Sorin Istrail is professor of computer science and will hold the first chaired professorship at Brown's Center for Computational Molecular Biology.
Tracie Sweeney is a senior associate director in the Office of Public Affairs and University Relations.

The career path for many people follows a well-mapped route. My professional journey, however, has taken me from government work, to industry, and to academia; from computer science, to biology, to physics, and to computational biology. In my computational biology journey, each step, every partnership, has taken place in an "intellectual Camelot" - communities of intellectual culture working on exceedingly hard problems. Places like Sandia Labs, where people worked in the shadows of the brilliant minds of the Manhattan Project to advance the nation's science, engineering, and defense projects. Like Celera Genomics, where an interdisciplinary team of scientists made landmark advances in genomics.

> "There exists today a very elaborate system of formal logic, and specifically, of logic as applied to mathematics. This is a discipline with many good sides, but also with certain serious weaknesses. ...Everybody who has worked in formal logic will confirm that it is one of the technically most refractory parts of mathematics. The reason for this is that it deals with rigid, all-or-none concepts, and has very little contact with the continuous concept of the real or of complex number, that is, with mathematical analysis. Yet analysis is the technically most successful and best-elaborated part of mathematics. Thus formal logic is, by the nature of its approach, cut off from the best cultivated portions of mathematics, and forced onto the most difficult part of mathematical terrain, into combinatorics." - John von Neumann

Combinatorics, as the most refractory part of mathematics, is one of the connecting threads of my story. And indeed, I was trained to appreciate both analysis and mathematical logic. World-class mathematicians Solomon Marcus and Sergiu Rudeanu, my advisers when I was a computer science doctoral student in Romania, were, respectively, specialists in mathematical analysis and mathematical logic.

ABOVE John von Neumann is widely regarded as the greatest scientist of the 20th century after Einstein.

I was fond of Johnny von Neumann since graduate school, and my American journey, especially in New Mexico, the Land of Enchantment, brought me closer to him. Let me introduce Johnny with the words of Norman Macrae, his biographer:

> "John von Neumann is widely regarded as the greatest scientist of the 20th century after Einstein. Born in Budapest in 1903, John von Neumann grew up in one of the most extraordinary of scientific communities. From his arrival in America in the mid 1930s - with bases in Boston, Princeton, Washington, and Los Alamos - von Neumann pioneered and participated in the major scientific and political dramas of the next three decades, leaving his mark on more fields of scientific endeavor than any other scientist. Von Neumann's work in areas such as game theory, mathematics, physics, and meteorology formed the building blocks for the most important discoveries of the century: the modern computer, game theory, the atomic bomb, radar, and artificial intelligence, to name a few. From the laboratory to the highest levels of government, he was an essential driver of these world-changing discoveries."

SANDIA

In 1992, on my first day at Sandia National Laboratories in Albuquerque, my manager Ernie Brickell handed me a pile of books and said, "You are the Computational Biology Project at Sandia. Apply for grants from the DOE." The next day, I flew to New Jersey for a three-week computational biology tutorial workshop at Rutgers University. There, I met Michael Waterman. He visited me regularly at Sandia (and later at Celera), and over the years became a dear friend and collaborator. Through computational biology by way of New Mexico, it was Michael who brought me closest to von Neumann. When I returned from the workshop, I prepared a grant application aimed at the DOE's Applied Mathematics Program (MICS), which was the continuation of the Applied Mathematics Program started at DOE by von Neumann while he was a member of the Atomic Energy Commission. Fred Howes, the MICS program manager, was in love with computational biology. With his passionate support over the years, I established and led the Computational Biology Project, the only biology program at Sandia at that time.

The Protein Folding Problem

Synergy and serendipity, which often have a hand in scientific advances, played a part in my entry to the world of protein folding in 1994. I had been invited to talk about genomic mapping at a Telluride workshop titled "Open Problems in Computational Biology." On the eve of my presentation, I was listening to Ron Unger's talk on protein folding when he revealed to the audience that nature can solve NP-complete problems, because in some obscure model, the protein folding problem was proved NP-complete. The following day, I shot down his argument using a series of cartoons, based on the cartoons from the Garey and Johnson book, that I had developed overnight.

The ensuing passionate discussions that Ron and I shared during long walks in beautiful Telluride exposed me for the first time to this most-famous open problem. My cartoons advocated using approximation algorithms. Because of them, Ron challenged me to find approximation algorithms for Ken

Dill's HP model, a simplified protein lattice model studied for decades by hundred of researchers. If you are so critical of my way, Ron challenged, you give it a go, and see how hard it is.

