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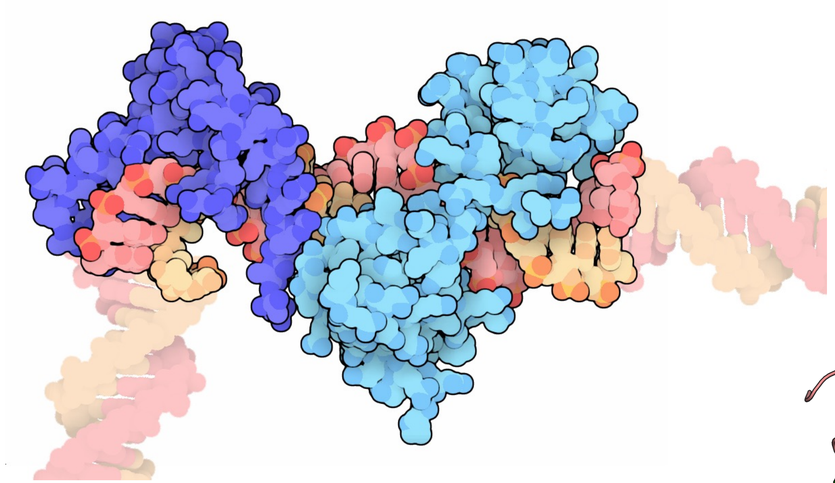
Introduction

