

The Provost's Innovation Initiative

What follows is a discussion with interviewees as part of the Provost's innovation initiative.

Faculty Member Innovation Spotlight

Michael I. Miller: Pattern Theorist and Biomedical Engineer

1. What you have done in your academic career that you think has been most creative or innovative?

Over the past two decades I have pioneered a field in medical imaging called Computational Anatomy, in which we attempt to build image understanding systems of human shape and form. Image understanding has been one of the holy grails of biomedical imaging over the past several decades: building knowledge representations from the millions and millions of measurements generated by three dimensional images from MRI machines, or even from video cameras on your iPhones.

You can think of image understanding as analogous to computational linguistics. We would like to parse medical images into their knowledge representations, as well as into their anatomical and physiological structural representations. We would also like to build a machine which renders diagnoses based on the hundreds of millions of variables coming from the scanners. This type of image understanding corresponds to a machine being able to make a declaration.: "this scan corresponds to a patient with temporal lobe aphasia" or "this scan corresponds to an individual converting to mild cognitive disorder".

The impressionist painters explored this dichotomy: millions of data points on the one hand, and semantic knowledge on the other. Think of Seurat and the Pointillist movement: from an endless number of data points, global gestalts emergeⁱ.

Noam Chomsky, who developed his linguistic theories of natural language in the second half of the 20th century, parses this dichotomy as the interplay between surface and deep structures. In language, surface structure is analogous to acoustic sound, with its multiplicity of isolated frequencies, while deep structure is the human brain's highly organized syntactic and semantic representation of the surface data points of sound. The highly organized internal representation is the meaning!

I refer to the acquisition and manipulation and inference on these deep structures as *understanding*, and in the same sense building them from images in the world *image understanding*. Whether these deep structures are built, represented, or constructed either by machines or by the human brain, I shall term this as UNDERSTANDING. We are on the edge now of being able to build machines that that have 'image understanding' capabilities.

Picasso, of course, was one of the great image understanders – in his remarkable *Man Smoking a Pipe*, 1915,ⁱⁱ he exploded the surface structures of points with extraordinary contradictions, yet was simultaneously able to maintain, embedded in the canvas, the knowledge representation of a *man smoking the pipe*. In the linguistic sphere Chomsky pushed similar buttons deconstructing the surface and simultaneously exploring the deep structures with sentences like *time flies like an arrow, fruit-flies like bananas, and you have feebly growing down on your chin*. Picasso and Chomsky were remarkable.

In both these cases, at the heart of understanding is *parsing*; associating with one representation or set of coordinates another representation or set of coordinates. Parsing in the dense continuum engages the classical notions of map making, which is why we call the parsing technology in the field of Computational Anatomyⁱⁱⁱ generating a *DiffeoMap*, essentially building a correspondence between every point in the individual's coordinate system with every point in the reference or atlas coordinate system.

Once the *DiffeoMap* of your brain is generated, the symbolic and knowledge representation that is available in the reference or atlas coordinate system about anatomy and physiology becomes available for understanding the individual's coordinates. The pre-fix *Diffeo* comes from *diffeomorphism* which corresponds to a particular kind of structure-preserving mapping.

2. What previous ideas was this innovation built on?

Over the past 20 years it has been my desire to make the study of human shape and form – and more specifically the study of neuroanatomy and MRI based brain imaging – into a precise mathematical science, much the same the way that Shannon made communication theory in the 20th century a precise mathematical science. Of course, to paraphrase a famous line from a presidential debate, I am no Claude Shannon. Nonetheless as the son of a New Yorker part of the Greatest Generation^{iv} who made it back from World War II, thankfully, I have never lacked great aspiration.

Before Shannon, communication was largely a study of devices, and until recently Medical imaging has been largely dominated by devices as well. But this is changing as massive databases come on line. If we are to understand the links between genomics a quaternary code and the phenotypes of structural and functional growth seen through the growth and channels, we are going to have to be able to quantify the Shannon representations of channel capacity. It is likely that robustness is the single most important surviving aspect of the evolutionary process; the role of the genotype has to be, at least in part, to condition the organism to its transformational challenges. I was fortunate to work with Donald Snyder at Washington University – my intersection with information theory was through my work with Don.

The greatest influence on the development of Computational Anatomy and Imaging Informatics came from Ulf Grenander. Ulf was originally a Cramer student in Sweden. and wrote the influential book with Szego on *Toeplitz Forms and their Applications*^v, a best seller for Electrical Engineers working in communications of stationary time-series. I took my first of several sabbatical years at Brown in the 90s participating in Grenander's Pattern Theory group.

