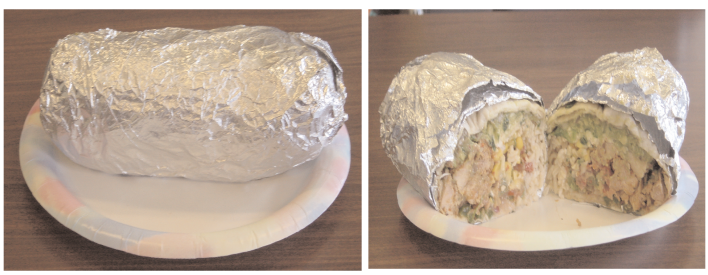
Bacterial Burritos, Mixed Metaphors and a Man in the Middle:

A Scientific Life at the Crossroads of Biology, Chemistry and Engineering

by Derek A. Cabrera[1]

As I sat for an interview with Cornell Assistant Professor of chemical and biochemical engineering, Matthew DeLisa, I found myself struggling to parse and reconcile the mix of metaphors and diverse visualizations he uses to explain his research. Then I realized that when your science is at the cutting edge of human understanding, it helps to have a mixed bag of metaphors and analogies, visualizations and examples. The universe is complex, perhaps no more so than inside a single bacterial cell, and when you're on the verge of new scientific discoveries you use whatever conceptual or technological tool that works best for the job. Sometimes this means you invent a totally new methodology in order to study protein to protein interactions and sometimes it means you have to mix a few metaphors in order to conceptualize what a cell is really like. Of course, this runs counter to the common stereotype of the clean rationality of science. But while the product of science—the groundbreaking discovery or the polished journal publication—is handsome and tidy, the process of science is a messy and complex business. The process of science is as much artistic as it is scientific, intuitive as it is rational, and metaphorical as it is literal.

DeLisa alternatively describes the features of bacterial cells in terms of biology and engineering, complex evolution and purposive design, as burrito and as machine, both messy and mechanical. "Bacteria are like a burrito" DeLisa explains, "both are stuffed with amazing complexity." He continues, "Cells are an amazing collection of machines. Previously, cells were thought of as these squishy things and you had all these molecules floating around randomly. But it turns out that the vast majority of chemical reactions are carried out by proteins that are clustered together in spatial



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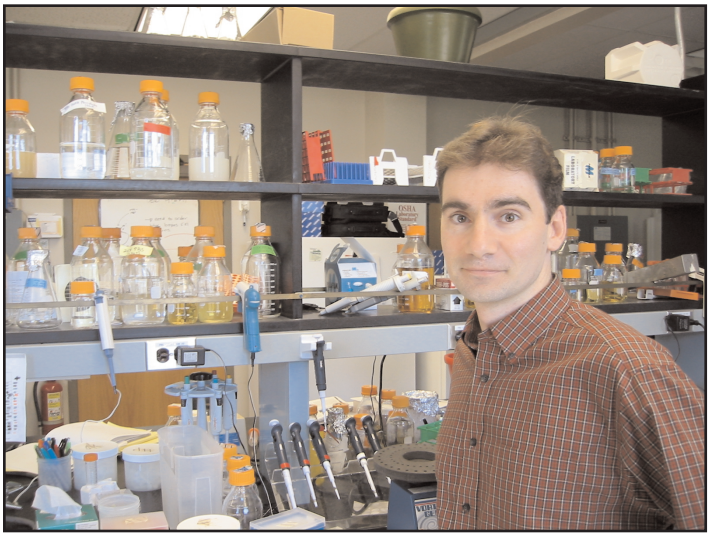

proximity to one another. It's not just random collisions; instead, if there are a series of proteins that carry out a function, then they are all somehow close together in the cell. Instead of as just loose associations, the cell is like a machine where all the parts need to work together."

One gets the impression that DeLisa has a rare case of scientific schizophrenia in which he oscillates between reductionism and holism, between the engineering of a well-oiled machine and the biology of complex squishy stuff. But DeLisa's condition is no scientific malady. He is representative of a new and revolutionary breed of scientists for which the classical battle between polarized scientific epistemologies does not cause cognitive dissonance. DeLisa's scientific work lives in the middle, at the boundary between paradigms. DeLisa's mind is more like the cluttered lab of an inventor than it is like the spotless assembly line for the chassis of a Ford Taurus. His ideas are evolving and adaptive, rather than designed, and while his scientific interconnections are bound by duct tape and tacky from drying glue, they are also ground breaking and new.

