Biomedical Imaging Informatics

9

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After reading this chapter, you should know the answers to these questions:

- What makes images a challenging type of data to be processed by computers when compared to non-image clinical data?
- Why are there many different imaging modalities, and by what major two characteristics do they differ?
- How are visual and knowledge content in images represented computationally? How are these techniques similar to representation of non-image biomedical data?
- What sort of applications can be developed to make use of the semantic image content made accessible using the Annotation and Image Markup model?
- What are four different types of image processing methods? Why are such methods assembled into a pipeline when creating imaging applications?
- What is an imaging modality with high spatial resolution? What is a modality that provides functional information? Why are most imaging modalities not capable of providing both?
- What is the goal in performing segmentation in image analysis? Why is there more than one segmentation method?
- What are two types of quantitative information in images? What are two types of semantic information in images? How might this information be used in medical applications?
- What is the difference between image registration and image fusion? What are examples of each?

9.1 Introduction

Imaging plays a central role in the health care process. The field is crucial not only to health care, but also to medical communication and education, as well as in research. In fact much of our recent progress, particularly in diagnosis, can be traced to the availability of increasingly sophisticated imaging techniques that not only show the structure of the body in incredible detail, but also show the function of the tissues within the body.

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Although there are many types (or modalities) of imaging equipment, the images the modalities produce are nearly always acquired in or converted to digital form. The evolution of imaging from analog, film-based acquisition to digital format has been driven by the necessities of cost reduction, efficient throughput, and workflow in managing and viewing an increasing proliferation in the number of images produced per imaging procedure (currently hundreds or even thousands of images). At the same time, having images in digital format makes them amenable to image processing methodologies for enhancement, analysis, display, storage, and even enhanced interpretation.

Because of the ubiquity of images in biomedicine, the increasing availability of images in digital form, the rise of high-powered computer hardware and networks, and the commonality of image processing solutions, digital images have become a core data type that must be considered in many biomedical informatics applications. Therefore, this chapter is devoted to a basic understanding of the unique aspects of images as a core data type and the unique aspects of imaging from an informatics perspective. Chapter 20, on the other hand, describes the use of images and image processing in various applications, particularly those in radiology since that field places the greatest demands on imaging methods.

The topics covered by this chapter and Chap. 20 comprise the growing discipline of biomedical imaging informatics (Kulikowski 1997), a subfield of biomedical informatics (see Chap. 1) that has arisen in recognition of the common issues that pertain to all image modalities and applications once the images are converted to digital form. Biomedical imaging informatics is a dynamic field, recently evolving from focusing purely on image processing to broader informatics topics such as representing and processing the semantic contents (Rubin and Napel 2010). At the same time, imaging informatics shares common methodologies and challenges with other domains in biomedical informatics. By trying to understand these common issues, we can develop general solutions that can be applied to all images, regardless of the source.

The major topics in biomedical imaging informatics include image acquisition, image content representation, management/storage of images, image processing, and image interpretation/computer reasoning (Fig. 9.1). **Image acquisition** is the process of generating images from the modality and converting them to digital form if they are not intrinsically digital. **Image content representation** makes the information in images accessible to machines for processing. **Image management/storage** includes methods for storing, transmitting, displaying, retrieving, and organizing images. **Image processing** comprises methods to enhance, segment, visualize, fuse, or analyze the images. **Image interpretation/computer reasoning** is the process by which the individual viewing the image renders an impression of the medical significance of the results of imaging study, potentially aided by computer methods. Chapter 20 is primarily concerned with information systems for image management and storage, whereas this chapter concentrates on these other core topics in biomedical imaging informatics.

An important concept when thinking about imaging from an informatics perspective is that images are an *unstructured data type*; as such, while machines can readily manage the raw image data in terms of storage/retrieval, they cannot easily access image contents (recognize the type of image, annotations made on the image, or anatomy or abnormalities within the image). In this regard, biomedical imaging informatics shares much in common with natural language processing (NLP; Chap. 8). In fact, as the methods of computationally representing and processing images is presented in this chapter, parallels to NLP should be considered, since there is synergy from an informatics perspective.

