Introduction

R. Nick Bryan

The title of this book refers to two components – *science* and *imaging*. Science, by usual definitions, has two aspects: a body of knowledge and a methodology. The former is the organized body of information that we have gained about ourselves and our environment by rigorous application of the latter. The scope of the scientific body of knowledge is vast; indeed, it is the total knowledge we have of our universe and everything in it. However, there is a restriction on this knowledge: it must have been derived through the scientific method. This carefully circumscribed method uses observation and experimentation in a logical and rational order to describe and explain natural phenomena. Scientific imaging, which is the specific topic of this presentation, likewise has two aspects: it is a body of knowledge – knowledge gained from the application of imaging – and a scientific methodology to answer scientific questions. While both of these elements, knowledge and methodology, are equally important, this book will focus on the methodological aspects of scientific imaging. However, this methodology will be extensively illustrated by examples from the commensurate body of knowledge. Hopefully the reader will be able to appreciate not only how to make and analyze a scientific image, but also what might be learned by doing so.

In a very broad sense, science is the study of the universe and all aspects of its components. It is the goal of science to understand and be able to explain everything about us. This goal is perhaps unachievable, but that does not diminish its importance or its validity. Science has greatly expanded our knowledge of the world, and it continues to do so. However, there are great voids in our knowledge about our world that provide the rationale and stimulus for future scientific activity – activity in which imaging will be a central element. Imaging has played, plays, and will continue to play a critical role in scientific investigation for two main reasons: the nature of the universe and human nature.

Though it may appear presumptuous, this presentation of the science of imaging will begin by addressing the general question of the universe: the whole space–time continuum in which we exist along with all the energy and matter within it. While vastly more complex than we can currently comprehend, this universe (U) can be grossly simplified, in the macroscopic sense, as the collection of all mass (m) and energy (E) distributed over three-dimensional space (x,y,z) evolving with time (t). This conceptualization of the universe can be formally expressed as:

$$U = (m, E)(x, y, z)(t) \qquad (1)$$

Science is the study of this spatial and temporal distribution of mass and energy. What makes imaging so critical to this enterprise is that mass and energy are not spread uniformly across space. This fact is readily appreciated by observing almost any aspect of nature, and it is beautifully illustrated by *The Powers of 10*, a film by Charles and Ray Eames illustrating the universe from its largest to its smallest elements, in 42 logarithmic steps (Figure 1). What is perhaps even more striking than the spatial magnitude, i.e., size, of the universe is its spatial complexity, reflected by extraordinary spatial variation at all levels. Mass and energy tend to be aggregated in local collections, albeit collections which vary greatly in their mass/energy make-up, spatial distribution, and temporal characteristics. Some collections are small, discrete masses that are relatively stable over time, like a diamond, while others are enormous, diffuse, rapidly evolving energy fields, like the electromagnetic radiation of a pulsar. Broadly defined, a coherent collection of mass/energy may be considered as a pattern or object: the former

Introduction to the Science of Medical Imaging, ed. R. Nick Bryan. Published by Cambridge University Press. © Cambridge University Press 2010.

