A Collaboratory for Interactive Molecular Modeling

Project Overview

Resource for Biocomputing, Visualization, and Informatics

University of California, San Francisco

Resource objectives:

To create and apply computational and visualization methods for solving a wide range of genomic and molecular recognition problems within the complex sequence→structure→function triad.

- Characterization and interpretation of genomic data, including knowledge discovery and transfer.
- Development, application, and dissemination of analysis methodologies and tools in computational structural biology.
- Theoretical and applied research in understanding how protein structures deliver function.

Sequence → Structure → Function

Challenges:

- Prediction of structure from sequence
- Prediction of function from sequence
- Understanding of evolutionary changes
- Engineering proteins for specialized function
- Applications in pharmacogenomics and pharmacogenetics

Potential for major impact on…

- Drug discovery
- Prediction of drug response
- Avoidance of toxic effects in many individuals

Collaboratory goals:

Develop a collaboratory environment for carrying out interactive three-dimensional molecular modeling studies for research and training

- Multiple scientists at remote locations to interactively manipulate shared, complex three-dimensional molecular models (as similar as possible to “face-to-face” collaborations)
- Full semantics for the modification of an object by any collaborative participant
  - access to the object's data, not just the object's graphical representation
  - individual participants can perform operations privately first, then present results in collaborative session

Motivation

Solid evidence of benefit of "face-to-face" scientific collaboration through a common visually-based work environment

- 1,000's of multiple author publications
- direct observation of interaction among visiting scientists
- direct reports that "collaboration promotes new ideas"

Desire to extend environment to remote scientists

- promote more frequent and spontaneous collaboration sessions
- encourage new collaborations

Desire to utilize remote collaborative environments in new ways

- Training
- Improved feedback for software development

Typical scenario

Input commands (typed keywords or menu selections) on one workstation, display and execute these commands on all other participating collaborative workstations

- Displayed molecules move in tandem on all workstations simultaneously in response to input from any participant

Provide independent control for each participant

- separately shaped or colored mouse cursors for highlight interesting facets of a molecular model
- interactive control of rotations, translations and scaling
- “private” window for testing ideas
- participants can join and/or leave an on-line session at any time

Why interactive graphics?

