VALIDATION OF NONSTATIONARY MODEL OF ATRIOVENTRICULAR NODE CONDUCTION IN ATRIAL FIBRILLATION

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In 24 hours RR sequences of inter beat intervals during atrial fibrillation, the scatter plot of mean and standard deviation over fixed length segments shows a strong linear correlation. We introduce a non stationary mathematical model, based on Zeng and Glass model of atrioventricular node conduction, and show that the simulated RR sequences display the same strong linear correlation.

1. Introduction

In normal human heart the main pacemaker is the sinus node, located in the right atrium; the electrical activation propagates from the sinus node through the atria and then to the ventricles in such a way that each atrial contraction corresponds to a ventricular one. The only conducting pathway between the atria and the ventricles is the atrioventricular node. Atrial fibrillation is an arrhythmia characterized by rapid irregular contraction of the atrial myocardium; electrical stimulations are filtered by the atrioventricular node, which propagates some of them to the ventricles, while others are blocked.

The ventricular contractions are represented by the R peaks of the ECG. The time interval between two consecutive R peaks is called RR interval; the RR intervals sequence extracted from the 24 hours Holter recording defines a time series of about 100,000 elements. In long term RR series of fibrillating subjects many qualitatively different kind of regimes may be observed in the same subject. For example, in Figure 1 two different regimes are evident in the second recording. The first regime (roughly the first 15000 beats) is similar to an RR sequence of a normal subject, while the second is typical of chronic fibrillation, as is the regime in the first

recording.

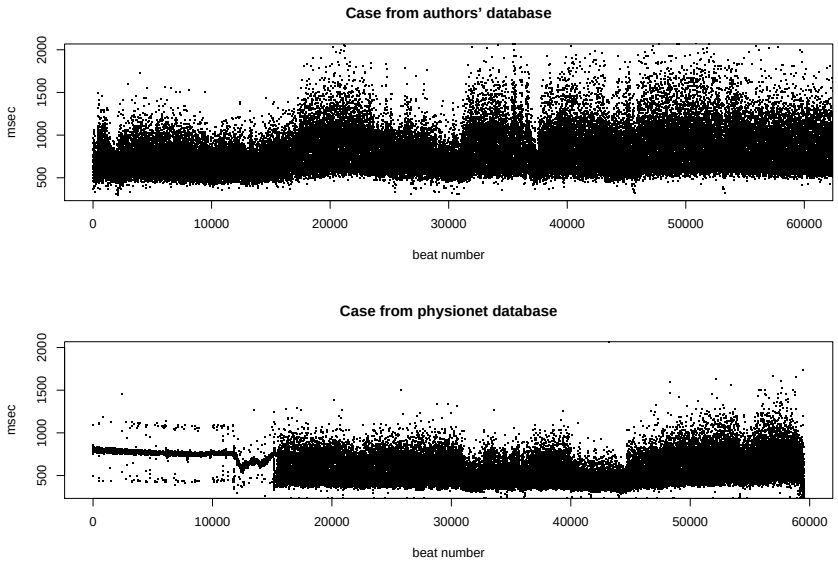

Figure 1. Plots of RR series. In the second panel one can easily recognize two qualitatively different regimes, unlike in the first panel.

We base our analysis on data from two different databases. The first has been provided to us from the Cardiology Department of our University and consists of 24 hours recordings of chronic fibrillation cases. We analyze cases whose RR sequence have a unique regime for the whole recording, like the first panel in the Figure 1. The second database is MIT-BIH Atrial Fibrillation Database, freely available on the web at `http://www.physionet.org/physiobank/database/`. This database consists of 10 hours RR recordings and contains a much more varied typology of fibrillation cases, some of which, like the second panel of Figure 1, have long enough segments with regime comparable to the one of the first panel in the same Figure.

In chronic atrial fibrillation, during the regime like the first panel of Figure 1, the RR time series exhibits very large fluctuations and weak and short range dependence (see for instance [1], [2], [3]). This series exhibits also a non stationary behavior, mainly due to long term humoral stimulation. In our opinion, one of the main features of this non stationary behavior is the

one noticed in [6], [1]: more precisely in [1] we have observed that dividing the series into segments of length between 300 and 1000 beats, the scatter plot of mean and standard deviation over these segments shows a strong linear correlation (see Figure 2).

