Symposium Honoring Mike Rowe and Jack Rush
Gaithersburg, 9 September 2005

Determination of Dynamic 3D Structures of Peptides in Membranes Using Diffraction and MD Simulations

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University of California at Irvine

CNBT Cold Neutrons for Biology and Technology

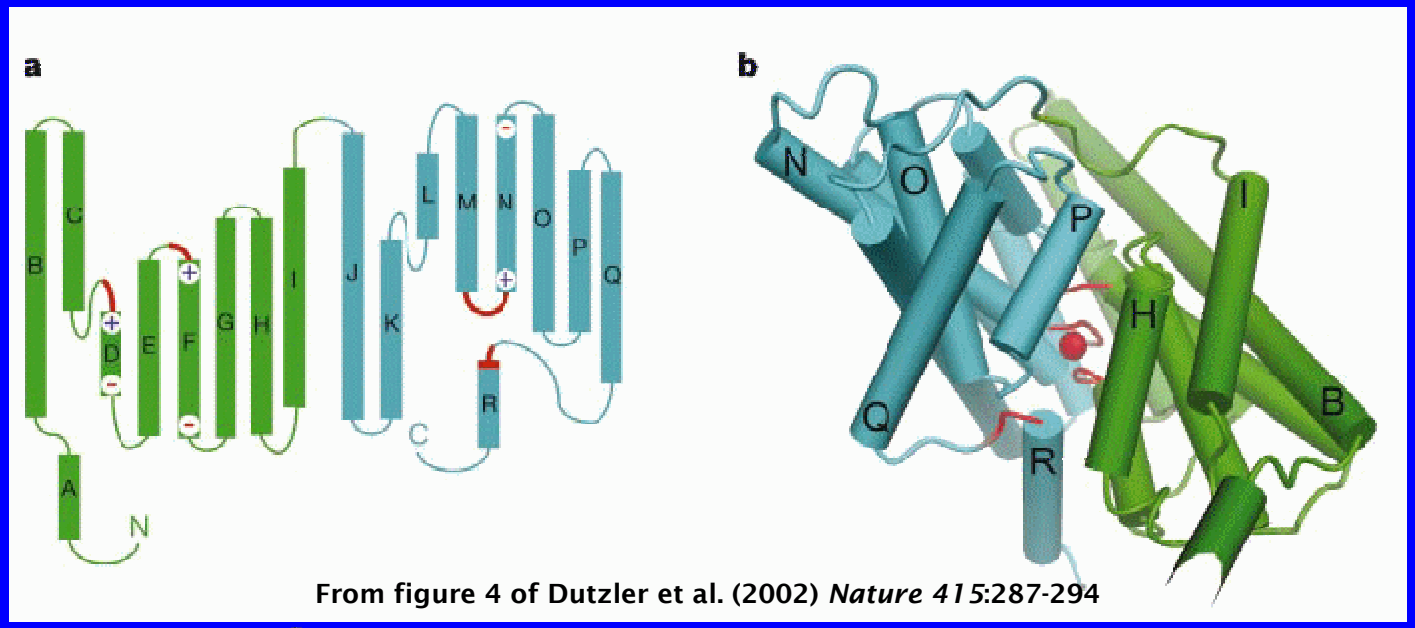
University of California at Irvine
TEMPO GROUP
Theory and Experiments in Membrane Protein Organization

LIPID MAPS

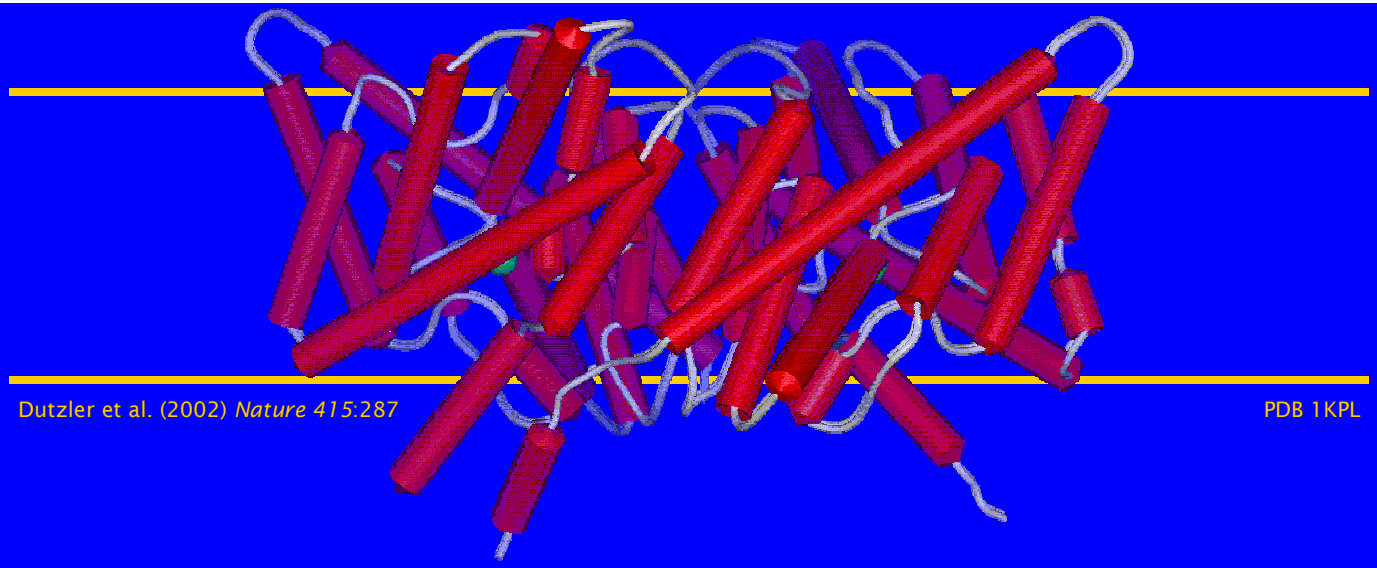
CNBT

Cold Neutrons for Biology and Technology

The Chloride Channel



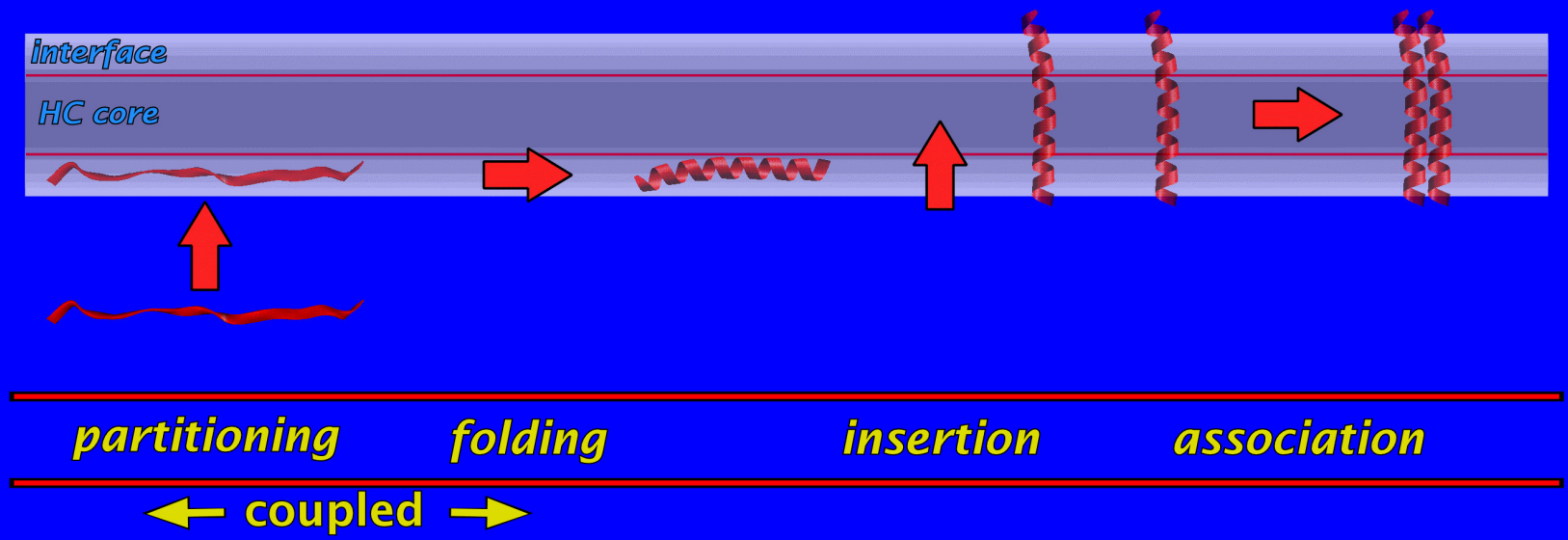
From figure 4 of Dutzler et al. (2002) *Nature 415*:287-294



