

## IMPROVED INTEGRATE-AND-FIRE MODEL FOR RSA

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**ABSTRACT.** A simple operational model of heart rate variability is described, accounting in particular for the respiratory sinus arrhythmia, and is fitted to some interbeat interval sequences recorded from normal subjects at rest. The model performance is evaluated using a test based on the nonlinear prediction approach. Moreover, a short comparative account of two similar models described in the literature is given.

**1. Introduction.** Understanding the origin of physiological rhythms and characterising their interactions are fundamental issues of the current research in physiology and nonlinear dynamics [10, 17]. In particular, this holds true for the heartbeat and respiratory activity.

Now, although it is well known that these two systems are coupled, it is an open issue as to how and how much they are phase-synchronised, and only recently some evidence of their transient synchronisation has been brought forward [13, 14], and new analytical tools have been devised to detect it locally [12].

To answer this and related questions, some operational models of the process underlying cardiac activity have recently been proposed, which are quite simple, but still can render its main dynamical features [4, 5, 11].

The model we propose, a stochastic integrate-and-fire model suitably modulated to account for the respiratory sinus arrhythmia (RSA), effectively reproduces the structure of the experimental data [4]. To evaluate the model performance, we also devised a Q-test statistic, based on the concept of nonlinear prediction.

In the present paper the procedure for fitting the model to the experimental datafiles has been improved, thus leading to better fits (corresponding to lower values of the test statistic), and the set of datafiles has been enlarged. Moreover, a comparison between our proposed model and similar ones recently published [5, 11] is outlined in section 4 (Discussion).

## 2. Materials and methods.

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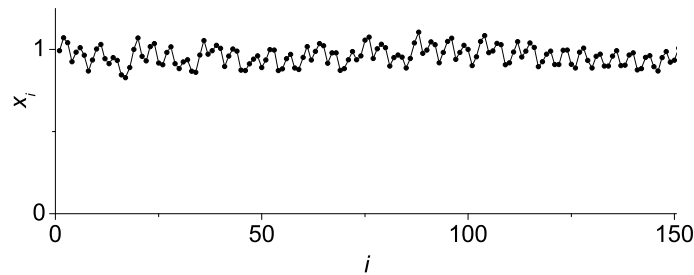


FIGURE 1. Part of the tachogram of the M1 sequence of RR intervals

**2.1. Experimental protocol.** In an experimental session aimed at characterizing the cognitive response of waking, healthy subjects, either hypnotizable or not, a number of biological signals were recorded in sixteen young healthy volunteers (ages 18 to 28) during periods of relaxation and under different cognitive stimulations. In particular, on the ECG signal recorded at 256 Hz the series of interbeat RR intervals  $x_i, i = 1, 2, \dots, n$ , was measured. Figure 1 shows the tachogram of file M1 ( $n = 400$  RR intervals). In the first investigation, these data were analysed to extract the embedded respiratory components [2]. The RR time series used in this paper have been obtained from the ECGs recorded during five minutes of quiet, sitting relaxation. Nine epochs from five subjects have been taken into account as representative of the most "regular" patterns: namely, those yielding a damped oscillatory autocorrelation function and a distinct high frequency (HF) peak in the spectrum. Most of them exhibit a clear respiratory modulation with about a four-beat period. Moreover, many epochs yield consistent negative values (see the Table 1 below) for the skewness of the first differences  $y_i = x_{i+1} - x_i$ ; i.e. the quantity

$$\gamma = \frac{\sum y_i^3}{(\sum y_i^2)^{3/2}}. \quad (1)$$

This nonlinear statistic, also called slope asymmetry or time asymmetry of the  $x_i$  sequence, captures the difference between the rise times (upward part) and fall times (downward part) of the oscillations of the  $x_i$  series. In other words, it measures the extent to which the  $x_i$  series looks different if reversed in time, and therefore it is an indicator of some type of nonlinearity [6].

**2.2. Model definition.** The proposed model, which bears some resemblance to that proposed 25 years ago for a generic biological oscillator [8, 9], consists of a stochastic integrate-and-fire unit<sup>1</sup> whose input signal—the so-called activity—is held constant until the spike (heartbeat) is fired while the threshold  $s(t)$  oscillates periodically exhibiting a time asymmetric profile (see also [4]). This oscillation, of period  $T$ , expresses the respiratory modulation of RR intervals, while its slope

<sup>1</sup>In its deterministic version, this model integrates the input signal (which can be constant or modulated, smooth or noisy) once the integral reaches a threshold value; then a spike is fired, the integral is reset to zero, and the integration starts again. The spike firing corresponds to the occurrence of a typical event of the heart activity cycle, for instance the R wave.

skewness accounts for the negative value of most investigated time series. Although its precise time-dependence is not critical, we have generally used the form

$$s(t) = s_0 + m \sin \{ \alpha [\varphi(t) - \pi] \}, \quad (2)$$

where  $\varphi(t) = 2\pi t(\text{mod}T)/T$  and  $|\alpha| \leq 1$ . Hence, while  $\varphi$  sweeps the  $(0, 2\pi)$  interval again and again, the sin function argument sweeps the interval  $(-\alpha\pi, \alpha\pi)$ . So for  $|\alpha| = 1$  the threshold profile is sinusoidal, but it becomes more and more discontinuous and asymmetric as  $|\alpha|$  decreases from 1 to, say, 0.5—note that negative  $\gamma$  values correspond to positive values of  $\alpha$ .

