



Exploring Biomolecular Structures with NCBI's iCn3D

Alexa M. Salsbury, Ph.D. and E. Sally Chang, Ph.D.

<https://bit.ly/NCBI-iCn3D-DiscoverBMB-24>

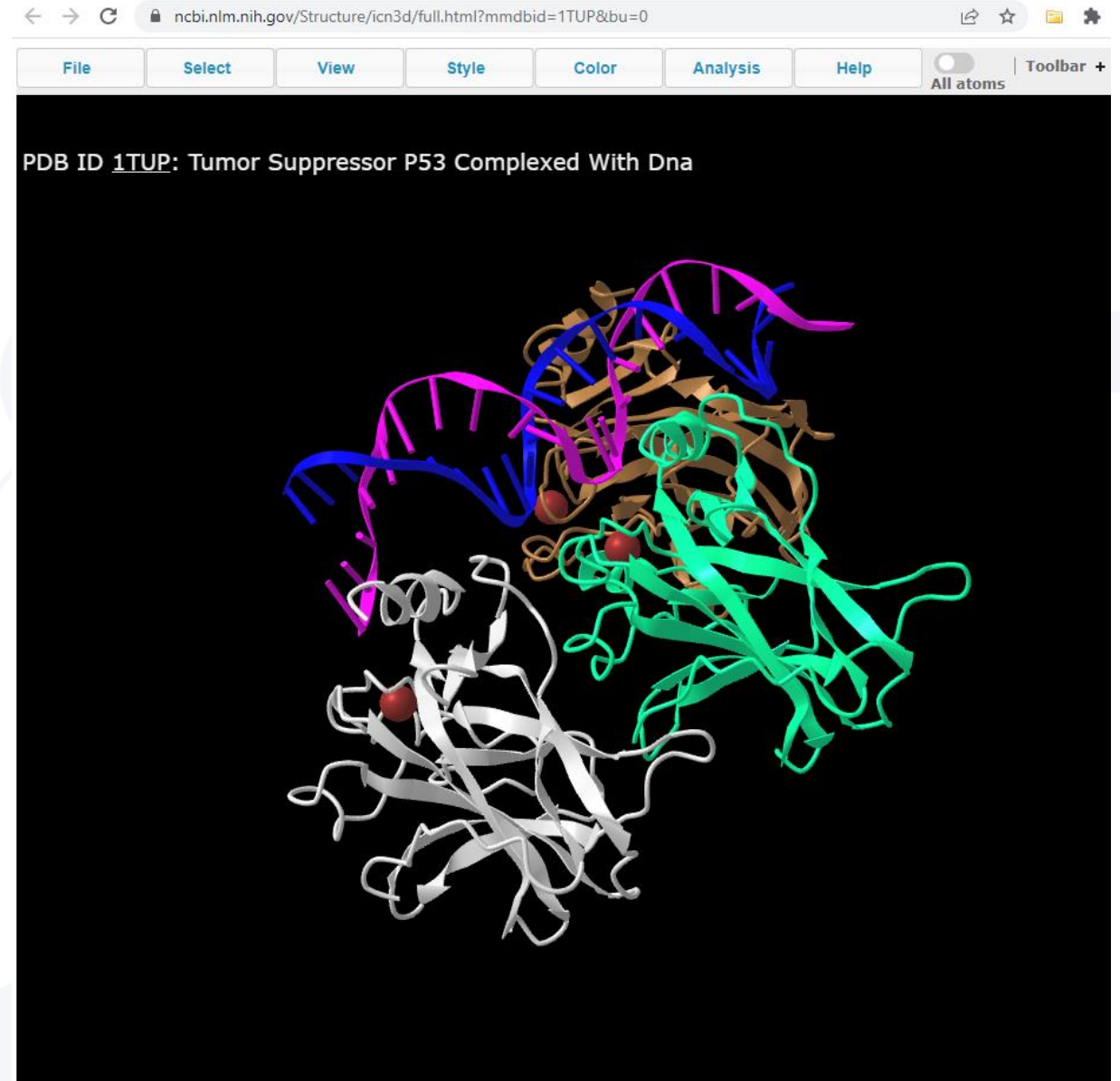


National Library of Medicine
National Center for Biotechnology Information



Overview

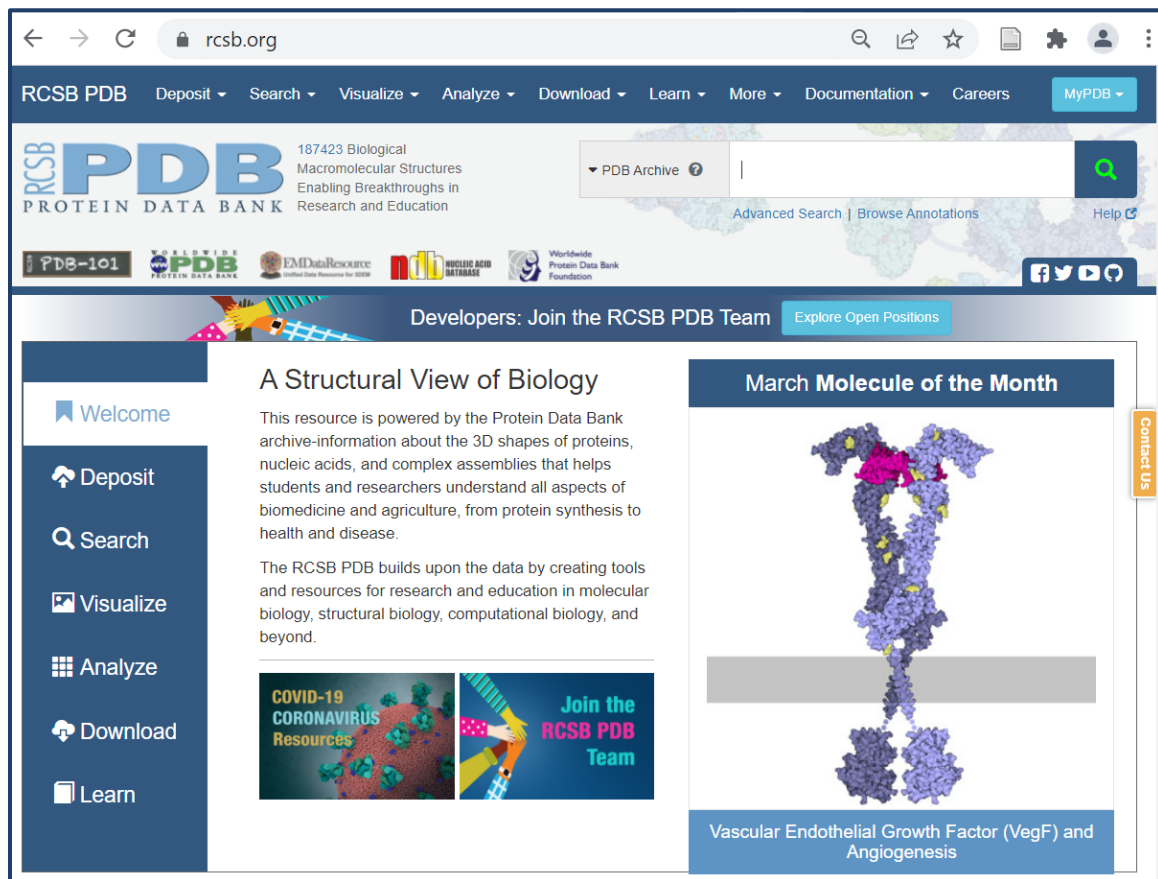
- Background
- iCn3D Fundamentals (Selection, Coloring, Style, and Sharing)
- Group Work
 - [Example 1](#): TP53 Mutation Analysis
 - [Example 2](#): TP53 from Structure to Function
 - [Example 3](#): Compare Crystal and AlphaFold TP53 Structures
- Group Discussion & Event wrap-up



Experimental techniques

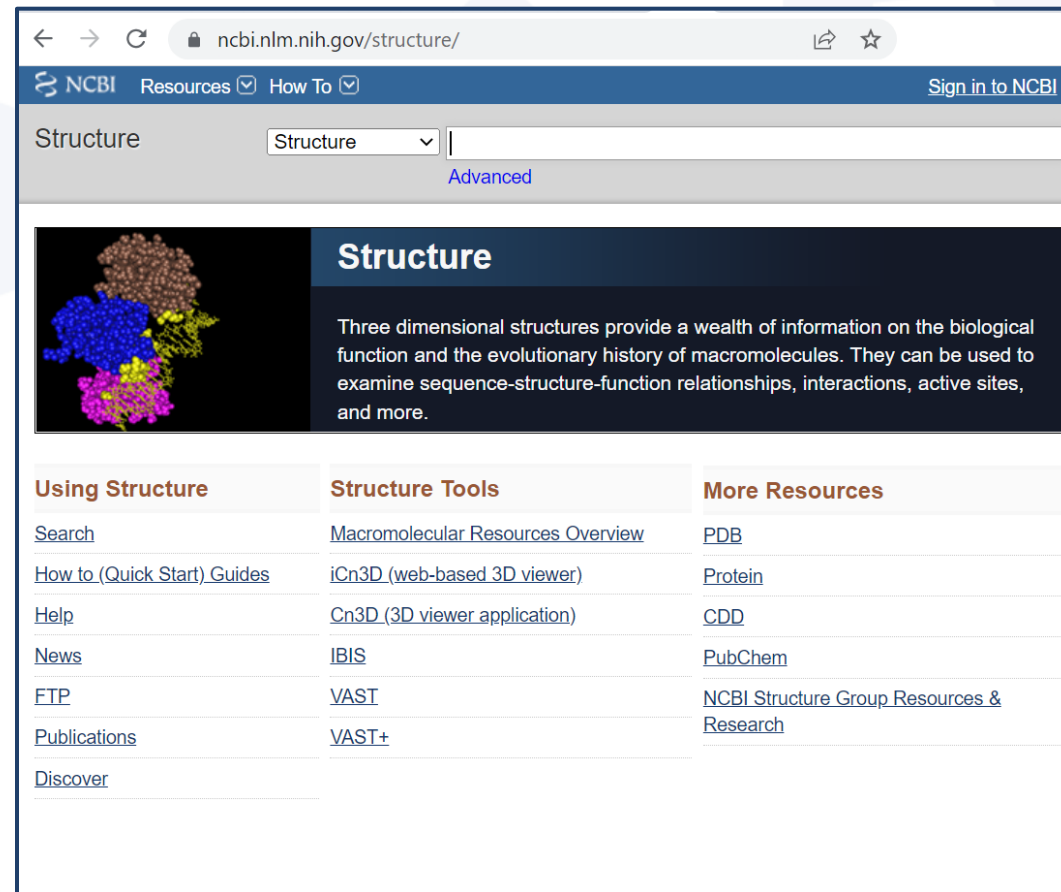
	Advantages	Disadvantages
X-ray crystallography	<ul style="list-style-type: none">• Well developed• High resolution• Broad molecular weight range	<ul style="list-style-type: none">• Difficult sample prep• Static crystalline state
NMR	<ul style="list-style-type: none">• High resolution• 3D structure in solution• Good for dynamic study	<ul style="list-style-type: none">• Difficult sample prep• High sample purity needed• Static crystalline state captured
Cryo-EM	<ul style="list-style-type: none">• Simple sample prep• Structure in native state• Small sample size needed	<ul style="list-style-type: none">• Lower resolution• Works best for samples with high molecular weight• Equipment can be expensive, but costs are decreasing

Where do I find experimentally determined structures?



