AMAT 342 Lecture 12, 10/3/19

Today: Edit distance examples
Another example of a metric from biology/chem

Review: Let S be the set of DNA sequences, (i.e., strings of letters A, T, C, G of any length).

Def: The edit distance $d_{edit} : S \times S \to [0, \infty)$, is given by

$d_{edit}(x, y)$ = minimum # el. ops. required to transform x into y.

Elementary Operations:
- change one letter
- insert one letter
- remove one letter

Example: $x = ATA$
$y = TAT$

$x = ATA \longrightarrow AT \longrightarrow TAT = y.$

There's no single elementary operation transforming x into y, so $d_{edit}(x, y) = 2$.

Exercise: $x = ATCG$ $\quad d_{edit}(x,y) = ?$
$y = GGTCG$ $\quad$ Ans: 2.

$ATCG \to GTCG \to GGTCG$

Let's verify that d_{edit} is a metric:

- Property 1) is clearly satisfied
- An elementary operation can always be undone by an elementary operation, so $d_{edit}(x,y) = d_{edit}(y,x)$.
- To establish triangle ineq. need to show that $\forall x,y,z \in S,\ d(x,z) \leq d(x,y) + d(y,z)$.
  Let $d(x,y) = m$, $d(y,z) = n$.
  Then there's a sequence α of elementary ops. transforming x to y, and a sequence β of elt. ops. transforming y to z. Then α followed by β is a sequence of $m+n$ elt. ops. transforming x to z. Thus $d(x,z) \leq m+n$.

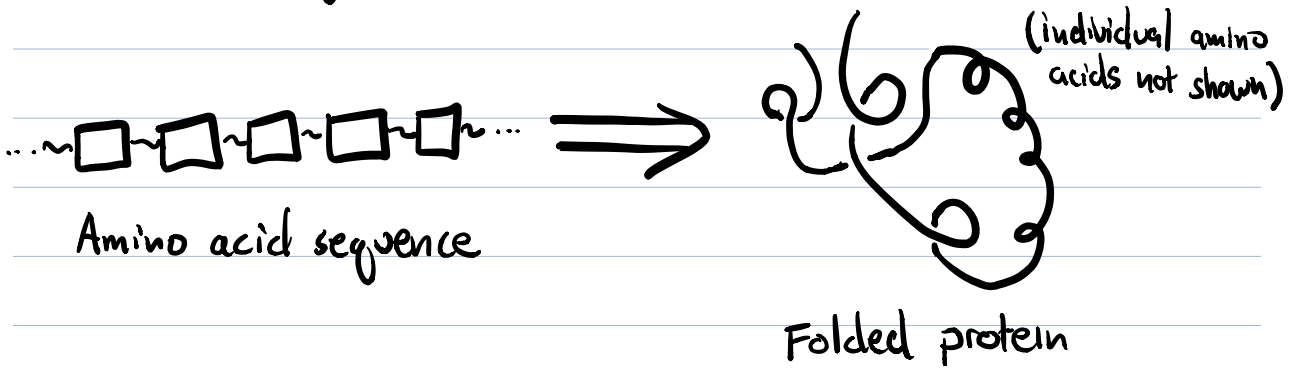
Another example of a metric space from biology

Background: The primary function of DNA is to serve as a blue-print from which proteins are constructed.

Simplified definition of a protein:
A protein is a string of subunits called amino acids connected by covalent bonds.

There are 20 different amino acids, with names like "arginine", "lysine," and "tryptophan."

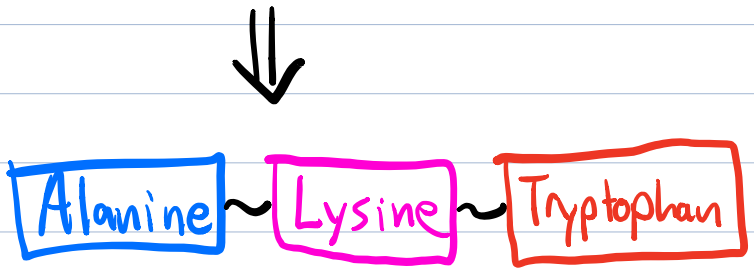
Proteins fold into complex 3-D structures, with essential biological function (eg. enzymes, neurotransmitters)



DNA sequences called Genes specify the amino acid sequence of protein.

Rough explanation: Three nucleotides specify one amino acid.

Ex: CGA TTT ACC



Determining the amino acid sequence from the DNA sequence is very easy.

