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PRESSURE CALCULATION IN MOLECULAR DYNAMICS SIMULATIONS OF MOLECULAR CRYSTALS

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In molecular dynamics simulations the pressure is usually calculated with molecules as basic units. This approach fails for a polymer, and it is shown that pressure calculation on the basis of individual atoms is equally well possible, even though the forces on the atoms are not pair-additive. The only disadvantage is the need for a larger pressure time constant in simulations where the volume is adjusted to an external pressure. The formalism is tested on the α -D-glucose monohydrate crystal. Some comments are made on the calculation of the temperature in the leap-frog scheme.

KEY WORDS: Molecular dynamics simulation, pressure equation, α -D-glucose

INTRODUCTION

Molecular dynamics simulation of crystals provides a good test for the quality of force fields. Not only can detailed results like cell parameters, atomic positions and vibrational amplitudes be compared with accurate experimental data [1], but also the thermal stability of the crystal can be studied: for well-behaved crystals the symmetry should be retained and in other cases experimentally observed disorder should be reproduced. An exciting prospect is the application of molecular dynamics simulation to *ab-initio* prediction of crystal structures [2].

To determine the cell parameters the simulations must be performed at ambient pressure. The necessary pressure calculations are usually performed using molecules as basic units. For large molecules (especially polymers) this procedure runs into difficulties, and we found that a calculation on an atomic basis has considerable advantages. After a discussion of the theory this will be illustrated for the monoclinic crystal of α -D-glucose monohydrate.

THEORY

We start with the instantaneous anisotropic pressure tensor

$$P_{\alpha\beta} V = \sum_i m_i v_{i\alpha} v_{i\beta} + W_{\alpha\beta} \quad (1)$$

where $\alpha, \beta = x, y, z$ and \mathbf{W} is the virial:

$$W_{\alpha\beta} = \sum_i r_{i\alpha} F_{i\beta} \quad (2)$$

where \mathbf{F}_i is the force on atom i . In Equations 1 and 2 m_i , \mathbf{r}_i and \mathbf{v}_i refer to the masses, coordinates and velocities, respectively, of atom i . These equations follow from a generalization of the derivation of the isotropic pressure equation given, for instance, in Reference [3]. A simplification is possible when the potential energy can be written as the sum of pair interactions $U_{ij}(r_{ij})$:

$$W_{\alpha\beta} = - \sum_i \sum_{j < i} \frac{1}{r_{ij}} \frac{\partial U_{ij}}{\partial r_{ij}} (r_{i\alpha} - r_{j\alpha}) (r_{i\beta} - r_{j\beta}) \quad (3)$$

where only *differences* in atomic coordinates are involved. This allows the use of the minimum image method [3]. However, as intramolecular interactions cannot be expressed as a sum of pair interactions it is common to use a variant of Equation 1 which is based on *molecular* interactions:

$$P_{\alpha\beta} V = \sum_s M_s V_{s\alpha} V_{s\beta} - \sum_i \sum_{j < i} \frac{1}{r_{ij}} \frac{\partial U_{ij}}{\partial r_{ij}} (R_{s\alpha} - R_{t\alpha}) (r_{i\beta} - r_{j\beta}) \quad (4)$$

where i and j belong to different molecules s and t , respectively, and the capitalized symbols M_s , \mathbf{V}_s and \mathbf{R}_s refer to the molecular centers of mass of these molecules [3]. (Note that a "molecule" may be any unit which interacts with other such units in a pair-additive way). For short, we shall refer to the "atomic" pressure (Equation 1) versus the "molecular" pressure (Equation 4).

