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Equipartition Principle for Internal Coordinate Molecular Dynamics

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Abstract

The *principle of equipartition of (kinetic) energy* for all-atom Cartesian molecular dynamics states that each momentum phase space coordinate on the average has ½**kT** of kinetic energy in a canonical ensemble. This principle is used in molecular dynamics simulations to initialize velocities, and to calculate statistical properties such as entropy. Internal coordinate molecular dynamics (ICMD) models differ from Cartesian models in that the overall kinetic energy depends on the generalized coordinates and includes cross-terms. Due to this coupled structure, no such equipartition principle holds for ICMD models. In this paper we introduce non-canonical *modal coordinates* to recover some of the structural simplicity of Cartesian models and develop a new equipartition principle for ICMD models. We derive low-order recursive computational algorithms for transforming between the modal and physical coordinates. The equipartition principle in modal coordinates provides a rigorous method for initializing velocities in ICMD simulations thus replacing the ad hoc methods used until now. It also sets the basis for calculating conformational entropy using internal coordinates.

1 Introduction

The equipartition theorem[1] for canonical ensembles is one of the fundamental principles used in the statistical mechanics theory for molecular systems. This theorem can be used to show that the *principle of equipartition of energy* holds for Cartesian molecular models.[1,2] For the kinetic energy, this principle states that each momentum coordinate in the canonical phase space has ½**kT** of thermal energy on the average (where **k** is the Boltzmann constant and **T** is the thermodynamic temperature). This equipartition principle is used for initializing atomic velocities in Cartesian molecular dynamics simulations with a Boltzmann distribution of thermal energy. The equipartition theorem has also been used to connect the classical variance to the quantum harmonic oscillator to derive the equations for calculating absolute entropies using internal coordinates.[3]

In contrast with Cartesian models, *internal-coordinate molecular dynamics (ICMD)* models utilize relative, instead of absolute, generalized coordinates. A well known example of ICMD internal coordinates are the *bond length/angle/torsional (BAT)* coordinates[4] which, while providing an alternative coordinate representation, retain the full system degrees of freedom. Another example of ICMD models is the *torsion angle molecular dynamics*

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The supplementary material contains the detailed steps in Tolman's derivation[22] of the equipartition relationship in Eq. 4. This information is available free of charge via the Internet at http://pubs.acs.org.

(TAMD) model. These are BAT models, with additional holonomic constraints that freeze the bond and angle coordinates. Thus TAMD models have a smaller number of coordinates than the Cartesian or BAT models.[5–8] While the TAMD models are attractive for tracking the low frequency motion in biomolecules, they give rise to qualitatively different dynamics compared to Cartesian models. Unlike the Cartesian case, the Hamiltonian for ICMD models is not *separable* because the kinetic energy depends not just on the momentum, but also on the generalized coordinates. The consequent dynamical cross-coupling among the coordinates makes the ICMD models more complex. This increases the difficulty in deriving energy conserving integration schemes similar to Velocity Verlet for Cartesian models.

The intuitive presumption that constrained ICMD models behave as the limiting case of increasingly stiff Cartesian models was shown to be incorrect in a series of careful investigations.[9–11] It was shown that statistical mechanics ensemble averages of conformation dependent quantities from constrained ICMD models differed systematically from those obtained using arbitrarily stiff Cartesian models. The recognition of these differences led Fixman to propose the use of a mass matrix tensor based compensating potential to correct for such discrepancies[12] and its validity has been verified via numerical experiments.[13–15] The difficulty in evaluating the compensating potential and its gradient have led researchers to investigate evaluation techniques[16,17] and the development of a spatial operators based solution and low-order computational algorithms.[18,19]

Therefore it is important to address these differences between ICMD and Cartesian models to make the ICMD simulations more robust and straightforward to use for biomolecular simulations. This work takes a step forward in maturing the understanding and use of ICMD models. We show that the application of the equipartition theorem to the ICMD model does not yield an equipartition principle analogous to that for Cartesian models. Instead, the ensemble averages involve configuration dependent, and coupled coordinates, that are not easy to interpret or use. We introduce a coordinate transformation to define new ICMD *modal coordinates*. These modal coordinates transform the system kinetic energy into a decoupled form similar to that for Cartesian models. Moreover, we show that an equipartition principle analogous to that for Cartesian models holds for these modal coordinates. This principle holds even though the modal coordinates are not canonical coordinates in the Hamiltonian sense.

The transformations between the physical ICMD velocity/momentum coordinates and the modal coordinates involve the square root of the configuration dependent ICMD mass matrix and its inverse. These matrices can be especially expensive to evaluate for constrained ICMD models. We use spatial operators to develop analytical expressions for these coordinate transformation matrices based on closed-form spatial operator factorizations of the ICMD mass matrix and its inverse. Subsequently, these operator expressions lead to recursive, low-order computational algorithms for carrying out the coordinate transformations that entirely avoid the explicit evaluation of the coordinate transformation matrices. The equipartition principle in modal coordinates can now be applied to assigning initial velocities to the internal coordinates according to Boltzmann distribution. We have demonstrated the use of modal coordinate velocities for velocity initialization in the TAMD simulations of protein structure folding and refinement.[20,21] The theoretical groundwork presented in this paper sets the stage for future calculations of other properties such as conformational entropy from ICMD models.

