CHAPTER 2

ANALYSIS OF CONCURRENT, COUPLED, AND CORRELATED PROCESSES

The human body is a complex integration of a number of biological systems with several ongoing physiological, functional, and possibly pathological processes. Most biological processes within a body are not independent of one another; rather, they are mutually correlated and bound together by physical or physiological control and communication phenomena. Analyzing any single process without due attention to others that are concurrent, coupled, or correlated with the process may provide only partial information and pose difficulties in the comprehension of the process. Then, the problem is, how do we recognize the existence of concurrent, coupled, and correlated phenomena? How do we obtain the corresponding signals and identify the correlated features? Unfortunately, there is no simple or universal solution or rule to apply to this problem.

Ideally, an investigator should explore the system or process of interest from all possible angles and use multidisciplinary approaches to identify several potential sources of information. The signals so obtained may be electrical, mechanical, biochemical, or physical, among the many possibilities, and may exhibit interrelationships confounded by peculiarities of transduction, time delays, multipath transmission or reflection, waveform distortions, and filtering effects that may need to be accounted for in their simultaneous analysis. Events or waves in signals of interest

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may be nonspecific and difficult to identify and analyze. How could we exploit the concurrency, coupling, and correlation present between processes or related signals to gain better understanding of the system or systems of interest?

2.1 Problem Statement

Determine the correspondences, correlation, and interrelationships present between concurrent signals related to a common underlying physiological system or process, and identify their potential applications.

The statement above represents, of necessity at this stage of the discussion, a vague and generic problem. The case studies and applications presented in the following sections provide a few illustrative examples dealing with specific systems and problems. Signal processing techniques for the various tasks identified in the case studies are developed in the chapters that follow. Note that the examples cover a diverse range of systems, processes, and signals. The specific problem of your interest will very likely not be directly related to any of the case studies presented here. It is expected that a study of the examples provided will expand the scope of your analytical skills and lead to improved solutions for your specific case.

2.2 Illustration of the Problem with Case Studies

2.2.1 The ECG and the PCG

A clinical ECG record typically includes 12 channels of sequentially or simultaneously recorded signals, and can be used on its own to diagnose many cardiac diseases. This is mainly due to (a) the simple and readily identifiable waveforms in the ECG, and the innumerable studies that have firmly established clinical ECG as a standard procedure. The PCG, on the other hand, is a more complex signal. PCG waveforms cannot be visually analyzed except for the identification of gross features such as the presence of murmurs, time delays as in a split S2, and envelopes of murmurs. An advantage with the PCG is that it may be listened to; auscultation of heart sounds is more commonly performed than visual analysis of the PCG signal. However, objective analysis of the PCG requires the identification of components, such as S1 and S2, and subsequent analysis tailored to the nature of the components.

Given a run of a PCG signal over several cardiac cycles, visual identification of S1 and S2 is possible if there are no murmurs between the sounds, and if the heart rate is low such that the S2 – S1 (of the next beat) interval is longer than the S1 – S2 interval (as expected in normal situations). At high heart rates and with the presence of murmurs or premature beats, identification of S1 and S2 could be difficult.

Problem: *Identify the beginning of S1 in a PCG signal and extract the heart sound signal over one cardiac cycle.*

Solution: The ECG and PCG are concurrent phenomena, with the noticeable difference that the former is electrical while the latter is mechanical (sound or vibra-

tion). It is customary to record the ECG with the PCG; see Figures 1.42 and 1.44 for examples.

The QRS wave in the ECG is directly related to ventricular contraction, as the summation of the action potentials of ventricular muscle cells (see Section 1.2.5). As the ventricles contract, the tension in the chordae tendineae and the pressure of retrograde flow of blood toward the atria seal the AV valves shut, thereby causing the initial vibrations of S1 [33] (see Section 1.2.9). Thus, S1 begins immediately after the QRS complex. Given the nonspecific nature of vibration signals and the various possibilities in the transmission of the heart sounds to the recording site on the chest, detection of S1 on its own is a difficult problem.

As shown in Sections 3.5.1, 4.3.1, and 4.3.2, detection of the QRS is fairly easy, given that the QRS is the sharpest wave in the ECG over a cardiac cycle; in fact, the P and T waves may be almost negligible in many ECG records. Thus, the QRS complex in the ECG is a reliable indicator of the beginning of S1 and may be used to segment a PCG record into individual cardiac cycles: from the beginning of one QRS (and thereby S1) to the beginning of the next QRS and S1. This method may be applied visually or via signal processing techniques: The former requires no further explanation but is expanded upon in Section 2.3; the latter is dealt with in Section 4.10.

2.2.2 The PCG and the carotid pulse

Identification of the diastolic segment of the PCG may be required in some applications in cardiovascular diagnosis [130]. Ventricular systole ends with the closure of the aortic and pulmonary valves, indicated by the aortic (A2) and pulmonary (P2) components of S2 (see Section 1.2.9). The end of contraction is also indicated by the T wave in the ECG, and S2 appears slightly after the end of the T wave (see Figure 1.42). S2 may be taken to be the end of systole and the beginning of ventricular relaxation or diastole. (*Note:* Shaver et al. [74] and Reddy et al. [75] have included S2 in the part of their article on systolic sounds.) However, as in the case of S1, S2 is also a nonspecific vibrational wave that cannot be readily identified (even visually), especially when murmurs are present.

Given the temporal relationship between the T wave and S2, it may appear that the former may be used to identify the latter. This, however, may not always be possible in practice, as the T wave is often a low-amplitude and smooth wave and is sometimes not recorded at all (see the normal beats in Figure 1.27). ST segment elevation (as in Figure 1.27) or depression (as in Figure 1.46) may make even visual identification of the T wave difficult. Thus, the T wave is not a reliable indicator to use for identification of S2.

Problem: *Identify the beginning of S2 in a PCG signal.*

Solution: Given the inadequacy of the T wave as an indicator of diastole, we need to explore other possible sources of information. Closure of the aortic valve is accompanied by deceleration and reversal of blood flow in the aorta. This causes a sudden drop in the pressure within the aorta, which is already on a downward slope due to the end of systolic activity. The sudden change in pressure causes an *incisura*

or notch in the aortic pressure wave (see Figures 1.45 and 1.46). The aortic pressure signal may be obtained using catheter-tip sensors [74, 75], but the procedure would be invasive. Fortunately, the notch is transmitted through the arterial system and may be observed in the carotid pulse (see Section 1.2.10) recorded at the neck.