I recently got a glimpse of this interdisciplinary process when he shared his work on the fundamental principles of cell biology, chemical engineering, laboratory evolution and de novo design. DeLisa explains, "The metaphors are really important to help explain the science and also to put the science into perspective. But in the lab on a daily basis, I don't know if people are

thinking about it in those terms." DeLisa explains the origin of the machine metaphor, "In 1998, Bruce Alberts, who is a leading cell biologist, wrote a beautiful paper in the journal, *Cell*. He did a wonderful job of articulating how cells are in fact these collections of machines. This metaphor can be taken pretty far. For example, you take an electron microscopy image of a bacterial motor in which you can see the shape and structure of this complex of proteins and place it next to a real human derived motor and you say, 'okay, there's a stator, there's a rotor and... wow, they seem to share a lot of the same parts.' But, at the same time, it's not true of most machines. There's not quite this exact parallel between the human marvels of mechanical engineering and that inside of bacterial cells."

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DeLisa's lab explores not just what a cellular machine does, but what it is capable of doing. So, while he attempts to deepen his understanding of the chemistry and biology of nature, he is also thinking about the possibilities that have never been expressed by nature, but that could be.

> While my work involves a lot of biology, there's also a lot of engineering involved. First, we need to understand the moving parts and forces inside the cell. Then there's a whole new world awaiting us: of rationally altering machines inside of cells and, eventually, of taking machines out of the cell and beginning to interface them with non-cellular entities, and building devices that are organic/inorganic combinations of proteins that might drive something that's non-biological.

DeLisa differentiates between top-down and bottom-up approaches to biochemical engineering:

> Right now, most approaches are top down—they start with all of the pieces and tweak, remove or add one—we start with something we already know. But a lot of interesting questions stem from if you come from the bottom up—if you start with nothing, how would you, in a simple fashion, piece together proteins in a way that might drive cell motion. So how would you build the bacterial motor, not with the set of proteins you are given but just a blank sheet of paper – how would you build that? And right now, we have no idea how to do that. But hopefully, if you came back and interviewed me in 20 years, I would tell you, 'you need these four pieces and you can drive a cell by rotation of flagella.'

DeLisa has positioned his lab "in the middle" of these two approaches. "We want to develop genetic and recombinant DNA techniques that combine traditional thinking about things as one gene or one protein at a time while moving beyond that into areas like systems biology and functional genomics that say, 'let's look at everything all at once.' What we're trying to do is to find somewhere in between. We don't want to look at every gene and every protein all simultaneously, that would be difficult. We'd like to begin thinking about a collection of five to ten of these genes and the proteins they encode – how they work together, how they assemble, how they interact and how those interactions dictate what the machine does." By developing an understanding of the function of these cellular machines, DeLisa thinks that design principles can be identified that can, "be changed to make the cell do something different." For example, DeLisa's lab looks at, "the proteins that make up a cell transporter, that might transport a molecule from one side of the cell membrane to another side of the membrane. We try to understand how it works and then we can change the way it works by manipulating the proteins at the level of their coded sequence and change it so that it has a higher flux of transport. Or, it could transport a greater array of molecules than the ones that it's normally assigned to transport."

The audacity of DeLisa's research is in its simplicity: learn nature's design principles and then re-engineer them to do something different than nature has ever thought of doing. He explains, "Cells have very specific programs that they need to follow in their lifetime and this is something that's come down through evolution. Most of the things they do every day, while they're useful to the cell, may not be useful to solving a problem that faces society today. For example, in cleaning up a toxic waste site or making a non-natural drug that cells don't normally have any need to make. But it seems that a lot of the machinery in these cells—even if you just change it slightly—can help us to realize some of these solutions. So what we

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are trying to do is build on naturally existing systems or machines. Understand what they do naturally and how they do that and then make a change to that machinery, a rational change we hope, that might give it a wider range of function. That might allow it to do something it previously didn't do."

