Profile of Ken A. Dill

A protein is a chain of amino acids that has been folded into a precise shape, explains statistical physicist Ken Dill, a recently elected member of the National Academy of Sciences and director of the Laufer Center for Physical and Quantitative Biology at Stony Brook University in New York. A protein with 100 amino acids can ball up in a staggering number of ways: roughly 3^{200} (1). Yet each protein molecule balls up into the exact shape needed to perform its desired role in the body. Even more impressive–the folding often occurs within milliseconds.

How, researchers like Dill have long wondered, does the protein know just what to do? More than answer a grand challenge in biology, predicting the secrets behind how a protein folds could pave the way for pharmaceutical drugs that target errant proteins. From the 1980s to the 1990s, Dill devised a theory to explain protein folding in terms of funnel-shaped energy landscapes. Today, that theory, which shows how amino acids in a protein chain can glom together in different ways and still arrive at the same protein shape, has emerged as the accepted view of how proteins fold (1, 3).

In his recent inaugural article, Dill (4) expanded from looking at the physics of a single protein to looking at all of the proteins inside a cell—a collection known as the proteome. Dill has found that proteomes have evolved to optimize performance inside their host cell. For instance, he says, his models show that cells are packed with the perfect number of proteins, a situation that he likens to a good party. Too few guests (or proteins) and the party fizzles out, he says. Too many guests and it becomes too crowded for one guest to travel across the room to talk to someone else. "Proteins and cells are remarkably optimal little physical machines," Dill says.

From Tinkerer to Researcher

Born in 1947 in Oklahoma City, Oklahoma, Dill spent his childhood tinkering. "I liked to fix old broken TV sets and make little transistor gizmos," he says. His interest in math and physics, he says, was partly inherited from his father, an engineer at the local telephone company.

As he grew older, Dill began to tackle more sophisticated problems. For a high school science fair project, Dill created a theory of algebraic rings using Fibonacci numbers, a project requiring long hours on computers generously made available to students at the Oklahoma Gas and Electric Company. One night, he became so entrenched in his work that his frantic parents called the police to find him. "Only then did I realize that it was four in the morning," Dill says.

Ken A. Dill.

In 1966, Dill entered the Massachusetts Institute of Technology in Cambridge, Massachusetts, as a math major. "I was really into problems having no practical importance," he says. However, by his sophomore year, he realized how much he liked physics and switched to mechanical engineering to bridge his interests. To see if he was cut out for research, Dill stayed on at the Massachusetts Institute of Technology for a fifth year and completed a master's degree in bioengineering. The field was still relatively new, and Dill began researching how nerve cells conduct pain throughout the body. "We built some electronics to monitor neural signals," says Dill, who was in charge of constructing the equipment and experimenting on anesthetized cats. The work convinced Dill of his love for research.

Dill decided to pursue a PhD in the University of California at San Diego's fledgling biology department in 1971. Initially, he says, he wanted to tackle a fundamental question: how did life originate from a hodgepodge of chemicals? However, that question proved too daunting for him at the time, and therefore, Dill began working with chemist and National Academy of Science member Bruno H. Zimm to understand the biophysics of DNA molecules (5, 6).

How Proteins Fold

By the time he finished his doctorate in 1978, however, Dill had become consumed with a third question—one that would ultimately shape his life's work. Around the time that Dill began his doctoral studies, Christian B. Anfinsen won the Nobel Prize in Chemistry for figuring out that proteins fold of their own accord. Specifically, when the researchers disrupted a protein called ribonuclease, the protein unraveled like yarn from a ball. However, when the conditions were restored, the protein once again formed a ball. Figuring out just how a string of amino acids folds into the precise protein shape needed by the body soon emerged as one of the hottest questions in biology. Scientists coined it the protein-folding problem.

After defending his thesis, Dill accepted a postdoctoral position with Nobel Laureate Paul Flory at Stanford University in Palo Alto, California, to research protein folding, albeit indirectly. Given proteins' chemical complexity, Dill began by researching a simpler system (7, 8): micelles. Micelles are surfactants (the same components of soaps and detergents), and like proteins, they contain a water-loving exterior and water-phobic—or oily—interior. Unlike proteins, however, micelles lack a distinct physical structure. Dill hoped that mapping micelles' amorphous structure would provide insights into the regimented internal world of proteins.

When he finished his postdoctoral work in 1981, however, Dill remained unsure about how to connect his work with micelles to proteins. While driving his beat-up Rambler across the country from California to his new teaching position at the University of Florida at Gainesville, "I had a lot of time to think about protein folding," Dill says. He realized that Flory's earlier insights into polymers, or chemical chains with repeat units, might hold a clue. Flory had found that polymer chains fold into a huge number of shapes in infinite space. However, cram those chains into a tight space like spaghetti in a carryout box, and the folding possibilities shrink exponentially (9). Dill began to suspect that proteins might also have just a small number of shapes when they were compact.