The dicrotic notch (D) in the carotid pulse signal bears a delay with respect to the corresponding notch in the aortic pressure signal, but has the advantage of being accessible in a noninvasive manner. (Similar events occur in the pulmonary artery, but provide no externally observable effects.) See Figures 1.42 and 1.44 for examples of three-channel PCG – ECG – carotid pulse recordings that illustrate the D – S2 – T relationships. The dicrotic notch may be used as a reliable indicator of the end of systole or beginning of diastole that may be obtained in a noninvasive manner. The average S2 – D delay has been found to be $42.6\ ms$ with a standard deviation (SD) of $5\ ms$ [131] (see also Tavel [72]), which should be subtracted from the dicrotic notch position to obtain the beginning of S2.

Signal processing techniques for the detection of the dicrotic notch and segmentation of the PCG are described in Sections 4.3.3, 4.10, and 4.11.

2.2.3 The ECG and the atrial electrogram

Most studies on the ECG and the PCG pay more attention to ventricular activity than to atrial activity — and, even then, more to left ventricular activity than to the right. Rhythm analysis is commonly performed using QRS complexes to obtain interbeat intervals known as RR intervals. Such analysis neglects atrial activity.

Recollect that the AV node introduces a delay between atrial contraction initiated by the SA node impulse and the consequent ventricular contraction. This delay plays a major role in the coordinated contraction of the atria and the ventricles. Certain pathological conditions may disrupt this coordination and may even cause AV dissociation [33]. It then becomes necessary to study atrial activity independent of ventricular activity and establish their association, or lack thereof. Thus, the interval between the P wave and the QRS (termed the PR interval) would be a valuable adjunct to the RR interval in rhythm analysis. Unfortunately, the atria, being relatively small chambers with weak contractile activity, cause a small and smooth P wave in the external ECG. Quite often, the P wave may not be recorded or seen in the external ECG; see, for example, leads I and V3 – V6 in Figure 1.34.

Problem: *Obtain an indicator of atrial contraction to measure the PR interval.*

Solution: One of the reasons for the lack of specificity of the P wave is the effect of transmission from the atria to the external recording sites. An obvious solution would be to insert electrodes into one of the atria via a catheter and record the signal at the source. This would, of course, constitute an invasive procedure. Jenkins et al. [132, 133] and Jenkins [51, 52] proposed a unique and interesting procedure to obtain a strong and clear signal of atrial activity: they developed a pill electrode that could be swallowed and lowered through the esophagus to a position close to the left atrium (the bipolar electrode pill being held suspended by wires about $35\ cm$ from the lips). The procedure may or may not be termed invasive, although an object is inserted into the body (and removed after the procedure), as the action required

is that of normal swallowing of a tablet-like object. The gain required to obtain a good atrial signal was $2-5$ times that used in ECG amplifiers. With a $5-100\ Hz$ bandpass filter, Jenkins et al. obtained an SNR of 10.

Figure 2.1 shows recordings from a normal subject of the atrial electrogram from the pill electrode and an external ECG lead. Atrial contraction is clearly indicated by a sharp spike in the atrial electrogram. Measurement of the PR interval (or the AR interval, as called by Jenkins et al.) now becomes an easy task, with identification of the spike in the atrial electrogram (the "A" wave, as labeled by Jenkins et al.) being easier than identification of the QRS in the ECG.

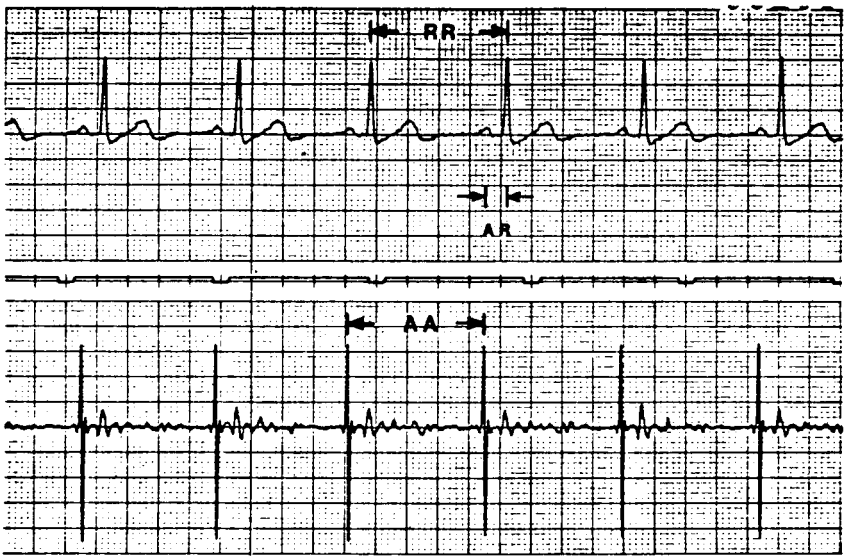

Figure 2.1 Pill-electrode recording of the atrial electrogram (lower tracing) and the external ECG (upper tracing) of a normal subject. The pulse train between the two signals indicates intervals of 1 s. Reproduced with permission from J.M. Jenkins, D. Wu, and R. Arzbaecher, Computer diagnosis of abnormal cardiac rhythms employing a new P-wave detector for interval measurement, *Computers and Biomedical Research*, 11:17–33, 1978. ©Academic Press.

Figure 2.2 shows the atrial electrogram and external ECG of a subject with ectopic beats. The PVCs have no immediately preceding atrial activity. The first PVC has blocked the conduction of the atrial activity occurring immediately after, resulting in a compensatory pause before the following normal beat. The second PVC has not blocked the subsequent atrial wave, but has caused a longer-than-normal AV delay and an aberrant conduction path, which explains the different waveshape of the consequent beat. The third PVC has not affected the timing of the following SA-node-initiated pulse, but has caused a change in waveshape in the resulting QRS-T by altering the conduction path [51, 52, 132, 133].

Jenkins et al. developed a four-digit code for each beat, as illustrated in Figure 2.2. The first digit was coded as

0: abnormal waveshape or
1: normal waveshape,
as determined by a correlation coefficient computed between the beat being processed and a normal template (see Sections 3.5.1, 4.4.2, 5.4.1, and 5.8). The remaining three digits encoded the nature of the RR, AR, and AA intervals, respectively, as
0: short,
1: normal, or
2: long.
The absence of a preceding A wave related to the beat being analyzed was indicated by the code $\times$ in the fourth digit (in which case the AR interval is longer than the RR interval). Figure 2.2 shows the code for each beat. Based upon the code for each beat, Jenkins et al. were able to develop a computerized method to detect a wide variety of arrhythmia.

