22. Biophysical Reaction Dynamics

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 $\gg k_BT$. 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_BT 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

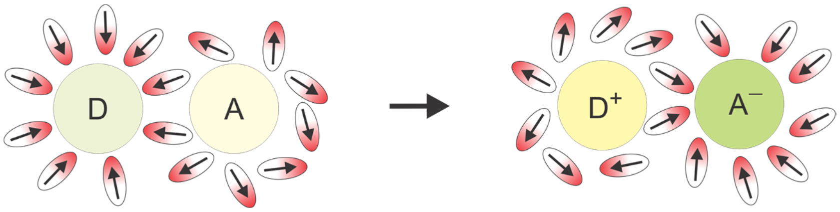
Refers to many types of variables that are used to describe the structure or configuration of a system. For instance, this may refer to the positions of atoms in a MD simulation as a function of time $\{\mathbf{r}^N, t\}$, or these Cartesian variables might be transformed onto a set of internal coordinates (such as bond lengths, bond angles, and torsion angles), or these positions may be projected onto a different collective coordinate.

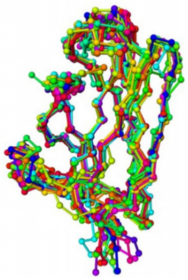
Unlike our simple lattice models, the transformation from atomic to collective coordinate is complex when the objective is to calculate a partition function, since the atomic degrees of freedom are all correlated.

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: $q \sim \Phi_A - \Phi_D$.

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

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

  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

$$A = -k_B T \ln Z$$

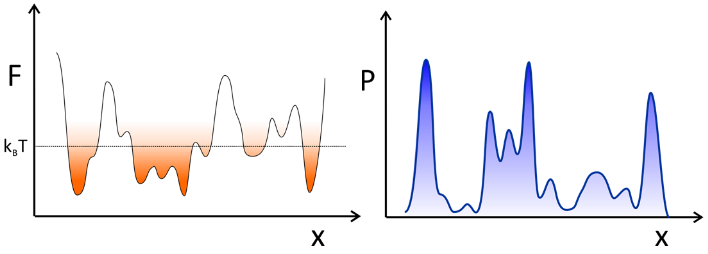
where Z is the partition function. The free energy is a number that reflects the thermally weighted number of microstates available to the system. The free energy determines the relative probability of occupying two states of the system:

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

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

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

$P(x)$ 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 <u>except</u> 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.

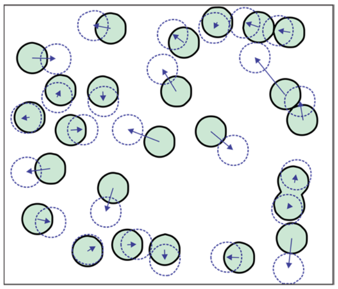
Configuration

- 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 labelled ‡, 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.

