MATHEMATICAL TECHNIQUES IN STRUCTURAL BIOLOGY

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Contents

0. Introduction

These are notes about using mathematics to study the molecular structure of molecules, especially long organic molecules like DNA and proteins. In both crystallography and NMR structure determination, mathematics plays an important role.

Distance geometry and discrete differential geometry are useful in structure determination using NMR data. Molecules can be studied using matrices of distances between pairs of atoms. The study of such matrices is called distance geometry. Proteins and DNA are also long strings of atoms that can be modeled using differential geometry of curves. These techniques also apply to other questions in shape theory and robotics.

Crystallography uses a different method. The molecule is modeled using level surfaces of a positive function giving the electron density at a point in space. This function is expanded as a Fourier series and the experiment gives information on the coefficients of the series.

Section 1 discusses the structure of DNA. The discovery in 1953 of the double helical structure of the DNA molecule by Watson and Crick initiated a revolution in biology. First, it dramatically showed that the structure of a molecule can give a clear picture of how it functions. In this case the double helical structure of DNA shows how it replicates itself and transmits genetic information in the form of a code. This helped initiate the subject of bioinformatics.

Secondly, the discovery by Watson and Crick of the structure of DNA showed that molecular structures can be discovered by a considering chemical properties, experimental data, and geometry. Ball and stick models and paper cutouts were used to understand the geometry of the molecule. In the computer era, all the relevant data is incorporated databases, and computers are able to manipulate the structure. This is computational structural biology and molecular dynamics. Section 9 gives a brief introduction to this.

There was a key piece of evidence that helped in the discovery of the structure of DNA, an X-ray diffraction pattern found by Rosalind Franklin. The relationship between the structure and the diffraction pattern was well known to Crick, and he knew from the diffraction pattern that DNA was some kind of helix. Section 6 discusses how the electron density function of crystals is computed from diffraction intensities using Fourier series.

Section 2 discusses proteins The discovery using X-ray crystallography of the structures of the proteins myoglobin by John Kendrew in 1958 and hemoglobin by Max Perutz in 1959 showed how the arrangement of the atoms in these structures reveals how these proteins function. There are a large number of atoms in myoglobin, approximately 1200 not including hydrogens, and visualizing the arrangement of them in 3D space is difficult. A graphic artist, Irving Geis, created pictures to make the arrangement clear. The advent of computer graphics enabled those studying proteins to see graphic renditions using ribbon diagrams and rotate them with a mouse. The ribbon diagram is a graphic created by Jane S. Richardson to indicate a sequence of atoms in a helical formation. These helices are called secondary structures. Secondary structures such as alpha helices, beta sheets, and coiled coils are discussed in section 5 on torsion angles, in section 3 on the Frenet formula, and in section 8 on the discrete Frenet frame.

Protein structures are stored in a database called the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank. Each protein whose structure has been found has a file in which the coordinates in space of the center of each atom is stored. This is called a *pdb file* and it is basically a list of atoms and their coordinates in 3D space. A protein viewer program reads this file and converts it to a graphic. At this writing there are about 86,000 files in the Protein Data Bank. A description of these files is given in section 5.

In any discussion of shapes we are dealing with the geometry of space. The most fundamental mathematical tool at our disposal is the group of Euclidean motions. The sense preserving motions can be described in terms of rotations and translations, and these can be put in matrix form. These transformations are important in understanding symmetries such as the ones seen in crystals. The simplest symmetries are given by translations and a structure with translational symmetries is called a lattices. Lattices can also have rotational symmetries but these are limited by the crystallographic restriction (section 6). Rotation matrices can also be thought of as right-handed orthonormal frames. Frames and rotation matrices are discussed in sections 3 and 4.

The fact that each peptide bond in a protein has the same geometry allows us to consider the euclidean motion form one peptide bond to the next. These trasformations are related to the Frenet formulas in the differential geometry of curves.

In studying and manipulating protein structures, it is useful to have a parameter space, a sequence of numbers which almost completely describes the structure. The set of coordinates of the atoms is too large a set. Some distances and angles between bonded atoms remain nearly the same for all proteins, and the backbone of a protein is a long string of atoms. The result is that structure can be described by a sequence of torsion angles. Torsion angles are discussed in section 5, and the way they are used to describe a structure is discussed in section 8 on the discrete Frenet frame.

Two techniques for finding protein structures are X-ray crystallography and NMR. Each technique has a set of mathematics tools used to find the structure from the data. X-ray crystallography relies on the theory of space groups describe the structure of the crystal, and on Fourier analysis to reveal the details of the atoms in the unit cell. These ideas are described in section 6.

NMR uses distance constraints or orientational constraints. Distance constraints are studied using distance and gram matrices described in section 7. Described there is the technique of calculating a sequence of coordinates from a distance matrix. This techniques is used in proving the Cayley Menger theorem and interpreting Cayley Menger determinants. Orientational constraints are used in solid state NMR and give information about the coordinates of the unit magnetic field directions in the Frenet frames along the molecule. Discrete Frenet frames are discussed in section 8. The Frenet formula derived in this section can be used to derive the Denavit-Hartenberg formula used in robotics.

One of the major goals of structural bioinformatics is to find the structure of a protein from the sequence of amino acids. Most techniques to accomplish this require the use of an energy function on a configuration space for the protein and a method of finding a configuration minimizing the energy. These ideas are briefly discussed in the section on protein folding, section 9 and illustrate using Frenet frames and the simple example of an alpha helix.

1. Molecular Genetics: DNA

This section reviews a few basic facts about genetics and DNA. There is a lot of information available from the Department of Energy. They have a primer on molecular genetics available on the web. This is a short course in some techniques in molecular biology used to find DNA sequences.

1.1. **Genetic code.**

DNA is a long molecule consisting of a string of base-pairs. Each base is a molecule called a nucleotide. There are four of these: Adenine, Cytosine, Guanine, and Thymine. We abbreviate these with the letters A, C, G, T. A long string of these four letters creates a code word, a gene, which gives instructions for the manufacturing of a protein.

The reason that the code can be duplicated and passed along is that the nucleotides pair only in certain ways: A pairs with T, and C pairs with G. These are called complementary base pairs. When the string of base pairs is pulled apart, we get two strings of complementary basepairs, each containing the same information. The discovery that genetic information is coded this lead to a branch of *bioinformatics* that investigates the similarity between long strings of letters A, T, C, G.

The big breakthrough in thinking about genetic information as digital information came with the landmark paper by Watson and Crick in 1953. This is a very short paper and easy to read. It reminds you that some important discoveries are based on simple observations. Knowledge of the geometry of molecules and chemical bonds and some clever geometric thinking were used to find the structure of DNA from only a few experimental facts. This is the prototype of how mathematics and chemistry are used to discover facts about biology.

In this lecture we discuss the geometry of the DNA base pairing. Some of the features of DNA structure are similar to protein structure, discussed in the next chapter. For example, the formation of helices and hydrogen bonds is found in both DNA and proteins. Also the pentagons and hexagons seen in the bases are similar to the ones seen on protein side-chains.

1.2. **The geometry of DNA.**

The reason that DNA functions the way it does is due to the geometrical structure of the bases. In figure 1 are close up views of the way nucleotides pair in a DNA structure.

The structure of DNA was discovered by Watson and Crick by studying the geometry of the DNA basepairs. The shapes of the molecules and the distribution of charges on them forces them to bond together only in pairs A-T and C-G. The weak bonds between the bases, indicated by the dashed lines, are called *hydrogen bonds.* The pair A-T is held together by 2 hydrogen bonds and the pair C-G by 3 hydrogen bonds. The bonds are caused by the electrical attraction between the positive and negative charges on the atoms as indicated.

1.3. **The double helix.**

The basepairs are strung together by a sugar-phosphate backbone, and form a double helix. Figures 2 and 3 show in detail how the base pairs fit into the helix.

A big clue for Watson and Crick was an x-ray diffraction photo (figure 4) of purified DNA fibers. This photo was obtained by Rosalind Franklin in the laboratory of Maurice Wilkins. The inner cross pattern of spots indicated to Watson and Crick that DNA was some sort of helix.

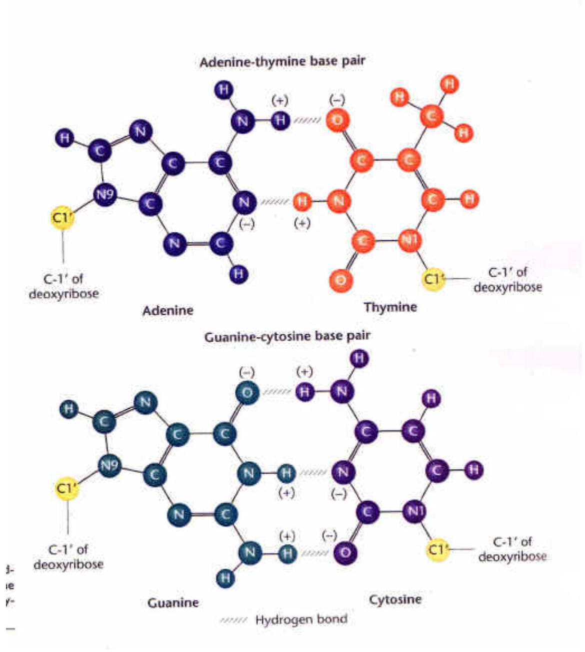


Figure 1. DNA basepairs showing the geometry of the hydrogen bonds

The relationship between the diffraction pattern and the structure of a molecule will be discussed later in the book.

1.4. **Larger organization of DNA.** In the human organism, DNA is organized into 23 pairs of chromosomes. Chromosomes are tightly wound strands of DNA. The strands are very long and without the presence of certain enzymes, DNA would become tangled and knotted. The way that DNA is ordered in chromosomes and the way it is unknotted by the enzymes is a current topic of research which uses ideas from geometry and topology.

1.5. **DNA and proteins.** The key to understanding the effect of genetics on health and disease is to understand that genes code for proteins. It is these proteins which determine the characteristics of organisms. Proteins and the genetic code will be discussed in the next lecture.

1.6. Problems.

(1) From the Watson and Crick paper, what would be the approximate length of a straight DNA helix of 10^6 basepairs?

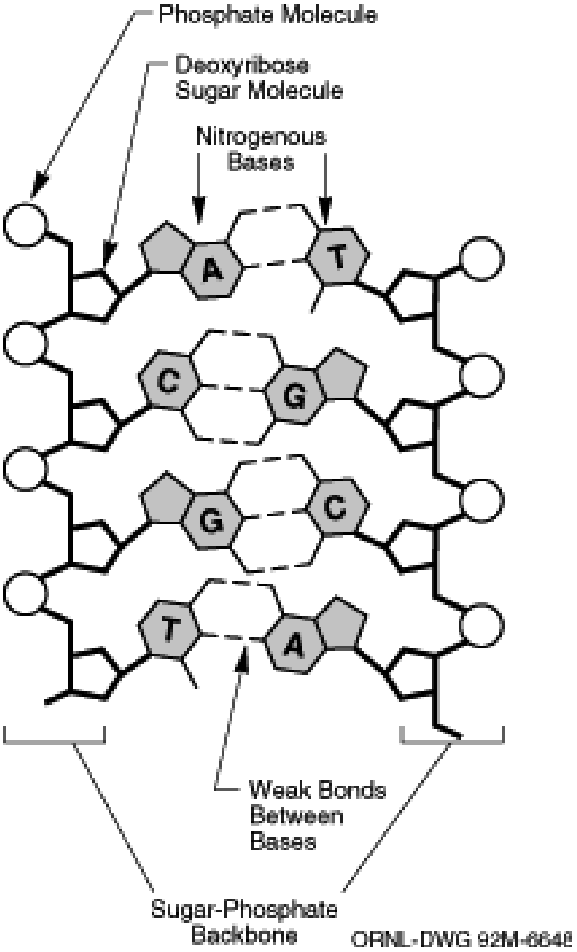


Figure 2. DNA structure

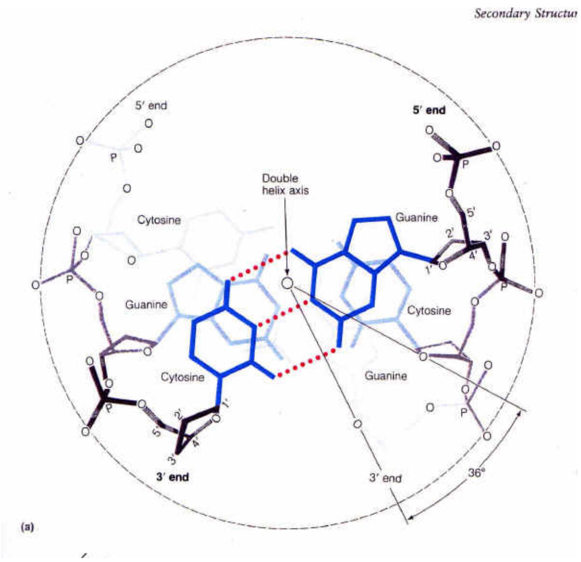


Figure 3. DNA helix indicating 10 basepairs per 360 degree turn of the helix.

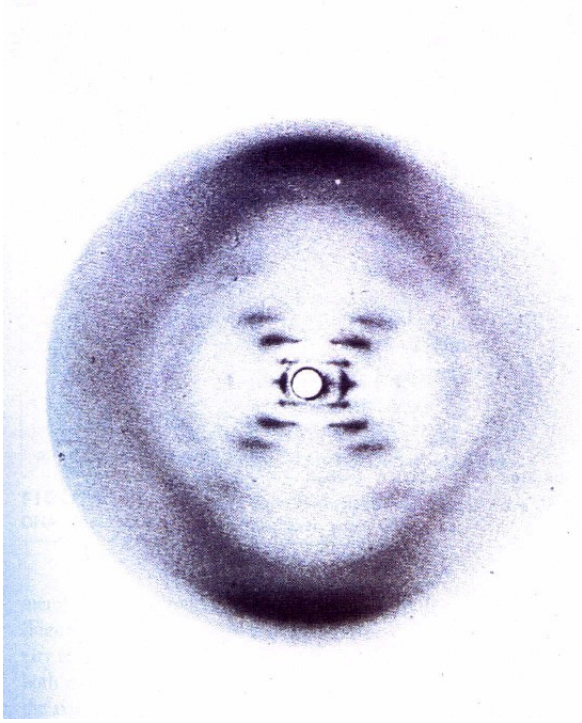


Figure 4. Rosalind Franklin's x-ray diffraction picture of DNA

2. Molecular Genetics: Proteins

2.1. **Amino Acids.** Proteins are long molecules composed of a string of amino acids. There are 20 commonly seen amino acids. These are given in table 1 with their full names and with one and three letter abbreviations for them. The capital letters in the name give a hint on how to remember the one letter code

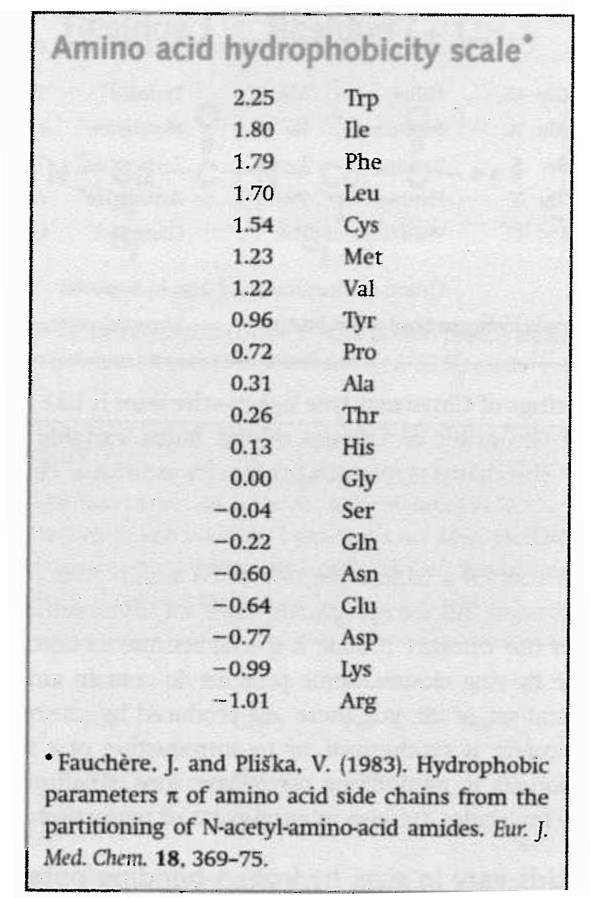
To a molecular biologist, each of these amino acids has its own personality in terms of shape and chemical properties. Often the property can be given a numerical value based on experimental measurements. One example, the hydropathy index, is given in figure 5. This measures how much the amino acid dislikes dissolving in water. An amino acid with a high hydropathy index, isoleucine, for example, can be thought of as not mixing with water, or being oily. Some less precise classifications simply divide the amino acids into two categories, *hydrophilic* (with low hydropathy index) and *hydrophobic* (with high hydropathy index). Either of these classifications can be used in computer programs for finding protein structures.

Alanine	Ala	A
Cysteine	Cys	C
Aspartic AciD	Asp	D
Glutamic Acid	Glu	E
Phenylalanine	Phe	F
Glycine	Gly	G
Histidine	His	H
Isoleucine	Ile	I
Lysine	Lys	K
Leucine	Leu	L
Methionine	Met	M
AsparagiNe	Asn	N
Proline	Pro	P
Glutamine	Gln	Q
ARginine	Arg	R
Serine	Ser	S
Threonine	Thr	T
Valine	Val	V
Tryptophan	Trp	W
TYrosine	Tyr	Y

Table 1. Amino acids and their abbreviations.

2.2. **The genetic code.** Based on the discovery of the structure of DNA as a long word in a four letter alphabet, the key to genetics was found to be a code. A sequence of three letters is a code for one of the 20 amino acids. A string of $3n$ letters codes for a protein with n amino acids and gives the sequence in which the amino acids are strung together.

Attempts were made to discover the code by logical reasoning, but the code was found by experiments expressing proteins from manufactured sequences of DNA. It was found, for example, that TGC codes for the amino acid Cystine. Also TAA codes for STOP, which means that the string of amino acids stops, and the protein is complete.



Amino acid hydrophobicity scale*

2.25	Trp
1.80	Ile
1.79	Phe
1.70	Leu
1.54	Cys
1.23	Met
1.22	Val
0.96	Tyr
0.72	Pro
0.31	Ala
0.26	Thr
0.13	His
0.00	Gly
−0.04	Ser
−0.22	Gln
−0.60	Asn
−0.64	Glu
−0.77	Asp
−0.99	Lys
−1.01	Arg

*** Fauchère, J. and Pliška, V. (1983). Hydrophobic parameters π of amino acid side chains from the partitioning of N-acetyl-amino-acid amides.** *Eur. J. Med. Chem.* **18**, 369–75.

FIGURE 5. Figure from *Introduction to Protein Architecture*, by Arthur Lesk showing a hydrophobicity scale for amino acids

2.3. **Amino acid template.** We are interested in the 3D structure of proteins. Proteins are composed of amino acids bound together, so first we look at amino acid structures. All amino acids have a COOH carboxyl and NHH amide part. The part which distinguishes different amino acids is called the side chain or residue. See figure 6

The structure of the amino acids can be learned by first learning their side chain topology. The topology tells only how the atoms are connected; more information is needed before you know the 3D structure. The additional information consists of other parameters called *torsion angles.* Figure 7 (from a paper of Ponder and Richards) gives the topology of the amino acids along with information on how the atoms and torsion angles are labeled. The figure also indicates how many torsion angles are needed to determine the structure. We will discuss this in more detail in a later chapter and refer back to the figure often.

2.4. **Tetrahedral geometry.** The geometry of the amino acids is partially determined by the tetrahedral geometry of the carbon bond. The bond directions for

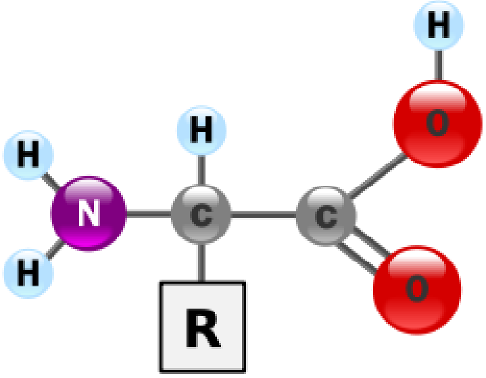


FIGURE 6. Template for amino acid. R denotes the side chain, or residue. The NHH is called an amide group and the COOH a carboxyl group.

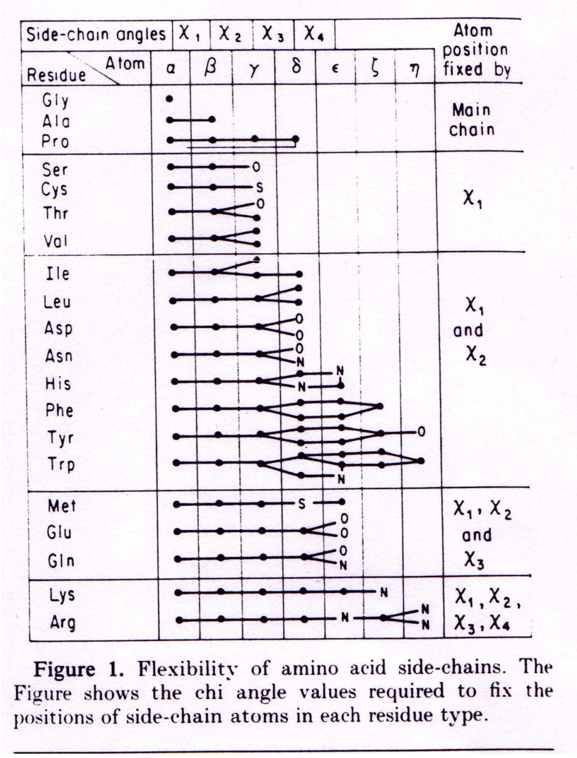


Figure 1. Flexibility of amino acid side-chains. The Figure shows the chi angle values required to fix the positions of side-chain atoms in each residue type.

FIGURE 7. Side chain topology

carbon are approximately the same as from the centroid of a regular tetrahedron to the vertices.

To get an idea of the geometry of a tetrahedron, a regular four-sided solid, you can construct one in *Maple*. Here is a *Maple* file to construct a tetrahedron. The tetrahedron can be rotated with the mouse.

The bond angles at a carbon bonded to four atoms are all approximately 110 degrees as if the carbon is the center of a tetrahedron and the bonded atoms are at the vertices. To see this verify that the points $A = (1, 1, 1)$, $B = (1, -1, -1)$, $C = (-1, 1, -1)$ and $D = (-1, -1, 1)$ are vertices of a tetrahedron by noting that the distance between any two of the points is $2\sqrt{2}$. They are also all a distance of $\sqrt{3}$ from the origin so the origin is the center of the tetrahedron. Now the angle θ between any two of the bonds, for example A and B, is given by

$$\cos\theta = A \cdot B/|A||B| = -1/3.$$

Compute that $\theta = \arccos(-1/3) \approx 109.47°$.

2.5. **Amino acid structure.** Figure 8 shows a typical structure of the amino acid leucine. Configuration of side chains are sometimes called rotamers because the tetrahedral geometry at the carbon bonds stays the same and the only degree of freedom is rotation about the carbon bonds.

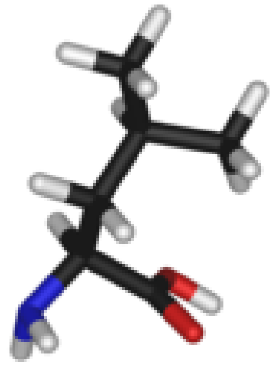


FIGURE 8. Structure of leucine shown in a computer graphics stick model. Hydrogens are white, carbons black, oxygens red, and nitrogens blue.

2.6. **The peptide bond.** To form a protein, amino acids are bonded together in sequence making a long chain. The bond between adjacent amino acids is called the *peptide bond.* The carboxyl group of one amino acid and the amide group of the subsequent amino acid lose an oxygen and two hydrogens, i. e., water (figure 9).

The bond is approximately planar; the six atoms involved in the bond lie in a plane, called the *peptide plane.* The electrons associated with these atoms form a cloud called the π orbital. There is a special geometry associated with the peptide plane shown in figure 10.

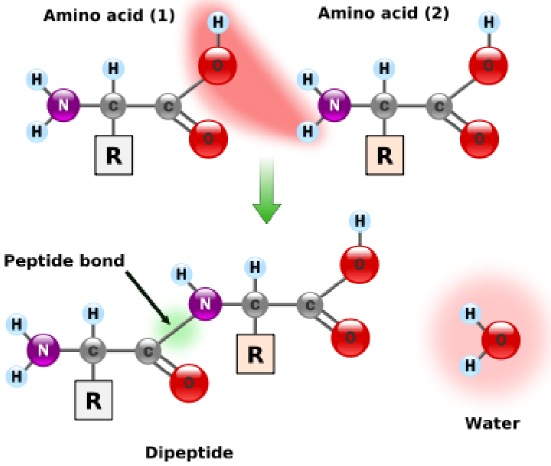


Figure 9. Peptide Bond. When two amino acids bond together in forming a proteins, they give off one molecule of water.

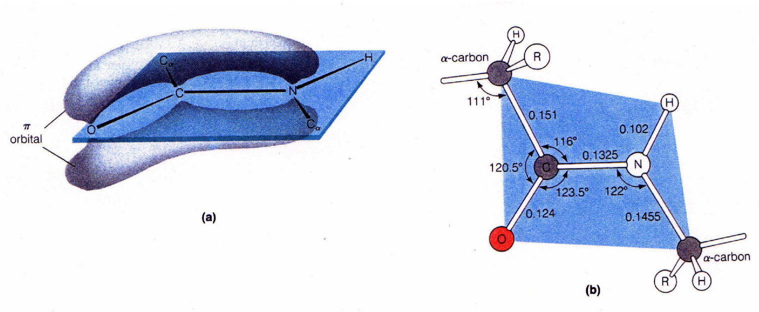


Figure 10. Peptide plane geometry. a) shows the distribution of electrons in the bond. b) shows the bond angles and distances as determined from structures determined by X-ray crystallography. This information is often used when modeling proteins.

2.7. **Protein structure.** As amino acids are bonded together they form into a specific shape called the *fold*. The structure of a protein is hard to see because of the number of atoms involved.

Before the era of computer graphics, only an artist could render an understandable picture of a protein. One such artist was Irving Geis. Here (figure 11) is his painting of sperm whale myoglobin, the first protein structure to be discovered. There is a website devoted to artistic renditions of molecules by Irving Geis and others. These renditions have been replaced by computer graphics which rely on ribbon diagrams.

