Our Mathematical Protectors

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Chapter 1

Preface

I am a mathematics professor at the University of Massachusetts Lowell. For the past twenty years I have also collaborated with researchers at the University of Massachusetts Medical School and elsewhere on medical imaging and radiation therapy. My work involved developing mathematical methods for generating pictures from x-ray, PET and MRI scanning data and algorithms for intensity-modulated radiation therapy. After twenty years, the fundamental formulas in this field had become old friends. When I was diagnosed with lymphoma, in March of 2011, I suddenly found myself on the other side of the scanners and began to see these old mathematical friends in a new and unexpected light. My friend David Barton helped me to find the words to describe this new view.

Cancer patients often turn to meditation, music, or art for help in dealing with the disease. In the recent Brush Gallery exhibition *On and Off the Wall*, the Lowell artist and cancer survivor David Barton introduced the visitors to his fierce defenders, surreal humanoid sculptures horrible enough to confront any invading cancer cells. His artist's vision of surrounding himself with monsters for protection is a bit like the way certain cultures like to place carved lions and dragons on their front steps. I realized that David's idea of having defenders was also the way I was starting to feel. My defenders, mathematicians, physicists, and their equations, may not look quite so horrible, but they are real and quite powerful.

After I saw David Barton's fierce creatures in the *On and Off the Wall* show at the Brush a few months back, and read in his artist's statement how he regards these creatures as his protectors, I began to see that I now regarded familiar equations as weapons to be brandished against an evil invader. I began trying to experience each equation visually, rather than mathematically, its fierce, forbidding, powerful, even otherworldly, hieroglyphics a talisman capable of tracking down the menacing foe and exposing it to deadly attack. The scientists who had developed these weapons, not as horrible-looking as David's creature in Figure 1.1, were now my protectors, as well as yours.

Figure 1.1: One of David Barton's protectors.

In the few pages that follow I will introduce you to several of the most powerful of these weapons and to the superheroes who forged them. The point is not to understand the mathematics, any more than the point of David's work is to understand the physiology of his creature's respiratory system. Try to view the strangeness of the equations as a source of their power, as you would David's monsters.

My ignorance of biology, chemistry and medicine prevents me from discussing those superheroes who invented Rituxan and the other miracle drugs and who provided the diagnoses and treatment that have made me cancer-free. I apologize to them if I appear to minimize their roles.

Chapter 2

Paul Dirac and His Equation

The famous physicist Eugene Wigner once wrote that what struck him as the most remarkable thing he had encountered during his life as a scientist was, as he called it, the "unreasonable effectiveness of mathematics". Why is it that, when we attempt to understand the workings of nature through mathematical models like differential equations, we often succeed? The story of Paul Dirac and his famous equation illustrates quite well the point Wigner was making.

The man in Figure 2.1 is the mathematician Paul Dirac, often called "the British Einstein" . He doesn't look too fierce. But he is definitely one of our protectors. Almost all of us cancer survivors have had a PET scan, a marvelous invention that owes its existence to the genius of this man. Those who knew him often remarked on his "strangeness" ; recent studies have suggested that both Dirac and his father were autistic.

Look at this equation:

$$i\hbar\frac{\partial\psi}{\partial t} = \frac{\hbar c}{i}\left(\alpha_1\frac{\partial\psi}{\partial x_1} + \alpha_2\frac{\partial\psi}{\partial x_2} + \alpha_3\frac{\partial\psi}{\partial x_3}\right) + \alpha_4 mc^2\psi.$$

It looks pretty fierce, and it is. Admit it! When you first looked at it, you wanted to run away and hide; that is certainly the way I feel when I see it. Imagine how a cancer cell must feel! This is Dirac's Equation from quantum mechanics, which predicted the existence of the positron and eventually led to PET scans.

In 1930 Dirac added his equation, now inscribed on the wall of Westminster Abbey, to the developing field of quantum mechanics. This equation agreed remarkably well with experimental data on the behavior of electrons in electric and magnetic fields, but it also seemed to allow for nonsensical solutions, such as spinning electrons with negative energy.

