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Normal modes for large molecules with arbitrary link constraints in the mobile block Hessian approach

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In a previous paper [Ghysels *et al.*, J. Chem. Phys. **126**, 224102 (2007)] the mobile block Hessian (MBH) approach was presented. The method was designed to accurately compute vibrational modes of partially optimized molecular structures. The key concept was the introduction of several blocks of atoms, which can move as rigid bodies with respect to a local, fully optimized subsystem. The choice of the blocks was restricted in the sense that none of them could be connected, and also linear blocks were not taken into consideration. In this paper an extended version of the MBH method is presented that is generally applicable and allows blocks to be adjoined by one or two common atoms. This extension to all possible block partitions of the molecule provides a structural flexibility varying from very rigid to extremely relaxed. The general MBH method is very well suited to study selected normal modes of large macromolecules (such as proteins and polymers) because the number of degrees of freedom can be greatly reduced while still keeping the essential motions of the molecular system. The reduction in the number of degrees of freedom due to the block linkages is imposed here directly using a constraint method, in contrast to restraint methods where stiff harmonic couplings are introduced to restrain the relative motion of the blocks. The computational cost of this constraint method is less than that of an implementation using a restraint method. This is illustrated for the α -helix conformation of an alanine-20-polypeptide. © 2009 American Institute of Physics. [DOI: 10.1063/1.3071261]

I. INTRODUCTION

The calculation of normal modes of not only an extended molecular system such as polypeptides and proteins but also polymer chains, supramolecular assemblies, systems embedded in a solvent, (macro)molecules adsorbed within porous materials, etc., is still a computationally intensive task that often goes beyond the capabilities of currently available computational hardware and software. The calculation of normal modes—often referred to as normal mode analysis (NMA)—is, however, essential for many purposes, ranging from the evaluation of chemical kinetics and thermodynamic properties such as entropies and free energies to the analysis of infrared and Raman spectra.^{1–6}

Frequency calculations need the construction of the full (all-atom) Hessian determined by the complete set of $3N_a$ degrees of freedom (with N_a the number of atoms). For large systems such as proteins, this can be beyond computational means. Even when feasible, the resulting huge amount of normal modes is often hard to analyze and interpret, and there is a need to filter out the relevant motions.

Another complicating factor in the NMA of extended systems is the fact that the geometry of these systems is often not fully optimized. An example of such a partial optimization is the simulation of reactions at surfaces, where the reactive center's geometry is optimized but the rest of the sur-

face is kept fixed during the optimization.⁷ The computation of the frequencies in such partially optimized systems is far from trivial. The main problem is that the global system is in nonequilibrium, and application of the standard NMA procedure is wrong, leading to wrong frequencies,⁸ which may even include a series of spurious imaginary frequencies.

One is frequently confronted with this kind of problems, and a proper solution is strongly needed. Appropriate methods have already been published recently: one of them is the mobile block Hessian (MBH) approach,⁸ although other related methods exist, which will be discussed later. The key concept of the MBH is the partitioning of the system into several blocks of atoms that move as rigid bodies during the vibrational analysis. Atoms that do not belong to any block are considered as free atoms. Forces on the atoms within the blocks may still be present because of the partial optimization; however, the position of the free atoms and the position and orientation of each block are assumed to be optimized.

In general, any system can be partitioned into blocks. Within each block the level of theory used for the optimization can differ and the atoms of some blocks may be nonoptimized. Blocks can be connected to each other by means of chemical bonds or nonbonding interactions or they can share one or two atoms. The usefulness and merit of this block concept have already been proven in some application fields: (i) The partition of a protein into blocks containing multiple amino-acid residues was shown to be very efficient for determining the normal modes of large proteins.^{9,10} (ii) In

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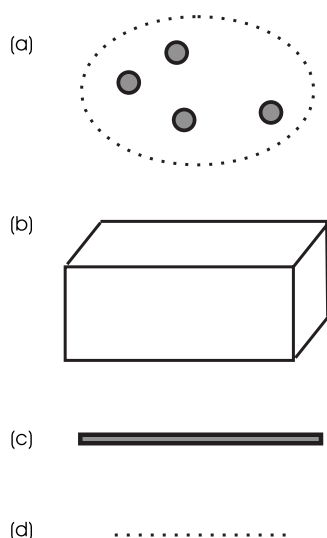


FIG. 1. Ingredients for a schematic depiction of a block partition of a molecule: an assembly of free atoms (a), and rigid nonlinear (b) or linear (c) blocks. A dotted line between two ingredients represents a chemical bond or nonbonding interaction (d).

chemical reactions only a fraction of the atoms is directly involved in bond breaking and forming or in a change in bond order, and the internal geometry of “spectator” chemical groups may be fixed.^{11–15}

A Cartesian formulation of the MBH approach was presented in Ref. 16, allowing a simple implementation in existing modeling packages. Up to now the MBH approach is already implemented in the last upgrade of CHARMM (Ref. 17) and Q-CHEM,¹⁸ and will be available too in the next release of ADF.¹⁹ The ability of MBH to accurately predict reaction rate constants has been validated in Ref. 13. It was shown there that, on condition of a suitable choice of the blocks, MBH includes the motions that are essential for a correct description of the reaction.

The choice of the blocks is crucial for the functionality of MBH and depends on what the real study object is. Normal modes usually involve the correlated motion of a number of atoms, but they can be divided into two main categories: the low-frequency modes where large parts of the molecule are involved moving in a collective way, and the local modes at higher frequency, localized in a specific part of the molecule, like the C=O stretch of the amide carbonyl group in polypeptides and proteins.⁴ Both categories have their practical usefulness in the prediction of chemical and physical properties, and in either case block choices can be introduced for an accurate reproduction of the relevant normal modes.⁸ The overlap with the full Hessian normal modes was used as a measure for the quality of the approximate MBH modes. Other measures are possible, for instance, by gauging how much an approximate normal mode deviates from an eigenvector of the full Hessian matrix.²⁰

Once the blocks have been fixed and optimized according to a certain level of theory, the internal motions in each block are frozen: blocks move as rigid bodies, but their relative motion is still free (apart from constraints imposed by common atoms). This is illustrated in Fig. 1, displaying the various ingredients entering possible partitions of a molecule

into blocks: (a) assemblies of free atoms, (b) linear and nonlinear rigid blocks containing atoms whose internal coordinates are frozen, and (c) dotted lines connecting the various bodies if no atom is shared by two or more blocks. This serves as a reminder that neighboring blocks without common atoms are not moving completely independently, but are connected by chemical bonds or nonbonding interactions. The ingredients of Fig. 1 can now be adjoined together in several ways, as specified in Fig. 2. For each topology a molecular example is given. The previous MBH method was restricted to a partitioning of the system following the scheme displayed in Fig. 2(a). This limits the block choices available in the existing MBH method: linear blocks were excluded and all blocks were assumed to be nonadjoined (i.e., connected by chemical bonds or nonbonding interactions only, with no adjoining atoms shared between the blocks).

The introduction of adjoining atoms in the partition scheme of a molecule, in particular, is a promising generalization of the MBH concept in systems with a large number of atoms because of the serious reduction in the degrees of freedom. One can distinguish between singly adjoined blocks connected by one common adjoining atom as displayed [see Figs. 2(b)–2(d)] and doubly adjoined or hinge blocks connected by two common adjoining atoms [see Fig. 2(e)]. Apart from global translation/rotation, two singly adjoined nonlinear blocks have three additional degrees of freedom (instead of six for nonadjoined blocks), while two hinge blocks have one degree of freedom corresponding to a hinge-bending motion. Multiple adjoined blocks can lead to a ring structure as shown in Fig. 2(f). All topologies can be constructed by combining all nonadjoined and adjoined (non)linear blocks.

The MBH method has been extended in a recent paper,²¹ to accommodate adjoined blocks sharing one or two atoms, as shown in Figs. 2(b)–2(f). It was found that the adjoined MBH model works well in extended systems where one is mainly interested in the low-frequency modes. For example, in peptide chains, the peptide unit is known to be quite rigid. The MBH approach with adjoined blocks then enables to connect various peptide units by the C_α atom. The main advantage of the adjoined blocks is that the number of degrees of freedom is further decreased, which is highly recommended in the case of extended systems with thousands of atoms.