The screenshot shows the RCSB PDB website. The header includes navigation links like Deposit, Search, Visualize, Analyze, Download, Learn, More, Documentation, and Careers. The main content area features a search bar, a sidebar with links to Welcome, Deposit, Search, Visualize, Analyze, Download, and Learn, and a central section titled "A Structural View of Biology" with text about the PDB archive and a "Join the RCSB PDB Team" button. A "March Molecule of the Month" section displays a 3D structure of Vascular Endothelial Growth Factor (VegF) and Angiogenesis.

RCSB Protein Data Bank



The screenshot shows the NCBI Structure Database website. The header includes navigation links like Resources and How To. The main content area features a search bar, a sidebar with links to Search, How to (Quick Start) Guides, Help, News, FTP, Publications, and Discover, and a central section titled "Structure" with text about three-dimensional structures and a "Join the NCBI Structure Group Resources & Research" button.

NCBI Structure Database

Protein Data Bank ([PDB](https://www.rcsb.org/))

- New Structures are deposited daily

Each structure contains:

- 3D atomic coordinates
- Mandatory Metadata
 - Author Information
 - Primary citation
 - Experimental Data
 - Polymer sequence(s)- proteins, DNA, RNA
 - Small Chemical component structures- ligands, inhibitors, etc.

6LU7

The crystal structure of COVID-19 main protease in complex with an inhibitor N3

DOI: [10.2210/pdb6LU7/pdb](https://doi.org/10.2210/pdb6LU7/pdb)

Classification: [VIRAL PROTEIN](#)

Organism(s): [Severe acute respiratory syndrome coronavirus 2](#), [synthetic construct](#)

Expression System: [Escherichia coli BL21\(DE3\)](#)

Mutation(s): No 

Deposited: 2020-01-26 **Released:** 2020-02-05

Deposition Author(s): [Liu, X.](#), [Zhang, B.](#), [Jin, Z.](#), [Yang, H.](#), [Rao, Z.](#)

Experimental Data Snapshot

Method: X-RAY DIFFRACTION

Resolution: 2.16 Å

R-Value Free: 0.235

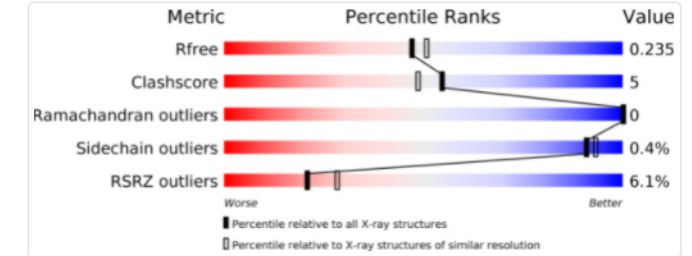
R-Value Work: 0.202

R-Value Observed: 0.204

wwPDB Validation

[3D Report](#)

[Full Report](#)



Literature

[Download Primary Citation](#)

Structure of Mpro from SARS-CoV-2 and discovery of its inhibitors.

[Jin, Z.](#), [Du, X.](#), [Xu, Y.](#), [Deng, Y.](#), [Liu, M.](#), [Zhao, Y.](#), [Zhang, B.](#), [Li, X.](#), [Zhang, L.](#), [Peng, C.](#), [Duan, Y.](#), [Yu, J.](#), [Wang, L.](#), [Yang, K.](#), [Liu, F.](#), [Jiang, R.](#), [Yang, X.](#), [You, T.](#), [Liu, X.](#), [Yang, X.](#), [Bai, F.](#), [Liu, H.](#), [Liu, X.](#), [Guddat, L.W.](#), [Xu, W.](#), [Xiao, G.](#), [Qin, C.](#), [Shi, Z.](#), [Jiang, H.](#), [Rao, Z.](#), [Yang, H.](#)

(2020) *Nature* **582**: 289-293


PubMed: [32272481](#) [Search on PubMed](#)

DOI: [10.1038/s41586-020-2223-y](https://doi.org/10.1038/s41586-020-2223-y)

Primary Citation of Related Structures:

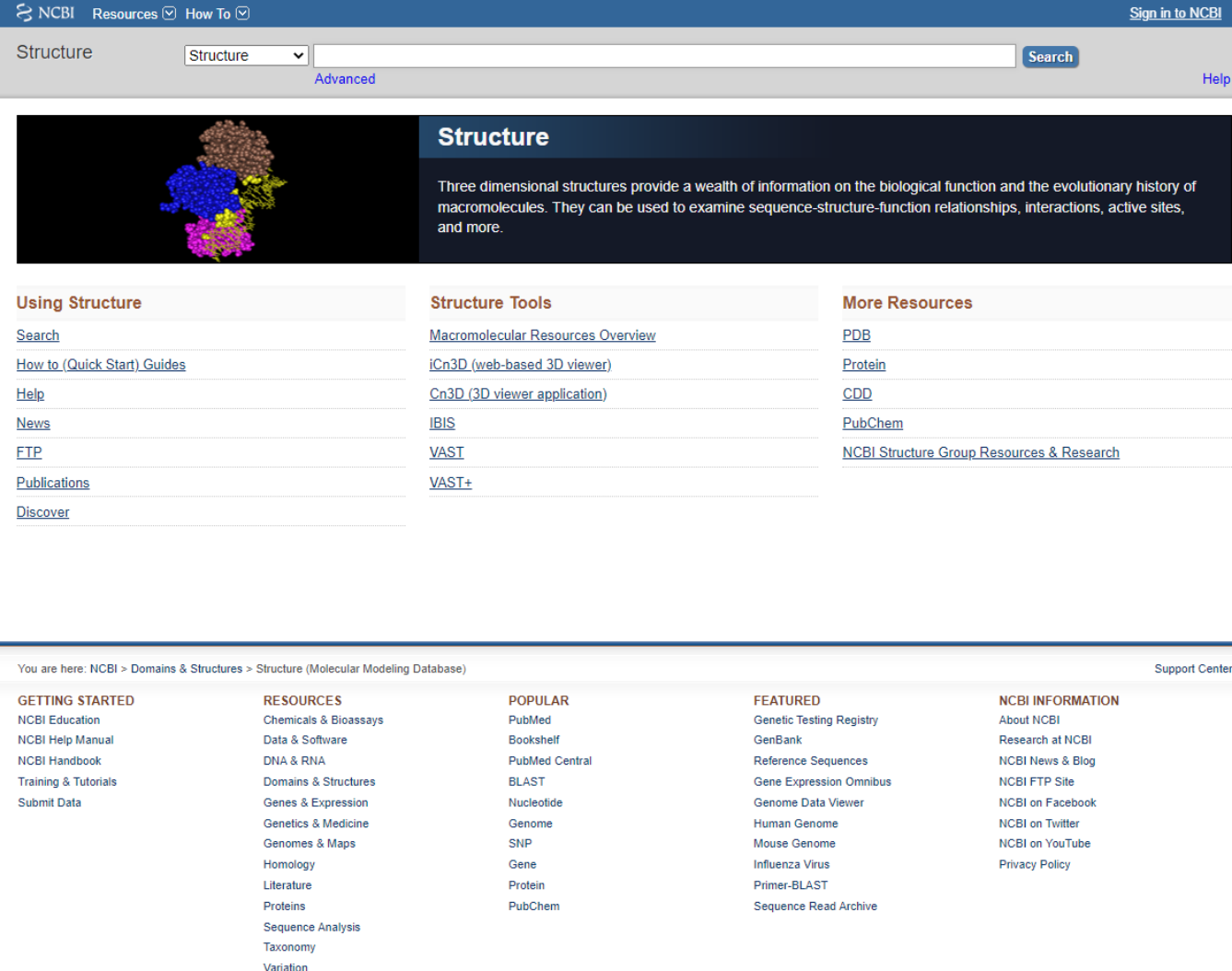
[7BQY](#), [6LU7](#)

PubMed Abstract:

A new coronavirus, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is the aetiological agent responsible for the 2019-2020 viral pneumonia outbreak of coronavirus disease 2019 (COVID-19)¹⁻⁴. Currently, there are no targeted therapeutic agents for the treatment of this disease, and effective treatment options remain very limited ... 

