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Comment

Reply to the paper by Stachó et al. “On the Elber–Karplus reaction path-following method and related procedures” [Chem. Phys. Lett. 311 (1999) 328]

Ron Elber^{a,*}, Martin Karplus^{b,c}

^a Department of Computer Science, 4130 Upson Hall, Cornell University, Ithaca, NY 14853, USA

^b Laboratoire de Chimie Biophysique, ISIS, Université Louis Pasteur, 67000 Strasbourg, France

^c Department of Chemistry and Chemical Biology, Harvard University, Cambridge, MA 02138, USA

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Abstract

Stachó, Dömötör and Bán [Chem. Phys. Lett. 311 (1999) 328] criticize the method developed by Elber and Karplus for finding reaction paths in large molecules. In this Comment we demonstrate that the statements and mathematical development on which Stachó et al. base their criticism are either false or well known from published work. © 1999 Elsevier Science B.V. All rights reserved.

The abstract of the manuscript of Stachó et al. [1] opens with the strong statement: “It is shown through a mathematical proof and by using simple test examples that the fundamental principles of the method of Elber and Karplus (EK) [2] for determining reaction paths are incorrect”. One would expect that such a statement would be supported by the appropriate evidence. This is not the case. The so-called ‘proof’ presented by Stachó et al. [3] is erroneous and the test examples they present are numerically flawed. Stachó et al. also make statements that indicate they did not read or pay attention to key discussions in EK [2], as well as in related papers. Moreover, in a recent conference report [4], Stachó et al. wrote:

“The popular global curve variation Elber–Karplus method [22] [equations and reference numbers correspond to those used in the quoted paper] is based upon the minimization of the energy average (with respect to the arc length) along the curve joining the two minima corresponding to the reactant and the product. Unfortunately, it can easily be shown that this method is mathematically false.” The statement was published without justification.

Given the above, we feel it is necessary to respond to Stachó et al.

Before addressing specific claims of Stachó et al., it is useful to review briefly the nature of the method proposed by EK and the description of its limitations given in the original paper published more than 10 years ago [2]. EK proposed a simple method for computing reaction paths that was designed to be applicable to large systems (e.g. proteins) because it

* Corresponding author. Fax: +1-607-2554428; e-mail: ron@cs.cornell.edu

does not require the use of Hessian matrices. It was clearly stated in the original manuscript that the EK formulation was an *approximate* procedure. “It is important to point out that the method proposed in Eqs. (4)–(7) *defines* the reaction path by minimizing the *average* value of the potential energy along the path. The more standard approaches are usually concerned with finding the path with the lowest barrier [1,2,3]”.

The EK method proposed to optimize a line integral to obtain a path \vec{l}_{\min} . \vec{l}_{\min} is *defined* to be the reaction coordinate; the line integral is given by

$$S = \frac{\int_R^P U(\vec{l}) \cdot |d\vec{l}|}{\int_R^P |d\vec{l}|} \equiv \langle U \rangle_{\vec{l}} \quad (1)$$

where S is the functional to be optimized, $U(\vec{l})$ is the energy function, R and P denote the positions of the reactants and product minima, respectively, and \vec{l} is a vector pointing along the path. In the implementation of the method, a discretized form of the line integral defined by

$$S(\vec{R}_o, \vec{R}_M; \vec{l}) \cong \frac{1}{L} \sum_{i=1}^M U(\vec{R}_i) |\Delta \vec{l}_i| \quad (2)$$

was used. Here $U(\vec{R}_i)$ is the energy as a function of the N -dimensional position vector \vec{R} representing the coordinates of the system of interest, \vec{R}_o and \vec{R}_M are the coordinates of the fixed end points, and R_i is the value of R at the end point of the interval $\Delta \vec{l}_i$, defined as

$$\Delta \vec{l}_i = \vec{R}_i - \vec{R}_{i-1} \quad (3)$$

Restraints were introduced of the form $\lambda(|\Delta \vec{l}_i| - \langle |\Delta \vec{l}| \rangle)^2$, where λ is a parameter that determines the range of the allowed fluctuations in $\Delta \vec{l}_i$, relative to the average value (over all i), $\langle |\Delta \vec{l}| \rangle$. This keeps the points approximately equidistant and avoids artefactual solutions in which the grid points cluster around the initial and final configurations. To eliminate rigid-body translations and rotations in the optimization, additional restraints were introduced [2].