I returned to Sandia and, with Bill Hart, a newly arrived postdoctoral fellow, we solved the problem in a few months. Our approximation algorithm with mathematically guaranteed error bounds would fold every HP lattice protein to a folded conformation with energy of better than 3/8 of optimal energy (number of contacts). Our paper was published in STOC 95 and then in the Journal of Computational Biology. Although the result was theoretical for a lattice protein model, Science magazine announced shortly after the news that Sandia's computer scientists had hit pay dirt with research on protein folding – and the deep computer science concept of "approximation algorithm with guaranteed error bounds" began to make the rounds among researchers involved in protein folding. It opened a new area of study, and dozens of follow-up papers, with similar results in many crystal lattices, have been published since.

> "The most vitally characteristic fact about mathematics is, in my opinion, its quite peculiar relationship to the natural sciences. ... In modern empirical sciences it has become more and more a major criterion of success whether they have become accessible to the mathematical method or to the near-mathematical methods of physics. Indeed, throughout the natural sciences an unbroken chain of successive pseudomorphoses, all of them pressing toward mathematics, and almost identified with the idea of scientific progress, has become more and more evident. Biology becomes increasingly pervaded by chemistry and physics, chemistry by experimental and theoretical physics, and physics by very mathematical forms of theoretical physics. ... This double face is the face of mathematics, and I do not believe that any simplified, unitarian view of the thing is possible without sacrificing the essence."
> -John von Neumann

This double face of mathematics is at the heart of the flaw in Ron's argument. NP-completeness is about mathematical models. Considering both the model and the "modelee" (the protein folding process) of the same type violates von Neumann "double face of mathematics" axiom. Even then, the argument does not work because the model is not only a simplification, but a generalization as well, of the modelee.

The 3D Ising Model Problem

From my first week at Sandia, a colleague down the hall, Bill Camp, started talking to me about the Ising model. I had no background in statistical mechanics and thermodynamics, so his conversations often were hard to follow. One thing was clear: His enthusiasm was infectious.

He shared with me some of the problem's fascinating history, and in doing so, passed the torch to me from his former PhD advisor, Michael Fisher, a member of an extraordinary team that between 1925 and 1972 worked on the 3D Ising Model Problem.

ABOVE At his son Larry's Bar-Mitzvah in the Ulam Ballroom at the Double Tree Hotel in Albuquerque. Sorin (left) with son Larry and John Conway, the John von Neumann Professor at Princeton.

In 1944, future Nobelist Lars Onsager provided the first exactly solved model that exhibits a mathematically provable phase transition. The model was the Ising model of ferromagnetism on the two-dimensional square lattice. It became statistical mechanics' Holy Grail for a 2D model.

Onsager's solution energized some of the most brilliant physicists and mathematicians in the quest for the generalization of the method for three dimensions. Decades of research conducted by the likes of such Nobelists as Onsager, Feynman, Fermi, and mathematicians such as Mark Kac and Michael Fisher uncovered new methods, but no exactly solvable three-dimensional model. In 1985, Kac described the period:

> "The three dimensional case does exhibit a phase transition but exact calculation of its properties has proved hopelessly difficult. The two-dimensional case ... was solved by Lars Onsger in 1944. Onsager's solution, a veritable "tour de force" of mathematical ingenuity and inventiveness, uncovered a number of surprising features and started a series of investigations, which continue to this day. The solution was difficult ... and George Uhlenbeck urged me to simplify it. 'Make it human' was the way he put it. ... Even Feynman got into the act. He attended two lectures I gave in 1952 at Caltech and came with the clearest and sharpest formulation of what was needed to fill the gap. The only time I have ever seen Feynman take notes was during the two lectures. Usually, he is miles ahead of the speaker but following combinatorial arguments is difficult for all mortals."

Funding pressures pushed me to start working on this area, so I started reading a textbook on statistical mechanics. In less than two years, I realized that the random walk of my career had prepared me to understand this extraordinarily beautiful computational problem and its complexity. In my STOC 2000, I published a theorem: "The world of the Ising Model is flat!": For each and every 3D Ising model (in its standard studied versions), computing the partition function was NP-complete. The impact of this Flatland theorem earned it a listing (No. 7) in the Advanced Scientific Computing category of the top 100 most distinguished achievements in the DOE's first 25 years.

