

## Classical Normal Mode Analysis: Harmonic Approximation

The vibrations of a molecule are given by its normal modes. Each absorption in a vibrational spectrum corresponds to a normal mode. The four normal modes of carbon dioxide, Figure 1, are the symmetric stretch, the asymmetric stretch and two bending modes. The two bending modes have the same energy and differ only in the direction of the bending motion. Modes that have the same energy are called degenerate. In the classical treatment of molecular vibrations, each normal mode is treated as a simple harmonic oscillator.

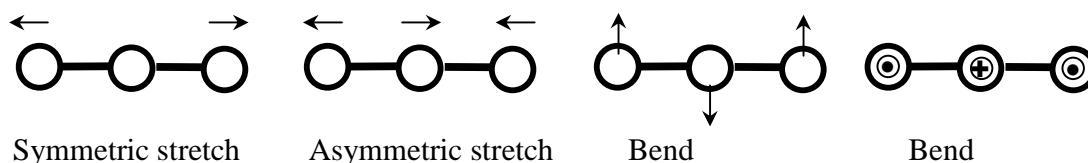


Figure 1. Normal Modes for a linear triatomic molecule. In the last bending vibration the motion of the atoms is in-and-out of the plane of the paper.

In general linear molecules have  $3N-5$  normal modes, where  $N$  is the number of atoms. The five remaining degrees of freedom for a linear molecule are three coordinates for the motion of the center of mass ( $x$ ,  $y$ ,  $z$ ) and two rotational angles. Non-linear molecules have three rotational angles, hence  $3N-6$  normal modes.

The characteristics of normal modes are summarized below.

### Characteristics of Normal Modes

1. Each normal mode acts like a simple harmonic oscillator.
2. A normal mode is a concerted motion of many atoms.
3. The center of mass doesn't move.
4. All atoms pass through their equilibrium positions at the same time.
5. Normal modes are independent; they don't interact.

In the asymmetric stretch and the two bending vibrations for  $\text{CO}_2$ , all the atoms move. The concerted motion of many of the atoms is a common characteristic of normal modes. However, in the symmetric stretch, to keep the center of mass constant, the center atom is stationary. In small molecules all or most all of the atoms move in a given normal mode; however, symmetry may require that a few atoms remain stationary for some normal modes. The last characteristic, that normal modes are independent, means that normal modes don't exchange energy. For example, if the symmetric stretch is excited, the energy stays in the symmetric stretch.

The background spectrum of air, Figure 2, shows the asymmetric and symmetric stretches and the bending vibration for water, and the asymmetric stretch and bending vibrations for  $\text{CO}_2$ . The symmetric stretch for  $\text{CO}_2$  doesn't appear in the Infrared; a Raman spectrum is needed to measure the frequency of the symmetric stretch. These absorptions are responsible for the vast majority of the greenhouse effect. We will also use  $\text{CO}_2$  as an example, below.

The normal modes are calculated using Newton's equations of motion.<sup>1-4</sup> Molecular mechanics and molecular orbital programs use the same methods. Normal mode calculations are available on-line.<sup>5</sup>

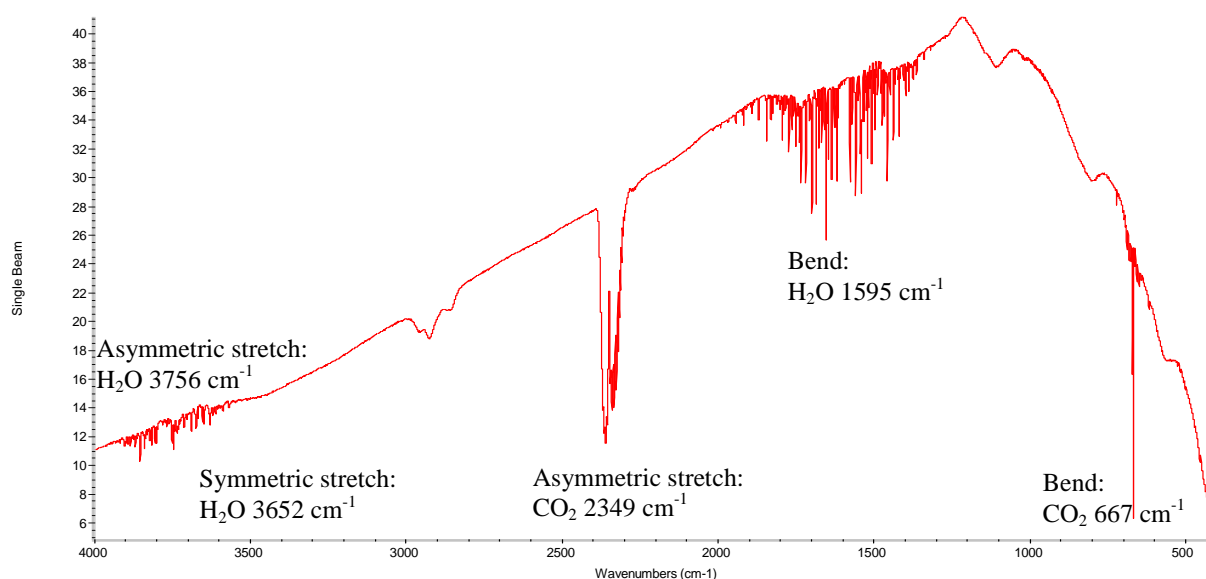


Figure 2. The Infrared spectrum of air. This spectrum is the background scan from an FT-IR spectrometer.