Computing Dynamics

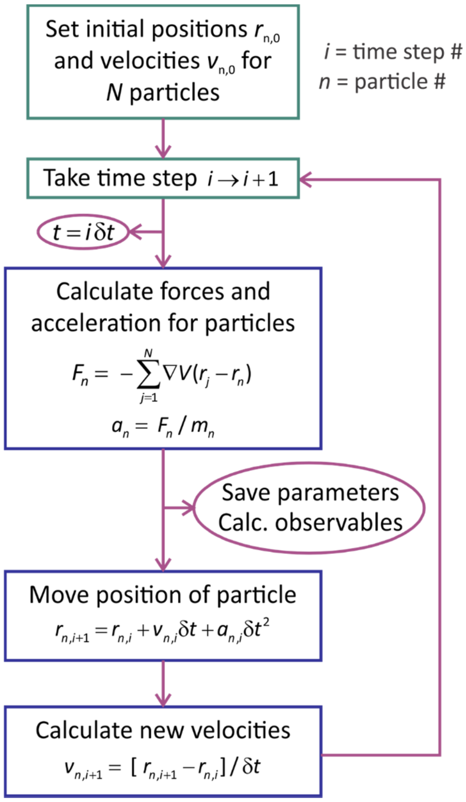


There are a number of ways of computationally modeling time-dependent processes in molecular biophysics. These methods integrate equations of motion for the molecular degrees of freedom evolving under a classical force–field interaction potential, a quantum mechanical Hamiltonian, or an energy landscape that could be phenomenological or atomistically detailed. Examples include using classical force fields to propagate Newton's equation of motion, integrating the Schrödinger equation, or integrating the Langevin equation on a potential of mean force. Since our interest is more on the description of computational or experimental data, this will just be a brief overview.

Classical Dynamics from a Potential (Force Field)

An overview of how to integrate Newton's equation of motion, leaving out many important details. This scheme, often used in MD simulations, is commonly called a Verlet integration.

1) Set initial positions **r** and velocities **v** of particles. For equilibrium simulations, the velocities are chosen from a Maxwell–Boltzmann distribution.
2) Take small successive steps in time δt, calculating the velocities and positions of the particles for the following time step.
   - At each time step calculate the forces on each particle by calculating the gradient of the potential with respect to **r**: $\mathbf{F}(\mathbf{r}) = -\nabla V(\mathbf{r})$. The force is proportional to the acceleration $\mathbf{a} = \mathbf{F}/m$, where m is the mass of the particle.
   - Now propagate the position of each particle n in time from time step i to time step $i+1$ as $\mathbf{r}_{n,i+1} = \mathbf{r}_{n,i} + \mathbf{v}_{n,i}\,\delta t + \mathbf{a}_{n,i}\,\delta t^2$. This is a good point to save information for the system at a particular time.
   - Calculate the new velocity for each particle from $\mathbf{v}_{n,i+1} = [\mathbf{r}_{n,i+1} - \mathbf{r}_{n,i}]/\delta t$.
3) Now, you can increment the time step and repeat step iteratively.



Langevin Dynamics

Building on our discussion of Brownian motion, the Langevin equation is an equation of motion for a particle acting under the influence of a fixed potential U, friction, and a time-dependent random force. Writing it in one dimension:

$$ma = f_{\text{potential}} + f_{\text{friction}} + f_{\text{random}}\left(t\right)$$

$$m\frac{\partial^2 x}{\partial t^2} = -\frac{\partial U}{\partial x} - \zeta\frac{\partial x}{\partial t} + f_r\left(t\right)$$

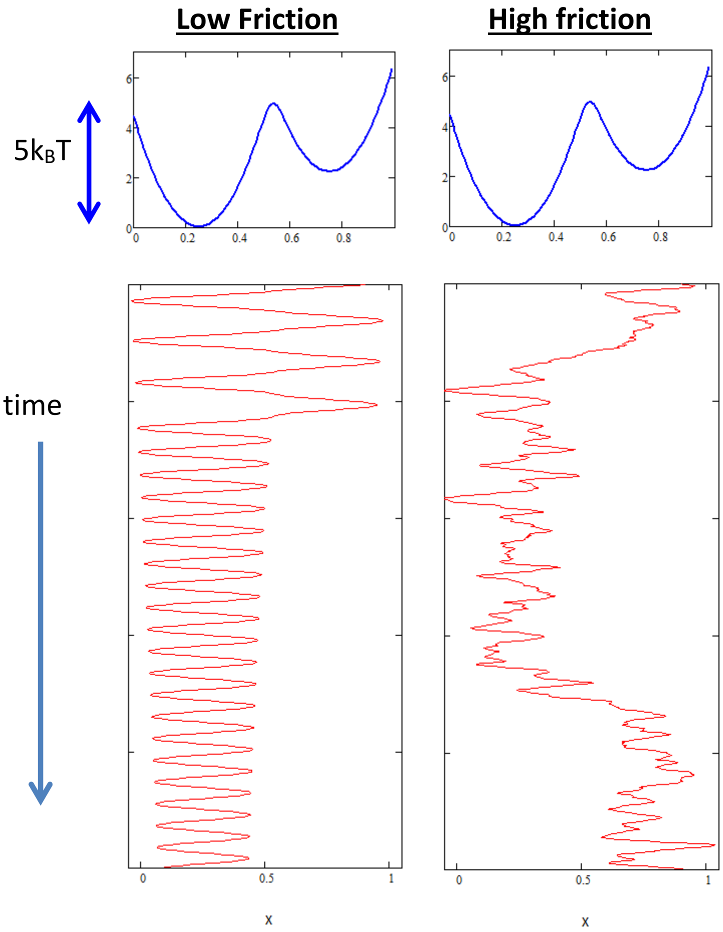
The random force reflects the equilibrium thermal fluctuations acting on the particle, and is the source of the friction on the particle. In the Markovian limit, the friction coefficient ζ and the random force $f_r(t)$ are related through a fluctuation–dissipation relationship:

