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BASIC CONCEPTS OF MEDICAL INSTRUMENTATION

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The invention, prototype design, product development, clinical testing, regulatory approval, manufacturing, marketing, and sale of a new medical instrument add up to a complex, expensive, and lengthy process. Very few new ideas survive the practical requirements, human barriers, and inevitable setbacks of this arduous process. Usually there is one person who is the "champion" of a truly new medical instrument or device. This person—who is not necessarily the inventor—must have a clear vision of the final new product and exactly how it will be used. And most important, this person must have the commitment and persistence to overcome unexpected technical problems, convince the naysayers, and cope with the bureaucratic apparatus that is genuinely needed to protect patients.

Important new ideas rarely flow smoothly to widespread clinical use. There are probably one hundred untold failure stories for each success story! New inventions usually are made by the wrong person with the wrong contacts and experience, in the wrong place at the wrong time. It is important to understand the difference between a crude feasibility prototype and a well-developed, reliable, manufacturable product. Patents are important to protect ideas during the development process and to provide incentives for making the financial investments needed. Many devices have failed because they were too hard to use, reliability and ruggedness were inadequate, marketing was misdirected, user education was lacking, or service was poor and/or slow.

An evolutionary product is a new model of an existing product that adds new features, improves the technology, and reduces the cost of production. A revolutionary new product either solves a totally new problem or uses

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a new principle or concept to solve an old problem in a better way that displaces old methods. A medical instrument that improves screening, diagnosis, or monitoring may not add value by improving patient outcome unless improvements in the application of therapy occur as a result of using the medical instrument.

1.1 TERMINOLOGY OF MEDICINE AND MEDICAL DEVICES

Most biomedical engineers learn the physical sciences first in the context of traditional engineering, physics, or chemistry. When they become interested in medicine, they usually take at least a basic course in physiology, which does not describe disease or pathologic terminology. The book *Medical Terminology: An Illustrated Guide* (Cohen and DePetris, 2013) is recommended. It emphasizes the Latin and Greek roots in a workbook format (with answers) that includes clinical case studies, flash cards, and simple, clear illustrations. An unabridged medical dictionary such as *Dorland's Illustrated Medical Dictionary*, 30th ed. (Dorland, 2003), is often useful. Physicians frequently use abbreviations and acronyms that are difficult to look up, and ambiguity or errors result. Six references on medical abbreviations are given (Cohen and DePetris, 2013; Davis, 2011; Firkin and Whitworth, 2001; Haber, 1988; Hamilton and Guides, 1988; Heister, 1989). Medical eponyms are widely used to describe diseases and syndromes by the name of the person who first identified them. Refer to *Dictionary of Medical Eponyms* (Firkin and Whitworth, 2001).

The name used to describe a medical instrument or device should be informative, consistent, and brief. The annual *Health Devices Sourcebook* (Anonymous, 2013a) is a directory of U.S. and Canadian medical device products, trade names, manufacturers, and related services. This book uses internationally accepted nomenclature and a numerical coding system for over 5000 product categories. The *Product Development Directory* (Anonymous, 1996) lists all specific medical products by the FDA standard product category name since enactment of the Medical Devices Amendments in April 1976. The *Encyclopedia of Medical Devices and Instrumentation*, 2nd edition (Webster, 2006), vols. 1–6 has many detailed descriptions. But beware of borrowing medical terminology to describe technical aspects of devices or instruments. Confounding ambiguities can result.

Recent information on medical instrumentation can be found by searching World Wide Web servers such as www.fda.gov, www.uspto.gov, Library Online Catalogs, and journal electronic databases such as Engineering Village, Science Citation Index, and PubMed.

1.2 GENERALIZED MEDICAL INSTRUMENTATION SYSTEM

Every instrumentation system has at least some of the functional components shown in Figure 1.1. The primary flow of information is from left to right. Elements and relationships depicted by dashed lines are not essential. The major difference between this system of medical instrumentation and conventional instrumentation systems is that the source of the signals is living tissue or energy applied to living tissue.

MEASURAND

The physical quantity, property, or condition that the system measures is called the measurand. The accessibility of the measurand is important because it may be internal (blood pressure), it may be on the body surface (electrocardiogram (ECG) potential), it may emanate from the body (infrared radiation), or it may be derived from a tissue sample (such as blood or a biopsy) that is removed from the body. Most medically important measurands can be grouped in the following categories: biopotential, pressure, flow, dimensions (imaging), displacement (velocity, acceleration, and force),

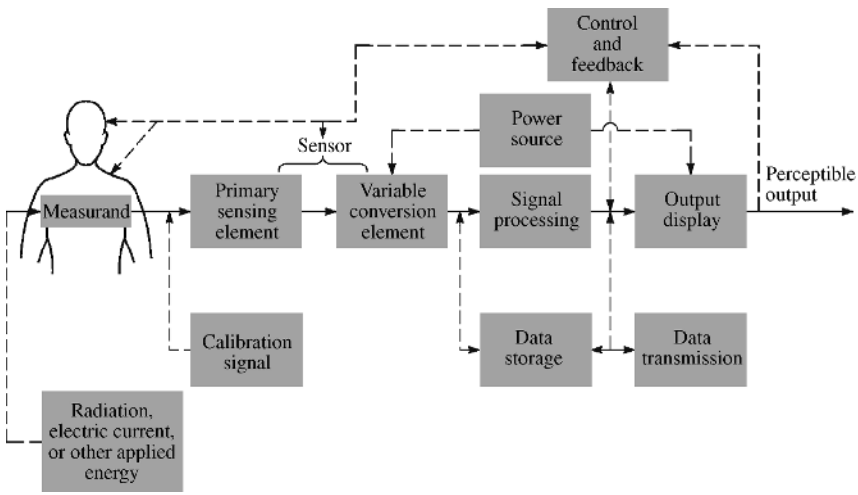

Figure 1.1 Generalized instrumentation system The sensor converts energy or information from the measurand to another form (usually electric). This signal is then processed and displayed so that humans can perceive the information. Elements and connections shown by dashed lines are optional for some applications.

impedance, temperature, and chemical concentrations. The measurand may be localized to a specific organ or anatomical structure.

SENSOR

Generally, the term *transducer* is defined as a device that converts one form of energy to another. A sensor converts a physical measurand to an electric output. The sensor should respond only to the form of energy present in the measurand, to the exclusion of all others. The sensor should interface with the living system in a way that minimizes the energy extracted, while being minimally invasive. Many sensors have a primary sensing element such as a diaphragm, which converts pressure to displacement. A variable-conversion element, such as a strain gage, then converts displacement to an electric voltage. Sometimes the sensitivity of the sensor can be adjusted over a wide range by altering the primary sensing element. Many variable-conversion elements need external electric power to obtain a sensor output.

SIGNAL CONDITIONING

Usually the sensor output cannot be directly coupled to the display device. Simple signal conditioners may only amplify and filter the signal or merely match the impedance of the sensor to the display. Often sensor outputs are converted to digital form and then processed by a microcontroller (Tompkins and Webster, 1981). For example, signal filtering may reduce undesirable sensor signals. It may also average repetitive signals to reduce noise, or it may convert information from the time domain to the frequency domain.

OUTPUT DISPLAY

The results of the measurement process must be displayed in a form that the human operator can perceive. The best form for the display may be numerical or graphical, discrete or continuous, permanent or temporary—depending on the particular measurand and how the operator will use the information. Although most displays rely on our visual sense, some information (Doppler ultrasonic signals, for example) is best perceived by other senses (here, the auditory sense). User controls and the output display should conform to the *Human Factors Engineering Guidelines and Preferred Practices for the Design of Medical Devices* [ANSI/AAMI, 2009/R(2013)] (Anonymous, 2013b).

AUXILIARY ELEMENTS

A calibration signal with the properties of the measurand should be applied to the sensor input or as early in the signal-processing chain as possible. Many forms of control and feedback may be required to elicit the measurand, to adjust the sensor and signal conditioner, and to direct the flow of output for display, storage, or transmission. Control and feedback may be automatic or manual. Data may be stored briefly to meet the requirements of signal conditioning or to enable the operator to examine data that precede alarm conditions. Or data may be stored before signal conditioning, so that different processing schemes can be utilized. The data can be transmitted wirelessly to remote displays at nurses' stations, medical centers, or medical data-processing facilities.

1.3 ALTERNATIVE OPERATIONAL MODES

DIRECT–INDIRECT MODES

Often the desired measurand can be interfaced directly to a sensor because the measurand is readily accessible or because acceptable invasive procedures are available. When the desired measurand is not accessible, we can use either another measurand that bears a known relation to the desired one or some form of energy or material that interacts with the desired measurand to generate a new measurand that is accessible. Examples include cardiac output (volume of blood pumped per minute by the heart), determined from measurements of respiration and blood gas concentration or from dye dilution; morphology of internal organs, determined from x-ray shadows; and pulmonary volumes, determined from variations in thoracic impedance plethysmography.

SAMPLING AND CONTINUOUS MODES

Some measurands such as body temperature and ion concentrations change so slowly that they may be sampled infrequently. Other quantities such as the electrocardiogram and respiratory gas flow may require continuous monitoring. The frequency content of the measurand, the objective of the measurement, the condition of the patient, and the potential liability of the physician all influence how often medical data are acquired. Many data that are collected may go unused.

GENERATING AND MODULATING SENSORS

Generating sensors produce their signal output from energy taken directly from the measurand, whereas modulating sensors use the measurand to alter the flow of energy from an external source in a way that affects the output of the sensor. For example, a photovoltaic cell is a generating sensor because it provides an output voltage related to its irradiation, without any additional external energy source. However, a photoconductive cell is a modulating sensor; to measure its change in resistance with irradiation, we must apply external energy to the sensor.

ANALOG AND DIGITAL MODES

Signals that carry measurement information are either *analog*, meaning continuous and able to take on any value within the dynamic range, or *digital*, meaning discrete and able to take on only a finite number of different values. Most currently available sensors operate in the analog mode, although some inherently digital measuring devices have been developed. Increased use of digital signal processing has required concurrent use of analog-to-digital and digital-to-analog converters to interface computers with analog sensors and analog display devices. Researchers have developed indirect digital sensors that use analog primary sensing elements and digital variable-conversion elements (optical shaft encoders). Also quasi-digital sensors, such as quartz-crystal thermometers, give outputs with variable frequency, pulse rate, or pulse duration that are easily converted to digital signals.

The advantages of the digital mode of operation include greater accuracy, repeatability, reliability, and immunity to noise. Furthermore, periodic calibration is usually not required. Digital numerical displays are replacing most analog meter movements because of their greater accuracy and readability. Most clinicians prefer digital displays when they are determining whether a physiological variable is within certain limits and when they are looking at a parameter that can change quickly, such as beat-to-beat heart rate.

REAL-TIME AND DELAYED-TIME MODES

Of course sensors must acquire signals in real time as the signals actually occur. The output of the measurement system may not display the result immediately, however, because some types of signal processing, such as averaging and transformations, need considerable input before any results can be produced. Often such short delays are acceptable unless urgent

feedback and control tasks depend on the output. In the case of some measurements, such as cell cultures, several days may be required before an output is obtained.

1.4 MEDICAL MEASUREMENT CONSTRAINTS

The medical instrumentation described throughout this book is designed to measure various medical and physiological parameters. The principal measurement and frequency ranges for each parameter are major factors that affect the design of all the instrument components shown in Figure 1.1. To get a brief overview of typical medical parameter magnitude and frequency ranges, refer to Table 1.1. Shown here are approximate ranges that are intended to include normal and abnormal values. Most of the parameter measurement ranges are quite low compared with nonmedical parameters. Note, for example, that most voltages are in the microvolt range and that pressures are low (about 100 mm Hg = 1.93 psi = 13.3 kPa). Also note that all the signals listed are in the audio frequency range or below and that many signals contain dc and very low frequencies. These general properties of medical parameters limit the practical choices available to designers for all aspects of instrument design.

Many crucial variables in living systems are inaccessible because the proper measurand–sensor interface cannot be obtained without damaging the system. Unlike many complex physical systems, a biological system is of such a nature that it is not possible to turn it off and remove parts of it during the measurement procedure. Even if interference from other physiological systems can be avoided, the physical size of many sensors prohibits the formation of a proper interface. Either such inaccessible variables must be measured indirectly, or corrections must be applied to data that are affected by the measurement process. The cardiac output is an important measurement that is obviously quite inaccessible.

Variables measured from the human body or from animals are seldom deterministic. Most measured quantities vary with time, even when all controllable factors are fixed. Many medical measurements vary widely among normal patients, even when conditions are similar. This inherent *variability* has been documented at the molecular and organ levels, and even for the whole body. Many internal anatomical variations accompany the obvious external differences among patients. Large tolerances on physiological measurements are partly the result of interactions among many physiological systems. Many feedback loops exist among physiological systems, and many of the interrelationships are poorly understood. It is seldom feasible to control or neutralize the effects of these other systems on the measured variable. The most common method of coping with this variability is to assume

Table 1.1 Medical and Physiological Parameters

Parameter or Measuring Technique	Principal Measurement Range of Parameter	Signal Frequency Range, Hz	Standard Sensor or Method
Ballistocardiography	0–7 mg	dc–40	Accelerometer, strain gage
	0–100 μm	dc–40	Displacement linear variable differential transformer
Bladder pressure	1–100 cm H_2O	dc–10	Strain-gage manometer
Blood flow	1–300 ml/s	dc–20	Flowmeter (electromagnetic or ultrasonic)
Blood pressure, arterial			
Direct	10–400 mm Hg	dc–50	Strain-gage manometer
Indirect	25–400 mm Hg	dc–60	Cuff, auscultation
Blood pressure, venous	0–50 mm Hg	dc–50	Strain gage
Blood gases			
P_{O_2}	30–100 mm Hg	dc–2	Specific electrode, volumetric or manometric
P_{CO_2}	40–100 mm Hg	dc–2	Specific electrode, volumetric or manometric
P_{N_2}	1–3 mm Hg	dc–2	Specific electrode, volumetric or manometric
P_{CO}	0.1–0.4 mm Hg	dc–2	Specific electrode, volumetric or manometric
Blood pH	6.8–7.8 pH units	dc–2	Specific electrode
Cardiac output	4–25 liter/min	dc–20	Dye dilution, Fick
Electrocardiography	0.5–4 mV	0.01–250	Skin electrodes
Electroencephalography	5–300 μV	dc–150	Scalp electrodes
Electrocorticography and brain depth	10–5000 μV	dc–150	Brain-surface or depth electrodes
Electrogastrography	10–1000 μV	dc–1	Skin-surface electrodes
	0.5–80 mV	dc–1	Stomach-surface electrodes
Electromyography	0.1–5 mV	dc–10,000	Needle electrodes
Eye potentials			
Electro-oculogram	50–3500 μV	dc–50	Contact electrodes
Electroretinogram	0–900 μV	dc–50	Contact electrodes
Galvanic skin response	1–500 kΩ	0.01–1	Skin electrodes

Table 1.1 *(Continued)*

Parameter or Measuring Technique	Principal Measurement Range of Parameter	Signal Frequency Range, Hz	Standard Sensor or Method
Gastric pH	3–13 pH units	dc–1	pH electrode; antimony electrode
Gastrointestinal pressure	0–100 cm H_2O	dc–10	Strain-gage manometer
Gastrointestinal forces	1–50 g	dc–1	Displacement system, linear variable differential transformer
Nerve potentials	0.01–3 mV	dc–10,000	Surface or needle electrodes
Phonocardiography	Dynamic range 80 dB, threshold about 100 μPa	5–2000	Microphone
Plethysmography (volume change)	Varies with organ measured	dc–30	Displacement chamber or impedance change
Circulatory	0–30 ml	dc–30	Displacement chamber or impedance change
Respiratory functions			
Pneumotachography (flow rate)	0–600 liter/min	dc–40	Pneumotachograph head and differential pressure
Respiratory rate	2–50 breaths/min	0.1–10	Strain gage on chest, impedance, nasal thermistor
Tidal volume	50–1000 ml/breath	0.1–10	Above methods
Temperature of body	32–40 °C 90–104 °F	dc–0.1	Thermistor, thermocouple

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empirical statistical and probabilistic distribution functions. Single measurements are then compared with these *norms* (see Section 1.8).

Nearly all biomedical measurements depend either on some form of energy being applied to the living tissue or on some energy being applied as an incidental consequence of sensor operation. X-ray and ultrasonic imaging techniques and electromagnetic or Doppler ultrasonic blood flowmeters depend on externally applied energy interacting with living tissue. Safe levels of these various types of energy are difficult to establish, because many mechanisms of tissue damage are not well understood. A fetus is particularly vulnerable during the early stages of development. The heating of tissue is one effect that must be limited, because even reversible

physiological changes can affect measurements. Damage to tissue at the molecular level has been demonstrated in some instances at surprisingly low energy levels.

Operation of instruments in the medical environment imposes important additional constraints. Equipment must be reliable, easy to operate, and capable of withstanding physical abuse and exposure to corrosive chemicals. Electronic equipment must be designed to minimize electric-shock hazards (Chapter 14). The safety of patients and medical personnel must be considered in all phases of the design and testing of instruments. The Medical Device Amendments of 1976 and the Safe Medical Devices Act of 1990 amend the Federal Food, Drug, and Cosmetics Act to provide for the safety and effectiveness of medical devices intended for human use (Section 1.26).

1.5 CLASSIFICATIONS OF BIOMEDICAL INSTRUMENTS

The study of biomedical instruments can be approached from at least four viewpoints. Techniques of biomedical measurement can be grouped according to the *quantity that is sensed*, such as pressure, flow, or temperature. One advantage of this classification is that it makes different methods for measuring any quantity easy to compare.

A second classification scheme uses the *principle of transduction*, such as resistive, inductive, capacitive, ultrasonic, or electrochemical. Different applications of each principle can be used to strengthen understanding of each concept; also, new applications may be readily apparent.

Measurement techniques can be studied separately for each *organ system*, such as the cardiovascular, pulmonary, nervous, and endocrine systems. This approach isolates all important measurements for specialists who need to know only about a specific area, but it results in considerable overlap of quantities sensed and principles of transduction.

Finally, biomedical instruments can be classified according to the *clinical medicine specialties*, such as pediatrics, obstetrics, cardiology, or radiology. This approach is valuable for medical personnel who are interested in specialized instruments. Of course, certain measurements such as blood pressure are important to many different medical specialties.

1.6 INTERFERING AND MODIFYING INPUTS

Desired inputs are the measurands that the instrument is designed to isolate. *Interfering inputs* are quantities that inadvertently affect the instrument as a consequence of the principles used to acquire and process the desired inputs.

If spatial or temporal isolation of the measurand is incomplete, the interfering input can even be the same quantity as the desired input. *Modifying inputs* are undesired quantities that indirectly affect the output by altering the performance of the instrument itself. Modifying inputs can affect processing of either desired or interfering inputs. Some undesirable quantities can act as both a modifying input and an interfering input.

A typical electrocardiographic recording system, shown in Figure 1.2, illustrates these concepts. The desired input is the electrocardiographic voltage V_{ecg} that appears between the two electrodes on the body surface. One interfering input is 60 Hz noise voltage induced in the shaded loop by environmental ac magnetic fields. The desired and the interfering voltages are in series, so both components appear at the input to the differential amplifier. Also, the difference between the capacitively coupled displacement currents flowing through each electrode and the body to ground causes an interfering voltage to appear across Z_{body} between the two electrodes and two interfering voltages across Z_1 and Z_2, the electrode impedances.

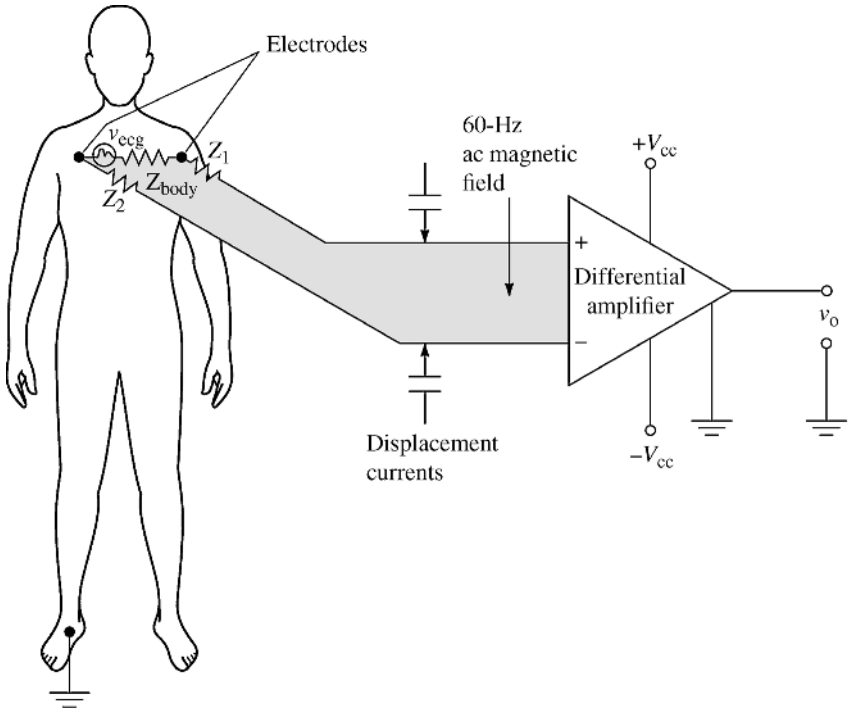


Figure 1.2 Simplified electrocardiographic recording system Two possible interfering inputs are stray magnetic fields and capacitively coupled noise. Orientation of patient cables and changes in electrode–skin impedance are two possible modifying inputs. Z_1 and Z_2 represent the electrode–skin interface impedances.

An example of a modifying input is the orientation of the patient cables. If the plane of the cables is parallel to the ac magnetic field, magnetically introduced interference is zero. If the plane of the cables is perpendicular to the ac magnetic field, magnetically introduced interference is maximal.

1.7 COMPENSATION TECHNIQUES

The effects of most interfering and modifying inputs can be reduced or eliminated either by altering the design of essential instrument components or by adding new components designed to offset the undesired inputs. The former alternative is preferred when it is feasible, because the result is usually simpler. Unfortunately, designers of instruments can only rarely eliminate the actual source of the undesired inputs. We shall discuss several compensation methods for eliminating the effects of interfering and modifying inputs.

INHERENT INSENSITIVITY

If all instrument components are inherently sensitive only to desired inputs, then interfering and modifying inputs obviously have no effect. For the electrocardiograph, an example is the twisting of the electrode wires to reduce the number of magnetic flux lines that cut the shaded loop in Figure 1.2. The voltage of the induced noise is proportional to the area of that loop. The effects of electrode motion can be reduced by techniques described in Section 5.5.

NEGATIVE FEEDBACK

When a modifying input cannot be avoided, then improved instrument performance requires a strategy that makes the output less dependent on the transfer function G_d. The negative feedback method takes a portion of the output, H_f, at any instant of time and feeds it back to the input of the instrument. This output-dependent signal is subtracted from the input, and the difference becomes the effective system input. For input, x_d, and output y, we can write

$$(x_d - H_f y)G_d = y \tag{1.1}$$

$$x_d - G_d = y(1 + H_f G_d) \tag{1.2}$$

$$y = \frac{G_d}{1 + H_f G_d} x_d \tag{1.3}$$

G_d usually includes amplification, so $H_f G_d \gg 1$ and $y \cong (1/H_f)(x_d)$. This well-known relationship shows that only the feedback element, H_f, determines the output for a given input. Of course, this strategy fails if H_f is also affected by modifying inputs. Usually the feedback device carries less power, so it is more accurate and linear. Less input-signal power is also needed for this feedback scheme, so less loading occurs. The major disadvantage of using this feedback principle is that dynamic instability leading to oscillations can occur, particularly if G_d contains time delays. The study of feedback systems is a well-developed discipline that cannot be pursued further here (Kuo and Golnaraghi, 2009).

SIGNAL FILTERING

A filter separates signals according to their frequencies. Most filters accomplish this by attenuating the part of the signal that is in one or more frequency bands. A more general definition for a filter is "a device or program that separates data, signals, or material in accordance with specified criteria" (IEEE, 1997).

Filters may be inserted at the instrument input, at some point within the instrument, or at the output of the instrument. In fact, the limitations of people's senses may be used to filter unwanted signal components coming from display devices. An example is the utilization of flicker fusion for rapidly changing images from a real-time ultrasonic scanner.

Input filtering blocks interfering and modifying inputs but does not alter the desired input. Filter elements may be distinct devices that block or pass all inputs, or they may be embodied in a single device that selectively blocks only undesired inputs. Many designers do not use input filters that are electric circuits but use instead mechanical, pneumatic, thermal, or electromagnetic principles to block out undesired environmental inputs. For example, instruments are often shock-mounted to filter vibrations that affect sensitive instrument components. Electromagnetic shielding is often used to block interfering electric and magnetic fields, such as those indicated in Figure 1.2.

Electronic filters are often incorporated at some intermediate stage within the instrument. To facilitate filtering based on differences in frequency, mixers and modulators are used to shift desired and/or undesired signals to another frequency range where filtering is more effective. Computers are used to filter signals on the basis of template-matching techniques and various time-domain signal properties. These filters may even have time- or signal-dependent criteria for isolating the desired signal.

Output filtering is possible, though it is usually more difficult because desired and undesired output signals are superimposed. The selectivity needed may be easier to achieve with higher-level output signals.

OPPOSING INPUTS

When interfering and/or modifying inputs cannot be filtered, additional interfering inputs can be used to cancel undesired output components. These extra intentional inputs may be the same as those to be canceled. In general, the unavoidable and the added opposing inputs can be quite different, as long as the two output components are equal so that cancellation results. The two outputs must cancel despite variations in all the unavoidable interfering inputs and variations in the desired inputs. The actual cancellation of undesired output components can be implemented either before or after the desired and undesired outputs are combined. Indeed, either the intentional or the unavoidable interfering input signal might be processed by G_d. The method of opposing inputs can also be used to cancel the effects of modifying inputs.

