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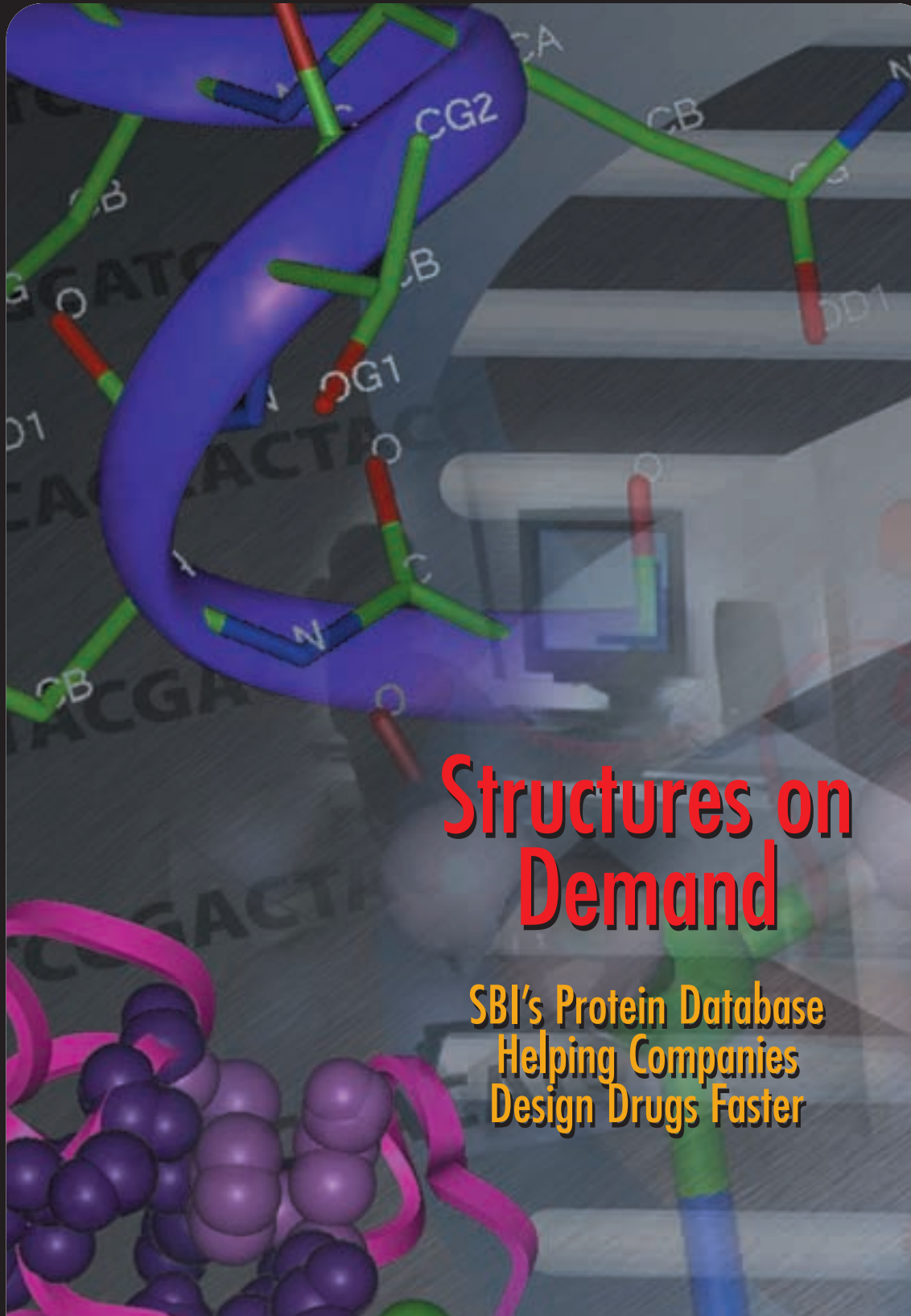
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Structures on Demand

SBI's Protein Database
Helping Companies
Design Drugs Faster



Welcome to the First Issue of strubix.com

Behind Every Great Structure

This is the first issue of strubix.com magazine from Structural Bioinformatics, Inc. Our goal for this publication is to educate and inform scientists in the pharmaceutical industry about new developments and expanding applications in the area of protein modeling.