### Harmonic Oscillator Review

Let's first review the simple harmonic oscillator. Consider a mass  $m$ , supported on a spring with force constant  $k$ . Hooke's Law for the restoring force for an extension,  $x$ , is  $F = -kx$ . In other words, if the spring is stretched a distance  $x > 0$ , the restoring force will be negative, which will act to pull the mass back to its equilibrium position. The potential energy for Hooke's Law is obtained by integrating

$$F = -\frac{dV}{dx} = -kx \quad (1)$$

$$\text{to give } V = \frac{1}{2} k x^2 \quad (2)$$

In molecular mechanics and molecular orbital calculations, the force constant is not known. However, the force constant can be calculated from the second derivative of the potential energy.

$$k = \frac{d^2 V}{dx^2} \quad (3)$$

The Hooke's Law force is substituted into Newton's Law:

$$F = ma \quad \text{or} \quad m \frac{d^2 x}{dt^2} = -kx \quad (4)$$

and solved to obtain the extension as a function of time:

$$x(t) = A \sin(2\pi\nu t) \quad (5)$$

where  $\nu$  is the fundamental vibration frequency and  $A$  is the amplitude of the vibration. Taking the second derivative of the extension gives

$$\frac{d^2 x}{dt^2} = -4\pi^2 \nu^2 x \quad (6)$$

Substituting Eq 6 back into Eq 4 gives:

$$-4\pi^2 \nu^2 m x = -kx \quad (7)$$

which is the basis for the classical calculation of the normal modes of a molecule.

### Normal Mode Analysis

For molecules the x, y, z coordinates of each atom must be specified. The coordinates are:

Atom 1:  $X_1, Y_1, Z_1$ ,      Atom 2:  $X_2, Y_2, Z_2$ ,      etc. ....

The extensions are the differences in the positions and the equilibrium positions for that atom:

Atom 1:  $x_1 = X_1 - X_{1,eq}$        $y_1 = Y_1 - Y_{1,eq}$        $z_1 = Z_1 - Z_{1,eq}$       (8)

Atom 2:  $x_2 = X_2 - X_{2,eq}$        $y_2 = Y_2 - Y_{2,eq}$        $z_2 = Z_2 - Z_{2,eq}$

Atom i:  $x_i = X_i - X_{i,eq}$        $y_i = Y_i - Y_{i,eq}$        $z_i = Z_i - Z_{i,eq}$

Where  $X_{i,eq}$ ,  $Y_{i,eq}$ , and  $Z_{i,eq}$  are the equilibrium (energy minimized) positions for atom i. For example, if  $x_1$ ,  $y_1$ , and  $z_1$  are all zero, then atom 1 is at its equilibrium position. Molecular mechanics or molecular orbital calculations are used to find the potential energy of the molecule as a function of the position of each atom,  $V(x_1, y_1, z_1, x_2, y_2, z_2, x_3, y_3, z_3, \dots, x_N, y_N, z_N)$ .

The second derivative of the potential energy can then be used to calculate the force constants, Eq 3. However, there are now  $3N \times 3N$  possible second derivatives and their corresponding force constants. For example,

$$\frac{\partial^2 V}{\partial x_1^2} = k_{xx}^{11} \quad (9)$$

is the change of the force on atom 1 in the x-direction when you move atom 1 in the x-direction. Similarly,

$$\frac{\partial^2 V}{\partial x_1 \partial y_2} = k_{xy}^{12} \quad (10)$$

is the change of the force on atom 1 in the x-direction when you move atom 2 in the y-direction. The various types of force constants are shown in Figure 3.

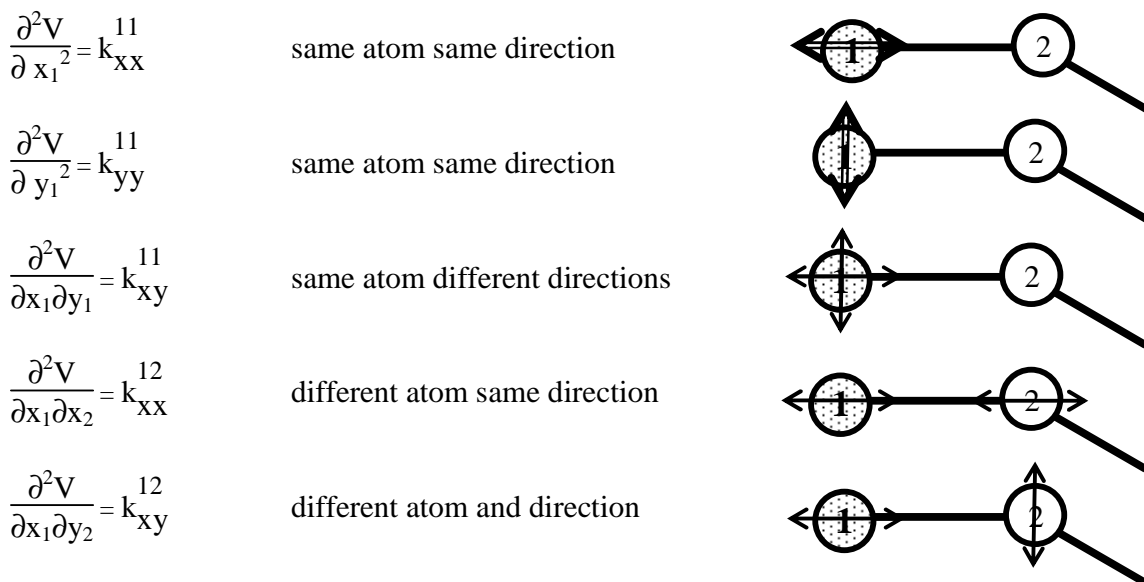


Figure 3. Types of second derivatives and force constants

These force constants are not the force constants for individual bonds, they are force constants for the motion of a single atom subject to all its neighbors, whether directly bonded or not. The

