Vibrational Dynamics of Atoms in Proteins

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I. ABSTRACT

Biological macromolecules expand with increasing temperature and this dynamic expansion is associated with the onset of function. The expansion is typically characterized by the mean square vibrational displacement (MSD), \( \langle u^2 \rangle \), of specific atoms such as hydrogen within the macromolecules. We show that the observed expansion and change in slope of \( \langle u^2 \rangle \) with temperature at a dynamical transition temperature, \( T_D \), can be reproduced within a simple model of the dynamics, an atom in an anharmonic potential, \( V(u) \). Given \( V(u) \), only the temperature is varied in the model. A simple Gaussian potential or a potential containing a hard wall is particularly effective in reproducing the observed change in the slope of \( \langle u^2 \rangle \) with temperature around \( T_D \).

II. INTRODUCTION

Many biological macromolecules undergo a dynamical transition\(^{1–10} \) or cross-over at a temperature \( T_D \sim 200 – 230 \) K. The cross-over can be characterized by a significant increase in the slope of the mean square displacement (MSD), \( \langle u^2 \rangle \), of atoms in the molecule with temperature at \( T_D \). Above \( T_D \), the \( \langle u^2 \rangle \) is large, the macromolecule is more flexible and atoms in the macromolecule traverse larger distances and sample new environments. This dynamical cross-over is associated with the onset of function or activity in the macromolecule.

In the classical limit and in a harmonic approximation\(^4,9 \), the MSD arising from vibration is \( \langle u^2 \rangle = k_B T/\phi \) where \( k_B \) is the Boltzmann constant, \( T \) is the temperature and \( \phi \) is a harmonic force constant. An increase in slope of \( \langle u^2 \rangle \) vs. \( T \) at \( T \approx T_D \) suggests a reduction in the effective force constant \( \phi \) at \( T \approx T_D \). Close inspection of the data reveals that the slope begins to increase somewhat at lower temperatures \( (T \approx 100 \) K) and the changes with temperature are continuous\(^9 \). However, there remains a marked change in slope at \( T_D \). The magnitude of the change in slope depends on the degree of hydration of the protein\(^2,4–6 \) and many other factors. The observed change in slope can be reproduced in molecular dynamics simulations of proteins\(^1,8 \).

The change in slope is observed in hydrated proteins, in DNA and in RNA. Typical examples are hydrated lysozyme\(^1 \), myoglobin\(^9 \) and purple membrane bacteriorhodopsin\(^2,5 \). The \( \langle u^2 \rangle \) is determined in neutron scattering\(^4,9,10 \), X-ray and Mossbauer spectroscopy\(^10,11 \) and in dielectric spectroscopy\(^5 \). In neutron scattering, the \( \langle u^2 \rangle \) of hydrogen atoms is predominantly observed, usually hydrogen bound in molecules (e.g. methyl groups). In Mossbauer spectroscopy the \( \langle u^2 \rangle \) of \( ^{57}Fe \) is observed. The sudden change in slope of \( \langle u^2 \rangle \) at \( T_D \) has been attributed to a change in the “effective elasticity” of the protein\(^7 \), to a “glass” transition in the protein\(^9,12,13 \), to thermally activated transitions that modify the trapping cages\(^9,14 \) and to a fragile-strong cross-over in the hydration water surrounding the macromolecule\(^15 \).

Our goal is simply to illustrate that a marked change in the slope of \( \langle u^2 \rangle \) with \( T \) can arise from the vibrational dynamics of an atom in an anharmonic potential well. This can arise, for example, in a Gaussian potential well, in which the curvature (effective force constant) decreases with increasing distance of the atom from the minimum of the well (with increasing \( \langle u^2 \rangle \)). In the Gaussian well example, the increase in slope with \( T \) is gradual. However, if the potential has hard wall and soft wall components in it, an abrupt change in slope of \( \langle u^2 \rangle \) with \( T \) can be obtained. We consider a single particle in a 1D well and use the self-consistent harmonic (SCH) theory\(^16–19 \) to describe the dynamics of the particle in the well. The essential feature of the SCH model is that the optimum harmonic force constant \( \phi \) is obtained as the second derivative of the potential averaged over the vibrational distribution of the particle in the well. As the \( \langle u^2 \rangle \) increases, a wider region of the well is sampled and the force constant, \( \phi \), can change (e.g. decrease) with increasing \( \langle u^2 \rangle \). This decrease leads to an increase in slope of \( \langle u^2 \rangle \) with temperature at \( T_D \) as is observed.