$$\left\langle f_r\left(t\right)\right\rangle = 0$$

$$\left\langle f_r\left(t\right) f_r\left(t_0\right)\right\rangle = 2\zeta k_B T\ \delta\left(t - t_0\right)$$

Also, the diffusion constant is $D = k_B T/\zeta$, and the time scale for loss of velocity correlations is $\tau_c = \gamma^{-1} = m/\zeta$. The Langevin equation has high and low friction limits. In the low friction limit ($\zeta \to 0$), the influence of friction and random force is minimal, and the behavior is dominated by the inertial motion of the particle. In the high friction limit, the particle's behavior, being dominated by ζ, is diffusive. The limit is defined by any two of the following four linearly related variables: ζ, D, T, and $\langle f_r^2 \rangle$. The high and low friction limit are also referred to as the low and high temperature limits: $\langle f_r^{\,2}\rangle / 2\zeta = k_B T$.

Example: Trajectory for a particle on a bistable potential from Langevin dynamics



Representations of Dynamics

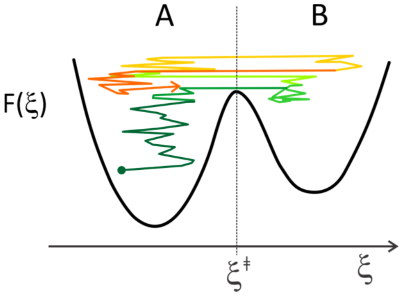
We will survey different representation of time-dependent processes using examples from one-dimension.

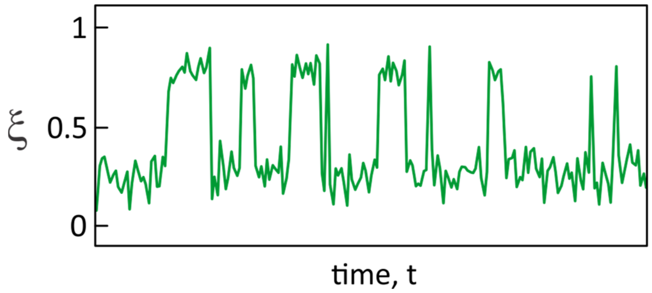
Trajectories

Watch the continuous time-dependent behavior of one or more particles/molecules in the system.

Time-dependent structural configurations

A molecular dynamics trajectory will give you the position of all atoms as a function of time $\{\mathbf{r}^N, t\}$. Although there is an enormous amount of information in such a trajectory, the raw data is often overwhelming and not of particularly high value itself. However, it is possible to project this high dimensional information in structural coordinates onto one or more collective variables ξ that forms a more meaningful representation of the dynamics, ξ(t). Alternatively, single molecule experiments can provide a chronological sequence of the states visited by molecule.



