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DESCRIBING THE EQUATION OF MOTION IN DIHEDRAL ANGLES — A METHOD FOR *IN SILICO* FOLDING OF PROTEINS

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The successful deciphering of the human genom has highlighted an old challenge in protein science: for most of the resolved protein sequences we do not know the corresponding structures and functions. Neither do we understand in detail the mechanism by which a protein folds into its biologically active form. Computer experiments offer one way to evaluate the sequence-structure relationship and the folding process but are extremely difficult for detailed protein models. This is because the energy landscape of all-atom protein models is characterized by a multitude of local minima separated by high energy barriers. Here, we describe an algorithm that allows one to partially overcome this multiple-minima problem. For this purpose a formulation of Lagrange's equation of motion for proteins described by internal coordinates is presented. Unlike in the previous work, not only velocities and accelerations are described by bond length, bond angles and dihedral angles, but a complete formalism is presented that includes also the positions of atoms and rotation vectors.

Успешное декодирование генома человека выдвинуло на первый план старую проблему изучения белков: для большинства расшифрованных последовательностей белков мы не знаем соответствующие структуры и функции. Точно так же мы не понимаем механизм, по которому белок переходит в биологически активную форму. Компьютерные эксперименты позволяют найти способ вычисления соотношения «последовательность–структура» и фолдинга, но он становится крайне сложным при описании подробных моделей белков. Это происходит потому, что энергетический ландшафт полноатомных моделей белков характеризуется множеством локальных минимумов, разделенных высокоэнергетическими барьерами. Здесь представлен алгоритм, позволяющий частично преодолеть эту проблему множественных минимумов. С этой целью формулируются уравнения движения Лагранжа для белков, описываемых внутренними координатами. В отличие от предыдущей работы с помощью длины связи, угла связи и двугранного угла не только описываются скорости и ускорения, но и строится полный формализм, включающий также положения атомов и векторы вращения.

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INTRODUCTION

One of the most common and important classes of molecules in living systems are proteins. Muscles and connective tissues are formed by them, and as enzymes, they catalyze and regulate biochemical reactions in the cell. Greatly differing in size and structure, all proteins are chemically linear chain molecules with the twenty naturally occurring amino acids as monomers. Locally, regular elements like helices, sheets and turns are formed, but the biological function of a protein is decided by its unique overall three-dimensional shape that is specified solely by the sequence of amino acids.

The sequence of amino acids that make up a protein is set in the genome. Hence, after the successful completion of the human genome project one knows in principal the chemical composition of all proteins in the human body. However, for most of the resolved protein sequences one does not know the corresponding structures. Since proteins are only functional if they fold into their specific shape, it is important to understand how the structure and function of proteins emerge from their sequence of amino acids.

One possibility to unveil the sequence-structure (function) relationship are computer experiments. Most proteins exist at room temperature in a *unique* structure that one can identify with the lowest *potential* energy conformation. However, simulations at these temperatures are extremely difficult for detailed protein models. This is because the energy landscape of all-atom protein models is characterized by a multitude of local minima separated by high energy barriers. This multitude of potential traps is at least in part due to the large number of degrees of freedom in regular molecular dynamics simulations of proteins.

In many biophysical and biochemical simulations the motion of the atoms is constraint and the number of degrees of freedom is less than $3N$, where N is the number of systems. In such a case it becomes advantageous to go to a set of internal coordinates that reflect the true degrees of freedom of the system. An example are proteins, where the length of chemical bonds and the bond angles fluctuate little, and therefore their movement can often be neglected. In fact, the ECEPP force field Ref. [5] assumes explicitly such a fixed geometry, and a configuration of a protein is described as a set of dihedral angles ϕ, ψ, ω (for the backbone) and χ's (for the side chains).

The advantages of such an approach are obvious: the time evolution of much less variables needs to be calculated. For instance, the pentapeptide Met-enkephaline has 75 atoms. In Cartesian coordinates one has to solve 225 equations of motions, in internal coordinates, however, only 24 equations of motion (assuming bond length and bond angles fixed as assumed in the ECEPP force field). Consequently, attempts were already made earlier to derive the equation of motions of a protein in internal coordinates. To our knowledge, the first such an attempt can be found in Ref. [1]. However, the equations derived in this work are not fully about internal coordinates as some variables are still expressed in Cartesian coordinates. Here, we take up their approach and present a formulation that allows a formulation of the equation of motion of a protein solely in internal coordinates. Most of the construction and notation in our work follows Ref. [1]. We present both a general description that allows also in principal for variable bond length or bond angles, and the simplified equations for the case where these quantities are kept fixed.

1. DEFINITIONS AND NOTATIONS

An important instrument in our study is the unit vector which has only direction. Because of the natural correspondence between unit vectors and points on the unit sphere one can discuss directions using spherical trigonometry.

For instance, the unit vectors $\hat{\mathbf{a}}$, $\hat{\mathbf{b}}$ and $\hat{\mathbf{c}}$ are regarded as vertices of the spherical triangle in Fig. 1. The angles α, β and $\gamma \in \langle 0; \pi \rangle$ between pairs of the vectors generate sides of this triangle.

Since we will represent all torsion angles on the unit sphere, we need to distinguish convex and concave dihedral angles. One way, according to Ref. [4], is to consider them as angles

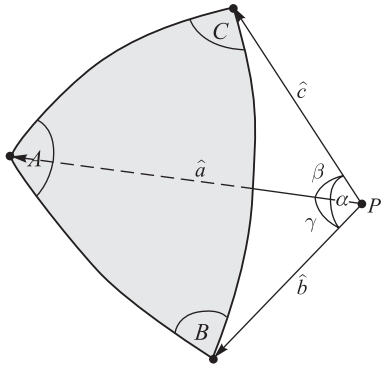

Fig. 1. Representation of unit vectors on the unit sphere

with a counterclockwise orientation. So, if the angle $A \in (-\pi;\ \pi\rangle$ in Fig. 1 is positive, then it poses the angle $\sphericalangle(\hat{\mathbf{b}}, \hat{\mathbf{a}}, \hat{\mathbf{c}})$, as a dihedral angle between faces represented by pairs $\hat{\mathbf{a}}$, $\hat{\mathbf{b}}$ and $\hat{\mathbf{a}}$, $\hat{\mathbf{c}}$ in this counterclockwise order. We shall write $A = \sphericalangle(\hat{\mathbf{c}}, \hat{\mathbf{a}}, \hat{\mathbf{b}})$, if it is negative. Note that we use here and otherwise in the text mathematical terms as defined and explained in Ref. [6].