2.8. **Secondary structure.** The organization of the atoms of a protein is complex but certain regular features appear. The most common are the alpha-helix and the beta-sheet (figures 12 and 13). These are referred to as *secondary structures* and can be visualized using ribbon diagrams created by computer programs called protein

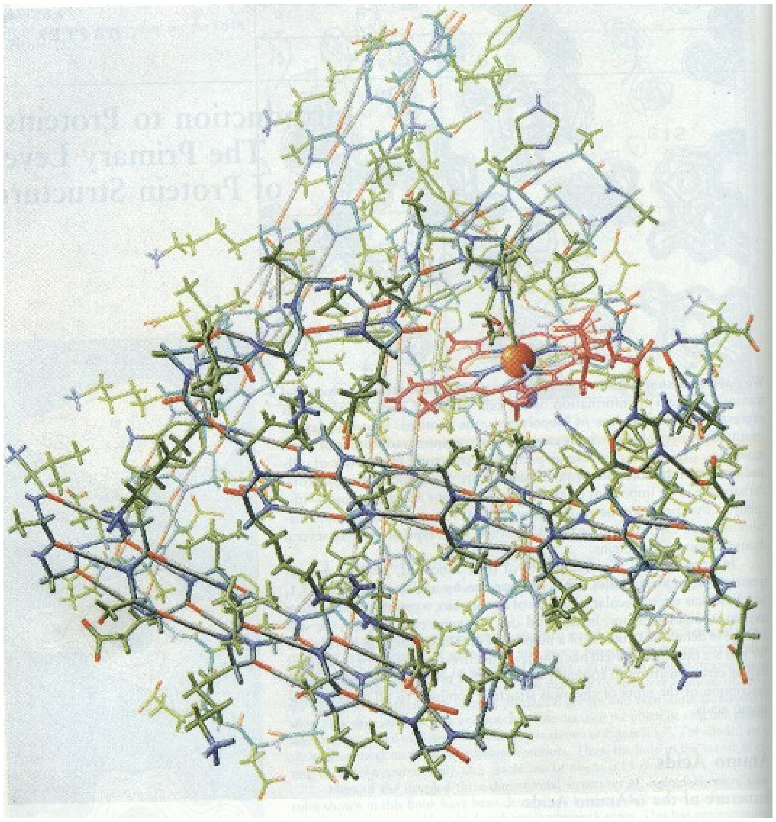


FIGURE 11. Painting by Irving Geis of a stick model of sperm whale myoglobin.

viewers. These can be found online at the Protein Data Bank website. See figures 14 and 15. The spiraling ribbons are alpha-helixes and the straight ribbons are beta-sheets. The original structure of sperm whale myoglobin by John Kendrew in the the Protein Data Bank under the code 1mbn.

Figures 12 and 13 are a detailed view of the alpha helix and the beta sheet. The structures are distinguished by the hydrogen bonding patterns. In an alpha helix the hydrogen bonds join atoms nearby in the chain; in a beta sheet the hydrogen bonds join atoms between two different parts of the chain.

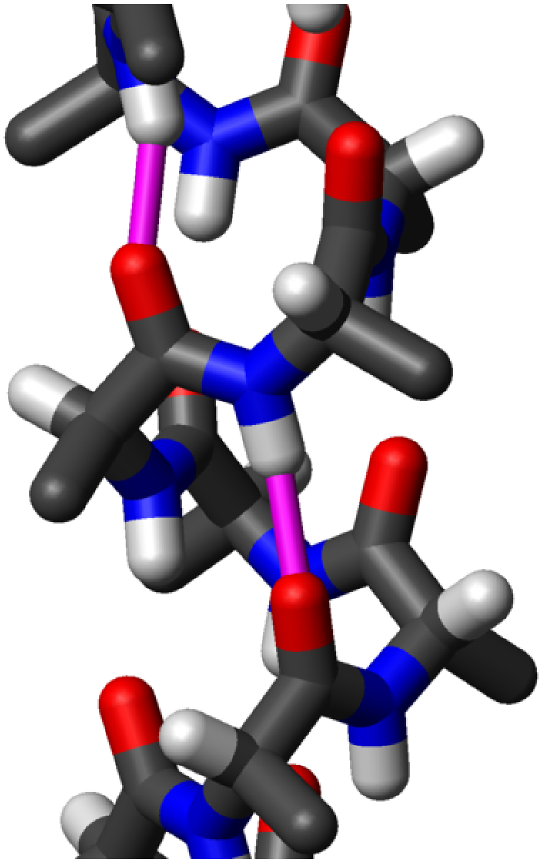


Figure 12. Stick diagram of the backbone of an alpha helix, showing the hydrogen bonds in pink. Carbons are black, nitrogens blue, oxygens red, and hydrogens white.

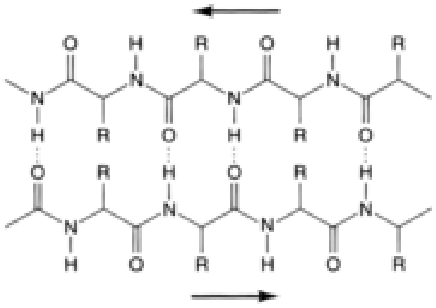


Figure 13. Diagram showing as dotted lines hydrogen bonds between protein strands in a beta sheet.

FIGURE 14. Ribbon diagram for the protein myoglobin. The curled ribbons indicate alpha helices. There are no beta sheets in this structure. The strings are called *loops* and have no particular structure.

FIGURE 15. Part of the protein carboxopeptidase A containing both an alpha helix and a beta sheet. The uncurled ribbons indicate strands of beta sheets.

3. Frames and moving frames

In 3D space, a sequence of 3 linearly independent vectors $\mathbf{v}_1, \mathbf{v}_2, \mathbf{v}_3$ is called a frame, since it gives a coordinate system (a frame of reference). Any vector $\mathbf{v}$ can be written as a linear combination $\mathbf{v} = x\mathbf{v}_1 + y\mathbf{v}_2 + z\mathbf{v}_3$ of vectors in the frame and x, y, z are called the coordinates of $\mathbf{v}$ in this frame. A frame is the same as an invertible linear transformation and an orthonormal frame is the same as an orthogonal transformation.

A frame called the Frenet frame is useful in the study of curves. It is called a moving frame because there is one at each point on the curve, and the points are considered as a function of a parameter t often thought of as time. The idea of a Frenet Frame can be adapted to study the shape of of long molecules such as DNA and proteins, as will be discussed in a later chapter.

3.1. Basic definitions.

A sequence of three vectors $\mathbf{v}_1, \mathbf{v}_2$, $\mathbf{v}_3$ can be made into the columns of a 3×3 matrix denoted $(\mathbf{v}_1, \mathbf{v}_2, \mathbf{v}_3)$. If the determinant of this matrix is not 0, then the sequence of vectors is called a *frame* and the vectors are *linearly independent*. We will not distinguish between the frame and the matrix.

The vectors

$$\mathbf{e}_1 = \begin{pmatrix} 1 \\ 0 \\ 0 \end{pmatrix} \quad \mathbf{e}_2 = \begin{pmatrix} 0 \\ 1 \\ 0 \end{pmatrix} \quad \mathbf{e}_3 = \begin{pmatrix} 0 \\ 0 \\ 1 \end{pmatrix}$$

form a frame $(\mathbf{e}_1, \mathbf{e}_2, \mathbf{e}_3)$ which is the identity matrix $\mathbf{I}$. This is called the *standard basis* or *lab frame.*

The determinant of the matrix $(\mathbf{v}_1, \mathbf{v}_2, \mathbf{v}_3)$ is equal to the *scalar triple product*,

$$\mathbf{v}_1 \cdot (\mathbf{v}_2 \times \mathbf{v}_3) = \det(\mathbf{v}_1, \mathbf{v}_2, \mathbf{v}_3).$$

If the determinant is positive, the frame is said to be *right-handed*, and if the determinant is negative, the frame is said to be *left-handed.*

3.2. Frames and gram matrices.

If $\mathbf{F} = (\mathbf{v}_1, \mathbf{v}_2, \mathbf{v}_3)$ is a matrix, the entry in row i, column j of the matrix $\mathbf{F}^{\mathrm{t}}\,\mathbf{F}$ is the dot product $\mathbf{v}_i \cdot \mathbf{v}_j$. This matrix is called the *gram matrix* of the vectors $\mathbf{v}_1, \mathbf{v}_2, \mathbf{v}_3$.

The frame is said to be an *orthogonal frame* if the vectors are mutually perpendicular, that is, $\mathbf{v}_i \cdot \mathbf{v}_j = 0$ for $i \neq j$. If all of the vectors are of length 1 in an orthogonal frame, it is called an *orthonormal frame.* The condition that $\mathbf{F}$ is an orthonormal frame can be written as

$$\mathbf{v}_i \cdot \mathbf{v}_j = \begin{cases} 1 & \text{if } i = j \\ 0 & \text{if } i \neq j. \end{cases}$$

This is equivalent to the gram matrix being the identity,

$$\mathbf{F}^{\mathrm{t}}\,\mathbf{F} = \mathbf{I}. \tag{1}$$

If $\mathbf{F}$ satisfies this condition it is said to be orthogonal. A frame that is not orthogonal is called *oblique.*

3.3. **Frames and rotations.** Vectors or points in space are usually given by column vectors whose entries are coordinates in the lab frame,

$$\mathbf{v} = \begin{pmatrix} a \\ b \\ c \end{pmatrix} = a\,\mathbf{e}_1 + b\,\mathbf{e}_2 + c\,\mathbf{e}_3.$$

For simplicity a vector will often be written as a row vector (a, b, c) instead of the column vector $(a, b, c)^{\mathrm{t}}$.

Any other frame $\mathbf{F}$ gives another set of coordinates to each point in $\mathbb{R}^3$. If $\mathbf{F} = (\mathbf{v}_1, \mathbf{v}_2, \mathbf{v}_3)$ then any $\mathbf{w}$ can be written as a linear combination of the vectors in $\mathbf{F}$ as

$$\mathbf{w} = x\,\mathbf{v}_1 + y\,\mathbf{v}_2 + z\,\mathbf{v}_3 \tag{2}$$

and (x, y, z) are said to be the coordinates in the frame $\mathbf{F}$.

Equation (2) can also be written conveniently in matrix form as

$$\mathbf{w} = \mathbf{F}\begin{pmatrix} x \\ y \\ z \end{pmatrix}. \tag{3}$$

An orthonormal frame $\mathbf{F}$ can also be thought of as a way to specify an *orthogonal transformation.* There is a unique transformation of space leaving the origin fixed and sending the lab frame $\mathbf{I} = (\mathbf{e}_1, \mathbf{e}_2, \mathbf{e}_3)$ to an orthogonal frame $\mathbf{F} = (\mathbf{u}_1, \mathbf{u}_2, \mathbf{u}_3)$ and this is given by

$$(x, y, z)^{\mathrm{t}} \to \mathbf{F}(x, y, z)^{\mathrm{t}}$$

so the transformation is given in lab frame coordinates by multiplication on the left by the matrix $\mathbf{F}$. If $(x, y, z)^{\mathrm{t}}$ are the coordinates in the lab frame before the rotation, then $\mathbf{F}(x, y, z)^{\mathrm{t}}$ are the coordinates in the lab frame after the rotation. We see that

$$\mathbf{F}\mathbf{e}_1 = \mathbf{u}_1 \quad \mathbf{F}\mathbf{e}_2 = \mathbf{u}_2 \quad \mathbf{F}\mathbf{e}_3 = \mathbf{u}_3$$

are the columns of the orthogonal matrix $\mathbf{F}$.

3.4. **Frames fixed at a point.** We have been thinking of frames as vectors with initial points at the origin. If the initial points are fixed at a point $\mathbf{p}$, the frame $\mathbf{F}$ is denoted $\{\mathbf{F}, \mathbf{p}\}$. The Euclidean motion that sends $\{\mathbf{I}, \mathbf{0}\}$ to $\{\mathbf{F}, \mathbf{p}\}$ is an orthogonal transformation $\mathbf{F}$ followed by translation by $\mathbf{p}$.

$$\mathbf{v} \to \{\mathbf{F}\mathbf{v}, \mathbf{p}\}.$$

3.5. **The Frenet Frame.** A *moving frame* is a frame $\mathbf{F}(t)$ which is a function of t. The frame is thought of as changing with time and is often thought of as moving along a curve. A curve in space is a vector function $\mathbf{x}(t)$ whose coordinates give the parametric equations for the curve. Think of $\mathbf{x}(t)$ as the position of an object at time t. If the initial points of the vectors of $\mathbf{F}(t)$ are at the point $\mathbf{x}(t)$ we write $\{\mathbf{F}(t), \mathbf{x}(t)\}$ and $\mathbf{F}$ is said to move along the curve $\mathbf{x}$.

A moving frame frequently used with a curve is the *Frenet* frame. The first vector in the frame is the *unit tangent vector* $\mathbf{t}$ pointing along the curve in the direction of motion. The other vectors are the *normal vector* $\mathbf{n}$ and the *binormal vector* $\mathbf{b}$. The Frenet frame is defined as

$$\mathbf{F}(t) = (\mathbf{t}(t), \mathbf{n}(t), \mathbf{b}(t))$$

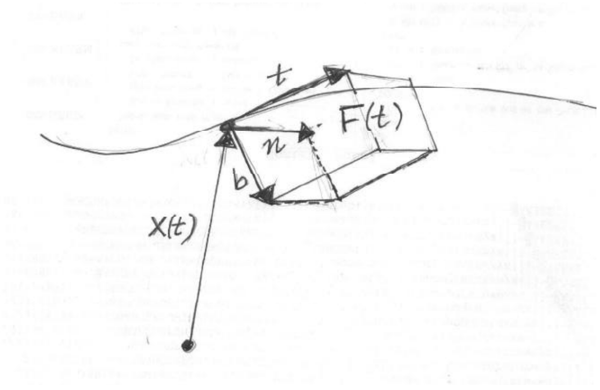


FIGURE 16. A moving frame (Frenet frame).

where

$$\begin{aligned}\mathbf{t}(t) &= \frac{d\mathbf{x}/dt}{|d\mathbf{x}/dt|}\\ \mathbf{n}(t) &= \frac{d\mathbf{t}/dt}{|d\mathbf{t}/dt|}\\ \mathbf{b}(t) &= \mathbf{t}(t)\times\mathbf{n}(t).\end{aligned} \tag{4}$$

For the frame to be defined at a point we must have $d\mathbf{x}/dt \neq 0$ and $d\mathbf{t}/dt \neq 0$. The speed is

$$ds/dt = |d\mathbf{x}/dt|\,,$$

so the unit tangent is the derivative of the position vector with respect to distance,

$$\mathbf{t}(t) = \frac{d\mathbf{x}/dt}{ds/dt} = d\mathbf{x}/ds.$$

By (4), $(\mathbf{t}, \mathbf{n}, \mathbf{b})$ is a right handed frame, and the lengths of $\mathbf{t}$ and $\mathbf{n}$ are 1. To see that it is an orthonormal frame, it is enough to show that $\mathbf{t}$ and $\mathbf{n}$ are perpendicular. This is shown by differentiating

$$\mathbf{t}\cdot\mathbf{t} = 1$$

using the product rule, to get

$$2\mathbf{t}\cdot(d\mathbf{t}/dt) = 0.$$

This is also geometrically evident, since $\mathbf{t}(t)$ can be thought of as a curve on a sphere of radius 1. Any tangent vector to the curve at a point must be perpendicular the radius of the sphere through the point, and therefore perpendicular to $\mathbf{t}$.

3.5.1. *Example of a Frenet Frame.* Consider a helix of radius r and pitch $2\pi p$ where the *pitch* of the helix is defined as the change in the z coordinate per turn of the helix. The equation of the helix is

$$\mathbf{h}(r,p)(t) = (r\cos t, r\sin t, p\,t). \tag{5}$$

One complete turn of the helix corresponds to t going from 0 to 2π. During this time the z coordinate changes by $2\pi p$ which is the pitch.

The Frenet frame for the helix is computed by (4) to be

$$\mathbf{F} = \begin{pmatrix} -c\,\sin t & -\cos t & s\,\sin t \\ c\,\cos t & -\sin t & -s\,\cos t \\ s & 0 & c \end{pmatrix}, \tag{6}$$

where

$$c = \frac{r}{\sqrt{r^2+p^2}} \quad s = \frac{p}{\sqrt{r^2+p^2}}.$$

Note that the normal $\mathbf{n} = (-\cos t, -\sin t, 0)$ is parallel to the xy plane and points from the point $\mathbf{h}(t)$ towards the z axis which is the axis of the helix.

The Frenet frame of a helix given in (6) can be computed using *Maple.* Maple demo

3.6. **The coiled-coil.** Francis Crick used a curve called the coiled-coil to describe the backbone structures of proteins like collagen, which is found in fibrous tissue in the body. He made his atomic structure by placing the alpha carbon atoms of a protein at equally spaced parameter values along the curve. The equation for this curve uses the Frenet frame for a helix.

The coiled coil is drawn by drawing a circle at a radians per second in the $\mathbf{n}$, $\mathbf{b}$ plane of the Frenet frame of helix (5) while traversing the helix. If this circle has radius r_2 then the vector equation of the coiled-coil is

$$C(t) = \mathbf{h}(t) + r_2\,(\cos at\,\mathbf{n} + \sin at\,\mathbf{b})$$

where $\mathbf{h} = \mathbf{h}(r_1, p)$ is the equation of the helix. The equation can also be written as

$$C(t) = \mathbf{h}(t) + r_2\mathbf{F}(t)(0, \cos at, \sin at)^{\mathrm{t}} \tag{7}$$

where $\mathbf{F}$ is the Frenet frame for $\mathbf{h}$. The curve coils around a tube of radius r_2 about the helix $\mathbf{h}$. In the moving frame the coil appears as a circle.

The helix $\mathbf{h}$ is called the *major helix*, and r_1 is the radius of the major helix. The coiled-coil C is called the *minor helix*, and r_2 is the radius of the minor helix. The major helix can be thought of as a curved axis for the minor helix. One turn of the major helix corresponds to a variation of t by 2π; one turn of the minor helix corresponds to a variation of t by $2\pi/a$. Thus there are a turns of the minor helix per turn of the major helix. (See figure 17 of a coil with with $a = 4$)

Maple demo of coiled coil

3.7. **The Frenet formula.** Curvature and torsion are defined by the derivative of the Frenet frame. The derivative of a matrix is similar to the derivative of a vector, it is computed by replacing each entry in the matrix by its derivative.

A square matrix $\mathbf{A}$ is said to be *skew symmetric* if

$$\mathbf{A}^{\mathrm{t}} = -\mathbf{A}.$$

Note that that the entries on the diagonal of a skew-symmetric matrix are 0. An important fact is

If $\mathbf{A}(t)$ *is orthogonal then* $\mathbf{A}^{\mathrm{t}}\,\dfrac{d\mathbf{A}}{dt}$ *is skew-symmetric.*

This can be seen by taking the derivative of

$$\mathbf{A}^{\mathrm{t}}\,\mathbf{A} = \mathbf{I}$$

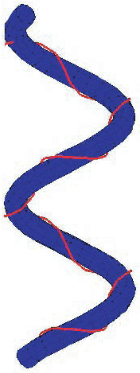


FIGURE 17. A coiled coil with 4 turns of the minor helix per turn of the major helix.

using the product rule to get

$$\frac{d\mathbf{A}^{\mathrm{t}}}{dt}\,\mathbf{A} + \mathbf{A}^{\mathrm{t}}\,\frac{d\mathbf{A}}{dt} = 0.$$

It follows that for the Frenet frame, $\mathbf{F}^{\mathrm{t}}(d\mathbf{F}/ds)$ is skew symmetric. In the case of the Frenet Frame the 3,1 and 1,3 entries in the matrix are zero, because the 3,1 entry is $\mathbf{b}\cdot(d\mathbf{t}/ds)$ and $d\mathbf{t}/ds$ is parallel to $\mathbf{n}$ and therefore perpendicular to $\mathbf{b}$. Now curvature and torsion are defined by the *Frenet formula*,

$$\mathbf{F}^{\mathrm{t}}\frac{d\mathbf{F}}{ds} = \begin{pmatrix} 0 & -\kappa & 0 \\ \kappa & 0 & -\tau \\ 0 & \tau & 0 \end{pmatrix} \tag{8}$$

where κ is *curvature* and τ is *torsion*. Since $\mathbf{F}^{\mathrm{t}}\mathbf{F} = \mathbf{I}$, equation (8) can also be written

$$\frac{d\mathbf{F}}{ds} = \mathbf{F}\begin{pmatrix} 0 & -\kappa & 0 \\ \kappa & 0 & -\tau \\ 0 & \tau & 0 \end{pmatrix}. \tag{9}$$

Since

$$\frac{d\,\mathbf{F}}{ds} = \left(\frac{d\,\mathbf{t}}{ds}, \frac{d\,\mathbf{n}}{ds}, \frac{d\mathbf{b}}{ds}\right),$$

equating the columns of (9) gives

$$\begin{aligned} \frac{d\mathbf{t}}{ds} &= \kappa\mathbf{n} \\ \frac{d\mathbf{n}}{ds} &= -\kappa\mathbf{t} + \tau\mathbf{b} \\ \frac{d\mathbf{b}}{ds} &= -\tau\mathbf{n}. \end{aligned}$$

These are also called the Frenet formulas, but (8) is a convenient way to write them in matrix form. It follows by taking the dot products of the first two equations with $\mathbf{n}$ and $\mathbf{b}$ respectively that

$$\kappa = \frac{d\mathbf{t}}{ds}\cdot\mathbf{n} \qquad \tau = \frac{d\mathbf{n}}{ds}\cdot\mathbf{b}. \tag{10}$$

The curvature measures how the curve deviates from being a straight line. If the curve is a line, then $\kappa = 0$. The torsion how it deviates from being in a plane. If the curve is in a plane, then **t** and **n** are in the plane and **b** is the normal to the plane, so $\tau = 0$. Using the Frenet formula an equation for the curve can be determined from the function κ and τ.

In the example of the helix (5) the curvature is a constant $r/(r^2 + p^2)$ and the torsion is constant $p/(r^2 + p^2)$. In general the curvature and torsion are functions of the parameter t.

3.8. **Problems.**

(1) Let
$$\mathbf{x}(t) = (r\cos t, r\sin t, p\,t)$$
be a helix. Show that the curvature is a constant $r/(r^2+p^2)$ and the torsion is constant $p/(r^2 + p^2)$.

(2) Use Maple and the Frenet Formula
$$\mathbf{F}^{\mathrm{t}}\frac{d\mathbf{F}}{ds} = \begin{pmatrix} 0 & -\kappa & 0 \\ \kappa & 0 & -\tau \\ 0 & \tau & 0 \end{pmatrix}$$
to find the curvature and torsion of the curve $(3t - t^3, 3t^2, 3t + t^3)$. You can use the procedure presented in the lecture for computing the Frenet Frame **F**.

(3) Show that
$$\mathbf{v}_1 \cdot (\mathbf{v}_2 \times \mathbf{v}_3) = \det(\mathbf{v}_1, \mathbf{v}_2, \mathbf{v}_3).$$

4. Orthogonal transformations and Rotations

A matrix is defined to be orthogonal if the entries are real and

$$\mathbf{A}'\,\mathbf{A} = \mathbf{I}. \tag{11}$$

Condition (11) says that the gram matrix of the sequence of vectors formed by the columns of $\mathbf{A}$ is the identity, so the columns are an orthonormal frame. An orthogonal matrix defines an orthogonal transformation $\mathbf{v} \to \mathbf{A}\mathbf{v}$ by mutiplying column vectors on the left.

Condition (11) also shows that $\mathbf{A}$ is a rigid motion preserving angles and distances. The dot product of two vectors is the same before and after an orthogonal transformation. This can be written as

$$\mathbf{A}\mathbf{v} \cdot \mathbf{A}\mathbf{w} = \mathbf{v} \cdot \mathbf{w}$$

for all vectors $\mathbf{v}$ and $\mathbf{w}$. This is true by the definition (11) of orthogonal matrix since

$$\begin{aligned}\mathbf{A}\mathbf{v} \cdot \mathbf{A}\mathbf{w} &= (\mathbf{A}\mathbf{v})'\mathbf{A}\mathbf{w} = \mathbf{v}'\mathbf{A}'\mathbf{A}\mathbf{w} \\ &= \mathbf{v}'\mathbf{I}\mathbf{w} = \mathbf{v}'\mathbf{w} = \mathbf{v} \cdot \mathbf{w}.\end{aligned}$$

Thus lengths and angles are preserved, since they are functions of the dot product.

The orthogonal transformation form a *group* since we can multiply two of them and get an orthogonal transformation. This is because if $\mathbf{A}$ and $\mathbf{B}$ are orthogonal, then $\mathbf{A}'\mathbf{A} = \mathbf{I}$ and $\mathbf{B}'\mathbf{B} = \mathbf{I}$. So

$$(\mathbf{A}\mathbf{B})'\mathbf{A}\mathbf{B} = \mathbf{B}'\mathbf{A}'\mathbf{A}\mathbf{B} = \mathbf{I},$$

showing that $\mathbf{AB}$ is also orthogonal. Likewise the inverse of an orthogonal transformation is orthogonal transformation.

Orthogonal transformations have determinant 1 or -1 since by (11) and properties of determinant,

$$\begin{aligned}(\det \mathbf{A})^2 &= \det(\mathbf{A}')\det \mathbf{A} \\ &= \det(\mathbf{A}'\,\mathbf{A}) \\ &= \det \mathbf{I} = 1.\end{aligned}$$

4.1. The rotation group.

Orthogonal transformations with determinant 1 are called rotations, since they have a fixed axis. This is discussed in more detail below. The rotations also form a group, since if $\det \mathbf{A} = 1$ and $\det \mathbf{B} = 1$ then

$$\det(\mathbf{AB}) = \det \mathbf{A} \det \mathbf{B} = 1.$$

If we think of an orthogonal matrix $\mathbf{A}$ as a frame

$$\mathbf{A} = (\mathbf{v}_1, \mathbf{v}_2, \mathbf{v}_3),$$

then the determinant is the scalar triple product

$$\mathbf{v}_1 \cdot (\mathbf{v}_2 \times \mathbf{v}_3).$$

The frame is right handed if the triple product is 1 and left handed if it is -1. The frame is the image of the right handed standard frame

$$(\mathbf{e}_1, \mathbf{e}_2, \mathbf{e}_3) = \mathbf{I}$$

under the transformation $\mathbf{A}$. Thus $\mathbf{A}$ preserves orientation (right-handedness) if the determinant is 1.

4.1.1. *Rotations and cross products.* Rotations are orthogonal transformations which preserve orientation. This is equivalent to the fact that they preserve the vector cross product:

$$\mathbf{A}(\mathbf{v} \times \mathbf{w}) = \mathbf{A}\mathbf{v} \times \mathbf{A}\mathbf{w}, \tag{12}$$

for all rotations $\mathbf{A}$ and vectors $\mathbf{v}$ and $\mathbf{w}$. Recall the right hand rule in the definition of the cross product (fig 18). The cross product is defined in terms of lengths and angles and right-handedness, all of which remain unchanged after rotation.

The fact that $\mathbf{A}$ preserves the cross product can also be proved using only the fact that $\mathbf{A}'\mathbf{A} = \mathbf{I}$ and $\det \mathbf{A} = 1$ (see problem 1).