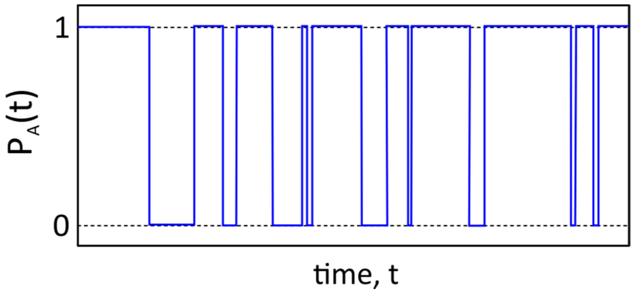


State trajectories: Time-dependent occupation of states

A discretized representation of which state of the system the particle occupies. Requires that you define the boundaries of a state.

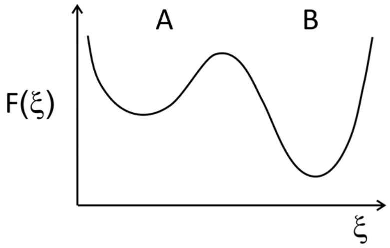
Example: A two state trajectory for an equilibrium $A \rightleftarrows B$, where the time-dependent probability of being in state A is:

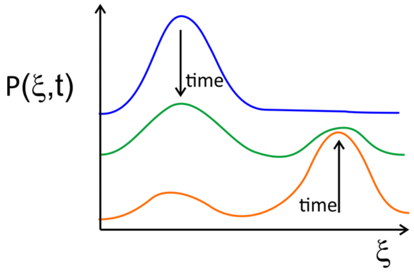
$$P_A(t) = \begin{cases} 1 \; if \; \xi(t) < \xi^{\ddagger} \\ 0 \; if \; \xi(t) > \xi^{\ddagger} \end{cases}$$



Time-Dependent Probability Distributions and Fluxes

With sufficient sampling, one can average over trajectories in order to develop a time-dependent probability distribution P(ξ,t) for the non-equilibrium evolution of an initial state.

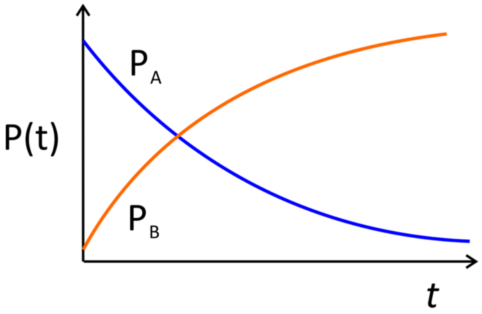




State Populations: Kinetics

- Average over states to get time-dependent populations of those states.

$$\int_{\text{state A}} P(\xi,t)\,d\xi = P_A(t)$$



- Alternatively, one can obtain the same information by analyzing waiting time distributions from state trajectories, as described below.
- The kinetics can be modeled with rate equations/master equation: $\dot{P} = \mathbf{k}P$.

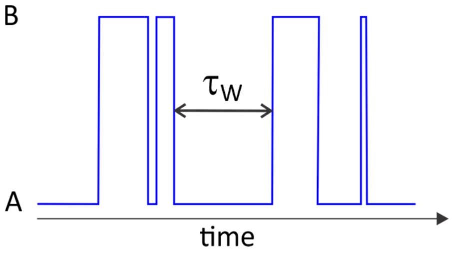
Time-Correlation Functions

Time-correlation functions are commonly used to characterize trajectories of a fluctuating observable. These are described below.

Analyzing Trajectories

Waiting-Time Distributions, Pw

τ_W:	Waiting time between arriving and leaving a state
P_k:	or $P(k,t)$ Probability of making k jumps during a time interval, t. → Survival probability
P_w:	Probability of waiting a time τ_w between jumps? Waiting time distribution → FPT distribution



Let's relate these…

Assume independent events. No memory of history – where it was in trajectory.

Flux: $\frac{dP_R}{dt} = J$

J: Probability of jump during Δt. Δt is small enough that $J \ll 1$, but long enough to lose memory of earlier configurations.

