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PERSPECTIVE

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# New theoretical methods for the exploration of functional landscapes

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## Abstract

Molecular functionality can be often directly attributed to given properties of the electronic wavefunction. Analogous to the potential energy surface, these properties can be represented as a function of the nuclear coordinates, giving rise to molecular "functional landscapes." However, so far there has been no possibility for their systematic investigation. This perspective aims to discuss the development of new theoretical methods based on the multistate extension of the metadynamics approach, employing electronic collective variables. This emerging methodology allows to explore functional landscapes and to gain a deeper understanding of the structure–function relation in molecules and complex molecular systems in the ground and excited electronic state.

**KEYWORDS**
electronic collective variables, electronic wavefunction, metadynamics, structure–function relation

## 1 | MOTIVATION AND SCOPE

The Born-Oppenheimer (BO) approximation[1], which allows to treat electrons and nuclei separately, builds the theoretical cornerstone of one of the fundamental concepts in chemistry: The idea of molecular structure. Within the BO framework, chemical reactions and light-induced phenomena can be considered as the structural evolution of the molecular system on one or multiple electronic potential energy surfaces (PES). The underlying molecular "functionality," enabling the studied processes, often correlates to direct properties of the electronic wavefunction. For example, the strength of the transition dipole moment determines the efficiency in light-harvesting processes [2], while in catalytic reactions, properties such as the charge distribution or the singlet-triplet gap define the intrinsic activity of the catalysts as well as their reaction route [3–5]. Processes such as energy transfer can take place efficiently upon (partial) charge transfer character of the wavefunction [6]. Here the diabatic analysis of the electronic wavefunction delivers (indirect) properties, which can be clearly assigned to the functional performance. Since the electronic wavefunction exhibits a direct dependence on the nuclear coordinates of the molecule, also its properties are directly dependent on the structural evolution of the system. Therefore, a detailed knowledge on the structure–function relation in molecular systems is not only of intellectual interest, but it would deliver useful information for the design of new materials for tailored functional processes. Furthermore, it would allow assigning experimental information on electronic properties (such as spectroscopic data) to structural motifs. In principle, in analogy to the PES, the considered electronic properties can be plotted as a function of nuclear coordinates, providing a global picture of the structure–function correlation which we have introduced as "functional landscapes" [7]. However, their rational investigation bears several challenges. In our recent work, we presented the fundamentals of a new methodology for an "automatic sampling of quantum property manifolds" (ASQPM) that allows to automatically extract molecular conformations from regions on the PES bearing "high" functionality in the ground, the excited state or a manifold

of (coupled) states, as it allows to detect molecular geometries for which the respective property of the electronic wavefunction is maximal. Here, we wish to present the recent developments of this promising methodology, that employs electronic collective variables (CVs) in order to explore the functional landscape of molecular systems. Therefore, the first section shortly summarizes the most prominent methodologies that allow for investigation of the PES, while the second section elucidates the concept of "functional landscapes," also addressing the challenges that have to be overcome for their rational investigation. Subsequently, the recently developed methodologies based on the multistate extension of the metadynamics are outlined, and the underling algorithm is discussed in detail, accompanied by a short discussion of the results of two recent examples of applications. Finally, an outlook for further applications and methodological developments is given.

## 2 | POTENTIAL ENERGY SURFACE

With the introduction of the BO approximation comes a useful artifact, that is, the PES depicting the relation between energy (and thus: Stability) and nuclear geometry. Theoretical chemistry has developed a plethora of strategies to investigate the PES: Optimization routines for finding the local minima and maxima, algorithms to sample the configurational space searching for the global minimum (e.g., basin hopping[8]), strategies to find the minimum energy pathway between stationary points (e.g., nudged elastic band method[9, 10]), as well as methods for simulation of real-time molecular dynamics (MD). A sophisticated way of sampling the free energy surface, which contains both the contribution of the PES as well as the temperature-dependent entropy contribution consists in accelerated MD techniques, such as for example the metadynamics, introduced by Parrinello and coworkers [11–16]. This approach uses classic CVs to drive transitions between different barrier-separated basins on the PES, thus allowing for systematic sampling of the PES as well as the determination of free energies. A wide variety of classic CVs has been implemented, ranging from simple geometrical quantities to complex variables constructed by machine learning [15, 17]. The method finds broad application in the frame of force field simulations for example, for investigation of folding mechanisms in proteins [18], while studies based on quantum chemical metadynamics simulations are still relatively rare [19, 20].