Obviously, this simplification fails in the case of a polymer where it is impossible to define such a molecule. With this application in mind we return to Equation 2, and rewrite it in a form where only interatomic distances occur. This is surprisingly easy. The intermolecular potential energy is treated as in Equation 3. The intramolecular potential energy is invariant for a translation of an entire molecule. It follows that the sum of all internal forces is zero:

$$\sum_{i=1}^n \mathbf{F}_i^{(k)} = 0 \quad (5)$$

for every internal coordinate k , with $n = 2$ for bond lengths, $n = 3$ for bond angles and $n = 4$ for torsional angles. So the contribution of this internal coordinate to the virial is:

$$\sum_{i=1}^n r_{i\alpha} F_{i\beta}^{(k)} = \sum_{i=1}^n (r_{i\alpha} - r_{j\alpha}) F_{i\beta}^{(k)} \quad (6)$$

where one of the atoms (j) is arbitrarily chosen. Since $\mathbf{F}_i^{(k)}$ is the gradient of an intramolecular potential which could in principle be written as a function (more complex than a sum) of interatomic distances, it could be expressed as

$$\mathbf{F}_i^{(k)} = - \sum_{j \neq i} \frac{\partial U^{(k)}}{\partial r_{ij}} \frac{\mathbf{r}_i - \mathbf{r}_j}{r_{ij}} \quad (7)$$

It follows that the atomic pressure tensor is symmetric at every instant. The molecular pressure has that property only after time averaging.

Special care is necessary when bond lengths are constrained by the procedure SHAKE [4]. This procedure calculates position shifts $\Delta \mathbf{r}_i$ to compensate for changes in bond lengths that would result from an unconstrained calculation [3]:

$$\Delta \mathbf{r}_i = \mathbf{G}_i (\Delta t)^2 / m_i \quad (8)$$

where \mathbf{G}_i is the constraint force on atom i and Δt is the time step. The shifts are calculated by iteratively solving the equations

$$m_i \Delta \mathbf{r}_i = \sum_j \lambda_{ij} (\mathbf{r}_i - \mathbf{r}_j) (\Delta t)^2 \quad (9)$$

where the summation is over all atoms j involved in a constraint bond to atom i . The parameters λ_{ij} are determined by the condition that all constraint bond lengths must have the prescribed value. Since $\lambda_{ij} = \lambda_{ji}$ the contribution of the constraint forces to the atomic virial is given by:

$$\sum_i r_{i\alpha} G_{i\beta} = \sum_i \sum_{j < i} \lambda_{ij} (r_{i\alpha} - r_{j\alpha}) (r_{i\beta} - r_{j\beta}) \quad (10)$$

where the summation is over all constraint atom pairs i, j . The first term of Equation 1 remains unchanged, although the relationship between its average diagonal elements and the temperature is changed due to the different number of degrees of freedom.

After time averaging all diagonal elements of the pressure tensor should be equal to the reference pressure P_0 , and the off-diagonal elements should be zero. Berendsen *et al* [5] have devised an elegant method to accomplish this: after each time step in the simulation all coordinates are rescaled by the transformation

$$\mathbf{r}_i \rightarrow \mu \mathbf{r}_i \quad \text{with} \quad \mu = 1 + \frac{\beta \Delta t}{3\tau_p} (\mathbf{P} - P_0 \mathbf{1}) \quad (11)$$

where β is the isothermal compressibility and τ_p is a pressure relaxation time. (Note that these authors use a different definition of the virial). It is seen that the change in position introduced by this scaling, $\Delta \mathbf{r}_i / \Delta t$, is proportional to the excess pressure. In another approach [6, 7, 8] it is the *second* time derivative of \mathbf{r}_i that is proportional to the excess pressure. As argued by Berendsen *et al* [5], this may lead to unwanted oscillations, whereas use of Equation 11 quickly leads to a stable situation with $\langle \mathbf{P} \rangle = P_0 \mathbf{1}$.

Of course, the scaling of Equation 11 also applies to the axes **a**, **b**, **c** of the simulation box (normally small multiples of the crystallographic cell constants). Application of Equation 11 will result in a rotation of the whole system. But periodic boundary conditions assume symmetry in certain directions, e.g. the **a** axis must remain coincident with the x axis, and the **b** axis must lie in the (x, y) plane. So a compensating rotation should be performed after the scaling. We have shown elsewhere [1] that this can be accomplished by replacing μ by

$$\begin{pmatrix} \mu_{xx} & \mu_{xy} + \mu_{yx} & \mu_{xz} + \mu_{zx} \\ 0 & \mu_{yy} & \mu_{yz} + \mu_{zy} \\ 0 & 0 & \mu_{zz} \end{pmatrix} \quad (12)$$