The probability of seeing k jumps during a time interval t, where t is divided into N intervals of width Δt ($t = N\Delta t$) is given by the binomial distribution

$$P(k,N) = \frac{N!}{k!(N-k)!} J^k (1-J)^{N-k} \tag{1}$$

Here $N \gg k$. Define rate λ in terms of the average number of jumps per unit time

$$\lambda = \frac{\langle k \rangle}{t} = \frac{1}{\langle \tau_W \rangle}$$

$$J = \lambda \Delta t \quad \longrightarrow \quad J = \frac{\lambda t}{N}$$

Substituting this into eq. (1) **Error! Reference source not found.**. For $N \gg k$, recognize

$$(1-J)^{N-k} \approx (1-J)^N = \left(1 - \frac{\lambda t}{N}\right)^N \approx e^{-\lambda t}$$

The last step is exact for lim $N \to \infty$.

Poisson distribution for the number of jumps in time t.

$$\langle P(k,t) \rangle = \langle \lambda t \rangle = \frac{\lambda t}{\langle P^2(k,t) \rangle^{1/2}} = (\lambda t)^{1/2}$$

Fluctuations: $\sigma / \left\langle P\left(k,t\right)\right\rangle = (\lambda t)^{-1/2}$

OK, now what about P_w the waiting time distribution?

Consider the probability of not jumping during time *t*:

$$P_k\left(0,\ t\right) = e^{-\lambda t}$$

As you wait longer and longer, the probability that you stay in the initial state drops exponentially. Note that $P_k(0,\ t)$ is related to P_w by integration over distribution of waiting times.

$$\int_t^\infty P_w(t')dt' = P(0,t) = e^{-\lambda t}$$

$$\int_t^\infty P_w\,dt \rightarrow \text{ probability of staying for t}$$

$$\int_0^t P_w dt \rightarrow \text{ probability of jumping within t}$$

Probability of jumping between *t* and *t*+Δ*t*:

$$P_w(t)\,\Delta t = \overbrace{\left(1-\langle k\rangle\Delta t_1\right)\left(1-\langle k\rangle\Delta t_2\right)\ldots\left(1-\langle k\rangle\Delta t_N\right)}^{\text{Probability of no decay for time }<t}\overbrace{k\Delta t}^{\text{decay on last}}$$

$$= \left(1-\langle k\rangle\Delta t\right)^N k\Delta t \approx ke^{-kt}\Delta t$$

$$P_w = \lambda e^{-\lambda t}$$

$$\left\langle \tau\right\rangle = \int_0^\infty t p_w(t)t$$

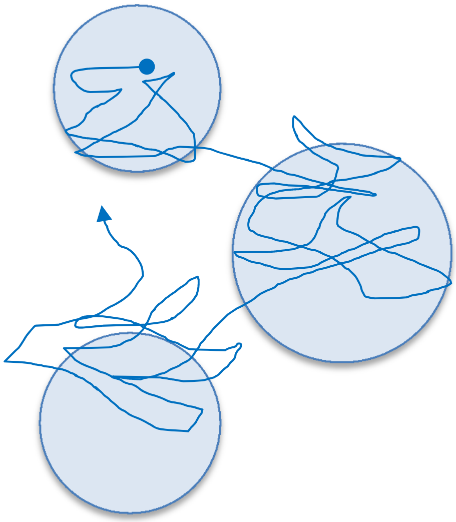
$$\left\langle \tau_w\right\rangle = 1/\lambda$$

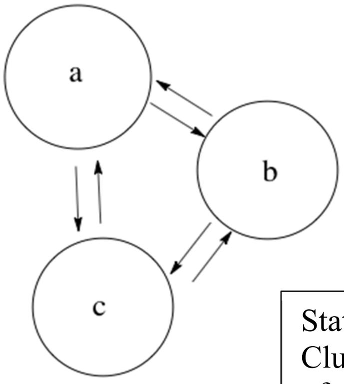
$$\left\langle \tau_w^2\right\rangle - \left\langle \tau_w\right\rangle^2 = \left(1/\lambda\right)^2$$

→ the average waiting time is the lifetime (1/λ)

Reduction of Complex Kinetics from Trajectories

- Integrating over trajectories gives probability densities.
- Need to choose a region of space to integrate over and thereby define states:





States:
Clustered regions of phase space that have high probability or long persistence.