## 3 | THE CONCEPT OF FUNCTIONAL LANDSCAPES

While a variety of methods for identification of energetic extrema on the PES is available, so far there has been no possibility to systematically detect the regions of the PES corresponding to a functionality of interest. Such regions might be located at minima at the PES and in that case, the considered molecule would exhibit an "intrinsic functionality," while "indirect functionality" might also be found for structures at non-stationary points on the PES, which are only thermally populated or transiently visited during the (reactive) structural evolution, enabling the respective functional process. Finally, structures bearing "high" functionality can also be out of any reactive or thermal reach when they are energetically separated. So far, only indirect ways such as (relaxed) scanning of the PES and the investigation of the electronic wavefunctions along the scanning modes or analysis along pathways from (accelerated) MD techniques provided information on the structure–function relation. In principle, since the functionality can often be assigned to the properties of the electronic wavefunction, within the BO approximation, in analogy to the PES, these properties can be represented as a hypersurface, and be considered as "functional landscape" (cf. Figure 1). By drawing the negative of the value of the electronic property of interest$-P(R)$, this landscapes bear minima that correspond to structures with high functionality and, in analogy to the PES can in principle be identified employing related algorithms as those developed for the detection of minimum energy structures. The rational investigation of these landscapes would allow to get a direct picture of the structure–function correlation in a molecule or complex molecular system (e.g., coupled monomers or compounds that interact with the surrounding). However, this is not straight-forward for several reasons, as the function does not include any information about the energy and thus stability of the system. A constraint for reasonable arrangements of the atoms constituting the considered molecular system and therefore, additional conditions have to be introduced, defining a "physically meaningful space," in which the landscape should be screened. Furthermore, this landscape might have ill-behaving features, exhibiting for example, peaks or large barriers that complicate its systematic investigation. In our recent work, we introduced a methodology based on the idea of Parrinello's metadynamics for the ASQPM in the ground-, excited and coupled states and, (i) considered the electronic energy as CV, which we used for the automatic exploration of energy crossing points between electronic states. Upon further generalization we (ii) introduced electronic CVs that can represent any quantum-mechanical property of the electronic wavefunction allowing to automatically explore functional landscapes. The details of the developed methodology and the underlying algorithm will be presented in detail in the following subsections.

## 4 | MULTISTATE METADYNAMICS FOR EXPLORATION OF CONICAL INTERSECTION SEAMS

Photochemical processes are governed by conical intersections (CIs) between the adiabatic PES at which the energy gap becomes zero, as in these regions strong nonadiabatic coupling leads to efficient population transfer between the involved electronic states. In principle, a CI between states

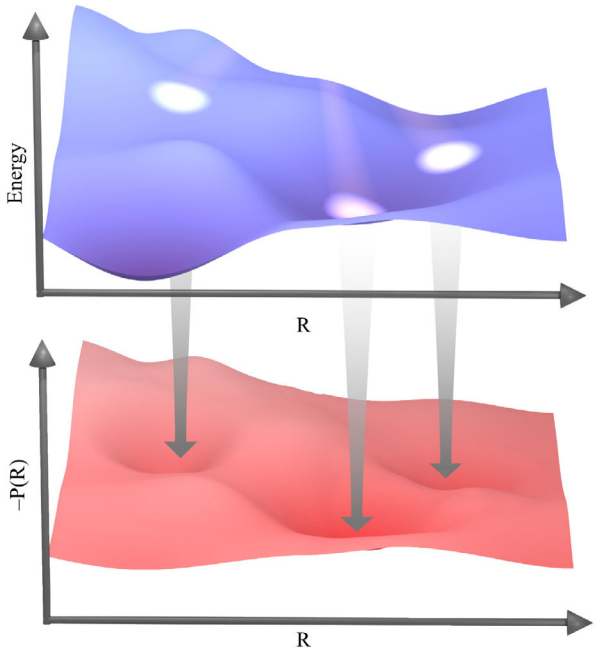



**FIGURE 1** Artwork illustrating the concept of functional landscapes. In the upper part, the potential energy surfaces (PES) is shown with illuminated regions in which the molecular system bears high functionality. In the lower part, the corresponding functional landscape−$P(R)$ is shown, with minima at molecular conformations with high functionality