Automatic real-time corrections are implied for the method of opposing inputs just described. Output corrections are often calculated by computer methods and applied after data are collected. This requires quantitative knowledge of the interfering and/or modifying input at the time of the measurement and also of how these inputs affect the output. This method is usually cumbersome, loses real-time information, and is often used only for rather static interfering inputs, such as temperature and atmospheric pressure.

An example of using the opposing-input method is to intentionally induce a voltage from the same 60 Hz magnetic field present in Figure 1.2 to be amplified and inverted until cancellation of the 60 Hz noise in the output is achieved. An obvious disadvantage of this method is that the amplifier gain has to be adjusted whenever the geometry of the shaded loop in Figure 1.2 changes. In electronic circuits that must operate over a wide temperature range, *thermistors* (temperature-dependent resistors) are often used to counteract unavoidable temperature-dependent changes in characteristics of active circuit elements, such as transistors and integrated circuits.

1.8 BIOSTATISTICS

The application of statistics to medical data is used to design experiments and clinical studies; to summarize, explore, analyze, and present data; to draw inferences from data by estimation or hypothesis testing; to evaluate diagnostic procedures; and to assist clinical decision-making (Dawson-Saunders and Trapp, 2004).

Medical research studies can be *observational studies*, wherein characteristics of one or more groups of patients are observed and recorded, or *experimental intervention studies*, wherein the effect of a medical

procedure or treatment is investigated. The simplest observational studies are *case-series* studies that describe some characteristics of a group. These studies are without control subjects, in order only to identify questions for further research. *Case-control* observational studies use individuals selected because they have (or do not have) some outcome or disease and then look backward to find possible causes or risk factors. *Cross-sectional* observational studies analyze characteristics of patients at one particular time to determine the status of a disease or condition. *Cohort* observational studies prospectively ask whether a particular characteristic is a precursor or risk factor for an outcome or disease. Experimental clinical trials are *controlled* if the outcome for patients administered a drug, device, or procedure is compared to the outcome for patients given a placebo or another accepted treatment. The trials are *uncontrolled* if there is no such comparison. *Concurrent controls* are best, because patients are selected in the same way and for the same time period. *Double-blind* study with *randomized* selection of patients to treatment options is preferred, because this design minimizes investigator and patient bias. Medical outcome studies that show cost-effective improvements in patient health are increasingly required prior to adoption and reimbursement for new medical technologies (Anonymous, 2001).

Quantitative data are measured on a continuous or discrete *numerical scale* with some precision. Qualitative data values that fit into categories are measured on *nominal scales* that show the names of the categories. An *ordinal scale* is used when the categories exhibit an inherent order. Descriptive statistics are useful to summarize data and their attributes. *Distributions* of empirical or theoretical data reflect the values of a variable or characteristic and the frequency of occurrence of those values.

Measures of the middle, or central tendency, include the well-known *mean*, which is the sum of observed values divided by the number of observations. The mean, found as follows,

$$\overline{X} = \frac{\sum X_i}{n} \tag{1.4}$$

works best as the measure of central tendency for symmetric distributions. The *median* is the value for which half the observations are smaller and half are larger; it is used for skewed numerical data or ordinal data. The *mode* is the observation that occurs most frequently; it is used for bimodal distributions. The *geometric mean* is the *n*th root of the product of the observations:

$$\text{GM} = \sqrt[n]{X_1 X_2 X_3 \cdots X_n} \tag{1.5}$$

It is used with data on a logarithmic scale.

Measures of spread or dispersion of data describe the variation in the observations. The *range*, which is the difference between the largest and smallest observations, is used to emphasize extreme values. The *standard deviation* is a measure of the spread of data about the mean. It is computed as follows:

$$s = \sqrt{\frac{\sum (X_i - \overline{X})^2}{n-1}} \tag{1.6}$$

It is used with the mean for symmetric distributions of numerical data. Regardless of the type of symmetric distribution, at least 75% of the values always lie between $\overline{X} - 2s$ and $\overline{X} + 2s$. The *coefficient of variation* is calculated as follows:

$$\text{CV} = \left(\frac{s}{\overline{X}}\right)(100\%) \tag{1.7}$$

It standardizes the variation, making it possible to compare two numerical distributions that are measured on different scales. A *percentile* gives the percentage of a distribution that is less than or equal to the percentile number; it may be used with the median for ordinal data or skewed numerical data. The *interquartile range* is the difference between the 25th and 75th percentiles, so it describes the central 50% of a distribution with any shape. The *standard error of the mean*, SEM (standard deviation of the mean) $s_{\overline{X}} = s/\sqrt{n-1}$, expresses the variability to be expected among the *means* in future samples, whereas the *standard deviation* describes the variability to be expected among *individuals* in future samples.

EXAMPLE 1.1 Your samples from a population are 1, 1, 3, 5, 5. Estimate the mean $\overline{X}$, the standard deviation s, and the standard deviation of mean $s_{\overline{X}}$.

ANSWER Mean $\overline{X}$ = (sum of values)/(number of values) = $(1+1+3+5+5)/5 = 3$ standard deviation $s = \{[(1-3)^2 + (1-3)^2 + (3-3)^2 + (5-3)^2 + (5-3)^2]/(5-1)\}^{1/2} = (16/4)^{1/2} = 2$ standard deviation of mean $s_{\overline{X}} = s/\sqrt{n-1} = 2/\sqrt{5-1} = 1$.

Often we need to study relationships between two numerical characteristics. The *correlation coefficient* r is a measure of the relationship between numerical variables X and Y for paired observations.

$$r = \frac{\sum (X_i - \overline{X})(Y_i - \overline{Y})}{\sqrt{\sum (X_i - \overline{X})^2 (Y_i - \overline{Y})^2}} \tag{1.8}$$

The correlation coefficient ranges from –1 for a negative linear relationship to +1 for a positive linear relationship; 0 indicates that there is no linear relationship between X and Y. The correlation coefficient is independent of the units employed to measure the variables, which can be different. Like the standard deviation, the correlation coefficient is strongly influenced by outlying values. Because the correlation coefficient measures only a straight-line relationship, it may be small for a strong curvilinear relationship. Of course, a high correlation does *not* imply a cause-and-effect relationship between the variables.

Estimation and hypothesis testing are two ways to make an inference about a value in a population of subjects from a set of observations drawn from a sample of such subjects. In estimation, *confidence intervals* are calculated for a statistic such as the mean. The confidence intervals indicate that a percentage—say 95%—of such confidence intervals contain the true value of the population mean. The confidence intervals indicate the degree of confidence we can have that they contain the true mean. Hypothesis testing reveals whether the sample gives enough evidence for us to reject the *null hypothesis*, which is usually cast as a statement that expresses the opposite of what we think is true. A *P-value* is the probability of obtaining, if the null hypothesis is true, a result that is at least as extreme as the one observed. The *P-value* indicates how often the observed difference would occur by chance alone if, indeed, nothing but chance were affecting the outcome. Recent trends favor using estimation and confidence intervals rather than hypothesis testing.

Methods for measuring the accuracy of a diagnostic procedure use three pieces of information. The *sensitivity* [TP/(TP + FN)] of a test is the probability of its yielding true positive (TP) results in patients who actually have the disease. A test with high sensitivity has a low *false-negative* (FN) rate. The *specificity* [TN/(TN + FP)] of a test is the probability of its yielding negative results in patients who do not have the disease. A test with high specificity has a low *false-positive* (FP) rate; it does not give a FP result in many patients who do not have the disease. The third piece of information is the *prior probability*, or prevalence [(TP + FN)/(TN + TP + FN + FP)] of the condition prior to the test (all diseased persons divided by all persons). There are several methods for revising the probability that a patient has a condition on the basis of the results of a diagnostic test. Taking into consideration the results of a diagnostic procedure is only one part of the complex clinical decision-making process. Decision tree analysis and other forms of decision analysis that include economic implications are also used in an effort to make optimal decisions (Webster, 2004).

1.9 GENERALIZED STATIC CHARACTERISTICS

To enable purchasers to compare commercially available instruments and evaluate new instrument designs, quantitative criteria for the performance of instruments are needed. These criteria must clearly specify how well an instrument measures the desired input and how much the output depends on interfering and modifying inputs. Characteristics of instrument performance are usually subdivided into two classes on the basis of the frequency of the input signals.

Static characteristics describe the performance of instruments for dc or very low-frequency inputs. The properties of the output for a wide range of constant inputs demonstrate the quality of the measurement, including nonlinear and statistical effects. Some sensors and instruments, such as piezoelectric devices, respond only to time-varying inputs and have no static characteristics.

Dynamic characteristics require the use of differential and/or integral equations to describe the quality of the measurements. Although dynamic characteristics usually depend on static characteristics, the nonlinearities and statistical variability are usually ignored for dynamic inputs, because the differential equations become difficult to solve. Complete characteristics are approximated by the sum of static and dynamic characteristics. This necessary oversimplification is frequently responsible for differences between real and ideal instrument performance.

ACCURACY

The *accuracy* of a single measured quantity is the difference between the true value and the measured value divided by the true value. This ratio is usually expressed as a percent. Because the true value is seldom available, the accepted true value or reference value should be traceable to the National Institute of Standards and Technology.

The accuracy usually varies over the normal range of the quantity measured, usually decreases as the full-scale value of the quantity decreases on a multirange instrument, and also often varies with the frequency of desired, interfering, and modifying inputs. Accuracy is a measure of the total error without regard to the type or source of the error. The possibility that the measurement is low and that it is high are assumed to be equal. The accuracy can be expressed as percent of reading, percent of full scale, ± number of digits for digital readouts, or ±1/2 the smallest division on an analog scale. Often the accuracy is expressed as a sum of these. For example, on a digital device: ±0.01% of reading ±0.015% of full-scale ±1 digit. If accuracy is

expressed simply as a percentage, full scale is usually assumed. Some instrument manufacturers specify accuracy only for a limited period of time.

PRECISION

The *precision* of a measurement expresses the number of distinguishable alternatives from which a given result is selected. For example, a meter that displays a reading of 2.434 V is more precise than one that displays a reading of 2.43 V. High-precision measurements do not imply high accuracy, however, because precision makes no comparison to the true value.

RESOLUTION

The smallest incremental quantity that can be measured with certainty is the *resolution*. If the measured quantity starts from zero, the term *threshold* is synonymous with *resolution*. Resolution expresses the degree to which nearly equal values of a quantity can be discriminated.

REPRODUCIBILITY

The ability of an instrument to give the same output for equal inputs applied over some period of time is called *reproducibility* or *repeatability*. Reproducibility does not imply accuracy. For example, a broken digital clock with an AM or PM indicator gives very reproducible values that are accurate only once a day.

STATISTICAL CONTROL

The accuracy of an instrument is not meaningful unless all factors, such as the environment and the method of use, are considered. Statistical control ensures that random variations in measured quantities that result from all factors that influence the measurement process are tolerable. Any systematic errors or bias can be removed by calibration and correction factors, but random variations pose a more difficult problem. The measurand and/or the instrument may introduce statistical variations that make outputs unreproducible. If the cause of this variability cannot be eliminated, then statistical analysis must be used to determine the error variation. The estimate of the true value can be improved by making multiple measurements and averaging the results.

STATIC SENSITIVITY

A static calibration is performed by holding all inputs (desired, interfering, and modifying) constant except one. This one input is varied incrementally over the normal operating range, resulting in a range of incremental outputs. The static sensitivity of an instrument or system is the ratio of the incremental output quantity to the incremental input quantity. This ratio is the static component of G_d for desired inputs within the range of the incremental inputs. The incremental slope can be obtained from either the secant between two adjacent points or the tangent to one point on the calibration curve. The static sensitivity may be constant for only part of the normal operating range of the instrument, as shown in Figure 1.3(a). For input–output data that indicate a straight-line calibration curve, the slope m and intercept b for the line with the minimal sum of the squared differences between data points and the line are given by the following equations:

$$m = \frac{n\sum x_d y - (\sum x_d)(\sum y)}{n\sum x_d^2 - (\sum x_d)^2} \tag{1.9}$$

$$b = \frac{(\sum y)(\sum x_d^2) - (\sum x_d y)(\sum x_d)}{n\sum x_d^2 - (\sum x_d)^2} \tag{1.10}$$

$$y = mx_d + b \tag{1.11}$$

where n is the total number of points and each sum is for all n points. The static sensitivity for modulating sensors is usually given per volt of excitation, because the output voltage is proportional to the excitation voltage. For example, the static sensitivity for a blood pressure sensor containing a strain-gage bridge might be $50\ \mu V \cdot V^{-1} \cdot mm\ Hg^{-1}$.

ZERO DRIFT

Interfering and/or modifying inputs can affect the static calibration curve shown in Figure 1.3(a) in several ways. Zero drift has occurred when all output values increase or decrease by the same absolute amount. The slope of the sensitivity curve is unchanged, but the output-axis intercept increases or decreases as shown in Figure 1.3(b). The following factors can cause zero drift: manufacturing misalignment, variations in ambient temperature, hysteresis, vibration, shock, and sensitivity to forces from undesired directions. A change in the dc-offset voltage at the electrodes in the ECG example in Figure 1.2 is an example of zero drift. Slow changes in the dc-offset voltage do not cause a problem, because the ECG amplifier is ac-coupled. Fast changes due to motion of the subject do cause low-frequency artifact to appear at the output.

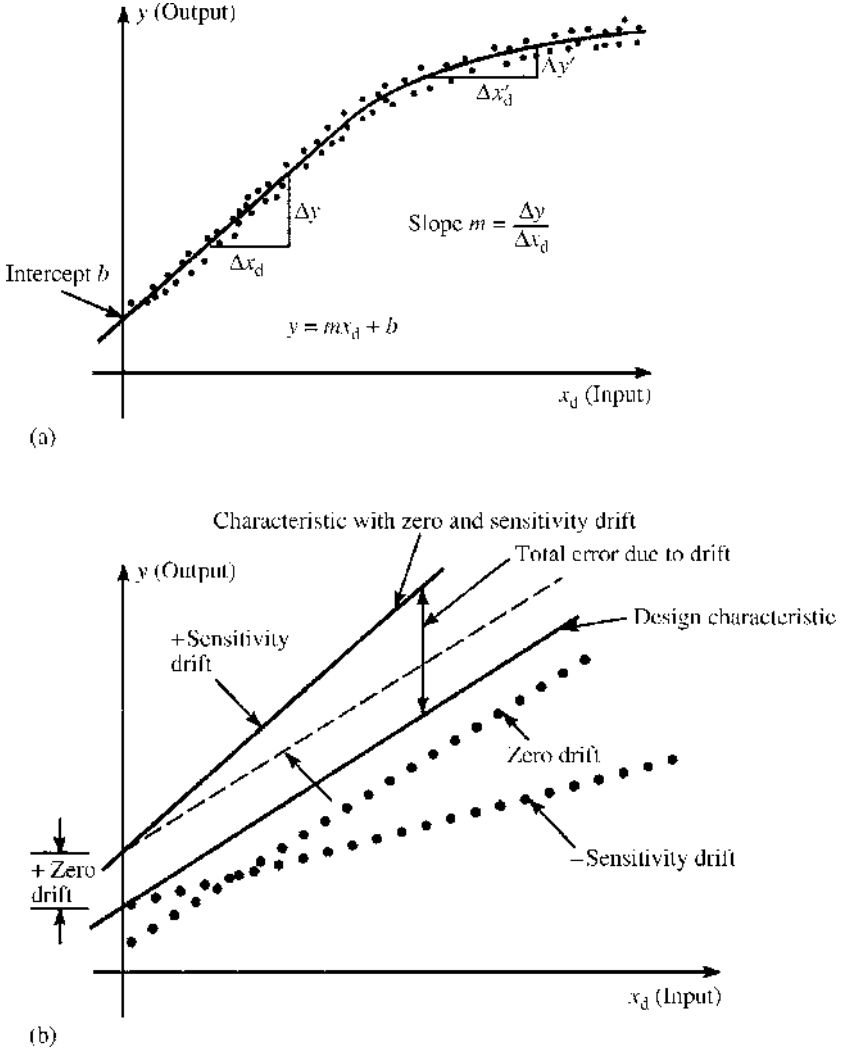


Figure 1.3 (a) Static-sensitivity curve that relates desired input x_d to output y. Static sensitivity may be constant for only a limited range of inputs. (b) Static sensitivity: zero drift and sensitivity drift. Dotted lines indicate that zero drift and sensitivity drift can be negative. [Part (b) modified from *Measurement Systems: Application and Design*, by E. O. Doebelin. Copyright 1990 by McGraw-Hill, Inc. Used with permission of McGraw-Hill Book Co.]

SENSITIVITY DRIFT

When the slope of the calibration curve changes as a result of an interfering and/or modifying input, a drift in sensitivity results. Sensitivity drift causes error that is proportional to the magnitude of the input. The slope of the calibration curve can either increase or decrease, as indicated in Figure 1.3(b). Sensitivity drift can result from manufacturing tolerances, variations in power supply, nonlinearities, and changes in ambient temperature and pressure. Variations in the ECG-amplifier voltage gain as a result of fluctuations in dc power-supply voltage or change in temperature are examples of sensitivity drift.

LINEARITY

A system or element is linear if it has properties such that, if y_1 is the response to x_1, and y_2 is the response to x_2, then $y_1 + y_2$ is the response to $x_1 + x_2$, and Ky_1 is the response to Kx_1. These two requirements for system linearity are restated in Figure 1.4(a).

They are clearly satisfied for an instrument with a calibration curve that is a straight line.

Keep in mind, however, that high accuracy does not necessarily imply linearity. In practice, no instrument has a perfect linear response, so a measure of deviation from linearity is needed. *Independent nonlinearity* expresses the maximal deviation of points from the least-squares fitted line as either $\pm A\%$ of the reading or $\pm B\%$ of full scale, whichever is greater (that is, whichever permits the larger error). This linearity specification is shown in Figure 1.4(b). For up-scale readings, the percent-of-reading figure is desirable because most errors are proportional to the reading. For small readings near zero, however, percentage of full scale is more realistic because it is not feasible to test for small percent-of-reading deviations near zero. All data points must fall inside the "funnel" shown in Figure 1.4(b). For most instruments that are essentially linear, if other sources of error are minimal, the accuracy is equal to the nonlinearity.

INPUT RANGES

Several maximal ranges of allowed input quantities are applicable for various conditions. Minimal resolvable inputs impose a lower bound on the quantity to be measured. The normal linear operating range specifies the maximal or near-maximal inputs that give linear outputs.

The static linear range and the dynamic linear range may be different. The maximal operating range is the largest input that does not damage the

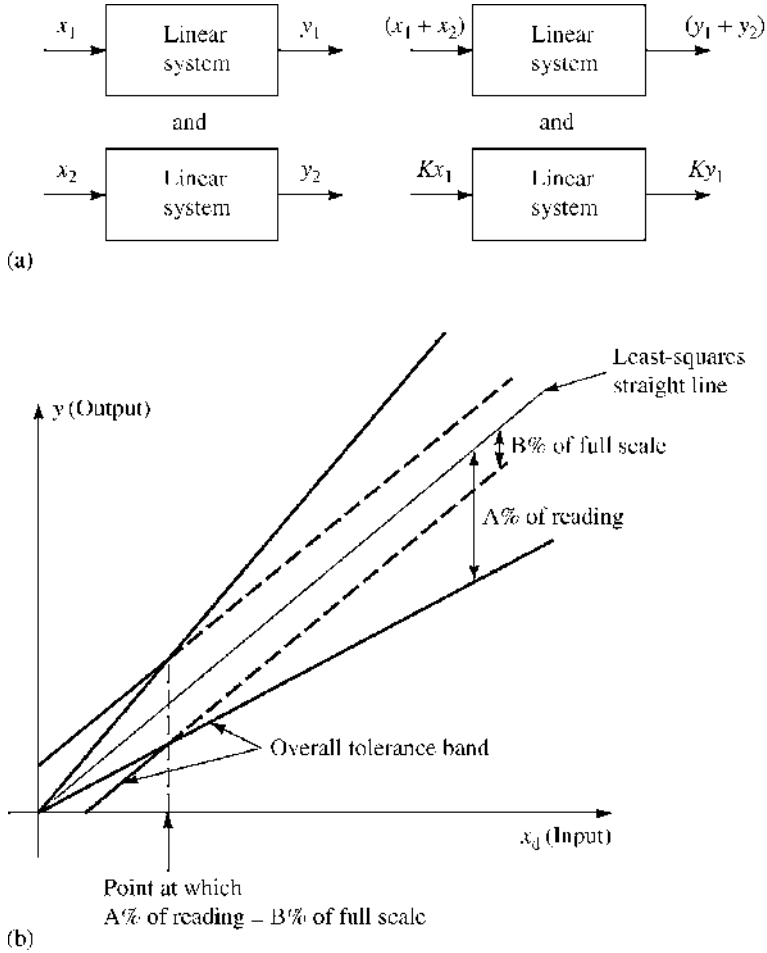


Figure 1.4 (a) Basic definition of linearity for a system or element. The same linear system or element is shown four times for different inputs. (b) A graphical illustration of independent nonlinearity equals ±A% of the reading, or ±B% of full scale, whichever is greater (that is, whichever permits the larger error). [Part (b) modified from *Measurement Systems: Application and Design*, by E. O. Doebelin. Copyright 1990 by McGraw-Hill, Inc. Used with permission of McGraw-Hill Book Co.]

instrument. Operation in the upper part of this range is more likely to be nonlinear. Finally, storage conditions specify environmental and interfering input limits that should not be exceeded when the instrument is not being used. These ranges are not always symmetric with respect to zero input,

particularly for storage conditions. Typical operating ranges for blood pressure sensors have a positive bias, such as +200 mm Hg to −60 mm Hg (+26.6 to −8.0 kPa).

INPUT IMPEDANCE

Because biomedical sensors and instruments usually convert nonelectric quantities into voltage or current, we introduce a generalized concept of input impedance. This is necessary so that we can properly evaluate the degree to which instruments disturb the quantity being measured. For every desired input X_{d1} that we seek to measure, there is another implicit input quantity X_{d2} such that the product $X_{d1} \cdot X_{d2}$ has the dimensions of power. This product represents the instantaneous rate at which energy is transferred across the tissue–sensor interface. The generalized input impedance Z_x is the ratio of the phasor equivalent of a steady-state sinusoidal *effort* input variable (voltage, force, and pressure) to the phasor equivalent of a steady-state sinusoidal *flow* input variable (current, velocity, and flow).

$$Z_x = \frac{X_{d1}}{X_{d2}} = \frac{\text{effort variable}}{\text{flow variable}} \tag{1.12}$$

The power P is the time rate of energy transfer from the measurement medium.

$$P = X_{d1} \cdot X_{d2} = \frac{X_{d1}^2}{Z_x} = Z_x X_{d2}^2 \tag{1.13}$$

To minimize P, when measuring effort variables X_{d1}, we should make the generalized input impedance as large as possible. This is usually achieved by minimizing the flow variable. However, most instruments function by measuring minute values of the flow variable, so the flow variable cannot be reduced to zero. On the other hand, when we are measuring flow variables X_{d2}, small input impedance is needed to minimize P. The loading caused by measuring devices depends on the magnitude of the input impedance $|Z_x|$ compared with the magnitude of the source impedance $|Z_s|$ for the desired input. Unfortunately, biological source impedances are usually unknown, variable, and difficult to measure and control. Thus, the instrument designer must usually focus on maximizing the input impedance Z_x for effort-variable measurement. When the measurand is a flow variable instead of an effort variable, it is more convenient to use the admittance $Y_x = 1/Z_x$ than the impedance.

EXAMPLE 1.2 In a design, Figure E1.2 circuit consisting of a linear potentiometer to measure the arc configuration in hospital beds monitor backrest elevation which helps ensure the proper angle is maintained for patients was implemented. A 5 V excitation source was used and the length of the potentiometer was 5 cm. The measurement system used to test the arc configuration has input impedance (RL) = 1 kΩ. Assuming that the wiper is in the middle of the potentiometer whose value is 1000 Ω. What is the sensitivity of the potentiometer system? What is the error in the measurement of voltage caused due to low value of input impedance?

ANSWER Sensitivity of the potentiometer system is 1000 Ω/5 cm = 200 Ω/cm.

Applying Kirchhoff current law (KCL) we have

$$I_1 = I_2 + I_3 \tag{E1.1}$$

Applying Kirchhoff voltage law (KVL) to loop ABCA, we have

$$-500\,I_1 - 1000\,I_3 + 5 = 0 \tag{E1.2}$$

Applying KVL to loop ACA, we have

$$-500I_1 - 500I_2 + 5 = 0 \tag{E1.3}$$

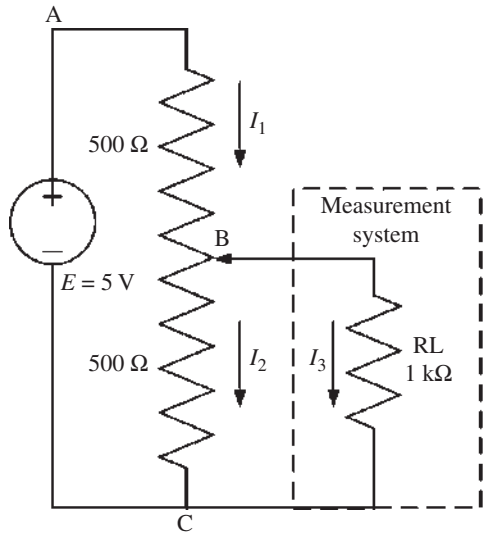


Figure E1.2 Measurement system load resistance is 1 kΩ.