Although I provided a "negative solution" to the problem in only a number of model settings, the "Flatland" nature of my result, matching the large volume of failed attempts, received a lot of attention. "NP-completeness," the most treasured paradigm in computer science, is a deep concept. In both the

protein folding and the 3D Ising models, such rigorous "impossibility" results provide rational vindication of failed efforts. And deep down, they identify combinatorial substructures of the models responsible for intractability.

> "The exactness of mathematics is well illustrated by proofs of impossibility. When asserting that doubling the cube ...is impossible, the statement does not merely refer to a temporary limitation of human ability to perform this feat. It goes far beyond this, for it proclaims that never, no matter what, will anybody ever be able to [double the cube]. No other science, or for that matter no other discipline of human endeavor, can even contemplate anything of such finality." - Mark Kac and Stan Ulam, 1968

The Kac-Ulam impossibility proof, although supreme, has "mutated" weaker versions of impossibility, such as NP-completeness. As von Neumann warned us:

> "...the very concept of 'absolute' mathematical rigor is not immutable. The variability of the concept of rigor shows that something else besides mathematical abstraction must enter into the makeup of mathematics... Something nonmathematical, somehow connected with the empirical sciences or with philosophy or both, does enter essentially..."

Science writers' talents flourish in environments with a high density of technical advances. I benefited over the years from the attention of some of the most talented – Barry Cipra (Science), Neal Singer (Sandia), and Phil Ball (Nature). They find beautiful metaphors to convey complexity: "adulterous proteins," "to fold or not to fold," "Why in Superbowl of statistical mechanics, famous players could never cross the goal line," "Ising on the cake," "Statistical physicists phase out a dream." Of these, the most innovative of all was the SIAM News article by Barry Cipra, an award-winning author on the Ising model. Describing my NP-completeness proof of the 3D Ising model, he used Dante's Inferno verses/poems for each of the main steps in my proof .[8]

In the late 1990s, several events - coincidental and otherwise - again changed the course of my career.

In 1997, Michael Waterman, Pavel Pevzner and I started an annual international conference, RECOMB (Research in Computational Molecular Biology), which has become, arguably, the top conference in computational biology. It just celebrated its 10th birthday this month with a meeting in Venice. Michael, who worked with Stan Ulam at Los Alamos, introduced me to a number of other personalities from that era: François Ulam, Gian-Carlo Rota, Nick Metropolis, Bill Beyer. In Michael, the RECOMB community heard the inspiring echoes of Ulam and von Neumann, two mathematicians in love with biology.

Fred Howes' untimely death in 1999 was the day the music died. (RECOMB honors his legacy with a Distinguished Service Award. In 2004, Dick Karp delivered the Fred Howes Award Lecture.) Weeks after Fred's death, Gene Myers enticed me to come to Celera to meet Craig Venter.

And the spirit of von Neumann cast itself over me once again: On the happy occasion of my son Larry's Bar-Mitzvah (held in the Ulam Ballroom at the Doubletree Hotel in Albuquerque), we were honored to have John H. Conway, the John von Neumann Professor at Princeton University, as a guest at the celebration.

ABOVE RECOMB 1997 Conference Banquet: Eric Lander, Michael Waterman, David Botstein, Sorin Istrail, Bill Beyer, Nick Metropolis

CELERA

My time at Sandia was followed by five years at another "intellectual Camelot" - Celera Genomics, where my role as senior director of the Informatics Research (IR) team was to lead the computational biology effort in the post-genome assembly phase. By creating powerful software libraries of tools for assembly comparison, annotation, mass spectrometry, SNPs and haplotypes, arrays, protein folding, and literature data mining, the IR team became, arguably, the leading computational biology group in the industry.

My interview at Celera was memorable. In my meeting with Craig Venter, I asked about the role of algorithms at Celera. He responded without hesitation: "Algorithms are the make or break of Celera." As "Speed Matters" was the company motto, I joined Celera two weeks later. One by one, all my close collaborators from Sandia as well as former students soon joined my group. "Where do you find all these geeks?" one assistant asked. "Is there a secret club?"

Each and every one of these extraordinarily talented colleagues, geeks or not, became stars of the Celera team. Some of the most opinionated, workaholic overachievers sat around the table to brainstorm, wearing smiles as if to ask "You are going to tell me what to do?"