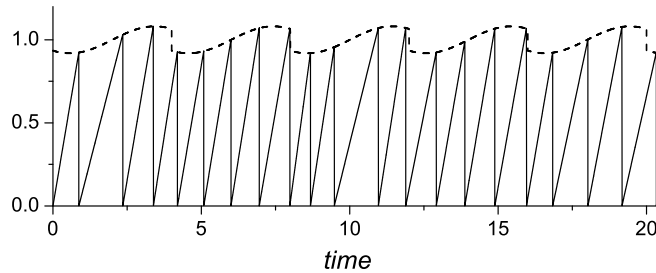


FIGURE 2. Model operation: the dashed line represents the beating threshold and the solid line the integral function. The parameters have the values:  $s_0 = 1$ ,  $T = 4$ ,  $m = 0.08$ ,  $\sigma = 0.2$ ,  $a_1 = 0.5$ ,  $\alpha = 0.7$ .

All of the remaining dynamics are accounted for by a stochastic component introduced in the following way. The activity signal (i.e., the rate of rising of the integral function), changes from one interval to another assuming the autocorrelated stochastic values (corresponding to a discrete sampling of the Ornstein-Uhlenbeck process)

$$\eta_i = a_0 + a_1\eta_{i-1} + \sigma\xi_i, \quad i = 1, 2, \dots \quad (3)$$

In this equation the  $\xi_i$  innovations are uncorrelated and Gaussian-distributed with zero mean and unit variance,  $a_1 \in [0, 1)$ , and  $a_0 = 1 - a_1$ ; it is worth noting that  $a_1$  gives the first coefficient of the exponential autocorrelation function of the sequence  $\{\eta_i\}$ . The mean value of  $\{\eta_i\}$  is thus unity, and its variance is given by

$$\nu = \langle (\eta_i - 1)^2 \rangle = \frac{\sigma^2}{1 - a_1^2}. \quad (4)$$

Figure 2 illustrates the model operation.

**2.3. Goodness of fit test.** To optimize the data fit by the model proposed in this paper, a measure of the goodness of fit is necessary. To this aim a kind of t-test statistic has been drawn from the nonlinear prediction method, an efficient tool of nonlinear time series analysis [3, 5, 16], whose rationale is that the analysed time series possesses some—possibly nonlinear—determinism, which in turn is a synonym of predictability; that is, the possibility of using the system knowledge to predict its evolution. Let us define it operationally with reference to any given RR interval series  $\{x_i\}$ ,  $i = 1, 2, \dots, n$ . First, an embedding space with a dimension of 4

and unity lag time is built by means of the delay vectors  $\mathbf{x}_i = (x_{i-3}, x_{i-2}, x_{i-1}, x_i)$ ,  $i = 4, 5, \dots, n$ , which represent the system states—noteworthy, the four components span about one respiration cycle. Then for each vector  $\mathbf{x}_i$  the nearest neighbour  $\mathbf{x}_k$  not sharing any component with  $\mathbf{x}_i$  is determined within the embedding phase space, and the one-step-ahead value  $x_{k+1}$  is adopted as the prediction for  $x_{i+1}$ . The difference  $\delta_i = x_{k+1} - x_{i+1}$  is the prediction error. This is repeated for as many delay vectors as possible and the normalised prediction error  $\epsilon_0$  of the time series is obtained by dividing the root mean square (r.m.s.) of errors  $\delta_i$  by the standard deviation of the time series (equal to the r.m.s. error of the rough prediction afforded by the time series mean)<sup>2</sup>. This quantity, which usually is less than unity, measures the predictability of the original series  $\{x_i\}$ . At this point ten series  $\{y_i^j\}$ ,  $j = 1, \dots, 10$ , with the same length as  $\{x_i\}$ , are generated by the model always adopting a given set of parameter values, and the normalised prediction error of the original series  $\epsilon_m^j$  is computed using each model realisation as reference (or learning) set. That means that the prediction for  $x_{i+1}$  is obtained, with a procedure somewhat resembling that used in the mutual prediction method of analysis [15], by determining in the embedding space of vectors  $\mathbf{y}_i^j$  the nearest neighbour to  $\mathbf{x}_i$  (let's call it  $\mathbf{y}_k^j$ ) and then taking  $y_{k+1}^j$ . Our goodness of fit statistic is defined as the ratio  $Q = (\epsilon_m - \epsilon_0) / \Delta\epsilon_m$ , where  $\epsilon_m$  and  $\Delta\epsilon_m$  are the average and the standard deviation of the values  $\epsilon_m^j$ , respectively. The lower the  $Q$  value, the better the description of the data afforded by the model; in particular, for  $Q \leq 1.96$ , the null hypothesis that the model-generated interval sequences came from the same system as the original RR sequence cannot be rejected ( $p = 0.05$ ).