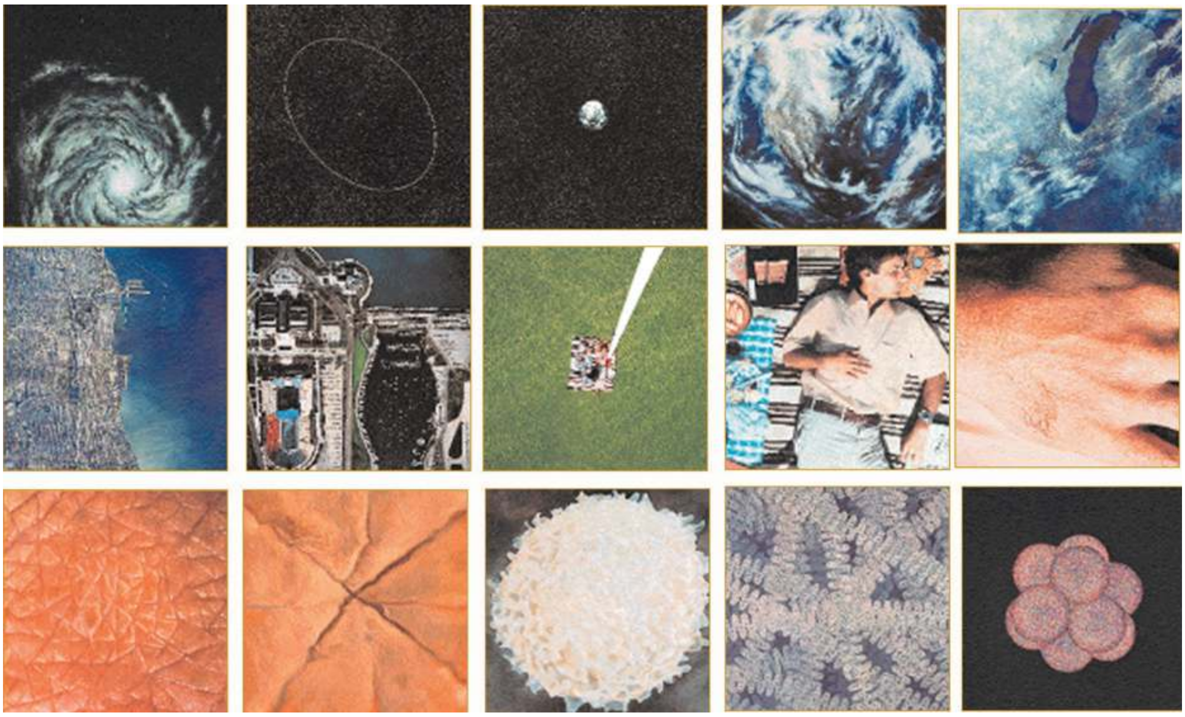

Figure 1. Spatial heterogeneity of the universe by the Powers of 10 by C. and R. Eames (www.powersof10.com). © 1977 Eames Office, LLC. Used with permission.

more diffuse and obtuse, the latter more discrete and well-defined. The critical point is that the universe is spatially and temporally heterogeneous. What is *here* is different than what is *there*! What is *here* today may be *there* tomorrow! Furthermore, this concept of spatial heterogeneity applies to most objects within the universe. From afar, the earth might be viewed as a simple, discrete object; however, on closer inspection its geographic heterogeneity is striking. There is a hierarchy of patterns and objects characterized by spatial heterogeneity at all levels. Biological systems, particularly a complex organism such as a human body, are incredibly heterogeneous objects, macroscopically and microscopically. Within the abdomen, the liver may be near to, but is distinctly separate from, the right kidney (Figure 2). Furthermore, this spatial heterogeneity is not just physical or anatomic, but also functional. The liver uses energy to make bile (among many other things), while the kidney makes urine. At the microscopic level organs are spatially segregated, with renal glomerular cells that filter urine distinct from nearby blood vessels. It is this intrinsic, spatially heterogeneous nature of the universe and objects within it that makes imaging so important to science.

In order to understand why imaging is so important to science, it is necessary to understand what an image is. In general, an image is defined as a representation of something, usually an object or local collection of objects (a scene). There are many different kinds of images: mental, auditory, abstract, direct, etc. Some images are permanent, others fleeting; some precise, others vague; some imaginary, others real. For purposes of this presentation, an image is defined as a representation or reproduction of a scene containing patterns or objects that explicitly retains and conveys the spatial aspects of the original. Specifically, we shall be dealing with what I call "scientific" images. A scientific image is an attempt to produce an accurate or high-fidelity reproduction of pattern(s) or object(s) based on spatially dependent measurements of their mass and/or energy contents. An image is a spatially coherent display of mass/energy measurements. This definition of an image can be formalized as:

$$I = f(m, E)(x, y, z)(t) \tag{2}$$

Note that this is virtually the same as Equation 1, except that it is formally presented as a mathematical function, and the elements do not represent actual