The extension of the standard MBH to adjoined blocks was performed by introducing dummy atoms (see Sec. 2 of Ref. 21). An adjoining atom shared by several blocks is formally duplicated in each of those blocks. Adding a strong harmonic coupling between the dummies, the system behaves as if the blocks were linked. This technique was shown to work well, but has a significant disadvantage in the sense that the introduction of the dummy atoms leads to an extension of the dynamical system. Thereby the dimension of the Hessian temporarily increases in size, and for very large molecular systems this can be quite bothersome and time consuming. Moreover, the strong coupling between the dummies can cause numerical instabilities in the diagonalization of the Hessian for very large systems.

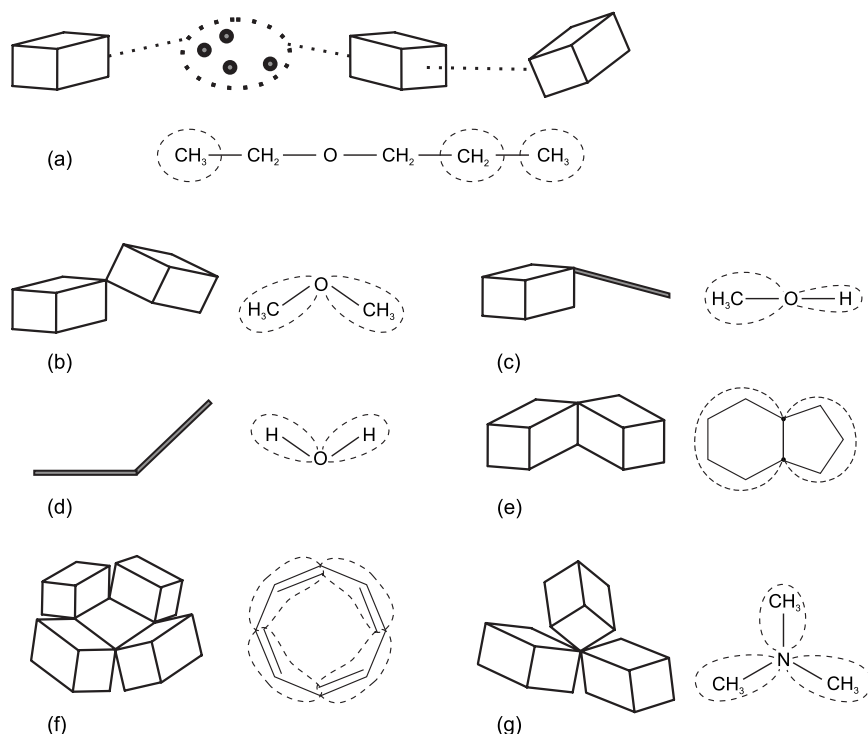


FIG. 2. With the ingredients of Fig. 1 various topologies can be constructed. In each case a molecular example is given. (a) An example of nonadjoined blocks. Nonlinear blocks have six; linear blocks have five degrees of freedom. [(b)–(d)] Some examples of adjoined blocks with one adjoining atom. (e) A hinge-type connection with blocks having two adjoining atoms gives rise to a hinge-bending motion with one rotational degree of freedom. (f) A ring structure consisting of singly adjoined blocks. (g) Example of three blocks with one adjoining atom, shared by the three blocks.

In order to overcome these shortcomings of the dummy atom concept, an exact and more direct treatment of the MBH with adjoined blocks is proposed in this paper. The main idea is to introduce block parameters for each block and then, in a second step, to impose the link constraints on the set of block parameters. The implementation avoids the extra degrees of freedom inherent to dummy atoms and is able to perform a MBH analysis for any arbitrary topology, even in the case of a ring structure of blocks.

Besides MBH there are other models in literature for the calculation of normal mode frequencies in extended systems. In particular, the partial Hessian vibrational analysis (PHVA) approach should be mentioned. It has been introduced by Head and co-workers^{22,7} and further investigated by Li and Jensen.¹² Normal modes are computed for the system with the fixed atoms frozen at their reference positions as if they were given an infinite mass and only the relaxed atoms can participate in the vibrations. An improved version of the PHVA was presented by Head,^{23,11,24} but this method requires the knowledge of an additional off-diagonal block of the Hessian. Another application of the partial Hessian approach is given by Besley and Metcalf.⁴ They compute a partial Hessian comprising the derivatives of the energy with respect to the movement of some selected atoms of relevance for their final goal. Their method has been applied successfully for the calculation of the amide I band in polypeptides and proteins. They limited the selection to the carbon and oxygen atoms of the backbone carbonyl groups and the amide nitrogens. NMA based on a simplified energy functional is also frequently used in biophysical chemistry.¹⁰ The Hessian matrix can also be reduced using group theoretical

methods based on the symmetry properties of the macromolecule. For highly symmetric systems this procedure is very appropriate and provides an excellent description of the low-frequency normal modes of proteins, which are linked to large-amplitude collective motions.²⁵ Once the symmetry becomes low and the molecular system involves heterogeneous distributions of different chemical groups, the concept of blocks has been introduced.^{26,27} The merit of the block normal mode (BNM) method as an effective coarse-grained NMA approach is that the cost of computation is dramatically reduced as compared to taking full account of intermolecular interactions. BNM is closely related to the rotations-translations of blocks (RTB) method developed by Tama *et al.*,⁹ which proved to be very efficient and adequate for NMA of proteins. The RTB method relies on the hypothesis that the low-frequency normal modes of proteins can be described as pure rigid-body motions of blocks of consecutive amino-acid residues. These frequencies seem to depend little on the size of the block (number of amino acids per block), strongly supporting the above hypothesis. By construction, RTB (or BNM) and MBH (in particular, the previous version) show large similarities: rigid blocks having six degrees of freedom (translation-rotation). The main difference lies in the fact that MBH is able to compute accurately normal modes in nonequilibrium (partially optimized) block systems, by taking into account gradient correction terms. These corrections are not involved in RTB (or BNM). In addition RTB (or BNM) is suitable for handling proteins, while the application field of MBH is much broader. Another method for NMA in large biomolecular systems is the vibrational subsystem analysis (VSA) method presented by Woodcock *et*

*al.*²⁸ This method is a partitioning scheme that separates (and integrates out) the motion of the environment from the user-defined subsystem. It is ideally suited for hybrid quantum mechanical/molecular mechanical potentials. A comparative study of the different approaches (PHVA, MBH, and VSA) will be presented in a forthcoming study.

In Sec. II we first present a more general formulation of the MBH, where the size of the blocks is arbitrary. A block can consist of one atom (corresponding to a free atom in the previous formulation of Ref. 8) or it may be a linear or nonlinear genuine block. Accordingly the block's number of degrees of freedom is three, five, or six. This view on the partition allows a transparent formulation of the MBH equations in terms of Cartesian quantities. The Cartesian gradient and Hessian are available in the output logfile of most simulation programs, such that the present MBH formulation is generally applicable. In Sec. III we then demonstrate that link constraints can be added in an elegant way. The only condition to be taken into account is that the geometry of the system should be partially optimized, such that the position/orientation of each block is optimized. In Sec. IV a practical numerical scheme resumes the steps in a general MBH analysis, indicating how MBH can be implemented. In Sec. V we report the results from the simulation of a α -helical peptide chain with 20 alanine residues.

II. ALL-BLOCK FORMULATION OF MBH

A. Transformations as dynamical variables

The MBH approach was introduced in previous papers^{8,16} as a flexible tool for performing vibrational analysis in the case of molecular systems where only a partial optimization is performed. Within the molecule, groups of neighboring atoms are identified as blocks, and the internal geometry (which need not be the equilibrium geometry) in each block is kept fixed during the motion. The different blocks have no atoms in common, but it is convenient to think of them as connected by chemical bonds or nonbonding interactions [see Fig. 2(a)].

