Molecular Dynamics of PAMAM Dendrimers

K.M. Anis Rahman[1], Christopher J. Durning and Nicholas J. Turro
Department of Chemical Engineering and Applied Chemistry
Columbia University, New York, NY 10027.

5/9/1999

Abstract

A series of poly(amido amine) dendrimers were constructed by atomistic simulation under Cerius2 environment on a Silicon Graphics computer. A systematic molecular dynamics calculation has been carried out on energy minimized structure of generations 0 through 6. Several dynamic properties have been predicted. These predictions provide insight about expected behavior of the real system and are useful in designing experiments to measure such properties. For instance, the radii of gyration computed from model structures agree with the experimentally determined values.

Contents:

---

[1] Corresponding email: a.rahman@arphotonics.net

A. Introduction

Molecular dynamics (MD) is a force-field based simulation method that is useful to understand atomic level mechanism of physical phenomena at nonzero temperatures on a picosecond timescale. In contrast, molecular mechanics refers to methods that do not include temperature effects. The usefulness of MD in probing fundamental properties of macromolecules has been recognized by applying it to various systems [1,2]. For instance, it was recognized via MD that the atoms in a protein molecule are in a state of constant motion [1]. Since the timescale of this motion is of the order of picosecond, experimental techniques are not often able to resolve the instantaneous motion of the molecule. Computer simulation tools provide us with the ability to visualise the molecular conformation on this extremely small timescale. For example, Fig. 1 depicts 5 conformations of a generation 3 poly(amidoamine) (PAMAM) dendrimer molecule in vacuum. The last picture (45.7 ps) of Fig. 1 has the lowest energy.

In this article we first review the theoretical premise of MD as implemented by Cerius2 simulation environment[†]. We then report the results of MD calculations of several generations of poly(amido amine) (PAMAM) dendrimers carried out on a Silicon Graphics computer. In particular, the constant-volume/constant-temperature dynamics (also called NVT dynamics) calculations were performed to probe a number of physical properties. The NVT dynamics allow the system to exchange heat with the environment at a controlled temperature and constant volume. The algorithm allows one to control the kinetic

[†] Cerius2 is a registered trade mark of Molecular Simulation Inc.

35 ps

45.1 ps

45.5 ps

45.6 ps

45.7 ps
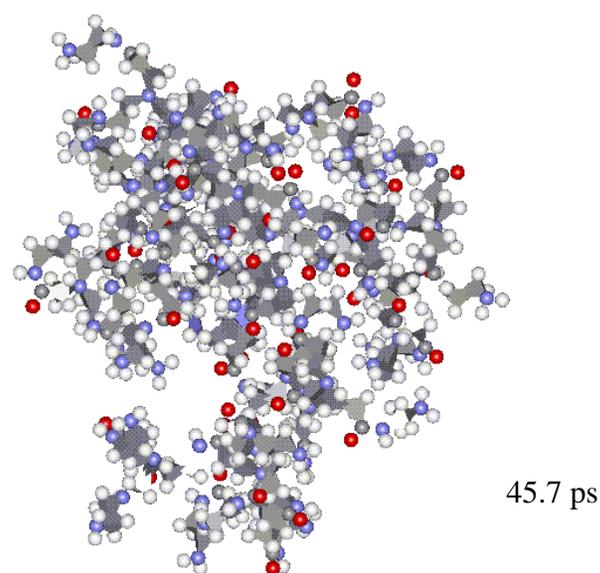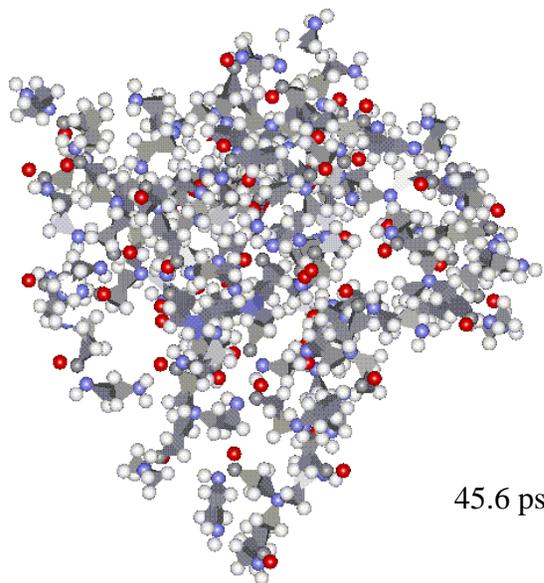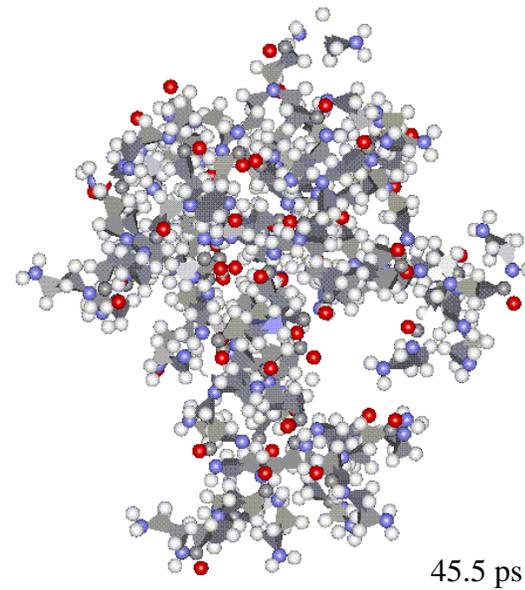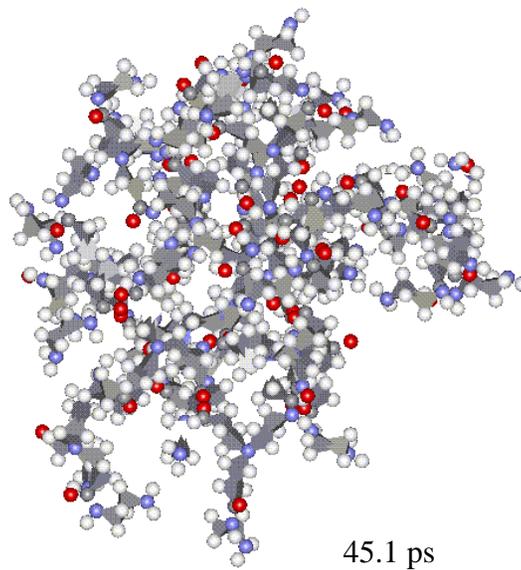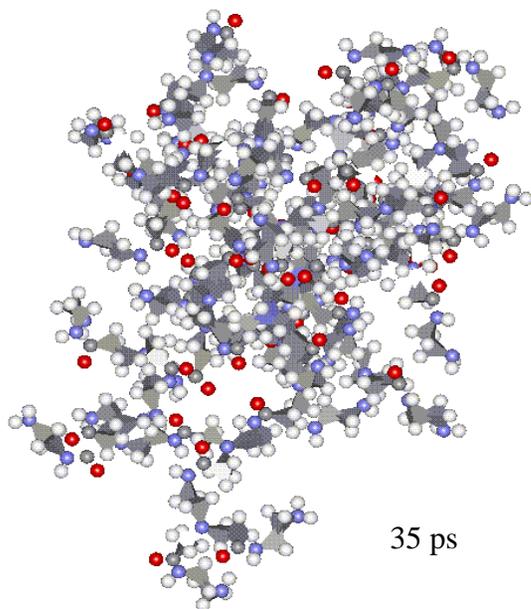
temperature of a system to quickly bring it to equilibrium at a given temperature or, alternatively, one can control the thermodynamic temperature to generate the correct statistical ensemble, so that probability of occurrence of a certain configuration obeys the laws of statistical mechanics. The initial input temperature is used for generating a Maxwell-Boltzmann distribution of initial atomic velocities. Velocities are assigned randomly to individual atoms so that the distribution is around the specified target temperature.

