1

Introduction

1.1 OVERVIEW

Signal processing in neuroscience and neural engineering includes a wide variety of algorithms applied to measurements such as a one-dimensional time series or multidimensional data sets such as a series of images. Although analog circuitry is capable of performing many types of signal processing, the development of digital technology has greatly enhanced the access to and the application of signal processing techniques. Generally, the goal of signal processing is to enhance signal components in noisy measurements or to transform measured data sets such that new features become visible. Other specific applications include characterization of a system by its input-output relationships, data compression, or prediction of future values of the signal.

This text introduces the whole spectrum of signal analysis: from data acquisition (Chapter 2) to data processing, and from the mathematical background of the analysis to the implementation and application of processing algorithms. Overall, our approach to the mathematics will be informal, and we will therefore focus on a basic understanding of the methods and their interrelationships rather than detailed proofs or derivations. Generally, we will take an optimistic approach, assuming implicitly that our functions or signal epochs are linear, stationary, show finite energy, have existing integrals and derivatives, and so on.

Noise plays an important role in signal processing in general; therefore, we will discuss some of its major properties (Chapter 3). The core of this text focuses on what can be considered the "***golden trio***" in the signal processing field:

1. **Averaging** (Chapter 4)
2. **Fourier analysis** (Chapters 5–7)
3. **Filtering** (Chapters 10–13)

Most current techniques in signal processing have been developed with linear time invariant (LTI) systems as the underlying signal generator or analysis module (Chapters 8 and 9). Because we are primarily interested

in the nervous system, which is often more complicated than an LTI system, we will extend the basic topics with an introduction into the analysis of time series of neuronal activity (***spike trains***, Chapter 14), analysis of nonstationary behavior (***wavelet analysis***, Chapters 15 and 16), and finally on the characterization of time series originating from ***nonlinear systems*** (Chapter 17).

1.2 BIOMEDICAL SIGNALS

Due to the development of a vast array of electronic measurement equipment, a rich variety of biomedical signals exist, ranging from measurements of molecular activity in cell membranes to recordings of animal behavior. The first link in the biomedical measurement chain is typically a ***transducer*** or ***sensor***, which measures signals (such as a heart valve sound, blood pressure, or X-ray absorption) and makes these signals available in an electronic format. Biopotentials represent a large subset of such biomedical signals that can be directly measured electrically using an ***electrode*** pair. Some such electrical signals occur "spontaneously" (e.g., the electroencephalogram, EEG); others can be observed upon stimulation (e.g., evoked potentials, EPs).

1.3 BIOPOTENTIALS

Biopotentials originate within biological tissue as potential differences that occur between compartments. Generally the compartments are separated by a (bio)membrane that maintains concentration gradients of certain ions via an active mechanism (e.g., the Na^+/K^+ pump). Hodgkin and Huxley (1952) were the first to model a biopotential (the action potential in the squid giant axon) with an electronic equivalent. A combination of ordinary differential equations (ODEs) and a model describing the nonlinear behavior of ionic conductances in the axonal membrane generated an almost perfect description of their measurements. The physical laws used to derive the base ODE for the equivalent circuit are ***Nernst, Kirchhoff,*** and ***Ohm's laws*** (Appendix 1.1). An example of how to derive the differential equation for a single ion channel in the membrane model is given in Chapter 8, Figure 8.2.

1.4 EXAMPLES OF BIOMEDICAL SIGNALS

1.4.1 EEG/ECoG and Evoked Potentials (EPs)

The electroencephalogram (EEG) represents overall brain activity recorded from pairs of electrodes on the scalp. In clinical neurophysiology,

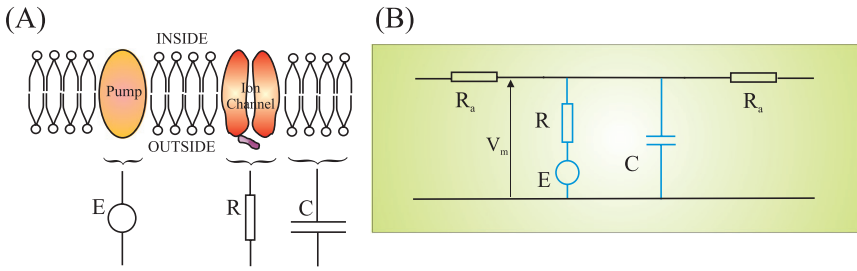

Figure 1.1 The origin of biopotentials. Simplified representation of the model described by Hodgkin and Huxley (1952). (A) The membrane consists of a double layer of phospholipids in which different structures are embedded. The ion pumps maintain gradient differences for certain ion species, causing a potential difference (E). The elements of the biological membrane can be represented by passive electrical elements: a capacitor (C) for the phospholipid bilayer and a resistor (R) for the ion channels. (B) In this way, a segment of membrane can be modeled by a circuit including these elements coupled to other contiguous compartments via an axial resistance (R_a).