The next year, Dirac realized that what the equation was calling for was *anti-matter*, a particle with the same mass as the electron, but with a positive charge. In the summer of 1932, Carl Anderson, working at Cal Tech, presented clear evidence for the existence of such a particle, which we now call the *positron*. What seemed like the height of science fiction in 1930 has become commonplace today.

When a positron collides with an electron their masses vanish and two gamma ray photons of pure energy are produced. These photons then move off in opposite directions. In positron emission tomography (PET) certain positron-emitting chemicals, such as glucose with radioactive fluorine chemically attached, are injected into the patient. When the PET scanner detects two photons arriving at the two ends of a line segment at (almost) the same time, called *coincidence detection*, it concludes that a positron was emitted somewhere along that line. This is repeated thousands of times. Once all this data has been collected, the mathematicians take over and use these clues to reconstruct an image of where the glucose is in the body. It is this image that the doctor sees.

We are able to see tumors using PET scans because most tumors, particularly the fast-growing ones, gobble up most of the glucose before their slower-growing neighbors have a chance. Most of the glucose, and therefore most of the radioactivity, resides then in the cancerous cells. A picture of where the radioactivity is will then be a picture of where the cancer is.

The same idea lies behind chemotherapy. Aggressive cancers, as well as other healthy, but fast-growing, cells, like hair cells and taste buds, eat more of the chemicals than do their slower-growing neighbors. The cancer cells die, you lose your hair and food starts to taste awful, but the rest of you survives.

Figure 2.1: Paul Dirac: his equation predicted positrons.

Figure 2.2: A pet getting a PET scan? Not quite.

Chapter 3

Allan Cormack and His CAT Scan

Look at the photo in Figure 3.1. He doesn't look so horrible, but the weapon he invented is fierce; it has changed medical diagnostics forever. My wife Eileen and I once shared a Chinese meal with him in the 1980's and I am sure that nobody else in the restaurant had any idea who he was. The man is Allan Cormack. He shared the Nobel Prize in 1979 for inventing the CAT scan.

Originally from South Africa, Allan Cormack was, for much of his adult life, a professor at Tufts. In the mid-1950's Cormack worked on radiation therapy in Cape Town. The main problem, then as now, is how to guide the radiation beams and adjust their strengths to have the desired effects without damaging the healthy organs of the patient. Cormack realized that, if he could get a look at the insides of the patient, he could improve the radiation treatment.

X-rays are weakened as they pass through the body of the patient. The degree of weakening tells us something about the amount of material that got in the way of the beam along its journey, but does not, by itself, tell us precisely where on that journey the weakening happened. You may think of arriving three hours late after a road trip and blaming it on traffic. Your listener now knows that there was a certain amount of traffic along your route, but does not know precisely where you encountered it.

To figure out just where the material, the "stuff" , is inside the patient, we pass many such beams through the patient, at many different angles. The weakening associated with each of the beams provides many clues about the distribution of material within the patient. Mathematics can then put all these clues together and give us a picture of just where the material is concentrated. This is the CAT scan image.

To get a feel for the problem that must be solved, imagine a checker board on which I have written a number in each of the sixty-four squares; your job is to figure out what numbers I have written. You can't see the numbers, but I tell you the sums of the numbers along each of the rows and along each of the columns. This is your data, from which you must figure out what I wrote in the squares. In CAT, each of the squares – and many more than sixty-four are used – are the pixels of the picture, the numbers tell us how much "stuff" resides within each pixel, and the sums correspond to the measured weakening of the x-ray beams as they pass through the patient.

It is common today to speak of all kinds of scans, PET scans, SPECT scans, CT, MRI, and ultrasound, as CAT scans, but originally a CAT, or CT, scan meant using x-rays in computer-assisted tomography. The word "tomography" comes from the Greek work "tomos", meaning part or slice; our word "atom" means "without parts".

Both PET and SPECT scans rely on metabolism and so must be performed on living beings, principally people and small animals. The pig in Figure 2.2 is having his heart imaged using SPECT, as part of a research effort to study the effectiveness of certain SPECT imaging algorithms. The hearts of pigs are similar to our own, which makes the pig a good subject for this study.

