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Radiology Paging a Good Mathematician

Why Math Can Contribute More to Medicine Than You Might Think

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Flying Blind

Magnetic resonance imaging, as anybody who's watched *Grey's Anatomy* knows, is a powerful diagnostic tool. It can reveal a wealth of information about the body's structure and physiology, and is the radiologist's tool of choice for assessing many pathologies. This exciting diagnostic tool is an outgrowth of the quantum mechanics elucidated by great scientific minds in the preceding century. To cut a long story very short, the nuclei of atoms that have an odd number of protons or neutrons will absorb radio frequency energy of a specific wavelength when they are in a strong magnetic field. If we pulse them with energy of the proper wavelength, they will give off an electromagnetic signal; this phenomenon is called nuclear magnetic resonance. We can measure this signal, and convert it into an image.

And this is where the mathematician comes in. The signal that these nuclei give off is not immediately useful. It is initially measured as a current running through a wire. Converting this signal into an image requires a good deal of mathematical know-how, involving Fourier transforms and a nebulous dimension known as *K*-space—neither of which is particularly well understood by your average radiologist. In other words, most of the doctors who are responsible for reading MRI studies know virtually nothing about how the images are constructed. I venture to say that few other areas of medicine—or any other profession, for that matter—suffer such a disconnect between the researchers who develop a procedure and the clinicians who deliver it to patients. As magnetic resonance procedures become more common and complex, this chasm will be increasingly precipitous.

The contribution of math to radiology does not end once images are constructed. The simple, grayscale MRI scans, such as those in Figure 1, are nothing more than raw signal intensity maps. In other words, they tell us which regions of the body are giving off the strongest signal in response to the radio frequency pulse. These signal intensity maps can be processed to reveal a host of physiological information. At every level, this image analysis relies on basic mathematical principles. And again, physicians rarely understand these principles.

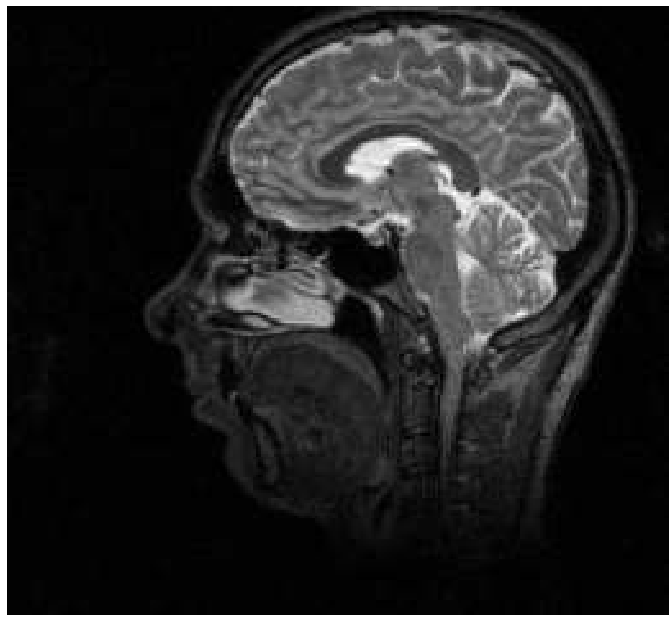

Figure 1. An MRI image of a healthy male head. This image was constructed by digitizing and processing the signal associated with a current in a wire at various points in time.

I hope that by illustrating—albeit not rigorously—a few of the applications of math to magnetic resonance, I will convince some budding mathematicians to become physicians. I also hope that the medical community will more fully embrace mathematics and actively encourage math students to enter the biomedical world. In closing, I will briefly touch on other medical fields that would benefit from a few more mathematicians.

Signal to Image: The Fourier Transform, *K*-space, and Other Such Fun

When an MRI apparatus (known as an imaging coil) receives a signal, we measure the current running thorough a wire. Now, without getting too far into the details, we determine just where in the body a signal is coming from by applying what is known in the business as a *frequency encoding gradient*. This gradient causes the shape of the signal function to vary; the stronger the gradient, the more the shape is altered. By applying linear gradients to a patient along several axes, we can determine precisely where the signal originated.

The raw signals that our imaging coil receives are digitized and placed in a 2-dimensional matrix known as *K*-space. *K*-space is not a terribly complex principle, but it still gives the willies to less mathematically attuned doctors. To understand *K*-space, we must first consider the mathematical beauty of the Fourier transform.