the electrodes are placed according to an international standard (the 10–20 system or its extended version, the 10–10 system shown in Fig. 1.2A). In special cases, brain activity may also be directly measured via electrodes on the cortical surface (the electrocorticogram, ECoG, Fig. 1.2B) or via depth electrodes implanted in the brain. Both EEG from the scalp and intracranial signals are evaluated for so-called foreground patterns (e.g., epileptic spikes) and ongoing background activity. This background activity is typically characterized by the power of the signal within different frequency bands:

Delta rhythm (δ): 0–4 Hz
Theta rhythm (θ): 4–8 Hz
Alpha rhythm (α): 8–12 Hz
Beta rhythm (β): 12–30 Hz
Gamma rhythm (γ): the higher EEG frequencies, usually 30~70 Hz

Very high EEG frequency components (not routinely considered in clinical EEG review) are ω (~60–120 Hz, retinal origin), ρ (~250 Hz, hippocampal ripples), and σ (~600 Hz, thalamocortical bursts).

Another common class of neurophysiological signals used for clinical tests are auditory-, visual-, and somatosensory-evoked potentials (AEP, VEP, and SSEP, respectively). These signals represent the brain's response to a standard stimulus such as a tone burst, click, light flash, change of a visual pattern, or an electrical pulse delivered to a nerve. When the brain

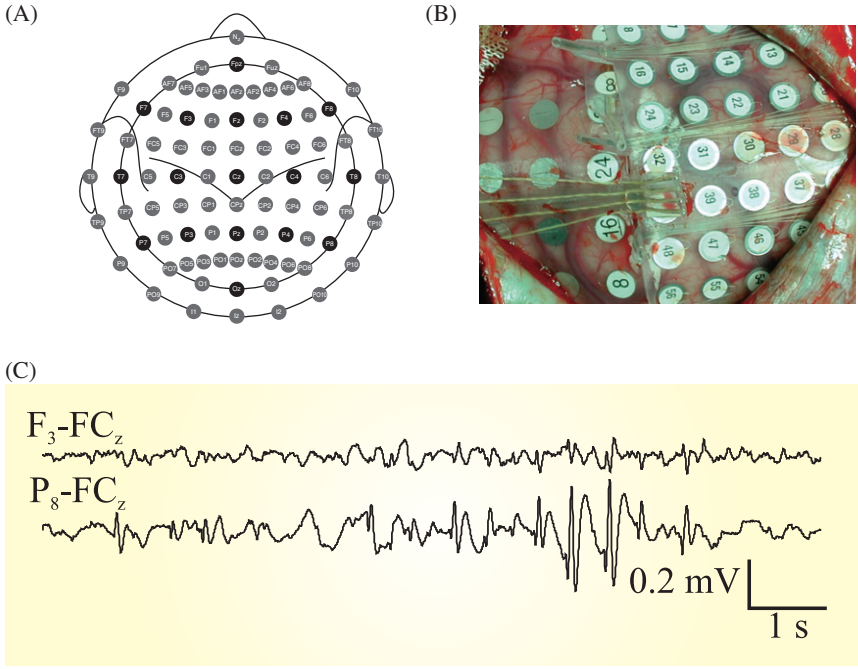

Figure 1.2 (A) An overview of the EEG 10–20 scalp electrode placement system (indicated as black dots). The diagram also shows the standard regional labels based on overlaying cranial bones: Fp–prefrontal, F–frontal, C–central, P–parietal, O–occipital, and T–temporal (intermediate positions indicated as gray dots: AF, FC, CP, PO). Even numbers are on the right side (e.g., C_4) and odd numbers are on the left side (e.g., C_3); larger numbers are farther from the midline. Midline electrodes are coded as z–zero positions (e.g., C_z). From Oostenveld and Praamstra, *Clinical Neurophysiology*, 112, 2001, 713–719. (B) An example of surgically placed cortical electrodes in a patient with epilepsy. In this application, the electrode placement is determined by the location of the epileptic focus. (C) An example of two EEG traces recorded from the human scalp, including a burst of epileptiform activity with larger amplitudes on the posterior-right side (P_8-FC_z, representing the subtraction of the FC_z signal from the P_8 signal) as compared to the frontal-left side (F_3-FC_z). The signals represent scalp potential plotted versus time. The total epoch is 10 s.