Unlike PET and SPECT, x-ray tomography CT can be used on corpses (King Tut has had a CT scan) and in industry. For such uses the dosages can be much higher than is safe for people and the quality of the images much greater.

I nearly had an industrial-strength CT scan once. My colleague Yair Censor and I were working on a Saturday in a building next to a construction site. As it happened, one of us moved the window shade. Within a minute or two, security folk descended on us; it turned out that x-ray CT was about to be used on the beam welds next door and our building should have been evacuated.

Once we have the data from the scanner, we have many choices of which mathematical algorithms to use to reconstruct the picture. Some algorithms do better than others, and generally we try to select an algorithm that is known to work well on the kind of image we are dealing with. In Figure 3.2 we see an original (simulated) head slice in the upper right and two different reconstructions in the lower row, both obtained using the same data, but different algorithms. The difference is that the reconstruction on the left also made use of prior information that the picture we expected to see looked somewhat like the one in the upper left.

Figure 3.1: Allan Cormack, who won the Nobel Prize for the CAT scan.

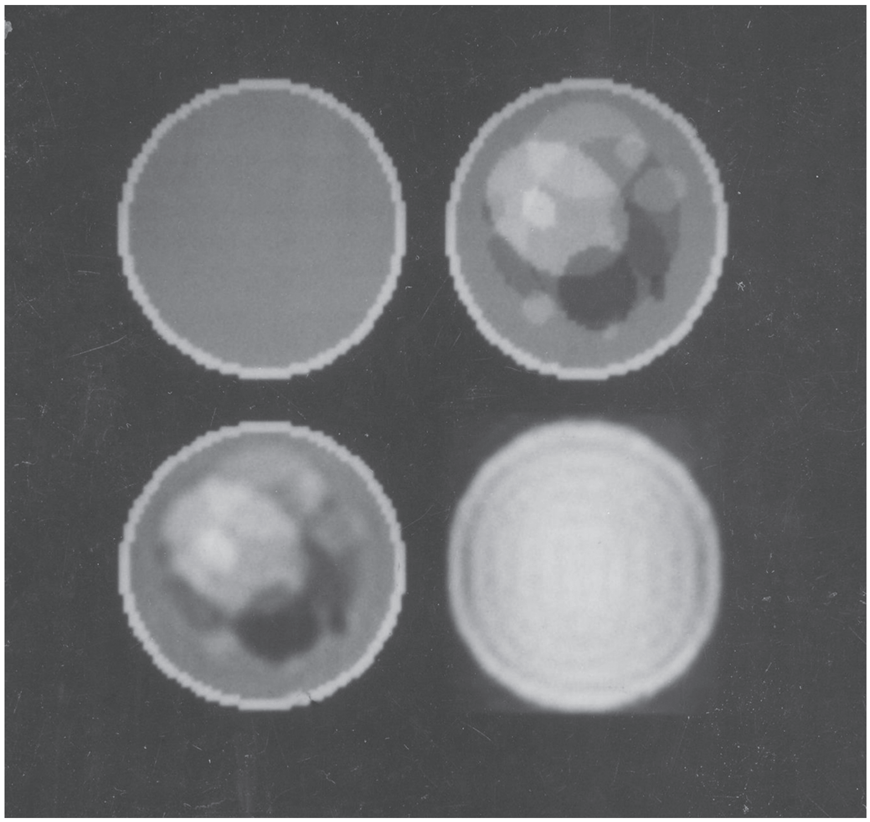

Figure 3.2: Extracting information in image reconstruction.

Chapter 4

Raymond Damadian and His MRI

One of the first things you get after a cancer diagnosis, usually after the biopsy, is an MRI scan. This leads us to another of the mathematical weapons in the arsenal:

$$S(t) = e^{i\omega_0 t} \int \int \rho(x, y) e^{i\gamma G_y y T} e^{i\gamma G_x x t} dx dy.$$

This equation describes the signals received by a magnetic-resonance imaging (MRI) scanner. The gentleman in Figure 4.1 is Raymond Damadian, who invented the MRI and should have received the Nobel prize in 2004.