The rigid-body motion of such a block b can be conveniently described by six parameters $p_{b\alpha}$ ($\alpha=1, \dots, 6$) of a translation/rotation group. The instantaneous positions $\mathbf{r}_A(t)$ of the atoms A in the block are simply generated by applying a common transformation with parameters p_b to the reference positions \mathbf{r}_A^0 ,

$$\mathbf{r}_A(t) = \mathbf{g}(\mathbf{r}_A^0, p_b(t)), \quad \forall A \in b. \quad (1)$$

The parametrization of the transformation group is arbitrary, but we will stick to the convention introduced in Ref. 8 of successively rotating along the fixed z -, y -, and x -axes of a space-fixed frame, followed by a translation,

$$\mathbf{g}(\mathbf{r}, p) = \begin{pmatrix} p_1 \\ p_2 \\ p_3 \end{pmatrix} + \begin{pmatrix} 1 & 0 & 0 \\ 0 & \cos p_4 & -\sin p_4 \\ 0 & \sin p_4 & \cos p_4 \end{pmatrix} \times \begin{pmatrix} \cos p_5 & 0 & \sin p_5 \\ 0 & 1 & 0 \\ -\sin p_5 & 0 & \cos p_5 \end{pmatrix} \begin{pmatrix} \cos p_6 & -\sin p_6 & 0 \\ \sin p_6 & \cos p_6 & 0 \\ 0 & 0 & 1 \end{pmatrix} \times \begin{pmatrix} x \\ y \\ z \end{pmatrix}. \quad (2)$$

The group variables p_b are used as the dynamical variables. Starting from a reference geometry that is optimized with respect to the p_b variables of the various blocks, the normal modes of this dynamical system can be calculated in a graceful way, while respecting the invariance under global rotations and translations of the molecular potential energy surface (PES).

In Ref. 16 the fixed-geometry blocks were treated separately from the remaining atoms, which could translate freely. This somewhat complicated the resulting expressions. In addition, linear blocks (which have only five degrees of freedom) were not considered explicitly. To remove these limitations, this section provides a unified framework solely in terms of block transformation parameters. This will facilitate, in the next stage, the development of the formalism in the presence of adjoining atoms.

We therefore assume that *all* the atoms in the molecule have been partitioned into blocks. The motion of the atoms in a block is still given by Eq. (1), but now three types of blocks are distinguished, depending on the number of its degrees of freedom d_b . The transformation $\mathbf{g}(\mathbf{r}_A^0, p_b)$ in Eq. (1) then depends on the number d_b of block variables as determined by the type of block.

- (1) For a normal block (containing at least three noncollinear atoms), $d_b=6$ and all parameters p_1, \dots, p_6 are needed.
- (2) For a single-atom block, $d_b=3$ and only the translational parameters p_1, p_2, p_3 are retained in the transformation (1).
- (3) For a linear block (containing two or more collinear atoms), $d_b=5$. The translational parameters p_1, \dots, p_3 and two of the rotational parameters are now retained in the block transformation (1). For such a linear block, we must exclude rotations about a particular axis (e.g., the μ -axis with $\mu=x, y$, or z) of the space-fixed frame. Note that in this case the block transformations no longer form a group. However, for the purpose of deriving the normal modes it is sufficient that the transformation is twice differentiable and covers all possible positions of the linear block near its reference position. As we shall see, the latter condition is always fulfilled, unless the reference position of the linear block happens to be orthogonal to the μ -axis; this can be simply avoided by a suitable choice of μ , e.g., as the axis with largest projection $|\mathbf{r}_{A\mu}^0 - \mathbf{r}_{B\mu}^0|$ for two atoms in the linear block.

TABLE I. Coefficients $D^{(\alpha)}$ and $C^{(\alpha\alpha')}$ defined in Eq. (4), expressing the first and second derivatives of the transformation in Eq. (1). The $v_{b\beta}^{(\alpha)}$ coefficients are defined in Eq. (13). The Levi-Civita symbol $\epsilon_{\lambda\mu\nu}$ equals 1 (-1) if $\lambda\mu\nu$ is a cyclic (anticyclic) permutation of xyz and zero otherwise.

α	$D_{A\mu}^{(\alpha)}$	α	α'	$C_{A\mu}^{(\alpha\alpha')}$	d_b	α	β	$v_{b\beta}^{(\alpha)} = (\partial \Psi_{b\beta} / \partial P_{\alpha})_0$
1	$\delta_{\mu x}$	1	1-6	0	3	1-6	1-3	$D_{A\beta}^{(\alpha)}$
2	$\delta_{\mu y}$	2	1-6	0	6	1-6	1-6	$\delta_{\alpha\beta}$
3	$\delta_{\mu z}$	3	1-6	0	5	1-6, $\neq 3+\mu$	1-3	$\delta_{\alpha\beta}$
4	$\sum_{\lambda} \epsilon_{\lambda\mu\lambda} r_{A\lambda}^0$	4	4	$\delta_{\mu x} r_{Ax}^0 - r_{A\mu}^0$			4-6, $\neq 3+\mu$	$\delta_{\alpha\beta}$
5	$\sum_{\lambda} \epsilon_{\lambda\mu y} r_{A\lambda}^0$		5	$\delta_{\mu y} r_{Ax}^0$		3+ μ	1-3	$\sum_{\gamma\delta} \epsilon_{\beta\gamma\delta} \frac{(r_{A\gamma}^0 r_{B\delta}^0 - r_{A\gamma}^0 r_{B\delta}^0)}{r_{A\mu}^0 - r_{B\mu}^0}$
6	$\sum_{\lambda} \epsilon_{\lambda\mu z} r_{A\lambda}^0$		6	$\delta_{\mu z} r_{Ax}^0$			4-6, $\neq 3+\mu$	$-\frac{(r_{A\gamma}^0 r_{B\delta}^0 - r_{A\gamma}^0 r_{B\delta}^0)}{r_{A\mu}^0 - r_{B\mu}^0}$
		5	5	$\delta_{\mu y} r_{Ay}^0 - r_{A\mu}^0$				
		6	6	$\delta_{\mu z} r_{Ay}^0$				
		6	6	$\delta_{\mu z} r_{Az}^0 - r_{A\mu}^0$				

For a particular block, the allowed transformations on the coordinates of its atoms thus depend on a number d_b of block variables, determined by the type of block. Note that the reduced set of p -variables in the case of a linear block or free atom can be complemented with zeros for the missing variables in the transformation $\mathbf{g}(\mathbf{r}_A^0, p_b)$ in Eq. (1). To avoid confusion, we will denote by \hat{p}_b this complemented set of six parameters.

B. Derivation of the normal mode equations

The PES expressed in the set of $\{p_{b\alpha}\}$ variables becomes

$$\tilde{V}(\{p_b\}) = V(\{\mathbf{g}(\mathbf{r}_A^0, \hat{p}_{b(A)})\}), \quad (3)$$

where $V(\{\mathbf{r}_A\})$ is the PES in Cartesian coordinates and $b(A)$ is the block to which atom A belongs.

Derivation of the normal modes proceeds using the same notations as in Ref. 16, i.e., $G_{A\mu} = (\partial V / \partial r_{A\mu})_0$ and $H_{A\mu, A'\mu'} = (\partial^2 V / \partial r_{A\mu} \partial r_{A'\mu'})_0$ for the gradient and Hessian of the PES in Cartesian coordinates, evaluated at the reference point, and

$$D_{A\mu}^{(\alpha)} = \frac{\partial g_{\mu}}{\partial p_{\alpha}}(\mathbf{r}_A^0, 0), \quad C_{A\mu}^{(\alpha\alpha')} = \frac{\partial^2 g_{\mu}}{\partial p_{\alpha} \partial p_{\alpha'}}(\mathbf{r}_A^0, 0) \quad (4)$$

for the first and second derivatives of the transformation (2) with respect to the p_{α} parameters, evaluated at the identity ($p_{\alpha}=0$). The $D^{(\alpha)}$ and $C^{(\alpha\alpha')}$ coefficients are tabulated in Table I.