1.1 Generalized equipartition theorem

Let $\mathscr{H}(q, p)$ and $\mathscr{L}\left(q, \dot{q}\right)$ denote the Hamiltonian and the Lagrangian respectively for a n-dimensional dynamical system, with $q \in \mathscr{R}^n$ denoting the generalized coordinates and $p \in \mathscr{R}^n$ the conjugate momenta. The elements of p satisfy

$$p_i = \frac{\partial \mathscr{L}\left(q, \dot{q}\right)}{\partial \dot{q}_i} \quad (1)$$

For a temperature, **T**, the canonical ensemble partition function, $\mathscr{Z}(\mathbf{T})$, is defined as[1]

$$\mathscr{Z}(\mathbf{T}) = \frac{1}{h^n} \int_{-\infty}^{\infty} dp_1 \cdots \int_{-\infty}^{\infty} dp_n \int_{-\alpha_1}^{\gamma_1} dq_1 \cdots \int_{-\alpha_n}^{\gamma_n} dq_n \quad e^{-\mathscr{H}(q,p)/kT} \quad (2)$$

where h is Planck's constant, and the α_i and γ_i integration limits are determined by the geometry of the problem. The ensemble average of a function $f(q,p)$ is

$$\langle f(q, p) \rangle = \frac{1}{h^n \mathscr{Z}(\mathbf{T})} \int_{-\infty}^{\infty} dp_1 \cdots \int_{-\infty}^{\infty} dp_n \int_{-\alpha_1}^{\gamma_1} dq_1 \cdots \int_{-\alpha_n}^{\gamma_n} dq_n \quad f(q, p)\, e^{-\mathscr{H}(q,p)/kT} \quad (3)$$

In particular, with y_i and y_j denoting a pair of phase space coordinates, the equipartition theorem[1,22] states that the ensemble average of the function $f(q, p) = y_i \frac{\partial \mathscr{H}(q, p)}{\partial y_j}$ is

$$\left\langle y_i \frac{\partial \mathscr{H}(q, p)}{\partial y_i} \right\rangle = kT \delta_{i=j} \quad (4)$$

where $\delta_{i=j}$ denotes the Dirac delta function which is unity only when $i = j$ and zero otherwise. A more detailed derivation of this result using integration by parts is included in the supplementary material.

In this powerful theorem, the y_i and y_j coordinates can be any of the elements of the q or p coordinates. However, the theorem does require that the q and p be canonical phase space coordinates. Gathering up the ensemble average values in Eq. 4 for all i and j, we can re-express it in matrix form as

$$\left\langle y \nabla_y \mathscr{H}(q, p) \right\rangle = \begin{pmatrix} \left\langle y_1 \frac{\partial \mathscr{H}(q,p)}{\partial y_1} \right\rangle & \cdots & \left\langle y_1 \frac{\partial \mathscr{H}(q,p)}{\partial y_{2n}} \right\rangle \\ \vdots & \vdots & \vdots \\ \left\langle y_{2n} \frac{\partial \mathscr{H}(q,p)}{\partial y_1} \right\rangle & \cdots & \left\langle y_{2n} \frac{\partial \mathscr{H}(q,p)}{\partial y_{2n}} \right\rangle \end{pmatrix} = kT I_{2n} \quad (5)$$

where I_{2n} denotes the $2n \times 2n$ identity matrix.

1.2 Cartesian molecular dynamics model

The Hamiltonian for an Cartesian molecular dynamics model with n atoms has the form

$$\mathscr{H}(x, p) = \sum_{i=1}^{3n} p_i^2 / 2\mathrm{m}_i + \mathscr{U}(x) \quad (6)$$

where $x \in \mathscr{R}^{3n}$ denotes the atom position generalized coordinates, $\mathscr{U}(x)$ the potential energy, and p_i a linear momentum component for an atom with mass m_i. For this Hamiltonian it follows from the Eq. 4 equipartition theorem (with $y_i = y_j = p_i$) that

$$\left\langle p_i^2/2\mathfrak{m}_i \right\rangle = kT/2 \quad (7)$$

This implies that the average kinetic energy in each conjugate momentum coordinate is **kT**/2. This result is also referred to as the *principle of equipartition of kinetic energy*.[1,2] This singular principle is a consequence of the following special properties of the Cartesian Hamiltonian in Eq. 6:

- the quadratic (or harmonic) form of the kinetic energy
- the absence of cross terms in the kinetic energy expression
- the *separable* nature of the Hamiltonian, i.e., the kinetic energy is independent of the generalized coordinates.

2 ICMD models

While Cartesian models use the absolute location of the atoms with respect to a reference frame as generalized coordinates, ICMD models use atom-atom relative coordinates as generalized coordinates. The bond length/angle/torsional (BAT) coordinates are well known examples of such ICMD coordinates. BAT coordinates provide an alternative representation of the phase space while retaining the dimensionality of the Cartesian model's coordinate space. Torsion angle molecular dynamics (TAMD) ICMD models are BAT models with additional holonomic constraints that freeze the bond and angle degrees of freedom. TAMD models thus have fewer coordinates than the corresponding BAT or Cartesian models.