Solving Eqs. (E1.1) to (E1.3), we get voltage measured will be 2 V.

$$\%\text{error} = 100(2.5 - 2)/2.5 = 20\%$$

1.10 GENERALIZED DYNAMIC CHARACTERISTICS

Only a few medical measurements, such as body temperature, are constant or slowly varying quantities. Most medical instruments must process signals that are functions of time. It is this time-varying property of medical signals that requires us to consider dynamic instrument characteristics. Differential or integral equations are required to relate dynamic inputs to dynamic outputs for continuous systems. Fortunately, many engineering instruments can be described by ordinary linear differential equations with constant coefficients. The input $x(t)$ is related to the output $y(t)$ according to the following equation:

$$a_n \frac{d_n y}{dt^n} + \cdots + a_1 \frac{dy}{dt} + a_0 y(t) = b_m \frac{d^m x}{dt^m} + \cdots + b_1 \frac{dx}{dt} + b_0 x(t) \qquad (1.14)$$

where the constants $a_i (i = 0, 1, \ldots, n)$ and $b_j (j = 0, 1, \ldots, m)$ depend on the physical and electric parameters of the system. By introducing the differential operator $D^k \equiv d^k()/dt^k$, we can write this equation as

$$(a_n D^n + \cdots + a_1 D + a_0) y(t) = (b_m D^m + \cdots + b_1 D + b_0) x(t) \qquad (1.15)$$

Readers familiar with Laplace transforms may recognize that D can be replaced by the Laplace parameter s to obtain the equation relating the transforms $Y(s)$ and $X(s)$. This is a *linear* differential equation, because the linear properties stated in Figure 1.4(a) are assumed and the coefficients a_i and b_j are not functions of time or the input $x(t)$. The equation is *ordinary*, because there is only one independent variable y. Essentially such properties mean that the instrument's methods of acquiring and analyzing the signals do not change as a function of time or the quantity of input. For example, an autoranging instrument may violate these conditions.

Most practical instruments are described by differential equations of zero, first, or second order; thus $n = 0, 1, 2$, and derivatives of the input are usually absent, so $m = 0$.

The input $x(t)$ can be classified as transient, periodic, or random. No general restrictions are placed on $x(t)$, although, for particular applications, bounds on amplitude and frequency content are usually assumed. Solutions

for the differential equation depend on the input classifications. The step function is the most common transient input for instrumentation. Sinusoids are the most common periodic function to use because, through the Fourier-series expansion, any periodic function can be approximated by a sum of sinusoids. Band-limited white noise (uniform-power spectral content) is a common random input because one can test instrument performance for all frequencies in a particular bandwidth.

TRANSFER FUNCTIONS

The transfer function for a linear instrument or system expresses the relationship between the input signal and the output signal mathematically. If the transfer function is known, the output can be predicted for any input. The *operational transfer function is the ratio* $y(D)/x(D)$ as a function of the differential operator D.

$$\frac{y(D)}{x(D)} = \frac{b_m D^m + \cdots + b_1 D + b_0}{a_n D^n + \cdots + a_1 D + a_0} \tag{1.16}$$

This form of the transfer function is particularly useful for transient inputs. For linear systems, the output for transient inputs, which occur only once and do not repeat, is usually expressed directly as a function of time, $y(t)$, which is the solution to the differential equation.

The *frequency transfer function* for a linear system is obtained by substituting $j\omega$ for D in (1.16).

$$\frac{Y(j\omega)}{X(j\omega)} = \frac{b_m (j\omega)^m + \cdots + b_1 (j\omega) + b_0}{a_n (j\omega)^n + \cdots + a_1 (j\omega) + a_0} \tag{1.17}$$

where $j = +\sqrt{-1}$ and ω is the angular frequency in radians per second. The input is usually given as $x(t) = A_x \sin(\omega t)$, and all transients are assumed to have died out. The output $y(t)$ is a sinusoid with the same frequency, but the amplitude and phase depend on ω; that is, $y(t) = B(\omega) \sin[\omega t + \varphi(\omega)]$. The frequency transfer function is a complex quantity having a magnitude that is the ratio of the magnitude of the output to the magnitude of the input and a phase angle φ that is the phase of the output $y(t)$ minus the phase of the input $x(t)$. The phase angle for most instruments is negative. We do not usually express the output of the system as $y(t)$ for each frequency, because we know that it is just a sinusoid with a particular magnitude and phase. Instead, the amplitude ratio and the phase angle are given separately as functions of frequency.

The dynamic characteristics of instruments are illustrated below by examples of zero-, first-, and second-order linear instruments for step and sinusoidal inputs.

ZERO-ORDER INSTRUMENT

The simplest nontrivial form of the differential equation results when all the a's and b's are zero except a_0 and b_0.

$$a_0 y(t) = b_0 x(t) \tag{1.18}$$

This is an algebraic equation, so

$$\frac{y(D)}{x(D)} = \frac{Y(j\omega)}{X(j\omega)} = \frac{b_0}{a_0} = K = \text{static sensitivity} \tag{1.19}$$

where the single constant K replaces the two constants a_0 and b_0. This zero-order instrument has ideal dynamic performance, because the output is proportional to the input for all frequencies and there is no amplitude or phase distortion.

A linear potentiometer is a good example of a zero-order instrument. Figure 1.5 shows that if the potentiometer has pure uniform resistance, then the output voltage $y(t)$ is directly proportional to the input displacement $x(t)$, with no time delay for any frequency of input. In practice, at high frequencies, some parasitic capacitance and inductance might cause slight distortion. Also, low-resistance circuits connected to the output can load this simple zero-order instrument. Example 1.2 shows a zero-order system and the loading effect.

FIRST-ORDER INSTRUMENT

If the instrument contains a single energy-storage element, then a first-order derivative of $y(t)$ is required in the differential equation.

$$a_1 \frac{dy(t)}{dt} + a_0 y(t) = b_0 x(t) \tag{1.20}$$

This equation can be written in terms of s as

$$(\tau D + 1) y(t) = K x(t) \tag{1.21}$$

where $K = b_0/a_0$ = static sensitivity and $\tau = a_1/a_0$ = time constant.

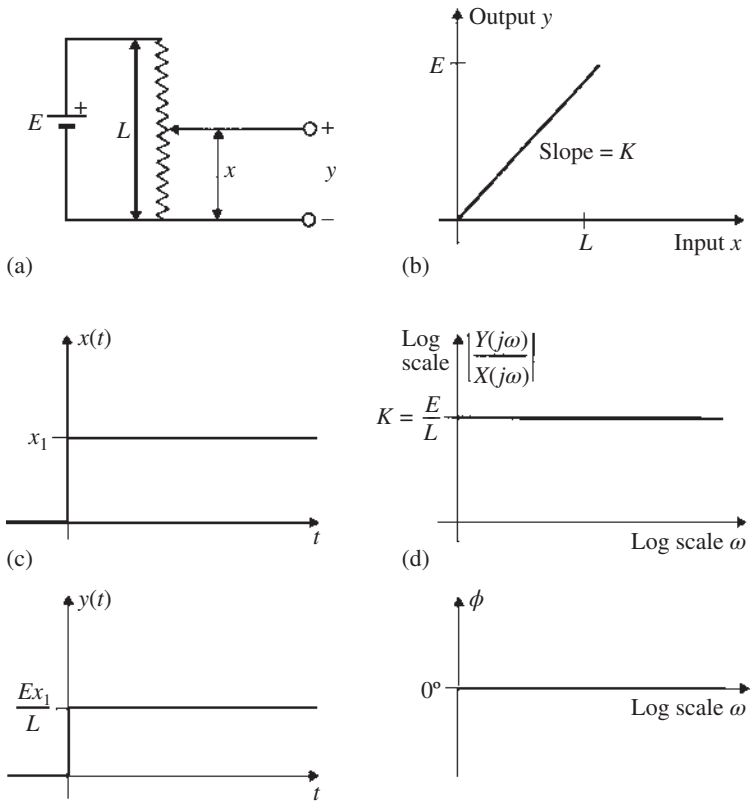


Figure 1.5 (a) A linear potentiometer, an example of a zero-order system. (b) Linear static characteristic for this system. (c) Step response is proportional to input. (d) Sinusoidal frequency response is constant with zero phase shift.

Exponential functions offer solutions to this equation when appropriate constants are chosen. The operational transfer function is

$$\frac{y(D)}{x(D)} = \frac{K}{1 + \tau D} \tag{1.22}$$

and the frequency transfer function is

$$\frac{Y(j\omega)}{X(j\omega)} = \frac{K}{1 + j\omega\tau} = \frac{K}{\sqrt{1 + \omega^2\tau^2}} \angle\phi; \angle\phi = arctan(-\omega\tau/1) \tag{1.23}$$

The *RC* low-pass filter circuit shown in Figure 1.6(a) is an example of a first-order instrument. The input is the voltage $x(t)$ and the output is the voltage $y(t)$ across the capacitor. The first-order differential equation for this circuit is $RC[dy(t)/dt] + y(t) = Kx(t)$. The static-sensitivity curve given in Figure 1.6(b) shows that static outputs are equal to static inputs. This is verified by the differential equation because, for static conditions, $dy/dt = 0$. The step response in Figure 1.6(c) is exponential with a time constant $\tau = RC$.

$$y(t) = K\left(1 - e^{-t/r}\right) \tag{1.24}$$

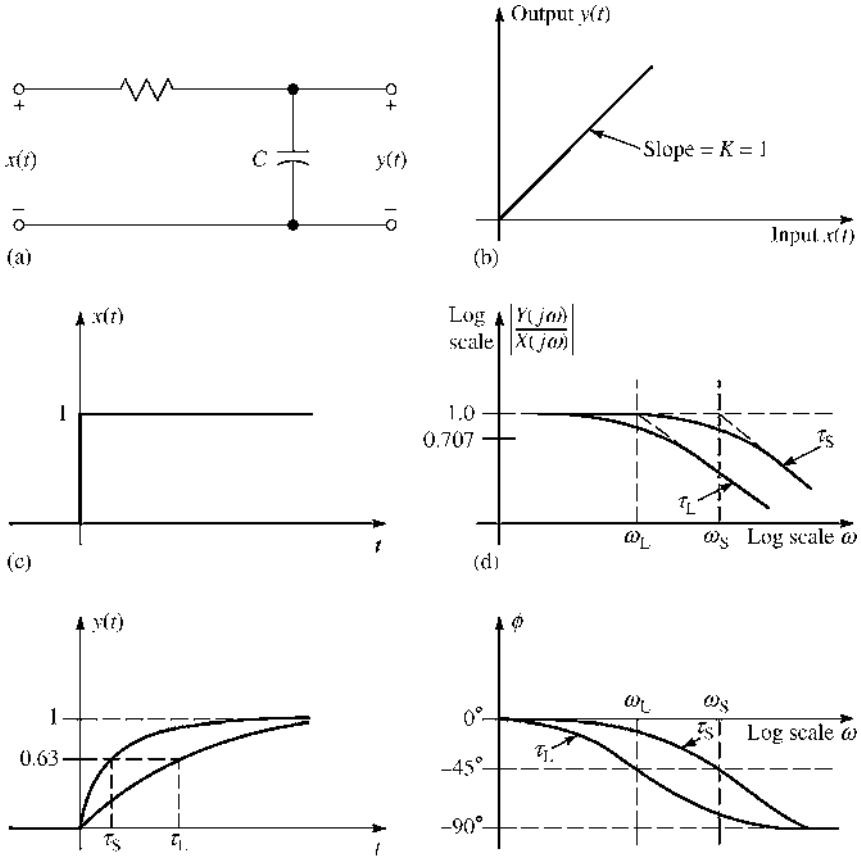


Figure 1.6 (a) A low-pass *RC* filter, an example of a first-order instrument. (b) Static sensitivity for constant inputs. (c) Step response for large time constants (τ_L) and small time constants (τ_S). (d) Sinusoidal frequency response for large and small time constants.

The smaller the time constant, the faster the output approaches the input. For sinusoids, (1.23) and Figure 1.6(d) show that the magnitude of the output decreases as frequency increases. For larger time constants, this decrease occurs at lower frequency.

When $\omega = 1/\tau$, the magnitude is $1/\sqrt{2} = 0.707$ times smaller, and the phase angle is –45°. This particular frequency ω is known as the *corner, cut-off*, or *break* frequency. Figure 1.6(d) verifies that this is a low-pass filter; low-frequency sinusoids are not severely attenuated, whereas high-frequency sinusoids produce very little output voltage. The ordinate of the frequency-response magnitude in Figure 1.6(d) is usually plotted on a log scale and may be given in units of decibels (dB), which are defined as $\text{dB} = 20\log_{10}|Y(j\omega)/X(j\omega)|$. A mercury-in-glass thermometer is another example of a low-pass first-order instrument.

EXAMPLE 1.3 A first-order low-pass instrument has a time constant of 20 ms. Find the maximal sinusoidal input frequency that will keep output error due to frequency response less than 5%. Find the phase angle at this frequency.

ANSWER

$$\frac{Y(j\omega)}{X(j\omega)} = \frac{K}{1 + j\omega\tau}$$

$$\left|\frac{K}{1 + j\omega\tau}\right| = \frac{K}{\sqrt{1 + \omega^2\tau^2}} = 0.95\,\text{K}$$

$$\left(\omega^2\tau^2 + 1\right)(0.95)^2 = 1$$

$$\omega^2 = \frac{1 - (0.95)^2}{(0.95)^2\left(20 \times 10^{-3}\right)^2}$$

$$\omega = 16.4\ \text{rad/s}$$

$$f = \frac{\omega}{2\pi} = 2.62\ \text{Hz}$$

$$\phi = \tan^{-1}\left(\frac{-\omega\tau}{1}\right) = -18.2^\circ$$

If R and C in Figure 1.6(a) are interchanged, the circuit becomes another first-order instrument known as a *high-pass filter*. The static characteristic is zero for all values of input, and the step response jumps immediately to the step voltage but decays exponentially toward zero as time increases. Thus $y(t) = Ke^{-t/\tau}$. Low-frequency sinusoids are severely attenuated, whereas high-frequency sinusoids are little attenuated. The sinusoidal transfer function is $Y(j\omega)/X(j\omega) = j\omega\tau/(1 + j\omega\tau)$.

EXAMPLE 1.4 From a 2 kV source in series with a 20 kΩ resistor, calculate the time required to charge a 100 μF defibrillator capacitor to 1.9 kV.

ANSWER Circuit is shown in Figure 1.6(a). Use (1.24) $v_C = V - Ve^{-\frac{t}{RC}}$

$$1900\,\text{V} = 2000\text{V} - 2000\text{V} \cdot e^{-\frac{t}{(20{,}000\Omega)(100\times 10^{-6}\text{F})}}$$

$$-100\,\text{V} = -2000\text{V} \cdot e^{-\frac{t}{(20{,}000\Omega)(100\times 10^{-6}\text{F})}}$$

$$0.05 = e^{-\frac{t}{(20{,}000\Omega)(100\times 10^{-6}\text{F})}}$$

$$\ln 0.05 = -\frac{t}{2\Omega \cdot \text{F}}$$

$$t = 5.99\,\text{s}$$

EXAMPLE 1.5 Temperature-guided radiofrequency catheter ablation was attempted with the catheter tip set to 70 °C to heat the affected tissue. A type J thermocouple (sensitivity of 50 μV/°C and time constant of 2 s) was used to measure this temperature. The thermocouple could be modeled as a first-order system. Write the first-order system model for this thermocouple. Use MATLAB code to plot the response of the thermocouple when it is suddenly exposed to the catheter tip temperature of 70 °C. How much time does it take to reach a steady state reading?

ANSWER The model for the first-order system is shown in (1.20) and (1.21). The thermocouple could be modeled as:

$$2\frac{dy(t)}{dx(t)} + y(t) = 50\times 10^{-6}\,x(t)$$

The transfer function for this system could be written as:

$$G = \frac{K}{\tau s + 1}$$

$$K = 50\times 10^{-6}; \quad \tau = 2\,\text{s}$$

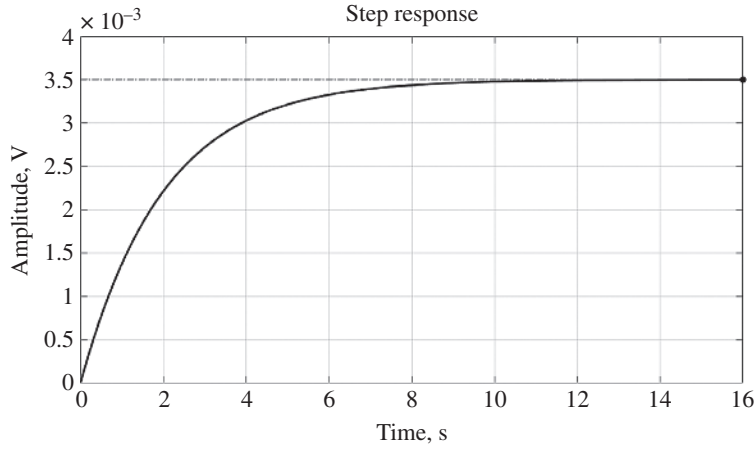


Figure E1.5 Step response for the thermocouple system The steady-state value is reached in approximately 10 s.

The MATLAB code for the step response (see Figure E1.5) is given below:

```
%% Step response for the thermocouple system
K = 50 * power(10,-6); % static sensitivity K = 50 μV/°C
tau = 2;               % time constant tau = 2 s
u = 70;                % step change of 70 °C
s = tf('s');
% to specify a TF model using a rational function in
% Laplace variable, s
G = K/(tau*s+1);            % transfer function
figure, step(u*G); grid on;
ylabel('Amplitude, V'); xlabel('Time, s');
```

SECOND-ORDER INSTRUMENT

An instrument is second order if a second-order differential equation is required to describe its dynamic response.

$$a_2 \frac{d^2y(t)}{dt^2} + a_1 \frac{dy(t)}{dt} + a_0 y(t) = b_0 x(t) \tag{1.25}$$

Many medical instruments are second order or higher, and low pass. Furthermore, many higher-order instruments can be approximated by second-order characteristics if some simplifying assumptions can be made.

The four constants in (1.25) can be reduced to three new ones that have physical significance:

$$\left[\frac{D^2}{\omega_n^2} + \frac{2\zeta D}{\omega_n} + 1\right] y(t) = Kx(t) \tag{1.26}$$

where

$$K = \frac{b_0}{a_0} = \text{ static sensitivity, output units divided by input units}$$

$$\omega_{\mathrm{n}} = \sqrt{\frac{a_0}{a_2}} = \text{ undamped natural frequency, rad/s}$$

$$\zeta = \frac{a_1}{2\sqrt{a_0 a_2}} = \text{ damping ratio, dimensionless}$$

Again exponential functions offer solutions to this equation, although the exact form of the solution varies as the damping ratio becomes greater than, equal to, or less than unity. The operational transfer function is

$$\frac{y(D)}{x(D)} = \frac{K}{\dfrac{D^2}{\omega_n^2} + \dfrac{2\zeta D}{\omega_n + 1}} \tag{1.27}$$

and the frequency transfer function is

$$\begin{aligned}\frac{Y(j\omega)}{X(j\omega)} &= \frac{K}{(j\omega/\omega_n)^2 + (2\zeta j\omega/\omega_n) + 1} \\ &= \frac{K}{\sqrt{\left[1 - (\omega/\omega_0)^2\right]^2 + 4\zeta^2\omega^2/\omega_n^2}} \angle\phi;\ \angle\phi = \arctan\frac{2\zeta}{\omega/\omega_n - \omega_n/\omega}\end{aligned} \tag{1.28}$$

A mechanical force-measuring instrument illustrates the properties of a second-order instrument (Doebelin, 1990). Mass, spring, and viscous-damping elements oppose the applied input force $x(t)$, and the output is the resulting displacement $y(t)$ of the movable mass attached to the spring [Figure 1.7(a)]. If the natural frequency of the spring is much greater than the frequency components in the input, the dynamic effect of the spring can be included by adding one-third of the spring's mass to the mass of the moving elements to obtain the equivalent total mass M.

Hooke's law for linear springs is assumed, so the spring constant is K_{s}. Dry friction is neglected and perfect viscous friction is assumed, with constant B.

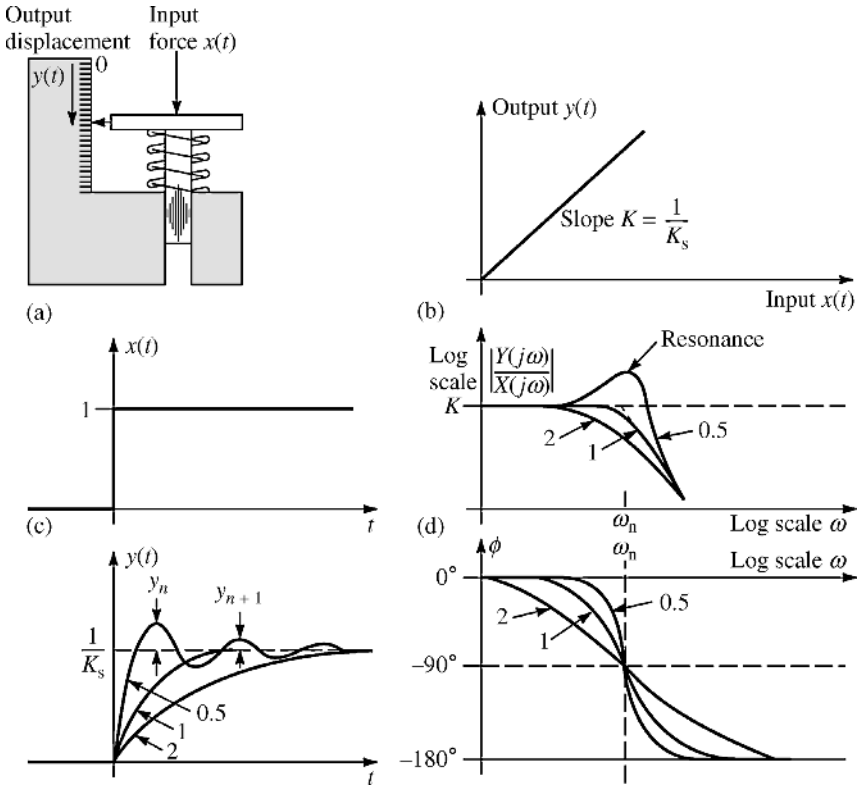


Figure 1.7 (a) Force-measuring spring scale, an example of a second-order instrument. (b) Static sensitivity. (c) Step response for overdamped case $\zeta = 2$, critically damped case $\zeta = 1$, and underdamped case $\zeta = 0.5$. (d) Sinusoidal steady-state frequency response, $\zeta = 2$, $\zeta = 1$, $\zeta = 0.5$. (*Measurement Systems: Application and Design*, by E. O. Doebelin. Copyright 1990 by McGraw-Hill, Inc. Used with permission of McGraw-Hill Book Co.)

To eliminate gravitational force from the equation, we adjust the scale until $y = 0$ when $x = 0$. Then the sum of the forces equals the product of mass and acceleration.

$$x(t) - B\frac{dy(t)}{dt} - K_s y(t) = M\frac{d^2y(t)}{dt^2} \tag{1.29}$$

This equation has the same form as (1.26) when the static sensitivity, undamped natural frequency, and damping ratio are defined in terms of K_s, B, and M, as follows:

$$K = \frac{1}{K_s} \tag{1.30}$$

$$\omega_n = \sqrt{\frac{K_s}{M}} \tag{1.31}$$

$$\zeta = \frac{B}{2\sqrt{K_s M}} \tag{1.32}$$

The static response is $y(t) = Kx(t)$, as shown in Figure 1.7(b). The step response can have three forms, depending on the damping ratio. For a unit-step input, these three forms are
Over damped, $\zeta > 1$:

$$y(t) = -\frac{\zeta + \sqrt{\zeta^2 - 1}}{2\sqrt{\zeta^2 - 1}} Ke^{\left(-\zeta + \sqrt{\zeta^2 - 1}\right)\omega_n t} + \frac{\zeta - \sqrt{\zeta^2 - 1}}{2\sqrt{\zeta^2 - 1}} Ke^{\left(-\zeta - \sqrt{\zeta^2 - 1}\right)\omega_n (t)} + K \tag{1.33}$$

Critically damped, $\zeta = 1$:

$$y(t) = -(1 + \omega_n t)Ke^{-\omega_n t} + K \tag{1.34}$$

Underdamped, $\zeta < 1$:

$$\begin{aligned} y(t) &= -\frac{e^{-\zeta\omega_n t}}{\sqrt{1 - \zeta^2}} K \sin\left(\sqrt{1 - \zeta^2}\omega_n t + \phi\right) + K \\ \phi &= \arcsin\sqrt{1 - \zeta^2} \end{aligned} \tag{1.35}$$

Examples of these three step responses are represented in Figure 1.7(c). Only for damping ratios less than unity does the step response overshoot the final value. Equation (1.35) shows that the frequency of the oscillations in the underdamped response in Figure 1.7(c) is the damped natural frequency $\omega_d = \omega_n\sqrt{1 - \zeta^2}$. A practical compromise between rapid rise time and minimal overshoot is a damping ratio of about 0.7.

EXAMPLE 1.6 For underdamped second-order instruments, find the damping ratio ζ from the step response.

