SEARCH FOR THE MOST STABLE STRUCTURES ON POTENTIAL ENERGY SURFACES*

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Dedicated to Professor Rudolf Zahradnik on the occasion of his 70th birthday. Many scientists of my generation owe a lot to Professor Rudolf Zahradnik. For us he is and will remain always an example of a curious human being, who devoted his life to knowledge and science and who's scientific achievements are admired by lots of his followers all over the world. We are also indebted to him for a unique friendly and scientific climate of our contacts. Last but not least we would like to stress also his exceptional qualities as a citizen. Thanks to such people as Professor Zahradnik, we in Poland were always sure that the truth will win in his country. We are really happy that this his and our dream came true.

Smoothing techniques for global optimization in search for the most stable structures (clusters or conformers) have been a novel possibility for the last decade. The techniques turned out to be related to a variety of fundamental laws: Fick's diffusion equation, time-dependent and time-independent Schrodinger equations, Smoluchowski dynamics equation, Bloch equation of canonical ensemble evolution with temperature, Gibbs free-energy principle. The progress indicator of global optimization in those methods takes different physical meanings: time, imaginary time, Planck constant, or the inverse absolute temperature. Despite this large spectrum of physical phenomena, the resulting global optimization procedures have a remarkable common feature. In the case of the Gaussian Ansatz for the wave function or density distribution, the underlying differential equations of motion for the Gaussian position and width are similar for all these phenomena. In all techniques the smoothed potential energy function plays a central role rather than the potential energy function itself. The smoothed potential results from a Gaussian convolution or filtering out high frequency Fourier components of the original potential energy function. During the minimization, the Gaussian position moves according to the negative gradient of the smoothed potential energy function. The Gaussian width is position dependent through the curvature of the potential energy function, and evolves according to the following rule. For sufficiently positive curvatures (close to minima of the smoothed potential) the width decreases, thus leading to a smoothed potential approaching the original potential energy function, while for negative curvatures (close to maxima) the width increases leading eventually to the disappearance of humps of the original potential energy function. This allows for crossing barriers separating the energy basins. Some methods result in an additional term, which increases the width, when the potential becomes flat. This may be described as a feature allowing hunting for distant minima.

Key words: Global optimization; Energy minimum; Stable structure; Fick's diffusion equation; Schrodinger equation; Bloch equation; Gibbs free-energy principle.

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Practically any attempt to make a scientific or commercial domain more quantitative leads to a problem of the optimal solution, *e.g.* a position or/and value of the absolute minimum of a function. Generally, finding optimal solution by a method begins by defining a starting point in the corresponding space of variables. However, this often creates a problem that one then obtains a *locally* optimal solution, *i.e.* only that one, which is accessible from a particular starting point. Nothing indicates where to search for the global optimal solutions, *i.e.* the global minimum of a function. The problem is not solvable in general. However, one finds important and urgent to reach the globally optimal or even suboptimal solution in computer science, physics, chemistry, biology, technology, economics, social sciences, *etc*. In these cases the problem does not need to be solved generally. It may be, that the task is solvable only for some useful class of functions, or (more likely) the methods to be elaborated will assure a significant increase of the success rate even in finding suboptimal solutions.

In chemistry one finds at least two domains where this is of prime importance. First, is the search for the most stable conformation of a flexible molecule, and second, the most stable configuration of an ensemble of atoms or molecules. In the last case we find the problem of the most stable isomer, the most stable products of chemical reactions and the most stable supramolecular structure. In the present state of quantum chemistry this question is in a large part ignored. How can it be that we are so successful in the application of the quantum chemistry tools to chemical problems? Well, the answer lies in the fact that molecules most treated so far in quantum chemistry have a low number of conformers (note, that we always prefer small or rigid molecules for our computers). Note also, that calculations for a large and flexible molecule are performed almost exclusively for a particular geometry, most often the X-ray geometry, because otherwise one is confronted with the difficulty described above.

