# Calculation of Classical Trajectories with Boundary Value Formulation

R. Elber

Department of Computer Science, Cornell University, 4130 Upson Hall, Ithaca NY 14853
ron@cs.cornell.edu

Ron Elber

Ron Elber: *Calculation of Classical Trajectories with Boundary Value Formulation*, Lect. Notes Phys. **703**, 435–451 (2006)
DOI 10.1007/3-540-35273-2_12

An algorithm to compute classical trajectories using boundary value formulation is presented and discussed. It is based on an optimization of a functional of the complete trajectory. This functional can be the usual classical action, and is approximated by discrete and sequential sets of coordinates. In contrast to initial value formulation, the pre-specified end points of the trajectories are useful for computing rare trajectories. Each of the boundary-value trajectories ends at desired products. A difficulty in applying boundary value formulation is the high computational cost of optimizing the whole trajectory in contrast to the calculation of one temporal frame at a time in initial value formulation.

## 1 Introduction

Calculation of classical trajectories of molecular systems is a powerful tool for studying the thermodynamics and the kinetics of biophysical problems. Indeed the availability of numerous computer packages and journals devoted to such simulations suggests that these studies are extremely popular, and are influencing many fields. It is therefore no surprise that a number of chapters in this book are devoted to the use of classical dynamics in condensed matter physics.

The emphasis in other chapters of this book is on initial value solution of classical equations of motion (e.g. the Newton's equations). The Newton's equations are second order differential equations – $M\ddot{X} = -dU/dX$, where $X\left(X \in R^{3N}\right)$ is the coordinate vector. Throughout this chapter $X$ is assumed to be a Cartesian vector, $M$ is a $3N \times 3N$ (diagonal) mass matrix, and $U$ is the potential energy. A widely used algorithm that employs the coordinates and the velocities ($V$) at a specific time and integrates the equations of motion in small time steps is the Verlet algorithm [1]:

$$\begin{aligned} X_{i+1} &= X_i + V_i \cdot \Delta t - \left(\Delta t^2/2M\right) \cdot (dU/dX_i) \\ V_{i+1} &= V_i - \left(\Delta t^2/2M\right) \cdot (dU/dX_i + dU/dX_{i+1}) \end{aligned} \tag{1}$$

where $i$ is the index of the integration step, $\Delta t$ is the step size, and the division by the matrix, means the inverse. There are two limitations of this popular initial value formulation that are worth mentioning: (i) The time step, $\Delta t$, must be small to maintain numerical stability, and (ii) It is difficult to end a trajectory solved with an initial value approach in a pre-determined and desired final state.

The small size of the time step restricts the calculation to rapid processes. Even for fast molecular events (nanoseconds) millions of femtosecond steps are required to reach the nanosecond time scale. Longer time scales are important for simulating many biophysical events and are not reachable with routine calculations (e.g. rapid protein folding occurs at the microseconds and milliseconds time scales).

The second limitation is more subtle. In principle, if the final state is strongly attractive with a large radius of convergence, we anticipate that the

trajectory will quickly stop at the end state, making the sampling of reactive trajectories relatively easy. This is a key idea behind the calculation of the transmission coefficient [2] and the transition path sampling [3]. These techniques initiate trajectories at improbable configurations that are intermediates between the reactants and products. By integrating the trajectory in the forward and backward directions to the two attractive end states it is possible to generate a complete reactive trajectory. Nevertheless, if the desired final states are not strong attractors it becomes difficult to sample reactive trajectories.

A complementary approach to the initial value formulation is the calculation of trajectories as a solution of a boundary value problem. In this approach the two end points are given as input to the calculations. It is therefore obvious that the trajectories will end at the pre-set interesting configurations. This simple construction solves the second limitation on initial value calculations that we mentioned above. Of course if the end points are not known and only the beginning configuration is available (e.g. the protein folding problem), then the initial value approach is the only viable option.

The second limitation is harder to tackle rigorously, however as we discuss in Sects. 3.3 and 3.4, the boundary value approach can be used to suggest approximate solutions with much larger time steps. Increasing the time step is much harder to achieve with initial value formulation.

## 2 Basic Theory

We consider the classical action $S$ [4] for a collection of $N$ particles, defined by

$$S = \int_0^t \left( \frac{1}{2} \dot{X}^t M \dot{X} - U(X) \right) d\tau \equiv \int_0^t (T - U) d\tau \equiv \int_0^t L d\tau \tag{2}$$