can be understood as a hyperdimensional seam, whose degeneracy is lifted in two dimensions [21–24]. A variety of strategies has been developed for the optimization of minimum energy crossing points (MECP) along this seam, based on gradient projection [25], penalty functions [26], or Lagrange–Newton techniques [27]. However, all these procedures account for an initial guess provided by chemical intuition or the outcome of nonadiabatic dynamics simulations. Furthermore, recent work has pointed out the important role of CIs in coherent vibronic dynamics involving nonadiabatic driving forces that arise due to the vibrational motion along the tuning modes [28]. Studies characterizing the full intersection seam have so far been relied on symmetry considerations[29] or employing algorithms such as the nudged elastic band method[30] and anharmonic downward distortion following [31–34]. Transition states on the intersection seam have been explored by an analytical second-order description and used for connecting multiple crossing points [35, 36].

## 4.1 | Multistate metadynamics algorithm

The essential idea of the multistate metadynamics for exploration of CIs[37] is to consider the energy gap between the ground and excited electronic states as an electronic CV that serves to drive the molecule toward the CI seam starting from an arbitrary ground state nuclear conformation (e.g., the energetic minimum structure). The idea to use an energy gap as a reaction coordinate originates from the Marcus theory of the electron transfer[38]. There, it is shown that the energy gap is a linear function of the reaction coordinate. In previous work, Fuxreiter et al. employed the diabatic energy gap to sample the reaction coordinate and locate the transition states in the ground electronic state[39]. However, the definition of suitable diabatic states is partly based on chemical intuition. In our work, the energy gap between adiabatic, electronic states that can be readily obtained using various quantum chemical methods, is chosen. Therefore, a biased MD simulation is carried out, while the molecule is propagated using the Newtonian equations of motion augmented by an additional history-dependent bias potential $V_G(t)$

$$m_i \ddot{\mathbf{R}}_i = -\nabla_i (E_g + V_G(t)), \tag{1}$$

for the $i$-th particle with the ground state BO PES $E_g$. The employed bias potential is updated at regular time steps $\tau_G$ upon addition of Gaussian-shaped functions:

$$V_G(t) = \sum_{t'=\tau_G, 2\tau_G, \ldots}^{t} w \exp\left( -\frac{(\Delta E_{\text{meta}}(t) - \Delta E_{\text{meta}}(t'))^2}{2\delta s^2} \right) \times \Theta(\Delta E_{\text{meta}}(t') - \epsilon), \tag{2}$$

and depends on the modified energy gap $\Delta E_{\text{meta}}$, with $\delta s$ and $w$ representing the fixed width and height of the Gaussian function, respectively. Within a MD simulation starting from any arbitrary molecular structure, the bias potential drives the system toward the CI seam by lowering the value of the energy gap. As the crucial feature of our algorithm, the bias potential is updated only if the value of the gap is larger than a defined numerical threshold $\epsilon$. This is realized by the presence of the Heaviside function $\Theta(\Delta E_{\text{meta}} - \epsilon)$ in Equation (2). Once the intersection seam is

reached, the gap value becomes lower than the threshold and a further biasing potential $V_{ge}$ is introduced into the off-diagonal elements of the (so far diagonal) molecular electronic Hamiltonian according to:

$$\mathbf{H_{BO}} = \begin{pmatrix} E_g & 0 \\ 0 & E_e \end{pmatrix} \rightarrow \mathbf{H_{meta}} = \begin{pmatrix} E_g & V_{ge} \\ V_{ge} & E_e \end{pmatrix}, \tag{3}$$