As in NLP, a major purpose of the methods of imaging informatics is to extract particular information; in biomedical informatics the goal is often to extract information about the structure of the body and to collect features that will be useful for characterizing abnormalities based on morphological alterations. In fact, imaging provides detailed and diverse information very useful for characterizing disease, providing an "imaging

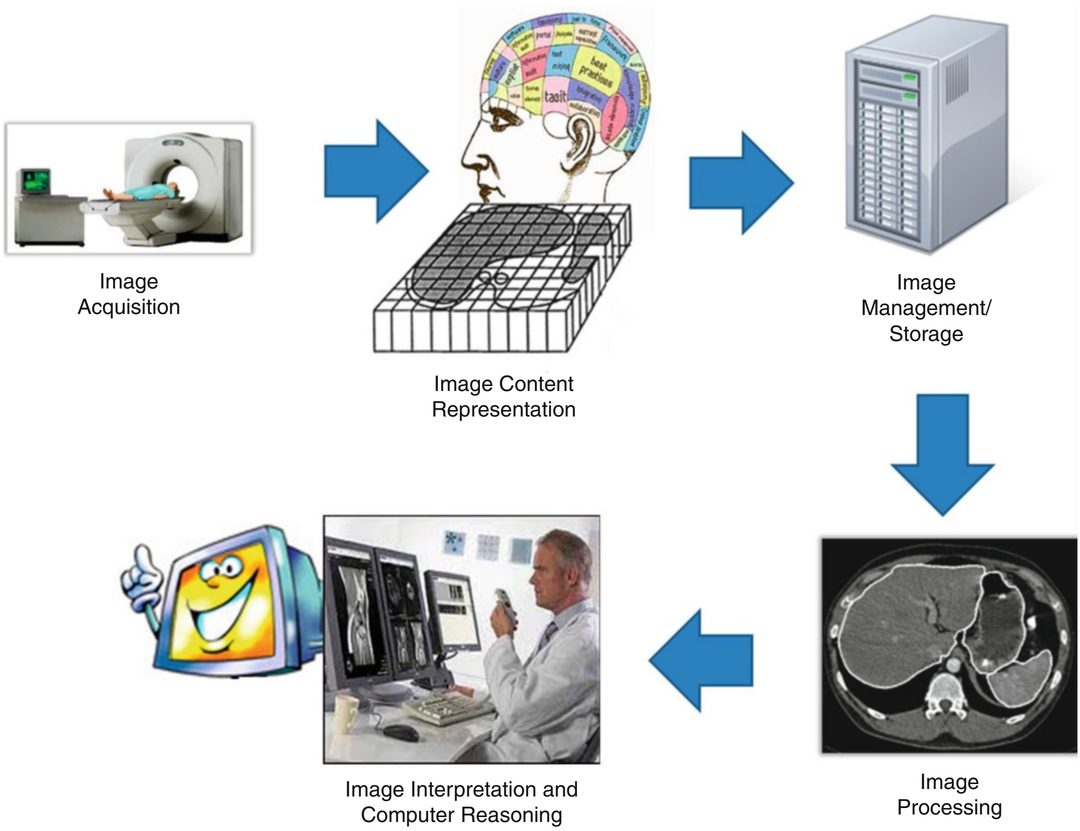

Fig. 9.1 The major topics in biomedical imaging informatics follow a workflow of activities and tasks commencing with include image acquisition, followed by image content representation, management/storage of images, image processing, and image interpretation/computer reasoning

phenotype” useful for characterizing disease, since “a picture is worth a thousand words.[1]” However, to overcome the challenges posed by the unstructured image data type, recent work is applying semantic methods from biomedical informatics to images to make their content explicit for machine processing (Rubin and Napel 2010). Many of the topics in this chapter therefore involve how to represent, extract and characterize the information that is present in images, such as anatomy and abnormalities. Once that task is completed, useful applications that process the image contents can be developed, such as image search and decision support to assist with image interpretation.

[1]Frederick Barnard, “One look is worth a thousand words,” Printers’ Ink, December, 1921.

While we seek generality in discussing biomedical imaging informatics, many examples in this chapter are taken from a few selected domains such as brain imaging, which is part of the growing field of **neuroinformatics** (Koslow and Huerta 1997). Though our examples are specific, we attempt to describe the topics in generic terms so that the reader can recognize parallels to other imaging domains and applications.

