

22.1: Concepts and Definitions

Time-dependent problems in molecular biophysics: How do molecular systems change? How does a molecular system change its microscopic configuration? How are molecules transported? How does a system sample its thermodynamically accessible states?

Two types of descriptions of time-dependent processes:

1. **Kinetics:** Describes the rates of interconversion between states. This is typically measured by most experiments. It does not directly explain how processes happen, but it can be used to predict the time-dependent behavior of populations from a proposed mechanism.
2. **Dynamics:** A description of the time-evolving molecular structures involved in a process, with the objective of gaining insight into mechanism. At a molecular level, this information is typically more readily available from dynamical simulations of a model than from experiments.

There is no single way to describe biophysical kinetics and dynamics, so we will survey a few approaches. The emphasis here will be on the description and analysis of time-dependent phenomena, and not on the experimental or computational methods used to obtain the data.

Two common classes of problems:

1. **Barrier crossing or activated processes:** For a solution phase process, evolution between two or more states separated by a barrier whose energy is $\gg k_B T$. A description of “rare events” when the system rapidly jumps between states. Includes chemical reactions described by transition-state theory. → We’ll look at two state problems.
2. **Diffusion processes:** Transport in the absence of significant enthalpic barriers. Many small barriers on the scale of $k_B T$ lead to “friction”, rapid randomization of momenta, and thereby diffusion.

Now let’s start with some basic definitions of terms we will use often:

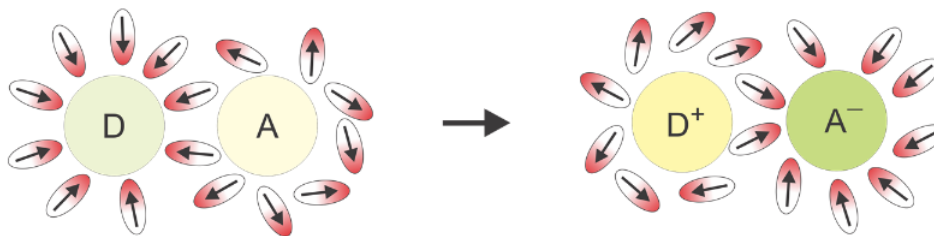
Coordinates

Refers to many types of variables that are used to describe the structure or configuration of a system. For instance, this may refer to the positions of atoms in a MD simulation as a function of time $\{\mathbf{r}^N, t\}$, or these Cartesian variables might be transformed onto a set of internal coordinates (such as bond lengths, bond angles, and torsion angles), or these positions may be projected onto a different collective coordinate. Unlike our simple lattice models, the transformation from atomic to collective coordinate is complex when the objective is to calculate a partition function, since the atomic degrees of freedom are all correlated.

Collective coordinate

- A coordinate that reflects a sum/projection over multiple internal variables—from a high-dimensional space to a lower one.

Example: Solvent coordinate in electron transfer. In polar solvation, the position of the electron is governed by the stabilization by the configuration of solvent dipoles. An effective collective coordinate could be the difference in electrostatic potential between the donor and acceptor sites: $q \Phi_A - \Phi_D$.



Example: RMSD variation of structure with coordinates from a reference state.

$$RMSD = \sqrt{\frac{1}{n} \sum_{i=1}^n (\mathbf{r}_i - \mathbf{r}_i^0)^2} \quad (22.1.1)$$

where r is the position of an atom in an n atom molecule.

- Sometimes the term “order parameter” gets used to describe a collective coordinate. This term originated in the description of changes of symmetry at phase transitions, and is a more specific term than order parameter. While order parameters are collective variables, collective variables are not necessarily order parameters.

Reaction coordinate

- An internal variable that describes the forward progress of a reaction or process.
- Typically an abstract quantity, and not a simple configurational or geometrical coordinate. In making a connection to molecular structure, often the optimal reaction coordinate is not known or cannot be described, and so we talk about a “good reaction coordinate” as a collective variable that is a good approximate description of the progress of the reaction.

Energy Landscape

A structure is characterized by an energy of formation. There are many forms of energy that we will use, including free energy (G, A), internal energy or enthalpy (E, H), interaction potential (U, V), ... so we will have to be careful to define the energy for a problem. Most of the time, though, we are interested in free energy.

The energy landscape is used to express the relative stability of different states, the position and magnitude of barriers between states, and possible configurational entropy of certain states. It is closely related to the free energy of the system, and is often used synonymously with the potential of mean force. The energy landscape expresses how the energy of a system (typically, but it is not limited to, free energy) depends on one or more coordinates of the system. It is often used as a free energy analog of a potential energy surface. For many-particle systems, they can be presented as a reduced dimensional surface by projecting onto one or a few degrees of freedom of interest, by integrating over the remaining degrees of freedom.

“Energy landscapes” represent the free energy (or rather the negative of the logarithm of the probability) along a particular coordinate. Let’s remind ourselves of some definitions. The free energy of the system is calculated from .

$$A = -k_B T \ln Z \quad (22.1.2)$$

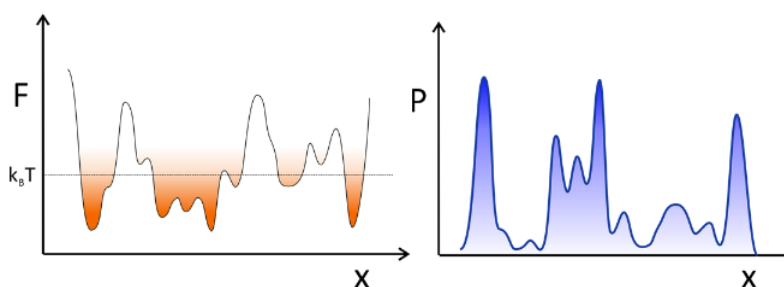
where Z is the partition function. The free energy is a number that reflects the thermally weighted number of microstates available to the system. The free energy determines the relative probability of occupying two states of the system:

$$\frac{P_A}{P_B} = e^{-(A_A - A_B)/k_B T} \quad (22.1.3)$$

The energy landscape is most closely related to a potential of mean force

$$F(x) = -k_B T \ln P(x) \quad (22.1.4)$$

P(x) is the probability density that reflects the probability for observing the system at a position x. As such it is equivalent to decomposing the free energy as a function of the coordinate x. Whereas the partition function is evaluated by integrating a Boltzmann weighting over all degrees of freedom, P(x) is obtained by integrating over all degrees of freedom except x.



States

We will use the term “state” in the thermodynamic sense: a distinguishable *minimum* or *basin* on free energy surface. States refer to a region of phase-space where you persist long compared to thermal fluctuations. The regions where there is a high probability of observing the system. One state is distinguished from another kinetically by a time-scale separation. The rate of evolving within a state is faster than the rate of transition between states.

Configuration

- Can refer to a distinct microstate or a structure that has been averaged over a local energy basin. You average over configurations (integrate over q) to get states (macrostates).

Transition State

- The transition state or transition–state ensemble, often labeled \ddagger , refers to those barrier configurations that have equal probability of making a transition forward or backward.
- It's not really a “state” by our definition, but a barrier or saddle point along a reaction coordinate.

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