A Rational Approach to Ring Flexibility in Internal Coordinate Dynamics

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Internal coordinate molecular dynamics (ICMD) is an efficient method for studying biopolymers, but it is readily applicable only to molecules with tree topologies, that is with no internal flexible rings. Common examples violating this condition are prolines and loops closed by S-S bridges in proteins. The most important such case, however, is nucleic acids because the flexibility of the furanose rings always plays an essential role in conformational transitions both in DNA and RNA. There are a few long-known theoretical approaches to this problem, but, in practice, rings with fixed bond lengths are closed by adding appropriate harmonic distance restraints, which is not always acceptable especially in dynamics. This paper tries to overcome this handicap of ICMD and proposes a rational strategy which results in practical numerical algorithms. It gives a unified analytical treatment which shows that this problem is very close to the difficulties encountered by the method of constraints in Cartesian coordinate dynamics, and certain ideas of the latter appear helpful in the context of ICMD. The method is affordable for large molecules and generally applicable to all kinds of rings. A specific implementation for five-membered rings is described and tested for a proline-rich polypeptide and a decamer DNA duplex. In both cases conditions are found which make possible time steps around 10 fs in ICMD calculations.

I. INTRODUCTION

Internal coordinate molecular dynamics (ICMD, see Ref. 1 for a historical review) is a recent approach to the simulation of flexible polymers which, unlike the traditional one, employs torsions and, if desired, valence angles and bond lengths as generalized coordinates in the equations of motion. It originates from the Euler-Lagrange-Hamilton formalism of classical mechanics and makes possible modeling of polymers as chains of rigid bodies, which automatically eliminates the most severe time step limitations characteristic for Newtonian MD. In addition, it drastically reduces the configurational space of flexible molecules, which is very useful for conformational searches and for refinement of experimental structures by simulated annealing.

Treatment of flexible cycles is an inherently difficult task for ICMD. The possibility of applying this method to large polymers rests upon recursive algorithms which are applicable only when the molecule is topologically isomorphous to a tree. Any non-rigid cycle, therefore, makes the whole system unsuitable for ICMD. Although a few possible approaches to this problem can be readily sketched, until now, no practical solution has been reported. This difficulty is most critical for simulations of nucleic acids because the five-membered sugar rings connect the bases with the sugar-phosphate backbone, and their relative orientations are, therefore, determined by the pseudorotation states of the sugars. As a result, nucleic acids are completely beyond the scope of ICMD although one cannot say that the problem did not attract attention.

This paper describes a rational solution of the problem of ring flexibility in ICMD. The new approach has much in common with the recent methods of constraints in Newtonian dynamics. The similarity between the difficulties created by ring flexibility in ICMD, and bond length constraints in Newtonian MD, is intuitively clear. Both these problems can be consistently treated by using projection operators in linear spaces, which results in a unified formalism. A fruitful idea used, sometimes implicitly, in Newtonian constraint dynamics is that projection operators can be applied directly in the finite-difference form of the equations of motion. This simplifies computations because certain terms in the analytical equations can be omitted, and immediately results in a time-reversible symplectic numerical integrator.

A specific implementation for the most practically important case of five-membered rings is described and tested here. It employs our earlier analytical approach to ring flexibility but can also be adapted to alternative methods, for instance, with various pseudorotation equations. Numerical algorithms suitable for other specific cases, such as S-S bridges in proteins, are also tested, but such cases are not studied here in detail. For five-membered rings in proteins and nucleic acids specific conditions that make possible time steps around 10 fs are considered.

II. RESULTS AND DISCUSSION

Overview of Earlier Approaches

In this section we outline the general view of the problem of ring flexibility and try to divide it into distinct separable tasks. This problem has been first addressed by
FIG. 1. Schematic representation of a loop of rigid bodies. To impose a tree topology loop (a) must be considered as broken, which can be done in many ways, for example, as in loops (b) or (c). Rigid bodies shown as open circles are joined by hard sticks in pivots shown as closed circles.

Gö and Scheraga[16] who formulated the following general approach later followed by others. Consider the example in Fig. 1. Suppose we want to describe a flexible loop (a) with certain internal coordinates that determine variable angles at pivots and lengths of bonds. A correct definition of internal coordinates always requires that the molecule is represented as a regular tree, which means that, conceptually, loop (a) in Fig. 1 must be considered broken in agreement with a certain tree topology, while a correct loop closure is maintained by applying appropriate constraining conditions. Hereafter this construction is referred to as the underlying tree. The constrained underlying tree gives the desired model with correctly closed loops, but, in derivations, its unconstrained movements are also sometimes considered. Structures (b) and (c) in Fig. 1 demonstrate that there are numerous ways to define the underlying tree of any given loop.

Now suppose we need to sample from the ensemble of closed loop conformations. Internal coordinates can be denoted as an n-vector \( q \) and they should vary concertedly so that the \( k \) scalar constraining conditions

\[
C_\mu(q) = 0, \quad \mu = 1,..., k. \tag{1}
\]

are not violated. By inverting Eqs. (1), a set of \( k \) internal coordinates can be, in principle, computed from the rest, which may be written as

\[
q^d = q^d(q^f) \tag{2}
\]

where \( q^d \) and \( q^f \) are the \( k \)-vector of dependent and \( (n-k) \)-vector of independent variables, respectively. Now \( q^f \) can be freely varied within the range of solubility of Eqs. (1). Dependant coordinates \( q^d \) computed by Eq. (2) always provide a correct loop closure in the underlying tree. Time derivatives of Eq. (2) read

\[
\dot{q}^d = \frac{\partial q^d}{\partial q^f} \dot{q}^f \tag{3a}
\]

\[
\ddot{q}^d = \frac{\partial \dot{q}^d}{\partial q^f} \dot{q}^f + \frac{\partial q^d}{\partial q^f} \ddot{q}^f + \frac{\partial q^d}{\partial q^f} \frac{d}{dt} \frac{\partial q^d}{\partial q^f} \tag{3b}
\]

where \( \frac{\partial q^d}{\partial q^f} \) is a \( k \times (n-k) \) matrix. This approach may be called consistent because, following to the basic idea of internal coordinates, it reduces the number of independent variables to the true number of conformational degrees of freedom.

