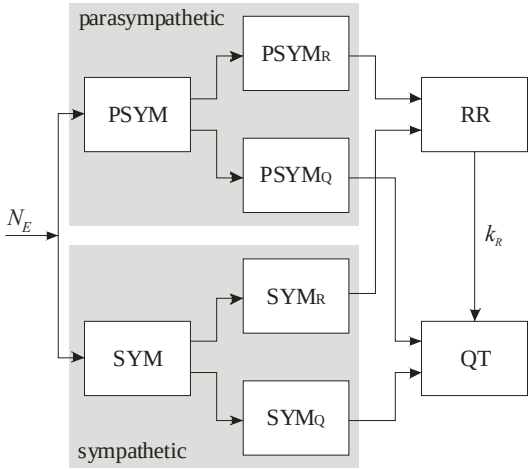

Figure 7: Parallel model with direct RR-QT confinement

Results

The simulation results were compared to the 10 most representative sets of experimental data. The criterion for choosing records was noiseless signal with considerable changes in the sequences of RR and QT intervals as responses to impulse stimulation. The aim of the work was to define properties of controlling subsystems. We have identified some of the model parametres as time constants of the filters (T_{SRp}, T_{PRp}, T_{SQp}, T_{PQp} and/or T_{SRs}, T_{PRs}, T_{SQs}, T_{PQs}), time delays (τ_{SQp}, τ_{PQp} and/or τ_{SQs}, τ_{PQs}) and gain factors (k_{SQp}, k_{PQp} and/or k_{SQs}, k_{PQs}). We used Matlab® Optimization Toolbox as an optimization tool. A root mean square error between simulated and real experimental data has been used for an optimization and its minimum was searched by the gradient method. The identification results for two different types of records are summarized in Table 1:

a. direct dependency QT on RR intervals – shortening of the RR intervals is followed by the shortening of QT intervals (Figure 8a)
b. unusual relationship between RR and QT that is not explained yet – shortening of the RR causes almost immediate *prolonging* of the sequences of QT intervals (Figure 8b).

Table 1: Summary of optimized parameters for two different relationships between sequences of RR and QT intervals (compared serial and parallel models, Figure 5 and Figure 6)

record 1 (velvet-s el 1-2002-04-24)		record 2 (nikita - s el - 2002-04-24)	
parallel model	serial model	parallel model	serial model
T_{SRp} = 25 s	T_{SRs} = 25 s	T_{SRp} = 4 s	T_{SRs} = 4 s
T_{PRp} = 25 s	T_{PRs} = 25 s	T_{PRp} = 4 s	T_{PRs} = 4 s
T_{SQp} = 20 s	T_{SQs} = 19 s	T_{SQp} = 17 s	T_{SQs} = 18 s
T_{PQp} = 18 s	T_{PQs} = 17 s	T_{PQp} = 15 s	T_{PQs} = 18 s
τ_{SQp} = 20 s	τ_{SQs} = 18 s	τ_{SQp} = 6.4 s	τ_{SQs} = 4 s
τ_{PQp} = 20 s	τ_{PQs} = 20 s	τ_{PQp} = 4.4 s	τ_{PQs} = 1.2 s
k_{SQp} = – 4.9	k_{SQs} = – 5.1	k_{SQp} = – 3.8	k_{SQs} = – 4.2
k_{PQp} = – 4.4	k_{PQs} = – 4.6	k_{PQp} = – 4.2	k_{PQs} = – 4.6

Discussion

If we compare corresponding parameters of the serial and parallel models (Table 1, Figure 5 and Figure 6) we see similar values not only for RR intervals (it is expected because RR branch in the parallel model is same as in the serial model) but also to QT intervals.

The resulting frequency response (sympathetic and/or parasympathetic) of the QT branch in the parallel model can be represented by the first-order filter and in the serial model the resulting frequency response is the second-order filter (two serially plugged in first-order filters).

From an analysis of sequences of RR and QT intervals we have found out that their useful spectra are in the frequency band of <0; 0.02> Hz. Due to close similarity of both the frequency responses (see Figure 9) described by eq. (4) in the mentioned frequency band

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(with the maximum difference of about 0.4÷0.6 dB at 0 Hz), we are not able to decide which of the two above described models is more suitable to define true structure of the control mechanisms of myocardium.

(a) record 1 (velvet - s el 1 – 2002-04-24)

(b) record 2 (nikita - s el – 2002-04-24)