responds to specific stimuli, the evoked electrical response is usually more than 10 times smaller than the ongoing EEG background activity. Signal averaging (Chapter 4) is commonly applied to make the brain's evoked activity visible. An example of an averaged SSEP is shown in Figure 1.3. The averaging approach takes advantage of the fact that the response is time locked with the stimulus, whereas the ongoing EEG background is not temporally related to the stimulus.

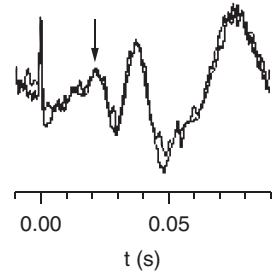

Figure 1.3 A somatosensory-evoked potential (SEP) recorded from the human scalp as the average result of 500 electrical stimulations of the left radial nerve at the wrist. The stimulus artifact (at time 0.00) shows the time of stimulation. The arrow indicates the N20 peak at ~20 ms latency. From Spiegel et al., *Clinical Neurophysiology*, 114, 2003, 992–1002.

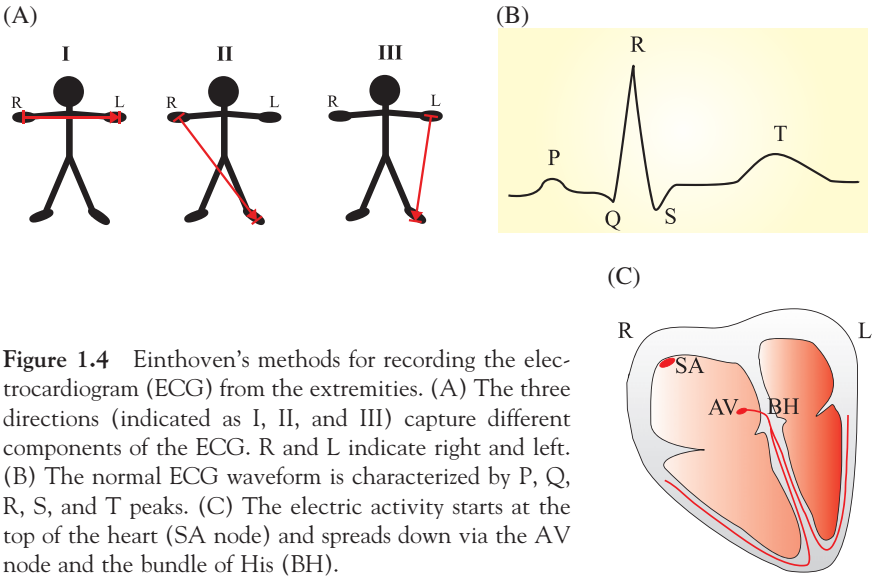

Figure 1.4 Einthoven's methods for recording the electrocardiogram (ECG) from the extremities. (A) The three directions (indicated as I, II, and III) capture different components of the ECG. R and L indicate right and left. (B) The normal ECG waveform is characterized by P, Q, R, S, and T peaks. (C) The electric activity starts at the top of the heart (SA node) and spreads down via the AV node and the bundle of His (BH).

1.4.2 ECG (EKG)

The activity of the heart is associated with a highly synchronized muscle contraction preceded by a wave of electrical activity. Normally, one cycle of depolarization starts at the sinoatrial (SA) node and then moves as a wave through the atrium to the atrioventricular (AV) node, the bundle of His, and the rest of the ventricles. This activation is followed by a repolarization phase. Due to the synchronization of the individual cellular activity, the electrical field generated by the heart is so strong that the electrocardiogram (ECG; though sometimes the German abbreviation EKG, for Elektrokardiogram, is used) can be measured from almost everywhere on the body. The ECG is usually characterized by several peaks, denoted alphabetically P-QRS-T (Fig. 1.4B). The P-wave is associated with

the activation of the atrium, the QRS-complex, and the T-wave with ventricular depolarization and repolarization, respectively. In clinical measurements, the ECG signals are labeled with the positions on the body from which each signal is recorded. An example of Einthoven's I, II, and III positions are shown in Figure 1.4A.