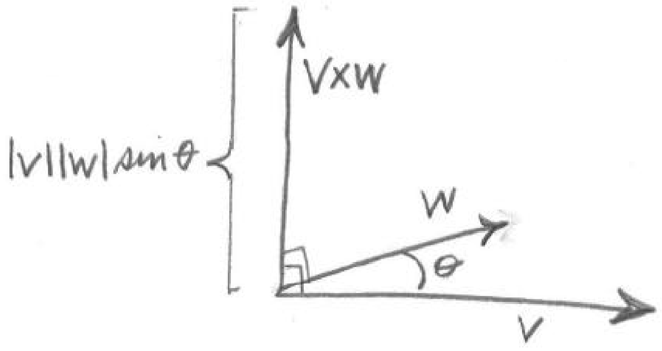


FIGURE 18. The geometric definition of the cross product. The direction of $\mathbf{v}\times\mathbf{w}$ is determined by the right hand rule. The fingers of the right hand should point from $\mathbf{v}$ to $\mathbf{w}$ and the thumb in the direction of the cross-product. The length of the cross product is $|\mathbf{v}||\mathbf{w}|\sin\theta$.

4.1.2. *Two dimensions.* In two dimensions, every rotation is of the form

$$\mathrm{R}(\theta) = \begin{pmatrix} \cos\theta & -\sin\theta \\ \sin\theta & \cos\theta \end{pmatrix}. \tag{13}$$

See section 10 problem 4.

Note that

$$\mathrm{R}(\theta)\mathrm{R}(\phi) = \mathrm{R}(\theta + \phi) = \mathrm{R}(\phi)\mathrm{R}(\theta),$$

so that rotations in two dimension commute.

4.1.3. *Three dimensions.* In three dimensions, matrices for rotation about coordinate axes have a form related to the 2 dimensional rotation matrices:

- Rotation about the x axis

$$\mathrm{R}_x(\theta) = \begin{pmatrix} 1 & 0 & 0 \\ 0 & \cos\theta & -\sin\theta \\ 0 & \sin\theta & \cos\theta \end{pmatrix}$$

Rotation about the y axis

$$\mathrm{R}_y(\theta) = \begin{pmatrix} \cos\theta & 0 & \sin\theta \\ 0 & 1 & 0 \\ -\sin\theta & 0 & \cos\theta \end{pmatrix}$$

Rotation about the z axis

$$\mathrm{R}_z(\theta) = \begin{pmatrix} \cos\theta & -\sin\theta & 0 \\ \sin\theta & \cos\theta & 0 \\ 0 & 0 & 1 \end{pmatrix}.$$

All rotations are counterclockwise about the axis indicated in the subscript. The rotations $\mathrm{R}_z(\theta)$, are exactly the ones that leave the vector $\mathbf{e}_3 = (0, 0, 1)'$ fixed and can be identified with rotation in the xy plane. Similarly for R_x and R_y.

The rotations $\mathrm{R}_x(\theta)$ commute,

$$\begin{aligned} \mathrm{R}_x(\theta)\mathrm{R}_x(\phi) &= \mathrm{R}_x(\theta + \phi) \\ &= \mathrm{R}_x(\phi)\mathrm{R}_x(\theta). \end{aligned}$$

Similarly rotations $\mathrm{R}_y(\theta)$ commute and rotations $\mathrm{R}_z(\theta)$ commute. In general, however, rotations in three dimensions do not commute. For example,

$$\mathrm{R}_x(\pi)\mathrm{R}_z(\pi/2) = \begin{pmatrix} 0 & -1 & 0 \\ -1 & 0 & 0 \\ 0 & 0 & -1 \end{pmatrix}$$

but

$$\mathrm{R}_z(\pi/2)\mathrm{R}_x(\pi) = \begin{pmatrix} 0 & 1 & 0 \\ 1 & 0 & 0 \\ 0 & 0 & -1 \end{pmatrix}.$$

Since rotations form a group we can get other rotations by multiplying together rotations of the form R_x, R_y, and R_z. It can be shown that any rotation $\mathbf{A}$ can be written as a product of three rotations about the y and z axes,

$$\mathbf{A} = \mathrm{R}_z(\alpha)\mathrm{R}_y(\gamma)\mathrm{R}_z(\delta). \tag{14}$$

The angles α, γ, δ are called *Euler angles* for the rotation $\mathbf{A}$. See problem 6

The proof that any rotation $\mathbf{A}$ can be written as above in terms of Euler angles relies on a simple fact. Any unit vector $\mathbf{u}$ can be written in terms of spherical coordinates as

$$\mathbf{u} = \begin{pmatrix} \sin\phi\cos\theta \\ \sin\phi\sin\theta \\ \cos\phi \end{pmatrix}, \tag{15}$$

and $\mathbf{u}$ can be obtained from $\mathbf{e}_3$ by two rotations

$$\mathbf{u} = \mathrm{R}_z(\theta)\mathrm{R}_y(\phi)\mathbf{e}_3. \tag{16}$$

4.2. **Complex form of a rotation.** In dimension 2 it is convenient to use complex numbers to write rotations. Rotation by an angle θ is given by

$$\zeta \to e^{i\theta}\zeta \tag{17}$$

where $\zeta = x + iy$. Writing $\bar{\zeta} = x - iy$ the rotation

$$\begin{pmatrix} x \\ y \end{pmatrix} \to \begin{pmatrix} \cos\theta & -\sin\theta \\ \sin\theta & \cos\theta \end{pmatrix} \begin{pmatrix} x \\ y \end{pmatrix}$$

is transformed into

$$\begin{pmatrix} \zeta \\ \bar{\zeta} \end{pmatrix} \to \begin{pmatrix} e^{i\theta} & 0 \\ 0 & e^{-i\theta} \end{pmatrix} \begin{pmatrix} \zeta \\ \bar{\zeta} \end{pmatrix}$$

which is convenient because the matrix is diagonal. The elements on the diagonal are eigenvalues of

$$\begin{pmatrix} \cos\theta & -\sin\theta \\ \sin\theta & \cos\theta \end{pmatrix}.$$

A similar method works in three dimensions for rotation about the z axis. First perform a change of coordinates. Letting $\zeta = x + iy$ the transformation

$$\begin{pmatrix} x \\ y \\ z \end{pmatrix} \to \begin{pmatrix} \cos\theta & -\sin\theta & 0 \\ \sin\theta & \cos\theta & 0 \\ 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} x \\ y \\ z \end{pmatrix}$$

becomes

$$\begin{pmatrix} \zeta \\ \bar{\zeta} \\ z \end{pmatrix} \to \begin{pmatrix} e^{i\theta} & 0 & 0 \\ 0 & e^{-i\theta} & 0 \\ 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} \zeta \\ \bar{\zeta} \\ z \end{pmatrix}$$

transforming the matrix for the rotation into a diagonal matrix. The diagonal entries are the eigenvalues of $R_z(\theta)$.

4.3. **Eigenvalues of a rotation.** First we show that *the eigenvalues of an orthogonal matrix have absolute value 1.*

To see this, suppose

$$\mathbf{A}\mathbf{v} = \lambda\mathbf{v} \tag{18}$$

for a non-zero vector $\mathbf{v}$. Taking the adjoint,

$$\mathbf{v}^*\mathbf{A}^* = \overline{\lambda}\mathbf{v}^*. \tag{19}$$

Since $\mathbf{A}$ is real, $\mathbf{A}^* = \mathbf{A}'$, and multiplying (18) and (19) and using the fact that $\mathbf{A}'\mathbf{A} = \mathbf{I}$ get

$$\mathbf{v}^*\mathbf{v} = |\lambda|^2\mathbf{v}^*\mathbf{v}$$

and hence

$$|\lambda|^2 = 1,$$

and thus all eigenvalues have absolute value 1.

If λ is an eigenvalue of $\mathbf{A}$,

$$\mathbf{A}\mathbf{v} = \lambda\mathbf{v}$$

for some non-zero vector $\mathbf{v}$. Taking conjugate of both sides,

$$\overline{\mathbf{A}}\bar{\mathbf{v}} = \bar{\lambda}\bar{\mathbf{v}}.$$

Since $\mathbf{A}$ is real, $\overline{\mathbf{A}} = \mathbf{A}$ so $\bar{\lambda}$ is an eigenvector corresponding to eigenvector $\bar{\mathbf{v}}$. It follows that the eigenvalues of an orthogonal matrix A are

$$\pm 1 \qquad \lambda \qquad \bar{\lambda}$$

where $\lambda = e^{i\theta}$. The determinant of $\mathbf{A}$ is the product of the eigenvalues, so for a rotation matrix the first eigenvalue above is 1. There is a real eigenvector $\mathbf{u}$ corresponding to the eigenvalue 1. This is left as an exercise (section 10 problem 6). The line though this vector $\mathbf{u}$ is called the *axis of the rotation.* .

By dividing by the length, we may suppose that $\mathbf{u}$ above is a unit vector. As in (16) write $\mathbf{u} = \mathbf{B}\mathbf{e}_3$ where $\mathbf{B}$ is a rotation. Since $\mathbf{u}$ is left fixed by A,

$$\mathbf{A}\mathbf{B}\mathbf{e}_3 = \mathbf{B}\mathbf{e}_3.$$

Thus $\mathbf{B}^{-1}\mathbf{A}\mathbf{B}$ leaves $\mathbf{e}_3$ fixed and so

$$\mathbf{B}^{-1}\mathbf{A}\mathbf{B} = R_z(\theta)$$

for some angle θ. (See problem 2.)

We have shown that every rotation is conjugate to a rotation about the z axis. In other words, every rotation $\mathbf{A}$ can be written in the form $\mathbf{A} = \mathbf{B}R_z(\theta)\mathbf{B}'$ for a rotation $\mathbf{B}$ and some angle θ. This is just a way of saying that by an orientation preserving change of variables we can take the z axis $\mathbf{e}_3$ along the axis of the rotation $\mathbf{A}$. Since $\mathbf{A}$ and $R_z(\theta)$ are conjugate, they have the same eigenvalues, So the eigenvalues of $\mathbf{A}$ are $1, e^{i\theta}, e^{-i\theta}$, where θ is the angle of rotation. The vector $\mathbf{u}$ is called the axis of the rotation.

Now we define the matrix $\mathrm{R}\left(\mathbf{u}, \theta\right)$, rotation an angle θ about the axis $\mathbf{u}$. We showed that every rotation $\mathbf{A}$ can be written

$$\mathbf{A} = \mathbf{B}R_z(\theta)\mathbf{B}' \tag{20}$$

where $\mathbf{B}\mathbf{e}_3 = \mathbf{u}$. In this case we write

$$\mathbf{A} = \mathrm{R}\left(\mathbf{u}, \theta\right).$$

We can check that $\mathbf{B}R_z(\theta)\mathbf{B}'$ is the same for any choice of rotation $\mathbf{B}$ with $\mathbf{B}\mathbf{e}_3 = \mathbf{u}$ (problem 3), so $\mathrm{R}\left(\mathbf{u}, \theta\right)$ is uniquely defined. Note that $\mathrm{R}\left(\mathbf{e}_1, \theta\right) = R_x(\theta)$, $\mathrm{R}\left(\mathbf{e}_2, \theta\right) = R_y(\theta)$, $\mathrm{R}\left(\mathbf{e}_3, \theta\right) = R_z(\theta)$.

When (20) holds, $\mathbf{A}$ is said to be *conjugate* to $R_z(\theta)$. Equation (20) says that under a change of coordinates given by a rotation $\mathbf{B}$, $\mathrm{R}\left(\mathbf{u}, \theta\right)$ looks like $R_z(\theta)$. Another way to think geometrically is that $\mathrm{R}\left(\mathbf{u}, \theta\right)$ is given by first rotating $\mathbf{u}$ to the z axis, then rotating an angle θ about the z axis, then rotating the z axis back to $\mathbf{u}$.

4.4. **Properties of rotations.** A few of the main properties of rotations are summarized here. In what follows, $\mathbf{u}$ is a unit vector and $\mathbf{v}$ and $\mathbf{w}$ are real vectors, and $\mathbf{A}$ is a rotation,

$$\mathrm{R}\left(\mathbf{u}, \theta\right) = \mathrm{R}\left(-\mathbf{u}, -\theta\right) \tag{21}$$

$$\mathbf{A}\mathbf{v} \cdot \mathbf{A}\mathbf{w} = \mathbf{v} \cdot \mathbf{w} \tag{22}$$

$$\mathbf{A}\mathbf{v} \times \mathbf{A}\mathbf{w} = \mathbf{A}(\mathbf{v} \times \mathbf{w}) \tag{23}$$

$$\mathbf{u} \cdot \left(\mathrm{R}\left(\mathbf{u}, \theta\right)\mathbf{v} - \mathbf{v}\right) = 0 \tag{24}$$

$$\mathbf{A}\mathrm{R}\left(\mathbf{u}, \theta\right)\mathbf{A}^{-1} = \mathrm{R}\left(\mathbf{A}\mathbf{u}, \theta\right) \tag{25}$$

$$\begin{aligned}\mathrm{R}\left(\mathbf{u}, \theta\right)\mathbf{v} = {} & \cos\theta\left(\mathbf{v} - (\mathbf{u} \cdot \mathbf{v})\mathbf{u}\right) \\ & + \sin\theta\, \mathbf{u} \times \mathbf{v} + (\mathbf{u} \cdot \mathbf{v})\mathbf{u}\end{aligned} \tag{26}$$

We can write (26) in a different form. If $\mathbf{u} = (a, b, c)'$ write

$$\mathbf{S_u} = \begin{pmatrix} 0 & -c & b \\ c & 0 & -a \\ -b & a & 0 \end{pmatrix}$$

Then

$$\mathrm{R}\,(\mathbf{u}, \theta) = \cos\theta\,\mathbf{I} + (1 - \cos\theta)\mathbf{u}\mathbf{u}' + \sin\theta\,\mathbf{S_u} \tag{27}$$

The identities (22) was shown above. For (23), see problem 1. The proofs of (24) and (25) are left as an exercise (see exercise 4).

Here is a proof of (26). The idea is to change variables so that $\mathbf{u}$ becomes $\mathbf{e}_3$ and then the formula becomes obvious. Let $\mathbf{A}$ be a rotation such that $\mathbf{Au} = \mathbf{e}_3$ and let $\mathbf{w} = \mathbf{Av}$. Using (25) and applying $\mathbf{A}$ to both sides of the equation, it becomes

$$\mathrm{R}\,(\mathbf{e}_3, \theta)\,\mathbf{w} = \cos\theta\,(\mathbf{w} - (\mathbf{e}_3 \cdot \mathbf{w})\mathbf{e}_3) + \sin\theta\,(\mathbf{e}_3 \times \mathbf{w}) + (\mathbf{e}_3 \cdot \mathbf{w})\mathbf{e}_3.$$

Writing $\mathbf{w} = (x, y, z)'$ the equation becomes

$$\mathrm{R}\,(\mathbf{e}_3, \theta) \begin{pmatrix} x \\ y \\ z \end{pmatrix} = \cos\theta \begin{pmatrix} x \\ y \\ 0 \end{pmatrix} + \sin\theta \begin{pmatrix} -y \\ x \\ 0 \end{pmatrix} + \begin{pmatrix} 0 \\ 0 \\ z \end{pmatrix},$$

which is clear from the definition of $\mathrm{R}\,(\mathbf{e}_3, \theta)$.

4.5. **Problems.**

(1) (a) Show that if $\det \mathbf{A} = 1$, then

$$\mathbf{v}_1 \cdot (\mathbf{v}_2 \times \mathbf{v}_3) = \mathbf{Av}_1 \cdot (\mathbf{Av}_2 \times \mathbf{Av}_3)$$

for all vectors $\mathbf{v}_1, \mathbf{v}_2, \mathbf{v}_3$.

(b) If in addition $\mathbf{A}'\mathbf{A} = \mathbf{I}$, so that $\mathbf{A}$ preserves the dot product, show that

$$\mathbf{A}(\mathbf{v}_2 \times \mathbf{v}_3) = \mathbf{Av}_2 \times \mathbf{Av}_3$$

for all vectors $\mathbf{v}_2, \mathbf{v}_3$.

(2) Suppose $\mathbf{A}'\mathbf{A} = \mathbf{I}$ and $\det \mathbf{A} = 1$ and $\mathbf{Ae}_3 = \mathbf{e}_3$ show that $\mathbf{A}$ is of the form

$$\begin{pmatrix} \cos\theta & -\sin\theta & 0 \\ \sin\theta & \cos\theta & 0 \\ 0 & 0 & 1 \end{pmatrix}.$$

Use section 10 problem 13.

(3) Suppose $\mathbf{B}_1$ and $\mathbf{B}_2$ are rotations with $\mathbf{B}_1\mathbf{e}_3 = \mathbf{B}_2\mathbf{e}_3$. Show that $\mathbf{B}_1 R_z(\theta)\mathbf{B}_1^{-1} = \mathbf{B}_2 R_z(\theta)\mathbf{B}_2^{-1}$.

(4) Prove that if $\mathbf{A}$ is a rotation, then

$$\mathbf{A}\mathrm{R}\,(\mathbf{u}, \theta)\,\mathbf{A}^{-1} = \mathrm{R}\,(\mathbf{Au}, \theta).$$

(5) Show that any rotation $\mathbf{A}$ can be written as a product of three rotations about the y and z axes,

$$\mathbf{A} = \mathrm{R}_z(\alpha)\mathrm{R}_y(\gamma)\mathrm{R}_z(\delta).$$

The angles α, γ, δ are called *Euler angles* for the rotation $\mathbf{A}$. (Hint: Write $\mathbf{Ae}_3$ in spherical coordinates.)

(6) Every rotation can be written as a product of three rotations in the form $R_z(\alpha)R_y(\gamma)R_z(\delta)$, and the angles α, γ and δ are called Euler angles. Write $R_x(\theta)$ in that form and find Euler angles for R_x. (The formula $\mathbf{A}R(\mathbf{u},\theta) = R(\mathbf{A}\mathbf{u},\theta)\mathbf{A}$ might be useful.)

(7) Let $\mathbf{u} = (1,-1,1)/\sqrt{3}$. Use (27) to find the matrix for $R(\mathbf{u}, 2\pi/3)$.

(8) If $\mathbf{u} = (a,b,c)'$ write

$$S_{\mathbf{u}} = \begin{pmatrix} 0 & -c & b \\ c & 0 & -a \\ -b & a & 0 \end{pmatrix}.$$

Suppose that $\mathbf{u}$ is a unit vector (with real entries) so that $|\mathbf{u}|^2 = \mathbf{u}'\mathbf{u} = 1$.

(a) Show that $S_{\mathbf{u}}\mathbf{u} = \mathbf{0}$.

(b) Show that

$$S_{\mathbf{u}}^2 = \mathbf{u}\mathbf{u}' - \mathbf{I}$$

(9) With $S_{\mathbf{u}}$ as in the previous problem with $\mathbf{u}$ a unit vector,

(a) Show that

$$S_{\mathbf{u}}^3 = -S_{\mathbf{u}}$$

(b) Show that

$$S_{\mathbf{u}}^{2n} = (-1)^n(\mathbf{I} - \mathbf{u}\mathbf{u}') \text{ for } n \geq 1$$

and

$$S_{\mathbf{u}}^{2n+1} = (-1)^n S_{\mathbf{u}} \text{ for } n \geq 0$$

5. Torsion angles and pdb files

In the study of space curves, the Frenet frame is used to define torsion and curvature, and these are used to describe the shape of the curve. A long molecule such as DNA or a protein can be thought of as a curve in space. Rather than being described by continuous functions, it is described by line segments which represent covalent bonds between atoms. The concept of curvature and torsion from differentiable curves can be adapted to study the structure of these molecules. Curvature corresponds to the angle between adjacent bonds, and torsion corresponds to the torsion angle discussed here.

5.1. **Torsion Angles.** In the study of molecular structure, torsion angles are frequently used to describe the shape of the molecule. In figure 19, we see four atoms $\mathbf{p}_1$, $\mathbf{p}_2$, $\mathbf{p}_3$, and $\mathbf{p}_4$. Think of the vectors $\mathbf{p}_j$ as vectors giving the coordinates of the centers of the atoms. Let

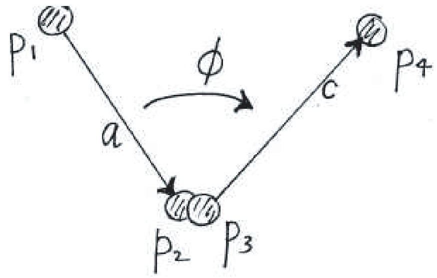


Figure 19. Torsion angle $\phi = \mathrm{Tor}\,(\mathbf{p}_1, \mathbf{p}_2, \mathbf{p}_3, \mathbf{p}_4)$. The angle is measured in the plane perpendicular to $\mathbf{b} = \mathbf{p}_3 - \mathbf{p}_2$.

$$\begin{aligned} \mathbf{a} &= \mathbf{p}_2 - \mathbf{p}_1 \\ \mathbf{b} &= \mathbf{p}_3 - \mathbf{p}_2 \\ \mathbf{c} &= \mathbf{p}_4 - \mathbf{p}_3. \end{aligned} \tag{28}$$

and let $P\mathbf{a}$ and $P\mathbf{c}$ be the projections of $\mathbf{a}$ and $\mathbf{c}$ respectively onto the plane perpendicular to $\mathbf{b}$. The angle, ϕ from $-P\mathbf{a}$ to $P\mathbf{c}$, measured counterclockwise around $\mathbf{b}$, is the torsion angle. Denote this angle as

$$\phi = \mathrm{Tor}\,(\mathbf{p}_1, \mathbf{p}_2, \mathbf{p}_3, \mathbf{p}_4)\,.$$

It is important to note that this angle is measured not between the two vectors $-\mathbf{a}$ and $\mathbf{c}$, but between their projections onto the plane perpendicular to $\mathbf{b}$.

Since the torsion angle depends only on the vectors $\mathbf{a}$, $\mathbf{b}$, $\mathbf{c}$ also write

$$\phi = \tau\,(\mathbf{a}, \mathbf{b}, \mathbf{c})\,.$$

In this case the torsion angle is also called the *dihedral angle.* The angle is usually measured in degrees and chosen in the interval $(-180, 180]$.

The dihedral angle can be thought of as the angle between two planes (See figure 20). It is the angle counterclockwise from the normal vector $\mathbf{a} \times \mathbf{b}$ of the plane containing $\mathbf{a}$ and $\mathbf{b}$ to the normal vector $\mathbf{b} \times \mathbf{c}$ of the plane containing $\mathbf{b}$ and $\mathbf{c}$. Both $\mathbf{a} \times \mathbf{b}$ and $\mathbf{b} \times \mathbf{c}$ are in the plane perpendicular to $\mathbf{b}$

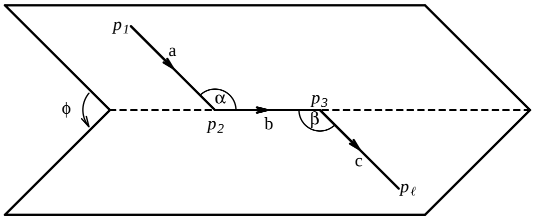


FIGURE 20. The torsion angle ϕ as the angle between planes.

$$\phi = \mathrm{Tor}\left(\mathbf{p}_1, \mathbf{p}_2, \mathbf{p}_3, \mathbf{p}_4\right) = \tau\left(\mathbf{a}, \mathbf{b}, \mathbf{c}\right).$$

Angles α and β are bond angles.

5.2. **The arg function.** The torsion angle can be defined in terms of the argument of a vector or complex number. Define θ to be the *argument* of a vector $(x, y) \neq (0, 0)$, written $\theta = \arg(x, y)$, if $-180° < \theta \leq 180°$ and

$$\cos\theta = x/\sqrt{(x^2 + y^2)}$$
$$\sin\theta = y/\sqrt{(x^2 + y^2)}.$$

We can also write the argument in terms of complex numbers. The angle $\theta = \arg(x, y)$ if $x + iy$ is written in polar form

$$x + iy = re^{i\theta}.$$

In Maple the command to find the argument of a complex number is `argument`.

Note that if $\mathbf{i}, \mathbf{j}, \mathbf{k}$ is the standard basis then the argument can be written as a dihedral angle,

$$\arg(x, y) = \tau\left(-\mathbf{i}, \mathbf{k}, x\mathbf{i} + y\mathbf{j}\right). \tag{29}$$

The angle ϕ of the spherical coordinates of a 3D vector

$$\mathbf{p} = (\cos\theta, \sin\theta\cos\phi, \sin\theta\sin\phi)$$

can also be thought of as a dihedral angle,

$$\phi = \tau\left(-\mathbf{i}, \mathbf{k}, \mathbf{p}\right). \tag{30}$$

5.3. **The torsion angle formula.** We give a formula for computing the dihedral angle, hence the torsion angle, in terms of the argument.

The Dihedral Angle Formula. For vectors $\mathbf{a}$, $\mathbf{b}$, and $\mathbf{c}$ for which the torsion angle is defined,

$$\tau\left(\mathbf{a}, \mathbf{b}, \mathbf{c}\right) = \arg\left(-|\mathbf{b}|^2\mathbf{a}\cdot\mathbf{c} + (\mathbf{a}\cdot\mathbf{b})(\mathbf{b}\cdot\mathbf{c}), |\mathbf{b}|\mathbf{a}\cdot(\mathbf{b}\times\mathbf{c})\right). \tag{31}$$

Proof. Recall that the left hand side is the angle from $\mathbf{a} \times \mathbf{b}$ to $\mathbf{b} \times \mathbf{c}$ measured counterclockwise around $\mathbf{b}$.

Notice that both sides of (31) are unchanged if $\mathbf{a}, \mathbf{b}, \mathbf{c}$ are replaced by $\mathbf{Aa}, \mathbf{Ab}$, and $\mathbf{Ac}$ for a rotation $\mathbf{A}$. So we can assume $\mathbf{b}$ is in the direction of $\mathbf{e}_3$. Likewise the equation unchanged if $\mathbf{b}$ is replaced by $\lambda\mathbf{b}$ for $\lambda > 0$ (dilation), so we can assume $\mathbf{b} = \mathbf{e}_3$.

The equation is unchanged if $\mathbf{a}$ is replaced by its projection $\mathbf{a} - (\mathbf{a} \cdot \mathbf{b})\mathbf{b}$ perpendicular to $\mathbf{b}$. So we can assume $\mathbf{a}$ is perpendicular to $\mathbf{b}$. As above we can rotate and dilate so that $\mathbf{a} = \mathbf{e}_2$. Let $\mathbf{c} = (x, y, z)'$. Then (31) is equivalent to

$$\tau\left(\mathbf{e}_2, \mathbf{e}_3, (x, y, z)\right) = \arg\left(-y, x\right)$$

which is true because the left hand side is the angle from $\mathbf{e}_2 \times \mathbf{e}_3 = \mathbf{e}_1$ to

$$\mathbf{e}_3 \times (x, y, z) = (-y, x, 0).$$

Here is a Maple worksheet to compute torsion angles.