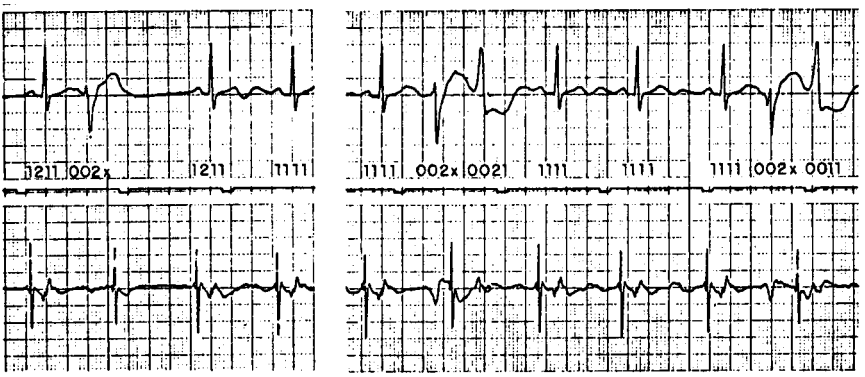

Figure 2.2 Atrial electrogram (lower tracing) and the external ECG (upper tracing) of a subject with ectopic beats. The pulse train between the two signals indicates intervals of 1 s. Reproduced with permission from J.M. Jenkins, D. Wu, and R. Arzbaecher, Computer diagnosis of abnormal cardiac rhythms employing a new P-wave detector for interval measurement, *Computers and Biomedical Research*, 11:17–33, 1978. ©Academic Press.

2.2.4 Cardiorespiratory interaction

The heart rate is affected by normal breathing due to the coupling and interaction existing between the cardiac and respiratory systems [134–139]. Figure 2.3 shows two recordings of the ECG of a normal subject taken a few minutes apart, the first with the subject breathing normally and the second with the subject holding his breath. Baroreceptors in the aorta detect changes in the aortic transmural pressure associated with variations in the intrapleural pressure with respiration. A decrease in the intrapleural pressure during inspiration causes the vagus nerve activity to be impeded, which causes an increase in the heart rate during inspiration. Therefore, as

a subject carries on breathing normally, there could be substantial variations in the heart rate and RR intervals.

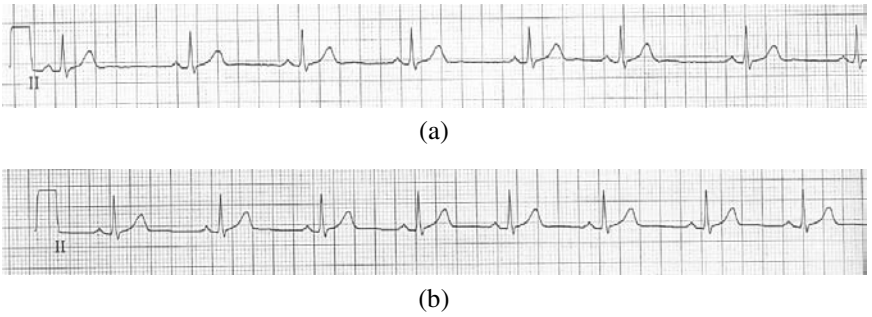

Figure 2.3 ECG signal of a subject (a) with the subject breathing normally, and (b) with the subject holding breath. Signal courtesy of E. Gedamu and L.B. Mitchell, Foothills Hospital, Calgary.

Breathing also affects the transmission of the heart sounds from the cardiac chambers to the chest surface. Durand et al. [140] recorded intracardiac and chest-surface PCG signals and derived the dynamic transfer function of the heart – thorax acoustic system in dogs. Analysis of the synchronization and coupling within the cardiorespiratory system could require sophisticated analysis of several signals acquired simultaneously from the cardiac and respiratory systems [141]. A few techniques for the analysis of heart-rate variability (HRV) based upon RR interval data are described in Sections 7.2.2, 7.8, and 8.11.

2.2.5 The importance of HRV

Even under resting and apparently steady conditions, the intervals between heart beats and the heart rate are not constant. Variability of the RR interval and heart rate is a normal and healthy physiological phenomenon. Reduced HRV in patients following acute myocardial infarction has been observed to be related to poor prognosis [142,143]. Malik and Camm [142] noted that HRV is the single most important predictor of patients at high risk of sudden death and ventricular arrhythmia.

As noted in Section 1.2.5, cardiac rhythm is controlled by the ANS. Section 2.2.4 presented a discussion on the effects of normal breathing on the heart rate due to the coupling and interaction between the cardiac and respiratory systems. The ANS is divided into the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS). The SNS and PNS do not work in opposition to one another, but interact in a complex and dynamic manner, with the interactions modulated by secondary messengers [144]. The PNS can inhibit sympathetic nerve activity, and sympathetic activation can inhibit parasympathetic activation [144]. Vagal tone or tonic parasympathetic activation is stronger than the sympathetic tone at rest. The parasympathetic

influence on the heart rate is mediated by the release of acetylcholine by the vagus nerve; sympathetic stimulation is mediated by the release of epinephrine. HRV has been noted as a noninvasive signature of the interaction and balance between the effects of the PNS and SNS on the heart [145]; see Kamath et al. [146] for a recent compilation of several works on this topic.

Olshansky et al. [144] studied the role of the PNS in heart failure and made the following observations. The resting rate of a normal heart is governed by a parasympathetic mechanism. The resting heart rate, which is an indicator of vagus nerve function, can predict mortality. Increase in the parasympathetic component of HRV and higher vagus nerve activity result in slower heart rate and better outcome in terms of cardiac health. In cases of heart failure, the regulation of heart rate by parasympathetic activation is poor. High resting heart rate typically leads to adverse outcomes. They also noted that the high-frequency components of HRV are associated with the vagus nerve and the parasympathetic effect, that the low-frequency components are due to sympathetic and parasympathetic activation, and, furthermore, that parasympathetic activation and its physiological effects are attenuated in cases of heart failure. Olshansky et al. observed that the electrophysiological benefits of parasympathetic activation include antiinflammatory effects, reduced heart rate, increased HRV, and direct antiarrhythmic effects. Whereas high levels of sympathetic activity are associated with poor prognosis, a high level of parasympathetic activation could provide protection. Based on these observations, Olshansky et al. indicated that direct or indirect vagus nerve stimulation could have beneficial effects on clinical outcomes.

See Malik et al. [147] for recommendations on measurement, physiological interpretation, and clinical use of HRV. See Sections 7.2.2, 7.8, and 8.11 for discussions on methods for the analysis of HRV.

2.2.6 The EMG and VMG

The EMG signal has been studied extensively and the relationship between EMG signal parameters and muscle contraction level has been established [30, 37]. It is known that the root mean-squared (RMS) and mean frequency values of the EMG increase with increasing muscle contraction until fatigue sets in, at which point both values begin to decrease. In this situation, while the muscle output measured is mechanical contraction (using force or strain transducers), the signal analyzed is electrical in character. A direct mechanical signal related to basic muscle-fiber or motor-unit phenomena may be desired in some situations.