In much of MRI, it is the distribution of hydrogen in water molecules that is the object of interest, although the imaging of phosphorus to study energy transfer in biological processing is also important. Because the magnetic properties of blood change when the blood is oxygenated, increased activity in parts of the brain can be imaged through *functional* MRI (fMRI). Non-radioactive isotopes of gadolinium are often injected as contrast agents because of their ability to modify the magnetic properties of tissues.

The hydrogen atoms act like little tops, spinning in all directions. When a very strong magnetic field is turned on, enough of these spinning tops line up so that a detectable signal is received when the magnetic field is changed. The MRI machine picks up these signals and mathematics is used to determine just where the signals originated. The result is a picture of the distribution of these molecules, as in Figure 4.2. Regions with more water show up brighter than others, soft tissue and tumors brighter than bone or air.

A recent article in The Boston Globe describes a new application of MRI, as a guide for the administration of ultra-sound to kill tumors and perform bloodless surgery. In MRI-guided focused ultra-sound, the sound waves are focused to heat up the regions to be destroyed and real-time MRI imaging shows the doctor where this region is located and if the sound waves are having the desired effect. The use of this technique in other areas is also being studied: to open up the blood-brain barrier to permit chemo-therapy for brain cancers; to cure hand tremors, chronic pain, and some effects of stroke, epilepsy, and Parkinson's disease; and to remove uterine fibroids.