III. DYNAMICAL MODEL

To describe the dynamics of a particle in a potential \( V(u) \) we employ the self consistent harmonic (SCH) theory of dynamics\(^16–19 \). In the SCH theory the aim is to determine the harmonic force constant \( \phi \) that best describes the anharmonic dynamics. The harmonic model can be introduced via a trial harmonic Hamiltonian \( H_h \) and density matrix \( \rho_h \). The optimum \( \phi \) can be determined by minimizing the Helmholtz free energy. The result is that the usual harmonic force constant \( \phi(u) = (d^2V/du^2)_{u=0} \), the second derivative evaluated at the minimum of the well \( u = 0 \), is replaced by

\[
\phi = \int du \rho(u) \frac{d^2V(u)}{du^2}, \tag{1}
\]
the second derivative averaged over the vibrational distribution $\rho(u)$ in the well. The distribution is

$$\rho(u) = [2\pi(u^2)]^{-1/2}e^{-u^2/2(u^2)},$$  \hspace{1cm} (2)

a Gaussian since we are assuming a harmonic model. The mean square displacement $\langle u^2 \rangle$ is given by the usual harmonic expression,

$$\langle u^2 \rangle = \frac{\hbar}{2M\omega} \coth\left(\frac{k_BT}{\hbar\omega}\right),$$  \hspace{1cm} (3)

where $M$ is the particle mass and $\omega^2 = \phi/M$ is the harmonic frequency and $\hbar$ is Planck’s constant divided by $2\pi$. In the classical limit, $T \geq \theta_E = h\omega/k_B$, Eq. 3 reduces to

$$\langle u^2 \rangle = \frac{k_BT}{\phi}$$  \hspace{1cm} (4)

Eqs. 1 to 3 constitute the SCH theory. It is implemented by iterating Eqs. 1, 2 and 3 until consistent beginning, for example, with an estimated value of $\langle u^2 \rangle$. The SCH can be derived by summing a class of anharmonic terms as well as by minimizing the free energy or ground state energy at $T=0$ K.

IV. RESULTS

A. Harmonic Potentials

Our model of an atom in a macromolecule is a single particle in a 1D potential well. We begin with a harmonic well to introduce the model and consider low temperature to determine a low temperature model force constant, $\phi_L$, and to set the length scales. The harmonic potential is $V(u) = (1/2)\phi_L u^2$, $d^2V/du^2 = \phi_L$, the oscillator (SHO) frequency is $\omega^2 = \omega_L^2 = \phi_L/M$ and in the classical limit the $\langle u^2 \rangle$ is Eq. 4 with $\phi = \phi_L$. We choose a mass $M = 20$ Amu which is intended to represent hydrogen bonded in a molecule.

At low temperature, $T \lesssim 120$ K, the observed $\langle u^2 \rangle$ versus $T$ in biological macromolecules is well described by a straight line, as in Eq. 4. We choose the low temperature force constant in our model, so that $\langle u^2 \rangle = k_BT/\phi_L$ reproduces the observed straight line $\langle u^2 \rangle_{\text{obs}}$ vs. $T$ at low $T$. We select, arbitrarily, myoglobin hydrated with 0.38 $g$ of $D_2O$ per g of protein as observed by Doster et. al.\textsuperscript{9}. To fix $\phi_L$ we introduce a convenient temperature $T_0$, arbitrarily choosing $T_0 = 240$ K, and extrapolate the observed myoglobin low temperature $\langle u^2 \rangle$ to $T_0$ and determine the length $u_0^2 \equiv \langle u^2 \rangle_{\text{obs}} = k_BT_0/\phi_L$. This extrapolation of the low temperature myoglobin $\langle u^2 \rangle$ data is shown as a solid line in Fig. 1 giving $u_0^2 = 0.1 \text{ A}^2$ at $T_0 = 240$ K. Clearly, the low temperature force constant is $\phi_L/k_B = T_0/u_0^2$. We also use $u_0$ and $T_0$ as convenient length and temperature scales, respectively.

