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Editorial

Two minds create a third: an exploration of the universe, cancer, and symmetry with Donald S. Coffey

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Donald S. Coffey was a leader, educator and mentor until the very end of his life and career. In this article, one of his students and friends offers a personal view. He touches on both men's exploration of minds, matter and information, as well as their combined efforts to understand and simplify cancer's complexity by applying the principles of symmetry.

A new beginning

Looking back, I find it for many reasons odd that Don Coffey and I never met until almost two decades into my career at Johns Hopkins. At that point, Don was already distinguished in his field, having spent forty years at Hopkins and taken on the directorship of the Brady Urological Institute Research Laboratory. I was a Professor of Radiology and Neuroscience and could at the time be found working away in typical insular manner on all things molecular imaging, a new field that my many coworkers and I had developed at Hopkins in the early 1980's. Don was familiar with many of the radiologists and nuclear medicine founders and educators in the Russell H. Morgan Department of Radiology, including Henry N. Wagner, my boss and mentor, Russell H. Morgan himself, Paul S. Wheeler, and William W. Scott, among many others. And as would later transpire, we had more than just these mutual connections in common.

My relationship with him was remarkable from our first meeting. In late 1998, I had just returned from a Schering Foundation conference on the newly evolving field of aptamers. (Aptamers are RNA polymers that fold into 3-dimensional structures with highly potent and specific binding properties and, accordingly, are highly desirable for *in vivo* molecular imaging). Excited by the potential applications of these molecules, I immediately went on a hunt for scientists in the area conducting aptamer research. There was a single result: Don Coffey. This was the first time I appreciated, as I would many times over the coming years, that Don was always thinking and working on the cusp of the new. He had decided to take up aptamer research so early in the development of the field as he followed his own dictum, which many who were close to him will recognize: "If it's true, what does it imply?" I didn't realize at the time, but a new phase of my education was just beginning.

This early connection proved fruitful. His graduate student at that time, Shawn E. Lupold, Don and I conceived and wrote a research proposal for funding research on PSMA aptamers for imaging prostate cancer. And later, Shawn, Martin G. Pomper in nuclear medicine and a sizable group of medicinal chemists developed PSMA imaging to its current state as one of the most significant new imaging technologies for cancer imaging and radionuclide treatment.

Phase two

Don and I stayed in touch over the next few years. Then, we stumbled on another new area of mutual interest: microtubules. Don had long been interested in microtubules, actin, myosin and other long protein polymers. He was the first to show that they compose a critically important cell structure: the nuclear matrix [1-3]. As we now know, the nuclear matrix mechanically supports the cell in a tensegritylike manner and plays a central role in molecular transport and information transfer. My own interest, however, concerned the role of microtubules in the brain as possible sites for quantum information processing and transfer. I had been thinking about the proven role of quantum mechanics in phenomena as varied as photosynthesis and birds' abilities to navigate over long distances. This led me to the hypothesis that the vast computational and creative capacity of the human brain must have more behind it than just a super Macintosh computer doing mathematical calculations. "How could we image this", I asked myself.

I remember the day when I told Don what I was thinking. While Don was clearly dedicated to cancer, the topic that had led him to Johns Hopkins, I knew he was also deeply interested in the human brain. (We would talk forever on history, evolution, creativity, and imagination). When I shared my thoughts on quantum mechanics and the brain there was an undeniable 'ah ha' moment between us that led to a 'Cambrian explosion' in the sorts of topics and ideas we would explore over the final decade of his life. Even then, we would often say to each other, in surprise, "I didn't know you were interested in that!".

Don taught me a lesson relevant to all scientists: don't avoid exploring topics outside your area of specialized knowledge and expertise. Answers to vexing and unsolved problems can often lie in surprising places. The long list of other topics that we began to address around 2006 included: information, self-organization, phase transitions, Boolean networks, emergence, evolution, time, consciousness, cosmology, artificial and human intelligence and a mix of topics in the arts, writing, meaning, and existence. There were no rules.

In an effort to draw together only a small part of these conversations in some concrete way, we chose to address the subject of symmetry breaking in an article, on which more later. And we often returned to physics and its role in the natural universe, including human imagination and creativity. Mind and matter was the theme. Don often marveled at the fact the human brain accomplishes all that it does, including sending men to the moon, on the power of a small light bulb: 20 Watts. Such simple facts constantly amazed him, and indeed, he was a strong proponent of simplicity. A book we read closely and on which we often relied was Manfred Eigen's *From Strange Simplicity to Complex Familiarity: A Treatise on Matter, Information, Life and Thought* [4]. And one of Don's favorite examples of the power of simplicity, which he returned to time and again, was Watson and Crick's discovery of the structure of DNA: no big science involving gigantic computers and endless number crunching, just basic human intuition.

Don's life before his scientific career also played a major role in his obsession with simplicity. He had worked under James "Big Jim" W. Currie at the Baltimore Westinghouse Electronic Corporation doing research and development in many areas, including inflatable antennas (while, impressively, at the same time working a Hopkins lab glassware washing shift at night). Even many decades on, Don would recall Big Jim's frequent exhortation: "Coffey, that's too complicated. We have to find a simpler solution". He came to view this as a guiding principle in his scientific work.