Qualitative

Generates pictures

Quality vs. interactive real-time

Value lies not in numbers themselves, but insights gained

Idea generator

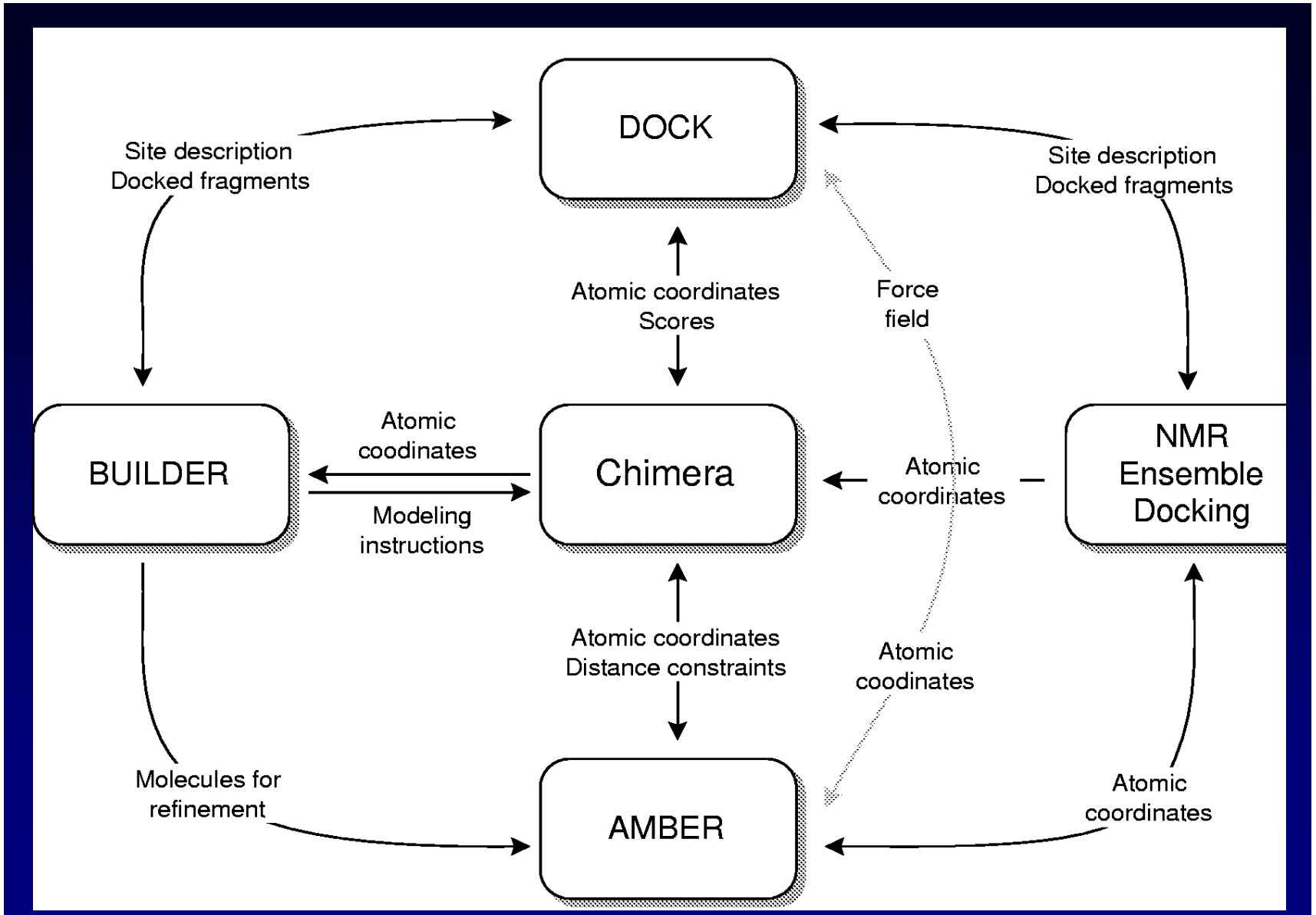
Complementary to experimental methods

- X-ray crystallography
- NMR spectroscopy
- Mass spectroscopy

Structure-Based Drug Design

Facile and comprehensive system for determining the structures of proteins and nucleic acids in solution and designing new ligands and drugs

- Integrated Software Tools for Structure-Based Drug Design Applications [figure 1]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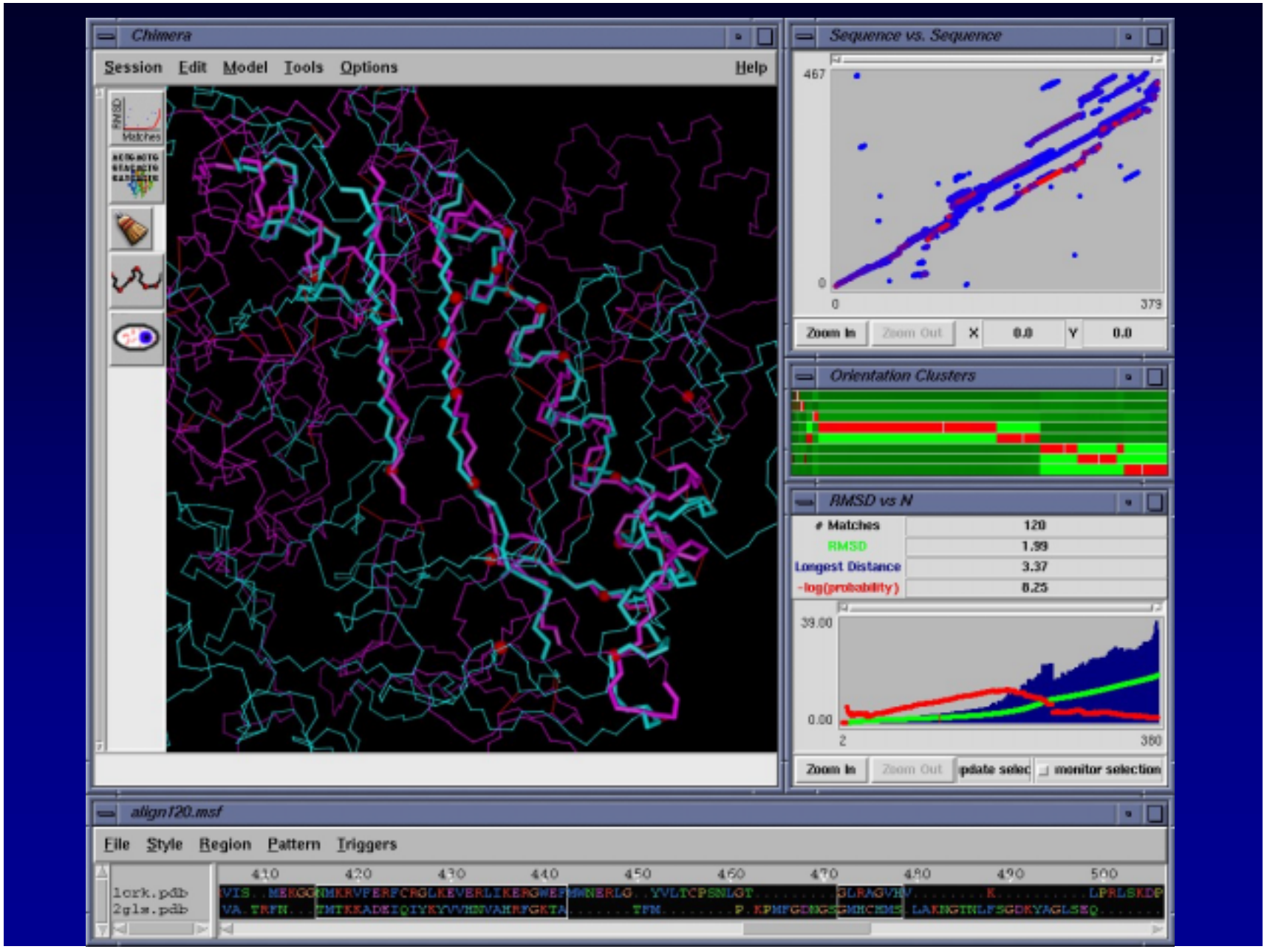
UCSF's Chimera