ANSWER To obtain the maximums for the underdamped response, we take the derivative of (1.35) and set it to zero. For $\zeta < 0.3$, we approximate

positive maximums when the sine argument equals $3\pi/2$, $7\pi/2$, and so forth. This occurs at

$$t_n = \frac{3\pi/2 - \phi}{\omega_n\sqrt{1-\zeta^2}} \quad \text{and} \quad t_{n+1} = \frac{7\pi/2 - \phi}{\omega_n\sqrt{1-\zeta^2}} \tag{1.36}$$

The ratio of the first positive overshoot y_n to the second positive overshoot y_{n+1} [Figure 1.7(c)] is

$$\frac{y_n}{y_{n+1}} = \frac{\left(\frac{K}{\sqrt{1-\zeta^2}}\right)\left(\exp\left\{-\zeta\omega_n\left[\frac{(3\pi/2-\phi)}{\omega_n\sqrt{1-\zeta^2}}\right]\right\}\right)}{\left(\frac{K}{\sqrt{1-\zeta^2}}\right)\left(\exp\left\{-\zeta\omega_n\left[\frac{(7\pi/2-\phi)}{\omega_n\sqrt{1-\zeta^2}}\right]\right\}\right)} \tag{1.37}$$

$$= \exp\left(\frac{2\pi\zeta}{\sqrt{1-\zeta^2}}\right)$$

$$\ln\left(\frac{y_n}{y_{n+1}}\right) = \Lambda = \frac{2\pi\zeta}{\sqrt{1-\zeta^2}}$$

where Λ is defined as *logarithmic decrement*. Solving for ζ yields

$$\zeta = \frac{\Lambda}{\sqrt{4\pi^2 + \Lambda^2}} \tag{1.38}$$

For sinusoidal steady-state responses, the frequency transfer function (1.28) and Figure 1.7(d) show that low-pass frequency responses result. The rate of decline in the amplitude frequency response is twice the rate of that decline for first-order instruments. Note that resonance phenomena can occur if the damping ratio is too small. Also note that the output phase lag can be as much as 180°, whereas for single-order instruments, the maximal phase lag is 90°.

EXAMPLE 1.7 Figure E1.7(a) shows a physical model of a catheter–sensor system. The catheter is 1 m long, 6 French diameter and filled with water at 20 °C. The internal radius (r) of the catheter is 0.46 mm; volume modulus of elasticity ($E_d = \Delta P/\Delta V$) of the diaphragm is 0.49×10^{15} N/m^5; viscosity (η) of water at 20 °C = 0.001 Pa·s; density (ρ) of water = 1×10^3 kg/m^3. The physical model of a catheter–sensor system could be mathematically represented

using a second-order differential equation and the electrical equivalent *RLC* circuit is, where

$$R_c = \frac{8\eta L}{\pi r^4}; L_c = \frac{\rho L}{\pi r^2}; C_d = \frac{1}{E_d}$$

Use LTspice or PSpice simulation software (these software are freely available online through the respective companies) to simulate the frequency response curve for the catheter–sensor system. Describe the damping ratio for this system.

ANSWER Figure E1.7(b) shows the electrical equivalent R, L, and C model for the catheter–sensor system is $R = 5.687 \times 10^{10}$ Pa·s/m^3; $L = 1.504 \times 10^9$ kg/m^4; $C = 2.041 \times 10^{-15}$ m^5/N.

The AC analysis of the *RLC* circuit using LTspice results in the frequency response shown in Figure E1.7(c). The natural frequency for the sensor is about 90 Hz and it resembles the response for an underdamped system.

TIME DELAY

Instrument elements that give an output that is exactly the same as the input, except that it is delayed in time by τ_d, are defined as *time-delay elements*. The mathematical expression for these elements is

$$y(t) = K(t - \tau_d), \qquad t > \tau_d \tag{1.39}$$

These elements may also be called analog delay lines, transport lags, or dead times. Although first-order and second-order instruments have negative phase angles that imply time delays, the phase angle varies with frequency, so the delay is not constant for all frequencies. For time delays, the static characteristic is the constant K, the step response is specified by (1.39), and the sinusoidal frequency response for magnitude and phase is

$$\frac{Y(j\omega)}{X(j\omega)} = Ke^{-j\omega\tau_d} \tag{1.40}$$

Time delays are present in transmission lines (electric, mechanical, hydraulic blood vessels, and pneumatic respiratory tubing), magnetic tape recorders, and some digital signal-processing schemes. Usually these time delays are to be avoided, especially in instruments or systems that involve feedback, because undesired oscillations may result.

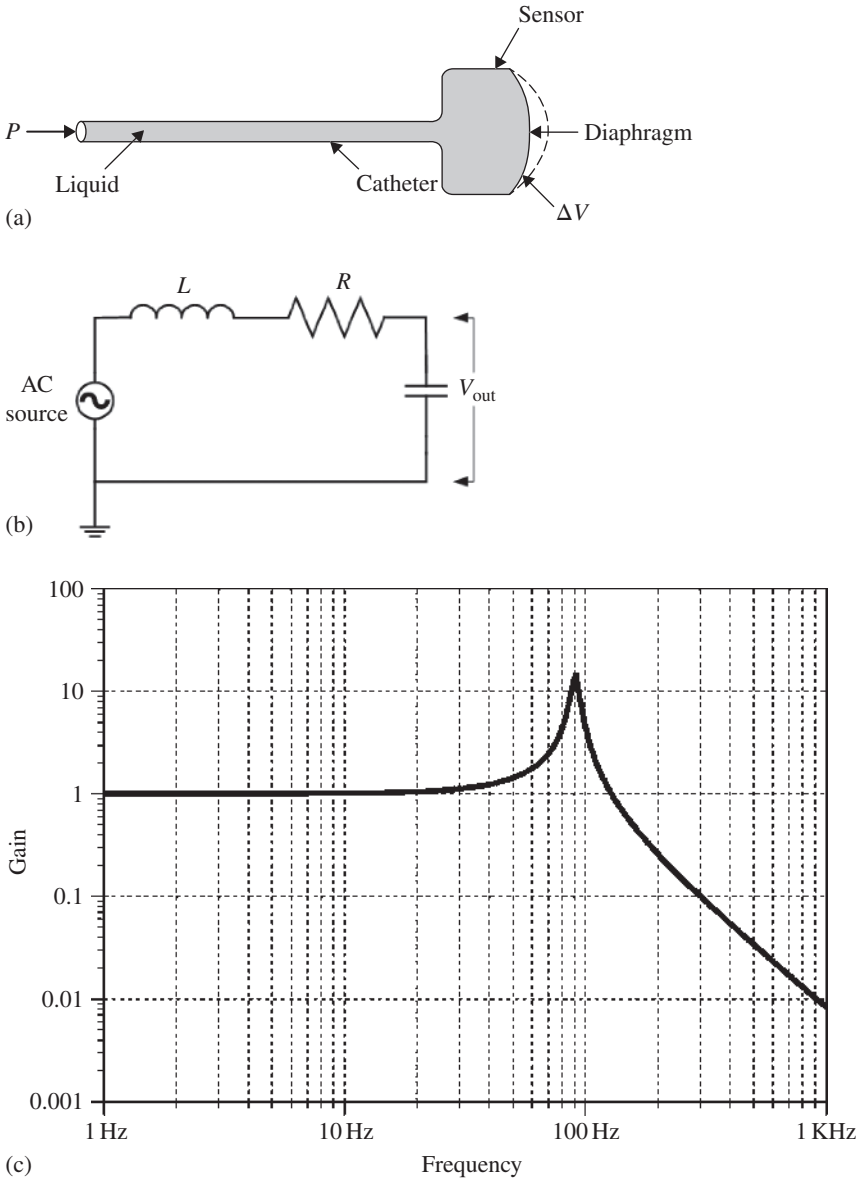


Figure E1.7 (a) A physical model of a catheter–sensor system. (b) Electrical equivalent R, L, and C model for the catheter-sensor system. (c) Frequency response of the RLC circuit.

If the instrument is used strictly for measurement and is not part of a feedback-control system, then some time delay is usually acceptable. The transfer function for undistorted signal reproduction with time delay becomes $Y(j\omega)/X(j\omega) = K \angle (-\omega\tau_d)$. Our previous study of time-delay elements shows that the output magnitude is K times the input magnitude for all frequencies and that the phase lag increases linearly with frequency.

The transfer-function requirements concern the *overall* instrument transfer function. The overall transfer function of linear elements connected in series is the product of the transfer functions for the individual elements. Many combinations of nonlinear elements can produce the overall linear transfer function required. Various forms of modulation and demodulation are used, and unavoidable sensor nonlinearities can sometimes be compensated for by other instrument elements.

1.11 AMPLIFIERS AND SIGNAL PROCESSING

Most bioelectric signals are small and require amplification. Amplifiers are also used for interfacing sensors that sense body motions, temperature, and chemical concentrations. In addition to simple amplification, the amplifier may also modify the signal to produce frequency filtering or nonlinear effects. This section emphasizes the *operational amplifier* (op amp), which has revolutionized electronic circuit design. Most circuit design was formerly performed with discrete components, requiring laborious calculations, many components, and large expense. Now a 20-cent op amp, a few resistors, and a knowledge of Ohm's law are all that is needed.

IDEAL OP AMPS

An *op amp* is a high-gain dc differential amplifier. It is normally used in circuits that have characteristics determined by external negative-feedback networks.

The best way to approach the design of a circuit that uses op amps is first to assume that the op amp is ideal. After the initial design, the circuit is checked to determine whether the nonideal characteristics of the op amp are important. If they are not, the design is complete; if they are, another design check is made, which may require additional components.

IDEAL CHARACTERISTICS

Figure 1.8 shows the equivalent circuit for a nonideal op amp. It is a dc differential amplifier, which means that any differential voltage, $v_d = (v_2 - v_1)$, is multiplied by the very high gain A to produce the output voltage v_o.

To simplify calculations, we assume the following characteristics for an ideal op-amp:

1. $A = \infty$ (gain is infinity)
2. $v_o = 0$, when $v_1 = v_2$ (no offset voltage)
3. $R_d = 0$ (input impedance is infinity)
4. $R_o = 0$ (output impedance is zero)
5. Bandwidth = ∞ (no frequency-response limitations) and no phase shift

Later in the chapter we shall examine the effect on the circuit of characteristics that are not ideal.

Figure 1.9 shows the op-amp circuit symbol, which includes two differential input terminals and one output terminal. All these voltages are

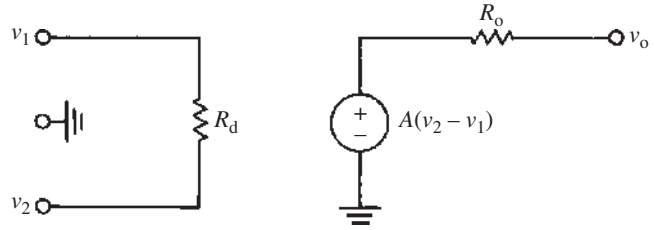


Figure 1.8 Op-amp equivalent circuit The two inputs are v_1 and v_2. A differential voltage between them causes current flow through the differential resistance R_d. The differential voltage is multiplied by A, the gain of the op amp, to generate the output-voltage source. Any current flowing to the output terminal v_o must pass through the output resistance R_o.

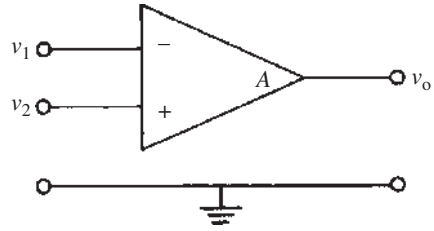


Figure 1.9 Op-amp circuit symbol A voltage at v_1, the inverting input, is greatly amplified and inverted to yield v_o. A voltage at v_2, the noninverting input, is greatly amplified to yield an in-phase output at v_o.

measured with respect to the ground shown. Power supplies, usually ±15 V, must be connected to terminals indicated on the manufacturer's specification sheet (Horowitz and Hill, 1989; Jung, 1986).

TWO BASIC RULES

Throughout this chapter we shall use two basic rules (or input terminal restrictions) that are very helpful in designing op-amp circuits.

RULE 1 *When the op-amp output is in its linear range, the two input terminals are at the same voltage.*

This is true because if the two input terminals were not at the same voltage, the differential input voltage would be multiplied by the infinite gain to yield an infinite output voltage. This is absurd; most op amps use a power supply of ±15 V, so v_o is restricted to this range. Actually the op-amp specifications guarantee a linear output range of only ±10 V, although some saturate at about ±13 V. A single supply is adequate with some op amps, such as the LM358 (Horowitz and Hill, 1989).

RULE 2 *No current flows into either input terminal of the op amp.*

This is true because we assume that the input impedance is infinity, and no current flows into an infinite impedance. Even if the input impedance were finite, Rule 1 tells us that there is no voltage drop across R_d, so therefore no current flows.

1.12 INVERTING AMPLIFIERS

CIRCUIT

Figure 1.10(a) shows the basic inverting-amplifier circuit, widely used in instrumentation, using, for example, a TL032 op amp. Note that a portion of v_o is fed back via R_f to the negative input of the op amp. This provides the inverting amplifier with the many advantages associated with the use of negative feedback—increased bandwidth, lower output impedance, and so forth. If v_0 is ever fed back to the positive input of the op amp, examine the circuit carefully. Either there is a mistake or the circuit is one of the rare ones in which a regenerative action is desired.

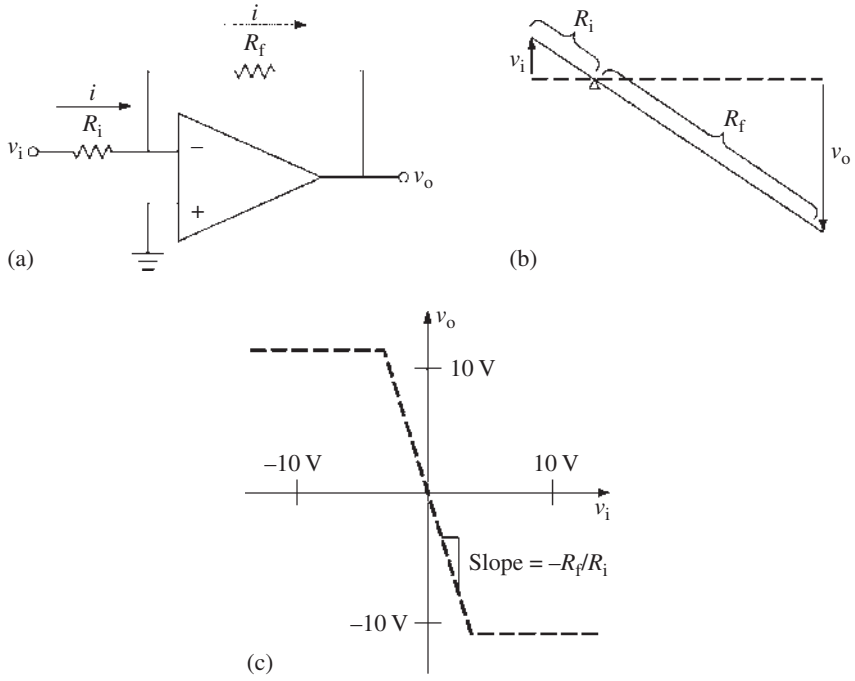


Figure 1.10 (a) An inverting amplifier. Current flowing through the input resistor R_i also flows through the feedback resistor R_f. (b) A lever with arm lengths proportional to resistance values enables the viewer to visualize the input–output characteristics easily. (c) The input–output plot shows a slope of $-R_f/R_i$ in the central portion, but the output saturates at about ±13 V.

EQUATION

Note that the positive input of the op amp is at 0 V. Therefore, by Rule 1, the negative input of the op amp is also at 0 V. Thus, no matter what happens to the rest of the circuit, the negative input of the op amp remains at 0 V, a condition known as a *virtual ground*.

Because the right side of R_i is at 0 V and the left side is v_i, by Ohm's law the current i through R_i is $i = v_i/R_i$. By Rule 2, no current can enter the op amp; therefore, i must also flow through R_f. This produces a voltage drop across R_f of iR_f. Because the left end of R_f is at 0 V, the right end must be

$$v_o = -iR_f = -v_i \frac{R_f}{R_i} \qquad \text{or} \qquad \frac{v_o}{v_i} = \frac{-R_f}{R_i} \tag{1.41}$$

Thus, the circuit inverts, and the *inverting-amplifier* gain (not the op-amp gain) is given by the ratio of R_f to R_i.

LEVER ANALOGY

Figure 1.10(b) shows an easy way to visualize the circuit's behavior. A lever is formed with arm lengths proportional to resistance values. Because the negative input is at 0 V, the fulcrum is placed at 0 V, as shown. If R_f is three times R_i, as shown, any variation of v_i results in a three-times-bigger variation of v_0. The circuit in Figure 1.10(a) is a voltage-controlled-current-source (VCCS) for any load R_f (Jung, 1986). The current i through R_f is v_i/R_i so v_i controls i. Current sources are useful in electrical impedance plethysmography for passing a fixed current through the body (Section 8.7).

INPUT–OUTPUT CHARACTERISTIC

Figure 1.10(c) shows that the circuit is linear only over a limited range of v_i. When v_o exceeds about ±13 V, it *saturates* (limits), and further increases in v_i produce no change in the output. The linear swing of v_o is about 4 V less than the difference in power-supply voltages. Although op amps usually have power-supply voltages set at ±15 V, reduced power-supply voltages may be used, with a corresponding reduction in the saturation voltages and the linear swing of v_o.

SUMMING AMPLIFIER

The inverting amplifier may be extended to form a circuit that yields the weighted sum of several input voltages. Each input voltage v_{i1}, v_{i2}, …, v_{ik} is connected to the negative input of the op amp by an individual resistor, the conductance of which ($1/R_{ik}$) is proportional to the desired weighting.

EXAMPLE 1.8 The output of a biopotential preamplifier that measures the electro-oculogram (Section 4.7) is an undesired dc voltage of ±5 V due to electrode half-cell potentials (Section 5.1), with a desired signal of ±1 V superimposed. Design a circuit that will balance the dc voltage to zero and provide a gain of −10 for the desired signal without saturating the op amp.

ANSWER Figure E1.8(a) shows the design. We assume that v_b, the balancing voltage available from the 5 kΩ potentiometer, is ±10 V. The undesired voltage at v_i = 5 V. For v_a = 0, the current through R_f is zero. Therefore, the sum of the currents through R_i and R_b is zero.

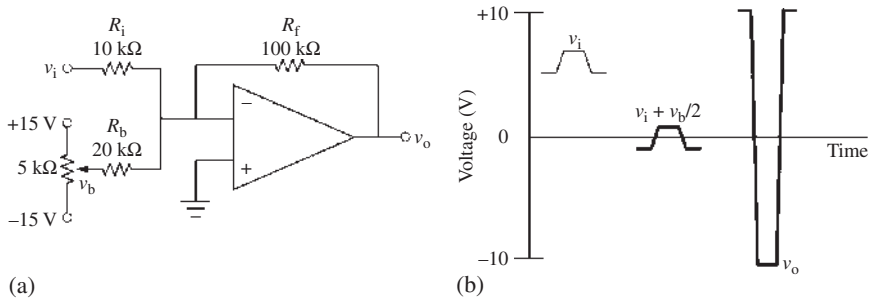


Figure E1.8 (a) This circuit sums the input voltage v_i plus one-half of the balancing voltage v_b. Thus, the output voltage v_o can be set to zero even when v_i has a nonzero dc component. (b) The three waveforms show v_i, the input voltage; $(v_i + v_b/2)$, the balanced-out voltage; and v_o, the amplified output voltage. If v_i were directly amplified, the op amp would saturate.

$$\frac{v_i}{R_i} + \frac{v_b}{R_b} = 0$$

$$R_b = \frac{-R_i v_b}{v} = \frac{-10^4(-10)}{5} = 2 \times 10^4\ \Omega$$

For a gain of –10, (1.41) requires R_f/R_i, =10, or R_f, =100 kΩ. The circuit equation is

$$v_o = -R_f\left(\frac{v_i}{R_i} + \frac{v_b}{R_b}\right)$$

$$v_o = -10^5\left(\frac{v_i}{10^4} + \frac{v_b}{2 \times 10^4}\right)$$

$$v_o = -10\left(v + \frac{v_b}{2}\right)$$

The potentiometer can balance out any undesired voltage in the range ±5 V, as shown by Figure E1.8(b).

1.13 NONINVERTING AMPLIFIERS

FOLLOWER

Figure 1.11(a) shows the circuit for a unity-gain follower. Because v_i exists at the positive input of the op amp, by Rule 1, v_i must also exist at the negative input. But v_0 is also connected to the negative input. Therefore, $v_o = v_i$, or the

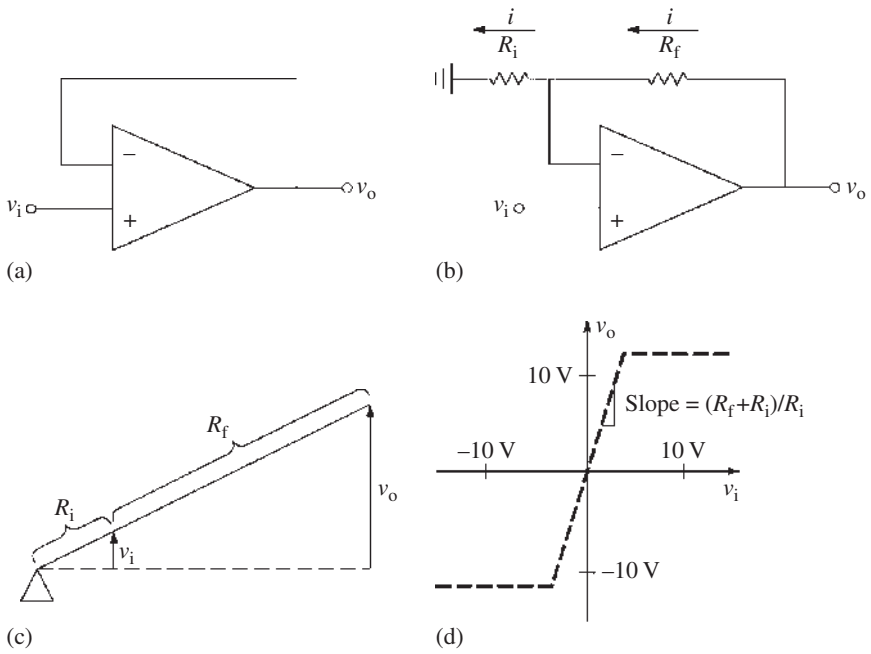


Figure 1.11 (a) A follower, $v_o = v_i$. (b) A noninverting amplifier, v_i, appears across R_i, producing a current through R_i that also flows through R_f. (c) A lever with arm lengths proportional to resistance values makes possible an easy visualization of input–output characteristics. (d) The input–output plot shows a positive slope of $(R_f + R_i)/R_i$ in the central portion, but the output saturates at about ±13 V.

output voltage follows the input voltage. At first glance it seems nothing is gained by using this circuit; the output is the same as the input. However, the circuit is very useful as a *buffer*, to prevent a high source resistance from being loaded down by a low-resistance load. By Rule 2, no current flows into the positive input, and therefore the source resistance in the external circuit is not loaded at all.

NONINVERTING AMPLIFIER

Figure 1.11(b) shows how the follower circuit can be modified to produce gain. By Rule 1, v_i appears at the negative input of the op amp. This causes current $i = v_i/R_i$ to flow to ground. By Rule 2, none of i can come from the negative input; therefore, all must flow through R_f. We can then calculate $v_o = i(R_f + R_i)$ and solve for the gain.

$$\frac{v_o}{v_i} = \frac{i(R_f + R_i)}{iR_i} = \frac{R_f + R_i}{R_i} \tag{1.42}$$

We note that the circuit gain (not the op-amp gain) is positive, always greater than or equal to 1; and that if $R_i = \infty$ (open circuit), the circuit reduces to Figure 1.11(a).

Figure 1.11(c) shows how a lever makes possible an easy visualization of the input–output characteristics. The fulcrum is placed at the left end, because R_i is grounded at the left end. v_i appears between the two resistors, so it provides an input at the central part of the diagram. v_o travels through an output excursion determined by the lever arms.

Figure 1.11(d), the input–output characteristic, shows that a one-op-amp circuit can have a positive amplifier gain. Again saturation is evident.

1.14 DIFFERENTIAL AMPLIFIERS

ONE-OP-AMP DIFFERENTIAL AMPLIFIER

The right side of Figure 1.12(a) shows a simple one-op-amp differential amplifier. Current flows from v_4 through R_3 and R_4 to ground. By Rule 2, no current flows into the positive input of the op amp. Hence, R_3 and R_4 act as a simple voltage-divider attenuator, which is unaffected by having the op amp attached or by any other changes in the circuit. The voltages in this part of the circuit are visualized in Figure 1.12(b) by the single lever that is attached to the fulcrum (ground).

By Rule 1, whatever voltage appears at the positive input also appears at the negative input. Once this voltage is fixed, the top half of the circuit behaves like an inverting amplifier. For example, if v_4 is 0 V, the positive input of the op amp is 0 V and the $v_3 - v_o$ circuit behaves exactly like an inverting amplifier. For other values of v_4, an inverting relation is obtained about some voltage intermediate between v_4 and 0 V. The relationship can be visualized in Figure 1.12(b) by noting that the two levers behave like a pair of scissors. The thumb and finger holes are v_4 and v_3, and the points are at v_o and 0 V.