5.4. **Protein torsion angles.**

5.4.1. *Protein backbone torsion angles.* The atoms along a protein backbone are C_α-C-N-C_α-C-N-$\mathrm{C}_\alpha\ldots$ in a sequence repeating every third atom. If each atom has a set of coordinates, the torsion angles along the backbone of a protein are named as follows

- the angle $\mathrm{Tor}\left(\mathrm{C}, \mathrm{N}, \mathrm{C}_\alpha, \mathrm{C}\right)$ is the ϕ torsion angle
- the angle $\mathrm{Tor}\left(\mathrm{N}, \mathrm{C}_\alpha, \mathrm{C}, \mathrm{N}\right)$ is the ψ torsion angle
- the angle $\mathrm{Tor}\left(\mathrm{C}_\alpha, \mathrm{C}, \mathrm{N}, \mathrm{C}_\alpha\right)$ is the ω torsion angle

Moving along the backbone we get a sequence of ϕ, ψ and ω torsion angles that can be used to describe the structure of the backbone.

5.4.2. *Protein sidechain torsion angles.* We can also get torsion angles by moving along a side chain. The greek letter subscripts for the atoms along the side chain are indicated in figure 21. For example, the sequence of atoms C_α, C_β, C_γ, C_δ of Lysine determine the χ_2 torsion angle. The atoms C_α, C_β, C_γ, S of Methionine determine the χ_2 torsion angle.

For the χ_1 angle, the first atom used for the torsion angle is the N on the backbone. For example,

- for Leucine, the angle $\mathrm{Tor}\left(\mathrm{N}, \mathrm{C}_\alpha, \mathrm{C}_\beta, \mathrm{C}_\gamma\right)$ is the χ_1 torsion angle
- for Threonine, the angle $\mathrm{Tor}\left(\mathrm{N}, \mathrm{C}_\alpha, \mathrm{C}_\beta, \mathrm{O}\right)$ is the χ_{1_2} torsion angle (when there are two χ_1 angles, another subscript is added).

5.5. **Protein Data Bank files.** Structures of all known proteins are stored online at the Protein Data Bank. The files there are called *pdb files.* The structural information contained in the file is a list of three coordinates, (x, y, z), for the centers of every atom in the molecule (although hydrogen atoms are left out because they are small and their positions can be determined from the positions of the other atoms). For example, a file identified as 1E0P contains the coordinates for a protein called bacteriorhodopsin. Here is part of the file which can be downloaded from the RCSB Protein Data Bank:

```
ATOM   1557  CB  ILE A 205     -14.646  17.302  50.448  1.00 21.52 C
ATOM   1558  CG1 ILE A 205     -13.253  16.800  50.104  1.00 19.39 C
ATOM   1559  CG2 ILE A 205     -15.422  17.496  49.149  1.00 22.80 C
ATOM   1560  CD1 ILE A 205     -13.299  15.453  49.472  1.00 18.37 C
ATOM   1561  N   PHE A 206     -12.336  19.006  52.127  1.00 22.92 N
```

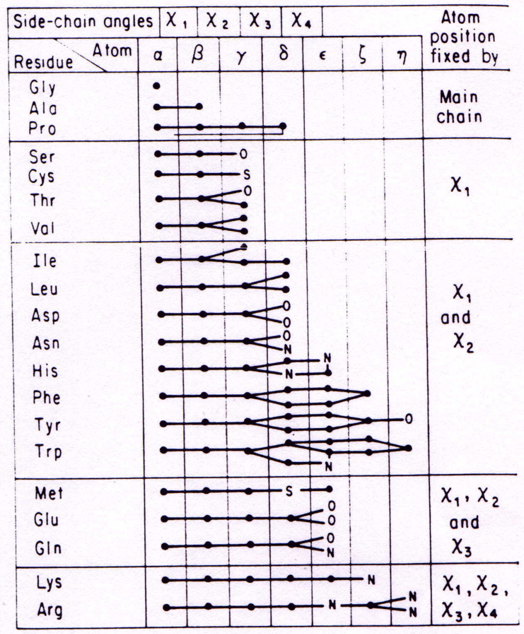


Figure 1. Flexibility of amino acid side-chains. The Figure shows the chi angle values required to fix the positions of side-chain atoms in each residue type.

FIGURE 21. Naming convention for torsion angles along the sidechains of a protein

```
ATOM   1562  CA  PHE A 206     -11.262  18.905  53.109  1.00 23.61 C
ATOM   1563  C   PHE A 206     -11.438  19.982  54.171  1.00 26.34 C
```

The x, y and z coordinates are contained in columns 7, 8, and 9 respectively. Other important information is

- column 2, the number of the atom in the list
- column 3, the position of the atom in the protein using the naming convention in table (21). Note that, for example, CB is written instead of C_β.
- column 4, the three letter code for the amino acid
- column 5, the number of the amino acid in the list of amino acids (residues) along the protein.

5.6. **Ramachandran diagram.** The ϕ, ψ pairs of torsion angles for each amino acid along the backbone of a protein can be plotted as points in a rectangle, and this plot is called a *Ramachandran plot.* The ω torsion angle in generally considered to be 180° since the peptide bond is planar. The Ramachandran plot gives information about the secondary structure of the protein. (See figure 5.6.)

A regular protein backbone structure is one where all of the ω torsion angles are 180 degrees and all of the ϕ, ψ pairs at alpha carbons have the same value. The diagram below indicates the types of structures we get for different pairs. A regular alpha helix, for example, corresponds to $(\phi, \psi) = (-60°, -50°)$. The level curves

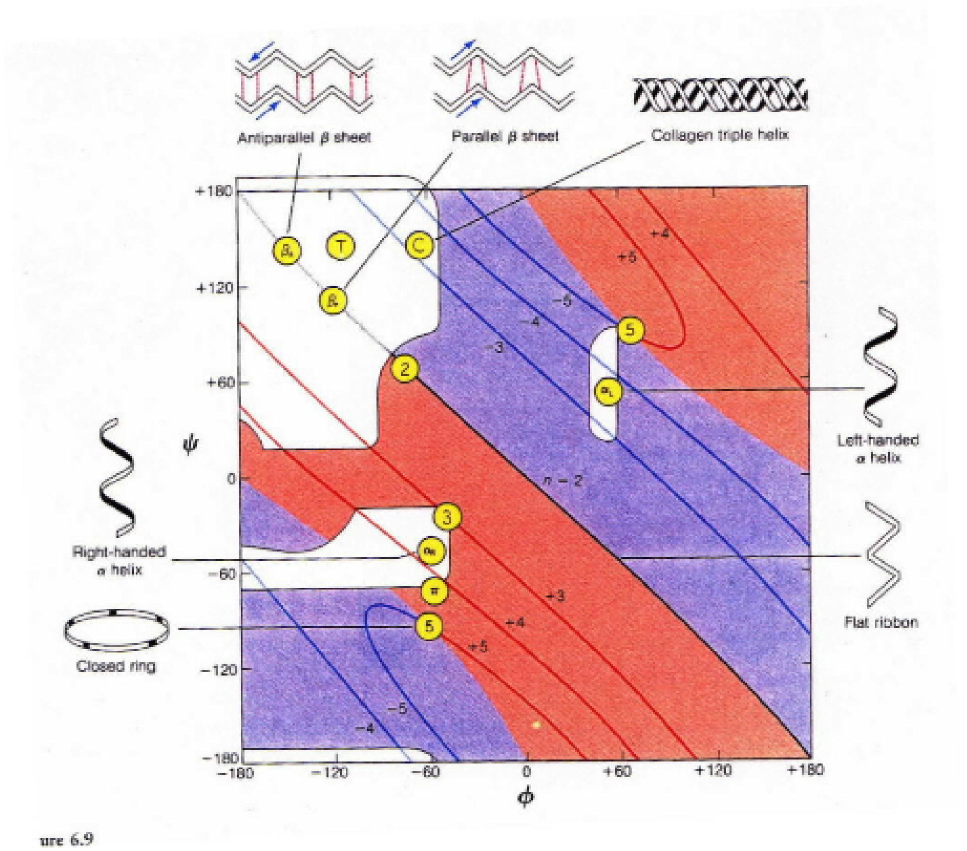


Figure 22. The Ramachandran plot giving the number of residues per turn of the helix.

indicate the number of residues per turn, the number of amino acids for each 180 degree turn about the axis of the helix, for the corresponding regular structure. All of the structures can be thought of as helices with various numbers of residues per turn.

5.7. **Torsion angles on the diamond packing.** The diamond packing is a set of points in space where the centers of carbons of a diamond crystal lie. The diamond packing is obtained from the face centered cubic lattice (the set of points with integer coordinates adding up to an even number) by adding to it points of the face centered cubic lattice moved over by the vector $(1/2, 1/2, 1/2)$. So

$$\text{Diamond packing} = \text{fcc} \cup \{\text{fcc} + (1/2, 1/2, 1/2)\}\,.$$

By moving on a path through the diamond packing you can get torsion angles of 180, 60, and -60 only (or undefined if two consecutive vectors are parallel). Since the -60 degree torsion angles are close to the ones for alpha helices, attempts have been made to model proteins by putting atoms in a protein on points in a diamond packing. Maple demo

5.8. **Appendix, properties of cross product.** Here are some useful formulas involving the cross product and the dot product

$$(\mathbf{a} \times \mathbf{b}) \cdot (\mathbf{c} \times \mathbf{d}) = (\mathbf{a} \cdot \mathbf{c})(\mathbf{b} \cdot \mathbf{d}) - (\mathbf{a} \cdot \mathbf{d})(\mathbf{b} \cdot \mathbf{c})$$
$$\mathbf{a} \times (\mathbf{b} \times \mathbf{c}) = (\mathbf{a} \cdot \mathbf{c})\mathbf{b} - (\mathbf{a} \cdot \mathbf{b})\mathbf{c}$$

5.9. **Problems.**

(1) Suppose a pdb file contains the following lines

```
ATOM    813  N   ARG O 113     -25.027  14.899 -17.838  1.00  8.68           N
ATOM    814  CA  ARG O 113     -24.794  13.442 -17.751  1.00  8.96           C
ATOM    815  C   ARG O 113     -24.526  13.069 -16.312  1.00  9.33           C
ATOM    816  O   ARG O 113     -24.431  13.934 -15.454  1.00  8.24           O
ATOM    817  CB  ARG O 113     -23.838  12.955 -18.888  1.00  7.62           C
ATOM    818  CG  ARG O 113     -24.493  12.701 -20.214  1.00  7.02           C
ATOM    819  CD  ARG O 113     -23.954  12.682 -21.559  1.00  4.59           C
ATOM    820  NE  ARG O 113     -24.914  12.545 -22.637  1.00  4.39           N
ATOM    821  CZ  ARG O 113     -24.964  12.763 -23.899  1.00  5.44           C
ATOM    822  NH1 ARG O 113     -24.081  13.156 -24.830  1.00  5.82           N
ATOM    823  NH2 ARG O 113     -26.153  12.663 -24.592  1.00  8.39           N
ATOM    824  N   THR O 114     -24.536  11.769 -16.002  1.00 11.55           N
ATOM    825  CA  THR O 114     -24.313  11.347 -14.633  1.00 11.92           C
ATOM    826  C   THR O 114     -22.940  10.686 -14.493  1.00 11.89           C
ATOM    827  O   THR O 114     -22.473   9.949 -15.295  1.00 11.88           O
ATOM    828  CB  THR O 114     -25.467  10.527 -13.954  1.00 11.40           C
ATOM    829  OG1 THR O 114     -26.730  11.163 -14.288  1.00 10.92           O
ATOM    830  CG2 THR O 114     -25.425  10.484 -12.405  1.00 11.83           C
```

   (a) Write in sequence the numbers of the atoms used to compute the χ_2 torsion angle for ARG. Use Maple and the torsion angle formula to compute the χ_2 torsion angle.

   (b) Using the coordinates above, use Maple to find (in degrees) the angle C_α-C-O in THR.

(2) Using the formula in the notes for torsion angle, show that

$$\mathrm{Tor}(\mathbf{p}_1, \mathbf{p}_2, \mathbf{p}_3, \mathbf{p}_4) = \mathrm{Tor}(\mathbf{p}_4, \mathbf{p}_3, \mathbf{p}_2, \mathbf{p}_1).$$

6. X-ray Crystallography, Lattices, and Fourier Series

Most of the information that we have on protein structure comes from x-ray crystallography. The basic steps in finding a protein structure using this method are:

- a high quality crystal is formed from a sample of protein
- the crystal is placed in an x-ray beam and the intensities of the diffraction spots are measured
- after finding the phases, an electron density map is computed from the diffraction intensities and phases using Fourier analysis. The phases cannot be found from experimental data, but are guessed by methods not discussed here.
- The coordinates of the atoms are found from the electron density.
- The structure is refined by checking that, for example, the atoms do not get too close to each other.

What follows is a brief discussion of some of the mathematics involved in finding the electron density from the diffraction intensities and phases. This requires studying Fourier series for functions periodic on lattices.

6.1. **Lattices.** The basic structure of a crystal is that of a lattice. A crystal is formed by several copies of the same protein in a pattern which fills a unit cell. The unit cell is a parallelepiped which is then used as a tile whose translations fill up space. For mathematical simplicity, we can suppose that there are an infinite number of copies of the same protein.

A lattice is easy to describe mathematically. A lattice L in three dimensions is generated by three linearly independent vectors $\mathbf{a}, \mathbf{b}, \mathbf{c}$; it is the set of all points $h\,\mathbf{a}+k\,\mathbf{b}+l\mathbf{c}$ where h, k and l are integers. A unit cell is the set of points $x\mathbf{a}+y\mathbf{b}+z\mathbf{c}$ for $0 \leq x \leq 1$, $0 \leq y \leq 1$, $0 \leq z \leq 1$. Similarly we can define a lattice in two dimensions as the set of integer combinations of two linearly independent vectors $\mathbf{a}$ and $\mathbf{b}$ and the unit cell is the parallelogram formed by the points $x\mathbf{a} + y\mathbf{b}$ for $0 \leq x \leq 1$, $0 \leq y \leq 1$. In the pdb file for a crystal structure, you can find the lengths of and angles between the vectors $\mathbf{a}, \mathbf{b}$ and $\mathbf{c}$ which generate the lattice for the crystal. If, for example, we look at the Protein Data Bank entry for the protein 2MBH, we find that the lengths of the vectors are $a = 108.24$. $b = 63.13$, $c = 54.54$. The angles between the vectors are $\alpha = 90.00$, $\beta = 110.85$, and $\gamma = 90.00$. The angles are measured in degrees. The angle α is between $\mathbf{b}$ and $\mathbf{c}$, the angle β is between $\mathbf{a}$ and $\mathbf{c}$ and the angle γ is between $\mathbf{a}$ and $\mathbf{b}$.

The origin of the coordinate system can be put at any point crystallized protein. If the origin is placed at an atom in the protein, then every lattice point will be on exactly the same atom in another copy of the protein in the lattice.

6.1.1. *Examples of lattices.* First consider two dimensions. The vectors $\mathbf{a} = (1, 0)$ and $\mathbf{b} = (0, 1)$ generate the *square lattice.* The vectors $\mathbf{a} = (1, 0)$ and $\mathbf{b} = (1/2, \sqrt{3}/2)$ generate the *hexagonal lattice.*

In three dimension the vectors $\mathbf{a} = (1, 0, 0)$, $\mathbf{b} = (0, 1, 0)$, and $\mathbf{c} = (0, 0, 1)$ generate the *cubic lattice.* The vectors $\mathbf{a} = (1, 1, 0)$, $\mathbf{b} = (1, 0, 1)$, $\mathbf{c} = (0, 1, 1)$ generate the *face centered cubic lattice.* The face centered cubic lattice can also be described as the set of points (x, y, z) with integer coordinates such that $x + y + z$ is even.

For an illustration of lattices see the Maple demo.

The lattices described above are examples of lattices with symmetries. A symmetry of a lattice is a rotation such that the rotation and its inverse maps every point in the lattice onto another point of the lattice. We say the rotation leave the lattice unchanged. The square lattice, for example, is left unchanged by 90 degree rotation, an order 4 symmetry since the product of 4 rotations of 90 degrees is the identity. The hexagonal lattice is left unchanged by 60 degree rotation, an order 6 symmetry. The cubic lattice is left fixed by 90 degree rotation about any coordinate axis. These are order 4 symmetries. The face centered cubic lattice is left fixed by 120 degree rotation about the axis in the direction $(1, 1, 1)$. This is an order 3 symmetry.

6.2. **The crystallographic restriction.**

A symmetry of the lattice for a crystal shows up in a symmetry of the diffraction pattern. It can be proved mathematically that the symmetry of a lattice has the crystallographic restriction: it has no rotational symmetries of order 5 or greater than 6. The crystallographic restriction can be stated as follows.

A lattice in the plane or in three-dimensional space cannot have rotational symmetries of order 5 or of order greater than 6.

Proof Here is a proof in dimension 2. The proof in dimension 3 is similar.

Let L be a two dimensional lattice generated by vectors $\mathbf{a}$ and $\mathbf{b}$,

$$L = \{h\,\mathbf{a} + k\,\mathbf{b} \mid \text{ } h \text{ and } k \text{ are integers}\}\,.$$

Suppose that the rotation

$$R = \begin{pmatrix} \cos\theta & -\sin\theta \\ \sin\theta & \cos\theta \end{pmatrix} \tag{32}$$

is a symmetry of L, that is, R moves L onto itself. Since $R\,\mathbf{a}$ and $R\,\mathbf{b}$ are in L,

$$\begin{aligned} R\,\mathbf{a} &= h_1\,\mathbf{a} + k_1\,\mathbf{b} \\ R\,\mathbf{b} &= h_2\,\mathbf{a} + k_2\,\mathbf{b} \end{aligned} \tag{33}$$

for integers h_1, h_2, k_1, k_2.

Using the frame $(\mathbf{a}, \mathbf{b})$ write (33) as

$$R\,(\mathbf{a}, \mathbf{b}) = (\mathbf{a}, \mathbf{b})\,M$$

or

$$(\mathbf{a}, \mathbf{b})^{-1}\,R\,(\mathbf{a}, \mathbf{b}) = M \tag{34}$$

where

$$M = \begin{pmatrix} h_1 & h_2 \\ k_1 & k_2 \end{pmatrix}.$$

The trace of a matrix A ($\operatorname{tr} A$) is the sum of its diagonal entries. A basic fact in linear algebra is that

$$\operatorname{tr}A = \operatorname{tr}(B^{-1}AB)$$

for all invertible matrices B. Applying this to (34),

$$\operatorname{tr} R = 2\cos\theta = \operatorname{tr} M = h_1 + k_2. \tag{35}$$

Now from (35) it follows that $2\cos\theta$ is an integer, and so must be equal to -2, -1, 0, 1, or 2. Thus the only possibilities for θ are 0°, ±60°, ±90° , ±120°, and 180° and this proves the crystallographic restriction in dimension 2. □

6.3. **Diffraction.** Molecules arranged in a lattice are arranged in many sets of parallel planes. You can see this by plotting a lattice, for example the face centered cubic lattice, in Maple and rotating it (Maple demo).

An X-ray beam focused on a crystal creates a pattern of diffraction spots. The position of an X-ray diffraction spot depends on the distance d between the parallel planes creating it, the normal vector for the planes, and the wave length of the x-rays.

The simplest and oldest rule of diffraction is Bragg's law derived by the English physicists Sir W.H. Bragg and his son Sir W.L. Bragg in 1913,

$$2\,d\,\sin\theta = n\,\lambda \tag{36}$$

where θ is the angle of incidence of the x-ray, λ is the wave length of the x-ray, and n is some integer. The formula holds when refraction yields a bright spot at angle θ.

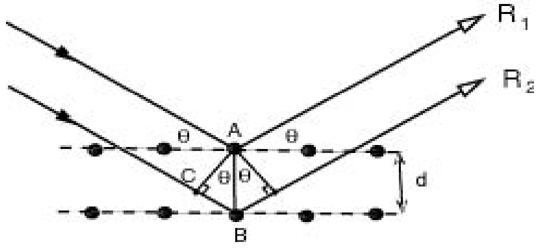


FIGURE 23. Illustration of Braggs Law. R_1 and R_2 are diffracted X-rays. The angle θ is the angle of incidence with planes containing the indicated atoms. Bragg's law can be derived by looking at the triangle ABC. The extra distance travelled by R_2 is $2\overline{\mathrm{BC}}$.

The formula is explained by looking at figure 23. If d is the distance between the planes, the ray R_2 travels a distance of $2\,d\,\sin\theta$ farther than R_1. If this is an integer multiple of the wavelength, the two rays are in phase after reflection and create a bright spot. Otherwise there is cancellation and no spot is seen.

Here is a link to a Java applet illustrating Bragg's Law.

6.3.1. *Mathematical statement of Bragg's law.* Bragg's law is an equation for the phase difference between two sine waves. We say the functions $\sin\frac{2\pi}{\lambda}x$ and $\sin\frac{2\pi}{\lambda}(x+p)$ have phase difference $\frac{p}{\lambda}$ cycles. The wave length is λ for both.

A sine wave with amplitude 1 and wavelength λ moving in the direction of the unit vector u_1 can be written as

$$\sin\left[\frac{2\pi}{\lambda}x\cdot u_1\right]. \tag{37}$$

where x is a vector representing a point in space. This represents, at a fixed time, an x-ray beam moving in the direction u_1. The reflection off a point x_0 along a line through x_0 in the direction u_2, the wave has the equation

$$\sin\left[\frac{2\pi}{\lambda}\left(x\cdot u_2 + x_0\cdot(u_1-u_2)\right)\right]. \tag{38}$$

This can be seen by checking that (37) and (38) agree at $x = x_0$.

Similarly the reflection off the point x_1 along a line through x_1 in the same direction u_2, the wave has the equation

$$\sin\left[\frac{2\pi}{\lambda}\left(x\cdot u_2 + x_1\cdot(u_1-u_2)\right)\right]. \tag{39}$$

See figure 24. The difference in phase between (38) and (39) is

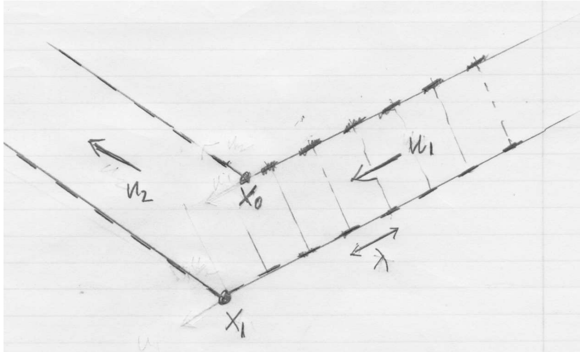


FIGURE 24. x-rays of wavelength λ reflecting off two atoms at points x_0 and x_1. Incoming rays in direction u_1 are parallel. Outgoing rays in direction u_2 are possibly out of phase.

$$\frac{1}{\lambda}(x_1-x_0)\cdot(u_1-u_2) \tag{40}$$

cycles, and when the difference is a integer n,

$$(x_1-x_0)\cdot(u_1-u_2) = n\lambda, \tag{41}$$

the outgoing waves are in phase at the point at infinity in the direction u_2.

Suppose x_0 and x_1 are points in a lattice, so they differ by a lattice vector $x_1 - x_0 = \mathbf{v}$. Equation (41) shows that all such reflections are in phase if

$$\mathbf{v}\cdot(u_1-u_2) = n\lambda \tag{42}$$

for all lattice vectors $\mathbf{v}$. For fixed n, (42) says that x_0 and x_1 lie in parallel planes perpendicular to $u_1 - u_2$.

Equation (42) is the mathematical expression of Bragg's law (36). To see this, note that $(x_1 - x_0) \cdot (u_1 - u_2) = d|u_1 - u_2|$ and $|u_1 - u_2| = 2\sin\theta$.

It says, for example, that on the integer lattice, since $\mathbf{v}$ always has integer coordinates, we get reflections in the direction u_2 from the planes normal to $u_1 - u_2$ only if $(u_1 - u_2)/\lambda = (h, k, l)$ also has integer coordinates. The reflection spot in the direction u_2 is labelled (h, k, l) for integers h, k, and l. They come from planes on the integer lattice parallel to the plane $hx + ky + lz = 0$.

6.4. **Electron density.** In crystallography, it is not the atoms of a molecule that are seen, but the electrons surrounding the atoms. To describe an electron cloud, a non-negative number giving the density of electrons is assigned to each point in the crystal. This number can be thought of as the amount of charge per unit volume. Although the information about protein structure is given in the form of a file containing the coordinates of each atom, in reality what the crystallographer sees is the electron density. The points representing the centers of the atoms are extrapolated from the electron density function using a computer.

Suppose that a molecule is crystallized into a lattice consisting of all integer combinations of vectors $\mathbf{a}, \mathbf{b}$ and $\mathbf{c}$. Let $r(x, y, z)$ be the electron density at the point $x\,\mathbf{a} + y\,\mathbf{b} + z\mathbf{c}$, where x, y and z are real numbers, not necessarily integers. The function r is called the electron density function. If a level surface of the electron density function is plotted in one unit cell, it will look as in figure 25 for 6 Angstrom resolution and figure 26 for for 1A resolution.

The level surface shows more structural detail at higher (1 Angstrom) resolution.

The electron density map is the level surface of a function computed from a Fourier series. Here is how Maple deals with level curves of functions of two variables and level surfaces of functions of three variables.

The electron density function is given by a function of three variable which is period 1 in each of the variables. Since the crystal is unchanged if it translated by $\mathbf{a}, \mathbf{b}$ or $\mathbf{c}$, the electron density is the same at

$$(x+1)\mathbf{a} + y\mathbf{b} + z\mathbf{c}$$

as at

$$x\mathbf{a} + y\mathbf{b} + z\mathbf{c}.$$

Thus r has period 1 in the variable x,

$$r(x, y, z) = r(x+1, y, z).$$

A similar equation holds for the variables y and z. The electron density function is a periodic function, of period 1 in each of the three variables.

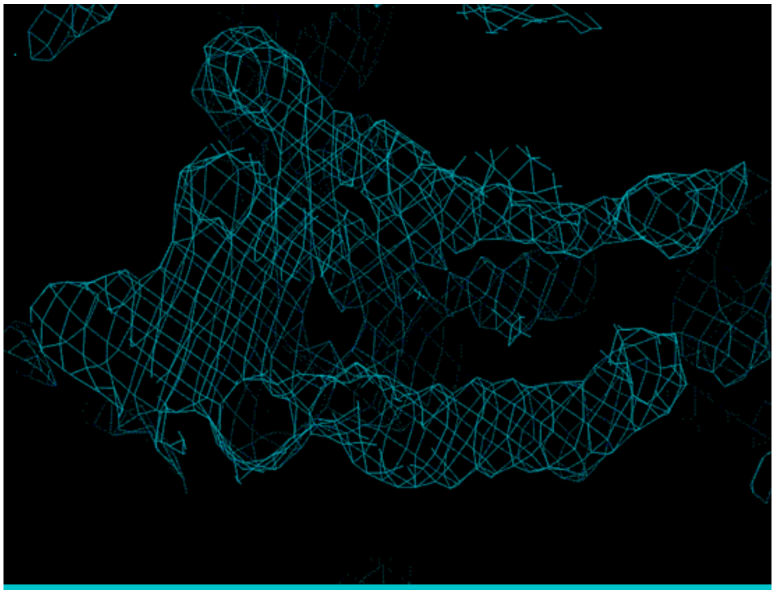


Figure 25. An electron density map of a molecule at 6 Angstrom resolution. The atoms are not clearly seen.