The above reasoning reveals the first task to be considered, that is, inversion of Eqs. (1) or, in other words, construction of a correctly closed ring geometry for any given \( q^f \). This is generally difficult because Eqs. (1) are non-linear. Practical solutions exist only in a few special cases, notably, there are relatively simple algorithms for loop closure with flexible valence angles [13,15,16]. For the important case of five-membered rings, pseudorotation equations give the most economical solution.\[12\] The second task is the calculation of dependent velocities and accelerations, but usually this presents no serious difficulties.

The possibility to apply this general strategy in ICMD was first addressed in Ref. [13]. Explicit equations of motion in independent variables can be obtained by linear transformations of the familiar ICMD equations for the unconstrained underlying tree. It is useful to reproduce this result here in a compact form. Let us construct \( n \times (n-k) \) matrix \( P \) as

\[
P = \frac{\partial q}{\partial q^f}. \tag{4}
\]

Every column in \( P \) is composed of partial derivatives of all internal coordinates with respect to a certain independent variable. Thus, each column has one unit element, \( n-k-1 \) zeroes and \( k \) derivatives of dependent variables. Any vector \( \dot{q}^f \) yields velocities of the underlying tree

\[
\dot{q} = P \dot{q}^f
\]

that fulfill the loop closure conditions. Similarly, the constrained accelerations are given by

\[
\ddot{q} = P \ddot{q}^f + P \dot{q}^f. \tag{5}
\]

Consider the unconstrained motion of the underlying tree. The corresponding equations of motion can be written as

\[
M(q) \ddot{q} = f(q) + u(q, \dot{q}), \tag{6}
\]

where \( M(q) \), \( f(q) \) and \( u(q, \dot{q}) \) are the mass matrix, the vector of generalized forces and the inertial term, respectively. In Ref. [13] equations for independent variables in a correctly constrained underlying tree were obtained by summing up scalar lines in Eq. (6) corresponding to dependent variables with coefficients from matrix \( P \), and excluding \( \dot{q}^d \) with the help of Eq. (3a). These calculations may be equivalently expressed in a matrix form as

\[
P^* M \dot{q}^f = P^* \left( f + u - M \dot{q}^f \right) \tag{7}
\]
where the asterisk denotes transposition. All accelerations for the constrained underlying tree are computed by substituting \( \ddot{\mathbf{q}} \) into Eq. \((\mathbb{3})\). For the following discussion it is convenient to rewrite it as

\[
\ddot{\mathbf{q}} = \left[ \mathbf{P} (\mathbf{P}^T \mathbf{M})^{-1} \mathbf{P}^T \mathbf{M} \right] \mathbf{M}^{-1} (\mathbf{f} + \mathbf{u}) + (\mathbf{I} - \mathbf{P} (\mathbf{P}^T \mathbf{M})^{-1} \mathbf{P}^T \mathbf{M}) \dot{\mathbf{P}} \dot{\mathbf{q}}^f. \tag{7}
\]

Equations \((\mathbb{6})\) and \((\mathbb{7})\) clearly show that the performance of any numerical algorithm originating from the consistent approach is limited by the necessity of inverting the \((n - k) \times (n - k)\) mass matrix \(\mathbf{P}^T \mathbf{M} \mathbf{P}\). This no longer corresponds to a tree topology therefore the fast recursive algorithms \([\mathbb{8}][\mathbb{9}]\) are inapplicable and, at least at present, only straightforward inversion is possible, which needs \(O[(n - k)^3]\) computations. In practice a reasonable maximum number of variables for calculations with a straightforward mass matrix inversion is around 100. This approach, therefore, is hardly practical for S-S bridges and prolines in globular proteins. A minimalist representation of nucleic acids needs about eight degrees of freedom per nucleotide, which comprises two pseudorotation variables for a furanose ring, one torsion for the base and all backbone torsions. Thus, a decamer duplex would be quite manageable since matrices of separate strands are inverted separately, but a hairpin of the same lengths would be more difficult.

This difficulty could be avoided, in principle, if we did not divide internal coordinates into dependent and independent variables. For instance, we could compute all reaction forces in a closed loop and include them explicitly into equations of motion of the unconstrained tree, which should give correct closed loop dynamics. This idea has been elaborated in robot mechanics \([\mathbb{4}]\) and, at least theoretically, it should result in an \(O(n)\) algorithm. Note also that this would be equivalent to the introduction of holonomic constraints explicitly, similarly to the well-known method of constraints in Cartesian coordinate dynamics \([\mathbb{1}]\). In a certain sense such an approach may be called inconsistent because the resultant system is constrained both implicitly and explicitly, but we will see below that this appears more efficient.

### Projection Operators

In this section we briefly recall a few necessary facts concerning projection operators in linear spaces. Consider a mechanical system of \( N \) free particles. Its configuration is determined by an \( n \)-vector of Cartesian coordinates \( \mathbf{x} \), where \( n = 3N \). Forces applied to particles are given by an \( n \)-vector \( \mathbf{f} \). The possible values of \( \mathbf{f} \) cover a full \( n \)-dimensional vector space \( \mathcal{L}^n \).

Now let us assume that our particles are bound to move along some hypersurface defined by a constraint equation

\[ C(\mathbf{x}) = 0 \]

and that initially they are placed at point \( \mathbf{x}_0 \) with zero velocities. Vector

\[ \mathbf{g} = \nabla C \bigg|_{\mathbf{x} = \mathbf{x}_0}, \]

where \( \nabla \) is a multidimensional gradient operator, is orthogonal to the constraint hypersurface and all its orthogonal vectors form an \((n - 1)\)-dimensional subspace in \( \mathcal{L}^n \) called tangent hyperplane \( \mathcal{P}^{n-1} \). The particles are held on the constraint hypersurface by reaction forces given by vector \( \mathbf{f}^\perp \) collinear to \( \mathbf{g} \). Together with \( \mathbf{f} \) this vector must give \( \mathbf{f}^\parallel \in \mathcal{P}^{n-1} : \)

\[ \mathbf{f}^\parallel = \mathbf{f} + \mathbf{f}^\perp = \mathbf{f} + \alpha(\mathbf{f}) \mathbf{g} \tag{8} \]

where \( \alpha(\mathbf{f}) \) is a scalar function.