DETAILS OF THE SIMULATION

As a test substance α -D-glucose monohydrate was chosen, as this substance was already simulated in earlier work [1]. The crystal structure is $P2_1$ with two asymmetric units per cell [9]. The simulation box was made from $3 \times 4 \times 2$ unit cells (48 glucose.H₂O units) to obtain box dimensions of about 20 Å in all directions. No further symmetry was imposed. The GROMOS force field [10] was used with SPC/E parameters [11] for the crystal water, and the addition of a bending force constant of 95 kcal mol⁻¹ rad⁻² for the anomeric O-C-O group. Charges for hydroxyl H atoms were +0.40 e, for hydroxyl O atoms -0.55 e, and for the ring O atom -0.36 e; adjacent C atoms made up the balance. The GROMOS program was modified to allow the calculation of the atomic pressure.

Unless specified otherwise, the simulations were performed with loose coupling to a temperature bath of 298 K with a coupling time constant [5] of 0.1 ps. The time step was $\Delta t = 0.002$ ps. The compressibility $\beta = 4.9 \times 10^{-5}$ bar⁻¹ [5] was taken over from water, the precise value being unimportant as it is divided by the adjustable parameter τ_p (Equation 11) which was taken to be 2 ps. Bond lengths were kept fixed by use of the SHAKE procedure [4] with a relative tolerance of 10^{-5} . The cut-off radius was 8 Å without Ewald corrections, and the pair list was updated every 10 steps. The calculations were performed on a personal computer enhanced with an i860 processor supplied by DSM, Munich; a 10 ps simulation took 20 hours computing time. The simulations using atomic pressure were about 2% faster than with the molecular pressure: the simplification of the calculation of the nonbonded interactions (no center of gravity is needed) outweighs the greater complexity of the intramolecular virial.

Some aspects of the calculations are sensitive to roundoff errors. On the computer used for this work we noted that an overall drift velocity arose, corresponding systematically to a translation of up to 0.5 Å in 10 ps. Energy and pressure are unaffected by this drift, but when equivalent molecules are averaged using fixed symmetry elements the results are disastrous. So we reset the velocity of the center of gravity to zero every 0.1 ps. Furthermore, the calculation of the constraint contributions to the atomic virial (Equation 10) starts suffering from roundoff errors for time steps smaller than 0.001 ps. This danger is obvious from inspection of Equation 9. However, since SHAKE is used just to prevent the necessity of small time steps, this does not seem a very serious drawback.

RESULTS

Starting from the experimental crystal structure (without energy minimization), the system was equilibrated for 10 ps at constant volume. The resulting velocities and

coordinates were used as a starting point for further work. First the simulation was continued for another 10 ps under the same conditions, and then the box was allowed to adjust itself against an external pressure $P_0 = 1$ bar. Figure 1 shows the evolution of the pressure, calculated both on atomic and molecular bases for a 30 ps period, and Figure 2 the changes in the parameters of the crystallographic cell. The numerical values are given in Tables 1 and 2; results for constant pressure were collected after stabilization of the box parameters.

For the simulations at variable volume with the atomic pressure the time constant $\tau_p = 2$ ps turned out to be a lower limit: at $\tau_p = 1$ ps the cell parameters started to oscillate with increasing amplitude, and the calculation ran wild. The explanation is given in Figure 3: although the long-term root mean square fluctuations of the pressure are not extremely different for the two approaches (Figure 1), the short-term oscillations are considerably more pronounced for the atomic pressure. The corresponding simulation using the molecular pressure was stable down to at least $\tau_p = 0.5$ ps. However, as Figure 2 shows, such a short time constant is not really needed to obtain volume and pressure adjustment in a reasonable period, and perturbs the system unnecessarily.

The average temperatures are a few degrees too low. This can be attributed to the fact that the time step of 0.002 ps is not quite adequate. Reduction of the time step to $\Delta t = 0.001$ ps is helpful, but for the atomic pressure at variable volume this necessitated an increase in the pressure time constant to $\tau_p = 5$ ps to avoid catastrophic oscillations. As discussed above, roundoff in SHAKE (Equation 9) starts playing a role here. The average temperature was now 298.6 K and the other results were identical. So the algorithm is independent of the time step, as it should be, despite the apparent dependence on Δt in Equations 8–10.