2. INTERNAL VARIABLES

Ignoring global translations and rotations our aim is to describe the internal motion of all atoms in the language of internal coordinates. Let us suppose that the positions and motions of all atoms of a molecular conformation are given in internal coordinates. In this case, a **tree** structure on the set of all atoms follows, as the positions of the atoms can be described by relations to neighbours. In this picture, atoms can be considered as nodes and bonds as edges of the tree. Note that in order to complete the tree, some virtual intermolecular edges need to be added. An appropriate elimination of edges (**Steiner tree**) keeps all nodes in a sparse tree conformation. An arbitrary node is now chosen as the root of this tree and anchors the system to a fixed point in the space. This origin has the position vector $\mathbf{r_1}$ and needs to be considered as an additional virtual node.

Each atom is connected with the origin by exactly one branch. The height of the node is the number of elements in such a branch. Because every quantity arising in our expressions corresponds to a node in particular branch only, it is indexed just by the height of the related node.

We distinguish three internal coordinates for a node (i.e., atom) characterized by a vector $\mathbf{r_i}$ that points inside a given branch onto an atom $\bar{\mathbf{r}}_\alpha$, which has the global index α. The first one is the torsion (dihedral) angle $\Phi_i = \sphericalangle(-\hat{\mathbf{f}}_{\mathbf{i-1}}, \hat{\mathbf{f}}_{\mathbf{i}}, \hat{\mathbf{f}}_{\mathbf{i+1}})$, where $\hat{\mathbf{f}}_{\mathbf{i}} = \dfrac{\mathbf{1}}{\|\mathbf{f_i}\|}\mathbf{f_i}$ is the unit vector for $\mathbf{f_i} = \mathbf{r_i} - \mathbf{r_{i-1}}$. So, $\sphericalangle(\hat{\mathbf{f}}_{\mathbf{i-1}}, \hat{\mathbf{f}}_{\mathbf{i}}, \hat{\mathbf{f}}_{\mathbf{i+1}}) = \mathbf{\Phi_i} \pm \pi$ according to the sign of Φ_i (Fig. 3). A change of Φ_i determines the rotation of the following part of the tree around the line defined by the node and $\hat{\mathbf{f}}_{\mathbf{i}}$. The second variable is the bond angle ω_i between $-\hat{\mathbf{f}}_{\mathbf{i}}$ and $\hat{\mathbf{f}}_{\mathbf{i+1}}$. So, the angle between $\hat{\mathbf{f}}_{\mathbf{i}}$ and $\hat{\mathbf{f}}_{\mathbf{i+1}}$ is $\pi - \omega_i$. Its drift designs the rotation around the node and $\hat{\mathbf{e}}_{\mathbf{i}} = \dfrac{\mathbf{1}}{\|\mathbf{e_i}\|}\mathbf{e_i}$, where $\mathbf{e_i} = \mathbf{f_{i+1}} \times \mathbf{f_i}$ is a vector product. Finally, we have the bond

length $b_{i+1} = \|\mathbf{f_{i+1}}\|$, which determines a shift to the next part of the tree and we can write $\mathbf{f_{i+1}} = \mathbf{b_{i+1}}\hat{\mathbf{f}}_{\mathbf{i+1}}$.

The index i grows from 1 at the origin level, across 2 at the root, to the height n_α of the last atom $\mathbf{r}_{\mathbf{n}_\alpha} = \bar{\mathbf{r}}_\alpha$ of the branch (Figs. 2, 3). The indexing is specified for each branch separately. The three coordinates Φ_i, ω_i and b_{i+1} associated with the ith node on the branch are not equivalent. The torsion angle Φ_i affects the positions of $\hat{\mathbf{e}}_\mathbf{i}$ and $\hat{\mathbf{f}}_{\mathbf{i+1}}$, the vectors of variables ω_i and b_{i+1}, and ω_i affects $\hat{\mathbf{f}}_{\mathbf{i+1}}$, but not vice versa. Several internal coordinates of the same type are at a furcate node, but each one is on a different branch. So, our indexing up the branch is still valid.

We need two more nonparallel vectors $\hat{\mathbf{x}}$ and $\hat{\mathbf{y}}$ in addition to the origin to define the positions of the atoms in space. These two vectors are chosen here without loss of generality as perpendicular and of unit length. They define a Cartesian coordinate system together with

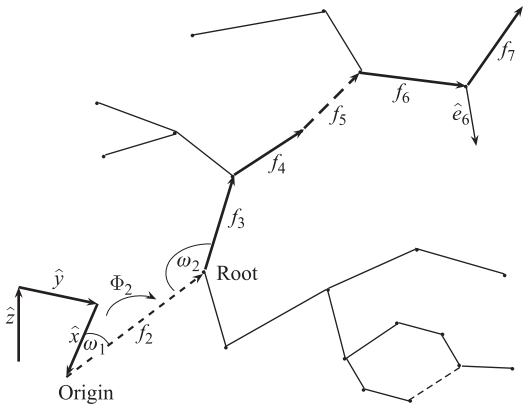

Fig. 2. Internal coordinates along a branch

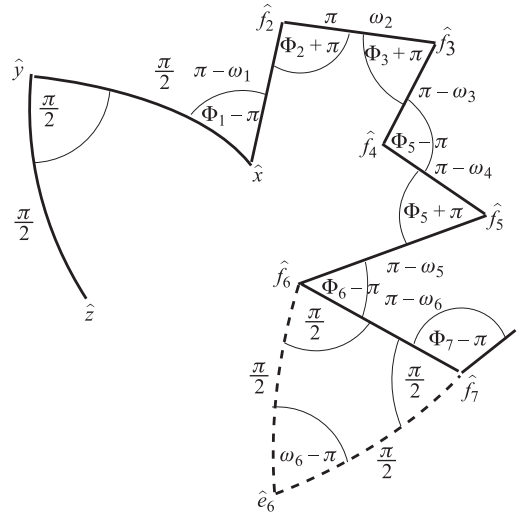

Fig. 3. Relevant vectors of the initial part of a branch (scheme)

the origin O and the vector of the third coordinate axis $\hat{\mathbf{z}} = \hat{\mathbf{x}} \times \hat{\mathbf{y}}$. The position of any node of a global index α and of a height n_α is together with Cartesian coordinates defined by a sequence of internal coordinates $(\Phi_1, \omega_1, b_2, \Phi_2, \omega_2, b_3, \ldots, \Phi_{n_\alpha - 1}, \omega_{n_\alpha - 1}, b_{n_\alpha})$ along the incident branch, where $\Phi_1 = \sphericalangle(-\hat{\mathbf{y}}, \hat{\mathbf{x}}, \hat{\mathbf{f}}_{\mathbf{2}})$, $\Phi_2 = \sphericalangle(-\hat{\mathbf{x}}, \hat{\mathbf{f}}_{\mathbf{2}}, \hat{\mathbf{f}}_{\mathbf{3}})$ and ω_1 is the angle between $-\hat{\mathbf{x}}$ and $\hat{\mathbf{f}}_{\mathbf{2}}$ (Figs. 2, 3). The first three coordinates Φ_1, ω_1, b_2 anchor the system in space. The nonfixed internal coordinates generate the set of all **generalized variables**.