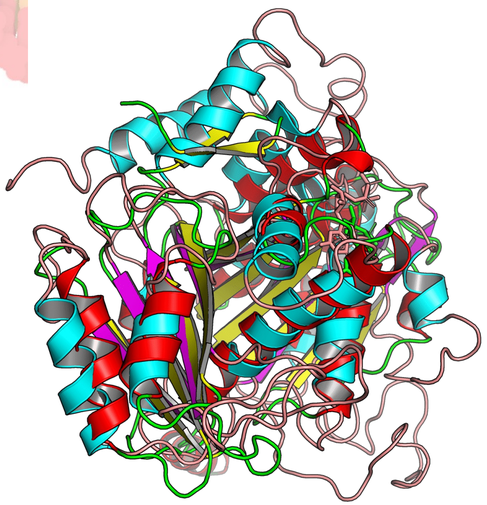
L1, Structural Bioinformatics

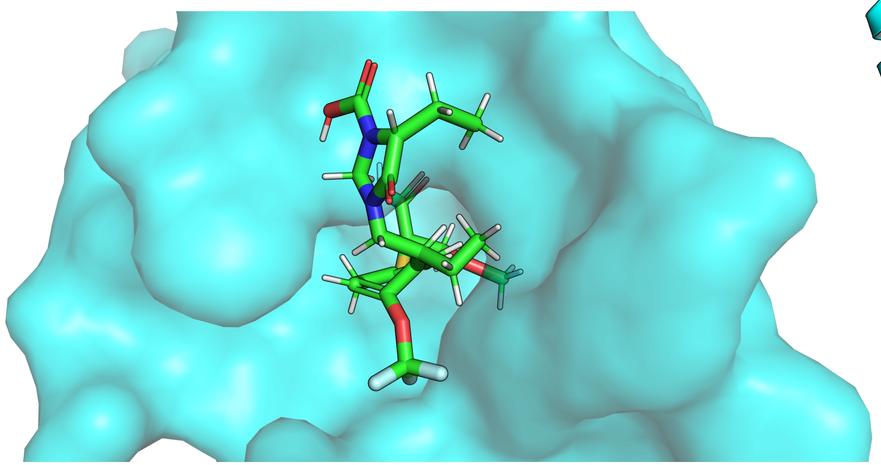
WiSe 2023/24, Heidelberg University

Structural Bioinformatics

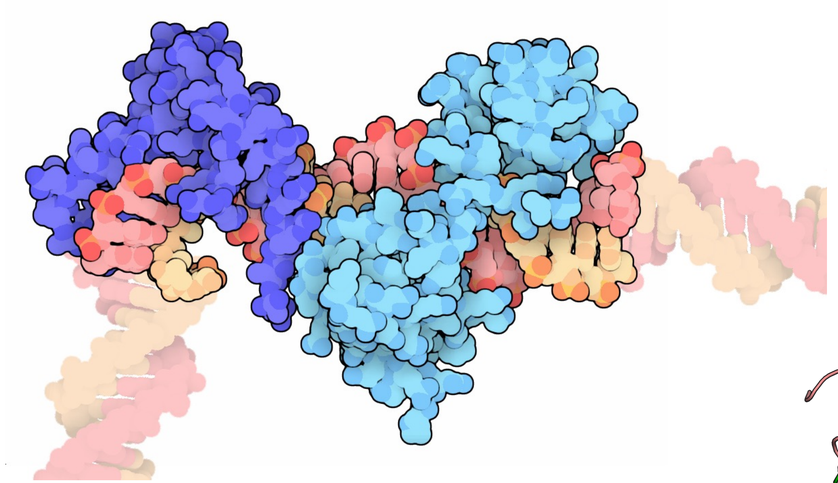
Structural Bioinformatics

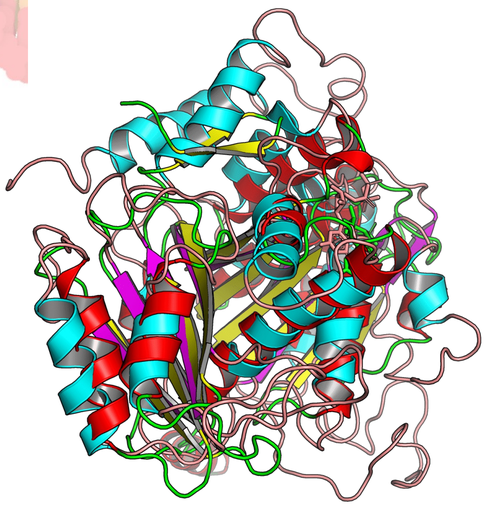


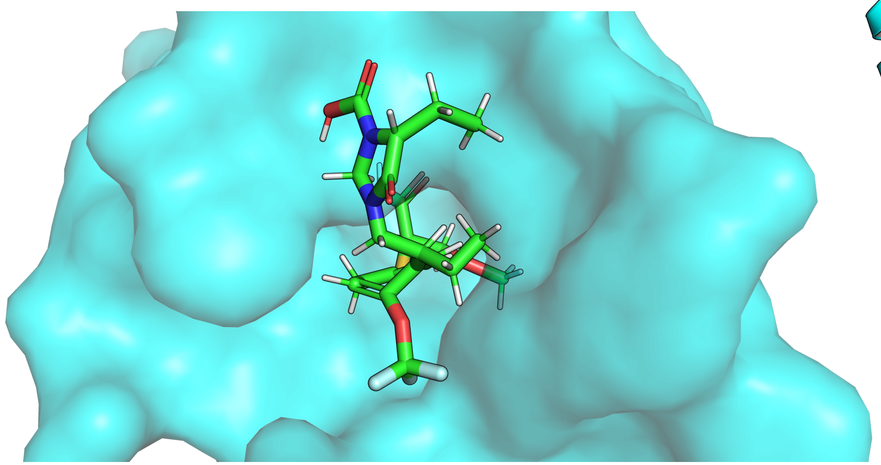


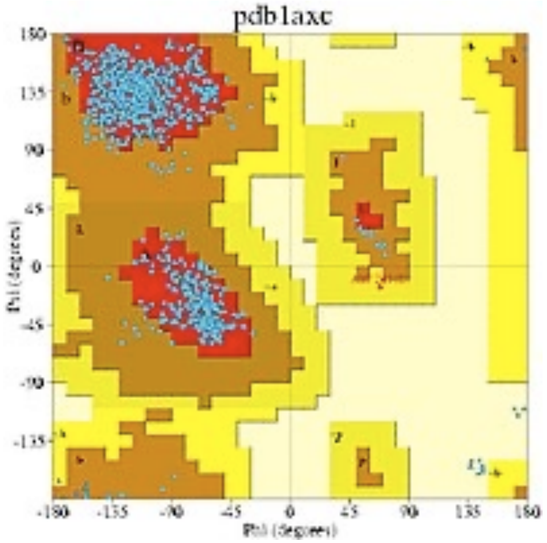


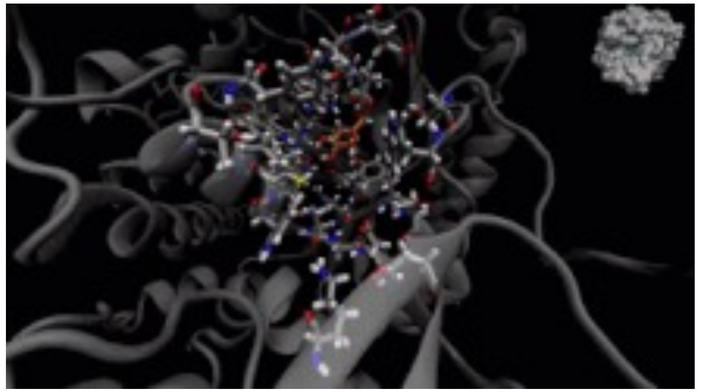
Structural Bioinformatics



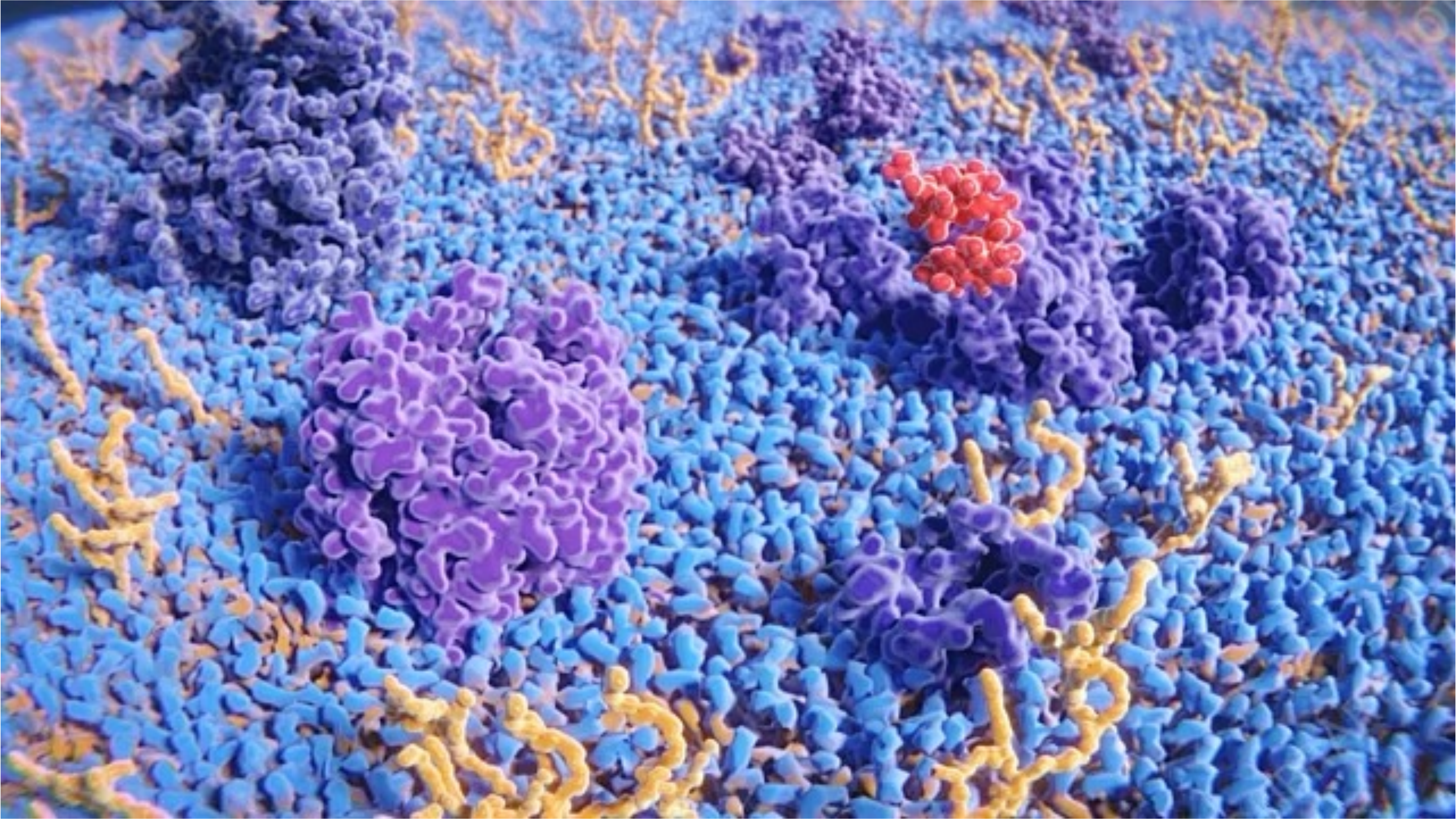








Source: Wikipedia.org

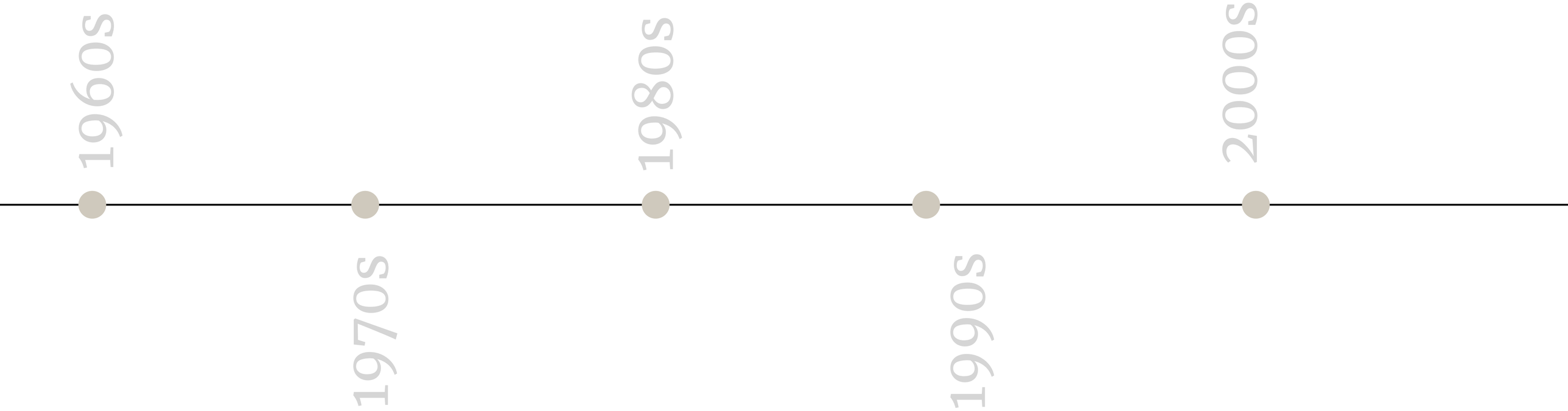


Overview

1. A Brief History of the Field
2. Where we are and where we are headed
3. This course
4. To-Dos for you!

Where do we come from?

Bioinformatics did not start structural, and not with DNA



Jeff Gauthier and others, A brief history of bioinformatics, *Briefings in Bioinformatics*, Volume 20, Issue 6, November 2019, Pages 1981–1996, https://doi.org/10.1093/bib/bby063

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1960s

PROTEIN SEQUENCE ASSEMBLY+ALIGNMENT

Edman Sequencing, Dayhoff, Needleman-Wunsch (1970)

1970s

1980s

1990s

2000s

```
            Thr-His-Glu-Cys         [Peptide]
                    Glu-Cys-Ala-Thr [Peptide]
        Lys-Thr-His                 [Peptide]
Met-Ile-Lys                         [Peptide]
-------------------------------------------
Met-Ile-Lys-Thr-His-Glu-Cys-Ala-Thr [Protein]
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THE SHIFT TO DNA

Sanger Sequencing, Phylogenetics

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THE PC MOVEMENT

Open-source, Journals, Perl&Python

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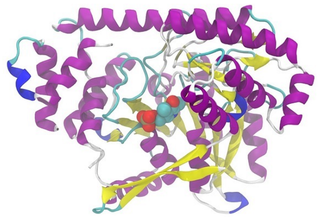

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WWW, GENOMES & STRUCTURES

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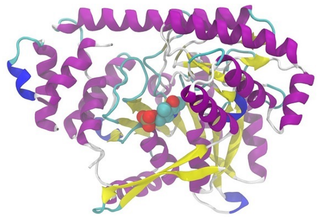

2000s

HIGH THROUGHPUT

NGS, Compute Clusters, PDB 3000 -> 8000 entries

```
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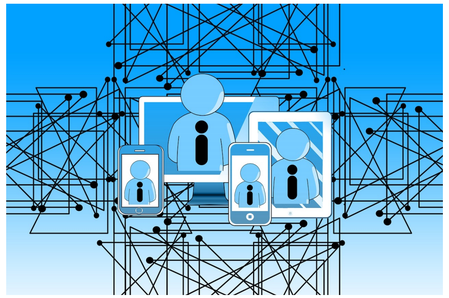