If no bond constraints are applied, the time step has to be reduced to 0.0005 ps to obtain a stable simulation, both for atomic and molecular pressure. Even then, from time to time the hydrogen atom of the anomeric hydroxyl group came too close to the ring oxygen atom and obtained temporarily an unrealistic acceleration. This is a deficiency of the force field noted earlier [12]. However, for the present purpose it is sufficient to see that the results for stable parts of the trajectory are not very different from the constraint calculations (see the Tables). The pressure fluctuations are larger, but not so much as one might have expected. Again, the increase in frequency is more important than the increase in amplitude.

Finally, corrections for the truncation of the long range interactions at

Table 1 Pressure and r.m.s. fluctuations (in kbar) from simulations at constant volume.

Simulation	Ia	Im	IIa	IIIm	IIIa	IIIIm
Δt (ps)		0.002		0.0005		0.002
Time (ps)		10		5		10
Temperature (K)	296.2		299.8		294.1	
Energy (kJ mol ⁻¹)	94.0		129.1		69.6	
P_{xx}	-5.9(2.2)	-5.9(1.2)	-6.2(3.5)	-6.2(1.4)	-9.2(2.2)	-8.9(1.2)
P_{yy}	-5.1(1.0)	-5.1(0.8)	-6.0(2.7)	-6.0(0.8)	-9.2(1.0)	-8.3(0.7)
P_{zz}	-2.0(1.9)	-2.0(1.2)	-2.0(3.5)	-2.0(1.4)	-7.7(2.0)	-7.7(1.1)
P_{yz}	0.0(0.9)	0.0(0.8)	0.1(1.2)	0.1(0.7)	0.0(0.9)	0.0(0.8)
P_{zx}	1.5(1.4)	1.5(1.5)	1.4(1.7)	1.4(1.5)	2.3(1.3)	2.5(1.4)
P_{xy}	0.0(0.9)	0.0(1.2)	0.1(1.6)	0.1(1.3)	0.0(0.9)	0.0(1.3)

I: Standard conditions; II: no SHAKE; III: with Ewald corrections (see text for details); a: atomic pressure; m: molecular pressure.

Table 2 Cell parameters and r.m.s. fluctuations (Å, degrees) for simulations at adjustable volume.

<i>Simulation</i> <i>Δt (ps)</i> <i>Time (ps)</i>	<i>Ia</i>	<i>Im</i> 0.002 20	<i>Ila</i>	<i>Ilm</i> 0.0005 5	<i>IIla</i>	<i>IIIm</i> 0.002 10	<i>Xray</i>
Temperature (K)	295.4	296.0	297.2	297.8	293.9	294.2	
Energy (kJ mol ⁻¹)	88.5	88.6	122.5	122.8	60.5	61.7	
<i>a</i>	8.742(6)	8.738(7)	8.744(15)	8.750(11)	8.782(8)	8.783(9)	8.803
<i>b</i>	4.946(4)	4.947(4)	4.933(8)	4.928(7)	4.891(11)	4.932(8)	5.085
<i>c</i>	9.710(6)	9.712(6)	9.732(11)	9.738(6)	9.518(6)	9.454(11)	9.708
<i>β</i>	95.37(7)	95.42(6)	95.63(19)	95.64(13)	93.92(19)	93.53(16)	97.67

I: Standard conditions; II: no SHAKE; III: with Ewald corrections (see text for details); a: atomic pressure; m: molecular pressure; Xray: experimental data [9].