NCBI's Structure Database

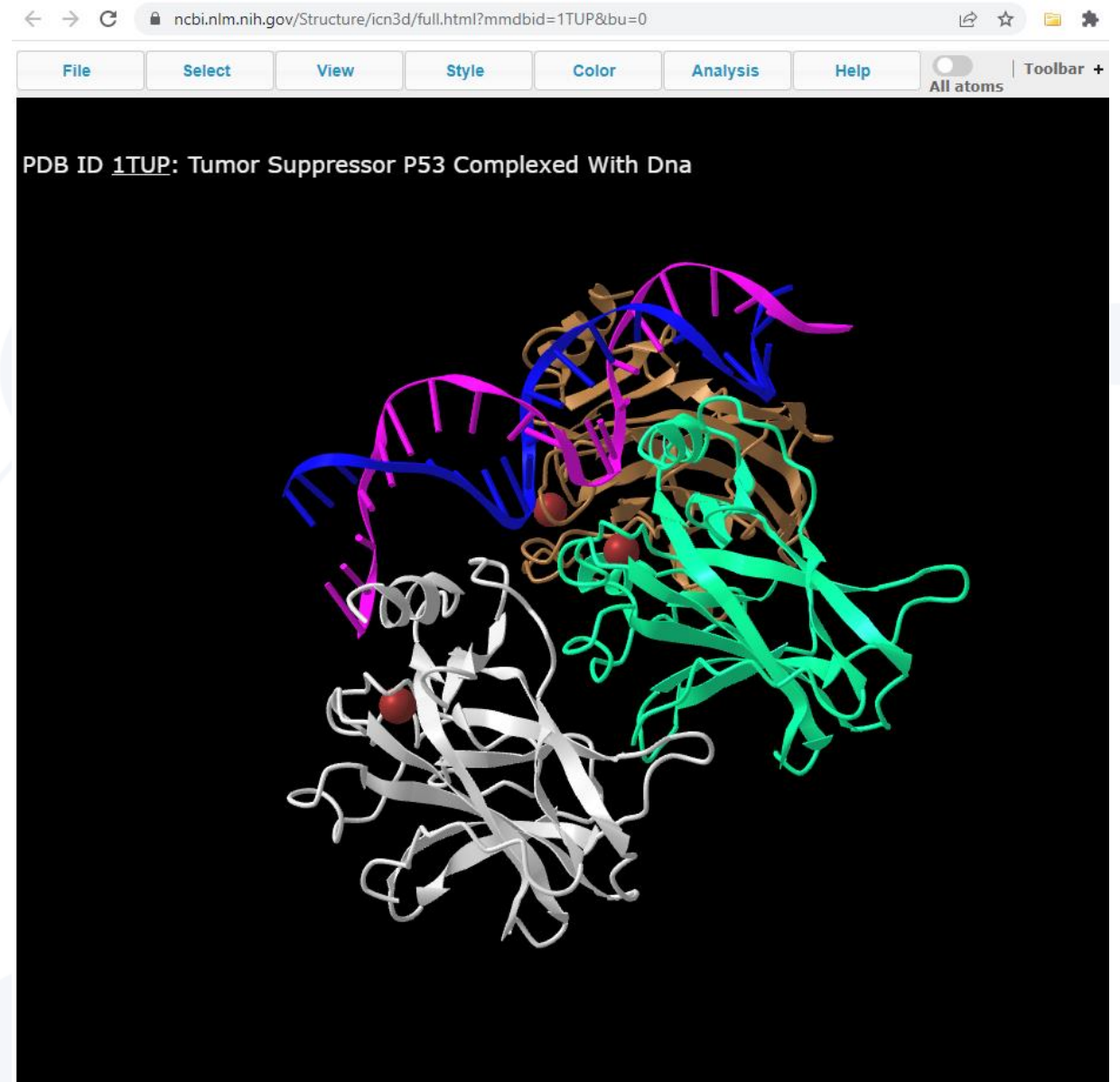
- Updated monthly
- Derived from PDB records
- Additional information added, including:
 - Explicit chemical graph information
 - Validation (secondary structure elements)
 - Includes taxonomy
- Connects 3D to associated literature, molecular data, chemical data, and other NCBI tools



The screenshot displays the NCBI Structure Database homepage. At the top, there is a navigation bar with links for 'NCBI', 'Resources', and 'How To', along with a 'Sign in to NCBI' link. Below this is a search bar with a dropdown menu set to 'Structure' and a 'Search' button. A 'Help' link is also present. The main content area features a large image of a 3D molecular structure on the left and a text box on the right stating: 'Three dimensional structures provide a wealth of information on the biological function and the evolutionary history of macromolecules. They can be used to examine sequence-structure-function relationships, interactions, active sites, and more.' Below this, there are three columns of links: 'Using Structure' (Search, How to (Quick Start) Guides, Help, News, FTP, Publications, Discover), 'Structure Tools' (Macromolecular Resources Overview, iCn3D (web-based 3D viewer), Cn3D (3D viewer application), IBIS, VAST, VAST+), and 'More Resources' (PDB, Protein, CDD, PubChem, NCBI Structure Group Resources & Research). At the bottom, there is a footer section with five columns of links: 'GETTING STARTED' (NCBI Education, NCBI Help Manual, NCBI Handbook, Training & Tutorials, Submit Data), 'RESOURCES' (Chemicals & Bioassays, Data & Software, DNA & RNA, Domains & Structures, Genes & Expression, Genetics & Medicine, Genomes & Maps, Homology, Literature, Proteins, Sequence Analysis, Taxonomy, Variation), 'POPULAR' (PubMed, Bookshelf, PubMed Central, BLAST, Nucleotide, Genome, SNP, Gene, Protein, PubChem), 'FEATURED' (Genetic Testing Registry, GenBank, Reference Sequences, Gene Expression Omnibus, Genome Data Viewer, Human Genome, Mouse Genome, Influenza Virus, Primer-BLAST, Sequence Read Archive), and 'NCBI INFORMATION' (About NCBI, Research at NCBI, NCBI News & Blog, NCBI FTP Site, NCBI on Facebook, NCBI on Twitter, NCBI on YouTube, Privacy Policy). A 'Support Center' link is located in the bottom right corner.

iCn3D

- Interactive, web-based 3D structure viewer
 - No installation needed!
- Users can
 - Visualize structure in 1D, 2D, and 3D
 - View sequence and structure alignments
 - Probe perturbations
 - And more!



3D Viewer Feature Comparison

	Web- based	1D Sequence	2D Diagram	Annotation	Align	Share Link	Script	Jupyter Notebook	Virtual Reality	3D Printing
iCn3D	✓	✓	✓	✓	✓ ^a	✓ ^b	✓ ^c	✓ ^d	✓	✓
Mol*	✓	✓	Web	Web						
Aquaria	✓	✓		✓					✓	
Chimera		✓		✓					✓	✓
PyMol		✓		✓			✓			
Cn3D		✓	Web	✓	✓					

^a: iCn3D aligns structures (PDB or AlphaFold) based on structures or sequences.

^b: iCn3D sharable links could be a [short URL](#) or a URL containing the [address of an iCn3D PNG Image](#)

^c: iCn3D supports command-line analysis with either [Python scripts](#) or [Node.js scripts](#)

^d: iCn3D can also be [used in Jupyter Notebook](#)

iCn3D Features of Interest

- iCn3D aligns structures (PDB or AlphaFold) based on structures or sequences.
- iCn3D sharable links (<https://structure.ncbi.nlm.nih.gov/icn3d/share.html?XCxR6fSTmXHxR3o1A>)
- iCn3D supports command-line analysis with either [Python scripts](#) or [Node.js scripts](#)
- iCn3D can also be used in Jupyter Notebook (<https://pypi.org/project/icn3dpy>)
- 3D printing: structure.ncbi.nlm.nih.gov/icn3d/share.html?wt4TDqzhC2rhCYTD7
- Contact map: structure.ncbi.nlm.nih.gov/icn3d/share.html?rnMbe26tNsAjJLGK9
- Precalculated symmetry: structure.ncbi.nlm.nih.gov/icn3d/share.html?bGH1BfLsiGFhhTDn8
- Symmetry dynamically: structure.ncbi.nlm.nih.gov/icn3d/share.html?6NvhQ45XrnbuXyGe6
- Electron density map: structure.ncbi.nlm.nih.gov/icn3d/share.html?QpqNZ3k65ToYFvUB6
- EM map: structure.ncbi.nlm.nih.gov/icn3d/share.html?L4C4WYE85tYRiFeK7
- Transmembrane protein: structure.ncbi.nlm.nih.gov/icn3d/share.html?jMN16mJyR9STUx6E6
- Solvent Accessible Area: structure.ncbi.nlm.nih.gov/icn3d/share.html?xKSyfd1umbKstGh29

iCn3D Shortcuts

Rotate

- **Left mouse button** can be used to rotate the structure
- **Key L** - left
- **Key J** - right
- **Key I** - up
- **Key M** - down
- **Shift + Key L** - left 90°
- **Shift + Key J** - right 90°
- **Shift + Key I** - up 90°
- **Shift + Key M** - down 90°

Zoom

- **Middle mouse button** OR **Left Mouse + Shift** - can be used to zoom
- **Key Z** - zoom in
- **Key X** - zoom out

Translate

- **Right mouse button** OR **Left Mouse + Ctrl** - can be used to translate the structure to a different location within the 3D window
- **Keyboard arrows**

Select

- **Alt + Click (PC)** or **Option + Click (Mac)**- can be used to select atom/residue/strand , hold **Ctrl + Click** to add another

A faint, light blue molecular structure graphic is visible in the background, consisting of several interconnected circles (nodes) of varying sizes, representing atoms and bonds in a chemical network.

iCn3D Fundamentals Demo

<https://bit.ly/NCBI-iCn3D-DiscoverBMB-24>

Group Exercises

- We will now split into groups to work on one of the three examples:

Example 1: TP53 Mutation Analysis

Example 2: TP53 from Structure to Function

Example 3: Compare Crystal and AlphaFold TP53 Structures

- Review the objectives on each of these pages and decide on an example that best suites your learning goals. Work with your group and NCBI experts on completing the steps and rendering an image(s) with iCn3D.

Continue learning about iCn3D

Tutorials and help documents are available [here](#):

The screenshot displays the iCn3D web interface, which is part of the U.S. National Library of Medicine and NCBI National Center for Biotechnology Information. The interface features a top navigation bar with the NIH logo and the text "U.S. National Library of Medicine" and "NCBI National Center for Biotechnology Information". Below this, the "iCn3D" logo is prominently displayed, followed by the text "AlphaFold-related gallery with live examples".