The equilibrium position of the blocks is taken as the reference point, i.e., the gradients in the $p_{b\alpha}$ variables,

$$\tilde{G}_{b\alpha} = \left(\frac{\partial \tilde{V}}{\partial p_{b\alpha}} \right)_0 = \sum_{A \in b, \mu} G_{A\mu} D_{A\mu}^{(\alpha)} = 0, \quad (5)$$

all vanish. The Hessian in the $p_{b\alpha}$ variables then becomes

$$\begin{aligned} \tilde{H}_{b\alpha, b'\alpha'} &= \left(\frac{\partial^2 \tilde{V}}{\partial p_{b\alpha} \partial p_{b'\alpha'}} \right)_0 \\ &= \sum_{A \in b, \mu} \sum_{A' \in b', \mu'} H_{A\mu, A'\mu'} D_{A\mu}^{(\alpha)} D_{A'\mu'}^{(\alpha')} \\ &\quad + \delta_{b, b'} \sum_{A \in b, \mu} G_{A\mu} C_{A\mu}^{(\alpha\alpha')}. \end{aligned} \quad (6)$$

This form is identical to the Hessian derived in Eq. 65 of Ref. 16 except that now the indices α pertaining to a certain block b need not correspond to all six parameters of the full translation/rotation group, but can be restricted to five or three in order to accommodate linear blocks or single atoms. The same remark applies to the mass matrix [Eq. 59 in Ref. 16],

$$\tilde{M}_{b\alpha, b'\alpha'} = \delta_{b, b'} \sum_{A \in b, \mu} m_A D_{A\mu}^{(\alpha)} D_{A\mu}^{(\alpha')}, \quad (7)$$

and to the normal mode equations themselves, which will not be repeated here.

C. Zero modes of the Hessian

Invariance of the PES under a global translation/rotation with (six) parameters P_{α} can be expressed as

$$\tilde{V}(\{p_b\}) = V(\{\mathbf{g}(\mathbf{r}_A^0, \Phi(\hat{p}_{b(A)}, P))\}), \quad (8)$$

where $\Phi(p, p')$ represents the six parameters of the combined transformation $\mathbf{g}(\mathbf{g}(\mathbf{r}, p), p') = \mathbf{g}(\mathbf{r}, \Phi(p, p'))$ (see Ref. 16).

For a particular block, $\Phi(\hat{p}_{b(A)}, P)$ represents a six-parameter transformation that takes the atoms of the block to new positions. Since any position of the block can be uniquely described by d_b parameters, the effect of this six-parameter transformation $\Phi(\hat{p}_{b(A)}, P)$ on the block atoms can always be replaced by an equivalent d_b -parameter transformation, $\Psi_b(p_b, P)$. The latter is completely determined by the equivalence relation

$$\forall A \in b: \mathbf{g}(\mathbf{r}_A^0, \hat{\Psi}_b(p_b, P)) = \mathbf{g}(\mathbf{r}_A^0, \Phi(p_b, P)). \quad (9)$$

The final translation/rotation invariance of the PES can now be expressed as

$$\tilde{V}(\{p_b\}) = \tilde{V}(\{\Psi_b(p_b, P)\}). \quad (10)$$

Taking the second derivative of Eq. (10) with respect to $p_{b\alpha}$ and P_β , and neglecting gradient terms on account of Eq. (5), one obtains

$$\begin{aligned} 0 &= \left(\frac{\partial^2 \tilde{V}}{\partial p_{b\alpha} \partial P_\beta} \right)_0 \\ &= \sum_{b' \alpha' \alpha''} \tilde{H}_{b\alpha'', b' \alpha'} \left(\frac{\partial \Psi_{b\alpha''}}{\partial p_{b\alpha}} \right)_0 \left(\frac{\partial \Psi_{b' \alpha'}}{\partial P_\beta} \right)_0. \end{aligned} \quad (11)$$

Since $\Psi_b(p_b, 0) = p_b$ one always has $(\partial \Psi_{b\alpha''} / \partial p_{b\alpha})_0 = \delta_{\alpha, \alpha''}$, and Eq. (11) can be simplified as

$$0 = \sum_{b' \alpha'} \tilde{H}_{b\alpha, b' \alpha'} \left(\frac{\partial \Psi_{b' \alpha'}}{\partial P_\beta} \right)_0. \quad (12)$$

By inspection, Eq. (12) implies that the Hessian \tilde{H} has six zero eigenvalues with corresponding eigenvectors $v^{(\beta)}$, whose components are given by

$$v_{b\alpha}^{(\beta)} = \left(\frac{\partial \Psi_{b\alpha}}{\partial P_\beta} \right)_0. \quad (13)$$

The $v_{b\alpha}^{(\beta)}$ are tabulated in Table I. Most of the required first-order derivatives follow straightforwardly from Eq. (9) evaluated at $p_b=0$,

$$\forall A \in b: \mathbf{g}(\mathbf{r}_A^0, \hat{\Psi}_b(0, P)) = \mathbf{g}(\mathbf{r}_A^0, P). \quad (14)$$

The only nontrivial case occurs for a linear block ($d_b=5$). Suppose the rotations around the μ -axis are excluded and we want to find $v^{(\beta)}$ for $\beta=3+\mu$. Then Eq. (14) implies that the positions of two atoms A and B of the linear block after an infinitesimal rotation about the μ -axis must be reproduced by a combination of infinitesimal translations and rotations about the two other axes. With (μ, κ, λ) in cyclical order, $(\delta a_\mu, \delta a_\kappa, \delta a_\lambda)$ the rotation angles about the respective space-fixed axes, and $(\delta t_\mu, \delta t_\kappa, \delta t_\lambda)$ the corresponding translation parameters, we can use a first-order expansion of Eq. (2) and express the equivalence of the positions of A and B under both transformations. This leads to three equations for atom A ,

$$\begin{aligned} \delta t_\kappa + \delta a_\lambda r_{A\mu}^0 &= -\delta a_\mu r_{A\lambda}^0, \\ \delta t_\lambda - \delta a_\kappa r_{A\mu}^0 &= \delta a_\mu r_{A\kappa}^0, \\ \delta t_\mu - \delta a_\lambda r_{A\kappa}^0 + \delta a_\kappa r_{A\lambda}^0 &= 0, \end{aligned} \quad (15)$$

and three analogous ones for atom B , which should be solved for the five unknown variables $\delta t_\mu, \delta t_\kappa, \delta t_\lambda, \delta a_\kappa$, and δa_λ . Provided that $r_{A\mu}^0 \neq r_{B\mu}^0$ (or equivalently, that the linear block is not orthogonal to the μ -axis), there is a unique solution

$$\delta a_\lambda = -(\delta a_\mu) \frac{r_{A\lambda}^0 - r_{B\lambda}^0}{r_{A\mu}^0 - r_{B\mu}^0},$$

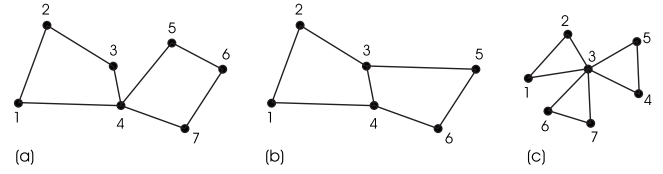


FIG. 3. Example of adjoining atoms. (a) Two blocks $[1,2,3,4], [4,5,6,7]$ having one adjoining atom (4) in common. Keeping the position of $[1,2,3,4]$ fixed, the relative motion of $[4,5,6,7]$ is limited to rotations about an axis through the adjoining atom. (b) Two blocks $[1,2,3,4], [3,4,5,6]$ having two adjoining atoms (3,4) in common (=hinge). Keeping the position of $[1,2,3,4]$ fixed, the relative motion of $[3,4,5,6]$ is limited to hinge-bending motions about the axis through the two adjoining atoms. (c) Three blocks $[1,2,3], [3,4,5], [3,6,7]$ having one adjoining atom (3) in common. The share number of atom 3 is 3.

$$\begin{aligned} \delta a_\kappa &= -(\delta a_\mu) \frac{r_{A\kappa}^0 - r_{B\kappa}^0}{r_{A\mu}^0 - r_{B\mu}^0}, \\ \delta t_\lambda &= (\delta a_\mu) \frac{r_{A\mu}^0 r_{B\kappa}^0 - r_{A\kappa}^0 r_{B\mu}^0}{r_{A\mu}^0 - r_{B\mu}^0}, \\ \delta t_\kappa &= (\delta a_\mu) \frac{r_{A\lambda}^0 r_{B\mu}^0 - r_{A\mu}^0 r_{B\kappa}^0}{r_{A\mu}^0 - r_{B\mu}^0}, \\ \delta t_\mu &= (\delta a_\mu) \frac{r_{A\kappa}^0 r_{B\lambda}^0 - r_{A\lambda}^0 r_{B\kappa}^0}{r_{A\mu}^0 - r_{B\mu}^0}. \end{aligned} \quad (16)$$

This solution determines precisely the first-order derivatives of Ψ_b appearing in Eq. (13) and gives rise to the corresponding components of $v^{(\beta)}$ as listed in Table I.