Few would argue that knowledge of protein structure isn't critical for structure-based drug discovery and rational experimental design throughout the life sciences. However, some researchers remain skeptical that protein models can, in many cases, replace experimentally-determined protein structures.



While rational drug design is predicated on the knowledge of a three-dimensional structure, experimentally-determined structures for most proteins are unavailable - and are likely to remain so for some time. Consequently, pharmaceutical projects routinely proceed with little or no information about the shape of the protein target.

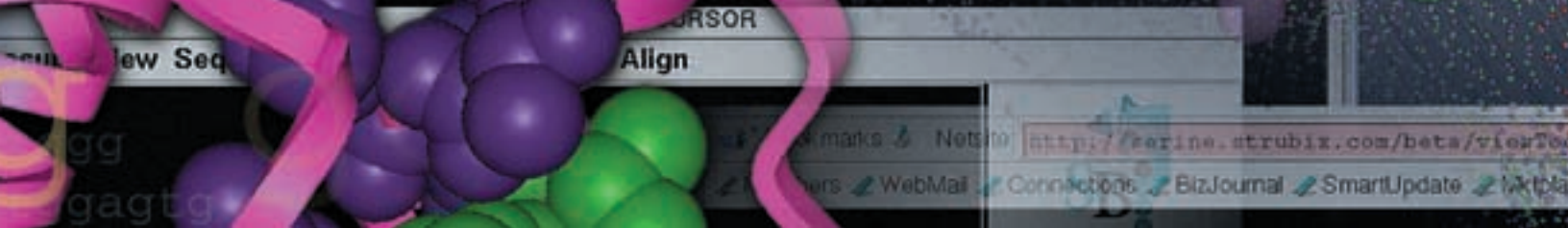
Similarly, structural information for related proteins, critical to understanding specificity differences or mechanisms of action, is frequently not available.

Through SBdBase™, SBI directly addresses this shortcoming in a practical way by providing instantly accessible, high-quality three-dimensional models of proteins for which no crystal structures are available. In addition, our GeneWeb™ interface allows the user to compare his or her own proprietary protein structures in the context of sequence or structurally-related SBI modeled structures. This comparison offers users novel insights regarding differences in structure, specificity, dynamic flexibility, biochemical and biophysical properties, and function, which can be quickly identified and highlighted for consideration and use throughout the research team.

SBI is dedicated to rapidly expanding the availability and multiple uses of protein structure in all aspects of pharmaceutical research, and to facilitating the central role, visibility and technical contributions of structural scientists in rational experimental design throughout the life sciences. As a forward-looking company, our vision is becoming reality as evidenced by: (1) our easily accessible, comprehensive protein structural database (SBdBase™), (2) our work in the application of large-scale protein modeling to pharmacogenomics (SVdBase™ modules), and (3) our commitment to highlighting and communicating the importance and growing role of the protein structural scientist in pharmaceutical research through this forum and additional publications accessible through our website www.strubix.com. I am confident that together we will continue to break new ground in the creation and use of protein models and look forward to many success stories from SBI and our customers that will be reported in future issues of strubix.com magazine. We encourage you to contact us (see contact information) on any matters, questions, comments or ideas which you may have relating to the generation or use of protein structural information.

Edward T. Maggio, Ph.D.
President and CEO





The dramatic increase in gene sequences and the accelerated identification of new pharmaceutical targets has increased interest in predicting three-dimensional protein structure, not only for modeling and structure-based design but also for molecular biology and other areas of biology. Experimental methods such as X-ray crystallography and NMR spectroscopy simply cannot keep pace with the rate of new sequences being discovered. Yet, protein structural information is critical to understanding function, ligand binding and specificity among other things. Protein structure affords powerful advantages to modern drug-discovery research.