We solve for the gain by finding v_5.

$$v_5 = \frac{v_4 R_4}{R_3 + R_4} \tag{1.43}$$

Then, solving for the current in the top half, we get

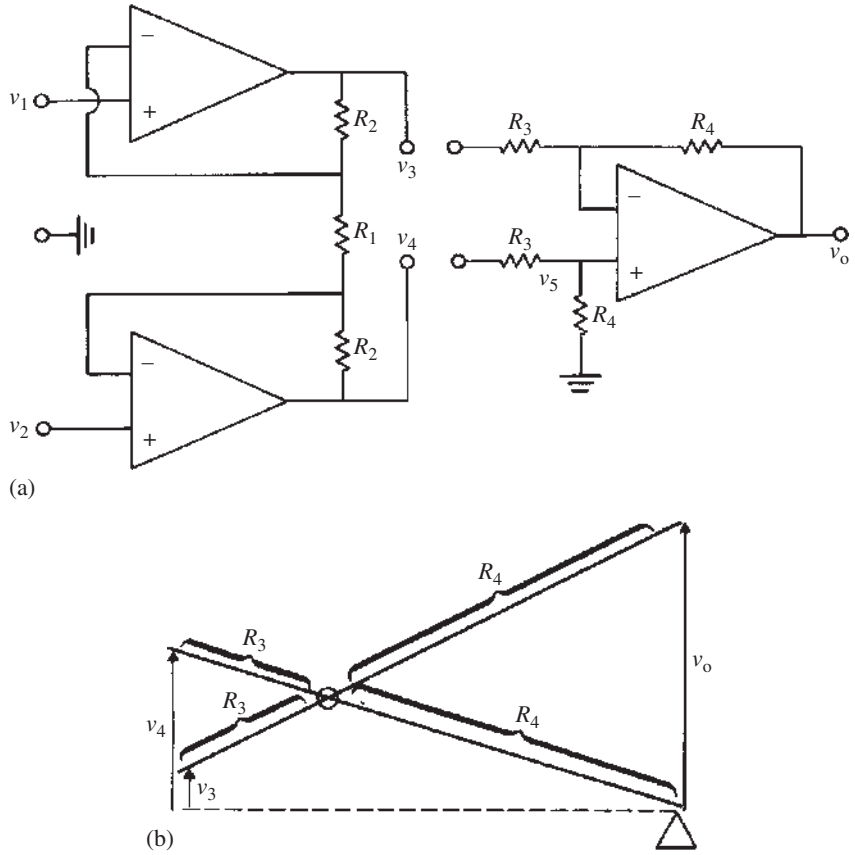


Figure 1.12 (a) The right side shows a one-op-amp differential amplifier, but it has low input impedance. The left side shows how two additional op amps can provide high input impedance and gain. (b) For the one-op-amp differential amplifier, two levers with arm lengths proportional to resistance values make possible an easy visualization of input–output characteristics.

$$i = \frac{v_3 - v_5}{R_3} = \frac{v_5 - v_o}{R_4} \tag{1.44}$$

Substituting (1.43) into (1.44) yields

$$v_o = \frac{(v_4 - v_3)R_4}{R_3} \tag{1.45}$$

This is the equation for a differential amplifier. If the two inputs are hooked together and driven by a common source, with respect to ground, then the *common-mode voltage* v_c is $v_3 = v_4$. Equation (1.45) shows that the ideal output is 0. The differential amplifier-circuit (not op-amp) *common-mode gain* G_c is 0. In Figure 1.12(b), imagine the scissors to be closed. No matter how the inputs are varied, $v_o = 0$.

If on the other hand $v_3 \neq v_4$, then the differential voltage $(v_4 - v_3)$ produces an amplifier-circuit (not op-amp) *differential gain* G_d that from (1.45) is equal to R_4/R_3. This result can be visualized in Figure 1.12(b) by noting that as the scissors open, v_o is geometrically related to $(v_4 - v_3)$ in the same ratio as the lever arms, R_4/R_3.

No differential amplifier perfectly rejects the common-mode voltage. To quantify this imperfection, we use the term *common-mode rejection ratio* (CMRR), which is defined as

$$\text{CMRR} = \frac{G_d}{G_c} \tag{1.46}$$

This factor may be lower than 100 for some oscilloscope differential amplifiers and higher than 10,000 for a high-quality biopotential amplifier.

EXAMPLE 1.9 A blood pressure sensor uses a four-active-arm Wheatstone strain-gage bridge excited with 5 V dc. At full scale, each arm changes resistance by ±0.3%. Design an amplifier that will provide a full-scale output over the op amp's full range of linear operation. Use the minimal number of components.

ANSWER From (2.6), $\Delta v_o = v_i \Delta R/R = 5\,\text{V}\ (0.003) = 0.015\,\text{V}$. Gain = 20/0.015 = 1333. Assume $R = 120\,\Omega$. Then the Thevenin source impedance = 60 Ω. Use this to replace R_3 of Figure 1.12(a) right side. Then, $R_4 = R_3 \times \text{gain} = 60\,\Omega \times 1333 = 80\,\text{k}\Omega$.

EXAMPLE 1.10 Derive the expression of differential mode gain (G_d) and common-mode gain (G_c) for one-op-amp differential amplifier with unmatched resistors.

ANSWER Figure E1.10 shows the one-amp differential amplifier with differential signal (V_{dm}) and common-mode signal (V_{cm}) such that the output voltage (V_{out}) is given as

$$V_{out} = G_d \times V_{dm} + G_c \times V_{cm}$$

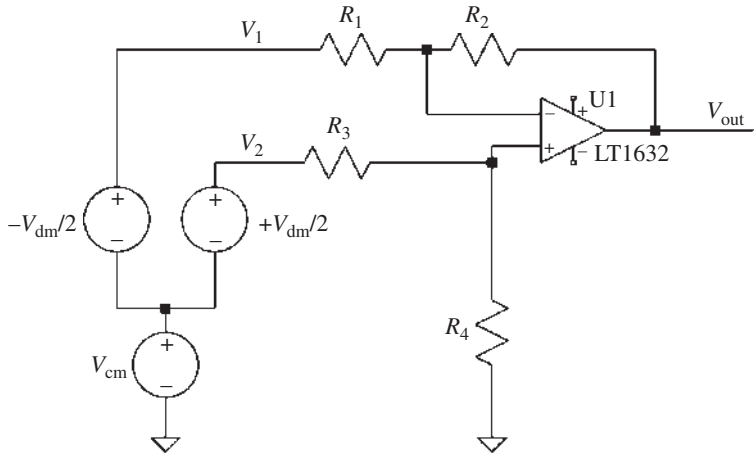


Figure E1.10 The differential signal given as $V_{dm} = (V_2 - V_1)$ and the common-mode signal given as $V_{cm} = (V_2 + V_1)/2$.

$$V_{dm} = (V_2 - V_1) \tag{E1.4}$$

$$V_{cm} = (V_2 + V_1)/2 \tag{E1.5}$$

$$V_2 = V_{cm} + (V_{dm}/2) \tag{E1.6}$$

$$V_1 = V_{cm} - (V_{dm}/2) \tag{E1.7}$$

$$V_{out} = \left(1 + \frac{R_2}{R_1}\right)\left(\frac{R_4}{R_3 + R_4}\right) V_2 - \left(\frac{R_2}{R_1}\right) V_1 \tag{E1.8}$$

Substituting Eqs. (E1.6) and (E1.7) in (E1.8) we get

$$V_{out} = \left(\frac{R_1R_4 + R_2R_3 + 2R_2R_4}{2R_1(R_3 + R_4)}\right) V_{dm} + \left(\frac{R_1R_4 - R_2R_3}{R_1(R_3 + R_4)}\right) V_{cm} \tag{E1.9}$$

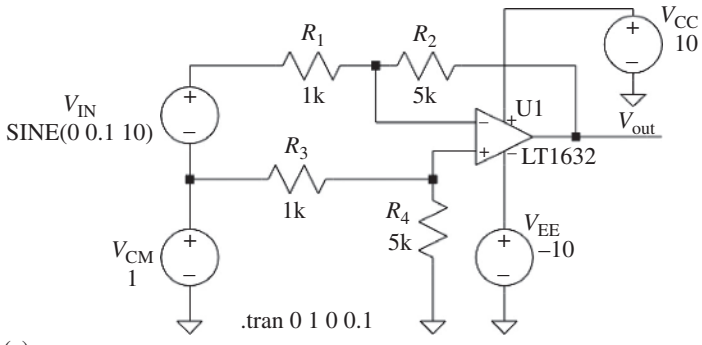
From (E1.9) we have

$$\text{Differential gain } G_d = \left(\frac{R_1R_4 + R_2R_3 + 2R_2R_4}{2R_1(R_3 + R_4)}\right)$$

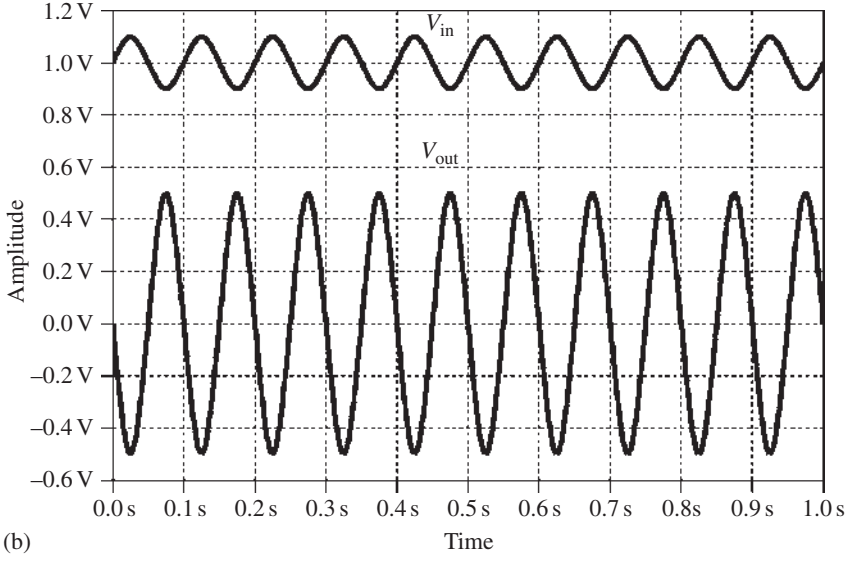
$$\text{Common} - \text{mode gain } G_c = \left(\frac{R_1R_4 - R_2R_3}{R_1(R_3 + R_4)}\right)$$

EXAMPLE 1.11 You have a physiological signal (represented as a sinusoid signal) with amplitude of 100 mV, frequency of 10 Hz, and a dc offset of 1 V. Design a one-op-amp differential amplifier with gain of 5 to amplify the signal and remove the dc offset. Use LTspice simulation to determine the common-mode gain if the value of resistor R2 in Figure E1.11(a) changes by 1%.

ANSWER One-op-amp differential amplifier with gain of 5 is shown in Figure E1.11(a). The offset to the signal is represented as a common-mode voltage $V_{CM} = 1$ V.



(a)



(b)

Figure E1.11 (a) One-op-amp differential amplifier with gain of 5. (b) Input signal (100 mV with 1 V offset) and amplified output signal with no offset.

Since R_2 changes by 1%, we have the new $R_2 = 5.05\,\text{k}\Omega$. For the LTspice simulation, set amplitude for $V_{IN} = 0\,\text{V}$ using statement SINE(0 0 10), $V_{CM} = 1\,\text{V}$, and LTspice directive as .tran 0 1 0 0.1. Run the simulation and observe the V_{OUT} on the graph as shown in Figure E1.11(b), which is about −8.33 mV. Thus, the common-mode gain $G_c = 8.33\,\text{mV}/1\,\text{V}$.

THREE-OP-AMP DIFFERENTIAL AMPLIFIER

The one-op-amp differential amplifier is quite satisfactory for low-resistance sources, such as strain-gage Wheatstone bridges (Section 2.3). But the input resistance is too low for high-resistance sources. Our first recourse is to add the simple follower shown in Figure 1.11(a) to each input. This provides the required buffering. Because this solution uses two additional op amps, we can also obtain gain from these buffering amplifiers by using a noninverting amplifier, as shown in Figure 1.11(b). However, this solution amplifies the common-mode voltage, as well as the differential voltage, so there is no improvement in CMRR.

A superior solution is achieved by hooking together the two R_i's of the noninverting amplifiers and eliminating the connection to ground. The result is shown on the left side of Figure 1.12(a). To examine the effects of common-mode voltage, assume that $v_1 = v_2$. By Rule 1, v_1 appears at both negative inputs to the op amps. This places the same voltage at both ends of R_1. Hence, current through R_1 is 0. By Rule 2, no current can flow from the op-amp inputs. Hence, the current through both R_2's is 0, so v_1 appears at both op-amp outputs and the G_c is 1.

To examine the effects when $v_1 \neq v_2$, we note that $v_1 - v_2$ appears across R_1. This causes a current to flow through R_1 that also flows through the resistor string R_2, R_1, R_2. Hence, the output voltage

$$v_3 - v_4 = i(R_2 + R_1 + R_2)$$

whereas the input

$$v_1 - v_2 = iR_1$$

The differential gain is then

$$G_d = \frac{v_3 - v_4}{v_1 - v_2} = \frac{2R_2 + R_1}{R_1} \tag{1.47}$$

Since the G_c is 1, the CMRR is equal to the G_d, which is usually much greater than 1. When the left and right halves of Figure 1.12(a) are combined, the resulting three-op-amp amplifier circuit is frequently called an *instrumentation*

amplifier. It has high input impedance, a high CMRR, and a gain that can be changed by adjusting R_1. This circuit finds wide use in measuring biopotentials (Section 6.7), because it rejects the large 60 Hz common-mode voltage that exists on the body.

Instrumentation amplifier (for example, LT1920) combines the three op amps of Figure 1.12 into a single package where gain can be adjusted by a single external resistor.

1.15 COMPARATORS

SIMPLE

A comparator is a circuit that compares the input voltage with some reference voltage. The comparator's output flips from one saturation limit to the other, as the negative input of the op amp passes through 0 V. For v_i greater than the comparison level, $v_o = -13$ V. For v_i less than the comparison level, $v_o = +13$ V. Thus, this circuit performs the same function as a *Schmitt trigger*, which detects an analog voltage level and yields a logic level output. The simplest comparator is the op amp itself, as shown in Figure 1.9. If a reference voltage is connected to the positive input and v_i is connected to the negative input, the circuit is complete. The inputs may be interchanged to invert the output. The input circuit may be expanded by adding the two R_1 resistors shown in Figure 1.13(a). This provides a known input resistance for the circuit and minimizes overdriving the op-amp input. Figure 1.13(b) shows that the comparator flips when $v_i = -v_{ref}$. To avoid

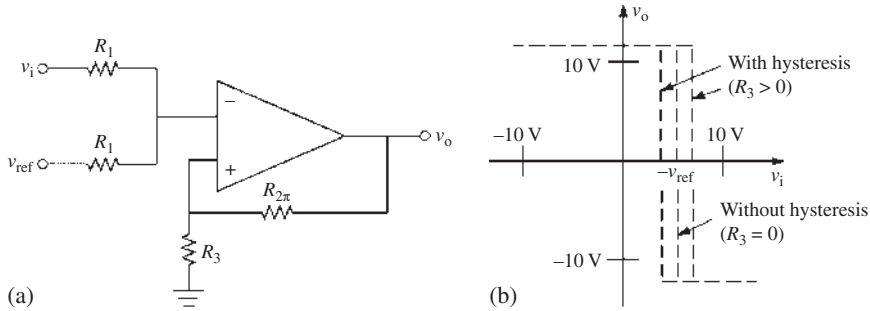


Figure 1.13 (a) Comparator. When $R_3 = 0$, v_o indicates whether $(v_I + v_{ref})$ is greater or less than 0 V. When R_3 is larger, the comparator has hysteresis, as shown in (b), the input–output characteristic.

building a separate power supply for v_{ref}, we can connect v_{ref} to the −15 V power supply and adjust the values of the input resistors so that the negative input of the op amp is at 0 V when v_i is at the desired positive comparison level. When negative comparison levels are desired, v_{ref} is connected to the +15 V power supply.

WITH HYSTERESIS

For a simple comparator, if v_i is at the comparison level and there is noise on v_i, then v_o fluctuates wildly. To prevent this, we can add hysteresis to the comparator by adding R_2 and R_3, as shown in Figure 1.13(a). The effect of this positive feedback is illustrated by the input–output characteristics shown in Figure 1.13(b). To analyze this circuit, first assume that $v_{ref} = -5$ V and $v_i = +10$ V. Then, because the op amp inverts and saturates, $v_0 = -13$ V. Divide v_o by R_2 and R_3 so that the positive input is at, say, −1 V. As v_i is lowered, the comparator does not flip until v_i reaches +3 V, which makes the negative input equal to the positive input, −1 V. At this point, v_0 flips to +13 V, causing the positive input to change to +1 V. Noise on v_i cannot cause v_0 to flip back, because the negative input must be raised to +1 V to cause the next flip. This requires v_i to be raised to +7 V, at which level the circuit can flip back to its original state. From this example, we see that the width of the hysteresis is four times as great as the magnitude of the voltage across R_3. The width of the hysteresis loop can be varied by replacing R_3 by a potentiometer.

EXAMPLE 1.12 A physiological signal (represented by a sinusoidal signal of 10 Hz) is amplified such that it has a voltage swing from −1 V to +10 V. However, along with signal, the noise overriding the signal gets amplified too. Design a comparator with hysteresis of window of 4 V, such that the comparator flips to $V_{OH} = +12$ V when the input is 0 V and $V_{OL} = -12$ V when the input is 4 V. Provide LTspice simulation results for the comparator (Figure E1.12).

ANSWER For Figure 1.13(a) shown:

The voltage at the + terminal of the op-amp $V^+ = [R_3/(R_2 + R_3)] \times V_o$

The voltage at the − terminal of the op-amp $V^- = (V_i + V_{ref})/2$

The differential voltage $V_d = V^+ - V^- = [R_3/(R_2 + R_3)] \times V_o - (V_i + V_{ref})/2$

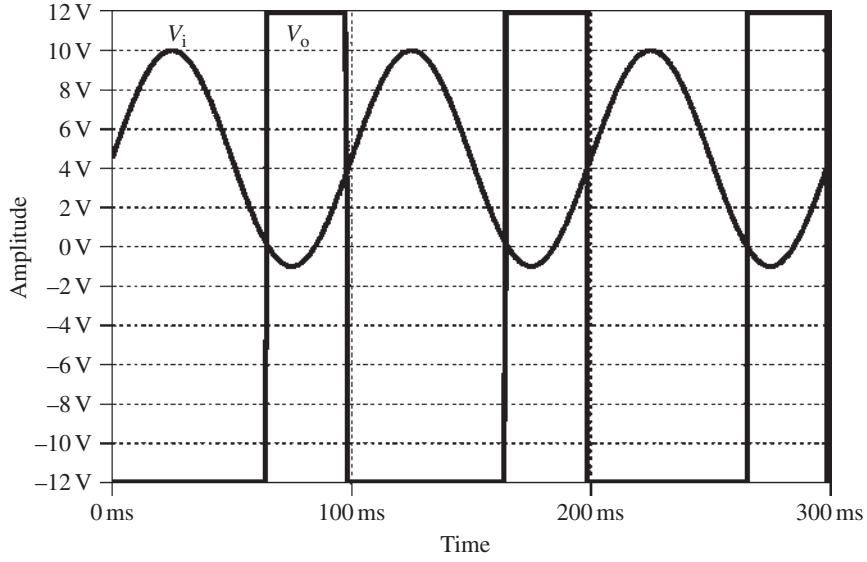


Figure E1.12 LTspice simulation for the comparator with hysteresis design.

The threshold voltage at $V_d = 0$ is given as $V_T = [R_3/(R_2 + R_3)] \times V_o$

The upper threshold is given as $V_{TU} = [R_3/(R_2 + R_3)] \times (12) = (V_i + V_{ref})/2$; when $V_i = 4$ V

The lower threshold is given as $V_{TL} = [R_3/(R_2 + R_3)] \times (-12) = (V_i + V_{ref})/2$; when $V_i = 0$ V

Solving the above two equations, we have $V_{ref} = -2$ V. Select $R_3 = 1$ kΩ and $R_2 = 11$ kΩ

1.16 RECTIFIERS

Simple resistor–diode rectifiers do not work well for voltages below 0.7 V, because the voltage is not sufficient to overcome the forward voltage drop of the diode. This problem can be overcome by placing the diode within the feedback loop of an op amp, thus reducing the voltage limitation by a factor equal to the gain of the op amp.

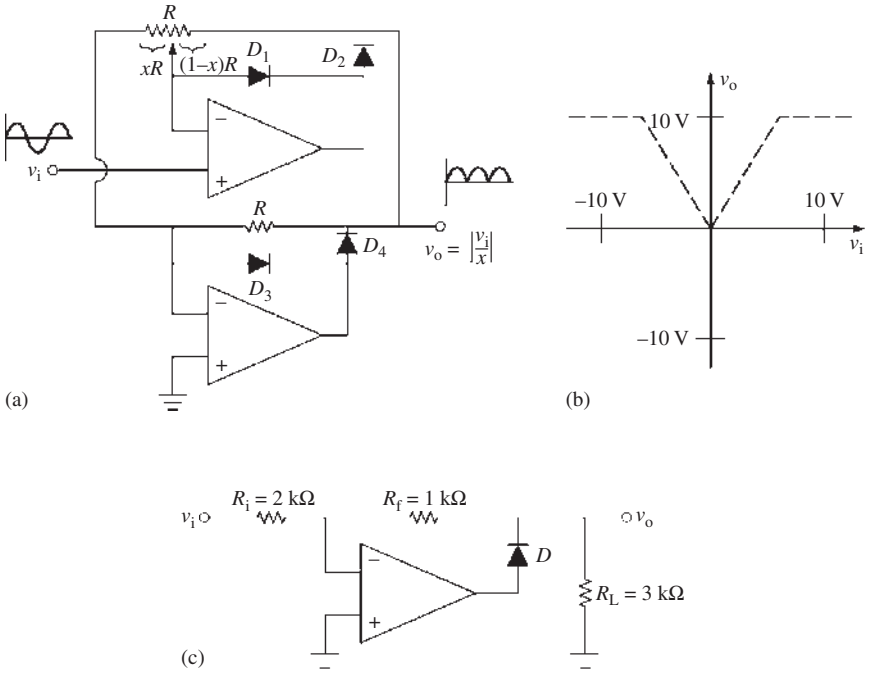


Figure 1.14 (a) Full-wave precision rectifier. For $v_i > 0$, the noninverting amplifier at the top is active, making $v_o > 0$. For $v_i < 0$, the inverting amplifier at the bottom is active, making $v_o > 0$. Circuit gain may be adjusted with a single pot. (b) Input–output characteristics show saturation when $v_o > +13$ V. (Reprinted with permission from *Electronics Magazine*, copyright December 12, 1974; Penton Publishing, Inc.) (c) One-op-amp full-wave rectifier. For $v_i < 0$, the circuit behaves like the inverting amplifier rectifier with a gain of +0.5. For $v_i > 0$, the op amp disconnects and the passive resistor chain yields a gain of +0.5.

Figure 1.14(a) shows the circuit for a full-wave precision rectifier (Graeme, 1974b). For $v_i > 0$, D_2 and D_3 conduct, whereas D_i and D_4 are reverse biased. The top op amp is a noninverting amplifier with a gain of $1/x$, where x is a fraction corresponding to the potentiometer setting. Because D_4 is not conducting, the lower op amp does not contribute to the output.

For $v_i < 0$, D_1 and D_4 conduct, while D_2 and D_3 are reverse biased. At the potentiometer wiper v_i serves as the input to the lower op-amp inverting amplifier, which has a gain of $-1/x$. Because D_2 is not conducting, the upper

op amp does not contribute to the output. And because the polarity of the gain switches with the polarity of v_i, $v_o = |v_i/x|$.

The advantage of this circuit over other full-wave rectifier circuits (Wait *et al.*, 1975, p. 173) is that the gain can be varied with a single potentiometer and the input resistance is very high. If only a half-wave rectifier is needed, either the noninverting amplifier or the inverting amplifier can be used separately, thus requiring only one op amp. The perfect rectifier is frequently used with an integrator to quantify the amplitude of electromyographic signals (Section 6.8).

Figure 1.14(c) shows a one-op-amp full-wave rectifier (Tompkins and Webster, 1988). Unlike other full-wave rectifiers, it requires the load to remain constant, because the gain is a function of load.

EXAMPLE 1.13 For the circuit shown in Figure E1.13(a), determine the relation between V_{in} and V_{OUT}.

ANSWER During the –ve half of V_{in} diode D_1 is reversed biased and diode D_2 is forward biased as shown in Figure E1.13(b).

Step I: Applying KCL at node Z (current entering the node = current leaving the node), we have

$(V_{in} - 0)/R_1 = (0 - V')/(R_2 + R_4) + (0 - V')/R_3$

$V_{in} = -3/2V'$

Step II: Applying KCL at node C, we have

$(0 - V'/(R_2 + R_4) = (V' - V_{out})/R_5$

$V_{out} = 3/2\ V'$

From Steps I and II, we have during the –ve half of V_{in}, $V_{out} = -V_{in}$

During the +ve half of V_{in}, we have diodes D_2 is reversed biased and D_1 is forward biased as shown in the Figure E1.13(c).

Step III: Applying KCL at node Z (current entering the node = current leaving the node), we have

$(V_{in} - 0)/R_1 = (0 - V')/(R_2)$

$V_{in} = -3/2V'$

Step IV: Applying KCL at node C, we have

$(0 - V')/(R_2) = (0 - V_{out})/R_5$

$V_{out} = -V'$

From Steps III and IV, we have during the +ve half of V_{in}, $V_{out} = +V_{in}$.

The circuit behaves as a full-wave rectifier.

The V_{in} and V_{out} waveforms using LTspice simulation are shown in Figure E1.13(d) and (e), respectively.