Once a dynamics session is run successfully, the results (stored in a "trajectory" file) then can be analyzed to calculate a number of physical quantities. Several types of analyses can be performed. The list include statistical analysis of properties, calculation of diffusion constants from mean-square displacements, calculation of the dipole-dipole autocorrelation function and power spectrum, and analysis of property fluctuations. Data can also be analyzed to obtain the velocity autocorrelation function and power spectrum. Structural analysis can also be performed, where the radial distribution function is calculated and the structure factor is obtained from Fourier transform of the radial distribution function.

B. A Review of Molecular Dynamics Method

In this section we present a general review of the key components of MD method. The aim here is to gain a "feeling" about subsequent computation, therefore, details have been omitted. The complete mathematical description of a molecule, including both quantum mechanical and relativistic effects, is a formidable problem, due to the small scales and large velocities. However, molecular mechanics and dynamics are based on empirical data that implicitly incorporate all the relativistic and quantum effects. A given problem, in general, is described by the nonrelativistic, time-independent form of the Schrödinger equation,

$$H\Psi(R,r) = E\Psi(R,r)\,, \qquad (1)$$

where, H is the Hamiltonian for the system, E is the energy and ψ is the wavefunction, R is the coordinate of nucleus and r is the coordinate of electron.

Eq. (1) is quite general but too complex for any practical numerical computation. Since the electrons are several thousands of times lighter than the nuclei, and therefore possess a much faster motion, Born and Oppenheimer (1927) proposed that the motion of the electrons can be decoupled from that of the nuclei, giving two separate equations. The first equation describes the electronic motion:

$$H\Psi(r;R) = E\Psi(r;R) \qquad (2)$$

and depends only parametrically on the positions of the nuclei. Eq (2) defines an energy $E(R)$, which is a function of only the coordinates of the nuclei. This energy is usually called the *potential energy surface*. The second equation then describes the motion of the nuclei on this potential energy surface $E(R)$:

$$H\Phi(R) = E\Phi(R) \qquad (3)$$

A direct solution of Eq. (2) is the area of *ab initio* quantum chemical computation. There are many codes that provide such *ab initio* computation facility, such as Gaussian, CADPAC, Hondo, GAMESS, DMol, and Turbomole. Semiempirical codes such as ZINDO, MNDO, MINDO, MOPAC, and AMPAC also solve Eq. (2), but they approximate many of the integrals with empirical functions. The common feature of these programs, though, is that they solve for the electronic wavefunction and energy as a function of nuclear coordinates. In contrast,

simulation engines provide an empirical fit to the potential energy surface.

B. 1. Empirical Fit to the Potential Energy Surface

Solution of Eq. (3) provides the structure or time evolution of a model. As written, Eq. (3) is the Schrödinger equation for the motion of the nuclei on the potential energy surface. In principle, Eq. (2) could be solved for the potential energy E, and then Eq. (3) could be solved. However, the effort required to solve Eq. (2) is extremely large, so usually an empirical fit to the potential energy surface, commonly called a forcefield (V), is used. Since the nuclei are relatively heavy objects, quantum mechanical effects are often insignificant, in which case Eq. (3) can be replaced by Newton's equation of motion:

$$-\frac{dV}{dr} = m\frac{d^2R}{dt^2} \qquad (4)$$

B. 2. Molecular Dynamics and Mechanics

The solution of Eq. (4) using an empirical fit to the potential energy surface $E(R)$ is called molecular dynamics (MD). On the other hand, molecular mechanics ignores the time evolution of the system and focuses on finding particular geometries and their associated energies (commonly known as *conformation*) and other static properties, such as, equilibrium structures, transition states, relative energies, and harmonic vibrational frequencies. Since MD computation process keeps track of the system configuration at each step of evolution, a series of dynamic properties can be obtained by analyzing the trajectories.

B. 3. The forcefield

The set of energy components used for the empirical fit to the potential energy surface is called the *forcefield*. It contains the necessary building blocks for the calculations of energy and

force. The goal of a forcefield is to describe entire classes of molecules with reasonable accuracy. The forcefield engine interpolates and extrapolates from the empirical data of the small set of models used to parameterize the forcefield to a larger set of related models. Some forcefields aim for high accuracy for a limited set of element types, thus enabling good prediction; other forcefields aim for the broadest possible coverage of the periodic table, with necessarily lower accuracy.

The interaction components in a forcefield is described in terms of a model's internal degrees of freedom i.e., bonds, angles, and torsions. This approach stems from the analogy of vibrating balls connected by springs to describe molecular motion. However, it must be noted that such models have limitations.

B. 4. The Energy Expression

The actual coordinates of a model combined with the forcefield data create the energy expression for the model. This energy expression is the equation that describes the *potential energy surface* of a particular model as a function of its atomic coordinates. The potential energy of a system can be expressed as a sum of valence (or bond), crossterm, and nonbond interactions.

Most simulation engines provide a number of forcefields – individual forcefield varies in the total number of terms used and the functional forms used to describe those terms. For example, a general, summed forcefield has the following form [3]:

$$V(R) = \sum_b D_b[1 - \exp(-a(b - b_0))]^2 + \sum_\theta H_\theta(\theta - \theta_0)^2 + \sum_\phi H_\phi[1 + s\cos(n\phi)]$$
$$+ \sum_\chi H_\chi \chi^2 + \sum_b \sum_{b'} F_{bb'}(b - b_0)(b' - b_0') + \sum_\theta \sum_{\theta'} F_{\theta\theta'}(\theta - \theta_0)(\theta' - \theta_0')$$
$$+ \sum_b \sum_\theta F_{b\theta}(b - b_0)(\theta - \theta_0) + \sum_\theta \sum_{\theta'} F_{\theta\theta'\phi}(\theta - \theta_0)(\theta' - \theta_0')\cos\phi \qquad (5)$$
$$+ \sum_\chi \sum_{\chi'} F_{\chi\chi'}\chi\chi' + \sum_i \sum_{j>i} \left[\frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^6} + \frac{q_i q_j}{r_{ij}} \right].$$

Here, the first four terms are sums that reflect the energy needed to stretch bonds (b), bend

angles (θ) away from their reference values, rotate torsion angles (ϕ) by twisting atoms about the

bond axis that determines the torsion angle, and distort planar atoms out of the plane formed by

the atoms they are bonded to (χ). The next five terms are cross terms that account for

interactions between the four types of internal coordinates. The final term represents the

nonbond interactions as a sum of repulsive and attractive Lennard-Jones terms as well as

Coulombic terms, all of which are function of the distance r_{ij} between atom pairs. The forcefield

defines the functional form of each term in this equation as well as the parameters such as D_b, α,

and b_0. The forcefield also defines internal coordinates such as b, θ, ϕ, and χ as a function of the

Cartesian atomic coordinates, although this is not explicit in Eq. (5). For more details on

forcefields available to C2 simulation engine, please consult MSI manual [3] or their web page at

the url:

   http://www.chem.cmu.edu/courses/09-560/docs/msi/ffbsim/2_Forcefields.html.