3. THE HYBRID FORM OF THE EQUATIONS OF MOTION

We start from the Lagrangian equations of motion in the form

$$\frac{d}{dt}\left(\frac{\partial L}{\partial \dot{\theta}}\right) - \frac{\partial L}{\partial \theta} = 0 \text{ for any generalized variable } \theta, \tag{1}$$

where $\dot{\theta} = \dfrac{\partial \theta}{\partial t}$. Substituting $\displaystyle\sum_{\alpha}\left(\frac{1}{2} m_\alpha \dot{\mathbf{r}}_\alpha^{\,2}\right) - U$ for the Lagrangian function L we obtain

$$-\frac{\partial U}{\partial \theta} = \sum_{\alpha \in D[\theta]} m_\alpha \left[\frac{d}{dt}\left(\dot{\mathbf{r}}_\alpha \frac{\partial \dot{\mathbf{r}}_\alpha}{\partial \dot{\theta}}\right) - \dot{\mathbf{r}}_\alpha \frac{\partial \dot{\mathbf{r}}_\alpha}{\partial \theta}\right] = \sum_{\alpha \in D[\theta]} m_\alpha \ddot{\mathbf{r}}_\alpha \frac{\partial \mathbf{r}_\alpha}{\partial \theta}, \tag{2}$$

where U is the potential energy; α is the global index for atoms; m_α is the mass and $\bar{\mathbf{r}}_\alpha$ is the position vector of the αth atom; $\dot{\mathbf{r}}_\alpha = \dfrac{\partial \bar{\mathbf{r}}_\alpha}{\partial t}$, $\ddot{\mathbf{r}}_\alpha = \dfrac{\partial^2 \bar{\mathbf{r}}_\alpha}{\partial t^2}$ and $D[\theta]$ is the set of global indices of all atoms affected by the variable θ. Our goal is to express the right side of (2) by internal variables only.

Following the ideas of the authors of Ref. [1] with simplification applied in Ref. [3], one can obtain $-\dfrac{\partial U}{\partial \theta}$ as a sum of scalar products

$$\begin{aligned}
-\frac{\partial U}{\partial \Phi} &= \sum_{\alpha \in D[\Phi]} \left(\hat{\mathbf{f}}_{\mathbf{k}} \times \mathbf{r}_{\alpha/\mathbf{k}}\right) m_\alpha \ddot{\mathbf{r}}_\alpha, \\
-\frac{\partial U}{\partial \omega} &= \sum_{\alpha \in D[\omega]} \left(\hat{\mathbf{e}}_{\mathbf{k}} \times \mathbf{r}_{\alpha/\mathbf{k}}\right) m_\alpha \ddot{\mathbf{r}}_\alpha, \\
-\frac{\partial U}{\partial b} &= \sum_{\alpha \in D[b]} \hat{\mathbf{f}}_{\mathbf{k+1}} \mathbf{m}_\alpha \ddot{\mathbf{r}}_\alpha,
\end{aligned} \tag{3}$$

where k is the height of the node associated with the generalized variable θ (Φ_k, ω_k or b_{k+1} on the branch to each atom with a global number $\alpha \in D[\theta]$), the vector $\mathbf{r}_{\alpha/\mathbf{i}}$ is given by

$\mathbf{r}_{\alpha/\mathbf{i}} = \bar{\mathbf{r}}_\alpha - \mathbf{r}_\mathbf{i}$, and $\ddot{\mathbf{r}}_\alpha$ is the acceleration of the αth atom. This vector can be written as

$$\begin{aligned}\ddot{\mathbf{r}}_\alpha = \sum_{i=1}^{n_\alpha-1} \Big[\Big(\ddot{\Phi}_i \hat{\mathbf{f}}_i + \ddot{\omega}_i \hat{\mathbf{e}}_i \Big) \times \mathbf{r}_{\alpha/\mathbf{i}} + \ddot{\mathbf{b}}_{\mathbf{i+1}} \hat{\mathbf{f}}_{\mathbf{i+1}} + \mathbf{2}\dot{\mathbf{\Phi}}_\mathbf{i}\dot{\omega}_\mathbf{i} \Big(\hat{\mathbf{f}}_\mathbf{i} \times \hat{\mathbf{e}}_\mathbf{i} \times \mathbf{r}_{\alpha/\mathbf{i}} \Big) + \\ + \dot{\Phi}_i^2 \Big(\hat{\mathbf{f}}_\mathbf{i} \times \hat{\mathbf{f}}_\mathbf{i} \times \mathbf{r}_{\alpha/\mathbf{i}} \Big) + \dot{\omega}_i^2 \left(\hat{\mathbf{e}}_\mathbf{i} \times \hat{\mathbf{e}}_\mathbf{i} \times \mathbf{r}_{\alpha/\mathbf{i}} \right) \Big] + \\ + 2 \sum_{i=2}^{n_\alpha-1} \sum_{m=1}^{i-1} \Big[\Big(\dot{\Phi}_m \hat{\mathbf{f}}_\mathbf{m} + \dot{\omega}_\mathbf{m} \hat{\mathbf{e}}_\mathbf{m} \Big) \times \Big(\dot{\Phi}_i \hat{\mathbf{f}}_\mathbf{i} + \dot{\omega}_\mathbf{i} \hat{\mathbf{e}}_\mathbf{i} \Big) \times \mathbf{r}_{\alpha/\mathbf{i}} \Big] + \\ + 2 \sum_{i=1}^{n_\alpha-1} \sum_{m=1}^{i} \Big[\Big(\dot{\Phi}_m \hat{\mathbf{f}}_\mathbf{m} + \dot{\omega}_\mathbf{m} \hat{\mathbf{e}}_\mathbf{m} \Big) \times \dot{b}_{i+1} \hat{\mathbf{f}}_{\mathbf{i+1}} \Big] , \quad (4)\end{aligned}$$

where $\dot{\theta} = \dfrac{d\theta}{dt}$, $\ddot{\theta} = \dfrac{d^2\theta}{dt^2}$, $\hat{\mathbf{f}}_\mathbf{1} = \hat{\mathbf{x}}$, $\mathbf{a} \times \mathbf{b} \times \mathbf{c}$ stands for $\mathbf{a} \times (\mathbf{b} \times \mathbf{c})$ and the members of all sums are indexed along the branch to the αth atom. If any internal coordinate θ is fixed, the corresponding velocity $\dot{\theta}$ and acceleration $\ddot{\theta}$ are zero. Our task is to express vectors in the formulas (3) and (4) by internal coordinates.