complete list of these force constants is called the Hessian, which is a  $3N \times 3N$  matrix. Eq 7 is then applied for each force constant.<sup>1,2</sup>

$$\begin{aligned}
 -4\pi^2\nu^2 m_1x_1 &= -k_{XX}^{11}x_1 - k_{XY}^{11}y_1 - k_{XZ}^{11}z_1 - k_{XX}^{12}x_2 - k_{XY}^{12}y_2 - \dots - k_{XZ}^{1N}z_N & (11) \\
 -4\pi^2\nu^2 m_1y_1 &= -k_{YX}^{11}x_1 - k_{YY}^{11}y_1 - k_{YZ}^{11}z_1 - k_{YX}^{12}x_2 - k_{YY}^{12}y_2 - \dots - k_{YZ}^{1N}z_N \\
 & \vdots \\
 -4\pi^2\nu^2 m_2x_2 &= -k_{XX}^{21}x_1 - k_{XY}^{21}y_1 - k_{XZ}^{21}z_1 - k_{XX}^{22}x_2 - k_{XY}^{22}y_2 - \dots - k_{XZ}^{2N}z_N \\
 & \vdots \\
 -4\pi^2\nu^2 m_Nz_N &= -k_{ZX}^{N1}x_1 - k_{ZY}^{N1}y_1 - k_{ZZ}^{N1}z_1 - k_{ZX}^{N2}x_2 - k_{ZY}^{N2}y_2 - \dots - k_{ZZ}^{NN}z_N
 \end{aligned}$$

In words, the right-hand sides of the above equations simply state that the total force on atom  $i$  is the sum of the forces of all the atoms on atom  $i$ . In addition, we need to keep track of the  $x$ ,  $y$ , and  $z$  directions for each atom. There are a total of  $3N \times 3N$  terms on the right. All these terms are confusing. A simple example will help at this point.

For our example consider a symmetrical linear triatomic molecule that can only vibrate along the  $x$ -axis, Figure 4.  $\text{CO}_2$  is a good example of a symmetrical linear triatomic.

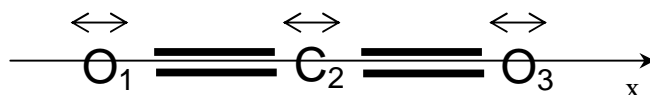


Figure 4. A symmetrical triatomic molecule with vibrations limited along the internuclear axis.

Because we have limited the vibrations to the  $x$ -axis, which is the internuclear axis, this model will provide the symmetric and asymmetric stretching modes, only. Eqs 11 then reduce to

$$-4\pi^2\nu^2 m_1x_1 = -k_{XX}^{11}x_1 - k_{XX}^{12}x_2 - k_{XX}^{13}x_3 \quad (12)$$

$$-4\pi^2\nu^2 m_2x_2 = -k_{XX}^{21}x_1 - k_{XX}^{22}x_2 - k_{XX}^{23}x_3 \quad (13)$$

$$-4\pi^2\nu^2 m_3x_3 = -k_{XX}^{31}x_1 - k_{XX}^{32}x_2 - k_{XX}^{33}x_3 \quad (14)$$

since we only need to keep the  $x$ -terms. Several numerical techniques are available to solve linear sets of simultaneous equations such as this. Conventionally, however, the problem is simplified by converting to mass weighted coordinates, for example:

$$\tilde{x}_1 = \sqrt{m_1} x_1 \quad \tilde{x}_2 = \sqrt{m_2} x_2 \quad , \text{ etc.} \quad (15)$$

and mass weighted force constants:

$$\tilde{k}_{XX}^{12} = \frac{k_{XX}^{12}}{\sqrt{m_1}\sqrt{m_2}} \quad (16)$$

In the new mass weighted coordinates, Eqs 12-14 become:

$$-4\pi^2\nu^2 \tilde{x}_1 = -\tilde{k}_{XX}^{11} \tilde{x}_1 - \tilde{k}_{XX}^{12} \tilde{x}_2 - \tilde{k}_{XX}^{13} \tilde{x}_3 \quad (17)$$

$$-4\pi^2\nu^2 \tilde{x}_2 = -\tilde{k}_{XX}^{21} \tilde{x}_1 - \tilde{k}_{XX}^{22} \tilde{x}_2 - \tilde{k}_{XX}^{23} \tilde{x}_3 \quad (18)$$

$$-4\pi^2\nu^2 \tilde{x}_3 = -\tilde{k}_{XX}^{31} \tilde{x}_1 - \tilde{k}_{XX}^{32} \tilde{x}_2 - \tilde{k}_{XX}^{33} \tilde{x}_3 \quad (19)$$

For example, we can show that Eq 17 is equivalent to Eq 11, by substituting Eqs 15 and 16 into Eq 17.

$$-4\pi^2\nu^2 \sqrt{m_1} x_1 = -\frac{k_{XX}^{11}}{\sqrt{m_1}\sqrt{m_1}} \sqrt{m_1} x_1 - \frac{k_{XX}^{12}}{\sqrt{m_1}\sqrt{m_2}} \sqrt{m_2} x_2 - \frac{k_{XX}^{13}}{\sqrt{m_1}\sqrt{m_3}} \sqrt{m_3} x_3 \quad (20)$$

Canceling mass terms and multiplying both sides by  $\sqrt{m_1}$  gives Eq 11.