A central menu is visible, listing options: "About iCn3D", "Live Gallery", "Tutorial >", "Search Structure", "Citing iCn3D", "Source Code >", "Develop >", and "Help Doc". A sub-menu for "Tutorial >" is open, showing "Use iCn3D", "iCn3D Videos", "URL Parameters", and "Commands".

Two protein structure visualizations are shown side-by-side. The left visualization is for UniProt ID A0A044R7Z7: ALPHAFOLD MONOMER V2. It shows a blue ribbon structure with a red helix and a green helix. The right visualization is for UniProt ID Q08426: ALPHAFOLD MONOMER V2. It shows a blue ribbon structure with a yellow helix and a green helix. Both visualizations include a "Sequences and Annotations" panel on the right, which displays protein details and annotations.

Below the left visualization, the text reads: "AlphaFold structures with conserved domain and 3D domain annotations (Uniprot ID A0A044R7Z7)". Below the right visualization, the text reads: "AlphaFold structures with SNP and ClinVar annotations (Uniprot ID Q08426)".

Continue learning about NCBI Resources

- Join us for workshops, webinars, or codeathons!

[NCBI Insights Blog](#)

- Follow us on social media:



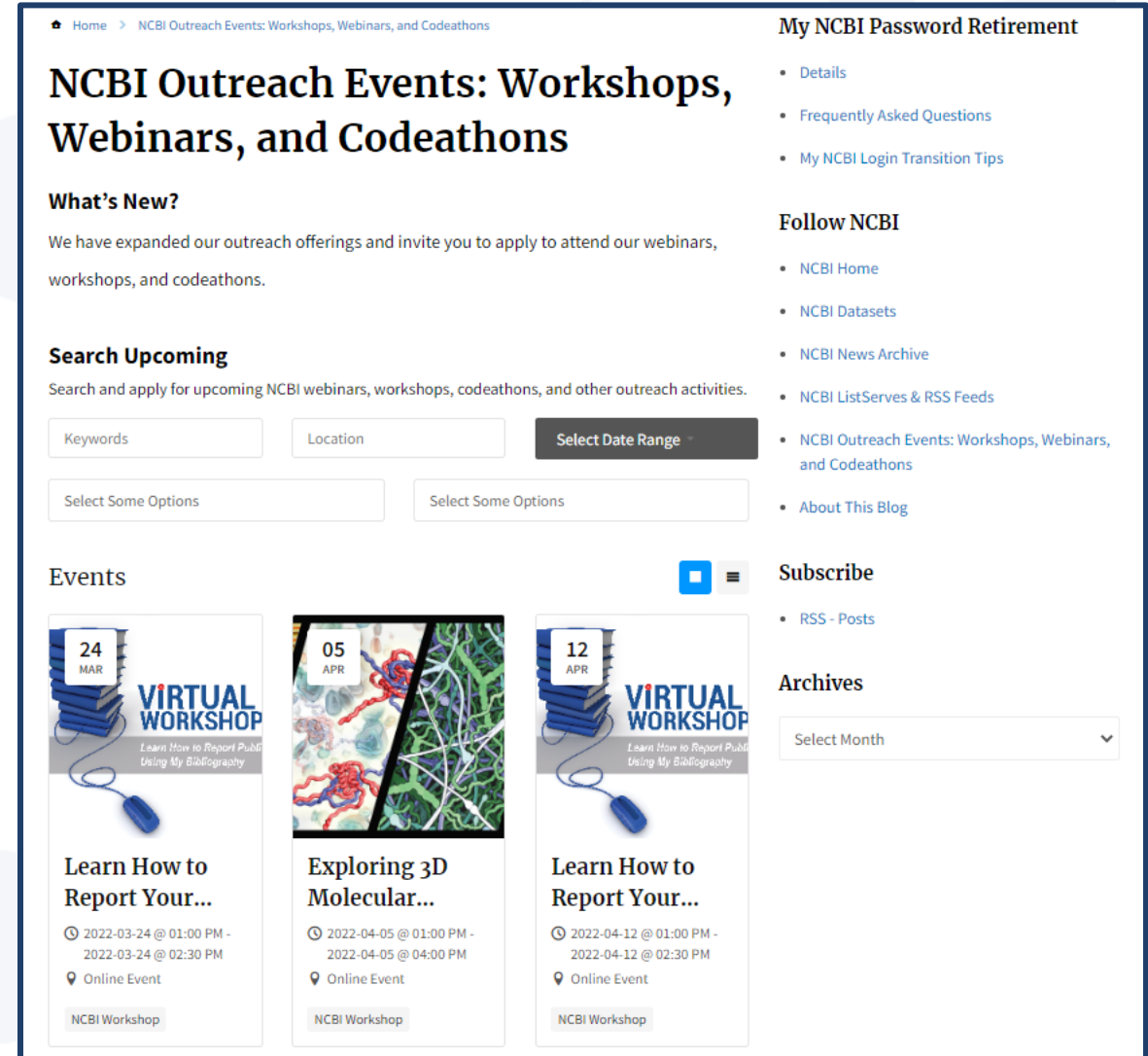
[X](#)



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[Facebook](#)



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NCBI Outreach Events: Workshops, Webinars, and Codeathons

What's New?
We have expanded our outreach offerings and invite you to apply to attend our webinars, workshops, and codeathons.

Search Upcoming
Search and apply for upcoming NCBI webinars, workshops, codeathons, and other outreach activities.

Keywords Location Select Date Range

Select Some Options Select Some Options

Events

- 24 MAR**
VIRTUAL WORKSHOP
Learn How to Report Your...
2022-03-24 @ 01:00 PM - 2022-03-24 @ 02:30 PM
Online Event
NCBI Workshop
- 05 APR**
Exploring 3D Molecular...
2022-04-05 @ 01:00 PM - 2022-04-05 @ 04:00 PM
Online Event
NCBI Workshop
- 12 APR**
VIRTUAL WORKSHOP
Learn How to Report Your...
2022-04-12 @ 01:00 PM - 2022-04-12 @ 02:30 PM
Online Event
NCBI Workshop

My NCBI Password Retirement

- Details
- Frequently Asked Questions
- My NCBI Login Transition Tips

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E. Sally Chang, PhD

Poster (338):

Using NCBI Resources to Develop
Case Studies for Student-Directed
Discovery



Tuesday, March 26
5:30 - 6:30 pm CT

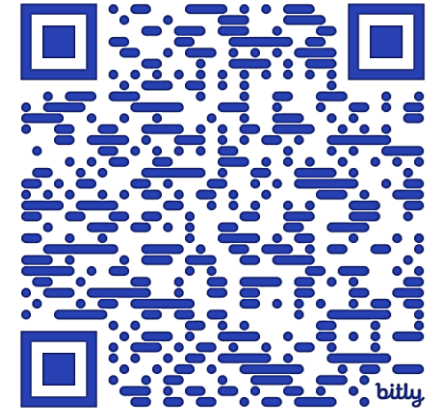


Learn more about NCBI
Education at today's poster
session!




BioEd Summit:
*Crafting Student-Centric
Curricula with NCBI Resources*
An NCBI Training Event for Science Educators

NIH Campus
Bethesda, MD
August 5-9, 2024



bit.ly/NCBI-BioEdSummit2024



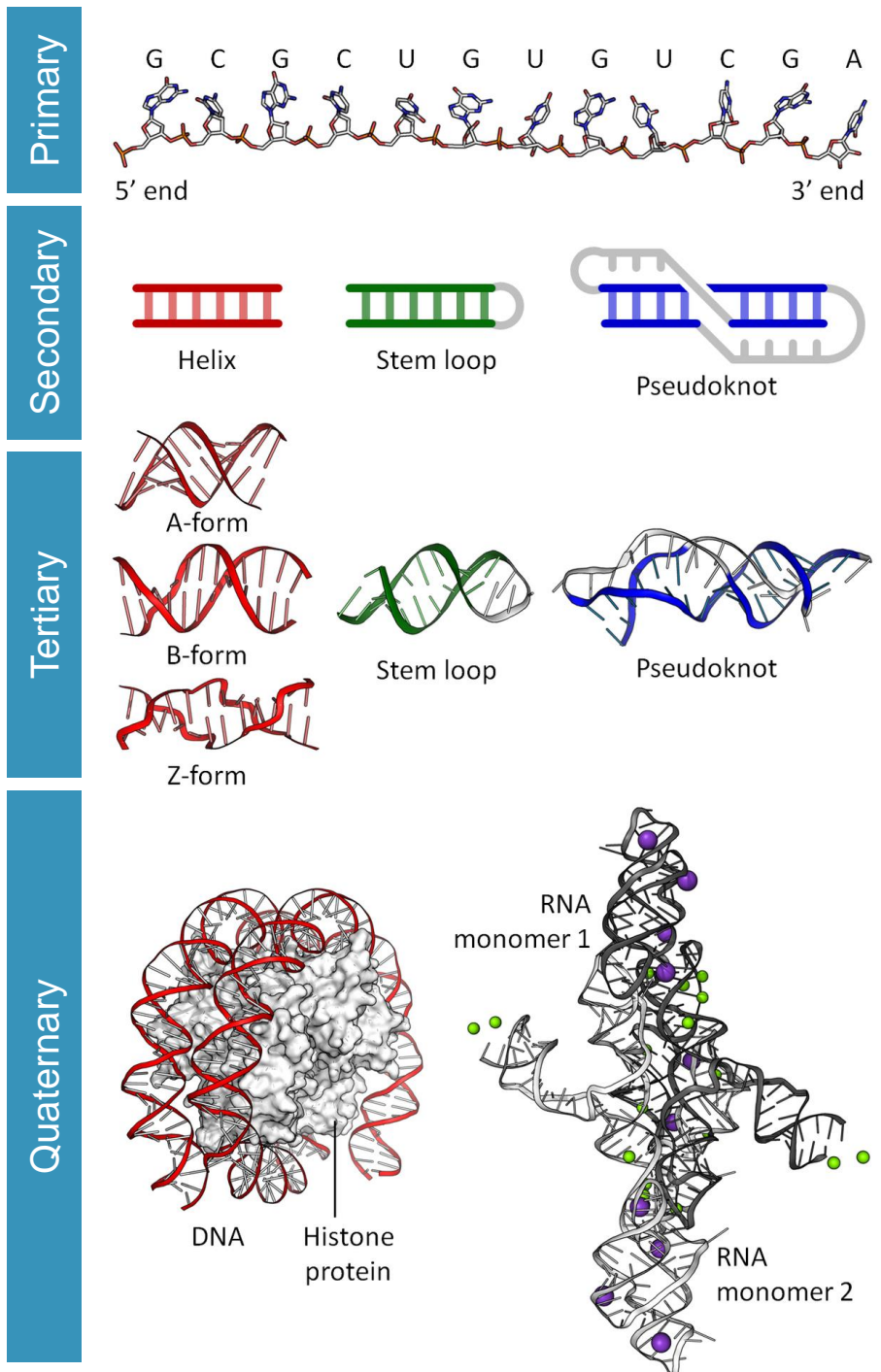


Exploring Biomolecular Structures with NCBI's iCn3D Supplemental Learning Materials

Alexa M. Salsbury, Ph.D. and E. Sally Chang, Ph.D.