Dutzler et al. (2002) *Nature 415*:287

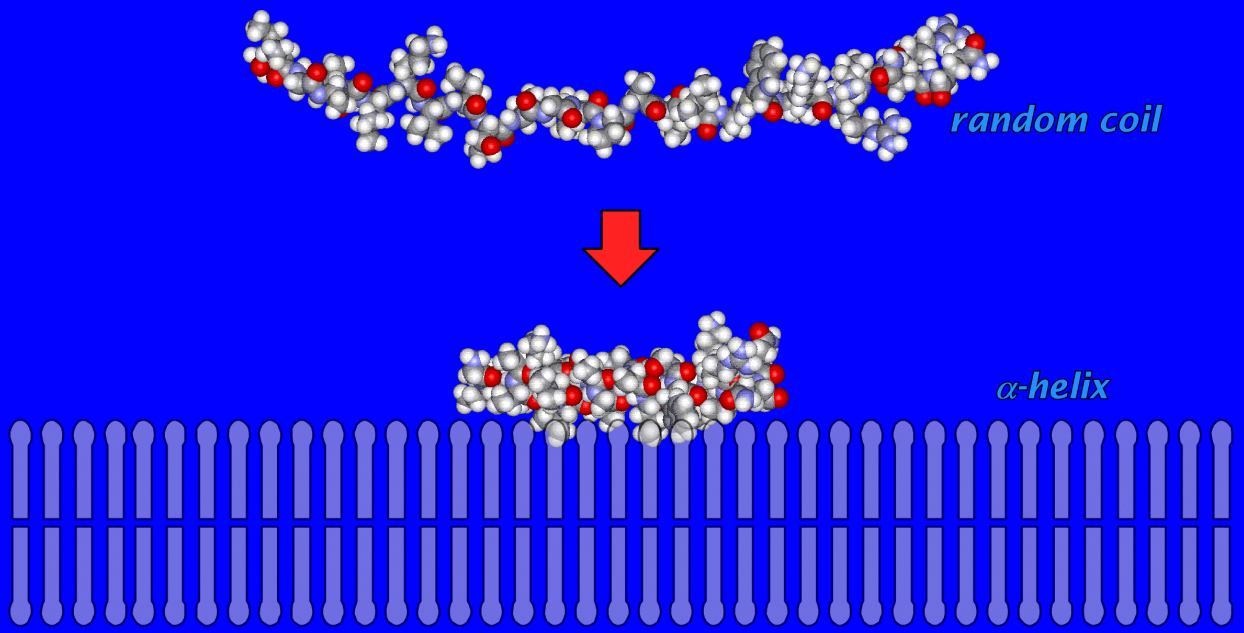
PDB 1KPL

Experiment-Based Whole-Residue Free Energy Scales



[Crit_thermo_vers2.cnv]

Melittin Partitioning



[MLT_folding_idea_1.CNV]

Structure of Fluid Lipid Bilayers:

Joint Refinement of X-ray and Neutron Data

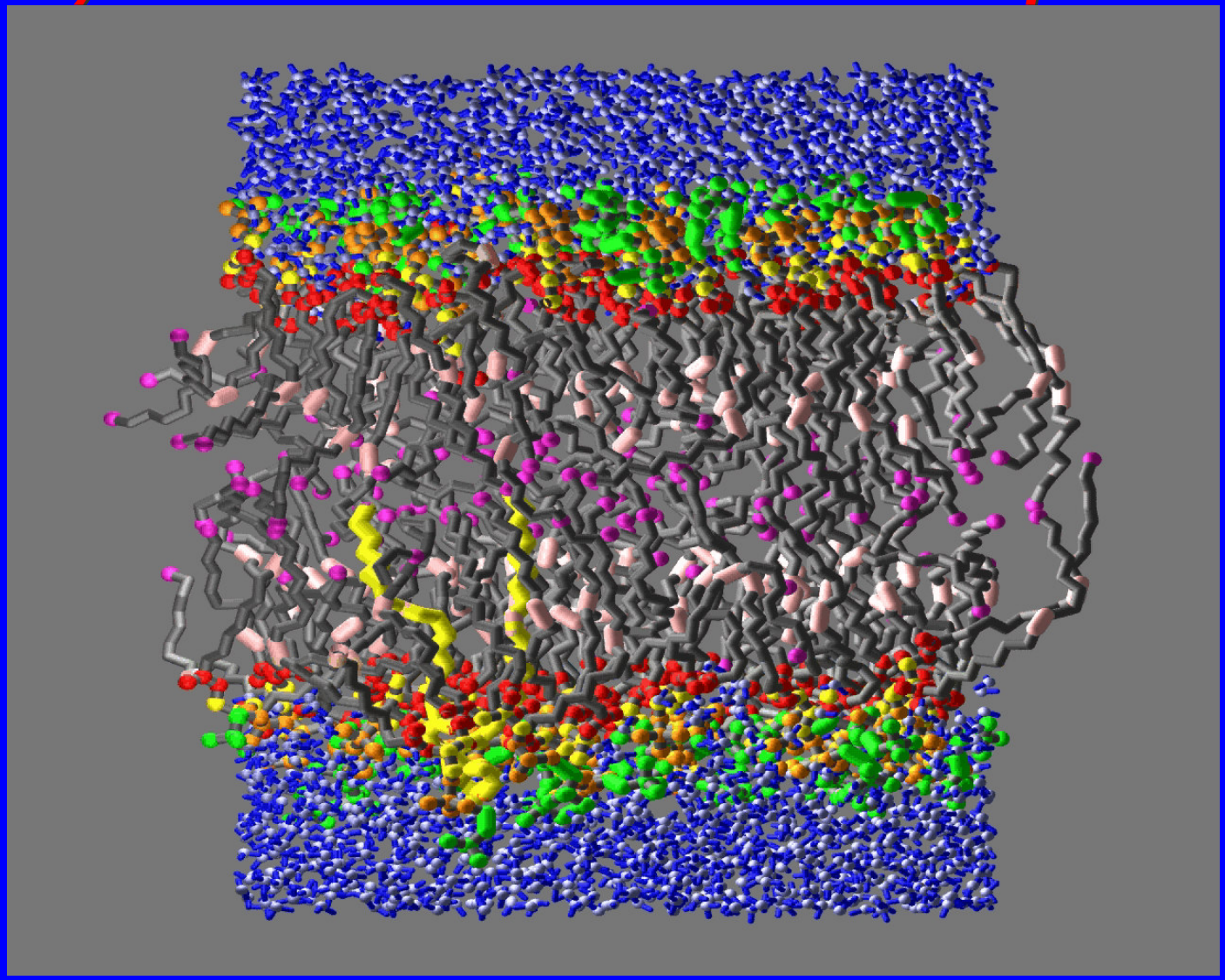
Disposition of Melittin in Bilayers:

Absolute-Scale Refinement

Dynamic 3D Models:

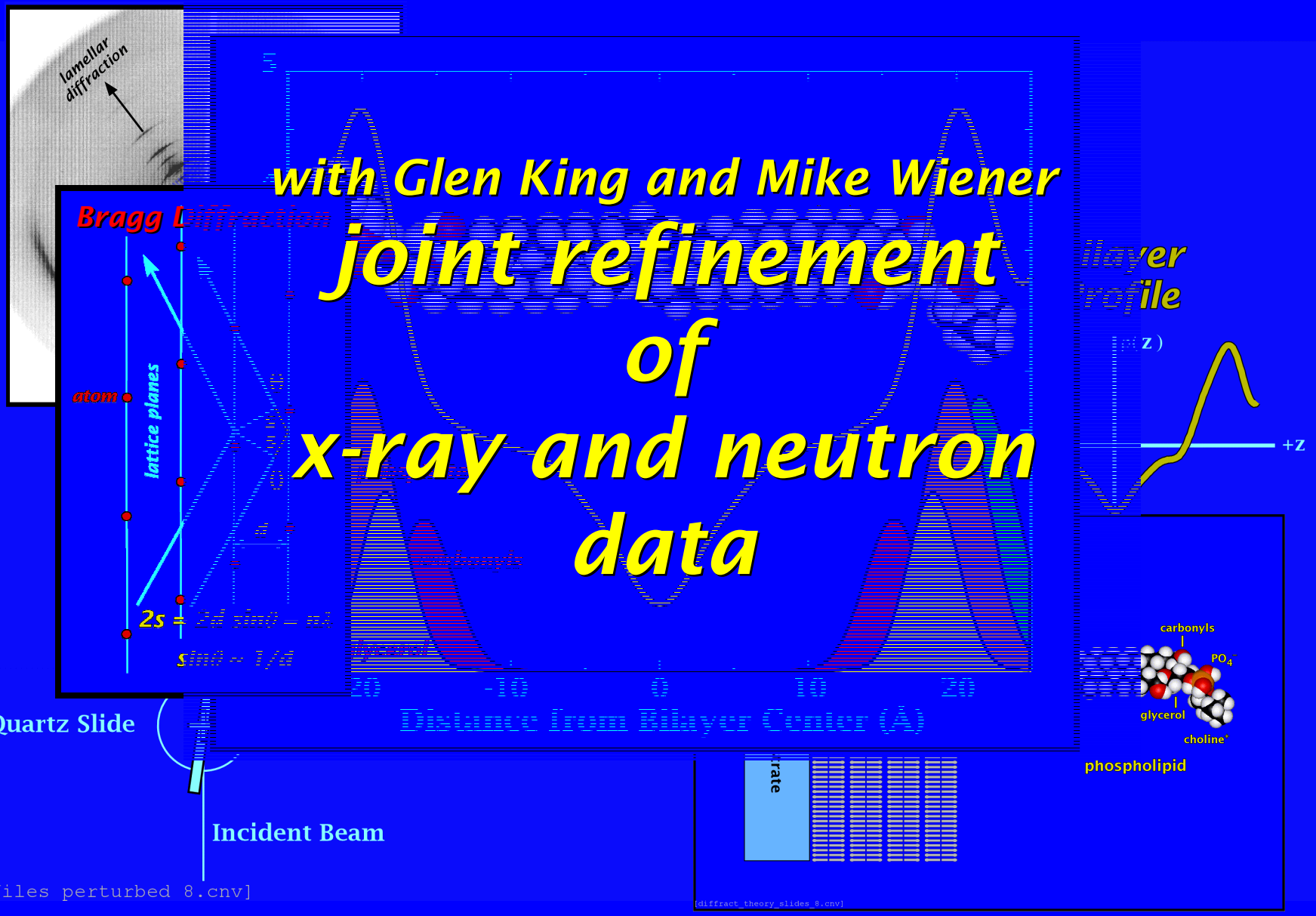
Restrained MD Simulations

The bilayer structure-determination problem….