C. Application of Molecular Dynamics to PAMAM Dendrimers

C.1. Energy Components and Radius of Gyration

        In what follows, we describe the results of constant-volume/constant-temperature (NVT)

dynamics calculations carried out on several generations of PAMAM dendrimers. The molecules

were first constructed by atomistic simulation using a script that runs under Cerius2. The script

implements an algorithm that first produces a structure of lowest full generation with minimum

energy conformation. The next higher generation is then built by adding repeat units to the

minimum energy of previous generation, and so on. However, as built, the final structure is not a

minimum energy state, mainly because of van der Waals overlapping. Therefore, the initial

geometries of each generation were optimized by energy minimization procedure. The

conformational structure was obtained by molecular mechanics using a CFF91 [5,6] force field.

Fig. 2 shows the energy minimized structure of generation 0 through 6 ($G0$–$G6$) PAMAM

dendrimers. This structure was then subjected to 50 ps of molecular dynamics at 300 K. Fig. 3

shows the time-evolution of various energy components of a generation 3 ($G3$) PAMAM

dendrimer molecule and Fig. 4 shows the variation of the radius of gyration, R_g, of the same

molecule during the dynamics. We subsequently used the R_g values for monolayer model

calculations [7]. Fig. 5 shows the time-evolution of radius of gyration of $G1$ through $G6$

PAMAM dendrimers. Several dynamic properties computed from the MD calculations for

several generations of PAMAM dendrimers are discussed here.

C.2. Self-Diffusion

Diffusion is the process whereby an initially non-uniform concentration profile is

smoothed in the absence of flow or drift. Diffusion is generally caused by the molecular motion

of the particles in the ensemble; this motion is described by Fick's law [7]. Diffusion of a

labeled species among otherwise identical solvent molecules is called self-diffusion.
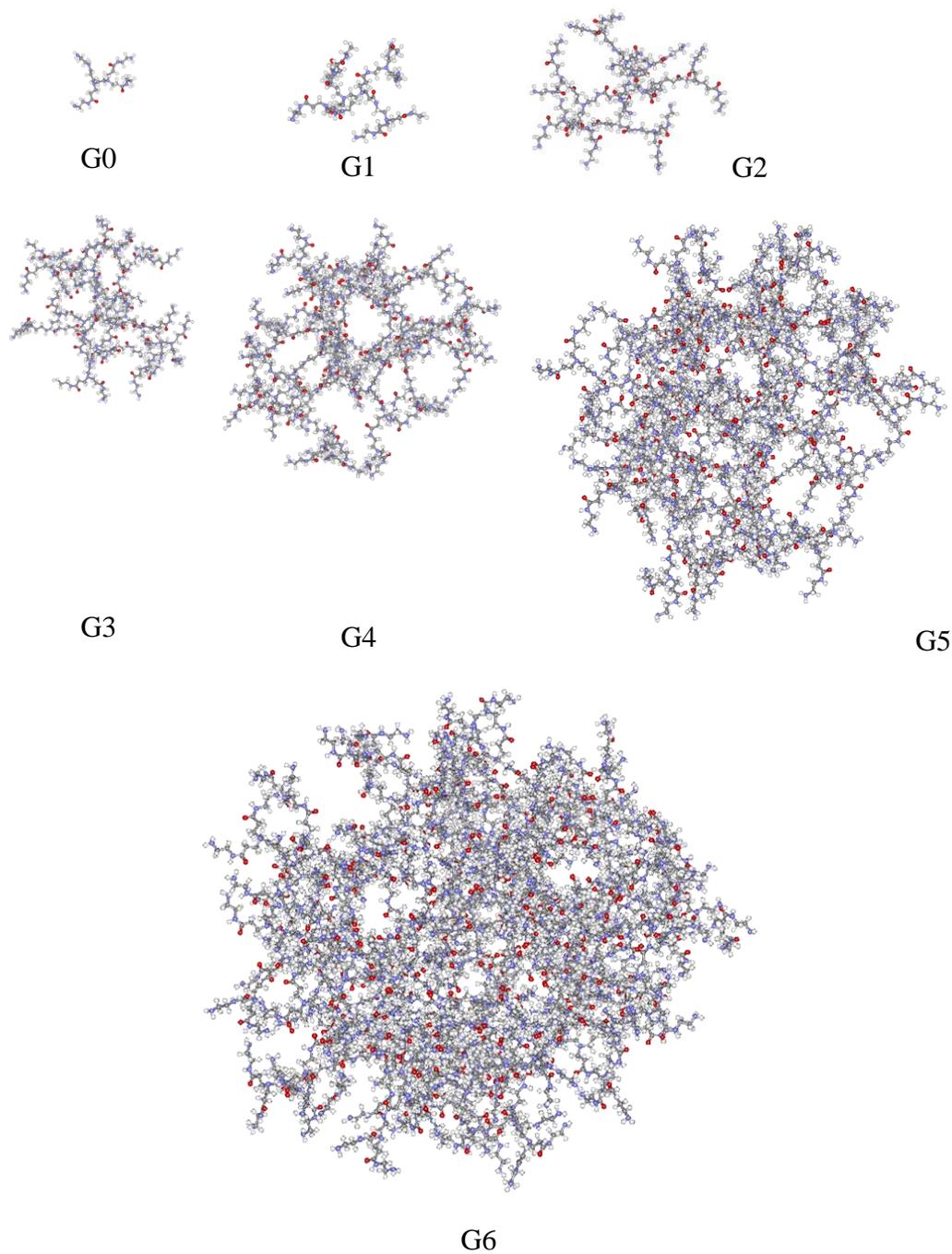
G0

