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 2

Description of heart-rate variability data in accordance with a physiological model for the genesis of heart beats

In this chapter we present a survey of different heart-rate variability (HRV) signals. We propose the IPFM model as a physiologically attractive device for a phenomenological description of HRV.

2.1 Abstract

A survey is presented of techniques which transform heart-rate variability data into a signal that is both visually informative and accessible for analysis. The Instantaneous Heart-Rate (IHR) signal is introduced, i.e. the signal having the value of the heart rate (inverse interbeat interval) during the interval concerned. The IHR signal differs from the standard Delayed Heart-Rate (DHR) signal, which is always one beat late.

The relationship is discussed between the different representation methods and the Integral Pulse Frequency Modulation (IPFM) model, the latter being a physiologically plausible model for the transformation of a continuous input signal (e.g., nervous influence on the cardiac pacemaker) into a series of events (heart beats). It is shown that when the IHR signal is used as input of the IPFM model, the event series from which the signal was derived, appears at the output. Hence, if the IPFM model is accepted as a model of the pacemaker, the IHR signal may be considered as an approximation of the neural (sympathetic and parasympathetic) influence on the pacemaker. In addition we show that the appearance of the IHR signal is less affected by trigger errors or extrasystoles than the standard DHR signal.

It is concluded that the most attractive time-domain representation of physiological event series consists of the IHR signal, because this signal, being conceptually and computationally simple, is consistent with the IPFM model.

2.2 Introduction

Heart beats are often considered as point events, i.e. the individual characteristics (shape, amplitude) of each beat are neglected, but its time of occurrence or, equivalently, the interval between successive beats is taken as the only relevant variable. A number of methodological problems are specific to the analysis of point event signals.

First, variations of the interval length are not easily discerned from the raw signal, the electrocardiogram (ECG). Hence, another representation method is needed to display the signal. Second, in the study of the heart-rate response to a prescribed stimulus, it is often necessary to average a number of responses. But it is not immediately clear how such an average can be obtained; one cannot simply add the event series in question. Applications occur in the study of heart-rate responses to mental tasks (e.g., Somsen et al., 1983) or to standing up (Borst et al., 1982). Finally, special data processing techniques are required when heart rate is related to another physiological signal such as respiration (Angelone and Coulter, 1964; Womack, 1971; Sroufe, 1971; Hirsch and Bishop, 1981) or blood pressure (Chapter 5, or DeBoer et al., 1983).

Existing methods for the statistical analysis of series of point events were developed for stochastic series of events and are not always suited for the analysis of physiological point event signals (Cox and Lewis, 1966; Cox and Isham, 1980; De Kwaadsteniet, 1982). Therefore techniques are needed that convert the point event signals into a form that is accessible to standard system analysis techniques (e.g., averaging, spectral analysis). In addition, the converted signal should preferably be visually informative.

In the next section (Survey of Methods) we compare a number of techniques that are used for this conversion. Some of these techniques produce a signal having a well-defined value at all times, e.g. the well known heart-rate signal, derived from the R-waves in the electrocardiogram. Similar signals have been defined using the interbeat interval instead of the heart rate. Other techniques produce a signal resembling a series of equidistantly sampled data, e.g. the interval series. We concentrate our survey on representation methods that are both conceptually and computationally simple.

In many physiological processes the timing of successive point events is governed by a continuously varying signal. For example, in heart-rate variability studies the deviations from a perfectly regular cardiac rhythm are explained by a fluctuating nervous drive. One is tempted to retrieve some properties of the underlying driving signal from the observed series of events. For this a model of the interaction between the supposed underlying signal and the point process is needed. The Integral Pulse Frequency Modulation (IPFM) model appears to be attractive both in describing nervous spike-trains (Bayly, 1968; Bruckstein and Zeevi, 1979) and in the study of heart-rate variability (Hyndman and Mohn, 1975b). We discuss some properties of the IPFM model in section 3 of this chapter and point out the relationship between this model and the various descriptive techniques presented. We state a preference for a descriptive heart-rate variability signal that is in accordance with the IPFM model. The model is also relevant for the continuing discussion regarding **rate** versus **interval** in the description of "heart-rate variability" (Graham, 1978a,b; Heslegrave et al., 1979; Jennings et al., 1981).
In the following we use the terminology and some examples from heart-rate variability studies; in these studies the R-wave of the ECG is usually considered as the event. Our conclusions, however, are equally valid for other physiological event series, such as trains of nerve spikes.

2.3 **Survey of methods for the description of a series of point events**

Figs.1 and 2 illustrate a number of techniques that convert a series of point events (Fig.1a) into a more tractable signal (Figs.1b-e, 2a-d). The ECG data of Fig.1a are from a young adult breathing at a frequency of 0.1 Hz. The R-wave in the ECG was taken as the event of interest. Inspiration and expiration were detected by a nose-thermistor (vertical dashed lines). One notices the large respiratory sinus arrhythmia.
The method of Fig.1b is used most often for converting a series of R-R intervals into a continuously defined signal; the heart-rate value, i.e. the inverse of the interbeat interval, is plotted at the **end** of the interval. This value is used as the heart-rate signal until the next event occurs (zero order hold -- the drawn line in Fig.1b). The signal is easily realized by some analogue or digital device capable of inverting the interval length and holding the value for some time. The signal can be plotted and inspected on line during an experiment. It will be called the **Delayed Heart-Rate** signal (**DHR** signal) in this chapter, because it has a latency of