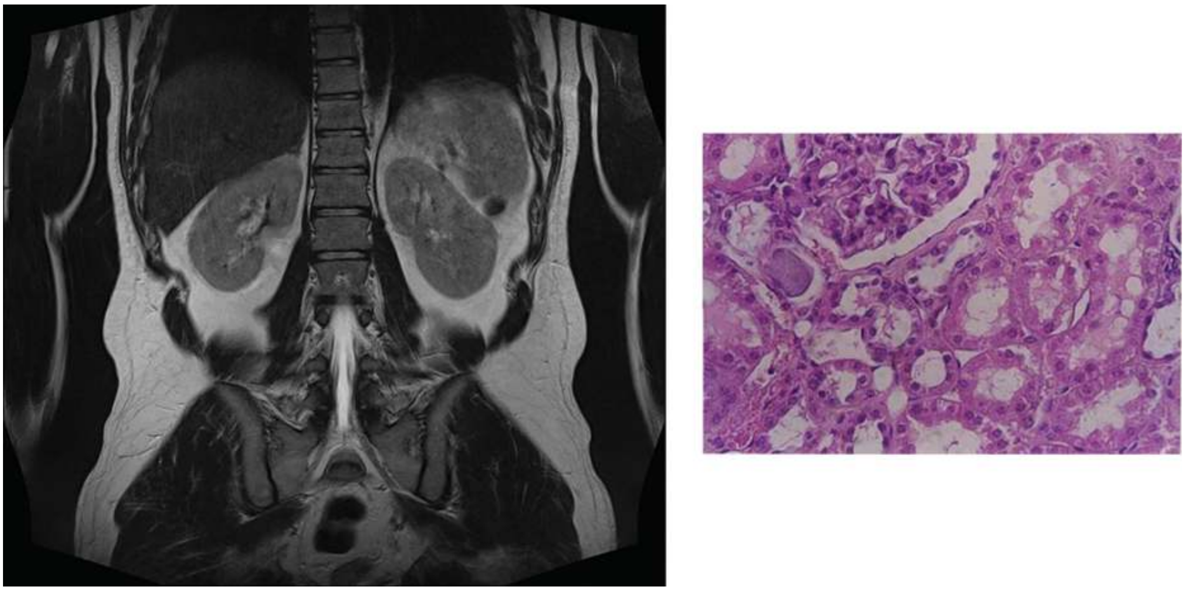

Figure 2. Macroscopic and microscopic spatial heterogeneity of the abdomen (magnetic resonance imaging) and kidney (light microscopy), respectively.

mass, energy, space, or time, but *measurements* of these physical features of the universe or of an object. Measurements of mass and energy are often modeled as signals, particularly in the engineering environment. There are many ways that these measurements can be made and subsequently displayed; this incredible smorgasbord of phenomena will be a large part of our story.

The original painting of a white pelican by Audubon is an image that is based on "measurements" of the amplitude and wavelength of visible light by the observer's (Mr. Audubon's) eye (Figure 3). The light signal measurements are spatially dependent. The light signal from the bird's left wing is more intense and of broader frequency (whiter) than the signal from the bird's left leg. Mr. Audubon's visual system integrated this signal and spatial information into an internal or mental image that he then rendered via his psychomotor system, a brush, paint, and canvas into a reproduction or representation of the original object, a pelican.

In this example, the imaging "system" was Mr. Audubon, his gun and his painting tools. The image is scientific because it is an attempt at a faithful, high-fidelity reproduction of the natural object under investigation, a pelican. Essentially all scientific images are variants of this theme: some kind of imaging device makes spatially dependent signal measurements and then renders a reproduction based on these measurements. An image such as this explicitly preserves and conveys spatial information as well as that relative to mass/energy.

Images such as these are robust forms of data. Such data are the descriptive heart of natural science. They reflect a rigorous interrogation of an object. The more faithfully, i.e., accurately, the image reflects the object, the higher the potential scientific quality of the image. Of obvious but special note is the fact that an image is the only way to fully investigate a spatially heterogeneous object. Non-spatially dependent scientific measurements may be, and often are, made, but they can never fully describe a spatially heterogeneous object. Measuring the amplitude and wavelength of light reflected from a pelican without explicit spatial information tells us something about the object, perhaps enough to distinguish a white pelican from a flamingo, although perhaps not enough to distinguish a white pelican from a swan. On the other hand, the barest of spatial information can convey a wealth of information. An image is necessary to fully describe and distinguish spatially heterogeneous objects.

This presentation on scientific imaging will proceed in a series of steps, beginning with a brief but more refined definition of a pattern, object, or sample – the thing to be imaged. Then the general principles of measurement will be reviewed. It should be emphasized that science is greatly, if not completely, dependent on