EK argued that the path so defined may be a useful approximation to the steepest descent path (SDP), and a number of numerical examples were provided. For cyclohexane and the alanine dipeptide,

the results were shown to agree with those obtained with other methods. Since the main purpose of introducing this approximate method was to be able to study large molecules, it was applied to a conformational transition of the protein myoglobin with 1531 atoms; the latter could not be checked because there were no other methods that could be applied to such a large system when the paper was published.

Since its introduction, the EK method has been used successfully by others for a variety of applications. An example is the study of the potential surface for water dynamics by Tanaka and Ohmine in 1989 [5]; other references to applications are given in Stachó et al. [1]. In addition, the EK method has served as the basis for refinements [6,7] and for the development of alternative improved methods for large systems [8–12]. A useful overview of methods for path optimization from small molecules to proteins is given by Schlegel [13] and by Elber [14].

There is some confusion as to what Stachó et al. mean by “incorrect”. Since it was clearly pointed out in EK [3] that the reaction path obtained from the line integral is not the steepest descent path, in general, a proof confirming this would be nothing new. Nevertheless, it is of interest to consider the “proof” of Stachó et al. [3] that the average energy functional cannot be the steepest descent path (SDP). To demonstrate that this statement is false, we introduce a simple counter-example. Consider a two-dimensional energy surface with the potential energy

$$U(x, y) = kx^2 + y^4 - y^2 \quad (4)$$

The line integral connecting the two minima along the y -axis ($x = 0$) is the steepest descent path. The SDP is also a minimum of the average energy along the same path and is obtainable by the EK procedure.

To paraphrase their “proof”, Stachó et al. [1] introduce some “elementary mathematical tools”. One of these is an unusual construction of points that cannot lead to a *continuous* path from R to P , as required by the definition of the line integral and so the discussion appears to be irrelevant to the formulation of EK [2]. They also performed a variational analysis. This analysis (see below) could have been a useful investigation to pinpoint exactly the difference between the SDP and the EK path. However, their analysis is wrong, as based on the text of the forth-

coming paper [3] that was provided to us. Below we provide the correct formulation and discuss the difference between the SDP path and EK path.

In the variational analysis, the path vector, \vec{l} , is parameterized by a scalar, say $t \in [0,1]$. Euler–Lagrange ‘equations of motion’ are derived for $\vec{l}(t)$ from the requirement that the functional be a minimum. Stachó et al. [3] attempted this derivation, but they made an error so that their result is incorrect. To make the comparison simpler, we use their path parameterization in which the distribution of points along the spatial path is determined by:

$$\left[\frac{d\vec{l}}{dt} \cdot \frac{d\vec{l}}{dt} \right]^{1/2} \equiv \int_R^P |d\vec{l}| \equiv L$$

$$\langle U(\vec{l}) \rangle_{\vec{l}} = \int_0^1 U(\vec{l}(t)) dt$$

The second formula follows from the definition of the path length.

The differential equation of Stachó et al. (Eq. (2) in Ref. [3]), has an essential error in that the Hessian $D^2U(\vec{l}(t))$ should not be there. The error leads to the incorrect result that $U(\vec{l}(t))$ is a monotonically decreasing function of t (Eq. (5) in Ref. [3]) and to their conclusion that the EK path is not valid.

The correct ‘equation of motion’ derived by straightforward variational analysis is:

$$L \cdot \nabla U(\vec{l}(t)) - \frac{1}{L} \left\langle \nabla U, \frac{d\vec{l}}{dt} \right\rangle \frac{d\vec{l}}{dt} - \frac{1}{L} (U - \langle U(\vec{l}) \rangle_{\vec{l}}) \frac{d^2\vec{l}}{dt^2} = 0$$

Following the definition of the length of the path, L , given in Eq. (5), we note that if ∇U is exactly parallel (or antiparallel) to $(d\vec{l})/(dt)$ (the usual situation in the SDP), the first two terms vanish. The third term, $(1/L)(U - \langle U(\vec{l}) \rangle_{\vec{l}}) d^2\vec{l}/dt^2$ which in general is not zero, contributes to the deviation of the EK path from the SDP. It is small when the path curvature, $d^2\vec{l}/dt^2$ is small. The counter-example in Eq. (4) has zero curvature, so that the EK path is exact for this case. Hence, Eq. (4) provides a counter example to the ‘proof’ of Ban et al. that the line

integral does not exist. *Not only the line integral exists for the model potential (4) but the resulting curve is also the steepest descent path. This counter example demonstrates that the ‘general proof’ of Bán et al. is incorrect.*

Application of the EK method has shown that the path produced by the EK functional is physically reasonable and close to the SDP path if the path curvature is small. Adding a penalty for a high curvature is not unreasonable, since highly curved paths are unlikely in systems at finite temperatures. For example, the MaxFlux algorithm of Huo and Straub [10] depends on the path length and leads preferably to shorter paths.