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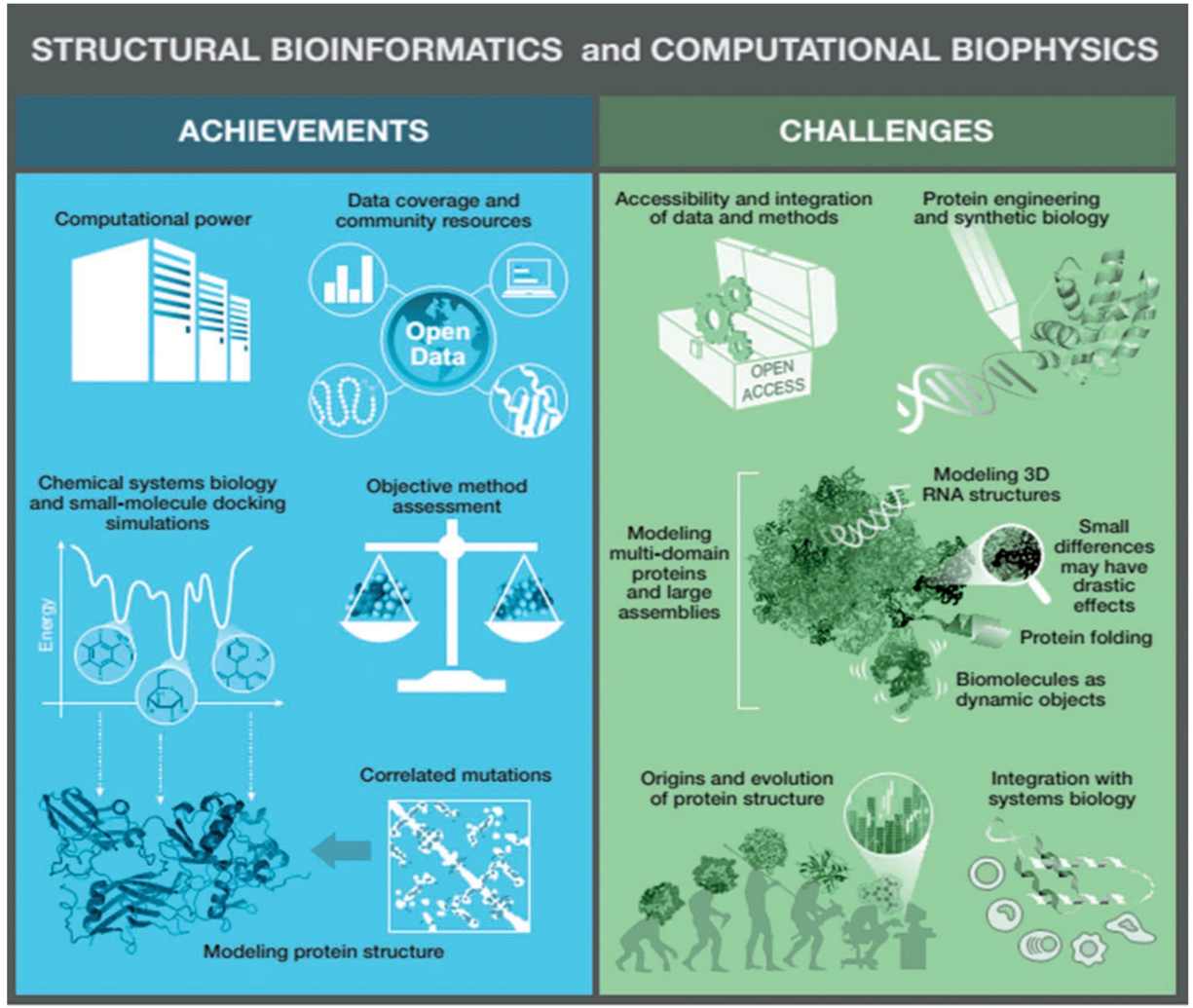
Where are we today?

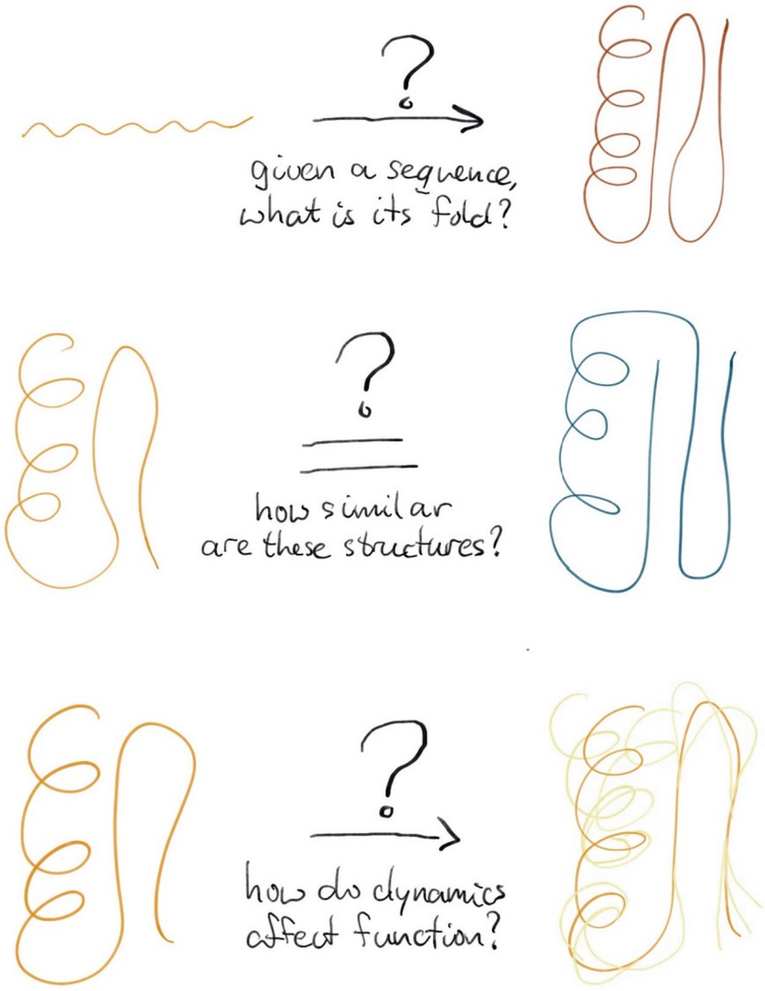
Achievements in Structural Bioinformatics (2014)



Bioinformatics, Volume 31, Issue 1, January 2015, Pages 146–150, https://doi.org/10.1093/bioinformatics/btu769.

What are the question we ask?

And how can we answer them?



Protein Structure
Prediction
AlphaFold2

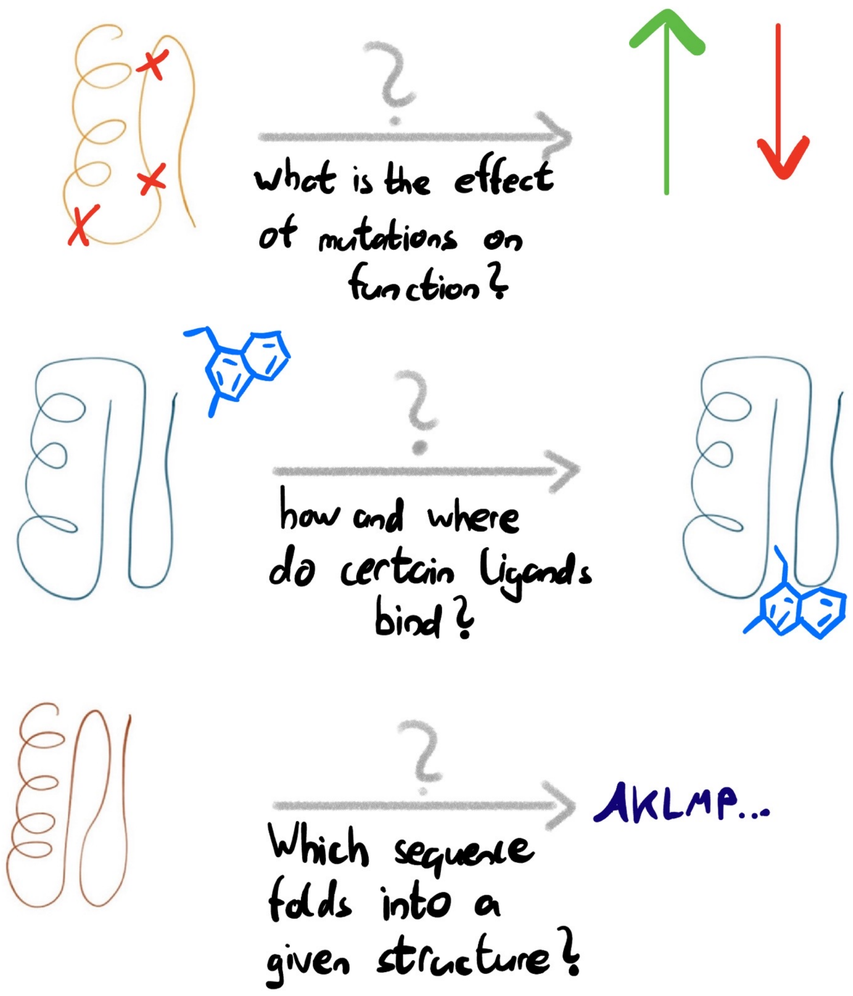
Sequence Alignments
Structure Alignments
Classification

MD Simulations
Protein Design

Feenstra & Abeln, 2014-2023 Intro Prot Struc Bioinf

What are the question we ask?

And how can we answer them?