But accurately determining the 3-D structure of the protein from the amino acid sequence is challenging

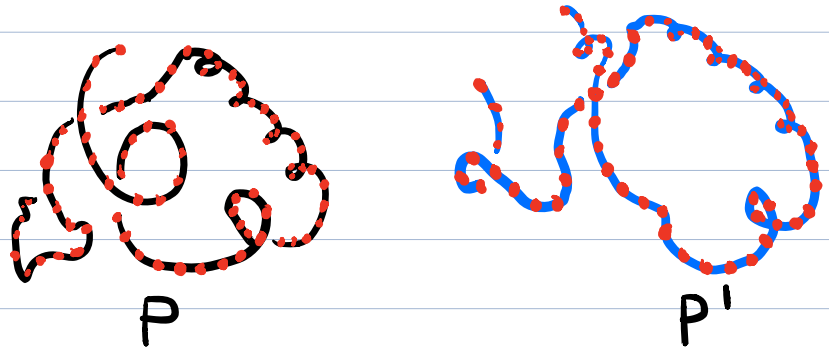
This is called the "protein structure prediction problem."
- one of the fundamental problems of computational biology
- applications to drug discovery
- biannual competitions on this problem called CASP
- lots of software available.

Note: In favorable cases, the structure can be determined by experiment, e.g., by a technique called x-ray crystallography. But this is expensive, time consuming.

and requires a lot of skill.

Computers are used to get fast solutions.

Question: Suppose I know the folded structure P of a protein. How do I measure the accuracy of a predicted structure P'?



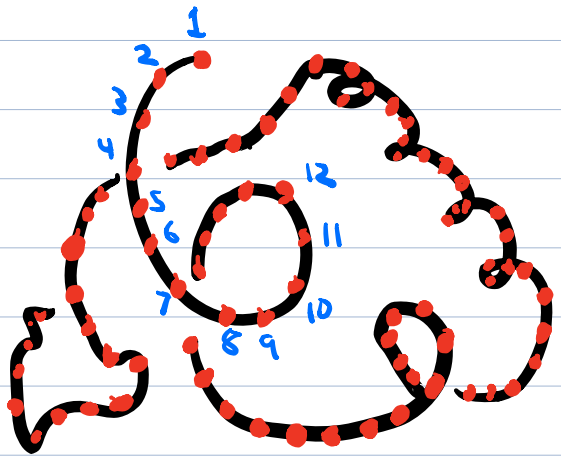
To assess the performance of a structure prediction method, e.g. in a competion like CASP, we need an answer.

Standard Answer: Compute a metric called **RMSD** (root mean squared deviation) between P and P'.

RMSD is a fundamental tool in the study of molecules.

How to represent the 3-D structure of a protein P mathematically

- Order the atoms of the protein (choice of order doesn't matter).



P

- Let O^n denote the set of all ordered subsets of $\mathbb{R}^3$ of size n. We think of P as an element of O^n.

- For $P \in O^n$, denote the i^{th} point in P by (x_i, y_i, z_i)

- Define a function $V: O^n \to \mathbb{R}^{3n}$ by

$$V(P) = (x_1, y_1, z_1, x_2, y_2, z_2, \ldots, x_n, y_n, z_n).$$

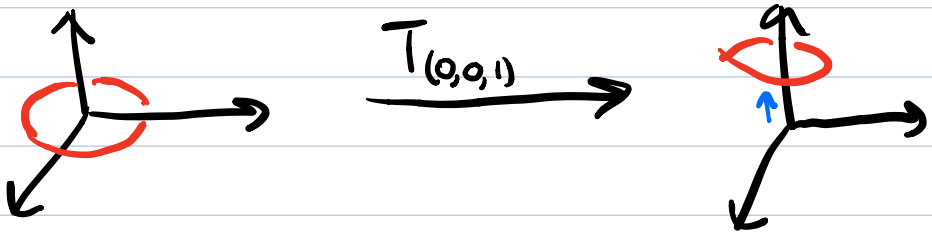
V is invertible!

This represents the protein's 3-D structure as a single point in a high-dimensional space!

Note: This representation throws away a lot of info about the protein (atom type, bond info), but for many applications, that is ok.