Eq 17-19 are most easily written in the equivalent matrix form:

$$-\begin{pmatrix} \frac{k_{XX}^{11}}{\sqrt{m_1}\sqrt{m_1}} & \frac{k_{XX}^{12}}{\sqrt{m_1}\sqrt{m_2}} & \frac{k_{XX}^{13}}{\sqrt{m_1}\sqrt{m_3}} \\ \frac{k_{XX}^{21}}{\sqrt{m_2}\sqrt{m_1}} & \frac{k_{XX}^{22}}{\sqrt{m_2}\sqrt{m_2}} & \frac{k_{XX}^{23}}{\sqrt{m_2}\sqrt{m_3}} \\ \frac{k_{XX}^{31}}{\sqrt{m_3}\sqrt{m_1}} & \frac{k_{XX}^{32}}{\sqrt{m_3}\sqrt{m_2}} & \frac{k_{XX}^{33}}{\sqrt{m_3}\sqrt{m_3}} \end{pmatrix} \begin{pmatrix} \tilde{x}_1 \\ \tilde{x}_2 \\ \tilde{x}_3 \end{pmatrix} = -4\pi^2\nu^2 \begin{pmatrix} \tilde{x}_1 \\ \tilde{x}_2 \\ \tilde{x}_3 \end{pmatrix} \quad (21)$$

The mass weighted force constants give a symmetric matrix. In other words, the corresponding off diagonal elements are equal. Eq 21 is an eigenvalue-eigenvector equation. The eigenvalues are the negative of the squared normal mode frequencies. The eigenvectors are the mass weighted normal coordinate displacements (see Appendix). Many efficient algorithms exist for solving eigenvalue equations.<sup>6</sup>

*The Hessian and Energy Minimization* The matrix of force constants is the matrix of the second derivatives of the potential energy. This matrix is also called the Hessian. The Hessian also plays a central role in energy minimization techniques. The use of the Hessian is necessary to minimize the energy of all the atoms in the molecule.

### Numerical Example for Carbon Dioxide

The CO<sub>2</sub> example will provide some insight for understanding Eq 21. First, we need to discuss units. The fundamental vibration frequency for a harmonic oscillator is

$$\nu_o = \frac{1}{2\pi} \sqrt{\frac{k}{m}} \quad \text{or} \quad 4\pi^2\nu^2 = \frac{k}{m} \quad (22)$$

with k in N m<sup>-1</sup> and m in kg molecule<sup>-1</sup>. Normally, vibrational spectra are plotted versus wavenumber, instead of frequency. To convert to wavenumbers,  $\tilde{\nu}$  :

$$\tilde{\nu} = \frac{1}{\lambda} \quad \text{or} \quad \nu = \frac{c}{\lambda} = c\tilde{\nu} \quad (23)$$

If  $\tilde{\nu}$  is in  $\text{cm}^{-1}$ ,  $c$  should be given in  $\text{cm s}^{-1}$ . Using  $\tilde{\nu}$  in  $\text{cm}^{-1}$  and  $m$  in  $\text{g mol}^{-1}$ , Eq 22 becomes:

$$\frac{4\pi^2 c^2 \tilde{\nu}^2}{1000 \text{ g/kg } N_A} = \frac{k}{m} \quad (24)$$

or solving for the frequency squared in wavenumbers gives a convenient conversion factor

$$\tilde{\nu}^2 = \frac{k/m}{5.8921 \times 10^{-5}} \quad (25)$$

Now for our example. The  $\text{CO}_2$  stretches are experimentally measured to be  $1340 \text{ cm}^{-1}$  for the symmetric stretch and  $2349 \text{ cm}^{-1}$  for the asymmetric stretch, Fig. 2. Lets roughly see if we can calculate these values through a normal mode analysis using our simplified one-dimensional model. First we will need all the force constants. However, some force constants are related by symmetry, since the left and right hand sides of the molecule are the same.

$$\text{By symmetry :} \quad k_{\text{XX}}^{11} = k_{\text{XX}}^{33} \quad k_{\text{XX}}^{12} = k_{\text{XX}}^{23} \quad (26)$$

The terms that exchange the atom labels are also equivalent, since atom 1 interacting with atom 2 gives the same result as atom 2 interacting with atom 1. In matrix terms, these corresponding off-diagonal terms are equivalent for a symmetric matrix.

$$\text{Symmetric matrix:} \quad k_{\text{XX}}^{12} = k_{\text{XX}}^{21} \quad k_{\text{XX}}^{23} = k_{\text{XX}}^{32} \quad (27)$$