Consider the normalized *Sinc* function, given by

$$Sinc(k) = \frac{\sin(\pi k)}{\pi k}.$$

This function is very common in signal processing, and should be familiar to anybody with a background in analysis, electrical engineering, or image processing. An interesting and useful feature of this function is that its Fourier transform is the rectangle function.

$$f(x) = \int_{-\infty}^{\infty} Sinc(k) e^{-i2\pi kx} dk = \begin{cases} 1, \text{ for } |x| \le 1/2 \\ 0, \text{ for all other } x \end{cases}.$$

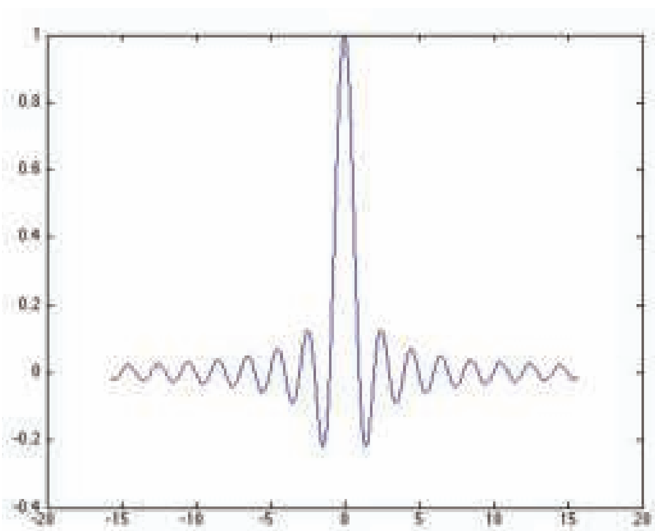

Figure 2. The normalized Sinc function shown over the range -4π to 4π. Note that the frequency is initially 2, and progressively increases. Also, the maximum magnitude is 1, just as the Fourier transform suggests.

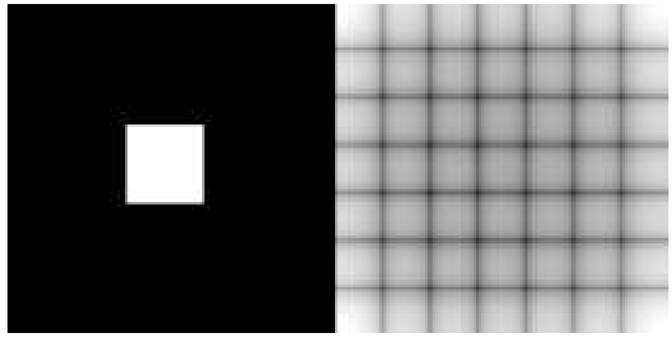

Figure 3. The 2-dimensional rectangle function and its Fourier transform.

We think of the domain of f as frequency, and its range as magnitude. In other words, this function $f(x)$ exists in a world with frequency on the x-axis and magnitude on the y-axis. So, the Fourier transform takes us from the time domain (k) to the frequency domain (x). After applying the transform, the signal is described as a function of frequency, rather than as a function of time.

At first, this result appears purely academic. But like so many things that seem interesting only to theoretical mathematicians, it is actually very useful. You see, the rectangle function contains all the information necessary to reconstruct the *Sinc* function. The rectangle function exactly reflects the range of periods contained in the *Sinc* function. In fact, the relationship is given by $T = 1/x$, where T is the period of a function and x is the frequency of its Fourier transform. A quick glance at Figure 2 confirms that the period of the *Sinc* function is 2 between –1 and 1, and grows as one moves away from the origin. Moreover, the magnitude of the rectangle function equals the maximum magnitude of the *Sinc* function.

Interestingly, taking the Fourier transform of this function's Fourier transform will give us back the original function!

$$\int_{-\infty}^{\infty} f(x) e^{-i2\pi kx} dx = \int_{-1/2}^{1/2} e^{-i2\pi kx} dx = \frac{\sin(\pi k)}{\pi k}.$$

The power of this result should be apparent.

Let's consider what happens when we extend this result to two dimensions. The first panel in Figure 3 shows a two-dimensional representation of the rectangle function, where the white regions represent the maximum magnitude (that is, 1) and the black regions represent the minimum magnitude (which is zero). If we take the Fourier transform of this two-dimensional function, we arrive in a space that looks like the second panel. Notice how the magnitude oscillates along the x- and y-axes.