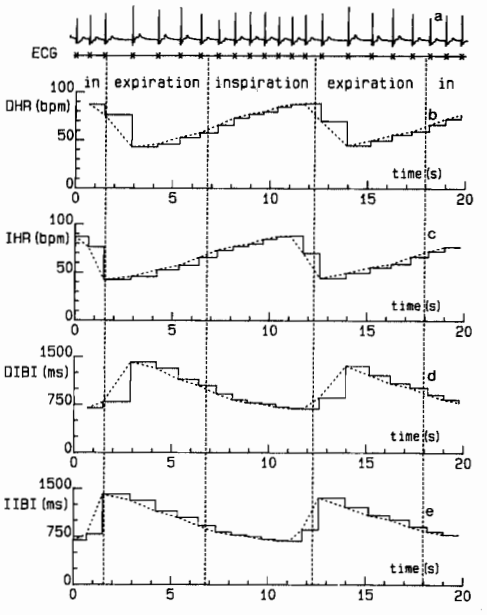


Fig.2-1 Survey of heart-rate variability signals

Fig.2-1a Electrocardiogram (ECG) from a young adult during forced breathing with a frequency of 0.1 Hz, and event series (*) derived from the R-waves in the ECG. The vertical dashed lines separate inspiratory and expiratory periods.

Fig.2-1b (Drawn line:) Standard (Delayed) Heart-Rate signal (DHR signal) derived from the event series in Fig.1a. Its value during an interval equals the inverse of the preceding interval length. The DHR signal is used in most studies on heart-rate variability. The dashed line shows the linear interpolation of the heart-rate values. (bpm=beats per minute)

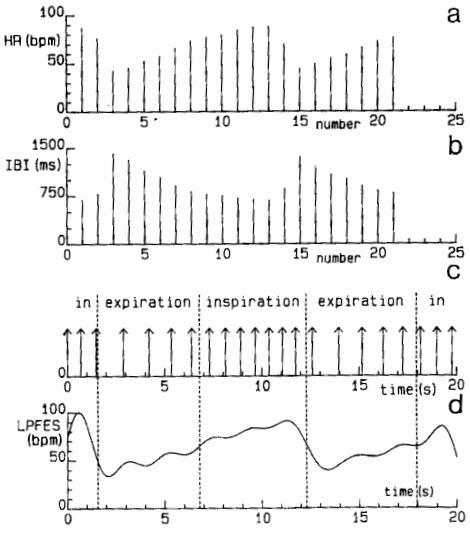
Fig.2-1c (Drawn line:) Instantaneous Heart-Rate signal (IHR signal); the value during an interval equals the inverse of the length of the interval concerned. The dashed line presents the linear interpolation.

Figs.2-1d, 2-1e Similar to Figs.1b,c, but now the interval value is plotted instead of the heart rate (DIBI=Delayed Interbeat Interval, IIBI=Instantaneous Interbeat Interval)

one beat in respect to the length of the interval; a high value of the heart-rate signal implies the preceding interval to be short, but the length of the present interval is unknown. Some delay is inherent to all on-line registration methods, because the length of an interval is obviously only known after its termination. The latency can be diminished by linear interpolation (Fig.1b, dashed line), which, however, cannot be performed on line. Luczak and Laurig (1973) discussed some properties of the signals in Fig.1b.

The method shown in Fig.1c has no latency; the value of the heart rate is plotted from the **start** of the interval concerned. This signal cannot be realized on line. Again the constant interpolation (drawn) and the linear interpolation (dashed) are shown. In this case the linear interpolation leads to a certain amount of prediction: the value during an interval is increasing if the next interval will be longer than the present one. The constant interpolation signal will be called the

Fig.2-2 Survey of heart-rate variability signals (continued from Fig.1).
Fig.2-2a Heart-rate (HR) series; the successive inverse interval lengths are plotted equidistantly, i.e. as a function of the interval number.
Fig.2-2b Interbeat interval (IBI) series: the intervals are plotted as a function of the interval number.
Fig.2-2c Representation of the events (heart beats) as mathematical delta-functions (spikes).
Fig.2-2d Low Pass Filtered Event Series (LPFES), i.e. the signal of Fig.2c passed through an ideal low pass filter with a cut-off frequency of 0.5 Hz.



Instantaneous Heart-Rate signal (IHR signal), because its value during an interval is derived from the length of the interval concerned. A low-pass filtered version of this signal was discussed by Lange and Hartline (1979).
Figs.1b and 1c show the apparent time relationship between the heart-rate signal and respiration to be different for the two representational methods. In Fig.1b the decrease in heart rate seems to coincide with the onset of expiration, but in Fig.1c the decrease starts clearly before this moment.
Instead of the heart rate, one also uses the **interbeat interval (IBI)** as the amplitude of the produced signal. The result is shown in Figs.1d and 1e, where the interval length is plotted at the end (Delayed IBI signal or DIBI) and the beginning (Instantaneous IBI signal or IIBI) of the interval, respectively. As in Figs.1b,c the constant interpolation (drawn) and the linear interpolation (dashed) are shown.

Other techniques that make the event series tractable are presented in Fig.2. In figs.2a and 2b successive heart-rate values (HR) and interval lengths (IBI), respectively, are plotted as a function of interval number instead of as a function of time (**heart-rate series** and **interval series**). Since the values are, by definition, equidistantly spaced, they may be analysed by means of Digital Fourier Transform or similar techniques. However, the latter two representations are not suited to relate an event series (e.g., heart beats) to a continuous signal (e.g., respiration),