Problem: *Obtain a mechanical signal that is a direct indicator of muscle-fiber or motor-unit activity to study muscle contraction and force development.*

Solution: The VMG, as introduced in Section 1.2.13, is a vibration signal measured from a contracting muscle. The signal is a direct manifestation of the contraction of muscle fibers and, as such, represents mechanical activity at the muscle-fiber or motor-unit level. The VMG is the mechanical counterpart and contemporary of the EMG. Although no direct relationship has been established between the force outputs of individual motor units and the net force output of the muscle, it has been

shown that the RMS and mean frequency parameters of the VMG signal increase with muscle force output, in patterns that parallel those of the EMG. Thus, the VMG may be used to quantify muscular contraction [85].

Given the simplicity and noninvasive nature of EMG and VMG measurement, simultaneous analysis of the two signals is an attractive and viable application. Such techniques may find use in biofeedback and rehabilitation [86]. Figure 2.4 shows simultaneous EMG – VMG recodings at two levels of contraction of the rectus femoris muscle [86]. Both signals are interference patterns of several active motor units even at low levels of muscle effort and cannot be analyzed visually. However, a general increase in the power levels of the signals from the lower effort to the higher effort case may be observed. Signal processing techniques for simultaneous EMG – VMG studies are described in Section 5.11.

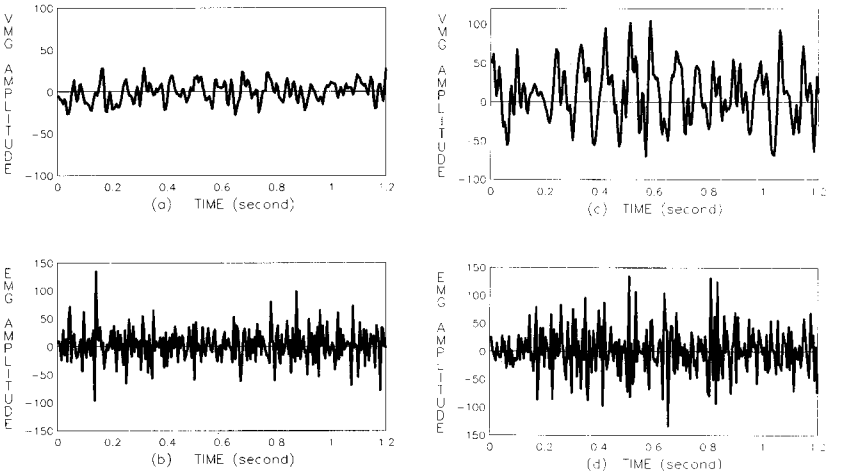

Figure 2.4 Simultaneous EMG – VMG records at two levels of contraction of the rectus femoris muscle. (a) VMG at 40% of the maximal voluntary contraction (MVC) level. (b) EMG at 40% MVC. (c) VMG at 60% MVC. (d) EMG at 60% MVC. Reproduced with permission from Y.T. Zhang, C.B. Frank, R.M. Rangayyan, and G.D. Bell, Relationships of the vibromyogram to the surface electromyogram of the human rectus femoris muscle during voluntary isometric contraction, *Journal of Rehabilitation Research and Development*, 33(4): 395–403, 1996. ©Department of Veterans Affairs.

2.2.7 The knee joint and muscle vibration signals

We saw in Section 1.2.14 that the vibration (VAG) signals produced by the knee joint during active swinging movement of the leg may bear diagnostic information. However, the VMG associated with the rectus femoris muscle that must necessarily be active during extension of the leg could appear as an interference and corrupt the VAG signal [125].

Problem: *Suggest an approach to remove muscle-contraction interference from the knee-joint vibration signal.*

Solution: The VMG interference signal gets transmitted from the source muscle location to the VAG recording position at the skin surface over the patella (knee cap) through the intervening muscles and bones (see Figure 3.11 and Section 3.3.6). Although the interference signal has been found to be of very low frequency (around $10\ Hz$), the frequency content of the signal varies with muscular effort and knee-joint angle. The rectus femoris muscle and the knee-joint systems are coupled dynamic systems with vibration characteristics that vary with activity level, and hence over time; thus, simple highpass or bandpass filtering of the VAG signal is not an appropriate solution.

An approach to solve the problem would be to record the VMG signal at the rectus femoris at the same time as the VAG signal of interest is acquired from the patella position. Adaptive filtering and noise cancellation techniques [124, 125, 148] could then be applied, with the VAG signal as the primary input and the VMG signal as the reference input. Assuming that the VMG signal that arrives at the patella is strongly correlated with the VMG signal at the rectus femoris and not correlated with the VAG signal of interest, the adaptive filter should remove the interference and estimate the desired VAG signal. Details of adaptive filters are provided in Sections 3.9 and 3.14.

2.3 Application: Segmentation of the PCG into Systolic and Diastolic Parts

Problem: *Show how the ECG and carotid pulse signals may be used to break a PCG signal into its systolic and diastolic parts.*

Solution: A cardiac cycle may be divided into two important parts based upon ventricular activity: systole and diastole. The systolic part starts with S1 and ends at the beginning of S2; it includes any systolic murmur that may be present in the signal. The diastolic part starts with S2, and it ends just before the beginning of the S1 of the next cardiac cycle. (The aortic and pulmonary valves close slightly before the A2 and P2 components of S2. Therefore, systole may be considered to have ended just before S2. Although Shaver et al. [74] and Reddy et al. [75] have included S2 in the part of their article on systolic sounds, we shall include S2 in the diastolic part of the PCG.) The diastolic part includes any diastolic murmur that may be present in the signal; it might also include S3 and S4, if present, as well as AV valve opening snaps, if any.

We saw in Section 2.2.1 that the QRS complex in the ECG may be used as a reliable marker of the beginning of S1. We also saw, in Section 2.2.2, that the dicrotic notch in the carotid pulse may be used to locate the beginning of S2. Thus, if we have both the ECG and carotid pulse signals along with the PCG, it becomes possible to break the PCG into its systolic and diastolic parts.

Figure 2.5 shows three-channel PCG – ECG – carotid pulse signals of a subject with systolic murmur due to aortic stenosis (the same as in Figure 1.44), with the systolic and diastolic parts of the PCG marked in relation to the QRS and D events.

The demarcation was performed by visual inspection of the signals in this example. Signal processing techniques to detect the QRS and D waves are presented in Section 4.3. Adaptive filtering techniques to break the PCG into stationary segments without the use of any other reference signal are described in Section 8.10.

