SANS and Modeling of Bio-macromolecular Complexes

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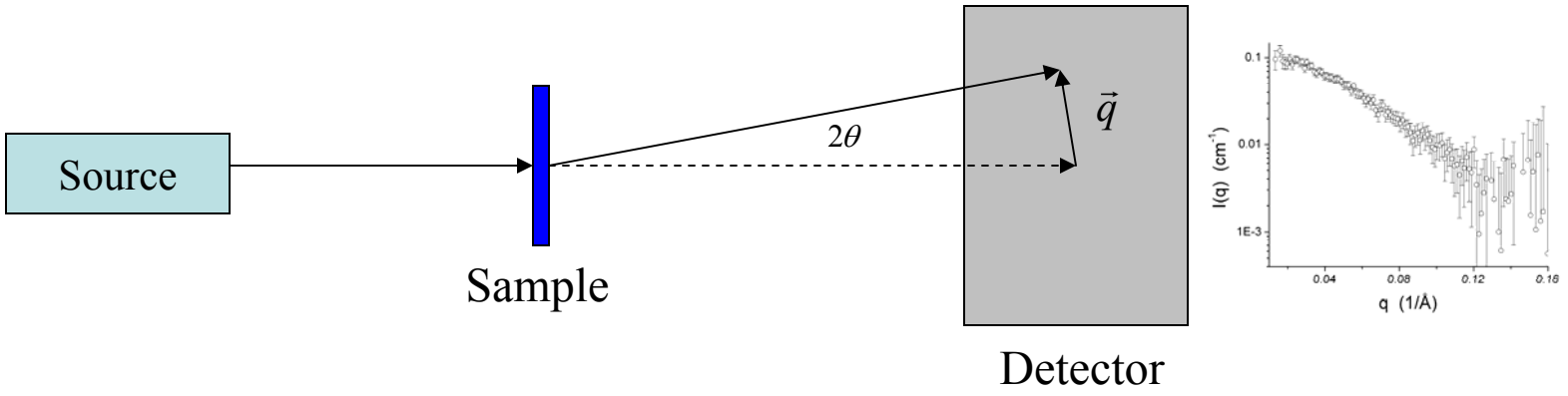
SANS is a powerful tool for studying Bio-macromolecular complexes

- Samples a large range of length scales
  - 5-2000 Å
- Samples are in dilute solution
- Directly complementary to SAXS



$$I(q) = \left| \left\langle \int_V (\rho(\vec{r}) - \rho_s) e^{-i\vec{q}\bullet\vec{r}} d^3 r \right\rangle \right|^2$$

$$|\vec{q}| = (4\pi \sin\theta)/\lambda$$

SANS benefits from the difference between the interaction of the neutron with hydrogen and deuterium

Atom	H	D	C	N	O	S
f_X, 10^{-12} cm	0.282	0.282	1.69	1.97	2.16	4.51
f_N, 10^{-12} cm	-0.374	0.667	0.665	0.940	0.580	0.285

- It is often possible to substitute deuterium for hydrogen with minimal impact on structure and function
- Bio-macromolecular complexes can often be dissolved in D2O and H2O/D2O mixtures
- The use of contrast variation provides additional information on the internal structures of complexes

Small-angle scattering provides information complementary to crystallography and NMR

- Does not provide structural information at the same level of detail as crystallography and NMR
- Provides size and shape information on macromolecular complexes and systems not amenable to other techniques
- Loss in information due to rotational averaging
  - 3D structure, but 1D data

Modeling of SAS data enables visualization of structure and interpretation of function

What kinds of modeling are available?

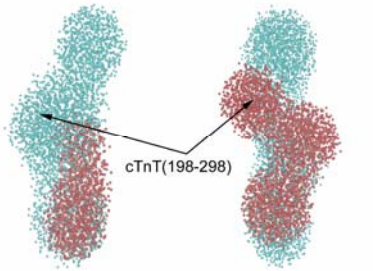
…and some authors…

- Spherical Harmonics
  - Svergun, Stuhrmann, Grossman, etc.
- Aggregates of Spheres
  - Svergun, Heller, Doniach, Chacón, etc.
- Sets of High-resolution Structures
  - Svergun, Heller, etc.
- Simple Shapes and Custom Approaches for Specific Problems
  - Henderson, Zhao, Gregurick, Heller, etc.