The coordinates are stored in the vector $X$ ($X^t$ denotes a transposed vector) and throughout this manuscript we use Cartesian coordinates only. A dot denotes a time derivative. The mass matrix $M$ is diagonal, $T$ is the kinetic energy, $U$ is the potential energy, and $L$ is the Lagrangian. We seek trajectories such that the total time, $t$, and the end points of the trajectories, $X(0)$ and $X(t)$, are fixed, and the action is stationary with respect to path variations. With the above conditions the Newton's equations of motion are obtained by a standard variation of the classical path [4]. Let $\eta(\tau)$ be an arbitrary displacement vector from a path, $X(\tau)$. The stationary condition of the action is obtained from the expression below

$$S\left[X\left(\tau\right)+\eta\left(\tau\right)\right]-S\left[X\left(\tau\right)\right]=\int_0^t\left(\frac{1}{2}\left(\dot{X}^t+\dot{\eta}^t\right)M\left(\dot{X}+\dot{\eta}\right)-U\left(X+\eta\right)\right)d\tau$$
$$-\int_0^t\left(\frac{1}{2}\left(\dot{X}^t\right)M\left(\dot{X}\right)-U\left(X\right)\right)d\tau \tag{3}$$

To the first order in the displacement $\eta$ we have

$$S\left[X\left(\tau\right)+\eta\left(\tau\right)\right]-S\left[X\left(\tau\right)\right]\cong\int_0^t\left(\dot{X}^tM\dot{\eta}-\left[dU\left(X\right)/dX\right]^t\cdot\eta\right)d\tau=0 \tag{4}$$

Integrating by parts $\int_0^t \dot{X}^tM\dot{\eta}\cdot d\tau=\left[\dot{X}^tM\eta\right]_0^t-\int_0^t \ddot{X}^tM\eta\cdot d\tau$, and setting the variation on the boundaries to zero $(\eta\left(0\right)=\eta\left(t\right)=0)$ we have for an arbitrary variation $\eta$

$$\begin{aligned}&S\left[X\left(\tau\right)+\eta\left(\tau\right)\right]-S\left[X\left(\tau\right)\right]\cong-\int_0^t\left(\ddot{X}^t\cdot M+\left[dU\left(X\right)/dX\right]^t\right)\cdot\eta d\tau=0\\&\Rightarrow M\ddot{X}+\frac{dU}{dX}=0\end{aligned} \tag{5}$$

This is (of course) the expression for the Newton's equations of motion. The above derivation is well known and can be found in any textbook on mechanics (e.g. Landau and Lifshitz [4]). It shows the equivalence of the variation principle and the usual differential form of the equations of motion. It is also the basis for introducing initial value numerical solvers, using a finite difference to represent the second derivatives with respect to time, for example

$$M\frac{X_{i+1}+X_{i-1}-2X_i}{\Delta t^2}+\frac{dU}{dX_i}=0 \tag{6}$$

We obtain an initial value solver by exchanging variables on both sides of the equation to give $X_{i+1}=2X_i-X_{i-1}-M^{-1}\Delta t^2\frac{dU}{dX}$. This equation can be solved in steps. Given $X_{i-1}$ and $X_i$ we can produce $X_{i+1}$, and so on.

It is useful to introduce another analytical variant of the classical action that suggests a different perspective on the boundary value formulation of classical mechanics and a corresponding initial value solver. We consider a system of a constant total energy $E=(T+U)$. We write $U=E-T$ and substitute in (2) $S=\int_0^t\left(2T-E\right)d\tau=\int_0^t 2T\cdot d\tau-Et$. Define $Q=M^{1/2}X$, mass weighted coordinates, which we now use in the expression for the kinetic energy $\int_0^t \dot{X}^tM\dot{X}\cdot d\tau=\int_0^t \dot{Q}^2\cdot d\tau$. The last expression can also be written as $\int_{Q(0)}^{Q(t)}\dot{Q}dQ$ $(dQ\equiv\dot{Q}d\tau)$. Collecting the pieces, we now have a new expression for the action

$$S = \int_{Q(0)}^{Q(t)} \dot{Q} dQ - Et \tag{7}$$

Note that $\dot{Q}$ and $dQ$ are parallel vectors. Therefore their inner product $\dot{Q} \cdot dQ$ can be written as $|\dot{Q}| \cdot |dQ|$ which allows for the final twist of (7). We return to the expression of the energy and write

$$E = \frac{1}{2}\dot{Q}^t \dot{Q} + U(Q) \;\; \Rightarrow \left|\dot{Q}\right| = \sqrt{2(E - U(Q))} \tag{8}$$

Our new expression for the action therefore becomes

$$S = \int_{Q(0)}^{Q(t)} \sqrt{2(E - U(Q))} dQ - Et \tag{9}$$

The boundary conditions of (9) are the same as of the usual classical action in (2) (fixed end points and total time). However, separation of variables is now self-evident. The second term on the right hand side of the equation ($Et$) is independent of the coordinates (the energy is a constant). Similarly the first term is independent of time. In fact, it is not necessary to write $dQ = \dot{Q} d\tau$. Any parameterization of the trajectory with respect to a scalar variable $s$ which is monotonic between the points $Q(0)$ and $Q(t)$ will do ($dQ = (dQ/ds)\, ds$). It means that variation of the integral part of the right hand side of (9) with respect to the coordinates can be done with no reference to time. We therefore consider a variation with the abbreviated action [5]