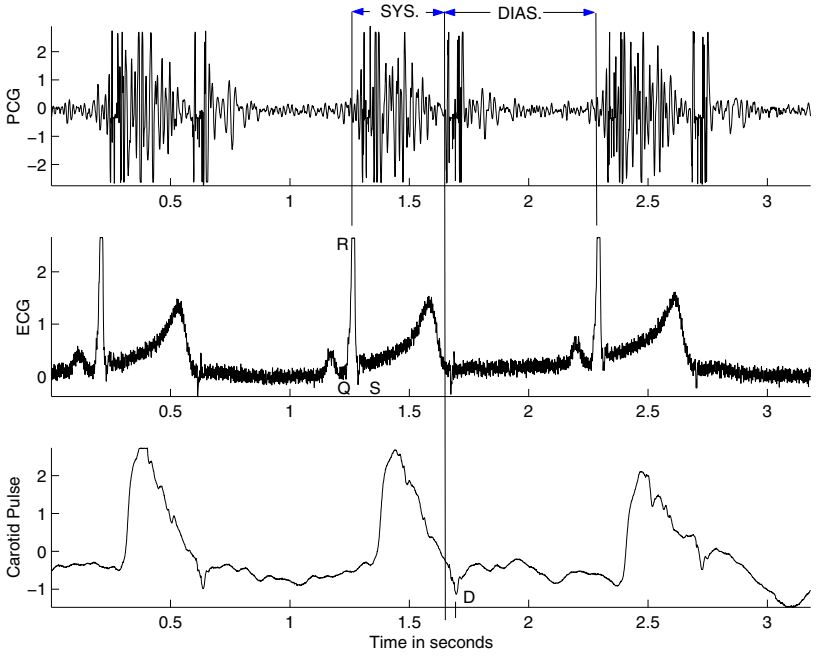

Figure 2.5 Demarcation of the systolic (SYS.) and diastolic (DIAS.) parts of the PCG signal in Figure 1.44 by using the ECG and carotid pulse as reference signals. The QRS complex and the dicrotic notch D are marked on the ECG and carotid pulse signals, respectively.

2.4 Application: Diagnosis and Monitoring of Sleep Apnea

Problem: *Propose approaches based on biomedical signal analysis to detect sleep apnea. Analyze the problem taking into consideration the various physiological systems that are either part of the problem or are affected by the resulting condition.*

Solution: The term "apnea" indicates a condition in which one stops breathing for several seconds, usually during sleep [127, 149–152]. The term "hypopnea" indicates a condition when airflow is diminished. According to Chesson et al. [153], the general condition of disordered breathing during sleep includes the conditions of apnea, defined as cessation or near cessation of respiration for a minimum period of 10 s; hypopnea, defined as a reduction in airflow for a minimum period of 10 s; and episodes of increased respiratory effort due to partial upper-airway obstruction. See Alshaer et al. [105] and Bradley and Floras [154] for additional conditions that de-

fine apnea and hypopnea. Disordered breathing during sleep causes fragmentation of sleep and lack of adequate rest. The total number of episodes of apnea and hypopnea per hour of sleep is defined as the apnea–hypopnea index (AHI). Whereas a patient affected by sleep apnea may stop breathing $10 - 100$ times per hour in episodes of duration $10 - 30$ s each, the diagnosis of sleep apnea is typically based on an AHI threshold of 10 to 15 [154].

Causes of sleep apnea include the lack of neural input from the CNS to the diaphragm to cause contraction and breathing, known as central sleep apnea (CSA), or collapse of the upper airway, referred to as obstructive sleep apnea (OSA). CSA involves disruption of breathing control where breathing does not match the metabolic requirements. In contrast, OSA is predominantly an anatomical disorder in which the upper airway does not remain open. During sleep, when muscle tone is reduced or absent, the airway collapses and the individual can no longer breathe sufficiently to maintain normal blood gases; as a result, the level of oxygen drops and that of carbon dioxide rises. OSA is the most common type of sleep apnea.

A common symptom of OSA is snoring, a respiratory noise caused by airflow through a partially obstructed airway. An episode of apnea is typically followed by arousal, allowing breathing to resume and blood gases to return to normal levels; there could be movements of the body or the limbs during such occasions of arousal. Frequent and numerous such arousals reduce the quality of sleep and the amount of rest obtained. Chronic reduction of oxygen levels and arousals increase SNS activity, and could cause numerous complications, including daytime sleepiness, hypertension, heart failure, depression, cardiac arrhythmia, and stroke. An effective treatment for OSA is continuous positive airway pressure (CPAP) applied via a face or nasal mask; the pressure applied inflates the upper airway and prevents it from collapsing.

Sleep apnea leads to decreased levels of oxyhemoglobin in the blood. Oxygen transported by blood is bound to hemoglobin in red blood cells. The absorption of different wavelengths of light by hemoglobin changes when it is bound to oxygen; thus, oxyhemoglobin appears red and deoxyhemoglobin appears blue. A finger-tip sensor with a light emitting diode (LED) and a photo sensor, known as a finger-tip pulse oximeter, or a CO-oximeter is commonly used to estimate the level of oxyhemoglobin. Using such a device, the absorption levels for red and infrared light are compared to estimate the proportion of oxyhemoglobin to deoxyhemoglobin in the blood. The measure known as SpO_2 is defined as the ratio of the amount of oxyhemoglobin to deoxyhemoglobin; SaO_2 is defined as the ratio of the amount of arterial-blood oxyhemoglobin to the sum of all types of hemoglobin.

One approach to detect sleep apnea is to measure oronasal airflow by using a pneumotachometer; however, due to the inconvenient nature of this approach, indirect indicators of airflow through the nose and mouth may be obtained by using an oronasal thermistor or by nasal pressure measurement [105, 106]. Respiratory inductance plethysmography is an indirect way of assessing airflow via movement of thoracic or abdominal belts; the signal obtained is proportional to volumetric displacement of the lungs [105, 106, 155].

2.4.1 Monitoring of sleep apnea by polysomnography

Polysomnography (PSG) [153, 156, 157], which involves multichannel recording of several biomedical signals and parameters, is the current standard for the evaluation of sleep-related problems, including sleep apnea. Some of the signals and parameters measured are respiratory effort, airflow, oxygenation, sleep state, EMG of the submental muscle (beneath the chin), EMG of the legs, the electrooculogram (EOG), EEG, ECG, and snoring sound. PSG requires the subject to sleep overnight in a laboratory.

Figure 2.6 shows eight channels selected from a 14-channel PSG data set of a patient with OSA [105]. Periods of diminished airflow to the lungs and consequently low SaO_2 levels are evident. Also seen are related intervals of increased submental EMG activity, snoring, and increased thoracic and/or abdominal activity related to recovery of respiration following episodes of apnea. (Artifact in the submental EMG channel has caused baseline movement; filters may be used to remove such artifact.) SaO_2 values are seen to increase following periods of increased ventilation, but fall again as OSA causes reduced airflow to the lungs. The leg EMG channel shows activity related to leg movement during periods of recovery from episodes of apnea, but is contaminated with the ECG.