Rigid motions

- A **translation** in $\mathbb{R}^3$ is a function $T_{\vec{v}}: \mathbb{R}^3 \to \mathbb{R}^3$ given by $T_{\vec{v}}(\vec{x}) = \vec{x} + \vec{v}$ for some fixed $\vec{v} \in \mathbb{R}^3$

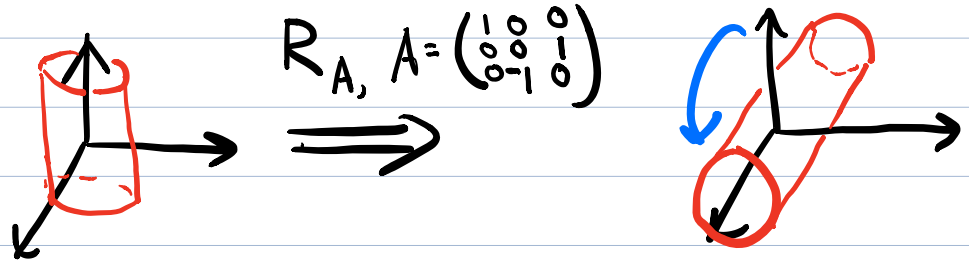


Interpretation: $T_{\vec{v}}$ shifts a geometric object in the direction $\vec{v}$ without rotating.

- A **rotation** in $\mathbb{R}^3$ is a function $R_A: \mathbb{R}^3 \to \mathbb{R}^3$ of the form

$$R_A(\vec{x}) = A\vec{x}$$ where A is a 3×3 matrix with determinant 1

Interpretation: R_A rotates a geometric object about the origin in $\mathbb{R}^3$.



A rigid motion in $\mathbb{R}^3$ is a translation followed by a rotation, i.e., a function

$$\varphi : \mathbb{R}^3 \to \mathbb{R}^3 \text{ of the form}$$

$$\varphi = R_A \circ T_{\vec{v}}.$$

(R_A: rotation; $T_{\vec{v}}$: translation)

Let E be the set of all rigid motions in $\mathbb{R}^3$.

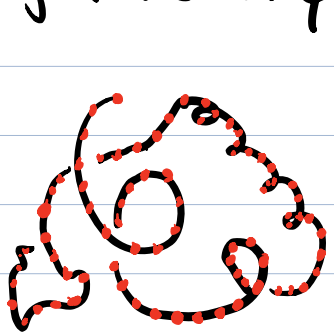
Definition: Let P, P' be 3-D structures for a given protien with n atoms, regared as subsets of $\mathbb{R}^3$ of size n.

$$RMSD(P, P') = \min_{\varphi \in E} \frac{1}{\sqrt{n}} d_2(V(P), V(\varphi(P'))).$$

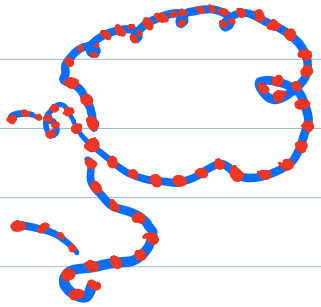
(d_2: ordinary Euclidean distance; φ: rigid motion of P')

Interpretation: To compute $RMSD(P, P')$,

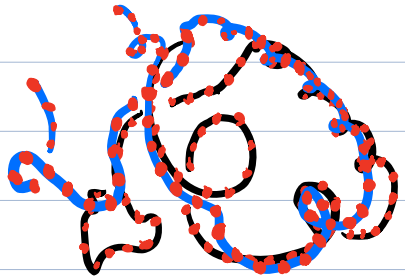
1) Align P and P' as well as possible via a rigid motion φ



P



P'



P and $\varphi(P')$

2) Represent P and $\varphi(P')$ as points $V(P), V(\varphi(P'))$ in $\mathbb{R}^{3n}$.

3) RMSD is the Euclidean distance between these points, normalized so that RMSD doesn't tend to grow as # of atoms grows.

Formally, we regard this as a function

$$\text{RMSD}: O^n \times O^n \to [0, \infty).$$

This function is symmetric and satisfies the triangle inequality, but we can have

$\text{RMSD}(P, P') = 0$ if $P \neq P'$ but $\varphi(P) = P'$ for some rigid motion φ.

Here's how we get a genuine metric here:

Define an equivalence relation $\sim$ on O^n by

$P \sim Q$ iff $\exists$ a rigid motion $\varphi: \mathbb{R}^3 \to \mathbb{R}^3$ with $\varphi(P) = Q$.

<u>Fact</u>: $\text{RMSD}(P, Q) = \text{RMSD}(P', Q')$ if $P \sim P'$ and $Q \sim Q'$

(Exercise: Prove this).

As a consequence, $\text{RMSD}: O^n \times O^n \to [0, \infty)$ descends to a genuine metric on $O^n/\sim$.