This essential element of the algorithm leads to a local modification of the PES, which is obtained upon diagonalization of $\mathbf{H_{meta}}$. The molecule continues to evolve on the locally modified PES with the effective energy gap

$$\Delta E_{meta} = \sqrt{(E_g - E_e)^2 + 4V_{ge}^2}, \tag{4}$$

The gap between the Eigenstates of the modified Hamiltonian is enlarged by the contribution of the off-diagonal bias $V_{ge}$. With the $\Theta$-function in Equation (2), $V_G$ acts in the way that large values of $\Delta E_{meta}$ are biased and therefore, the molecular system is driven to the next intersection point. Notice, that $V_{ge}$ is made dependent on an additional, structural CV $s_{CI}$ that allows to distinguish between different molecular configurations. In that way, the return to the already sampled regions of the CI seam is prevented and the dynamics is forced to evolve toward unexplored regions. Complementary to $V_G$, $V_{ge}$ is updated only if $\Delta E_{meta}$ is below $\epsilon$ by adding a Gaussian potential according to:

$$V_{ge}(t) = \sum_{t'=\tau_G, 2\tau_G, \ldots}^{t} w \exp\left(-\frac{(s_{CI}(t) - s_{CI}(t'))^2}{2\delta s^2}\right) \times \Theta(\epsilon - \Delta E_{meta}(t')), \tag{5}$$

To summarize, initially, $\Delta E_{meta}$ equals the BO gap $\Delta E_{BO}$ as long as no Gaussians are added to the off-diagonal bias $V_{ge}$, and $\mathbf{H_{meta}}$ reduces to $\mathbf{H_{BO}}$. At the beginning of the simulation, $\Delta E_{meta}$ is larger than $\epsilon$, therefore, $V_G$ is updated in periodic time steps, driving the system toward the CI seam. When $V_G$ is strong enough and the system reaches the CI seam, $V_{ge}$ is updated. Diagonalization of $\mathbf{H_{meta}}$ "opens" the energy gap and the dynamics is continued on the modified PES. $V_{ge}$ forces the change of the current value of the CV $s_{CI}$, while $V_G$ drives the system back to the intersection seam. Reaching the next structural motif of the CI seam, another Gaussian is added to $V_{ge}$, biasing the current CI-structure. This procedure is repeated (see Figure 2) until the whole part of the intersection seam within the configuration space that is spanned by $s_{CI}$ is automatically explored and thus, "unzipped." Within the simulation, calculations of the BO energy gradient of the ground state are carried out and can in principle be obtained by a whole spectrum of electronic structure methods. Furthermore, the gradient of the modified energy gap is needed in order to calculate the force in Equation (1), which can be obtained according to the expression:

$$\nabla(\Delta E_{meta}) = \frac{\Delta E_{BO} \nabla(\Delta E_{BO}) + 4V_{ge}\nabla(V_{ge})}{\Delta E_{meta}}, \tag{6}$$

This requires also the calculation of the excited state energy gradient and the differentiation of $V_{ge}$:

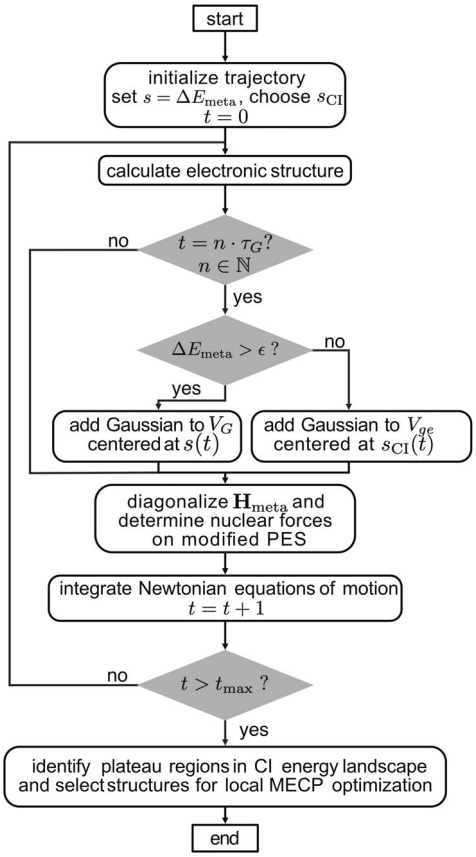
$$\nabla(V_{ge}) = \sum_{t'=\tau_G, 2\tau_G, \ldots}^{t} w \exp\left(-\frac{(s_{CI}(t) - s_{CI}(t'))^2}{2\delta s^2}\right) \times \Theta(\epsilon - \Delta E_{meta}(t')) \times \left(-\frac{s_{CI}(t) - s_{CI}(t')}{\delta s^2} \nabla(s_{CI}(t))\right), \tag{7}$$