For an ICMD model with $\mathcal{N}$ configuration degrees of freedom, we use $\theta \in \mathcal{R}^{\mathcal{N}}$ to denote its set of generalized coordinates. The ICMD model's kinetic energy depends on a configuration dependent mass matrix $\mathcal{M}(\theta) \in \mathcal{R}^{\mathcal{N}\times\mathcal{N}}$ and takes the form

$$\mathcal{K}_e(\theta, p) = \frac{1}{2}\dot{\theta}^* \mathcal{M}(\theta)\,\dot{\theta} = \frac{1}{2} p^* \mathcal{M}^{-1}(\theta)\, p \quad (8)$$

where the conjugate momenta vector $p \in \mathcal{R}^{\mathcal{N}}$ is given by the expression

$$p = \mathcal{M}(\theta)\,\dot{\theta} \quad (9)$$

The x^* notation used here denotes the transpose of a vector or matrix x. The $\mathcal{M}(\theta)$ mass matrix is symmetric and positive definite. Unlike the case of Cartesian models, the ICMD mass matrix is configuration dependent and dense. As a consequence, the system kinetic energy includes cross-terms from the generalized velocity and momentum components (in contrast with Eq. 6 for Cartesian models). The ICMD Hamiltonian is

$$\mathcal{H}(\theta, p) = \frac{1}{2} p^* \mathcal{M}^{-1}(\theta)\, p + \mathcal{U}(\theta) \quad (10)$$

Observe that the dependency of the kinetic energy on the generalized coordinates implies that the Hamiltonian is *not separable*. The ICMD partition function, $\mathcal{Z}(\mathbf{T})$, is

$$\mathcal{Z}(\mathbf{T}) = \frac{1}{h^{\mathcal{N}}} \int_{-\infty}^{\infty} dp_1 \cdots \int_{-\infty}^{\infty} dp_{\mathcal{N}} \int_{-\alpha_1}^{\gamma_1} d\theta_1 \cdots \int_{-\alpha_{\mathcal{N}}}^{\gamma_{\mathcal{N}}} d\theta_{\mathcal{N}} \quad e^{-\left[\frac{1}{2} p^* \mathcal{M}^{-1}(\theta) p + \mathcal{U}(\theta)\right]/kT} \quad (11)$$

From Eq. 10 it follows that

$$\frac{\partial \mathscr{H}(\theta, p)}{\partial p_j} = \frac{\partial p^*}{\partial p_j} \mathscr{M}^{-1}(\theta)\, p = \mathrm{e}_j^* \cdot \dot{\theta} = \dot{\theta}_j \quad (12)$$

e_j^* above denotes a vector with all zero elements except for the j^{th} element being 1. Using the equipartition theorem Eq. 4 we thus obtain

$$\left\langle p_i \frac{\partial \mathscr{H}(\theta, p)}{\partial p_j} \right\rangle \overset{12}{=} \left\langle p_i \dot{\theta}_j \right\rangle \overset{4}{=} kT\delta_{i=j} \quad (13)$$

The ‘‘ $\overset{12}{=}$ ’’ and ‘‘ $\overset{4}{=}$ ’’ notation identifies the equation(s) used to establish equalities. While the ensemble average term on the left has the units of energy, it does not lend itself to an interpretation as a principle of equipartition of kinetic energy. This is because p_i depends on multiple velocity coordinates and not just $\dot{\theta}_i$.

Combining Eq. 13 together for all i and j, the overall ensemble averages can be expressed in matrix form as

$$\left\langle \dot{\theta}\ p^* \right\rangle \overset{8}{=} \left\langle \mathscr{M}^{-1}(\theta)\, p\, p^* \right\rangle \overset{13}{=} kTI_{\mathscr{N}} \quad (14)$$

Unlike the Cartesian Eq. 7, there is no clear way to use this ensemble average relationship to assign the thermal energy across the ICMD model degrees of freedom with a Boltzmann distribution.

2.1 Modal coordinates

Since the ICMD mass matrix $\mathscr{M}(\theta)$ is symmetric and positive definite, there exists an invertible matrix $m(\theta) \in \mathscr{R}^{\mathscr{N}\times\mathscr{N}}$ such that

$$\mathscr{M}(\theta) = \mathfrak{m}(\theta)\, \mathfrak{m}^*(\theta) \quad (15)$$

Let $\ell(\theta) \in \mathscr{R}^{\mathscr{N}\times\mathscr{N}}$ denote the inverse of m(θ) so that

$$\mathfrak{m}^{-1}(\theta) = \ell(\theta) \quad \text{and} \quad \mathscr{M}^{-1}(\theta) \overset{15}{=} \ell^*(\theta)\, \ell(\theta) \quad (16)$$

Define the *modal coordinates* $v \in \mathscr{R}^{\mathscr{N}}$ as

$$v(\theta, p) \triangleq \mathfrak{m}^*(\theta)\, \dot{\theta} \overset{9,16}{=} \ell(\theta)\, p \quad (17)$$

The ‘‘ $\triangleq$ ’’ notation should be read as “is defined as” and is used within definitional expressions. Using the v modal coordinates, the Eq. 10 Hamiltonian can be expressed as

$$\mathscr{H}(\theta, v) \overset{15}{=} \frac{1}{2} v^* v + \mathscr{U}(\theta) \quad (18)$$

In contrast with Eq. 10, the kinetic energy in this Hamiltonian expression has a decoupled structure without any cross-terms involving the v_i elements. In addition, the kinetic energy no longer explicitly depends on the θ generalized coordinates. These properties are the motivation for referring to these coordinates as “modal” coordinates.