As I worked closely with Craig, I admired his extraordinary ability to make the impossible possible through his inspiring leadership. Exciting and inspiring leadership, as well as the magnitude of the problem ahead, molded us in such a way that each person, prima donna or not, came to rely upon the others in order to achieve lasting contributions.

"Our CPAs are hopefully behind the times when they estimate a company's net worth in terms of material assets. All businesses today depend ... on the creative thinking of a few eccentric individuals. ... Talent seldom grows in isolation. More often, it benefits from the encouragement and challenge of similar talent. Talent is created by teamwork as much as good teamwork is made up of talent. The most successful teams at the National Labs ... are made up of scientists and engineers who think and work in very similar patterns, and who have learned to spot and appreciate each other's complementary skills. ... Scientific teams are fragile. It takes years, as well as a dose of good luck, to assemble a successful scientific team, and it takes one stroke of the pen to destroy it. Once a research group is broken up, it is all but impossible to put it together again, and a national asset is forever lost." - Nick Metropolis, 1993

The members of the IR team were exceptional, some of the most talented computer scientists and software engineers I had the pleasure to work with. Each taught me a lot and could well join the ranks of my beloved teachers. At Celera, we could not wait to come to work - although everyone worked basically 24 hours a day. We designed some of the most powerful algorithms; we performed some of the largest supercomputing computations. Due to private industry's large investment, we had the fortune to see and analyze for the first time whole genomes and various other immense data sets generated by biotechnology. Buses of high school students would visit the site, and press releases were distributed almost every day. Companies around the globe wanted to work with Celera. Craig was invited to the White House. It was an extraordinary time of our lives. The world was alive. And one day in 2002, the largest DNA sequencing factory on earth was called to national duty to help with DNA identification of the remains of the 9/11 victims. Celera called it the Soaring Eagle project. A tremendous company-wide effort was made because, at that time, speed truly mattered.

Not long after Craig returned from his meeting with President Clinton at the White House, a day came when at Celera the music died: On that dark Monday, we learned that Craig left the company.

Comparison of Genome Assemblies

To understand the state of genomics before Celera, a good reference can be found in a book by Freeman Dyson:

"The human genome project began in 1990 and is supposed to be finished in 2005. In 1999 more than half the time has passed but less than a tenth of the genome has been sequenced. ...In my opinion, the decision of the administrators of the genome project, to finish the sequencing of the entire human genome by year 2005 using existing methods, was unwise. The decision was driven by politics and not by the needs of science and medicine. ...In science, to change the objectives of a program in the light of new discoveries is a sign of wisdom. In politics, it is a sign of weakness. Unfortunately, politics prevailed over science. ...The human genome project at the current cost is not sustainable. ...The cost of sequencing must be reduced, and the speed increased, by a factor of a hundred or a thousand."
- *The Sun, the Genome, and the Internet* (Oxford University Press 1999)

Craig Venter's departure was soon followed by Gene Myers'. For his farewell party, we formed the IR Band that played *IR Genomes*, based upon John Lennon's *Grow Old with Me*:

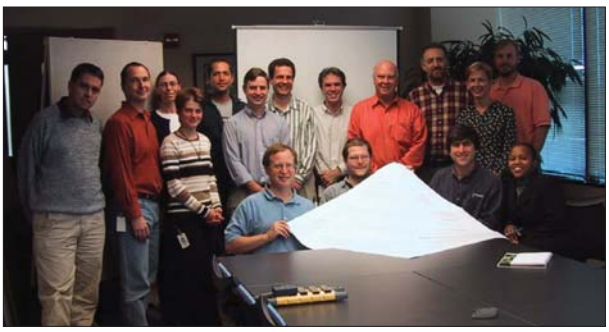
For genomes like you and me
The best is yet to be
When the time has come
We will be as one

We did great things together
Genomics is forever!

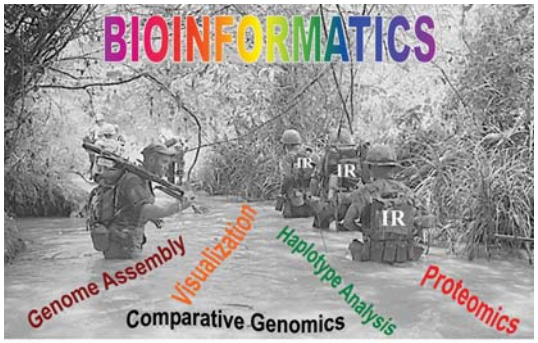
The president of Applied Biosystems, Michael Hunkapiller, and his staff understood immediately that the IR group was the "bioinformatics special forces," and we began to work closer with Applied Biosystems. One day, I told him that my group's members were restless, and I asked him to speak with them. In that teleconference, Michael said there is no such thing as permanent employment in private industry, but that IR had the next best thing.