**2.4. Fitting the model to the data.** A simple operational procedure was used in each case to determine the best parameter values of the model (i.e. those minimizing the  $Q$  value). Namely,  $s_0$  was set at the mean RR interval of the original sequence,  $T$  at the reciprocal of the respiratory peak frequency in the tachogram spectrum, and  $m$  at twice the square root of the power in the respiratory peak of the spectrum. For the other parameters the starting values  $\alpha = 0.8$ ,  $a_1 = 0.85$  and  $\sigma = 0.02$  were adopted, and then small adjustments were performed, bearing in mind that the SA value increases (almost linearly) with  $(1 - \alpha)$ , while  $\sigma$  and  $a_1$  gather the information about the low-frequency components of the tachogram spectrum.

**3. Results.** Before showing how the proposed model can be fitted to the experimental datafiles, let us summarize the characterization of its behaviour obtained by generating many sequences of intervals, each corresponding to a different set of values of the model parameters<sup>3</sup>. In fact, the model performance is determined by six parameters: four concern the modulation of the firing threshold (i.e.,  $T$ ,  $s_0$ ,  $m$  and  $\alpha$ ), while two are related to the input signal  $\eta_i$  ( $a_1$  and  $\sigma$ ). In this preliminary analysis of the model performance,  $T$  was set at 4 or about 4 and  $s_0$  at 1, while the values 1 and 0.7 were adopted for  $\alpha$ , and  $m$  and  $\sigma$  were set at 0.05 and 0.02, respectively. We soon realized that to allow the model to reproduce the slow drift of the running mean interval in the tachograms, thus getting a realistic broadening of the respiratory peak in the corresponding spectra, the noise signal had to be

<sup>2</sup>It is usually  $\epsilon_0 < 1$ ; also, the lower  $\epsilon_0$  the higher the predictability, or determinism, of the investigated series.

<sup>3</sup>Of course, the precise sequence obtained for each set of parameter values does depend on the particular noise realisation and initial conditions, but its general features do not

definitely autocorrelated, with parameter  $a_1$  set at values as high as 0.8-0.9. Moreover, for all investigated files, we drew the scatter plot of the first difference series  $\{y_i\}$ , also called the first-order variability diagram [1]; those obtained from M1, M2, M3 and M8 datafiles exhibited a three-clouded structure [4, 7] to reproduce which the model must be provided, in addition to a strongly autocorrelated noise, with a time-asymmetric threshold modulation (with  $\alpha \cong 0.8$ ). As an example, the left panel of Figure 3 shows the variability diagram for file M1, while the right panel reports the one obtained from the model-generated sequence of intervals.

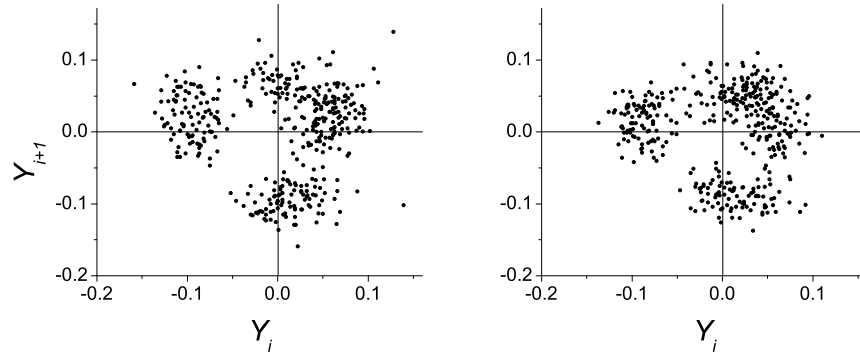


FIGURE 3. First-order variability diagrams of file M1 (left panel) and a model-generated sequence (right panel).

Now let us examine how the model can generate sequences of intervals that effectively mimic the experimental ones. To accomplish this, the model parameters have to be set to such values that the generated sequences reproduce the dynamics of the experimental ones as well as possible, thus lowering the  $Q$  statistic described in the Methods section. The overall results are reported for each data file in the Table below.