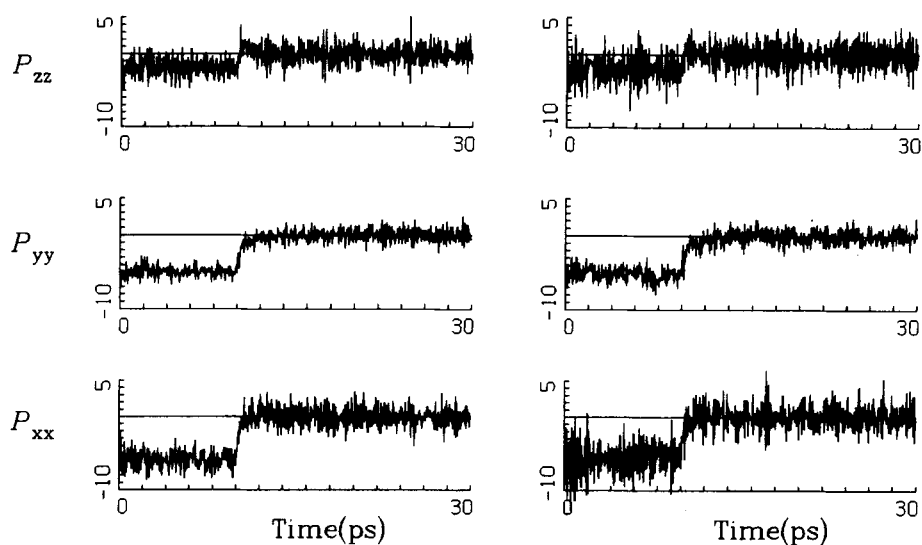


Figure 1 Evolution of the diagonal elements of the molecular pressure (left) and the atomic pressure (right) in kbar. First 10 ps: volume constant; last 20 ps: volume adjusted to obtain an average pressure of 1 bar.

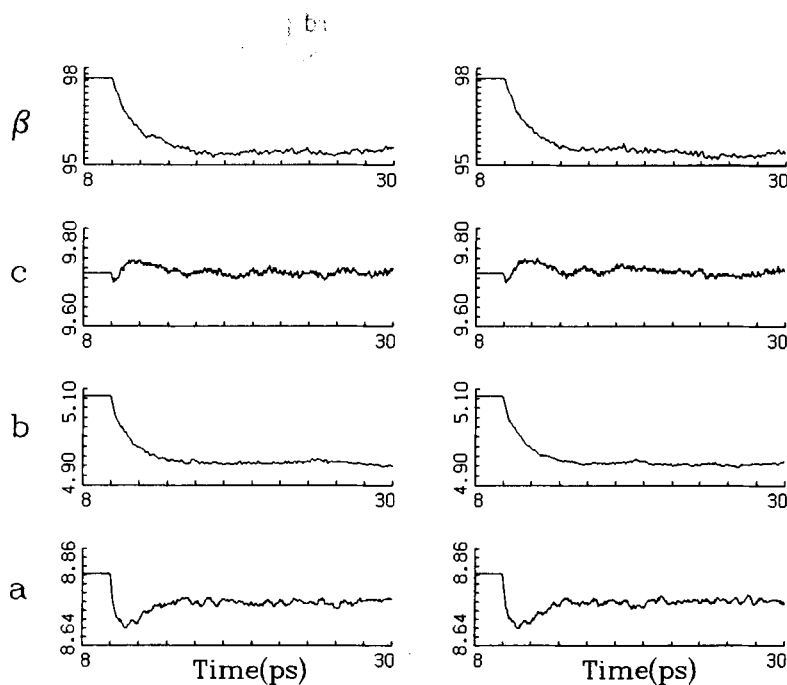


Figure 2 Evolution of the cell parameters (Å, degrees) calculated on the basis of molecular pressure (left) and atomic pressure (right).