Celera followed the course advocated by Dyson and found tremendous success, which was not universally well received. Ridiculous papers were published - revisionist histories that reminded me of communist Romania and read like manifestos rather than science.

Once the National Center for Biotechnology Information (NCBI) announced the Human Genome Assembly "finish line," the time was right to evaluate the first human genomes of 2001. At Craig and Michael's request, I became the lead "prosecutor" of Celera's case, with a responsibility as first author of the paper that would put to rest the revisionists' mutterings. A year later, after a tremendous team effort, we published what I call our "lighthouse" paper - computational analysis as permanent as the bricks housing these beacons of light - in the Proceedings of the National Academy of Sciences. Some of the largest biological-inspired computations to date were used for the paper. As was promised in Celera's first paper, the publication of our "lighthouse" paper made public all Celera human genome assemblies and the Celera assembly code, all available in the NIH/NCBI databases.



ABOVE The dream team of authors of the "lighthouse" paper: (standing, left to right) Bjarni Halldorson, Aaron Halpern, Hagit Shatkay, Liliana Florea, Ross Lippert, Nathan Edwards, Granger Sutton, Russell Turner, Craig Venter, Sorin Istrail, Karin Remington, Ian Dew; (sitting, left to right) Clark Mobarry, Brian Walenz, "the Father of all DotPlots," Jason Miller, Merissa Henry.



The Informatics Research Group blazes the way through the bioinformatics jungle, leaving behind a trail of success.

APPLIED BIOSYSTEMS
SPECIAL FORCES

LEFT Front and back images that appeared on the Informatics Group t-shirts. Tranquility and Crisium were the two conference rooms of the Informatics Research team. The T-shirt was to celebrate winning "The Fight for Tranquility."

The Regulatory Genome

After the 2001 publication of the first assemblies of the human genomes, we wondered about the next big problem to solve. Craig told us that drug design was next in line. A remarkable parade of companies presented their technologies to us. Everybody, it seemed, wanted to work with Celera. Craig wanted us to work on the most difficult of cancers: pancreatic cancer.

At that time, I thought the focus of my group should include genomic regulation, because gene regulation is a major component of the disease mechanism. And in this area, the top experimentalist is Caltech's Eric Davidson, whom I had met in Tokyo when he presented a keynote address at a RECOMB conference. At that time, Eric expressed an interest in having Celera sequence the sea urchin. I brought him to Celera to see Craig.

Since then, the most exciting area of my research is my collaboration with Eric on genomic regulatory networks. Our paper "Logic functions of the genomic cis-regulatory code" provided a first repertoire of building block gates of genomic regulation. Eric reeled me in with a story about his mentor, Max Delbruck, his next-door neighbor at Caltech. Max encouraged Eric to start learning mathematics, and even provided a postdoc to teach him. Eric does not tell stories without a motive, so, thinking a bit, I got the message. I told him that I would take the "Delbruck-Davidson challenge" and I would start learning experimental biology. Like his mentor, Eric's students have been my instructors for what he calls my "boot camp training" in wet lab developmental regulatory networks.

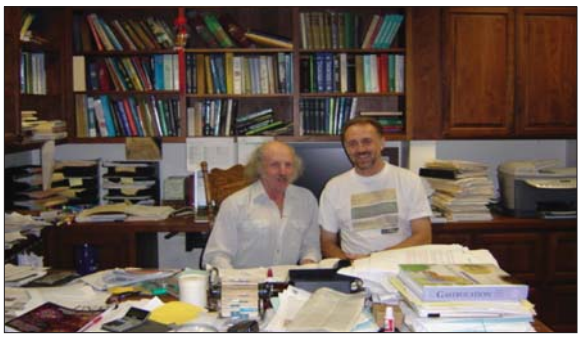
Using the sea urchin genome, Eric is today the leading liberator of quantitative principles of cell regulation trapped in the qualitative, descriptive world of biology without genomic sequence. Just like he does in his Caltech Lab, Eric unites all of us – biologists, physicists, biochemists, engineers, and computer scientists – in a research renaissance questing after the functional meaning of DNA. From such research will ultimately come, by experimental demonstration, the revelation of the long-sought laws of regulatory biology.