….High Thermal Disorder

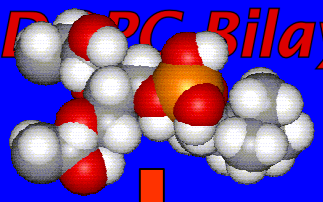
Principles of Lamellar Bilayer Diffraction



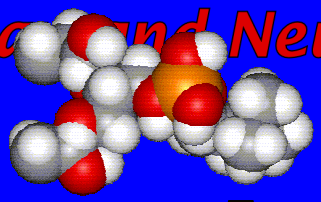
Joint Refinement of X-ray and Neutron Data

Wiener & White (1991) Biophys. J. 59:174-185

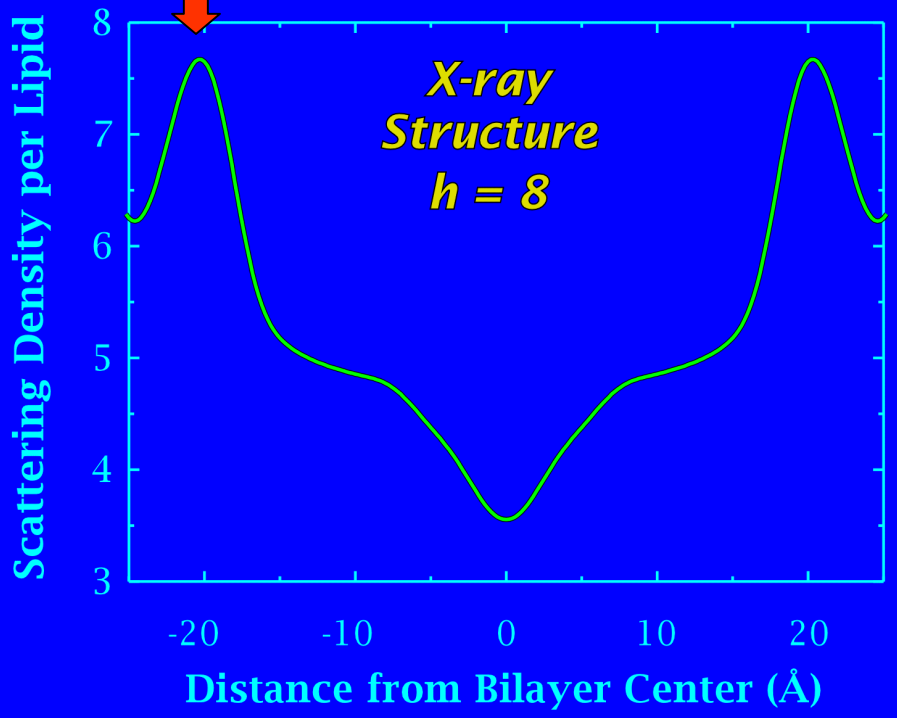
DMPC Bilayer Profiles by X-ray and Neutron Diffraction