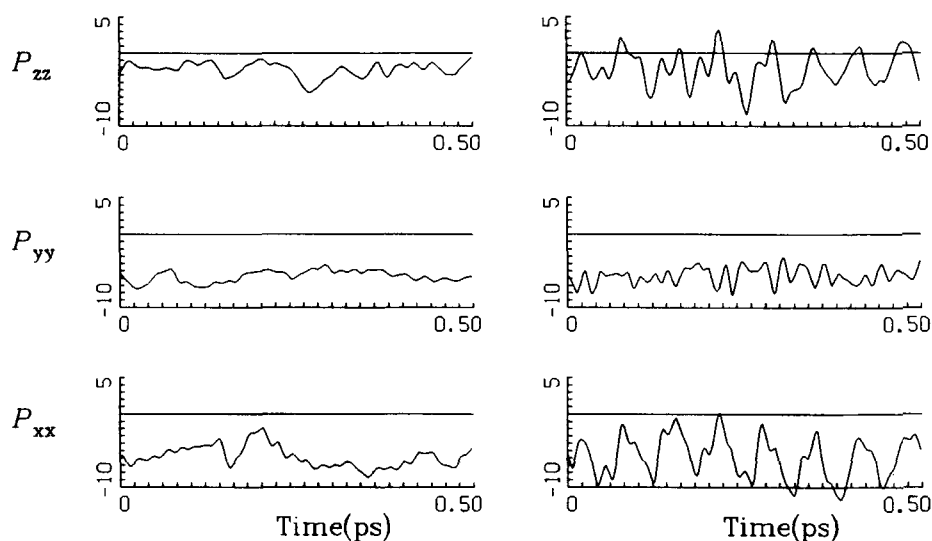


Figure 3 Detail of Fig. 1: the first 0.5 ps at constant volume.

$R_c = 8 \text{ \AA}$ were made using convergence acceleration by the Ewald method. This was done for Coulomb interaction as well as for Lennard Jones r^{-6} attraction, using formulas given by Karasawa and Goddard [13]. (Nosé and Klein [8] give a slightly different formula for the Coulomb terms. Their approach scales molecular centres of gravity rather than all atoms, which is less suitable for our purposes.) We have reported the implementation of this method in the GROMOS program in a previous paper [1]. The convergence parameters were $\eta = 2.5 \text{ \AA}$ for the Coulomb interaction and $\eta = 2.0 \text{ \AA}$ for the Lennard-Jones attraction; cut-off parameters were $R_c = 7.0 \text{ \AA}$ in real space and $H_c = 0.50 \text{ \AA}^{-1}$ in reciprocal space. These parameters are sufficient to obtain an energy within 1 kJ mol^{-1} of the value obtained using larger cut-off radii. It is seen in the Tables that the effect on the energy is enormous; in effect, this calculation should be regarded as done with a different force field. Pressures and cell parameters are somewhat different from the results of the standard procedure. Moreover, the differences between the two approaches are larger than before. This is not surprising, since the Ewald procedure requires that the pressure is calculated on an atomic basis [1]. The computing time was almost doubled.

THE TEMPERATURE

Why are the temperatures for a time step 0.002 ps too low? One would expect that decreasing the temperature coupling constant would help, but that turned out not to be the case. The origin of the problem was then located in the implementation of the leap-frog algorithm ([3], p. 80.) Here the kinetic energy at time t is calculated from the velocities which are found from

$$\mathbf{v}(t) = \frac{1}{2} [\mathbf{v}(t + \frac{1}{2}\Delta t) + \mathbf{v}(t - \frac{1}{2}\Delta t)] \quad (13)$$

This is done because the velocities in the leap-frog algorithm are only defined at times $t \pm \frac{1}{2}\Delta t$. But then the kinetic energy should also be calculated at these time points, and averaged to get the kinetic energy at time t . Averaging the velocities rather than their squares always produces a kinetic energy which is too low. After making this change in the program the temperatures became 299.5 ± 6.5 K and 297.9 ± 6.6 K without and with Ewald corrections, respectively (atomic pressure, volume adjustable).

Now the temperature for the standard simulation is higher than 298 K which is only to be expected: the use of a cut-off radius increases the temperature for molecular systems. Using the Ewald corrections should eliminate this effect, and indeed the temperature improves. The error introduced by Equation 13 increases when accelerations are large, which explains that the problem becomes manifest for a crystal sooner than for a liquid.

DISCUSSION

Berendsen *et al* [5] have stated that for non-additive pair interactions the pressure must be calculated on a molecular basis. We have shown that a calculation on an atomic basis is also possible; it is even necessary for a polymer where no separate molecules can be defined. The algorithm is simple and somewhat faster than the calculation on a molecular basis. A slight disadvantage is the need for a larger pressure time constant for simulations at adjustable volume, but this is desirable anyhow in order to disturb the system as little as possible.

After completion of this work a very elaborate discussion of the same subject was published by Theodorou *et al* [14]. They derived an improved equation for the molecular pressure which is also valid for polymer systems and which can be used in Monte Carlo simulations too.

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