We use $\phi_L/k_B$ as the low temperature force constant in all potentials. When the potential well $V(u)$ is not harmonic, we adjust the parameters in $V(u)$ (in units of $k_B$) so that the low temperature force constant is $(d^2V/du^2)_{u=0} = (\phi_L/k_B) = T_0/u_0^2$. In this way all potentials have the same initial slope of $\langle u^2 \rangle$ vs. $T$ at low temperature and they differ only in their higher temperature behaviour ($T \gtrsim T_0/2$).

FIG. 1: (a) The mean square vibrational displacement, (MSD), $\langle u^2 \rangle$, given by (Eq. 3) of an atom in a harmonic well. The slope of $\langle u^2 \rangle$ vs. $T$ in the classical limit, $T \geq \theta_E$, is given by $\langle u^2 \rangle = k_BT/\phi_L$. We choose the low temperature force constant $\phi_L$ in our model so that it reproduces the observed slope of myoglobin at low temperature, i.e. $u_0^2 = \langle u^2 \rangle_{\text{obs}} = k_BT_0/\phi_L$, where $u_0^2 = 0.1 \text{ A}^2$ is the observed MSD at temperature $T_0$. (b) The vibrational distribution $\rho(x)$ in harmonic well $v(x) = V(u)/k_BT_0$, $x = u/u_0$ at three temperatures.

The inset of Fig. 1a shows the harmonic potential $V(u) = (1/2)\phi_L u^2$ in the dimensionless length...
For a particle in a Gaussian potential, the Schrödinger (SCH) model is the same as the harmonic approximation. The constant $\phi$ for all temperatures where $\langle \phi \rangle$ shows the harmonic potential and vibrational distribution $\rho(x)$ in the Gaussian well at three temperatures.

Fig. 2a shows the $\langle u^2 \rangle$ predicted by the SCH theory for a particle in a Gaussian potential,

$$ V(x) = V(x)/k_B T_0 $$

Using $\phi_L/k_B = T_0/u_0^2$, $v(x) = (1/2)x^2$. Fig. 1b shows the harmonic potential and vibrational distribution $\rho(x) = [2\pi(x^2)]^{-1/2} \exp[-x^2/2\langle x^2 \rangle]$ at three temperatures where $\langle x^2 \rangle = \langle u^2 \rangle/u_0^2$. Since $d^2v(x)/dx^2 = 1$ for all $x$ for the harmonic potential, the SCH force constant $\phi$ given by Eq. 1 remains $\phi = \phi_L$ at all $T$ independent of the width of $\rho(x)$. For a harmonic potential, the SCH model is the same as the harmonic approximation.

### B. Symmetric Potentials

Fig. 2a shows the $\langle u^2 \rangle$ in a potential well composed of two harmonic components characterized by force constants $\phi_L$ and $\phi_H$. The slope crosses over gradually from a low (L) temperature to high (H) temperature value. (b) The $\rho(x)$ for a potential composed of two harmonic components.

$$ V(u) = -A e^{-\alpha u^2}, $$

where $A$ and $\alpha$ are adjustable parameters. In this case $d^2V/du^2$ decreases with increasing $u$ and the SCH force constant $\phi$, given by Eq. 1, decreases with increasing temperature as the vibrational distribution, $\rho(u)$, broadens. The slope of $\langle u^2 \rangle$ vs. $T$ ($\langle u^2 \rangle = k_B T/\phi$) therefore increases with increasing temperature as shown in Fig. 2a. Thus using a simple model of anharmonic effects (e.g. the SCH model) and a simple potential (a Gaussian), a variation of $\langle u^2 \rangle$ with temperature as observed in biological macromolecules can be reproduced. The degree of change in slope of $\langle u^2 \rangle$ vs. $T$ with increasing temperature depends entirely on the parameters chosen in the Gaussian potential. In the example shown in...
Fig. 4: The $\langle u^2 \rangle$ for an atom in a potential well composed of two harmonic components with a barrier separating the two components (see inset). The $\langle u^2 \rangle$ vs. temperature and $\rho(x)$ (not shown) is similar to that in Fig. 3b.