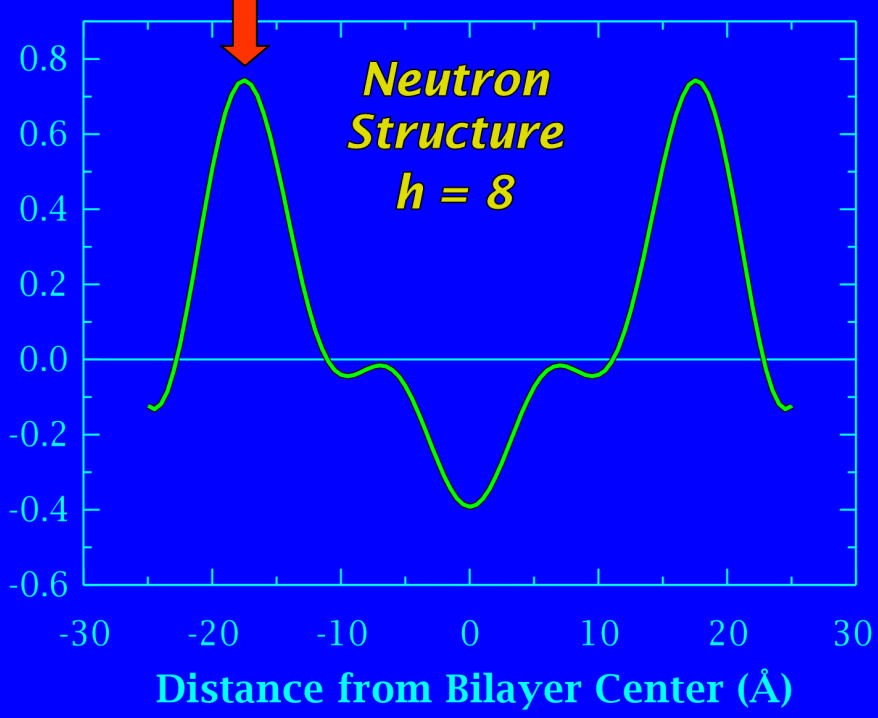


phosphate

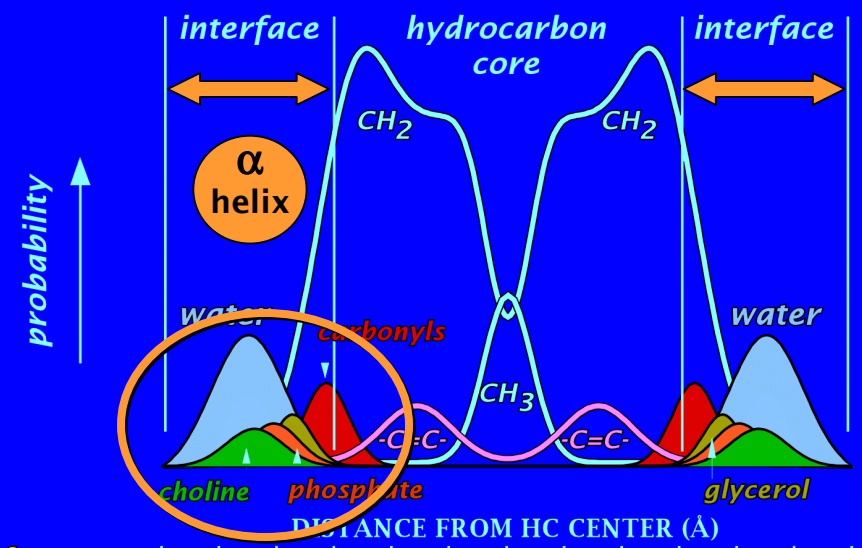


carbonyls



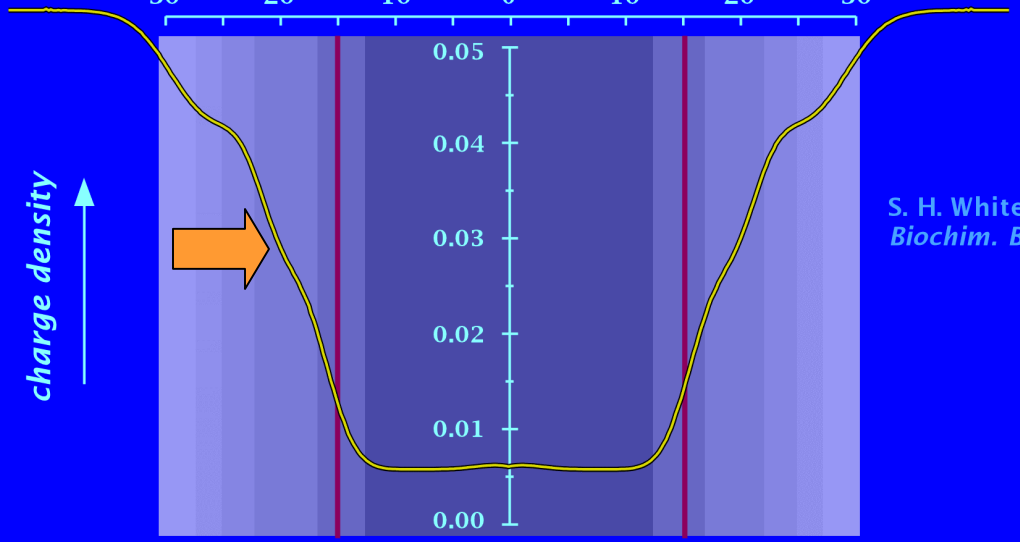


DOPC Structure Summary



M. C. Wiener & S. H. White (1992)
Biophys. J. 61:434-447

Bilayer Polarity Profile

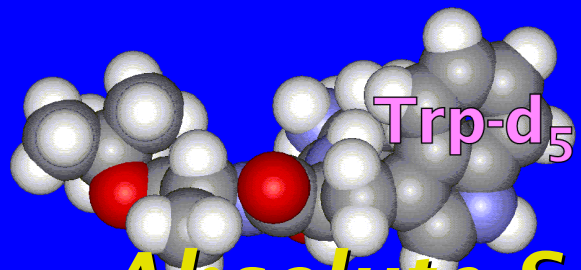


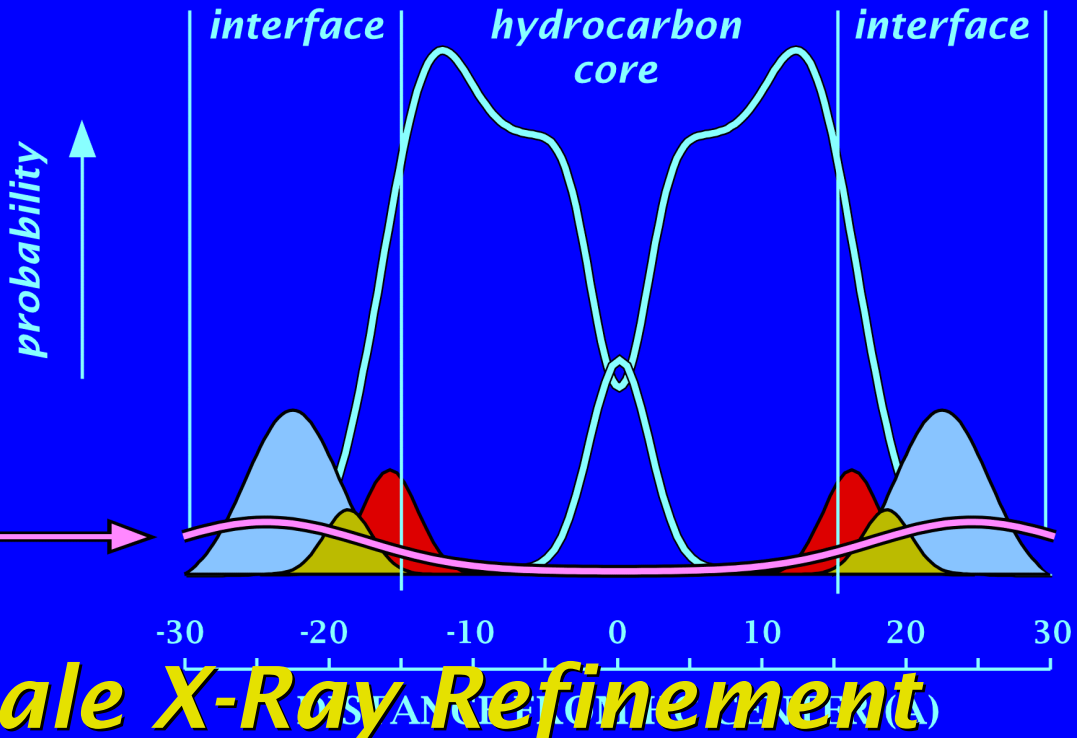
S. H. White & W. C. Wimley (1998)
Biochim. Biophys. Acta 1376:339-352

[profiles_perturbed_10.cnv]

Small Peptides Are Located in the Bilayer Interface

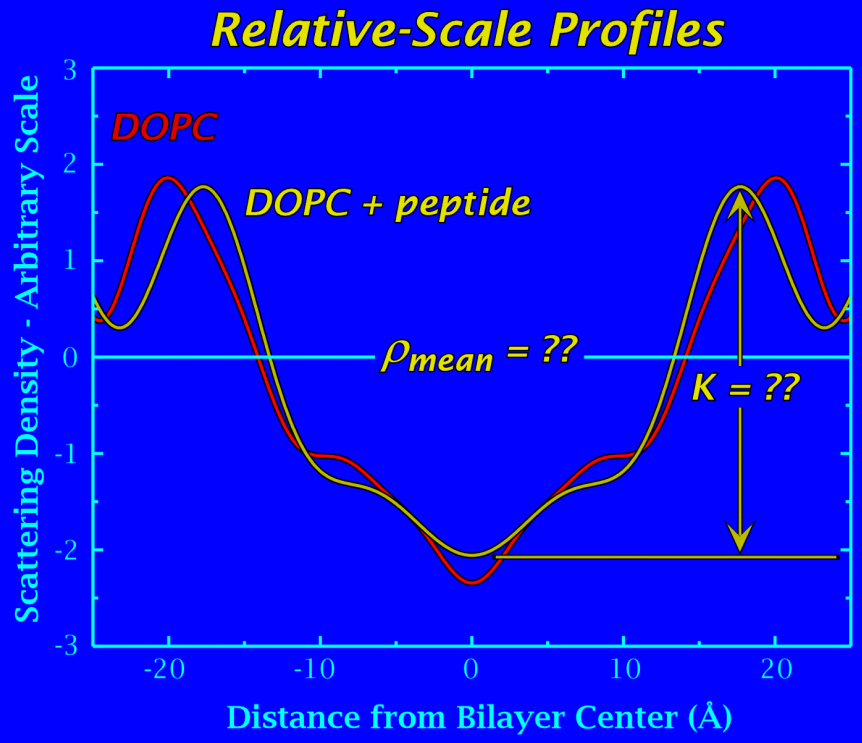
location of
Ala-Trp-Ala-O-*tert*-Butyl
determined by neutron diffraction
Jacobs & White (1989)
Biochemistry 28:3421