"We must emphasize a statement which I am sure you have heard before, but which must be repeated again and again. It is that the sciences do not try to explain, they hardly even try to interpret, they mainly make models. By a model is meant a mathematical construct which, with the addition of certain verbal interpretations, describes the observed phenomena... Furthermore, it must satisfy certain esthetic criteria – that is, in relation to how much it describes, it must be rather simple. ...Once cannot tell exactly how "simple" simple is. ...Simplicity is largely a matter of historical background, of previous conditioning, of antecedents, of customary procedures, and it is very much a function of what is explained by it."
– John von Neumann

The gene regulatory network models built in the Davidson lab are flagships that satisfy von Neumann's esthetic axiom. These models are updated continuously by the causality-driven scientific method cycle: description-prediction-experimental validation.

For five years, my father dealt with cancer. The doctor taking care of him, Thomas Devers of New Britain, Connecticut, was a physician of extraordinary dedication and professionalism. He was also a fan of Celera. Each time I visited my father in the New Britain Hospital, where he was being treated for advanced pancreatic cancer, the doctor, with a sparkle in his eyes, would ask about Celera. During one of my bedside stays, I told the doctor that I needed to return to work. "Is that OK?" I asked, fearful of what his answer might be. "Go back [to Celera] and save the world," Doctor Devers said. My father passed away a few months later.

Five years earlier, when my father had been diagnosed with pancreatic cancer, an Internet search brought him to surgeon Jeffery Matthews, a doctor affiliated with Harvard Medical School. Doctor Matthews performed an extraordinary procedure to remove the cancerous tissue from my father's pancreas. My father did not believe in impossible problems; he believed there is always a solution – and the harder the problem, the more interesting it was to solve. He survived Romanian Nazi labor camps, and throughout his adult life was a businessman of highest caliber. One problem he could not solve was his cancer. He was my inspiration.



ABOVE Sorin (right) and Eric Davidson, the Norman Chandler Professor at California Institute of Technology, discuss their ongoing research involving the regulatory genome of sea urchins.

The Axioms

Michael Hunkapiller kept his promise. The IR group survived until the very day he left the company. In industry, once the job is done, it moves on. Nothing personal; just business. All of us in IR moved on as well. Each of us became academics.

I believe von Neumann would have liked each of the four problems discussed in this article. They all have a von Neumannesque flavor in their exceeding difficulty and symbiosis of computer science, biology, physics, statistical mechanics, and mathematical logic. As a computer scientist, it was wonderful to see computer science ready for the Genomic Era. From protein folding and the Ising model to the genome assembly and the regulatory genome, deep biology themes such as evolution, genome structure, biomolecular structure, and cell regulation intertwined with computer science and statistical methods to unveil the genomic mysteries. We need to continue von Neumann's unfinished research program toward a new theory of information and computation for the living cell, in which the "refractory" combinatorics/logic and "best cultivated" analysis come together via a concept of thermodynamic error. Inspired by the cell, we need to uncover the principles of information processing using millions of processors working asynchronously. New computing architecture paradigms based on self-diagnosis and self-repair will help us build von Neumann models for cellular information processing.

My professional ramblings in computational biology have taken me to two Camelots: the National Lab/Sandia; and Celera. Last fall, dressed in academic regalia and listening to President Simmons at Opening Convocation, I realized that I had arrived at another Camelot: Brown. President Simmons spoke with pride about the incoming freshman class, remarking that 15 percent and 13 percent of the class had perfect SAT scores in English and math, respectively. With a back-of-the-envelope calculation guessing that at most 3 percent are perfect in both, it follows that one in four Brown freshman is perfect in either English or math. The students in my "Algorithmic Foundations of Computational Biology" class are extraordinary as well. With such students, plus a department that is a world-class temple for computer science, and the Center for Computational Molecular Biology, which is in the process of recruiting top talent, the sky is the limit."

How do you search for an intellectual Camelot? I believe von Neumann would have liked this question. He would try to find the axioms for it. Based on my experiences, I would venture a guess:

Axiom 1. Randomness is beautiful.
Axiom 2. Work on the hardest problems.
Axiom 3. Continuously search for teachers.
Axiom 4. Scientific teams are fragile.
Axiom 5. A crisis is a terrible thing to waste.
Axiom 6. And in the end, the love you take is equal to the love you make.

C!

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