2.4.2 Home monitoring of sleep apnea

Although PSG is a comprehensive and accurate method for diagnosing sleep apnea, it is expensive, inconvenient, and often not available. To address these difficulties, practical home-monitoring systems have been developed and are commercially available for the diagnosis and follow-up of sleep apnea. One such system [150] captures the following signals to diagnose patients suspected of having sleep apnea: SpO_2 using a finger-tip pulse oximeter; heart rate, also from the pulse oximeter; pulse amplitude; nasal airflow (through measurement of pressure with a nasal cannula); snoring sound signal using a microphone attached to the throat; and body position using an accelerometer. Additional signals that may be acquired are respiratory airflow (with a pneumotachograph, when CPAP is used); mask pressure (when CPAP is used); respiratory movements; EMG of the legs (for the diagnosis of periodic leg movement); and EMG of the masseter (jaw muscle, for the diagnosis of bruxism).

Figure 2.7 shows a segment of four channels of signals (duration $= 4\ min$) from a home apnea monitor for a subject with mild sleep apnea. Concurrent episodes of increasing heart rate and snoring sound are seen in relation to the two brief episodes of apnea (periods of no or low variations in the nasal pressure signal just before the markers for 32 and 33 min).

Figure 2.8 shows a segment of four channels of signals (of duration 5 min) from an apnea monitor for a subject with severe apnea. Several episodes of substantial hemoglobin desaturation are seen in the record. It is evident that periods of apnea are directly associated with episodes of snoring, reduced SpO_2, and increased heart rate. The clinical report of the study indicated that the patterns of airflow and oxygen saturation signals seen in the figure are compatible with an obstructive condition.

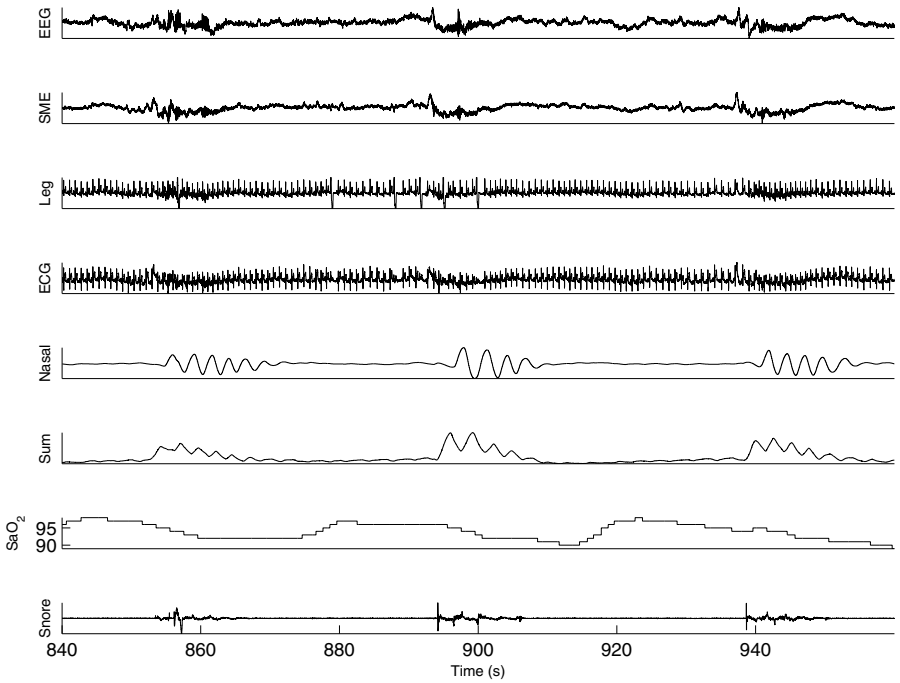

Figure 2.6 Top to bottom: EEG (F4), submental EMG (SME), leg EMG, ECG, airflow (nasal pressure cannula), sum of thoracic and abdominal activity (sum, from respiratory inductance plethysmography), SaO_2 %, and snoring sound signals selected from a 14-channel PSG record of a patient with OSA. Amplitude information has been removed from all channels except SaO_2 % to reduce clutter. Data obtained from Hisham Alshaer and T. Douglas Bradley, Sleep Research Laboratory of the University Health Network Toronto Rehabilitation Institute, Toronto, Ontario, Canada, with permission [105, 106].

See Koley and Dey [158] for the description of a system to detect apnea and hypopnea using the SpO_2 signal from a finger-tip oximeter.

2.4.3 Multivariate and multiorgan analysis

Bianchi et al. [159] proposed a multivariate and multiorgan approach for the analysis of cardiorespiratory variability signals with application to the analysis of sleep and sleep-related disorders. This approach emphasizes that the ANS influences several organs and systems, including the cardiovascular, respiratory, and endocrine-metabolic systems; it also indicates a direct connection to the central and peripheral nervous systems. Bianchi et al. [159] conducted PSG studies including the following signals: three EEG leads (C3–A2, C4–A1, and O2–A1), two EOG leads, three EMG leads (chin, right tibia, and left tibia), one ECG lead, nasal and oral airflow using thermistors, and thoracic and abdominal respiration with piezoelectric belts.

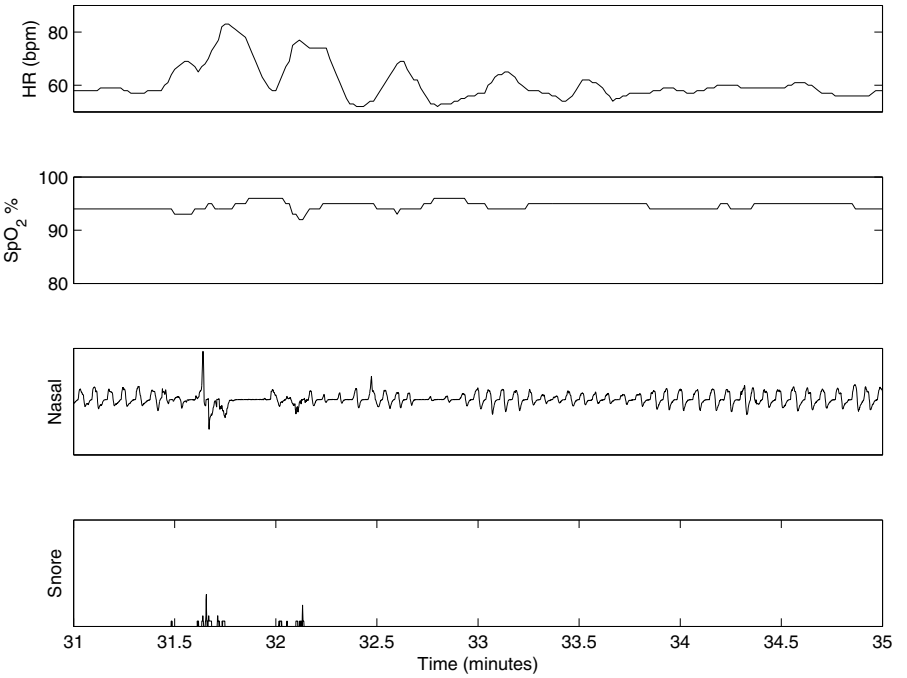

Figure 2.7 Top to bottom: Heart rate, SpO_2, nasal pressure, and snoring sound signals from a home apnea monitoring record of a moderately symptomatic subject. Amplitude information has been removed from the nasal pressure and snoring sound channels to reduce clutter. Data courtesy of R. Platt, SagaTech Electronics Inc., Calgary, Alberta, Canada, sagatech.ca.