Molecular visualization system providing:

- Interactive manipulation of multiple molecular structures
- Real-time rendering of models in several formats
  - ball-and-stick, ribbons, molecular surfaces...
  - Takes advantage of available high-performance graphics hardware
- Support for non-molecular objects
  - points, vectors, spheres, cylinders, polygons...
- Both menu and command line modes of interaction
  - Command emulator for compatibility with MidasPlus
  - "Power users" prefer command line based system
- Extensible functionality without access to source code through a high-level, dynamically-loadable programming language (Python)
  - Allows ideas for new functionality to be quickly tested
- Use of standard APIs ensure portability to many platforms
  - Windows 98/NT/2000, Compaq Alpha, SGI, Linux, …


Chimera
Session Edit Model Tools Options Help
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1ork.pdb
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Research plan

Phased implementation approach

- 1:1
- 1:N
- N:N

Multiple testbed research projects

- Molecular Mechanisms of Mutagenesis and DNA Repair: Recognition of Damaged DNA
- Drug specificity of Dihydrofolate Reductase
- Structural Aspects of type 1 Collagen in imperfecta Osteogenesis
- Feedback to Chimera developers

Training at two levels

- active learning for local and remote Chimera users
- active learning of molecular recognition and drug design principles for biologists and chemists

Technologies employed

Chimera

- Collaboratory being implemented as extension to basic system

COTS desktop videoconferencing

- Prefer standards-based, platform independent tools (e.g. vic and rat)
- High quality audio imperative, low frame rate video just fine

Low-latency networking

- Initial session startup may require high bandwidth, but otherwise only modest bandwidth needs envisioned (this needs to be evaluated)
  - Internet 2?
  - Campus local area network?
  - DSL/Cable modem?

Networking issues

Parameters affecting network performance

- bandwidth
- latency
- delay variance
- connection quality
- multicast support
- quality-versus-price tradeoffs

Collaboratory data connection characteristics

- lower bandwidth requirements than videoconferencing (especially audio)
- need high reliability (I.e. low packet loss)
- bursts of activity will by typical

Project status

Funding began in August 1999

Project staffing has been a challenge

Design and initial implementation recently completed

- demonstration at Saturday afternoon session

Initial deployment to selected user research community during winter 2000

Testbed projects and evaluation to follow

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Additional information

- http://www.cgl.ucsf.edu/chimera