It follows that the six zero-mode eigenvectors of the Hessian are analytically known for any given block structure of the molecule. Just as in Ref. 16 one has the option of decoupling them explicitly from the intrinsic normal modes, using congruent transformations on \tilde{H} and \tilde{M} .

III. MBH FOR SYSTEMS WITH LINK CONSTRAINTS

A. Formulating the link constraints

In this section the previous MBH method is generalized to adjoined blocks, a significant extension opening a lot of new perspectives (see Sec. I). From now on we assume that the relative motion of some of the blocks is no longer independent, but obeys some constraints. This can be described by allowing some atoms, henceforth called adjoining atoms, to belong to two (or more) blocks. Using adjoining atoms to connect blocks, a large variety of topologies becomes possible (see Fig. 2). In addition, some of the blocks may be linear and have one degree of freedom less than normal blocks. It is clear that highly complex situations can arise. It turns out, however, that the normal modes can still be handled easily within the MBH framework.

After the partitioning of the molecular system into blocks (nonadjoined-adjoined-free atoms) each atom A is characterized by the share number s_A (i.e., the number of blocks to which A belongs), and the corresponding block indices $b(A)_1, \dots, b(A)_{s_A}$. Some examples are schematically displayed in Fig. 3. The positions of the atoms are still gov-

erned by the transformations (1). However, the transformation parameters $\{p_b\}$ of the blocks are no longer independent variables when adjoining atoms are present. An adjoining atom belongs to more than one block, and the fact that the position of the adjoining atom must be the same when transformed according to any of these blocks imposes constraints among the parameters of the blocks to which the adjoining atom belongs. For an adjoining atom L , which is shared by s_L blocks $b(L)_1, b(L)_2, \dots, b(L)_{s_L}$, these constraints can be neatly expressed as

$$\mathbf{g}(\mathbf{r}_{L, \hat{p}_{b(L)_1}}^0) = \mathbf{g}(\mathbf{r}_{L, \hat{p}_{b(L)_2}}^0) = \dots = \mathbf{g}(\mathbf{r}_{L, \hat{p}_{b(L)_{s_L}}}^0). \quad (17)$$

When all adjoining atoms are considered, the set of constraints of the form in Eq. (17) therefore impose relationships between the group parameters $\{p_b\}$, identifying the allowed motions in the presence of adjoining atoms.

These relationships may also be viewed as defining an allowed hypersurface $p_b \equiv p_b(y)$ in $\{p_b\}$ space, which can be parametrized in terms of k independent variables $y_\pi, \pi = 1, \dots, k$. These y variables will be taken as the dynamical variables in the NMA. The number k of independent degrees of freedom is as yet unknown and depends on the number of adjoining atoms and the topological structure of the links between the various blocks. Constructing a complete functional dependence $p_b(y)$ can be hideously complicated. For the purpose of a vibrational analysis, however, we only need small excursions from the reference geometry. As we shall see, this simplifies things considerably.

B. Construction of the Hessian

The PES expressed in terms of the y coordinates becomes

$$W(y) = \tilde{V}(\{p_b(y)\}) = V(\{\mathbf{g}(\mathbf{r}_{A, \hat{p}_{b(A)_1}}^0(y))\}). \quad (18)$$

Because of the constraints in Eq. (17), it is immaterial which block $b(A)_i$ is chosen to describe the motion of an adjoining atom in the Cartesian PES on the right of Eq. (18): for simplicity we always take the first block $b(A)_1$.

We assume that the reference geometry has been optimized in the presence of the adjoining atom constraints, i.e. it is gradient-free for all the independent variables y_π ,

$$0 = G'_\pi = \left(\frac{\partial W}{\partial y_\pi} \right)_0 = \sum_{b\alpha} \tilde{G}_{b\alpha} \left(\frac{\partial p_{b\alpha}}{\partial y_\pi} \right)_0. \quad (19)$$

The Hessian at the reference geometry is easily calculated using Eq. (18),

$$H'_{\pi, \tau} = \left(\frac{\partial^2 W}{\partial y_\pi \partial y_\tau} \right)_0 = \sum_{b\alpha} \sum_{b'\alpha'} \tilde{H}_{b\alpha, b'\alpha'} \left(\frac{\partial p_{b\alpha}}{\partial y_\pi} \right)_0 \left(\frac{\partial p_{b'\alpha'}}{\partial y_\tau} \right)_0 + \sum_{b\alpha} \tilde{G}_{b\alpha} \left(\frac{\partial^2 p_{b\alpha}}{\partial y_\pi \partial y_\tau} \right)_0. \quad (20)$$

The gradient and Hessian elements that appear in Eqs. (19) and (20) can be expressed in terms of the Cartesian ones using Eqs. (5) (not necessarily zero in this case) and (6). It is important, however, to realize that Eqs. (5) and (6) are only valid for a strict partition of the atoms, where each atom belongs to a unique block. In the present situation such a partition is done automatically by selecting the first block for each atom. The general expressions (valid for systems with or without adjoining atoms) therefore read

$$\tilde{G}_{b\alpha} = \sum_{A \in b, \mu} G_{A\mu} D_{A\mu}^{(\alpha)} \delta_{b, b(A)_1}, \quad (21)$$

$$\begin{aligned} \tilde{H}_{b\alpha, b'\alpha'} &= \sum_{A \in b, \mu} \sum_{A' \in b', \mu'} H_{A\mu, A'\mu'} D_{A\mu}^{(\alpha)} D_{A'\mu'}^{(\alpha')} \\ &\quad \times \delta_{b, b(A)_1} \delta_{b', b(A')_1} \\ &\quad + \delta_{b, b'} \sum_{A \in b, \mu} G_{A\mu} C_{A\mu}^{(\alpha\alpha')} \delta_{b, b(A)_1}. \end{aligned} \quad (22)$$

Solution of the unknown coefficients $(\partial p_{b\alpha}/\partial y_\pi)_0$ and $(\partial^2 p_{b\alpha}/\partial y_\pi \partial y_\tau)_0$ in Eqs. (19) and (20) is surprisingly easy. Using the y variables, the constraint equations in Eq. (17) can be re-expressed as identities. We have, for all Cartesian components μ and all adjoining atoms L , a sequence of $s_L - 1$ identities,

$$g_\mu(\mathbf{r}_{L, \hat{p}_{b(L)_1}}^0(y)) = g_\mu(\mathbf{r}_{L, \hat{p}_{b(L)_2}}^0(y)) \dots = g_\mu(\mathbf{r}_{L, \hat{p}_{b(L)_{s_L}}}^0(y)). \quad (23)$$

The first and second derivatives of Eq. (23) with respect to the y variables can be worked out using the chain rule,

$$\sum_{\alpha} D_{L\mu}^{(\alpha)} \left(\frac{\partial p_{b(L)_1\alpha}}{\partial y_\pi} \right)_0 = \sum_{\alpha} D_{L\mu}^{(\alpha)} \left(\frac{\partial p_{b(L)_2\alpha}}{\partial y_\pi} \right)_0 \dots = \sum_{\alpha} D_{L\mu}^{(\alpha)} \left(\frac{\partial p_{b(L)_{s_L}\alpha}}{\partial y_\pi} \right)_0, \quad (24)$$

$$\begin{aligned} \sum_{\alpha\alpha'} C_{L\mu}^{(\alpha\alpha')} \left(\frac{\partial p_{b(L)_1\alpha}}{\partial y_\pi} \right)_0 \left(\frac{\partial p_{b(L)_1\alpha'}}{\partial y_\tau} \right)_0 + \sum_{\alpha} D_{L\mu}^{(\alpha)} \left(\frac{\partial^2 p_{b(L)_1\alpha}}{\partial y_\pi \partial y_\tau} \right)_0 &= \sum_{\alpha\alpha'} C_{L\mu}^{(\alpha\alpha')} \left(\frac{\partial p_{b(L)_2\alpha}}{\partial y_\pi} \right)_0 \left(\frac{\partial p_{b(L)_2\alpha'}}{\partial y_\tau} \right)_0 + \sum_{\alpha} D_{L\mu}^{(\alpha)} \left(\frac{\partial^2 p_{b(L)_2\alpha}}{\partial y_\pi \partial y_\tau} \right)_0 \\ \dots &= \sum_{\alpha\alpha'} C_{L\mu}^{(\alpha\alpha')} \left(\frac{\partial p_{b(L)_{s_L}\alpha}}{\partial y_\pi} \right)_0 \left(\frac{\partial p_{b(L)_{s_L}\alpha'}}{\partial y_\tau} \right)_0 \\ &\quad + \sum_{\alpha} D_{L\mu}^{(\alpha)} \left(\frac{\partial^2 p_{b(L)_{s_L}\alpha}}{\partial y_\pi \partial y_\tau} \right)_0, \end{aligned} \quad (25)$$

in terms of the familiar MBH coefficients $D_{L\mu}^{(\alpha)}$ and $C_{L\mu}^{(\alpha\alpha')}$ tabulated in Table I.