because no direct relationship exists between the heart-rate series or interval series and the time. When, however, the event series is to be related to a signal that is also defined beat-to-beat (e.g., systolic blood pressure values), one of the representation methods in figs.2a or 2b can be used (Chapter 5, or De Boer et al., 1983). A different way of transforming the series of events into a continuously defined (but not continuous !) signal is shown in Fig.2c: each event is replaced by a mathematical **delta-function** (spike), so the signal can be described as $p(t)=\sum_k \delta(t-t_k)$, t_k being the time of occurrence of an event. This mathematically well-defined procedure does not create an easily interpretable signal.
Low-pass filtering of the spike-series of Fig.2c produces a continuous signal, the **Low Pass Filtered Event Series** (LPFES, Fig.2d). This signal was recommended as a heart-rate variability signal by Hyndman and Mohn (1975b) and by Rompelman et al. (1977). We calculated the curve in Fig.2d using an ideal low pass filter with cut-off frequency of 0.5 Hz (Hyndman and Mohn, 1975b). This amounts to the replacement of the spike series $\sum_k \delta(t-t_k)$ by $\sum_k \sin(2\pi f_{max}(t-t_k))/(\pi(t-t_k))$, with f_{max}=0.5 Hz. An efficient algorithm for calculating the LPFES was published by French and Holden (1971); see also Peterka et al. (1978) and Chapter 3.A2. The dimension of the LPFES is s^{-1}, or, as indicated in Fig.2d, beats per minute (bpm).

Figs.1 and 2 show that many different possibilities exist for the representation of an event series. The relationship between the input (respiration) and output (the signals derived from the event series) seems rather different for these figures. To make a motivated choice for one of the descriptive signals, models for the genesis of the spike-train have to be considered. In the following section we discuss the relationship between a simple but attractive model and some of the above-mentioned techniques.

2.4 The Integral Pulse Frequency Modulation (IPFM) model

The model we choose for the description of spike generation is the Integral Pulse Frequency Modulation (IPFM) model, also known as the Integrate to Threshold (ITT) model. Fig.3a shows how this model transforms a continuous, positive signal m(t) into a spike-train p(t) in a physiologically plausible way. In the analogy between the model and the cardiac pacemaker, m(t) is linked to the amount of accelerating nervous influence on the pacemaker, and the spiketrain p(t) stands for the series of heart beats.

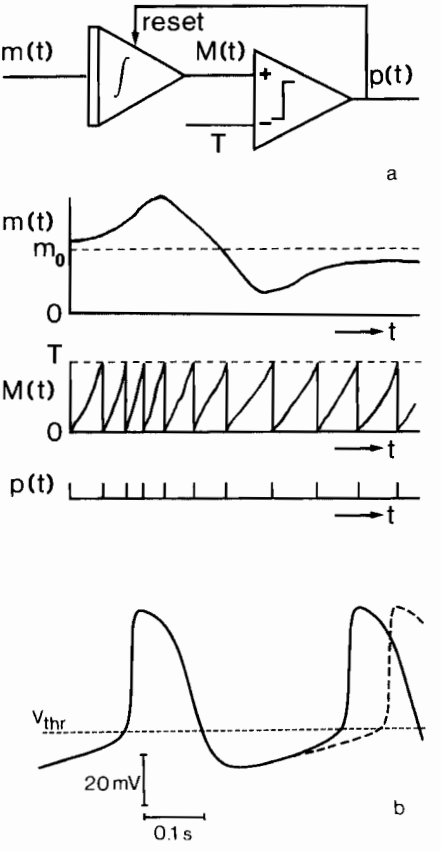


Fig.2-3a Diagram of the Integral Pulse Frequency Modulation model (IPFM model), transforming a continuous signal m(t) (= autonomic nervous influence) into an event series p(t) (= heart beats). The input signal m(t) — consisting of a steady-state value m_0 and a varying contribution $m_1(t)$ — is integrated and when the integrated value M(t) (= membrane potential) exceeds the threshold T, an event occurs and the integrator is reset.

Fig.2-3b Membrane potential $V_m(t)$ (equivalent to M(t) in Fig.3a) of a cardiac pacemaker cell without (drawn) and with (dashed) parasympathetic stimulation. The stimulation causes a diminished rate of rise of the membrane potential towards the threshold V_{thr} (equivalent to T). (Figure redrawn from experimental curves from our laboratory).

The signal $m(t)=m_0+m_1(t)$ is integrated until its integrated value, M(t), exceeds a fixed reference value T (threshold). Then an event occurs and the integrator is reset. Here M(t) resembles the actual membrane potential $V_m(t)$ of a cardiac pacemaker cell. The potential rises steadily towards the threshold V_{thr} and an action potential occurs when the threshold is reached (Fig.3b, drawn line). The rate of rise of $V_m(t)$ is dV_m/dt and has mean value m_0; this so-called rate of diastolic depolarization may change under control of the autonomic nerves.

The neural influence is represented in the model by $m_1(t)$, consisting of a mixture of sympathetic (accelerating) and parasympathetic (decelerating) contributions. A negative value of $m_1(t)$, equivalent to the preponderance of parasympathetic nervous influence, decreases the rate of rise of $V_m(t)$ and causes the interval-length to increase (Fig.3b -- dashed line). On the other hand, a dominant sympathetic influence (= a positive value of $m_1(t)$) increases the rate of rise and advances the next beat.

In this way a modulating signal m(t) leads to an event series p(t); the event series is only uniquely defined if the time of the first event, t_o, is known. Successive event-times t_k are mutually related by the expression $\int_{t_k}^{t_{k+1}} m(t)dt=T$, or $M(t_{k+1})-M(t_k)=T$. If $m_I(t)=0$ for all t, then $m(t)=m_o$, and the series consists of events at a constant spacing equal to T/m_o.