9.2 Image Acquisition

In general, there are two different strategies in imaging the body: (1) delineate *anatomic structure* (anatomic/structural imaging), and (2) determine *tissue composition or function* (functional imaging) (Fig. 9.2). In reality, one does not

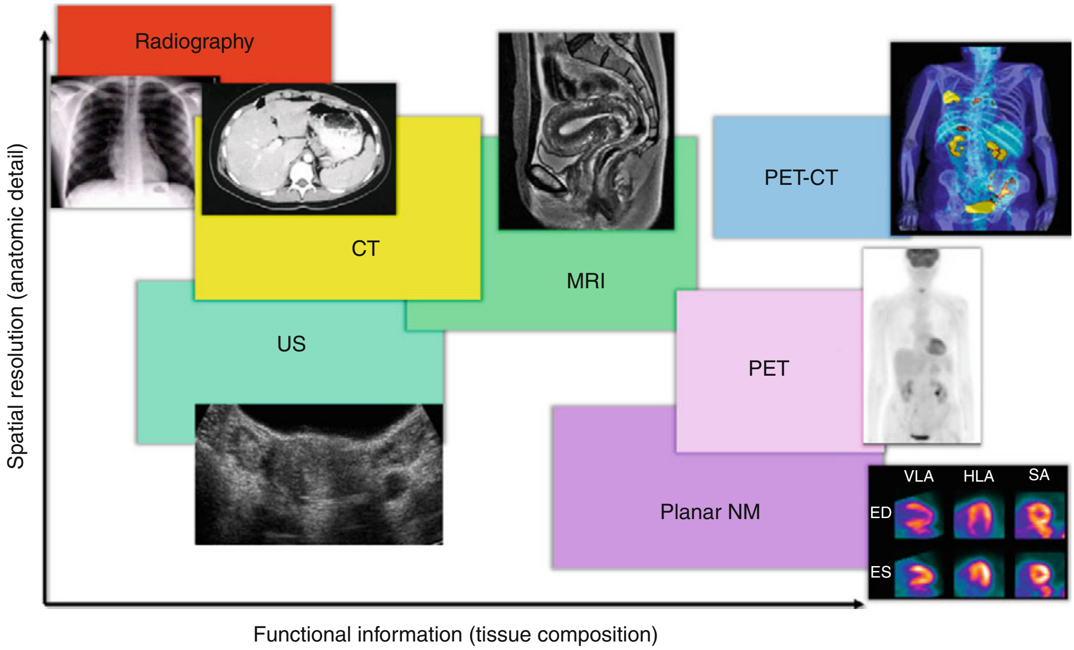

Fig. 9.2 The various radiology imaging methods differ according to two major axes of information of images, spatial resolution (anatomic detail) and functional information depicted (which represents the tissue composition—e.g., normal or abnormal). A sample of the more common imaging modalities is shown

choose between anatomic and functional imaging; many modalities provide information about both morphology and function. However, in general, each imaging modality is characterized primarily as being able to render high-resolution images with good contrast resolution (anatomic imaging) or to render images that depict tissue function (functional imaging).

9.2.1 Anatomic (Structural) Imaging

Imaging the structure of the body has been and continues to be the major application of medical imaging, although, as described in Sect. 9.2.2, functional imaging is a very active area of research. The goal of anatomic imaging is to accurately depict the structure of the body—the size and shape of organs—and to visualize abnormalities clearly. Since the goal in anatomic imaging is to depict and understand the structure of anatomic entities accurately, high spatial resolution is an important requirement of the imaging method (Fig. 9.2). On the other hand, in anatomic imaging, recognizing tissue function (e.g., tissue ischemia, neoplasm, inflammation, etc.) is not the goal, though this is crucial to functional imaging and to patient diagnosis. In most cases, imaging will be done using a combination of methods or modalities to derive both structural/anatomic information as well as functional information.

9.2.2 Functional Imaging

Many imaging techniques not only show the structure of the body, but also the function, where for imaging purposes function can be inferred by observing changes of structure over time. In recent years this ability to image function has greatly accelerated. For example, ultrasound and angiography are widely used to show the functioning of the heart by depicting wall motion, and ultrasound Doppler can image both normal and disturbed blood flow (Mehta et al. 2000). Molecular imaging (Sect. 9.2.3) is increasingly able to depict the expression of particular genes superimposed on structural images, and thus can also be seen as a form of functional imaging.

A particularly important application of functional imaging is for understanding the cognitive activity in the brain. It is now routinely possible to put a normal subject in a scanner, to give the person a cognitive task, such as counting or object recognition, and to observe which parts of the brain light up. This unprecedented ability to observe the functioning of the living brain opens up entirely new avenues for exploring how the brain works.

