Characteristic time of crossing a long free energy barrier

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This short paper presents a simple approximate analytical estimate of the characteristic time of crossing a high, long and arbitrary bumpy free energy barrier in a course of chemical, biochemical or physical reaction.

Many important reactions, such as polymerization or aggregation, include crossing of a long free energy barrier [1-4] (Fig. 1).

FIG. 1: Scheme of a polymerization reaction. Circles are free monomers in solution. Rhombs are monomers in a form appropriate for polymerization. This form is unstable for free monomers; very short polymers are also unstable; long polymers are stable. \( k_{i\rightarrow i+1} \) is the transition rate constant for passing from state \( i \) to the next state \( i+1 \) at the reaction pathway; \( k_{i+1 \rightarrow i} \) is the rate constant for the reverse transition from \( i+1 \) to \( i \) state.

Despite the abundance of such reactions (see, e.g., Fig. 2 as one more example), I, to my surprise, failed to find in literature a general formula to estimate their characteristic times.

FIG. 2: Scheme of a free energy change along a pathway of \( \beta \)-sheet formation [5]. Each turn of the chain increases the chain’s free energy, as well as the first extended chain region (separate \( \beta \)-strand), while each subsequent \( \beta \)-strand of the sheet decreases the free energy, so that a large \( \beta \)-sheet is stable.

It was not difficult to obtain an estimate of the characteristic time of crossing of a long, arbitrary bumpy but high free energy barrier (see equation (5) below), and this formula was included as equation (8.19) in [5] without a proof or analysis.
Consider the kinetics of a reversible process

\[
\begin{array}{ccccccc}
0 & \xrightarrow{k_{1-2,0}} & 1 & \xrightarrow{k_{2-1,1}} & \cdots & \xrightarrow{k_{M-M+1, M}} & M+1 \xrightarrow{k_{M+1-M, M}} & \text{finish}
\end{array}
\]

where \( k_{i-\alpha i+1} \) is the transition rate constant of passing from state \( i \) to \( i+1 \), and \( k_{i+1-\alpha i} \) of the reverse transition from \( i+1 \) to \( i \) (we will assume that \( F_0 \), the free energy of the “start” state, is higher than that \( F_{M+1} \), the free energy of the “finish” state).

The Moscow scientist Rakowski gave a general solution of the system of kinetic differential equations corresponding this process in 1907 [6]; but now we are interested in a simple estimate of the rate of such a specific process, in which the free energy of the intermediate states (1, ..., \( M \)) is much higher than the free energy of the initial state 0 and the final state \( M+1 \). This estimate can be based on the "quasi-stationary approximation", widely used in chemical kinetics [7 - 11].

Due to a high free energy \( F_i \) of all intermediate states \( 1 \leq i \leq M \), the number of molecules \( n_i \) in each intermediate state is very small as compared to their number \( n_0 + n_{M+1} \) in the initial and final states. Therefore, the rate of change of \( n_i \) is very small as compared to the rate of change of \( n_0 \) or \( n_{M+1} \). Thus, in the "zero" approximation, one can assume that \( \frac{dn_i}{dt} = 0 \) for intermediate states 1,...,\( M \), and therefore the flow rate is constant along the reaction pathway:

\[
-\frac{dn_i}{dt} = k_{0-\alpha i}n_0 - k_{i-\gamma i}n_i = k_{i-\gamma i}n_i - k_{2-\gamma 1}n_2 = \cdots = k_{M-M+1}n_M - k_{M+1-\alpha M+1}n_{M+1} = \frac{dn_{M+1}}{dt}.
\]

Denoting the flow rate \( -\frac{dn_i}{dt} \) as \( I \), one has a system of equations

\[
\begin{align*}
\begin{cases}
  k_{0-\gamma 0}n_0 - k_{1-\gamma 1}n_1 = I \\
  \cdots \\
  k_{i-\gamma i}n_{i-1} - k_{i+1-\gamma i}n_i = I \\
  \cdots \\
  k_{M-M+1}n_M - k_{M+1-\gamma M+1}n_{M+1} = I,
\end{cases}
\end{align*}
\]

or

\[
\begin{align*}
\begin{cases}
  n_0 - (k_{i-\gamma i}/k_{0-\gamma 0})n_1 = I \tau_i \\
  \cdots \\
  n_{i-1} - (k_{i-\gamma i}/k_{i-1-\gamma i})n_i = I \tau_i \\
  \cdots \\
  n_{M+1} - (k_{M+1-\gamma M+1}/k_{M-M+1})n_{M+1} = I \tau_{M+1},
\end{cases}
\end{align*}
\]

where \( \tau_i = 1/k_{i-\gamma i} \) is the passage ("state \( i-1 \)"-to-"state \( i \)"") time.

