Protein folding kinetics

- $e^N$ local energy minima (configurations) connected via transitions
- Random walk on network from initial to native state
- States and transition probabilities obtained from simulations

Additional Reading


Markov Modeling

• Describes temporal evolution of state of the system

• No memory; transition probabilities only depend on current state; satisfied by MD trajectories

• Time domain (continuous or discrete); state space (continuous or discrete)

• Statistical description: What is probability that member of the ensemble of systems will be in a given state at time \( t \)?

• How does one choose set of states for Markov model of protein dynamics---continuous degrees of freedom yields infinite number of states? *Number of native contacts...but not specific enough*
Lumping of States: From 11 to 3

• Are transitions among aggregated states (A, B, C) Markovian?
  • Yes, at sufficiently long time scales.
• How does one decide on lumping scheme?
Mathematical Description

\[ \begin{align*}
\text{Elements} & \text{ non-negative} \\
\text{Columns sum to 1} \\
\text{Eigenvalues} \mu_i \leq 1: \ T \Phi = \mu \Phi \\
\Phi(\mu=1) & \text{ gives steady-state probability distribution}
\end{align*} \]

\[ T_{ij} \to, \text{ from} \]

\[ P_i((n+1)\tau) = T_{ij}(\tau)P_j(n\tau) \]

\[ T_{ij}P_j(t \to \infty) = T_{ji}P_i(t \to \infty) \]  
**Detailed balance (no net flow)**

\[ P(n\tau) = \sum_i c_i \mu_i^n \Phi_i \]

\[ \mu_i^n = \mu_i^{t/\tau} = e^{-t/\tau_i\text{decay}}; \tau_i\text{decay} = -\frac{\tau}{\ln \mu_i} \]

\[ \begin{align*}
\text{N}_s-1 \text{ eigenvalues determine relaxation rates}
\end{align*} \]
**Figure 1.** Representation of the Markov transition matrix for the example problem described in the text. Only “off-diagonal” values of the matrix are explicitly shown. The diagonal elements can be deduced from the fact that the sum of all transition probabilities out of any state is unity. The nine *microstates* of the nine-state system are indicated by numbers. Three *macrostates*, indicated by letters, are formed by lumping groups of three microstates together, as shown.
Transition Matrix

\[
T_{ij} = \begin{pmatrix}
0.99 & 0.005 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0.01 & 0.99 & 0.01 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0.005 & 0.986 & 0.004 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0.004 & 0.976 & 0.01 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0.02 & 0.98 & 0.02 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0.01 & 0.976 & 0.004 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0.004 & 0.946 & 0.025 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0.004 & 0.946 & 0.025 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0.05 & 0.95 & 0.05 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0.025 & 0.95
\end{pmatrix}
= 1
\]

Lumped Transition Matrix

\[
T_{ij}^{lump} = \begin{pmatrix}
2.996/3 & 0.004/3 & 0 \\
0.004/3 & 2.992/3 & 0.004/3 \\
0 & 0.004/3 & 2.996/3
\end{pmatrix}
= 1
\]

\[
L_{2 \times 2} (T) = \begin{pmatrix}
\frac{a_1 + a_2 + a_3 + a_4}{2} & \frac{b_1 + b_2 + b_3 + b_4}{2} \\
\frac{c_1 + c_2 + c_3 + c_4}{2} & \frac{d_1 + d_2 + d_3 + d_4}{2}
\end{pmatrix}
\]
**State Probabilities**

![Graph showing state probabilities over time](image)

**Figure 2.** Transition functions, showing the probability of being in various states as a function of time given that the system was in state 5 of the nine-state system at time $t > 0$ (solid lines), or given that it was in state 2 of the lumped three-state system at time $t > 0$ (dashed lines). For the nine-state case, the rapidly decreasing function represents the diagonal function $T_{5,5}$, and the two most rapidly rising functions represent the probability of being in states 4 or 6. For the three-state system, the decreasing function represents the diagonal function $T_{B,B}$, and the two more rapidly rising functions represent the probability of being in states A or C.
Results from Toy Model

- **9 microstates**
- **L(T^n)**
- **(L(T))^n**

Larger deviations; practical
Figure 3. Eigenvalues as a function of time for a nine- (solid lines) and a three-state (dashed lines) system. Each system has one eigenvalue of unity for all lag times. The eigenvalues of the nine-state system show the expected exponential decay of a Markov process. Those of the three-state system need not, because they represent a process that is not necessarily Markovian.
Eigenvalue Spectra

Small deviations

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Figure 5. Lifetime distributions for the lumped three-state system. On each plot the solid line represents observed lifetime distributions; dashed line represents the distribution that would be expected if the behavior were Markovian and had a mean lifetime that was equal observed mean lifetime. Panels A–C show data for state A of the three-state system using time lags of 10, 20, and 50 sampling periods, respectively. Similar data for state B of the three-state system are shown in panels D–F (again, with time lags of 10, 20, and 50).