$$S_{abbrev} = \int_{Q_{init}}^{Q_{final}} \sqrt{2(E - U(Q))} dQ \tag{10}$$

One should keep in mind that the new abbreviated action poses no constraint on time. Another way of thinking about the elimination of time is to shift the total energy by a constant, $C$, such that $E' = E - C = 0$. In this case (9) becomes identical to (10). Note that the potential energy $U$ is shifted in a similar way to the total energy $U' = U - C$. This keeps the value of $E - U$ unchanged. The time is arbitrary and is no longer fixed as in the usual definition of the action. The time can be computed in retrospect once the stationary path is obtained using the standard classical mechanics formula $t = \int_{Q_{init}}^{Q_{final}} \frac{d|Q|}{\sqrt{2(E-U(Q))}}$ (the integration is over the previously determined classical path in $3N$ space).

The variation of $S_{abbrev}$ is done in a similar way to the variation of the usual classical action. The parameterization of $Q$ ($Q(s)$) we have in mind is in terms of the arc length $ds = \sqrt{dQ^t dQ}$

$$S_{abbrev}\left[Q+\eta\right]-S_{abbrev}\left[Q\right]=\int_{Q_{init}}^{Q_{final}}\sqrt{2\left(E-U\left(Q+\eta\right)\right)}d\sqrt{\left(Q+\eta\right)^{t}\left(Q+\eta\right)}$$
$$-\int_{Q_{init}}^{Q_{final}}\sqrt{2\left(E-U\left(Q\right)\right)}\sqrt{dQ^{t}\cdot dQ} \tag{11}$$

The expansion of the length element to the first order in $\eta$ is as follows

$$\sqrt{d\left(Q+\eta\right)^{t}\cdot d\left(Q+\eta\right)}\cong\sqrt{dQ^{t}\cdot dQ+2d\eta^{t}\cdot dQ}=ds\left(1+\frac{d\eta^{t}}{ds}\cdot\frac{dQ}{ds}\right)$$

where $\frac{dQ}{ds}\equiv e_Q$ is a unit vector in the direction of the path $Q$.

We now have

$$S_{abbrev}\left[Q+\eta\right]-S_{abbrev}\left[Q\right]\cong\int_{0}^{s_f}\frac{-\eta^{t}\cdot dU/dQ}{\sqrt{2\left(E-U\left(Q\right)\right)}}ds+\int_{0}^{s_f}\sqrt{2\left(E-U\left(Q\right)\right)}\frac{d\eta}{ds}\frac{dQ}{ds}ds$$
$$=\int_{0}^{s_f}\left(\frac{-\eta^{t}\cdot dU/dQ}{\sqrt{2\left(E-U\left(Q+\eta\right)\right)}}+\frac{\left(e_Q^{t}\cdot dU/dQ\right)\left(\eta^{t}\cdot e_Q\right)}{\sqrt{2\left(E-U\left(Q+\eta\right)\right)}}+\sqrt{2\left(E-U\left(Q\right)\right)}\frac{de_Q^{t}}{ds}\cdot\eta\right)ds$$

and we finally write an equation of motion in $s$ which is the arc-length of the classical path

$$\frac{d^2Q}{ds^2}=-\frac{1}{2\left(E-U\left(Q\right)\right)}\left(\frac{dU}{dQ}-\left(e_Q^{t}\cdot\frac{dU}{dQ}\right)\left(e_Q\right)\right) \tag{12}$$

This equation is similar to the Newton's equation (remember that $Q$ is weighted by the mass) except that the component of the force in the direction perpendicular to the path is projected out and the mass is replaced by twice the kinetic energy. From the differential equation a finite difference formula for $Q$ as a function of $s$ can be obtained similarly to the initial difference formula we have for $X$ as a function of the time $t$. This equation is not so popular with initial value solvers since the term $E-U$ can go to zero, or becomes (numerically) even negative causing significant implementation problems.

If we multiply (10) by $e_Q^{t}$ from the left we obtain

$$e_Q^{t}\cdot\frac{d^2Q}{ds^2}=\frac{dQ}{ds}\frac{d^2Q}{ds^2}=\frac{1}{2}\frac{d}{ds}\left(\frac{dQ}{ds}\right)^2=0\ \rightarrow\left|e_Q\right|=\text{constant}$$

The last result is however not new since (by definition!) $\left|\frac{dQ}{ds}\right|\equiv\left|e_Q\right|=1$. Hence, the equations of motion (12) are only for the component of the coordinate vector that is perpendicular to the path. The motion along the path is determined by the definition of $s$.