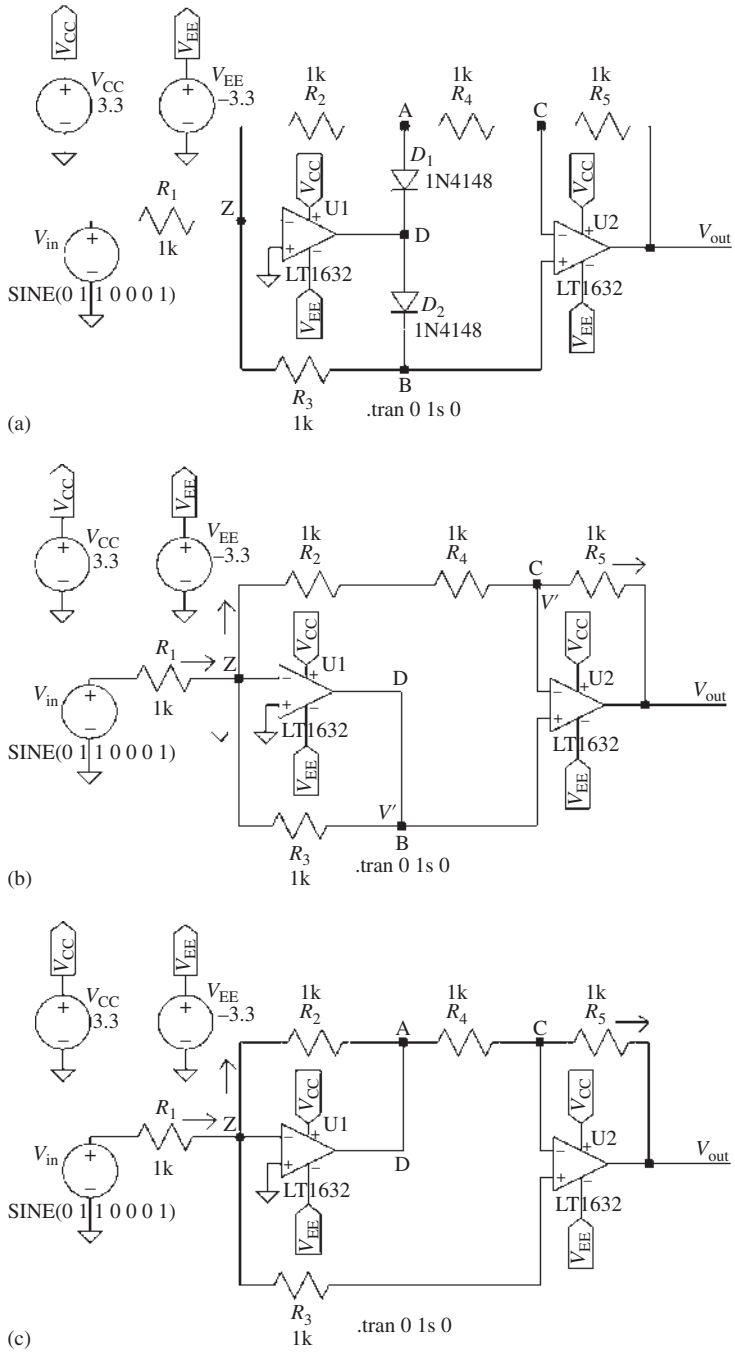
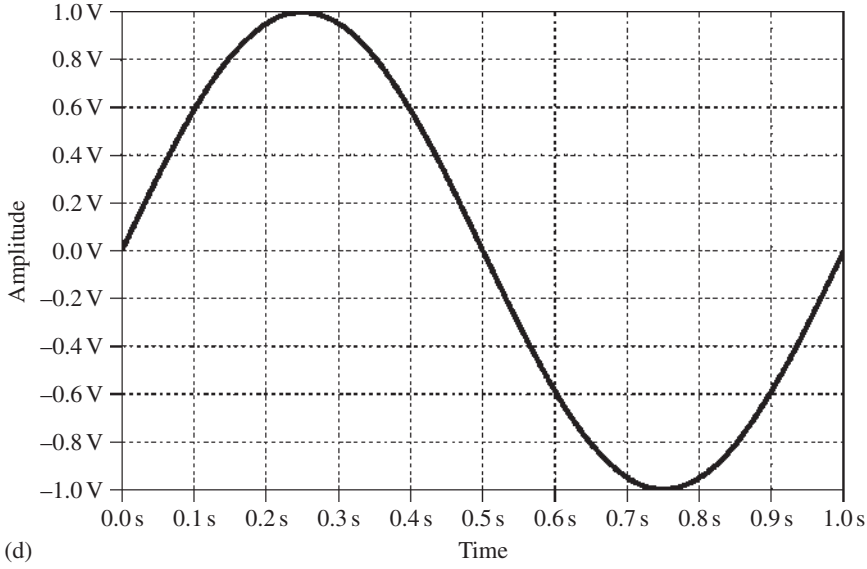
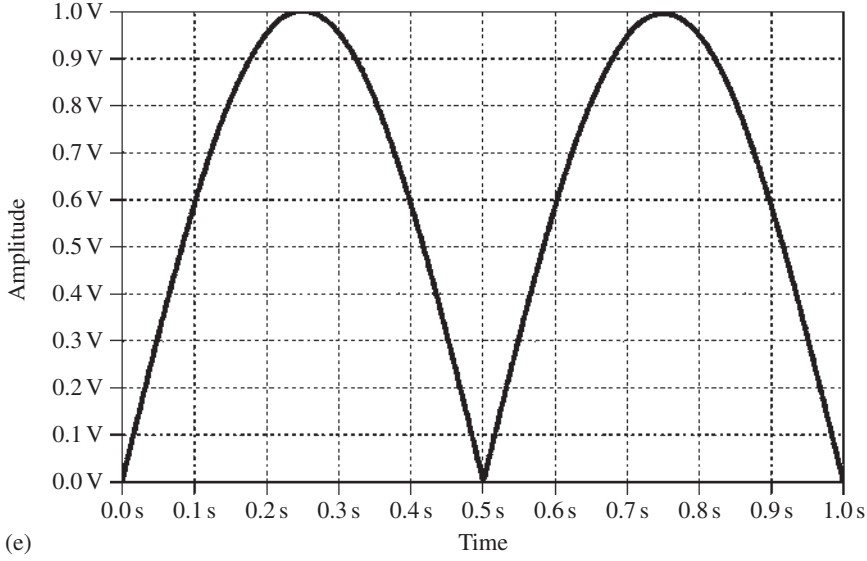


Figure E1.13 (a) The input V_{in} is sinusoidal signal with $V_p = 1$ V centered at ground. The diodes D_1 and D_2 are forward and reversed biased depending on the polarity of V_{in} signal. (b) Equivalent circuit during the –ve half of V_{in}. (c) Equivalent circuit during the +ve half of V_{in}. (d) V_{in} and (e) V_{out} for the full-wave rectified circuit.



(d)



(e)

Figure E1.13 (*Continued*)

1.17 LOGARITHMIC AMPLIFIERS

The logarithmic amplifier makes use of the nonlinear volt–ampere relation of the silicon planar transistor (Jung, 1986).

$$V_{BE} = 0.060 \log \left(\frac{I_C}{I_S} \right) \tag{1.48}$$

where

$$\begin{aligned} V_{BE} &= \text{base – emitter voltage} \\ I_C &= \text{collector current} \\ I_S &= \text{reverse saturation current, } 10^{-13} \text{ A at } 27^\circ\text{C} \end{aligned}$$

The transistor is placed in the *transdiode* configuration shown in Figure 1.15(a), in which $I_C = v_i/R_i$. Then, the output $v_o = V_{BE}$ is logarithmically related to v_i as given by (1.48) over the approximate range 10^{-7} A $< I_C < 10^{-2}$ A. The approximate range of v_o is –0.36 to –0.66 V, so larger ranges of v_o are sometimes obtained by the alternate switch position shown in Figure 1.15(a). The resistor network feeds back only a fraction of v_o in order to boost v_o and uses the same principle as that used in the noninverting amplifier. Figure 1.15(b) shows the input–output characteristics for each of these circuits.

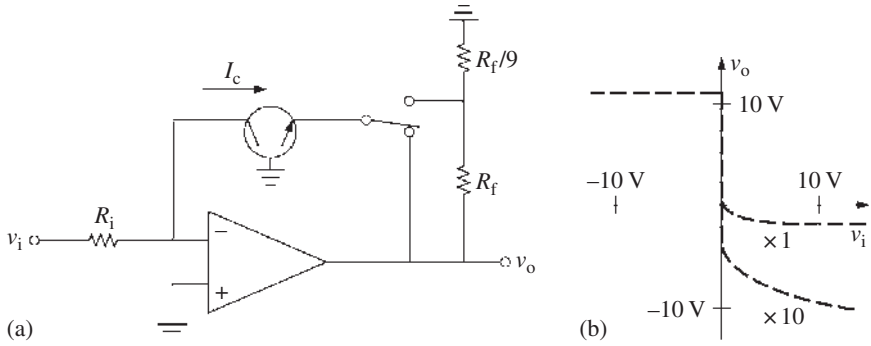


Figure 1.15 (a) A logarithmic amplifier makes use of the fact that a transistor's V_{BE} is related to the logarithm of its collector current. With the switch thrown in the alternate position, the circuit gain is increased by 10. (b) Input–output characteristics show that the logarithmic relation is obtained for only one polarity; ×1 and ×10 gains are indicated.

Because semiconductors are temperature-sensitive, accurate circuits require temperature compensation. Antilog (exponential) circuits are made by interchanging the resistor and semiconductor. These log and antilog circuits are used to multiply a variable, divide it, or raise it to a power; to compress large dynamic ranges into small ones; and to linearize the output of devices with logarithmic or exponential input–output relations. In the spectrophotometer (Section 11.1), the logarithmic converter can be used to convert transmittance to absorbance.

1.18 INTEGRATORS

So far in this chapter, we have considered only circuits with a flat gain-versus-frequency characteristic. Now let us consider circuits that have a deliberate change in gain with frequency. The first such circuit is the integrator. Figure 1.16 shows the circuit for an *integrator,* which is obtained by closing switch S_i. The voltage across an initially uncharged capacitor is given by

$$v = \frac{1}{C}\int_0^{t_1} i\,dt \tag{1.49}$$

where i is the current through C and t_1 is the integration time. For the integrator, for v_i positive, the input current $i = v_i/R$ flows through C in a direction to cause v_o to move in a negative direction. Thus,

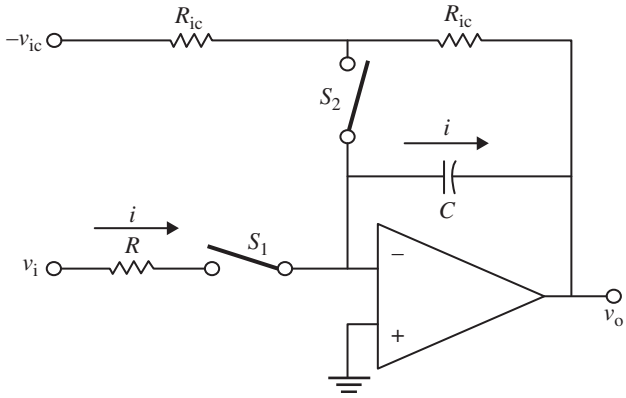


Figure 1.16 A three-mode integrator With S_1 open and S_2 closed, the dc circuit behaves as an inverting amplifier. Thus, $v_o = v_{ic}$ and v_o can be set to any desired initial condition. With S_i closed and S_2 open, the circuit integrates. With both switches open, the circuit holds v_o constant, making possible a leisurely readout.

$$v_o = -\frac{1}{RC}\int_0^{t_1} v_i dt + v_{ic} \tag{1.50}$$

This shows that v_o is equal to the negative integral of v_i, scaled by the factor $1/RC$ and added to v_{ic}, the voltage due to the initial condition. For $v_o = 0$ and v_i = constant, $v_o = -v_i$ after an integration time equal to RC. Because any real integrator eventually drifts into saturation, a means must be provided to restore v_o to any desired initial condition. If an initial condition of $v_o = 0$ V is desired, a simple switch to short out C is sufficient. For more versatility, S_1 is opened and S_2 closed. This dc circuit then acts as an inverting amplifier, which makes $v_o = v_{ic}$. During integration, S_1 is closed and S_2 open. After the integration, both switches may be opened to hold the output at the final calculated value, thus permitting time for readout. The circuit is useful for computing the area under a curve, as technicians do when they calculate cardiac output (Section 8.2).

The frequency response of an integrator is easily analyzed because the formula for the inverting amplifier gain (1.41) can be generalized to any input and feedback impedances. Thus, for Figure 1.16, with S_1 closed,

$$\begin{aligned}\frac{V_o(j\omega)}{V_i(j\omega)} &= -\frac{Z_f}{Z_i} = -\frac{1/j\omega C}{R} \\ &= -\frac{1}{j\omega RC} = -\frac{1}{j\omega\tau}\end{aligned} \tag{1.51}$$

where $\tau = RC$, $\omega = 2\pi f$, and f = frequency. Equation (1.51) shows that the circuit gain decreases as R increases, Figure 1.17 shows the frequency response, and Eq. (1.51) shows that the circuit gain is 1 when $\omega\tau = 1$.

1.19 DIFFERENTIATORS

Interchanging the integrator's R and C yields the differentiator shown in Figure 1.18.

The current through a capacitor is given by

$$i = C\frac{dv}{dt} \tag{1.52}$$

If dv_i/dt is positive, i flows through R in a direction such that it yields a negative v_0. Thus,

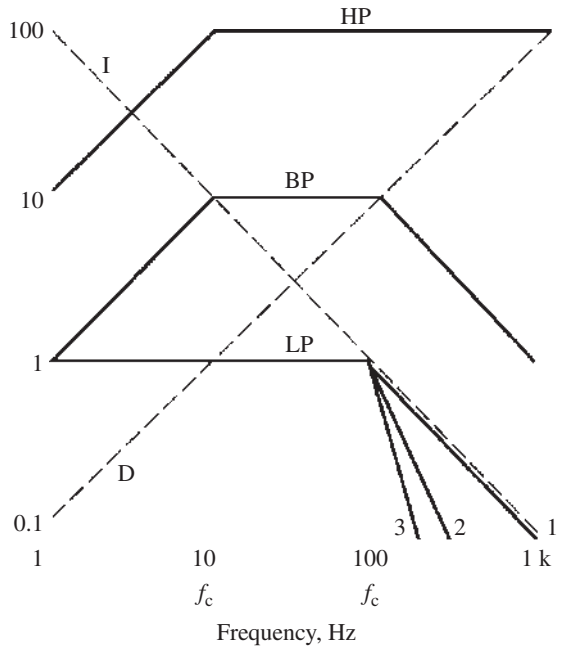


Figure 1.17 Bode plot (gain versus frequency) for various filters Integrator (I); differentiator (D); low pass (LP), 1, 2, 3 section (pole); high pass (HP); bandpass (BP). Corner frequencies f_c for high-pass, low-pass, and bandpass filters.

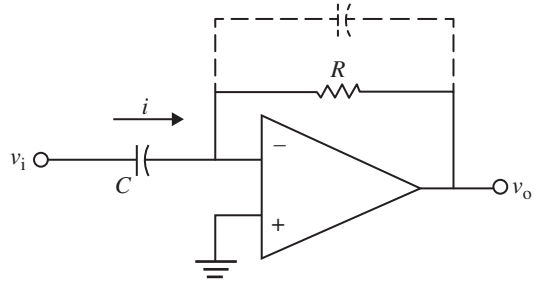


Figure 1.18 A differentiator The dashed lines indicate that a small capacitor must usually be added across the feedback resistor to prevent oscillation.

$$v_o = -RC\frac{dv_i}{dt} \tag{1.53}$$

The frequency response of a differentiator is given by the ratio of feedback to input impedance.

$$\frac{V_o(j\omega)}{V_i(j\omega)} = -\frac{Z_f}{Z_i} = -\frac{R}{1/j\omega C} \\ = -j\omega RC = -j\omega\tau \tag{1.54}$$

Equation (1.54) shows that the circuit gain increases as f increases and that it is equal to unity when $\omega\tau = 1$. Figure 1.17 shows the frequency response.

Unless specific preventive steps are taken, the circuit tends to oscillate. The output also tends to be noisy, because the circuit emphasizes high frequencies. A differentiator followed by a comparator is useful for detecting an event, the slope of which exceeds a given value—for example, detection of the R wave in an electrocardiogram.

1.20 ACTIVE FILTERS

LOW-PASS FILTER

Figure 1.6(a) shows a low-pass filter that is useful for attenuating high-frequency noise. A low-pass active filter can be obtained by using the one-op-amp circuit shown in Figure 1.19(a). The advantages of this circuit are that it is capable of gain and that it has very low output impedance. The frequency response is given by the ratio of feedback to input impedance.

$$\frac{V_o(j\omega)}{V_i(j\omega)} = -\frac{Z_f}{Z_i} = -\frac{\dfrac{(R_f/j\omega C_f)}{[(1/j\omega C_f) + R_f]}}{R_i} \\ = -\frac{R_f}{(1 + j\omega R_f C_f)R_i} = -\frac{R_f}{R_i}\frac{1}{1 + j\omega\tau} \tag{1.55}$$

where $\tau = R_f C_f$. Note that (1.55) has the same form as (1.23). Figure 1.17 shows the frequency response, which is similar to that shown in Figure 1.6 (d). For $\omega \ll 1/\tau$, the circuit behaves as an inverting amplifier (Figure 1.10), because the impedance of C_f is large compared with R_f. For $\omega \gg 1/\tau$, the circuit behaves as an integrator (Figure 1.16), because C_f is the dominant feedback impedance. The *corner frequency* f_c, which is defined by the intersection of the two asymptotes shown, is given by the relation $\omega\tau = 2\pi f_c\tau = 1$. When a designer wishes to limit the frequency of a wide-band amplifier, it is not necessary to add a separate stage, as shown in Figure 1.19(a), but only to add the correct size C_f to the existing wide-band amplifier.

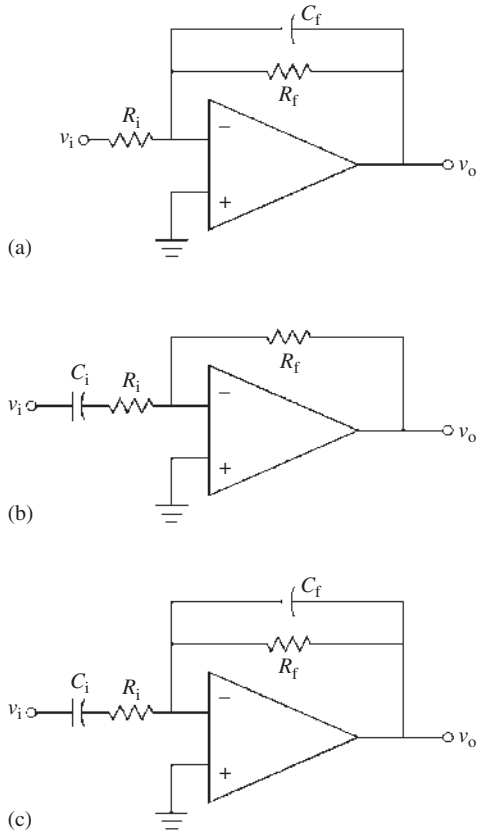


Figure 1.19 Active filters (a) A low-pass filter attenuates high frequencies. (b) A high-pass filter attenuates low frequencies and blocks dc. (c) A bandpass filter attenuates both low and high frequencies.

HIGH-PASS FILTER

Figure 1.19(b) shows a one-op-amp high-pass filter. Such a circuit is useful for amplifying a small ac voltage that rides on top of a large dc voltage, because C_i, blocks the dc. The frequency-response equation is

$$\begin{aligned}\frac{V_o(j\omega)}{V_i(j\omega)} &= -\frac{Z_f}{Z_i} = -\frac{R_f}{1/j\omega C_i + R_i} \\ &= -\frac{j\omega R_f C_i}{1 + j\omega C_i R_i} = -\frac{R_f}{R_i}\frac{j\omega\tau}{1 + j\omega\tau}\end{aligned} \tag{1.56}$$

where $\tau = R_i C_i$. Figure 1.17 shows the frequency response. For $\omega \ll 1/\tau$, the circuit behaves as a differentiator (Figure 1.18), because C_i is the dominant input impedance. For $\omega \gg 1/\tau$, the circuit behaves as an inverting amplifier, because the impedance of R_i is large compared with that of C_i. The corner frequency f_c, which is defined by the intersection of the two asymptotes shown, is given by the relation $\omega\tau = 2\pi f_c \tau = 1$.

BANDPASS FILTER

A series combination of the low-pass filter and the high-pass filter results in a *bandpass filter*, which amplifies frequencies over a desired range and attenuates higher and lower frequencies. Figure 1.19(c) shows that the bandpass function can be achieved with a one-op-amp circuit. Figure 1.17 shows the frequency response. The corner frequencies are defined by the same relations as those for the low-pass and the high-pass filters. This circuit is useful for amplifying a certain band of frequencies, such as those required for recording heart sounds or the electrocardiogram.

ALL-PASS FILTER

All-pass filters keep the amplitude of the signal intact for all frequencies; however, they add a phase shift. They are used to compensate for phase changes of the signal.

EXAMPLE 1.14 Design a first-order all-pass filter that has phase shift of 0° at dc, -180° at higher frequency, and -90° at corner frequency f_c about 500 Hz. Provide LTspice simulation for the frequency and phase response.

ANSWER Figure E1.14(a) shows the circuitry and Figure E1.14(b) shows the gain and phase response for a unity gain all-pass filter. For low frequencies, the capacitor acts as an open circuit with $V_{out} = V_{in}$ and phase shift of 0°. For high frequencies, the capacitor acts as a short circuit and it behaves as an inverting amplifier with unity gain and a phase shift of -180°. At corner frequency, $f_c = 1/(2\pi RC) = 1/(2\pi \times 10 \times 10^3 \times 31.8 \times 10^{-9}) \approx 500$ Hz of the low-pass filter, the circuit introduces a phase shift of -90°.

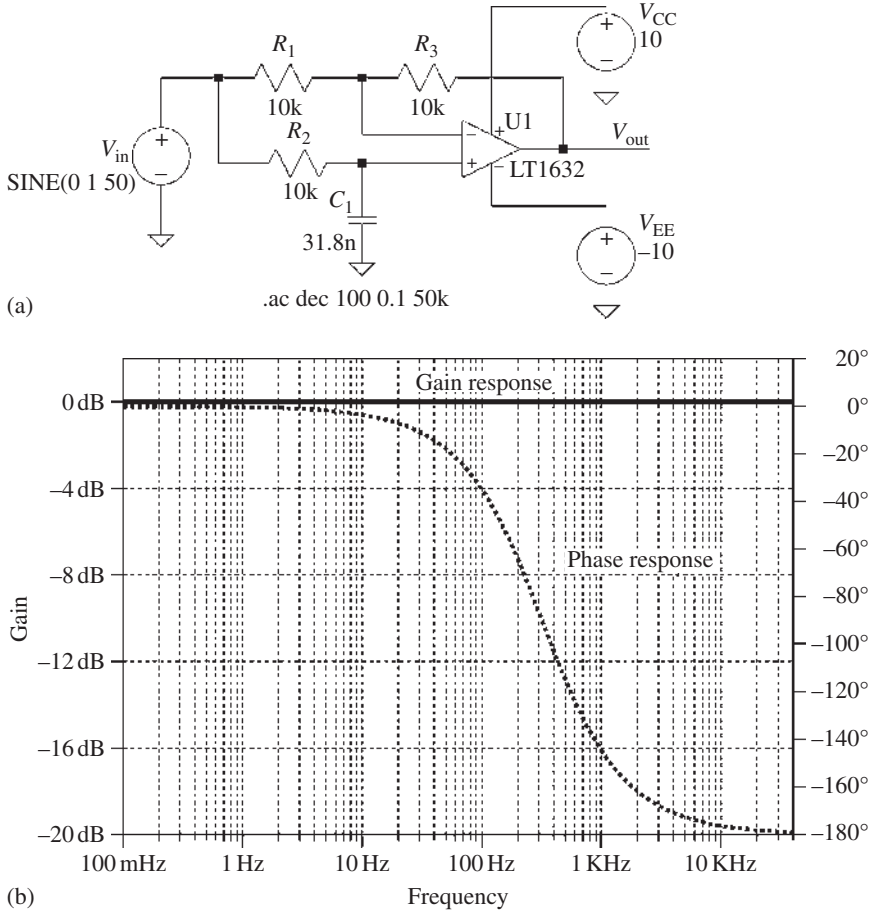


Figure E1.14 (a) Circuit design of unity gain active all-pass filter. (b) Gain and phase response for all-pass filter with phase shift of –90° at about 500 Hz.

HIGHER ORDER FILTER

While the first-order filters described above may be simple to design, they offer a roll-off slope of –20 dB/decade attenuation for frequencies beyond the corner frequency f_c. This might not be adequate to remove unwanted signal frequencies and thus demands the need to design higher order filters with steeper roll-offs. Detailed review of higher order filter is beyond the scope of this chapter and could be obtained through Van Valkenburg (1982). However, we can use some widely available software tools such as Analog

Devices—Analog Filter Wizard, Texas Instruments—WEBENCH® Filter Designer, Microchip—Filter® Filter Design Software for design purposes and at least gain some understanding into some of the filter characteristics.

EXAMPLE 1.15 Design a second-order low-pass filter with a unity gain, corner frequency of 500 Hz, and 0 dB ripple in the pass band. Calculate the corner frequency change when you make selection for capacitor from E24 series (5% tolerance) and resistor from E96 series (1% tolerance).

ANSWER Using the Analog Devices—Analog Filter Wizard tool, we can design a single-stage second-order Butterworth filter to have a corner frequency of 500 Hz and 0 dB ripple in the pass band. Figure E1.15 shows the Sallen–Key topology for the second-order filter.

Selecting the capacitor from the E24 series (5% tolerance) and resistor from the E96 series (1% tolerance) yields $R_1 = 75\,\text{k}\Omega$, $R_2 = 1.33\,\text{M}\Omega$, $C_1 = 330\,\text{pF}$, and $C_2 = 3.3\,\text{nF}$.