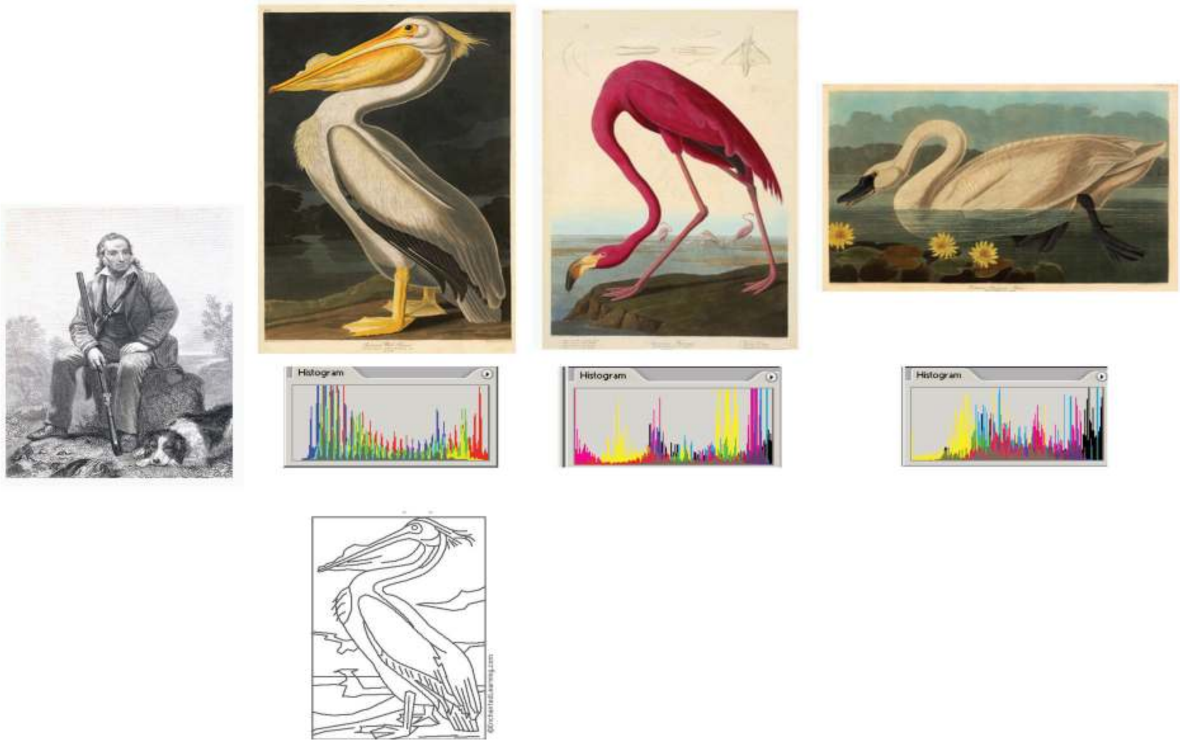

Figure 3. John James Audubon and his watercolors of a pelican, flamingo, and swan, with accompanying light spectrograms plus line drawing of pelican. Paintings used with permission: Audubon, John James, by J. Woodhouse Audubon (1974.46); others by John J. Audubon: American White Pelican (1863.17.311), Greater Flamingo (1863.17.431), Tundra swan (1863.17.411), all from the collection of The New-York Historical Society http://emuseum.nyhistory.org/code/emuseum.asp; drawing used with permission of EnchantedLearning.com.

measurements. This applies to descriptive as well as experimental science. Oddly, measurements, especially accurate, quantitative measurements, have been a major challenge and weakness of scientific imaging. There are no explicit measurements, much less numbers, associated with Audubon's paintings. Roentgen made the first x-ray image (of his wife's hand) with a mechanical apparatus that performed no explicit mathematical operation and produced no numbers (Figure 4). Today a radiologist typically interprets a CT scan of the brain in an empirical, qualitative, non-quantitative fashion. However, this aspect of scientific imaging is rapidly changing, and this is one of the major stimuli for this book. Today's CT scan may be interpreted qualitatively by the human eye, but the actual image is numeric, digital, and was created by a very sophisticated machine using advanced mathematics (Figure 5). Furthermore, the interpretation or analysis of scientific images will increasingly be performed with the aid of a computer in a quantitative fashion. Robust scientific images demand a strong quantitative component. Therefore this text will introduce the basic mathematics of scientific imaging, which includes the superset of measurement as well as the related topics of probability and statistics.

The unique aspect of imaging is the inclusion of spatial information. *Space* is the central element of imaging. This is evident in the formulae of the universe and of an image. Scientific imaging requires the explicit measurement of space, in addition to the measurements of mass or energy. The nature and importance of space seems intuitively obvious to humans. However, space is a very complex ideation that has multiple definitions and related applications that will require significant exposition and illustration. This will be important for understanding how human observers deal with images and their content. Psychologically it turns out that space is not as innate a concept as one might think: people actually have to learn what space is. As a result of this learning process, there is significant variability among different individuals' conceptions and perception of space, which can influence how they view and interpret images.