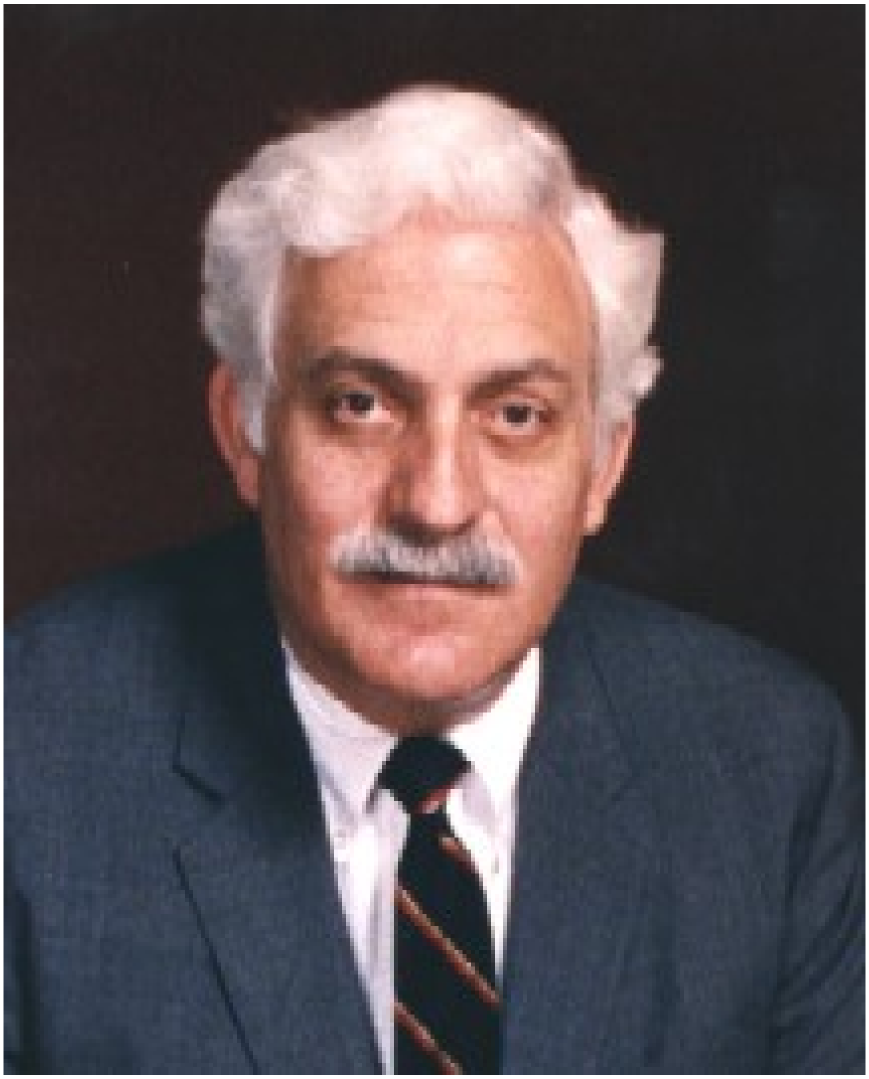

Figure 4.1: Raymond Damadian: inventor of MRI.

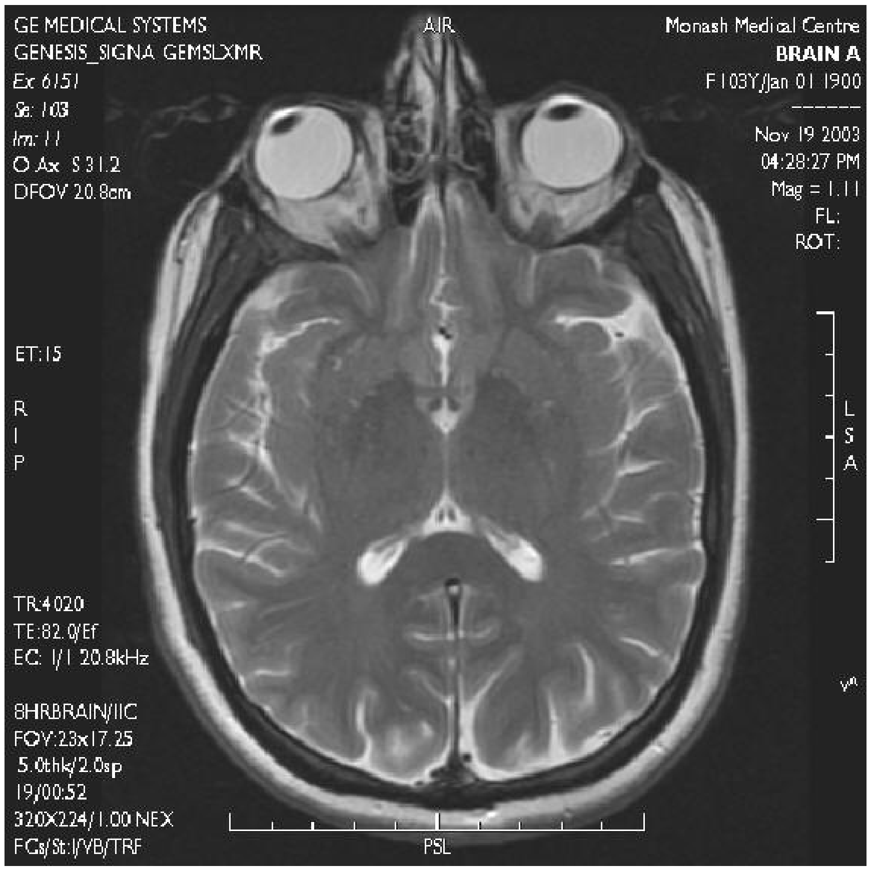

Figure 4.2: An MRI head scan. Check out the eyeballs.

Chapter 5

John Tukey and His Fast Fourier Transform (FFT)

The title of this chapter reminds me of the Tom Swift adventure books that I read as a child in the 1950's. They always had titles like "Tom Swift and his Nuclear-Powered Backyard Swing Set" . But the Fast Fourier Transform is real and it is fast. Co-invented by the mathematician John Tukey (see Figure 5.1) and James Cooley in 1965, the Fast Fourier Transform, always called the FFT, has revolutionized image processing; without it, all the digital imaging that fills our modern world would be impossible. With it, medical images can be created from scanning data in almost real time, instead of weeks. Professor Tukey doesn't look too fierce in the photo, but, in person, he did bear some slight resemblance to one of David Barton's terrible creatures.