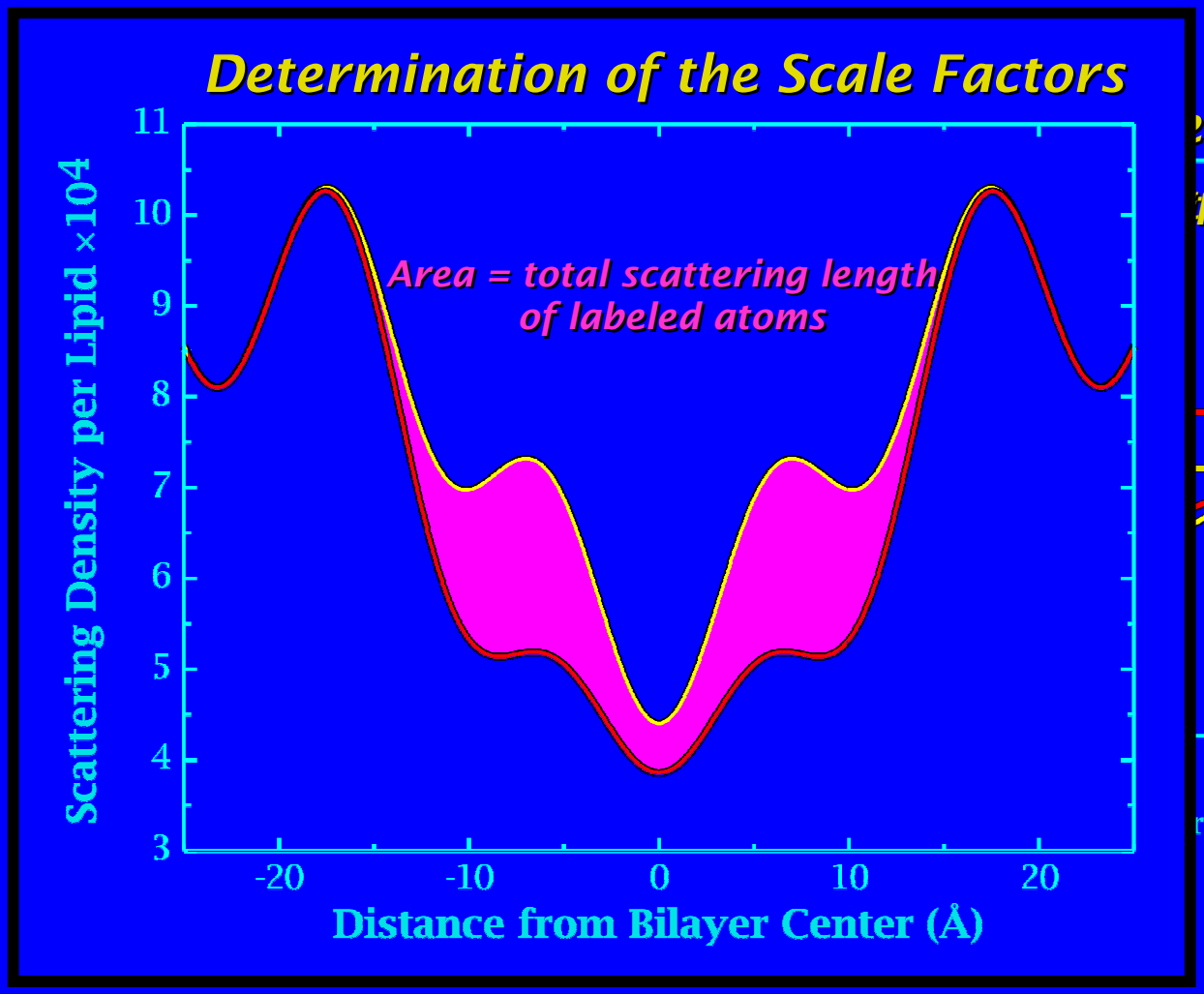
Absolute-Scale X-Ray Refinement

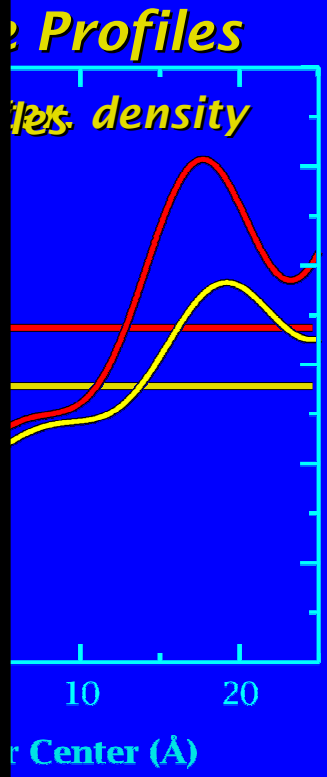
Finding Peptides in Bilayers:
The Importance of Absolute Scaling



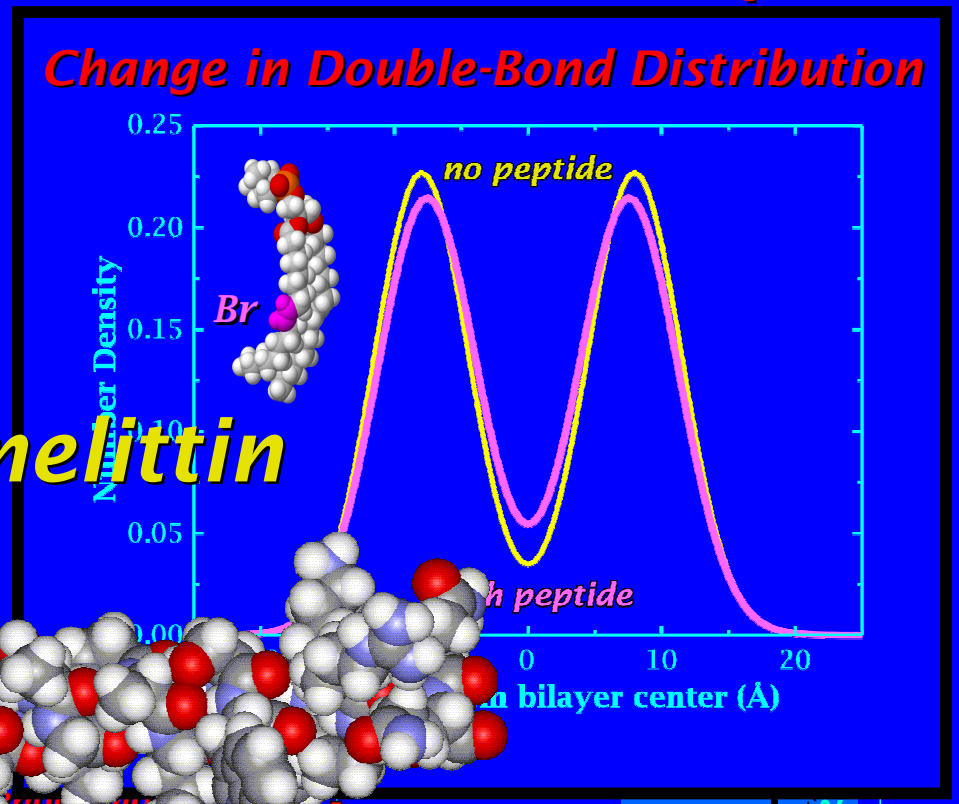
[profiles_perturbed_6.cnv]

Placing Membrane Profiles on the Absolute Scale

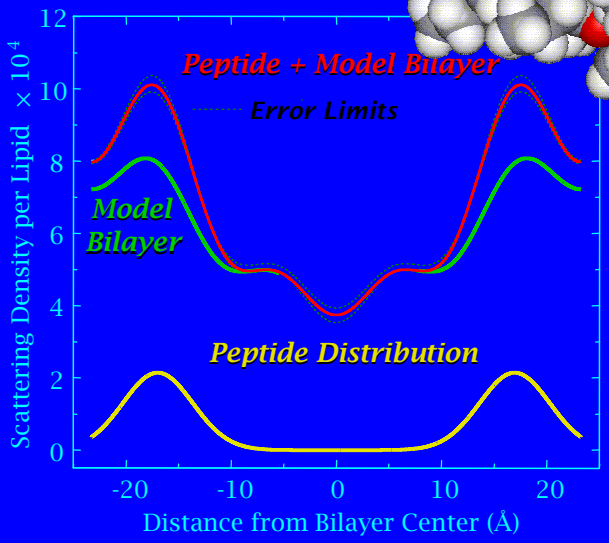




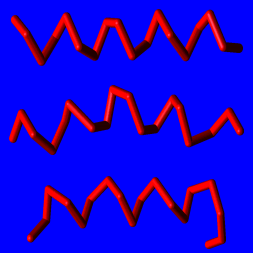
Absolute-Scale Structure Determination and Refinement