G1

G2

G3

G4

G5

G6

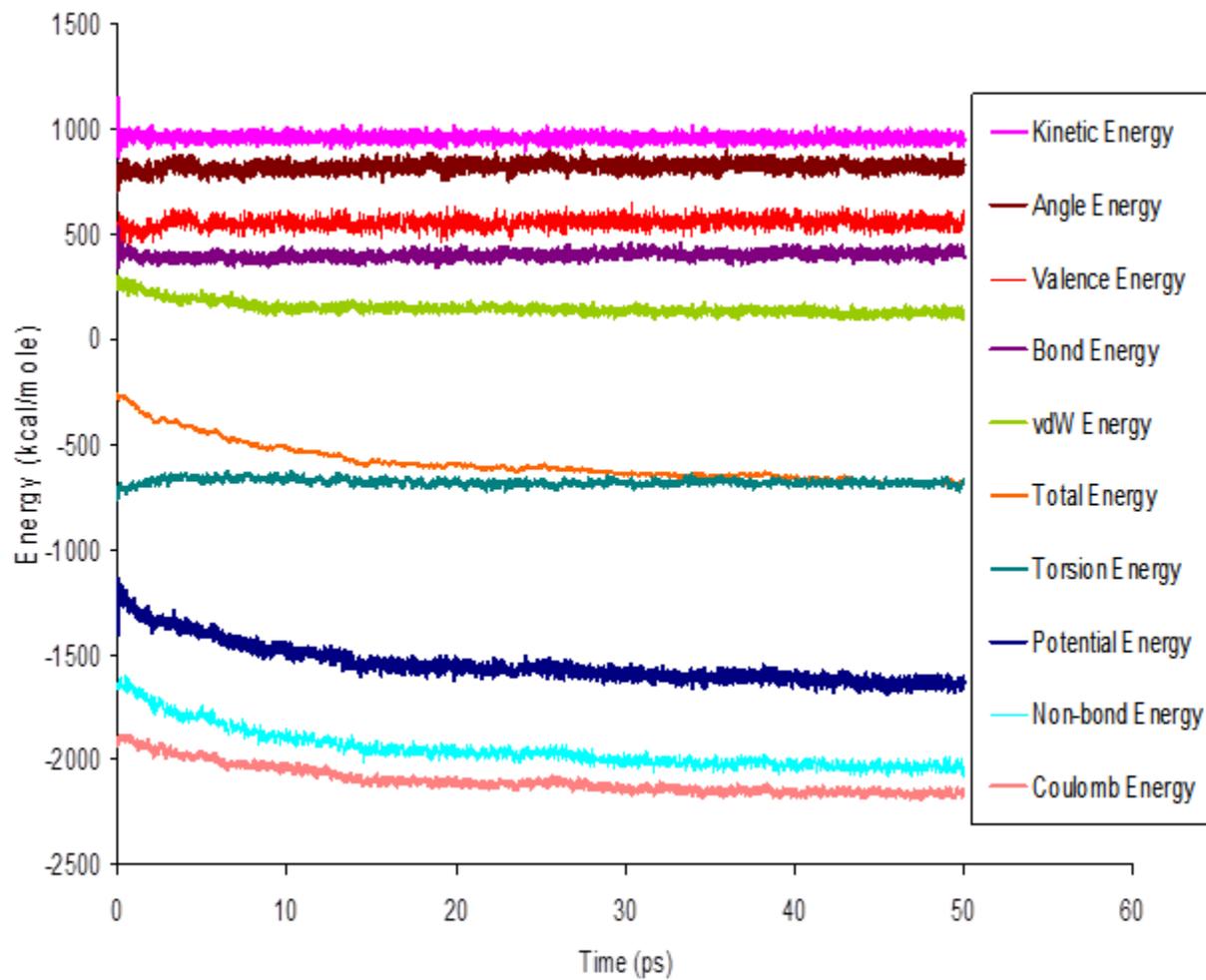Fig 2. "Frozen-in-time" structure of PAMAM dendrimers (not in scale).

Figure 3. Variation of energy components during time-evolution of a G3 PAMAM dendrimer molecule calculated in vacuo.
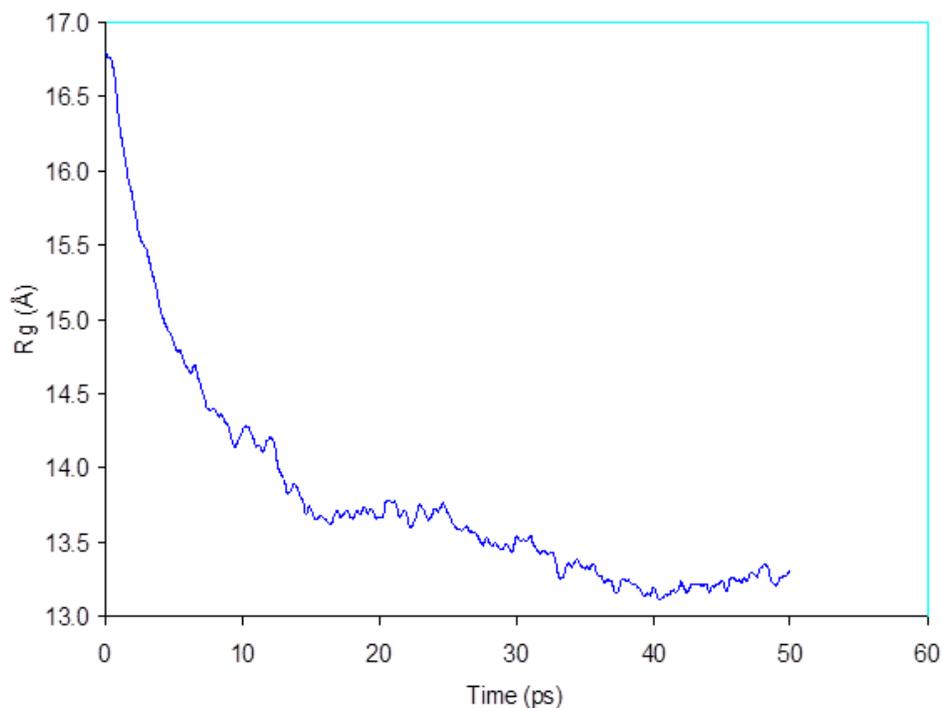
Figure 4. Time-evolution of radius of gyration of a *G*3 molecule during dynamics calculation in vacuo. The initial *R*g (=16.8Å) fell to a stable value of 13.25Å after 50 ps of dynamics.
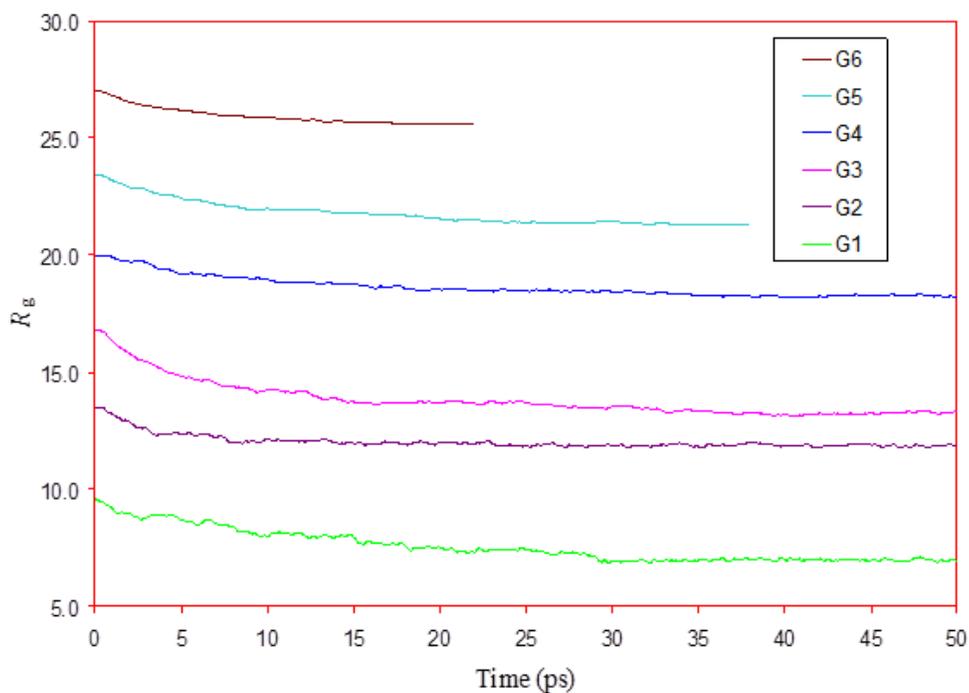