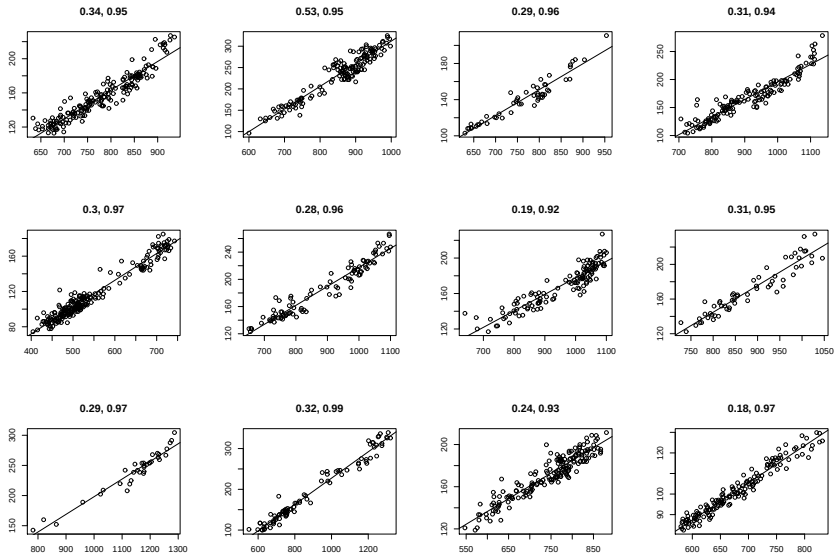

Figure 2. Scatter plot of the pairs (mean, standard deviation) for segments of length 500 of interventricular intervals time series in atrial fibrillation of 11 cases from authors' database and a plot (last panel) simulated using a non stationary adaption of Zeng and Glass model. For each plot are given the slope of the linear fit and the value of the correlation.

We have analyzed the MIT-BIH Atrial Fibrillation Database in order to find the extent to which the above observed feature is present in a sample with different typologies of fibrillation. We have selected only those cases which present long enough regimes similar to the one shown in the first plot of Figure 1. For example we have considered the second case of Figure 1, since the regime from beat 15000 to the end meets this requirement. The results about the correlation in the scatter plot of mean and standard deviation are shown in Figure 3, where we use the same labels as in `physionet` web site. We believe that only the cases corresponding to diagrams with strong linear correlation refer to a kind of atrial fibrillation similar to the one in our database.

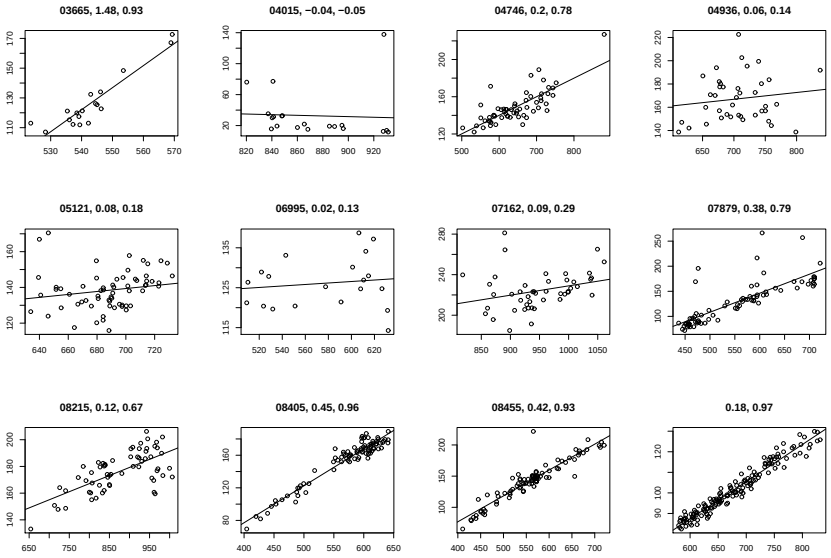

Figure 3. Scatter plot of the pairs (mean, standard deviation) for segments of length 500 of interventricular intervals time series in atrial fibrillation of 11 cases from MIT-BIH databaseand a plot (last panel) simulated using a non stationary adaption of Zeng and Glass model. For each plot are given the slope of the linear fit, the value of the correlation and the label as in `physionet` web site (except for the last).

