Beat-to-beat blood-pressure fluctuations and heart-rate variability in man: physiological relationships, analysis techniques and a simple model

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Chapter 5
Beat-to-beat variability
of heart interval and blood pressure

This chapter describes a simple beat-to-beat model of the cardiovascular system. Cross-correlation techniques are used to test the validity of the model.

5.1 Abstract
We propose a set of three mathematical equations to model the beat-to-beat properties of the fast blood-pressure regulation system. The equations are based on the following physiological considerations: 1) The length of the RR-interval is dependent on the systolic pressure (baroreflex). 2) The pulse pressure is dependent on the length of the preceding interval (due to the restitution properties of the myocardium and to Starling's law). 3) During diastole the pressure decay can be described by a Windkessel-equation.

As preliminary results we found that blood-pressure data from hypertensive patients which showed respiratory sinus arrhythmia agreed well with equations 1) and 3), and that data from a patient with atrial fibrillation agreed with equations 2) and 3).

5.2 Introduction
In the intact organism variations in heart interval (HI) and in blood pressure (BP) are interconnected: a changing BP influences the HI through the baroreflex, and cardiovascular properties transform a changing HI into variations of BP. In most studies of the cardiovascular system, a continuous signal is derived from the momentaneous heart-rate (i.e. the inverse of the HI) by an interpolation-procedure and the mean blood pressure is used as descriptor of the blood-pressure signal. The advantage of this approach is that relationships between these continuous signals can be studied using standard systems analysis techniques. However, this approach is not well suited for the study of fast variations of HI and BP with characteristic times of less than, say, 3 seconds (≈ 3 beats), for then it is not longer possible to neglect the pulsatile character of the BP-signal and the concept of a continuous heart-rate becomes meaningless.
Unfortunately, no clear-cut methods are known for the study of the unprocessed cardiovascular signals, consisting of the series of intervals (which can be considered as a series of point events) and the pulsatile blood-pressure signal, from which a large number of parameters may be extracted (systolic, diastolic and mean pressure, maximal systolic rate of pressure rise, etc.).

As our group is studying the fast (vagally mediated) baroreflex properties (Karemaker, 1980; Karemaker and Borst, 1980), a description of the beat-to-beat variability of HI and BP was needed. We present such a description and discuss its use in blood-pressure data from a number of patients.

5.3 A beat-to-beat model of the cardiovascular system.

A diagram of the fast loop for blood-pressure regulation is shown in Fig.1. The blood pressure is considered as the input signal for the baroreceptors. These pressure-sensitive devices, located in the carotid arteries and in the aorta, send afferent information to the Central Nervous System (CNS). The CNS processes this information and accordingly influences the length of the heart interval by modulating the amount of efferent signals it sends towards the SA-node of the heart via the vagal nerve. The length of the heart interval combined with the cardiovascular properties, determine the blood pressure, thus closing the loop of Fig.1. Evidently, in the diagram only the fast (parasympathetic) regulation is included and not the slower sympathetic one, influencing inotropic state, peripheral resistance and other important parameters of the cardiovascular system.

![Diagram of the fast blood-pressure regulation loop.](image-url)
We based our mathematical model of the HI-BP-system on the loop of Fig.1, taking into account known physiological relationships. Fig.2 shows the notation we adopted. $S_n$, $D_n$, and $P_n$ are the systolic, diastolic and pulse pressures during RR-interval $I_n$. We modelled the beat-to-beat properties of the HI-BP-system by the following set of three equations. The first one describes the influence of BP on HI, the other two equations describe how the BP is affected by the HI.

Eqn.1. $I_n = a_0 S_n + c_1$  
baroreflex

Eqn.2. $P_n ( = S_n - D_n ) = \sqrt{I_{n-1}} + c_2$  
estitution and Starling

Eqn.3. $D_n = c_3 S_{n-1} \exp(-I_{n-1}/T)$  
Windkessel

In Eqn.1 a linear relation between systolic pressure $S_n$ and interval $I_n$ is assumed to model the fast baroreflex properties. The coefficient $a_0$ is a measure of baroreflex sensitivity, related to the one introduced by Smyth and coworkers (1969). The equation must be changed if -- e.g. through sympathetic drive -- the interval shortens below approximately 700 ms (85 beats per minute). Then the interval $I_n$ becomes dependent on the preceding systolic pressure $S_{n-1}$, due to the delay of around 500 ms between the baroreceptor sensing the blood pressure and the effect on the heart interval (Pickering and Davies, 1973; Borst and Karemaker, 1980):

Eqn.1'. $I_n = a_1 S_{n-1} + c_4$

Eqn.2 is based on the restitution properties of ventricular muscle -- an increased interval between beats implies a more powerful contraction and thus a larger pulse pressure (cf. Pidgeon et al., 1982) -- and on Starling's law: an increased ventricular filling (as caused by a longer interval between beats) enhances the force of contraction.
We felt justified to use linearized relations in Eqns.1 and 2, as we first of all want to describe the semi-steady state, where only small excursions from the mean values occur.

Eqn.3 is a Windkessel-description of the diastolic pressure decay between two beats.