The corner frequency is given as

$$f_c = \frac{1}{2\pi\sqrt{R_1 \times R_2 \times C_1 \times C_2}} = 483\ \text{Hz}$$

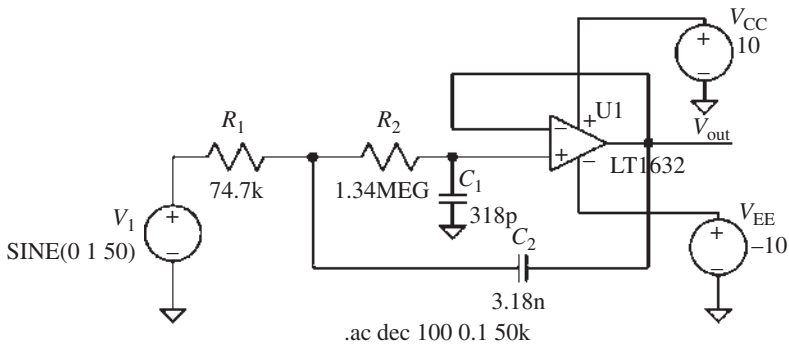


Figure E1.15 Sallen–Key topology for second-order filter design.

1.21 FREQUENCY RESPONSE

Up until now, we have found it useful to consider the op amp as ideal. Now, we shall examine the effects of several nonideal characteristics, starting with that of frequency response.

OPEN-LOOP GAIN

Because the op amp requires very high gain, it has several stages. Each of these stages has stray or junction capacitance that limits its high-frequency response in the same way that a simple *RC* low-pass filter reduces high-frequency gain. At high frequencies, each stage has a –1 slope on a log–log plot of gain versus frequency, and each has a –90° phase shift. Thus, a three-stage op amp, such as type 709, reaches a slope of –3, as shown by the dashed curve in Figure 1.20. The phase shift reaches –270°, which is quite satisfactory for a comparator, because feedback is not employed. For an

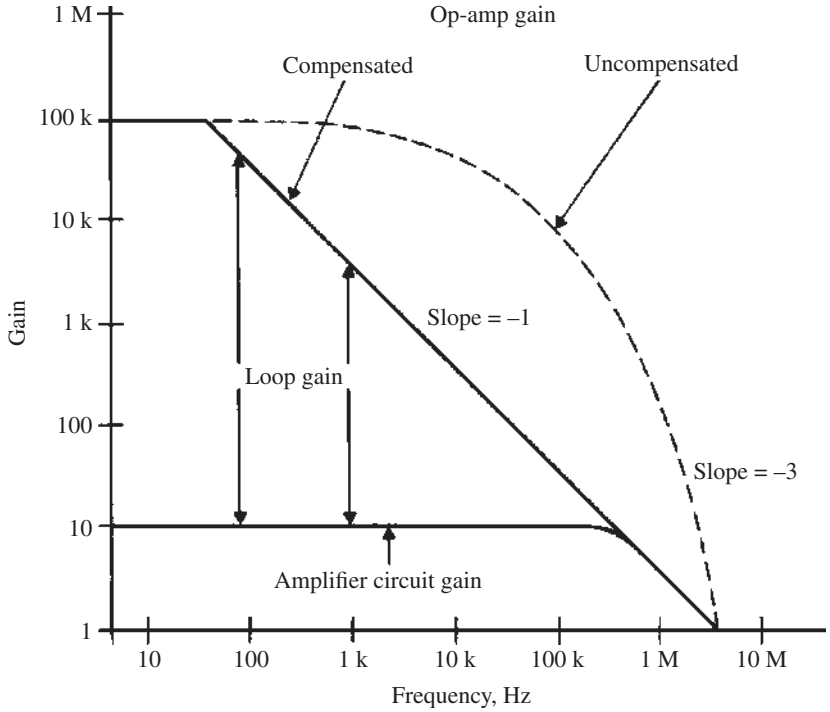


Figure 1.20 Op-amp frequency characteristics Early op amps (such as the 709) were uncompensated, had a gain greater than 1 when the phase shift was equal to –180°, and therefore oscillated unless compensation was added externally. A popular op amp, the 411, is compensated internally, so for a gain greater than 1, the phase shift is limited to –90°. When feedback resistors are added to build an amplifier circuit, the loop gain on this log–log plot is the difference between the op-amp gain and the amplifier–circuit gain.

amplifier, if the gain is greater than 1 when the phase shift is equal to –180° (the closed-loop condition for oscillation), there is undesirable oscillation.

COMPENSATION

Adding an external capacitor to the terminals indicated on the specification sheet moves one of the *RC* filter corner frequencies to a very low frequency. This compensates the uncompensated op amp, resulting in a slope of –1 and a maximal phase shift of –90°. This is done with an internal capacitor in the 411, resulting in the solid curve shown in Figure 1.20. This op amp does not oscillate for any amplifier we have described. This op amp has very high dc gain, but the gain is progressively reduced at higher frequencies, until it is only 1 at 4 MHz.

CLOSED-LOOP GAIN

It might appear that the op amp has very poor frequency response, because its gain is reduced for frequencies above 40 Hz. However, an amplifier circuit is never built using the op amp open loop, so we shall therefore discuss only the circuit closed-loop response. For example, if we build an amplifier circuit with a gain of 10, as shown in Figure 1.20, the frequency response is flat up to 400 kHz and is reduced above that frequency only because the amplifier-circuit gain can never exceed the op-amp gain. We find this an advantage of using negative feedback, in that the frequency response is greatly extended.

LOOP GAIN

The loop gain for an amplifier circuit is obtained by breaking the feedback loop at any point in the loop, injecting a signal, and measuring the gain around the loop. For example, in a unity-gain follower [Figure 1.11(a)], we break the feedback loop and then the injected signal enters the negative input, after which it is amplified by the op-amp gain. Therefore, the loop gain equals the op-amp gain. To measure loop gain in an inverting amplifier with a gain of –1 [Figure 1.10(a)], assume that the amplifier-circuit input is grounded. The injected signal is divided by 2 by the attenuator formed of R_f and R_i, and is then amplified by the op-amp gain. Thus, the loop gain is equal to (op-amp gain)/2.

Figure 1.11 shows the loop-gain concept for a noninverting amplifier. The amplifier-circuit gain is 10. On the log–log plot, the difference between the op-amp gain and the amplifier-circuit gain is the loop gain. At low frequencies, the loop gain is high and the closed-loop amplifier-circuit characteristics are determined by the feedback resistors. At high frequencies, the

loop gain is low and the amplifier-circuit characteristics follow the op-amp characteristics. High loop gain is good for accuracy and stability, because the feedback resistors can be made much more stable than the op-amp characteristics.

GAIN-BANDWIDTH PRODUCT

The gain-bandwidth product of the op amp is equal to the product of gain and bandwidth at a particular frequency. Thus, in Figure 1.20 the unity-gain-bandwidth product is 4 MHz, a typical value for op amps. Note that along the entire curve with a slope of –1, the gain-bandwidth product is still constant, at 4 MHz. Thus, for any amplifier circuit, we can obtain its bandwidth by dividing the gain-bandwidth product by the amplifier-circuit gain. For higher-frequency applications, op amps such as the OP-37E are available with gain-bandwidth products of 60 MHz.

SLEW RATE

Small-signal response follows the amplifier-circuit frequency response predicted by Figure 1.20. For large signals there is an additional limitation. When rapid changes in output are demanded, the capacitor added for compensation must be charged up from an internal source that has limited current capability I_{max}. The change in voltage across the capacitor is then limited, $dv/dt = I_{max}/C$, and dv_o/dt is limited to a maximal slew rate (15 V/μs for the 411). If this slew rate S_r is exceeded by a large-amplitude, high-frequency sine wave, distortion occurs. Thus, there is a limitation on the sine-wave *full-power response*, or maximal frequency for rated output,

$$f_p = \frac{S_r}{2\pi V_{or}} \tag{1.57}$$

where V_{or} is the rated output voltage (usually 10 V). If the slew rate is too slow for fast switching of a comparator, an uncompensated op amp can be used, because comparators do not contain the negative-feedback path that may cause oscillations.

1.22 OFFSET VOLTAGE

Another nonideal characteristic is that of offset voltage. The two op-amp inputs drive the bases of transistors, and the base-to-emitter voltage drop may be slightly different for each. Thus, so that we can obtain $v_o = 0$, the

voltage ($v_1 - v_2$) must be a few millivolts. This offset voltage is usually not important when v_i is 1–10 V. But when v_i is on the order of millivolts, as when amplifying the output from thermocouples or strain gages, the offset voltage must be considered.

NULLING

The offset voltage may be reduced to zero by adding an external nulling pot to the terminals indicated on the specification sheet. Adjustment of this pot increases emitter current through one of the input transistors and lowers it through the other. This alters the base-to-emitter voltage of the two transistors until the offset voltage is reduced to zero.

DRIFT

Even though the offset voltage may be set to 0 at 25 °C, it does not remain there if temperature is not constant. Temperature changes that affect the base-to-emitter voltages may be due to either environmental changes or to variations in the dissipation of power in the chip that result from fluctuating output voltage. The effects of temperature may be specified as a maximal offset voltage change in volts per degree Celsius or a maximal offset voltage change over a given temperature range, say –25 to +85 °C. If the drift of an inexpensive op amp is too high for a given application, tighter specifications (0.1 μV/°C) are available with temperature-controlled chips. An alternative technique modulates the dc as in chopper-stabilized and varactor op amps (Tobey *et al.*, 1971).

NOISE

All semiconductor junctions generate noise, which limits the detection of small signals. Op amps have transistor input junctions, which generate both noise-voltage sources and noise-current sources. These can be modeled as shown in Figure 1.21. For low source impedances, only the noise voltage v_n is important; it is large compared with the i_nR drop caused by the current noise i_n. The noise is random, but the amplitude varies with frequency. For example, at low frequencies the noise power density varies as $1/f$ (flicker noise), so a large amount of noise is present at low frequencies. At the mid-frequencies, the noise is lower and can be specified in rms units of $V \cdot Hz^{-1/2}$. In addition, some silicon planar-diffused bipolar integrated-circuit op amps exhibit bursts of noise, called *popcorn noise* (Wait *et al.*, 1975).

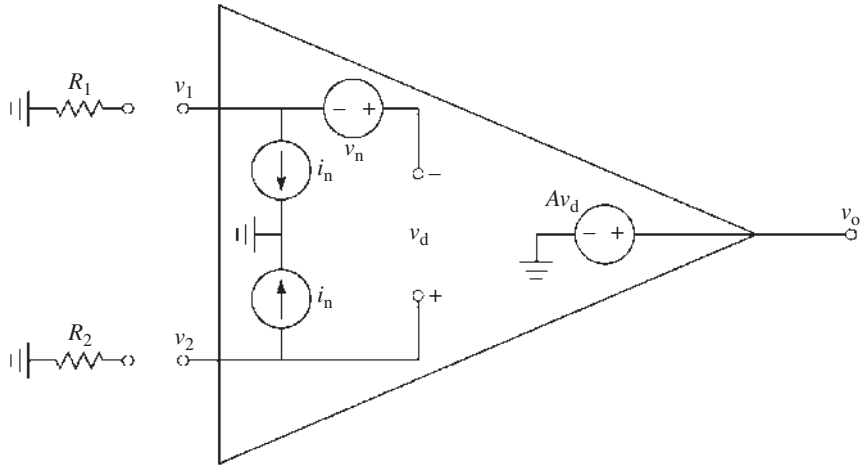


Figure 1.21 Noise sources in an op amp The noise-voltage source v_n is in series with the input and cannot be reduced. The noise added by the noise-current sources can be minimized by using small external resistances.

1.23 BIAS CURRENT

Because the two op-amp inputs drive transistors, base or gate current must flow all the time to keep the transistors turned on. This is called *bias current*, which for the 411 is about 200 pA. This bias current must flow through the feedback network. It causes errors proportional to feedback-element resistances. To minimize these errors, small feedback resistors, such as those with resistances of 10 kΩ, are normally used. Smaller values should be used only after a check to determine that the current flowing through the feedback resistor, plus the current flowing through all load resistors, does not exceed the op-amp output current rating (20 mA for the 411).

DIFFERENTIAL BIAS CURRENT

The difference between the two input bias currents is much smaller than either of the bias currents alone. A degree of cancellation of the effects of bias current can be achieved by having each bias current flow through the same equivalent resistance. This is accomplished for the inverting amplifier and the noninverting amplifier by adding, in series with the positive input, a compensation resistor the value of which is equal to the parallel combination

of R_i and R_f. There still is an error, but it is now determined by the difference in bias current.

DRIFT

The input bias currents are transistor base or gate currents, so they are temperature-sensitive, because transistor gain varies with temperature. However, the changes in gain of the two transistors tend to track together, so the additional compensation resistor that we have described minimizes the problem.

NOISE

Figure 1.21 shows how variations in bias current contribute to overall noise. The noise currents flow through the external equivalent resistances so that the total rms noise voltage is

$$v \cong \left\{ \left[v_n^2 + (i_n R_1)^2 + (i_n R_2)^2 + 4\kappa T R_1 + 4\kappa T R_2 \right] \mathrm{BW} \right\}^{1/2} \tag{1.58}$$

where

R_1 and R_2 = equivalent source resistances
v_n = mean value of the rms noise voltage, in $\mathrm{V} \cdot \mathrm{Hz}^{-1/2}$, across the frequency range of interest
i_n = mean value of the rms noise current, in $\mathrm{A} \cdot \mathrm{Hz}^{-1/2}$, across the frequency range of interest
κ = Boltzmann's constant (Appendix)
T = temperature, K
BW = noise bandwidth, Hz

The specification sheet provides values of v_n and i_n (sometimes v_n^2 and i_n^2), thus making it possible to compare different op amps. If the source resistances are 10 kΩ, bipolar-transistor op amps yield the lowest noise. For larger source resistances, low-input-current amplifiers, such as the field-effect transistor (FET) input stage, are best because of their lower current noise. Ary (1977) presents design factors and performance specifications for a low-noise amplifier.

For ac amplifiers, the lowest noise is obtained by calculating the characteristic noise resistance $R_n = v_n/i_n$ and setting it equal to the equivalent source resistance R_2 (for the noninverting amplifier). This is accomplished by

inserting a transformer with turns ratio 1:N, where $N = (R_n/R_2)^{1/2}$, between the source and the op amp (Jung, 1986).

1.24 INPUT AND OUTPUT RESISTANCE

INPUT RESISTANCE

The op-amp differential-input resistance R_d is shown in Figures 1.8 and 1.22. For the FET-input 411, it is 1 TΩ, whereas for bipolar junction transistor (BJT)-input op amps, it is about 2 MΩ, which is comparable to the value of some feedback resistors used. However, we shall see that its value is usually not important because of the benefits of feedback. Consider the follower shown in Figure 1.22. In order to calculate the amplifier-circuit input resistance R_{ai}, assume a change in input voltage v_i. Because this is a follower,

$$\begin{aligned} \Delta v_o &= A\Delta v_d = A(\Delta v_i - \Delta v_o) \\ &= \frac{A\Delta v_i}{A+1} \\ \Delta i_i &= \frac{\Delta v_d}{R_d} = \frac{\Delta v_i - \Delta v_o}{R_d}\frac{\Delta v_i}{(A+1)R_d} \\ R_{ai} &= \frac{\Delta v_i}{\Delta i_i} = (A+1)R_d \cong R_d \end{aligned} \tag{1.59}$$

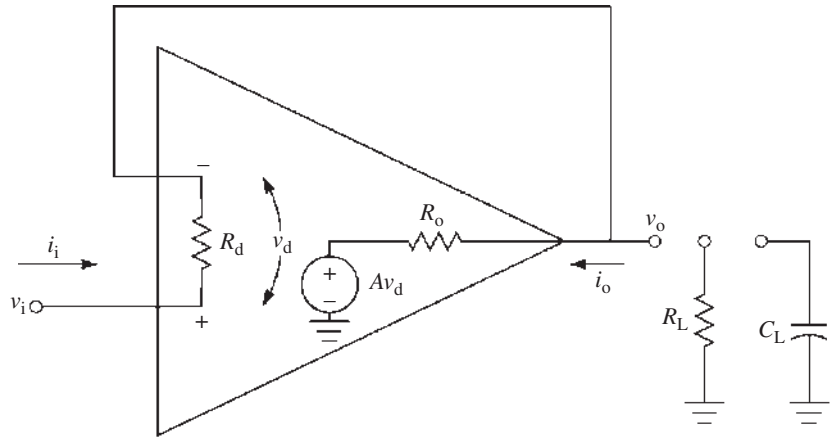


Figure 1.22 The amplifier input impedance is much higher than the op-amp input impedance R_d. The amplifier output impedance is much smaller than the op-amp output impedance R_o.

Thus, the amplifier-circuit input resistance R_{ai} is about $(10^5) \times (2\,M\Omega) = 200\,G\Omega$. This value cannot be achieved in practice, because surface leakage paths in the op-amp socket lower it considerably. In general, all noninverting amplifiers have a very high input resistance, which is equal to R_d times the loop gain. This is not to say that very large source resistances can be used, because the bias current usually causes much larger problems than the amplifier-circuit input impedance. For large source resistances, FET op amps such as the 411 are helpful.

The input resistance of an inverting amplifier is easy to determine. Because the negative input of the op amp is a virtual ground,

$$R_{ai} = \frac{\Delta v_i}{\Delta i_i} = R_i \tag{1.60}$$

Thus, the amplifier-circuit input resistance R_{ai} is equal to R_i, the input resistor. Because R_i is usually a small value, the inverting amplifier has small input resistance.

OUTPUT RESISTANCE

The op-amp output resistance R_o is shown in Figures 1.8 and 1.22. It is about $40\,\Omega$ for the typical op amp, which may seem large for some applications. However, its value is usually not important because of the benefits of feedback. Consider the follower shown in Figure 1.22. In order to calculate the amplifier-circuit output resistance R_{ao}, assume that load resistor R_L is attached to the output, causing a change in output current Δi_o. Because i_o flows through R_o, there is an additional voltage drop $\Delta i_o R_o$.

$$\begin{aligned} -\Delta v_d = \Delta v_o &= A\Delta v_d + \Delta i_o R_o = -A\Delta v_o + \Delta i_o R_o \\ (A+1)\Delta v_o &= \Delta i_o R_o \\ R_{ao} = \frac{\Delta v_o}{\Delta i_o} &= \frac{R_o}{A+1} \cong \frac{R_o}{A} \end{aligned} \tag{1.61}$$

Thus, the amplifier-circuit output resistance R_{ao} is about $40/(10^5) = 0.0004\,\Omega$, a value negligible in most circuits. In general, all noninverting and inverting amplifiers have an output resistance that is equal to R_o divided by the loop gain. This is not to say that very small load resistances can be driven by the output. If R_L shown in Figure 1.22 is smaller than $500\,\Omega$, the op amp saturates internally, because the maximal current output for a typical op amp is 20 mA. This maximal current output must also be considered when driving large capacitances C_L at a high slew rate. Then the output current

$$i_o = C_L \frac{dv_o}{dt} \tag{1.62}$$

The $R_o - C_L$ combination also acts as a low-pass filter, which introduces additional phase shift around the loop and can cause oscillation. The cure is to add a small resistor between v_o and C_L, thus isolating C_L from the feedback loop.

To achieve larger current outputs, the current booster is used. An ordinary op amp drives high-power transistors (on heat sinks if required). Then, we can use the entire circuit as an op amp by connecting terminals v_1, v_2, and v_o to external feedback networks. This places the booster section within the feedback loop and keeps distortion low.

1.25 DESIGN CRITERIA

As shown, many factors affect the design of biomedical instruments. The factors that impose constraints on the design are of course different for each type of instrument. However, some of the general requirements can be categorized as signal, environmental, medical, and economic factors. Figure 1.23 shows how these factors are incorporated into the initial design and development of an instrument.

Note that the type of sensor selected usually determines the signal-processing equipment needed, so an instrument specification includes more than just what type of sensor to use. To obtain a final design, some compromises in specifications are usually required. Actual tests on a prototype are always needed before final design decisions can be made. Changes in performance and interaction of the elements in a complex instrument often dictate design modifications. Good designs are frequently the result of many compromises throughout the development of the instrument. In Chapter 2, we shall examine basic methods of sensing biomedical quantities to ensure that many sensor design alternatives are considered (King and Fries, 2003).

1.26 COMMERCIAL MEDICAL INSTRUMENTATION DEVELOPMENT PROCESS

A commercial medical instrument project has many phases, and the size of the team needed grows as the project progresses. Ideas often come from people working where health care is delivered, because clinical needs are most evident there. Physicians, nurses, clinical engineers, and sales personnel are therefore good sources of ideas. Industry engineers and marketing personnel should spend time in hospitals observing how their products are actually

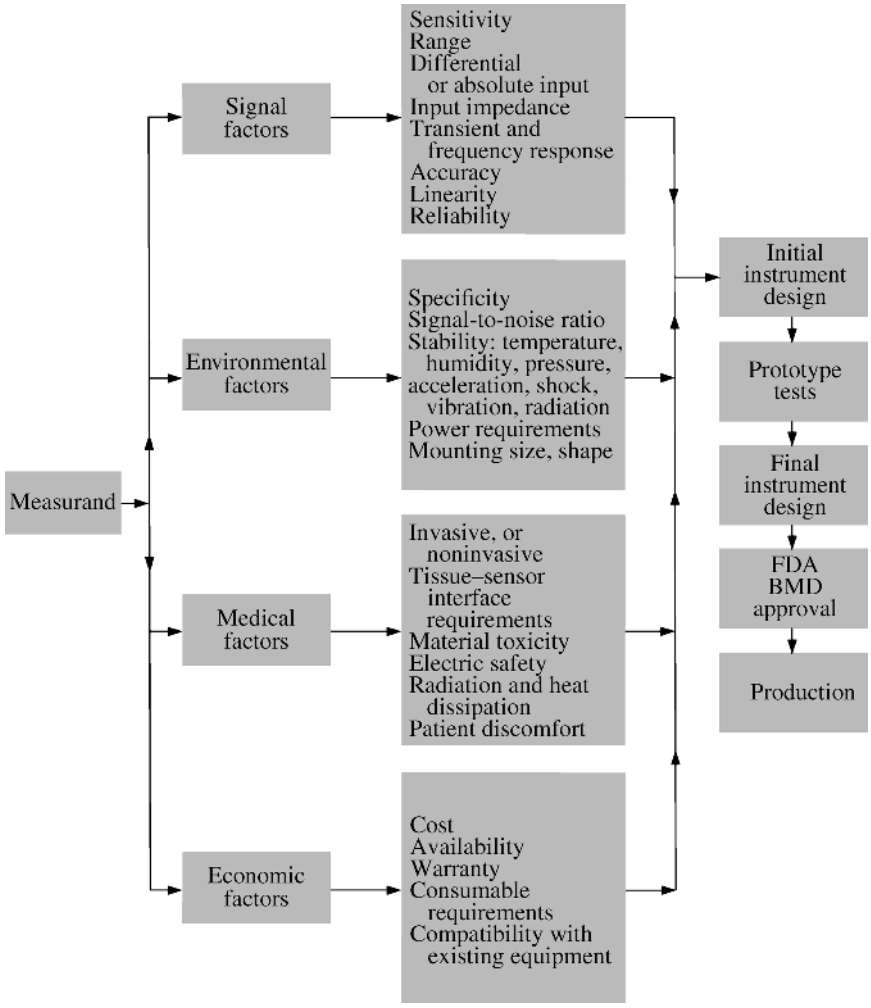


Figure 1.23 Design process for medical instruments Choice and design of instruments are affected by signal factors, and also by environmental, medical, and economic factors. (Revised from *Transducers for Biomedical Measurements: Application and Design*, by R. S. C. Cobbold. Copyright 1974, John Wiley & Sons, Inc. Used by permission of John Wiley & Sons, Inc.)

being used (and misused). Unsolicited inventions are often presented to industry. Most companies have one or more people who are responsible for evaluating new ideas, so it is very important for those who want to propose a new idea to be in contact with a person who can understand the idea and who has the authority to proceed with a detailed evaluation. A simple,

signed nondisclosure agreement is adequate (but essential) to protect patent rights when detailed ideas are discussed.

At this early stage even the best ideas are crudely defined, and they are often not appreciated until at least a preliminary *feasibility analysis* is done. The feasibility analysis and written *product description* should consider the medical need for the product, its technical feasibility, and how well it fits with the company's current or planned product lines and sales methods. Determining medical feasibility entails examining the clinical need for the product, including patient indications, number of patients, clinical specialty, and exactly how, why, and by whom the device will be utilized. Marketing research and analysis can be useful for evolutionary products but are not reliable for revolutionary products, especially when a change in medical practice is required. Technical feasibility analysis should include a description of the core technologies needed, suitability of existing or readily modifiable components, breakthroughs or inventions required, systems analysis, and preliminary cost estimates. A functional prototype that includes the sensor, primary signal processing elements, and other new or unique components should be built and tested on animals and humans as early as possible. The manufacturing feasibility analysis should be done early, when major alternative technologies can still be selected. A brief business plan should assess financial aspects, personnel requirements, competition, patents, standards, manufacturing requirements, sales and service requirements, and the time schedule for the project. Experience has shown that abbreviating the feasibility phase or adding features after this phase usually causes disasters later. A detailed feasibility review should be required at the end of this phase. If the results are not clearly favorable, the project should be abandoned or the feasibility phase should be continued.

After a favorable feasibility review is complete, a detailed *product specification* must be written to describe all the product features. Included should be numerical values for performance, many internal testing requirements, user interface requirements, environmental testing requirements, and even the size, weight, and color of the instrument. The product specification should say everything about "what" is required but nothing about "how" it is to be achieved. This gives design engineers important flexibility. The product specification is used by design and development engineers, test equipment design engineers, quality assurance engineers, and manufacturing engineers throughout the product life cycle. The product specification remains a confidential document in most companies; only the main external performance specifications appear in user technical manuals and promotional materials.

