Full STEM Ahead Long Island: Structural Biology and Drug Discovery

Resources for Your Classroom

Background: The field of structural biology requires expertise in the areas of physics, chemistry, biochemistry, molecular biology, and computational science. The structural biologist plays an important role in the understanding of how molecules are built. Using a variety of imaging techniques, the structural biologist views three-dimensional shapes of molecules to learn how they function and interact. Applications could lead to the design of new medicines and treatments of diseases.

There are different tools and techniques that scientists use to study cells, viruses, and molecules, such as proteins. To study a protein, first it is put into a chemical solution that forces it to assemble into a crystal lattice. Then, the protein crystal is imaged with Cryo-electron microscopy (Cryo-EM) or X-ray crystallography, imaging techniques performed at local research laboratories, Cold Spring Harbor Laboratory and Brookhaven National Laboratory. Scientists analyze the data using computer modeling to create images of their samples and study native proteins in their natural folded state with structure and function intact, or sometimes mutant proteins.

Photon sciences at Brookhaven National Laboratory is led by the National Synchrotron Light Source II (NSLS-II). The NSLS-II provides world-leading capabilities for X-ray imaging and high-resolution energy analysis. This user facility is open to users including academia, industry and local students.

Careers in structural biology include x-ray crystallographers, physicists, chemists, biochemists, molecular biologists, computational scientists, engineers and technicians.

Objective: Introduce students to the field of structural biology and the techniques and tools they use to determine shape and function of biological molecules and how changes to the structure affects their function. This has implications for the discovery of new drugs.

Vocabulary:

Structural biology	Protein	X-ray crystallography	Synchrotron
Structure	Hydrophobic	Hydrophilic	Backbone
Alpha helix	Beta sheet	Amino acids	Cryo-electron microscopy (Cryo-EM)

Procedure:

Introduction

Proteins are large complex molecules that play many critical roles in the body. They are extremely diverse in terms of size, composition and function. The U.S. National Library of Medicine provides an introduction to proteins which can be accessed here: What are proteins and what to they

do?. There are four different levels of protein structures- primary, secondary, tertiary and quaternary. The primary structure is the sequence of amino acids in the protein. Secondary structure refers to the alpha helix and beta sheets. The tertiary structure includes the 3-D shape of entire protein, such as the disulfide bridges and electrostatic bonds. All proteins have primary, secondary and tertiary structures. Only some proteins have quaternary structure, which is the arrangement of multiple protein subunits. Images of these structures can be found here: Protein Structures.

Build a Protein Model

To become familiar with the fundamentals of protein structure, make a model. Using the 3-D Molecular Designs Protein Folding activity as a guide, begin by gathering materials you have available in your home or classroom. If you don't have a toober available, any rigid yet bendable material will do, such as a pipe cleaner, heavy gauge wire, or wired-ribbon. Next, as a substitute for thumb tacks, try beads, yarn, or markers. You'll need five different colors of each to represent amino acids.

Foldit

The function of proteins is highly dependent on the shape of the particular protein (structure determines function). After solving protein structures, scientists looks for other molecules that will bind to the protein and alter it's function. Foldit, a website where students can solve puzzles for science, allows students and community to test different structures and molecules. Go to Foldit where we will start with the basic protein structures. The Science Behind Foldit will give users a better understanding how the game contributes to science; it can be found here: The Science Behind Foldit. This webpage also lists a number of publications that have been produced from Foldit.

Once you reach the homepage, head to the right hand side and click on 'Are you new to Foldit? Click here' link. Foldit offers options for Windows, Mac and Linux based computer systems. After successfully downloading the appropriate program, open the Foldit application. Click Play! and Ok. Foldit will ask for a login. There are two options, to create an account and play online, or play offline. Playing online allows you to upload your score, download new puzzles, and see other players. After choosing a preferred method of play, click play offline or play online.

To begin, Foldit will present you with a challenge. Each challenge represents a level in the game. To successfully complete each level, the user must make adjustments to the proteins or side chains. It may represent a clash, misfolding, etc. Read the directions carefully- these interactions also occur in real proteins and it will help you to understand how and why proteins fold into their different shapes.