Multiplying equation for each \( \tau_i \) (with \( i > 1 \)) by \((k_{i-\gamma i}/k_{0-\gamma 0})\) \( \cdots (k_{i-\gamma i}/k_{i-1-\gamma i}) \) and summing all these equations, one obtains:

\[
n_0 - (k_{i-\gamma i}/k_{0-\gamma 0}) \cdots (k_{M+1-\gamma M+1}/k_{M-M+1})n_{M+1} = [\tau_i + \cdots + \tau_{M+1}](k_{i-\gamma i}/k_{0-\gamma 0}) \cdots (k_{M+1-\gamma M+1}/k_{M-M+1}) \cdot I.
\]

Using the well-known [10] ratio \( k_{i-\gamma i}/k_{j-\gamma j} = \exp\left[\frac{F_j - F_i}{k_B T}\right] \), which follows from that that the equilibrium populations \( n_i^0 \) and \( n_j^0 \) of states \( i \) and \( j \) must satisfy both to the kinetic equation \( n_i^0 k_{i-\gamma i} = n_j^0 k_{j-\gamma j} \) and the thermodynamic relation \( n_i^0/F_i = \exp\left[-\frac{F_j - F_i}{k_B T}\right] \) (where \( T \) is temperature and \( k_B \) the Boltzmann constant), one obtains

\[
n_0 - \exp\left[\frac{F_M+1 - F_0}{k_B T}\right] n_{M+1} = [\tau_i + \cdots + \tau_{M+1}] \exp\left[\frac{F_M - F_0}{k_B T}\right] \cdot I.
\]

Thus,
\[ I = \frac{n_0 \exp \left[ \frac{F_{M+1} - F_0}{k_BT} \right] n_{M+1}}{\sum_{j=1}^{M+1} \tau_j \exp \left[ \frac{F_{j-1} - F_0}{k_BT} \right]} \] (3)

If \( n_{M+1} \ll n_0 \) and \( F_{M+1} < F_0 \), then \( n_0 >> \exp \left[ \frac{F_{M+1} - F_0}{k_BT} \right] n_{M+1} \), so that

\[ I \approx \frac{n_0}{\sum_{j=1}^{M+1} \tau_j \exp \left[ \frac{F_{j-1} - F_0}{k_BT} \right]} \] (4)

Thus, our task, in fact, is reduced to the calculation of the flux in an irreversible reaction

\[ \begin{array}{cccccc}
0 & \xrightarrow{k_{i-1 \to i}} & 1 & \xrightarrow{k_{i \to i+1}} & \cdots & \xrightarrow{k_{M \to M+1}} & M+1 \xrightarrow{\text{finish}} M \to M+1
\end{array} \]

The characteristic time of passage of all \( n_0 \) particles from the initial state 0 to \( M+1 \) is

\[ t_{0 \to \cdots \to M+1} = n_0 / I \approx \sum_{j=1}^{M+1} \tau_j \exp \left[ \frac{F_{j-1} - F_0}{k_BT} \right]. \] (5)

Here \( F_{j-1} - F_0 \) is the free energy state \( j-1 \) counted off the free energy of the initial state 0. Note that the intermediates of a high free energy make a major contribution to the passage time, and that intermediates of a very low free energy (see the right parts of Figs. 1, 2) make a such a low contribution to the passage time that it can be neglected.