Nucleic Acid Structure

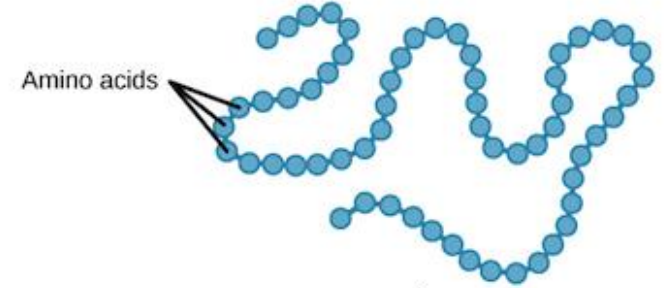
- **Primary**- sequence of nucleotides
- **Secondary**- base pairing interactions between polymers (DNA) or within a single polymer (RNA)
- **Tertiary**- 3D folding pattern
- **Quaternary**- interactions of nucleic acids with other molecules (DNA, RNA, or Protein)



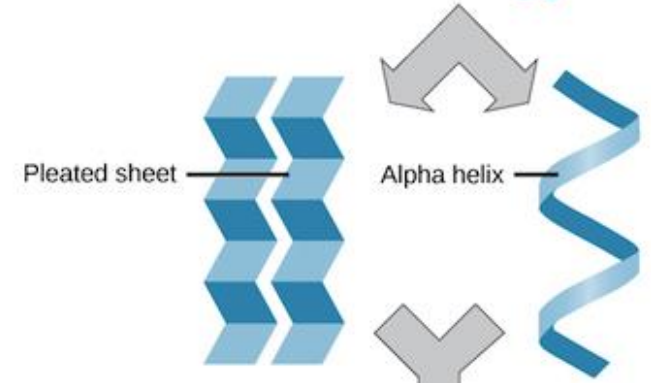
Protein Structure

- **Primary**- sequence of amino acids
- **Secondary**- hydrogen bonding of the peptide backbone that causes amino acids to fold into a repeating pattern
- **Tertiary**- 3D folding pattern of a protein due to side chain interactions
- **Quaternary**- protein consisting of more than one polypeptide

Primary



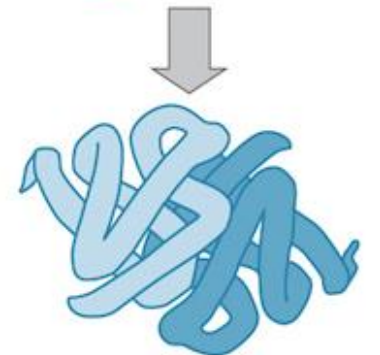
Secondary



Tertiary



Quaternary



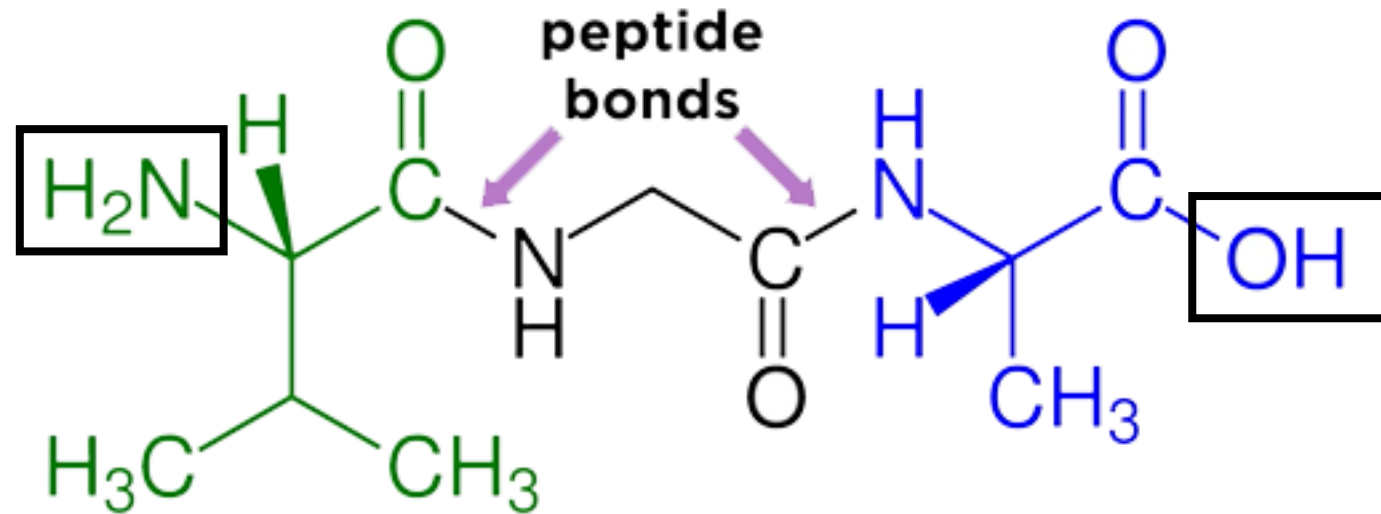
Terminology

N-terminus

(ends in amino group)

C-terminus

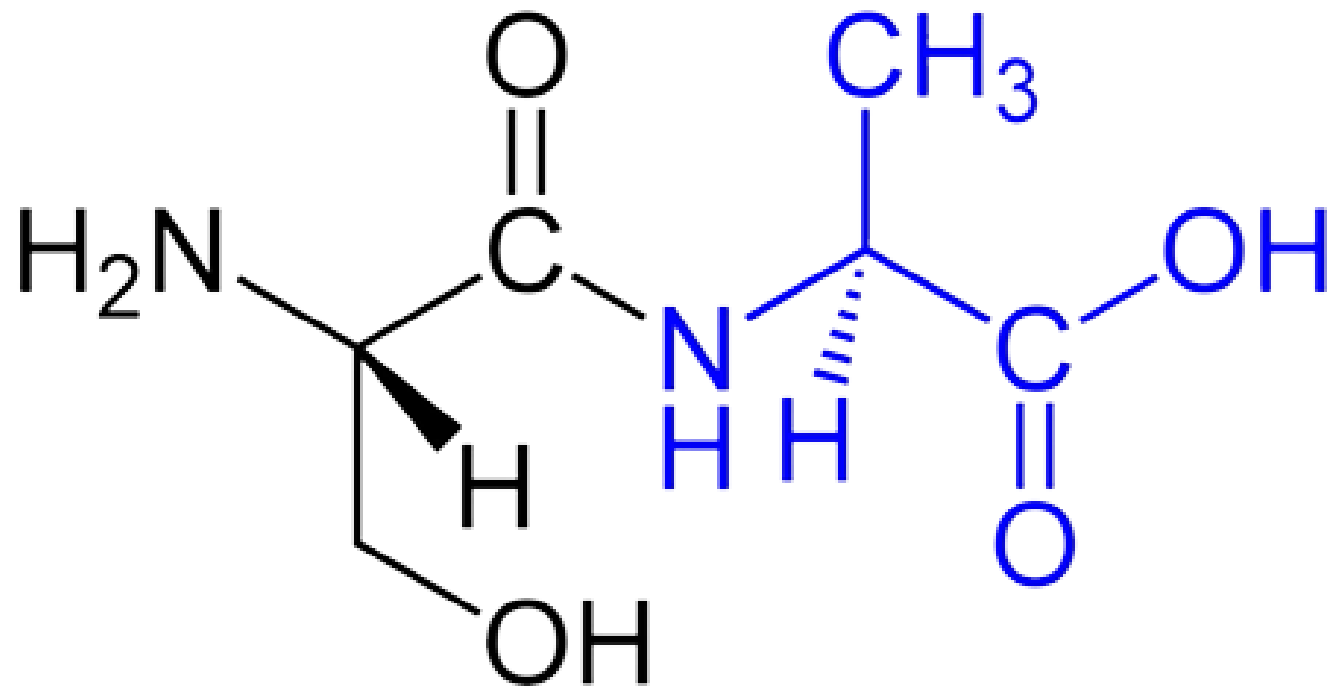
(ends in carboxyl group)