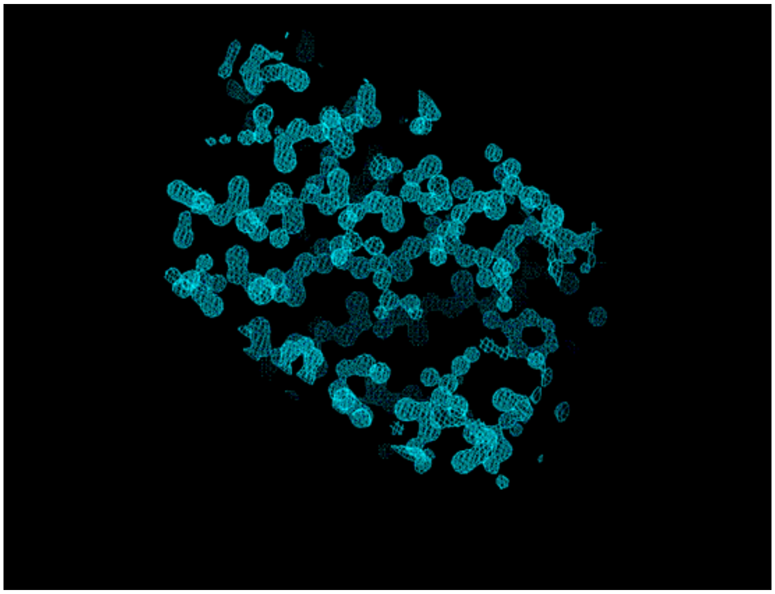


Figure 26. Electron density function of a molecule at 1 Angstrom. The position of each atom is clearly seen.

Periodic functions are studied using Fourier series. We begin by looking at the theory for one variable. This will generalize to the three variable case which we are interested in.

6.5. **Fourier series.** The electron density function is constructed using Fourier Analysis. Fourier analysis is the approximation of periodic functions by sines and cosines. The basic idea of Fourier analysis is that any real valued function $f(x)$ of period 1 can be approximated by sums of the type

$$a_0 + \sum_{j=1}^{n} [a_j \cos(2\pi jx) + b_j \sin(2\pi jx)] \tag{43}$$

for suitable choice of the real coefficients a_j and b_j and for n large enough. A sum of type (43) is called a Fourier series.

The surprising part about Fourier's discovery is that even a discontinuous function such as a square wave can be approximated by a Fourier series. For example, consider the period 1 square wave defined on the interval $[0, 1]$ by the function

$$f(x) = \begin{cases} 0, & \text{if } \frac{1}{4} < x < \frac{3}{4} \\ 2, & \text{otherwise.} \end{cases} \tag{44}$$

This is a function of period 1, and $\int_0^1 f(x)\,dx = 1$. The Fourier cosine series

$$1 + \sum_{j=0}^{n} a_j \cos 2\pi(2j+1)x \tag{45}$$

with coefficients

$$a_j = \frac{4(-1)^j}{\pi(2j+1)} \tag{46}$$

approximates f closely for large n. Here is a Maple demo

6.5.1. *Complex form of Fourier series.* We will discuss how the coefficients of a Fourier series are computed. The simplest formula uses the complex form of the Fourier series. Complex numbers give a convenient way of writing Fourier series, even for real functions.

The complex form of Fourier series is based on Euler's formula

$$e^{ix} = \cos x + i \sin x.$$

from which it follows that

$$\cos 2\pi jx = \frac{e^{2\pi ijx} + e^{-2\pi ijx}}{2}$$

and

$$\sin 2\pi jx = \frac{e^{2\pi ijx} - e^{-2\pi ijx}}{2i}.$$

Substituting these expressions in the general form for the Fourier sum (43) get

$$\sum_{j=-n}^{n} c_j e^{2\pi ijx} \tag{47}$$

where

$$c_j = \frac{1}{2}(a_j - ib_j), \quad j = 1, \ldots, n$$

$$c_0 = a_0$$

and

$$c_{-j} = \bar{c_j}, \quad j = 1, \ldots, n.$$

So now we have a sum (47) of complex functions equal to the real sum (43). The sum (47) adds up to a real function since every term $c_j e^{2\pi i j x}$ is added to its conjugate $\overline{c_j} e^{-2\pi i j x}$.

If

$$f(x) = \sum_{j=-n}^{n} c_j e^{2\pi i j x} \tag{48}$$

then the Fourier coefficients can be recovered from the function f by the formula

$$c_k = \int_0^1 f(x) e^{-2\pi i k x} dx. \tag{49}$$

This can be seen by multiplying both sides of (48) by $e^{-2\pi i k x}$ and integrating, noting that

$$\int_0^1 e^{2\pi i(j-k)x} dx = \begin{cases} 0, & \text{if } j \neq k \\ 1, & \text{if } j = k. \end{cases}$$

Here is a demo in Maple of complex Fourier series. It is left as an exercise (problem 3 with $a = 1/4$) to show that formula (49) gives coefficients (46) for the square wave (44).

The Fourier coefficients, like all complex numbers, have an absolute value and an argument, that is, we can write them in polar form as

$$c_j = |c_j| e^{i\delta_j}. \tag{50}$$

The number δ_j is called the phase and $|c_j|$ the norm. These are the phases referred to in the crystallography phase problem.

6.5.2. *Delta function.* The square wave function (44) is an example of an approximation to a periodic 1 Dirac delta function. The periodic delta function $\delta_{\mathbb{Z}}$, or the delta function of the one dimensional integer lattice $\mathbb{Z}$, is thought of as a "function" of period 1 such that

$$\int_{-1/2}^{1/2} \delta_{\mathbb{Z}}(x) f(x)\, dx = f(0) \tag{51}$$

for any smooth periodic function $f(x)$. In particular,

$$\int_{-1/2}^{1/2} \delta_{\mathbb{Z}}(x)\, dx = 1.$$

There is no function that has these properties, but the delta function can be thought of as the limit as $M \to \infty$ of square waves such as

$$f(x) = \begin{cases} \frac{M}{2}, & \text{if } n - \frac{1}{M} < x < n + \frac{1}{M},\ n \text{ an integer;} \\ 0, & \text{otherwise,} \end{cases} \tag{52}$$

of which (44) is the special case $M = 4$. Similarly by replacing 0 by a in (51), get the definition of the periodic delta function $\delta_{\mathbb{Z}+a}$.

A way to think about electron density function of a crystal and the phase problem is to use a delta function. Think of the periodic delta function $\delta_{\mathbb{Z}+a}$ in one dimension as describing the electron density of a crystal formed by a single atom of zero radius and mass 1 at each point $a + n$ where n is an integer. Better, think of it as approximated by a function which is non-negative but zero except near a and which integrates near a to 1. By (49), the Fourier coefficients of $\delta_{\mathbb{Z}+a}$ are given by

$$c_j = e^{-2\pi i j a}. \tag{53}$$

So $\delta_{\mathbb{Z}+a}$ can be approximated by

$$\delta_{\mathbb{Z}+a}(x) \approx \sum_{k=-N}^{N} e^{2\pi i k(x-a)} \tag{54}$$

for large N. Look at the Maple worksheet to see what this function looks like. In fact, simplifying the right hand side of (54) gives

$$\delta_{\mathbb{Z}+a}(x) \approx \frac{\sin\left[2\pi\left(N+\frac{1}{2}\right)(x-a)\right]}{\sin[\pi(x-a)]}. \tag{55}$$

The phase of c_j is $-2\pi j a$ and the norm is 1. If we did not know the phase but put 0 for the phase instead, then the coefficients c_j would all be 1 and we would get an atom at $x = 0$ instead of $x = a$. This illustrates the importance of knowing the phases in computing the electron density function.

6.6. **Three variable Fourier series.** Fourier series can be used to analyze periodic functions in any number of variables, for example the electron density function ρ for a 3D crystal.

Given a real function $\rho(x, y, z)$ of period 1 in each variable, it can be approximated by a triple sum of the form

$$\sum_{h=-n}^{n} \sum_{k=-n}^{n} \sum_{l=-n}^{n} c_{hkl} e^{2\pi i(hx+ky+lz)}$$

written more compactly as

$$f(x, y, z) = \sum_{hkl} c_{hkl} e^{2\pi i(hx+ky+lz)} \tag{56}$$

where

$$c_{-h,-k,-l} = \bar{c}_{hkl}$$

since the function is real, and where $|h|$, $|j|$, and $|k|$ are $\leq n$ where n is a large enough integer. Writing the complex Fourier coefficient in polar form as

$$c_{hkl} = |c_{hkl}|e^{i\alpha_{hkl}},$$

the number α_{hkl} is the *phase*.

Similar to (49) the Fourier coefficients of (56) are

$$c_{hkl} = \int_0^1 \int_0^1 \int_0^1 f(x, y, z)e^{-2\pi i(hx+ky+lz)}dx\, dy\, dz. \tag{57}$$

In x-ray crystallography, the values $|c_{hkl}|$ are measured from the intensities of the spots in the diffraction pattern. The phases α_{hkl} must be supplied by other means to find the electron density function. This is called the *phase problem.* There are mathematical techniques for finding the phases but also some guess work is involved.

6.6.1. *Delta function.* Similar to the delta function for the one dimensional integer lattice, the delta function $\delta_{\mathbb{Z}^3}$ for the three dimensional integer lattice, or cubic lattice, can be approximated by a finite sum of the form (56) with $c_{hkl} = 1$ for all integer triples hkl. Also $\delta_{\mathbb{Z}^3+a}$ is approximated by setting the Fourier coefficients $c_\ell = e^{-2\pi i a\cdot\ell}$ where $\ell = (h, k, l)$.

6.7. **Diffraction pattern and Fourier series.**

Here we show how the diffraction intensities give the absolute values of the Fourier coefficients of the electron density function. We show this when the molecule is a single point and the electron density is a delta function. The general case follows from this by adding delta functions for all the atoms in the molecule.

Consider the electron density of a single atom of mass m modeled approximately as m times a delta function. For simplicity, assume the lattice of the crystal is the integer lattice, $\mathbb{Z}^3$. In order to get a finite Fourier sum consider just a part of the lattice,

$$L = \{(x, y, z)|\ x, y, z \text{ integers }, -N \leq x \leq N, -N \leq y \leq N, -N \leq z \leq N\}$$

for N large. Now write the electron density function for atoms at points $x_0 + \ell$, $\ell \in L$ as

$$\rho(x) = m\sum_{\ell\in L} e^{-2\pi i x_0\cdot\ell}e^{2\pi i x\cdot\ell}. \tag{58}$$

The Fourier coefficients of the electron density function are $c_\ell = me^{-2\pi i x_0\cdot\ell}$ for $\ell \in L$. Note that $\rho(x)$ is an approximation of the delta function $\delta_{x_0+\mathbb{Z}^3}$.

Now look at the diffraction pattern. As before, consider the reflection of an x-ray beam moving in the direction u_1, reflected in the direction u_2 from all of these atoms. The equation for the beam reflected from the atom at x_0 is given as (38). The computation simplifies if we replace the sine function by the complex exponential. Also assume that the intensity of the reflected beam is proportional to the electron density m at the point. Then the outgoing beam has equation

$$m \exp\left[\frac{2\pi i}{\lambda}\left(x\cdot u_2 + x_0\cdot(u_1-u_2)\right)\right] \tag{59}$$

giving the amplitude and phase for the beam at a point x in space. The beam from the entire lattice of points is the sum of the intensities of each point in the lattice,

$$\begin{aligned} w(x) &= \sum_{\ell\in L} m\exp\left[\frac{2\pi i}{\lambda}\left(x\cdot u_2 + (x_0+\ell)\cdot(u_1-u_2)\right)\right] \\ &= m\exp\left[\frac{2\pi i}{\lambda}x\cdot u_2\right]\exp\left[\frac{2\pi i}{\lambda}x_0\cdot(u_1-u_2)\right]\sum_{\ell\in L}\exp\left[\frac{2\pi i}{\lambda}\ell\cdot(u_1-u_2)\right]. \end{aligned} \tag{60}$$

Writing $\ell^* = (u_1-u_2)/\lambda$ equation (60) becomes

$$w(x) \approx m\exp\left[\frac{2\pi i}{\lambda}x\cdot u_2\right]\exp\left[2\pi i x_0\cdot\ell^*\right]\delta_{\mathbb{Z}^3}(\ell^*) \tag{61}$$

since

$$\delta_{\mathbb{Z}^3}(\ell^*) \approx \sum_{\ell\in L}\exp\left[2\pi i\ell\cdot\ell^*\right].$$

Integrating it with respect to ℓ^* near a lattice point gives the value of 1. It follows that the total reflected wave for $(u_1-u_2)/\lambda$ near ℓ^* is

$$m\exp\left[\frac{2\pi i}{\lambda}x\cdot u_2\right]\exp\left[2\pi i x_0\cdot\ell^*\right] \tag{62}$$

where x is a point along the reflected beam. (Since all the beams are parallel in the direction u_2, we merge them all into one beam at infinity where they are collected.) The expression (62) is $c_{\ell^*}\exp\left[\frac{2\pi i}{\lambda}x\cdot u_2\right]$ where c_{ℓ^*} is the ℓ^* Fourier coefficient of the electron density function (58). Since only the amplitude of the beam can be measured from the intensity of the diffraction spot, the data gives only $|c_{\ell^*}| = m$, the absolute value of the Fourier coefficient, and not the phase.

Using the above method of argument, it can be shown that the same result holds when we add electron densities of atoms to get the electron density of a molecule. Only the absolute value of the Fourier coefficient can be determined from the diffraction pattern.

6.8. **Problems.**

(1) The face centered cubic (fcc) lattice is generated by the basis vectors

$$(0,1,1),(1,1,0),(1,0,1),$$

which means it is the set of all vectors of the form

$$a(0,1,1)+b(1,1,0)+c(1,0,1)$$

where a, b, and c are integers. Show that this lattice is also the set of vectors (p, q, r) where p, q, and r are integers and $p+q+r$ is even.

(2) Show that the rotations

$$\begin{pmatrix} 0 & 1 & 0 \\ 0 & 0 & -1 \\ -1 & 0 & 0 \end{pmatrix} \text{ and } \begin{pmatrix} 0 & 0 & 1 \\ 1 & 0 & 0 \\ 0 & 1 & 0 \end{pmatrix}$$

are symmetries of the fcc lattice.

(3) For $0 < a < 1/2$ let $f_a(x)$ be the square wave defined on the interval $-1/2 \leq x \leq 1/2$ by

$$f_a(x) = \begin{cases} \frac{1}{2a} & \text{if } -a < x < a \\ 0 & \text{otherwise} \end{cases}$$

  (a) Find the Fourier coefficients c_k of the Fourier series

$$\sum_{k=-\infty}^{\infty} c_k e^{2\pi i k x}$$

  for f_a.

  (b) Show that for every k, $c_k \to 1$ as $a \to 0$. (Remark: the coefficients $c_k = 1$ are the coefficients of the delta function $\delta_{\mathbb{Z}}$)

(4) The Heaviside function can be used to construct square waves. Using Maple plot the functions Heaviside(x) and

$$f(x) = \text{Heaviside}(1/4 - x) + \text{Heaviside}(1/4 + x) - 1$$

for $-1 < x < 1$.

(5) Use plot3d in Maple to plot the function

$$g(x, y) = f(x)f(y)$$

for $-1 < x < 1$, $-1 < y < 1$ and where f is the function in problem 4.

(6) For a function $f(x, y)$ of period 1 in each variable the Fourier series is defined by

$$\sum_{h=-N}^{N} \sum_{k=-N}^{N} c_{h,k} e^{2\pi i(hx+ky)}$$

where

$$c_{h,k} = \int_0^1 \int_0^1 f(x, y) e^{-2\pi i(hx+ky)}\, dxdy$$

are the Fourier coefficients. Let N be 2. Find the Fourier coefficients for the function g in the previous problem. Use Maple to plot the Fourier series and compare it with the graph of g. Try $N = 3$ and $N = 4$.

(7) Suppose

$$f(x) = \sum_{j=-n}^{n} c_j e^{2\pi i j x}$$

with $c_{-j} = \overline{c_j}$ for all j so that f is a real valued function. Let

$$g(x) = \int_0^1 f(t) f(x+t)\, dt.$$

Show that

$$g(x) = \sum_{j=-n}^{n} |c_j|^2 e^{2\pi i j x}.$$

Note: In crystallography the three dimensional analog of g is called the Patterson function for f. It is determined by the norms of the Fourier coefficients of f and not the phases.

7. Nuclear Magnetic Resonance and distance geometry

Nuclear Magnetic Resonance (NMR) is another method besides crystallography that can be used to find structures of proteins. NMR spectroscopy is the observation of spins of atoms and electrons in a molecule that is placed in a magnetic field. The spins precess at a frequency in the radio frequency range and the frequency can be detected by the electrical signal that it generates.

We briefly discuss the physics of NMR, and then describe *distance geometry*, a mathematical theory that can be used to find the protein structure from some types of NMR data.

7.1. **Larmor frequency.** Spins placed in a magnetic field precess; they wobble like a spinning top. Only certain isotopes of molecules found in organic compounds have spins that react to the magnetic field; the most common ones used in proteins are ^{1}H, ^{13}C, ^{15}N. The isotopes ^{13}C and ^{15}N are not in common abundance, so specially prepared protein samples must be used.

The frequency of precession is called the *Larmor frequency* and it is determined mainly by the type of atom and the strength of the magnetic field. The basic NMR equation is,

$$\omega = \gamma B_0 \tag{63}$$

where

$\omega =$ the Larmor frequency, i.e., the angular frequency of the precession in radians per second

$\gamma =$ gyromagnetic ratio, a constant depending on the type of the atom

$B_0 =$ the intensity of the magnetic field

7.2. **Splitting and chemical shift.** Equation (63) assumes that the detected frequency depends only on the atom and the intensity of the magnetic field. There is another factor, however. The magnetic field intensity B_0 is not the same everywhere in the molecule; it is affected by neighboring atoms and electrons. Neighboring spins have their own magnetic field and this perturbs the field of the magnet and changes the frequency of precession.

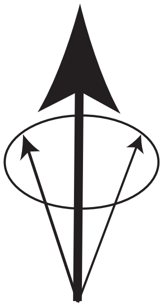


Figure 27. An NMR experiment is the observation of the precession of nuclear spins in the presence of a magnetic field. The large arrow represents the magnetic field of the magnet, the small arrow represents magnetic field of the nucleus which is precessing like a spinning top as the tip of the arrow moves on the indicated circle.

This is illustrated by the NMR spectrum of the hydrogen atoms in the molecule Toluene (figure 28). The spectrum is a Fourier transform of the electrical signal showing the intensities (vertical axis) of certain frequencies (horizontal axis). The spectrum can be thought of as the absolute values of Fourier coefficients for the function giving the signal as a function of time. It the signal is the real part of $s(t) = \sum_{j=1}^{n} a_j e^{2\pi i \omega_j t}$ then the spectrum gives absolute values $|a_j|$, $j = 1 \dots n$ at frequencies ω_j cycles per second.

The spectrum of Toluene shows that the peak frequencies cluster around two values. Also a reference signal is shown for hydrogens which are not part of any molecule. The frequencies of the hydrogens in the molecule are different (shifted) from the reference signal. The observed difference is divided by the frequency of the reference signal times 10^6, and the change in frequency is reported in *parts per million* or *ppm*. The change is called a *chemical shift*. The spectrum shows that the 3 methyl hydrogens (to the right) are shifted less that the other 5 hydrogens. From the symmetry of the molecule it is easy to see that the peak on the right comes from the methyl hydrogens, the hydrogens on the CH_3 group at the end of the molecule. This is because they all have the same relation to the rest of the molecule which causes the shift.

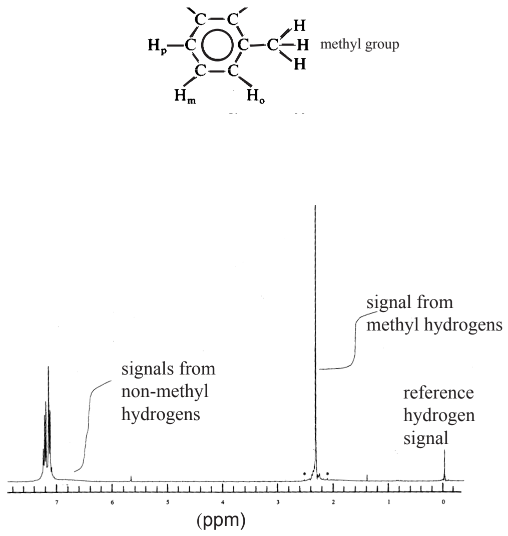


Figure 28. The spectrum of Toluene. In a magnetic field, the hydrogens spins in the molecule precess at different frequencies depending on the surrounding atoms and electrons. This is because the neighboring atoms and electrons have spins which contribute to the magnetic field. In Toluene the frequencies are seen in two separate ranges shifted from the reference signal.

The spectrum of Toluene shows that we can infer facts about the shape of a molecule by looking at the spectrum. This suggests that we can find chemical structures of larger molecules by NMR. However the spectrum of a protein is much more difficult to interpret. Below is the NMR spectrum of all the hydrogens in the protein thioredoxin indicating which part of the molecule the hydrogen signals are coming from. Although some aspects of the structure can be deduced from the spectrum, it would be difficult to find coordinates of the atoms from this spectrum.

There is another type of spectrum (figure 30) called a 2D NOESY spectrum. This experiment observes two frequencies from an atom, so the intensity is a function of two variables. The figure shows level curves for high intensity, which looks like a set of points. These can be used to estimate distances between atoms. Such estimates are called *distance constraints.* Distance constraints can be used to find atomic coordinates using techniques of distance geometry. Similar spectra can be used to find *orientational constraints* which measure angles rather than distances. Orientational constraint measure the angle between covalent bond vectors and the vector giving the direction of the magnetic field.

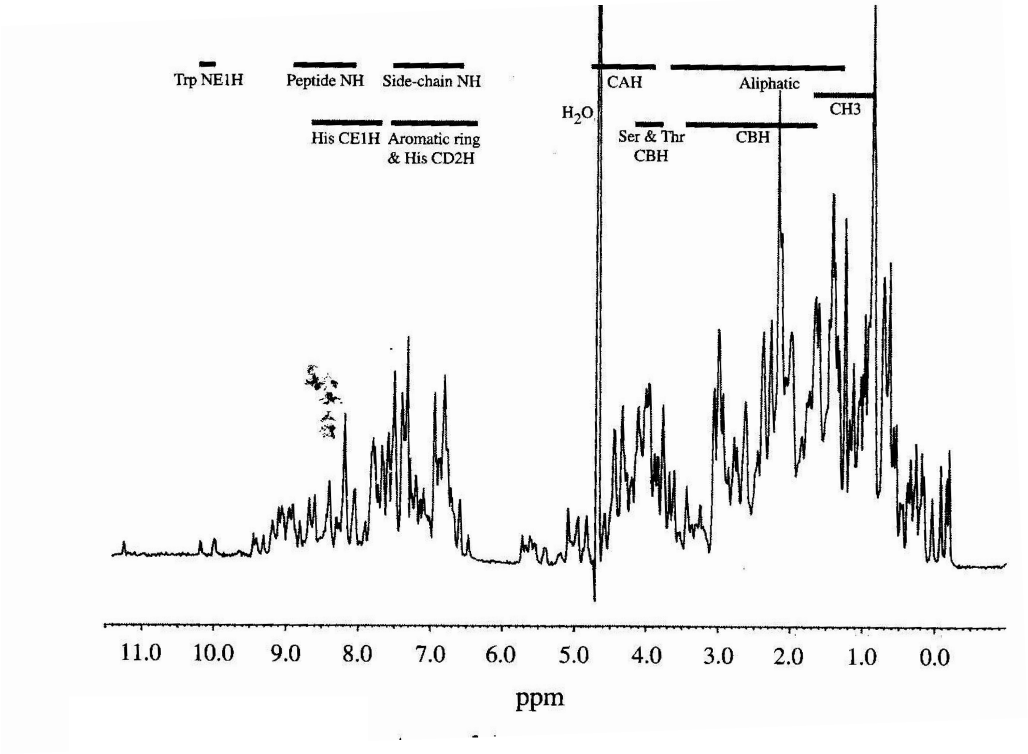


FIGURE 29. The hydrogen NMR spectrum of the protein thioredoxin. Indicated on the spectrum are the parts of the protein responsible for each part of the signal. The signal is shifted according to the unique chemical environment of each part of the protein.

7.3. **Distance geometry.** Determination of the structure of a protein from distance constraints caused renewed interest in an old branch of mathematics called *distance geometry.* A protein structure is a list of coordinates for the atoms. Rather than coordinates, we could consider a list of distances between atoms. Distances, unlike coordinates, are invariant under rotation and translation, so they are also useful in shape analysis.

Consider a sequence of points in 3D space. Information about distances between a sequence of points can be put into a matrix called a *distance matrix.* The atoms in a structure are numbered 1 to n. The distance matrix is an $n \times n$ matrix. The entry in row i and column j is the *square of the distance* between points i and j. The object of distance geometry is to find coordinates of the points from the distance matrix.

There is no unique list of coordinates since a rotated and translated set of coordinates gives the same distance matrix, however, coordinates can be found which

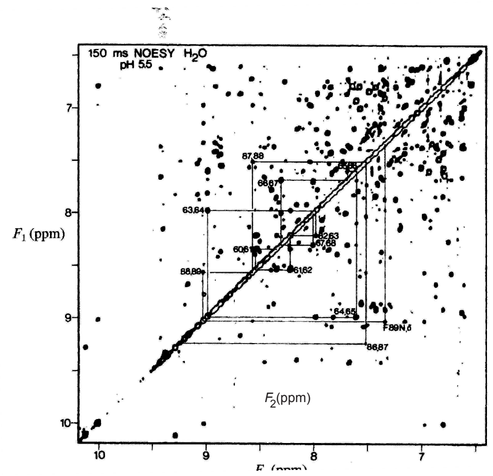


FIGURE 30. NOESY spectrum of thioredoxin. A labeled point in the spectrum indicates that the signal comes from the interaction between a certain pair of hydrogen atoms. That the two hydrogen atoms interact indicates that they are not far apart. The distance between the atoms can be estimated by the intensity of the signal.

are unique up to a Euclidean motion. The situation is analogous to viewing a pdb file. Protein viewers change all the coordinates in the structure through rotations and translations, but the shape of the protein and the distances between atoms stays fixed.