Protein Engineering

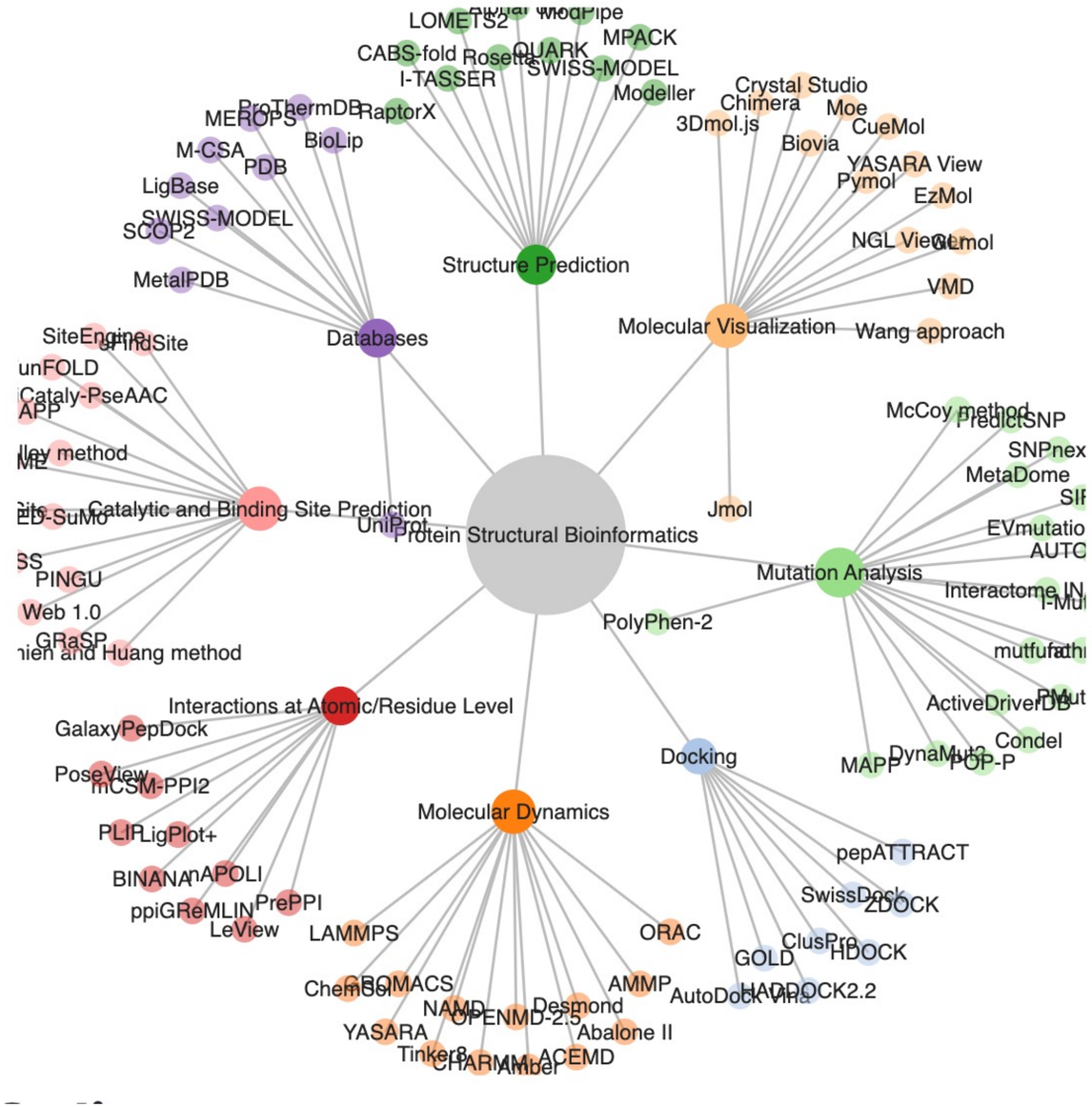
Docking
Drug Design

Inverse Folding
Protein Design

Feenstra & Abeln, 2014-2023 Intro Prot Struc Bioinf

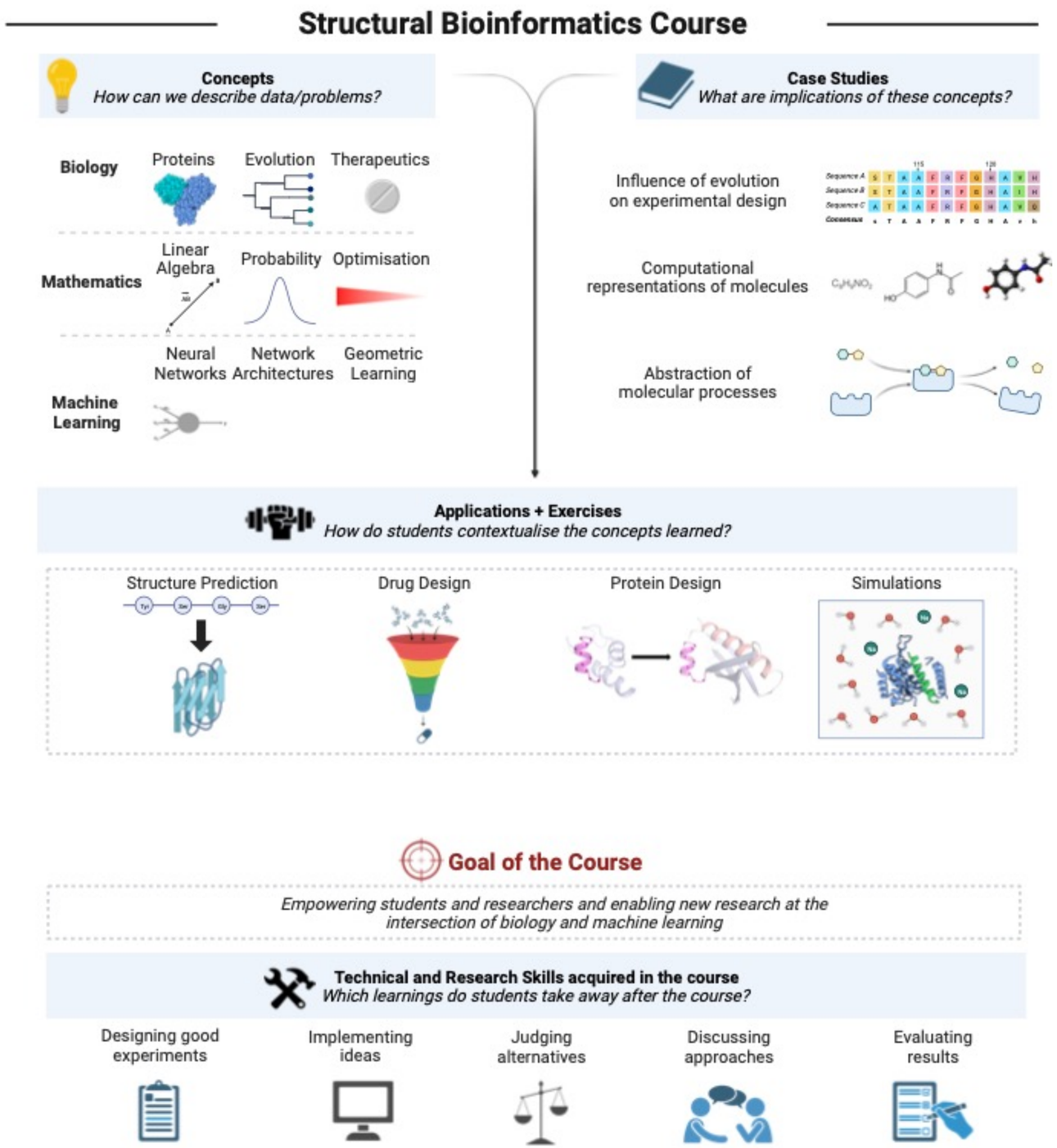
What are the tools at our disposal?

PreStO



This course

What will we talk about?



This course

Lecture	Biology	Mathematics	CS/Machine Learning	Case Studies
L1: Introduction	Protein structure, history of the field	Intro to linear algebra + probability	Biological file formats + handling	PDB files
L2: ML Basics	-	Optimisation, gradient descent	Neural networks, basic notions	PyTorch
L3: ML Architectures	Computational representation of proteins	Matrix Algebra	CNNs, RNNs, transformers	AlexNet, transformers
L4: Language, Evolution and Bioinformatics	Homology, phylogeny	Distance metrics, clustering	Language models, data leakage	ESM
L5: Geometric Deep Learning	Computational representation of generic molecules	Invariance, equivariance, group theory	Graph Neural Networks (GNNs), geometric graph learning	GCN, GAT, EGNN
L6: Protein Structure Prediction	Structure-Function relationship, coevolution, protein dynamics/ interactions	End-to-end differentiability, quaternions	Inductive biases in model building, self-supervised learning	AlphaFold2, ESMFold
L7: Generative Modelling	-	distribution learning, score functions	Function modelling vs generative modelling, VAEs, diffusion models	Autoregressive VAEs, DDPMs
L8: Protein Design	Sequence- vs structure-based methods, catalysis, functional motifs	SO(3) group equivariance	Equivariant diffusion models	Rosetta, RFDiffusion, ProteinMPNN
L9: Simulations	Protein dynamics, conformational flexibility, structure ensembles	Numerical vs analytical integration, Newton's equations of motion	Performance/accuracy trade-off, coarse-graining, multiprocessing	GROMACS, Allegro
L10: Drug Design	Protein-ligand interactions, virtual screening	-	Rephrasing a problem as a generative one, data-driven vs rule-based methods	AutoDock, DIffDock, DiffSBDD
L11: Further Topics and Conclusion	Summary and Conclusion	Summary and Conclusion	Summary and Conclusion	-

Know your tools

Pymol – Python - Proteins

PyTorch

To-Dos for you!

1. Enter the Discord server
2. Install Pymol
3. Read the Python Post and do Google Colab Intro
4. Do the first exercises!

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Math Primer 1: Linear Algebra

L1, Structural Bioinformatics

WiSe 2023/24, Heidelberg University
Kieran Didi

Overview

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Scalars

- A scalar is a single number
- Integers, real numbers, rational numbers, etc.
- We denote it with italic font:

$$a, n, x$$

(Goodfellow 2016)

Vectors

- A vector is a 1-D array of numbers:

$$\boldsymbol{x} = \begin{bmatrix} x_1 \\ x_2 \\ \vdots \\ x_n \end{bmatrix}. \tag{2.1}$$

- Can be real, binary, integer, etc.