valine-glycine-alanine

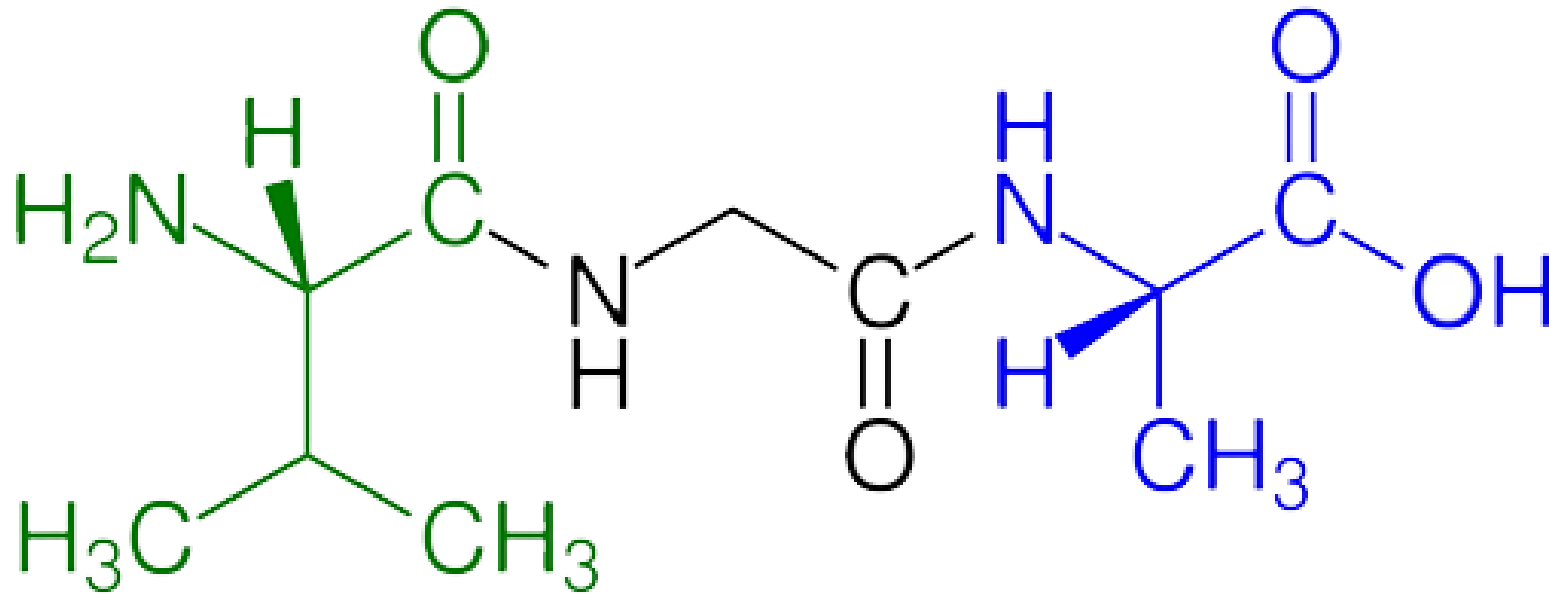
Terminology

dipeptide (2 amino acids)



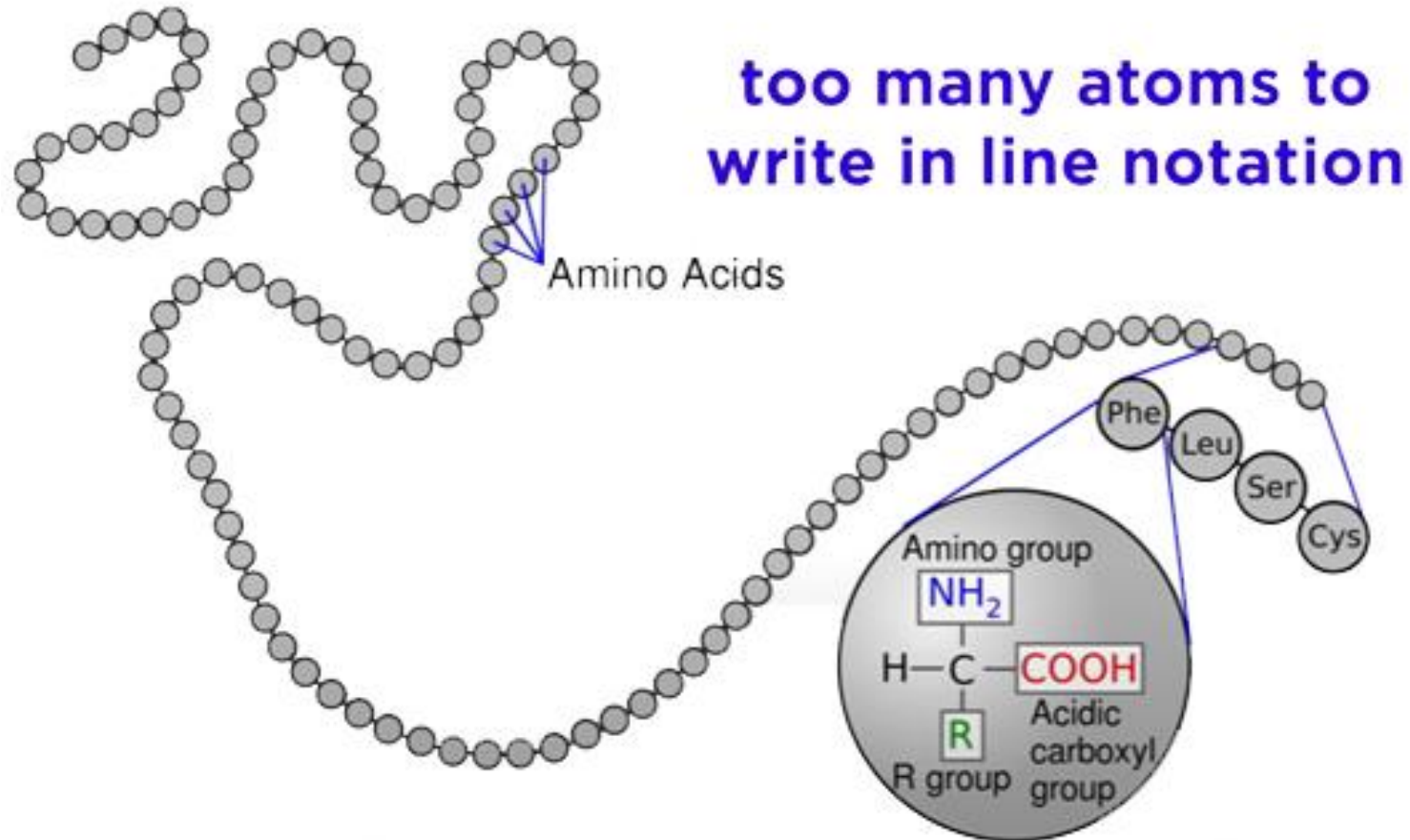
Terminology

oligopeptide (3-10 amino acids)



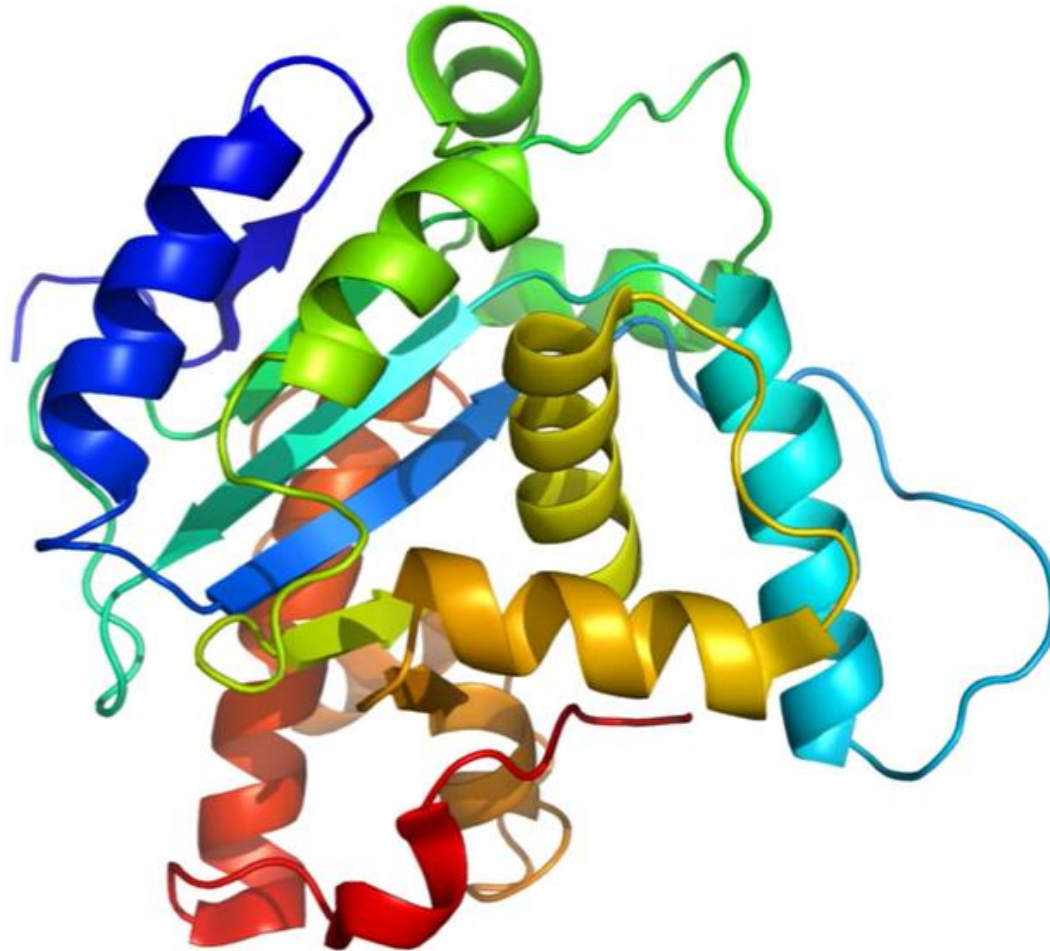
Terminology

polypeptide (>10 amino acids)