1.4.3 Action Potentials

The activity of single neurons can be recorded using microelectrodes with tip diameters around 1 μm. If both recording electrodes are outside the cell, one can record the extracellular currents associated with the action potentials. These so-called extracellular recordings of multiple neuronal action potentials in series are also referred to as spike trains. Alternately, if one electrode of the recording pair is inside the neuron, one can directly measure the membrane potential of that cell (Fig. 1.5). Action potentials are obvious in these intracellular recordings as large stereotypical depolarizations in the membrane potential. In addition, intracellular recordings can reveal much smaller fluctuations in potential that are generated at synapses.

1.5 ANALOG-TO-DIGITAL CONVERSION

The nature of biomedical signals is analog (i.e., continuous both in amplitude and time). Modern data acquisition and analysis frequently depend on digital signal processing (DSP), and therefore the signal must be converted into a discrete representation. The time scale is made discrete by sampling the continuous wave at a given interval; the amplitude scale is made discrete by an analog-to-digital converter (***A/D converter*** or ***ADC***), which can be thought of as a truncation or rounding of a real-valued measurement to an integer representation.

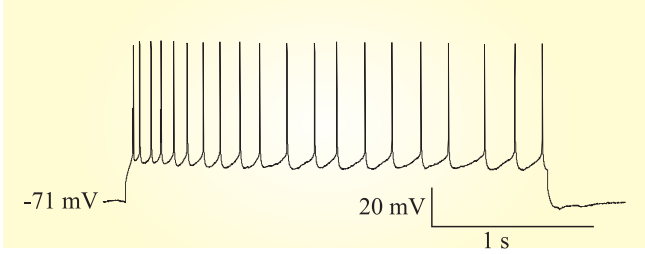

Figure 1.5 Action potentials from a neocortical neuron evoked by an intracellular current injection. The recording was performed using the patch clamp technique.

An important characteristic of an ADC is its amplitude resolution, which is measured in bits. A simplified example with a 3-bit converter (giving $2^3 = 8$ levels) is shown in Figure 1.6. Usually converters have at least an 8-bit range, producing $2^8 = 256$ levels. In most biomedical equipment, a 16-bit range ($2^{16} = 65{,}536$ levels) or higher is considered state of the art.

As Figure 1.6 shows, the resolution of the complete analog-to-digital conversion process expressed in the potential step per digitizer unit (e.g., μV/bit) is not uniquely determined by the ADC but also depends on the analog amplification. After the measurements are converted, the data can be stored in different formats: integer, real/float, or (ASCII). It is common to refer to 8 bits as a byte and a combination of bytes (e.g., 4 bytes) as a word.

1.6 MOVING SIGNALS INTO THE MATLAB ANALYSIS ENVIRONMENT

Throughout this book, we will explore signal processing techniques with real signals. Therefore, it is critical to be able to move measurements into the analysis environment. Here we give two examples of reading recordings of neural activity into MATLAB. To get an overview of file types that can be read directly into MATLAB, you can type: help fileformats in the MATLAB command window. Most files recorded with biomedical

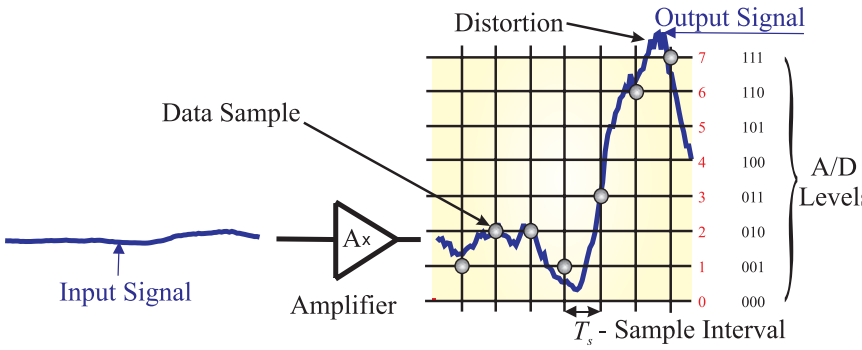

Figure 1.6 Analog-to-digital conversion (ADC). An example of an analog signal that is amplified A× and digitized showing seven samples taken at a regular sample interval T_s and a 3-bit A/D conversion. There are $2^3 = 8$ levels (0–7) of conversion. The decimal (0–7) representation of the digitizer levels is in red, and the 3-bit binary code (000–111) is in black. In this example, the converter represents the output signal values between the A/D levels as integer values rounded to the closest level. (In this example, the converter rounds intermediate levels to the nearest discrete level.)