The 1980s were a fortuitous time. At the University of Florida, Dill began

This is a Profile of a recently elected member of the National Academy of Sciences to accompany the member's Inaugural Article on page 17876 in issue 44 of volume 108.

crunching the numbers and discovered that a protein can only ball up into a small number of compact structures, among which is the protein's actual shape (2). Dill also married his sweetheart, Jolanda Schreurs, whom he met while completing his postdoctorate studies at Stanford. Dill moved back to California, this time to the University of California at San Francisco, where he and his wife raised two sons, Tyler and Ryan.

Protein Poetry

However, all was not perfect. Although Dill published his theory on protein folding and stability in 1985, it would take more than a decade for people outside his small academic circle to take notice. At the time, Dill says, few people saw the relevance of statistical mechanics to the protein-folding problem. Additionally, without a vocabulary to talk about his finding, people failed to grasp the significance behind the statistics. "If you tell people about the shape of an entropy function, their eyes glaze over," Dill says. Therefore, he and a few others began framing the situation in more poetic prose. In 1987, for instance, he referred to protein folding as a problem of "funnels, not tunnels" (10). "People had been thinking of protein folding as a needle in a haystack problem and pondered whether there were special 'tunnels' through the haystack to find the needle. So I used that terminology," Dill says.

The funnel idea finally caught on in the mid-1990s, years after his initial paper on protein folding. In 1987, he published a paper illustrating the funnel idea with a cartoon in which a protein chain starts out sitting at the top of a funnel (3). The laws of thermodynamics say that, like skiers down a mountainside, a system such as a folding polymer will spiral down, and its constituent amino acids begin to ball up. "Like skiers all arriving at the same lodge, the folding protein gets systematically closer to the desired protein shape as it moves down the funnel," Dill says. "And it gets there pretty fast." The funnel theory finally caught on. "Experimentalists in the field started to refer to this as a new view of protein folding," Dill says.

Interestingly, Dill's insights into how to use statistical physics to explain protein folding helped him answer one of his earlier questions: how might life have originated? Dill's work shows that the question can be answered through probability. All life on earth arose from just 20 amino acids. To produce life, however, those amino acids would have had to line up along the protein chain in just the right way as to allow the resulting protein to fold into something lifelike. The odds of getting a particular amino acid into slot number one along the chain is 1 of 20; for slot two, those odds drop to 1 of 400, and for slot three, the odds are all the way down to 1 of 8,000 and so on. "Creationists argue that it would be astronomically impossible for life to happen by random processes, because there is no way you could get the right string of bead colors to get the protein needed for life," Dill says.

But Dill considered that the wrong question. Rather than asking how to string together amino acids in just the right order, he asked how you could string them together to get the desired shape, regardless of how the amino acids were ordered in the chain. When Dill plugged random strings of amino acids into computer models, he found that a significant fraction of those beaded chains folded up into something lifelike (11). "That little switch in framing the question," Dill says, "upped the odds of life appearing spontaneously by a hundred orders of magnitude."

Building Life's Building Blocks from Scratch

Eventually, Dill moved from modeling proteins on a computer to actively trying to replicate them. Most polymer materials in use today, like plastic and rubber, are monotonous repeats of the same small molecule bead hooked together along the chain. However, what if, Dill wondered, polymers could be constructed using particular sequences of amino acid-like building blocks. Could they fold, like proteins do, into versatile structures? Could we create new materials out of foldable polymers?

In the early 1990s, Dill's wife, a pharmacologist at the drug manufacturer Chiron Corporation, introduced Dill to her then-colleague Ronald Zuckermann. Zuckermann had invented an artificial molecule known as a peptoid, a protein-like structure made up of human-made materials (12). Zuckermann and Dill wanted to see if they could create peptoids with protein-folding abilities. It was an ambitious goal. Although protein biologists had made decades of headway into cataloguing the different types of proteins in the world, polymer chemists had had only a few years. By way of comparison, Dill says, the protein databank today includes the precise anatomic structure of 70,000 proteins; the peptoid databank has fewer than 10.

Nonetheless, by 2005, Zuckermann and Dill had showed that it was possible to make foldable peptoids (13). Dill and Zuckermann then showed that they could make peptoids that can bind zinc—a crucial element in the body—as strongly as proteins do (14). That proof of concept could have powerful applications in the real world. For instance, human-made molecules with protein-like binding abilities could become next-generation biosensors. Such biosensors could selectively bind and deactivate toxins in the environment, even at extremely low concentrations, Dill says.

