BCHM669A   Methods for Biomolecular Structure Determination in Solution
FALL 2023

Course meets in Biomolecular Sciences Bldg, Rm 2118, Mo/Wed 11:00am-12:15pm

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This graduate level course is designed as an introduction to modern methods for determining structures of biological macromolecules in solution. It covers both low-resolution methods, such as small-angle X-ray and neutron scattering (SAXS, SANS), and high-resolution method which is NMR. The course will introduce theoretical background of these methods and discuss their applications to biological problems, including determination of the structure and dynamics of biomacromolecules and characterization of macromolecular interactions. The course covers fundamentals of nuclear magnetic resonance (NMR), including quantum-mechanical treatment, vector models, and product operator formalism. The students will learn NMR pulse sequence design (including product operator formalism), principles of multidimensional NMR, methods for protein signal assignment and structure calculation, studies of protein-ligand interactions, and NMR approaches to protein dynamics.

Course prerequisites: calculus, undergraduate level biochemistry and physical chemistry.

Topics Wish List (subtopics not necessarily in this order)**:**
1. *Small-Angle X-ray and Neutron Scattering*:
     general principles of scattering, scattering in solution, Debye formula, Guinier plot, pair distribution function, relationship between molecular structure and scattering profile, small-angle X-ray scattering (SAXS) and applications to biological macromolecules, small-angle neutron scattering (SANS) and applications to biological macromolecules and their complexes, contrast variation.
2. *Nuclear Magnetic Resonance, basics*:
     general principles of NMR spectroscopy, classical/vector description, Bloch equations, chemical shift, quantum mechanical description of NMR spectroscopy, spin-Hamiltonian, eigenstates, transitions, product operator formalism and how to use it, understanding NMR pulse sequences.
3. *Multidimensional NMR Spectroscopy*:
     From 1-D to 2-D to n-D, homonuclear coherence transfer and mixing: COSY, NOESY, TOCSY; heteronuclear coherence transfer: INEPT, HSQC, HMQC, TROSY.
4. *Experimental aspects of NMR*:
     quadrature detection, sign discrimination, coherence selection, phase cycling, gradients; data processing: window function, zero-filling, linear prediction, isotope filtering/editing; solvent-signal suppression; computer simulations of the outcome of NMR experiments.
5. *NMR for biomolecular structure determination*:
     NOEs, J-couplings, H-bonding; spin system assignment, NOESY signal assignment, triple-resonance methods for spin system typing, sequential assignment; 2° structure prediction (J-couplings, Karplus equation, H-D exchange, CSI); from NOEs to structure, example of structure assignment and calculation.

6. *NMR for protein dynamics studies:*
   nuclear spin relaxation as a unique tool to study biomolecular dynamics; overall and internal motions.
7. *Additional NMR methods for structure determination*:
   long-range orientational constraints from molecular alignment (residual dipolar couplings) and anisotropic rotational diffusion, paramagnetic effects (relaxation enhancement, pseudo-contact shifts), CSA tensors.
8. *NMR methods to study protein-ligand interactions*:
   mapping interaction interfaces, from fast to slow exchange, determining binding affinities and stoichiometries.
9. Fluorescence Resonance Energy Transfer (FRET) and Electron Paramagnetic Resonance-based (DEER) methods for distance measurements.

Textbooks:
1. M. Levitt, Spin Dynamics: basics of nuclear magnetic resonance, Wiley, 2001
2. G. Rule, T. K. Hitchens, Fundamentals of Protein NMR Spectroscopy, Springer, 2005
3. Cavanagh et al., Protein NMR Spectroscopy. Academic Press, 1996
4. F. Van de Ven, Multidimensional NMR in Liquids, Wiley-VCH.

Grading:
Homework reading and problems (not graded) will be assigned during the semester. Students will be given four major midterm projects that will be due in class on the assigned dates. The scores on all four projects will be added, and the final grades will be based on the total score. Contributions to the total grade:

Project #1	25%
Project #2	25%
Project #3	25%
Project #4	25%

You will be guaranteed an A if your total score is above 85% and a B if it is above 60% of the maximum possible total score.

Academic integrity. Students are expected to observe the University's *Code of Academic Integrity* (**http://www.president.umd.edu/policies/iii100a.html**). Cheating on the exams or projects is not acceptable and will be met with zero tolerance. All work submitted for grading in this course (i.e. examinations and homework projects) must be the original work of the student whose name is on the work.

This syllabus was updated on 08/27/2023.