It is clear that Eq. \((\mathbb{5})\) applies to any vector \( \mathbf{f} \in \mathcal{L}^n \). It is known also that the sum of any two free forces \( \mathbf{f}_1 + \mathbf{f}_2 \) gives the corresponding sum \( \mathbf{f}_1^\parallel + \mathbf{f}_2^\parallel \), and that \( \mathbf{f} \) multiplied by a constant results in the same multiplication of \( \mathbf{f}^\parallel \). In other words, Eq. \((\mathbb{5})\) in fact defines a linear mapping \( \mathbf{f} \rightarrow \mathbf{f}^\parallel \) from \( \mathcal{L}^n \) to \( \mathcal{P}^{n-1} \), and, consequently, it can be expressed as

\[ \mathbf{f}^\parallel = \mathbf{T} \mathbf{f} \tag{9} \]

where \( \mathbf{T} \) is an \( n \times n \) matrix.

By construction, \( \mathbf{T}^2 = \mathbf{T} \), that is \( \mathbf{T} \) represents a projection operator. Any such matrix can be calculated as

\[ \mathbf{T} = (\mathbf{I} - \nabla C) (\mathbf{I} - \mathbf{D} (\mathbf{G}^T \mathbf{D})^{-1} \mathbf{G}^*) \tag{10} \]

where \( \mathbf{I} \) is the unit matrix, \( \mathbf{D} \) and \( \mathbf{G} \) are basis matrices of the right and left zero spaces of \( \mathbf{T} \), respectively. By definition, vector \( \mathbf{e} \) belongs to the right zero space of \( \mathbf{T} \) if \( \mathbf{T} \mathbf{e} = 0 \). Such vectors form a linear subspace \( \mathcal{D}^k \) in \( \mathcal{L}^n \) and \( n \times k \) matrix \( \mathbf{D} \) in Eq. \((\mathbb{10})\) consists of \( k \) of its basis vectors. It is readily verified that \( \mathbf{T} \mathbf{D} = 0 \). Matrix \( \mathbf{G} \) is constructed in the same way, and it is seen that \( \mathbf{G}^T \mathbf{T} = 0 \). The two zero spaces \( \mathcal{D}^k \) and \( \mathcal{G}^k \) always have the same dimension and they define a unique projection operator.

The physical meaning of \( \mathcal{D}^k \) and \( \mathcal{G}^k \) is clear from the above example. \( \mathcal{D}^k \) determines the direction of projection. Equation \((\mathbb{5})\) shows that, in our example, the corresponding basis consists of a single vector \( \mathbf{g} \). In turn, \( \mathcal{G}^k \) is the orthogonal complement to the tangent hyperplane \( \mathcal{P}^{n-k} \). In our example \( \mathcal{G}^2 \) it is identical to \( \mathcal{D}^1 \), and so we have

\[ \mathbf{T} = 1 - \mathbf{g} (\mathbf{g}^* \mathbf{g})^{-1} \mathbf{g}^* \]

Finally, consider

\[ \tilde{\mathbf{T}} = \mathbf{D} (\mathbf{G}^T \mathbf{D})^{-1} \mathbf{G}^*. \tag{11} \]

It is readily verified that \( \tilde{\mathbf{T}} \) is also a projecting operator. It projects upon \( \mathcal{D}^k \) along the orthogonal subspace of \( \mathcal{G}^k \), that is, along the tangent hyperplane \( \mathcal{P}^{n-k} \), thus making
a complimentary pair with $\mathbf{T}$. Equations (10) and (11) can also be applied to a single projection, which gives two alternative representations. In both cases, the operator is defined by the direction and the hyperplane of the projection. However, in case of Eq. (10) one has to substitute the direction itself and the orthogonal complement for the plane, whereas in Eq. (11) the opposite combination is required.

The Analytical Equations of Constraint Dynamics

In this section we derive the basic equations of motion for constraint dynamics directly from the above projection considerations. These equations are well-known, but our main interest is in the reasoning rather than in the result because similar arguments will later lead us to the required numerical algorithm.

We consider again a system with $n$ degrees of freedom described by an $n$-vector $\mathbf{q}$ and the equations of motion (3). We assume that these equations can be somehow derived and solved without major difficulties. For Newtonian MD these are equations for unconstrained molecules while in the case of ICMD these are equations for trees of rigid bodies. These two models thus play similar roles in our reasonings.

Now let us impose on our system a certain number of explicit constraints defined by Eq. (4). For clarity, from now on we drop superscripts denoting dimensions of subspaces. Equations (4) define a $(n-k)$-dimensional hyper-surface in $\mathcal{L}$ and the system is held on it by generalized reactions $\mathbf{f}^\perp \in \mathcal{G}$ where $\mathcal{G}$ is the subspace of orthogonal vectors

$$\mathbf{g}_\mu = \nabla C_\mu(\mathbf{q})$$

with an $n \times k$ basis matrix $\mathbf{G}$. A straightforward derivation of equations of motion for the constrained system would require evaluation of $\mathbf{f}^\perp$ with subsequent substitution into the r.h.s. of Eq. (3):

$$\mathbf{M} \dot{\mathbf{q}} = \mathbf{f} + \mathbf{u} + \mathbf{f}^\perp. \quad (12)$$

Calculation of reactions can be bypassed as follows.