Functional brain imaging modalities can be classified as *image-based* or *non-image based*. In both cases it is taken as axiomatic that the functional data must be mapped to the individual subject's anatomy, where the anatomy is extracted from structural images using techniques described in the previous sections. Once mapped to anatomy, the functional data can be integrated with other functional data from the same subject, and with functional data from other subjects whose anatomy has been related to a template or probabilistic atlas. Techniques for generating, mapping and integrating functional data are part of the field of Functional Brain Mapping, which has become very active in the past few years, with several conferences (Organization for Human Brain Mapping 2001) and journals (Fox 2001; Toga et al. 2001) devoted to the subject.

9.2.2.1 Image-Based Functional Brain Imaging

Image-based functional data generally come from scanners that generate relatively low-resolution volume arrays depicting spatially-localized activation. For example, **positron emission tomography** (PET) (Heiss and Phelps 1983; Aine 1995; Alberini et al. 2011) and **magnetic resonance spectroscopy** (MRS) (Ross and Bluml 2001) reveal the uptake of various metabolic products by the functioning brain; and **functional magnetic resonance imaging** (fMRI) reveals changes in blood oxygenation that occur following neural activity (Aine 1995). The raw intensity values generated by these techniques must be processed by sophisticated statistical algorithms to sort out how much of the observed intensity is due to cognitive activity and how much is due to background noise.

As an example, one approach to fMRI imaging is language mapping (Corina et al. 2000). The subject is placed in the **magnetic resonance imaging** (MRI) scanner and told to silently name objects shown at 3-s intervals on a head-mounted display. The actual objects ("on" state) are alternated with nonsense objects ("off" state), and the fMRI signal is measured during both the on and the off states. Essentially the **voxel** values at the off (or control) state are subtracted from those at the on state. The difference values are tested for significant difference from non-activated areas, then expressed as t-values. The voxel array of t-values can be displayed as an image.

A large number of alternative methods have been and are being developed for acquiring and analyzing functional data (Frackowiak et al. 1997). The output of most of these techniques is a low-resolution 3-D image volume in which each voxel value is a measure of the amount of activation for a given task. The low-resolution volume is then mapped to anatomy guided by a high-resolution structural MR dataset, using one of the linear registration techniques described in Sect. 9.4.7.

Many of these and other techniques are implemented in the SPM program (Friston et al. 1995), the AFNI program (Cox 1996), the Lyngby toolkit (Hansen et al. 1999), and several commercial programs such as Medex (Sensor Systems Inc. 2001) and Brain Voyager (Brain Innovation B.V. 2001). The FisWidgets project at the University of Pittsburgh is developing an approach that allows customized creation of graphical user interfaces in an integrated desktop environment (Cohen 2001). A similar effort (VoxBox) is underway at the University of Pennsylvania (Kimborg and Aguirre 2002).

The ultimate goal of functional neuroimaging is to observe the actual electrical activity of the neurons as they perform various cognitive tasks. fMRI, MRS and PET do not directly record electrical activity. Rather, they record the results of electrical activity, such as (in the case of fMRI) the oxygenation of blood supplying the active neurons. Thus, there is a delay from the time of activity to the measured response. In other words these techniques have relatively poor temporal resolution (Sect. 9.2.4). **Electroencephalography** (EEG) or **magnetoencephalography** (MEG), on the other hand, are more direct measures of electrical activity since they measure the electromagnetic fields generated by the electrical activity of the neurons. Current EEG and MEG methods involve the use of large arrays of scalp sensors, the output of which are processed in a similar way to CT in order to localize the source of the electrical activity inside the brain. In general this "source localization problem" is underconstrained, so information about brain anatomy obtained from MRI is used to provide further constraints (George et al. 1995).

9.2.3 Imaging Modalities

There are many different approaches that have been developed to acquire images of the body. A proliferation in imaging modalities reflects the fact that there is no single perfect imaging modality; no single imaging technique satisfies all the desiderata for depicting the broad variety of types of pathology, some of which are better seen on some modalities than on others. The primary difference among the imaging modalities is the energy source used to generate the images. In radiology, nearly every type of energy in the electromagnetic spectrum has been used, in addition to other physical phenomena such as sound and heat. We describe the more common methods according to the type of energy used to create the image.