In [4], Zeng and Glass proposed a model of atrioventricular node conduction that allows to calculate the sequence of ventricular responses to atrial stimulations, based on conduction properties of atrioventricular node. This model has recently received an experimental validation in [5] based on intra cardiac recordings of atrial and ventricular activities. Both [4] and [5] refers to short atrial and ventricular intervals sequences, which can be naturally modeled as stationary sequences.

In this paper we extend Zeng and Glass model along two different directions. The first one consists of replacing constant parameters with random ones. With this modification, the histogram of the inter beat ventricular intervals shown in the second panel of Figure 5 resembles that of real data, unlike the one obtained from constant parameters and shown in the first panel of Figure 5.

The second extension consists of a non stationary version of the model, obtained by introducing a further randomness in the mean values of the parameters. Using this non stationary model we find that simulated RR

series show the same strong linear correlation between mean and standard deviation observed in real data.

Our non stationary model has been obtained by introducing minimal modifications of Glass and Zeng model and still reproduces some important features of observed RR sequences. In particular it is not necessary to introduce randomness also in the standard deviation of the parameters. The model automatically produces the observed variation in the standard deviation of RR intervals. For this reason we believe that this non stationary model has an interesting mathematical structure. This paper is a first exploration of the properties of the model, preliminary to a complete mathematical analysis of it.

2. Model of atrioventricular node function

In this section we describe the Zeng and Glass model of atrioventricular node function [4], [5]. We denote by $A_1, A_2, ...$ the sequence of activation times of atria and by $V_1, V_2, ...$ the sequence of activation times of ventricles. The atrioventricular node function selects from the A_i's a subsequence $A_{q(i)}$ of *transmitted atrial activations*. The *conduction time* AV_i is defined as the time that the electrical stimulation starting at $A_{q(i)}$ takes to be transmitted through the atrioventricular node. If the activation is transmitted, the subsequent ventricular activation occurs at time $V_i = A_{q(i)} + AV_i$. After this ventricular activation the atrioventricular node is in a *refractory period* of duration θ. If the new atrial activation time $A_{q(i)+1}$ is less than $V_i+\theta$ the stimulation is blocked and the refractory period is prolonged by a period δ. This blocking and prolongation is repeated several times, until an atrial activation falls after the expiration of the refractory period. When this happens the stimulation is conducted. We define the random variable $n(i)$ as the minimum positive number of atrial activations after $A_{q(i)}$ such that $A_{q(i)+n(i)}$ is transmitted. The interval from the end of the refractory period to the first conducted atrial activation is called *recovery time*. The length of this interval is

$$RA_i = A_{q(i)+n(i)} - (V_i + \theta + (n(i) - 1)\delta).$$

The model is completed by assigning the *recovery curve*, which gives the conduction time as a function of the the recovery time. This function is a decreasing exponential

$$AV_i = \gamma + \alpha e^{-RA_i/\tau}$$

where γ is the minimum conduction time through the atrioventricular node. The time of the $i+1$-th ventricular activation is

$$V_{i+1} = V_i + \theta + (n(i) - 1)\delta + AV_i.$$

The conditions $q(1) = 1$ and $q(i+1) = q(i) + n(i)$ define the subsequence $A_{q(i)}$ of conducted atrial activations. In order to define the initial values we also put $V_1 = A_1 + \gamma + \alpha$. In this way each pair $(A_{q(i+1)}, V_{i+1})$ depends only on the pair $(A_{q(i)}, V_i)$.

In [5] the following values of parameters, expressed in msec, are given

$$\gamma = 65, \quad \alpha = 290, \quad \tau = 55, \quad \theta = 114, \quad \delta = 81$$

The following times play an important role in the model: the interatrial intervals $A_{i+1} - A_i$ and the interventricular intervals $V_{i+1} - V_i$. Note that the RR sequence is just the sequence of interventricular intervals. The interatrial intervals are simulated by a sequence of independent variables with common normal distribution a of mean 146 and standard deviation 16, i.e $a \sim N(146, 16^2)$. These values for mean and standard deviation of a are taken from the measures in [5]. Using these values in the simulation, the resulting interventricular intervals have a mean of 669 msec. The conduction ratio, defined as the fraction of atrial activations over ventricular ones, is 4.59, confirming the results in [5]. We have checked moreover that the fraction of conducted atrial activation is highly sensitive to the values of δ and ultimately no atrial activation is conducted when δ approaches the mean value of a.