Structures on Demand

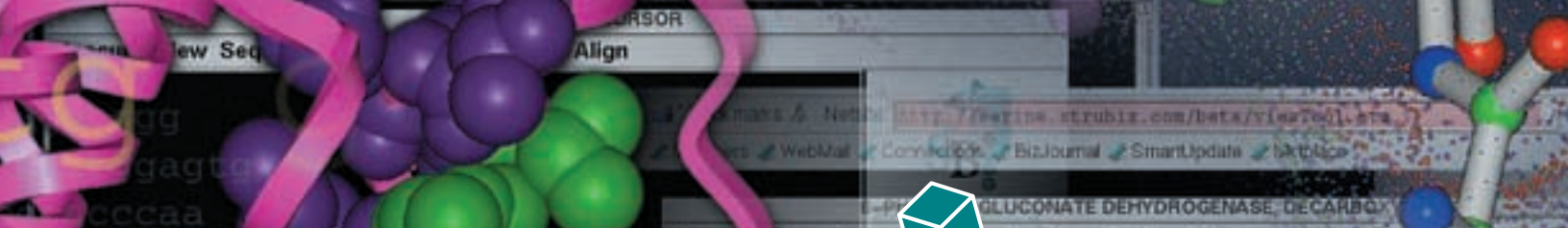
SBI's Protein Database Helping Companies Design Drugs Faster

by Jayant Ghiara, Ph.D.

Certain advantages derive intrinsically from structure and can be realized by simple examination. The identification of residues important to function or to binding is tentative, at best, from sequence alone because noncontiguous parts of the sequence are brought together during protein folding. Today, protein models are widely used to engineer therapeutic protein products, to identify medicinal peptides and important protein-surface epitopes for pharmaceutical use, to engineer stability and for applications in everything from protein expression systems to gene therapy to the design and optimization of small-molecule drugs.

It is not currently possible to predict the three-dimensional structure of a protein from its amino acid sequence alone, although efforts and improvements are steadily being made in this area. Most protein modeling methods rely on similarity to known structures (greater than about 25-30% sequence identity), and this approach has become reasonably reliable, particularly when practiced by an expert. Commercial and academic software is available, from a variety of sources, that automatically generate the three-dimensional structure of proteins from sequence information. Automatically-generated structures may be used for very qualitative purposes but are generally considered unacceptable for drug design





Protein models from SBdBase™ provide immediate access to protein structures invaluable to all aspects of pharmaceutical research and structure-based drug design.

where a higher degree of accuracy is needed. Inevitably, human intervention is necessary to improve upon these first results.

SBI automates some steps but combines this with irreplaceable human experience and handling. The modeling technique is best described as comparative modeling augmented by proprietary *ab initio* and energy-based methods, including proprietary loop modeling and structure refinement techniques developed in-house. SBI modelers use a combination of proprietary algorithms along with some of the best available academic and commercial techniques for comparative modeling, with protocols tailored to specific protein families.

Modeling is a challenge that varies with the problem and generally precludes the use of a single, set protocol. Nevertheless, there are many commonalities. Sequence alignment is initially based on sequence similarity, with extensive manual adjustments made to automated homologous sequence alignments. Adjustments are typically based on structurally and functionally-important regions as determined from biological/functional data, sometimes significantly reducing the scored "% identity" from the original alignments. Manual intervention is also required when aligning sequences that have insertions and/or deletions with respect to one another. Models consistent with the alignment are constructed. The models are refined using energy-based methods and surface