Today, the applications of DeLisa's work are primarily in the pharmaceutical industry. He recently won the NYSTAR James D. Watson Investigator Award, which is given to scientists in New York State whose work is deemed to have an impact on industry and the state economy. "The vast majority of applications is pharmaceutical, so our project to engineer protein transporters stems from the fact that these transporters have been used as one of the predominant mechanisms in producing recombinant proteins in bacteria." This work is especially germane to larger companies like Pfizer, Merck or Genentech who "regularly use one of these pathways for the production of biotherapeutics." DeLisa's lab also works on a project that explores the engineering of the ribosome. "We are looking at the limitations of the ribosome and its ability to make complex modular therapeutic proteins. But, instead of trying to change the sequence of the therapeutic protein, or instead of introducing a special factor that helps that particular protein fold, we're looking at the machinery that makes the protein. If you could change the machinery that synthesizes the protein then you might have a better shot a making that protein, as well as many other proteins that are difficult to produce using traditional approaches."

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It is no coincidence that this crosser of boundaries—between science and society, engineering and biology, athletics and academia—has landed in Cornell's new Life Sciences Initiative, an interdisciplinary effort to understand the mysteries of life itself. It is also not a coincidence that he started his lab at Cornell University—namesake of the industrialist Ezra Cornell and brainchild of the intellectual Andrew Dickson White—a University that was ahead of its time and innovative on so many fronts, not the least of which was its refusal to choose between the pragmatism of the industrialist and the intellect of the academic. Cornell himself established this multi-disciplinary vision when he said, "any person, any study." DeLisa explains that this interdisciplinary culture is what attracted him to Cornell and to the Initiative:

> The Life Sciences/Genomics Initiative just sounded like something that I wanted to be a part of. My interview was totally different at Cornell. Faculty from different departments across campus attended my seminar and my future research luncheon. It was just mind boggling that there was this sort of integration and interest. This kind of process ensures that faculty hires will work collaboratively, as opposed to working in a vacuum. So, to me, that was really exciting. There wasn't any other school that I went to that was doing anything like that. A lot of places talked about interdisciplinary research, but if you pressed them for an example, they would struggle to find one. At Cornell, I didn't have to press for an example – I was living it during the interviews.

DeLisa was hired to work at the interdisciplinary crossroads of the physical and natural sciences. "At the time I applied, Cornell was in the second phase of the genomics initiative. Phase one was strengthening the life sciences. Phase two was integrating between the life sciences and the physical sciences. As a result, there were resources available that gave my department the lateral mobility to attract a new faculty member that was a good fit." To be interdisciplinary requires a delicate balance on the part of faculty, departments and universities. Interdisciplinarity is not always rewarded in academia. The machinations of tenure are often unkind. But DeLisa thinks Cornell is the kind of place that supports such efforts:

> Cornell supports this type of [interdisciplinary] person. In general, scientists are all naturally moving toward this kind of research largely because multi-disciplinary efforts with diverse investigators allows for the tackling of very hard problems - problems that one person couldn't do. So being in a place where that was emphasized was important to me. There is also the problem of tenure and interdisciplinary research. As a junior faculty member, you walk a thin line. You have to establish your own independent research and show how it relies on your talents alone. In some universities, those things are suicide in terms of

tenure. At Cornell, I saw that I could start that right away, and that it was not seen as a negative. That was the kind of place I wanted to be.

DeLisa wasn't always a scientist, but he has always crossed disciplines. In college he was dedicated to his first love as a Division I soccer player. But he eventually found a new passion for science, "Science was something in school that excited me at the same levels that sports had done previously. But, I was a late bloomer as a scientist. It wasn't until I was a senior in college that I was really hooked." DeLisa brings these experiences to his work as teacher and mentor of aspiring scientists. "I think the best advice, which I didn't follow, is to get involved early. I see now that there are opportunities for students to be involved much earlier in cutting edge science, in ways that I never dreamed of. I have sophomores and juniors in a lab-based course that I teach who have already learned modern techniques of molecular biology like PCR. I assumed they learned this in a lab here at Cornell and it turns out that a lot of them have done it in high school programs.

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Other than looking through a microscope or occasionally dissecting a pig, I don't remember feeling that I was learning cutting edge biological techniques at such an early age. I think similar to how computers have infiltrated the daily life of three and four year olds, the same things are happening with science." DeLisa also provides a bridge between past and future academic and scientific worlds. He states, "What field to actually go into is a much tougher question. But ultimately, because of the way science is changing, those decisions are not as critical. I mean, if you actually were to build a university from scratch, the vertical alignment of colleges, and also of disciplines, might not take the same shape that you see today."