These equivalences leave four force constants that we need to guess. First focus on atom 1. By trial an error, a good guess for

$$k_{\text{XX}}^{11} = 1600 \text{ N m}^{-1} \quad (28)$$

This force constant gives the restoring force as atom 1 is moved. The resorting force,  $F = -kx$ , will be negative, pulling the atom back to its equilibrium position. Another way to state this is if atom 1 is moved forward to shorten the bond length then atom 1 will try to move back to keep the bond length constant. A reasonable guess for

$$k_{\text{XX}}^{12} = -k_{\text{XX}}^{11} \quad (29)$$

Here the 12-force constant is negative, and the restoring force,  $F = -kx$ , is positive. This positive force results because as you move atom 1's neighbor, atom 1 will try to follow along in the same direction to keep the bond length constant. The absolute value of the two force constants is the same since moving either atom 1 or atom 2 has the same effect on the bond length and, therefore, the force on atom 1. Now focus on atom 2. Lets guess that it is twice as hard to move atom 2 as it is to move atom 1, since moving atom 2 effects two bonds:

$$k_{\text{XX}}^{22} = 2 k_{\text{XX}}^{11} = 3200 \text{ N m}^{-1} \quad (30)$$

Finally, we will assume that

$$k_{\text{XX}}^{13} = 0. \quad (31)$$

We assume that atom 3 doesn't affect atom 1 significantly because the two atoms aren't directly bonded. Substituting Eqs 26-31 into Eq 21 gives the mass weighted force constant matrix. The row and columns correspond to the three different atoms, O<sub>1</sub>, C<sub>2</sub>, and O<sub>3</sub>, respectively.

$$\begin{matrix} & \begin{matrix} \text{O}_1 & \text{C}_2 & \text{O}_3 \end{matrix} \\ \begin{matrix} \text{O}_1 \\ \text{C}_2 \\ \text{O}_3 \end{matrix} & \begin{pmatrix} \frac{1600}{\sqrt{16}\sqrt{16}} & -\frac{1600}{\sqrt{16}\sqrt{12}} & 0 \\ -\frac{1600}{\sqrt{12}\sqrt{16}} & \frac{3200}{\sqrt{12}\sqrt{12}} & -\frac{1600}{\sqrt{12}\sqrt{16}} \\ 0 & -\frac{1600}{\sqrt{16}\sqrt{12}} & \frac{1600}{\sqrt{16}\sqrt{16}} \end{pmatrix} \end{matrix} = \begin{pmatrix} -100 & 115.47 & 0 \\ 115.47 & -266.67 & 115.47 \\ 0 & 115.47 & -100 \end{pmatrix} \quad (30)$$

The "eigen" Web applet is available to solve the eigenvalue problem.<sup>7</sup> Computer algebra programs like Maple and Mathematica are also handy for solving eigenvalue problems. The output of the "eigen" applet is shown below. The eigenvalues are listed with "E=". The normal mode frequencies are easily calculated using the units conversion factor from Eq 25.

Eigenvector 1: E=-0.000976903 ≈ 0

0.603024

0.522229

0.603024

Eigenvector 2: E=-100

-0.707107

0

0.707107

Eigenvector 3: E=-366.669

-0.369272

0.852805

-0.369272

Symmetric stretch:

$$\tilde{\nu} = \sqrt{\frac{100}{5.892 \times 10^{-5}}} = 1303 \text{ cm}^{-1}$$

Asymmetric stretch:

$$\tilde{\nu} = \sqrt{\frac{366.67}{5.892 \times 10^{-5}}} = 2495 \text{ cm}^{-1}$$

(for about 5% errors)

The three numbers below each eigenvalue are the normal coordinates. For example, the normal coordinates for the second eigenvector show atom 1 (-0.707) moving in the opposite direction as atom 3 (0.707), while atom 2 remains stationary (0). For the CO<sub>2</sub> example we have motion only in the x-direction, so there are only three coordinates listed, one for each atom. In general to display the motion of the atoms during the vibration, the atom coordinates are calculated for atom i as:

$$X_i = X_{i,\text{eq}} + \frac{\tilde{x}_i}{\sqrt{m_i}} q \quad Y_i = Y_{i,\text{eq}} + \frac{\tilde{y}_i}{\sqrt{m_i}} q \quad Z_i = Z_{i,\text{eq}} + \frac{\tilde{z}_i}{\sqrt{m_i}} q \quad (33)$$

where  $q = \sin(2\pi\nu t)$ . For example, for the asymmetric stretch for CO<sub>2</sub> for the first O atom,

$$X_1 = X_{1,\text{eq}} + -0.369 \sin(2\pi\nu t) \quad (34)$$

$$Y_1 = Y_{1,\text{eq}} + 0.853 \sin(2\pi\nu t)$$

$$Z_1 = Z_{1,\text{eq}} + -0.369 \sin(2\pi\nu t)$$

The first eigenvalue is zero, because it corresponds to the motion of the center of mass of the molecule in the x-direction. You can also tell that the first eigenvector is for the motion of the molecule as a whole because all the normal coordinates have the same sign, that is all the atoms

are traveling in the same direction. For fully three-dimensional problems, the first 5 eigenvalues, for linear molecules, or 6 eigenvalues, for nonlinear molecules, will correspond to translation and rotation. (Spartan, however, doesn't show you these first eigenvalues, but other programs do.)

You can tell that eigenvalue 2 is for the symmetric stretch, since the normal coordinates for the oxygen atoms are opposite to each other (i.e.  $-0.707$  and  $0.707$  respectively) and the carbon atom doesn't move. In the asymmetric stretch, eigenvalue 3, the oxygen atoms move backward while the carbon atom moves forward.