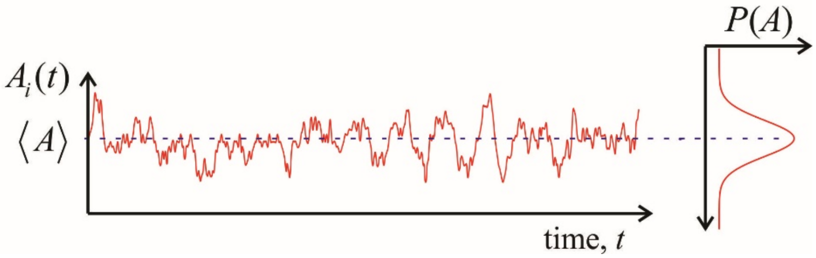
- States: Clustered regions of phase space that have high probability or long persistence.
- Markovian states: Spend enough time to forget where you came from.
- Master equation: Coupled first order differential equations for the flow of amplitude between states written in terms of probabilities.

$$\frac{dP_m}{dt} = \sum_n k_{n\to m} P_n - \sum_n k_{m\to n} P_m$$

$k_{n\to m}$ is rate constant for transition from state n to state m. Units: probability/time. Or in matrix form: $\dot{P} = \mathbf{k}P$ where $\mathbf{k}$ is the transition rate matrix. With detailed balance, conservation of population all initial conditions will converge on equilibrium.

Time-Correlation Functions

Time-correlation functions are commonly used to characterize the dynamics of a random (or stochastic) process. If we observe the behavior of an internal variable *A* describing the behavior of one molecule at thermal equilibrium, it may be subject to microscopic fluctuations.



Although there may seem to be little information in this noisy trajectory, this dynamics is not entirely random, since they are a consequence of time-dependent interactions with the environment. We can provide a statistical description of the characteristic time scales and amplitudes to these changes by comparing the value of *A* at time *t* with the value of *A* at a later time *t'*. We define a time-correlation function as the product of these values averaged over an equilibrium ensemble:

$$C_{AA}\left(t-t'\right) \equiv \left\langle A\left(t\right) A\left(t'\right)\right\rangle \tag{2}$$

Correlation functions do not depend on the absolute point of observation (*t* and *t'*), but rather the time interval between observations (for stationary random processes). So, we can define the time interval $\tau \equiv t - t'$, and express our function as $C_{AA}\left(\tau\right)$.

We can see that when we evaluate C_{AA} at $\tau = 0$, we obtain the mean square value of *A*, $\langle A^2 \rangle$. At long times, as thermal fluctuations act to randomize the system, the values of *A* become uncorrelated: $\lim_{\tau\to\infty} C_{AA}\left(\tau\right) = \left\langle A\right\rangle^2$. It is therefore common to redefine the correlation function in terms of the deviation from average

$$\delta A \equiv A - \left\langle A\right\rangle \tag{3}$$

$$C_{\delta A\delta A}\left(t\right) = \left\langle \delta A\left(t\right)\delta A\left(0\right)\right\rangle = C_{AA}\left(t\right) - \left\langle A\right\rangle^2 \tag{4}$$

Then $C_{\delta A\delta A}\left(0\right)$ gives the variance for the random process, and the correlation function decays to zero as $\tau \to \infty$. The characteristic time scale for this relaxation is the correlation time, τ_c. which we can obtain from

$$\tau_c = \frac{1}{\left\langle \delta A^2\right\rangle}\int_0^\infty dt\, \left\langle \delta A\left(t\right)\delta A\left(0\right)\right\rangle \tag{5}$$