Now think for a second about the image in Figure 1. Each pixel in the image falls somewhere on a shading continuum between black and white; in between lie various shades of gray. This is simply a graphical representation of a data matrix where each pixel lives as a number between zero and 1. The closer to 1 a number is, the whiter the corresponding pixel will be. If we take a one-dimensional "strip" from this image, we will obtain a series of numbers that can be fit to a curve. This curve will be fairly complex – *but it has a direct relation with its Fourier transform,* just as the *Sinc* function does.

Now, consider taking the Fourier transform of each one-dimensional strip from Figure 1. It's not hard to imagine the resulting one-dimensional Fourier transforms filling a 2-dimensional space—in fact, this is exactly what we saw a few moments ago with the 2D rectangle function. Now for the punch line: the space filled by these Fourier transforms is *K*-space. In other words, the 2-dimensional data matrix we obtain by digitizing the various signal components—which, recall, are differentiated by the gradient applied to them—is directly related to the final image we want by a fascinating mathematical identity.

So, the images of your brain that doctors examine are constructed by taking the inverse Fourier transform of a digital data matrix. Stig Ljunggren and Donald Tweig independently proved this result in 1983. Since then, it has become the foundation of MR image construction. To understand the latest advances in scanning technology, you need to know *K*-space and the Fourier transform.

Deriving Physiological Parameters from Images: More Work for the Mathematically Inclined

One nice aspect of magnetic resonance is that it gives us more than pretty pictures. In many cases, we can derive physiological information from the signal intensity images con-

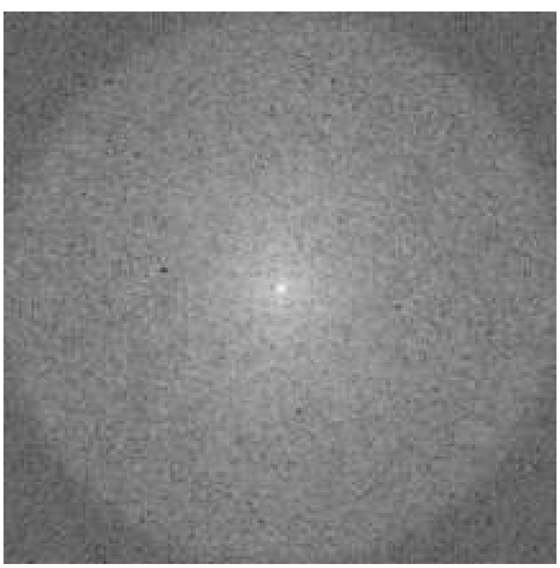

Figure 4. *K*-space corresponding to the brain scan in Figure 1. The image space is the inverse Fourier transform of the data matrix represented here.

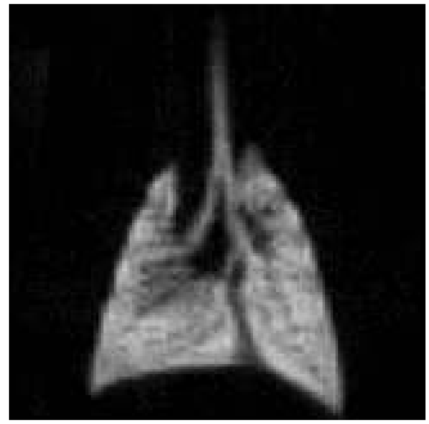

Figure 5. Signal intensity image of rat lungs obtained by ventilating airspaces with hyperpolarized ^{3}Helium.

structed in the previous section. Such quantitative, regional information about an organ can be extraordinarily useful. However, pulling such information from the images requires a good deal of mathematical and computing knowledge. The ceiling on how much data we can extract from MR studies is ultimately set by researchers' quantitative skills.

Recent advances in lung imaging have made it possible to measure regional indicators of pulmonary function. These regional measurements represent a huge step forward in pulmonary medicine, which has historically relied on global pulmonary function tests. Such tests tell us nothing about where in the lung defects occur or how widespread they are. One extremely important regional parameter is *fractional ventilation*, the ratio of gas in a given region exchanged with each breath.