Fig. 2b, the $\rho(x)$ begins to sample regions of $V(x)$ where $d^2V/dx^2$ is quite small (even negative) at a temperature of $T \approx 250$ K. Thus the SCH force constant $\phi$ decreases rapidly with increasing $T$ for $T \gtrsim 250$ K and the slope of $\langle u^2 \rangle = k_B T/\phi$ increases rapidly with increasing $T$ for $T \gtrsim 250$ K.

Fig. 3a shows the MSD $\langle u^2 \rangle$ for a particle in a potential that is the sum of two harmonic potentials as depicted in the inset of Fig. 3a and in Fig. 3b. At low temperature, the slope of $\langle u^2 \rangle$ is set by the large force constant $\phi_L$. This slope is indicated by the short dashed line in Fig. 3a. At high temperature the slope of $\langle u^2 \rangle$ is set by the much smaller force constant $\phi_H$ that characterizes the shallow harmonic well at large values of $x$. The steeper slope of $\langle u^2 \rangle$ at higher temperatures is indicated by the long dashed line in Fig. 3a. The temperature ($T \sim 150$ K) at which the slope crosses over from a low to a higher value depends on the energy at which the $V(x)$ crosses over from a large force constant $\phi_L$ to the smaller one, $\phi_H$. The $\phi_H$ is adjustable. The cross-over from the low (L) to high (H) temperature slope will always be gradual because the distribution $\rho(x)$ continues to sample the steep well potential near $x = 0$ at higher temperature, as shown in Fig. 3b.

In Fig. 4 we show $\langle u^2 \rangle$ for a potential that is again the sum of two harmonic components but with a barrier between the two components. This potential leads to a $\langle u^2 \rangle$ which has the same basic character as that shown in Fig. 3a. Thus introducing a barrier and displacing the minimum of the shallow potentials to finite values of $x$ makes little difference to $\langle u^2 \rangle$. The $\langle u^2 \rangle$ in Fig. 3a and Fig. 4 are very similar probably because both potentials are symmetric about $x = 0$. The $\rho(x)$ are also similar and therefore the $\rho(x)$ for the potential depicted in Fig. 4 is not shown.

FIG. 5: (a) The MSD, $\langle u^2 \rangle$, for a double well potential. The height of the barrier (at $x_B = 0.75$) between the two wells (see inset) is relatively small, $V(x_B)/k_B T_0 \approx 0.2$. (b) The $\rho(x)$ for a particle in a double well potential. The center of $\rho(x)$, $\Delta$ moves from one well ($\Delta = 0$) at $T = 0$ K to the midpoint between the two wells ($\Delta = x_B$) at a relatively low temperature. The slope at high temperature is set by the harmonic well force constant (H) at larger $x$.

C. Asymmetric Potentials

The four potentials $V(x)$ considered so far are symmetric around the origin ($x = 0$), i.e. symmetric around the center of the low temperature well. This means that as temperature is increased, although $\langle x^2 \rangle$ increases, the vibrational distribution $\rho(x)$ remains centered around $x = 0$. We now consider potentials that are asymmetric around $x = 0$. This means that the center point of $\rho(x)$ will change with temperature. To accommodate this we generalize $\rho(x)$ to

$$\rho(x) = [2\pi(x^2)]^{-1/2}e^{-(x-\Delta)^2/2(x^2)}$$

(6)
where as before $\langle x^2 \rangle = \langle u^2 \rangle / u_0^2$. The SCH $\langle x^2 \rangle$ and $\phi$ are obtained as before. The $\Delta$ is obtained by minimizing the potential energy $\langle V(x) \rangle$ as a function of $\Delta$. Since we are in the classical limit, minimization of the free energy reduces to minimization of the potential energy.