Overview of SBI's Augmented Homology Modeling Strategy

Sequence homology search

Alignment within family

3D template selection

3D fold, structural motif

Structure-based sequence alignment

Maximal alignment of helices and strands

Alignment of functional residues

Alignment of active sites and binding sites

Initial 3D model construction

Energy-based refinement

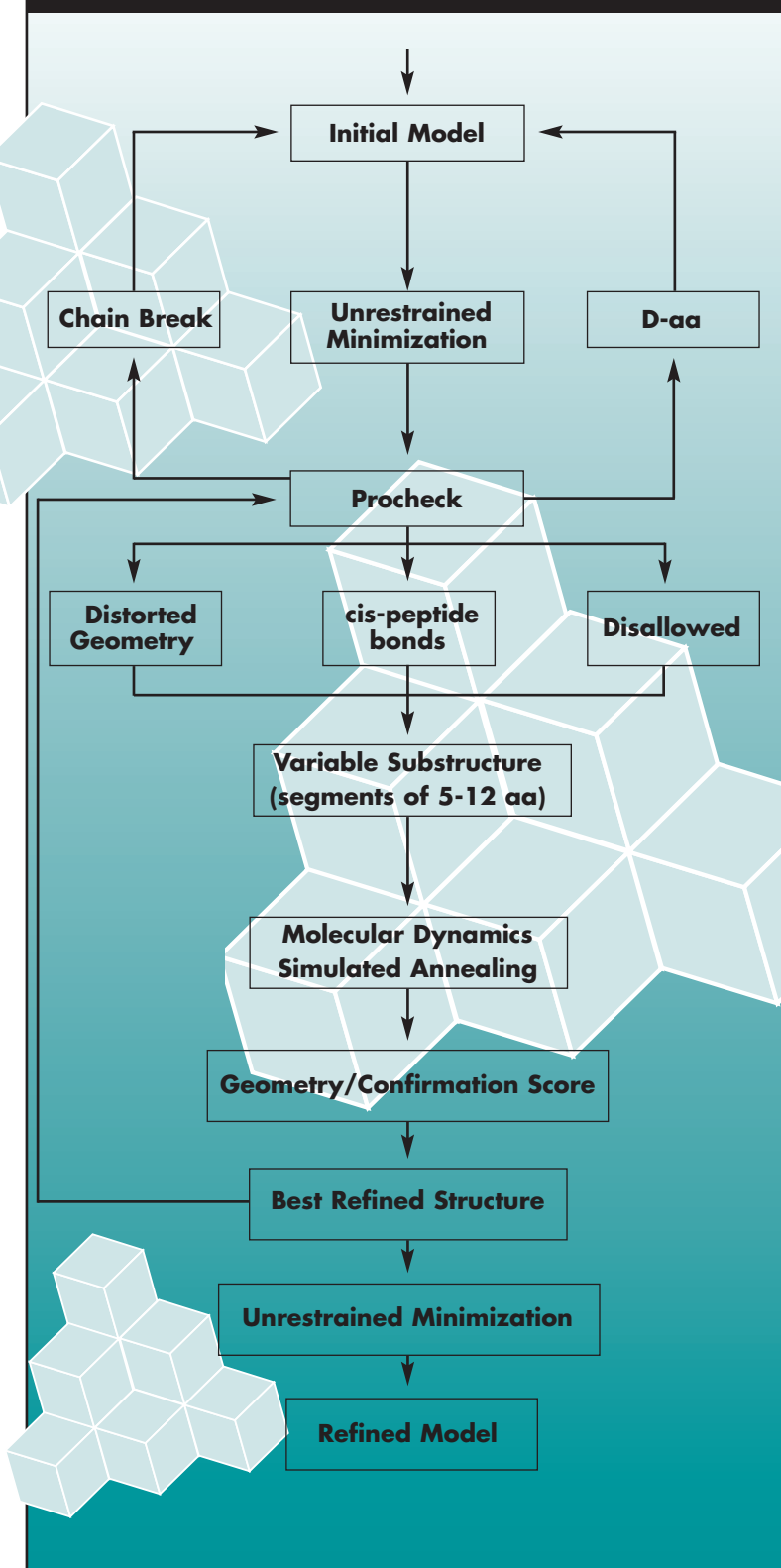
Loop generation by *ab initio* mechanics methods

Quality control and molecular dynamics to evaluate reliability of the model





Flow Chart of the SBI Refinement Procedure



SBI addresses the need for high-quality, instantly-accessible three-dimensional models of protein drug targets and structurally-related family members for which no crystal structures are available.

loops are predicted using in-house proprietary molecular mechanics-based protocols. A suite of quality control methods is used to check for packing, solvent accessibility and local strain in the structures (Ponnuswamy, Prabhakaran and Manavalan, 1980; Prabhakaran and Ponnuswamy, 1980; Maiorov, V. and R. Abagyan, 1998). Stereochemical consistency of the structures is evaluated using PROCHECK™ (Laskowski et al., 1993), and energy-based methods are also used to evaluate structural quality (Case et al., 1997; Dudek, Ramnarayan and Ponder, 1998).

Efforts are underway to develop new, advanced computational methods to predict protein structures that, together with concerted efforts to solve structures of new protein folds, hold the promise of predicting structure from almost any protein sequence. As one example, a research group at SBI Advanced Technologies A/S, a subsidiary of SBI located in Hoersholm, Denmark, has trained multiple neural networks to predict secondary structure with an unprecedented degree of accuracy. Other advanced methods based on new theories about protein folding are in development and may lead to dramatic improvements in the computational determination of protein structure.