## 3 Numerical Algorithm

The two equations of motion we discussed so far can be found in classical mechanics text books (the differential equations of motion as a function of the arch-length can be found in [5]). Amusingly, the usual derivation of the initial value equations starts from boundary value formulation while a numerical solution by the initial value approach is much more common. Shouldn't we try to solve the boundary value formulation first? As discussed below the numerical solution for the boundary value representation is significantly more expensive, which explains the general preference to initial value solvers. Nevertheless, there is a subset of problems for which the boundary value formulation is more appropriate. For example boundary value formulation is likely to be efficient when we probe paths connecting two known end points.

An algorithm to solve the boundary value formulation uses the local stationary conditions on the action and seeks a simultaneous solution for the coordinates at all times. Consider a set of discrete coordinates that we use to approximate the trajectory $\{X_1, ..., X_N\}$ where the initial and final coordinate sets of the trajectory, $X_1$ and $X_N$, are fixed. We have $N-2$ (possibly non-linear) coupled equations for the coordinates of the remaining time slices based on the local stationary conditions

$$M\frac{2X_i - X_{i+1} - X_{i-1}}{\Delta t^2} + \frac{dU}{dX_i} \equiv r_i = 0\ , \quad i = 2, \ldots, N-1 \tag{13}$$

The set of unknown are the $X_i$-s, and the goal is to set all the $r_i$-s (the residuals) to zero. The same condition is obtained if we first discretize the classical action and consider a stationary condition of the discrete classical action as a function of the intermediate coordinates

$$S = \sum_{i=1}^{N-1}\left[M\frac{\left(X_{i+1} - X_i\right)^2}{2\Delta t^2} - U\left(X_i\right)\right]^2 \Delta t \tag{14}$$

The difference (13) is recovered from (14) by the requirement that the action will be stationary with respect to all intermediate coordinates $X_i$, $i = 2, \ldots, N-1$, i.e. $\partial S/\partial X_i = 0$

### 3.1 The Action is not a Minimum

It is important to emphasize that the stationary solution of the action functional (the classical trajectory) is not necessarily a minimum. This means that a straightforward minimization of $S$ as a function of all the intermediate coordinates is not possible in the general case. The action can be optimized if the matrix of its second derivatives with respect to the intermediate coordinates is definite (positive or negative) to support direct minimization of $S$ or $-S$. As a simple example that $S$ need not be definite, we consider a one-dimensional

case and compute the second derivatives of the discrete action in (14) with respect to the intermediate coordinates

$$\frac{\Delta t}{M}\frac{\partial^2 S}{\partial X_j \partial X_k} = 2\delta_{j,k} - \delta_{j,k+1} - \delta_{j,k-1} - \frac{\Delta t^2}{M}\frac{\partial^2 U}{\partial X_j \partial X_k}\delta_{j,k} \tag{15}$$

The last term on the right hand side of the equation is diagonal in the time slices. For stable systems (convex potentials) such as the harmonic oscillator, $(U(X) = \frac{1}{2}k(X - X_{eq})^2)$, it is negative. The first three terms form a tri-diagonal matrix proportional to a discrete representation of the operator $\frac{d^2}{dt^2}$. The eigenvectors of this operator are of the form: $A\exp(-i\lambda j)$ where $A$ and $\lambda$ are constants and $i \equiv \sqrt{-1}$. The eigenvalues are $2(1 - \cos(\lambda))$. The eigenvalues of the tri-diagonal matrix vary from zero to four (the precise spread depends on the boundary conditions and the discretization of time). On the other hand the last diagonal term (the potential derivatives) tends to be negative in stable systems. Therefore the sum of the time derivative operator and the diagonal term has the potential of creating a non-definite matrix. This is indeed the case for numerous applications. We cannot be more specific since the relative size of the two terms is related to concrete choice of potential and to the total time under consideration.

A transition from a definite to a non-definite matrix occurs even for the simple case of the harmonic oscillator as a function of the total time. In general, the shorter the time, the smaller the term with the potential derivatives and the matrix as a whole is more positive. At sufficiently long time we expect some of the eigenvalues to reverse their sign and become negative, making the matrix indefinite.

### 3.2 Minimization of a Target Function

The above discussion suggests that we cannot minimize the action directly to compute classical trajectories. We focus instead on the residuals (13). One boundary value formulation that we frequently use minimizes the squares of the residual vectors, i.e., we define a target function $T$ that we wish to minimize as a function of all the intermediate coordinates $X_j, j = 2, ..., N-1$.