An HRV signal was obtained from the ECG as a sequence of RR intervals. The results obtained indicated that respiratory activation and tachycardia precede periodic leg movement, which was taken to correlate with sympathetic preactivation. Bianchi et al. observed that autonomic changes could be the first manifestation of central activity involving other peripheral systems, and precede related changes in the EEG and EMG. They also observed that HRV may start a few cardiac beats before short arousals, an arousal being considered as a homeostatic mechanism to recover cardiorespiratory functionality. The results were taken to indicate the existence of strong coupling between the ANS and CNS during sleep, and that a mismatch in the coupling strength may lead to pathological situations. It was noted that therapeutic strategies should not be targeted to a single organ or system but should take into consideration the interactions among various systems.

Cerutti [160] presents compelling arguments for an integrated approach for analysis of signals arising from coupled and correlated biological or physiological systems. Figure 2.9 shows four traces of signals including the EEG, EMG from the tibia, RR intervals, and respiration from a patient with myoclonus (involuntary twitching or jerking of a muscle) during sleep. Repeated jerking of the leg, known as the restless

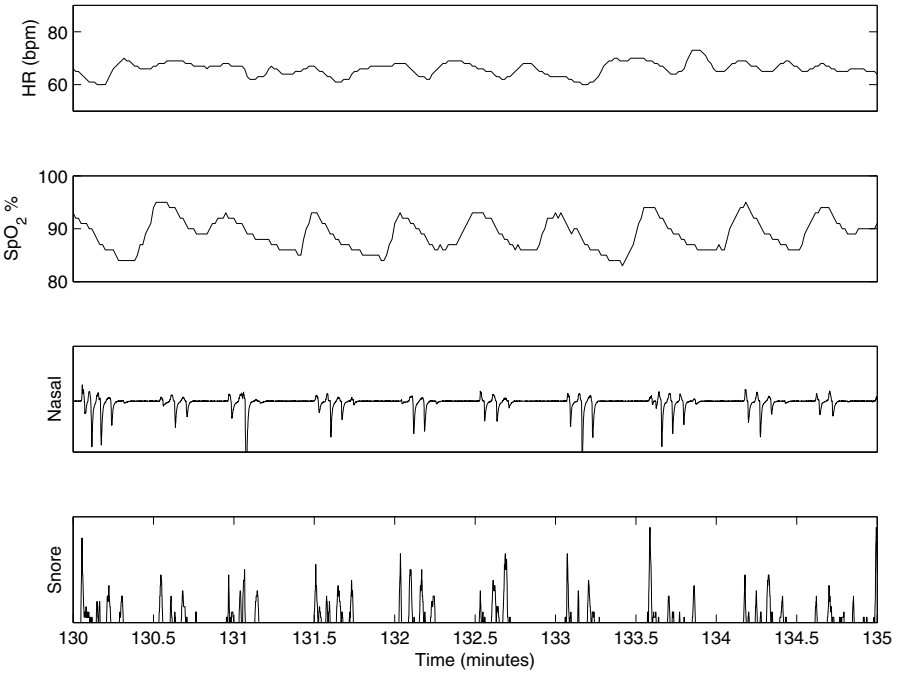

Figure 2.8 Top to bottom: Heart rate, SpO_2, nasal pressure, and snoring sound signals from a home apnea monitoring record of a subject with severe sleep apnea. Amplitude information has been removed from the nasal pressure and snoring sound channels to reduce clutter. Data courtesy of R. Platt, SagaTech Electronics Inc., Calgary, Alberta, Canada, sagatech.ca.

leg syndrome, is associated with sleep disruption and apnea, among several other disorders. The signals in Figure 2.9 demonstrate synchronization between arousal events in the EEG, spikes of activity related to myoclonus in the tibial EMG, increased heart rate (diminished RR intervals), and decreased respiratory activity. (See Somers et al. [161] for a discussion on the autonomic and hemodynamic responses to OSA and high sympathetic nerve activity in patients with OSA.)

In order to simplify the process of monitoring sleep apnea, several researchers have studied various secondary markers of apnea and hypopnea. Contrary to the multivariate approach described above, it might be desirable to be able to detect apnea by using only one or a small number of signals obtained by minimally intrusive ways. It is well known that the heart rate varies with respiration [134]; see Section 2.2.4 and Figure 2.3. Based on this knowledge, researchers have attempted to derive information related to respiration from HRV signals (see Sections 7.2.2, 7.8, and 8.11 for discussions on HRV). Episodes of apnea have been observed to be accompanied by cyclical variations in RR intervals of ECG signals, demonstrating bradycardia during apnea followed by tachycardia upon return to normal respiration. de Chazal et al. [162] proposed methods to derive a surrogate signal related to res-