In the long-time limit, the sum of the off-diagonal bias elements converges to the intersection seam along which the electronic CV is maximal. In case of the energy gap as a CV, the intersection seam corresponds to the CI.

## 4.2 | Role of the CV $s_{CI}$

Besides the electronic CV, that represents the functionality of interest, the discussed algorithm employs a second, structural CV: $s_{CI}$, that serves to distinguish between the geometrical configurations of the considered system, allowing to modify the CI seam only at already reached geometries. Furthermore, it spans the configurational space in which the CI seam is explored. Therefore, $s_{CI}$ should be unique for any geometry on the intersection seam, which is a sophisticated condition. In principle, the geometrical distance matrix can deliver unambiguous numbers; however, for complex systems, its calculation is time consuming. In search for a generally applicable CV that does not limit the sampling space, scalar

**FIGURE 2** Flowchart illustrating the multistate metadynamics algorithm




invariants like the lowest eigenvalue or other topographical indices of the density matrix[40] have been proven to be good candidates and the most general approach consists in the choice of the 3D-Wiener number *W*[41] defined as:

$$W = \frac{1}{2}\sum_{i}^{N}\sum_{j}^{N} d_{ij}, \tag{8}$$

as a CV for the off-diagonal bias $s_{\mathrm{CI}}$ where *N* is the number of atoms and $d_{ij}$ are interatomic distances. Comparison of different conditions chosen for the multistate dynamics simulations reveal that in organic molecules, it is often justified to consider only non-hydrogen distances. The value of *W* correlates with the molecular shape, due to the reduction of dimensionality, there is no unique mapping of the Wiener number to structure, meaning that $f-3$-dimensional isosurfaces are biased rather than single configurations on the $f-2$-dimensional intersection seam, where *f* is the number of internal degrees of freedom. This limitation can be overcome by running multiple trajectories with differing initial conditions, leading to a satisfying structural variability. Alternatively, social permutation invariant coordinates describing the bond network around a given atom by evaluating the largest Eigenvalue and the corresponding Eigenvector of the contact matrix might be a sophisticated choice [42]. For other purposes, it might be of interest to choose the second CV in a way that the sampled configuration space is limited to a particular geometrical subspace. As an example, photochemically and -physically relevant CI geometries of (aromatic) planar ring systems often exhibit "out-of-plane" puckering modes of parts of the molecular system, which can be described in an elegant way employing Cremer–Pople parameters [43]. In a recent multistate metadynamics study in the frame of CASSCF methodology, we have employed the Cremer–Pople parameters as structural CV in order to investigate the CI seam of adenine, as presented in Figure 3A,B. In that way, we have been able to obtain a global representation of the intersection seam identifying the MECP that play a relevant role in the light-induced processes of adenine, as proven by atomistic real-time dynamics simulations [44].

## 5 | AUTOMATIC SAMPLING OF QUANTUM PROPERTY MANIFOLDS

By generalizing the discussed methodology using any kind of properties of the electronic wavefunction as electronic CVs, the multistate metadynamics approach can be applied for an "ASQPM," which can be considered as functional landscapes both in the ground and excited state. In a first application we employed the approach for the investigation of biradicality landscapes [7].