Changing Policy

In the 1990s, Dill's work with the Biophysical Society opened his eyes to a critical gap in academic funding. Funding for most academic research in the United States is carefully parceled out by field, Dill says. For instance, biology is largely funded through the National Institutes of Health, whereas physics is funded through the Department of Energy and the National Science Foundation. Such segmentation leaves little room for scientists bridging fields, Dill says.

Through various leadership roles at the Biophysical Society, including a stint as president from 1998 to 1999, Dill devoted much of his time to trying to close that gap. During his early days with the society, he wrote an article highlighting the critical need to bridge funding and research in the life and physical sciences as a way to strengthen biomedicine's roots (15). In 2002, Dill and his colleagues built a coalition of 15 research societies and spent the next several years lobbying lawmakers on Capitol Hill. "We passed out white papers to any warm body in Washington," Dill says.

Their efforts began to snowball, and others joined in. In November of 2004, the National Institutes of Health hosted a multiagency meeting on the subject. That same month, Dill met with Representative Nancy Pelosi (D-California) and Bruce Alberts, then-president of the National Academy of Sciences. The following year, the National Academy of Sciences developed a call to action (16), and both parties in the House of Representatives developed innovation agendas. The popular press soon caught on as well. By 2007, the National Research Council had begun studying the issue (17).

Now, as director of the new Laufer Center at Stony Brook University, Dill continues his work at the interface between statistical physics and biology. Dill wants to know, for instance, why proteins do not precipitate inside cells, where they are so densely packed. Although it makes for a great party, the cells should, nonetheless, have left a little room for error, he explains. "Proteins are kind of sticky, and if you condense them in a tight space, they will stick together and cause problems. In Alzheimer's, for instance, proteins glom together," Dill says.

Additionally, Dill is developing theoretical and computer methods for delving deeper into protein physics: how proteins aggregate, how they form fibrils, how they bind to drug molecules, and how they interact with water, for example. He hopes that deeper knowledge of the physical underpinnings will help advance biological discovery and drug development.

Sujata Gupta, *Freelance Science Writer*

1. Service RF (2008) Problem solved* (*sort of). *Science* 321:784–786.
2. Dill KA (1985) Theory for the folding and stability of globular proteins. *Biochemistry* 24:1501–1509.
3. Dill KA, Chan HS (1997) From Levinthal to pathways to funnels. *Nat Struct Biol* 4:10–19.
4. Dill KA, Ghosh K, Schmit JD (2011) Physical limits of cells and proteomes. *Proc Natl Acad Sci USA* 108:17876–17882.
5. Dill KA (1979) Theory for the separation of very large DNA molecules by radial migration. *Biophys Chem* 10: 327–334.
6. Dill KA, Zimm BH (1979) A rhelogical separator for very large DNA molecules. *Nucleic Acids Res* 7:735–749.
7. Dill KA, Flory PJ (1981) Molecular organization of micelles and vesicles. *Proc Natl Acad Sci USA* 78:676–680.
8. Dill KA, et al. (1984) The molecular conformations in surfactant micelles. *Nature* 309:42–45.
9. Flory PJ (1949) The configuration of real polymer chains. *J Chem Phys* 17:303–311.
10. Dill KA (1987) *The Stabilities of Globular Proteins Protein Engineering*, eds Oxender DL, Fox CF (Liss, New York), p 187.
11. Lau KF, Dill KA (1990) Theory for protein mutability and biogenesis. *Proc Natl Acad Sci USA* 87:638–642.
12. Zuckermann RN, Kerr JM, Kent SBH, Moos WH (1992) Efficient method for the preparation of peptoids [oligo(N-substituted glycines)] by submonomer solid-phase synthesis. *J Am Chem Soc* 114:10646–10647.
13. Lee BC, Zuckermann RN, Dill KA (2005) Folding a nonbiological polymer into a compact multihelical structure. *J Am Chem Soc* 127:10999–11009.
14. Lee BC, Chu TK, Dill KA, Zuckermann RN (2008) Biomimetic nanostructures: Creating a high-affinity zinc-binding site in a folded nonbiological polymer. *J Am Chem Soc* 130:8847–8855.
15. Dill KA (1999) Strengthening biomedicine's roots. *Nature* 400:309–310.
16. Committee on Prospering in the Global Economy of the 21st Century: An Agenda for American Science and Technology, National Academy of Sciences, National Academy of Engineering, Institute of Medicine (2007) *Rising Above the Gathering Storm. Energizing and Employing America for a Brighter Economic Future* (National Academy Press, Washington, DC).
17. Committee on Forefronts of Science at the Interface of Physical and Life Sciences; National Research Council (2010) *Research at the Intersection of the Physical and Life Sciences* (National Academy Press, Washington, DC).