Fixing bond length and bond angles, Eqs. (3) and (4) reduce to the simplified versions

$$-\frac{\partial U}{\partial \Phi} = \sum_{\alpha \in D[\Phi]} \Big(\hat{\mathbf{f}}_\mathbf{k} \times \mathbf{r}_{\alpha/\mathbf{k}} \Big) m_\alpha \ddot{\mathbf{r}}_\alpha \quad (5)$$

and

$$\ddot{\mathbf{r}}_\alpha = \sum_{i=1}^{n_\alpha-1} \Big[\ddot{\Phi}_i \hat{\mathbf{f}}_\mathbf{i} \times \mathbf{r}_{\alpha/\mathbf{i}} + \dot{\mathbf{\Phi}}_\mathbf{i}^\mathbf{2} \Big(\hat{\mathbf{f}}_\mathbf{i} \times \hat{\mathbf{f}}_\mathbf{i} \times \mathbf{r}_{\alpha/\mathbf{i}} \Big) \Big] + 2 \sum_{i=2}^{n_\alpha-1} \sum_{m=1}^{i-1} \Big[\dot{\Phi}_m \hat{\mathbf{f}}_\mathbf{m} \times \dot{\mathbf{\Phi}}_\mathbf{i} \hat{\mathbf{f}}_\mathbf{i} \times \mathbf{r}_{\alpha/\mathbf{i}} \Big] . \quad (6)$$

4. EQUATIONS OF MOTION SOLELY WRITTEN IN INTERNAL COORDINATES

The Cartesian coordinates of $\hat{\mathbf{f}}_\mathbf{i}$ are the cosines of the angles between $\hat{\mathbf{f}}_\mathbf{i}$ and $\hat{\mathbf{x}}$, $\hat{\mathbf{y}}$, $\hat{\mathbf{z}}$. These cosines are (see Appendix)

$$\begin{aligned}\hat{\mathbf{f}}_\mathbf{i}(\mathbf{1}) &= (1,0,0)\mathbf{C_1} \cdots \mathbf{C_{i-1}} \cdot (\mathbf{1},\mathbf{0},\mathbf{0})^T, \\ \hat{\mathbf{f}}_\mathbf{i}(\mathbf{2}) &= (1,0,0)\mathbf{C_0} \cdot \mathbf{C_1} \cdots \mathbf{C_{i-1}} \cdot (\mathbf{1},\mathbf{0},\mathbf{0})^T, \\ \hat{\mathbf{f}}_\mathbf{i}(\mathbf{3}) &= (1,0,0)\mathbf{C_{-1}} \cdot \mathbf{C_0} \cdot \mathbf{C_1} \cdots \mathbf{C_{i-1}} \cdot (\mathbf{1},\mathbf{0},\mathbf{0})^T,\end{aligned} \quad (7)$$

where ^{T} is the operation of *transpose*, the dot represents here and in the following *matrix multiplication*, and the mth *compose matrix* is

$$\mathbf{C_m} = \begin{pmatrix} -\cos\omega_m & \sin\omega_m & 0 \\ -\sin\omega_m \cos\Phi_m & -\cos\omega_m \cos\Phi_m & -\sin\Phi_m \\ -\sin\omega_m \sin\Phi_m & -\cos\omega_m \sin\Phi_m & \cos\Phi_m \end{pmatrix} \quad (8)$$

as $\cos(\pi - \omega_m) = -\cos\omega_m$, $\sin(\pi - \omega_m) = \sin\omega_m$, $\cos(\Phi_m \pm \pi) = -\cos\Phi_m$ and $\sin(\Phi_m \pm \pi) = -\sin\Phi_m$. The initial angles are $\Phi_0 = \sphericalangle(-\hat{\mathbf{z}}, \hat{\mathbf{y}}, \hat{\mathbf{x}}) = -\dfrac{\pi}{2}$ and arbitrary Φ_{-1} and $\omega_0 = \omega_{-1} = \dfrac{\pi}{2}$ are the angles between $\hat{\mathbf{x}}$ and $-\hat{\mathbf{y}}$ or $\hat{\mathbf{y}}$ and $-\hat{\mathbf{z}}$ (Fig. 3).

As we have $(1,0,0)\mathbf{C_0} = (\mathbf{0},\mathbf{1},\mathbf{0})$ and $(1,0,0)\mathbf{C_{-1}}\cdot\mathbf{C_0} = (\mathbf{0},\mathbf{0},\mathbf{1})$, new compound version of (7) is

$$\hat{\mathbf{f}}_\mathbf{i} = \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix} \mathbf{C_1}\cdot\mathbf{C_2}\cdots\mathbf{C_{i-1}}\cdot(\mathbf{1},\mathbf{0},\mathbf{0})^T = \mathbf{C_1}\cdot\mathbf{C_2}\cdots\mathbf{C_{i-1}}\cdot(\mathbf{1},\mathbf{0},\mathbf{0})^T, \quad (9)$$

where the vector $\hat{\mathbf{f}}_\mathbf{i}$ is identified with its arithmetical representation. One can write

$$\hat{\mathbf{f}}_\mathbf{i} = \mathbf{C_1}\cdot\mathbf{C_2}\cdots\mathbf{C_{i-1}}\cdot\hat{\mathbf{x}} \quad (10)$$

extending this representation to the other vectors considered now as column matrices. As $(\mathbf{A}\cdot\mathbf{u})\times(\mathbf{A}\cdot\mathbf{v}) = \mathbf{A}\cdot(\mathbf{u}\times\mathbf{v})$ holds for any orthogonal matrix $\mathbf{A}$, we have $\hat{\mathbf{e}}_\mathbf{i} = \dfrac{\mathbf{1}}{\left\|\hat{\mathbf{f}}_{\mathbf{i+1}}\times\hat{\mathbf{f}}_\mathbf{i}\right\|}\times$ $(\hat{\mathbf{f}}_{\mathbf{i+1}}\times\hat{\mathbf{f}}_\mathbf{i}) = \dfrac{\mathbf{1}}{\sin\omega_\mathbf{i}}\mathbf{C_1}\cdot\mathbf{C_2}\cdots\mathbf{C_{i-1}}\cdot[(\mathbf{C_i}\cdot\hat{\mathbf{x}})\times\hat{\mathbf{x}}]$. This relation can be simplified as