The other argument in Stachó et al. [1] against the EK method is based on the fact that they failed when they tried to employ the EK method, in contrast to the success of other workers (see discussion above). Indeed Stachó et al. failed, but this is due to the fact that they did not follow the guidelines given in the EK paper [2]. In a sense, the conclusions (i)–(iii) of Stachó et al. [1] do not refer to the EK algorithm but to a ‘new’ algorithm of their own design.

The first two conclusions of Stachó et al. are: (i) ‘‘It has been proven that the line integral used in the methods employing the EK strategy without constraints has no minimum’’ and (ii) ‘‘Using polygons with points/vertices of discrete numbers and without using penalty functions the results obtained are not useful.’’

We agree that use of the EK method without ‘‘penalty functions’’ (restraints) is not useful. The EK algorithm always uses the penalty functions. It is meaningless to optimize the functional without high values for the penalty functions and we do not understand the purpose of this exercise performed by Stachó et al. Large penalties, to avoid rigid body translations and rotations, do not affect the value of the functional, and a large penalty on deviations from equal distances between the points is essential to approximate the line integral in Eq. (1). A visual inspection of Fig. 1 in Stachó et al. shows the results *do not* provide an adequate description of the line integral defined in Eq. (1). In our hands (Fig. 1, this paper), the EK method provides a reasonable approximation to the steepest descent path for the Müller–Brown potential. It is not exact for this case, as expected from the derivation given above.

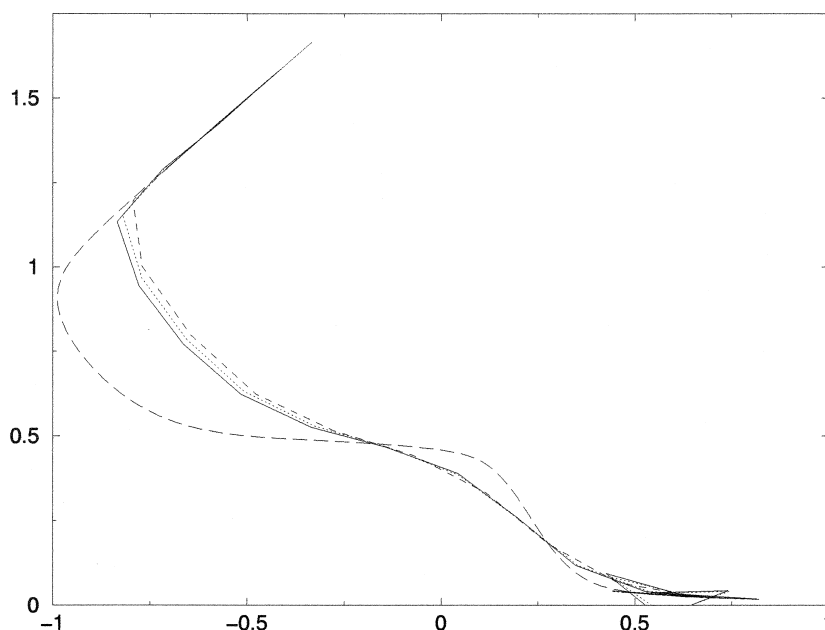


Fig. 1. Reaction path calculations on the Müller potential. Long dash, the steepest descent path. Three different EK paths are shown with force constants for equi-distance constraints of 4000 (dash), 8000 (dotted line) and 16000 (solid line). Rigid-body constraints are not necessary in this case. The force constant value does not affect significantly the shape of the path. In the calculations of the EK path 30 grid points were used (including the fixed points at the path edges). The optimization was performed by simulated annealing that was followed by 200 conjugate gradient minimization steps.

To amplify the point concerning the importance of restraints, which seems to have been missed by Stachó et al., we quote from Chiu et al. [6]: “EK recognized that a straightforward minimization of Eq. (2) would lead to two problems. The first arises from the fact that the lowest value of $S(\vec{R}_o, \vec{R}_M; \vec{l})$ will be obtained if all of the grid points moved to the initial or final configurations. This would be possible if there was no constraint put on the values of $|\Delta \vec{l}|$ and would lead to a nonsensical representation of Eq. (1).” Bán et al. argued that the aggregation of points (piling up of the points) is a novel discovery of their study. Even before Chiu et al. [6], Czerminski and Elber discussed this problem in their 1990 paper [11] and proposed a solution by introducing an additional repulsion term. This problem has nothing to do with the existence of the line integral but rather with how to construct a useful numerical representation of it.