For any particular $\pi(=1, \dots, k)$, Eq. (24) expresses the fact that the first-order derivatives of the transformation parameters, $(\partial p_{b\alpha}/\partial y_\pi)_0 = x_{b\alpha}^{(\pi)}$, must be a solution $x^{(\pi)}$ to the homogeneous linear system of $3\Sigma_L(s_L-1)$ equations

$$Kx^{(\pi)} = 0, \quad (26)$$

where the matrix K has entries (with L specifying the adjoining atom; $\mu=1, \dots, 3$; and $i=1, \dots, s_L-1$),

$$K_{\mu Li, b\alpha} = \begin{cases} D_{L\mu}^{(\alpha)} & \text{if } b = b(L)_i \\ -D_{L\mu}^{(\alpha)} & \text{if } b = b(L)_{i+1} \\ 0 & \text{otherwise.} \end{cases} \quad (27)$$

The linear system (26) therefore immediately determines the number of independent y variables, as the dimension of the null space of the matrix K . It is convenient to choose for the $x_{b\alpha}^{(\pi)}$ an orthonormal basis of the null space of K , so that

$$\sum_{b\alpha} x_{b\alpha}^{(\pi)} x_{b\alpha}^{(\tau)} = \delta_{\pi\tau}. \quad (28)$$

Note that if too many constraints are carelessly imposed on the relative motions of the blocks, the whole system may be “locked” and move as a single rigid body. This would be detected by a matrix K having a null space of dimension equal to 6.

For a particular combination $\pi\tau$, Eq. (25) then fixes the corresponding second-order derivatives of the transformation parameters, $(\partial^2 p_{b\alpha}/\partial y_\pi \partial y_\tau)_0 = x_{b\alpha}^{(\pi\tau)}$, as a solution $x^{(\pi\tau)}$ of the set of inhomogeneous equations,

$$Kx^{(\pi\tau)} = y^{(\pi\tau)}, \quad (29)$$

where the vector on the right has components

$$y_{\mu Li}^{(\pi\tau)} = \sum_{\alpha\alpha'} C_{L\mu}^{(\alpha\alpha')} [x_{b(L)_{i+1}\alpha}^{(\pi)} x_{b(L)_{i+1}\alpha'}^{(\tau)} - x_{b(L)_i\alpha}^{(\pi)} x_{b(L)_i\alpha'}^{(\tau)}]. \quad (30)$$

The solution $x^{(\pi\tau)}$ of Eq. (29) is not unique; it is determined up to an arbitrary vector in the null space of K , i.e.,

$$x^{(\pi\tau)'} = x^{(\pi\tau)} + \sum_{\rho} \lambda_{\rho} x^{(\rho)} \quad (31)$$

is also a solution for arbitrary λ_{ρ} . However, this does not lead to an ambiguity when evaluating the second term in the Hessian of Eq. (20),

$$\sum_{b\alpha} \tilde{G}_{b\alpha} x_{b\alpha}^{(\pi\tau)'} = \sum_{b\alpha} \tilde{G}_{b\alpha} \left[x_{b\alpha}^{(\pi\tau)'} + \sum_{\rho} \lambda_{\rho} x_{b\alpha}^{(\rho)} \right]. \quad (32)$$

On account of Eq. (19), the combination

$$\sum_{b\alpha} \tilde{G}_{b\alpha} x_{b\alpha}^{(\rho)} = 0 \quad (33)$$

vanishes in an equilibrium point, and the Hessian in Eq. (20) is independent of the choice of λ_{ρ} .

We conclude that the Hessian expressed in the y variables is completely determined by solving the linear systems in Eqs. (26) and (29). Numerically, this can be done efficiently by performing a singular value decomposition (SVD) of the matrix K . When determining the null space of K , a

singular value is considered being zero if it is smaller than a small threshold value to account for numerical inaccuracies. In practice, this never leads to ambiguities.

Note that many different parametrizations $p_b(y)$ of the allowed relative motions of the constrained MBH blocks can be constructed; however, near the reference geometry the only freedom left is the choice of a particular basis for the null space of K . One can indeed show that the final normal mode equations are independent of this choice.

C. Derivation of the normal mode equations

With the Hessian given by Eq. (20), the further derivation of the normal modes proceeds in a standard fashion. The instantaneous velocities of the atoms in the molecule are given by the defining property

$$\dot{r}_{A\mu} = \sum_{\alpha\pi} \frac{\partial g_{\mu}}{\partial p_{\alpha}}(\mathbf{r}_A^0, \hat{p}_{b(A)_1}(y)) \left(\frac{\partial p_{b(A)_1\alpha}}{\partial y_{\pi}}(y) \right) \dot{y}_{\pi}. \quad (34)$$

Note that for a contribution of an adjoining atom to the kinetic energy, one can pick arbitrarily a block $b(A)$ to which A belongs; any other choice is equivalent on account of Eq. (24). The kinetic energy in the y variables, expanded to second order, therefore reads

$$T = \frac{1}{2} \sum_{A\mu} m_A \left(\sum_{\alpha\pi} D_{A\mu}^{(\alpha)} x_{b(A)_1\alpha}^{(\pi)} \dot{y}_{\pi} \right)^2 = \frac{1}{2} \sum_{\pi\tau} M'_{\pi\tau} \dot{y}_{\pi} \dot{y}_{\tau}. \quad (35)$$

The last identity in Eq. (35) defines the mass matrix M' corresponding to the use of y as the dynamical variables; its entries are given by

$$M'_{\pi\tau} = \sum_{A\mu} m_A \sum_{\alpha\alpha'} x_{b(A)_1\alpha}^{(\pi)} x_{b(A)_1\alpha'}^{(\tau)} D_{A\mu}^{(\alpha)} D_{A\mu}^{(\alpha')}. \quad (36)$$

The final normal mode equations are represented by the generalized eigenvalue problem of dimension k ,

$$H'v = \omega^2 M'v, \quad (37)$$

with ω the vibrational frequency and v the corresponding normal mode eigenvector.

D. Zero modes

If the *same* global rotation/translation P is applied to all the constrained blocks, the block parameters $p_b(y)$ change to new values, which evidently must also be on the allowed surface and are described by new values of the y variables. The connection can be made explicit by introducing a function $G(y, P)$ through

$$\Psi_b(p_b(y), P) = p_b(G(y, P)), \quad (38)$$

where Ψ_b was defined in Eq. (9).