$$T = \sum_{j=2,\ldots,N-1} r_j^t \cdot r_j \tag{16}$$

The global minimum of $T$ $(T = 0)$ is our approximation to a classical trajectory for a finite step size $\Delta t$. A typical calculation of a trajectory will start with an initial guess, say $X_j^0$ $j = 2, \ldots, N-1$ which in many applications we set to a straight line in Cartesian space, i.e. $X_j = X_1 + \frac{j-1}{N-1} \cdot (X_N - X_1)$. The optimization proceeds by optimization of the target function. For example using over-damped dynamics, we solve the following coupled stochastic equations

$$\begin{aligned} &\gamma \tfrac{dX_j}{d\tau} = -\nabla T_j + R_j \ , \quad j = 2, ...N-1 \\ &\langle R_i \rangle = 0 \ \ \langle R_i \left(0\right) R_i \left(\tau\right) \rangle = 4\gamma k_B \theta \delta \left(\tau\right) \end{aligned} \tag{17}$$

with the initial condition $\left\{X_j \left(\tau = 0\right) = X_j^0\right\}$. In the above equation $\tau$ is a fictitious time (with units of $1/\gamma$ - fictitious friction) that indexes the relaxation of the whole trajectory until the residuals are fully optimized (set to zero). $R_i$ is a white-noise random force chosen to satisfy the dissipation-fluctuation theorem, the relation in the second line of (17). In the simulation we gradually decrease the temperature, $k_B\theta$, from a high initial value to zero. Note that this annealing is for the whole classical trajectories and we simulated simultaneously changes in $N-2$ structures. This is more expensive that initial value formulation in which one structure is changing at a time. However, the algorithm of (17) brings us to a desired product and is considerably more stable as a function of integration step size.

There are important differences between the initial value formulation and the boundary value approach. Initial value solutions are based on interpolation forward in time one coordinate set after another. The boundary value approach is based on minimization of a target function of the whole trajectory. Minimization (and the study of a larger system) is more expensive in the boundary value formulation compared to initial value solver. However, the calculations of state to state trajectories and the abilities to use approximations (next section), make it a useful alternative for a large number of problems.

### 3.3 Large Step in Time

It is instructive to consider the solution of the coupled (13) for the harmonic oscillator demonstrating an important difference between the initial value solver and boundary value formulation. For simplicity we consider a harmonic oscillator with two degrees of freedom $Y^{(1)} \equiv X^{(1)} - X^{(1eq)}$ and $Y^{(2)} \equiv X^{(2)} - X^{(2eq)}$ where $X^{(1eq)}$ and $X^{(2eq)}$ are the equilibrium positions. The corresponding force constants are $c^{(1)}$ and $c^{(2)}$ respectively. We are particularly interested in the case of $c^{(1)} \gg c^{(2)}$.

$$\begin{aligned} &M \frac{2Y_j^{(k)} - Y_{j+1}^{(k)} - Y_{j-1}^{(k)}}{\Delta t^2} - c^{(k)} Y_j^{(k)} = r_j^{(k)} = 0 \ , \\ &j = 2, ..., N-1 \ , \quad k = 1, 2 \end{aligned} \tag{18}$$

The index $k$ refers to different degrees of freedom and the index $j$ to time slices.

It is possible to solve the coordinates $Y_j^{(k)}$ at different times as independent variables (like we do in practical calculation with boundary value formulation). However, for the stability analysis below it is useful to consider a solution of the type $Y_j^{(k)} = A_k \exp\left(i\lambda^{(k)} j\right)$, we have

$$A^{(k)}\left[2-2\cos\left(\lambda^{(k)}\right)-\frac{c^{(k)}\cdot\Delta t^2}{M}\right]=0 \text{ or } \cos\left(\lambda^{(k)}\right)=\left(1-\frac{\Delta t^2 c^{(k)}}{2M}\right) .$$

For a small $\Delta t$ we can find an appropriate solution for $\lambda^{(k)}$. Substituting it in the expression for $Y_j^{(k)}$ provides a sound approximation to the time evolution of the coordinates. The amplitudes $A^{(k)}$ and its conjugate solution are determined from the boundary conditions.

If the time step is not small (such that $\Delta t^2 > 2M/c^{(1)}$) an initial value solver becomes unstable. A solution to the finite difference equation can be found in which $\lambda^{(1)}$ is imaginary, and the cosine function is replaced by a hyperbolic cosine. This solution is not only a poor approximation but it is also numerically unstable. Using initial value solvers the above solution leads to exponential (unbound) growth of the coordinate as a function of time ($Y_j^{(1)} = A\exp(\lambda^{(1)} j)$).

Since we assume different force constants, we can still have an accurate and stable solution for the second mode if $\Delta t^2 \ll 2M/c^{(2)}$. However, even a small coupling between the degrees of freedom (as expected in practice) will make the solution for the two coordinates unstable. In typical simulations instability developed in one or a few coordinates rapidly spreads to the rest of the degrees of freedom and cannot be ignored.

Interestingly the behavior of the fast mode is different in boundary value formulation, resulting in a stable solution. In boundary value formulation we have two end coordinates with sensible values that are hard to fit to an exponentially growing function. A solution of the form $Y(t) = A\exp(\lambda t)$ is not likely to satisfy boundary value conditions with $Y(0)$ and $Y(t)$ bound by $a \cdot A$ where $a$ is of order of 1. The minimization of the target function $T$ finds a likely minimum for the residuals (and the trajectory) in which the amplitude is zero ($A = 0$) for all intermediate points. The solution is (of course) not exact since rapid oscillations have been removed. However, it is numerically stable which is surprising for a step size comparable or even larger than the (fast) oscillation period. It is also expected to be quite accurate if the coupling between the fast and the slow modes is rather weak [6] as is the case (for example) for fast bond vibrations in comparison to the slow overall diffusion of biological molecules.