How well did our simplified model work? The symmetric stretch is a little low and the asymmetric stretch is a little too high for a combined error of about 5%. It doesn't make sense to try to get the results to agree any better. We have neglected the bending vibration in our treatment, and using a molecular mechanics or molecular orbital program is much more accurate. However, you should try changing the force constant guesses a little to see the effects of each force constant. If you make a change that is not consistent with the force field in a real molecule, then the first eigenvalue will increase. Better sets of guesses give a smaller first eigenvalue.

### Normal Mode Analysis and Molecular Mechanics and Molecular Orbital Calculations

Our simple example of  $\text{CO}_2$  is not representative of the accuracy available for predicting normal mode frequencies. Molecular mechanics and molecular orbital calculations can quite accurately predict the frequencies for the vibrations of complex molecules. Results for  $\text{CO}_2$  are given in Table I. If you haven't gotten to molecular orbital theory yet, suffice it to say that you can calculate normal mode frequencies quite accurately.<sup>8,9</sup>

Table I. Molecular Mechanics and Molecular Orbital Based Normal Mode Analysis for  $\text{CO}_2$ .

Literature	MMFF	AM1	PM3	HF/ 6-31G*	MP2/ 6-311G**	pBP/DN*	BP/DN*	B3LYP/ 6-311G(d)
667	538	526	522	744	656	637	638	666
667	538	526	523	744	656	637	638	666
1340	912	1480	1408	1518	1344	1323	1319	1377
2349	1746	2565	2387	2585	2461	2363	2349	2438
error %	24.1%	15.5%	12.5%	11.6%	2.1%	2.7%	2.5%	1.7%

The MMFF molecular mechanics calculation poorly represents the accuracy for molecular mechanics in general, since the force field parameters aren't optimized for the unusual C=O bonds in  $\text{CO}_2$ . Molecular mechanics calculations are common and very useful for large biomolecules. Semi-empirical calculations at the AM1 or PM3 level are more accurate. Hartree-Fock, HF, calculations are even better, especially when MP2 electron-electron correlations are taken into account. Density functional methods like pBP, BP or B3LYP are now the best choice for careful analysis. Molecular orbital calculations are indispensable for helping to assign the vibration bands in Infrared and Raman spectroscopy.

### Anharmonicity

The preceding discussions assume all the vibrations are purely harmonic. Our treatment of molecular mechanics force fields showed that anharmonic corrections are often important for real molecules. What is the effect of anharmonicity on vibrational spectra and normal mode calculations? For weak anharmonicity, vibrational spectra also show overtones and sum and difference bands. Overtones are at integer multiples of the fundamental frequency,  $n\tilde{\nu}_A$ . Sum and



difference bands occur at  $\tilde{\nu}_A + \tilde{\nu}_B$ , and  $\tilde{\nu}_A - \tilde{\nu}_B$ , respectively. Frequencies from *ab initio* molecular orbital calculations are normally multiplied by 0.9 to correct for anharmonicity. In Table I, if the HF/6-31G\* values are multiplied by 0.9, the average deviation drops to 1%. Frequencies from molecular mechanics are usually too approximate to warrant anharmonicity corrections when comparing with vibrational spectra.

For strong anharmonicity, such as occurs for very loose and floppy vibrations, a more refined treatment is necessary.<sup>10</sup> Such vibrations include bond torsions that have low energy barriers, ring vibrations in large ring systems, and vibrations in hydrogen-bonded systems and molecular complexes. Unfortunately, such vibrations are often the most interesting, especially in studies of proteins and nucleic acids. Treating very flexible, low energy vibrations in biomolecules is an active area of current study.<sup>11-15</sup>

### Vibrations and Thermodynamics

Vibrations increase the Gibbs Free Energy of a substance. Vibrational enthalpy and entropy calculations are very useful in drug discovery for assessing the Gibbs Free Energy of binding.<sup>16</sup> Vibrations also play a central role in protein folding and protein flexibility.<sup>13-15</sup> The contribution of a vibration to the enthalpy and entropy of a substance is given by<sup>17</sup>

$$H_{\text{vib}} = \frac{1}{2} N_A h \nu_0 + \frac{N_A h \nu_0 e^{-h\nu_0/kT}}{1 - e^{-h\nu_0/kT}} \quad (35)$$

$$S_{\text{vib}} = -R \ln(1 - e^{-h\nu_0/kT}) + \frac{N_A h \nu_0 e^{-h\nu_0/kT}}{T (1 - e^{-h\nu_0/kT})} \quad (36)$$

where  $N_A$  is Avogadro's number,  $\nu_0$  is the frequency of the normal mode,  $h$  is Planck's constant, and  $k$  is Boltzmann's constant =  $R/N_A$ . The  $\frac{1}{2} N_A h \nu_0$  term in the enthalpy is the zero-point vibrational energy, which is the energy of the vibration at absolute zero temperature,  $H_{\text{vib}}(0)$ . Eqs 35 and 36 are summed for each normal mode vibration. Following a normal mode analysis, then, it is very easy to calculate the Gibbs Free Energy of a substance.