Unlike p, the v coordinates are *not* conjugate momenta of the θ generalized coordinates, and thus the (θ, v) pair are *not* canonical phase space coordinates in the Hamiltonian sense. Now we change the integration variables from the p_i momentum coordinates to the v_i modal

coordinates. Eq. 17 implies the following relationship between infinitesimal volumes in the two coordinate spaces:

$$\begin{aligned} & dv_1 \cdots dv_{\mathcal{N}} \\ & \quad = \det\{\ell\}\, dp_1 \cdots dp_{\mathcal{N}} \Rightarrow \det\{\mathcal{M}(\theta)\}^{\frac{1}{2}} dv_1 \cdots dv_{\mathcal{N}} \\ & \quad \overset{15,16}{=} dp_1 \cdots dp_{\mathcal{N}} \end{aligned} \tag{19}$$

Using this in Eq. 11, the partition function is given by

$$\begin{aligned} \mathcal{Z}(\mathbf{T}) \overset{18,19}{=} & \frac{1}{n^{\mathcal{N}}} \int_{-\infty}^{\infty} dv_1 \\ & \cdots \int_{-\infty}^{\infty} dv_{\mathcal{N}} \int_{-\alpha_1}^{\gamma_1} d\theta_1 \cdots \int_{-\alpha_{\mathcal{N}}}^{\gamma_{\mathcal{N}}} d\theta_{\mathcal{N}} \quad \det\{\mathcal{M}(\theta)\}^{\frac{1}{2}} \quad e^{-\left[\frac{1}{2}v^* v + \mathcal{U}(\theta)\right]/kT} \end{aligned} \tag{20}$$

The ensemble average of a function $f(\theta,p) \equiv f(\theta, v)$ is given by

$$\begin{aligned} \langle f(\theta, v)\rangle = & \frac{1}{h^{\mathcal{N}} \mathcal{Z}(\mathbf{T})} \int_{-\infty}^{\infty} dv_1 \\ & \cdots \int_{-\infty}^{\infty} dv_{\mathcal{N}} \int_{-\alpha_1}^{\gamma_1} d\theta_1 \cdots \int_{-\alpha_{\mathcal{N}}}^{\gamma_{\mathcal{N}}} d\theta_{\mathcal{N}} \quad f(\theta, v)\, \det\left\{\mathcal{M}^{\frac{1}{2}}(\theta)\right\} e^{-\left[\frac{1}{2}v^* v + \mathcal{U}(\theta)\right]/kT} \end{aligned} \tag{21}$$

Define

$$\mathcal{U}'(\theta) \triangleq \mathcal{U}(\theta) + \mathcal{U}_c(\theta), \quad \text{where} \quad \mathcal{U}_c(\theta) \triangleq \frac{1}{2} \ln \det\{\mathcal{M}(\theta)\} \tag{22}$$

Using this, Eq. 21 can be re-expressed as

$$\begin{aligned} \langle f(\theta, v)\rangle \overset{20,11}{=} & \frac{1}{h^{\mathcal{N}} \mathcal{Z}(\mathbf{T})} \int_{-\infty}^{\infty} dv_1 \\ & \cdots \int_{-\infty}^{\infty} dv_{\mathcal{N}} \int_{-\alpha_1}^{\gamma_1} d\theta_1 \cdots \int_{-\alpha_{\mathcal{N}}}^{\gamma_{\mathcal{N}}} d\theta_{\mathcal{N}}\, f(\theta, v)\, e^{-\left[\frac{1}{2}v^* v + \mathcal{U}'(\theta)\right]/kT} \end{aligned} \tag{23}$$

In particular, the ensemble average of $f(v) = v_i v_j$ is

$$\begin{aligned} \left\langle v_i v_j \right\rangle \overset{23}{=} & \frac{1}{h^{\mathcal{N}} \mathcal{Z}(\mathbf{T})} \int_{-\infty}^{\infty} dv_1 \cdots \int_{-\infty}^{\infty} dv_{\mathcal{N}} \int_{-\alpha_1}^{\gamma_1} d\theta_1 \cdots \int_{-\alpha_{\mathcal{N}}}^{\gamma_{\mathcal{N}}} d\theta_{\mathcal{N}}\, v_i v_j e^{-\left[\frac{1}{2}v^* v + \mathcal{U}'(\theta)\right]/kT} \\ = & \frac{1}{h^{\mathcal{N}} \mathcal{Z}(\mathbf{T})} \int_{-\infty}^{\infty} dv_1 \cdots \int_{-\infty}^{\infty} dv_{\mathcal{N}}\, v_i v_j e^{-\frac{1}{2}v^* v/kT} \int_{-\alpha_1}^{\gamma_1} d\theta_1 \cdots \int_{-\alpha_{\mathcal{N}}}^{\gamma_{\mathcal{N}}} d\theta_{\mathcal{N}} \quad e^{-\mathcal{U}'(\theta)/kT} \end{aligned} \tag{24}$$

Integrating over the generalized and modal coordinates we obtain

$$\left\langle v_i v_j \right\rangle \overset{24}{=} kT\delta_{i=j} \tag{25}$$

Recalling from Eq. 18 that $v_i^2/2$ is the kinetic energy for the v_i modal coordinate, this result implies that the $_i$ modal coordinate components are uncorrelated with each other, and moreover, the average kinetic energy in each of these coordinate elements is ½**kT**. The v_i modal coordinates are decoupled in a manner similar to that of the velocity and momentum coordinates for the Cartesian model. Thus Eq. 25 represents an equipartition principle for ICMD models that is the analog of the principle for Cartesian models in Eq. 7.

