## **Biophysicist in Profile**



Stephen L. Mayo

Few people know that *Stephen L. Mayo* is a former nationally ranked hang glider pilot. His interest in flying began while growing up on an Air Force base in San Antonio, and if he hadn't become a scientist, "a fighter pilot," says Mayo without hesitation, "(is) definitely what I would have wanted to do!"

Born in 1961, Mayo and his brothers *Anthony* and *Bradley* were Air Force brats, moving often to accommodate their father *Leon*'s military career. Mayo's mother *Nancy* worked part-time as a teacher's aide in grade school while raising the three boys.

Mayo himself briefly thought of entering the Air Force Academy, a notion that was quickly dismissed because he lacked 20/20 vision. Instead, he took up hang gliding and sail planes in graduate school, where he flew competitively. Although Mayo no longer hang glides, he still has a very strong interest in flying, and is considering

joining the Caltech flying club to get back into the air.

It's clear that many of Mayo's interests were born from things he experienced through his father. In fact, he credits his father for his interest in flying as well as his interest in science. After leaving the Air Force active duty, the elder Mayo went to work for the Army, teaching electronics communications at a military facility. "A lot of my science interest came from my father, who was really into technology," explains Mayo, "he would always have some home project, which involved building computers or televisions, or radios, etc." Watching his father work on projects inspired Mayo to work on his own. Mayo was about ten years old, his parents bought him a chemistry set for Christmas, which occupied him for hours on end.

Mayo entered Pennsylvania State University as an undergraduate, and in his sophomore year he entered the

newly formed honors program. Mayo describes the program as "really phenomenal" because it allowed him to work in a chemistry lab, a rare opportunity for a sophomore. A philosophy honors course taught by *Professor Flay* ("We used to call him Flay-to," Mayo remembers) was scheduled concurrently with the standard organic chemistry series. To resolve the conflict, Mayo approached the organic chemistry instructor, *Roy Olofson*, and told him he wanted to take his class, but "just take the tests." Mayo explained to Olofson

that he was "not going to go to any of the lectures, and wanted his permission Olofson laughed and to do that." responded that "Rather than doing that and getting honors units from a philosophy class, just work in my lab and get credit that way." So, at the beginning of Mayo's sophomore year, he began working in a synthetic organic chemistry lab and worked there for three years. During that time, Mayo accomplished a number of things from small molecule X-ray crystallography to writing computer graphics code. He completed his Bachelor of Science in Chemistry with Distinction and Honors in 1983.

When it came time to apply to grad schools, Mayo's undergraduate research advisor told him there was only one place for him. "I'll never forget the way he phrased it," Mayo says: "Caltech is the only place where you will survive."

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happy in the winter!"

In retrospect, Mayo says he understands why. The chemistry graduate program at Caltech was really top-notch and

allowed Mayo to do his own thing, and after living four years in State College, Pennsylvania, Mayo was ready for a warmer climate. "Happy Valley is not so happy in the winter!" he notes. Mayo ended up having three research advisors for his PhD thesis, and they put together an interdisciplinary research program that kept Mayo busy and interested.

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As a student at Caltech, Mayo worked on two different projects. His main thesis project area was looking at electron transfers in metalloproteins, which he worked on primarily with Harry Gray, with components done with Jack Richards and Judy Campbell. The main question was "How do electrons get from metal site A to metal site B within a metalloprotein?" At the time they were looking at electron transfer rates that were measured between naturally occurring internal and external metal binding sites that the group would prepare. The group put a ruthenium complex on the surface of the protein and then measured the rate constant for the transfer between the two sites. Mayo's project area was to use site-directed mutagenesis to control where the labeling would occur so that they could get a defined set of distances and orientations for the electron transfer event. The second project, done primarily with *Bill Goddard*, a computational chemist at Caltech, was to develop computational modeling tools to analyze proteins and to run molecular mechanic and dynamics simulations on proteins. The work involved a lot of software development and computer graphics, as well as computational chemistry work, which Mayo really enjoyed.

The work Mayo did with Goddard ultimately led to the formation of a

company, Molecular Simulations, Inc. (MSI). They started the company when Mayo was a first-year graduate student, and he worked there part-time. Between his first and second postdoctoral appointments, Mayo worked at MSI full-time for more than a year. He continued as a consultant with

the company through his second post-

doc and later, when he became a professor at Caltech. He is no longer affiliated with the company because as he says, "it's not atypical for scientific founders of a company to be banished after several years."