Is this difficulty serious? Let us take a polypeptide as an example. Approximate stable conformations of the backbone of a dipeptide (we ignore complication coming from the side-chain conformations) can be found from the so called Ramachandran map[1], which leads to about 10 different stable backbone conformations. This means, that a rough estimation of the number of stable conformers of an oligopeptide composed of $N + 1$ amino acids is of the order of 10^N, which is an astronomical number even for a relatively small molecule as compared to proteins (in the latter case, say, 200 amino acids). An important class of proteins – enzymes function in nature only in a specific conformation or a set of closely related conformations (native structure). Therefore, for such a case it is clear, that one has to determine somehow a way to find those conformations among plethora of others. There are only a few things that help us in such a formidable task. The first is that apparently it is not necessary to consider the molecular structure in the atomic representation, and the concept of pseudoatoms, or even pseudopeptides still preserving reasonable characteristics of the amino acids[2,3], may be used. The second one is that it turns out that for enzymes the energy-hypersur-

face structure has a hierarchical feature[4], *i.e.* there is a kind of a funnel effect biasing the search towards the global minimum. The reason for the funnel effect may be that for those proteins that fold easily to the native structure, the global minimum energy is considerably lower than that of other conformations[5,6], thus facilitating the funnel effect. Despite these advantages the problem seems to be extremely severe not only for enzymes, but also for molecules of a quite modest size. Nature however finds somehow its way to the native conformation, although it has to be admitted that it takes her seconds or even minutes sometimes, which is a large amount of time.

During the last decade or so a new idea of the global optimization has emerged[7,8], and has been later elaborated in a number of approaches[9–27]. The key word in these methods is smoothing or coarse-graining of the original potential energy hypersurface[28]. The deformed hypersurface supports much fewer minima, thus being much simpler and easier to operate during the global minimization.

In the present paper some general aspects of the global minimization will be stressed. Global minimization and smoothing are closely related to some of basic equations of physics: Fick's diffusion equation, time dependent and time independent Schrödinger equations, Bloch equation of canonical ensemble dependence on temperature, Gibbs free-energy equation, Smoluchowski dynamics. Some of the main features underlying the mechanism of this relation may be revealed, when one uses the Gaussian Ansatz, *i.e.* when one approximates the ensemble distributions or the wave functions by a single Gaussian function characterized by a position and a width. For the sake of simplicity all formulas of the present paper will be written for a one-dimensional potential V. We will assume that V supports such a large number of minima, that no trivial search for the global minimum position is likely to be successful.

There is an indication[24] that the global optimization schemes that come out from these equations are all of the same kind as if nature applied a quite robust method to find the most stable structure. The details of the method change from scheme to scheme, but the essence seems to remain the same.

FUNDAMENTAL EQUATIONS

Fick's Diffusion Equation

Let us denote the function to be minimized by $V(x)$, and assume that the function is given by an appropriate analytical formula. The x domain (usually multidimensional) may be divided into non-overlapping basins of attraction, each basin associated with a minimum of V. A basin is an open set of all those points, which when used as starting points of a steepest-descent minimization procedure, lead to the same minimum (an attractor). Thus, a basin is the same as a cell in Fukui's formulation of reaction paths[29]. Imagine now that one adds to $V(x)$ its second derivative V'' multiplied by t/N, with $t > 0$ and N a large natural number. This operation rises the new function (with respect to V) for

those x, for which $V'' > 0$, lowers the new function for x with $V'' < 0$ and leaves the value of the function unchanged for x with $V'' = 0$. In particular, all minima will be pushed up, all maxima will be lowered. This operation destabilizes all basins and eventually some of the basins may disappear. It has been shown[8] that, at a given t, when this operation is iteratively repeated N times and $N \to \infty$, one gets from V another function, $W(x,t)$, which for differentiable V reads as

$$W(x,t) = T(t)V(x) \tag{1}$$

with the operator T

$$T(t) = \exp\left(t\,\frac{\partial^2}{\partial x^2}\right) . \tag{2}$$

The operator T has the following eigenfunctions

$$T(t)\ \sin \omega x = a(t,\omega)\ \sin \omega x \tag{3}$$

$$T(t)\ \cos \omega x = a(t,\omega)\ \cos \omega x\ , \tag{4}$$

with the eigenvalues $a(t,\omega)$

$$a(t,\omega) = \exp\ (-t\omega^2)\ . \tag{5}$$

Let us consider a Fourier decomposition of V. As one can see from Eq. (*5*), $W(x,t = 0) = V(x)$. However, as seen from Eqs (*4*) and (*5*) for $t > 0$ the T operator damps all Fourier amplitudes exponentially with t, and more interestingly this damping is especially pronounced for high frequency components. Thus, the action of $T(t > 0)$ is smoothing or coarse-graining the original function V, *i.e.* filtering out high frequency components. The smoothing is larger for larger t and for larger ω. Admitting even non-continuous V, one may show[8] that the corresponding W satisfies the diffusion equation with the parameter t playing the role of *time*

$$\frac{\partial^2 W}{\partial x^2} = \frac{\partial W}{\partial t}\ . \tag{6}$$

Thus, W changes with t (time) as if it were a concentration or temperature distribution in a homogeneous body, with the starting distribution at $t = 0$ equal to $V(x)$.