Furthermore, space is a key concept of the mathematics of imaging, and mathematicians define, think

Figure 4. Conrad Roentgen and x-ray of his wife's hand, 1895. http://en.wikipedia.org/wiki/Wilhelm_R%C3%B6ntgen.

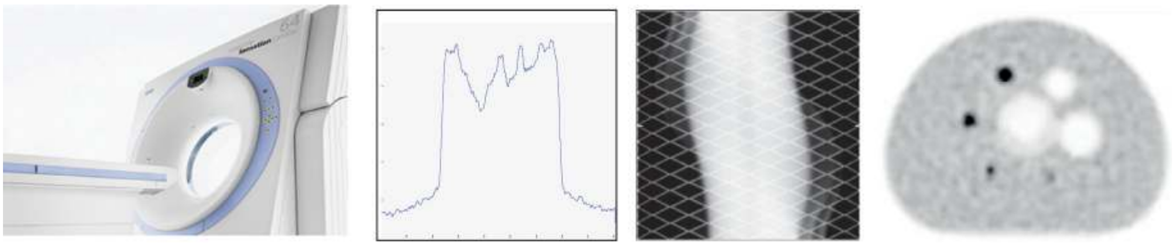

Figure 5. Contemporary CT scanner, CT data projection, reconstructed sinogram, and conventional Cartesian images of physical phantom containing seven rods of different sizes and radiodensities. Scanner photo courtesy of Siemens Healthcare. Others courtesy of J. S. Karp.

about, and use space very differently than many of the rest of us. Mathematical space is not only important conceptually, but also practically, as it is essential for scientific application.

Early cartographers might be considered the founders of scientific imaging, in that they first dealt with the explicit measurement and representation of real, physical space, in contrast to mathematicians, who dealt in abstract, metric space. Cartography is the science of spatially defined measurements of the earth (and other planets); maps form a subclass of scientific images. Early cartography focused on the new methodologies of space measurement in order to address the "where" (spatial) question. The very earliest maps were essentially one-dimensional, initially showing the order and then the distances between locations in one direction (Figure 6). Early spatial metrics were very crude, often in rough physical units such as spans (of a hand) or even more imprecise units of time equivalents (days of travel). This limited spatial view was expanded by the twelfth century to include refined two-dimensional flat maps, and by the fifteenth century three-dimensional globes of the world based on well-defined spatial units such as rods and sophisticated geometric concepts appeared. Early "mappers" paid less attention to the "what" question, the other essential component of an image. Usually there was only a rudimentary, qualitative description of "what" (post, village, river), located at a quantitatively defined location. However, the "what" of a cartographic map is

Figure 6. One-dimensional map of route from London, England to Beauvais, France by Dover ca 1250; two-dimensional map of Eurasia by al-Idrisi in 1154; three-dimensonal world globe by Martin Behaim in 1492, which still does not include America. London route owned by the British Library; image appeared in Akerman JR and Karrow RW, *Maps*, University of Chicago Press, 2007. Muhammad al-Idrisi's map appears on http://en.wikipedia.org/wiki/Tabula_Rogeriana. Globe photo courtesy of Alexander Franke, http://en.wikipedia.org/wiki/Erdapfel.

equivalent to the m,E measurement in a generic scientific image. Beginning in the seventeenth and eighteenth centuries, the introduction of more precise physical measurements of the "what" (number of people, temperature, wind direction) that was located at specific geographical locations resulted in rich *functional* maps that are not only exquisite, but classical examples of scientific images.