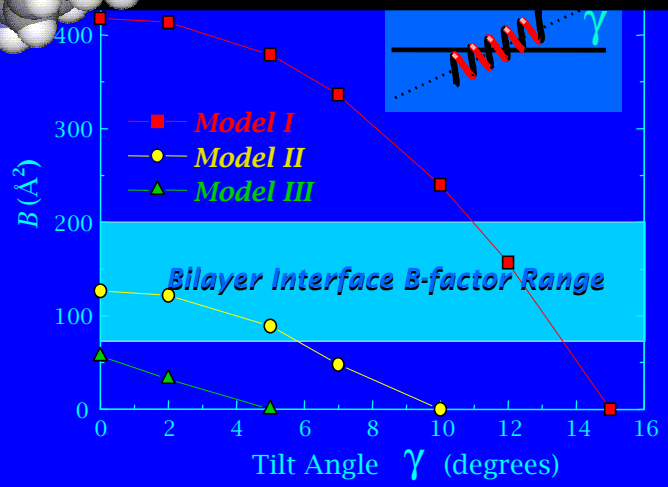


Step 3. Optimal Peptide D

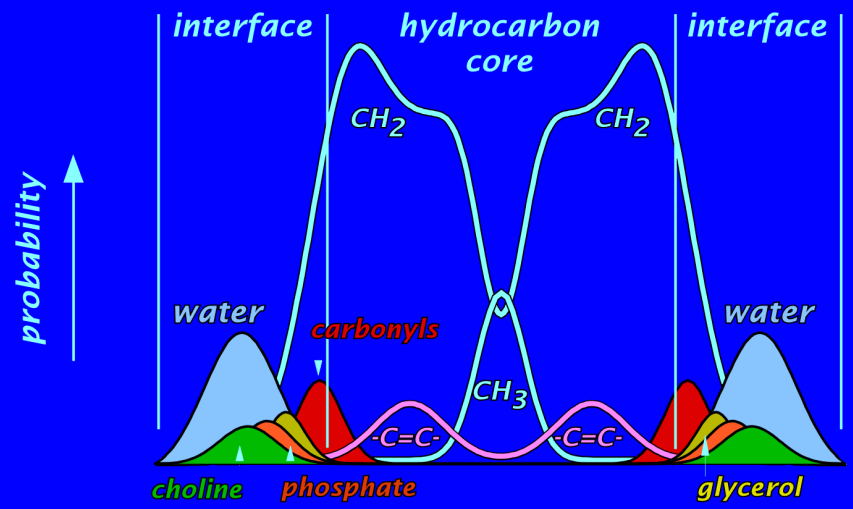


by Molecular Dynamics

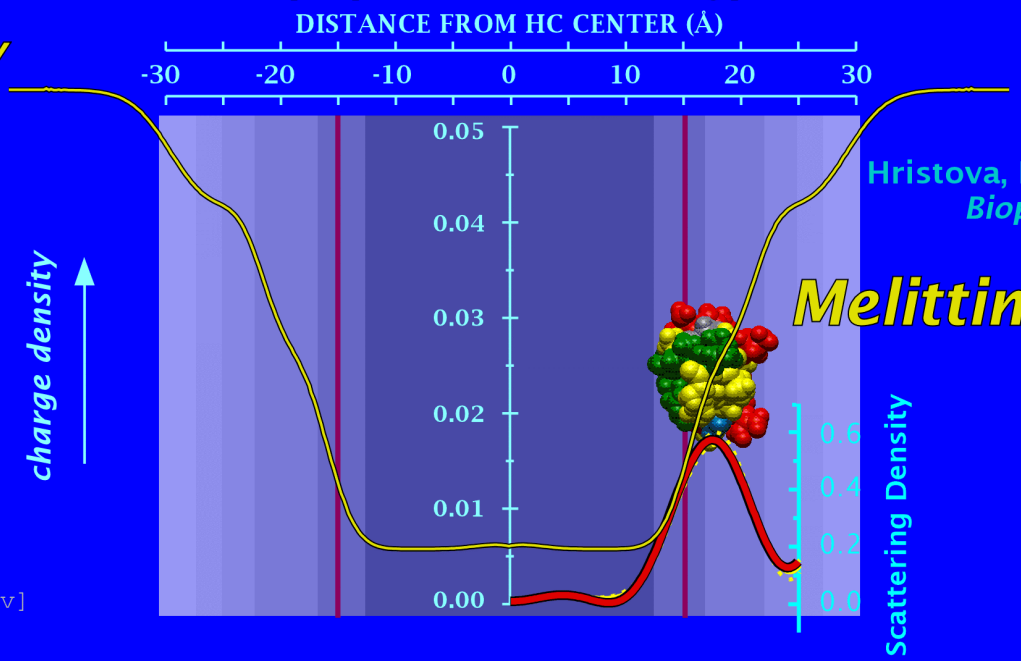




Disposition of Melittin in DOPC Bilayers



Bilayer Polarity Profile

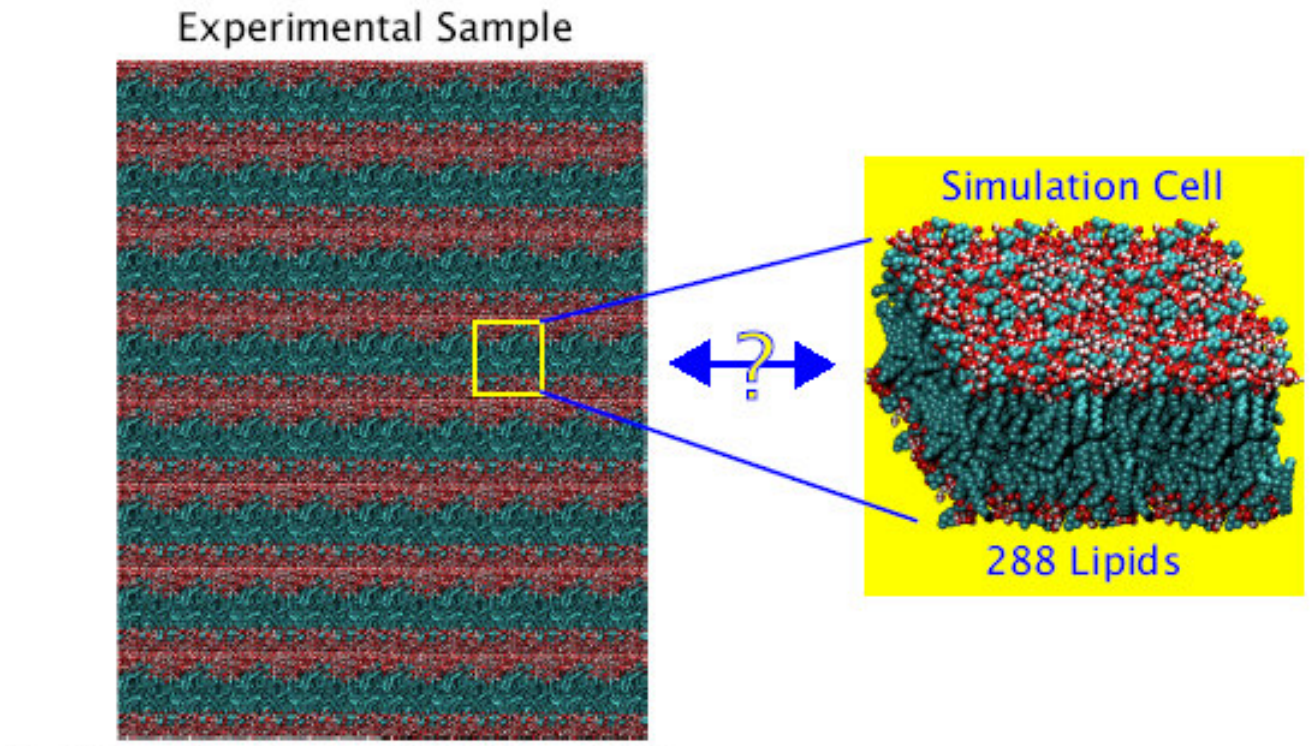


Hristova, Dempsey, & White (2001)
Biophys. J. 80:801-811

Melittin

[profiles_perturbed_14.cnv]

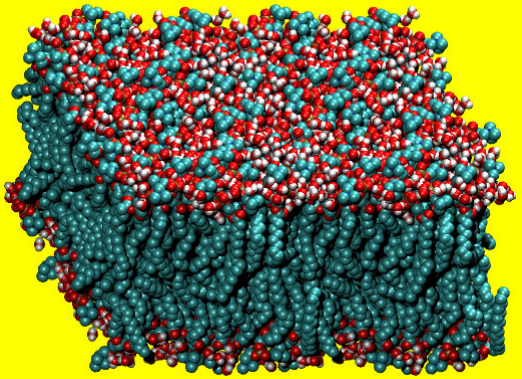
The Problem:
Combining Diffraction and MD Simulation Data



Transforming Between Real Space and Reciprocal Space

Compute Fourier Transform from Atomic Form Factors

$$F(s) = \sum_{\text{unit cell}} f_i(s) e^{2\pi i s r} \qquad f(s) = \sum_{j=1}^{4} a_j e^{-b_j [s/2]^2} + c$$



$$F_T(s) = \left\{ \sum_{n=0}^{N-1} e^{2\pi i s n d} \right\} F(s)$$

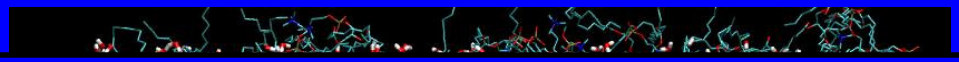
Product of Continuous Transform with the Interference Function samples Continuous Transform at intervals S=h/d

single bilayer

Fourier Transform

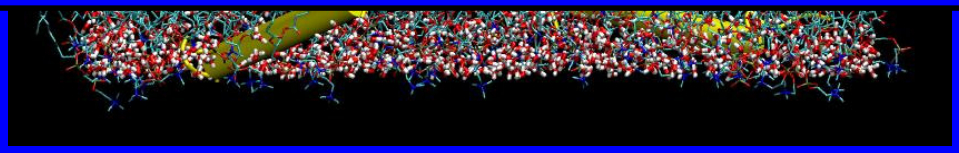
continuous transform

MD Simulation of Melittin in DOPC Bilayer



Apply Restraint Potentials to Double-Bonds and Water using x-ray Determined Positions and Widths

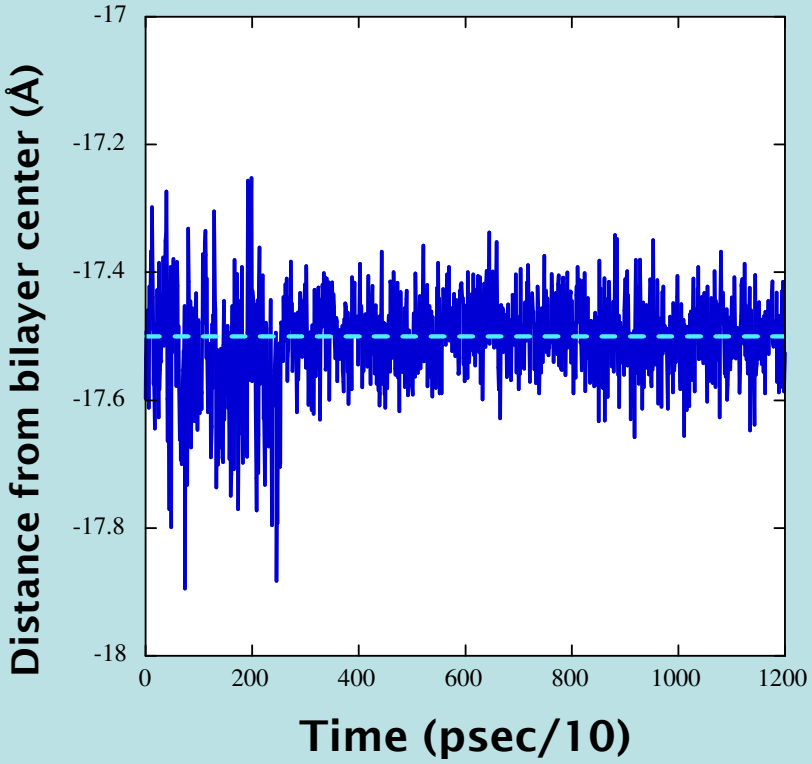
$$\phi(Z,\sigma) = K_Z(Z - Z^*)^2 + K_\sigma(\sigma - \sigma^*)^2$$