Setting to zero rapid oscillations that are difficult to integrate accurately is one model of the dynamics. Another model is to use mathematical white noise, attempting to capture the influence of the rapid oscillations on the slow modes. The finite difference equation is replaced by

$$M\frac{2Y_j^{(k)}-Y_{j+1}^{(k)}-Y_{j-1}^{(k)}}{\Delta t^2}-c^{(k)}Y_j^{(k)}=r_j^{(k)}=R_j^k\ , \quad j=2,\ldots,N-1\ . \tag{19}$$

The deviations from zero are modeled as Gaussian white noise such that $\left\langle R_j^k\right\rangle = 0$ and $\left\langle R_j^k R_m^k\right\rangle = b\delta_{jm}$ where $b$ is a constant. This procedure was used in the past to sample and optimize trajectories [7,8].

We noted above that if the coupling between the fast and slow modes is significant then the filtering may impact the slow modes as well. Consider an activated process, a transition from a deep minimum $A$ to another deep minimum $B$ passing over a significant energy barrier. This is a classical problem which is deceptively simple. The transition is slow on the average since the process is rare. However, both the vibrations within the well, and the time of transition over the barrier are fast. The application of the "filter" mentioned above will remove all the rapid oscillations. The filtered discrete trajectory will have some points "sitting" at the minimum of $A$ and some points "sitting" at the minimum of $B$. Hence, all the intrinsic dynamics are washed away if the integration time step, $\Delta t$, is greater than both the local vibration inverse frequency and the transition time scale. This is regardless of the additional (hidden) time scale in the system (the fact that the process is rare). It is therefore clear that the filtering of high frequencies in time is a useful approach to describe dynamics of slow modes, as long as slow modes with interesting motions and relatively weak coupling to the fast modes can be found in the system.

The length formulation of the classical action is better suited to describe transitions between the wells with large integration steps. This is since the overall distance between the states $A$ and $B$ is large in the length representation (even if it is short in time). The large overall distance is captured by the arc length formulation even if the typical integration step in length is not small. This is to be contrasted with a large time step that misses in this case the rapid transition time.

### 3.4 Large Step in Length

An interesting large step limit can be found in the length formulation. Consider the finite-difference residual-equation as a function of the arc-length.

$$\frac{Q_{s+1}+Q_{s-1}-2Q_s}{\Delta s^2} = \\ -\frac{1}{2\left(E-U\left(Q_s\right)\right)}\left(\frac{dU}{dQ_s}-\left(\left(\frac{Q_{s+1}-Q_s}{\Delta s}\right)^t\cdot\frac{dU}{dQ}\right)\cdot\frac{Q_{s+1}-Q_s}{\Delta s}\right) \tag{20}$$

with the additional requirement $|e_Q| \equiv \left|\frac{dQ}{ds}\right| \simeq \left|\frac{Q_{s+1}-Q_s}{\Delta s}\right| = 1$. Consider next the limit of a large step $\Delta s$ or a small curvature such that (note that the forces are independent of the step size $\Delta s$)

$$2\left(E-U\left(Q_s\right)\right)\frac{Q_{s+1}+Q_{s-1}-2Q_s}{\Delta s^2} \ll \frac{dU}{dQ_s} \tag{21}$$

We also require that the finite difference approximation to $e_Q$ is a sound approximation to the path slope. Under these circumstances the residual equations are dominated by the potential derivatives and can be approximately solved as

$$\left(\frac{dU}{dQ_s} - \left(\left(\frac{Q_{s+1}-Q_s}{\Delta s}\right)^t \cdot \frac{dU}{dQ}\right) \cdot \frac{Q_{s+1}-Q_s}{\Delta s}\right) = 0 \; s = 2, \ldots, N-1 \qquad (22)$$

$$\text{and} \left|\frac{Q_{s+1}-Q_s}{\Delta s}\right| = 1.$$

This is an identical equation for the minimum energy path [9, 10] or the so-called steepest descent path. The first implementation of an algorithm to compute minimum energy paths based on the above formula was the LUP (Locally Updated Planes) method [9] that did not include the constraint on the displacement size. This is formally correct since different parameterizations of the path are possible, but may lead to numerical problems in which the distances between the intermediates grow without control. This was adjusted to produce more stable algorithms by the Nudge Elastic Band approach [11] and later by the String method [10].

In summary the length formulation provides physically meaningful results at the small (exact result) and the large step (the minimum energy path) limits.