Figure 5. Time-evolution of *R*g of PAMAM dendrimers during dynamics simulation in vacou (*G*1−*G*6).

To compute the self-diffusion coefficient, one first must calculate the mean-square displacement (MSD), given by,

$$\text{MSD}(m) = \left\langle \left| r(t) - r \right|^2 \right\rangle = \frac{1}{n} \sum_{i=1}^{n} \left| r(m+i) - r(i) \right|^2 , \tag{6}$$

where, and m is the maximum number of points allowed for the MSD calculation (= max. simulation time in picoseconds) and $0 < m + n = k$, n being the number of data points used for averaging, i the increment and k the total number of frames. The MSD is computed as a function of the position of each diffusing particle. The self-diffusion constant is obtained using the Einstein relation [6]:

$$D = \frac{1}{6Nt} \left\langle \left| r(t) - r \right|^2 \right\rangle , \tag{7}$$

where, N is the number of atoms, r is the position of the particle at time t.

Fig. 6 shows the MSD vs. time graphs for $G1$- $G6$. The self-diffusion constant is determined from the slope of the least-squares linear fit line to the MSD. For instance, a least-squares fit to the linear portion (~30 ps) of MSD plot of generation 3 ($G3$) PAMAM dendrimer yields the self-diffusion coefficient $D = 8.4 \times 10^{-5} \ cm^2$/s. Fig. 7 shows the self-diffusion coefficients for several generations of this class of dendrimers.

C.3. Velocity Autocorrelation Function

The velocity autocorrelation (VAC) function is an equilibrium property of the system, it describes correlations between velocities at different times along an equilibrium trajectory. The VAC function can be used as an independent route to test the calculation of the diffusion coefficient via *Green-Kubo* relation [7]

$$D = \int_0^\infty d\tau \left\langle v_x(\tau) v_x(0) \right\rangle \tag{8}$$

where, $\tau = t' - t''$ is the time coordinate, v_x is the x-component of the particle velocity. In terms of MD trajectory, the autocorrelation function C $(= \langle v_x(\tau)v_x(0)\rangle)$ is defined as follows:

$$C(m) = \frac{1}{n}\sum_{i=1}^{n}V(m+i)\times V(i),$$ (9)

where, V is the velocity, m is the maximum number of points allowed for the autocorrelation function calculation (=max. simulation time in ps), $0 < m + n = k$, n is the number of data points used for averaging, i is the increment, and k is the total number of frames.
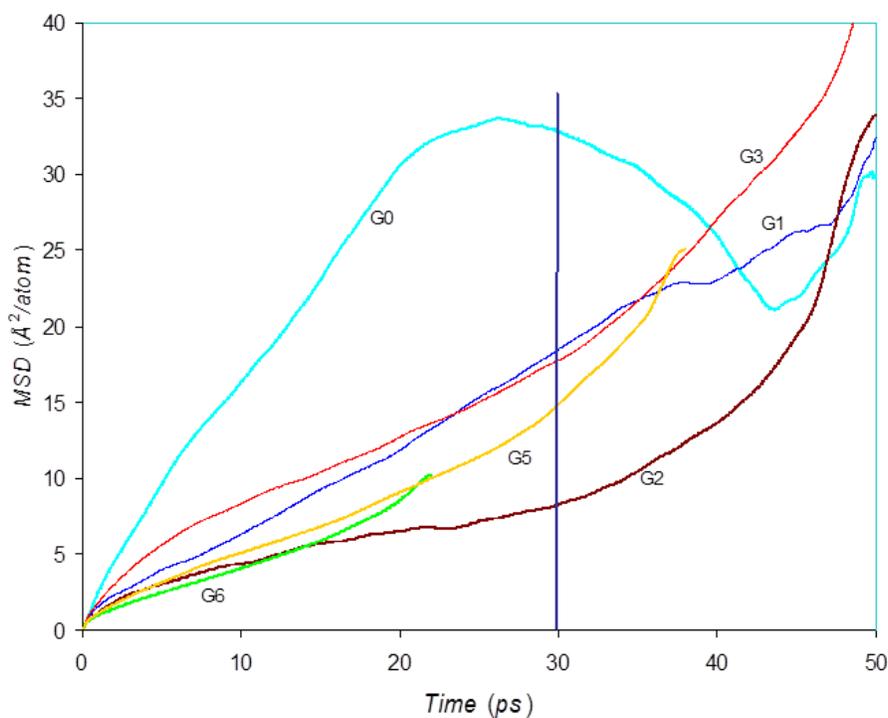

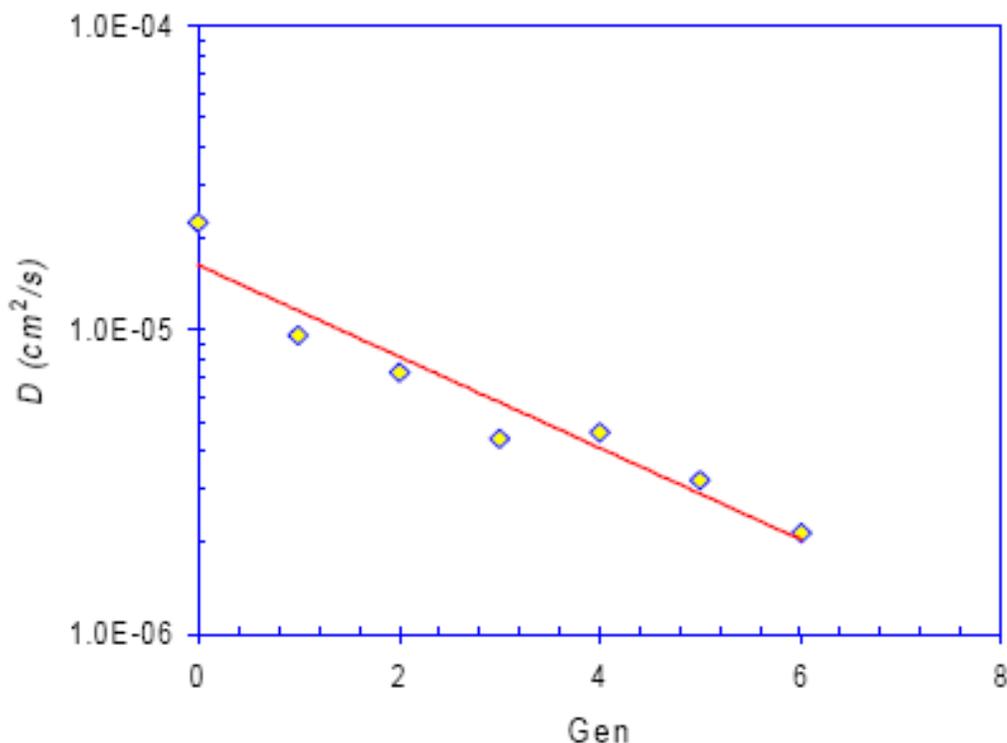Figure 6. *MSD* vs. time of *G*0-*G*6 PAMAM dendrimer.