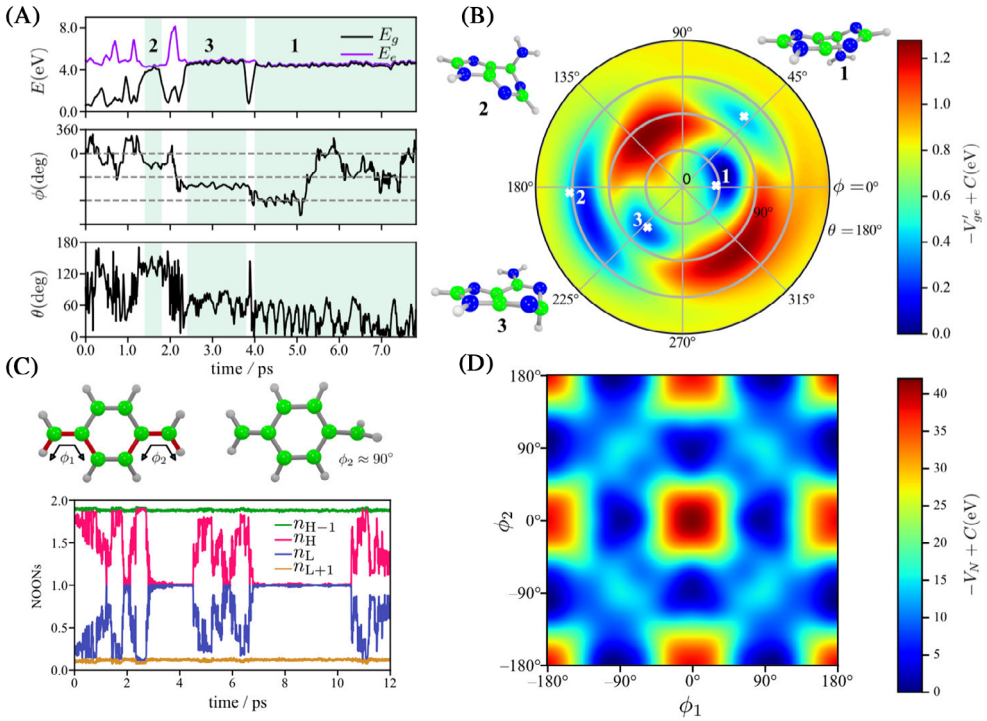



**FIGURE 3** (A) Energies of the ground and excited state (upper part) and the values of the Cremer-Pople parameters $\theta$, $\phi$ along the calculated multistate metadynamics trajectory for the exploration of the conical intersection seam of adenine (CASSCF level of theory). (B) Global conical intersection seam obtained from the multistate metadynamics along with the molecular conformations corresponding to the minimum energy crossing points. (C) Value of the frontier natural orbital occupation numbers (NOONs) along the calculated automatic sampling of quantum property manifolds (ASQPM) trajectory for p-xylylene (CASSCF level of theory), employing the NOON gap as electronic collective variable (CV) and the dihedral angles between the methyl group and the aromatic ring system as structural CV's, spanning the conformational space which is explored. (C) Resulting "biradicality landscape" of p-xylylene for the defined geometrical subspace with minima indicated by blue coloring

## 5.1 | Application to biradicality landscapes

Transiently formed biradical conformations play an important role in light-induced processes, for example, at CIs between the first excited and the ground BO states, mediating efficient non-radiative decay of excited molecules [45]. Also several bond forming reactions such as the photoinduced cycloaddition can process via biradical intermediates [46]. However, there is a growing interest in stabilized biradical compounds forming new classes of functional molecules with several potential applications: Organic biradical molecules serve as attractive candidates for optoelectronic applications such as singlet fission[47–50]. Therefore, a systematic investigation of the "biradicality landscape" can provide information about the structural evolution within light-induced (reactive) processes but might also guide the rational design of new biradical molecules. We consider the natural orbital occupation numbers (NOONs) as an electronic CV, which can be derived from the electronic wavefunction upon calculation of the one-electron reduced density matrix expanded into the molecular orbital basis. Diagonalization of the density matrix gives rise to a set of eigenvalue-eigenvector pairs, representing the reduced density matrix **D** in terms of natural orbitals (NO) $\varphi_i$ as

$$\mathbf{D}(\mathbf{x}_1,\mathbf{x}_{1'}) = \sum_i n_i \varphi_i^*(\mathbf{x}_1)\varphi_i(\mathbf{x}_{1'}), \tag{9}$$

NOs are the best possible approximation of the many-particle problem based on one-electron wavefunctions and therefore serve as an indicator for unpaired electrons in a molecular system. The corresponding eigenvalues $n_i$ are interpreted as NOONs[51, 52].