The three equations constitute a closed model of the HI-BP-system, leading to stable and acceptable values for I, S, D and P if realistic values of the constants \( a_0 \), \( \tau \), \( c_1 \), \( c_2 \) and \( c_3 \) are chosen. Evidently, the model does not explicitly incorporate respiratory arrhythmias or respiration-linked variations in blood pressure.

Combination of the three equations leads to the following recurrent relation for systolic pressures:

\[
S_{n+1} = c_3 \cdot S_n \cdot \exp\left(-\frac{(a_0 \cdot S_n + c_1)}{\tau}\right) + a_0 \cdot \frac{S_n}{\tau} + \frac{a_0}{\tau} \cdot c_1 + c_2
\]

This equation is of the shape \( S_{n+1} = f(S_n) \). If \( S \) is an equilibrium point of the equation, then \( S = f(S) \). The equilibrium point is locally stable if \( \frac{\partial f}{\partial S} < 1 \), or:

\[
\frac{D}{S} - a_0 \frac{D}{\tau} + a_0 < 1,
\]

with \( D \) the diastolic value belonging to the equilibrium value \( S \). As an example, values for \( D \), \( S \), \( \tau \) and \( a_0 \) can be taken from section 7.4.3 as 75 mmHg, 143 mmHg, 1850 ms and 13.2 ms/mmHg, respectively. Then the condition for stability becomes \( y < 0.08 \text{ mmHg/ms} \).

5.4 Cross-correlation of blood pressure and heart interval

We tested the model using arterial blood-pressure data from a number of hypertensive patients. For ease of calculation we introduced a new variable \( L_n \) (the logarithmic decrement) and rewrote Eqn.3 as:

\[
3'. \quad L_n \overset{\text{def}}{=} \log\left(\frac{S_{n-1}}{D_n}\right) = I_{n-1}/\tau + c_3 \quad (c_3 = -\log(c_3))
\]

To test the different equations, we computed correlation coefficients between \( I_n \) and \( S_n \) (Eqn.1), \( P_n \) and \( I_{n-1} \) (Eqn.2) and \( L_n \) and \( I_{n-1} \) (Eqn.3). However, more insight was obtained by computing cross-correlation functions (CC-functions) of the different blood-pressure variables (S, D, P and L) and interval (I). We calculated the CC-coefficients as (cf. Jenkins and Watts, 1968, Ch.8):

\[
r_X(k) = c_{XI}(k) / \left( c_{XX}(0),c_{II}(0) \right)^{1/2}
\]

with:

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if \( k \geq 0 \)

\[
c_{xI}(k) = \frac{1}{N} \sum_{i=1}^{N-k} (x_n - \bar{x}) \cdot (I_{n+k} - \bar{I})
\]

if \( k < 0 \)

\[
c_{xI}(k) = c_{xI}(-k)
\]

\( X_n \) stands for any of the blood-pressure variables \( S_n, D_n, P_n \) or \( L_n \). \( N \) is the number of data-points. The CC-coefficients \( r_{XI}(k) \) describe the linear correlation between the sets of values \( X_n \) and \( I_{n+k} \) (\( n = 1, N-k \)), i.e. the correlation between the value of a BP variable and the length of the interval \( k \) beats later (\( k > 0 \)) or earlier (\( k < 0 \)).

In some registrations, evident slow non-stationarities (trends) in BP and HI were present. In these cases, we used the differenced data for our calculations:

\[
I_n^d = I_n - I_{n-1}, \quad S_n^d = S_n - S_{n-1}, \quad \text{etc. (cf. Karemaker, 1980a,b)}.
\]

This lead to similar results as shown in the following figures.

5.5 Data from a patient with respiratory sinus arrhythmia

We present results for arterial pressure data from a hypertensive patient showing a marked respiratory sinus arrhythmia (RSA) when breathing freely. In Fig.3a a number of successive values of interval, systolic, diastolic and pulse pressure and of the logarithmic decrement \( L_n \) are shown. In the figure the respiratory influence is evident, the period being approximately 3 beats (or 3 s). The different CC-functions in Figs.3b-e show a similar periodicity, as is expected. The results presented in the figures are typical for a number of blood-pressure registrations we analyzed so far.

Fig.5-3a A number of consecutive values of interval and blood-pressure data from a hypertensive patient, showing respiratory sinus arrhythmia.
Figs. 3b-e Cross-correlation (CC-)functions of systolic pressure (S, Fig.3b), diastolic pressure (D, Fig.3c), pulse pressure (P, Fig.3d) and logarithmic decrement (L, Fig.3e) vs. interval length I as computed from the data of Fig.3a. For example, \( r_{51}(2) \) is the correlation coefficient between systolic pressure \( S_n \) and the length of the interval two beats later \( (t_{n+2}) \). According to the described model, the correlation values marked with an asterisk (•) should have high positive values. This is only the case in figs.3b and 3d, which corroborate eqn.1 (baroreflex) and eqn.3 (Windkessel), respectively.