The overall translational/rotational invariance of the potential surface can then be expressed as

$$W(y) = W(G(y, P)), \quad (39)$$

and must give rise to six eigenvectors with zero eigenvalue of the Hessian expressed in the y variables. The explicit form is easily found by taking the second-order derivative

$\partial^2/\partial y_\pi \partial P_\alpha$ of Eq. (39) at the reference configuration and at $P=0$,

$$0 = \sum_{\tau\rho} H'_{\tau\rho} \left(\frac{\partial G_\tau}{\partial y_\pi} \right)_0 \left(\frac{\partial G_\rho}{\partial P_\alpha} \right)_0 + \sum_{\tau} G'_\tau \left(\frac{\partial^2 G_\tau}{\partial y_\pi \partial P_\alpha} \right)_0. \quad (40)$$

The second term contains the gradient and vanishes automatically at the reference configuration, whereas the behavior of the G -function for small arguments leads to further simplifications. When the global transformation P in Eq. (38) is the identity ($P=0$), nothing changes, so $G_\tau(y,0)=y_\tau$ and

$$\left(\frac{\partial G_\tau}{\partial y_\pi} \right)_0 = \delta_{\pi,\tau}. \quad (41)$$

Substitution of the above results into Eq. (40) allows to recognize the presence of six eigenvectors $v^{(\alpha)}$ corresponding to global rotation/translation,

$$0 = \sum_{\rho} H'_{\tau\rho} v^{(\alpha)}_\rho, \quad (42)$$

where the components of the eigenvector are given by $v^{(\alpha)}_\rho = \partial G_\rho / \partial P_\alpha$.

In order to determine the analytic form of the eigenvectors one can consider a global transformation P applied to the reference geometry ($y=0$). According to Eq. (38) this leads to

$$\Psi_b(p_b(0), P) = \Psi_b(0, P) = p_b(G(0, P)). \quad (43)$$

Taking the first derivative $\partial/\partial P_\alpha$ at $P=0$ of the β component, one finds

$$\left(\frac{\partial \Psi_{b\beta}}{\partial P_\alpha} \right)_0 = \sum_{\tau} \left(\frac{\partial p_{b\beta}}{\partial y_\tau} \right)_0 \left(\frac{\partial G_\tau}{\partial P_\alpha} \right)_0 = \sum_{\tau} x^{(\tau)}_{b\beta} \left(\frac{\partial G_\tau}{\partial P_\alpha} \right)_0, \quad (44)$$

$$\beta = 1, \dots, d_b. \quad (44)$$

Multiplying with $x^{(\rho)}_{b\beta}$, summing over $b\beta$, and using the orthonormality properties (28) lead to

$$\left(\frac{\partial G_\rho}{\partial P_\alpha} \right)_0 = \sum_{b\beta} x^{(\rho)}_{b\beta} \left(\frac{\partial \Psi_{b\beta}}{\partial P_\alpha} \right)_0, \quad (45)$$

so that the eigenvectors are easily expressed in terms of known quantities.

IV. PRACTICAL IMPLEMENTATION OF THE MBH SCHEME

In this section the general MBH procedure is rephrased in matrix notation to facilitate a numerical treatment with standard linear algebra subroutines. The starting point is the Cartesian gradient and Hessian, as provided by most molecular modeling packages. If the package allows to extract the gradient and Hessian in user-defined coordinates, step 4 in the procedure below can be omitted.

- (1) **Choice of blocks and constraints.** Identify the blocks b in the molecular system, and their respective type and number d_b of transformation parameters. Assign the atoms to the various blocks, by listing for each atom A the blocks to which it belongs and the share number s_A .
- (2) **Partial optimization.** Optimize the energy while the

internal coordinates of each block are kept fixed. This can, e.g., be realized with the Z -coordinate formalism, as explained in Ref. 16, and determines the reference geometry $\{r_A^0\}$. For a linear block ($d_b=5$) one can now decide upon an axis ($\mu=x,y,z$) of the space-fixed frame and omit rotations around this axis, following the discussion in Sec. II A.

- (3) **Determination of the actual degrees of freedom.** With $s=\sum_A 3(s_A-1)$ and $d=\sum_b d_b$, construct the $s \times d$ matrix K according to Eq. (27). Perform a SVD, $K = VSW^T$, where W is an orthogonal $d \times d$ matrix, S is a diagonal $s \times d$ matrix containing the singular values, and V is an orthogonal $s \times s$ matrix. The number k of zero singular values equals the number of actual degrees of freedom, i.e., the number of y_π variables defined in Sec. III A. In practice, a singular value is considered zero below a small threshold value to account for numerical inaccuracy. The k columns of W corresponding to the zero singular values can be taken as the orthonormal basis vectors $x^{(\pi)}$ in Eq. (26), spanning the null space of K ; they are collected in a $d \times k$ matrix X .
- (4) **Construction of the $(d \times 1)$ gradient \tilde{G} and of the $d \times d$ Hessian \tilde{H} and mass matrix \tilde{M} .** These quantities correspond to using the d block parameters $p_{b\alpha}$ as dynamical variables, and can be obtained in terms of the Cartesian $(3N_a \times 1)$ gradient G and the $3N_a \times 3N_a$ Hessian H and mass matrix M . According to Eq. (21) they read $\tilde{G} = U^T G$, $\tilde{M} = U^T M U$, and $\tilde{H} = U^T H U + \tilde{R}$, where the $3N_a \times d$ transformation matrix U is defined as $U_{A\mu,b\alpha} = D_{A\mu}^{(\alpha)} \delta_{b,b(A)_1}$. In nonequilibrium, \tilde{H} receives a gradient correction \tilde{R} given by $\tilde{R}_{b\alpha,b'\alpha'} = \delta_{b,b'} \sum_{A \in b,\mu} G_{A\mu} C_{A\mu}^{(\alpha\alpha')} \delta_{b,b(A)_1}$. The coefficients $C^{(\alpha\alpha')}$ and $D^{(\alpha)}$ are tabulated in Table I.
- (5) **Construction of the $k \times k$ Hessian H' and mass matrix M' .** These quantities correspond to using the genuine independent variables y_π , $\pi=1, \dots, k$, as dynamical variables. According to Eqs. (20) and (36) they read $M' = X^T \tilde{M} X$ and $H' = X^T \tilde{H} X + R'$. In nonequilibrium, H' receives a gradient correction R' given by $R'_{\pi,\tau} = \sum_{b\alpha} \tilde{G}_{b\alpha} x^{(\pi\tau)}_{b\alpha}$. The $d \times 1$ vectors $x^{(\pi\tau)}$ are obtained as a solution to the inhomogeneous linear system in Eq. (29). Since the SVD of the matrix K has already been constructed in step 3, this requires little additional effort.
- (6) **Calculate the k eigenvalues and eigenvectors of $M'^{-1/2} H' M'^{-1/2}$.** These yield the desired frequencies and normal modes of the linked block system.

V. NUMERICAL APPLICATION

As an example of the procedure developed in this paper we here report the results of a peptide chain consisting of 20 L-alanine residues (20 side chains, 21 peptide bonds), hereafter referred to as (Ala)₂₀. This oligomer is long enough to model the secondary structure of a protein: here we choose the α -helix conformation. CHARMM was used for the geometry optimization and the Hessian calculation.¹⁷ A postpro-

TABLE II. Results for the low-lying normal modes in (Ala)₂₀. The full Hessian frequencies (units of cm⁻¹, first column) are compared to MBH results using several block choices, as indicated in Fig. 4. Frequencies calculated with the constraint or dummy atoms method [columns labeled (c) and (d), respectively] are identical within numerical precision. The last three lines contain some computational details: number of frequencies, dimension of matrices to be diagonalized, dimension of *K* matrix [see Eq. (27)] if constraints are used. In the case of the dummy atom method, the bracketed number is the dimension of the Cartesian Hessian in Eq. (6).