TABLE 1. Relevant features of the datafiles and parameter values of the model fit to them

file	$\gamma$ $\times 10^2$	Total power $\times 10^3$	HF power $\times 10^3$	$s_0$	$T$	$m$ $\times 10^2$	$\sigma$ $\times 10^2$	$a_1$	$\alpha$	$\epsilon_0$	$\epsilon_m$	$Q$
M1	-2.6	1.58	0.71	0.961	3.9	5.2	1.74	0.9	0.82	0.685	0.728	1.52
M2	-2.5	2.09	0.72	0.992	3.95	5.3	2.7	0.82	0.79	0.716	0.79	1.44
M3	-2.3	2.2	0.82	0.998	3.95	5.7	2.75	0.81	0.82	0.795	0.827	0.74
M8	-3.2	2.05	0.68	0.945	3.9	5.2	1.9	0.92	0.8	0.704	0.74	1.06
I1	-2.3	1.04	0.54	0.964	3.92	4.6	2.12	0.75	0.83	0.837	0.847	0.29
L1	-2.4	0.72	0.105	0.971	4.55	2.0	1.33	0.92	0.85	0.761	0.787	0.91
G1	-0.3	1.03	0.29	0.756	3.1	3.4	3.25	0.76	0.95	0.968	0.993	0.61
P2	-0.5	1.44	0.31	0.866	4.25	3.5	2.18	0.90	0.95	0.782	0.794	0.52
P4	0.6	1.54	0.43	0.9	4.25	4.1	2.42	0.87	1.0	0.833	0.872	0.90

They show, in this order, the value, the total spectral power, the power in the HF peak, then the model parameter values obtained by using the stated protocol, and finally the  $Q$  value (together with  $\epsilon_0$  and  $\epsilon_m$ ). The last values span a wide range: from 0.29 to 1.52, corresponding, for the probability that the original sequence and the model realisations come from the same system, to the values 0.77 and 0.13, respectively. Worthy of note, the figures reported in Table 1 do not change appreciably by using, to calculate  $Q$ , an embedding dimension of 5. On the whole, considering that the model is quite simple and mainly aimed at reproducing the RSA dynamics, we believe its performance to be satisfactory.

**4. Discussion.** As shown above, the proposed model can fairly well fit all RR sequences taken into account, although with rather different values of its parameters, in particular  $\gamma$  and the spectral powers (total and HF), as well as  $T$  and  $s_0$  (and their ratio). We believe that the model could be fit as well to any regular recorded sequence of some hundreds of RR intervals. Of course, the fit will not be perfect in all respects; in particular, the low-frequency part of the spectrum will not be reproduced in detail by the simulated sequences. But this is expected from such a simple operational model. Anyway, despite its evident limitations, the model can help us to answer some debated issues in the study of physiological rhythms, such as that of assessing, in the recorded activity, the possible phase synchronisation between heartbeat and breathing rhythms (see [4]).

An issue worth investigating in the near future is the possibility of improving the model without a major increase to its complexity. To this end, one should bear in mind the two models of HRV proposed recently and having some similarity with our model [5, 11]. In the first one [5], the input level of an integrate-and-fire device is additively modulated by two sinusoidal oscillators, simulating the respiratory and vasomotor influences, respectively. This model does not seem to fit the experimental data satisfactorily, particularly not the power spectra of the RR series, even when some Gaussian noise is added to the intervals. However, it would suggest us to seek to directly add in our model a second oscillator (accounting for the vasomotor input), even if a change-reduction-of the noisy component would be required at the same time.

In the second model [11], the heartbeat is still described by an integrate-and-fire system, but there the modulation accounting for RSA is on the firing threshold, as in the model proposed by us. However in that model, which is purely deterministic, a cardioventilatory coupling (CVC), the reverse influence of heartbeat on respiration, is included. The authors claim that their model "captures the essential features of the interactions between human cardiac and respiratory systems, when those interactions are simplified by anesthesia" and conclude that, although RSA alone might cause synchronisation between heartbeat and respiration, CVC is the dominant mechanism responsible for synchronising the two oscillators. Therefore CVC should be included in our model, possibly in the same way as performed in [11], but that would again require other changes, in particular to the noise component design.

As a last remark, we note that our model is potential to get tachograms with time-asymmetric respiratory modulation and thus  $\gamma$  values significantly non-vanishing, proved to be important for fitting our experimental data (it is enough to observe the correlation between the values of  $\gamma$  and those of  $\alpha$  in Table 1). Hence, also considering that it is quite easy to calculate, we take the liberty of inviting physiologists

to investigate whether a significant negative  $\gamma$  value measured on the experimental data<sup>4</sup> may encode for some interesting feature of the cardiorespiratory system.

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<sup>4</sup>The significance of the value can be assessed either by comparing it with the values obtained on suitable surrogate data or by simple inspection of the first-order variability diagram obtained from the data [4].