7.3.1. *Distance matrix example.* Label the rows and columns below by the letters a through h. The corresponding entry gives the square of the distance between the two corresponding points on the cube with sides of length 1 in figure 31.

$$\begin{pmatrix}
0 & 1 & 2 & 1 & 1 & 2 & 3 & 2 \\
1 & 0 & 1 & 2 & 2 & 1 & 2 & 3 \\
2 & 1 & 0 & 1 & 3 & 2 & 1 & 2 \\
1 & 2 & 1 & 0 & 2 & 3 & 2 & 1 \\
1 & 2 & 3 & 2 & 0 & 1 & 2 & 1 \\
2 & 1 & 2 & 3 & 1 & 0 & 1 & 2 \\
3 & 2 & 1 & 2 & 2 & 1 & 0 & 1 \\
2 & 3 & 2 & 1 & 1 & 2 & 1 & 0
\end{pmatrix}$$

For example, if v_a and v_g are vectors giving the coordinates of points a and g respectively, then the ag and ga entries in the matrix are $|v_a - v_g|^2$. The distances can be found from figure 31 or by writing out coordinates fro the vertices, $v_a = (0,0,0)$, $v_b = (0,1,0)$, etc.

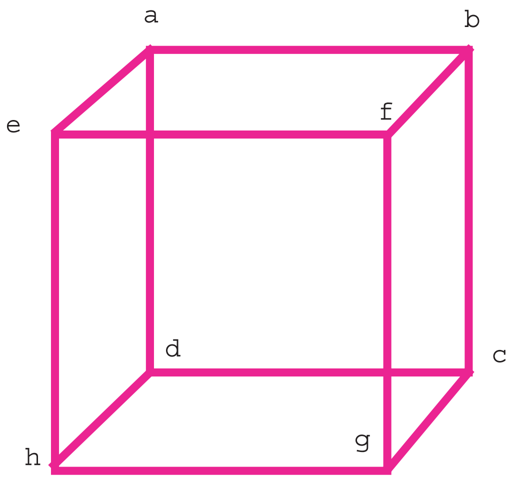


FIGURE 31. Cube (octahedron) with vertices labelled.

7.4. **Obtaining coordinates from a distance matrix.** The problem in distance geometry is to recover the coordinates of a sequence of points, up to a Euclidean motion of space, from the distance matrix. The solution is presented in this section.

Suppose there are $n+1$ vectors $\mathbf{v}_0 \dots \mathbf{v}_n$ giving the coordinates of $n+1$ points in 3D space. For simplicity, translate the points so that $\mathbf{v}_0 = 0$. Consider the vectors as columns of a $3 \times n$ matrix

$$\mathbf{M} = (\mathbf{v}_1, \dots, \mathbf{v}_n).$$

Finding the vectors $\mathbf{v}_j$ from the distance matrix follows in two steps

(1) find the gram matrix $\mathbf{G} = \mathbf{M}'\mathbf{M}$ from the distance matrix. The matrix $\mathbf{G}$ can be thought of as the *square of* $\mathbf{M}$.
(2) find $\mathbf{M}$ from the gram matrix $\mathbf{G}$. This can thought of as taking the *square root* of the gram matrix.

Note that the distance matrix is $(n+1) \times (n+1)$ and the gram matrix is $n \times n$.

7.4.1. *Gram matrix from distance matrix.* The entries in the distance matrix $\mathbf{D}$ are $|\mathbf{v}_j - \mathbf{v}_k|^2$, $j, k = 0, 1, \dots n$,

$$\mathbf{D} = \begin{pmatrix} 0 & |\mathbf{v}_1|^2 & |\mathbf{v}_2|^2 & \cdots & |\mathbf{v}_n|^2 \\ |\mathbf{v}_1|^2 & 0 & |\mathbf{v}_1 - \mathbf{v}_2|^2 & \cdots & |\mathbf{v}_1 - \mathbf{v}_n|^2 \\ |\mathbf{v}_2|^2 & |\mathbf{v}_2 - \mathbf{v}_1|^2 & 0 & \cdots & |\mathbf{v}_2 - \mathbf{v}_n|^2 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ |\mathbf{v}_n|^2 & |\mathbf{v}_n - \mathbf{v}_1|^2 & |\mathbf{v}_n - \mathbf{v}_2|^2 & \cdots & 0 \end{pmatrix} \tag{64}$$

The gram matrix $\mathbf{G}$ is given by

$$\mathbf{G} = \begin{pmatrix} \mathbf{v}_1 \cdot \mathbf{v}_1 & \mathbf{v}_1 \cdot \mathbf{v}_2 & \cdots & \mathbf{v}_1 \cdot \mathbf{v}_n \\ \mathbf{v}_2 \cdot \mathbf{v}_1 & \mathbf{v}_2 \cdot \mathbf{v}_2 & \cdots & \mathbf{v}_2 \cdot \mathbf{v}_n \\ \vdots & \vdots & \ddots & \vdots \\ \mathbf{v}_n \cdot \mathbf{v}_1 & \mathbf{v}_n \cdot \mathbf{v}_2 & \cdots & \mathbf{v}_n \cdot \mathbf{v}_n \end{pmatrix} \tag{65}$$

The gram matrix can be found from the distance matrix using the identity

$$-\,2\,\mathbf{v}_i \cdot \mathbf{v}_j = |\mathbf{v}_i - \mathbf{v}_j|^2 - |\mathbf{v}_i|^2 - |\mathbf{v}_j|^2. \tag{66}$$

All the information on the right hand side of this equation is in the distance matrix (64). Using (66) we can get the gram matrix from the distance matrix by row and column operations

(1) subtract the first row of $\mathbf{D}$ from each row
(2) subtract the first column from each column.

The result is $-2\mathbf{G}$ bordered by zeros the first row and column.

7.5. **Coordinates from the gram matrix.** Given $\mathbf{G}$ obtained from a distance matrix of vectors in 3D space, the problem is to find a square root of $\mathbf{G}$, a $3 \times n$ matrix $\mathbf{M}$ such that

$$\mathbf{G} = \mathbf{M}'\mathbf{M}. \tag{67}$$

This can be done by finding eigenvectors and eigenvalues. Since $\mathbf{G}$ can be written in the form (67), it has real, non-negative eigenvalues. Since $\mathbf{M}$ is $3 \times n$ there are at most 3 non-zero eigenvalues. See exercise 1

Write the eigenvectors of $\mathbf{G}$ as columns of a matrix $\mathbf{V}$ and the eigenvalues as diagonal entries in a diagonal matrix $\mathbf{E}$. Then

$$\mathbf{G}\mathbf{V} = \mathbf{V}\mathbf{E}. \tag{68}$$

Arrange the eigenvalues and eigenvectors so that

$$\mathbf{E} = \begin{pmatrix} \mathbf{E}_1 & \mathbf{0} \\ \mathbf{0} & \mathbf{0} \end{pmatrix} \tag{69}$$

where $\mathbf{E}_1$ is a diagonal matrix with 3 non-negative entries. Eigenvectors can always be found which are an orthonormal set,

$$\mathbf{V}'\mathbf{V} = \mathbf{V}\mathbf{V}' = \mathbf{I}. \tag{70}$$

The eigenvectors are orthogonal if the eigenvalues are distinct and they can be normalized by dividing by the length. If they are not distinct, an orthonormal set of eigenvectors can be found by the Gram-Schmidt orthogonalization procedure. Now (68) becomes

$$\mathbf{G} = \mathbf{V}\mathbf{E}\mathbf{V}'. \tag{71}$$

Write

$$\mathbf{V} = (\mathbf{V}_1, \mathbf{V}_2) \tag{72}$$

where $\mathbf{V}_1$ is a $3 \times n$ matrix whose columns are eigenvectors corresponding to the diagonal elements of $\mathbf{E}_1$, and where the columns of the $3 \times (n-3)$ matrix $\mathbf{V}_2$ have eigenvalue 0. The columns of $\mathbf{V}_2$ are in the kernel of $\mathbf{G}$, that is, they are eigenvectors corresponding to the eigenvalue 0, so $\mathbf{G}\mathbf{V}_2 = \mathbf{0}$. Using (71) and (72) we have

$$\mathbf{G} = \mathbf{V}_1\mathbf{E}_1\mathbf{V}_1'. \tag{73}$$

Now construct a diagonal matrix whose entries on the diagonal are the square roots of the entries of $\mathbf{E}_1$. Since the entries on the diagonal are non-negative, the square roots are also non-negative real numbers. Call this matrix $\sqrt{\mathbf{E}_1}$. From (73) it follows that

$$\mathbf{G} = \mathbf{V_1}\sqrt{\mathbf{E}_1}\sqrt{\mathbf{E}_1}\mathbf{V_1'}. \tag{74}$$

Letting

$$\mathbf{M} = \sqrt{\mathbf{E}_1}\mathbf{V_1'},$$

$\mathbf{G} = \mathbf{M}'\mathbf{M}$ and $\mathbf{M}$ is a $3 \times n$ matrix.

This procedure for finding coordinates is best illustrated using 4 points ($n = 4$). Find coordinates of points in 3D space giving the distance matrix

$$\begin{bmatrix} 0 & 2 & 1 & 1 \\ 2 & 0 & 3 & 1 \\ 1 & 3 & 0 & 2 \\ 1 & 1 & 2 & 0 \end{bmatrix}$$

Maple demo

Here is an example with $n = 5$. Find coordinates of points in 3D space giving the distance matrix

$$\begin{bmatrix} 0 & 2 & 1 & 1 & 2 \\ 2 & 0 & 3 & 1 & 2 \\ 1 & 3 & 0 & 2 & 1 \\ 1 & 1 & 2 & 0 & 1 \\ 2 & 2 & 1 & 1 & 0 \end{bmatrix}$$

Maple demo

Note that finding a sequence of vectors with the given distance matrix depends on the gram matrix being rank 3 and having non-negative eigenvalues. If there are small errors in the data, this will not be the case, but we can still solve the linear algebra problem with vectors in a space of dimension n. These vectors may have complex valued coordinates.

The above techniques are the basis for studying the Cayley-Menger theorem and Cayley-Menger determinants.

7.6. **Problems.**

(1) Suppose G and M are real matrices with $G = M'M$.
  (a) Show that all the eigenvalues of G are non-negative.
  (b) If M is a $3 \times n$ matrix show there can be at most 3 non-zero eigenvalues of G. (Hint: What is the dimension of the image of the linear transformation M? Same question for G.)

(2) Suppose M and N are 3×3 matrices whose columns are linearly independent vectors. Suppose the gram matrices $M'M$ and $N'N$ are equal. Show that there is an orthogonal matrix S such that $M = SN$.

(3) We say that A is a square root of G if $A'A = G$. Using Maple and the technique described in the notes, find a square root of

$$\begin{bmatrix} 3.0 & -1.0 & 0.0 \\ -1.0 & 3.0 & -2.0 \\ 0.0 & -2.0 & 6.0 \end{bmatrix}.$$

To avoid complicated expressions, do this problem numerically.

(4) Using Maple, find coordinates of points in 3D space having the distance matrix

$$\begin{bmatrix} 0 & 4 & 4 & 8 & 3 \\ 4 & 0 & 8 & 4 & 3 \\ 4 & 8 & 0 & 4 & 3 \\ 8 & 4 & 4 & 0 & 3 \\ 3 & 3 & 3 & 3 & 0 \end{bmatrix}.$$

You can use commands from the worksheet DistMatrix4 on the website. Give the answer to 2 decimal places.

8. DISCRETE FRENET FRAME

We saw in the previous section how distance geometry is useful in finding protein structures from NMR distance data. When the sample can be held rigid in relation to the magnetic field, another method is used based on *orientational constraints.* This method uses the NMR spectrum to find the coordinates of the unit magnetic field direction in frames rigidly attached to the protein. These frames are discrete versions of the Frenet frames discussed in section 3. We call such a frame a *Discrete Frenet Frame* (DFF). The DFF is also useful in the study of robotics and kinematics by transforming a rigid motions into a sequence of simpler ones.

8.1. **Discrete Frenet Frame.** In calculus, a curve in 3D space is given by a vector function of a variable t. Using derivatives of this function the curvature and torsion can be computed in terms of a Frenet frame, a moving frame along the curve, as discussed in section 3.

Organic chemistry includes the study of long molecules such as a proteins and DNA. The backbone of a protein can be thought of as a sequence of points at the center of atoms rather than as a continuous function of t. Using differences rather than derivatives a Frenet frame can be defined which is useful in analyzing the shape of the protein, and in finding protein structures using NMR orientational constraints.

8.2. **Definition of the discrete Frenet frame.** A sequence of points $\mathbf{v}_0, \ldots, \mathbf{v}_n$ is called a *discrete curve.* To picture the curve, consecutive points are joined with line segments, which in chemical applications are thought of as chemical bonds, usually covalent bonds. The backbone of a protein, for example, can be thought of as a discrete curve.

If no three consecutive points of a discrete curve are collinear, a sequence of orthonormal, right-handed frames

$$\mathbf{F}_k = (\mathbf{t}_k, \mathbf{n}_k, \mathbf{b}_k) \quad k = 1, \ldots, n$$

where

$$\mathbf{t}_k = \frac{\mathbf{v}_{k+1} - \mathbf{v}_k}{|\mathbf{v}_{k+1} - \mathbf{v}_k|}$$

$$\mathbf{b}_k = \frac{\mathbf{t}_{k-1} \times \mathbf{t}_k}{|\mathbf{t}_{k-1} \times \mathbf{t}_k|}$$

$$\mathbf{n}_k = \mathbf{b}_k \times \mathbf{t}_k$$

is defined called a *discrete Frenet frame (DFF)* for the curve. The unit vectors $\mathbf{t}$, $\mathbf{n}$ and $\mathbf{b}$ are analogous to the tangent, normal, and binormal for continuous curves. The tangent vector $\mathbf{t}_k$ points in the direction from $\mathbf{v}_k$ to the next point $\mathbf{v}_{k+1}$. The binormal vector $\mathbf{b}_k$ is perpendicular to the plane containing $\mathbf{t}_k$ and $\mathbf{t}_{k-1}$. Using the cross product formula

$$\mathbf{a} \times (\mathbf{b} \times \mathbf{c}) = (\mathbf{a} \cdot \mathbf{c})\mathbf{b} - (\mathbf{a} \cdot \mathbf{b})\mathbf{c}$$

the normal vector can be written as

$$\mathbf{n}_k = \frac{-\mathbf{t}_{k-1} + (\mathbf{t}_{k-1} \cdot \mathbf{t}_k)\ \mathbf{t}_k}{|-\mathbf{t}_{k-1} + (\mathbf{t}_{k-1} \cdot \mathbf{t}_k)\ \mathbf{t}_k|}$$

so it is in the plane containing $\mathbf{t}_k$ and $\mathbf{t}_{k-1}$ and perpendicular to $\mathbf{t}_k$.

8.3. **Torsion angles and bond angles.** Geometric properties of the curve can be expressed in terms of the DFF. We have already defined the torsion angle for each bond. The torsions angle at the bond from $\mathbf{v}_k$ to $\mathbf{v}_{k+1}$ to be

$$\phi_k = \tau\left(\mathbf{t}_{k-1}, \mathbf{t}_k, \mathbf{t}_{k+1}\right) \quad k = 1, \ldots, n-1$$

The *bond angle* or *curvature angle* θ_k at $\mathbf{v}_k$ is defined as the angle between the bond vector from $\mathbf{v}_{k-1}$ to $\mathbf{v}_k$ and the bond vector from $\mathbf{v}_k$ to $\mathbf{v}_{k+1}$,

$$\theta_k = \arccos(\mathbf{t}_{k-1} \cdot \mathbf{t}_k) \quad k = 1, \ldots, n$$

as in figure 32.

The bond angles and can also be defined using rotation matrices,

$$\mathbf{t}_k = \mathrm{R}\left(\mathbf{b}_k, \theta_k\right) \mathbf{t}_{k-1} \qquad (75)$$
$$\mathbf{b}_{k+1} = \mathrm{R}\left(\mathbf{t}_k, \phi_k\right) \mathbf{b}_k.$$

Both of these equations follow directly from the definition of the bond angle and the torsion angle.

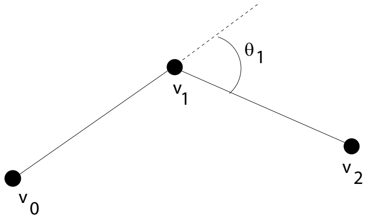


FIGURE 32. The angle θ_1 is the bond angle at $\mathbf{v}_1$. It is always between 0 and 90 degrees.

Now write the rotation from $\mathbf{F}_k$ to $\mathbf{F}_{k+1}$ in terms of the bond angle and the torsion angle. By (75) and the fact that $\mathrm{R}\left(\mathbf{u}, \theta\right)$ leaves $\mathbf{u}$ fixed,

$$\begin{aligned} \mathbf{b}_{k+1} &= \mathrm{R}\left(\mathbf{b}_{k+1}, \theta_{k+1}\right) \mathrm{R}\left(\mathbf{t}_k, \phi_k\right)\, \mathbf{b}_k \\ \mathbf{t}_{k+1} &= \mathrm{R}\left(\mathbf{b}_{k+1}, \theta_{k+1}\right) \mathrm{R}\left(\mathbf{t}_k, \phi_k\right)\, \mathbf{t}_k. \end{aligned} \qquad (76)$$

Since rotations preserve cross products and $\mathbf{n}_{k+1} = \mathbf{t}_{k+1} \times \mathbf{b}_{k+1}$, it follows from (76) that

$$\mathbf{n}_{k+1} = \mathrm{R}\left(\mathbf{b}_{k+1}, \theta_{k+1}\right) \mathrm{R}\left(\mathbf{t}_k, \phi_k\right)\, \mathbf{n}_k.$$

The previous three equations can be combined as

$$\mathbf{F}_{k+1} = \mathrm{R}\left(\mathbf{b}_{k+1}, \theta_{k+1}\right) \mathrm{R}\left(\mathbf{t}_k, \phi_k\right) \mathbf{F}_k. \qquad (77)$$

Now recall the property of rotations

$$\mathbf{F}\mathrm{R}\left(\mathbf{u}, \theta\right) = \mathrm{R}\left(\mathbf{F}\mathbf{u}, \theta\right) \mathbf{F}. \qquad (78)$$

where $\mathbf{F}$ is a rotation. Letting $\mathbf{F} = \mathrm{R}\left(\mathbf{t}_k, \phi_k\right)$, $\mathbf{u} = \mathbf{b}_k$, and $\theta = \theta_{k+1}$ get using (75) and (78) that

$$\mathrm{R}\left(\mathbf{t}_k, \phi_k\right) \mathrm{R}\left(\mathbf{b}_k, \theta_{k+1}\right) = \mathrm{R}\left(\mathbf{b}_{k+1}, \theta_{k+1}\right) \mathrm{R}\left(\mathbf{t}_k, \phi_k\right).$$

Now (77) becomes

$$\mathbf{F}_{k+1} = \mathrm{R}\left(\mathbf{t}_k, \phi_k\right) \mathrm{R}\left(\mathbf{b}_k, \theta_{k+1}\right) \mathbf{F}_k. \qquad (79)$$

Since $\mathbf{t}_k$ is the first column and $\mathbf{b}_k$ the third column of $\mathbf{F}_k$,

$$\mathbf{F}_k\, \mathbf{e}_1 = \mathbf{t}_k \text{ and } \mathbf{F}_k\, \mathbf{e}_3 = \mathbf{b}_k.$$

Now using (78) rewrite (79) as

$$\begin{aligned} \mathbf{F}_{k+1} &= \mathbf{F}_k\, \mathrm{R}\left(\mathbf{e}_1, \phi_k\right) \mathrm{R}\left(\mathbf{e}_3, \theta_{k+1}\right) \\ &= \mathbf{F}_k\, \mathrm{R}_x(\phi_k)\, \mathrm{R}_z(\theta_{k+1}). \end{aligned} \qquad (80)$$

By induction using (80),

$$\mathbf{F}_k = \mathbf{F}_0 \mathrm{R}_x(\phi_0)\,\mathrm{R}_z(\theta_1)\,\mathrm{R}_x(\phi_1)\,\mathrm{R}_z(\theta_2)\cdots\mathrm{R}_x(\phi_{k-1})\,\mathrm{R}_z(\theta_k). \tag{81}$$

So each frame can be written in terms of the the initial frame $\mathbf{F}_0$ and the sequence of bond and torsion angles using the rotation matrices R_x and R_z.

8.4. **The Euclidean Group.** The orthogonal group is the group of all rigid transformation of 3D space which leave the origin fixed. Every rigid transformation of space $\mathbf{T}$ is given by an orthogonal transformation and a translation,

$$\mathbf{T}\mathbf{w} = \mathbf{F}\mathbf{w} + \mathbf{v} \tag{82}$$

where $\mathbf{F}$ is an orthogonal transformation and $\mathbf{v}$ is a vector. The set of all such transformations is a group called the *Euclidean group*, denoted E(3), and an element of this group is called a *Euclidean transformation.*

The composition of two Euclidean transformations

$$\mathbf{T}_1\mathbf{w} = \mathbf{F}_1\mathbf{w} + \mathbf{v}_1$$
$$\mathbf{T}_2\mathbf{w} = \mathbf{F}_2\mathbf{w} + \mathbf{v}_2$$

is given by

$$\mathbf{T}_1(\mathbf{T}_2\mathbf{w}) = \mathbf{F}_1\mathbf{F}_2\mathbf{w} + (\mathbf{v}_1 + \mathbf{F}_1\mathbf{v}_2). \tag{83}$$

The transformation (82) has inverse

$$\mathbf{T}^{-1}\mathbf{w} = \mathbf{F}^{-1}\mathbf{w} - \mathbf{F}^{-1}\mathbf{v}. \tag{84}$$

A more convenient way to calculate composition of Euclidean transformations is to use 4×4 matrices. Associate the transformation (82) with the 4×4 matrix

$$\begin{pmatrix} \mathbf{F} & \mathbf{v} \\ \mathbf{0} & 1 \end{pmatrix} \tag{85}$$

where $\mathbf{0}$ denotes the zero row vector. Also associate the 3D vector $\mathbf{w}$ with the 4D vector

$$\begin{pmatrix} \mathbf{w} \\ 1 \end{pmatrix}.$$

Now

$$\begin{pmatrix} \mathbf{F} & \mathbf{v} \\ \mathbf{0} & 1 \end{pmatrix} \begin{pmatrix} \mathbf{w} \\ 1 \end{pmatrix} = \begin{pmatrix} \mathbf{F}\mathbf{w} + \mathbf{v} \\ 1 \end{pmatrix}$$

and the vector on the right is associated with the vector (82). Likewise

$$\begin{pmatrix} \mathbf{F}_1 & \mathbf{v}_1 \\ \mathbf{0} & 1 \end{pmatrix} \begin{pmatrix} \mathbf{F}_2 & \mathbf{v}_2 \\ \mathbf{0} & 1 \end{pmatrix} = \begin{pmatrix} \mathbf{F}_1\mathbf{F}_2 & \mathbf{v}_1 + \mathbf{F}_1\mathbf{v}_2 \\ \mathbf{0} & 1 \end{pmatrix} \tag{86}$$

and the matrix on the right is associated with the transformation (83). So the composition of Euclidean transformations in 3D space can be computed by multiplying the corresponding 4×4 matrices as in (86). For composition of Euclidean motions, (86) can be easier to program than (83) since it relies on matrix multiplication.

The matrix (85) can also be thought as the fixed frame $\mathbf{F}$ whose vectors have initial points at the point $\mathbf{v}$.

8.5. **DFF and the Euclidean Group.** Equation (81) gives the frame $\mathbf{F}_k$ as a function of the torsion angles and bond angles. The discrete curve cannot be determined from the frames alone. Distances between points are needed to find the points $\mathbf{v}_k$ of the curve. Let $s_k = |\mathbf{v}_{k+1} - \mathbf{v}_k|$ be the distance between two consecutive points. Since $\mathbf{t}_k = \mathbf{F}_k\,\mathbf{e}_1$ and

$$\mathbf{v}_{k+1} = \mathbf{v}_k + s_k\,\mathbf{t}_k, \tag{87}$$

the distances s_k give the extra information needed to find the points, which can be computed recursively from (87).

If the moving frame is thought of as an element of the Euclidean group in the form (89), a formula can be written similar to (80),

$$\mathbf{T}_{k+1} = \mathbf{T}_k \begin{pmatrix} \mathrm{R}_x(\phi_k) & s_k\mathbf{e}_1 \\ \mathbf{0} & 1 \end{pmatrix} \begin{pmatrix} \mathrm{R}_z(\theta_{k+1}) & \mathbf{0} \\ \mathbf{0} & 1 \end{pmatrix}. \tag{88}$$

where

$$\mathbf{T}_k = \begin{pmatrix} \mathbf{F}_k & \mathbf{v}_k \\ \mathbf{0} & 1 \end{pmatrix} \tag{89}$$

represents the Frenet frame $\mathbf{F}_k$ at the point $\mathbf{v}_k$. This recursion formula gives fixed Frenet frames at each point of the curve in terms of the initial frame, the bond angles θ_k, torsion angles ϕ_k, and distances s_k.

The bond angles, torsion angles and distances can be thought of as directions for driving (or flying) along the curve. The distances s_k between the points are like the differences in odometer readings between pont k and $k+1$. The bond angles θ_k are like right and left turns if $\theta_k = \pi/2$, except you may turn at any angle. Also you do not need to make turns in the same plane, the torsion angle ϕ_k tells how to move to a different plane.

8.6. **Application to Proteins.** Use of the DFF to study protein structure requires knowledge of the geometry of the bonds in peptide plane. The atoms along the protein backbone appear in sequence C_α, C, N, C_α, ... and can be thought of as points of a discrete curve. The bond angles at these atoms have been determined by crystallography studies and the values are 58° at nitrogen atoms, 64° at carbonyl carbon atoms, and 69° at the alpha carbons (see figure 33). (If the geometry at the alpha carbon is taken to be exactly tetrahedral, then the bond angle $\arccos\frac{1}{3} = 70.5°$ is used.) Distances between atoms in the peptide bond have also been determined. The distance from C_α to C is approximately 1.51, from C to N approximately 1.32 and from N to C_α approximately 1.45.