Unlike the case for Cartesian models, this equipartition principle holds even though (θ, v) are non-canonical coordinates. Indeed, no such principle holds for the (θ, p) canonical

coordinates. Together with the decoupled (no cross-terms) nature of the Eq. 18 kinetic energy expression, the "modal" properties of ν coordinates are seen to disentangle the dynamical cross-coupling between the canonical momentum coordinates for ICMD models. Combining Eq. 25 for all i and j elements we obtain the matrix expression

$$\langle vv^* \rangle = kTI_{\mathcal{N}} \quad (26)$$

Eq. 26 is the matrix version of the equipartition principle for ICMD models.

Having established the theory and nature of the equipartition principle for constrained and unconstrained ICMD models, we now turn to further exploring the properties of the m(θ) transformation matrix needed for defining the modal coordinates. In the following sections we derive closed-form analytical expressions that hold for general ICMD models for these quantities. These analytical expressions form the basis of low-order computational algorithms for working with modal coordinates, and consider the tractable use of our theoretical results in practical applications.

3 Physical to modal coordinate transformations

When working with multiple coordinate representations, as a practical matter(e.g. during molecular dynamics simulations) there is a need to be able to transform between the physical and modal coordinates. In our case we need to be able to go between the ν modal and the $\dot{\theta}$ physical velocities. From Eq. 17 we observe that the m(θ) and $\ell(\theta)$ matrices are needed to carry out these coordinate transformations so that

$$v = \mathfrak{m}^*(\theta)\,\dot{\theta} \quad \text{and} \quad \dot{\theta} = \ell^*(\theta)\,v \quad (27)$$

We now look into the issue of obtaining these coordinate transformation matrices. The configu-ration dependent $\mathcal{J}(\theta) \in \mathcal{R}^{3n\times\mathcal{N}}$ Jacobian matrix relates Cartesian generalized velocities $\dot{x}$ to the ICMD $\dot{\theta}$ velocities via the expression

$$\dot{x} = \mathcal{J}(\theta)\,\dot{\theta} \quad \text{where} \quad \mathcal{J}(\theta) \triangleq \begin{pmatrix} \frac{\partial x_1}{\partial \theta_1} & \cdots & \frac{\partial x_{\mathcal{N}}}{\partial \theta_{\mathcal{N}}} \\ \vdots & \vdots & \vdots \\ \frac{\partial x_{3n}}{\partial \theta_1} & \cdots & \frac{\partial x_{3n}}{\partial \theta_{\mathcal{N}}} \end{pmatrix} \quad (28)$$

This Jacobian can be used to obtain the following expression for the ICMD mass matrix

$$\mathcal{M}(\theta) = \mathcal{J}^*(\theta)\,\mathrm{M}\,\mathcal{J}(\theta) \quad (29)$$

where $\mathrm{M} \in \mathcal{R}^{3n\times 3n}$ denotes the constant, diagonal matrix with the atom masses along the diagonal. M is in fact the mass matrix for the Cartesian model.

For BAT models, $\mathcal{N} = 3n$, and $\mathcal{J}(\theta)$ is square and invertible. The structure of the BAT system Jacobian and its determinant play an important role in entropy studies for molecular systems.[10,23] Indeed, for BAT models m(θ) is simply

$$\mathfrak{m}(\theta) = \mathcal{J}^*(\theta)\,\mathrm{M}^{\frac{1}{2}} \quad (30)$$

This expression for m(θ) is both square and invertible and together with its inverse provides the desired coordinate transformation matrices for BAT ICMD models.

The situation is quite different once holonomic constraints are present such as for TAMD ICMD models. Due to the constraints, $\mathcal{N}<3n$. While Eq. 28 and Eq. 29 still hold, the $\mathcal{J}(\theta)$ matrix for constrained ICMD models is neither square, nor invertible. Thus Eq. 30 is no longer usable since it yields a non-square (and thus non-invertible) m(θ) matrix. An option then is to use Eq. 29 to explicitly evaluate the mass matrix followed by a numerical factorization step to obtain a square and invertible m(θ) matrix.

3.1 Analytical expressions for m(θ) and $\ell(\theta)$

In this section, we use spatial operators to develop analytical expressions that lead to recursive, low-order computational algorithms for transforming between the ν and $\dot{\theta}$ coordinates. The end result will be an algorithm that implements the Eq. 27 transformations without requiring the explicit evaluation of the m(θ) and $\ell(\theta)$ matrices. While these procedures are valid with or without holonomic constraints, they are essential when holonomic constraints are present. The developments we describe assume that the ICMD model has a tree topology (such as for BAT and TAMD models). The extensions for closed-chain topology models are possible using constraint embedding techniques[19] but are not discussed here.