3. Modifications of the model

We compare the sequence of interventricular intervals simulated with Zeng and Glass model to recorded sequences from the two databases. If the simulation is carried on according to Zeng and Glass model, the plot of the simulated sequence shows several horizontal lines corresponding to the number of times at which the atrial activation has been blocked (see the first panel of Figure 4). The same phenomenon can also be seen by looking at the histogram in the first panel of Figure 5; these features do not appear in recorded sequences.

Therefore we modify the model introducing random refractory times θ and δ. We sample δ and θ from normal distributions centered in the values 114 and 81 respectively (taken from [5]), with standard deviations 11 and 8 respectively (chosen by us as one tenth of the preceding values). In symbols, $\delta \sim N(81, 8^2)$ and $\theta \sim N(114, 11^2)$. This suffices to get an RR

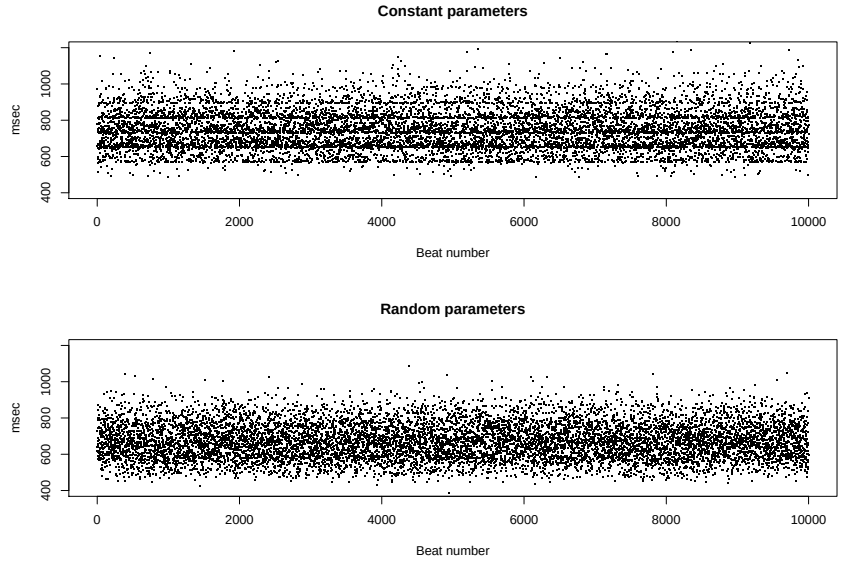

Figure 4. Plot of simulated time series of interventricular intervals. Top: model with fixed parameters $\theta = 114$ and $\delta = 81$; Bottom: model with random parameters $\theta \sim N(114, 11^2)$ and $\delta \sim N(81, 8^2)$. Notice that in the top figure dots aggregate to form regular horizontal lines.

sequence and an histogram resembling the real ones, as in the second panel of Figure 4 and 5.

According to the model as considered so far, the output of interventricular intervals can be satisfactorily modeled as a stationary sequence. Since real data recordings show a non stationary behavior, we define a non stationary version of the model choosing to variate the means of the following three parameters: interatrial intervals a, refractory time θ, prolongation time δ. More precisely we define a non stationary time series by gluing together stationary segments. In our simulations we have glued together 150 segments of length 500. If we choose to vary the parameter θ, each segment is obtained by simulating the model using the parameter $\theta \sim N(p, 11^2)$ where p is fixed and, when the segment is changed,p is taken from a uniform distribution i.e. $p \sim U(114 - 11, 114 + 11)$. We sample the remaining parameters according to, $a \sim N(146, 16^2)$ and $\delta \sim N(81, 8^2)$, independently of the segments.

When we choose to vary another parameter, we proceed in the same fashion; the mean of the parameter δ on each segment is taken from the