$$\hat{\mathbf{e}}_\mathbf{i} = \mathbf{C_1}\cdot\mathbf{C_2}\cdots\mathbf{C_{i-1}}\cdot\hat{\mathbf{u}}_\mathbf{i} \quad (11)$$

using that $\hat{\mathbf{u}}_\mathbf{i} = (\mathbf{0},-\sin\mathbf{\Phi_i},\cos\mathbf{\Phi_i})^T$. Similarly, $\mathbf{r}_{\alpha/\mathbf{i}} = \mathbf{b}_{\mathbf{i+1}}\mathbf{f}_{\mathbf{i+1}} + \mathbf{b}_{\mathbf{i+2}}\mathbf{f}_{\mathbf{i+2}} + \ldots + \mathbf{b}_{\mathbf{n}_\alpha}\mathbf{f}_{\mathbf{n}_\alpha}$ can be written as

$$\mathbf{r}_{\alpha/\mathbf{i}} = \mathbf{C_1}\cdot\mathbf{C_2}\cdots\mathbf{C_i}\cdot\mathrm{rot}(\mathbf{r}_{\alpha/\mathbf{i}}), \quad (12)$$

where $\mathrm{rot}(r_{\alpha/i}) = (b_{i+1}I_3 + C_{i+1}(b_{i+2}I_3 + C_{i+2}(b_{i+3}I_3 + \ldots + C_{n_\alpha-2}(b_{n_\alpha-1}I_3 + b_{n_\alpha}C_{n_\alpha-1}))\ldots)\hat{x}$ and $\mathbf{I_3}$ is the identity matrix of the third order.

Let us now define for non-negative integers i, j the *cumulative compose matrix*

$$\mathfrak{C}_{i,j} = \mathbf{C}_\mathbf{i}^T\cdot\mathbf{C}_{\mathbf{i-1}}^T\cdots\mathbf{C}_\mathbf{0}^T\cdot\mathbf{C_0}\cdots\mathbf{C_j} = \begin{cases} \mathbf{C_{i+1}}\cdot\mathbf{C_{i+2}}\cdots\mathbf{C_j}, & \text{if } i<j, \\ \mathbf{I_3}, & \text{if } i=j, \\ \mathbf{C}_\mathbf{i}^T\cdot\mathbf{C}_{\mathbf{i-1}}^T\cdots\ \mathbf{C}_{\mathbf{j+1}}^T, & \text{if } i>j. \end{cases} \quad (13)$$

These orthogonal matrices have several useful properties

$$\begin{array}{ll} \mathbf{C_i} = \mathfrak{C}_{\mathbf{i-1,i}}, & \mathbf{C_1}\cdot\mathbf{C_2}\cdots\mathbf{C_i} = \mathfrak{C}_{\mathbf{0,i}}, \\ \mathfrak{C}_{i,j}\cdot\mathfrak{C}_{j,k} = \mathfrak{C}_{i,k}, & \mathfrak{C}_{i,j}^T = \mathfrak{C}_{j,i}. \end{array} \quad (14)$$

All terms of (3) and (4) can now be written as

$$\begin{aligned} \hat{\mathbf{f}}_\mathbf{k}\times\mathbf{r}_{\alpha/\mathbf{k}} &= \mathfrak{C}_{0,k-1}\left[\hat{\mathbf{x}}\times\left(\mathbf{C_k}\cdot\mathrm{rot}(\mathbf{r}_{\alpha/\mathbf{k}})\right)\right], \\ \hat{\mathbf{e}}_\mathbf{k}\times\mathbf{r}_{\alpha/\mathbf{k}} &= \mathfrak{C}_{0,k-1}\left[\hat{\mathbf{u}}_\mathbf{k}\times\left(\mathbf{C_k}\cdot\mathrm{rot}(\mathbf{r}_{\alpha/\mathbf{k}})\right)\right], \\ \hat{\mathbf{f}}_{\mathbf{k+1}} &= \mathfrak{C}_{0,k-1}\mathbf{C_k}\cdot\hat{\mathbf{x}} \end{aligned} \quad (15)$$

and

$$\begin{aligned} \left(\ddot{\Phi}_i\hat{\mathbf{f}}_\mathbf{i} + \ddot{\omega}_\mathbf{i}\hat{\mathbf{e}}_\mathbf{i}\right)\times\mathbf{r}_{\alpha/\mathbf{i}} &= \mathfrak{C}_{0,i-1}\left[\left(\ddot{\Phi}_i\hat{\mathbf{x}} + \ddot{\omega}_\mathbf{i}\hat{\mathbf{u}}_\mathbf{i}\right)\times\left(\mathbf{C_i}\cdot\mathrm{rot}(\mathbf{r}_{\alpha/\mathbf{i}})\right)\right], \\ \ddot{b}_{i+1}\hat{\mathbf{f}}_{\mathbf{i+1}} &= \mathfrak{C}_{0,i-1}\mathbf{C_i}\cdot\ddot{\mathbf{b}}_{\mathbf{i+1}}\hat{\mathbf{x}}, \\ \dot{\Phi}_i\dot{\omega}_i\left(\hat{\mathbf{f}}_\mathbf{i}\times\hat{\mathbf{e}}_\mathbf{i}\times\mathbf{r}_{\alpha/\mathbf{i}}\right) &= \mathfrak{C}_{0,i-1}\left[\hat{\mathbf{x}}\times\hat{\mathbf{u}}_\mathbf{i}\times\left(\mathbf{C_i}\cdot\dot{\mathbf{\Phi}}_\mathbf{i}\dot{\omega}_\mathbf{i}\,\mathrm{rot}(\mathbf{r}_{\alpha/\mathbf{i}})\right)\right], \\ \dot{\Phi}_i^2\left(\hat{\mathbf{f}}_\mathbf{i}\times\hat{\mathbf{f}}_\mathbf{i}\times\mathbf{r}_{\alpha/\mathbf{i}}\right) &= \mathfrak{C}_{0,i-1}\left[\hat{\mathbf{x}}\times\hat{\mathbf{x}}\times\left(\mathbf{C_i}\cdot\dot{\mathbf{\Phi}}_\mathbf{i}^\mathbf{2}\,\mathrm{rot}(\mathbf{r}_{\alpha/\mathbf{i}})\right)\right], \\ \dot{\omega}_i^2\left(\hat{\mathbf{e}}_\mathbf{i}\times\hat{\mathbf{e}}_\mathbf{i}\times\mathbf{r}_{\alpha/\mathbf{i}}\right) &= \mathfrak{C}_{0,i-1}\left[\hat{\mathbf{u}}_\mathbf{i}\times\hat{\mathbf{u}}_\mathbf{i}\times\left(\mathbf{C_i}\cdot\dot{\omega}_\mathbf{i}^\mathbf{2}\,\mathrm{rot}(\mathbf{r}_{\alpha/\mathbf{i}})\right)\right], \end{aligned} \quad (16)$$