Spatial operators are a valuable technique for analyzing the dynamics of ICMD models and developing computational dynamics algorithms.[19] They have been used to develop the $O(\mathcal{N})$ algorithms for solving the ICMD equations of motion[6] that have been applied to study molecular dynamics problems.[20,21] The following describes key analytical spatial operator expressions for the square factorization and inversion of the mass matrix:[19]

$$\begin{aligned} \mathcal{M} &= \mathrm{H}\phi\mathrm{M}\phi^{*}\mathrm{H}^{*} \\ \mathcal{M} &= [\mathrm{I}+\mathrm{H}\phi\mathcal{K}]\,\mathcal{D}\,[\mathrm{I}+\mathrm{H}\phi\mathcal{K}]^{*} \\ [\mathrm{I}+\mathrm{H}\phi\mathcal{K}]^{-1} &= [\mathrm{I}-\mathrm{H}\psi\mathcal{K}] \\ \mathcal{M}^{-1} &= [\mathrm{I}-\mathrm{H}\psi\mathcal{K}]^{*}\mathcal{D}^{-1}\,[\mathrm{I}-\mathrm{H}\psi\mathcal{K}] \end{aligned} \tag{31}$$

The first expression defines the Newton-Euler operator factorization of the mass matrix $\mathcal{M}$ in terms of the H hinge articulation, the ϕ rigid body propagation and the M link spatial inertia operators. While this factorization has non-square factors, the second expression describes an alternative factorization involving only square factors with block diagonal $\mathcal{D}$ and block lower-triangular $[\mathrm{I}+\mathrm{H}\phi\mathcal{K}]$ matrices. This factorization involves new spatial operators that are associated with the *articulated body (AB)* forward dynamics algorithm[24,25] for the system. The next expression describes an analytical expression for the inverse of the $[\mathrm{I}+\mathrm{H}\phi\mathcal{K}]$ operator. Using this leads to the final analytical expression for the inverse of the mass matrix. These operator expressions hold generally for tree-topology systems irrespective of the number of bodies, the types of hinges, the specific topological structure and even for the case of non-rigid links.[19]

From the second equation in Eq. 31, we can identify a square m(θ) that satisfies Eq. 15's $\mathcal{M}(\theta)=m(\theta)\,m*(\theta)$ relationship to obtain the following analytical expressions for the desired coordinate transformation matrices for ICMD models:

$$\mathrm{m}(\theta)=[\mathrm{I}+\mathrm{H}\phi\mathcal{K}]\,\mathcal{D}^{\frac{1}{2}},\quad \ell(\theta)=\mathcal{D}^{-\frac{1}{2}}\,[\mathrm{I}-\mathrm{H}\psi\mathcal{K}] \tag{32}$$

We have thus obtained explicit expressions for the transformation matrices needed to go between the and the $\nu\dot{\theta}$ coordinates, and which lead to the following version of the transformation expressions in Eq. 27:

$$v=\mathscr{D}^{\frac{1}{2}}\left[\mathrm{I}+\mathrm{H}\phi\mathscr{K}\right]^{*}\dot{\theta},\quad \dot{\theta}=\left[\mathrm{I}-\mathrm{H}\psi\mathscr{K}\right]^{*}\mathscr{D}^{-\frac{1}{2}}v \quad (33)$$

Evaluation of either of the above expressions in principle requires $\mathrm{O}\left(\mathscr{N}^{2}\right)$ computations for the evaluation of the matrices and and the matrix/vector products.

However, the special internal structure of the spatial operators allows us to entirely avoid evaluating these matrices, and instead carry out the required matrix/vector products recursively with just $\mathrm{O}(\mathscr{N})$ cost[19,25] and the recursive algorithms corresponding to the Eq. 33 transformations are shown in Table 1. Each of these recursions proceeds from the ICMD base towards the tips of the ICMD tree. The algorithm on the left transforms the physical $\dot{\theta}$ velocities into the ν modal coordinates, while the algorithm on the right does the converse. The intermediate $\mathscr{V}(k)\in\mathscr{R}^{6}$ quantity in the recursions is the combined angular and linear velocity of the k^{th} coordinate frame. The computational cost of these algorithms scales linearly with the number of degrees of freedom. For notational simplicity, the algorithms in the table are for serial topology systems, and the more general tree topology versions are described in reference.[19]

In summary, the spatial operator results in this section provide a way to carry out the coordinate transformations with $\mathrm{O}(\mathscr{N})$ cost, and without requiring the expensive evaluation of any of the configuration dependent $\mathscr{M}$, m or ℓmatrices.

4 Theoretical implications for velocity initialization

At the start of a molecular dynamics simulation, initial velocities need to be assigned to the generalized velocity coordinates in a manner that is consistent with the Boltzmann distribution of thermal energy. The simulation temperature for the simulation determines the overall kinetic energy to be assigned to the system.

4.1 Cartesian models

For Cartesian simulations, the equipartition principle in Eq. 7 implies that the kinetic energy can be independently assigned to each of the $\dot{x}(i)$ velocity coordinates using an Boltzmann distribution with mean of ½**kT** such that

$$\left\langle \mathrm{M}^{\frac{1}{2}}\,\dot{x}\,\dot{x}^{*}\mathrm{M}^{\frac{1}{2}}\right\rangle = kTI_{3n} \quad (34)$$

4.2 Unconstrained ICMD models

Since the equipartition principle does not hold for the physical (θ, p) coordinates in an ICMD model, such a procedure cannot be directly used to initialize the $\dot{\theta}$ generalized velocities to properly distribute the thermal energy. Since the equipartition principle is available for Cartesian models, a commonly used option is to begin by assigning the $\dot{x}$ Cartesian atom velocities using the above described Cartesian equipartition principle, and then transition to the $\dot{\theta}$ ICMD generalized velocities. For the full-dimensional BAT ICMD models, such a transition to $\dot{\theta}$ is easily carried out using the relationship

$$\dot{\theta}\overset{28}{=}\mathscr{J}^{-1}(\theta)\,\dot{x} \quad (35)$$

We can check that this procedure is correct by verifying that the ICMD equipartition principle in Eq. 26 holds. Towards this, observe that

$$\langle vv^* \rangle \overset{30}{=} \left\langle \mathrm{M}^{\frac{1}{2}} \mathscr{J} \dot{\theta} \dot{\theta}^* \mathscr{J}^* \mathrm{M}^{\frac{1}{2}} \right\rangle \overset{35}{=} \left\langle \mathrm{M}^{\frac{1}{2}} \dot{x} \dot{x}^* \mathrm{M}^{\frac{1}{2}} \right\rangle \overset{34}{=} kTI_{3n} \quad (36)$$

Thus, as we might intuitively expect, we can conclude that for BAT coordinates, the procedure of initializing the Cartesian velocities, followed by a transformation to the BAT velocities via Eq. 35 is statistically correct.