In a perfect closed-shell configuration, all NOONs are zero or two, as electrons occupy the NOs in pairwise manner. The orbital with the lowest NOON close to two is called highest occupied natural orbital (HONO) with NOON $n_H$, while the orbital with the highest NOON close to zero is referred to as lowest unoccupied natural orbital (LUNO) with NOON $n_L$. However, in an open-shell configuration bearing an even total number of electrons, one or several pairs of NOs are singly occupied resulting in NOON values of one. Biradical represent a special case, in which two unpaired weakly interacting electrons are present, that is, $N/2-1$ NOs are doubly occupied, while the two NOs with NOON value $n_H$ and $n_L$ are approximately one. Therefore, the gap between $n_H$ and $n_L$ can be considered as a measure for the degree of biradicality, and thus be applied as a

clearly defined, electronic CV for a systematic sampling of the biradicality landscape. Again, the bias potential $V_G(t)$ is built up at regular time steps $\tau_G$ adding Gaussian-shaped functions along the electronic CV $\Delta n_{\text{meta}}$:

$$V_G(t) = \sum_{t'=\tau_G, 2\tau_G, \ldots}^{t} w_G \exp\left( -\frac{(\Delta n_{\text{meta}}(t) - \Delta n_{\text{meta}}(t'))^2}{2\delta {\Delta n_{\text{meta}}}^2} \right) \times \Theta(\Delta n_{\text{meta}}(t') - \epsilon), \tag{10}$$

In order to systematically sample the biradicality landscape, this time we introduce an additional off-diagonal coupling term $V_N$ into the sub-block of the density matrix $\mathbf{D_{diag}}$ containing the HONO and LUNO (represented by their NOON values $n_{\text{H}}$ and $n_{\text{L}}$). The corresponding submatrix than becomes:

$$\mathrm{D}_{\text{meta}} = \begin{pmatrix} n_{\text{L}} & V_N \\ V_N & n_{\text{H}} \end{pmatrix}, \tag{11}$$

and by diagonalization, we get an effective NOON gap:

$$\Delta n_{\text{meta}} = \sqrt{(n_{\text{L}} - n_{\text{H}})^2 + 4V_N^2}, \tag{12}$$

assuming values between 2 (closed shell structure) and 0 (bi- or polyradical structure), as long as $V_N$ is zero. The off-diagonal biasing potential $V_N$ again serves to force the system to move along the biradicality landscape. For this purpose, $V_N$ is updated every $\tau_G$ steps, if $\Delta n_{\text{meta}}$ drops below $\epsilon$, according to:

$$V_N(t) = \sum_{t'=\tau_G, 2\tau_G, \ldots}^{t} w_N \exp\left( -\sum_i \frac{(s_i(t) - s_i(t'))^2}{2\delta {s_i}^2} \right) \times \Theta(\epsilon - \Delta n_{\text{meta}}(t')), \tag{13}$$

In order to distinguish between different biradical geometries and prevent the simulation to visit the same part of the landscape several times, a set of additional (geometric) CVs $\{s_i\}$ is introduced. In the long-time limit, the off-diagonal elements converge to something which can be considered as a biradical intersection. However, its physical meaning is not straightforward. As we wish to restrict the simulation to the exploration of biradical structures rather than polyradicals, we make sure that all NOONs other than $n_{\text{L}}$ and $n_{\text{H}}$ are close to 0 or 2, achieved by introduction of two quadratic wall potentials acting on $n_{\text{L}+1}$ and $n_{\text{H}-1}$:

$$V_{\text{wall}}^{\text{L}+1} = \begin{cases} k(n_{\text{L}+1} - \epsilon_{\text{L}+1})^2 & \text{for } n_{\text{L}+1} > \epsilon_{\text{L}+1} \\ 0 & \text{for } n_{\text{L}+1} < \epsilon_{\text{L}+1} \end{cases}, \tag{14}$$

$$V_{\text{wall}}^{\text{H}-1} = \begin{cases} k(n_{\text{H}-1} - \epsilon_{\text{H}-1})^2 & \text{for } n_{\text{H}-1} < \epsilon_{\text{H}-1} \\ 0 & \text{for } n_{\text{H}-1} < \epsilon_{\text{H}-1} \end{cases}, \tag{15}$$