According to the IPFM model, the modulating function m(t) is a measure for the autonomic nervous influence, controlling heart rate. Hence it is attractive to try to reconstruct m(t), or equivalently its integral M(t), from the observed event series. However, m(t) cannot be recovered from the event series in a unique way. This is shown in Fig.4a; here M(t) is presented in a different way (drawn line). The observed event series fixes only the position of the dots in the figure, but any non-decreasing function passing through these dots is an acceptable candidate for M(t); m(t) is then found as the derivative of M(t). One should note that any signal m(t) constructed in the described way, when used as input of the IPFM model, reproduces exactly the event series from which it was derived.

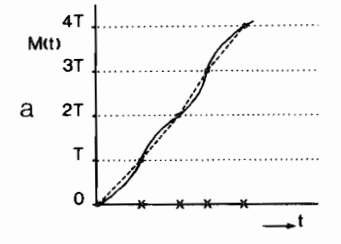


Fig.2-4a In this figure the values of M(t) during successive intervals are stacked above each other (drawn line; cf. Fig.3a). The observed event series fixes only the positions of the dots. The dashed line connecting the dots is a piecewise linear approximation of M(t); this leads to the representation of the event series as shown in Fig.1c (IHR signal).

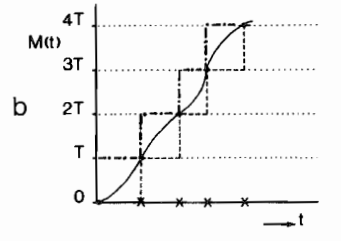


Fig.2-4b Approximation of M(t) by two different step-functions (dashed and dashed-dotted). Both step-functions lead to the representation of Fig.2c (delta-functions).

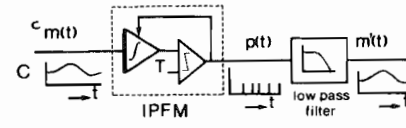


Fig.2-4c Diagram of the transformation of a continous signal m(t) into an event series p(t) by the IPFM model, and back into a continuous signal m'(t) (Low Pass Filtered Event Series or LPFES) by low pass filtering. See text.

A simple way to construct a function M(t) passing through the dots in Fig.4a consists of linear interpolation between successive dots (dashed line); the function m(t)=dM(t)/dt has a constant value between events and is proportional to the IHR function of Fig.1c (drawn line). When the IHR signal is fed into the IPFM model, the output of the integrator reaches threshold at times t_k, due to the equality of all areas under the curve between successive events t_{k-1} and t_k. So the IHR function is consistent with the IPFM model: if used as the input of this model, the original event series appears at the output. Therefore we consider the IHR signal to be an acceptable approximation of the "true" m(t), the autonomic neural influence on the pacemaker.

Another way to reconstruct the function M(t) from an observed event series, is by the use of step-functions as shown in Fig.4b. Both the dashed step-function, which seems to lag behind the true M(t)-signal, and the dashed-dotted line, which seems to lead M(t), produce an identical m(t)-signal consisting of a train of delta-functions, similar to the signal shown in Fig.2c; again, if the latter signal is used as input of the IPFM integrator the series of Fig.1a emerges. Thus a relationship exists between the IPFM model and the representation of an event series as a train of delta-functions.

The Low Pass Filtered Event Series (LPFES, section 2) is also related to the IPFM model. It is known that the LPFES, derived from the output signal from an IPFM model, resembles the input signal $m(t)=m_0+m_1(t)$ if two conditions are met (Bayly, 1968; Coenen et al., 1977; Chapter 4, or DeBoer et al., 1985a). First, $m_1(t)$ must be band-limited (i.e. the amount of modulation may not vary too quickly), and second, $m_1(t)$ must be much smaller than m_0 (i.e. slight modulation and consequently a rather constant heart rate). Under the stated conditions the LPFES, used as input of the IPFM model, will almost exactly reproduce the original spike-train. The operation of converting a continuous signal m(t) into a spike-train p(t) using the IPFM model, followed by low-pass filtering to produce the LPFES m'(t) is illustrated in Fig.4c.

None of the other representations in Figs.1 or 2 is consistent with the IPFM model.

2.5 The Instantaneous Heart Rate (IHR) signal

To illustrate further the adequacy of the IHR signal in retrieving the modulating function m(t), we show in Fig.5 the DHR and the IHR representation of the output

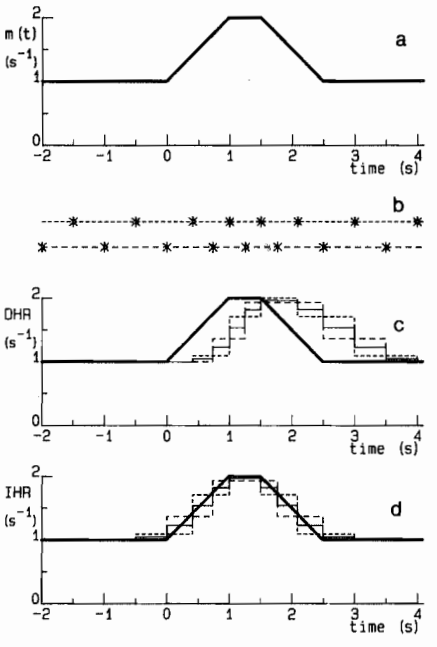


Fig.2-5a Input signal m(t) of an IPFM model with threshold T=1. At time t=0, m(t) is increased temporarily.

Fig.2-5b Two examples of output signals (event series) belonging to the input signal m(t) of Fig.5a. Note that an input signal of an IPFM model may lead to many different event series, depending on the time of occurrence t_o of the first event. Here: t_o=-1.5 s and t_o=-2 s for the upper and lower event series, respectively.

Fig.2-5c Calculated Delayed Heart-Rate (DHR) representation of the two event series of Fig.5b (dashed lines; the line types correspond with the ones in Fig.5b). Drawn line: mean of the two DHR signals. Heavy line: input signal m(t) (as in Fig.5a). Note the asymmetry and the delay in response.