### 3.5 The Gauss and Onsager-Machlup Actions

We have started from expressions for the classical action, replaced them by a local differential equation, and by a local difference equation which we solve either "as is" using relaxation methods (a topic that was not discussed in this manuscript) or by minimizing a target function $T$ ($T = \sum_{i=2,\ldots,N-1} r_i^2$). Can we "close the cycle" and find the continuous limit of the target function? The target function $G$ can be easily written down in the limit of a small time step providing a functional of the path

$$G\left[X\left(\tau\right)\right] = \int_0^t \left(M\frac{d^2X}{d\tau^2} + \frac{dU\left(X\right)}{dX}\right)^2 d\tau \qquad (23)$$

The functional above was used already by Gauss [12] to study classical trajectories (which explains our choice of the action symbol). Onsager and Machlup used path integral formulation to study stochastic trajectories [13]. The origin of their trajectories is different from what we discussed so far, which are mechanical trajectories. However, the functional they derive for the most probable trajectories, $O\left[X\left(\tau\right)\right]$ is similar to the equation above:

$$O\left[X\left(\tau\right)\right] = \int_0^t \left(M\frac{d^2X}{dt^2} - \gamma\frac{dX}{dt} + \frac{dU}{dX}\right)^2 d\tau \qquad (24)$$

A dissipative (friction) term is the difference between the Onsager and the Gauss actions. In principle the friction can be set to zero which makes the

optimal paths identical in the two actions. The optimal paths are obtained when the actions are zeroes.

These functionals are different from the usual classical action (see (2) and (10)). It is of interest to examine the variation of the Gauss action and its stationary solutions. It is clear that the global minimum of all paths of the Gauss action is when the differential equations of motion (Newton's law) are satisfied. Nevertheless, the possibility of alternative stationary solutions cannot be dismissed. This has practical ramifications since it is the Gauss action that we approximate when we minimize the sum of the residuals in (18). To the first order we have

$$\begin{aligned} &G\left[X\left(\tau\right)+\eta\right]-G\left[X\left(\tau\right)\right] \\ &\cong \int_0^t 2\left(M\frac{d^2X}{dt^2}+\frac{dU}{dX}\right)\left(M\frac{d^2}{dt^2}\eta+\frac{d^2U}{dX^2}\eta\right)dt \end{aligned} \tag{25}$$

Integrating by part and setting $\eta$ and $d\eta/dt$ to zero at the boundaries ($\tau = 0$ and $\tau = t$ ) we obtain the following Euler Lagrange equations

$$M\frac{d^2}{dt^2}\left(M\frac{d^2X}{dt^2}+\frac{dU}{dX}\right)+\frac{d^2U}{dX^2}\cdot\left(M\frac{d^2X}{dt^2}+\frac{dU}{dX}\right)=0\,. \tag{26}$$

We define $C \equiv \left(M\frac{d^2X}{dt^2}+\frac{dU}{dX}\right)$, which allows us to write (26) more compactly $M\frac{d^2C}{dt^2}+\frac{d^2U}{dX^2}C=0$. The Newtonian trajectories are the special case in which $C$ is equal to zero on the boundaries and everywhere else. There are however other solutions that may satisfy the variational principle and the boundary conditions. For illustration purposes we consider a one-dimensional harmonic oscillator for which $\frac{d^2U}{dX^2}=K$, the spring force constant. In this particular example $C$ itself becomes a harmonic oscillator $C = A\cos(\sqrt{\frac{K}{M}}t+\varphi) \equiv A\cos(\omega t+\phi)$ where $A, \omega$ and $\varphi$ are constants.

Substituting back the solution of $C$ in the Euler Lagrange equations for $X$ we obtain the equation for a forced harmonic oscillator.

$$M\frac{d^2X}{dt^2}+KX=A\cos\left(\omega t+\varphi\right)$$

Since the frequency of the external force is exactly on resonance with the free oscillator, the amplitude of the forced solution is unbound. Hence, the second stationary trajectory of the Gauss action (in addition to the Newtonian trajectory) is a solution with a growing amplitude (and energy) as a function of time. This solution is unlikely to be present in a boundary value formulation in which both end points have physically sound values. Note that the energy growth here has a different origin when compared to the numerical instability induced by a large step in the difference equation (Sect. 12.3.3).

The existence of multiple solutions (stationary paths of the action) suggests why in the discrete representation we need to use a global minimizer

like simulated annealing. On the other hand the last illustration for the harmonic oscillator suggests that the behavior of the alternative trajectories is markedly different from the Newtonian's trajectory and therefore relatively easy to detect.

## 4 Examples

In the last ten years or so, a number of studies addressing numerous molecular processes of physical and biophysical origins were investigated using the boundary value techniques that were presented here. With the time formulation we have studied a conformational transition in glycosyltransferase [14]. This study was (and still is) the largest system for which such a reactive trajectory was computed. More recent time formulation studies include ion permeation through the gramicidin channel [15], and an isomerization of a Lennard-Jones cluster [16]. Other studies of biophysical systems in the length formulation include folding of protein A [17], cytochrome C [18] and a helix formation of a short peptide [19]. Some of the calculations were performed for problems accessible to straightforward molecular dynamics which makes it possible to compare mechanisms. Other calculations were extended to domains of time inaccessible to the initial value approach making it possible to explore and examined in atomic details problems we were not able to study in the past.