4.3 Constrained ICMD models

For constrained ICMD models, this procedure for transforming Cartesian velocities to ICMD velocities breaks down. For the constrained case, $\mathscr{N} < 3n$ and the $\mathscr{J}(\theta)$ Jacobian is non-square and non-invertible, and Eq. 35 cannot be used. Instead, the Cartesian velocities need to be mapped to the lower-dimensional ICMD velocities space. Let $P \in \mathscr{R}^{\mathscr{N} \times 3n}$ denote such a mapping matrix so that

$$\dot{\theta} = P\dot{x} \quad (37)$$

We again evaluate $\langle vv^* \rangle$ along the lines of Eq. 36 to obtain

$$\langle vv^* \rangle = \mathfrak{m}^* PP^* \mathfrak{m} \quad kT \quad (38)$$

For this expression to be consistent with the ICMD equipartition principle in Eq. 26 requires that the P mapping matrix be such that $\mathrm{m}^* PP^* \mathrm{m}$ is the identity matrix. One value of P that satisfies this requirement is

$$P = \mathscr{M}^{-1} \mathrm{H} \phi \mathrm{M}^{\frac{1}{2}} \quad (39)$$

because then

$$\mathfrak{m}^* PP^* \mathfrak{m} \overset{39,31}{=} \mathfrak{m}^* \mathscr{M}^{-1} \mathscr{M} \mathscr{M}^{-1} \mathfrak{m} = \mathfrak{m}^* \mathscr{M}^{-1} \mathfrak{m} \overset{15,16}{=} \mathrm{I}_{\mathscr{N}}$$

This P is indeed the correct mapping matrix that ensures that the Cartesian model procedure for distributing thermal energy does so correctly for the ICMD model as well. Unlike the ad hoc projection techniques used in practice,[26] this procedure provides a thermodynamically rigorous method for initializing the velocities in ICMD models from Cartesian velocity assignments. While theoretically correct, a practical disadvantage is that the P matrix in Eq. 39 requires the expensive computation of the mass matrix inverse.

Instead, of this expensive Cartesian velocities based initialization technique, we can exploit the ICMD equipartition principle to develop a much simpler and direct procedure for correctly initializing (constrained and unconstrained) ICMD simulations where the kinetic energy assignment obeys the required Boltzmann distribution. The procedure makes use of the modal coordinates equipartition principle in Eq. 26 to initialize the ν_i ICMD velocity variables with mean ½**kT** energy distributed in accordance with the Boltzmann distribution. Once all the modal coordinates have been initialized, we convert them to $\dot{\theta}$, ICMD physical velocities, using the $\mathrm{O}(\mathscr{N})$ recursive algorithm on the right of Table 1 as was discussed in Section 3.1. Observe that in contrast with Eq. 39, this procedure does not require the explicit computation of the mass matrix inverse.

5 Conclusions

Cartesian MD models are widely used, and a rich body of accompanying theory has evolved that addresses a broad range of topics including statistical mechanics, free energy computations, canonical models, numerical integration techniques etc. to guide their correct use. In contrast, the use of ICMD models, especially constrained ICMD models, is not common. This stems from their added complexity as well as a lack of theoretical understanding of their behavior given the fundamentally different nature of such models. We have begun addressing several issues related to ICMD models to improve the effective use of ICMD simulations. In this paper we have derived the equipartition principle for ICMD models, by introducing a new set of non-canonical modal coordinates. This principle applies to both the unconstrained and constrained types of ICMD models. This sets the stage for rigorous velocity initialization and calculation of torsional entropy from ICMD trajectories.[5,6,9–11,18,27] We have implemented and tested the use of modal coordinate velocities in ICMD simulations and applied it to study protein folding and protein homology model refinement.[20,21] Much still remains to be done in developing, validating and maturing ICMD techniques in areas such as choice of constraints, structure preserving numerical integrators, entropy analysis and their application to problems such as studying protein domain motion, protein structure refinement etc.

Turning our attention to computational issues, we use spatial operators to obtain analytical expressions for the transformations needed to go between the modal and physical velocity coordinates. Additionally, we show that the transformations can be carried out via low-order recursive algorithms that entirely avoid the expensive need for computing the transformation matrices. The availability of such low-order computational algorithms allows us to consider ideas beyond theory and explore the use of modal coordinates for other ICMD dynamics problems.