Without delving too deeply into the physics involved, lung images like those in Figure 5 are obtained by ventilating the patient with hyperpolarized gases. It's not important to understand why we use these special gases. For now, it suffices to say that signal intensity is proportional to the degree of polarization of the gas and its concentration in a given space. Together, these two factors determine the net magnetization of the gas in a region, which in turn determines signal intensity.

Clearly, the concentration depends on how much helium is able to reach a region with each breath. So, distal regions of the lung will give off a smaller signal than regions near the trachea; also, pathologies that restrict the airways, such as asthma, will reduce signal. We define the amount of air in a region that is exchanged with each breath as fraction ventilation, and express it mathematically as

$$r = \frac{V_{fresh}}{V_{fresh} + V_{old}},$$

where V_{fresh} is the volume of fresh gas received per breath, and

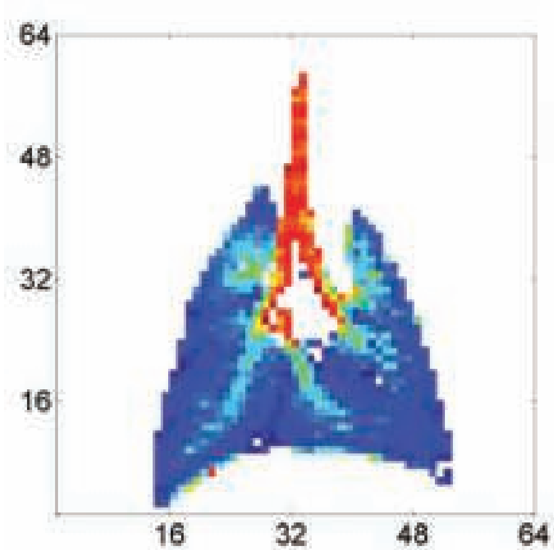

Figure 6. Estimation of fractional ventilation *r* throughout a rat lung obtained using the technique described. Note that gas exchange is significantly more efficient in the trachea than in distal airways, as we might expect.

V_{old} is the volume of old gas that remains in the lung. Helium's degree of polarization is affected by several factors, which I will describe shortly. Combining these two factors and accurately describing a signal in a given region requires some interesting mathematical models.

After a given number of polarized gas inhalations, the degree of magnetization M of gas in the lungs can be expressed as a function of fractional ventilation and factors that cause the nuclear magnetization to degrade. Since signal intensity is directly linked to this magnetization, we can determine M from our basic signal intensity images. If fractional ventilation were the only factor influencing magnetization, it would be given by the following expression after j breaths:

$$M(j) = M_0 \cdot r + M(j-1)\cdot(1-r),$$

where M_0 is the polarization in our helium reservoir. However, there are three other effects that we must account for.

Flip Angle Effect

Whenever we acquire an image, the gas depolarizes to some extent. The physics behind this phenomenon is well defined, so it is easily accounted for. There is an imaging parameter know as the "flip angle," which is directly related to the amount of depolarization. When we analyze MRI studies, we have *a priori* knowledge of this flip angle, which we designate α. The effect of image acquisition can be expressed as

$$e^{N\cdot\ln(\cos\alpha)},$$

where N is a constant representing the resolution of the image.

External Relaxation

The helium gas in our external reservoir is subject to depolarization, mostly from interactions with the walls of the container. This depolarization is known to be exponential. If we let τ represent the time interval between breaths and $T_{1,\,\mathrm{ext}}$ represent the interaction between the gas and the container walls, we can account for external relaxation with the expression

$$e^{\frac{-\tau}{T_{1,ext}}}.$$

This effect has been experimentally characterized.

Oxygen Interaction Effect

Interactions with oxygen cause the helium to depolarize; the precise nature of the helium-oxygen interaction is readily available in the chemical literature. This effect, like external relaxation, will lead to exponential depolarization. If we let PO_2 be the partial pressure of oxygen gas in the lungs, we can model the oxygen interaction effect as

$$T_{1,\,O_2} = \xi / PO_2,$$

where ξ is a physical constant.

We can combine these terms to build the following recursive model of magnetization buildup in the lungs with successive breaths:

$$M(j) = M_0 \cdot e^{\frac{\tau}{T_{1,ext}}} \cdot r + M(j-1)\cdot(1-r)\cdot e^{[N\cdot\ln(\cos\alpha) - \frac{\tau\cdot PO_2\cdot(1-r)^{j-1}}{\xi}]}.$$

Notice that if no image is acquired after a breath, α is zero, and the expression for flip-angle depolarization falls out.