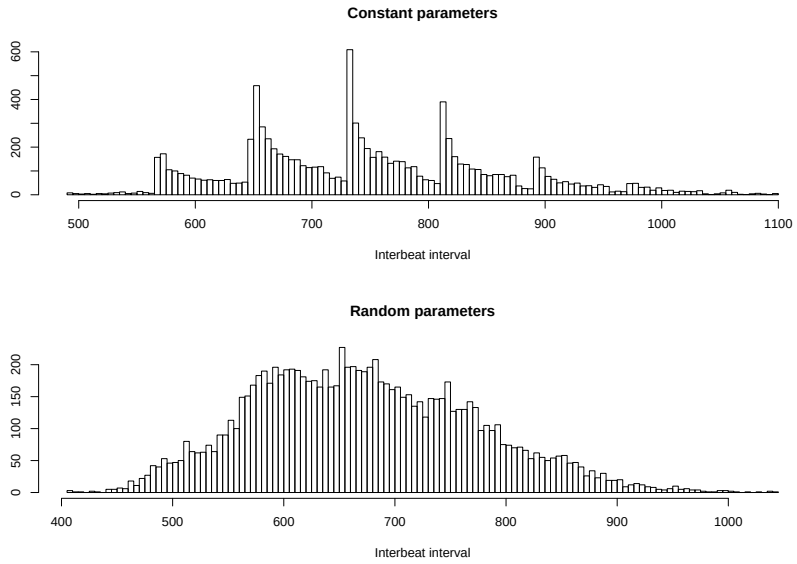

Figure 5. Histogram of interventricular intervals. Top: model with fixed parameters $\theta = 114$ and $\delta = 81$; Bottom: model with random parameters $\theta \sim N(114, 11^2)$ and $\delta \sim N(81, 8^2)$.

uniform distribution $U(81-8, 81+8)$ and the mean of a on each segment is taken from the uniform distribution $U(145-16, 145+16)$. Note that we change the distributions from which we sample the parameters on every segment by only varying the mean level while keeping the standard deviation fixed.

For each segment we compute mean and standard deviation and evaluate their scatter plot. If we vary the parameter a or the parameter δ on the segments, the scatter plot shows a strong linear correlation, very similar to the one observed in recorded sequences. When we vary the parameter θ this does not happen (see Figure 6).

Finally, when we vary the three parameters simultaneously and independently, the scatter plot of simulated sequences still shows the same features of the recorded ones as shown in the last panels of Figure 2 and 3.

The range of the uniform distribution from which are sampled the mean values of the parameters in the non stationary model is pretty narrow. Actually, if we allowed wider ranges, it becomes quite possible that atrial activations are very rarely conducted and also definitely blocked. The study

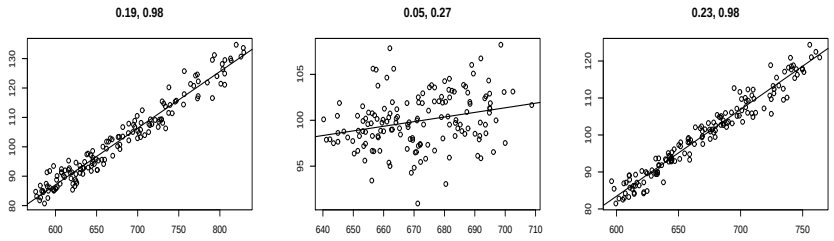

Figure 6. Scatter plots of the pairs (mean, standard deviation) for 150 segments of length 500 of interventricular intervals time series in simulations with non stationary model. In the first, second and third panel, the mean level of a, δ and θ respectively varies over the segments. For each plot are given the slope of the linear fit and the value of the correlation.

of the range of allowable parameters as well as the estimate of parameters from observed data seem to be interesting subjects for further investigation.

4. Conclusions

In this paper we have pointed out that several cases of atrial fibrillation in both authors' and MIT-BIH databases show strong linear correlation of the scatter plot of mean and standard deviation. This peculiar feature, that cannot be explained with a stationary model, can be simulated by introducing a non stationary modification of Zeng and Glass model of atrioventricular node conduction. We have checked that this feature appears as soon as the mean level of the parameters is randomly varied without changing their standard deviation. The parameters which are more directly linked to this feature are the mean interatrial interval and the mean prolongation of refractory time.

The results of our work seems to give a direct and non invasive validation of the model. We think that other non invasive validations are possible. In [2] we have observed that, in the database provided by the Cardiology Department of our University, most of detrended segments can be modeled as autoregressive sequences of order 0 or 1. We have checked that the same behavior is shared by those RR sequences of the MIT-BIH database whose scatter plots in Figure 3 have strong linear correlations. We believe, on the basis of a preliminary analysis, that Zeng and Glass model can explain also the order of the autoregressive model.

The non stationary version of Zeng and Glass model is suitable for describing 24 hours RR sequences of a particular type of atrial fibrillation.

For this reason, it would be important to investigate mathematically the model, but this seems to be very hard. Future investigation should be aimed at introducing some simplifications in order to make the model more tractable but still good enough to describe real data.

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