One can also obtain populations \( n_i \) of intermediate states in the course of reaction, using the recurrence relations following from the system (2) and equation (4):

\[ n_i = (k_{i-1 \to i} / k_{i \to i+1}) n_{i-1} - (k_{i \to i+1} / k_{i \to i-1}) \tau_i I = \exp \left[ \frac{F_{i-1} - F_i}{k_BT} \right] \{ n_{i-1} - \tau_i I \} \]

\[ = \exp \left[ \frac{F_0 - F_i}{k_BT} \right] n_0 - I \sum_{j=1}^{M+1} \tau_j \exp \left[ \frac{F_{j-1} - F_i}{k_BT} \right] \]

\[ = \exp \left[ \frac{F_0 - F_i}{k_BT} \right] \left\{ n_0 - \frac{n_0}{\sum_{j=1}^{M+1} \tau_j \exp \left[ \frac{F_{j-1} - F_0}{k_BT} \right]} \sum_{j=1}^{M+1} \tau_j \exp \left[ \frac{F_{j-1} - F_i}{k_BT} \right] \right\} \]

\[ = \exp \left[ \frac{F_0 - F_i}{k_BT} \right] n_0 - \frac{n_0}{\sum_{j=1}^{M+1} \tau_j \exp \left[ \frac{F_{j-1} - F_0}{k_BT} \right]} \sum_{j=1}^{M+1} \tau_j \exp \left[ \frac{F_{j-1} - F_i}{k_BT} \right] \]

\[ = \exp \left[ \frac{F_0 - F_i}{k_BT} \right] \left\{ n_0 - \frac{n_0}{\sum_{j=1}^{M+1} \tau_j \exp \left[ \frac{F_{j-1} - F_0}{k_BT} \right]} \right\} \]

\[ = \exp \left[ \frac{F_0 - F_i}{k_BT} \right] \frac{n_0}{\sum_{j=1}^{M+1} \tau_j \exp \left[ \frac{F_{j-1} - F_0}{k_BT} \right]} \]

\[ \text{for all } i = 0, 1, \ldots, M+1. \]

Note that any \( n_i \) may be represented as

\[ n_i = n_i^0 \frac{\sum_{j=1}^{M+1} \tau_j \exp \left[ \frac{F_{j-1} - F_0}{k_BT} \right]}{\sum_{j=1}^{M+1} \tau_j \exp \left[ \frac{F_{j-1} - F_0}{k_BT} \right]} \]

\[ n_i^0 = \exp \left[ \frac{F_0 - F_i}{k_BT} \right] n_0 \]

where \( n_i^0 \) is population of state \( i \), corresponding to its thermodynamic equilibrium with population \( n_0 \) of the initial state 0.

One can see that all \( n_i < n_i^0 \) at \( i > 0 \).

However, the solution obtained above seems to be not quite correct, since the system (2) is obtained under the assumption that \( \frac{dn_i}{dt} = 0 \) for all intermediates \( i = 1, \ldots, M \), and that only \( \frac{dn_0}{dt} = - \frac{dn_{M+1}}{dt} = -I \neq 0 \). On the other hand, equation (6) leads to non-zero derivatives \( \frac{dn_i}{dt} \) for all intermediate states \( i = 1, \ldots, M \):

\[ \frac{dn_i}{dt} = \exp \left[ \frac{F_0 - F_i}{k_BT} \right] \frac{\sum_{j=1}^{M+1} \tau_j \exp \left[ \frac{F_{j-1} - F_0}{k_BT} \right]}{\sum_{j=1}^{M+1} \tau_j \exp \left[ \frac{F_{j-1} - F_0}{k_BT} \right]} = -I \exp \left[ \frac{F_0 - F_i}{k_BT} \right] \frac{\sum_{j=1}^{M+1} \tau_j \exp \left[ \frac{F_{j-1} - F_0}{k_BT} \right]}{\sum_{j=1}^{M+1} \tau_j \exp \left[ \frac{F_{j-1} - F_0}{k_BT} \right]} = -I \frac{n_i}{n_0}. \] (8)
It is therefore necessary to consider the next, higher approximation taking into account the possible change of population of the intermediate states \( i \) (and, consequently, the possible change in the magnitude of the flux \( I_i \)) at different steps of the above shown irreversible reaction:

![Reaction diagram](attachment:image.png)