## 5 Summary

We have discussed numerous boundary value formulations of classical mechanics and the corresponding discrete versions that led to convenient numerical procedures. The boundary value approach has the following advantages compared to initial value formulation: (i) the initial and the final points are fixed, enabling the study of transition mechanisms between pre-specified states, (ii) A large time step is possible while maintaining the stability of the solution, and (iii) alternative representation (time, arc-length) are possible, adding to the flexibility of the calculation and interpretation. The disadvantage compared to initial value formulation is the much larger problem we have at our hand (a complete trajectory is optimized starting from an initial guess as compared to computing one structure at the time with initial value formulation). Another disadvantage is the requirement for two end points. When two end points are not available, the initial value formulation is preferred. Comparing the time and the length formulation with a large integration step, the length formulation is more appropriate for activated processes with a large integration step.

## Acknowledgements

This research is supported by NIH grant GM059796. I am grateful to Stacey Shirk for editorial assistance.

## References

1. L. Verlet (1967) Computer experiments on classical fluids I. Thermodynamics properties of Lennard Jones molecules. *Phys. Rev.* **98**, p. 159
2. D. Chandler (1978) Statistical mechanics of isomerization dynamics in liquids and transition-state approximation. *J. Chem. Phys.* **68**, pp. 2959–2970
3. C. Dellago, P. G. Bolhuis, and D. Chandler (1999) On the calculation of reaction rates in the transition path ensemble. *J. Chem. Phys.* **110**, pp. 6617–6625
4. L. D. Landau and E. M. Lifshitz (2000) *Mechanics*, third edition, Butterworth-Heinenann, Oxford, Chap. 1
5. L. D. Landau and E. M. Lifshitz (2000) *Mechanics*, third edition, Butterworth-Heinenann, Oxford, pp. 140–142
6. R. Olender and R. Elber (1996) Calculation of classical trajectories with a very large time step: Formalism and numerical examples. *J. Chem. Phys.* **105**, pp. 9299–9315
7. R. Elber, J. Meller and R. Olender (1999) A stochastic path approach to compute atomically detailed trajectories: Application to the folding of C peptide. *J. Phys. Chem. B* **103**, pp. 899–911
8. K. Siva and R. Elber (2003) Ion permeation through the gramicidin channel: Atomically detailed modeling by the stochastic difference equation. *Proteins, Structure, Function and Genetics* **50**, pp. 63–80
9. A. Ulitksy and R. Elber (1990) A new technique to calculate the steepest descent paths in flexible polyatomic systems. *J. Chem. Phys.* **96**, p. 1510
10. E. Weinan, R. Weiqing, and E. Vanden-Eijnden (2002) String method for the study of rare events. *Physical Review B* **66**, p. 52301
11. H. Jonsson, G. Mills, and K. W. Jacobsen (1998) Nudge Elastic Band Method for Finding Minimum Energy Paths of Transitions, in Classical and Quantum Dynamics in Condensed Phase Simulations. Edited by B.J. Berne, G. Ciccotti, D.F. Coker, World Scientific, p. 385.
12. C. Lanczos (1970) The variational principles of mechanics. University of Toronto Press
13. L. Onsager and S. Machlup (1953) *Phys. Rev.* **91**, p. 1505; *ibid.* (1953); **91**, p. 1512
14. J. C. M. Uitdehaag, B. A. van der Veen, L. Dijkhuizen, R. Elber, and B. W. Dijkstra (2001) Enzymatic circularization of a malto-octaose linear chain studied by stochastic reaction path calculations on cyclodextrin glycosyltransferase. *Proteins Structure Function and Genetics* **43**, pp. 327–335
15. K. Siva and R. Elber (2003) Ion permeation through the gramicidin channel: Atomically detailed modeling by the Stochastic Difference Equation. *Proteins Structure Function and Genetics* **50**, pp. 63–80
16. D. Bai and R. Elber, Calculation of point-to-point short time and rare trajectories with boundary value formulation. *J. Chemical Theory and Computation*, 2, 484–494(2006)

17. A. Ghosh, R. Elber, and H. Scheraga (2002) An atomically detailed study of the folding pathways of Protein A with the Stochastic Difference Equation. *Proc. Natl. Acad. Sci.* **99**, pp. 10394–10398
18. A. Cárdenas and R. Elber (2003) Kinetics of Cytochrome C Folding: Atomically Detailed Simulations. *Proteins, Structure Function and Genetics* **51**, pp. 245–257
19. A. Cárdenas and R. Elber (2003) Atomically detailed simulations of helix formation with the stochastic difference equation. *Biophysical Journal*, **85**, pp. 2919–2939