Due to the sorting of the NOONs, these two wall potentials restrict all NOONs other than $n_{\text{H}}$ and $n_{\text{L}}$ to values below $\epsilon_{\text{L}+1}$ or above $\epsilon_{\text{H}-1}$ and the full equation of motion for the nuclei becomes:

$$m_i \ddot{\mathbf{R}}_i = -\nabla_i \left( V_{\text{el}} + V_G + V_{\text{wall}}^{\text{L}+1} + V_{\text{wall}}^{\text{H}-1} \right), \tag{16}$$

with the original electronic potential $V_{\text{el}}$ obtained from the chosen electronic structure method.

Notice, that the nuclear gradients contain the differentiation of $\Delta n_{\text{meta}}$ with respect to the nuclear coordinates:

$$\nabla(\Delta n_{\text{meta}}) = \frac{(n_{\text{L}} - n_{\text{H}})\nabla(n_{\text{L}} - n_{\text{H}}) + 4V_N \nabla V_N}{\Delta n_{\text{meta}}}. \tag{17}$$

Furthermore, the gradients $\nabla n_{\text{H}}$ and $\nabla n_{\text{L}}$ are needed for the calculation of the wall potentials in Equations (14) and (15), which we get from numerical differentiation.

In a recent example, we have proven the applicability of the described method on the biradicality landscape of p-xylylene as a model system: while the planar molecule is known to exhibit closed-shell electron configuration, rotation of one of the methylene groups leads to biradical configuration. By employing the rotation angles as illustrated in Figure 3C,D, as structural CVs, the biradicality landscape within the chosen geometric subspace has been explored, indicating strongest biradical character for a molecular conformation bearing one planar methylene group while the other one is twisted by 90 degrees.

## 6 | PERSPECTIVE AND OUTLOOK

This perspective article aims to address the need for new theoretical methods and algorithms allowing for the rational prediction and investigation of the structure–function relation in molecular systems. It elucidates the concept of functional landscapes and discusses the challenges that have to be overcome for their rational investigation. Recent methodological developments based on the idea of the multistate metadynamics, employing electronic CVs, are presented, providing a promising strategy in the rational exploration of structure–function relations in complex molecular systems. The advantages of the method are outlined referring to recent examples of applications. In order to advance the ASQPM approach to a robust, generally applicable methodology, (i) solutions for the efficient calculation of the derivatives of the electronic CVs have to be developed, while (ii) the implementation of diverse electronic properties as well as electronic structure methods has to proceed. In particular, so far this method has been applied to properties with a defined maximal value, that is in case of the CIs, an energy gap of zero and in case of the biradicality, a NOON value of one for both frontier orbitals. Here, further generalization of the methodology is needed. Recent advances in metadynamics such as variationally enhanced sampling[53] may also in the future be extended to the multistate dynamics in order to enhance sampling of various kinds of functional landscapes. This is particularly attractive since the bias can be determined variationally by minimizing a given functional such that probability distribution of the CV is equal to predefined target distribution. The latter might be designed such that it is localized close to the functional landscape (e.g., intersection seam). A particularly attractive feature of this novel approach is that it can be combined with machine learning methods expressing the bias in the form of a neural network[54]. These advancements will significantly broaden the scope of applications, ranging from the investigation of catalytic systems to multi-molecular arrangements such as molecular aggregates. All recent and ongoing method development is implemented in our freely available metaFALCON program package[55].

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### CONFLICT OF INTEREST

The author declares no conflict of interest.

### AUTHOR CONTRIBUTIONS

**Merle I. S. Röhr:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; supervision; validation; visualization; writing-original draft; writing-review & editing.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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