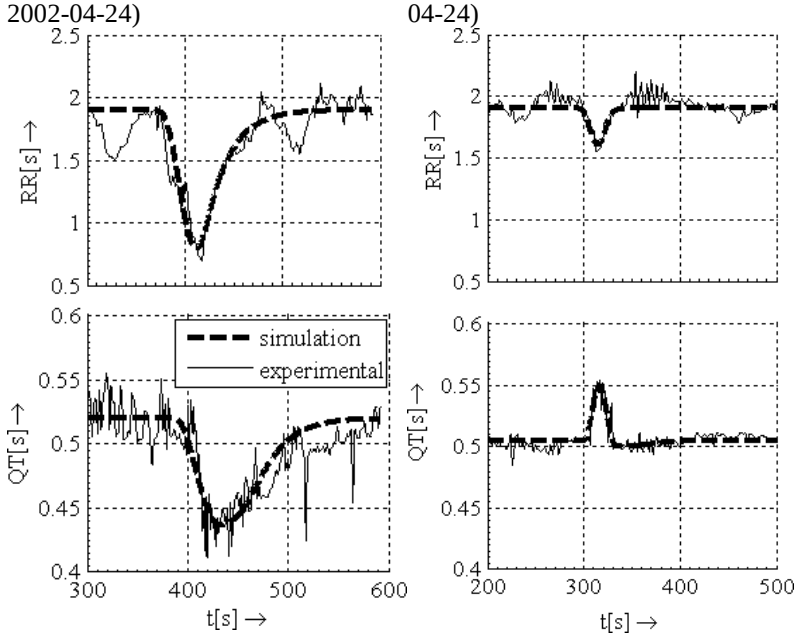

Figure 8: Experimental and simulated data generated by the optimized parameters (used structure depicted in Figure 6)

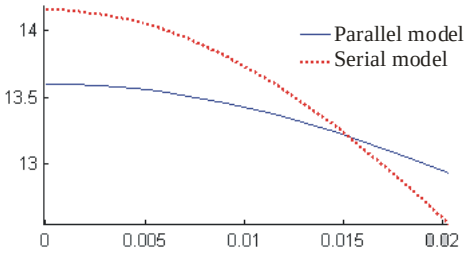

Figure 9: Frequency functions of the first-order filter (parallel model, Figure 6) and the second-order filter (serial model, Figure 5) in the sympathetic branch

Because of practical reasons corresponding to simplification of model analysis we have chosen the parallel model for future research. It has two mutually independent branches that are supposed to be analysed easier.

We tried also to solve the problem of direct RR-QT relationship: the parallel model (Figure 6, Table 1) was extended with additional control mechanism, simply described by the gain factor k_R (Figure 7). The parameter k_R was included in the basic set of parameters to be identified (see Table 1). The identified values of the basic set of parameters were then almost unchanged and the identified value of k_R was closed to zero. It means that relative influence of direct RR-QT control compared with sympathetic/parasympathetic QT control (SYM_Q, $PSYM_Q$) was <1.1, 2.1> %. These results made us sure that there is an insignificant influence of local mechanisms controlling the electrical activity of heart ventricles in healthy organism.

Having chosen the model structure (Figure 6) and identified its parameters we are able to explain fundamental causes of various behaviour of the QT intervals. We recognised almost linear dependency with positive slope constant between optimum parameters of τ_{SQ}, τ_{PQ}, and T_{SQ}, T_{PQ}. It is due to the fact that the developed model uses linear subsystems only (the non-linear functions $N_S = N_S(N_E)$ and $N_P = N_P(N_E)$ are used in their linear parts only, see also Figure 4) and the input signal N_E is used for both sympathetic and parasympathetic branch.

We have proved experimentally that the simple shape of the QT interval sequences with one local extreme (classes a. and b.) is generated by the model using very similar values of τ_{SQ}, τ_{PQ} and T_{SQ}, T_{PQ} in both the neural branches. If the supposition about the similarity of the above mentioned parameters is not valid then the signals N_S, N_P are mutually shifted in time. The mutual shift will cause a change of the QT sequence shape. In the case, one local extreme is substituted by biphasic waveform with local maximum and minimum (class c., Fig. 9).

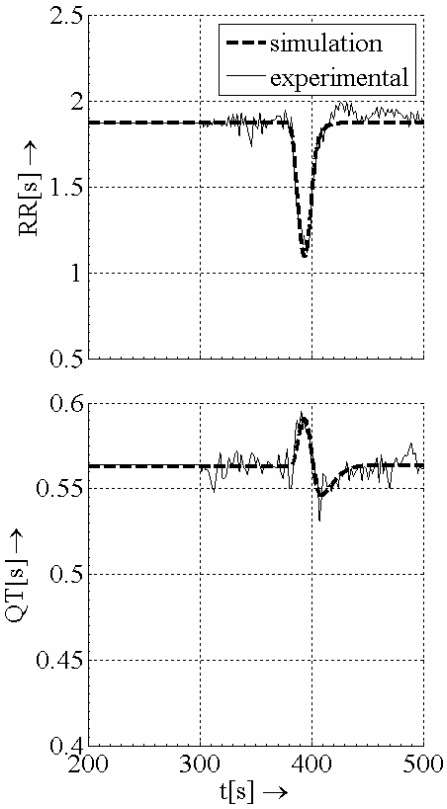

Figure 10: Bi-phase sequences of QT intervals (heda1)

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Dependency of parameters k_{PQ}, k_{SQ} can be approximated well by a linear relationship with a negative slope constant (see the x-y projection of the optimum path in Fig. 7 and Fig. 8)

$$k_{SQ} = a.k_{PQ} + b, \quad (6)$$

where the estimated values of coefficients $a = -2$ and $b = -13.5$ are roughly valid for all analysed records. If we suppose the simplified criteria $\tau_{SQ} = \tau_{PQ}$ and $T_{SQ} = T_P$, then the breaking point between the direct (Figure 8a) and inverse (Figure 8b) dependency of QT on RR intervals is set for $k_{SQ} = k_{PQ} = -4.5$. Then for $k_{SQ} > k_{PQ}$ we observe the direct dependency (class a.) and for $k_{SQ} < k_{PQ}$ the inverse dependency (class b.) of QT on RR intervals.

Acknowledgement

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