Fig. 5 shows the MSD for a particle in a double well potential. The double well potential selected consists of two harmonic wells (with force constant $\phi_L$) separated by a barrier. At low temperature, the particle is confined to the left well ($x = 0$) with $\Delta = 0$, as indicated by the $p(x)$ in Fig. 5b for $T = 60$ K. As temperature is increased the center of the $p(x)$ moves to the right until at high temperature ($T = 240$ K) the $p(x)$ is centered symmetrically between the two wells. In the example shown in Fig. 5, the barrier height between the two wells is relatively small (compared to $k_B T_0$) and $\Delta$ moves from $\Delta = 0$ to the midpoint between the two wells at a relatively low temperature. This double well potential does not reproduce the observed increase in slope of $\langle u^2 \rangle$ with increasing temperature well.

In Fig. 6a we show the MSD for a particle in an asymmetric potential which is intended to simulate a particle near a surface or a wall. The wall on the LHS of the potential is formed by continuing the large low temperature force constant $\phi_L$ (near $x = 0$) to high energy ($\sim 2k_B T_0$). On the RHS, the “barrier height” of the low temperature potential is low. Thus the particle can cross the barrier on the RHS and move to the right away from the wall at higher temperature. The potential on the RHS also has a well with a minimum or “well center” at $x \approx 3$. At higher temperature we anticipate that the particle will move toward the “well center”. As shown in Fig. 6a, the $\langle u^2 \rangle$ increases very rapidly at high temperature ($T \sim 250$ K) with $\langle u^2 \rangle$ vs. $T$ reaching a very steep slope at high temperature. The steep slope is associated with the particle moving rapidly away from the wall as $T$ is increased i.e. $\Delta(T)$ increasing rapidly with $T$ at higher temperature.

The potential shown in Fig. 6 is a simple but very flexible potential which can reproduce a large or small change in slope of $\langle u^2 \rangle$ vs. $T$ with the change in slope taking place at any desired temperature. It could also describe the eventual instability of a protein at an even higher temperature (as can the Gaussian potential). In Fig. 7 we show this potential with parameter (barrier height,
well center and $\phi_H$) selected to reproduce the $\langle u^2 \rangle$ observed by Doster et al.\textsuperscript{9} for hydrated myoglobin. Clearly, the change in slope seen in the data is well reproduced. In this potential, the slope at high temperature is set chiefly by the rate at which the particle is moving away from the wall (by the rate of change of $\Delta(T)$ with $T$) rather from the force constant $\phi_H$ describing the potential well on the RHS away wall. In this sense the physical origin of the slope of $\langle u^2 \rangle$ at higher temperature is quite different from that for the symmetric Gaussian potential shown in Fig. 2.

V. DISCUSSION

There are predominantly two approaches to revealing and understanding the dynamics of proteins. The first is experiment, chiefly neutron scattering experiments. The second is molecular dynamics (MD) simulation. The present work is a middle ground, an analytic approach using a simple model of the dynamics of an atom. The aim of the simple model is to bring understanding, since it surely falls short of being a realistic description of a complex biological macromolecules. The understanding in this case is that the main features of the observed $\langle u^2 \rangle$ versus $T$ can be reproduced by a vibrating particle in an anharmonic potential. The model is simply dynamics. The present dynamical model does not contain any thermally activated, transition rate processes as in the “two-state” model introduced by Frauenfelder et al.\textsuperscript{20}, Keller and Debrunner\textsuperscript{14} and Doster et al.\textsuperscript{9}. It does not contain any diffusive motion.

In the classical limit, which is reached at $T \gtrsim 100$ K, the present MSD is independent of the mass of the particle. The $\langle u^2 \rangle$ depends only on the potential, $V(u)$, selected and the temperature. The observed $\langle u^2 \rangle$ can be reproduced quite accurately using a Gaussian potential or a potential with a wall. In the Gaussian potential, the slope of $\langle u^2 \rangle$ can change rapidly with temperature at a dynamical transition temperature $T_D$, if the second derivative of $V(u)$ changes rapidly with $u$ at energies $V(u) \sim k_B T_D$. That is, if at energies $k_B T_D$, $V(u)$ becomes soft. A marked change in $\langle u^2 \rangle$ versus $T$ will take place at $T_D$ for any potential that has this property. For a potential with a wall, the slope of $\langle u^2 \rangle$ versus $T$ changes at $T_D$ because the particle moves away from the wall at $T \gtrsim T_D$. The slope is large for $T \geq T_D$ because the particle is moving rapidly away from the wall for $T \geq T_D$.

