Web alert

Protein folding

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Various genome projects are identifying thousands of new protein sequences every year, which has led to an expanded interest in protein folding. There are two parts to the protein folding problem: the first is predicting the three-dimensional structure of a protein from its amino-acid sequence; and the second — the focus of this Web alert — is to understand how proteins fold. Increased interest in protein folding has been fuelled by the belief that many human diseases (Alzheimer's and Parkinson's, for example) are caused by aggregation or misfolding of proteins. The FASEB Society has a valuable essay (aimed at the general public) that describes known diseases related to protein (mis)folding (www.faseb.org/opar/protfold/protein.html). It is possible that the selective pressures that act during evolution function to preserve amino-acid sequences that not only form structures that adequately perform specific biological functions, but also to preserve those that fold quickly enough to avoid aggregation or misfolded states.

Although a search for 'protein folding' using a search engine like AltaVista has more than 13,600 hits, the number of useful protein-folding resources is limited. A good place to start, to get acquainted with the people in the field, is the comprehensive list of protein-folding groups compiled by Heinrich Roder's laboratory at Fox Chase Cancer Center (http://www.fccc.edu/research/labs/roder/folding_groups.html), which contains links to more than 80 research teams working on various aspects of protein folding. Several of the scientists listed here have their own web pages, some of which are very creative, and include links to other useful sites.

Protein folding is quite different from small-molecule chemical reactions (in which covalent bonds are formed or broken in well-defined transition states), because of the many degrees of freedom allowed a polypeptide chain. In order to understand the complexity of protein-folding processes at the microscopic level, a statistical approach is required. The current theoretical and computational frontline, with respect to protein-folding dynamics, is well described in the Pittsburgh Supercomputing Center's interactive collection of articles from 1998 (http://www.psc.edu/science/lifeproc.html). In particular, the papers by C.L. Brooks III and P. Kollman are admirable. Vijay Pande's website (http://www.stanford.edu/group/pandegroup/#research) is also excellent, and includes movies of all-atom molecular-dynamics simulations of protein folding.

The Database of Macromolecular Movements (http://bioinfo.mbb.yale.edu/MolMovDB/) is another amusing site to visit. It contains short videos of motions in proteins (including a few examples of folding and unfolding). This site also includes free software tools for protein geometric analyses.

In order to place protein folding in its realistic *in vivo* context, there are additional factors to address. Around 5% of all proteins made in cells (often larger, multidomain proteins) require help from 'chaperonin' proteins to fold properly. To learn more about these reactions, visit the Chaperonin Home Page (http://bioc09.uthscsa.edu/~seale/Chap/chap.html) located at the University of Texas Health Science Center. This web page links to researchers in the field and lists thermodynamic data for a large number of mutants of the most famous chaperonin pair GroEL/GroES. The site also includes a protein-structure gallery and a recent paper alert.

20–30% of all proteins function within cellular membranes. It has not yet been resolved (from either a thermodynamic or a kinetic viewpoint) how such proteins are synthesized and then inserted into the membranes. An excellent resource for this topic is the web pages of Stephen White's laboratory at UC Irvine (start at http://blanco.biomol.uci.edu/mp_assembly.html). The general principles of membrane-protein structure and stability, the group's own research approach, a wealth of interesting links and downloadable key research papers are all available here.

In order to perform their biological functions, many proteins coordinate small cofactors such as metal ions. The recently created PROMISE database (http://bioinf.leeds.ac.uk/promise/) provides a wealth of information on these types of proteins (although there is not much on the proteins' folding properties yet). In addition, this site links to an impressive number of bioinorganic web resources.

The field of protein folding is growing at a fast pace, as is the number of researchers that need to keep up with the current literature and news. A perfect way to do this is to attend the Johns Hopkins Protein Folding Meeting, which has taken place each spring for the past five years. This meeting attracts the finest people in protein folding, and the conference covers all aspects of this fascinating field. The program for the 5th Meeting (taking place this month) can be viewed at http://www.jhu.edu/~ipmb/protein.html.

Protein folding is a rapidly expanding field that involves researchers from many disciplines. We expect new web resources to be developed that continue to facilitate discussion and collaboration.

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