Fig.2-5d Similar as Fig.5c, but now the Instantaneous Heart-Rate (IHR) signals are calculated. The mean IHR signal (drawn) is a fair approximation of the input signal m(t) (heavy line).

signal of an IPFM model. We assume m(t) to be the signal in Fig.5a; at time t=0, m(t) increases for a short period of time. This may be due to an external stimulus, causing a prompt but temporary withdrawal of parasympathetic influence from the pacemaker. Two possible series of events, produced by the signal of Fig.5a, are shown in Fig.5b. Our point is: how well can m(t) be retrieved from these event series ?

The dashed lines in Fig.5c are the two DHR signals, belonging to the event-series of Fig.5b; the drawn line is the mean of the DHR signals. The heavy line is m(t). In a similar way Fig.5d shows the IHR signals (dashed lines) and the mean IHR signal (drawn). The input signal m(t) is well retrieved using the IHR signal, even when averaging only two event series. The DHR signal is noticeably delayed and its shape is different from m(t). Due to the asymmetrical shape of the DHR signal, a mere shift of, say, one second of this signal does not suffice to recover the original shape of m(t).

The change in the IHR signal can slightly precede the change in the input signal m(t) when m(t) changes during an interval (Fig.5d). This is because the IHR signal reflects the shortening or lengthening from the start of the interval concerned. The anticipation is limited to one interval at the most. The DHR signal is always delayed in respect to the change in m(t).
In appendix 2 we give an analysis of the response of the DHR signal, the IHR signal and the LPFES signal to a sudden step in m(t).

Hyndman and Mohn (1975b) included a refractory period in the IPFM model, during which the input signal m(t) has no effect. This amounts to the assumption that in the cardiac pacemaker the autonomic influence arriving during the refractory period does not affect the interval length. However, though the effectiveness of the autonomic influence in shortening or lengthening the interval varies throughout the cardiac cycle, no such insensitive period exists (Brown and Eccles,1934; Levy et al., 1970). Therefore the inclusion of an insensitive period in the IPFM model does not seem to be an improvement.
One is tempted to equate the autonomic influence as represented by $m_1(t)$ in Fig.3a directly with the amount of nerve spike activity along the sympathetic and parasympathetic (vagal) nerves. It should be realized, however, that a delay exists between a change in neural activity and the first cardiac cycle length affected. In the dog the delay is about 0.2 s for vagal and 2 s for sympathetic influence (Warner and Russell, 1969; Levy et al., 1970). Recently similar latencies were described in man (Borst and Karemaker, 1983). Hence the signal $m_1(t)$ is hardly delayed in respect to the vagal influence, which causes the phasic heart rate responses, but is roughly two heart beats late in reproducing the sympathetic influence (tonic response). Especially in the study of fast heart rate responses (within a few seconds after a stimulus), the sympathetic influence can often be neglected and almost no delay will be observed.
Rompelman and coworkers (1977) introduced a modified IPFM model. They considered an interchange of the signals m(t) and T in the model of Fig.3a; this leads to a model exhibiting a constant rate of integration 1/T towards a varying threshold m(t). When the signal of Fig.1e (Instantaneous Interbeat Interval, IIBI) is used as input signal m(t) for this model, the event series of Fig.1a is reproduced once again. Thus the interval function is consistent with the modified IPFM model. However, cardiac pacemaker cells (and also nerve cells) are known to have rather

constant thresholds (Fig.3b). Therefore variations of interval length are more likely due to a fluctuating rate of rise of the membrane potential (IPFM model) than to a varying threshold (modified IPFM model). Consequently, we prefer the IHR signal to the IIBI signal.
The common use of heart rate rather than interval in clinical practice as well as by most authors of heart-rate variability studies seems indeed justified. However, to comply fully with the IPFM model, the heart-rate value should be plotted from the beginning of the interval (IHR) rather than from the end (DHR) as is usually done.

2.6 Discussion

In this chapter we compared a number of techniques that convert a series of heart beats, considered as an event series, into a more tractable signal. We concentrated on techniques that are simple in concept and that lead to signals which are easily obtained from the event series. When a purely descriptive approach is used, many possibilities exist (Figs.1 and 2). However, we recommend the use of a representation that is related to a physiologically plausible model for the genesis of event series.

The analogy between the cardiac pacemaker and the Integral Pulse Frequency Modulation (IPFM) model (Fig.3) should be discussed. The IPFM model transforms a continuous input signal (autonomic neural influence on the pacemaker) into a series of events (heart beats). In many cases this input signal (the autonomic influence) will be the parameter of interest. Therefore we examined which of the heart-rate variability signals shown in Figs.1 and 2 are consistent with the IPFM model and hence are to be preferred for the description of heart-rate variability. (In appendix 1 some further comments are made on the use of the IPFM model for the description of heart-rate variability.)
Only three of the signals in Figs.1 and 2 reproduce the original event series if they are used as input of the IPFM model. Hence only these three signals can be considered as approximations of the neural autonomic influence, governing the heart rate.
The representation of spikes as **mathematical delta-functions** (Fig.2c) is in accordance with the IPFM model, but is for many purposes as awkward as the original spike train and is visually not attractive. However, when a more elaborate analysis

of the heart-rate data is performed, these disadvantages need not be important any more. Indeed, this representation is appropriate for the use of spectral analysis methods (Chapters 3 and 4, or DeBoer et al., 1984, 1985a).

