Comprehensive model is first to map protein folding at atomic level

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Scientists at Harvard University have developed a computer model that, for the first time, can fully map and predict how small proteins fold into three-dimensional, biologically active shapes. The work could help researchers better understand the abnormal protein aggregation underlying some devastating diseases, as well as how natural proteins evolved and how proteins recognize correct biochemical partners within living cells.

The technique, which can track protein folding for some 10 microseconds -- about as long as some proteins take to assume their biologically stable configuration, and at least a thousand times longer than previous methods -- is described this week in the *Proceedings of the National Academy of Sciences*.

"For years, a sizable army of scientists has been working toward better understanding how proteins fold," says co-author Eugene I. Shakhnovich, professor of chemistry and chemical biology in Harvard's Faculty of Arts and Sciences. "One of the great problems in science has been deciphering how amino acid sequence -- a protein's primary structure -- also determines its three-dimensional structure, and through that its biological function. Our paper provides a first solution to the folding problem, for small proteins, at an atomic level of detail."

Fiendishly intricate, protein folding is crucial to the chemistry of life. Each of the body's 20 amino acids, the building blocks of proteins, is attracted or repulsed by water; it's largely these affinities that drive the

contorting of proteins into distinctive three-dimensional shapes within the watery confines of a cell. The split-second folding of gangly protein chains into tight three-dimensional shapes has broad implications for the growing number of disorders believed to result from misfolded proteins or parts of proteins, most notably neurodegenerative disorders such as Alzheimer's and Parkinson's diseases.

The model developed by Shakhnovich and colleagues faithfully describes and catalogs countless interactions between the individual atoms that comprise proteins. In so doing, it essentially predicts, given a string of amino acids, how the resulting protein will fold -- the first computer model to fully replicate folding of a protein as happens in nature. In more than 4,000 simulations conducted by the researchers, the computer model consistently predicted folded structures nearly identical to those that have been observed experimentally.

"This work should open new vistas in protein engineering, allowing rational control of not only protein folding, but also the design of pathways that lead to these folds," says Shakhnovich, who has studied protein folding for nearly two decades. "We are also using these techniques to better understand two fundamental biological questions: How have natural proteins evolved, and how do proteins interact in living cells to recognize correct partners versus promiscuous ones?"

Source: Harvard University