In their conclusion (iii) Stachó et al. state: “When using penalty functions, the resulting curve can be interpreted as a sort of RP approximation; however,

the larger the values of the parameters, the more the minimization of the penalty functions and not of the energy of the system will take place.” We agree with the first part, but again this is nothing more than what was stated in the original EK paper. As to the second part, restraint parameters have to be chosen appropriately; if they are very large, the optimization will be slow and inefficient. However, the final result should not be affected. The use of inappropriate restraints provides a partial explanation of the problems Stachó et al. appear to have in applying the EK method (e.g., see their Table 1).

As to conclusion (iv), we do not quote most of this since it only presents the opinion that the DDRP strategy of Stachó and Bán [1,15] is the best method to obtain the reaction path. We have not tested the DDRP method, so we have no comment on their opinion. The comment “The DDRP method does not require ... an initial straight line for the zero approximation of the RP” may be true but, of course, neither does the EK method.

In addition to the fundamental problems with the Stachó et al. papers [1,3] outlined above, they make many statements that are incorrect and/or confusing. We cite only a few of them in what follows.

- The abstract of Stachó et al. [1] states: “Therefore the method, including *its improved versions*, ... should be accepted with reservation”.

It is not clear what is meant by “improved versions”. Other algorithms developed by Elber and coworkers for determining reaction paths for large molecule systems, such as that of Ulitsky and Elber [12] and of Olender and Elber [8], compute the exact SDP. Correspondingly, the method of Fischer and Karplus [9] computes exact saddle points and from them the SDP.

- The following complicated sentence is in the introduction: “As to our mathematical investigation [29] the method of Olender and Elber [30] does not supply conventional RPs, however it operates with a new concept of the RP which is probably not a true SDP in the mathematical sense yet the solutions of such a variational problem may approximate or even replace the old concept of the RP”.

Ref. [29] of their paper, which is Ref. [3] of ours, does not investigate the procedure of Olender and Elber [8]. Moreover, as just pointed out, the Olender–Elber method does determine the SDP, so the purpose and meaning of this sentence of Stachó et al. is unclear.

- Also in the introduction, Stachó et al. argue that the EK method “is based on the principle stating that the RPs are energy average minimizing curves”.

As is clear from the quote given above from the EK paper, this is not true. We *defined* the reaction coordinate as the path that minimizes the average energy. We did not say that the resulting path is the same as the SDP, which is one possible way of choosing a reaction path. It is, in fact, not obvious that in large molecules the SDP is the best choice to describe kinetics and the use of functionals suggests useful alternatives [2,10,11,14].

- Also, in the introduction, Stachó et al. claim “there has been some confusion about which variant was used in a particular application [25–27]”.

The confusion is not in the papers. Their Refs. [25] and [27] *did not* use the EK method, as is clearly stated in these manuscripts.

We conclude by restating the claims of Bán et al. and our replies:

(1) *There is a “proof” that the line integral does not exist.* It is enough to provide one counter example to invalidate a “general proof”. We provide such a counter example. The potential model in Eq. (4) and the (correct) variational analysis show (for that counter example) that not only the line integral exists but that it yields the steepest descent path.

(2) *A variational principle proves that the EK method is not valid.* Bán et al. are “ready to admit” that their derivation is wrong.

(3) *The numerical study gives results that depend on the parameters.* We demonstrate in Fig. 1 that the results are parameter independent (provided that the constraints are satisfied). Bán et al. did not implement correctly the EK algorithm.

We further note that our reaction path code has been freely available on the network for a number of years as a part of the MOIL package for biomolecular modeling. At present it includes an upgraded version of the reaction path algorithm [11], and we encourage Bán et al. to use it. The commercial program CHARMM also includes the algorithm of [11] as implemented by B. Brooks.

There are numerous techniques to obtain reaction paths in small molecular systems [13]. A key difficulty in large molecular systems is the rapid growth in computational effort and the decrease in numerical stability. The EK method and related approaches were developed for computing reaction paths in macromolecules with thousands of degrees of freedom, with many minima, and with path multiplicity. Perhaps the DDRP approach [15] is applicable to such systems and can yield accurate values for the SDP in reasonable times. If so, such studies would be of greater interest than the EK method criticism presented by Stachó et al. (preceding paper), which we have shown to be invalid.

Acknowledgements

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