Ulf had already invented *Metric Pattern Theory*^{vi}, which addresses the understanding and representation of natural patterns in the world. In the 60's and 70's he recognized the importance to his work of placing natural patterns into metric space structures, i.e computing the distance between two patterns, analogous to the distance between two cities in a Michelin road map. He realized the importance for this of patterns which don't lend themselves to such flat spaces. Take two linguistic structures from Chomsky – how do you compare their closeness or proximity. Or alternatively, you would like to have a distance measure which claimed two drawings of a *man smoking a pipe* had small distance to each other, even if the surface structure was shattered as in the Picasso version *Man Smoking a Pipe, 1915*.

Or be able to compare successive measurements of a tumor and declare the treatment is efficacious.

Being able to quantitatively measure distances in high dimensional pattern space is an area of great interest now to the community – Metric Pattern Theory.

Ulf had certainly been influenced by D'Arcy Thompson's work *On Growth and Form*. Of course one of Ulf's many interests were the curved structures of group theory, working heavily on compact groups, and such as those from Sophus Lie's

construction of groups so useful in Physics. Naturally it turned out that my own pursuit of flows of *DiffeoMaps* as the correct model for representing growth and atrophy was to turn out to be a kind of generalized infinite dimensional Lie group. The statistical representation of the variations of human anatomy correspond to probabilities in the Lie algebra.

This recognition of the representation of anatomical variation and “Lie algebra” probabilities resulted in our definition of human anatomy as a mathematical orbit of an exemplar, or atlas, under the group of infinite dimensional diffeomorphisms. In this theory we have generative equations to generate the anatomical configurations, analogous to Chomsky’s generative structures, beginning with an exemplar and flowing differentially from one anatomical configuration to another.

3. Was your innovation the result of pure basic research, pure applied research, or use-inspired basic research?

Our innovation has been the result of all three; certainly it has always been my goal to make a contribution to medical image understanding and to understand the structure and function of the human brain.

We call the applications of these *DiffeoMap* technologies *High Throughput Imaging Informatics*. With high speed MR imaging and body scanning becoming routinely available, it forms the basis for Personalized or Precision medicine. It is now possible to *DiffeoMap* individuals, and understand them. The reduction of the millions of measurements to anatomical and physiological knowledge representation is the informatics. We are of course doing this within our own Medical School radiology department and nationally.

4. What challenges did you face?

In Computational Anatomy, the notion of parsing corresponds to global spatial positioning, or GPS. We are all familiar in our day to day lives with GPS, as it allows us to track our coordinates relative to world coordinates, so that at any moment our iPhone can tell us where the coffee shops are (StarbuckAPP), what coupons are available in the neighborhood (GrouponAPP), and where the closest highway entrance is (GoogleMapsAPP), and the orientation and pitch of the airplane we are flying in the fog. GPS allows us to place ourselves in the world of information.

For biomedical image understanding, the challenge has been accommodating the sheer amount of information and its staggering variation. Unlike the geographic data represented by the GPS in Google maps, human anatomy upon which information is registered is a continuum of highly varying structure, hence our DiffeoMapAPP produces infinite dimensional correspondences. The classic GPS representation is just 6 or 7 dimensional; representation of human form and function is of infinite, evolutionary complexity.

5. What role did collaboration with different disciplines and individuals play in your innovation?

Some scientists solve long standing challenges to the field. My strength lies not so much there, but rather in connecting the dots which appear at the interfaces of science, what is coming to be called Convergence Science.^{vii}

Biomedical engineering as a discipline was created at Johns Hopkins half a decade ago, and I was roughly in the fifth generation of students. Contributions in Biomedical Engineering of necessity involve a convergence of disciplines. In our national program project on dementia headed by Marilyn Albert, we are simultaneously studying the molecular basis of the changes in the brain, during conversion to mild cognitive disorder, as well as the functional connectivity during cognition across millimeter connectivity scales of 10^6 neurons.

For me personally, however, there seems to be yet another, deeper role of collaboration. I enjoy working on biomedical problems which can be reduced to highly conserved quantities, hence the roll of mathematics. Numerical and algebraic representation is the ultimate example of that knowledge reduction.