Thus, for all \( i = 1, \ldots, M+1 \) one obtains equations analogous to those presented in system (1),

\[
k_{i-1 \rightarrow i} n_{i-1} - k_{i \rightarrow i-1} n_i = \lambda_i I_i \quad \text{(where } I_i \equiv \frac{-d n_i}{d t} \text{ and the multiplier } \lambda_1 \equiv 1)\]

(1a)

and the recursive relations similar to those presented in system (2) and equation (6):

\[
n_i = \exp \left[ \frac{F_{i-1} - F_i}{k_B T} \right] \left[ n_{i-1} - (\tau_i \lambda_i) I_i \right].
\]

(2a)

After calculations similar to those done to derive equations (4), (6), one obtains:

\[
I \approx \frac{n_0}{\sum_{j=1}^{M+1} \tau_j \exp \left[ \frac{F_{j-1} - F_j}{k_B T} \right]}
\]

(4a)

and

\[
n_i = \exp \left[ \frac{F_0 - F_i}{k_B T} \right] n_0 \frac{\sum_{j=1}^{M+1} \tau_j \exp \left[ \frac{F_{j-1} - F_j}{k_B T} \right]}{\sum_{j=1}^{M+1} \tau_j \exp \left[ \frac{F_{j-1} - F_j}{k_B T} \right]}
\]

(6a)

or

\[
n_i = n_i^0 \frac{\sum_{j=1}^{M+1} \tau_j \exp \left[ \frac{F_{j-1} - F_j}{k_B T} \right]}{\sum_{j=1}^{M+1} \tau_j \exp \left[ \frac{F_{j-1} - F_j}{k_B T} \right]}
\]

(7a)

(cf. (6), (7)). Up to now, we did not do any approximations. Now we introduce a stationary approximation, i.e., we assume that each \( \frac{d n_i}{d t} = 0 \) (without this approximation, we would have to solve the complete system of linear differential equations considered in [6]). As a result (cf. (8)),

\[
\frac{dn_i}{dt} = \exp \left[ \frac{F_0 - F_i}{k_B T} \right] \frac{dn_0}{dt} \frac{\sum_{j=1}^{M+1} \tau_j \exp \left[ \frac{F_{j-1} - F_j}{k_B T} \right]}{\sum_{j=1}^{M+1} \tau_j \exp \left[ \frac{F_{j-1} - F_j}{k_B T} \right]} = -I \frac{n_i}{n_0}
\]

(8a)

where \( I \equiv \frac{-d n_i}{d t} \) is now described by equation (4a).

Equation (1a) and the above given scheme show that the flux

\[
\lambda_i I = -\frac{d}{dt} \left( \sum_{j=0}^{i-1} n_j \right).
\]

(9)

This means that \( \lambda_i I = I \sum_{j=0}^{i-1} \frac{n_j}{n_0} \), or

\[
\lambda_i = 1 + \sum_{j=1}^{i-1} \frac{n_j}{n_0}
\]

(10)

i.e., \( \lambda_i \) increases with \( i \).

However, since the population of each state, \( n_i \), in the course of reaction does not exceed \( n_j^0 \), the thermodynamically equilibrium population of the same state (see equation (7a)),

\[
\lambda_i \leq 1 + \sum_{j=1}^{i-1} \frac{n_j^0}{n_0} \equiv 1 + \sum_{j=1}^{i-1} \exp \left[ \frac{F_0 - F_j}{k_B T} \right],
\]

(11)

which means that all the values \( \lambda_i \) remain close to 1 if \( \sum_{j=1}^{i-1} \exp \left[ \frac{F_0 - F_j}{k_B T} \right] << 1 \), i.e., if the free
energies of the intermediate states $j = 1, \ldots, i-1$ are much, by many $k_BT$ higher than $F_0$.

This means that the estimate of characteristic reaction time obtained in equation (5) (and in (8.19) of [5]) is fairly accurate, provided that the free energy barrier at the reaction pathway is high.

In conclusion, I have to repeat that I was surprised when failed to find in literature a general formula (5) to estimate the characteristic time of crossing of arbitrarily bumpy but high free energy barrier, and I will be obliged to any reader who will send me the corresponding reference(s).

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