The function W that satisfies the diffusion equation can be expressed as the Fourier–Poisson integral, *i.e.* convolution of V with a Gaussian function

$$W(x_0,t) \equiv \langle V \rangle (x_0,t) = (4\pi t)^{-1/2} \int \mathrm{d}x V(x) \exp\left[-(x - x_0)^2 / 4t\right] \quad . \tag{7}$$

In ref.[8] one can find $\langle V \rangle$ derived for V being a polynomial, a Gaussian or Lorentz function as well as the so called standard test functions for global optimization methods. Note, that as $t \to 0$ the normalized Gaussian function tends to the Dirac delta function $\delta(x - x_0)$ and therefore for $t = 0$,

$$\langle V \rangle = V \quad . \tag{8}$$

After substituting $x_0 \to x$ the function $\langle V \rangle (x,t) = W(x,t)$ is used in the global minimization in the following way (reversing procedure[8]). First, one chooses a large value of $t = t_{\max}$ and calculates $W(x,t_{\max})$. This function (for non-degenerate global minima) will be convex for sufficiently large $t_{\max}$. By using a steepest descent minimization procedure one obtains its single minimum starting from any point of space, thus making the procedure independent of the starting point, which is a remarkable feature. This single minimum may serve as the starting point for a minimization of the $W(x,t_{\max} - \delta)$ with δ very small. Thus a new minimum is located. This minimum is used then as the starting point in the minimization of $W(x,t_{\max} - 2\delta)$, *etc*. Finally, one finds a minimum of the function $W(x,0) = V(x)$. This minimum in many cases[8–10,15] is the global minimum of V. In other words one uses the progress indicator $\alpha = t$ changing from ∞ to 0 and solves the differential equation

$$\frac{\mathrm{d}x_0}{\mathrm{d}\alpha} = -\left(\frac{\mathrm{d}}{\mathrm{d}x} \langle V \rangle (x,t) \right)_{x = x_0} \quad . \tag{9}$$

For the reason that will become clear later on, let us write that the change of t (a quantity related to the Gaussian width) with the progress indicator is trivial in the diffusion equation method: $\mathrm{d}t/\mathrm{d}\alpha = 1$.

Schrodinger Equation

The Schrodinger equation may be used to find the global minimum of a potential energy function. This can be done in two ways. Both are based on the known property of

the time-independent Schrodinger equation that the ground-state wave function usually has its single maximum close to the global minimum of the potential energy[14,17,18,30]. In this paragraph we would like to concentrate on the so called imaginary time Schrodinger equation technique designed by Straub and coworkers[20] for finding the global minimum.

One replaces the time variable t in the time dependent Schrodinger equation by $\tau = it/\hbar$ and then treats τ as a real variable, *i.e.* as if t were imaginary. The new equation describes the evolution of a function $\phi(x,\tau = 0)$, as the time τ tends to infinity

$$\phi(x,\tau) = \exp(-H\tau)\,\phi(x,0)\,, \tag{10}$$

where H is the system Hamiltonian. By expanding the starting function $\phi(x,0)$ into a set of the eigenfunction u_n of H one has

$$\phi(x,\tau) = \exp(-E_0\tau)\,\Sigma_n\, a_n\, u_n(x)\, \exp[-(E_n - E_0)\tau]\,. \tag{11}$$

Since $E_n - E_0 \geq 0$, for sufficiently large τ the dominant contribution to ϕ comes from the ground state, *i.e*, u_0 function corresponding to the energy E_0. This function hopefully has its maximum close to the global minimum of the potential energy. The idea behind the method is to start from a localized trial function and then follow its evolution, when $\tau \to \infty$. The resulting position of the function will hopefully indicate the global minimum of V.