Block choice	Full	[C _α] ¹		[C _α] ³		[C _α] ⁴		[C _α -N] ² + [C _α -C] ²	
constraint/dummy				c	d	c	d	c	d
	-0.0077	-0.0004	-0.0004	-0.0051	-0.0206	-0.0162	-0.0004	-0.0082	
	-0.0041	-0.0002	-0.0002	-0.0042	-0.0004	-0.0144	-0.0002	-0.0074	
	-0.0004	-0.0002	-0.0001	-0.0040	-0.0001	-0.0096	-0.0002	-0.0045	
	0.0002	0.0003	0.0003	-0.0029	0.0002	-0.0062	0.0003	-0.0020	
	0.0003	0.0003	0.0003	0.0030	0.0003	0.0031	0.0003	0.0083	
	0.0030	0.0004	0.0004	0.0050	0.0018	0.0067	0.0004	0.0101	
	4.0140	8.0850	6.6441	6.6441	6.5904	6.5904	7.1478	7.1479	
	7.5011	9.6303	8.8830	8.8830	8.8300	8.8300	9.7947	9.7947	
	9.3331	12.2977	11.5214	11.5214	11.4967	11.4967	12.2417	12.2418	
	10.8304	14.3976	13.3146	13.3146	13.2574	13.2574	15.1729	15.1729	
	13.0483	17.7756	15.6395	15.6395	15.5541	15.5542	17.4958	17.4958	
	15.8202	19.3651	19.6403	19.6403	19.5654	19.5654	23.9893	23.9893	
	18.6776	23.2107	23.0828	23.0828	22.9777	22.9777	27.0471	27.0471	
	20.3250	27.0383	24.6705	24.6705	24.5536	24.5536	30.6317	30.6316	
	24.6424	29.5497	30.9905	30.9905	30.8257	30.8257	36.2858	36.2858	
	27.9384	35.2907	32.7529	32.7529	32.5852	32.5853	41.2541	41.2541	
	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	
Frequencies	609	120	126	126	166	166	46	46	
Dimension	609	120	126	(729) 246	166	(789) 346	46	(849) 246	
Dimension <i>K</i>	-	-	120 × 246	-	180 × 346	-	240 × 246	-	

cessing program written in Python²⁹ extracts the Hessian from the CHARMM output file and calculates frequencies and modes in three ways: (1) the standard NMA with the full Hessian, (2) the MBH without adjoined blocks, and (3) the MBH with adjoined blocks. The latter calculation is performed both with the constraint method according to the above procedure or with the restraint method using dummy atoms.

Table II gives an overview of the lowest calculated frequencies and some computational parameters. In the first column one finds the full Hessian frequencies as a reference. In the other columns blocks were used as depicted in Fig. 4; a block choice is labeled by the notation [C_α]^{s_A} with s_A the share number of the C_α carbon atom. In block choice [C_α]¹, the MBH blocks are not adjoined to each other. Dummies nor link constraints are required for the vibrational analysis, and the former version of MBH can be used.

In block choice [C_α]³ the carbon atom connects three nonlinear blocks, in [C_α]⁴ the carbon atom connects one linear (the C–H bond) and three nonlinear blocks. In block choice [C_α-N]²+ [C_α-C]², the C_α-N bond and C_α-C bond are common between subsequent blocks, which illustrates the hinge-type connection. Those block choices are calculated with the adjoined version of the MBH, either by adding link constraints (c) or by introducing dummy atoms (d). Table II shows that the results are the same within meaningful numerical accuracy, hence both methods give equivalent results. The only difference to be noticed is in the lowest six frequencies, which should be zero on account of global ro-

tational and translational invariance. The deviation from zero is larger with the dummy atom approach because the introduced strong harmonic coupling tends to make the Hessian more ill conditioned and the numerical diagonalization less stable.

The introduction of blocks stiffens the systems, causing

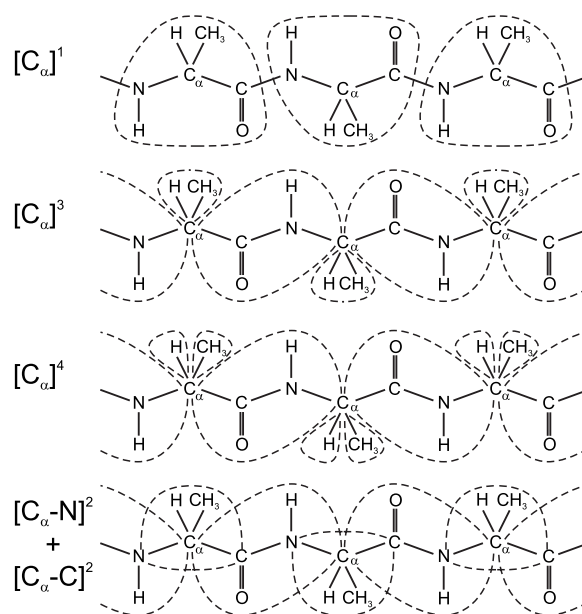


FIG. 4. Block choices for (Ala)₂₀. For clarity, only part of the chain is shown.

the frequencies to shift to higher values. As was observed by Tama *et al.*,⁹ this frequency shift is roughly linear and occurs in a rather systematic and predictable way. Comparing the nonadjoined $[C_\alpha]^1$ and the adjoined $[C_\alpha]^3$ block choice, we see that for a comparable number of frequencies (120 versus 126) the frequency overestimation is less for the block choice with adjoined blocks. Relaxation of the side chain-C-H angle as in $[C_\alpha]^4$ has little influence on the frequencies. In block choice $[C_\alpha-N]^2 + [C_\alpha-C]^2$ the large reduction in the number of frequencies (to only 8% of the original number) makes the overestimation higher.

The last lines of Table II contain some computational details for both methods. The number of frequencies depends on the number of blocks and how they are connected. When using the method with link constraints, the number of frequencies equals exactly the dimension (k) of the matrices to be diagonalized, i.e., the mass matrix and Hessian. The computational cost is dominated by the SVD of the $s \times d$ matrix K in Eq. (27), which scales as sd^2 (with $s < d$). In the restraint method, each dummy atom enlarges the dimension of the Cartesian Hessian in Eq. (6) by 3. Block choices $[C_\alpha]^3$, $[C_\alpha]^4$, and $[C_\alpha-N]^2 + [C_\alpha-C]^2$ have 40, 60, and 80 dummy atoms, respectively, and one has to manipulate considerably larger matrices. Finally a $d \times d$ matrix must be diagonalized. While the size of the present system is still rather modest, we do find that the constraint method has a more favorable overall computational cost, e.g., in block choice $[C_\alpha]^3$, the restraint method is a factor of 4 faster than in the dummy atom method.

The procedure of Sec. IV has also been tested for both fully and partially optimized structures and for a variety of topologies. Visualization of the modes showed that the blocks indeed vibrate as imposed by the link constraints. The test set (dimethylether, a series of alkanes, alanine dipeptide, crambin) is the same as those in Ref. 21, where the linked block dynamics were imposed with a restraint method using dummy atoms. While the frequencies were (virtually) identical in both methods, the present method has the advantage of being less computationally demanding. This advantage becomes more outspoken with increasing system size.

VI. CONCLUSION

In this paper the MBH model has been extended to any topology consisting of blocks (linear or nonlinear, unlinked or linked), as well as free atoms. The partitioning into blocks enables accurate frequency calculations of complex molecular systems due to the enormous reduction in the dimensionality of the problem (as the blocks have a rigid internal structure), and a further reduction can be obtained by imposing physically realistic link constraints between the blocks. Compared with other similar rotation/translation blocks (RTB/BNM) methods—frequently used in the polypeptide and protein world—the MBH routine incorporates gradient terms and thereby corrects for errors in the computed frequencies arising from partially optimized systems. Moreover, the option of introducing linkages between blocks is a new feature available in MBH but not in the other methods.

In the linked MBH scheme the blocks can move while

keeping their rigid internal structure and subject to the constraints that some of the blocks have common atoms. The geometry of this constrained system is optimized at a level of theory adapted to the size of the complex molecular system. As a result of the frozen internal structure of the blocks, as well as the presence of link constraints, the system is only partially optimized and the individual atoms are not force-free. Low frequencies correspond to collective motions and are the most interesting modes in the determination of physical and chemical properties of the system. But just these frequencies are the most sensitive to an improper handling of partially optimized systems.

The scheme proposed in this work is a general all-block formulation and may be regarded as a universal extension of the previous MBH procedure. In this way any complex molecular system can be partitioned, and in principle this should always be sufficient to make a frequency computation feasible. The new procedure makes use of a partial Hessian construction, and further matrix manipulations following known recipes. The procedure has been illustrated with the alanine-20-polypeptide.

One of the strong points of the scheme is the high flexibility, in the sense that any topology can be treated, even if it contains a mixture of free atoms, a branched chain of blocks, a ring structure of blocks, with or without linear blocks. Another important point is the absence of dummy atoms. As a consequence, the matrices to be diagonalized have considerably smaller dimensions than in the case where extra degrees of freedom are generated by the dummy atoms. Especially for large systems this is a big advantage of the constraint implementation of MBH with respect to the implementation with dummy atom restraints.

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