That was what was so remarkable about Chomsky for example, which often goes unnoticed. Of course he created the formalization of the syntactic structures we learned in 10th grade in English class attempting to model the evolutionary complexity of natural language. But he also wrote three remarkable papers in the 50's in *Information and Control* and *Information Theory* journals - as information theory was breaking post Turing's triumphant machine - which reduced the complexity and completeness of natural languages to algebraic structures, highly conserved equations of motion. Remarkable.

So his discipline had a deep impact on me, as I was doing single unit recording for my PhD years as a Sachs & Young student in the Auditory system, and not

only thinking about the surface structures of sounds and tones, but also about how the brain assimilated these into the deeper semantic structures. Pitch is the perfect example in the auditory system of a deeper structure. I remember debating this with Dan Gibson, a student from Biophysics who worked in Auditory cortex as we drove to Massachusetts to meet his father and Anne Bancroft who had been collaborating on the *Miracle Worker* and stopped along the way to visit with Marvin Minsky the father of Artificial Intelligence and “perceptrons” at his home in Brookline. So Chomsky was in the air, and his efforts in natural language inspired me towards attempting to mathematize human shape and form and its roll in connections of the brain, and on the definition of human shape and form as a mathematical structure. So I have collaborated with his field, even though I have never met Noam Chomsky personally.

But to think in less lofty ways about collaboration, I could never, on my own have pursued the Mathematical depth of the approaches we have taken, while also delivering technologies which are useful to practitioners. There have been many twists and turns here and they continue. Over the past 10 years, my collaboration with Alain Troune and Laurent Younes, mathematicians from *CNRS* and *Ecole Normale* outside of Paris, have resulted in a theory of diffeomorphic momentum appropriate for the deformable bodies of human shape and form, generalizing properly to infinite dimensions the classical notions of rigid bodies, fundamental in Newtonian mechanics. Diffeomorphic momentum is the direct analogue of linear and angular momentum from Newtonian mechanics, it has a natural conservation law analogous to the conservation of momentum for rigid bodies (bodies at rest and bodies in motion), and -an Euler equation the analogue of the Euler equation for rigid bodies.

So as you see from my descriptions, many of the contributions that I see as my most creative contributions result from collaboration.

6. How important is innovative thinking to success in your field? How has the concept of innovation influenced your thinking? What professional and personal circumstances led to what you would consider your biggest innovations?

Biomedical science is a convergence discipline, living at the interfaces. Biological and medical systems exist across 10 orders of magnitude in spatial scales and similarly temporal scales. Certainly the engineers who created the steam engine didn't have to endure this diversity of scales. Evolution didn't respect the separation of the disciplines.

The single most important component of my success has been the discipline that I have been privileged to be part of. The first half of the 20th century was the quantum age and Physics; Harvard and University of Chicago made their bet on that. The second half of the 20th century was the information age; MIT and Stanford bet on that.

50 years prior and during that period Medicine was created at Johns Hopkins and Biomedical engineering began. Being involved in that field early has been my good karma.

7. How has being part of a research university affected your ability to succeed in your work?

In thinking about my experience at the University, I have been very fortunate to have been shaped by a hugely disparate group of remarkable individuals. As part of Biomedical Engineering 30 years ago, I studied Anatomy, Biochemistry, and Physiology with people such as Albert Lehninger. I recall having Donald Coffee and Vernon Mountcastle each come and give seminars to the BME department. We had 4 new PhD students that year in the seminar sitting in one of the rows of that very small room in the Traylor building. The somatosensory homunculus was just being measured by the likes of Mike Merzenich, and Sol Snyder was just discovering opiate receptors. Victor McKusick was attending and advocating the principles that Physiology can't be understood without Anatomy, and 400 miles to the North at the source of Amtrak, Chomsky was speaking on the essential unification of semantics and syntax. Little did I realize how important structure and function would be in my career.

In my years away from Johns Hopkins, I have spent years with Ulf Grenander at Brown University in the metric pattern theory era.

Where else outside of the Research University could anyone have had these experiences?

8. What role has creativity played in your career?

Creativity has played a role. Sometimes the dots are as distant as the White Mountains to the Rockies. But just as importantly for me, has been faith, faith in the scientific method. My mathematical colleague Donald Geman points out that there is no one he knows who is more optimistic about the role of Mathematics in

solving problems in the world. I am reminded of the magnificent writings of Eugene Wigner titled "The Unreasonable Effectiveness of Mathematics in Natural Sciences"^{viii}. Quoting from Wigner, "we are in a position similar to that of a man who was provided with a bunch of keys and who, having to open several doors in succession, always hit on the right key on the first or second trial." I have always been amazed at how reliable and unfailing - belief in the the scientific method is. The doors just keep opening.