According to Eqn.1, a positive correlation between systolic pressure \( S_n \) and interval \( t_n \) is to be expected. Fig.3b shows for \( k = 0 \) a correlation value \( r = 0.75 \) (N = 25). This correlation can thus be explained from the baroreflex equation 1. The value of \( a_0 \) (the baroreflex sensitivity index) was found as 5.1 ms/mmHg. Fig.3c shows a negative correlation \( (r = -0.55) \) between diastolic pressure \( D_n \) and the length of the preceding interval \( t_{n-1} \). In Fig.3e a positive correlation between \( L_n \) and \( t_{n-1} \) is seen \( (r = 0.79) \), which is in accordance with Eqn. 3'. From the regression of \( L_n \) on \( t_{n-1} \) a value of \( \tau = 965 \) ms can be calculated, which is not unrealistic (Simon et al., 1979).
Eqn.2 implies a positive correlation between $P_n$ and $I_{n-1}$; however, only a moderately positive value was obtained from the data (Fig.3d for $k = -1$: $r = 0.36$). This lack of correlation is not caused by a curvilinear relationship between pulse pressure $P_n$ and preceding interval $I_{n-1}$, as was clear when a scatter plot of $P_n$ vs. $I_{n-1}$ was drawn. We conclude that in this patient the pulse pressure is scarcely related to the length of the preceding interval. Even lower correlation coefficients were found in data from some other patients.

5.6 Data from a patient with atrial fibrillation

In a similar way we analyzed blood-pressure data from a hypertensive patient, suffering from atrial fibrillation (Fig.4). In this disease the lengths of successive heart intervals vary in a fully random fashion (cf. Bootsma et al., 1970). No respiratory influence was apparent in BP- or HR-data from this patient (Fig.4a). The computed autocorrelation coefficients for interval and pressure-variables ($I$, $S$, $D$, and $P$) were for $k=0$ all near zero.

The CC-functions (Figs.4b-e) showed a significant non-zero correlation between $S_n$ and $I_{n-k}$ and between $P_n$ and $I_{n-k}$ only for $k = -1$ ($r = 0.74$ and $r = 0.85$ resp.; $N = 60$). Thus, no evidence was found for the validity of the baroreflex-equation 1. or 1.' (this equation implies a high correlation for $k = 0$ or $k = 1$). $S_n$ and $P_n$ were highly correlated in these data ($r = 0.92$). Our results confirm that in patients with atrial fibrillation the height of the pulse pressure $P_n$ is related to the length of the preceding interval $I_{n-1}$ (Einthoven and Korteweg, 1915; Meyler et al., 1968).

Fig.5-4a  Interval and pressure data from a patient suffering from atrial fibrillation.
A negative correlation between $D_n$ and $I_{n-1}$ ($r = -0.59$) and a positive correlation between $D_n$ and $I_{n-2}$ ($r = 0.58$) were found. This can be explained from Eqn.3, which, when linearized, implies a negative correlation between $D_n$ and $I_{n-1}$ and a positive one between $D_n$ and $S_{n-1}$, and hence between $D_n$ and $I_{n-2}$ (due to the high correlation between $S_n$ and $I_{n-1}$ and the autocorrelation coefficients being almost zero.) The correlation between $L_n$ and $I_{n-1}$ was positive ($r = 0.73$), in accordance with Eqn.3'. In addition, a slightly positive correlation between $L_n$ and $I_{n-2}$ was found ($r = 0.37$).

### 5.7 Conclusion

We presented three equations for the description of beat-to-beat properties of HI and BP. Two of these equations (the baroreflex-equation 1 and the Windkessel-equation 3) agreed well with experimental blood-pressure data from a number of hypertensive patients. The third one -- linking the pulse pressure to the
preceding interval (eqn.2) -- was not found to agree well with these data. However, in a hypertensive patient suffering from atrial fibrillation, the expected positive correlation between pulse pressure and preceding interval was found. The lack of correlation between pulse pressure and preceding interval can be explained by assuming important respiratory influence on the pulse pressure. Another explanation may be the leveling off of the restitution curve (contractility vs. interval) for intervals longer than 800-900 ms (Pidgeon et al., 1982).

Our results show a positive correlation between interval $I_n$ and systolic pressure $S_n$ in patients with RSA. We also found positive correlations between interval and mean pressure (i.e. the mean over one beat), which is in contrast to the results of Freyschuss and Melcher (1976), who found a positive correlation between mean pressure and instantaneous heart rate (which is the inverse of the interval) in healthy volunteers. However, whereas they imposed a fixed respiration rate of 0.1 Hz and a high tidal volume on their subjects, our patients were breathing freely. This difference in experimental conditions might explain the different results.

As conclusion, we state that a beat-to-beat description of the fast blood-pressure regulation loop is closer to the physiological phenomena than the standard description using artificially constructed continuous heart-rate and pressure signals.

5.8 Note on further discussion of the results of this chapter

This chapter contains the text of a paper written in 1982. Especially the use of spectral analysis techniques (Chapters 6, 7) has clarified some of the results described here: the effect of differencing, the BRS$^+$-measure of Karemaker (1980a,b), the apparent discrepancy with the results of Freyschuss and Melcher (1976). A further discussion of these matters is given in Chapter 8.1.5.