The **Low Pass Filtered Event Series** (LPFES, Fig.2d) is largely consistent with the IPFM model (see Fig.4c). The LPFES seems an attractive approximation of the autonomic influence because it is a smooth function of time. However, it has two important drawbacks: it is not easily computed from the event-series signal, and the non-causal filtering procedure implies that the effect (e.g., a rise in heart rate) may seem to precede its cause (a stimulus) by a large amount, especially if the rise is fast (see appendix 2).

The **Instantaneous Heart-Rate (IHR) signal** (Fig.1c, drawn line) is a step-like signal of which the value between two beats is equal to the inverse length of the inter-beat interval. This signal is consistent with the IPFM model and may hence be used as an approximation of the neural influence on the cardiac pacemaker. For the standard Delayed Heart-Rate (DHR) signal the rate value is plotted **after** the completion of the interval, but for the IHR signal it is plotted **during** the interval concerned. The signal can easily be obtained from an event series (though not on line). The IHR signal, being defined at each moment, is accessible for all signal analysis methods (e.g., averaging, see Fig.5d). This is an advantage compared with descriptive methods in which a heart-rate value is only defined once per second or once per beat (Graham, 1978b). If, for special purposes, one heart-rate value per second must be found, we suggest the use of the mean IHR value over this period. This is equivalent to the rate in beats/sec as advocated by Graham (1978b) If one needs to average phasic heart-rate responses to repeated stimuli such as standing up or respiration, ensemble averaging of the IHR signals is, thanks to the IHR's link with the IPFM model, better justified than averaging the standard (delayed) heart-rate signals or the interval series. Likewise, the time-averaged IHR signal is the most logical choice when a descriptor of the mean heart rate over a period is needed. It is easy to see that the time-averaged IHR signal is simply the number of beats in the considered period, thus agreeing with the usual measure of "beats per minute".

A final, practical advantage of the IHR signal over the DHR signal is in the representation of trigger-artefacts or extrasystoles (occurring even in healthy persons). This point is illustrated by the example of Fig.6. The ECG in Fig.6a shows a ven-

tricular extrasystole, followed by a compensatory pause; this amounts to a shortened interval, followed by a lengthened one. The DHR signal and the IHR signal derived from this ECG are shown in Figs.6b and 6c, respectively.
The DHR signal is rather unattractive because the high heart-rate value, due to the premature beat, lasts during the whole prolonged post-extrasystolic period. The IHR signal is the more logical choice, because the raised heart-rate value lasts only during the short interval and is easily discerned as an artefact.

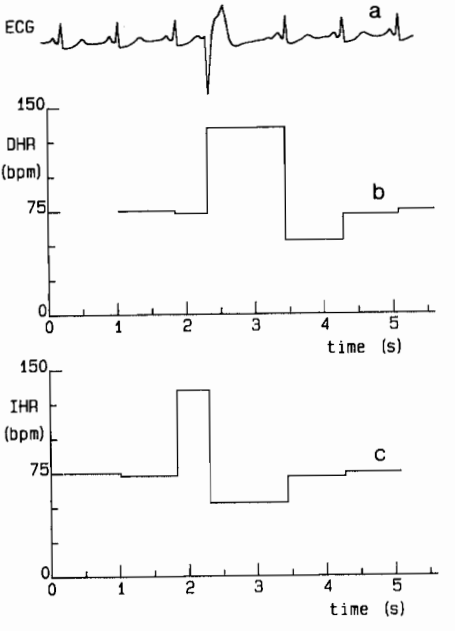


Fig.2-6a ECG with an isolated ventricular extrasystole.
Fig.2-6b DHR signal, derived from the ECG in Fig.6a. Note the excessive importance attributed to the high heart-rate value caused by the short-lasting interval before the extrasystole.
Fig.2-6c IHR signal. In this representation the importance of the shortened interval is reduced to proper proportions.

A number of potential objections to the use of the IHR signal are pertinent to point out. First, it is not possible to obtain the IHR signal on line during an experiment since there will always be a short delay (one beat). This, however, is of little importance when experiments are recorded on tape and analysed afterwards, or when a computer is used. Next, the signal is discontinuous at the moments of occurrence of an event and seems therefore less attractive as an approximation of the hidden modulating signal m(t). The discontinuities are a consequence of the fundamentally discontinuous event-series signal under consideration and cannot easily be overcome. The linearly interpolated signals in Figs.1b-e (dashed lines) are continuous, but not in accordance with the IPFM model. Low pass filtering of the IHR signal or the delta-train (LPFES, Fig.2d) will remove the discontinuities but is computationally complex. Another apparent drawback of the IHR signal is that a

change in the IHR signal can slightly precede its cause (e.g. a stimulus; see Fig.5d and Fig.A1d). Again, this is a property of the event series signal, which is defined only at the instants an event occurs.

All points considered, the IHR signal seems to us the most appropriate signal for the time-domain description of heart-rate vaiability data. The signal is consistent with the IPFM model, and if one accepts this model as a valid description of the cardiac pacemaker, the IHR signal can thus be considered as an approximation of the autonomic influence on the pacemaker. The IHR signal, having no delay in respect to the original event series, is especially useful in establishing correct timing relationships between the event series and other signals. In addition, the signal is easily obtained from the experimental data.