9.2.3.1 Light

The earliest medical images used visible light to create photographs, either of gross anatomic structures or, if a microscope was used, of histological specimens. Light is still an important source for creation of images, and in fact optical imaging has seen a resurgence of interest and application for areas such as molecular imaging (Weissleder and Mahmood 2001; Ray 2011) and imaging of brain activity on the exposed surface of the cerebral cortex (Pouratian et al. 2003). Visible light is the basis for an emerging modality called "optical imaging" and has promising applications such as cancer imaging (Solomon, Liu et al. 2011). Visible light, however, does not allow us to see more than a short distance beneath the surface of the body; thus other modalities are used for imaging structures deep inside the body.

9.2.3.2 X-Rays

X-rays were first discovered in 1895 by Wilhelm Conrad Roentgen, who was awarded the 1901 Nobel Prize in Physics for this achievement. The discovery caused worldwide excitement, especially in the field of medicine; by 1900, there already were several medical radiological societies. Thus, the foundation was laid for a new branch of medicine devoted to imaging the structure and function of the body (Kevles 1997).

Radiography is the primary modality used in radiology departments today, both to record a static image (Fig. 9.3) as well as to produce a real-time view of the patient (fluoroscopy) or a movie (cine). Both film and fluoroscopic screens were used initially for recording X-ray images, but the fluoroscopic images were too faint to be used clinically. By the 1940s, however, television and image-intensifier technologies were developed to produce clear real-time fluorescent

Fig. 9.3 A radiograph of the chest (Chest X-ray) taken in the frontal projection. The image is shown as if the patient is facing the viewer. This patient has abnormal density in the left lower lobe

images. Today, a standard procedure for many types of examinations is to combine real-time television monitoring of X-ray images with the creation of selected higher resolution film images. Until the early 1970s, film and fluoroscopy were the only X-ray modalities available. Recently, nearly all radiology departments have shifted away from acquiring radiographic images on film (analog images) to using digital radiography (Korner et al. 2007) to acquire digital images.

X-ray imaging is a projection technique; an X-ray beam—one form of ionizing radiation—is projected from an X-ray source through a patient's body (or other object) onto an X-ray array detector (a specially coated cassette that is scanned by a computer to capture the image in digital form), or film (to produce an non-digital image). Because an X-ray beam is differentially absorbed by the various body tissues based on the thickness and atomic number of the tissues, the X-rays produce varying degrees of brightness and darkness on the radiographic image. The differential amounts of brightness and darkness on the image are referred to as "image contrast;" differential contrast among structures on the image is the basis for recognizing anatomic structures. Since the image in radiography is a projection, radiographs show a superposition of all the structures traversed by the X-ray beam.

Computed radiography (CR) is an imaging technique that directly creates digital radiographs from the imaging procedure. Storage phosphor replaces film by substituting a reusable phosphor plate in a standard film cassette. The exposed plate is processed by a reader system that scans the image into digital form, erases the plate, and packages the cassette for reuse. An important advantage of CR systems is that the cassettes are of standard size, so they can be used in any equipment that holds film-based cassettes (Horii 1996). More recently, **Digital Radiography** (DR) uses charge-coupled device (CCD) arrays to capture the image directly.

Radiographic images have very high spatial resolution because a high photon flux is used to produce the images, and a high resolution detector (film or digital image array) that captures many line pairs per unit area is used. On the other hand, since the contrast in images is due to differences in tissue density and atomic number, the amount of functional information that can be derived from radiographic images is limited (Fig. 9.2). Radiography is also limited by relatively poor contrast resolution (compared with other modalities such as **computed tomography** (CT) or MRI), their use of ionizing radiation, the challenge of spatial localization due to projection ambiguity, and their limited ability to depict physiological function. As described below, newer imaging modalities have been developed to increase contrast resolution, to eliminate the need for X-rays, and to improve spatial localization. A benefit of radiographic images is that they can be generated in real time (fluoroscopy) and can be produced using portable devices.

Computed Tomography (CT) is an important imaging method that uses X-ray imaging to produce cross sectional and volumetric images of the body (Lee 2006). Similar to radiography, X-rays are projected through the body onto an array of detectors; however, the beam and detectors rotate around the patient, making numerous views at different angles of rotation. Using computer reconstruction algorithms, an estimate of absolute density at each point (volume element or **voxel**) in the body is computed. Thus, the CT image is a computed image (Fig. 9.4); CT did not become practical for generating high quality images until the advent of powerful computers