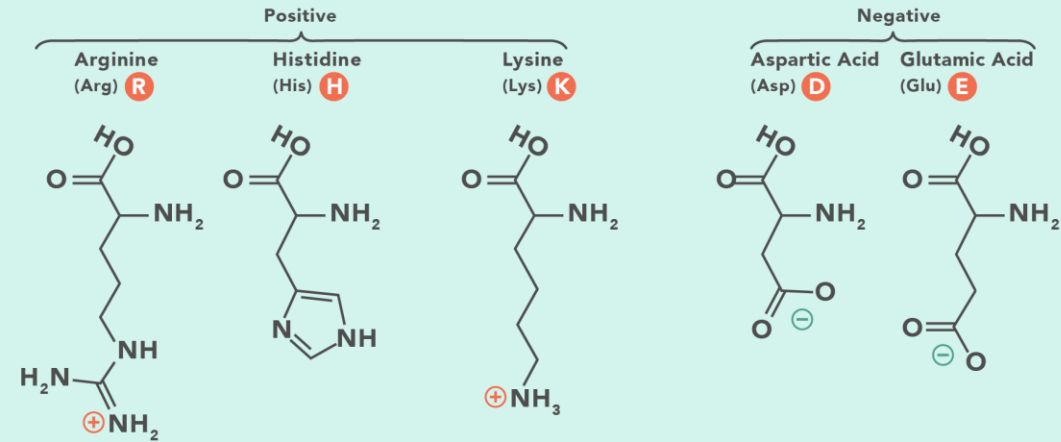


Terminology

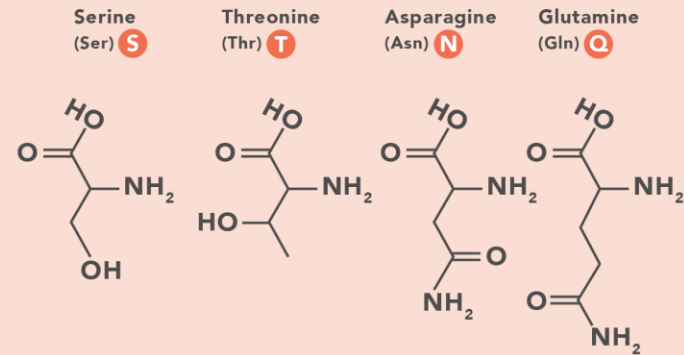
protein (generally 300-1000 amino acids)



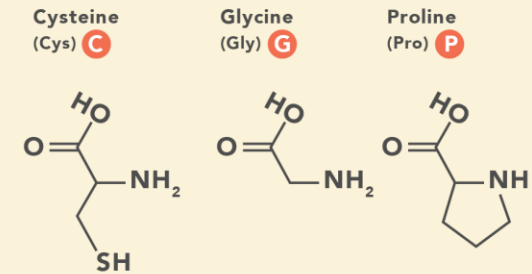
A. Amino Acids with Electrically Charged Side Chains



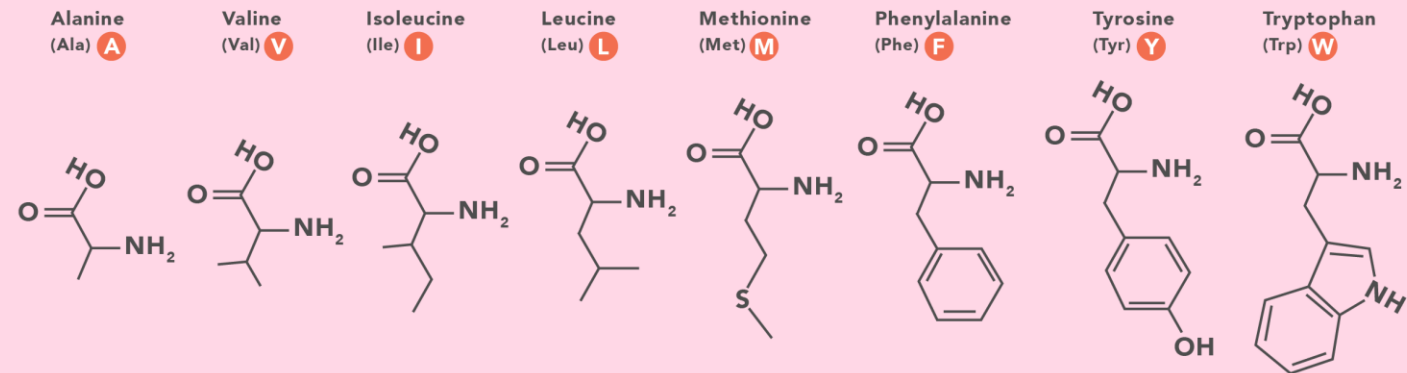
B. Amino Acids with Polar Uncharged Side Chains



C. Special Cases



D. Amino Acids with Hydrophobic Side Chains



Functional definition:

- Enzymes: Accelerate biochemical reactions
- Structural: Form biological structures
- Transport: Carry biochemically important substances
- Defense: Protect the body from foreign invaders

Structural definition:

- Globular: Complex folds, irregularly shaped tertiary structures
- Fibrous: Extended, simple folds -- generally structural proteins

Cellular localization definition:

- Membrane: In direct physical contact with a membrane; generally water insoluble.
- Soluble: Water soluble; can be anywhere in the cell

Experimental techniques



■ Single crystal X-ray diffraction (SC-XRD)

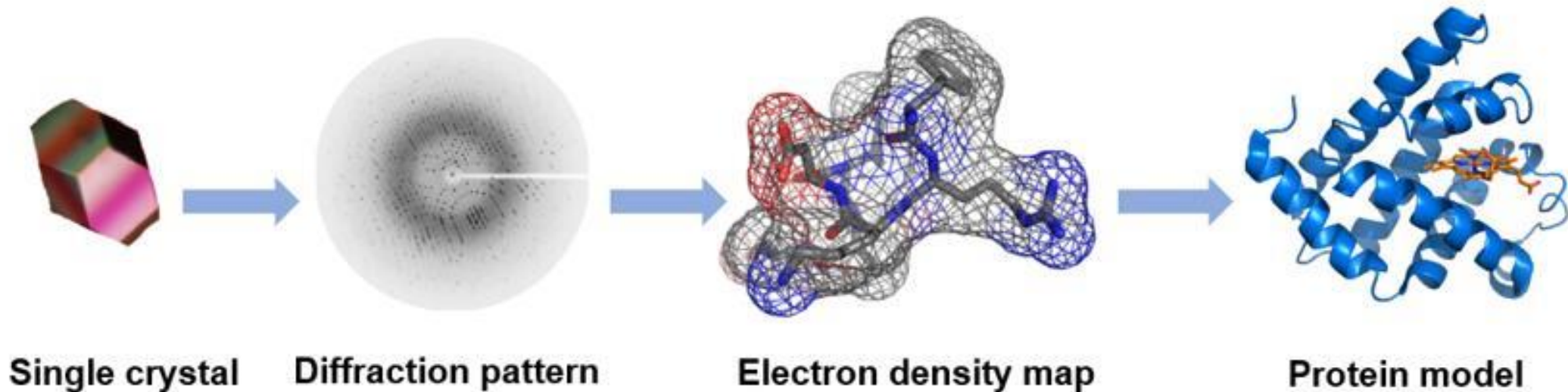
■ Nuclear magnetic resonance (NMR)

■ Cryo-electron microscopy (Cryo-EM)

Three main research techniques for structural biology.
According to the statistics of PDB (<https://www.rcsb.org/>)

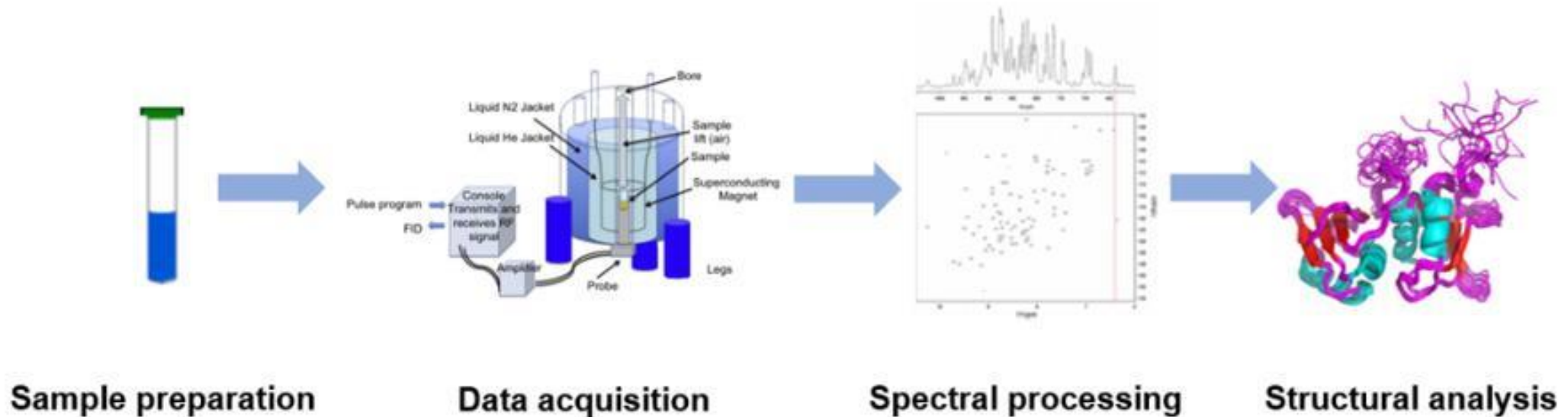
X-ray Crystallography

- Requires crystals, which can be hard to make
- Can handle very large proteins and complexes (e.g. ribosome)
- Provides a “flash picture” with little or no data about motions
- Can include packing artifacts from crystallization



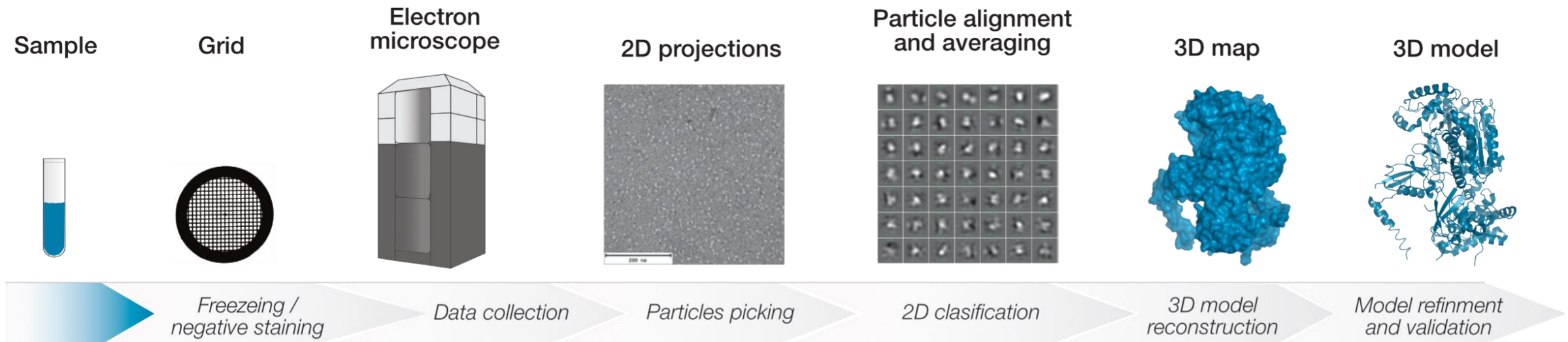
Nuclear Magnetic Resonance

- Requires highly concentrated, C13/N15-labeled protein solutions
- Limited to relatively small proteins (<30 kDa)
- Sensitive to molecular motions
- High protein concentrations may induce non-biological binding