- Example notation for type and size:

$$\mathbb{R}^n$$

(Goodfellow 2016)

Matrices

- A matrix is a 2-D array of numbers:

Row

$$\begin{bmatrix} A_{1,1} & A_{1,2} \\ A_{2,1} & A_{2,2} \end{bmatrix}. \tag{2.2}$$

Column

- Example notation for type and shape:

$$\boldsymbol{A} \in \mathbb{R}^{m \times n}$$

(Goodfellow 2016)

Tensors

- A tensor is an array of numbers, that may have
  - zero dimensions, and be a scalar
  - one dimension, and be a vector
  - two dimensions, and be a matrix
  - or more dimensions.

(Goodfellow 2016)

Matrix Transpose

$$(\boldsymbol{A}^\top)_{i,j} = A_{j,i}. \tag{2.3}$$

$$\boldsymbol{A} = \begin{bmatrix} A_{1,1} & A_{1,2} \\ A_{2,1} & A_{2,2} \\ A_{3,1} & A_{3,2} \end{bmatrix} \Rightarrow \boldsymbol{A}^\top = \begin{bmatrix} A_{1,1} & A_{2,1} & A_{3,1} \\ A_{1,2} & A_{2,2} & A_{3,2} \end{bmatrix}$$

Figure 2.1: The transpose of the matrix can be thought of as a mirror image across the main diagonal.

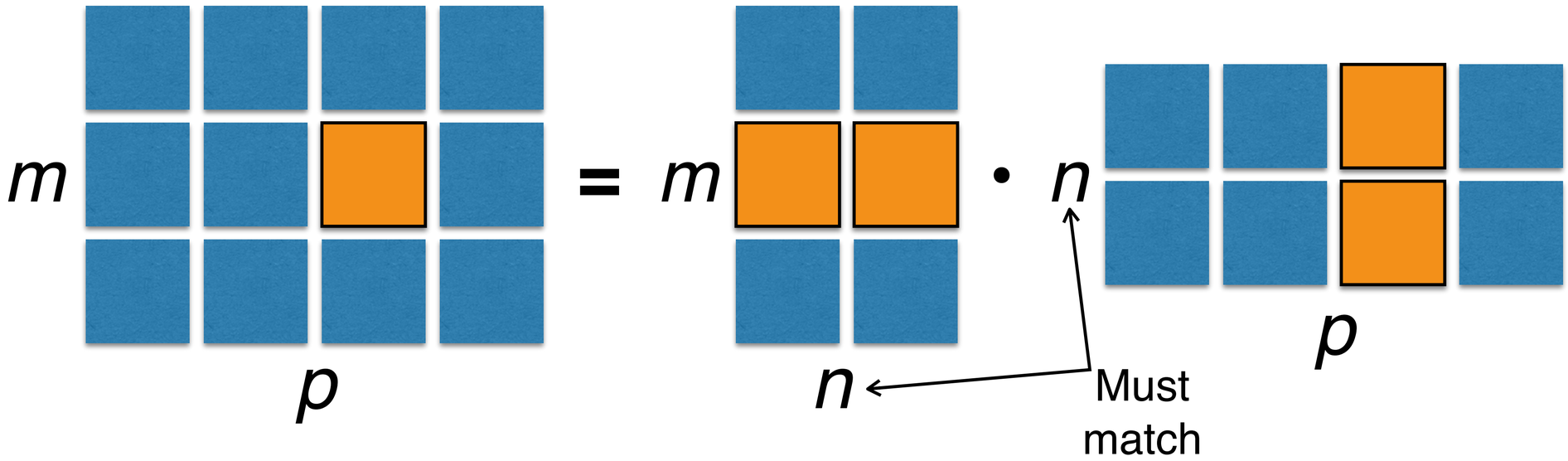
$$(\boldsymbol{AB})^\top = \boldsymbol{B}^\top \boldsymbol{A}^\top. \tag{2.9}$$

(Goodfellow 2016)

Matrix (Dot) Product

$$\boldsymbol{C} = \boldsymbol{A}\boldsymbol{B}. \tag{2.4}$$

$$C_{i,j} = \sum_k A_{i,k} B_{k,j}. \tag{2.5}$$



(Goodfellow 2016)

Identity Matrix

$$\begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}$$

Figure 2.2: *Example identity matrix*: This is $\boldsymbol{I}_3$.

$$\forall \boldsymbol{x} \in \mathbb{R}^n, \boldsymbol{I}_n \boldsymbol{x} = \boldsymbol{x}. \tag{2.20}$$

(Goodfellow 2016)

Systems of Equations

$$\boldsymbol{A}\boldsymbol{x} = \boldsymbol{b} \tag{2.11}$$

expands to

$$\boldsymbol{A}_{1,:}\boldsymbol{x} = b_1 \tag{2.12}$$

$$\boldsymbol{A}_{2,:}\boldsymbol{x} = b_2 \tag{2.13}$$

$$\dots \tag{2.14}$$

$$\boldsymbol{A}_{m,:}\boldsymbol{x} = b_m \tag{2.15}$$

(Goodfellow 2016)

Solving Systems of Equations

- A linear system of equations can have:
  - No solution
  - Many solutions
  - Exactly one solution: this means multiplication by the matrix is an invertible function

(Goodfellow 2016)

Matrix Inversion

- Matrix inverse:

$$\boldsymbol{A}^{-1}\boldsymbol{A} = \boldsymbol{I}_n. \tag{2.21}$$

- Solving a system using an inverse:

$$\boldsymbol{A}\boldsymbol{x} = \boldsymbol{b} \tag{2.22}$$

$$\boldsymbol{A}^{-1}\boldsymbol{A}\boldsymbol{x} = \boldsymbol{A}^{-1}\boldsymbol{b} \tag{2.23}$$

$$\boldsymbol{I}_n\boldsymbol{x} = \boldsymbol{A}^{-1}\boldsymbol{b} \tag{2.24}$$

- Numerically unstable, but useful for abstract analysis

Invertibility

- Matrix can't be inverted if…
  - More rows than columns
  - More columns than rows
  - Redundant rows/columns ("linearly dependent", "low rank")

Norms

- L^p norm

$$||\boldsymbol{x}||_p = \left(\sum_i |x_i|^p \right)^{\frac{1}{p}}$$

- Most popular norm: L2 norm, *p*=2
- L1 norm, *p*=1: $||\boldsymbol{x}||_1 = \sum_i |x_i|. \quad (2.31)$
- Max norm, infinite *p:* $||\boldsymbol{x}||_\infty = \max_i |x_i|. \quad (2.32)$

(Goodfellow 2016)

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Math Primer 2: Probability

L1, Structural Bioinformatics

WiSe 2023/24, Heidelberg University
Kieran Didi

Probability Mass Function

Describing discrete event space

- The domain of P must be the set of all possible states of x.
- $\forall x \in \mathrm{x}, 0 \leq P(x) \leq 1$. An impossible event has probability 0 and no state can be less probable than that. Likewise, an event that is guaranteed to happen has probability 1, and no state can have a greater chance of occurring.
- $\sum_{x \in \mathrm{x}} P(x) = 1$. We refer to this property as being **normalized**. Without this property, we could obtain probabilities greater than one by computing the probability of one of many events occurring.

Example: uniform distribution: $$P(\mathrm{x} = x_i) = \frac{1}{k}$$

Probability Density Function

Describing continuous event space

- The domain of p must be the set of all possible states of x.
- $\forall x \in \mathrm{x}, p(x) \geq 0$. Note that we do not require $p(x) \leq 1$.
- $\int p(x)dx = 1$.

Example: uniform distribution: $u(x; a, b) = \frac{1}{b-a}$.

The Sum Rule of Probability

How to calculate a marginal

$$\forall x \in \mathrm{x}, P(\mathrm{x} = x) = \sum_{y} P(\mathrm{x} = x, \mathrm{y} = y). \tag{3.3}$$

$$p(x) = \int p(x, y) dy. \tag{3.4}$$

Conditional Probability

A slice through the distribution

$$P(\mathrm{y} = y \mid \mathrm{x} = x) = \frac{P(\mathrm{y} = y, \mathrm{x} = x)}{P(\mathrm{x} = x)}.$$

The Chain Rule of Probability

How to factor a joint distribution

$$P(\mathrm{x}^{(1)}, \ldots, \mathrm{x}^{(n)}) = P(\mathrm{x}^{(1)}) \Pi_{i=2}^{n} P(\mathrm{x}^{(i)} \mid \mathrm{x}^{(1)}, \ldots, \mathrm{x}^{(i-1)}). \tag{3.6}$$

(Conditional) Independence

When can we consider events separately?

$$\forall x \in \mathrm{x}, y \in \mathrm{y},\ p(\mathrm{x} = x, \mathrm{y} = y) = p(\mathrm{x} = x)p(\mathrm{y} = y). \tag{3.7}$$

$$\forall x \in \mathrm{x}, y \in \mathrm{y}, z \in \mathrm{z},\ p(\mathrm{x} = x, \mathrm{y} = y \mid \mathrm{z} = z) = p(\mathrm{x} = x \mid \mathrm{z} = z)p(\mathrm{y} = y \mid \mathrm{z} = z). \tag{3.8}$$