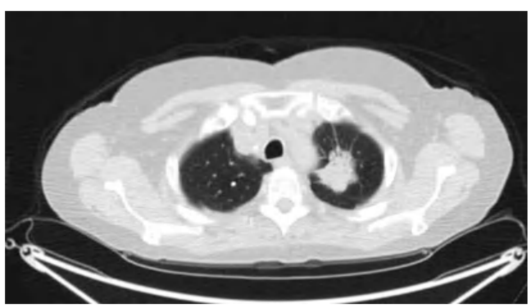

Fig. 9.4 A CT image of the upper chest. CT images are slices of a body plane; in this case, a cross sectional (axial) image of the chest. Axial images are viewed from below the patient, so that the patient's left is on viewer's right. This image shows a cancer mass in the left upper lobe of the lung

and development of computer-based reconstruction techniques, which represent one of the most spectacular applications of computers in all of medicine (Buxton 2009). The spatial resolution of images is not as high in CT as it is in radiography, however, due to the computed nature of the images, the contrast resolution and ability to derive functional information of tissues in the body is superior for CT than for radiography (Fig. 9.2).

9.2.3.3 Ultrasound

A common energy source used to produce images is **ultrasound**, which developed from research performed by the Navy during World War II in which sonar was used to locate objects of interest in the ocean. Ultrasonography uses pulses of high-frequency sound waves rather than ionizing radiation to image body structures (Kremkau 2006). The basis of image generation is due to a property of all objects called acoustical impedance. As sound waves encounter different types of tissues in a patient's body (particularly interfaces where there is a chance in acoustical impedance), a portion of the wave is reflected and a portion of the sound beam (which is now attenuated) continues to traverse into deeper tissues. The time required for the echo to return is proportional to the distance into the body at which it is reflected; the amplitude (intensity) of a returning echo depends on the acoustical properties of the tissues encountered and is represented in the image as brightness (more echoes returning to the source is shown as image brightness). The system constructs two-dimensional images (B-scans) by displaying the echoes from pulses of multiple adjacent one-dimensional paths (A-scans). Ultrasound images are acquired as digital images from the outset, and saved on computer disks. They may also be recorded as frames in rapid succession (cine loops) for real-time imaging. In addition, Doppler methods in ultrasound are used to measure and characterize the blood flow in blood vessels in the body (Fig. 9.5).

Since the image contrast in ultrasound is based on differences in the acoustic impedance of tissue, ultrasound provides functional information (e.g., tissue composition and blood flow). On the other hand, the flux of sound waves is not as dense as the photon flux used to produce images in radiography; thus ultrasound images are generally lower resolution images than other imaging modalities (Fig. 9.2).

Current ultrasound machines are essentially specialized computers with attached peripherals, with active development of three-dimensional imaging. The ultrasound transducer now often sweeps out a 3-D volume rather than a 2-D plane, and the data are written directly into a three-dimensional array memory, which is displayed using volume or surface-based rendering techniques (Ritchie et al. 1996).

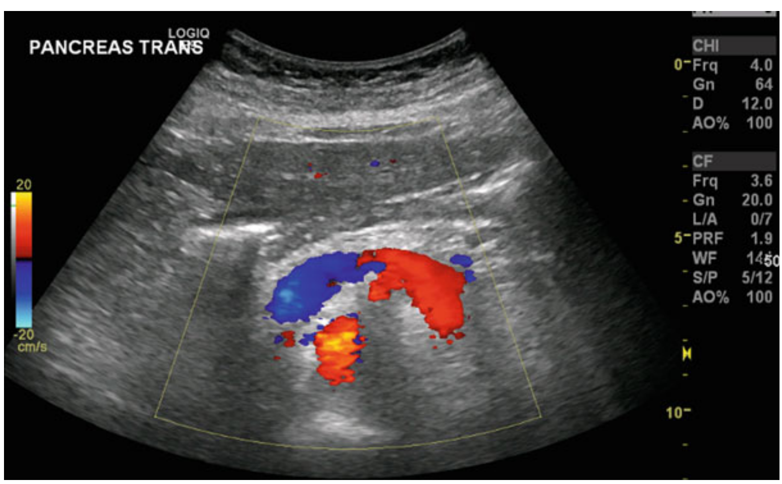

Fig. 9.5 An ultrasound image of abdomen. Like CT and MRI, ultrasound images are slices of a body, but because a user creates the images by holding a probe, any arbitrary plane can be imaged (so long as the probe can be oriented to produce that plane). This image shows an axial slice through the pancreas, and flow in nearby blood vessels (*in color*) is seen due to Doppler effects incorporated into the imaging method