8.6.1. *Excluded regions in Ramachandran plot.* In the Ramachandran plot, certain ϕ,ψ pairs are excluded because they cause clashes between atoms in adjacent peptide planes. Consider a pair of peptide planes bonded together with torsion angle ϕ and ψ and with standard peptide geometry as indicated in figure 33. We compute the distance $d(\mathrm{O},\mathrm{O}')$ between the O atoms as a function of ϕ,ψ. The prime indicates the second peptide plane. Think of the torsion angle pair (ϕ,ψ) as a configuration space (or parameter space) for a dipeptide. The pair (ϕ,ψ) completely

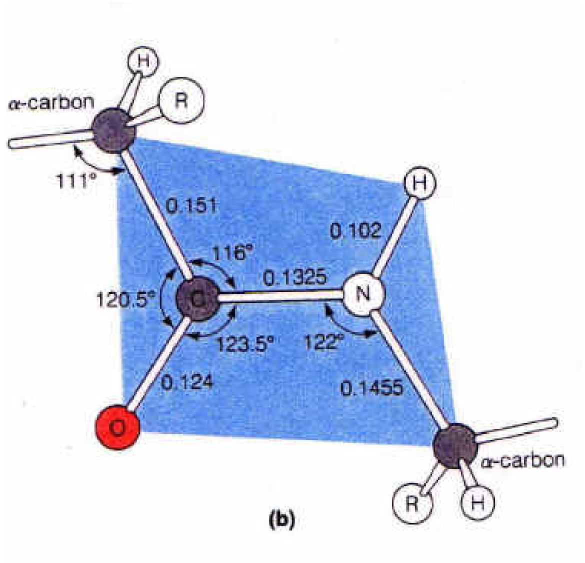


Figure 33. The geometry of the peptide plane as determined by crystallography studies. All of the atoms indicated lie in the blue plane.

k	1	2	3	4	5	6
v_k	O	C	N	C_α	C'	O'
θ_k		56.5°	58°	70°	64°	0
ϕ_k	0	0	ϕ	$\psi - 180°$	0	
s_k	1.24	1.325	1.455	1.51	1.24	

Table 2. Bond angles, and torsion angles, and distance parameters (in Angstroms) for the discrete curve from O to O′ in a dipeptide

determines the distance between all atoms. The protein segment from O to O′ is a discrete curve consisting of atoms O, C, N, C_α, C′, O′. The bond and torsion angles and distances along the curve are shown in table 2. Formula (80) can be used find the coordinates of O and O′ and graph the distance d(O,O′) as a function of ϕ, ψ (figure 34). The level curves of the function d(O,O′) shows regions of the ϕ, ψ plane where the oxygens O and O′ are too close. Since the radius of an oxygen atom is about 1.5 Angstroms, they certainly cannot get closer than a distance of 3. These excluded regions are shown on many Ramachandran diagrams (see figure 35).

Maple worksheet

8.7. **Period 3 structures.** The DFF can be used to study the helix parameters for period three secondary structures, the beta sheet and the alpha helix. Suppose

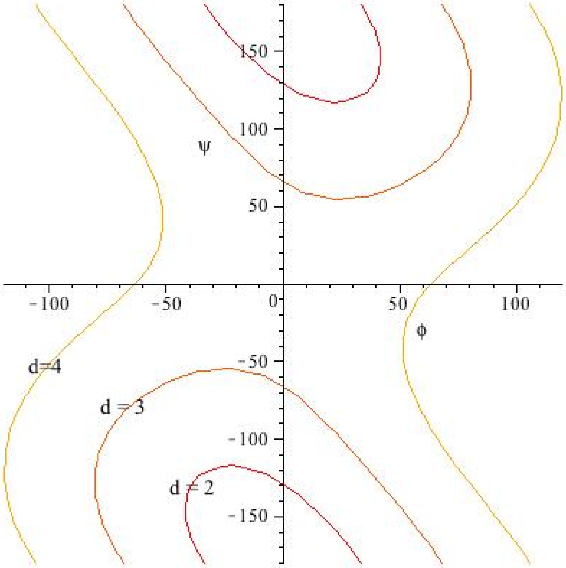


FIGURE 34. Contour plot distances $d(\mathrm{O},\mathrm{O}')$ between oxygens in adjacent peptide planes as function of ϕ and ψ. Points where the distance is less that 3 are excluded since the oxygens are too close.

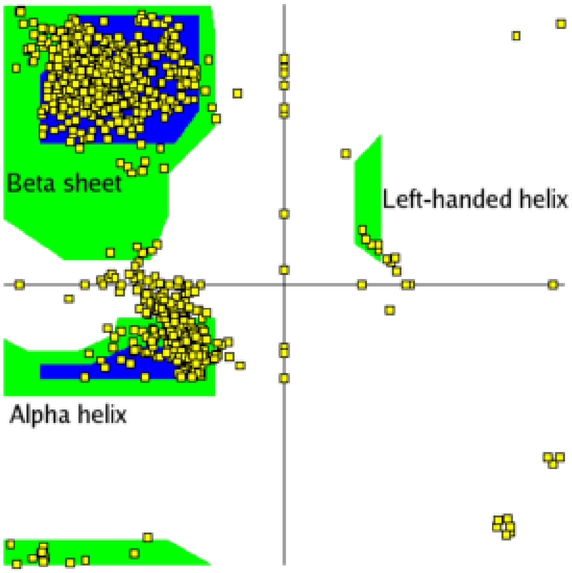


FIGURE 35. Ramachandran plot showing all ϕ, ψ pairs (in yellow boxes) from protein pdb ID 1AXC. Note from figure 34 the white region with no ϕ, ψ pairs includes places where $d(\mathrm{O},\mathrm{O}')$ is small.

there are n peptide planes with atoms $\mathbf{v}_{-1}, \mathbf{v}_0 \dots \mathbf{v}_{3n+1}$ with

$$\begin{aligned} \mathbf{v}_{3k} &= \text{the } k^{\text{th}} \text{ C}_\alpha \text{ atom} \\ \mathbf{v}_{3k+1} &= \text{ the } k^{\text{th}} \text{ carbonyl carbon atom} \\ \mathbf{v}_{3k+2} &= \text{ the } k^{\text{th}} \text{ nitrogen atom.} \end{aligned} \tag{90}$$

The bond angles are given approximately by

$$\theta_{3k} = 70^\circ \qquad \theta_{3k+1} = 65^\circ \qquad \theta_{3k+2} = 59^\circ \tag{91}$$

and the bond distances are

$$s_{3k} = 1.51 \qquad s_{3k+1} = 1.32 \qquad s_{3k+2} = 1.45 \tag{92}$$

for $k = 0, \dots, n$. For a period three structure, the torsion angles also repeat in sequences of three,

$$\phi_{3k} = \psi \qquad \phi_{3k+1} = 180^\circ \qquad \phi_{3k+2} = \phi \tag{93}$$

where ϕ and ψ are fixed torsion angles. We discuss later the restrictions on ϕ and ψ. The 180° angle is a consequence of the planarity of the three adjacent bones in the peptide plane.

Initializing, let $\mathbf{F}_0 = \mathbf{I}$ and $\mathbf{v}_0 = \mathbf{0}$. From (81) it follows that

$$\begin{aligned} \mathbf{F}_1 &= \mathrm{R}_x(\psi)\mathrm{R}_z(65^\circ) \\ \mathbf{F}_2 &= \mathbf{F}_1\mathrm{R}_x(180^\circ)\mathrm{R}_z(59^\circ) \\ \mathbf{F}_3 &= \mathbf{F}_2\mathrm{R}_x(\phi)\mathrm{R}_z(70^\circ) \end{aligned} \tag{94}$$

Since the structure is period three, i.e., the angles repeat in units of three,

$$\mathbf{F}_{3k} = \mathbf{F}_3^k \qquad \mathbf{F}_{3k+1} = \mathbf{F}_3^k\mathbf{F}_1 \qquad \mathbf{F}_{3k+2} = \mathbf{F}_3^k\mathbf{F}_2. \tag{95}$$

Letting $\hat{A}_k = \{\mathbf{F}_k; \mathbf{v}_k\}$, (95) holds for $\mathbf{F}$ replaced by $\hat{A}$. So multiplication can be done in the Euclidean group. The vector $\mathbf{v}_3$ is the vectors from alpha carbon 0 to alpha carbon 3 and is referred to as the *virtual bond vector*. It will be denoted simply as $\mathbf{v}$.

If T is any Euclidean transformation, and P is any point or set of points, we say that the set of points $T^n(P)$ is the *orbit of P under powers of T*. If P is a single point, the orbit is called a *helix* since all of the points in the orbit will lie on a helix curve whose axis is the axis of T. The above discussion shows that every peptide plane in a period three structure is the orbit of the first plane under powers of $\hat{A}_3$. The orbits of the atoms in the first peptide plane form helices. If the peptide plane geometry is fixed, then $\hat{A}_3$ is a function of ϕ and ψ only.

8.8. **Helix parameters.** To compute the parameters of protein secondary structure helices, the rotation $\mathbf{F}_3$ must first be written in the form $\mathrm{R}(\mathbf{u}, \theta)$. Remember that $\mathbf{u}$ is a unit eigenvalue of the rotation $\mathbf{F}_3$ corresponding to the eigenvalue 1 and $\theta = \tau(\mathbf{w}, u, \mathbf{F}_3\mathbf{w})$ for any $\mathbf{w}$ not parallel to $\mathbf{u}$. Also note that $1 + 2\cos\theta$ is the trace of $\mathbf{F}_3$ (sum of the diagonal entries).

There are two possible choices of $\mathbf{u}$. The choice is made so that $\mathbf{u} \cdot \mathbf{v} > 0$. The helix is right or left handed depending on whether $0 < \theta < 180°$ or $-180° < \theta < 0$.

The helix parameters associated with the protein helix are

(96)

$$\begin{aligned}
&h = \mathbf{u} \cdot \mathbf{v} = \text{rise per residue}\\
&n = 2\pi/\theta = \text{number of residues per turn}\\
&p = hn = \text{rise per turn}\\
&\mathbf{r} = \frac{1}{2}\left(\cot\frac{\theta}{2}\mathbf{u} \times \mathbf{v} + \mathbf{v} - (\mathbf{u} \cdot \mathbf{v})\mathbf{u}\right) = \text{shortest vector from } \mathbf{0} \text{ to the helix axis}\\
&|\mathbf{v}_k - \mathbf{r} - (\mathbf{u} \cdot \mathbf{v}_k)\mathbf{u}| = \text{distance of } \mathbf{v}_k \text{ from the axis of the helix}
\end{aligned}$$

If the alpha carbon is the origin of our coordinate system then

$$d = |\mathbf{r}| = \frac{\sqrt{|\mathbf{v}|^2 - h^2}}{2|\sin\frac{\theta}{2}|} \qquad (97)$$

$$= \text{distance of alpha carbons from the helix axis.}$$

Computing the products in (94), the helix parameters can be computed from the torsion angle ϕ and ψ. It is convenient to let

$$s = \frac{\phi + \psi}{2} \qquad t = \frac{\phi - \psi}{2}. \qquad (98)$$

Then

$$\begin{aligned}
\mathbf{v} &= \begin{pmatrix} 3.54 \\ 1.37\cos\psi \\ 1.37\sin\psi \end{pmatrix}\\
|\mathbf{v}| &= 3.80\\
\cos\frac{\theta}{2} &= -.82\sin s + .03\sin t\\
\sin\frac{\theta}{2}\mathbf{u} &= \begin{pmatrix} .82\cos s + .03\cos t \\ -.57\cos s + .04\cos t \\ -.57\sin s - .04\sin t \end{pmatrix}\\
d\sin\frac{\theta}{2} &= -.68\cos t + 2.9\cos s.
\end{aligned} \qquad (99)$$

To derive the equations 99 it is convenient to use quaternions to represent the rotations. For a unit traceless quaternion (vector) u define

$$e^{\theta u} = \cos\theta + \sin\theta\, u.$$

The rotation from one alpha carbon frame to the next is given by

$$e^{\frac{\psi}{2}I} e^{\frac{\alpha}{2}K} e^{\frac{\pi}{2}I} e^{\frac{\beta}{2}K} e^{\frac{\phi}{2}I} e^{\frac{\gamma}{2}K} \qquad (100)$$

where in the standard peptide geometry, $\alpha = 59°$, $\beta = 65°$, $\gamma = 70°$. We have

(101)

$$e^{\frac{\alpha}{2}K}e^{\frac{\pi}{2}I}e^{\frac{\beta}{2}K} = e^{\frac{\alpha}{2}K}Ie^{\frac{\beta}{2}K} = Ie^{-\frac{\alpha}{2}K}e^{\frac{\beta}{2}K} = Ie^{\frac{\beta-\alpha}{2}K} = \cos\frac{\alpha-\beta}{2}I + \sin\frac{\alpha-\beta}{2}J.$$

Since α and β differ by only 6 degrees, the above is close to I.

We compute (100) for the terms in (101) separately,

$$\begin{aligned}
&e^{\frac{\psi}{2}I}Ie^{\frac{\phi}{2}I}e^{\frac{\gamma}{2}K} = Ie^{sI}e^{\frac{\gamma}{2}K}\\
&= I\left(\cos s\,\cos\frac{\gamma}{2} + \sin s\,\cos\frac{\gamma}{2}I - \sin s\,\sin\frac{\gamma}{2}J + \cos s\,\sin\frac{\gamma}{2}K\right)\\
&= -\sin s\,\cos\frac{\gamma}{2} + \cos s\cos\frac{\gamma}{2}I - \cos s\sin\frac{\gamma}{2}J - \sin s\sin\frac{\gamma}{2}K
\end{aligned}$$

and

$$\begin{aligned}
&e^{\frac{\psi}{2}I}Je^{\frac{\phi}{2}I}e^{\frac{\gamma}{2}K} = Je^{tI}e^{\frac{\gamma}{2}K}\\
&= J\left(\cos t\,\cos\frac{\gamma}{2} + \sin t\,\cos\frac{\gamma}{2}I - \sin t\,\sin\frac{\gamma}{2}J + \cos t\,\sin\frac{\gamma}{2}K\right)\\
&= \sin t\,\sin\frac{\gamma}{2} + \cos t\,\sin\frac{\gamma}{2}I + \cos t\,\cos\frac{\gamma}{2}J - \sin t\,\cos\frac{\gamma}{2}K
\end{aligned}$$

so finally (100) is given by

(102)
$$\cos\delta\, I\, e^{sI}e^{\frac{\gamma}{2}K} + \sin\delta\, J\, e^{tI}e^{\frac{\gamma}{2}K}$$

where $\delta = \frac{\alpha-\beta}{2}$ is near 3°. Now substitute

$\cos 3^\circ \cos 35^\circ = .82 \quad \cos 3^\circ \sin 35^\circ = .57 \quad \sin 3^\circ \sin 35^\circ = .03 \quad \sin 3^\circ \cos 35^\circ = .04$

to get the equations for $\cos\frac{\theta}{2}$ and $\left(\sin\frac{\theta}{2}\right)\mathbf{u}$ in (98).

8.9. **Problems.**

(1) Consider the discrete curve along the FCC lattice given by the 5 points $p_1 = (0,0,0)$, $p_2 = (1,1,0)$, $p_3 = (1,2,1)$, $p_4 = (2,2,2)$, $p_5 = (3,3,2)$. Compute the bond angles $\theta_2, \theta_3, \theta_4$ and the torsion angles ϕ_2, ϕ_3. (You can write the torsion angle in terms of the arccosine function or the argument.)

(2) Consider the closed discrete curve given by the points

$$\mathbf{v}_j = \left(\cos\frac{j\pi}{3}, \sin\frac{j\pi}{3}, (-1)^j\frac{\sqrt{5}}{4}\right)'$$

for j = 0, …, 6. This models the discrete curve formed by the carbon atoms in the chair configuration of the molecule cyclohexane. Note that the molecule has symmetry. The set of points is left fixed by the rotation $R_z(2\pi/3)$.

  (a) Find the discrete Frenet frame, $\mathbf{F}_1$.
  (b) Find the unit tangent vectors $\mathbf{t}_0, \mathbf{t}_1, \ldots, \mathbf{t}_6$.
  (c) Show $\cos\theta_j = -\frac{1}{3}$, for $j = 1, \ldots, 6$ so the bond angles are compatible with a tetrahedral carbon bond.
  (d) Find the torsion angles $\phi_1, \ldots, \phi_6$.

FIGURE 36. Chair configuration of cyclohexane. Carbons are colored black.

9. PROTEIN FOLDING

The structure of proteins is described on several scales. The *primary structure* is the amino acid sequence which is coded in the gene for the protein. *Secondary structure* describes the chain forming alpha helices, beta sheets and loops. *Tertiary structure* describes how the helices, sheets and loops are assembled into a working unit. Review these concepts from the lecture on proteins.

Linus Pauling predicted the alpha helix secondary structure in 1948. His conjectured structure was based on his knowledge of covalent bonds and hydrogen bonds, and geometric reasoning using a piece of paper that he folded. Here is a copy of his sketch on the unfolded sheet of paper. He asked himself how the long chain of the protein backbone could be arranged so that the oxygens and the hydrogens on the backbone form a hydrogen bond. His folded paper (figure 37) brought the points A and B close together and created a hydrogen bond between the negatively charged oxygen and the positively charged hydrogen. The hydrogen bond completed a ring consisting of 13 atoms and showed a helix with 3.6 residues per turn. Structures of proteins were later obtained by crystallography, confirming Pauling's conjecture.

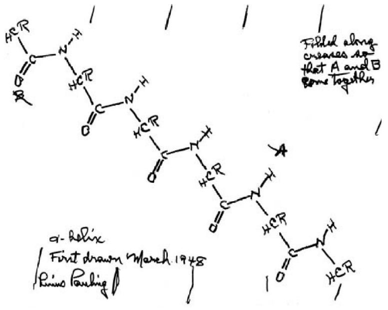


FIGURE 37. Paper folded by Linus Pauling in 1948 to predict the structure of the alpha helix.

All Pauling needed to make his discovery was the sequence of atoms and a knowledge about hydrogen bonds created by the electric force between the positively charged H bonded to N and the negatively charged. O bonded to C. This raises the question of whether protein structures can be determined from just the sequence of amino acids and all the forces between the atoms. Possibly with powerful computers and a knowledge of all the forces between atoms in a protein, the structure can be determined without experiments in the same way that Pauling did.

9.1. **Anfinsen's hypothesis.** The above question is related to Anfinsen's hypothesis, one of the basic tenants of structural genomics. It states that *information determining the structure of a protein resides in the chemistry of its amino acid sequence.* For example, it says that the amino acid sequence of Bacteriorhodopsin:

```
TGRPEWIWLALGTALMGLGTLYFLVKGMGVSDPDAKKFYAITT
LVPAIAFTMYLSMLLGYGLTMVPFGGEQNPIYWARYADWLFTT
PLLLLDLALLVDADQGTILALVGADGIMIGTGLVGALTKVYSY
RFVWWAISTAAMLYILYVLFFGFTSKAESMRPEVASTFKVLRN
VTVVLWSAYPVVWLIGSEGAGIVPLNIETLLFMVLDVSAKVGF
GLILLRSRAIFGE
```

determines the structure shown in figure 38 that we find in the pdb file 1E0P.

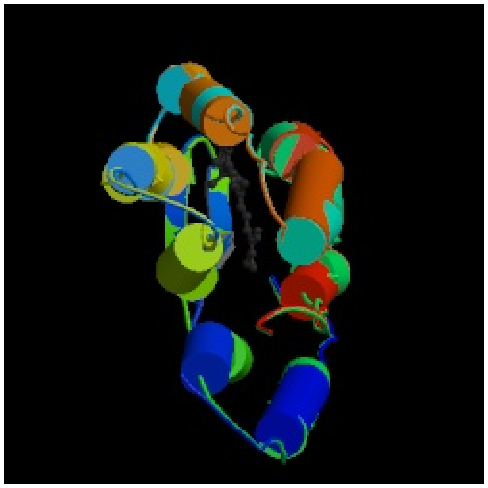


FIGURE 38. The structure of the protein Bacteriorhodopsin

The structure of the functional protein is called the *native state.* The process by which a protein folds into this structure from an extended chain is called *folding* (figure 39).

9.2. **Configuration space.** The basic question in protein folding is whether from the amino acid sequence and basic laws of physics the structure of a protein can be predicted using the power of a computer. This leads to the following questions:

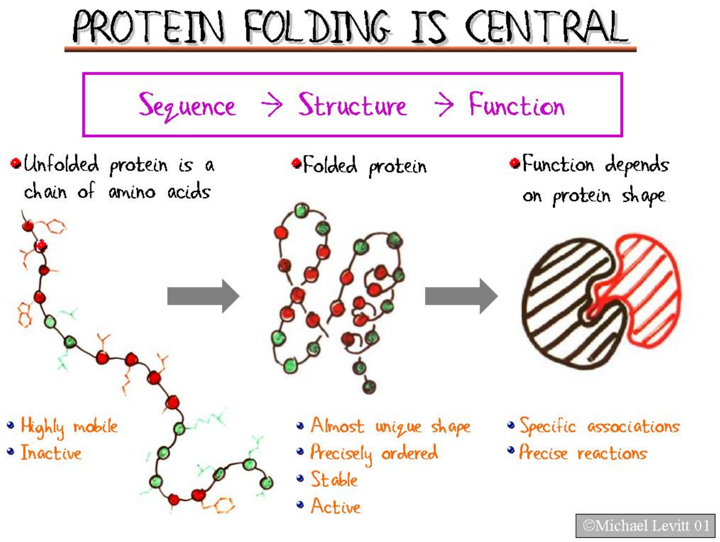


Figure 39. The relationship between protein sequence and protein function. Figure taken from Michael Levitt's Structural Biology and Computer Science course at Stanford.

- Is there a sequence of numbers that describes any possible shape, or configuration, of a protein?
- What energy function can we associate to set of all configurations of a protein with a given sequence of amino acids?
- Is the structure of a protein the solution to the problem of minimizing this energy function on the set of configurations?

To describe the set of all possible shapes of a protein, we need a *configuration space* described by a sequence of parameters. Recall that a structure is given in a pdb file as a list of three coordinates for each atom in the molecule. This configuration space is n dimensional where n is 3 times the number of atoms in molecule. For bacteriorhodopsin we can see from the pdb file that one chain has approximately has 1700 atoms. This gives $n = 5100$, a very large number of variables to work with. The fact that proteins find their native configuration in spite of the size of the configuration space is called *Levinthal's paradox.*

Levinthal's paradox: It would take a protein the present age of the universe to explore all possible configurations and find the minimum energy configuration. Yet proteins fold in microseconds.

9.3. **Reduced parametrizations.** For computation it is desirable to have a smaller number of parameters describing configuration space. It is not necessary to find the coordinates of every atom. Some atom positions are fixed by others. For example, if the coordinates of a carbon and two adjacent bonded atoms are known, the coordinates of any hydrogen bonded to the carbon can be found.

The size of the configuration space can also be reduced by using torsion angles for parameters instead of coordinates of atoms. The table of side chains is helpful for counting. Below in table 3 is listed the number of torsion angles per side chain, including main chain. On average there are about 4 (ϕ, ψ, χ) torsion angles per residue.

Table 3. Number of torsions angle needed to determine the structure of a side chain.

number of torsion angles	residues
2	Gly, Ala, Pro
3	Ser, Cys, Thr, Val
4	Ile, Leu, Asp, Asn, His, Phe, Try, Trp
5	Met, Glu, Gln
6	Lys, Arg

9.4. **Energy functions.** Pauling discovered the structure of the alpha helix by trying to bring a hydrogen and an oxygen in close proximity while keeping the geometry of the peptide bond and keeping some uniformity in the torsion angles at the alpha carbons. If d is the distance from the O to the H in the hydrogen bond, Pauling was trying to minimize d or equivalently to minimize $-1/d$. If q_1 is the charge on the O, a negative charge, and q_2 is the charge on H, a positive charge, then by Coulomb's law the electrostatic energy of the OH pair is q_1q_2/d. So Pauling was minimizing energy. The numbers q_1 and q_2 are called partial charges since they are less than 1 in absolute value, while the charge on one proton is $+1$ and the charge on one electron is -1.

This procedure can be greatly generalized by introducing the idea of an energy function, a function of all the parameters for the configuration space, and trying to find values of the parameters which minimize this function. One of the energy functions used is the van der Waals energy which is large if two molecules are close together. Minimizing the van der Waals energy keeps atoms from getting too close. The van der Waals energy is just one term in the total energy.

Another term in the energy function is the electrostatic energy which is large if two oppositely charged atoms are far apart. Minimizing the electrostatic energy function will includes making the distance between atoms in a hydrogen bond small. The electrostatic energy is another term in the total energy function. Many other types of energy functions can be added to get the total energy.

One collection of energy functions that is frequently used is CHARMM (Chemistry at HARvard Molecular Mechanics). The functions are simple quadratic functions of distances and angles, similar to the energy function for a spring. The

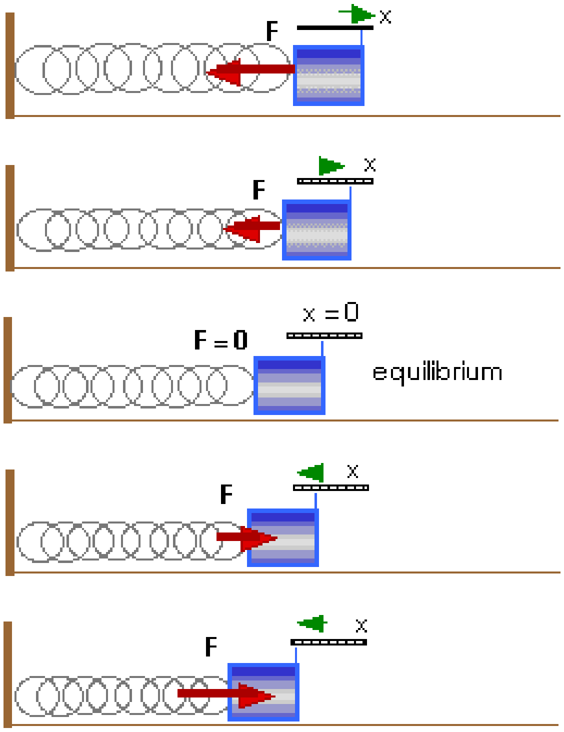


FIGURE 40. A spring in various states of displacement from equilibrium

energy can be thought of as the energy of a collection of springs describing the forces within the molecule.

9.4.1. *The energy of a spring.* We review the equation for the energy of a spring. If on a number line $x = 0$ represents the coordinate of the end of a spring at equilibrium, the force on the spring with the end moved to x is given by $F = -kx$ where $k > 0$ is the *spring constant*(figure 40). The energy to move the end of the spring to x is

$$E = \int_0^x ks\,ds = k\,\frac{x^2}{2}. \tag{103}$$

Force represents the rate of change of energy, $F = -dE/dx$. We can think of the force as a tendency to move to minimum energy (figure 41). The graph of the energy function is called the *energy landscape*. To find the minimum energy configuration, we look for valleys in the energy landscape. For this spring, the minimum energy is at $x = 0$, at the lowest point of the parabola.

9.4.2. *CHARMM Energy.* The main part of the CHARMM energy is a sum of six types of energy terms, each of which is a quadratic function analogous to the energy function of a spring.