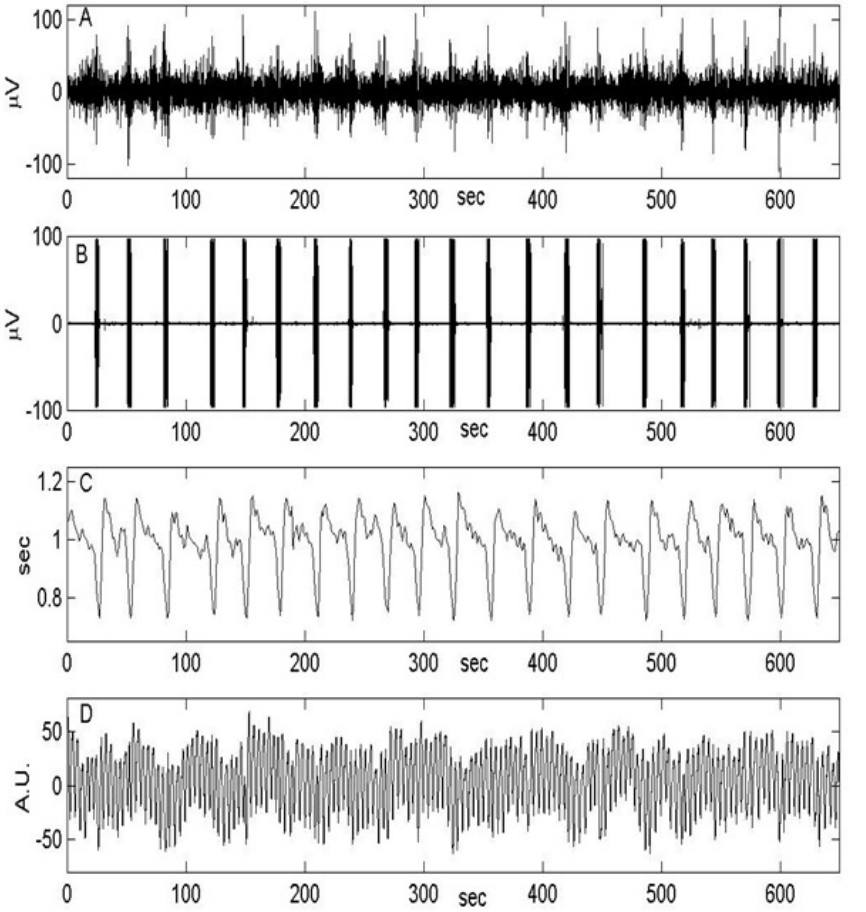

Figure 2.9 Top to bottom: EEG, EMG from the tibia, RR intervals, and respiration signal from a patient with myoclonus (involuntary twitching or jerking of a muscle) during sleep. Reproduced with permission from S. Cerutti, "Methods of biomedical signal processing: multiparametric and multidisciplinary integration toward a better comprehension of pathophysiological mechanisms," pp 3–31, Chapter 1 in *Advanced Methods of Biomedical Signal Processing,* Edited by S. Cerutti and C. Marchesi, IEEE and Wiley, New York, NY, 2011. ©IEEE.

piration from a single-lead ECG signal. Several features were derived from the RR intervals of the ECG signal and the surrogate respiration signal, including the mean, SD, correlation coefficients, measures of variation, and spectral density. Features based only on RR intervals provided a minute-by-minute rate of over 85% in the identification of episodes of apnea. Bsoul et al. [149] developed a real-time sleep apnea monitor using single-lead ECG. Measures were extracted from an HRV signal formulated using RR intervals and from a surrogate respiration signal derived from one-minute segments of the ECG signal for the detection of sleep apnea. High sensitivity of up to 96% was obtained.

Madhav et al. [163] proposed methods to derive respiratory activity from signals such as the ECG and the photoplethysmogram using modeling techniques. Arunachalam and Brown [164] proposed a real-time algorithm to estimate and remove baseline wander and obtain a surrogate respiration signal from an ECG signal. The respiration signal was estimated from the amplitude modulation of R waves in the ECG caused by breathing. See Khandoker et al. [165] for related studies.

Mendez et al. [166] proposed a method for the detection of OSA based on the ECG recorded during sleep. Several parameters were derived from the ECG signal using time-variant modeling techniques. One of the features giving good results in the detection of OSA was the coherence between the RR interval data and the area under the QRS wave. This result was considered to suggest that respiration not only causes respiratory sinus arrhythmia, but also modifies the ECG waveshape. The coherence feature was considered to be a direct representation of the relation between the respiratory aspects of OSA and their synchronization with the heart rate.

Patangay et al. [167] proposed methods for the detection of apnea based on features of ECG as well as PCG signals. It was observed that the decrease in intrathoracic pressure during OSA causes a decrease in the left-ventricular pressure; this, in turn, results in increasingly stronger left-ventricular contraction. As a result, the PCG signal during OSA, in particular the S1 amplitude, has a crescendo-like change in amplitude. A composite feature vector was prepared using subband decomposition of S1 amplitudes and RR intervals. A sensitivity of 85.5% and a specificity of 92.2% were obtained in the detection of episodes of OSA.

Alshaer et al. [105, 106] developed a specially designed face frame with a microphone to record breath sounds. They proposed single-channel signal processing techniques to detect sleep-disordered breathing (CSA or OSA) via characterization of the envelope and spectral properties of the breath sounds. Using a diagnostic limit of AHI ≥ 10 based on PSG, the overall accuracy of the breath-sound-based method was about 88%, with an overall correlation of AHI with PSG of 94%.

Notwithstanding the benefits of detecting apnea with a single signal, it should be noted that each such approach may present its own limitations and may not provide the desired degree of robustness or dependability in a clinical application. Similar to the acceptance of redundancy in the 12-lead system of ECG in clinical practice for the sake of the accompanying robustness, it may be desirable to use multiple signals from several systems that may demonstrate different effects or manifestations of apnea. Although substantial numbers of research studies are still being conducted on various issues related to OSA and CSA, as reviewed briefly in the present section,

systems and methods to detect and treat apnea are now commercially available [150, 168].

2.5 Remarks

This chapter has introduced the notion of using multiple channels of biomedical signals to obtain information on concurrent, coupled, and correlated phenomena with the aim of obtaining an improved understanding of physiological systems or obtaining reference signals for various purposes. The main point to note is that physiological systems are complex systems with multiple variables and outputs that should be studied from various approaches in order to gain multifaceted information. See Cerutti [160] and Baselli et al. [169] for discussions on several techniques and parametric models for the analysis of interactions between biomedical signals and systems.

Some of the problems described in the present chapter have been stated in fairly general terms due to the introductory nature of the chapter. The subsequent chapters present more illustrations of specific problems and applications of the notions gained from this chapter. A number of examples are provided in the chapters that follow to illustrate the use of multiple channels of signals to obtain clinically useful information.

2.6 Study Questions and Problems

1. A patient has ventricular bigeminy: Every second pulse from the SA node is replaced by a PVC with a full compensatory pause. (See Figure 9.9 for an illustration of bigeminy.) The firing rate of the SA node is regular at 80 beats a minute, and each ectopic beat precedes the blocked SA-node pulse by 100 ms.

   Draw a schematic three-channel representation of the ECG, the atrial electrogram (or the SA node's firing pattern), and the firing pattern of the ectopic focus for 10 beats, marking the time scale in detail. Identify the correspondences and relationships between the activities in the three channels.

2. Draw schematic representations of the ECG, PCG, and carotid pulse signals. Label all waves in the three signals. Identify their common relationships to events in the cardiac cycle.

2.7 Laboratory Exercises and Projects

(*Note:* The following projects require access to a physiological signal recording laboratory.)

1. Using a multichannel biomedical signal acquisition system, obtain simultaneous recordings of an ECG channel and a signal related to respiration (temperature, airflow, or pressure in the nostril). Study the variations in the RR interval with inspiration and expiration. Repeat the experiment with the subject holding his/her breath during the signal acquisition period.

2. Obtain simultaneous recordings of an ECG lead, the PCG, the carotid pulse, and the pulse at the wrist. Study the temporal correspondences (and delays) between events in the various channels.
3. Record an ECG lead and PCG signals from two or three auscultation areas (mitral, aortic, pulmonary, tricuspid, and apex: see Figure 1.31) simultaneously. Study the variations in the intensities and characteristics of S1 and S2 and their components in the PCGs from the various recording sites.