By taking time derivatives of Eq. (3) one obtains constraining conditions upon the tree velocities and accelerations

$$\mathbf{g}_\mu \dot{\mathbf{q}} = 0$$

$$\mathbf{g}_\mu \ddot{\mathbf{q}} + \dot{\mathbf{g}}_\mu \mathbf{q} = 0 \quad (13a)$$

$$\mathbf{g}_\mu \ddot{\mathbf{q}} + \dot{\mathbf{g}}_\mu \mathbf{q} = 0 \quad (13b)$$

Let us first consider the case $\dot{\mathbf{g}}_\mu = 0$. One can assume, for instance, that particles are moving along space-fixed surfaces. In this case the second term in Eq. (13b) is zero and we see that the constrained accelerations belong to the tangent hyper-plane $\mathcal{P}$. Note also that according to Eq. (12) constrained accelerations are obtained by correcting the corresponding unconstrained vector by $\mathbf{M}^{-1} \mathbf{f}^\perp$, that is, by a vector from a subspace with the basis matrix $\mathbf{M}^{-1} \mathbf{G}$. We see, therefore, that calculation of the constrained accelerations is nothing but a projection $\mathcal{L} \rightarrow \mathcal{P}$ along direction $\mathbf{M}^{-1} \mathbf{G}$. The corresponding operator is readily computed according to Eq. (10)

$$\mathbf{T} = (\mathbf{I} - \mathbf{T}) = \left[ \mathbf{I} - \mathbf{M}^{-1} \mathbf{G} (\mathbf{G}^* \mathbf{M}^{-1} \mathbf{G})^{-1} \mathbf{G}^* \right] \quad (14)$$

By applying it in Eq. (12) we obtain equations of motion

$$\ddot{\mathbf{q}} = \mathbf{T} \mathbf{M}^{-1} (\mathbf{f} + \mathbf{u}) = \left[ \mathbf{I} - \mathbf{M}^{-1} \mathbf{G} (\mathbf{G}^* \mathbf{M}^{-1} \mathbf{G})^{-1} \mathbf{G}^* \right] \mathbf{M}^{-1} (\mathbf{f} + \mathbf{u}). \quad (15)$$

Now consider the case $\dot{\mathbf{g}}_\mu \neq 0$. Equation (13b) indicates that, unlike velocities, the constrained accelerations no longer belong to $\mathcal{P}$, but lie in another hyper-plane which is shifted from the zero of the coordinates. It does not, therefore, represent a subspace in $\mathcal{L}$ and the constrained accelerations can no longer be obtained by a linear mapping like Eq. (4). Let us, however, decompose vector $\ddot{\mathbf{q}}$ as

$$\ddot{\mathbf{q}} = \ddot{\mathbf{q}}_\parallel + \ddot{\mathbf{q}}^\perp \quad (16)$$

where $\ddot{\mathbf{q}}_\parallel \in \mathcal{P}$ and $\ddot{\mathbf{q}}^\perp \in \mathcal{G}$. By substituting Eq. (10) into Eq. (12) we get

$$\mathbf{M} \ddot{\mathbf{q}}_\parallel = \mathbf{f} + \mathbf{u} - \mathbf{M} \ddot{\mathbf{q}}^\perp + \mathbf{f}^\perp. \quad (17)$$

Now we can again use operator $\mathbf{T}$ to compute $\ddot{\mathbf{q}}^\perp$ and, by substituting back to Eq. (14), obtain

$$\ddot{\mathbf{q}} = \mathbf{T} \mathbf{M}^{-1} (\mathbf{f} + \mathbf{u}) + \tilde{\mathbf{T}} \ddot{\mathbf{q}}^\perp \quad (18)$$

Thus, we still avoid explicit calculation of reactions if vector $\ddot{\mathbf{q}}^\perp$ is obtained separately. This is, fortunately, the case. By definition, $\ddot{\mathbf{q}}^\perp$ is a projection of $\ddot{\mathbf{q}}$ upon $\mathcal{G}$ along hyper-plane $\mathcal{P}$. The corresponding operator can be computed by Eq. (11). (Note that it differs from $\tilde{\mathbf{T}}$ in Eq. (4) by its target hyperplane,) By using Eqs. (11) and (13b) we get

$$\ddot{\mathbf{q}}^\perp = \mathbf{G} (\mathbf{G}^* \mathbf{G})^{-1} \mathbf{G}^* \ddot{\mathbf{q}} = -\mathbf{G} (\mathbf{G}^* \mathbf{G})^{-1} \mathbf{G}^* \ddot{\mathbf{q}} \quad (19)$$

and substitution of Eqs. (14) and (19) into Eq. (18) gives the required equation of motion

$$\ddot{\mathbf{q}} = \left[ \mathbf{I} - \mathbf{M}^{-1} \mathbf{G} (\mathbf{G}^* \mathbf{M}^{-1} \mathbf{G})^{-1} \mathbf{G}^* + \mathbf{M}^{-1} \mathbf{G} (\mathbf{G}^* \mathbf{M}^{-1} \mathbf{G})^{-1} \mathbf{G}^* \right] \mathbf{M}^{-1} (\mathbf{f} + \mathbf{u}) - \mathbf{M}^{-1} \mathbf{G} (\mathbf{G}^* \mathbf{M}^{-1} \mathbf{G})^{-1} \mathbf{G}^* \ddot{\mathbf{q}} \quad (20)$$

Note that for Cartesian coordinates this gives the same equation as that derived by using Lagrange multipliers. On the other hand, it is seen from Eqs. (4) and (10) that

$$\ddot{\mathbf{q}}^f = \tilde{\mathbf{P}} \ddot{\mathbf{q}}^f$$

and thus Eq. (4) is equivalent to Eqs. (18) and (20). They involve the same projection operation, but employ
two alternative representations of the operator. These two representations correspond to two alternative approaches to constraints in dynamics and dictate opposite trends in computational strategies. In case of Eq. (20) the projection operator is specified by the target plane and the orthogonal compliment to the projecting direction, that is according to Eq. (11). This leads to inversion of a \((n-k)\times(n-k)\) matrix and prompts a reduction of the degrees of freedom in the system. In contrast, in the case of Eq. (20) the operator is specified by the direction and the orthogonal compliment to the target plane, that is corresponding to Eq. (10), which results in inversion of constraints and, consequently, keeping a possibly large number of degrees of freedom. In the second case, matrix \(M^{-1}\) is used several times, but this is not computationally limiting and in practice Eq. (20) appears applicable to large systems.