Now, one may choose as the wave function a normalized Gaussian function

$$\phi(x,\tau) = (2\pi\sigma^2)^{-1/4} \exp\{-[(x - x_0)/2\sigma]^2\}\,, \tag{12}$$

where the width σ and the position x_0 depend on τ and $\int\phi^*\phi dx = 1$. For $\tau = 0$ one chooses some starting values of these parameters (hopefully the final results will not depend on this choice) and one solves the following set of differential equations

$$\frac{dx_0}{d\tau} = -2\sigma^2\left(\frac{d}{dx}\langle V\rangle(x,t)\right)_{x=x_0} \tag{13}$$

$$\frac{d\sigma}{d\tau} = \frac{\hbar^2}{2m} - 2\sigma^4\left(\frac{d^2}{dx^2}\langle V\rangle(x,t)\right)_{x=x_0}\,, \tag{14}$$

where $\langle V \rangle$ is exactly the same as that appearing in the diffusion equation method, the role of time t is played now by $\sigma^2/2$ and the imaginary time, τ, is the minimization progress indicator. Equations (*13*) and (*14*) are derived, respectively, after setting $(x - x_0)$ and $(x - x_0)^2$ for the operator A in the expression for the time derivative of the mean value of A

$$\frac{d\langle A \rangle}{d\tau} = (-\langle AH - HA \rangle + 2\langle A \rangle \langle H \rangle) \tag{15}$$

and the mean value defined as

$$\langle A \rangle = \langle \phi | A | \phi \rangle / \langle \phi | \phi \rangle \, . \tag{16}$$

Bloch Equation

The canonical ensemble of a system with the Hamilton function $H(x,p_x)$ in equilibrium with an external bath of temperature T has the phase space normalized distribution $\rho_{eq}(x,p_x)$

$$\rho_{eq}(x,p_x) = Q^{-1} \exp [-\beta H(x,p_x)] \tag{17}$$

with $\beta = 1/kT$ and $Q(\beta) = \int dx \, dp_x \exp(-\beta H)$. After differentiating with respect to β one obtains the Bloch equation

$$\frac{\partial \rho_{eq}}{\partial \beta} = -(H - \langle V \rangle) \rho_{eq} \, , \tag{18}$$

where $\langle \, \rangle$ stands for the average value calculated with the density distribution ρ_{eq}. After integrating over momentum p_x one obtains the so called reduced (normalized) density

$$\rho(x) = A^{-1} \exp [-\beta V(x)] \tag{19}$$

and the reduced Bloch equation

$$\frac{\partial \rho}{\partial \beta} = -(V - \langle V \rangle) \rho \tag{20}$$

with $A(\beta) = \int dx \exp(-\beta V)$ and the corresponding change of the definition of the average. The Bloch equation describes the evolution of the distribution density of the canonical ensemble, when the absolute temperature changes (in our case from $T = \infty$ to $T = 0$).

Now, one may introduce a Gaussian Ansatz for the reduced density

$$\rho(x_0,\sigma_1) = (2\pi\sigma_1)^{-1/2} \exp[-(x - x_0)^2/2\sigma_1] \ , \qquad (21)$$

where x_0 and σ_1, depend on the progress indicator β. Allowing change of both Gaussian parameters with β after inserting ρ into the reduced Bloch equation yields the following set of differential equations

$$\frac{dx_0}{d\beta} = -\sigma_1^2 \left(\frac{d}{dx} \langle V \rangle(x,t) \right)_{x = x_0} \qquad (22)$$

$$\frac{\partial\sigma_1}{\partial\beta} = -\sigma_1^4 \left(\frac{d^2}{dx^2} \langle V \rangle(x,t) \right)_{x = x_0} \ . \qquad (23)$$

Here β is the minimization progress indicator changing from $\beta = 0$ (or, $T = \infty$) to $\beta = \infty$ (or, $T = 0$). Hopefully, at $T = 0$ one obtains x_0 corresponding to the global minimum of V.

Gibbs Free-Energy Equation

The global minimum of the potential function does not necessarily describe the most stable structure. What counts is not only the depth of the potential energy well, but also its width. Therefore, the free energy of Gibbs is a more proper function to be minimized. Recently, Schelstraete and Verschelde[31] used the Gibbs variational principle to find the minimum free-energy configuration of a system. The Gibbs free energy $F(T)$ is defined as

$$F = \text{Min}\{\rho\}\{\Phi\} \ , \qquad (24)$$

$$\Phi = \int dx \, \rho(x) V(x) + kT \int dx \, \rho(x) \ln \rho(x) \ , \qquad (25)$$