The classical correlation function can be obtained from an equilibrium probability distribution as

$$C_{AA}(t-t') = \int dp \int dq \;\; A(p,q;t)\; A(p,q;t')\, P_{eq}(p,q) \tag{6}$$

In practice, correlation function are more commonly obtained from trajectories by calculating it as a time average

$$C_{AA}(\tau) = \overline{A(\tau)A(0)} = \lim_{T\to\infty} \frac{1}{T}\int_0^T dt' \;\; A_i(\tau+t')\,A_i(t') \tag{7}$$

If the time-average value of C is to be equal to the equilibrium ensemble average value of C, we say the system is ergodic.

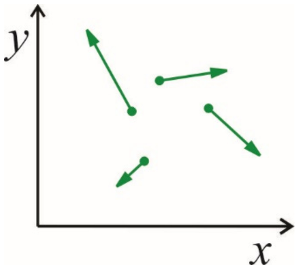
Example: Velocity Autocorrelation Function for Gas

A dilute gas of molecules has a Maxwell–Boltzmann distribution of velocities, for which we will focus on the velocity component along the $\hat{x}$ direction, v_x. We know that the average velocity is $\langle v_x \rangle = 0$. The velocity correlation function is

$$C_{v_x v_x}(\tau) = \langle v_x(\tau)\, v_x(0)\rangle$$

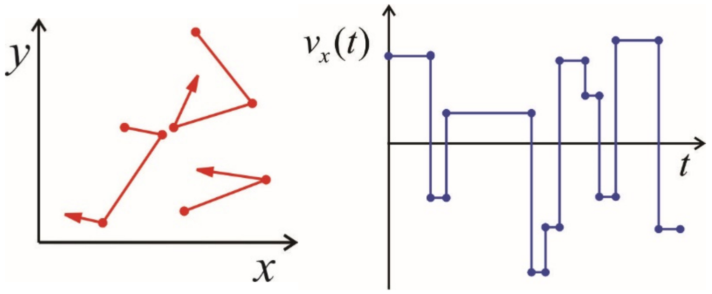
The average translational energy is $\frac{1}{2}m\langle v_x^2\rangle = k_B T/2$, so

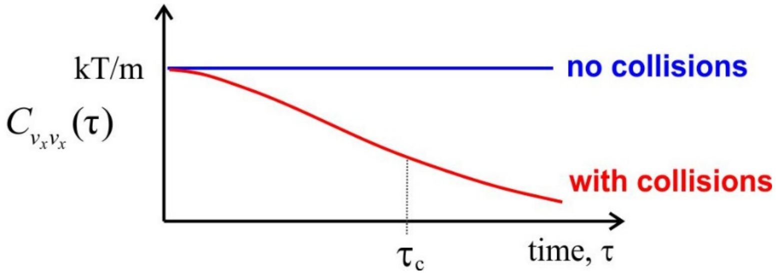
$$C_{v_x v_x}(0) = \langle v_x^2(0)\rangle = \frac{k_B T}{m}$$



For time scales that are short compared to the average collision time between molecules, the velocity of any given molecule remains constant and unchanged, so the correlation function for the velocity is also unchanged at k_BT/m. This non-interacting regime corresponds to the behavior of an ideal gas.

For any real gas, there will be collisions that randomize the direction and speed of the molecules, so that any molecule over a long enough time will sample the various velocities within the Maxwell–Boltzmann distribution. From the trajectory of x-velocities for a given molecule we can calculate $C_{v_x v_x}(\tau)$ using time averaging. The correlation function will drop on with a correlation time τ_c, which is related to mean time between collisions. After enough collisions, the correlation with the initial velocity is lost and $C_{v_x v_x}(\tau)$ approaches $\langle v_x^2\rangle = 0$. Finally, we can determine the diffusion constant for the gas, which relates the time and mean square displacement of the molecules: $\langle x^2(t)\rangle = 2D_x t$. From $D_x = \int_0^\infty dt\, \langle v_x(t) v_x(0)\rangle$ we have $D_x = k_B T \tau_c / m$. In viscous fluids τ_c / m is called the mobility.