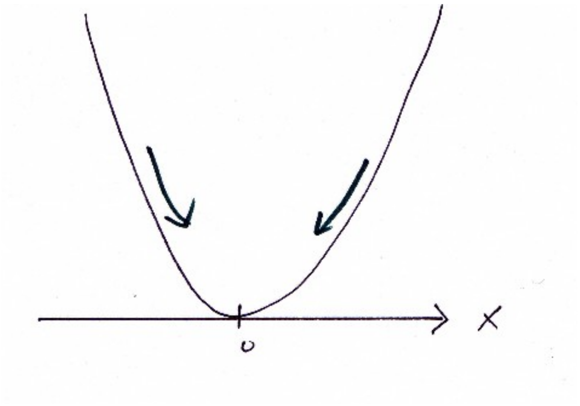


FIGURE 41. Energy landscape of a spring. the curve represents energy $E = kx^2/2$, with the minumum energy at $x = 0$. The force is the slope of the energy function. The force pushes the spring toward equilibrium at $x = 0$.

$$
\begin{array}{rcll}
V(x) = & \sum_b & c_\ell(b-b_0)^2 & b \text{ a bond length} \\
+ & \sum_\theta & c_a(\theta-\theta_0)^2 & \theta \text{ a bond angle} \\
+ & \sum_\tau & c_i(\tau-\tau_0)^2 & \tau \text{ a torsion angle} \\
+ & \sum_\omega & \operatorname{trig}(\omega) & \omega \text{ a dihedral angle} \\
+ & \sum_{i,j} & \frac{Q_iQ_j}{D\,r_{ij}} & r_{ij} \text{ dist. between charged pair} \\
+ & \sum & c_w\phi\left(\frac{R_i+R_j}{r_{ij}}\right) & r_{ij} \text{ dist. between pair}
\end{array}
\tag{104}
$$

Some further terms, accounting specifically for disulfide bonds and hydrogen bonds, are also present but will not be discussed here.

9.4.3. *Explanation of energy terms.* The Q_i are *partial charges* assigned to the atoms in order to approximate the electrostatic potential of the electron cloud. The constants labelled c are analogous to spring constants. These are estimated from principles of physical chemistry and values for these are included in the CHARMM package. D is the dielectric constant which is determined by the medium, usually water, in which the protein folds. It measures how strongly within the medium an electric charge is felt at a distance from the charge.

The quantities indexed by the subscript 0 are reference bond lengths, bond angles, and improper torsion angles near their equilibrium values; different constants apply depending on the chemistry and on their location in a functional group. The coefficients of the trigonometric terms $\operatorname{trig}(\omega)$ (linear combinations of cosines of multiples of ω) are also determined by the chemistry of the atoms.

The van der Waals interactions (defined by the final sum in the potential) depend on the interatomic pair potential φ which, in the simplest case, is taken as the

Lennard-Jones potential $\varphi(R_0/R)$ where

$$\varphi(x) = x^{12} - 2\,x^6.$$

Under this potential, two atoms are attracted if they are farther than R_0 apart and repel each other if they are less than R_0 apart.

That all of these constants are independent of the molecule is a basic assumption of molecular mechanics called *transferability*.

Slides from Michael Levitt's structural biology course at Stanford are helpful in understanding energy functions.

Finding the minimum of this complicated energy function is a hard computational problem.

9.5. **Example, the alpha helix.** As an illustration of minimizing an energy function, take a simple example of finding the ϕ, ψ parameters for an alpha helix as the solution of a minimum energy problem. We saw that in the discovery of the alpha helix, Pauling was trying to minimize d, or equivalently to minimize $-1/d$ where d is the distance between atoms forming a hydrogen bond. He was trying to find a configuration giving the shortest distance between the H and the O atoms in the bond. This can be thought of as minimizing the electrostatic energy given by the charges on the O and H atoms.

Assuming that the O and the H have three C_α atoms in between, and assuming that the ϕ, ψ torsion angles are the same at each C_α, the configuration space is 2 dimensional, consisting of the parameters ϕ and ψ. Looking at the discrete curve from the O to the H atom, and using the discrete Frenet frame and the bond, torsion, and distances given from protein geometry (see table 4), the distance d(O,H) can be computed as a function of ϕ and ψ. Figure 42 shows the level curves of this function. See the Maple worksheet for this computation.

10. Appendix 1: A Very Brief Linear Algebra Review

Linear Algebra, also known as matrix theory, is an important element of all branches of mathematics. Very often in this course we study the shapes and the symmetries of molecules. Motion of 3D space which leave molecules rigid can be described by matrices. Briefly mentioned in these notes will be quantum mechanics, where matrices and their eigenvalues have an essential role.

In all cases it is useful to allow the entries in the matrix to be complex numbers. If you have studied matrices only with real number entries, it is very easy to adapt to complex numbers. Almost all the rules of computations are the same.

TABLE 4. The hydrogen bond completes a chain of 13 bonded atoms along the protein forming a discrete curve. The bond angles, torsion angles and distances along this chain from O to H are given in this table.

k	atom	θ_k	ϕ_k	s_k
1	O			1.24
2	C	56.5°	0	1.32
3	N	58°	ϕ	1.45
4	C_α	69°	ψ	1.51
5	C	54°	180°	1.32
6	N	58°	ϕ	1.45
7	C_α	69°	ψ	1.51
8	C	54°	180°	1.32
9	N	58°	ϕ	1.45
10	C_α	69°	ψ	1.51
11	C	54°	180°	1.32
12	N	60°	0	1.02
13	H			

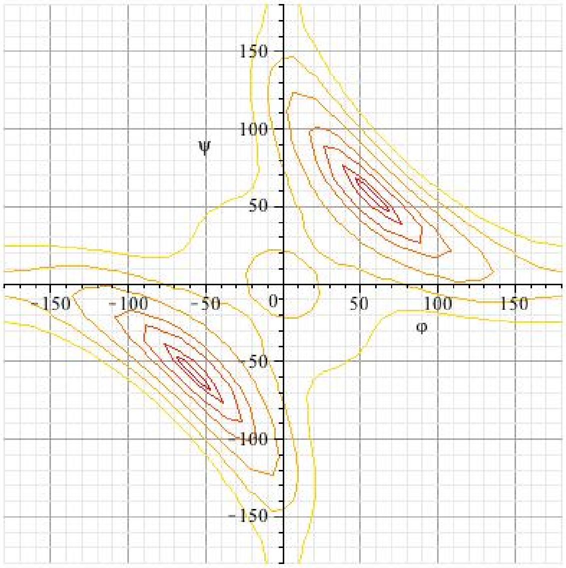


FIGURE 42. Level curves of $d(\mathrm{O,H})(\phi, \psi)$ showing a minimum near $(-50°, -50°)$, which are the parameters for a right handed alpha helix. There is also a minimum near $(50°, 50°)$ corresponding to a left handed alpha helix.

In doing computations with matrices it is useful to have a computer program such as *Maple* or *Matlab*. These tools make multiplication of matrices very easy, and they work with complex numbers. The main difference between *Maple* and

Matlab is that *Maple* can work symbolically, that is, you can use letter as well as numbers for entries. When using numbers, *Matlab* is often faster.

Below we give a review of a few basic ideas that will be used in the course.

10.1. **Matrices and Vectors.** *Example*:

$$\mathrm{A} = \begin{bmatrix} 2 & 1 \\ -1 & 3 \end{bmatrix}$$

A is a matrix with 2 rows and 2 columns i.e a 2 × 2 matrix.

A matrix with m rows and n columns is called an $m \times n$ matrix.

A matrix with the same number of rows and columns is called a square matrix.

3 × 3 square matrix:

$$\mathrm{B} = \begin{bmatrix} 3 & 1 & 7 \\ -1 & 2 & 0 \\ 0 & 1 & 5 \end{bmatrix}$$

3 × 2 matrix:

$$\mathrm{C} = \begin{bmatrix} 2 & 0 \\ -9 & 10 \\ 1 & 14 \end{bmatrix}$$

A 1 × 1 matrix is the same as a number or scalar,

$$3 = [3].$$

Matrices with 1 row are called row vectors and matrices with 1 column are called column vectors.

$$\mathrm{A} = \begin{bmatrix} 2 \\ 1 \end{bmatrix} \quad \mathrm{B} = \begin{bmatrix} 3 \\ 2 \\ 1 \end{bmatrix}$$

are column vectors.

$$\mathrm{C} = \begin{bmatrix} 2 & 1 \end{bmatrix} \quad \mathrm{D} = \begin{bmatrix} 3 & 2 & 1 \end{bmatrix}$$

are row vectors. Usually we will assume vectors are column vectors. A row vector can be converted into a column vector (or vice versa) by the transpose operation, which changes rows to columns.

Example:

$$\begin{bmatrix} 1 & -1 & 0 \end{bmatrix}' = \begin{bmatrix} 1 \\ -1 \\ 0 \end{bmatrix}$$

Complex numbers can be used in matrices.

A number $z = a + bi$ where a and b are real numbers and where $i^2 = -1$ is called a complex number. The number a is called the *real part*, $a = \operatorname{Re} z$ and b the imaginary part, $b = \operatorname{Im} z$.

If $z = a + bi$ where a and b are real numbers, then the *complex conjugate* of z is $\overline{z} = a - bi$. The number z is *real* if $b = 0$, or equivalently, $z = \bar{z}$.

Basic operations with matrices are:

- addition
- scalar multiplication
- multiplication

10.2. **Operations with matrices.** Addition: Add matrices by adding corresponding entries.

$$\begin{bmatrix} 2 & 1 \\ -1 & 3 \end{bmatrix} + \begin{bmatrix} i & 0 \\ 1 & 2 \end{bmatrix} = \begin{bmatrix} 2+i & 1 \\ 0 & 5 \end{bmatrix}$$

Every matrix entry is multiplied by the scalar.

$$2i \begin{bmatrix} 2 & 1 \\ -1 & 3 \end{bmatrix} = \begin{bmatrix} 4i & 2i \\ -2i & 6i \end{bmatrix}$$

Matrix Multiplication: Multiplication AB can be done only if the number of columns of A is the same as the number of rows of B. Each entry of the product is the dot product of a row of the first matrix with a column of the second.

Here is the product of a 3×3 matrix and a 3×1 matrix.

$$\begin{bmatrix} 2 & 1 & 3 \\ -1 & 1 & 2 \\ 3 & 1 & 1 \end{bmatrix} \begin{bmatrix} 1 \\ 0 \\ 2 \end{bmatrix} = \begin{bmatrix} 2 \cdot 1 + 1 \cdot 0 + 3 \cdot 2 \\ (-1) \cdot 1 + 1 \cdot 0 + 2 \cdot 2 \\ 3 \cdot 1 + 1 \cdot 0 + 1 \cdot 2 \end{bmatrix} = \begin{bmatrix} 8 \\ 3 \\ 5 \end{bmatrix}$$

Here is the product of two 3 × 3 matrices:

$$\begin{bmatrix} 2 & 1 & 3 \\ 1 & 0 & 1 \\ 2 & 1 & 0 \end{bmatrix} \begin{bmatrix} 1 & -1 & 0 \\ 1 & 2 & \frac{1}{2} \\ 3 & 0 & 1 \end{bmatrix} =$$

$$\begin{bmatrix} 2\cdot 1 + 1\cdot 1 + 3\cdot 3 & 2\cdot(-1) + 1\cdot 2 + 3\cdot 0 & 2\cdot 0 + 1\cdot\frac{1}{2} + 3\cdot 1 \\ 1\cdot 1 + 0\cdot 1 + 1\cdot 3 & 1\cdot(-1) + 0\cdot 2 + 1\cdot 0 & 1\cdot 0 + 0\cdot\frac{1}{2} + 1\cdot 1 \\ 2\cdot 1 + 1\cdot 1 + 0\cdot 3 & 2\cdot(-1) + 1\cdot 2 + 0\cdot 0 & 2\cdot 0 + 1\cdot\frac{1}{2} + 0\cdot 1 \end{bmatrix} =$$

$$\begin{bmatrix} 12 & 0 & 3.5 \\ 4 & -1 & 1 \\ 3 & 0 & .5 \end{bmatrix}$$

An important thing to remember about matrix multiplication is that it is *not commutative*; in general, AB ≠ BA. For example

$$\begin{bmatrix} 1 & 1 \\ 0 & 1 \end{bmatrix} \begin{bmatrix} 1 & 0 \\ 1 & 1 \end{bmatrix} = \begin{bmatrix} 2 & 1 \\ 1 & 1 \end{bmatrix}$$

$$\begin{bmatrix} 1 & 0 \\ 1 & 1 \end{bmatrix} \begin{bmatrix} 1 & 1 \\ 0 & 1 \end{bmatrix} = \begin{bmatrix} 1 & 1 \\ 1 & 2 \end{bmatrix}$$

Other operations are

- conjugation
- transpose
- adjoint
- inversion

If Z is a matrix then the matrix conjugate is formed by taking the complex conjugate of each entry.

Example: Let

$$Z = \begin{bmatrix} 1+i & 2 \\ 3-i & \frac{1}{2}+2i \end{bmatrix} = \begin{bmatrix} 1 & 2 \\ 3 & \frac{1}{2} \end{bmatrix} + \begin{bmatrix} 1 & 0 \\ -1 & 2 \end{bmatrix} i$$

$$= A + Bi$$

where

$$A = \begin{bmatrix} 1 & 2 \\ 3 & \frac{1}{2} \end{bmatrix}$$

and

$$B = \begin{bmatrix} 1 & 0 \\ -1 & 2 \end{bmatrix}$$

.

The matrix A is the real part of Z and the matrix B is the imaginary part of Z.

The conjugate of Z is

$$\overline{\mathrm{Z}} = \begin{bmatrix} 1-i & 2 \\ 3+i & \frac{1}{2}-2i \end{bmatrix}$$

or using the real and imaginary parts of the matrix,

$$\overline{\mathrm{Z}} = A - Bi$$

Some properties of the matrix congugate are:

$$\overline{\mathrm{AB}} = \overline{\mathrm{A}}\,\overline{\mathrm{B}}$$

$$\overline{(\mathrm{A}+\mathrm{B})} = \overline{\mathrm{A}} + \overline{\mathrm{B}}$$

The *transpose* of a matrix A, A′, is obtained by changing rows to columns (or equivalently, changing columns to rows).

Sometimes the transpose is denoted A′ rather than A^{t}.

$$\mathrm{A} = \begin{bmatrix} 2 & 1 & -1 \\ 0 & 1 & 2 \\ -1 & 0 & 1 \end{bmatrix} \qquad \mathrm{A}^{\mathrm{t}} = \begin{bmatrix} 2 & 0 & -1 \\ 1 & 1 & 0 \\ -1 & 2 & 1 \end{bmatrix}$$

Some properties of transpose are

$$(\mathrm{AB})^{\mathrm{t}} = \mathrm{B}^{\mathrm{t}}\mathrm{A}^{\mathrm{t}}$$
$$(\mathrm{A}+\mathrm{B})^{\mathrm{t}} = \mathrm{A}^{\mathrm{t}} + \mathrm{B}^{\mathrm{t}}$$

The *Hermitian transpose* or *adjoint* is the conjugate transpose given by

$$\mathrm{A}^* = \bar{\mathrm{A}}^{\mathrm{t}}.$$

Example:

$$\begin{bmatrix} 1, 2-i, 3 \end{bmatrix}^* = \begin{bmatrix} 1 \\ 2+i \\ 3 \end{bmatrix}$$

Example: For the matrix Z given above,

$$\mathrm{Z}^* = \overline{\mathrm{Z}^t} = \begin{bmatrix} 1-i & 3+i \\ 2 & \frac{1}{2}-2i \end{bmatrix}$$

Some properties of adjoint are

$$(\mathrm{AB})^* = \mathrm{B}^*\mathrm{A}^*$$
$$(\mathrm{A}+\mathrm{B})^* = \mathrm{A}^* + \mathrm{B}^*$$

10.3. **Matrix inverse.** The matrix I denotes a square matrix whose entries are a_{ij} where

$$a_{ij} = \begin{cases} 1 \text{ if } i = j \\ 0 \text{ if } i \neq j. \end{cases}$$

The matrix I is called the unit or *identity matrix.* Identity matrices come in different sizes:

$$\mathrm{I}_2 = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix} \quad \mathrm{I}_3 = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix}.$$

Let A be a square matrix. The inverse is a matrix A^{-1} such that $\mathrm{A}^{-1}\mathrm{A} = \mathrm{AA}^{-1} = I$.

The inverse of a 2×2 matrix is easy to find. If

$$\mathrm{A} = \begin{bmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{bmatrix}$$

then

$$\mathrm{A}^{-1} = \frac{1}{\alpha} \begin{bmatrix} a_{22} & -a_{12} \\ -a_{21} & a_{11} \end{bmatrix}$$

if $\alpha = a_{11}a_{22} - a_{12}a_{21} \neq 0$.

Not every square matrix has an inverse.

10.4. **Dot product.** Let $v = \begin{bmatrix} a \\ b \\ c \end{bmatrix}$ and $w = \begin{bmatrix} x \\ y \\ z \end{bmatrix}$ be two vectors, then the *dot product* is given by

$$v \cdot w = v^t w = \begin{bmatrix} a & b & c \end{bmatrix} \begin{bmatrix} x \\ y \\ z \end{bmatrix} = ax + by + cz$$

Let $v = \begin{bmatrix} 1+i \\ 1 \\ i \end{bmatrix}$ and $w = \begin{bmatrix} 2 \\ 1-i \\ 3 \end{bmatrix}$ then the *Hermitian dot product* is given by

$$\langle v, w \rangle = v^* w = \overline{v} \cdot w$$
$$= (1-i)2 + 1(1-i) + (-i)3$$
$$= 3 - 6\,i.$$

The length of a vector $|v|$ is given by

$$|v|^2 = \langle v, v\rangle.$$

Two vectors v and w are *orthogonal* or *perpendicular* if $\langle v, w\rangle = 0$. In general for real vectors

$$\langle v, w\rangle = |v||w|\cos\theta$$

where θ is the angle between the vectors.

10.5. **Matrix multiplication and dot product.** An $m \times n$ matrix can be considered as a list of n column vectors, $v_1, \ldots, v_n$, each $m \times 1$,

$$\mathrm{A} = [v_1, \ldots, v_n]$$

and the transpose as a list of row vectors

$$\mathrm{A}^{\mathrm{t}} = \begin{bmatrix} v_1^{\mathrm{t}} \\ \vdots \\ v_n^{\mathrm{t}} \end{bmatrix}.$$

If

$$\mathrm{B} = \begin{bmatrix} w_1^{\mathrm{t}} \\ \vdots \\ w_k^{\mathrm{t}} \end{bmatrix}$$

is a $k \times m$ matrix given as a list of k row vectors, $w_1^{\mathrm{t}}, \ldots, w_k^{\mathrm{t}}$, each $1 \times m$, then

$$\mathrm{BA} \ = \begin{bmatrix} w_1 \cdot v_1 & \ldots & w_1 \cdot v_n \\ \vdots & & \vdots \\ w_k \cdot v_1 & \ldots & w_k \cdot v_n \end{bmatrix}$$

is a matrix of dot products.

10.6. **Symmetric Matrices.** A matrix B is *symmetric* if $\mathrm{B} = \mathrm{B}^{\mathrm{t}}$

Example:

$$\begin{bmatrix} 3 & 1+i & 2 \\ 1+i & 0 & -5 \\ 2 & -5 & 2 \end{bmatrix}$$

is symmetric.

A matrix B is *self adjoint* (or *Hermitian symmetric*) if $\mathrm{B}^* = \mathrm{B}$

Example:

$$\begin{bmatrix} 2 & 1+i & \frac{1}{2}+2i \\ 1-i & 3 & 5 \\ \frac{1}{2}-2i & 5 & 4 \end{bmatrix}$$

is self adjoint.

10.7. **Determinant.** The determinant of a 2×2 matrix is given by

$$\det \begin{bmatrix} a & b \\ c & d \end{bmatrix} = \begin{vmatrix} a & b \\ c & d \end{vmatrix} = ad - bc.$$

For a 3×3 matrix,

$$\det \begin{bmatrix} a & b & c \\ d & e & f \\ g & h & k \end{bmatrix} = a \begin{vmatrix} e & f \\ h & k \end{vmatrix} - b \begin{vmatrix} d & f \\ g & k \end{vmatrix} + c \begin{vmatrix} d & e \\ g & h \end{vmatrix}.$$

This is called *expansion by minors.* Likewise the determinant is defined for any square matrix.

Properties of determinant:

$$\det \mathrm{AB} = \det \mathrm{A} \det \mathrm{B}$$

$$\det \mathrm{A} \neq 0 \text{ implies } \mathrm{A}^{-1} \text{ exists}$$

10.8. **Vector Cross Product.**

$$\begin{bmatrix} a \\ b \\ c \end{bmatrix} \times \begin{bmatrix} x \\ y \\ z \end{bmatrix} = \begin{bmatrix} bz - cy \\ -az + cx \\ ay - bx \end{bmatrix}.$$

$$= (bz - cy)\mathbf{i} - (az - cx)\mathbf{j} + (ay - bx)\mathbf{k}$$

where

$$\mathbf{i} = \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix} \quad \mathbf{j} = \begin{bmatrix} 0 \\ 1 \\ 0 \end{bmatrix} \quad \mathbf{k} = \begin{bmatrix} 0 \\ 0 \\ 1 \end{bmatrix}$$

The formula for cross product is often remembered by pretending that **i**, **j** and **k** are numbers and writing

$$\begin{bmatrix} a \\ b \\ c \end{bmatrix} \times \begin{bmatrix} x \\ y \\ z \end{bmatrix} = \det \begin{bmatrix} \mathbf{i} & \mathbf{j} & \mathbf{k} \\ a & b & c \\ x & y & z \end{bmatrix}$$

10.9. **Eigenvalue and Eigenvectors.** The scalar λ, a real or complex number, is an *eigenvalue* of a matrix A corresponding to an *eigenvector* $v \neq 0$ if $\mathrm{A}v = \lambda v$.

Example: 1

$$\begin{bmatrix} 2 & 1 \\ 1 & 2 \end{bmatrix} \begin{bmatrix} 1 \\ 1 \end{bmatrix} = 3 \begin{bmatrix} 1 \\ 1 \end{bmatrix}$$

The eigenvalue is 3, and an eigenvector is $[1, 1]^{\mathrm{t}}$. Note that $[2, 2]^{\mathrm{t}}$ is also an eigenvector.

Example: 2

$$\begin{bmatrix} 0 & -1 \\ 1 & 0 \end{bmatrix} \begin{bmatrix} 1 \\ -i \end{bmatrix} = \begin{bmatrix} i \\ 1 \end{bmatrix} = i \begin{bmatrix} 1 \\ -i \end{bmatrix}$$

The eigenvalue is i, and an eigenvector is $[1, -i]^t$.

Example: 3

$$\begin{bmatrix} 0 & -1 \\ 1 & 0 \end{bmatrix} \begin{bmatrix} 1 \\ i \end{bmatrix} = \begin{bmatrix} -i \\ 1 \end{bmatrix} = -i \begin{bmatrix} 1 \\ i \end{bmatrix}$$

The eigenvalue is $-i$, and an eigenvector is $[1, i]^t$.

Note that the equation in example 3 is the conjugate on the one in example 2.

Also note that a matrix with real entries can have complex eigenvalues and eigenvectors.

The eigenvalues of self adjoint matrices are real. This fact is essential in many areas of mathematics and is also a key fact in the mathematical formulation of quantum mechanics. Here is a proof:

If A is self adjoint and

$$\mathrm{A}v = \lambda v$$

then taking the adjoint of both sides gives since $\mathrm{A}^* = \mathrm{A}$,

$$v^*\mathrm{A} = \overline{\lambda} v^*.$$

Multiplying the first equation on the left by v^* and the second on the right by v gives

$$v^*\mathrm{A}v = \lambda |v|^2 = \overline{\lambda} |v|^2.$$

Since $|v| \neq 0$ we have $\overline{\lambda} = \lambda$ and so λ is real.

A consequence is that the eigenvalues of a symmetric real matrix are real.

10.10. **Rotation matrices.** In dimension 2, rotation of a column vector by an angle θ counterclockwise is given by multiplying on the left by the matrix

$$\begin{bmatrix} \cos\theta & -\sin\theta \\ \sin\theta & \cos\theta \end{bmatrix}.$$

In dimension 3 rotations about the three axes are given by

- Rotation an angle θ about the x axis
$$\mathrm{R}_x(\theta) = \begin{bmatrix} 1 & 0 & 0 \\ 0 & \cos\theta & -\sin\theta \\ 0 & \sin\theta & \cos\theta \end{bmatrix}$$
- Rotation an angle θ about the y axis
$$\mathrm{R}_y(\theta) = \begin{bmatrix} \cos\theta & 0 & \sin\theta \\ 0 & 1 & 0 \\ -\sin\theta & 0 & \cos\theta \end{bmatrix}$$
- Rotation an angle θ about the z axis
$$\mathrm{R}_z(\theta) = \begin{bmatrix} \cos\theta & -\sin\theta & 0 \\ \sin\theta & \cos\theta & 0 \\ 0 & 0 & 1 \end{bmatrix}.$$

Matrices can be found for rotation of any angle about any axis, where an axis is given by a non-zero vector.

10.11. **Problems.**

(1) Read about finding eigenvalues using Maple. Let
$$C = \begin{pmatrix} -4 & -3 & 3 & -3 \\ 3 & 2 & -3 & 3 \\ 3 & 3 & -4 & 3 \\ 6 & 6 & -6 & 5 \end{pmatrix}$$
Use Maple to find a non-zero vector X such that $CX = 2X$.

(2) Use Maple to find the inverses of the matrices
$$M = \begin{pmatrix} 1 & 2 & 3 \\ 3 & 4 & 5 \\ 3 & 5 & 6 \end{pmatrix} \text{ and } N = \begin{pmatrix} 2 & 2-i \\ 2+i & -2 \end{pmatrix}.$$

(3) Suppose A is self adjoint and that v_1 and v_2 are eigenvectors corresponding to distinct eigenvalues. Show that $v_1^* v_2 = 0$.

(4) If A is a real 2×2 matrix such that $A'A = I$ and $\det A = 1$, show that for some θ,
$$A = \begin{pmatrix} \cos\theta & -\sin\theta \\ \sin\theta & \cos\theta \end{pmatrix}.$$

(5) Let R_θ be the rotation matrix
$$\begin{pmatrix} \cos\theta & -\sin\theta \\ \sin\theta & \cos\theta \end{pmatrix}.$$
Show that
$$(R_\theta - I)(R_{-\theta} - I) = 2(1 - \cos\theta)I.$$

(6) Show that if A is real and has real eigenvalue λ, then there is a real vector (a vector with real coordinates) which is an eigenvector corresponding to λ.

(7) Let

$$\Sigma_1 = \begin{pmatrix} 0 & 1 \\ 1 & 0 \end{pmatrix} \qquad \Sigma_2 = \begin{pmatrix} 0 & -i \\ i & 0 \end{pmatrix} \qquad \Sigma_3 = \begin{pmatrix} 1 & 0 \\ 0 & -1 \end{pmatrix}.$$

Use Maple to verify the following identities:

$$\begin{gathered} \Sigma_1^2 = 1, \qquad \Sigma_2^2 = 1 \qquad \Sigma_3^2 = 1, \\ \Sigma_1\Sigma_2 = i\Sigma_3, \qquad \Sigma_2\Sigma_1 = -i\Sigma_3, \\ \Sigma_2\Sigma_3 = i\Sigma_1, \qquad \Sigma_3\Sigma_2 = -i\Sigma_1, \\ \Sigma_3\Sigma_1 = i\Sigma_2, \qquad \Sigma_1\Sigma_3 = -i\Sigma_2. \end{gathered}$$

(8) For the each of the matrices Σ_k in the previous problem, find vectors X and Y such that

$$\Sigma_k X = X \text{ and } \Sigma_k Y = -Y.$$