$$\left(\dot{\Phi}_m\hat{\mathbf{f}}_\mathbf{m}+\dot{\omega}_\mathbf{m}\hat{\mathbf{e}}_\mathbf{m}\right)\times\left(\dot{\Phi}_i\hat{\mathbf{f}}_\mathbf{i}+\dot{\omega}_\mathbf{i}\hat{\mathbf{e}}_\mathbf{i}\right)\times\mathbf{r}_{\alpha/\mathbf{i}}\overset{\mathbf{m}<\mathbf{i}}{=}\left(\mathfrak{C}_{\mathbf{0},\mathbf{m}-\mathbf{1}}(\dot{\mathbf{\Phi}}_\mathbf{m}\hat{\mathbf{x}}+\dot{\omega}_\mathbf{m}\hat{\mathbf{u}}_\mathbf{m})\right)\times$$
$$\times\left(\mathfrak{C}_{0,i-1}\left((\dot{\Phi}_i\hat{\mathbf{x}}+\dot{\omega}_\mathbf{i}\hat{\mathbf{u}}_\mathbf{i})\times(\mathbf{C_i}\cdot\mathrm{rot}(\mathbf{r}_{\alpha/\mathbf{i}}))\right)\right),$$

$$\left(\dot{\Phi}_m\hat{\mathbf{f}}_\mathbf{m}+\dot{\omega}_\mathbf{m}\hat{\mathbf{e}}_\mathbf{m}\right)\times\dot{b}_{i+1}\hat{\mathbf{f}}_{\mathbf{i+1}}\overset{\mathbf{m}\leqslant\mathbf{i}}{=}\left(\mathfrak{C}_{\mathbf{0},\mathbf{m}-\mathbf{1}}(\dot{\mathbf{\Phi}}_\mathbf{m}\hat{\mathbf{x}}+\dot{\omega}_\mathbf{m}\hat{\mathbf{u}}_\mathbf{m})\right)\times\left(\mathfrak{C}_{\mathbf{0},\mathbf{i}}\cdot\dot{\mathbf{b}}_{\mathbf{i+1}}\hat{\mathbf{x}}\right).$$

As a scalar product of vectors $\mathbf{a}$ and $\mathbf{b}$ can be also written as a matrix multiplication $\mathbf{a}^T\cdot\mathbf{b}$, and all matrices $\mathbf{C_i}$ and $\mathfrak{C}_{i,j}$ are orthogonal, an additional reduction is obtained by multiplication of the terms (15) and (16) in (3). This leads to our final equation of motion that is now based only on the internal coordinates:

$$\begin{aligned}
-\frac{\partial U}{\partial\Phi}&=\hat{\mathbf{x}}^T\sum_{\alpha\in\mathbf{D}[\mathbf{\Phi}]}\left(\mathbf{C_k}\cdot\mathrm{rot}(\mathbf{r}_{\alpha/\mathbf{k}})\right)\times\mathbf{m}_\alpha\mathbf{a}_{\mathbf{k},\alpha},\\
-\frac{\partial U}{\partial\omega}&=\hat{\mathbf{u}}_\mathbf{k}^T\sum_{\alpha\in\mathbf{D}[\mathbf{\Phi}]}\left(\mathbf{C_k}\cdot\mathrm{rot}(\mathbf{r}_{\alpha/\mathbf{k}})\right)\times\mathbf{m}_\alpha\mathbf{a}_{\mathbf{k},\alpha},\\
-\frac{\partial U}{\partial b}&=\left(\mathbf{C_k}\cdot\hat{\mathbf{x}}\right)^T\sum_{\alpha\in D[b]}m_\alpha\mathbf{a}_{\mathbf{k},\alpha}.
\end{aligned}\tag{17}$$

Here we assume

$$\begin{aligned}
\mathbf{a}_{\mathbf{k},\alpha}=\sum_{\mathbf{i}=\mathbf{1}}^{\mathbf{n}_\alpha-\mathbf{1}}\mathfrak{C}_{\mathbf{k}-\mathbf{1},\mathbf{i}-\mathbf{1}}\Big[&\left(\ddot{\mathbf{\Phi}}_\mathbf{i}\hat{\mathbf{x}}+\ddot{\omega}_\mathbf{i}\hat{\mathbf{u}}_\mathbf{i}\right)\times\left(\mathbf{C_i}\cdot\mathrm{rot}(\mathbf{r}_{\alpha/\mathbf{i}})\right)+\mathbf{C_i}\cdot\ddot{\mathbf{b}}_{\mathbf{i+1}}\hat{\mathbf{x}}+\\
&+\hat{\mathbf{x}}\times\hat{\mathbf{u}}_\mathbf{i}\times\left(\mathbf{C_i}\cdot\mathbf{2}\dot{\mathbf{\Phi}}_\mathbf{i}\dot{\omega}_\mathbf{i}\,\mathrm{rot}(\mathbf{r}_{\alpha/\mathbf{i}})\right)+\hat{\mathbf{x}}\times\hat{\mathbf{x}}\times\left(\mathbf{C_i}\cdot\dot{\mathbf{\Phi}}_\mathbf{i}^\mathbf{2}\,\mathrm{rot}(\mathbf{r}_{\alpha/\mathbf{i}})\right)+\\
&+\hat{\mathbf{u}}_\mathbf{i}\times\hat{\mathbf{u}}_\mathbf{i}\times\left(\mathbf{C_i}\cdot\dot{\omega}_\mathbf{i}^\mathbf{2}\,\mathrm{rot}(\mathbf{r}_{\alpha/\mathbf{i}})\right)\Big]+\\
&+2\sum_{i=2}^{n_\alpha-1}\sum_{m=1}^{i-1}\Big[\left(\mathfrak{C}_{k-1,m-1}\left(\dot{\Phi}_m\hat{\mathbf{x}}+\dot{\omega}_\mathbf{m}\hat{\mathbf{u}}_\mathbf{m}\right)\right)\times\\
&\times\left(\mathfrak{C}_{k-1,i-1}\left((\dot{\Phi}_i\hat{\mathbf{x}}+\dot{\omega}_\mathbf{i}\hat{\mathbf{u}}_\mathbf{i})\times(\mathbf{C_i}\cdot\mathrm{rot}(\mathbf{r}_{\alpha/\mathbf{i}}))\right)\right)\Big]+\\
&+2\sum_{i=1}^{n_\alpha-1}\sum_{m=1}^{i}\left[\left(\mathfrak{C}_{k-1,m-1}\left(\dot{\Phi}_m\hat{\mathbf{x}}+\dot{\omega}_\mathbf{m}\hat{\mathbf{u}}_\mathbf{m}\right)\right)\times\left(\mathfrak{C}_{k-1,i}\cdot\dot{b}_{i+1}\hat{\mathbf{x}}\right)\right].
\end{aligned}\tag{18}$$

Cumulative compose matrices $\mathfrak{C}_{k-1,i-1}$ are endowed by two indices in the previous form. But the first one is constant $k-1$ dependent on the height of the generalized variable θ.