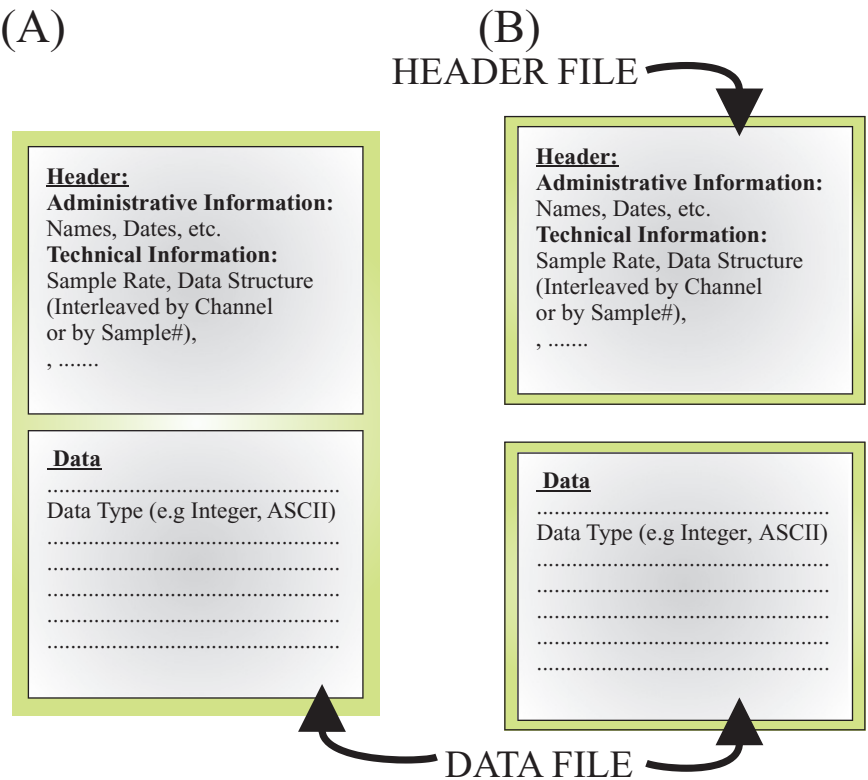

Figure 1.7 Data files. (A) An integrated file including both header information and data. Sometimes the header information is at the end of the file (tailer). (B) Separate header and data files.

equipment are not directly compatible with MATLAB and must be edited or converted. Usually this conversion requires either a number of steps to reformat the file or reading the file using the low-level fopen and fread commands. Since analog-to-digital converters typically generate integer values, most commercial data formats for measurement files consist of arrays of integer words. Such a file may contain some administrative information at the beginning (header) or end (tailer); in other cases, this type of measurement-related information is stored in a separate file (sometimes called a header file; see Fig. 1.7).

As an exercise, we will move data from two example data sets (included on the CD) into MATLAB; one set is an EEG recording (consisting of two files, data.eeg and data.bni), and the other is a measurement of a neuron's membrane potential (Cell.dat). Like many biomedical signals, these data

sets were acquired using a proprietary acquisition system with integrated hardware and software tools. As we will see, this can complicate the process of importing data into our analysis environment.

The membrane potential recording (Cell.dat) can be directly read with AxoScope or any software package that includes the AxoScope reader (free software that can be downloaded from the Axon Instruments Inc. website, www.axon.com). If you have access to this package, you can store a selection of the data in a text file format (*·tf). This file includes header information followed by the data itself (Fig. 1.7A). If you do not have access to the proprietary reader software, you can work with an output text file of AxoScope that is also available on the CD (Action_Potentials.atf). In order to load this file (containing the single-cell data) in MATLAB, the header must be removed using a text editor (such as WordPad in a Windows operating system). The first few lines of the file as seen in WordPad are shown here:

```
ATF    1.0
7      4
"AcquisitionMode=Gap Free"
"Comment="
"YTop=10,100,10"
"YBottom=-10,-100,-10"
"SweepStartTimesMS=72839.700"
"SignalsExported=PBCint,neuron,current"
"Signals="    "PBCint"      "neuron"      "current"
"Time (s)" "Trace #1 (V)" "Trace #1 (mV)" "Trace #1 (nA)"
72.8397       0.90332       -58.5938      0.00976563
72.84         0.898438      -58.5938      0
72.8403       0.90332       -58.7402      -0.00976563
....
```