In 1997 Mayo, together with a former graduate student *Bassil Dahiyat*, co-founded a second company, Xencor. The privately owned, California-based biotechnology company is founded on the protein design technology

pioneered in Mayo's lab at Caltech. Dahiyat, now chief scientific officer says that "Steve was, and is, committed to going after the most challenging scientific problems in protein structure, and really lives a high-risk/high-reward research approach." "We faced a lot of roadblocks," Dahiyat continues, "both technical and perceptions of our peers, during our work to establish protein design methodologies, yet he never wavered. He believed that what we

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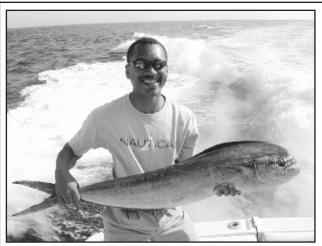
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were trying to do was both worth-while and achievable, and events have proven him out." Since then, Dahiyat says that Mayo has been instrumental in bringing a number of their competitors into Xencor, because

he recognizes that their work can bring significant benefit to the company's design efforts. "He clearly still insists on going for the bleeding edge developments in the protein structure field, which is true to form." At Xencor, computational protein design methods are used to design novel protein-based therapeutics. Mayo remains active in the company as the chair of the scientific advisory board.

In addition to Xencor, Mayo is Professor of Biology and Chemistry at California Institute of Technology, which Mayo describes as "awesome." He quotes one of his colleagues at Caltech that "being a professor is one of the last great jobs in America and I have to say that (it) is certainly a phenomenal thing." Mayo's joint appointment in



Stephen Mayo pictured with a Mahi Mahi he caught off the coast of Cabo San Lucas, Baja California, while at the World Molecular Engineering Network Thirteenth Annual Meeting on Structural Biology. The photo is courtesy of Carlos Barbas of the Scripps Research Institute.

biology and chemistry gives him even greater access to the "general interdisciplinary vibe," which he says is ingrained in the system. As an example, he describes the tradition that graduate students are admitted to different graduate programs—chemistry, biology, chemistry students, biochemistry, physics, etc.—which means that "once you're admitted as a grad student to any of these programs, you can work in anyone's lab, as long as they can support you. I've had physics students, students from computational science, biology students, and biochemistry students. So there's an incredibly low level of bureaucratic impediment to doing interdisciplinary work, and for my lab that's incredibly important because we do a combination of theoretical work, computational work, and experimental work...I need to have people with a really broad background in order to get all the stuff done. Caltech is set up in a way that really fosters this sort of endeavor."

Christopher Voigt, Mayo's former student and now assistant professor at UCSF, calls Mayo a "technophile." He says that Mayo's "electronics interest flowed naturally into computers and programming and he developed one of

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the first programs to study proteins in the early 1980s." Despite running a lab, Voigt says Mayo is still an "avid programmer and often would be utilizing his insomnia to

write code. His hands-on approach led to the coherent software package that dominates his lab's research."

For the past eight years, Mayo has also been a Howard Hughes Medical

Institute Investigator. "This has been absolutely phenomenal," he says, "because of the level of financial commitment that they provide for running a lab." This is particularly important in a lab that does interdisciplinary work, Mayo explains, because there is a need to be skilled in many different areas

with state-of-theart equipment. "We have several very large scale multiprocessor computer clusters to do computational work, but we also have a state of the art

experimental lab, which includes really extensive analytical equipment like circular dichroism spectrometers, and NMR spectrometers, etc.," Mayo explains. "Having the resources that Hughes provides allows me to really establish a truly state-of-the-art interdisciplinary environment where we can actually be on the cutting edge all the way across the spectrum, from computational to experimental work."