5. NUMERICAL SOLUTION

Fixing again bond length and bond angles, the first equation of (17) together with (18) simplify to

$$-\frac{\partial U}{\partial\Phi}=\hat{\mathbf{x}}^T\sum_{\alpha\in\mathbf{D}[\mathbf{\Phi}]}\left(\mathbf{C_k}\cdot\mathrm{rot}(\mathbf{r}_{\alpha/\mathbf{k}})\right)\times$$

$$\times m_\alpha \left\{ \sum_{i=1}^{n_\alpha - 1} \mathfrak{C}_{k-1,i-1} \left[\ddot{\Phi}_i \hat{\mathbf{x}} \times \left(\mathbf{C_i} \cdot \mathrm{rot}(\mathbf{r}_{\alpha/\mathbf{i}}) \right) + \hat{\mathbf{x}} \times \hat{\mathbf{x}} \times \left(\mathbf{C_i} \cdot \dot{\mathbf{\Phi}}_\mathbf{i}^\mathbf{2} \mathrm{rot}(\mathbf{r}_{\alpha/\mathbf{i}}) \right) \right] + \right.$$
$$\left. + 2 \sum_{i=2}^{n_\alpha - 1} \sum_{m=1}^{i-1} \left[\left(\mathfrak{C}_{k-1,m-1} \cdot \dot{\Phi}_m \hat{\mathbf{x}} \right) \times \left(\mathfrak{C}_{k-1,i-1} \left(\dot{\Phi}_i \hat{\mathbf{x}} \times (\mathbf{C_i} \cdot \mathrm{rot}(\mathbf{r}_{\alpha/\mathbf{i}})) \right) \right) \right] \right\}. \quad (19)$$

It is possible to solve the system (19) with numerical methods (see, e.g., Ref. [2]) as one can express $\ddot{\Phi}$'s explicitly. Adapting conventional methods for solving systems of differential equations we represent this system in a form

$$M(t, \mathbf{y}) \cdot \dot{\mathbf{y}} = \mathbf{f}(\mathbf{t}, \mathbf{y}). \quad (20)$$

We need unambiguous identification of internal coordinates and variables. They are identified by indices only within a particular branch. Hence, two different internal variables with the same index can occur inside the same Eq. (19). Let now

$$\begin{pmatrix} \Phi_{(1)} \\ \omega_{(1)} \\ b_{(1)} \end{pmatrix}, \begin{pmatrix} \Phi_{(2)} \\ \omega_{(2)} \\ b_{(2)} \end{pmatrix}, \ldots, \begin{pmatrix} \Phi_{(\iota)} \\ \omega_{(\iota)} \\ b_{(\iota)} \end{pmatrix}, \ldots, \begin{pmatrix} \Phi_{(N)} \\ \omega_{(N)} \\ b_{(N)} \end{pmatrix} \quad (21)$$

be a global indexing of triplets of internal coordinates and let

$$\bar{\mathbf{r}}_\mathbf{1}, \bar{\mathbf{r}}_\mathbf{2}, \ldots, \bar{\mathbf{r}}_\alpha, \ldots, \bar{\mathbf{r}}_\mathbf{M} \quad (22)$$

be a global indexing of position vectors of the nodes (atoms). One triplet of internal variables inside a branch is defined as $\begin{pmatrix} \Phi_i \\ \omega_i \\ b_{i+1} \end{pmatrix}$ above. Each triplet $\begin{pmatrix} \Phi_{(\iota)} \\ \omega_{(\iota)} \\ b_{(\iota)} \end{pmatrix}$ is associated just with one node $\bar{\mathbf{r}}_{\nu(\iota)}$. Several triplets can be associated with the same furcate node. Let $D[\Phi]$ be the set of all global indices of nodes, which are affected by internal variable Φ. For two internal variables $\Phi_{(\iota)}$ and $\Phi_{(\kappa)}$ is $D[\Phi_{(\iota)}] \cap D[\Phi_{(\kappa)}] \neq \varnothing$, if and only if $\Phi_{(\iota)}$ and $\Phi_{(\kappa)}$ lie on the same branch. In a such case, is this intersection one of the intersecting sets (let us denote $\Phi_{(\iota)} \prec \Phi_{(\kappa)} \Longleftrightarrow D[\Phi_{(\iota)}] \supset D[\Phi_{(\kappa)}]$)?

Let

$$\mathbf{C}_{(\iota)} = \begin{pmatrix} -\cos\omega_{(\iota)} & \sin\omega_{(\iota)} & 0 \\ -\sin\omega_{(\iota)}\cos\Phi_{(\iota)} & -\cos\omega_{(\iota)}\cos\Phi_{(\iota)} & -\sin\Phi_{(\iota)} \\ -\sin\omega_{(\iota)}\sin\Phi_{(\iota)} & -\cos\omega_{(\iota)}\sin\Phi_{(\iota)} & \cos\Phi_{(\iota)} \end{pmatrix} \quad (23)$$

and

$$\mathfrak{C}_{(\kappa,\lambda)} = \begin{cases} \mathbf{C}_{(\iota_\mathbf{1})} \cdot \mathbf{C}_{(\iota_\mathbf{2})} \cdots \mathbf{C}_{(\iota_{\mathbf{j-1}})}, & \text{if } \kappa = \iota_1 \text{ and } \lambda = \iota_j, \\ \mathbf{I_3}, & \text{if } \kappa = \lambda, \\ \mathbf{C}^T_{(\iota_{\mathbf{j-1}})} \cdot \mathbf{C}^T_{(\iota_{\mathbf{j-2}})} \cdots \mathbf{C}^T_{(\iota_\mathbf{1})}, & \text{if } \lambda = \iota_1 \text{ and } \kappa = \iota_j, \\ \mathbf{0_3}, & \text{if } D[\Phi_{(\kappa)}] \cap D[\Phi_{(\lambda)}] = \varnothing, \end{cases} \quad (24)$$

where $\mathbf{I_3}$ and $\mathbf{0_3}$ are identity and zero matrices and $(\iota_1, \iota_2, \ldots, \iota_j)$ are global indices of a sequence of successive triplets of internal coordinates increasing along the same branch. Moreover, let

$$\mathrm{rot}(r_{\alpha/\iota}) = (b_{(\iota_1)} I_3 + C_{(\iota_2)}(b_{(\iota_2)} I_3 + C_{(\iota_3)}(b_{(\iota_3)} I_3 + \ldots$$
$$\ldots + C_{(\iota_{j-1})}(b_{(\iota_{j-1})} I_3 + b_{(\iota_j)} C_{(\iota_j)})) \ldots)\hat{x}, \quad (25)$$

where $(\iota_1, \iota_2, \ldots, \iota_j)$ are indices of the increasing sequence of all successive internal coordinates impacting against the αth node and starting from $\iota_1 = \iota$.