A specific example will help to clarify the importance of normal mode analysis in thermodynamic considerations. Consider two different conformations of a molecule, A and B:



Examples include the trans and gauche isomers of butane or two conformations of a large protein. For low frequency vibrations Eq 36 simplifies and the entropy difference reduces to<sup>13</sup>

$$\Delta S_{\text{vib,conf}} = R \ln \left( \frac{2\pi\nu_{A1} 2\pi\nu_{A2} 2\pi\nu_{A3} \dots}{2\pi\nu_{B1} 2\pi\nu_{B2} 2\pi\nu_{B3} \dots} \right) \quad (38)$$

This entropy difference is called the configurational entropy difference. The numerator is the product of the low frequency normal modes for A, and the denominator is the product of the low frequency normal modes for B. Therefore, if B has lower frequency modes, the entropy of B will be larger and the entropy difference will favor B. In other words, the lower the mode frequencies, the more the conformation can rattle around, and the more that conformation is favored.

In molecular mechanics the enthalpy of formation of a molecule is given as:

$$\Delta_f H^\circ = \frac{3}{2} RT + \frac{3}{2} RT + RT + \text{bond energy} + \text{steric energy} + \text{vibrational contributions} \quad (41)$$

Normal mode analysis gives us the tools to calculate the vibrational contributions directly using Eq 35. For MM2 calculations a series of approximations are made for Eq 41. The zero point energy is often neglected in classical simulations, leaving the temperature dependent contribution from the second term of the vibrational enthalpy, Eq 35. This contribution to the enthalpy is plotted as a function of vibrational frequency in Figure 5.

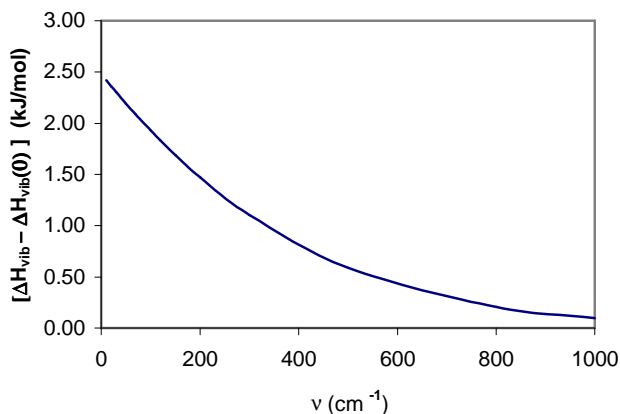


Figure 5. Contribution of a vibration to the Enthalpy of formation of a molecule above the zero point energy.

The contribution of vibrations becomes negligible for frequencies greater than about 500 cm<sup>-1</sup>. Therefore, only low frequency vibrations contribute strongly. Torsional motions around freely rotating bonds are often the lowest frequency normal modes in molecules. Other low frequency vibrations are often ignored. The vibrational contributions can then be approximated by torsional increments for each freely rotating bond:

$$\Delta_f H^\circ = \frac{3}{2}RT + \frac{3}{2}RT + RT + \text{bond energy} + \text{steric energy} + \text{torsional increments} \quad (42)$$

Our treatment of normal modes now will allow us to discuss these approximations in detail. Examples of low frequency vibrations are bending vibrations and ring vibrations as well as freely rotating bond torsions. Clearly for careful calculations more contributions than just the torsional increments for freely rotating bonds are necessary. In addition, Eq 42 completely neglects the zero point energies. Molecular orbital and molecular mechanics programs readily provide these thermodynamic contributions when normal mode analyses are done, so we don't need to make the extreme approximations inherent in Eq 42.

### Molecular Dynamics and Normal Mode Analysis

Molecular dynamics and normal mode analysis are really quite similar. Both include the kinetic and potential energy for the molecule. The force field is the same. They both calculate the Hessian and then integrate Newton's Laws of motion. The motions that you see in molecular dynamics simulations are in fact the normal modes of the molecule. The fluctuations of the atom positions in a molecular dynamics run can be used to extract the normal mode frequencies.<sup>14,18</sup>

The difference between molecular dynamics and normal mode analysis is that the equations of motion are integrated numerically in dynamics simulations, but sinusoidal solutions are assumed for normal mode analysis. In addition, in molecular dynamics the motions of all the normal modes are studied simultaneously, while in normal mode analysis one mode is studied at a time.

The techniques have their strengths and weaknesses. Eqns 35 and 36 show that the link between normal mode analysis and thermodynamics is direct and straightforward. Thermodynamic properties can be calculated from dynamics runs, but particular care must be taken to ensure adequate statistical sampling (i.e. using long time simulations). On the other hand, molecular dynamics more easily handles anharmonicity and explicit solvation.

### Valence Force Field Solutions

Normal mode analysis is particularly important in molecular spectroscopy. As a consequence, valence force field solutions have been worked out for many small molecule geometries. These solutions take a different approach to the problem. The force constants that are used are the force constants for individual bonds, rather than the force constants for moving atoms, e.g. Eq 9. Focussing on the bond force constants more closely corresponds to our “chemical intuition.” Another advantage of valence force field calculations is that algebraic solutions can be written. For example, for a symmetric triatomic molecule, where  $m_1 = m_3$ , the internal coordinates are defined as

$$\begin{aligned} q_1 &= r_{12} - r_o \\ q_2 &= r_{23} - r_o \\ \delta &= \theta - \theta_o \end{aligned} \quad (43)$$

The  $q$ 's are bond stretching terms and  $\delta$  is the bond bending term;  $r_{12}$  is the distance between atoms 1 and 2,  $r_o$  is the equilibrium bond length,  $\theta$  is the bond angle, and  $\theta_o$  is the equilibrium bond angle. The potential energy is chosen as:

$$V = \frac{1}{2} k_1 q_1^2 + \frac{1}{2} k_1 q_2^2 + k_\delta \delta^2 \quad (44)$$