Expectation

A weighted average of all possible outcomes

$$\mathbb{E}_{\mathbf{x}\sim P}[f(x)] = \sum_x P(x)f(x), \tag{3.9}$$

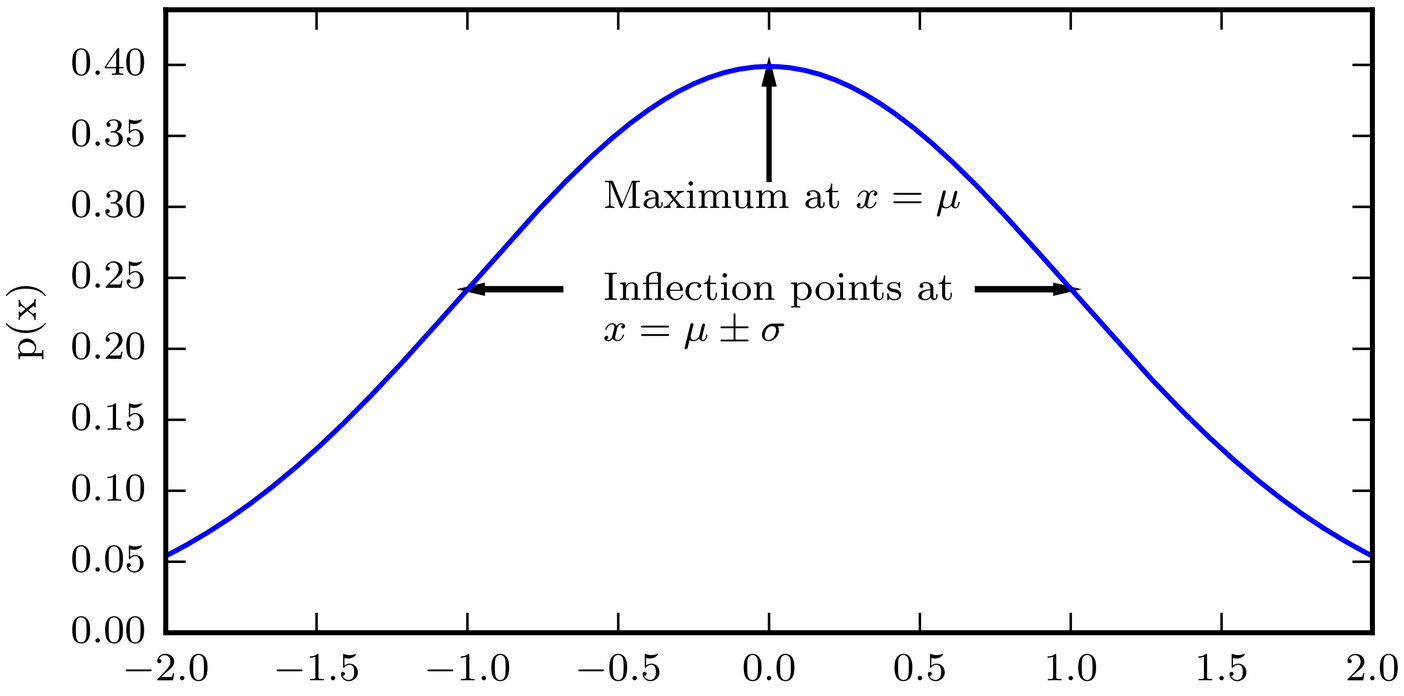
$$\mathbb{E}_{\mathbf{x}\sim p}[f(x)] = \int p(x)f(x)dx. \tag{3.10}$$

linearity of expectations:

$$\mathbb{E}_{\mathbf{x}}[\alpha f(x) + \beta g(x)] = \alpha\mathbb{E}_{\mathbf{x}}[f(x)] + \beta\mathbb{E}_{\mathbf{x}}[g(x)], \tag{3.11}$$

Gaussian Distribution

The bread-and-butter of ML



Gaussian Distribution

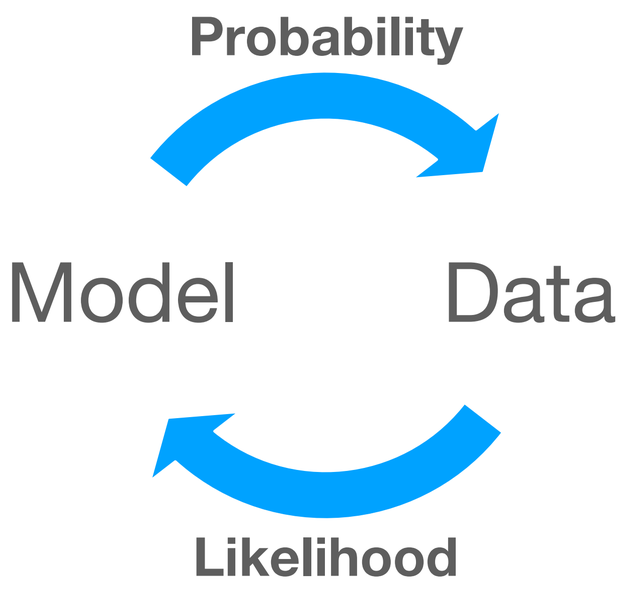
The bread-and-butter of ML

$$\mathcal{N}(x; \mu, \sigma^2) = \sqrt{\frac{1}{2\pi\sigma^2}} \exp\left(-\frac{1}{2\sigma^2}(x-\mu)^2\right). \tag{3.21}$$

$$\mathcal{N}(\boldsymbol{x}; \boldsymbol{\mu}, \boldsymbol{\Sigma}) = \sqrt{\frac{1}{(2\pi)^n \det(\boldsymbol{\Sigma})}} \exp\left(-\frac{1}{2}(\boldsymbol{x}-\boldsymbol{\mu})^\top \boldsymbol{\Sigma}^{-1}(\boldsymbol{x}-\boldsymbol{\mu})\right). \tag{3.23}$$