In the present model the change in slope of $\langle u^2 \rangle$ with $T$, with only $T$ itself varying, is captured because the dynamical model is non-perturbative. That is, derivatives of $V(u)$ at displacements $u \geq 0$ (described here by $\rho(u)$) are sampled. A perturbative theory of anharmonic effects in which derivatives of $V(u)$ at $(u = 0)$ only are included would probably not suffice. Also since we are in the classical limit, the vibrational distribution $\rho(u)$ should be interpreted as representing a statistical distribution of the displacements of an ensemble of identical, independent classical particles in the well at temperature, $T$.

The model can be adapted or adjusted to describe a specific protein by adjusting the low temperature force constant $\phi_L$ of the Gaussian is set to reproduce the low temperature slope of $\langle u^2 \rangle$ vs. $T$ in purple membrane (PM). The calculated $\langle u^2 \rangle$ at higher temperature for the Gaussian $V(u)$ reproduces the observed $\langle u^2 \rangle$ for PM (dashed-dotted line) well at higher temperature ($T \gtrsim 200$ K). The vibrational distribution $\rho(x)$ is shown in part (b).

FIG. 8: (a) The calculated MSD $\langle u^2 \rangle$ for a Gaussian potential well (solid line). The low temperature force constant $\phi_L$ of the Gaussian is set to reproduce the low temperature slope of $\langle u^2 \rangle$ vs. $T$ in purple membrane (PM). The calculated $\langle u^2 \rangle$ at higher temperature for the Gaussian $V(u)$ reproduces the observed $\langle u^2 \rangle$ for PM (dashed-dotted line) well at higher temperature ($T \gtrsim 200$ K). The vibrational distribution $\rho(x)$ is shown in part (b).
the observed $\langle u^2 \rangle$ versus $T$ in PM is well reproduced at low and at high temperature using a Gaussian potential. Note that the definition of $\langle u^2 \rangle$ in Refs.[1] and [2] (Fig. 8) for PM is twice the value used in Refs.[9] and [14] (Fig. 7) for myoglobin.

We have also applied the SCH dynamics to the “two-state” model potential introduced by Frauenfelder et al, Keller and Debrunner and Doster et al. This potential coupled with the SCH dynamics did not lead to a $\langle u^2 \rangle$ that agreed well with experiment - essentially because the thermally activated transitions central to this model are not included. Including the thermally activated transitions between the two states, as intended, is essential to obtain the good agreement with experiment that has been obtained using the “two state” model.

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APPENDIX A: THE SELF CONSISTENT HARMONIC THEORY

In this section we derive the self consistent harmonic theory for a single particle of mass $M$ in an arbitrary potential, $V(u)$ used in the present article. The particle is described by the Hamiltonian

$$\hat{H} = \hat{K} + V(u)$$  \hspace{1cm} (A-1)

where $\hat{K} = -(h^2/2M)d^2/du^2$ is the kinetic energy operator. We introduce a model harmonic Hamiltonian

$$\hat{H}_h = \hat{K} + \frac{1}{2} \phi u^2$$  \hspace{1cm} (A-2)

and corresponding harmonic density matrix

$$\rho_h = \frac{e^{-\beta \hat{H}_h}}{Tr(e^{-\beta \hat{H}_h})}$$  \hspace{1cm} (A-3)

where $\beta = (k_B T)^{-1}$. Expectation values evaluated using $\rho_h$ are

$$\langle \hat{O} \rangle_h = Tr(\rho_h \hat{O})$$  \hspace{1cm} (A-4)

where $\hat{O}$ is any operator. The corresponding model harmonic Helmholtz free energy is