The only term in this model that we don't know is r. So, we can solve this equation for r after ventilating the patient with our hyperpolarized gas. Figure 6 is an estimated ventilation map obtained using this technique. Although the image displayed was obtained from a rat, it is obvious that this information could help doctors make diagnoses in human patients.

Similar techniques allow us to assess a plethora of pulmonary parameters, such as blood perfusion, partial pressure of oxygen, and the rate of oxygen uptake into the blood. Quantitative methods also allow radiologists to study the function of other organs; for example, methods have been developed to measure electric activity in the brain in response to various stimuli. Development and refinement of these image processing techniques requires mathematical knowledge far beyond that of the average physician.

Some Other Things You Won't See on the MCAT

The medical applications of math are certainly not confined to radiology, and this discussion has barely scratched the surface of applications within that field. In addition to magnetic resonance, radiologists routinely use x-rays, ultrasound, gamma cameras, positron emission tomography, and computed tomography to assess pathologies. Math plays some role in all of these techniques. The latter two modalities acquire information at points in a plane that transects the patient, and rather advanced matrix algebra is required to transform this data into a useful image.

Developing new tools for processing and analyzing images requires researchers with a good math background. The exciting field of computer assisted diagnosis (CAD), which uses computers to analyze images and make diagnoses, may eventually produce software that assess images faster and more accurately than doctors. A young method known as digital radiography allows x-rays to be computerized, making images available within seconds of acquisition. This can have tremendous impact when a patient's life is on the line. I have personally seen the trauma team in the Emergency Department at the Hospital of the University of Pennsylvania make critical decisions within minutes of a patient's arrival based on digital radiography information. This would be impossible without modern computing tools.

You probably know of efforts to decode the human genome. Genomics is an exciting field with the potential to revolutionize medicine, from prevention to treatment. But the human genome is enormous—it contains about 3 billion molecular base pairs (the smallest information-containing unit in a cell) and about 25,000 protein-encoding genes. Without powerful mathematical tools, culling this dataset for patterns would be an unthinkable enterprise. But with the aid of powerful computers and good mathematicians, the dark secrets of many dreadful diseases may soon be known.

There is literally no end to biomedical uses for math. Models of bacterial growth are little more than first-order differential equations. Blood flow, muscle activity, and drug uptake can all be modeled using tools accessible to undergraduate mathematicians. There are countless ways that math students can contribute to medicine—but first they must make a commitment to the profession. The medical community does not, in my opinion, fully acknowledge how much mathematicians can give. The only way to change that is for good mathematicians to enter medicine and demonstrate what they can do. ■

For Further Reading

Students interested in magnetic resonance should find a copy of *MRI: The Basics*, by Ray H. Hashemi and William G. Bradley (Baltimore, MD: Lippincott Williams &Wilkins, 2003). An excellent online resource is `www.e-mri.org`, which includes a tutorial of *K*-space and the Fourier transform. If your interest was piqued by my discussion of lung imaging via hyperpolarized gases, I recommend Stephen Kadlecek's 2002 paper "Magnetic Resonance Imaging with Polarized Gases" (*American Scientist* 90, p. 540).

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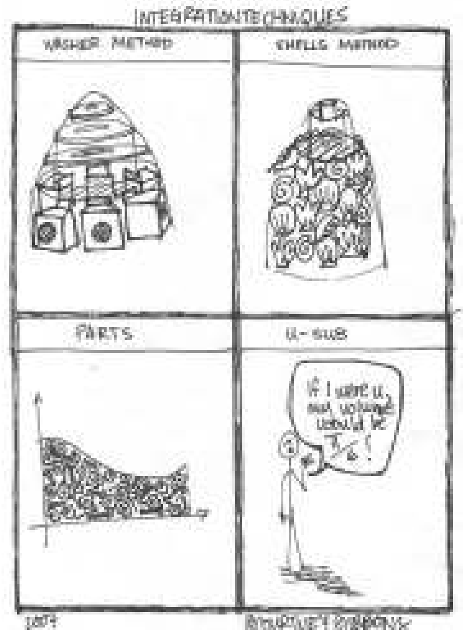

Cartoon by Courtney Gibbons.

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