Let us finally obtain quasi-Hamiltonian equations for the same system. For the unconstrained underlying tree these equations can be expressed as

\[
\dot{\mathbf{p}} = \mathbf{f}(\mathbf{q}) + \mathbf{w}(\mathbf{q}, \dot{\mathbf{q}}) \tag{21a}
\]

\[
\dot{\mathbf{q}} = M^{-1} \mathbf{p} \tag{21b}
\]

where \(\mathbf{p}\) is the \(n\)-vector of conjugate momenta and \(\mathbf{w}(\mathbf{q}, \dot{\mathbf{q}})\) is the corresponding inertial term. In order to get the equations for the constrained tree we just need to evaluate generalized reactions from Eqs. (13) and (20) and add them to the r.h.s. of Eq. (21b). The vector of reaction is

\[
\mathbf{f}^\perp = -\mathbf{G}(\mathbf{G}^\dagger M^{-1} \mathbf{G})^{-1} \left[ \mathbf{G}^\dagger \dot{\mathbf{q}} + \mathbf{G}^\dagger \mathbf{M}^{-1} (\mathbf{f} + \mathbf{u}) \right], \tag{22}
\]

and the resultant equations read

\[
\dot{\mathbf{p}} = \left[ \mathbf{I} - \mathbf{G} \left( \mathbf{G}^\dagger M^{-1} \mathbf{G} \right)^{-1} \mathbf{G}^\dagger \mathbf{G} \mathbf{M}^{-1} \right] \mathbf{f} + \mathbf{w} - \mathbf{G} \left( \mathbf{G}^\dagger M^{-1} \mathbf{G} \right)^{-1} \left( \mathbf{G}^\dagger \dot{\mathbf{q}} + \mathbf{G}^\dagger \mathbf{M}^{-1} \mathbf{u} \right) \tag{23a}
\]

\[
\dot{\mathbf{q}} = \mathbf{M}^{-1} \mathbf{p}. \tag{23b}
\]

The last equations are preferred because they are suitable for symplectic numerical integration and provide much better average properties of dynamic trajectories with large time steps.

**Numerical Algorithm**

Equations (23) have the same general form as Eq. (21) and are suitable for the implicit leapfrog integrator designed for the latter. However, here I prefer to follow the well-tested approach of the Newtonian MD, which avoids a straightforward integration of the analytical equations, and uses projection considerations to derive a high precision numerical algorithm. The main idea becomes clear from the following example. Consider an Euler step in Cartesian coordinates:

\[
\mathbf{v}_1 = \mathbf{v}_0 + \mathbf{M}^{-1} \left( \mathbf{f}_0 + \mathbf{f}_0^\perp \right) h \tag{24a}
\]

\[
\mathbf{x}_1 = \mathbf{x}_0 + \mathbf{v}_1 h \tag{24b}
\]

where \(h\) is the step size and subscripts refer to the time step number. Suppose coordinates \(\mathbf{x}_0\) and velocities \(\mathbf{v}_0\) satisfy constraints with absolute accuracy. Equation (24a) with an exact reaction \(\mathbf{f}_0^\perp\) computed by using Eq. (23), for instance, would give velocities \(\mathbf{v}_1\) with an approximation error of \(O(h^2)\). A similar error would be propagated to the constraint conditions at the next step. Note, however, that, according to Eq. (24b), we can minimize deviation of the trajectory from the next step constraint hyperplane \(\mathcal{P}_1\) by requiring that \(\mathbf{v}_1 \in \mathcal{P}_0\). Effectively, this means that, instead of the true reaction force \(\mathbf{f}_0^\perp\), we substitute into Eq. (24a) another vector which provides a projection of \(\mathbf{v}_0 + \mathbf{M}^{-1} \mathbf{f}_0^\perp\) upon \(\mathcal{P}_0\). Algorithm (24), therefore, becomes

\[
\mathbf{v}_1 = \mathbf{T}_0 \left( \mathbf{v}_0 + \mathbf{M}^{-1} \mathbf{f}_0^\perp \right) h \tag{25a}
\]

\[
\mathbf{x}_1 = \mathbf{x}_0 + \mathbf{v}_1 h \tag{25b}
\]

This basic idea is used in the SHAKE and LINKS algorithms of Cartesian MD where unconstrained bond lengths are corrected by using previous bond directions. The projection in Eq. (25a) does not eliminate the error in the constraints, but only gives the best first approximation. The residual error can be controlled by feedback schemes which add a small out-of-plane correction to the projected vector \(\mathbf{v}_1\) so as to eliminate accumulation.

Now consider the implementation of the above strategy for Eqs. (23). With our present notation the kernel of the implicit leapfrog integrator for Eq. (21) reads

\[
\mathbf{f}_n = \mathbf{f}(\mathbf{q}_n) \tag{26a}
\]

\[
\circ \quad \mathbf{q}_{n+\frac{1}{2}} = \mathbf{q}_{n-\frac{1}{2}} + \left( \dot{\mathbf{q}}_{n-\frac{1}{2}} + \dot{\mathbf{q}}_{n+\frac{1}{2}} \right) \frac{h}{2} \tag{26b}
\]

\[
\circ \quad \mathbf{p}_{n+\frac{1}{2}} = \mathbf{p}_{n-\frac{1}{2}} + \mathbf{f}_n h + \left( \mathbf{w}_{n-\frac{1}{2}} + \mathbf{w}_{n+\frac{1}{2}} \right) \frac{h}{2} \tag{26c}
\]

\[
\circ \quad \dot{\mathbf{q}}_{n+\frac{1}{2}} = \mathbf{M}^{-1} \mathbf{p}_{n+\frac{1}{2}} \tag{26d}
\]

\[
\circ \quad \mathbf{q}_{n+1} = \mathbf{q}_n + \dot{\mathbf{q}}_{n+\frac{1}{2}} h \tag{26e}
\]

where the conventional notation is used for denoting on-step and half-step values. The lines marked by circles are iterated until convergence of Eqs. (26b) and (26c). Reactions depend upon both coordinates and velocities, therefore, if computed explicitly, they should have been added to Eq. (26d) to give

\[
\mathbf{p}_{n+\frac{1}{2}} = \mathbf{p}_{n-\frac{1}{2}} + \mathbf{f}_n h + \left( \mathbf{w}_{n-\frac{1}{2}} + \mathbf{w}_{n+\frac{1}{2}} \right) \frac{h}{2} + \left( \dot{\mathbf{f}}^\perp_{n-\frac{1}{2}} + \dot{\mathbf{f}}^\perp_{n+\frac{1}{2}} \right) \frac{h}{2} \tag{26f}
\]