$$F_h = \langle \hat{H}_h \rangle_h - TS_h$$  
$$= \langle \hat{H}_h \rangle + (k_B T) Tr(\rho_h \log \rho_h)$$  
$$= k_B T \log 2 \sinh \left( \frac{1}{2} \beta \hbar \omega \right)$$  \hspace{1cm} (A-5)

where $\omega = (\frac{\phi}{\beta})^{1/2}$ is the model simple harmonic oscillator frequency. In terms of $\hat{H}_h$ the particle $\hat{H}$ is

$$\hat{H} = \hat{H}_h + V(u) - \frac{1}{2} \phi u^2.$$  \hspace{1cm} (A-6)

The basic concept is to use $\rho_h$ as a trial or model density matrix with which to evaluate the particle free energy. The trial particle free energy is

$$F_{\text{trial}} = \langle H \rangle_h + (k_B T) Tr(\rho_h \log \rho_h)$$  
$$= F_h + \langle V(u) \rangle_h - \frac{1}{2} \phi \langle u^2 \rangle_h.$$  \hspace{1cm} (A-7)

The $F_{\text{trial}}$ is an upper bound to the exact Helmholtz free energy, the Gibbs-Bogoliubov variational principle. We consider $F_{\text{trial}}$ as a functional of the model harmonic force constant $\phi$ and the MSD $\langle u^2 \rangle_h$. We minimize the $F_{\text{trial}}$ with respect to $\phi$ and $\langle u^2 \rangle_h$ independently holding the other variable constant to find the optimum $\phi$ and $\langle u^2 \rangle_h$. This variation gives

$$\frac{\delta F_{\text{trial}}}{\delta \langle u^2 \rangle_h} = \frac{1}{2} \frac{d^2 V(u)}{du^2} \langle u^2 \rangle_h - \frac{1}{2} \phi = 0$$  \hspace{1cm} (A-8)

$$\frac{\delta F_{\text{trial}}}{\delta \phi} = \frac{1}{2} \left( \frac{\hbar}{2 M \omega} \right) \coth \left( \frac{1}{2} \beta \hbar \omega \right) - \frac{1}{2} \langle u^2 \rangle_h = 0.$$  \hspace{1cm} (A-9)

The first term in Eq. A-8 is obtained by making a Taylor’s expansion of $\langle V(u) \rangle_h$ in Eq. A-7 about $V(0)$, $V(u) = e^{u(d/du)} V(0)$, and a cumulant expression of the exponential $\langle e^{u(d/du)} \rangle_h$. For, a harmonic system with Gaussian distributions, $\langle u \rangle_h = 0$ and all cumulants beyond the second cumulant vanish so that

$$\langle V(u) \rangle_h = \langle e^{u(d/du)} \rangle_h V(0)$$  
$$= e^{\frac{1}{2} \langle u^2 \rangle_h (d^2/du^2)} V(0).$$  \hspace{1cm} (A-10)

Differentiation with respect to $\langle u^2 \rangle_h$ then yields the first term in Eq. A-8 and Eq. A-8 leads immediately to Eq. A-1 with $\langle \rangle_h$ expressed as an average in configuration space. The average in configuration space can be obtained by Fourier transforming $V(u)$ and again using a cumulant expansion,
\[ \langle \nabla^2 V(u) \rangle_h = \nabla^2 \int dq V(q) e^{iqu} \langle e^{i u} \rangle_h \]
\[ = \nabla^2 \int dq V(q) e^{-\frac{1}{2}q^2} \langle u^2 \rangle_h \]
\[ = \int du e^{-\frac{1}{2}u^2} \langle u^2 \rangle_h \nabla^2 V(u) \quad (A-11) \]

where \( d/du \) is denoted by \( \nabla \). The first term in Eq. A-9 is obtained by differentiating Eq. A-5 for \( F_h \) with respect to \( \omega \) using \( \omega^2 = \phi/M \). Eq. A-9 leads immediately to Eq. 3. The \( \phi \) represents the optimum harmonic force constant representing a particle in an anharmonic well \( V(u) \) in which the particle has a MSD \( \langle u^2 \rangle \).