where $\rho(x) > 0$ is a density distribution of an ensemble, k is the Boltzmann constant, T is the temperature and Min $\{\rho\}$ means a minimum with respect to all possible normalized density distributions. The functional Φ is minimized by $\rho \approx \exp[-\beta V(x)]$, but this does not help finding the x corresponding to the largest ρ, *i.e.* the lowest value of V. If ρ is

approximated by the normalized Gaussian density with two parameters, the position x_0 and the width σ_1, Eq. (*21*), then the functional Φ becomes a function of two parameters only. From the condition

$$\frac{\partial \Phi}{\partial \sigma_1} = 0 \tag{26}$$

one obtains

$$\sigma_1^{-1} = \beta(2\pi\sigma_1)^{-1/2} \int \mathrm{d}x\, V(x)\, \{[(x - x_0)/\sigma_1]^2 - 1/\sigma_1\} \exp\,[-(x - x_0)^2/2\sigma_1] \ . \tag{27}$$

After substituting σ_1 of Eq. (*27*) into the functional Φ one obtains the so called effective diffusion potential

$$V_{\mathrm{D}}^{\mathrm{eff}}(x_0,T) = (2\pi\sigma_1)^{-1/2} \int \mathrm{d}x\, V(x) \exp\,[-(x - x_0)^2/2\sigma_1] - kT/2\,[ln\,(2\pi\sigma_1) + 1] \ , \tag{28}$$

composed of the energy (first term) and entropy (second term) contributions. The functional Φ at a given T is obtained from the condition $\partial V_{\mathrm{D}}^{\mathrm{eff}}/\partial x_0 = 0$. The effective diffusive potential $V_{\mathrm{D}}^{\mathrm{eff}}$ is not a convex function, but is much smoother than the original potential V. To allow for arbitrary starting points x_0 and σ_1, one may think of another strategy in the Gibbs free energy method. After finding that

$$\frac{\mathrm{d}F}{\mathrm{d}x_0} = \left(\frac{\mathrm{d}}{\mathrm{d}x} \langle V \rangle (x,t) \right)_{x = x_0} \tag{29}$$

and

$$\frac{\partial F}{\partial \sigma_1} = \frac{1}{2} \left(\frac{\mathrm{d}^2}{\mathrm{d}x^2} \langle V \rangle (x,t) \right)_{x = x_0} - \frac{kT}{2\sigma_1} \ , \tag{30}$$

one may introduce the progress indicator $\alpha = 1/kT$ and assure lowering Φ with respect to x_0 and σ_1, by solving the following set of equations

$$\frac{\mathrm{d}x_0}{\mathrm{d}\alpha} = -\left(\frac{\mathrm{d}}{\mathrm{d}x} \langle V \rangle (x,t) \right)_{x = x_0} \tag{31}$$

$$\frac{\partial \sigma_1}{\partial \alpha} = \frac{kT}{2\sigma_1} - \frac{1}{2}\left(\frac{\mathrm{d}^2}{\mathrm{d}x^2}\langle V\rangle(x,t)\right)_{x=x_0} \quad . \tag{32}$$

Now, let us comment on some important developments related to the effective diffused potential. As shown in ref.[31] the effective diffused potential is a Gaussian approximation to some exact effective potential and coincides with the first two terms in a series expansion of this exact effective potential. It has been proved that the potential is a *convex* function of the mean position (identical to x_0 in the Gaussian approximation). The single minimum of the function corresponds to the exact free energy of the system. Since this is also true for $T = 0$, the effective potential at $T = 0$ has the only minimum exactly at the position of the global minimum of a non-degenerate V (convex envelope). This proves that the idea of smoothing leads to the solution of the global minimum problem. It remains to wait for a progress in calculation of the exact effective potential for real systems.

Smoluchowski Equation

The Smoluchowski equation[32,33], related to the Fokker–Planck dynamics[34], gives the dynamics of an ensemble of particles (each of mass m) with the reduced density distribution ρ subject to a force F and the friction constant γ of a medium in contact with the bath of temperature T. The equation of motion reads

$$\frac{\partial \rho}{\partial t} = \frac{1}{m\gamma}\left[\frac{\partial}{\partial x}\left(-F(x) + kT\frac{\partial}{\partial x}\right)\right]\rho \quad . \tag{33}$$