2.A1 Appendix 1: A few additional remarks concerning the applicability of the IPFM model and the IHR signal for the time-domain description of heart-rate variability

a. In the IPFM model, variations in heart rate are due only to variations in the rate of diastolic depolarization. However, other physiological causes for a varying R-R interval include changes of the length of the action potential, of the atrio-ventricular conduction time (P-R interval), of the threshold value of the excitable cells, and of the value of the maximal diastolic potential.

b. The sensitivity of the cardiac pacemaker for neural -- and especially vagal -- information varies throughout the cardiac cycle, but is constant in the IPFM model. Also, the effect of a vagal volley on second and subsequent beats is nil in the IPFM model. However, both in the cat (Brown and Eccles, 1934) and in the rabbit (Karemaker, 1980), the vagal effect lasts for several beats (but the length of these beats is much shorter than in man).

c. It may seem somewhat bizarre that a continuously defined signal is sought to resemble the elusive signal m(t), which in the body consists of a spike-train along the sympathetic, accelerating nerves, together with a counteracting spike-train along the vagal, decelerating nerves. However, continuous signals are conceptually easier, and we first of all wanted to present a conceptually attractive description of heart rate variability.

d. A simple argument exists to prove that neither IHR signal nor LPFES signal lead or lag in comparison with the original spike-train: if the direction of time is reversed, both signals do not change.

e. Finally: a difference between DHR signal and IHR signal, and hence a preference for the IHR signal, exists only if one is interested in short-term heart-rate variability. If the time-scale is in tens of seconds or in minutes, the distinction between DHR and IHR becomes irrelevant.

2.A2 Appendix 2: Response of the DHR signal, the IHR signal and the LPFES signal to a sudden step in m(t)

We show the response of the various heart-rate variability signals to a sudden increase (Fig.A1a, drawn line) or decrease (dashed line) of the input signal m(t) of an IPFM model by 50%. (It should be realized that the IPFM-model, not being a linear system, is not fully characterized by its response to a step input.) The change of the input signal is taken at the time t=0. Examples of event series generated by these input signals are shown in Fig.A1b.

Fig.A1c shows the calculated standard (Delayed) Heart Rate signal (DHR signal) and Fig.A1d the calculated Instantaneous Heart Rate signal (IHR signal). As both the IHR signal and the DHR signal depend on the moment of increase or decrease of the input signal within the interval, three lines are presented in each case. The heavy lines present the mean DHR value (Fig.A1c) and the mean IHR value

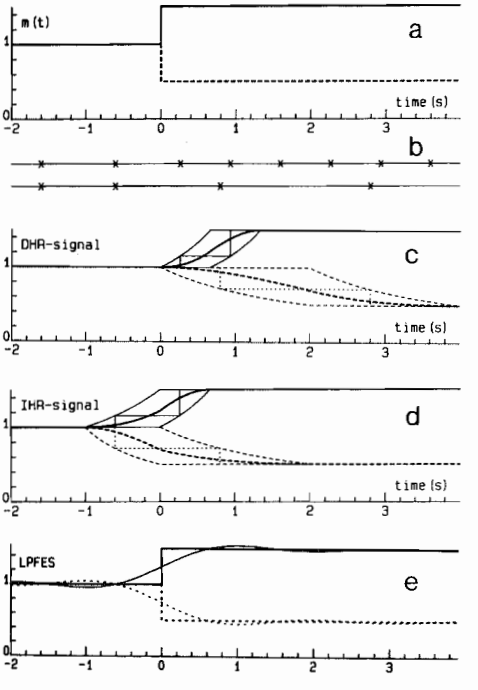


Fig.2-A1a Input signal m(t) of an IPFM-model with threshold T=1. At time t=0, m(t) is suddenly increased (drawn line) or decreased (dashed line) by 50%.

Fig.2-A1b Examples of output signals (event series) belonging to the input signal m(t) of Fig.A1a. The upper one is for an increasing, the lower one for a decreasing input signal.

Fig.2-A1c Calculated Delayed Heart Rate (DHR) representation of event series belonging to the increased (drawn line) and decreased (dashed line) input signal of Fig.A1a. Heavy lines: mean DHR signal, i.e. the ensemble average of many responses to a step change in m(t).

Fig.2-A1d Similar as Fig.A1c, but now the Instantaneous Heart Rate signal (IHR signal) is calculated. The timing of the response corresponds with the input signal.

Fig.2-A1e Average response of the LPFES signal (light lines) to a sudden positive or negative step of m(t) (heavy lines).

(Fig.A1d) which result when many heart rate responses to a sudden change in the modulating signal are averaged. It is assumed that the jump in m(t) occurs with equal probability throughout the interval. The lighter lines in Figs.A1c,d represent the range of single responses to the jump in m(t). In addition, the DHR signal and the IHR signal as obtained from the event series of Fig.A1b are shown (step-functions). The mathematical formulae used in the calculation of the curves in Figs.A1c,d are given in section 2.A2.1.

The change in the IHR signal (Fig.A1d) can slightly precede the change in the input signal m(t). This happens if during an interval a stimulus is given which immediately shortens the interval. The IHR signal reflects this shortening from the start of the interval concerned. The DHR signal is always delayed in respect to the change in m(t).

From Fig.A1 it is clear that the original modulating signal m(t) cannot be retrieved by simple averaging of the IHR or DHR signals. However, for less abrupt changes of m(t) than shown in Fig.A1 the IHR signal approximates the input signal more faithfully (cf. fig.5).

The averaged step response of the LPFES signal is the low pass filtered step itself, which for f_{max}=0.5 Hz is:

$$\overline{\text{LPFES}}(t) = 1 \pm (1/4 + (1/2\pi) \int_0^t (\sin(\varphi)/\varphi)\, d\varphi ,$$

with the sign corresponding with the sign of the step. This function is shown in fig.A1e; the drawn and the dashed heavy lines represent m(t) for a positive and a negative step, respectively, and the light lines are the average LPFES-signals. The response is symmetrical around t=0 s. It differs appreciably from the step from t=-1.5 s till t=1.5 s, which is a drawback for the use of the LPFES signal in the time-domain description of heart-rate variability.