Design and development uses the product specification to make a manufacturable prototype. For most instruments, functions must be partitioned into hardware and software before detailed design can begin. Circuit diagrams,

detailed software requirements, and mechanical designs are made by means of computer-aided-design (CAD) tools that allow such detailed simulations of functional operation that there is little need for "breadboard" prototypes. Design reviews focus on systems issues and problems that the company may encounter in meeting the product specification. True prototypes that are very similar to the final product are thus developed much earlier and can be used by test, design assurance, and manufacturing engineers. These prototypes are also tested on animals or human subjects to verify expected operation and performance at a few clinical testing centers. Data from these *clinical feasibility trials* (including repeated observations of users) should be studied closely, because design flaws that cause user frustration or errors must be discovered at this critical stage. A final *design review* should include test results for all specifications, clinical results including subjective user feedback, an assessment of manufacturability, and more detailed cost estimates.

Production engineers must be involved throughout the design and development process to avoid a redesign for manufacturability. Special production equipment usually has a long lead time. Many fixtures and automatic tests must be designed. All final documents that describe how the product is made must be released by the design and development engineers. Any changes made after the final design review must be authorized via an *engineering change order* (ECO). Small production runs are usually needed to discover problems and improve efficiency. Most medical instruments and devices are not produced in high volume, as consumer products are, so full automation of production is not cost-effective. Even after full production begins, some ECOs may be needed to correct problems that occur in the field. Any failures of medical devices must be documented, along with the corrective action taken.

Throughout the product life cycle, which includes the period after the product is no longer offered for sale, technical support for user questions and problems must be provided. Successful companies must be committed to repairing or replacing their products throughout the entire expected lifetime of the product.

1.27 REGULATION OF MEDICAL DEVICES

In 1976, the United States Congress passed what are known as the **Medical Device Amendments** (Public Law 94-295) to the Federal Food, Drug, and Cosmetics Act that dates back to the 1930s. In the Safe Medical Devices Act of 1990, further amendments were made (Pacela, 1991). The primary purpose was to ensure the safety and efficacy of new medical devices prior to marketing of the device. The law's definition of the term *medical device* is

Table 1.2 FDA Device Classifications

	Class I	Class II	Class III
Description	Minimal potential for harm to the user, often simpler in design than Class II or III devices	Most non-life sustaining medical devices	Sustain or support life, are implanted, or present potential unreasonable risk of illness or injury
Risk level	Low	Moderate	High
Regulatory controls	• General controls • Most devices are exempt from Premarket Notification 510(k) (substantial equivalence to a predicate device)	• General controls • Special controls • Most devices require Premarket Notification 510(k)	• General controls • Most devices require Premarket Approval
Examples	Manual toothbrush, medical gloves, elastic bandages, dental floss, enema kits, bedpans, ear irrigation kit, fluorometer	Infusion pumps, powered wheelchairs, contact lens, noninvasive blood pressure monitors, surgical drape	Implantable pacemakers, heart valve, aortic stent, artificial heart, bone graft, defibrillator, breast implants

SOURCE: Adapted from USFDA (2018a).

"any item promoted for a medical purpose that does not rely on chemical action to achieve its intended effect" (Kessler *et al*., 1987). Table 1.2 shows the classification of such devices into Class I to III was based on the principle that devices that pose greater potential hazards should be subject to more regulatory requirements. Software used in medical devices has become an area of increasing concern; several serious accidents have been traced to software bugs (Murfitt, 1990). Increased requirements for maintaining traceability of devices to the ultimate customer, postmarketing surveillance for life-sustaining and life-supporting implants, and hospital reporting requirements for adverse incidents were added to the law in 1990.

Along with the three classifications mentioned earlier, the novel medical devices are sometimes classified under the De Novo classification. It is a risk-based classification process for a novel medical device for which there is no legally market predicate device, and for which general controls alone, or general and special controls, provide reasonable assurance of safety and effectiveness for the intended use. Such devices are automatically designated Class III classification; however, a De Novo classification

request can be submitted to FDA for a risk-based evaluation for reclassification of the device into Class II or I [U.S. Food and Drug Administration (USFDA), 2019c].

Medical device manufacturers are required to perform registration, premarketing notification, record keeping, labeling, reporting of adverse experiences, and good manufacturing practices. The general controls are regulatory requirements authorized by the Food Drug & Cosmetic (FD&C) Act, under sections 501, 502, 510, 516, 518, 519, and 520 and apply to all three classes of medical devices shown in Table 1.2 (USFDA, 2018c).

The special controls are regulatory requirements for Class II devices, since the general controls alone are insufficient to provide reasonable assurance of the safety and effectiveness of the device. There is sufficient information presented to establish special controls to provide such assurance. These special controls are device-specific and include performance standards, postmarket surveillance, patient registries, special labeling requirements, premarket data requirements, and guidelines (USFDA, 2018c).

While, Premarket Approval (PMA) is the required process of scientific review to ensure the safety and effectiveness of Class III devices. The PMA process is more involved and includes the submission of clinical data to support claims made for the device (USFDA, 2018c).

The FDA has established classifications for approximately 1700 different generic types of device and grouped them into 16 medical specialties or "panels." Each of these generic types of devices is assigned into one of the three regulatory classes shown in Table 1.2, based on the level of control necessary to assure the safety and effectiveness of the device (USFDA, 2018b).

The product classification database accessible through the following link: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/classification.cfm contains these generic types of devices, and the associated codes developed by the FDA to support its regulatory and administrative processes (USFDA, 2019e).

The different categories into which medical devices are divided are described below which include classification rules and some examples.

Preamendments device (or old devices)—These are legally marketed devices in the United States before the enactment of Medical Devices Amendments in May 28, 1976 and have not been significantly changed or modified, and for which, a regulation requiring a PMA application has not been published by the FDA. Examples include analog electrocardiography machine, electrohydraulic lithotriptor, infant radiant warmer, and automated blood-cell separator (Kessler *et al.*, 1987; USFDA, 2019a, 2019e).

Postamendments device (or new devices)—These are legally marketed devices in the United States on or after May 28, 1976. These devices were put into same class as preamendments device if found to be

"substantially equivalent." Other postamendments devices were automatically placed into Class III. A manufacturer may petition to FDA for reclassification into Class I or II. Examples include magnetic resonance imager, defibrillator, bone-growth stimulator, hydrophilic contact lenses, absorbable sponge, and hepatitis B-antibody detection kit (*Federal Policies and the Medical Device Industry*, 1984; Kessler *et al*., 1987; USFDA, 2019e).

Substantially equivalent devices—These are postamendments devices found to be "substantially equivalent" to preamendments devices and put into the class as their preamendments counterpart and subjects to the same requirements. Those in Class III could eventually be required to demonstrate their safety and effectiveness. These substantially equivalent devices will be subject to testing and approval, if the FDA were to require testing and approval of the counterpart preamendments devices. Examples include digital electrocardiography machines, ELISA diagnostic kits, and devices used to test drug abuse (*Federal Policies and the Medical Device Industry*, 1984; Kessler *et al*., 1987; USFDA, 2019e).

Implantable devices—These devices are placed into surgically or naturally formed cavity of the human body, continuously for a period of 30 days or more. These are typically placed in Class III unless a lesser regulated class will ensure safety and effectiveness. Examples under Class III includes implantable cardiac pacemaker, aortic stent, and atrial defibrillator; under Class II includes implanted hearing aid, internal ear prosthesis, and intervertebral fusion device with bone graft; under Class I includes bone cap and pacemaker polymeric mesh bag (Kessler *et al*., 1987; USFDA, 2019b, 2019e).

Life-supporting or life-sustaining devices—These are devices that are essential to, or yield information that is essential to, the restoration or continuation of a bodily function important to sustain human life. These are primarily Class III and some Class II devices. Examples under Class III include electrical tumor treatment fields, drug-eluting permanent left ventricular pacemaker electrode, renal stent, and under Class II include hemodialysis system, apnea monitor, and gas machine for anesthesia (Kessler *et al*., 1987; USFDA, 2019b, 2019e).

Custom devices—These are devices for the purpose of treating a sufficiently rare condition, and are obtained through the written request from a physician. They are sufficiently unique such that conducting clinical investigations on such device would be impractical. These devices are not generally available in finished form and the production of the device if limited to no more five units per year. The manufacturer needs to provide FDA with an annual report on the custom devices supplied. Examples include device for patient with skeletal

dysplasia requiring a total hip replacement procedure to treat osteoarthritis, an artificial cervical disc replacement for reconstruction of the cervical disc following cervical discectomy to treat cervical radiculopathy, and toddler needing occipital condyle screws after surviving a severe car accident that left the toddler paralyzed from the neck down and in need of instrumentation to help hold up the head (USFDA, 2014).

Investigational devices—These medical devices are generally with an Investigational Device Exemption, and are used in controlled settings for the purpose of collecting data on safety and effectiveness, the information from which is used in support of a PMA or premarket notification 510(k) application (USFDA, 2013a).

Transitional devices—These are medical devices that were regulated as new drugs before May 28, 1976. Any Class III transitional device is automatically classified into Class III and governed by the PMA regulations. They could be petitioned for Class II and Class I status. Examples include intraocular lenses, injectable silicone, surgical sutures, bone hetrografts, gonorrhea diagnostic products, and injectable Teflon (Kessler *et al.*, 1987).

Humanitarian devices—These are medical devices for treatment or diagnosis of a disease or condition affecting not more than 8000 individuals in the United States per year. The humanitarian device exemption (HDE) is similar to PMA, but is exempt from effectiveness requirement; however, it is subject to certain profit and use restrictions. The use of such devices generally requires approval by an institutional review board (IRB) at the institution where the device is to be used. Examples include electrical stimulation bladder system, refractive corneal implant, pediatric ventricular assist device, and deep brain stimulator for obsessive compulsive disorder (USFDA, 2019d, 2019e).

Unclassified devices—These are preamendments medical devices for which classification regulation has not be promulgated, and require 510(k) premarket notification submission. Once the device is classified, it may require submission of a PMA, a 510(k), or be exempt from any premarket submission. Examples include rechargeable batteries for Class II or Class III devices, tactile hearing aid, ultrasonic surgical instrument, and acupressure device (USFDA, 2013b, 2019e).

Not-Classified devices—These are postamendments devices for which the FDA has not yet reviewed a marketing application or for which the FDA has not made a final decision on such a marketing application. Examples include 3D laser scanning system, air traffic control, black light, digital display monitor, blood virus applications software, and microplate assay software management (USFDA, 2013b, 2019e).

PROBLEMS

1.1 Find the independent nonlinearity, as defined in Figure 1.4(b), for the following set of inputs and outputs from a nearly linear system. Instrument was designed for an output equal to twice the input. Full scale is 20.

Inputs	0.50	1.50	2.00	5.00	10.00
Outputs	0.90	3.05	4.00	9.90	20.50

1.2 Find the correlation coefficient r for the set of five inputs and outputs given in Problem 1.1.

1.3 Derive the operational transfer function and the sinusoidal transfer function for an RC high-pass filter. Plot the step response and the complete frequency response (magnitude and phase).

1.4 A first-order low-pass instrument must measure hummingbird wing displacements (assume sinusoidal) with frequency content up to 100 Hz with an amplitude inaccuracy of less than 5%. What is the maximal allowable time constant for the instrument? What is the phase angle at 50 Hz and at 100 Hz?

1.5 A mercury thermometer has a cylindrical capillary tube with an internal diameter of 0.2 mm. If the volume of the thermometer and that of the bulb are not affected by temperature, what volume must the bulb have if a sensitivity of 2 mm/°C is to be obtained? Assume operation near 24 °C. Assume that the stem volume is negligible compared with the bulb internal volume. Differential expansion coefficient of Hg = 1.82×10^{-4} ml/(ml·C).

1.6 For the spring scale shown in Figure 1.7(a), find the transfer function when the mass is negligible.

1.7 Find the time constant from the following differential equation, given that x is the input, y is the output, and a through h are constants.

$$a = \frac{dy}{dt} + bx + c + hy = e\frac{dy}{dt} + fx + g$$

1.8 A low-pass first-order instrument has a time constant of 20 ms. Find the frequency, in hertz, of the input at which the output will be 93% of the dc output. Find the phase angle at this frequency.

1.9 A second-order instrument has a damping ratio of 0.4 and an undamped natural frequency of 85 Hz. Sketch the step response, and give numerical values for the amplitude and time of the first two positive maxima. Assume that the input goes from 0 to 1 and that the static sensitivity is 10.

1.10 Consider an underdamped second-order system with step response as shown in Figure 1.7(c). A different way to define logarithmic decrement is

$$\Gamma = \ln \frac{y_n}{y_{n+1}}$$

Here, n refers not to the number of positive peaks shown in Figure 1.7(c) but to both positive and negative peaks. That is, n increases by 1 for each half-cycle. Derive an equation for the damping ratio ζ in terms of this different definition of logarithmic decrement.

1.11 For Example 1.2, calculate the value of RL to reduce the error down to 5%.

1.12 (a) Design an inverting amplifier with an input resistance of 20 kΩ and a gain of −10. (b) Include a resistor to compensate for bias current. (c) Design a summing amplifier such that $v_o = -(10v_1 + 2v_2 + 0.5v_3)$.

1.13 The axon action potential (AAP) is shown in Figure 4.1. Design a dc-coupled one-op-amp circuit that will amplify the −100 mV to +50 mV input range to have the maximal gain possible without exceeding the typical guaranteed linear output range.

1.14 Use the circuit shown in Figure E1.8 to design a dc-coupled one-op-amp circuit that will amplify the ±100 μV EOG to have the maximal gain possible without exceeding the typical guaranteed linear output range. Include a control that can balance (remove) series electrode offset potentials up to ±300 mV. Give all numerical values.

1.15 Design a noninverting amplifier having a gain of 10 and R_i of Figure 1.11(b) equal to 20 kΩ. Include a resistor to compensate for bias current.

1.16 An op-amp differential amplifier is built using four identical resistors, each having a tolerance of ±5%. Calculate the worst possible CMRR.

1.17 Design a three-op-amp differential amplifier having a differential gain of 5 in the first stage and 6 in the second stage.

1.18 Design a comparator with hysteresis in which the hysteresis width extends from 0 to +2 V.

1.19 For an inverting half-wave perfect rectifier, sketch the circuit. Plot the input–output characteristics for both the circuit output and the op-amp output, which are not the same point as in most op-amp circuits.

1.20 Using the principle shown in Figure 1.15, design a signal compressor for which an input-voltage range of ±10 V yields an output-voltage range of ±4 V.

1.21 Design an integrator with an input resistance of 1 MΩ. Select the capacitor such that when $v_i = +10$ V, v_o travels from 0 to −10 V in 0.1 s.

1.22 In Problem 1.21, if $v_i = 0$ and offset voltage equals 5 mV, what is the current through R? How long will it take for v_o to drift from 0 V to saturation? Explain how to cure this drift problem.

1.23 In Problem 1.21, if bias current is 200 pA, how long will it take for v_o to drift from 0 V to saturation? Explain how to cure this drift problem.

1.24 Design a differentiator for which $v_o = -10$ V when $dv_i/dt = 100$ V/s.

1.25 Design a one-section high-pass filter with a gain of 20 and a corner frequency of 0.05 Hz. Calculate its response to a step input of 1 mV.

1.26 Design a one-op-amp high-pass active filter with a high-frequency gain of +10 (not −10), a high-frequency input impedance of 10 MΩ, and a corner frequency of 10 Hz.

1.27 Find $V_o(j\omega)/V_i(j\omega)$ for the bandpass filter shown in Figure 1.19(c).

1.28 Figure 6.16 shows that the frequency range of the AAP is 1 to 10 kHz. Design a one-op-amp active bandpass filter that has a midband input impedance of approximately 10 kΩ, a midband gain of approximately 1, and a frequency response from 1 to 10 kHz (corner frequencies).

1.29 Figure 6.16 shows the maximal single-peak signal and frequency range of the EMG. Design a one-op-amp bandpass filter circuit that will amplify the EMG to have the maximal gain possible without exceeding the typical guaranteed linear output range and will pass the range of frequencies shown.

1.30 Using 411 op amps, explain how an amplifier with a gain of 100 and a bandwidth of 100 kHz can be designed.

1.31 Refer to Figure 1.20. If the amplifier gain is 1000, what is the loop gain at 100 Hz?

1.32 For the differentiator shown in Figure 1.18, ground the input, break the feedback loop at any point, and determine the phase shift in each section. Explain why the circuit tends to oscillate.

1.33 For Problem 1.32, calculate the amplifier input and output resistances at 100 Hz, for inverting and noninverting amplifiers.

1.34 For Figure 1.22, what is the maximal capacitive load C_L that can be connected to a 411 without degrading the normal slew rate (15 V/μs) at the maximal current output (20 mA)?

1.35 You have an input sinusoidal signal of 1 Hz with $V_{peak} = 2.5$ V. However, you also have high frequency (50 Hz) noise with $V_{peak} = 300$ mV on top of your input. Design a comparator with hysteresis (shown in Figure P1.35) such that when:

$V_{in} \geq 2.0$ V, V_{out} goes from V_{cc} (3.3 V) to Gnd (0 V) and;

$V_{in} < 1.2$ V, V_{out} goes from Gnd (0 V) to V_{cc} (3.3 V)

Calculate values for R_1, R_2, and R_3. Use LTspice simulation to verify your design.

1.36 Identify following devices into Class I, Class II, or Class III, also determine if these are Life-Sustain/Support devices or Implant devices, and the Medical Specialty/Review Panel under which they belong to. Fill in the following table P1.36:

Devices: Antimicrobial Medical Glove, Medical Image Analyzer, Arthroscope Atrial Defibrillator, Infants cooling cap, Bone Heterograft, Ultrasonic cleaner for medical instruments, Blood pressure alarm, Angioscope, Artificial Heart, Neonatal Phototherapy Blanket, MR-guided focused ultrasound system, Continuous Glucose Monitor Retrospective Data Analysis Software, Femoral catheter, Cardiovascular permanent or temporary pacemaker electrode, Hemodialysis system for home use.

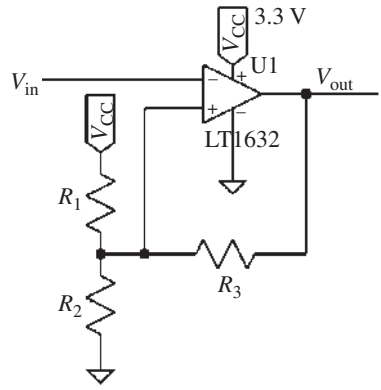


Figure P1.35 Comparator with hysteresis circuit.

Table P1.36 Medical Device Classification

Device	Class	Medical Specialty/ Review Panel	Life-Sustain/ Support	Implant
Antimicrobial Medical Glove				

1.37 You planned to use one-amp differential amplifier with gain 5 to amplify electrocardiogram signal as shown in Figure P1.37, such that $R_1 = R_3 = 10$ kΩ, $R_2 = R_4 = 50$ kΩ. However the skin–electrode impedances ($R_5 = 10$ kΩ and $R_6 = 20$ kΩ) differed by 10 kΩ causing a mismatch of input impedances values. The common-mode voltage V_{CM} observed was 10 mV. Use LTspice simulation to determine the common-mode gain for the system. What additions can you make to the circuit to address the mismatch of input impedances?

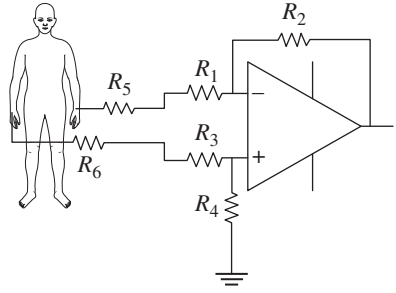


Figure P1.37 One-amp amplifier with skin–electrode impedances.

REFERENCES

Anonymous, *Health Devices Sourcebook*. Plymouth Meeting, PA: ECRI, 2013a.

Anonymous, *Human Factors Engineering Guidelines and Preferred Practices for the Design of Medical Devices*. ANSI/AAMI HE75, 2009/ (R) 2013. Arlington, VA: AAMI, 2013b.

Anonymous, *Medical Outcomes and Guidelines Sourcebook*. New York, NY: Faulkner and Gray, Inc., 2001.

Anonymous, *Product Development Directory*. Montvale, NJ: Medical Economics Co., 1996.

Ary, J. P., "A head-mounted 24-channel evoked potential preamplifier employing low-noise operational amplifiers." *IEEE Trans. Biomed. Eng*., 1977, BME-24, 293–297.

Cobbold, R. S. C., *Transducers for Biomedical Measurements: Principles and Applications*. New York: Wiley, 1974.

Cohen, B. J., and A. DePetris, *Medical Terminology: An Illustrated Guide*, 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2013.

Davis, N. M., *Medical Abbreviations: 32,000 Conveniences at the Expense of Communication and Safety*, 15th ed. Huntington Valley, PA: Neil M. Davis Associates, 2011.

Dawson-Saunders, B., and R. G. Trapp, *Basic and Clinical Biostatistics*, 4th ed. Norwalk, CT: Appleton & Lange, 2004.

Doebelin, E. O., *Measurement Systems: Application and Design*, 4th ed. New York: McGraw-Hill, 1990.

Dorland, N. W. (ed.), *Dorland's Illustrated Medical Dictionary*, 30th ed. Philadelphia: Saunders, 2003.

Federal Policies and the Medical Device Industry. Washington, DC: U.S. Congress, Office of Technology Assessment, OTA-H-230, October 1984.

Firkin, B. G., and J. A. Whitworth, *Dictionary of Medical Eponyms*, 2nd ed. London: Taylor & Francis, 2001.

Graeme, J. G., "Rectifying wide-range signals with precision, variable gain." *Electronics*, December 12, 1974b, 45(25), 107–109.

Haber, K., *Common Abbreviations in Clinical Medicine*. New York: Raven Press, 1988.

Hamilton, B., and B. Guides, *Medical Acronyms, Symbols and Abbreviations*, 2nd ed. New York: Neal-Schuman, 1988.

Heister, R., *Dictionary of Abbreviations in Medical Sciences*. New York: Springer, 1989.

Horowitz, P., and W. Hill, *The Art of Electronics*, 2nd ed. Cambridge, England: Cambridge University Press, 1989.

Institute of Electrical and Electronics Engineers (IEEE), *IEEE Standard Dictionary of Electrical and Electronic Terms*, 6th ed. Piscataway, NJ: Institute of Electrical and Electronics Engineers, 1997.

Jung, W. G., *1C Op-Amp Cookbook*, 3rd ed. Indianapolis: Howard W. Sams, 1986.

Kessler, D. A., S. M. Pape, and D. N. Sundwall, "The federal regulation of medical devices." *N. Engl. J. Med.*, 1987, 317(6), 357–366.

King, P. H., and R. C. Fries, *Design of Biomedical Devices and Systems*. New York: Dekker, 2003.

Kuo, B., and F. Golnaraghi, *Automatic Control Systems*, 9th ed. New York: Wiley, 2009.

Murfitt, R. R., "United States government regulation of medical device software: A review." *J. Med. Eng. Technol.*, 1990, 14(3), 111–113.

Pacela, A. F. (ed.), "Safe medical devices law: Sweeping changes for hospitals and the standards industry." *Biomed. Safety Stand*., Special Supplement No. 12, February 1991.

Ray, C. D. (ed.), *Medical Engineering*. Chicago: Year Book, 1974.

Tobey, G. E., J. G. Graeme, and L. P. Huelsman, *Operational Amplifiers: Design and Application*. New York: McGraw-Hill, 1971.

Tompkins, W. J., and J. G. Webster (eds.), *Design of Microcomputer-Based Medical Instrumentation*. Englewood Cliffs, NJ: Prentice-Hall, 1981.

Tompkins, W. J., and J. G. Webster (eds.), *Interfacing Sensors to the IBM PC*. Englewood Cliffs, NJ: Prentice-Hall, 1988.

U.S. Food and Drug Administration, *Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies*, 2013a. https://www.fda.gov/media/81784/download (accessed on October 13, 2019).

U.S. Food and Drug Administration, *Medical Device Classification Product Codes*, 2013b. https://www.fda.gov/media/82781/download (accessed on October 14, 2019).

U.S. Food and Drug Administration, *Custom Device Exemption Guidance for Industry and Food and Drug Administration*, 2014. https://www.fda.gov/media/89897/download (accessed on October 14, 2019).

U.S. Food and Drug Administration, *Classify Your Medical Device*, 2018a. https://www.fda.gov/medical-devices/overview-device-regulation/classify-your-medical-device (accessed on October 14, 2019).

U.S. Food and Drug Administration, *Device Classification Panels*, 2018b. https://www.fda.gov/medical-devices/classify-your-medical-device/device-classification-panels (accessed on October 14, 2019).

U.S. Food and Drug Administration, *Regulatory Controls*, 2018c. https://www.fda.gov/medical-devices/overview-device-regulation/regulatory-controls (accessed on October 14, 2019).

U.S. Food and Drug Administration, *Class I/II Exemptions*, 2019a. https://www.fda.gov/medical-devices/classify-your-medical-device/class-i-ii-exemptions (accessed on October 14, 2019).

U.S. Food and Drug Administration, *CFR Title 21*, 2019b. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=860.3 (accessed on October 14, 2019).

U.S. Food and Drug Administration, *De Novo Classification Request*, 2019c. https://www.fda.gov/medical-devices/premarket-submissions/de-novo-classification-request (accessed on October 14, 2019).

U.S. Food and Drug Administration, *Humanitarian Device Exemption*, 2019d. https://www.fda.gov/medical-devices/premarket-submissions/humanitarian-device-exemption (accessed on October 14, 2019).

U.S. Food and Drug Administration, *Product Classification*, 2019e. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm (accessed on October 14, 2019).

Van Valkenburg, M. E., *Analog Filter Design*. New York: Holt, Rinehart, and Winston, 1982.

Wait, J. V., L. P. Huelsman, and G. A. Korn, *Introduction to Operational Amplifier Theory and Applications*. New York: McGraw-Hill, 1975.

Webster, J. G. (ed.), *Bioinstrumentation*. Hoboken, NJ: Wiley, 2004.

Webster, J. G. (ed.), *Encyclopedia of Medical Devices and Instrumentation*, 2nd ed., Vols. 1–6. New York: Wiley, 2006.