The key equations in the FFT are these:

$$F_k = \sum_{m=0}^{M-1} f_{2m} e^{2\pi imk/M} + e^{2\pi ik/N} \sum_{m=0}^{M-1} f_{2m+1} e^{2\pi imk/M},$$

and

$$F_{k+M} = \sum_{m=0}^{M-1} f_{2m} e^{2\pi imk/M} - e^{2\pi ik/N} \sum_{m=0}^{M-1} f_{2m+1} e^{2\pi imk/M}.$$

The main idea is that the calculations required to do image processing often have a lot of hidden redundancy that the FFT avoids, thereby greatly reducing the number of calculations and therefore the time required to process the image.

Figure 5.1: John Tukey: co-inventor of the FFT.

Chapter 6

A Personal View

Once I had my cancer diagnosis, I began to view even my own work in medical imaging in a new light. For one thing, I felt that I was privileged to apply to practical, and even personal, situations what is often abstract and remote from daily concerns. As was the case with the other formulas I talked about in the previous chapters, my own equations began to seem like tools, weapons even, that might be used to ward off disease.

The software inside the scanners is not changed every time one of us publishes a new paper. The researchers in the field are engaged in a conversation among themselves, each new idea suggested by what has come before. Every so often, a company making scanners will adopt some recently presented algorithms to include in its next line of products. Each of us may have contributed some small piece to what ends up in the machines, but we never really know for sure.

Here are two methods that were developed for producing medical images, both of which I have had the opportunity to work on. The first is the "expectation maximization maximum likelihood" (EMML) method and the second is the "simultaneous multiplicative algebraic reconstruction technique" (SMART).

The iterative step for the EMML method is

$$x_j^{k+1} = (x^k)_j' = x_j^k \sum_{i=1}^{I} A_{ij} \frac{b_i}{(Ax^k)_i}.$$

The iterative step for the SMART is

$$x_j^{m+1} = (x^m)_j'' = x_j^m \exp\Big(\sum_{i=1}^{I} A_{ij} \log \frac{b_i}{(Ax^m)_i} \Big).$$

One problem with both of these methods is that they can be very slow. Figuring out how to modify these methods to make them faster was one of my goals. In 1995 I found a way to do it, the RBI-EMML algorithm, and added my own equation to the armory; here it is:

$$x_j^{k+1} = (1 - m_i^{-1} A_{ij}) x_j^k + m_i^{-1} A_{ij} \Big(x_j^k \frac{b_i}{(Ax^k)_i} \Big).$$

About 2006 I found myself involved in *intensity-modulated radiation therapy* (IMRT). The problem in radiation therapy, as Cormack knew in the 1950's, is how to adjust the intensities of the x-ray beams that enter the patient undergoing therapy so that tumors are killed but healthy organs are unharmed. A recent technique, known as IMRT, uses the mathematics of optimization to solve this problem. The advantage of IMRT is that, when done properly, higher doses of radiation can be used without risking damage to healthy organs.

Yair Censor, shown in Figure 6.1, is a mathematician who has been working in medical imaging and radiation therapy for over thirty years. I first met Yair in 1992 at the University of Pennsylvania and we have worked together ever since.

Figure 6.1: My colleague Yair Censor of the University of Haifa.

In 2005 I discovered a mathematical algorithm for solving a general optimization problem. Here it is:

$$x^{k+1} = P_C(x^k - \gamma A^T(I - P_Q)Ax^k).$$

Yair, then working with radiation therapists at Massachusetts General Hospital, modified my algorithm and showed how it could be used to develop protocols for IMRT. The lesson I drew from this is that we can never predict the possible uses of the mathematics we work on. I had chemotherapy, but did not have radiation therapy. I once joked that, if radiation had been needed, I would have rechecked my calculations.

I cannot pass up the only opportunity I will ever have to see my picture in the same document with those of Dirac, Cormack, Damadian, and Tukey, so I give you Figure 6.2.

Figure 6.2: Patient No. 5016259 in Mass General Hospital, summer of 2011.