Probability vs Likelihood

Evaluate data vs evaluate model

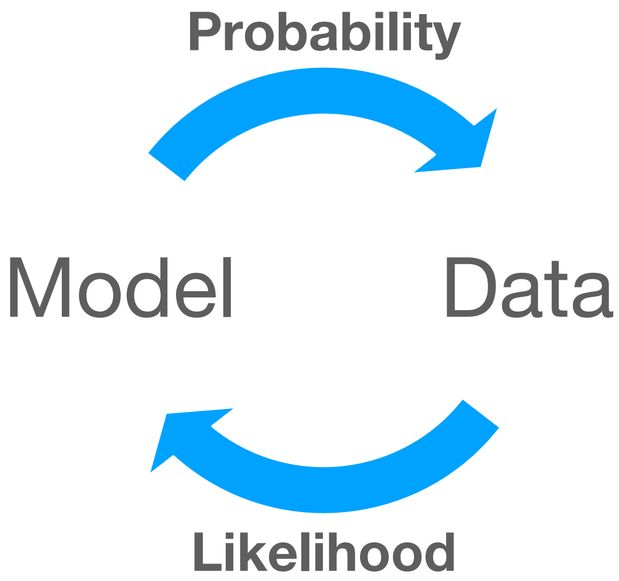


StatExchange Discussion

StatQuest Video

Probability vs Likelihood

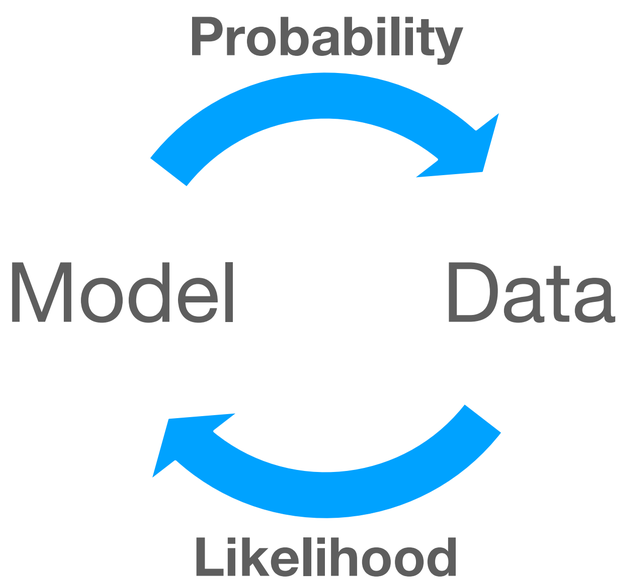
Evaluate data vs evaluate model

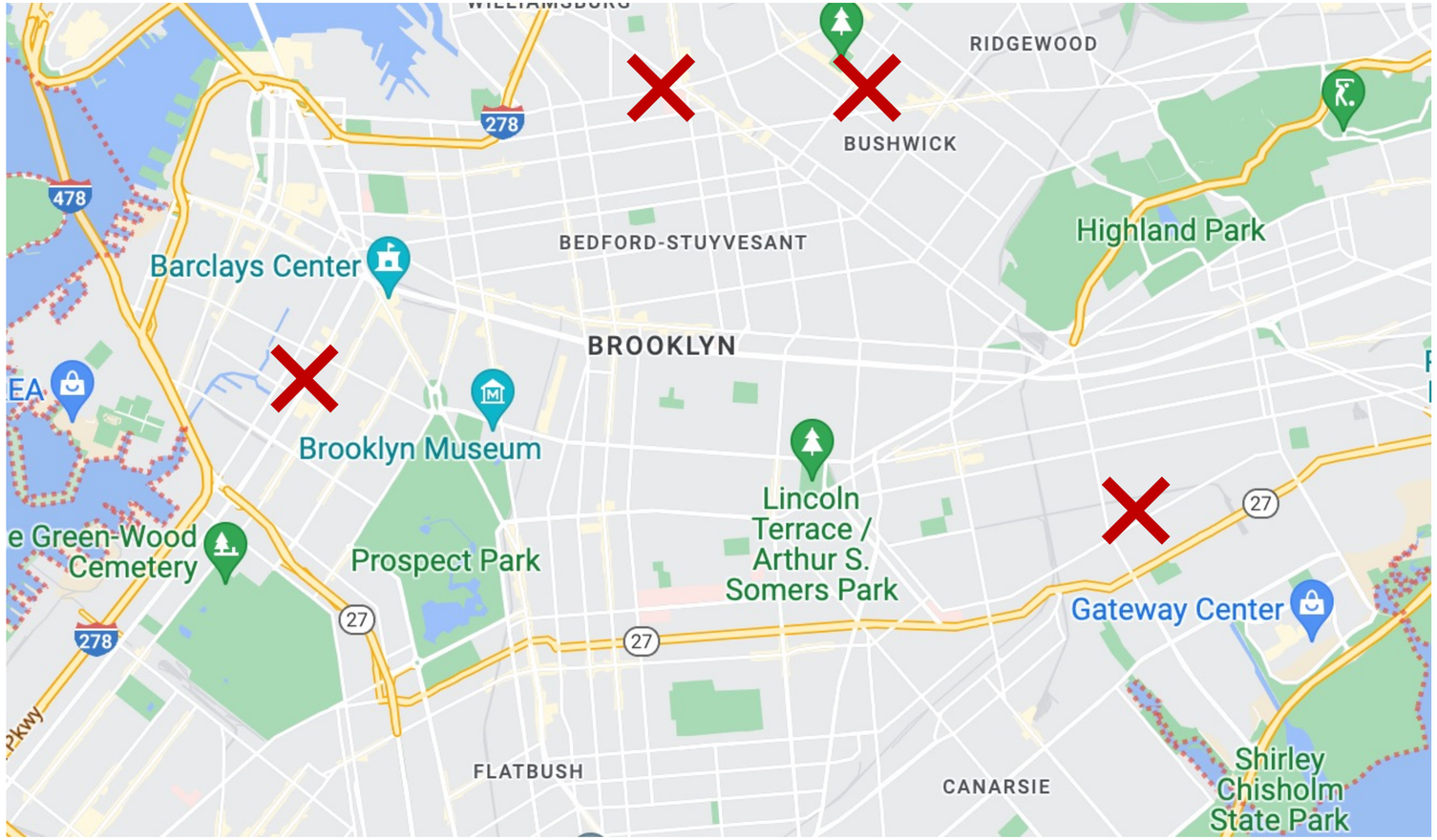


[StatExchange Discussion]
[StatQuest Video]