After deleting the header information, the file contains only four columns of data.

```
72.8397       0.90332       -58.5938      0.00976563
72.84         0.898438      -58.5938      0
72.8403       0.90332       -58.7402      -0.00976563
72.8406       0.898438      -58.6914      0.00488281
72.8409       0.90332       -58.6426      -0.00488281
...
```

This can be stored as a text file (Action_Potentials.txt) containing the recorded data (without header information) before loading the file into MATLAB. The MATLAB command to access the data is load Action_Potentials.txt -ascii. The intracellular data are presented in the third

column and can be displayed by using the command plot(Action_Potentials(:,3)). The obtained plot result should look similar to Figure 1.5. The values in the graph are the raw measures of the membrane potential in mV. If you have a background in neurobiology, you may find these membrane potential values somewhat high; in fact, these values must be corrected by subtracting 12 mV (the so-called liquid junction potential correction).

In contrast to the intracellular data recorded with Axon Instruments products, the EEG measurement data (Reader Software: EEGVue, Nicolet Biomedical Inc., www.nicoletbiomedical.com/home.shtml) has a separate header file (data.bni) and data file (data.eeg), corresponding to the diagram in Figure 1.7B. As shown in the figure, the header file is an ASCII text file, while the digitized measurements in the data file are stored in a 16-bit integer format. Since the data and header files are separate, MATLAB can read the data without modification of the file itself, though importing this kind of binary data requires the use of lower-level commands (as we will show). Since EEG files contain records of a number of channels, sometimes over a long period of time, the files can be quite large and therefore unwieldy in MATLAB. For this reason, it may be helpful to use an application like EEGVue to select smaller segments of data, which can be saved in separate files and read into MATLAB in more manageable chunks. In this example, we do not have to select a subset of the recording because we have a 10 s EEG epoch only. If you do not have access to the reader software EEGVue, you can see what the display would look like in the jpg files: data_montaged_filtered.jpg and data.jpg. These files show the display in the EEGVue application of the data.eeg file in a montaged and filtered version and in a raw data version, respectively.

The following MATLAB script shows the commands for loading the data from data.eeg:

```
% pr1_1.m
sr=400;                                % Sample Rate
Nyq_freq=sr/2;                         % Nyquist Frequency
fneeg=input('Filename (with path and extension) :', 's');
t=input('How many seconds in total of EEG ? : ');
ch=input('How many channels of EEG ? : ');
le=t*sr;                               % Length of the Recording
fid=fopen(fneeg, 'r', 'l');            % *) Open the file to read('r') and
                                          little-endian ('l')
EEG=fread(fid,[ch,le],'int16');        % Read Data -> EEG Matrix
fclose ('all');                        % Close all open Files
```

*) The little-endian byte ordering is only required when going from PC to Mac; in PC to PC data transfer the 'l' option in the fopen statement can be omitted.

Executing this script in a MATLAB command window or via the MATLAB script included on the CD (pr1_1.m) generates the following questions:

```
Filename (with path and extension) : data.eeg
How many seconds in total of EEG ? : 10
How many channels of EEG ? : 32
```

The answers to the questions are shown in bold. You can now plot some of the data you read into the matrix EEG with plot(-EEG(1,:)), plot(-EEG(16,:)), or plot(EEG(32,:)). The first two plot commands will display noisy EEG channels; the last trace is an ECG recording. The — (minus) signs in the first two plot commands are included in order to follow the EEG convention of showing negative deflections upward. To compare the MATLAB figures of the EEG with the traces in the proprietary EEGVue software, the basis montage (None-Ref) must be selected and filters must be turned off (if you don't have access to EEGVue reader to compare your result with the screen layout, see also the jpeg file showing the raw data data.jpg). Alternatively, you can quickly verify your result by checking channel 32 for occurrence of QRS complexes similar to the one shown in Figure 1.4B.