Such modal coordinates were originally identified as a set of diagonalizing coordinates that decoupled the ICMD (non-Hamiltonian) equations of motion.[19,28] A remarkable property of the modal coordinates is the orthogonality to the Coriolis forces term in the equations of motion - a property that does not hold for equations of motion based on physical velocity coordinates. This orthogonality property has been shown to simplify control and stability analysis for constrained ICMD like systems. We believe that modal coordinates hold promise for the development of model reduction and numerical integration techniques for ICMD dynamics that we plan to address in future research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Tolman, RC. Statistical Mechanics with Applications to Physics and Chemistry. Chemical Catalog Company; 1927.
2. Uline MJ, Siderius DW, Corti DS. J. Chem. Phys. 2008; 128:124301–124317. [PubMed: 18376913]
3. Schafer H, Mark AE, Gunsteren WF. V. J. Chem. Phys. 2000; 113:7809–7817.

4. Zuckerman, DM. Statistical Physics of Biomolecules: An Introduction. CRC Press; 2010. p. 356
5. Mazur AK, Abagyan RA. J. Biomol. Struct. Dyn. 1989; 6:815–832. [PubMed: 2619942]
6. Jain A, Vaidehi N, Rodriguez G. J. Comput. Phys. 1993; 106:258–268.
7. Chen J, Im W, Brooks CL III. J. Comput. Chem. 2005; 26:1565–1578. [PubMed: 16145655]
8. Schwieters CD, Clore GM. Journal of Magnetic Resonance. 2001; 152:288–302. [PubMed: 11567582]
9. Fixman M. Proc. Nat. Acad. Sci. USA. 1974; 71:3050–3053. [PubMed: 16578718]
10. Go N, Scheraga HA. Macromolecules. 1976; 9:535–542.
11. Gunsteren WFV, Karplus M. Macromolecules. 1982; 15:1528–1544.
12. Fixman M. J. Chem. Phys. 1978; 69:1527–1537.
13. Chandler D, Berne BJ. J. Chem. Phys. 1979; 71:5386–5387.
14. Gunsteren WFV. Molecular Phys. 1980; 40:1015–1019.
15. Pear MR, Weiner JH. J. Chem. Phys. 1979; 71:212–224.
16. Mülders T, Swegat W. Molecular Phys. 1998; 94:395–399.
17. Patriciu A, Chirikjian GS, Pappu RV. J. Chem. Phys. 2004; 121:12708–12720. [PubMed: 15606297]
18. Jain A. J. Comput. Phys. 1997; 136:289–297.
19. Jain, A. Robot and Multibody Dynamics: Analysis and Algorithms. Springer; 2011. p. 512
20. Balaraman GS, Park I-H, Jain A, Vaidehi N. J. Phys. Chem. B. 2011; 115:7588–7596. [PubMed: 21591767]
21. Park I-H, Gangupomu V, Wagner J, Jain A, Vaidehi N. J. Phys. Chem. 2012; 116:2365–2375.
22. Tolman RC. Phys. Rev. 1918; 11:261–275.
23. Herschbach DR, Johnston HS, Rapp D. J. Chem. Phys. 1959; 31:1652–1661.
24. Featherstone, R. Rigid Body Dynamics Algorithms. Springer Verlag; 2008.
25. Jain A. Multibody System Dynamics. 2011; 26:335–365. [PubMed: 22102791]
26. Chun HM, Padilla CE, Chin DN, Watanabe M, Karlov VI, Alper HE, Soosaar K, Blair KB, Becker OM, Caves LSD, Nagle R, Haney DN, Farmer BL. J. Comput. Chem. 2000; 21:159–184.
27. Hnizdo V, Gilson MK. Entropy. 2010; 12:578–590.
28. Jain A, Rodriguez G. IEEE T. Robotic. Autom. 1995; 11:571–584.

Table 1

Recursive, base-to-tip algorithms for converting between the $\dot{\theta}$ and ν coordinates using Eq. 33 for serial-topology systems.

$\boldsymbol{\nu} = \mathrm{D}^{\frac{1}{2}}[\mathrm{I} + \mathrm{H}\boldsymbol{\phi}\mathrm{K}]^{*}\dot{\boldsymbol{\theta}}$	$\dot{\boldsymbol{\theta}} = [\mathrm{I} - \mathrm{H}\boldsymbol{\psi}\mathrm{K}]^{*}\mathrm{D}^{-\frac{1}{2}}\boldsymbol{\nu}$
$\mathrm{V}(\mathrm{N}+1) = \mathbf{0}$	$\mathrm{V}(\mathrm{N}+1) = \mathbf{0}$
for $k = \mathrm{N} \cdots 1$	**for** $k = \mathrm{N} \cdots 1$
$\mathrm{V}^{+}(k) = \boldsymbol{\phi}^{*}(k+1,\, k)\mathrm{V}(k+1)$	$\mathrm{V}^{+}(k) = \boldsymbol{\phi}^{*}(k+1,\, k)\mathrm{V}(k+1)$
$\nu(k) = \mathrm{D}^{\frac{1}{2}}(k)\left[\dot{\theta}(k) + \mathrm{G}^{*}(k)\mathrm{V}^{+}(k)\right]$	$\dot{\theta}(k) = \mathrm{D}^{-\frac{1}{2}}(k)\nu(k) - \mathrm{G}^{*}(k)\mathrm{V}^{+}(k)$
$\mathrm{V}(k) = \mathrm{V}^{+}(k) + \mathrm{H}^{*}(k)\dot{\theta}(k)$	$\mathrm{V}(k) = \mathrm{V}^{+}(k) + \mathrm{H}^{*}(k)\dot{\theta}(k)$
end loop	**end loop**