Following the above strategy we require that \(\mathbf{f}^\perp_{n+\frac{1}{2}}\) provide a projection of the unconstrained predicted velocities upon \(\mathcal{P}_{n+\frac{1}{2}}\), which results in the following sequence of calculations.
\[ f_n = f(q_n) \]  
\[ q_n + \frac{1}{2} = q_n - \frac{1}{2} + \left( \dot{q}_n + \frac{1}{2} \dot{q}_{n+\frac{1}{2}} \right) \frac{h}{2} \]  
\[ \vec{p}_{n+\frac{1}{2}} = \vec{p}_n - \frac{1}{2} \vec{f}_n h + \left( \vec{w}_{n-\frac{1}{2}} + \vec{w}_{n+\frac{1}{2}} \right) \frac{h}{2} + f^+_n \frac{h}{2} \]  
\[ \dot{q}_n + \frac{1}{2} = T_{n+\frac{1}{2}} M^{-1}_{n+\frac{1}{2}} \vec{p}_{n+\frac{1}{2}} \]  
\[ \vec{p}_{n+\frac{1}{2}} = M_{n+\frac{1}{2}} \dot{q}_{n+\frac{1}{2}} \]  
\[ f^+_n \frac{h}{2} = \vec{p}_{n+\frac{1}{2}} - \vec{p}_{n-\frac{1}{2}} \]  
\[ q_{n+1} = q_n + \dot{q}_{n+\frac{1}{2}} h \]  

Equations (27) represent the kernel of the new algorithm. The prediction step necessary to enter the iterative cycle of Eqs. (27) is made by using the previous half-step values instead of \( \dot{q}_{n+\frac{1}{2}} \) and \( \vec{w}_{n+\frac{1}{2}} \) in Eqs. (27b) and (27c). It is clear, however, that, if not additionally controlled, the ideal ring geometry specified by Eqs. (1) would degrade because of the approximation errors in Eqs. (27). There are numerous case-specific ways to handle this problem and some of them are considered below.

**Implementation for Five-Membered Rings**

In this section we consider an implementation of the above algorithm with examples of specific solutions of the remaining practical difficulties, such as the construction of a correctly closed loop conformation and calculation of the projection operator. Our present implementation is specifically suited for five-membered rings and has been tested for proline-rich polypeptides and nucleic acids. Cystine bridges in proteins present a somewhat different case and should be treated separately.

Consider once more Fig.1. It is known since the first analysis by Gö and Scheraga [2] that the problem of loop closure in internal coordinates is generally reduced to six coupled equations. Loop (b) in Fig.1 shows where this number comes from. If the loop is broken as shown, each half of the broken rigid body has six degrees of freedom. In order to close the loop, six rigid body coordinates of the two parts must be equated. Structure (c) in the same figure shows, however, that the complexity of the problem can sometimes be reduced just by choosing a different underlying tree. We see that, if all angles are variable, closure in loop (c) needs only one distance constraint. The number of constraining conditions is always equal to the number of degrees of freedom taken from the underlying tree by the loop closure. All three loops in Fig.1 are similar, but the underlying tree in (b) has five degrees of freedom more than in (c). For our algorithm construction (c) is certainly preferable.

Let us now turn to five-membered rings. It is known that their internal motions are well described as pseudorotation with only two parameters [30]. Pseudorotation equations can give constraints Eqs. (1) in an explicitly inverted form, which simplifies calculations. However, such small rings are flexible only if valence angles vary and, therefore, any underlying tree has rather many degrees of freedom. Thus, the number of scalar constraints effectively introduced by the pseudorotation approach is very large even compared with loop (c) in Fig.1. On the other hand, as we just have seen, this number, in principle, can be reduced to one per ring, and this appears rather easy.

Figure 2 shows the underlying tree for a five-membered ring. Atoms are numbered 1,..,5, with this ordering in ribose or deoxyribose corresponding to C₄′, C₃′, C₂′, C₁′, O₅′ and the broken bond C₁′...O₄′. The ring conformation is determined by five valence and dihedral angles q₁,...,q₅ indicated by arrows. Let \( r_{11},...,r_5 \) denote atom position vectors and \( l_{ij} \) and \( e_{ij} \), \( i,j = 1,...,5 \) denote the interatomic distances and the corresponding unit vectors. Directions and positions of rotation axes of ring variables are specified by the unit vectors \( e_{11},...,e_5 \) and position vectors \( r_{m1},...,r_{m5} \), respectively. The constraint condition is

\[ C = |r_5 - r_1| - l_{15} = 0 \]  

We consider firstly calculation of the projection operator \( \mathbf{T} \). Each ring contributes to the basis matrix \( \mathbf{G} \) a single vector \( \mathbf{g} \) with only five non-zero components obtained by straightforward differentiation of Eq. (28):

\[ g_i = \partial C / \partial q_i = e_{1i} \times (r_5 - r_{m_i}) \]  

These computations are sufficient to evaluate \( \mathbf{T} \). In practice it is used in Eq. (27d) in the factorized form of Eq. (14), which results in several matrix-vector multiplications. Only the term \((\mathbf{G}^T \mathbf{M}^{-1} \mathbf{G})^{-1}\) needs to be
computed separately, and the cost of these computations appears minor. The product $k \times k$ matrix is small and essentially diagonal because constraints in different rings are only weakly coupled. In addition, I have found that this term converges faster than the overall iterative cycle, Eqs. (27b-d), and there is no need to recalculate it after the first two iterations.