Cryo-electron microscopy

- Requires expensive equipment
- Only small amount of sample
- Rapid freezing sample allows sample to maintain a closer-to-native state
- Useful for biomolecules with high molecular weight



NCBI Structure Database Search Tips

Entrez is a molecular biology database system that provides access to a wealth of NCBI data

- More [Entrez Help](#) is available on the NCBI website

Finding structures with Entrez

```
"term1"[field1] AND/OR/NOT "term2"[field2] AND/OR/NOT ...
```

- Use field limits and Boolean operators
- Put phrases in quotes

NCBI Structure Database Search Examples

Useful Search Fields

Organism

Ex. "Homo sapiens"[orgn]

Experimental Method

Ex. "NMR"[exp]

Chemical Name

"zinc"[chemical name]

PDB Description

Ex. "Tumor Suppressor
p53"[title]

[Filter]

Ex. "Complex DNA"[filter]

[More Search Field Options](#)

```
term1[field1] AND/OR/NOT term2[field2] AND/OR/NOT ...
```

```
"Homo sapiens"[orgn] AND "X-ray  
diffraction"[exp]
```

Search results

Items: 1 to 20 of 47803

```
"Homo sapiens"[orgn] AND "X-ray  
diffraction"[exp] AND "zinc"[chemical name]
```

Search results

Items: 1 to 20 of 6092

```
"Homo sapiens"[orgn] AND "X-ray  
diffraction"[exp] AND "zinc"[chemical  
name] AND "Complex DNA"[filter]
```

Search results

Items: 1 to 20 of 288

```
1TUP
```

PDB File

HEADER	ISOMERASE/DNA	04-OCT-07	2RGR
TITLE	TOPOISOMERASE IIA BOUND TO G-SEGMENT DNA		
COMPND	MOL_ID: 1;		
COMPND	2 MOLECULE: DNA TOPOISOMERASE 2;		
COMPND	3 CHAIN: A;		
COMPND	4 FRAGMENT: DNA BINDING AND CLEAVAGE DOMAIN (RESIDUES 419-		
COMPND	5 1177);		
COMPND	6 SYNONYM: DNA TOPOISOMERASE II;		
COMPND	7 EC: 5.99.1.3;		
COMPND	8 ENGINEERED: YES;		
COMPND	9 MOL_ID: 2;		
COMPND	10 MOLECULE: DNA;		
COMPND	11 CHAIN: C;		
COMPND	12 ENGINEERED: YES;		
COMPND	13 MOL_ID: 3;		
COMPND	14 MOLECULE: DNA;		
COMPND	15 CHAIN: D;		
COMPND	16 ENGINEERED: YES		
SOURCE	MOL_ID: 1;		
SOURCE	2 ORGANISM_SCIENTIFIC: SACCHAROMYCES CEREVISIAE;		
SOURCE	3 ORGANISM_COMMON: BAKER'S YEAST;		
SOURCE	4 ORGANISM		
SOURCE	5 GENE:		
SOURCE	6 EXPRES		
SOURCE	7 EXPRES		
SOURCE	8 EXPRES		
SOURCE	9 EXPRES		
SOURCE	10 EXPRES		
SOURCE	11 EXPRES		
SOURCE	12 MOL_ID		
SOURCE	13 SYNTHETIC		
SOURCE	14 MOL_ID		
SOURCE	15 SYNTHETIC		
REMARK	2		
REMARK	2	RESOLUTION.	3.00 ANGSTROMS.
REMARK	3		
REMARK	3	REFINEMENT.	
REMARK	3	PROGRAM	: PHENIX
REMARK	280		
REMARK	280	CRYSTAL	
REMARK	280	SOLVENT CONTENT, VS (%)	: 59.90
REMARK	280	MATTHEWS COEFFICIENT, VM (ANGSTROMS**3/DA)	: 3.07
REMARK	280		
REMARK	280	CRYSTALLIZATION CONDITIONS: 12-20% PEG 1000, 100-250 MM MGCL2,	
REMARK	280	100 MM SODIUM CACODYLATE, PH 7.0, VAPOR DIFFUSION, HANGING	
REMARK	280	DROP, TEMPERATURE 277K	
REMARK	290		

PDB File: Data

ATOM	46	N	THR	A	424	17.857	11.128	-95.193	1.00	57.50	N	
ANISOU	46	N	THR	A	424	7252	7857	6740	-72	842	107	N
ATOM	47	CA	THR	A	424	16.610	11.906	-95.142	1.00	56.73	C	
ANISOU	47	CA	THR	A	424	7153	7780	6623	-85	799	141	C
ATOM	48	C	THR	A	424	15.300	11.135	-94.959	1.00	55.10	C	
ATOM	49	O	THR	A	424	6950	7583	6224	-111	717	150	O
ATOM	50	CB	THR	A	424	16.451	12.75	15.406	1	60.37	18	C
ATOM	50	CB	THR	A	424	7628	8271	-94	20	18	C	
ATOM	51	OG1	THR	A	424	16.550	11.914	-97.557	1.00	63.33	O	
AN	51	OG1	THR	A	424	8049	8666	7346	-104	846	160	C
AT	51	CG2	THR	A	424	17.523	13.836	-96.462	1.00	61.80	200	C
AN	51	CG2	THR	A	424	77	7271	-81	860	200	C	

Name

Atom Number

Atom Name

Chain ID

Residue Name

Residue Number

X

Y

Z

Occupancy

Temperature Factor

Computational Structural Biology

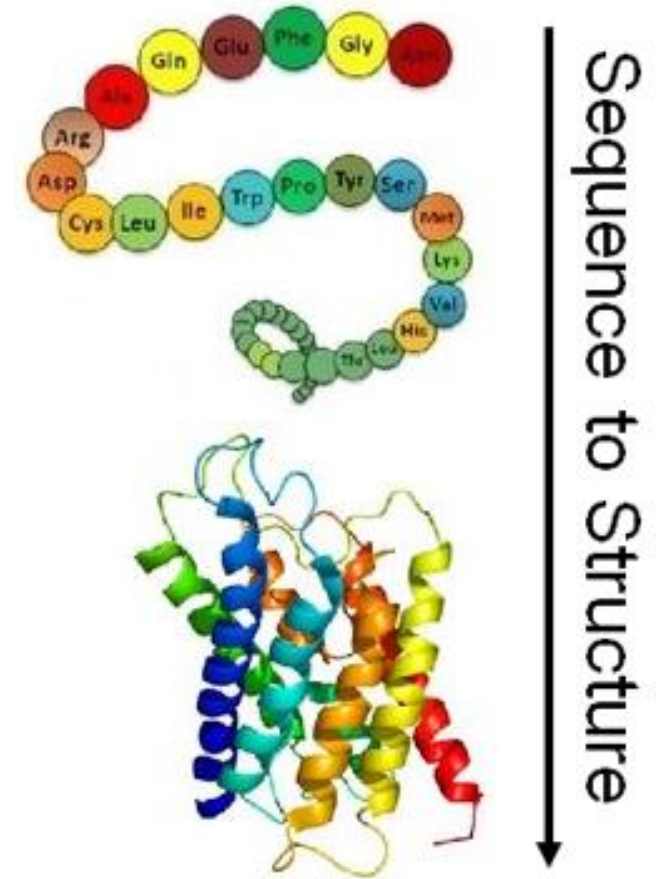
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- Molecular Docking- predicts the orientation of one molecule to another
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Computational Structural Biology

- Structure Prediction- inference of 3D structure from sequence data
- Molecular Docking- predicts the orientation of one molecule to another
- Molecular Dynamics Simulations- analyzes physical movements of atoms and molecules over time
- Rely on experimental information from public databases
 - NCBI Databases and RCSB Protein Data Bank

Structure Prediction Methods

- Comparative Modeling
 - Prediction is based on amino acid sequence and structures of similar molecules available
- Fold recognition
 - Predicts folded structure by aligning a protein of **unknown** structure and a protein of **known structure** for low levels of sequence identity (<25%)
- Ab initio
 - Predicts the structure of proteins from the sequence and using molecular energy calculations (Schrodinger equation)



Structure Prediction Example

Impact on COVID-19 research

- Researchers have provided key insights into the SARS-CoV-2 proteins through structure prediction
 - Identified critical residues
 - Contextualized variant perturbations
 - Improved understanding of molecular recognition
- Spike fusion glycoprotein example
 - Challenging to characterize experimentally
 - Modeling + molecular dynamics helped researchers understand the roles of glycans on the dynamics of the protein

Casalino et al, *Beyond Shielding: The Roles of Glycans in the SARS-CoV-2 Spike Protein*, PMID:33140034



Homology Modeling vs *Ab initio* Prediction

Ab initio Prediction	Comparative Modeling
Applicable to any sequence	Applicable to only those sequences with recognizable similarity to a template structure
Not very accurate ($>4\text{\AA}$ RMSD)	Fairly accurate ($<3\text{\AA}$ RMSD), similar to low resolution X-ray structure
Attempted for proteins of <100 residues	Not limited by size
Accuracy and applicability are limited by our understanding of the protein folding problem	Accuracy and applicability are limited by the number of known folds