Calculating a Correlation Function from a Trajectory

We can evaluate eq. (7) for a discrete and finite trajectory in which we are given a series of N observations of the dynamical variable A at equally separated time points t_i. The separation between time points is $t_{i+1} - t_i = \delta t$, and the length of the trajectory is $T = N\,\delta t$. Then we have

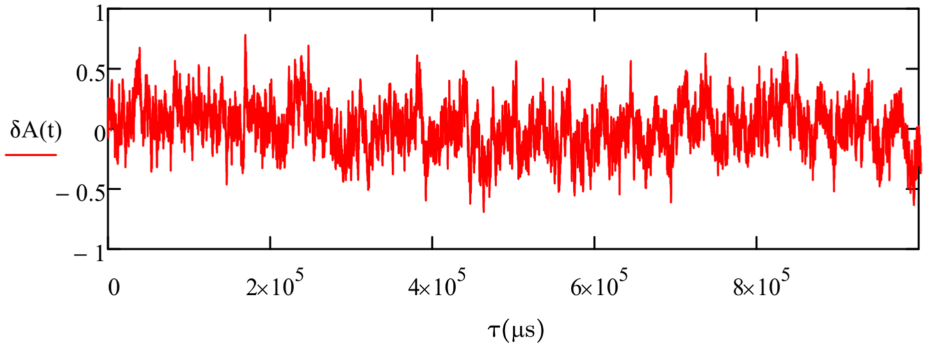
$$C_{AA} = \frac{1}{T}\sum_{i,j=1}^{N} \delta t\, A(t_i)A(t_j) = \frac{1}{N}\sum_{i,j=1}^{N} A_i A_j \tag{8}$$

where $A_i = A(t_i)$. To make this more useful we want to express it as the time interval between points $\tau = t_j - t_i = (j-i)\delta t$, and average over all possible pairwise products of A separated by τ. Defining a new count integer $n = j - i$, we can express the delay as $\tau = n\delta t$. For a finite data set there are a different number of observations to average over at each time interval (n). We have the most pairwise products—N to be precise—when the time points are equal ($t_i = t_j$). We only have one data pair for the maximum delay $\tau = T$. Therefore, the number of pairwise products for a given delay τ is $N - n$. So we can write eq. (8) as

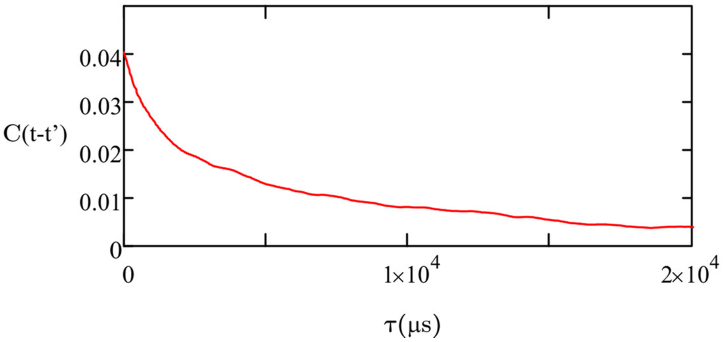
$$C_{AA}(\tau) = C(n) = \frac{1}{N-n}\sum_{i=1}^{N-n} A_{i+n} A_i \tag{9}$$

Note that this expression will only be calculated for positive values of n, for which $t_j \geq t_i$.

As an example consider the following calculation for fluctuations in fluorescence intensity in an FCS experiment. This trajectory consists of 32000 consecutive measurements separated by 44 μs, and is plotted as a deviation from the mean $\delta A(t) = A(t) - \langle A \rangle$.



The correlation function obtained from eq. (9) is



We can see that the decay of the correlation function is observed for sub-ms time delays. From eq. (5) we find that the correlation time is τ_C = 890 μs.