Figure 7. Self-diffusion coefficient computed from *MSD* for *G*1 to *G*6 PAMAM dendrimers.

One can compute a useful quantity, the *power spectrum*, by taking Fourier transform of the VAC function. The power spectrum gives the dynamic and vibrational properties of materials at elevated temperatures and also useful in predicting thermal effects on infrared or Raman spectra. The positions of peaks in the power spectrum give the frequencies of vibrational motions within the system being studied [8]. The frequency resolution of the power spectrum, $\Delta\omega$, is given by:

$$\Delta\omega = \frac{\pi}{t_{max}}$$

(10)

where t_{max} is time length of the analyzed data. Fig. 8 and 9 display the VAC and power spectrum of *G*3 PAMAM dendrimers.

C.4. Radial Distribution Function and Structure Factor

A radial distribution function (RDF) is the spherically averaged distribution of

interatomic vector lengths within a system. This information is useful in revealing overall structural properties such as packing, ordering, compressibility, and phase transitions. The following expression is used to calculate the unnormalized radial distribution function between two selected groups of atoms, *A* and *B*:

$$g_{AB}(r) = \left\langle \sum_{i \neq j} \delta\left(r - \left|r_{Ai} - r_{Bj}\right|\right) \right\rangle,$$

(11)

where, r_{Ai} is the position of the *i*th atom in group *A* and r_{Bj} is the position of the *j*th atom in group *B*.
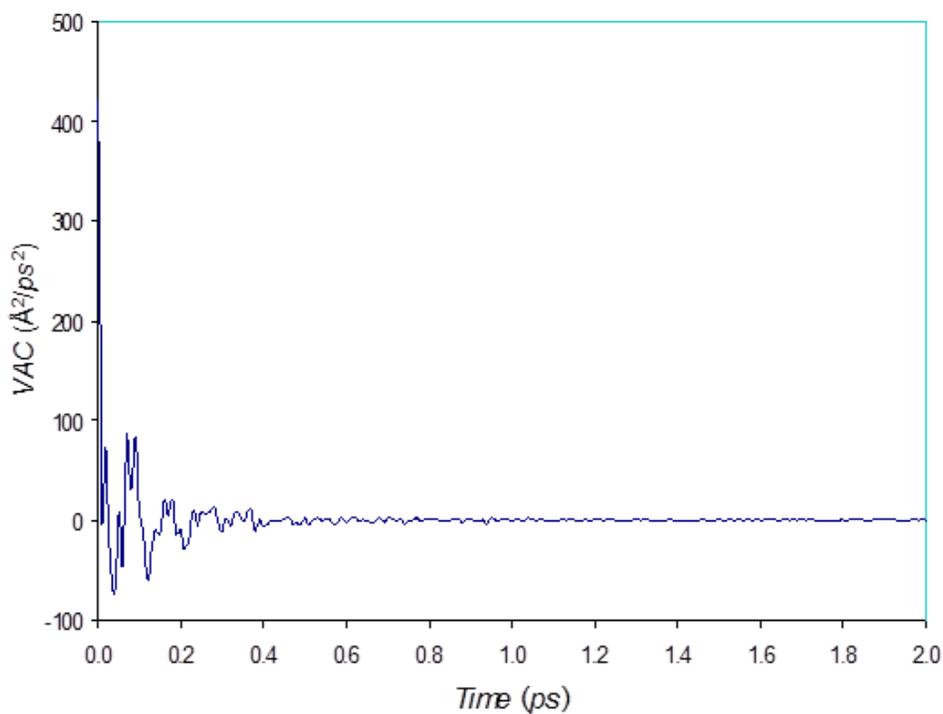
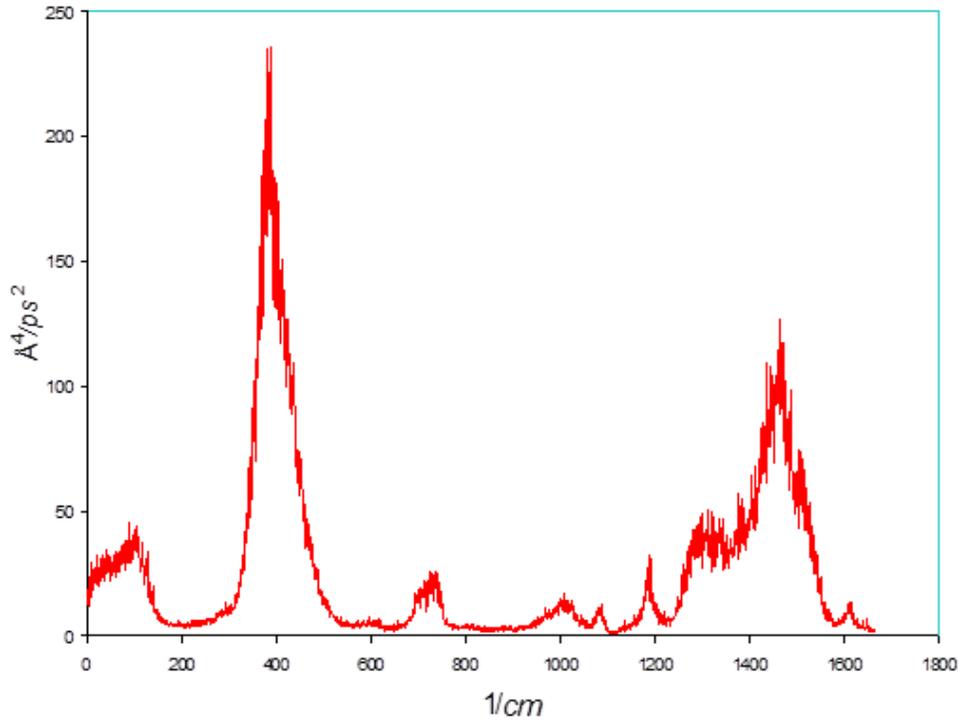Figure 8. VAC function computed for *G*3 PAMAM dendrimer.

Figure 9. Power spectrum of G3 PAMAM dendrimer. The peaks correspond to the frequencies of vibrational motions within a G3 molecule.