The small deviations of the constrained bond lengths $l_{15}$ caused by the approximation errors can be either eliminated by exact analytical ring closure or reduced to a low and stable level by feedback corrections. The analytical closure is simple. Let us take variables $q_1, \ldots, q_4$ as independent and compute the last valence angle $q_5$, so that Eq. (28) is fulfilled. Variables $q_1, \ldots, q_4$ specify positions of atoms 1,...,4 and the orientation of the plane of $q_5$ specified by vectors $e_{34}$ and an in-plane unit vector $e_{345}$ orthogonal to $e_{34}$. We may write

$$r_{45} = l_{45} (x e_{34} + y e_{345})$$

where $x$ and $y$ are the two unknown in-plane coordinates of the unit vector $e_5$. They are found from the constraint Eq. (28) and the normalization condition, which results in

$$x (e_{14} e_{34}) + y (e_{14} e_{345}) = \frac{l_{14}^2 - l_{15}^2 - l_{24}^2}{2 l_{14} l_{45}}$$

$$x^2 + y^2 = 1$$

This system is reduced to a square equation and gives a single $x > 0$ solution, which solves the task. Derivatives of the dependent angle $q_5$, which are normally used only for computing energy gradients during minimization, are

$$\frac{\partial q_5}{\partial q_i} = -g_i / g_5$$

The feedback algorithm is constructed as follows. Suppose, at the nth step, we have a non-zero value $C_n$ in Eq. (28). We require that

$$C_n + \lambda \frac{\partial C}{\partial q} \tilde{q} = 0,$$

which means that at the next time step the accumulated error must be zeroed to the first order. It is clear that for each ring only the component of $\tilde{q}$ orthogonal to the constraint hypersurface matters and from Eq. (32) it is evaluated as

$$\tilde{q}^n_{n+\frac{1}{2}} = -C_n \frac{\tilde{q}}{\|\tilde{q}\|^2}.$$

Vectors $g$ are mutually orthogonal and by combining Eqs. (33) for all rings we obtain a corresponding component $\tilde{q}^n_{n+\frac{1}{2}}$ for the whole molecule. To compute the correcting velocity $\tilde{q}^n_{n+\frac{1}{2}}$ we require that it result from a variation of reactions and thus belongs to the subspace with the basis matrix $M^{-1}G$. This gives a projection

$$\tilde{q}^n_{n+\frac{1}{2}} = T \tilde{q}^n_{n+\frac{1}{2}} = M^{-1}G (G^*M^{-1}G)^{-1} G^* \tilde{q}^n_{n+\frac{1}{2}}.$$ (34)

The last computation tends to reduce the extra mechanical work introduced by the algorithm. The correction obtained may be used inside the iterative cycle of the algorithm or just added to $\tilde{q}^n_{n+\frac{1}{2}}$ at the end. Also, $\tilde{q}^n_{n+\frac{1}{2}}$ can be computed for on-step or for half-step conformations, or both such vectors may be combined. These alternatives give a series of slightly different algorithms which are compared in the numerical tests below. Note, however, that both the analytical closure and the feedback schemes break the time reversibility of algorithm and should generally increase the drift of the total energy.

Numerical Examples

In the numerical tests presented below we address two issues. First, we test the accuracy of the ring closure provided by the new algorithm with and without additional corrections. Second, we check its stability with elevated time steps, notably, the possibility of step sizes around 10 fsec for proteins and nucleic acids. This specific value is targeted because it has been found optimal in a certain sense, for in-water simulations of proteins.

We consider two test examples: one for proteins and one for nucleic acids. The first is a 36 residue fragment of a collagen triple helix which involves 24 prolines (file 1bff in the protein database). Parameters for the amino acids were taken from the AMBER94 set. Except for prolines, all bond lengths and bond angles were fixed at standard values according to the standard geometry approximation. The second test system is a decamer DNA duplex (TA)$_{24}$. Nucleotide geometry was taken from FLEX force field to provide compatibility with JUMNA program, which was used for preparation of the initial duplex conformations. Except for sugar rings, the geometry of the nucleotides was fixed, that is the bases were rigid and all other bond lengths and bond angles were fixed. Calculations have been performed without explicit solvent by using the AMBER94 force field with a dielectric constant $\varepsilon = r$ and phosphate charges in DNA reduced by 0.5. These conditions emulate the effects of ion condensation and provide a reasonably accurate approximation in conformational analysis of nucleic acids.

Pyrrolidine and furanose rings are treated similarly by a single program. The furanose underlying tree has been detailed above. In the analogous construction for prolines the NC$_5$ bond is broken and replaced by a distance constraint. Our approach generally allows for arbitrary freezing of internal coordinates and thus can consider numerous different representations of such rings. Here we consider a model with only bond lengths fixed and all intra-cyclic valence angles free. These choices leave several fast bond angle bending modes active, notably, the scissor H-C-H mode with a frequency of around 1500
cm$^{-1}$. Theory says that for a step size of 10 fs, the maximum frequency should be 3 times lower. To achieve this, additional moments of inertia of 9 amu·Å$^2$ are applied to C-H bonds as described earlier. Following earlier conclusions, other hydrogen-only rigid bodies, like thymine methyls, have additional inertia of 4 amu·Å$^2$ added.

With these modifications, the pseudorotation normal modes with frequencies around 550 and 640 cm$^{-1}$ for DNA and collagen, respectively, become the fastest and they already correspond to a harmonic characteristic time step between 9 and 10 fs for leapfrog-equivalent integrators. However, with unfavorable collision angles, non-hydrogen ring atoms with all valence angles free have a considerably smaller effective inertia than similar atoms in models with fixed bond angles. In preliminary tests (not shown here) I observed an anharmonic limitation below 10 fs at normal temperature which could be overcome by an additional increase of the ring inertia. Here I show results obtained with the moments of ring C-C and C-O bonds increased by 15 amu·Å$^2$ and 2 amu·Å$^2$, respectively. This should make the inertias of all ring bonds similar and approximately equal to that of a water molecule, with a 50% increase for C-C bonds. As a side effect, the fastest pseudorotation frequencies are shifted down below the already lowered hydrogen scissor modes, and the latter thus remain the fastest in both test systems.