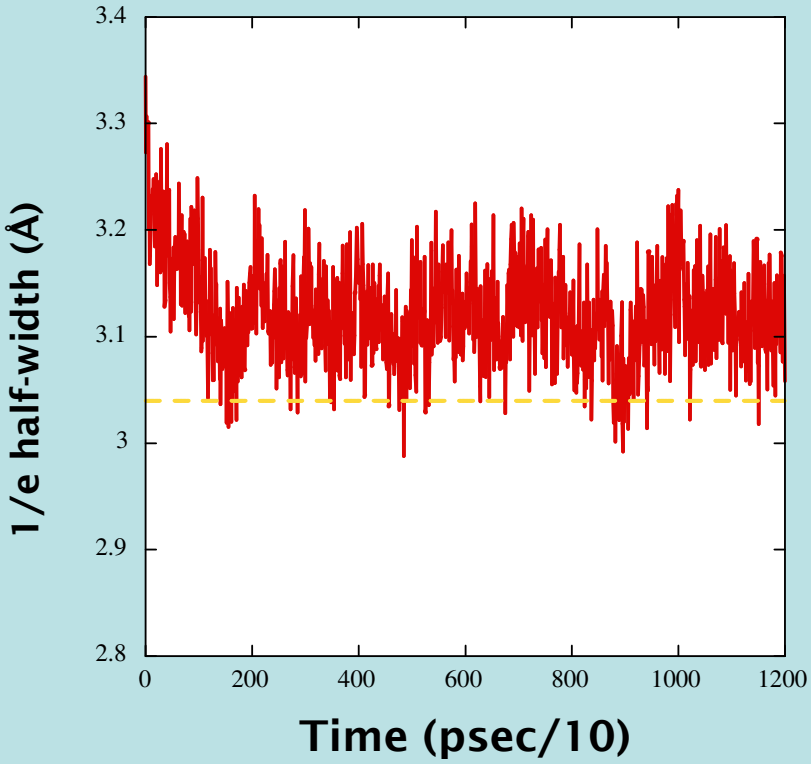


Trajectory of Simulation

Lower Leaflet

12 nsec simulation

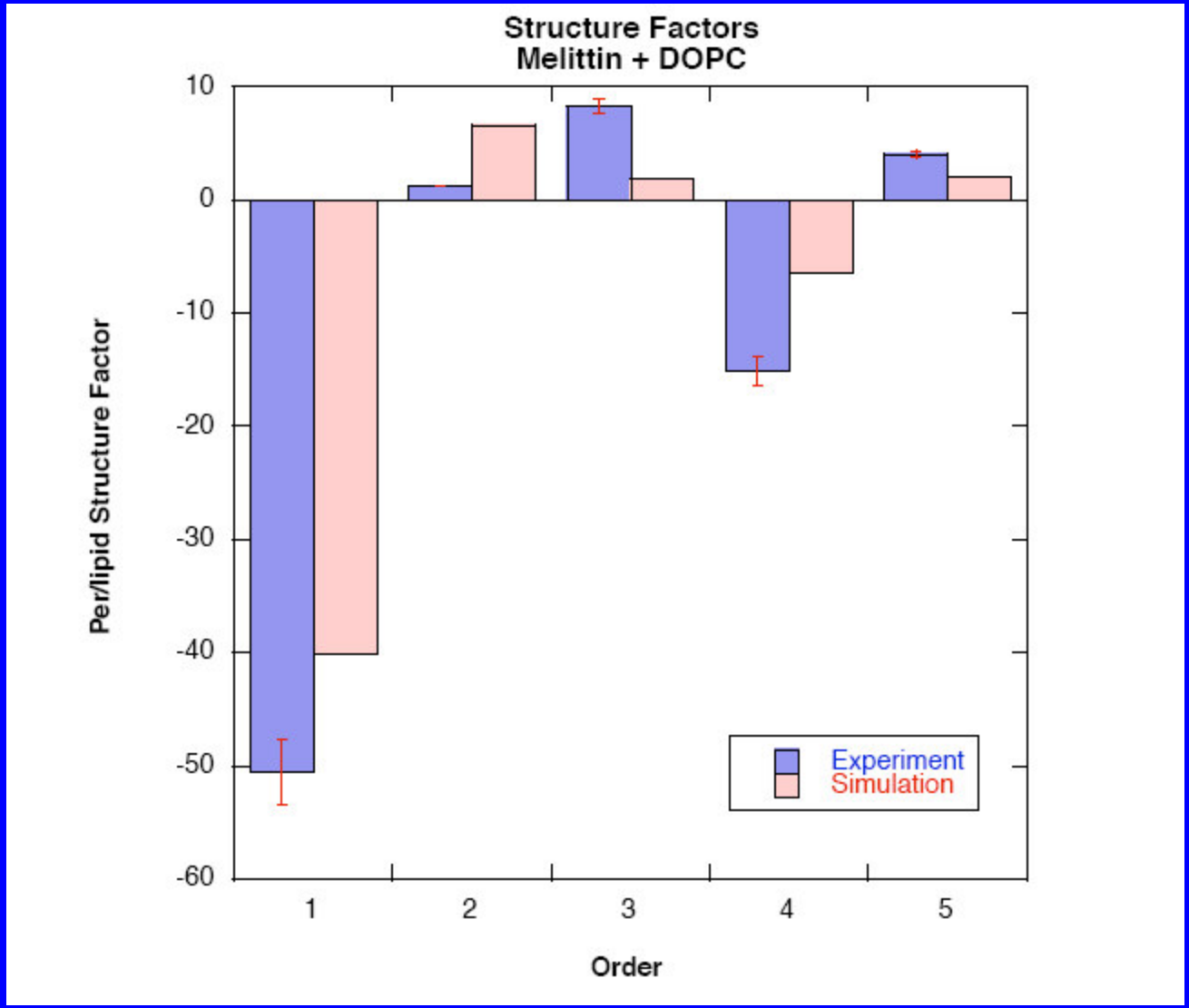




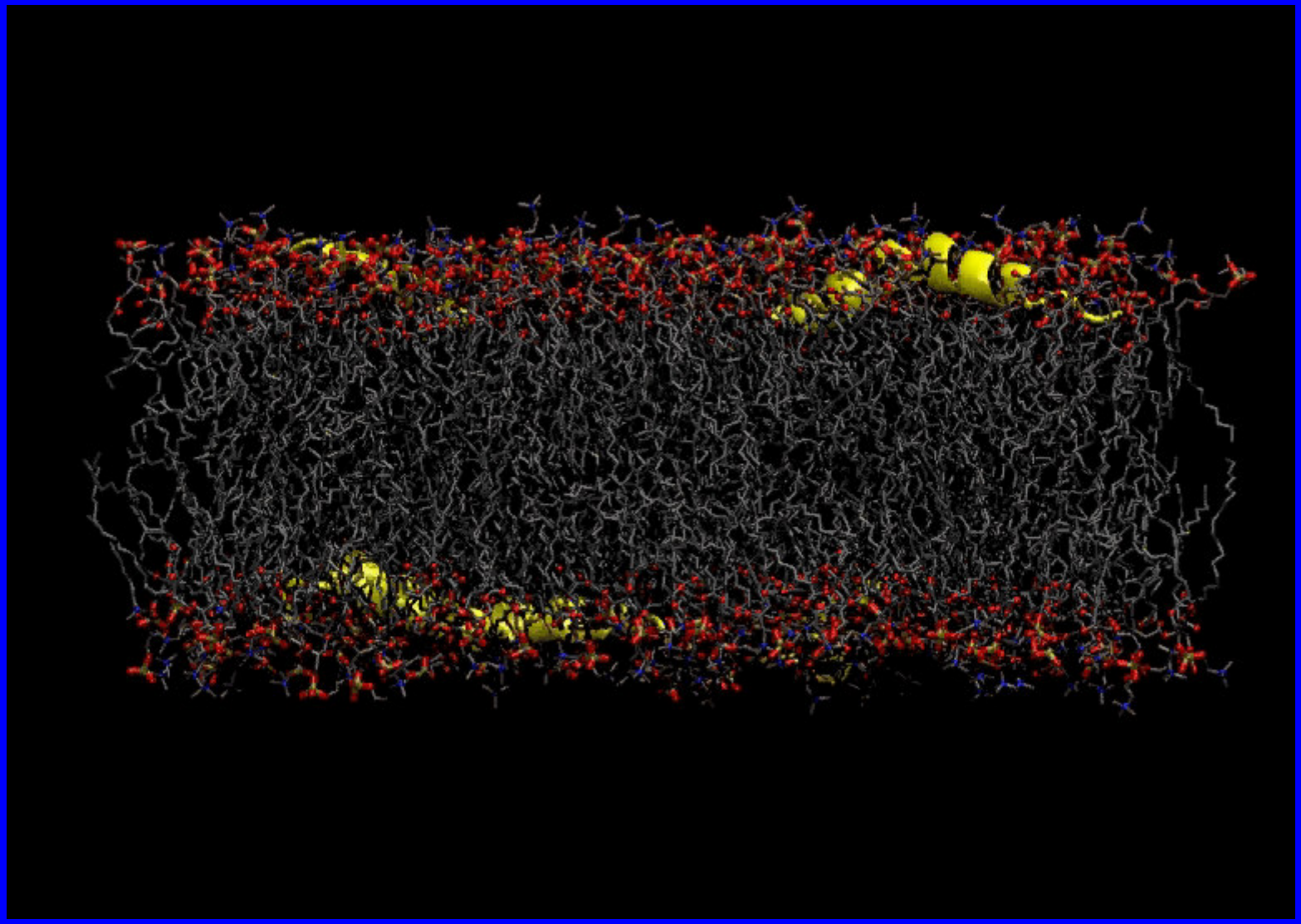
position

width

Comparison of Structure Factors



Melittin – the movie



Alex Ladokhin (Kansas University Med. Cntr.)