Even the lines of science and society are getting fuzzier. "I would suggest to anybody to just get involved in any way you can. So I think that even if science is not something you like, you should at least educate yourself to the point that you can turn on the local news and hear something about a genetically modified organism or hear about DNA cloning and at least have some understanding of what is being talked about. Because I think it's everybody's responsibility to have some innate understanding of these things that are affecting everybody's lives more so than ever." As cutting edge science increasingly becomes headline news, DeLisa, the scientist, finds himself crossing other boundaries and becoming citizen, regulator and even ethicist. To the general public, DeLisa's work can sound alternatively exciting and cool as well as Orwellian or even terrifying. This is a man who is using a deep understanding of biological nature to do things nature never thought of doing. I asked him about the public relations side of his job:

> Those are tough things to think about and I think the responsibility is now upon the scientists to start thinking about those things. I was just at a meeting where numerous scientists were suggesting that there is nothing that says we couldn't build an entire genome, an organism from scratch, from the bottom up. So, one of the questions that came forth at this meeting was, How do we regulate ourselves as scientists? As a reputable scientist, perhaps no one is scared of what you're going to do. However, if by publishing your work you provide a recipe for doing this or that, well, in this time of biological terror threats, I think it's important to figure out how you keep those types of things from being used in a malicious way.

DeLisa explains that Craig Venter, who led the sequencing of the human genome, recently demonstrated the assembly of an entire phage genome (a virus) from scratch. Using off the shelf pieces of DNA that could be ordered and assembled, such a virus could be engineered in an unsophisticated lab. DeLisa states, "Yes, it is scary. Its something I think about. It's tough because you're in your lab and you're shielded from a lot of this and you're driven to reach your goals but every once in a while it's important to think about those types of things. What the solution is right now, I don't know. But I think as long as enough of the smart people who are doing the work are also thinking about these things, the safeguards that are necessary will eventually be put in place."

While DeLisa approaches the future with caution, he is also excited by the possibilities. His penchant for boundary crossing and his strengths at the crossroads of biology and engineering have allowed

him to actually see evolution in action, something most of us, even Darwin himself, could only conceptualize. In post-doctoral work he did over a three year period, DeLisa and his colleagues engineered an entirely new pathway in the cell using techniques such as the laboratory evolution of a protein. They changed the amino acids in a protein's sequence and made the cell, "do things it didn't previously do." DeLisa's work built an entirely new pathway for creating what are called disulfide bonds (bonds between two cysteine amino acids in a protein). DeLisa remembers, "We were fortuitous in some ways. We had built this pathway that we thought was pretty interesting but we really didn't know anything about the mechanism of how we were doing it. Following a seminar, a colleague in the audience said he wanted to take a look at the protein we had engineered, because he had some ideas of what might actually be happening. It turned out that when he went to purify it into a solution, the protein that we made turned totally brown. This immediately told us that this protein we had made was binding iron. Yet, the protein that we started with never binds iron. So, we didn't intentionally say, 'Let's put iron in here and see what happens.' But, we actually took a protein that normally is a single protein by itself and through this process of laboratory evolution we created an entirely new protein. To take it one step further, what was really exciting about the work was that many people had done similar things, even using computer design, but did so without any resulting function. Not only had we incorporated iron, but our iron-binding protein had biological function that was able to replace an existing or normal pathway."

DeLisa hopes to cross new scientific boundaries in his lab in the coming years. "I want to extend this work on laboratory evolution and protein engineering to multi-protein systems. This excites me because I think it's something new and I think there's a lot of fertile ground out there for a group like ours with the skill set we have to make an impact in this area. So far, these techniques have only been applied to single protein systems. If we are able to do it, it will be, to my knowledge, the first use in this fashion. But it's a complex problem and just simply taking laboratory evolution that has previously been used for one protein at a time and applying it to multi-protein systems doesn't scale as simply as we would have hoped. So, coming up with ways around that and how we can incorporate more information into the problem, like protein crystal structure, and like computational protein design, is part of the challenge that we face. That's what excites me and that's what keeps me up nights."

At 31, DeLisa presumably has a lot of sleepless nights ahead, especially because he and his wife just crossed a new boundary into parenthood. Their son was born in December 2004. □