Stability and step size limits were evaluated with the testing technique and equilibration protocols proposed and analyzed in detail elsewhere. In this method, the test trajectory is repeatedly calculated always starting from exactly the same constant-energy hypersurface. In each run, certain system averages are evaluated and compared with “ideal” values, i.e. the same parameters obtained with a very small time step. The choice of such parameters has been discussed in detail earlier. Here we use only the total energy, $E = \bar{U} + \bar{K}$ and its drift ($E$-drift), where $\bar{U}$ and $\bar{K}$ are average potential and kinetic energies computed for integer steps and half-steps, respectively. As in the previous study, we take a deviation of $0.2\text{D}[\bar{U}]$, where $\text{D}[\cdot]$ denotes operator of variance, as the upper acceptable level for deviation of $E$. The step size maximum determined is denoted as $h_c$ and called “characteristic”. The $E$-drift is exactly zero for ideal harmonic systems and is thus a good indicator of anharmonic effects. Virtually harmonic conditions are simulated by reducing the temperature down to 0.1K with the same equilibration protocol as before. Relevant harmonic frequencies were evaluated from low temperature spectral densities of autocorrelation functions of appropriate generalized velocities. In all production runs the duration of the test trajectory was 10 psec.

The results of such testing are shown in Figs. and . For both model systems the low and normal temperature plots have characteristic qualitative differences, but $h_c$ does not change with temperature indicating that the time step limitations are harmonic. The $h_c$ values are close to the expected harmonic estimate. The small
difference observed between the two systems can be attributed to a three times larger number of hydrogen scissor modes in collagen. We see that the projection step in algorithm (27) does not deteriorate the high stability of the original leapfrog algorithm. We conclude also that our model for five-membered rings allows calculations with $h \approx 10$ fsec. The last conclusion has been checked by computing several nanosecond trajectories of different DNA oligomers (results not shown).

Plots in Figs. 5 and 6 are obtained by algorithm (27) without corrections of constrained bond lengths. Before considering the effects of such corrections let us look more carefully at how constraint distances behave in the above conditions. Since algorithm (27) keeps no information about the initial bond lengths a diffusive drift from initial values is possible. Note, however, that the constrained distances are just additional first integrals of the constrained equations of motion, like momenta or the total energy. For leapfrog-equivalent integrators deviations in first integrals caused by approximation errors are normally oscillatory rather than diffusive, and the drift may thus be small.

Figure 5 shows the time variation of a CN bond in proline during a 1 nsec trajectory. This trajectory has been computed for a single terminally blocked residue at normal temperature with the same conditions as above. It is seen that the fluctuations have many time scales, but even in the slowest one they are not evidently diffusive. The insertion plot shows that the high frequency amplitude of the fluctuations levels starting from the very first time step. It scales as $O(h^2)$ in agreement with the general properties of leapfrog-like algorithms (not shown). The high-frequency amplitude is evidently larger than diffusive deviations accumulated for tens of picoseconds, and, therefore, infrequent periodical corrections should be sufficient to keep deviations within this range. Such a possibility is illustrated by the solid line in the same figure where the analytical ring closure was applied once every 10 psec. One may note that this gives a reasonable and certainly the safest correction strategy.

Table 1 compares several correcting schemes discussed in the previous section. We noted above that numerous feedback algorithms are possible due to variation of two conditions. First, correction of generalized velocities can be added within the iterative cycle or after it. The last option, however, always yields a considerably higher E-drift and such algorithms are not included in Table 1. Second, there are two possible directions of the correcting vector computed for on-step rings and half-step rings, respectively. Only one of the two directions, or an average of the two vectors, can be used, or else they can alternate between time steps. In the last case, however, a dramatic loss of the overall stability of the algorithm is induced. Thus, among many variants only three feedback strategies included in Table 1 give acceptable results. The data have been obtained for 10 psec trajectories of the DNA decamer with a 10 fsec step size. Trajectories started from the same initial state with sugar rings closed exactly.

We noted above that any correcting algorithm is likely to increase the E-drift. It appears, however, that the increase is usually below the noise level for the step sizes of interest, which is clearly seen in Table 1 and Fig. 5. Except for half-step feedback corrections the E-drift is within the range of fluctuations in Fig. 5(b). A certain increase in E-drift is observed, however, with much smaller time steps as well as with $h > h_c$. Very good results are obtained with analytical ring closure, which seems to be the best choice for furanose and proline rings. It should be noted that, in this case, with any step size, iterations in Eqs. (27) converge only up to a relative accuracy of $10^{-5}$ and then start looping. This, however, does not seem to affect either the accuracy in terms of energy conservation, or the long time stability of the algorithm, which also has been checked for nanosecond trajectories.

Although feedback algorithms appear unnecessary for five-membered rings they still present significant interest especially for S-S bridges were both the analytical closure and the periodical corrections are not easy. Table 1 shows that, as expected, the three feedback algorithms improve the accuracy in the targeted rings. Improvements are not spectacular, but it is important to note that the corrected levels of deviations are stable in time. In this respect the last algorithm in Table 1, which manages to correct both on-step and half-step distances, is the most promising.
TABLE I. The quality of the ring closure obtained with different correcting strategies. Data from 10 psec trajectories of (TA)_5 starting from the same initial state with all rings closed exactly. Time step 10 fsec. The rms deviations of closing bond lengths from ideal values are shown, with corresponding maximal values given in brackets.

| Algorithm            | on-step rings ($\times 10^{-3}$Å) | half-step rings ($\times 10^{-3}$Å) | E-drift ($\times 10^{-2}$ kcal/psec) |
|----------------------|-----------------------------------|-----------------------------------|------------------------------------|
| No correction        | 1.50(11.3)                        | 0.757(6.34)                       | -9.23                              |
| Analytical closure   | 0(0)                              | 0(0)                              | -3.49                              |
| Feedback on-step     | 0.294(1.84)                       | 1.52(7.81)                        | 5.71                               |
| Feedback half-step   | 1.53(12.0)                        | 0.369(2.90)                       | -39.5                              |
| Feedback mixed       | 0.837(5.72)                       | 0.852(6.04)                       | -8.94                              |

III. CONCLUSIONS

This study is, to my knowledge, the first successful attempt to develop a practical ICMD approach to large molecules with internal flexible rings. It is shown here that is imposing explicit constraints upon a system already constrained implicitly, results in algorithms as fast and as stable as those for ICMD simulations of polymers with the tree topology. For the important case of five-membered rings in nucleic acids and proteins, calculations with time steps around 10 fsec are shown to be possible.

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