Michael Wiener (University of Virginia)

Kalina Hristova (Johns Hopkins)

Ryan Benz

Hirsh Nanda

Doug Tobias

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A Biotechnology Research Partnership supported by
NIH National Center for Research Resources

Neutron Jack

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Collaborating Partners

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Duke University

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Los Alamos National Laboratory

NIH (NIAAA)

.. ve

proteins in their native environment, including experiment-validated studies of dynamics

National Institute of Standards and Technology

NIST

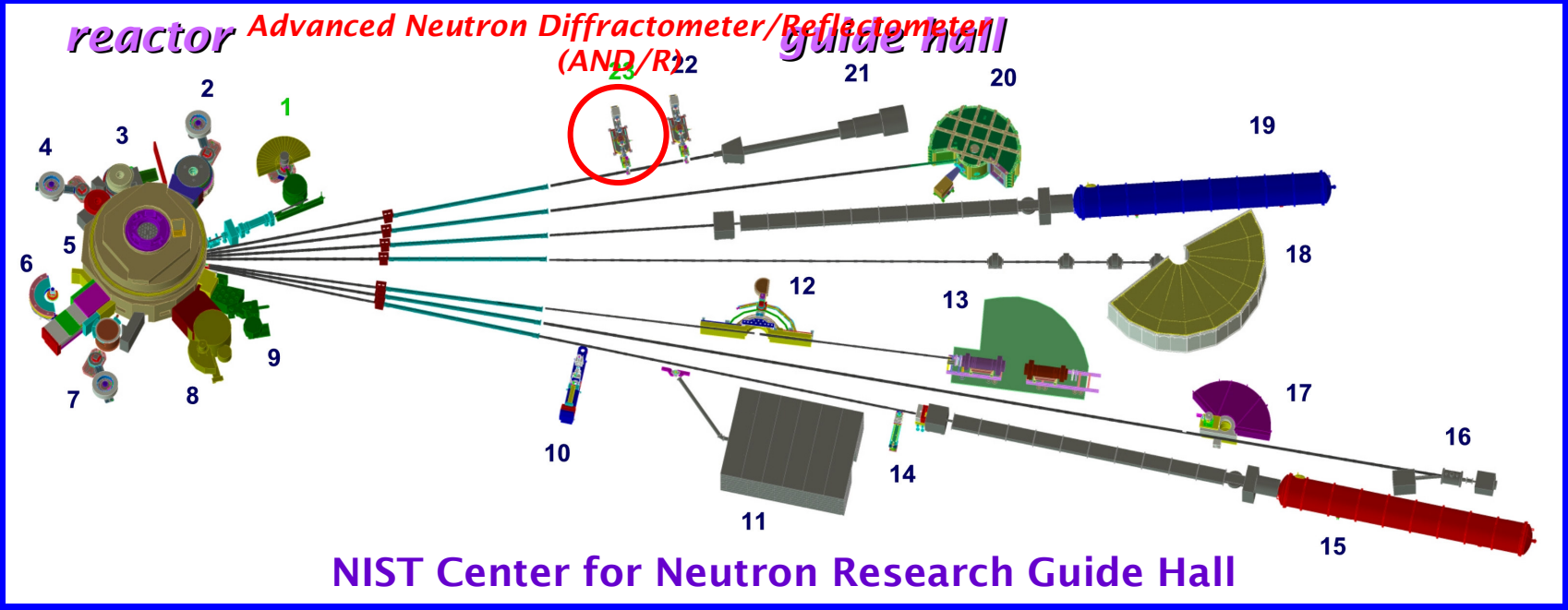
...working with industry to develop and apply technology, measurements and standards

NIST Center for Neutron Research

Gaithersburg, Maryland

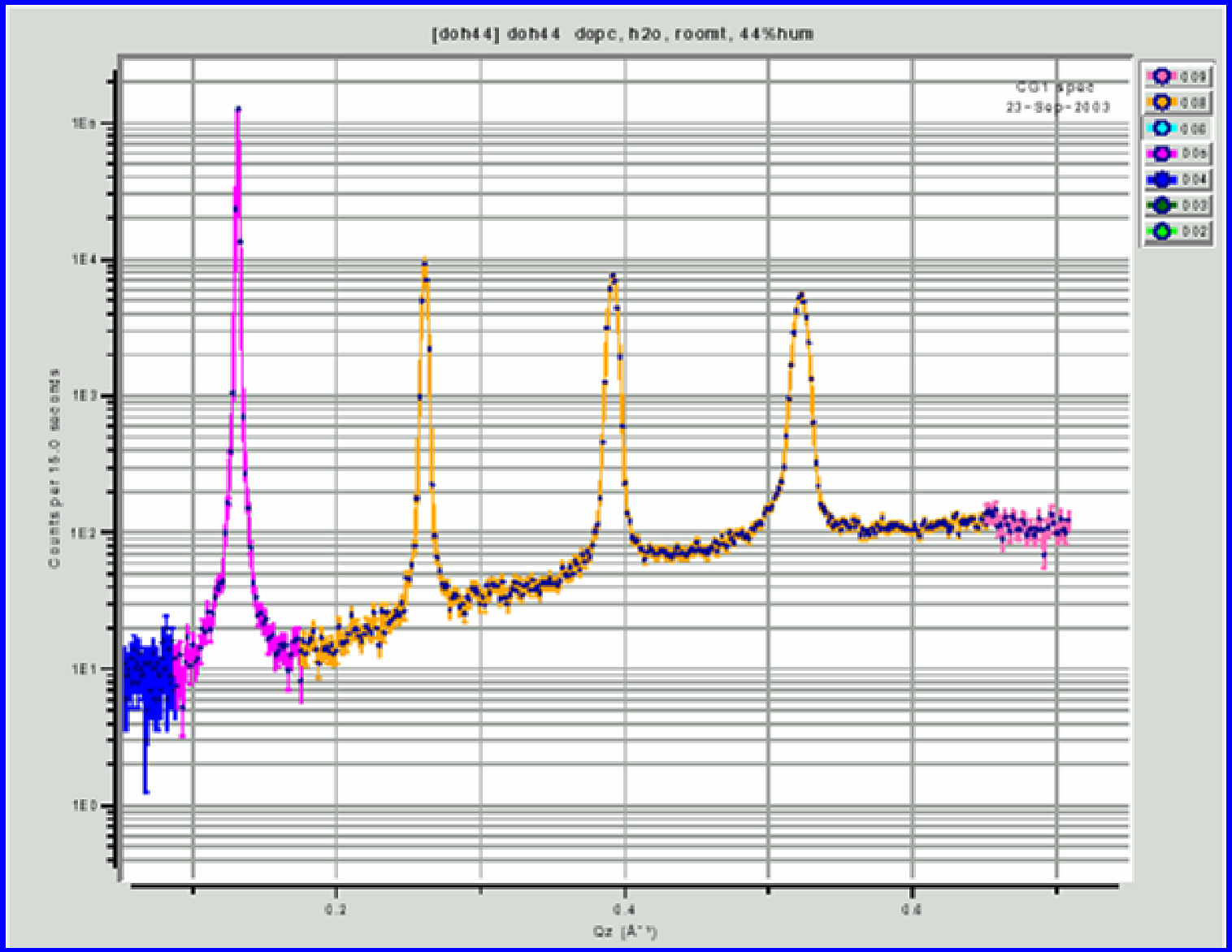
NIST Center for Neutron Research

Guide Hall and Instruments



AND/R: FIRST DATA!

DOPC Oriented Multilamellar Array, 44% RH



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Cold Neutrons for Biology and Technology

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RR14812

Facilities and Personnel

NCNR

AND/R + 10% of 30m SANS beam-time

64 node PC Cluster

Mathias Loesche (Johns Hopkins), Director

Chuck Majkrzak
Susan Krueger
Anne Plant
(Instrument Scientist)

Ella Mihailescu
Leonor Saiz
Ting Xu (2004)
(postdoc)

UC Irvine

64 node PC Cluster

Doug Tobias
Steve White (PI)

Francisco Castro-Roman
Ryan Benz
Jenifer Humphries
Alfredo Frietes

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Alfredo Frietes
Simon Jaud

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Huey Huang	Tom McIntosh	Kent Blasie	Mike Paulaitis	John Nagle