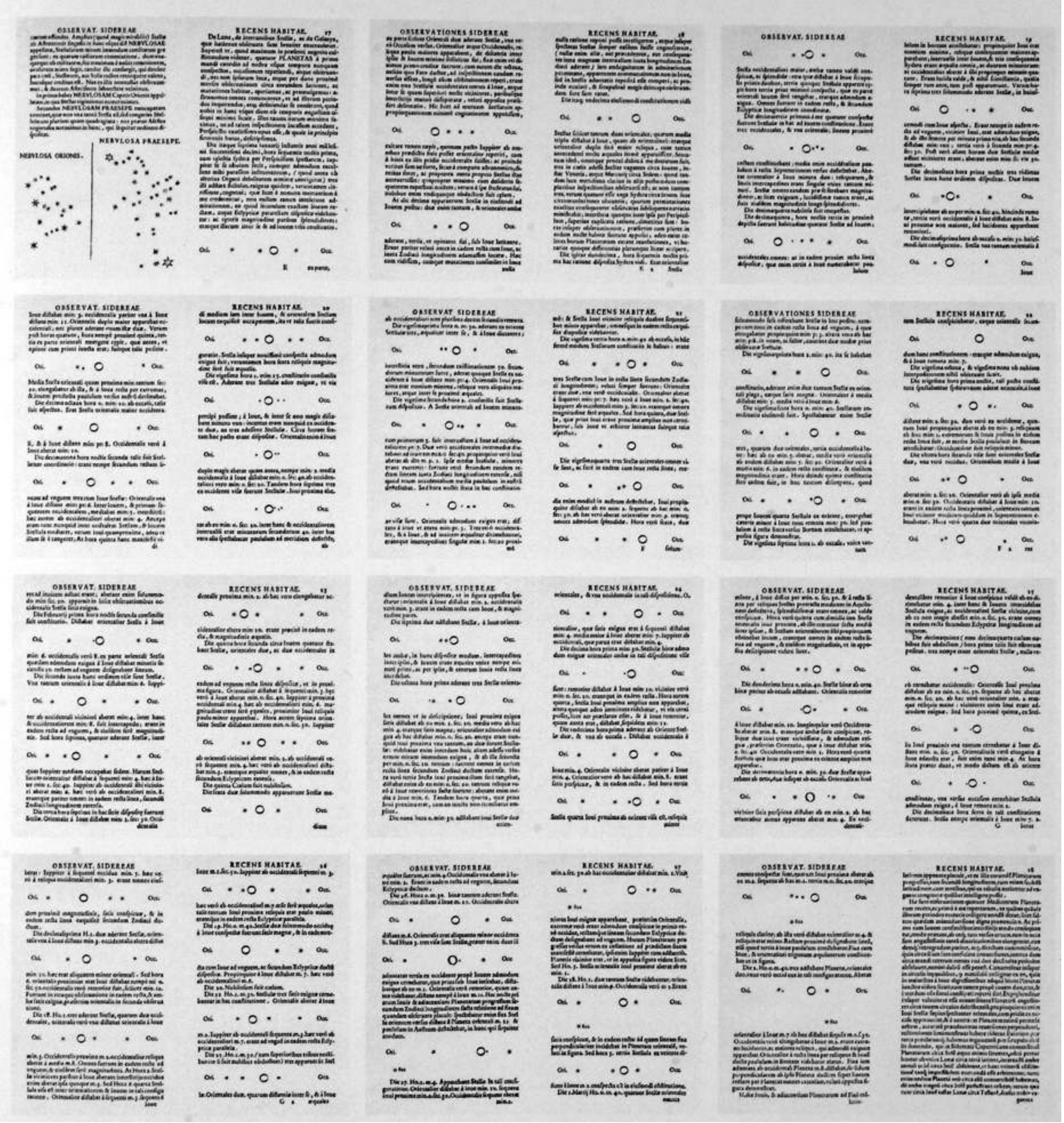

Figure 7. Notes from Galileo's notebook depicting a series of nightly observations of Jupiter and its four previously unknown moons. As appeared in Edward R. Tufte, *Beautiful Evidence*, Graphics Press LLC, Cheshire, Connecticut, 2006. Used with permission.

If there were to be challengers to cartographers as the first scientific imagers, it would have to be the astronomers (unless, that is, astronomy is deemed to be cartography of the skies, and astronomers thus the first cartographers). Certainly the two disciplines evolved very closely, as both are dependent on the same mathematical principles and related instrumentation for their spatial measurements. As with cartography, early astronomers focused on the spatial measurements of an image, with only crude measurements of the mass/energy of the objects they were observing. I would propose Galileo's astronomical observations of Jupiter's moons as perhaps the first modern scientific images (Figure 7). His work included not only careful

Figure 8. High-fidelity artist's rendering of dermatologic disease accurately depicts signal (color) and spatial components of image. Deliberate color distortion of the village of Marley by the Fauvist Vlaminck, and spatial distortion of Picasso in his portrait by the cubist Juan Gris. *Depiction of Infected Atopic Dermatitis*, by Dr. Louis Duhring, University of Pennsylvania. *Restaurant de la Machine at Bougival* by Maurice de Vlaminck, 1905, is at the Musée d'Orsay in Paris. Used with permission of Erich Lessing/Art Resource, NY and © 2009 Artists Rights Society (ARS), New York/ADAGP, Paris. Juan Gris' *Portrait of Picasso*, 1912, is at The Art Institute of Chicago. http://en.wikipedia.org/wiki/Juan_Gris.

measurements of mass/energy, space, and time, but also a mathematically tested and proven hypothesis. Contemporary scientific imaging now reflects very refined spatially dependent measurements of almost any imaginable body, object, view, or scene of our universe.