The excitement of symmetry

Symmetry was a topic of great fascination to Don. He marveled at its many manifestations in biology, physics, cosmology and art. He would often tell me, while he intuitively believed in and felt the importance of symmetry, he did not understand it.

He shared with me a formative experience that led to his interest in the subject: Eugene Wigner's visit to Don's high school in Bristol, Tennessee. Wigner was awarded the Nobel Prize in physics in 1963 "for his contributions to the theory of the atomic nucleus and the elementary particles, particularly through the discovery and application of fundamental symmetry principles". He was briefly the director of what is now the Oak Ridge National Laboratory in Oak Ridge, Tennessee, from 1946-47 before tiring of managerial duties and returning to Princeton. Don would have been 14 years old when Wigner was at Oak Ridge and came to talk to the students about science and, presumably, the importance of symmetry. Although Don struggled throughout high school due to his dyslexia, he recalled with complete clarity Wigner's visit and the impact it had on him. I first heard this story when I told Don one day, with excitement about an article I had read on

Wigner, his investigations of symmetry and his Nobel Prize. I was astounded when Don simply replied: “Oh yeah, I met him at my high school in Bristol”.

Our symmetry conversations sparked a line of thinking about symmetry and cancer. Clearly, cancer cells have a broken symmetry in their shape, which is key to pathological diagnosis, therapy and prognosis. Don’s flair for the dramatic was rarely better than during his *Human Destiny* talk when he would crumple an empty Coke can in his hands and toss it clattering across the stage floor: “That’s cancer”, he would say. But, what is the cause of the broken symmetry of a cancer cell at a molecular level? Why is the degree of symmetry loss so closely related to prognosis? How is homeostasis breaking related to symmetry breaking? These questions recalled my own early college education at Washington University in Saint Louis as a chemistry and physics major. Symmetry and symmetry breaking were constant features of my coursework and college research. In fact Washington University’s chemistry department became a leader in the field the post-war era in part because it attracted the nation’s top nuclear and radiochemists who had been working on the Manhattan Project at Los Alamos.

Wigner was also part of the Manhattan Project. In 1939 Wigner, with Leó Szilárd and Albert Einstein, wrote the Einstein-Szilárd letter, which prompted President Franklin D. Roosevelt to sign off ona project to develop atomic bombs. In a sense then, there was a symmetry in Don and my relationship before we even knew it.

As we later learned, symmetry breaking in cancer can take several forms beyond just geometric symmetry breaking. In our recent article *Symmetry and Symmetry Breaking in Cancer: A Foundational Approach to the Cancer Problem*, we explore cancer symmetry breaking from the additional perspectives of the symmetry of cancer networks, cancer’s combinatorial complexity and the fractal and scale independence of cancer features [5]. In each instance, the goal is to simplify the enormous complexity of cancer through symmetry, just as it can in physics and mathematics. Further, we show how concepts of network stabilizability and attack tolerance, whether applied to the national electrical grid, the internet or cancer, can be related to symmetry principles and quantitative symmetry measurement. The idea being that treatment could, in the future, be directed to vulnerable sites in broken cancer symmetry leading to the destruction of the cancer system network, either at the level of individual cells or within the cancer microenvironment.

An irony of symmetry’s regularity is that chaos too exhibits symmetric patterns. Another favorite book of Don’s was *Symmetry in Chaos* by Michael Field and Martin Gobulitsky [6]. The authors offer many beautiful examples of the symmetric patterns and the strange attractors of dynamic systems evolving chaotically in time. How is the symmetry of chaos related to the symmetry of non-chaotic systems or systems at the edge of chaos? What information does it impart? Does the symmetry of chaotic systems offer simplification or is it just a manifestation of inherent complexity? Is there any relevance to cancer? On the final point, Don had already shown in 1996 that cancer cells do manifest chaotic features, as outlined in an influential article: *Chaotic Oscillations in Cultured Cells: Rat Prostate Cancer* [7]. Once again, Don was on the forefront of the physical and mathematical sciences as applied to the complexity of cancer. His intuition concerning the relevance of old and new concepts at the foundational level of science and reality were unmatched. This intuition proved a constant feature of his efforts to create a unified view of the world.

Not the final chapter

Don continually marveled at both the complex and everyday aspects of life and the natural world. But he was not uncritical. While his life’s work was a series of metaphorical deep dives into all corners of cancer’s complexity, he was at the same time suspicious of said complexity. He believed it to be a distraction, a perpetual pit of cancer dead ends, resulting in an unending series of drug targets that too often led to more tumor heterogeneity and resistance.

Again he would return to the principles of Manfred Eigen’s *Complex Familiarity*. The path that is easy to follow, because it’s logical and right in front of you is not always the right one. In the cancer context it can lead to never-ending, often distracting, possibilities for research, funding and drug development. Big Jim Currie for his part would be aghast at the current state of our attempts to solve the cancer problem. The more positive suggestions in Eigen's *Strange Simplicity* are, however, what really gave Don 'palpitations', whether in the discovery of the structure of DNA or in the magic of a card trick. Complexity cannot be ignored, but Don Coffey would continue to strive for cancer's simple solution and so must we.

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