SBI ACQUIRES MAG'S GENEMINE™ TECHNOLOGY

SBI announced January 17, 2000 that the company has acquired the GeneMine™ technology from Molecular Applications Group (MAG), Palo Alto, CA. Along with its protein database technologies, SBI offers a unified platform of bioinformatics data retrieval, integration and visualization of protein sequence information in the context of protein structural information along with high quality protein structures. The system can collect and display an extensive array of information including homology clusters, homology fingerprints, active sites, functional motifs, post-translational modifications, metabolic pathway associations and sequence polymorphic regions and also includes a set of efficient, highly reliable protein modeling methodologies that were developed by MAG.

"GeneMine is extremely complementary to our protein structure database, SBdBase," said Dean Goddette, Ph.D., Vice President of Sales and Marketing at SBI. "The acquisition allows us to expand the content of our own database products while providing our customers with an expanded set of tools for analysis of protein sequence and structure."

SBdBASE™ VERSION 2.0 NOW AVAILABLE

A new, updated version of SBI's flagship SBdBase™ database of protein structures will be available in February 2000. The new version includes an entirely new user interface, which is more user friendly and intuitive. The new features enable the user to compare structurally-related proteins, import local structures for comparison and export reports, images and plots for presentations and reports. "This is a major enhancement of the functionality," said Dr. Ramnarayan, Chief Scientific Officer of SBI. "We are also laying the groundwork for better performance and future expandability of tools and features."

CTC LABORATORY SYSTEMS TO DISTRIBUTE SBdBASE™ IN JAPAN

SBI has signed an agreement designating CTCLS as the exclusive distributor of SBdBase™ in Japan. "We are very pleased to have CTCLS representing SBI in Japan," said Dr. Dean Goddette, Vice President of Marketing & Sales. "They have an excellent reputation and are highly regarded by their customers." CTCLS has traditionally been involved in the marketing and sales of drug discovery software in Japan.

"Bioinformatics is a key new area in Japan that will help accelerate drug discovery," said Mr. Kazuo Yamamoto, President of CTCLS. "SBdBase™ plays an integral part in plans to integrate bioinformatics and cheminformatics through the use of protein structure."



QUEST DIAGNOSTICS AND SBI ANNOUNCE STRATEGIC ALLIANCE FOR PHARMACOGENOMICS APPLICATIONS TO HEALTHCARE

Structural pharmacogenomics is the analysis of structural variations of drug targets resulting from genetic variations within a population. SBI will extend existing and generate new proprietary target-specific Structural Variant database SVdBase™ modules for a number of therapeutic targets based on Quest Diagnostics' clinical sequence databases. "The structural variant databases generated from our genotyping databases should provide a fertile new source of information helpful in the design of new antiviral compounds using the structure-based drug discovery approach pioneered by SBI," Dr. Bernard L. Kasten, Quest Diagnostics' Chief Laboratory Officer said. "It is possible that structure-based modeling may have important new applications for clinical testing and test reporting for the care of individual patients." Quest Diagnostics is one of the nation's leading providers of diagnostic testing, information and services to physicians, hospitals, managed care organizations, employers and government agencies.





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Some wait for Structure. Others get it from SBI.

Why wait for your protein structure? An increasing percentage of protein structures are available immediately through comparative modeling. SBdBase™ provides a powerful resource of professional-quality protein structures of pharmaceutically-relevant proteins. Easily accessible at the desktop through a web-based interface, you can view the structures online for guidance in labeling proteins for *in vitro* studies or for rationalizing alanine-scanning experiments. Alternatively, you can export the coordinates for docking studies, *de novo* design of inhibitors, mutagenesis studies, and much more!

SBdBase™

- Database of human protein structures
- Professional-quality comparative models
- Drug target emphasis
- Over 150 protein families
- Thousands of individual models



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Upcoming C o n f e r e n c e s

Integrative Bioinformatics

January 19-21, 2000
Zurich, Switzerland

Advances in Human Genome Biology & Technology

February 5-8, 2000
Marco Island, FL

Human Genome Project: Commercial Implications

February 28-March 1, 2000
San Francisco, CA

Gene Function Analysis

March 2-3, 2000
San Francisco, CA

ACS Spring National Meeting & Exposition

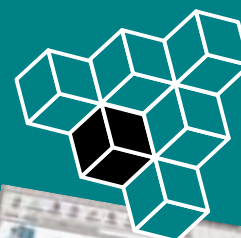
March 26-28, 2000
San Francisco, CA

Genomics, New Discoveries & Commercial Developments

March 29-31, 2000
Cambridge, United Kingdom

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