Mass/energy and spatial measurements are of two different physical domains and are relatively independent; however, a "complete picture" is dependent on the accurate amalgamation of the two. This combination of spatial and physical measurements is the methodological core of imaging and the source of its power. An artist may inadvertently or deliberately misrepresent or distort spatial or m,E information, but a scientist must not (Figure 8). Science requires that significant attention be given to the accuracy of spatially dependent measurements and their subsequent display and analysis.

In this book the basic concepts of a scientific image will be presented in Section 1 (Chapters 1–3), followed by a survey of contemporary biomedical imaging techniques in Section 2 (Chapters 4–10). Technology – in this context, instrumentation – is intimately related to scientific imaging. Imaging instruments generally include devices that improve on the human visual system to observe or measure objects within a scene, specifically including their spatial aspects. The Whipple Museum of the History of Science at the University of Cambridge is filled with fascinating scientific contraptions; notably, over 60% of these are imaging devices (Figure 9). While the human visual system alone may have been an adequate imaging device for a natural scientist in Audubon's time, or perhaps for a contemporary dermatologist, it is severely limited in terms of what types of objects or samples it can interrogate. Specifically, the unaided human visual system cannot image very small objects; it cannot image signals other than those within the wavelength of visible light; it cannot image below the surface of most objects; and it cannot image remote objects. The ongoing revolution in scientific imaging is defined by and dependent upon the discovery and development of new imaging devices that improve our ability to image not only with light signals (microscope, fundiscope), but also with different types of signals: x-rays for computed tomography (CT) scans, radio signals for magnetic resonance imaging (MRI), and sound waves for ultrasonography (US) (Figure 10). An important aspect of many newer imaging techniques is their non-destructive nature. While this feature greatly complicates the imaging process, it is obviously of great practical value for many applications. Prior to the late nineteenth century, imaging of the inside of the body required cutting into it, an event that took place after or immediately prior to death (Figure 11). Today, modern medical ultrasound provides universally compelling 3D images of a living, moving fetus with neither pain nor harm to baby or mother.

Once an image has been created, it must then be interpreted or analyzed, as elaborated on in Section 3 (Chapters 11–14). Traditionally this function has been performed by the human "eye" using empirical, qualitative methods dependent on visual psychophysics. This very human process is highly individualized, and thus it can be rather mundane or highly creative

Figure 9. Scientific imaging devices at the Whipple Museum, the University of Cambridge. Photo courtesy of the museum. www.hps.cam.ac.uk/whipple/index.html.