Once the RDF is calculated, the energy and pressure of the system can be readily obtained. The potential energy per particle can be obtained from

$$U = \frac{\rho}{2} \int_0^\infty u(r) g_{AB}(r) dr \qquad (12)$$

where, $u(r)$ is the pair potential and ρ is the number density.

The structure factor (SF) can be obtained by taking Fourier transform of the RDF. The SF enables one to gain information about overall structural properties such as packing, ordering, compressibility, and phase transitions. It is particularly useful in that it can be directly compared with X-ray diffraction data. The following 3D Fourier transform is used to calculate the SF from the RDF:

$$S_{AB}(k) = 1 + \rho\left(1 + \frac{1}{N}\right) \times \int dr[g_{AB}(r) - 1]e^{i\mathbf{k}\cdot\mathbf{r}} \qquad (13)$$

where, k is the wave vector, ρ is the atomic density (=N/V), N is the number of atoms and V is

the unit cell volume (for nonperiodic systems V = 1). Fig. 10 and 11 display the radial

distribution function and the structure factor for G3 PAMAM dendrimer.

C. 5. The Dipole-Dipole Correlation and Dipole Power Spectrum

The dipole moment is defined as the magnitude of the dipole vector. The dipole vector

and dipole-dipole correlation function can be calculated from MD trajectories. The Fourier

transform of the correlation function gives the dipole-dipole power spectrum. The power

spectrum of the dipole correlation function can be related to the infrared spectrum of the system

being studied. For a collection of point charges, the dipole vector is defined as:

$$dipole = 4.802 * Q_{\min}\left(Q_{COC}^+ - Q_{COC}^-\right) \qquad (14)$$

where, 4.802 is the factor necessary to convert the value to Debyes from angstroms and atomic

charges, $Q_{\min}$ is the smaller absolute value of the total positive charge and the total negative

charge, and $Q_{COC}^{\pm}$ are the center of charge (positive or negative), given by

$$Q_{COC}^{\pm} = \sum_i \frac{(q_i r_{i,a})}{\sum q_i}. \qquad (15)$$

Here, the sums run over all positive or negative charges as appropriate, q_i is the charge on atom i

and $r_{i,a}$ are the x, y, or z component of the coordinates of charge i. Fig. 12 and 13 display the

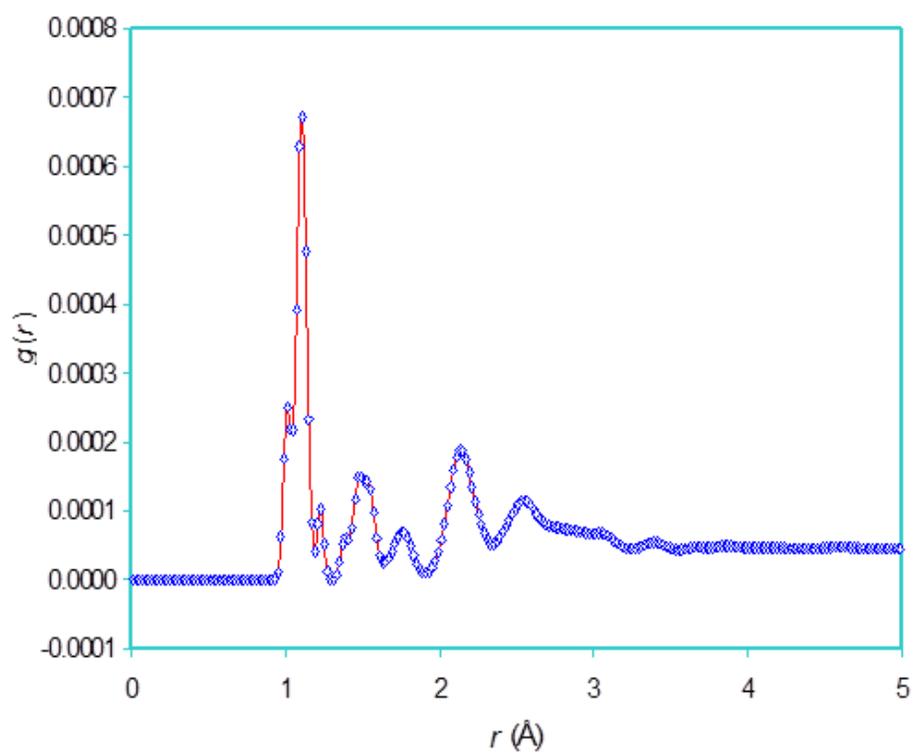dipole correlation function and the dipole power spectrum of a G4 PAMAM dendrimer.

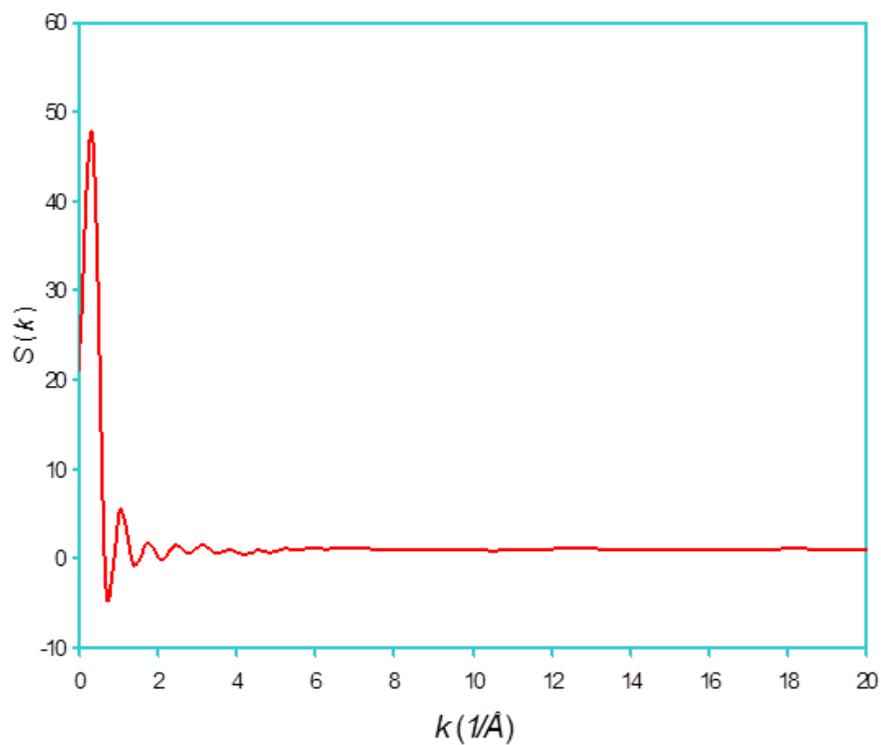Figure 10. The radial distribution function of a *G*3 PAMAM dendrimer molecule.

Figure 11. The structure factor of generation 3 PAMAM dendrimer.