Mayo was recently one of four from Caltech to be named to the National Academy of Sciences (NAS). "First I

app-

was surprised, because usually people are significantly older than I am when they get into the academy," he explains. "The timing was sur-

prising, but (I'm) very, very happy, and the recognition has certainly been very nice." Mayo is also a Rita Allen Foundation Scholar, a Searle Scholar, and a Packard Fellow. When asked to describe his greatest professional accomplishment, Mayo says it was his 1997 scientific paper entitled, *De novo protein design: Towards fully automated sequence selection*. In that paper, he and Dahiyat showed that one could design a protein on a computer and show in a laboratory that it

really works. This was a significant achievement because at the time, the level of skepticism was very high, and Mayo has always believed that the most compelling computational experiments have at the back end a

wet lab experiment that shows something important. In that paper, the group was able to develop a theoretical model and a computational model for how to design amino acid sequences and then show in the same paper that it actually works, and that a protein that folds to the right structure can be built. "For my career," Mayo says, "I think that it was the most significant thing I've done so far."

Mayo's future scientific goals relate to an idea he has been trying to develop that interesting questions in structural biology/computational biology will be best approached by using what they call a design paradigm. "Problems will be so complex that rather than utilizing and relying on the normal, simple perturbation paradigm, perturbing the system and seeing what it does, we're interested in this idea that in order to really gain deep insight you'll have to be able to design very complex systems—complex proteins, complex enzymes, etc.—

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and then explore questions about naturally occurring biological systems through this design approach." He describes as an example that "if you are interested in the evolution of protein structure and function, one interesting way to approach that problem is to try to design proteins in the lab and to impose upon your designs a computational model for how you think evolution could occur and then try to recapitulate that experimentally using a complex series of design proteins. In general we're trying to really establish and demonstrate that a design-based

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approach to study biology is going to be a viable and necessary way to gain deep insight going forward. The goal then is to really make sure that we actually have a technology base, in terms of software ultimately, that allows you to execute these complex designs. Whether it be for enzymology,

evolution, or signaling in cells or networks, etc., that there needs to be a technology infrastructure that allows researchers in general to go out to execute complex designs and allow them to probe the fundamental aspects of particular experimental systems." Mayo continues, "trying to understand the evolution of structure and function is one of the basic questions in biology: how do you evolve? How do you go

level."

from something that's not folded to something that is folded, something that's not functional to something that is functional? It really speaks to the fundamental aspects of what biology and evolution are. Will we get there in ten years? Yeah. Maybe. We'll see."

Mayo is a member of the Biophysical Society Minority Affairs Committee. He feels, however, that "we would get greater and more universal participation in science and technology fields in general by providing appropriate educational opportunities to children in K-12." His experience taught him that K-12 is the place where an interest in science is initially generated. "Unfortun-ately, the quality of edu-

cation is just incredibly non-uniform across the country and it seems invariably true that minority communities tend to have much weaker public school systems, so in order to get greater universal participation in science, we have to improve the educational system really starting at the K-12 level."

Mayo advises young scientists to get broad training in

mathematics and in the more physical sciences to be adequately prepared for the increasingly quantitative nature of science in biology, chemistry, biochemistry, and biophysical chemistry. He is on a number of graduate admissions committees at Caltech and is often surprised by how many students apply who have no real physical chemistry or math coursework beyond simple calculus.

In this same vein, Mayo is passing his love of science onto the next generation. Married for almost five years to wife, Julie, an MIT graduate who is a science writer for two labs at the City of the Hope Research Hospital, the couple are raising two sons, Derek, two and half years, and Jason six months. Mayo has found the last several years challenging in terms of trying to raise two boys and still putting in the time and effort required to run a vigorous research lab. Mayo brings Derek to his office almost every weekend, where he likes to play on the computer. "It's amazing what kids can do at that age now with computers," Mayo says, "he can actually start up his own educational games and play with them and turn them off. When he comes to my office, he likes to just hack around on my computers, not doing anything important, but just messing everything up." And the apple doesn't fall far from the tree. Just recently, father and son sat in Mayo's conference room and spent hours building different amino acids out of a modeling kit for making peptide protein models. "Derek obviously had no idea what they were," Mayo says, "but just the idea of plugging little balls and sticks together, he seems to find it enjoyable."

When they can fit it into their busy schedule the Mayo family enjoys the California climate by cruising up and down the coast, visiting various islands on their 40-foot powerboat. Whether sailing over seas, gliding through air, working on a technical solution to an experiment, or putting things together with his son, *Steve Mayo* has more than just a few cutting edge interests to utilize his insomnia.