Let the actual interval variable $\Phi = \Phi_{(\mu)}$. We can rewrite Eqs. (19) under this denotation onto

$$
\begin{aligned}
-\frac{\partial U}{\partial \Phi_{(\mu)}} = \\
&= \sum_{\iota=1}^{N} \ddot{\Phi}_{(\iota)} \hat{\mathbf{x}}^T \sum_{\alpha \in \mathbf{D}_{\iota\mu}} \mathbf{m}_\alpha \left(\mathbf{C}_{(\mu)} \cdot \mathrm{rot}(\mathbf{r}_{\alpha/\mu}) \right) \times \mathfrak{C}_{(\mu,\iota)} \left(\hat{\mathbf{x}} \times \left(\mathbf{C}_{(\iota)} \cdot \mathrm{rot}(\mathbf{r}_{\alpha/\iota}) \right) \right) + \\
&+ \sum_{\iota=1}^{N} \dot{\Phi}^2_{(\iota)} \hat{\mathbf{x}}^T \sum_{\alpha \in \mathbf{D}_{\iota\mu}} \mathbf{m}_\alpha \left(\mathbf{C}_{(\mu)} \cdot \mathrm{rot}(\mathbf{r}_{\alpha/\mu}) \right) \times \mathfrak{C}_{(\mu,\iota)} \left(\hat{\mathbf{x}} \times \hat{\mathbf{x}} \times \left(\mathbf{C}_{(\iota)} \cdot \mathrm{rot}(\mathbf{r}_{\alpha/\iota}) \right) \right) + \\
&+ 2 \sum_{\iota=1}^{N} \sum_{\Phi_{(\lambda)} \prec \Phi_{(\iota)}} \dot{\Phi}_{(\iota)} \dot{\Phi}_{(\lambda)} \hat{\mathbf{x}}^T \sum_{\alpha \in \mathbf{D}_{\iota\mu}} \mathbf{m}_\alpha \left(\mathbf{C}_{(\mu)} \cdot \mathrm{rot}(\mathbf{r}_{\alpha/\mu}) \right) \times \left(\mathfrak{C}_{(\mu,\lambda)} \cdot \hat{\mathbf{x}} \right) \times \\
&\qquad \times \left(\mathfrak{C}_{(\mu,\iota)} \left(\hat{\mathbf{x}} \times (\mathbf{C}_{(\iota)} \cdot \mathrm{rot}(\mathbf{r}_{\alpha/\iota})) \right) \right) \qquad (26)
\end{aligned}
$$

for $D_{\iota\mu} = D[\Phi_{(\iota)}] \cap D[\Phi_{(\mu)}]$ and $\mu = 1, 2, \ldots, N$.

Hence, one can replace these N differential equations of the second order by $2N$ equations of the first order (20) that can be solved with standard techniques:

$$
\dot{\Phi}_{(\mu)} = \Psi_{(\mu)}, \qquad (27)
$$

$$
\begin{aligned}
&\sum_{\iota=1}^{N} \dot{\Psi}_{(\iota)} \hat{\mathbf{x}}^T \sum_{\alpha \in \mathbf{D}_{\iota\mu}} \mathbf{m}_\alpha \left(\mathbf{C}_{(\mu)} \cdot \mathrm{rot}(\mathbf{r}_{\alpha/\mu}) \right) \times \mathfrak{C}_{(\mu,\iota)} \left(\hat{\mathbf{x}} \times \left(\mathbf{C}_{(\iota)} \cdot \mathrm{rot}(\mathbf{r}_{\alpha/\iota}) \right) \right) = \\
&- \sum_{\iota=1}^{N} \Psi^2_{(\iota)} \hat{\mathbf{x}}^T \sum_{\alpha \in \mathbf{D}_{\iota\mu}} \mathbf{m}_\alpha \left(\mathbf{C}_{(\mu)} \cdot \mathrm{rot}(\mathbf{r}_{\alpha/\mu}) \right) \times \mathfrak{C}_{(\mu,\iota)} \left(\hat{\mathbf{x}} \times \hat{\mathbf{x}} \times \left(\mathbf{C}_{(\iota)} \cdot \mathrm{rot}(\mathbf{r}_{\alpha/\iota}) \right) \right) - \\
&- 2 \sum_{\iota=1}^{N} \sum_{\Phi_{(\lambda)} \prec \Phi_{(\iota)}} \Psi_{(\iota)} \Psi_{(\lambda)} \hat{\mathbf{x}}^T \sum_{\alpha \in \mathbf{D}_{\iota\mu}} \mathbf{m}_\alpha \left(\mathbf{C}_{(\mu)} \cdot \mathrm{rot}(\mathbf{r}_{\alpha/\mu}) \right) \times \left(\mathfrak{C}_{(\mu,\lambda)} \cdot \hat{\mathbf{x}} \right) \times \\
&\qquad \times \left(\mathfrak{C}_{(\mu,\iota)} \cdot \left(\hat{\mathbf{x}} \times (\mathbf{C}_{(\iota)} \cdot \mathrm{rot}(\mathbf{r}_{\alpha/\iota})) \right) \right) - \frac{\partial U}{\partial \Phi_{(\mu)}} \qquad (28)
\end{aligned}
$$

for $\mathbf{y} = (\mathbf{\Phi_{(1)}}, \ldots, \mathbf{\Phi_{(N)}}, \mathbf{\Psi_{(1)}}, \ldots, \mathbf{\Psi_{(N)}})^T$.

CONCLUSION

We have developed equations of motion for proteins that, unlike earlier forms, rely only on internal coordinates. This is not only satisfying from a mathematical point of view, but also allows a formulation of molecular dynamics solely in internal coordinates. As the «hard» degrees of freedom are integrated out in such a description, this allows larger time steps. The resulting faster sampling is a necessary condition for even simulation of small proteins (of order ≈ 50 residues).

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