2.A2.1 Derivation of expressions for the IHR signal and the DHR signal, when the input signal is suddenly changed

a. The IHR signal

Without loss of generality we set the threshold T of the IPFM-model equal to 1. In addition we take m(t)=1 for t<0 and m(t)=a for t>0; thus a=1.5 and a=0.5 correspond to the two cases shown in Figs.A1. Our notation is illustrated in Fig.A2a. Let t_o be the start of the first interval affected by the change of m(t) ($-1<t_o<0$) and let t_1 be the end of it ($0<t_1<1/a$). The values t_o and t_1 are connected by the defining equation of the IPFM-model: $\int_{t_o}^{t_1} m(t)dt=1$, or $-t_o+at_1=1$. The Instantaneous Heart Rate signal -- thin line in Fig.A2a -- is a function of both the time t and t_o:

$IHR(t,t_o) = 1$ for $t < t_o$

$IHR(t,t_o) = 1/(t_1-t_o) = a/(1-t_o(a-1))$ for $t_o < t < t_1=(t_o+1)/a$

$IHR(t,t_o) = a$ for $t > t_1$

The extremes of this function for a fixed value of t are for $-1<t<0$: 1 if $t_o>t$, and $a/(1-t(a-1))$ if $t_o=t$. For $0<t<1/a$ the extremes are: $1/(1-t(a-1))$ if $t_1=t$, and a if $t_1<t$. These minimum and maximum values are shown in Fig.A1d (thin lines).

If t_o is assumed to be uniformly distributed between -1 and 0, the mean value (ensemble average) $\overline{IHR}(t)$ becomes:

For $-1 < t < 0$:

$$\overline{IHR}(t) = \int_{-1}^{0} IHR(t,t_o)dt_o = \int_{-1}^{t} a/(1-t_o(a-1))dt_o + \int_{t}^{0} dt_o =$$
$$= -t + (a/(a-1)).\ \log(a)-\log(1-t(a-1)).$$

For $0 < t < 1/a$:

$$\overline{IHR}(t) = \int_{-1}^{at-1} a.dt_o + \int_{at-1}^{0} a/(1-t_o(a-1))dt_o = a^2t-(a/(a-1)).\log(a-at(a-1))$$

For $t<-1$ and $t>1/a$, $\overline{IHR}(t)$ is equal to 1 and a, respectively. The value of $\overline{IHR}(t)$ is shown in Fig.A1d for a=1.5 (drawn heavy line) and for a=0.5 (dashed heavy line).

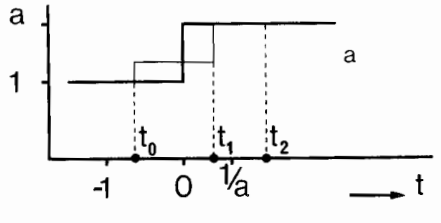


Fig.2-A2a Drawing of m(t) (heavy line) and of an exemplary IHR signal to explain in the notation as used in this Appendix. The value of m(t) jumps from 1 to a at time t=0. t_o is the start of the first interval affected by the change in m(t). t_1 is the end of this interval, t_2 of the next one.

b. **The DHR signal**

In the derivation of similar formulae for the Delayed Heart Rate signal two successive intervals must be considered (see Fig.A2b). t_0 and t_1 are defined as in the preceding, but now the time t_2 (end of the interval starting at t_1) comes also into play ($1/a < t_2 < 2/a$). The DHR signal reflects the change in heartrate from the time t_1. Relationships between the points of time t_0, t_1 and t_2 are $-t_0+at_1=1$ and $t_2=t_1+1/a$. The DHR signal -- thin line in Fig.A2b) -- is a function of t and t_0:

$$DHR(t,t_0) = 1 \qquad \text{for } t < t_1$$

$$DHR(t,t_0) = 1/(t_1-t_0) = a/(1-t_0(a-1)) \qquad \text{for } t_1 < t < t_2$$

$$DHR(t,t_0) = a \qquad \text{for } t > t_2$$

Extremes of the DHR function -- thin lines in Fig.A1c -- for a fixed value of t are for $0<t<1/a$: 1 if $t_1>t$, and $1/(1-t(a-1))$ if $t_1=t$. For $1/a<t<2/a$ the extremes are: $1/(1-(t-1/a)(a-1))$ if $t_2=t$, and a if $t_2<t$. The extreme values are shown in Fig.A1c (thin lines).

The mean value $\overline{DHR}(t)$ is:

For $0 < t < 1/a$:

$$\overline{DHR}(t) = \int_{-1}^{0} DHR(t,t_0)dt_0 = \int_{-1}^{at-1} a/(1-t_0(a-1))dt_0 + \int_{at-1}^{0} dt_0 =$$

$$= 1-at - (a/(a-1))\log(1-t(a-1))$$

For $1/a < t < 2/a$:

$$\overline{DHR}(t) = \int_{-1}^{at-2} a\,dt_0 + \int_{at-2}^{0} a/(1-t_0(a-1))dt_0 = at^2-a + (a/(a-1))\log(1-(at-2)(a-1))$$

For $t<0$ and $t>1/a$ $\overline{DHR}(t)$ is equal to 1 and a, respectively. $\overline{DHR}(t)$ is shown in Fig.A1c for a=1.5 (drawn heavy line) and a=0.5 (dashed heavy line).

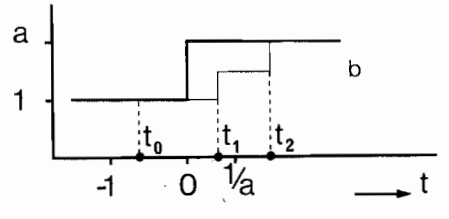


Fig.2-A2b Drawing of m(t) (heavy line) and of an exemplary DHR signal. The DHR signal changes at $t=t_1$, and it has a constant value 1/a from $t=t_2$.