When the Gaussian Ansatz, Eq. (*21*), is used, one obtains the following equation of motion[22] for the Gaussian position and width

$$\frac{\mathrm{d}x_0}{\mathrm{d}t} = -\frac{1}{m\gamma}\left(\frac{\mathrm{d}}{\mathrm{d}x}\langle V\rangle(x,t)\right)_{x=x_0} \tag{34}$$

$$\frac{\partial \sigma_1}{\partial t} = \frac{1}{m\gamma}\left[2kT - 2\sigma_1\left(\frac{\mathrm{d}^2}{\mathrm{d}x^2}\langle V\rangle(x,t)\right)_{x=x_0}\right] . \tag{35}$$

A UNIFYING STRATEGY

In the diffusion equation method of global minimization, the time t, measuring the Gaussian width, Eq. (*7*), decreased during the minimization according to the reversing procedure, and therefore was position independent. That made treatment of the humps

and valleys of the potential on equal footing, *i.e.* the maxima disappeared to the same extent as valleys. This was an unfavorable behavior for only minima contain information about the global minimum and the minima valleys were destroyed to a considerable extent by "melting" the humps. In the methods that were developed later, the Gaussian width is position dependent. First Straub and coworkers have shown[20] in the imaginary time Schrodinger equation method, that the humps disappear much faster than valleys do even when time t tends to infinity (or, the Planck constant $\hbar$ tends to zero). This means that even in the classical limit a kind of a classical tunneling appears. Similarly, Schelstraete and Verschelde[31] have shown that even for $T = 0$ the effective diffusive potential $V_D^{eff}(x_0,T)$ has humps lowered with respect to those of V.

One can see that despite of the variety of physical phenomena considered, the equations of motion for the Gaussian position and width are basically the same[24] (α denotes time minimization progress indicator)

$$\frac{dx_0}{d\alpha} = -A\left(\frac{d}{dx}\langle V\rangle(x,t)\right)_{x=x_0} \tag{36}$$

$$\frac{\partial\sigma}{\partial\alpha} = C - B\left(\frac{d^2}{dx^2}\langle V\rangle(x,t)\right)_{x=x_0} . \tag{37}$$

Here $A, B, C > 0$. In the diffusion equation $B = 0$, in the Bloch equation $C = 0$. Interestingly, time and T^{-1} play a similar role. This looks as if nature had a robust recipe to handle the global minimum problem by moving a position x_0 of an ensemble from its starting value to the final position close to the global minimum, when the time goes to infinity or the temperature or the Planck constant go zero.

The strategy consists of the following principles:

– At the current position x_0, the smoothed potential energy $\langle V\rangle$ has to be used instead of the original potential energy V. With the Gaussian Ansatz the smoothing is performed through an averaging the original potential about the point x_0 with the Gaussian weights.

– Smoothing is more pronounced for larger smoothing width. The width has a position dependent value.

– The current position changes with the progress indicator following the direction minus gradient of $\langle V\rangle$, calculated at x_0. The rate of this motion is different in various methods.

– The current width value decreases, where the curvature of $\langle V\rangle$ exceeds a positive treshold (close to minima) and increases where it is negative (maxima). This removes efficiently the barriers between the energy basins. The rate of this motion is also method dependent.

– When the system is trapped in a flat portion of the potential, the Gaussian width increases with the effect of hunting for distant minima. The hunting effect is present in the imaginary time Schroodinger equation method, the Smoluchowski dynamics and the Gibbs free-energy approach. The hunting disappears when the progress indicator approaches its final value, which is assured by the Planck constant or temperature, respectively, set to zero.

– The Gaussian Ansatz gives only an approximation to the true density distribution minimizing the Gibbs free energy. Therefore, when limiting ourselves to a single Gaussian at a non-zero temperature, an important ingredient of nature's recipe escapes, *i.e.* its ability to divide the distribution and populate other energy wells, as required by the exact solution $\rho \approx \exp[-\beta V(x)]$ of the Gibbs free energy functional.

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28. The first article that discussed a smoothing of the potential energy surface by a convolution transformation with a filter function was published by Stillinger[7]. When the filter was of the Gaussian shape with the width δ, it has been shown by Stillinger that the number of minima supported by a deformed hypersurface decreases exponentially with δ. In our paper (ref.[8]) a similar idea has been introduced independently with the following differences. First, smoothing has been used to serve as a global minimization tool. To this end a convexization of the energy hypersurface has been postulated and then the so called reversing procedure has been introduced, that hopefully links the minimum found for the smoothed function with that of the original potential. Second, smoothing concept is going beyond any convolution.
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