D. Summary

Molecular dynamics calculations have been carried out on poly(amido amine) dendrimers for generations 0 through 6 under Cerius2 environment on a Silicon Graphics computer. Dynamic properties have been predicted that are useful to understand the fundamental properties of these macromolecules. For instance, the radii of gyration computed from simulation agree with experimentally determined values [8]. These predictions should be helpful in designing experiments to measure such properties.
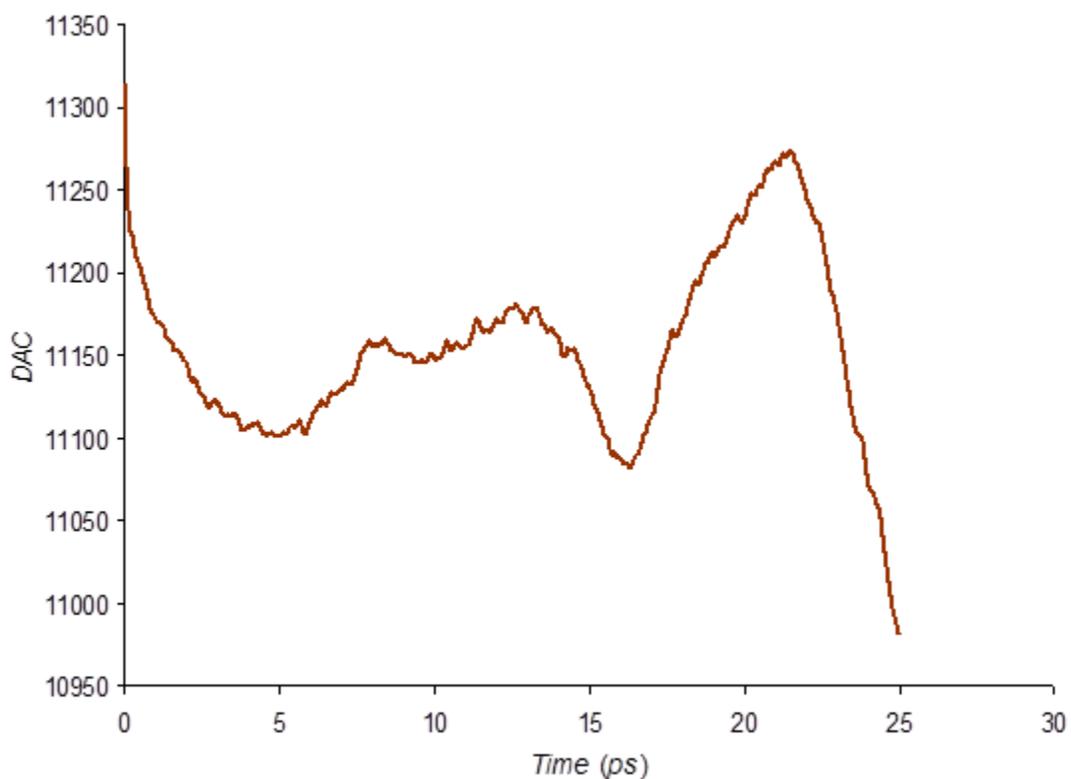
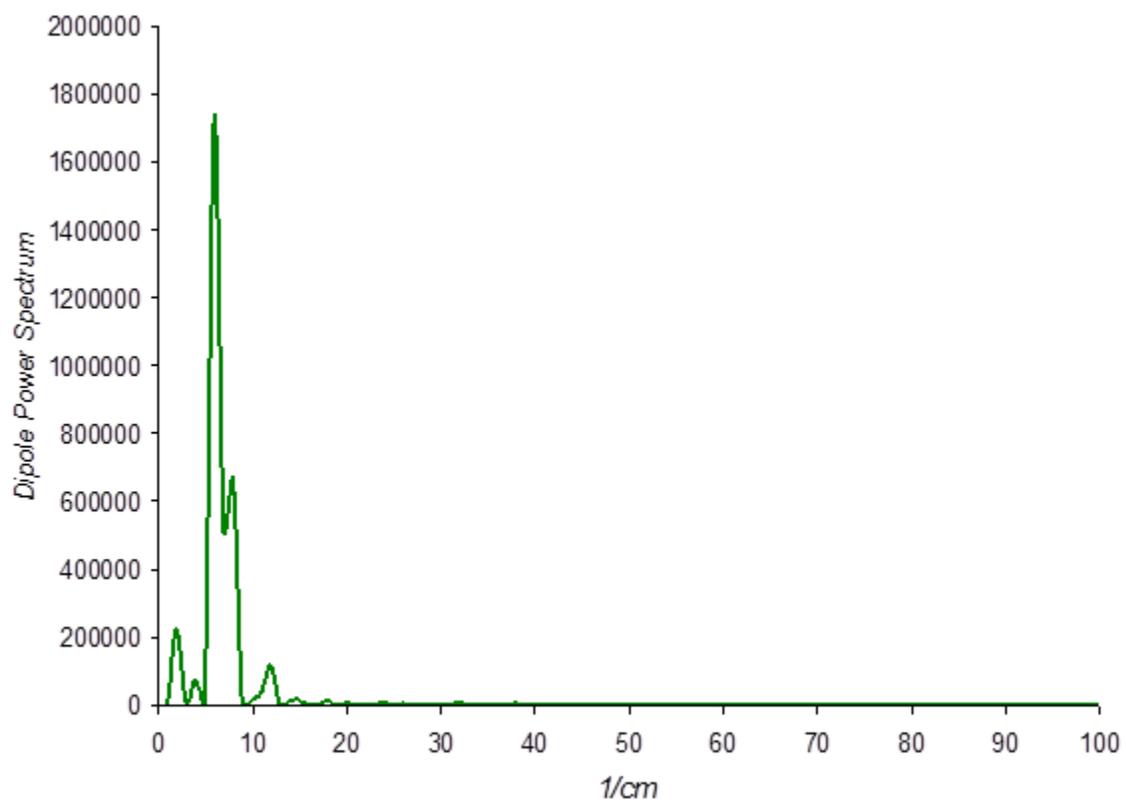Figure 12. Dipole autocorrelation function of a $G4$ PAMAM dendrimer.

Figure 13. Dipole power spectrum of a G4 PAMAM dendrimer.

E. References

1. M. Karplus and J. A. McCammon, "The Dynamics of Proteins," *Scientific Americans*, April 1986, 42-51.

2. B. Vessal, M. Amini and H. Akbarzadeh, "Molecular dynamics simulation of molten silica at high pressure," *J. Chem. Phys.*, **101** (9), 1994, 7823-7827.

3. MSI Manual, "Force-field based simulations," April, 1997.

4. K. M. A. Rahman, C. J. Durning and N. J. Turro, "Adsorption of Poly(amido amine) dendrimers on Gold," to be submitted to *Langmuir*.

5. J. R. Maple, U. Dinur and A. T. Hagler, *Proc. Natl. Acad. Sci. USA*, **85**, 1988, 5350-5354

6. O. Ermer, "Calculation of molecular properties using force fields. Applications in organic chemistry," *Structure and Bonding*, **27**, 1976, 161-211.

7. Daan Frenkel and Berend Smit, "Understanding Molecular Simulation," *Academic Press*, New York: 1996.

8. Jozef Bicerano, "Prediction of Polymer Properties," *Mercel Dekker*, New York: 1993.