The  $k_1$  force constant is for stretching the 1-2 or 2-3 bond. For  $\text{CO}_2$  this is the C=O stretch. The force constant for bond bending is  $k_\delta$ . The Hessian second derivatives can be obtained by taking explicit derivatives of Eq 44. For this potential energy form the normal mode frequencies are given by<sup>3,4</sup>

$$4\pi^2 v_{\text{asym}}^2 = \left( 1 + \frac{2m_1}{m_2} \sin^2 \frac{\theta_o}{2} \right) \frac{k_1}{m_1} \quad (45)$$

$$4\pi^2 (v_{\text{sym}}^2 + v_{\text{bnd}}^2) = \left( 1 + \frac{2m_1}{m_2} \cos^2 \frac{\theta_o}{2} \right) \frac{k_1}{m_1} + \frac{2}{m_1} \left( 1 + \frac{2m_1}{m_2} \sin^2 \frac{\theta_o}{2} \right) \frac{k_\delta}{r_o^2} \quad (46)$$

$$16\pi^4 (v_{\text{sym}}^2 v_{\text{bnd}}^2) = 2 \left( 1 + \frac{2m_1}{m_2} \right) \frac{k_1}{m_1^2} \frac{k_\delta}{r_o^2} \quad (47)$$

Eqs 46 and 47 show that the frequency of the symmetric stretch depends on the bending force constant. As mentioned above, our example for one-dimensional  $\text{CO}_2$  didn't include this effect.

The disadvantage of algebraic solutions is that they depend critically on the details of the potential energy function, e.g. Eq 44. If a stretch-bend interaction or Van der Waals terms are included, as in many molecular mechanics force fields, then Eqs 45-47 are no longer valid. In the early decades of vibrational spectroscopy, it was hoped that solutions to the normal mode problem could be used to determine the force constants for individual bonds, as in Eq 44. However, the dependence of the force constants on such over-simplified potential energy functions causes large errors. The attempt to determine bond force constants directly from spectra has therefore been abandoned. Equations such as 45-47 can still be useful in building our intuition about bond strengths, however the derived force constants must be treated as very approximate and can sometimes be misleading.

## Appendix

We wish to show more clearly the relationship between Eqs 17-19 and the normal coordinates, for the curious. First note that substituting Eq 5 into Eq 7 gives:

$$-4\pi^2 v^2 m A \sin(2\pi vt) = -k A \sin(2\pi vt) \quad (48)$$

Dividing both sides by the sin gives

$$-4\pi^2 v^2 m A = -k A \quad (49)$$

In other words, the equation applies to the time dependence of the vibration and also to the amplitude of the vibration separately. Therefore Eqs 12-14 and 17-19 allow us to solve for the amplitudes of the vibrations, where  $x_i, y_i, z_i$  can be read as the amplitudes of the waves in the  $x, y,$  and  $z$  directions for atom  $i$ . Similarly,  $\tilde{x}_i, \tilde{y}_i, \tilde{z}_i$  can be considered to be the corresponding mass weighted amplitudes. The time dependent values are then:

$$\tilde{x}_i(t) = \tilde{x}_i \sin(2\pi vt) \quad \tilde{y}_i(t) = \tilde{y}_i \sin(2\pi vt) \quad \tilde{z}_i(t) = \tilde{z}_i \sin(2\pi vt) \quad (50)$$

Dropping the "(t)" for convenience and converting back into non-mass weighted coordinates gives:

$$x_i = \frac{\tilde{x}_i}{\sqrt{m_i}} \sin(2\pi vt) \quad y_i = \frac{\tilde{y}_i}{\sqrt{m_i}} \sin(2\pi vt) \quad z_i = \frac{\tilde{z}_i}{\sqrt{m_i}} \sin(2\pi vt) \quad (51)$$

Converting from extensions into final coordinates using Eq 8 gives Eq 33.

Now you may have noted that Eqs 17-19 involve four unknowns ( $v, \tilde{x}_i, \tilde{y}_i,$  and  $\tilde{z}_i$ ) but only three equations. So to obtain unique solutions, some more information is necessary. We must add the requirement that the center of mass can't move:

$$m_1 x_1 + m_2 x_2 + m_3 x_3 = 0 \quad (52)$$

or equivalently in mass weighted coordinates:

$$\sqrt{m_1} \tilde{x}_1 + \sqrt{m_2} \tilde{x}_2 + \sqrt{m_3} \tilde{x}_3 = 0 \quad (53)$$

As we solve for each successive normal mode we also need to ensure that the vibrations don't interact. Mathematically this requires that the normal modes are orthogonal. For each pair of normal modes A and B, with normal coordinates  $\tilde{x}_{iA}$  and  $\tilde{x}_{iB}$ , respectively:

$$\tilde{x}_{1A} \tilde{x}_{1B} + \tilde{x}_{2A} \tilde{x}_{2B} + \tilde{x}_{3A} \tilde{x}_{3B} = 0 \quad (54)$$

Taken together, Eqs 17-19 and Eq 53 and 54 provide the unique set of normal modes satisfying the desired characteristics set out in the introduction. Solving these equations as a linear set of simultaneous equations is difficult. Luckily, solving the problem as an eigenvalue-eigenvector equation using Eq 21 automatically satisfies the requirement for orthogonality.

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