Challenge: Foldit regularly posts challenges that are related to current events, the spread and infection of COVID-19 is just one of many examples. Once you have mastered the puzzles, head to https://fold.it/portal/puzzles. This page lists the current puzzles that may be used by scientists to study structure, binding, function, etc. Note: these challenges will require the user to create and account and login to Foldit.

Protein Data Bank

The Protein Data Bank (PDB) is an open access digital data resource for biological and medicinal fields. It provides access to 3D structures for large biological molecules including proteins, DNA and RNA. Scientists publish their results including structures, functions and interactions. With these

constant additions, PDB users can stay up to date on new research and current events. The PDB recently published resources regarding SARS-CoV-2, the virus that causes COVID-19. 3-D images of the structure and additional resources can be found here: PDB COVID-19 Resources. Once you have more closely studied the structure of SARS-CoV-2, watch the video Fighting Coronavirus with Soap.

Students Doing Science

SPARK - Student Partnerships for Advanced Research and Knowledge: This program provides an opportunity for all high school students and their science educators to become visiting researchers to Brookhaven National Laboratory's scientific facilities— just like the thousands of scientific researchers use them for their research each year. Check out the SPARK website for information and watch a Vlog posted by one of the students:
http://www.bnl.gov/education/programs/program.php?q=231

SPARK overview video: https://vimeo.com/384863829/0bd4e512cf

LI High School Students Solve Protein Structures at Brookhaven's Light Source

https://www.bnl.gov/newsroom/news.php?a=216876

Structural Biology Pipeline Meets the High School Classroom

https://cdn.rcsb.org/rcsb-pdb/general_information/news_publications/newsletters/2018q4/corner.html

Science News

Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation

https://science.sciencemag.org/content/367/6483/1260

Cryo-EM Used in Novel Coronavirus Research to Support Vaccine, Treatment Development

https://www.thermofisher.com/blog/microscopy/cryo-em-used-in-novel-coronavirus-research-to-support-vaccine-treatment-development/

Scientists Visualize Structure of Key Enzyme that Makes Triglycerides

https://news.stonybrook.edu/facultystaff/scientists-visualize-structure-of-key-enzyme-that-makes-triglycerides/

Cracking the Case of the Norovirus

https://www.cshl.edu/cracking-the-case-of-the-norovirus/

Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved α-ketoamide inhibitors

https://science.sciencemag.org/content/early/2020/03/20/science.abb3405?utm_campaign=fr_sci_2020-03-20&et_rid=17097999&et_cid=3252868

What the Structure of the Coronavirus Can Tell Us

https://www.washingtonpost.com/graphics/2020/health/coronavirus-sars-cov-2-structure/

Video Clips, Articles and Lectures

Meet NSLS-II's Lisa Miller

https://www.bnl.gov/newsroom/news.php?a=214400

Crystallography at BNL

https://vimeo.com/user102290427/review/398246104/440f5e056a

Structural Biology: Studying living things as they giggle and wiggle

https://www.bnl.gov/video/index.php?v=524

Lesson Resources

How proteins are synthesized:

Protein synthesis: https://www.ck12.org/book/ck-12-human-biology/section/5.6/

Guide to understanding X-ray crystallography:

https://www.chem.ucla.edu/~harding/ec_tutorials/tutorial73.pdf

General overview of structural biology field, tools and techniques from National Institute of General Medical Sciences:

https://www.nigms.nih.gov/education/fact-sheets/Pages/structural-biology.aspx

Diamond Light Source simulations and worksheets:

https://www.diamond.ac.uk/Public/For-School/Resources/Simulations-and-Worksheets.html

Stony Brook University: Biochemistry and Structural Biology Graduate Program resources:

https://www.stonybrook.edu/commcms/bsb/resources/

Center for Biomolecular Modeling:

http://cbm.msoe.edu/

Cold Spring Harbor Laboratory

https://www.cshl.edu/

Brookhaven National Laboratory

https://www.bnl.gov/world/

National Synchrotron Light Source II Structural Biology group

https://www.bnl.gov/ps/programs/structural-biology.php