Energy Landscapes: Frequently Asked Questions

Thermodynamics

The microcanonical and canonical partition functions can be written as a superposition of contributions from the catchment basins of all the minima [1]:

$$\Omega(E) = \sum_i \Omega_i(E) \quad \text{and} \quad Z(T) = \sum_i Z_i(T),$$

where $\Omega_i(E)$ and $Z_i(T)$ are the microcanonical density of states and canonical partition function for local minimum i, respectively.

The potential energy surface is independent of mass, temperature and coordinate systems; $\Omega(E)$ and $Z(T)$ provide connections to the thermodynamic potentials in the microcanonical and canonical ensembles, namely entropy and free energy.

The canonical equilibrium occupation probability of minimum i is $p_i^{\rm eq}(T) = Z_i(T)/Z(T)$, and the corresponding free energy is $F_i(T) = -kT\ln Z_i(T)$. The free energy of transition state † is $F^\dagger(T) = -kT\ln Z^\dagger(T)$, where $Z^\dagger(T)$ does not include the mode corresponding to the negative Hessian eigenvalue.

In the canonical ensemble the equilibrium occupation probability and free energy of a group of minima, J are

$$p_J^{\rm eq}(T) = \sum_{j\in J} p_j^{\rm eq}(T) \quad \text{and} \quad F_J(T) = -kT\ln\sum_{j\in J} Z_j(T),$$

and the free energy of the transition states connecting J and L is then

$$F_{LJ}^\dagger(T) = -kT\ln\sum_{(lj)^\dagger} Z_{lj}^\dagger(T), \qquad l\in L,\ j\in J,$$

$$\text{with} \quad k_{LJ}^\dagger(T) = \sum_{(lj)^\dagger}\frac{p_j^{\rm eq}(T)}{p_J^{\rm eq}(T)}k_{lj}^\dagger(T) = \frac{kT}{h}\exp\left[-\frac{\Big(F_{LJ}^\dagger(T) - F_J(T)\Big)}{kT}\right].$$

Size Effects

The total (free) energy is extensive, and scales with system size, along with the energy range spanned by the lowest to highest minima. However, barrier heights and energy differences between minima directly connected by transition states (saddles of Hessian index one [2]) are intensive quantities.

The relative equilibrium occupation probabilities and rate constants [3] between these minima depend on ratios of intensive quantities, namely energy differences and kT. Hence the equilibrium concentration of a particular defect and the defect migration rate in a crystal do not depend on the size of the crystal [4, 5]. An inappropriate comparison of the extensive internal energy with intensive barriers leads to the conclusion that 'activated' processes cease to exist as the system size increases [6, 7].

Genuine finite size effects are certainly of interest, for example, the sharpening of heat capacity peaks for first order-type transitions [8].

Landscapes and Entropy

It can be helpful to think of the energy landscape in terms of analogies from a mountain range, following James Clark Maxwell in his article for *Philosophical Magazine* ‘On Hills and Dales’ in 1870 [9]. Transition states then correspond to watersheds, and steepest-descent paths to watercourses.

However, low-dimensional projections can also be misleading [10–17]. In particular, the system is never ‘above’ the potential energy surface: the potential energy function is defined for any configuration.

The effect of increasing the temperature is to shift the occupation probabilities to states with higher entropy and higher potential energy. The temperature gradients of the $p_i^{\rm eq}(T)$ can be related to peaks in the heat capacity [18].

We can distinguish two contributions to the entropy. There is an (anharmonic) vibrational entropy associated with each local minimum, determined by the phase volume contained within the basin of attraction.

The contribution associated with the multiplicity and distribution of the minima is the landscape entropy [19–21], or inherent structure [22] entropy, $S_{\rm IS}$.

Rotational contributions can also be included, but are usually dominated by the vibrational component, which is often treated in a harmonic normal mode approximation [1].

The landscape contribution is convoluted with the local vibrational densities of states to obtain the full configurational entropy, S_c.

We can calculate $S_{\rm IS}$ by sampling the potential energy density of local minima [21,23]. (Note that some authors refer to $S_{\rm IS}$ as the configurational entropy.)

We can also consider the local densities of states associated with distinct pathways between product and reactant states, and define a pathway entropy from the multiplicity of alternative routes mediated by different transition states [24–26].

Funnels, Relaxation, and Self-Organisation

The number of local minima and transition states increase exponentially with system size, [5, 22, 27] and the number of transition states per minimum is expected to increase linearly [4]. This increase in connectivity cannot be represented properly by surfaces in three dimensions [26].

However, efficient relaxation to the global minimum can be encoded in the landscape if there is a single funnel structure, corresponding to a set of kinetically convergent pathways [28]. This is the organisation we expect for naturally occurring proteins that have a single function [29, 30], and for 'magic number' clusters, such as buckminsterfullerene [31, 32].

In contrast, landscapes with distinct low energy structures separated by high barriers are considered 'frustrated' [29, 30]. We could also describe such multifunnel landscapes as 'rugged', but some authors associate this term with the existence of many local minima.

The existence of more local minima does not necessarily lead to more complex behaviour, since funnelled landscapes also exist for larger systems. Hence it may be best to refer to multifunnel landscapes as frustrated.

The presence of multiple low energy morphologies provides a mechanism to encode multifunctional properties [33]. Such multifunnel landscapes have been characterised for certain biomolecules [34, 35], which may constitute evolved multifunctional systems. Hence we have a design principle for achieving targeted properties, such as switches, for potential technological applications.

Disconnectivity Graphs

Disconnectivity graphs [31, 36] provide a powerful way to visualise the organisation of the energy landscape, and they can be constructed directly from a database of local minima and the transition states [2] that connect them. The contrast between single and multifunnel landscapes is clearly highlighted in this construction. A single funnel landscape suggests that the system will support efficient self-organisation, in terms of relaxation to the global minimum, while a molecular switch would probably correspond to a double funnel. Multifunnel landscapes, with competing alternative morphologies separated by a high barrier, produce challenges for sampling, with broken ergodicity and rare event dynamics, associated with multiple relaxation time scales [37, 38].

In these graphs the branches terminate at the energies of local minima, and the vertical scale is the potential (or free) energy. At regular energy thresholds we identify the sets of minima (superbasins) that can interconvert amongst themeselves without exceeding the threshold. The segregation into these disjoint sets of minima at each threshold is obtained from analysis of the database of minima and transition states, which constitutes a kinetic transition network [15, 17, 39, 40]. The superbasins of minima (nodes) split into smaller sets as the threshold decreases, and ultimately terminate at the energy of individual minima on the vertical axis.

Global thermodynamic and kinetic properties are calculated from the database of minima and transition states using standard tools of statistical mechanics and unimolecular rate theory, based on the energetics of these stationary points and their densities of states. The disconnectivity graphs provide a complementary visualisation of how the landscape is organised. Here the nodes are ordered on the horizontal axis according to how they split from the parent node in the level above. The children of each parent node can be ordered so that the superbasins containing the lowest energy minima are in the middle of each set; alternatively the superbasins with the most minima can be positioned centrally. The relative spacing on the horizontal axis is chosen according to the number of minima in each superbasin to allow room for further branching at lower energy thresholds.

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