Like the first few lines of header information in the single-cell data file shown earlier, the first few lines of the separate EEG header file (data.bni) contain similar housekeeping information. Again, this ASCII-formatted file can be opened with a text editor such as WordPad, revealing the following:

```
FileFormat = BNI-1
Filename = f:\anonymous_2f1177c5_2a99_11d5_a850_
00e0293dab97\data.bni
Comment =
PatientName = anonymous
PatientId = 1
......
```

APPENDIX 1.1

This appendix provides a quick reference to some basic laws frequently used to analyze problems in neurobiology and that are cited throughout this text (Fig. A1.1). A further explanation of these laws can be found in any basic physics textbook.

Ohm's law: The potential difference V (V, or volt) over a conductor with resistance R (Ω — Ohm) and current I (A, or ampère) can be related by

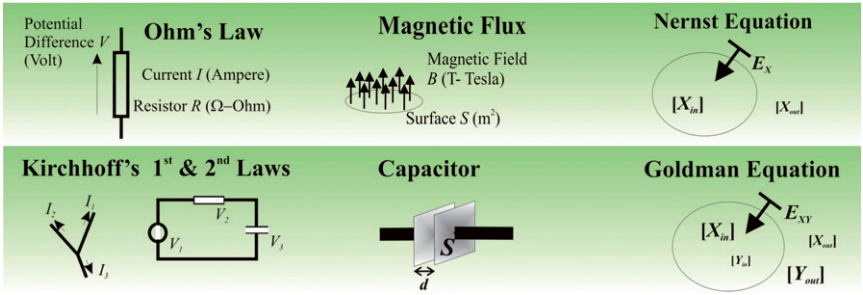

Figure A1.1 Overview of basic physics laws.

$$V = IR \tag{A1.1-1}$$

Kirchhoff's first law: At a junction, all currents add up to 0:

$$\sum_{i=1}^{N} I_i = 0 \tag{A1.1-2}$$

Kirchhoff's second law: In a circuit loop, all potentials add up to 0:

$$\sum_{i=1}^{N} V_i = 0 \tag{A1.1-3}$$

Magnetic flux induces a potential difference:

$$V = -\frac{d\Phi_B}{dt} \tag{A1.1-4}$$

Φ_B = the magnetic flux (Wb, or Weber) through a loop with surface area S (m^2) in a magnetic field of B (T-Tesla) (i.e., $\Phi_B = B\ S$).

The magnitude of the magnetic field B generated by a current I at a distance d (m — meter) is given by $B = \frac{\mu}{2\pi}\frac{I}{d}$ where μ = magnetic permeability (in a vacuum $\mu_0 = 4\pi\ 10^{-7}$).

Capacitance-related equations: The potential difference V between the two conductors of a capacitor is the quotient of charge Q (C, or Coulomb) and capacitance C (F, or Fahrad):

$$V = \frac{Q}{C} \quad \text{or} \quad Q = CV \tag{A1.1-5}$$

Current is the derivative of the charge Q:

$$i = \frac{dQ}{dt} \quad \text{and} \quad Q = \int i\,dt \tag{A1.1-6}$$

Capacitance C is proportional to the quotient of surface area S (m^2, or square meter) of the conductors and their interdistance d:

$$C = \varepsilon \frac{S}{d} \tag{A1.1-7}$$

ε = dielectric constant of the medium in between the conductors ($\varepsilon = 8.85\ 10^{-12}$ for a vacuum).

Nernst equation:

$$E_X = \frac{RT}{zF} \ln\left(\frac{[X_{out}]}{[X_{in}]}\right) \tag{A1.1-8}$$

This is the potential difference E_X created by a difference of concentrations of ion species X inside $[X_{in}]$ and outside $[X_{out}]$ the cell membrane. The constants R, T, and F are the gas constant, absolute temperature, and Avogadro's number, respectively. Parameter z denotes the charge of the ion, (e.g., +1 for Na^+ or K^+, –1 for Cl^-, and +2 for Ca^{2+}.

Goldman equation:

$$E_{XY} = \frac{RT}{F} \ln\left(\frac{p_X[X_{out}] + p_Y[Y_{out}]}{p_X[X_{in}] + p_Y[Y_{in}]}\right) \tag{A1.1-9}$$

This is similar to the Nernst equation, but here we consider the effect of multiple ion species (e.g., Na^+ and K^+). In this case, the concentrations are weighted by the membrane permeability of the ions, denoted p_{Na} and p_K, respectively.

In both the Nernst and Goldman equations, at room temperature (25°C) RT/F ln(. . .) can be replaced by

$$58\ \text{mV}\ \log_{10}(\ldots)$$