Probability vs Likelihood

Data x: Crime Locations



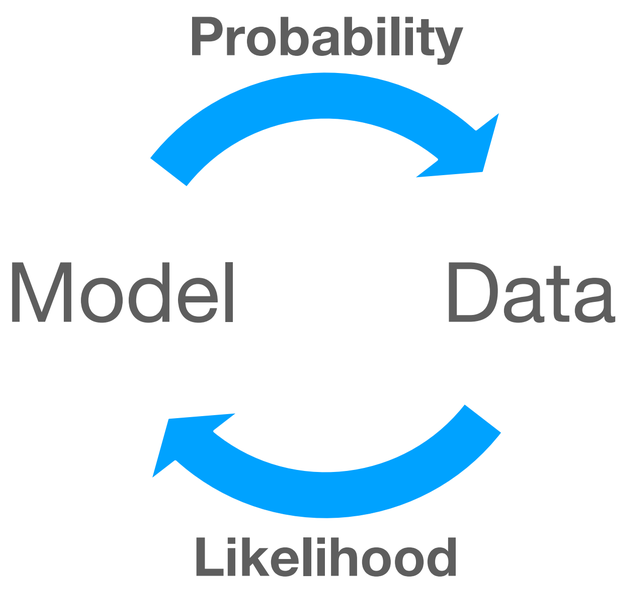


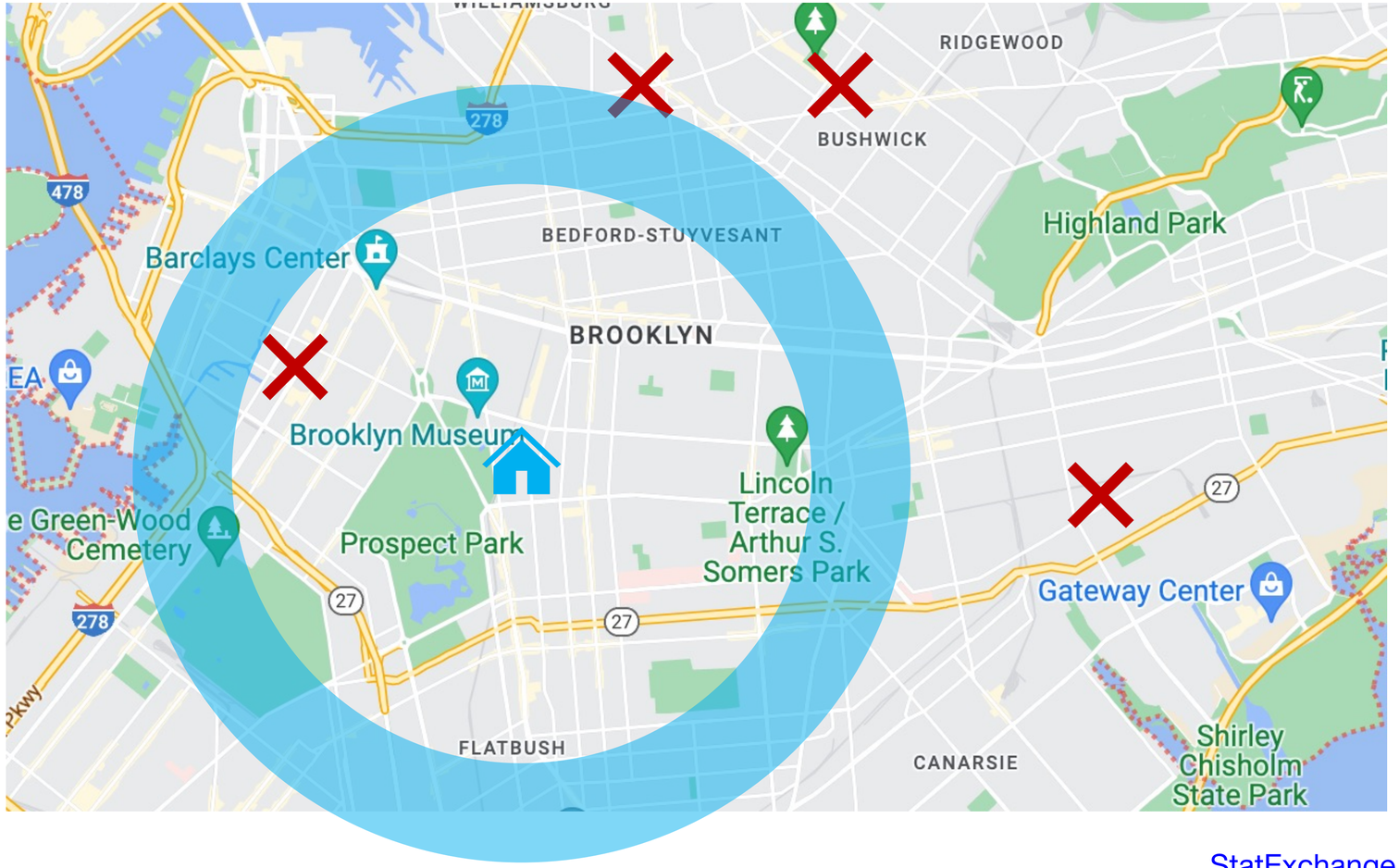
StatExchange Discussion

StatQuest Video

Probability vs Likelihood

Model Parameter θ: Criminal Location



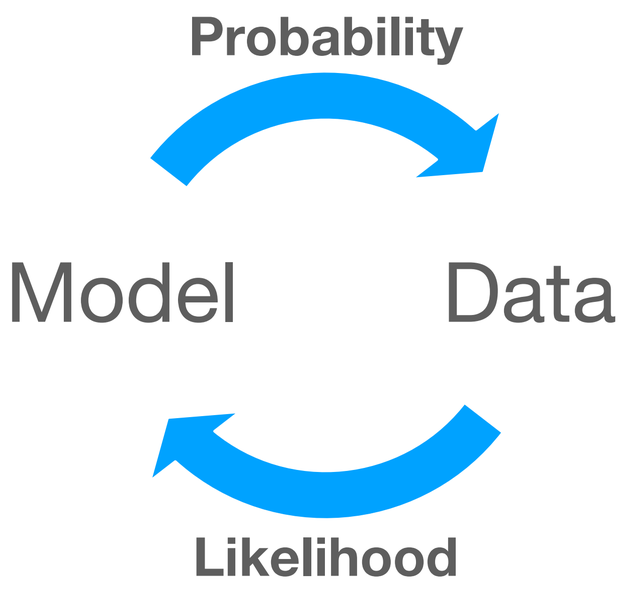


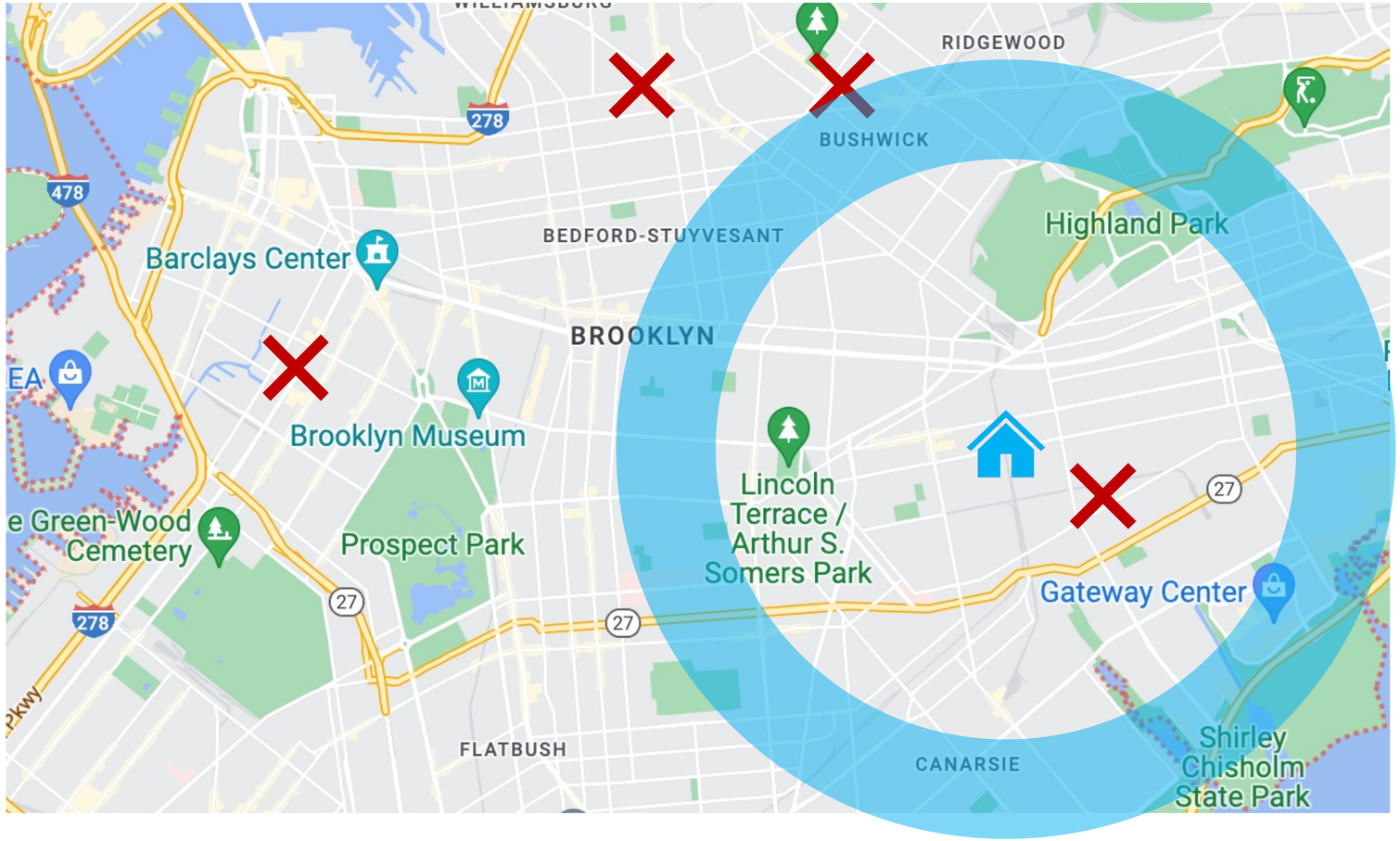
StatExchange Discussion

StatQuest Video

Maximum Likelihood

Modify parameters to make data maximally likely





[StatExchange Discussion]

[StatQuest Video]

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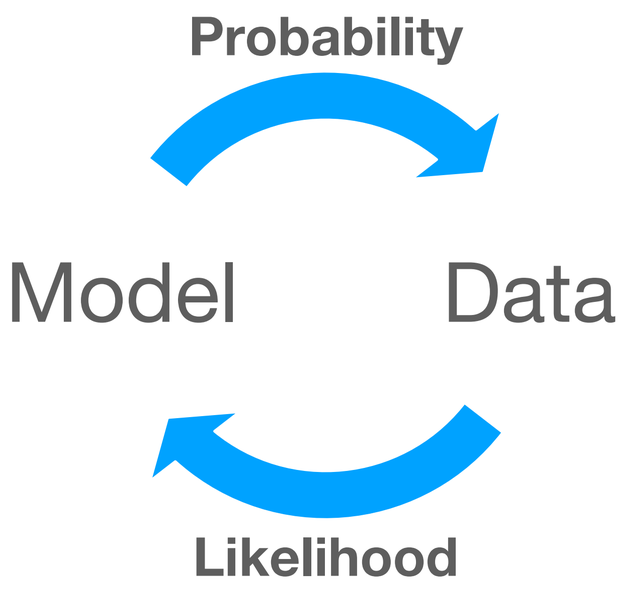

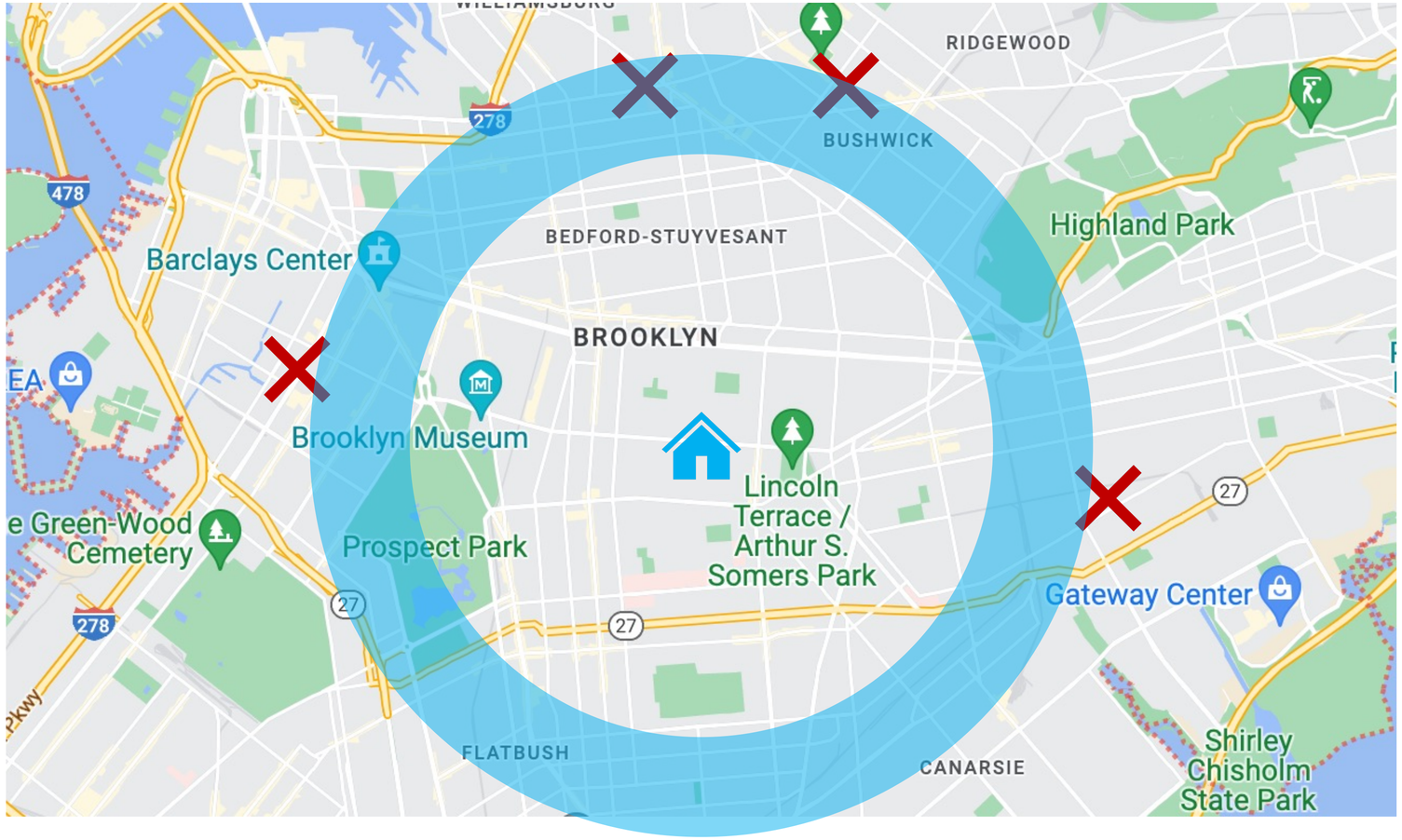

[StatExchange Discussion]

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Bayes' Rule

Incorporating prior knowledge

$$P(\mathrm{x} \mid \mathrm{y}) = \frac{P(\mathrm{x})P(\mathrm{y} \mid \mathrm{x})}{P(\mathrm{y})}. \tag{3.42}$$

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Frequentists versus Bayesians

Data is king vs appreciate prior knowledge and uncertainity

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