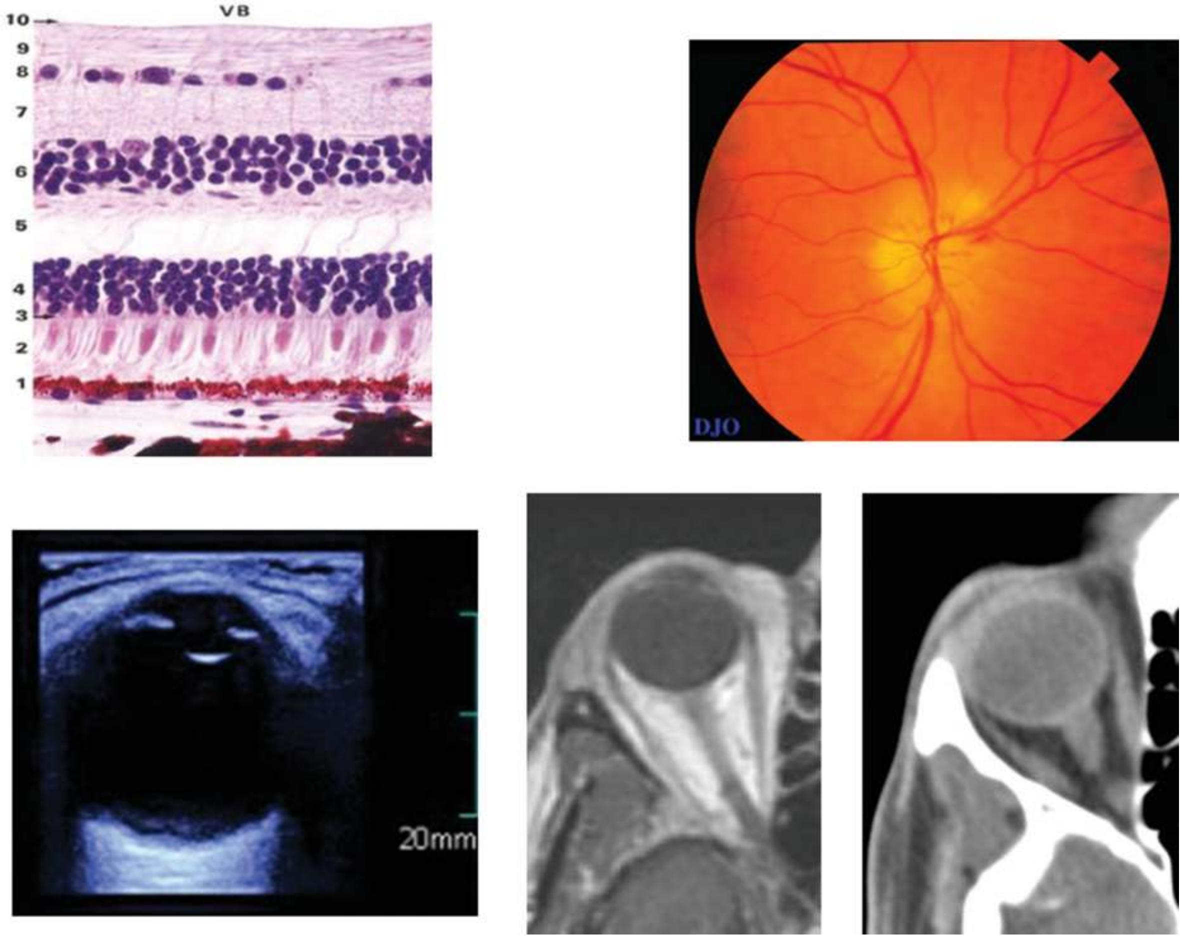

Figure 10. Multimodality images of the human eye: histological, fundiscopic, ultrasound, MRI, and x-ray CT. Histological image appeared in Young B and Heath JW, *Wheater's Functional Histology: A Text and Colour Atlas*, Churchill Livingstone, Edinburgh and New York, 2000. © Elsevier. Used with permission. Fundoscopic image appeared online in Neuro-ophthalmology Quiz 1 of *Digital Journal of Ophthalmology* by Shiuey Y, MD. www.djo.harvard.edu/site.php?url=/physicians/kr/468. Used with permission from *Digital Journal of Ophthalmology*.

Figure 11. Medieval invasive morphological imaging; contemporary non-invasive ultrasound imaging of fetus. *Dissection Scene*, from De Proprietatibus Rerum, by Bartolomeus Anglicus, late fifteenth century. Owned by Bibliothèque Nationale de France.

and “artistic.” There may be “art” not only in the creation of an image, but also great creativity in the interpretation of images. The artistic part of imaging is a function of the human observer and is probably inextricable as long as a human is involved in the creative and interpretative process. For aesthetics and the quality and variety of life, art is integral, important, and greatly desired. However, art can be a problem for scientific imaging. Art is intrinsically individualistic and therefore highly variable. Art is not restricted to “facts,” does not require accuracy, and allows for the deliberate distortion of reality. Art is not science. Therefore scientific imaging must strive to control carefully the artistic aspects of imaging. This is a major challenge as long as humans participate in the imaging process. Images are made to be seen, looked at, and observed by people. This does not mean that machines, computers, mathematical algorithms cannot play a role in creating or even analyzing images, but at some stage a human has to look at a picture or image.

Human involvement is an integral part of imaging because imaging is, at its most basic level, a communication tool. Imaging is a language in the broadest sense. Imaging is the language of space. Imaging is how we most efficiently depict and convey spatial information from one person to another. Imaging’s role as a communicating device is what keeps humans central to our discussion. The requisite involvement of humans in scientific imaging results in a persistent artistic component. While art is indeed an important element of scientific imaging, it is one that must be carefully coordinated with and, if necessary, subjugated to the methodological rules of science. The discussion of image analysis will include components related to the human visual system, psychophysics, and observer performance. Central to this discussion are information and communication theory relative to how effectively images convey information from one person to another. The incredible power of images to communicate should never be forgotten. “Seeing is believing” is deeply rooted in human psychology; indeed, it is human nature.