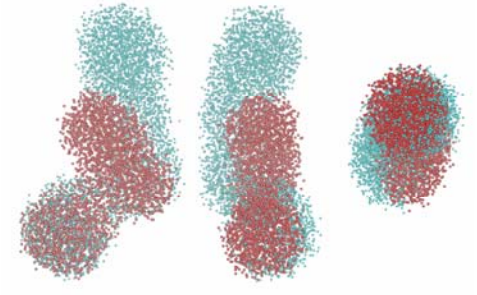
Creativity and time are the only real limits

Spherical Harmonic, Aggregate and Simple Shape Methods

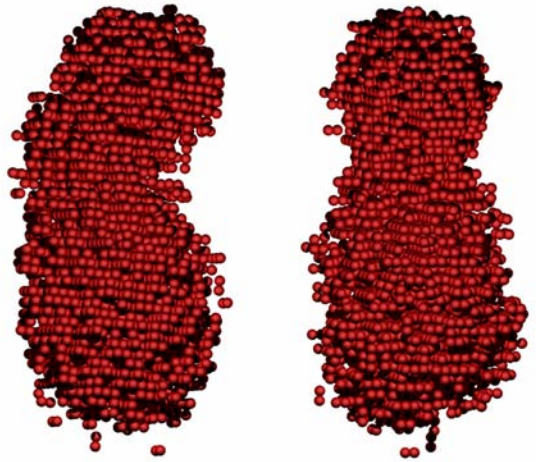
- No initial structural data exists of complete system
- Investigating conformational transitions



The location of Troponin T(198-298) was inferred using SANS with contrast variation



Bis-phosphorylation of Troponin I produces a bend in the structure.



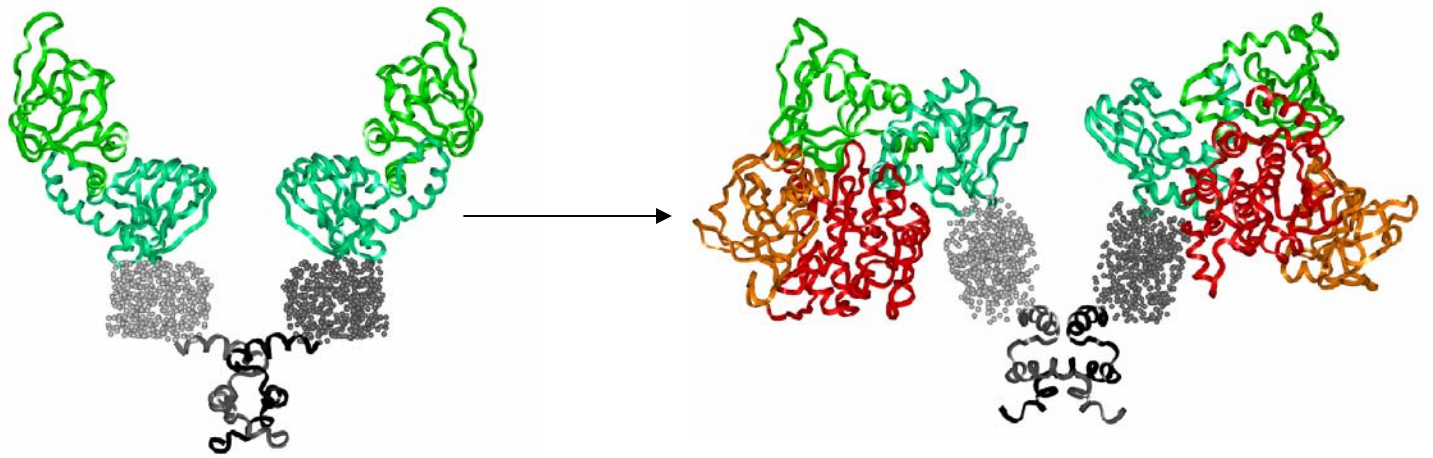
Models of human plasma vitronectin produced from SAXS data help visualize global conformation when only fragmentary structural information exists

Lynn, G. W., et al. (2005) *Biochemistry* **44**: 565-574.

Heller, W. T., et al. (2003) *Biochemistry* **42**: 7790-7800.

Modeling Building from Sets of High-resolution structures

- Structures of subunits of a complex have been determined by crystallography or NMR
- Mechanism for filling in missing sequences



The conformation of the regulatory dimer of protein kinase A changes in response to binding of the catalytic subunits

Heller, W. T., et al. (2004) *J. Biol. Chem.* **279**: 19084-19090.

Vigil, D., et al. (2004) *J. Mol. Biol.* **337**: 1183-1194.

The goal is to construct biologically relevant models using scattering data

Modeling is a core capability of the Center for Structural Molecular Biology and an integral part of our support of neutron scattering at ORNL

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