Comment on Molecular Mechanics for Chemical Reactions

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The hybrid quantum mechanical/molecular mechanical (QM/MM) methods are considered at present the only practical way of quantitative modeling of chemical reactions in macromolecules or solutions. Among QM/MM algorithms, the empirical valence bond (EVB) method stands out since it can be parametrized in a simple and intuitive way. The excellent performance of the parametrized valence bond (VB) approach in providing realistic potential energy surfaces was noticed already half a century ago, when Coulson and Danielsson[1] wrote that "the close liaison with experiment required in estimating the various elements $H_{\mu\nu}$ is the primary cause of this" (of the excellent numerical results). Still, the current success of the EVB method in macromolecular modeling grows from the approximation of the diagonal elements (H_{ii}) of the VB Hamiltonian by molecular mechanical (MM) force fields[2−5] and the design of an efficient coupling between the reacting core and its macromolecular or solution environment.[6] The EVB approach captures correctly the linear relationship between reaction and activation free energies (LFER) observed for many important reactions,[7] although it should be noted that EVB is not the only method capable of generating LFER from the intersecting diabatic states.[8,9] The crucial parts of the EVB model are the off-diagonal matrix elements (H_{ij}) that govern the extent of mixing of diabatic H_{ii} surfaces in the diagonalization procedure, which determines the ground-state potential energy surface for the given reaction. Consequently, new approaches to empirical adjustment of the H_{ij} elements keep being introduced.[10,12−15] Unfortunately, often the suggestion of an improved fitting procedure for H_{ij} is considered as a sufficient reason to create new acronyms for the EVB method.[16]

The latest addition to the EVB family (Table 1) is the multiconfigurational molecular mechanics (MC-MM) method of Truhlar and co-workers,[10,13] who extended and automated Chang and Miller's algorithm of fitting H_{ij} using ab initio Hessians. Although the design of a black-box fitting procedure for H_{ij} is undoubtedly attractive for applications of the EVB method in biochemistry, the addition of a new acronym will necessarily detract from the ability of theoretical papers using MC-MM methods to be understood by the biochemical community, where the EVB methodology has already shown a great impact (see, e.g., refs 17 and 18). To limit the extent of the confusion about the real meaning of various EVB acronyms, I would like to emphasize the following points:

(i) The EVB and AVB[11,19] approaches are identical theoretical concepts that involve three major ingredients: replacement of H_{ii} and H_{ij} integrals in the VB method by empirical functions; including the solvent effects in the VB Hamiltonian; representation of the parts of the solute and the solvent by adding molecular mechanics (MM) potential functions to the H_{ii} elements. The first of these ingredients was included in many studies prior to 1970, in particular in the remarkable study of the O−H···O hydrogen bond.[1] The remaining two ingredients are to the best of my knowledge due to Warshel and coworkers,[2−6] who also coined the acronym EVB.

(ii) The MC-MM method[10,13] is not unique (as its name might suggest) in mixing molecular-mechanics force fields, nor does it include more VB configurations than previous EVB models. Because the MC-MM acronym fails to convey the quantum nature of the method, it should be ideally reserved for a simple case of zero coupling (i.e., for cases when $H_{ij} = 0$). The zero-coupling multiconfigurational MM potential functions are frequently employed in the literature for statistical sampling of reaction surfaces in the *classical* molecular dynamics simulations. Typically, these simulations represent the starting point for a subsequent evaluation of EVB[17,18] or ab initio[20] free energies of biochemical reactions.

(iii) The only conceptual difference between the MC-MM and EVB (or AVB) methods is that the MC-MM model does not include, in its present formulation, the effect of the solvent on the reaction potential energy surface. However, it is quite possible that the solvent effects will be incorporated into the MC-MM method in the future.

In summary, it seems that replacing the MC-MM name by the universal EVB (or at least AVB) trademark would be beneficial for the image of computational biochemistry.

TABLE 1: Taxonomy of the EVB and Earlier Methods[a]

year	1954	1980	1991	1996	1997	1998	2001
acronym	VB[b]	EVB	EVB	AVB	extended EVB	MS-EVB	MC-MM
principal author	Coulson[1]	Warshel[2−6]	Miller[12]	McCammon[11,19]	Borgis[15]	Voth[14]	Truhlar[10,13]
no. of VB states	3	2−8	2	2−8	∼20	6−10	2
H_{ii}[c]	Morse	Morse + MM	Morse+MM	Morse+MM	Morse+MM	Morse+MM	MM
H_{ij}[c]	exp function	const or exp function	exp function	const	exp function	general function	general function
analytical forces[d]	no	yes	no	yes	yes	yes	yes
solvent[e]	no	in H_{ii}	no	in H_{ii}	in H_{ii}	in H_{ii} and H_{ij}	no
studied energy surf	H bonding	enzyme catal, soln reacns	double-well potentials	phospholipase catalysis	hydrated proton	hydrated proton	H transfer
syst size (no. of atoms)	3	2 to $\sim 10^4$	n/a	2 to $\sim 10^4$	∼400	∼400	3−13

[a] This table is biased toward authors who introduced new algorithms in the EVB family and therefore it should not be regarded as a comprehensive review of EVB applications. [b] Coulson's and Danielsson's paper is presented only as a representative example of early VB treatments that included empirical parametrization of the VB Hamiltonian. [c] Diagonal (H_{ii}) and off-diagonal (H_{ij}) elements of the VB Hamiltonian are considered to be empirical parameters fitted either to experimental or ab initio data. [d] Hellmann−Feynman forces. [e] Protein and/or solution environment.

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