So in this way I am creative and innovative.

9. How has mentoring undergraduate and graduate students affected your career?

I have always depended on my students. I have a number of PhD and masters students who have made significant contributions to our field.

But now I teach every year an undergraduate class as one of our four core classes to 100 Biomedical Engineers. Bill Siebert taught one of the core classes at MIT which all of their remarkable Electrical Engineering students in the 80's-90's would take every year; classes inspired by Bill Siebert. I would like to think that I am doing something good inspired by Bill Siebert. In our case, we are role modeling the analytical approach, teaching our Biomedical engineers the core value add that they bring to Biomedicine – the analytical method. These students will lead the Bioengineering world. I love my undergraduates.

10. Do you believe that a university can foster innovation? If so, how? How does the availability of research funding affect your ability to be innovative in your research?

Architects have appreciated this now for a long time – physical spaces matter. Creating spaces that allow our remarkable faculty to interact will result in collaborations, and will foster innovation.

I believe that research funding is very important. It has allowed me to think about the problems that have interested me.

11. Do you believe in the value of serendipity and sudden flashes of insight, or do you feel that effort and hard work have been most essential?

For me, invention comes through continued consciousness experience of the dots. Once I start to see something being connected, it stays in my mind continually and never leaves. Disparate events will be seen as being associated with the same abstraction.

So take for example the famous Picasso movie where he reduces painting to a generative grammar of strokes^{ix}. In graph theory we call them *simple moves*. I saw that at some point early in my career. It rattled around for a long time, until I could see that what he was doing was to reduce shape and form to generative grammars to force the viewer to appreciate the close interaction of physical form in shape space

When I first saw it I didn't know what to make of it. But it emerged clearly later as I could understand sequential inference in work I was doing on Jump-Diffusion processes. If only we could craft the proper metric space – Picasso metric – then machines would be able to see the connectedness of natural shape space. Of course that would remove some of the mystery.

12. Where do you believe your work will be headed next?

We will be connecting our work on the information representation of the structural and functional phenotypes at 1mm scale to the information representation of the genotype.

13. What inspires you to succeed in your work?

The joy of discovery. I am in my happy space when I am connecting the dots and writing. I always tell my popular brother that us University faculty are writers, just like him.

I continue to hope that my work can make a contribution. I also hope that I can make a contribution to this great University, Johns Hopkins, which has really been the starting point for me. I don't forget that day 35 years ago when my father and I parked the family car off of Rutland avenue and I interviewed while my dad sat in Larry Shramm's office in Traylor building and became best friends with Evelyn the then graduate program administrator.

Everything we do is about relationships. I am glad I am back at JHU.

Michael I. Miller, October 2011

ⁱ *Picnic on the Grand Jatte*,

http://en.wikipedia.org/wiki/File:A_Sunday_on_La_Grande_Jatte,_Georges_Seurat,_1884.jpg

ⁱⁱ [http://www.abacus-gallery.com/cgi-](http://www.abacus-gallery.com/cgi-bin/shop/shop.pl?fid=1285576982&cgifunction=form)

[bin/shop/shop.pl?fid=1285576982&cgifunction=form](http://www.abacus-gallery.com/cgi-bin/shop/shop.pl?fid=1285576982&cgifunction=form)

ⁱⁱⁱ <http://www.mendeley.com/research/computational-anatomy-an-emerging-discipline/>

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^h[http://www.alibris.com/search/books/qwork/6726466/used/Toeplitz%20forms%20and%20the](http://www.alibris.com/search/books/qwork/6726466/used/Toeplitz%20forms%20and%20the%20applicationstp://en.wikipedia.org/wiki/Greatest_Generation)
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^{vi} <http://www.amazon.com/General-Pattern-Theory-Mathematical-Structures/dp/0198536712>

^{vii} http://www.insidehighered.com/news/2011/01/05/is_convergence_the_new_big_idea_for_health_sciences

^{viii} [^] [Wigner, E. P. \(1960\). "The unreasonable effectiveness of mathematics in the natural sciences. Richard courant lecture in mathematical sciences delivered at New York University, May 11, 1959". *Communications on Pure and Applied Mathematics* **13**: 1–14. doi:10.1002/cpa.316013010](#)

^{ix} <http://www.youtube.com/watch?v=JU9oaD0e7uU&feature=related>