MODELING IN BIOLOGY STOCHASTIC PROCESSES AND NETWORKS

Courswork 2

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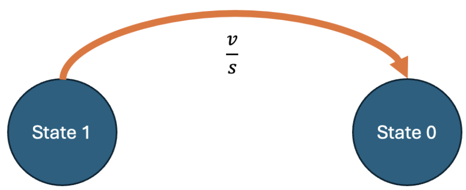
1 Question 1: Unimolecular decay

In this part of the question, only the decay processes are considered. The decay process is modeled as a two-state, continuous-time process, with $state_1$ as undecayed state and $state_0$ as a decayed state.

1.1 Graph and Rate Matrix

The Figure 1 represent the transfer of between two states and the rate matrix is stated in equation 1.



$$\mathbf{K} = \begin{pmatrix} 0 & \nu \\ 0 & -\nu \end{pmatrix} \tag{1}$$

Figure 1: Transition Graph

1.2 Obtain $p_0(t)$

Master Equation (equation 2) can be obtained by substituting the rate matrix (equation 1) in it. Since the state either be $state_1$ or $state_0$ $(p_1(t) + p_0(t) = 1)$, $p_1(t) = 1 - p_0(t)$. Using this information to subsitude $p_1(t)$ and $p_0(t)$ can be solved.

$$\frac{d}{dt}\begin{pmatrix} p_0(t) \\ p_1(t) \end{pmatrix} = \mathbf{K}\begin{bmatrix} p_0(t) \\ p_1(t) \end{bmatrix} = \begin{pmatrix} 0 & \nu \\ 0 & -\nu \end{pmatrix}\begin{bmatrix} p_0(t) \\ p_1(t) \end{bmatrix} \tag{2}$$

$$\frac{dp_0(t)}{dt} = \nu p_1 = \nu(1 - p_0(t)), \quad \frac{1}{1 - p_0(t)} dp_0(t) = \nu dt, \quad \int \frac{1}{1 - p_0(t)} dp_0(t) = \int \nu dt$$

$$-\ln|1 - p_0(t)| = \nu t + C, \quad |1 - p_0(t)| = e^{-\nu t - C}, \quad 1 - p_0(t) = \pm e^{-C} e^{-\nu t}$$

$$p_0(t) = 1 - C' e^{-\nu t}, \quad \because p_0(0) = 0, \quad \therefore 0 = 1 - C', C' = 1$$

$$p_0(t) = 1 - e^{-\nu t}$$

1.3 Distribution of Decay Times

To obtain the distribution of decay time $(p(t_{\text{dec}}))$, a relationship between $p_0(t)$ and $p(t_{\text{dec}})$ could be found and used to solve $p(t_{\text{dec}})$, since $p_0(t)$ already be calculated.

$$\because p(t_{\text{dec}})\delta t_{\text{dec}} = p_0(t_{\text{dec}} + \delta t_{\text{dec}}) - p_0(t_{\text{dec}}) = p_0(t_{\text{dec}}) + \frac{d}{dt_{\text{dec}}} p_0(t_{\text{dec}})\delta t_{\text{dec}} - p_0(t_{\text{dec}}) \text{ (Taylor Expansion)}$$

$$\therefore p(t_{\text{dec}}) = \frac{d}{dt_{\text{dec}}} p_0(t_{\text{dec}}) = \frac{d}{dt_{\text{dec}}}(1 - e^{-\nu t_{\text{dec}}}) = \nu e^{-\nu t_{\text{dec}}}$$

1.4 Mean and Variance of Decay Time

Mean($\langle T_{\text{dec}}\rangle$) and variance ($\text{VAR}(T_{\text{dec}})$) can be calculated by equation 3.

$$\langle T_{\text{dec}}\rangle = \int_0^\infty t_{\text{dec}} \cdot p(t_{\text{dec}})\, dt_{\text{dec}}, \quad \text{VAR}(T_{\text{dec}}) = \int_0^\infty (t_{\text{dec}} - \langle T_{\text{dec}}\rangle)^2 \cdot p(t_{\text{dec}})\, dt_{\text{dec}} \tag{3}$$

$$\begin{aligned}
\langle T_{\text{dec}}\rangle &= \int_0^\infty t_{\text{dec}} \cdot p(t_{\text{dec}})\, dt_{\text{dec}} = \int_0^\infty t_{\text{dec}} \cdot \nu e^{-\nu t_{\text{dec}}}\, dt_{\text{dec}} = \nu \int_0^\infty t_{\text{dec}} \cdot e^{-\nu t_{\text{dec}}}\, dt_{\text{dec}} \\
&= \nu(-\frac{t_{\text{dec}} e^{-\nu t_{\text{dec}}}}{\nu}\Big|_0^\infty + \int_0^\infty \frac{1}{\nu} e^{-\nu t_{\text{dec}}} dt_{\text{dec}}) = -t_{\text{dec}} e^{-\nu t_{\text{dec}}}\Big|_0^\infty + \int_0^\infty e^{-\nu t_{\text{dec}}} dt_{\text{dec}} \\
&= \int_0^\infty e^{-\nu t_{\text{dec}}} dt_{\text{dec}} = -\frac{1}{\nu} e^{-\nu t_{\text{dec}}}\Big|_0^\infty = \frac{1}{\nu} \\
\text{VAR}(T_{\text{dec}}) &= \int_0^\infty (t_{\text{dec}} - \langle T_{\text{dec}}\rangle)^2 \cdot p(t_{\text{dec}})\, dt_{\text{dec}} = \nu \int_0^\infty (t_{\text{dec}} - \frac{1}{\nu})^2 \cdot e^{-\nu t_{\text{dec}}}\, dt_{\text{dec}} \\
&= \nu \int_0^\infty (t_{\text{dec}}^2 - \frac{2t_{\text{dec}}}{\nu} + \frac{1}{\nu^2}) \cdot e^{-\nu t_{\text{dec}}}\, dt_{\text{dec}} \\
&= \nu \int_0^\infty t_{\text{dec}}^2 e^{-\nu t_{\text{dec}}} dt_{\text{dec}} - 2\int_0^\infty t_{\text{dec}} e^{-\nu t_{\text{dec}}} dt_{\text{dec}} + \frac{1}{\nu}\int_0^\infty e^{-\nu t_{\text{dec}}} dt_{\text{dec}} \\
&= \nu \int_0^\infty t_{\text{dec}}^2 e^{-\nu t_{\text{dec}}} dt_{\text{dec}} - \frac{2}{\nu^2} + \frac{1}{\nu^2} = \nu \int_0^\infty t_{\text{dec}}^2 e^{-\nu t_{\text{dec}}} dt_{\text{dec}} - \frac{1}{\nu^2} \\
&= \nu \left(-\frac{t_{\text{dec}}^2}{\nu} e^{-\nu t_{\text{dec}}}\Big|_0^\infty + \int_0^\infty \frac{2t_{\text{dec}}}{\nu} e^{-\nu t_{\text{dec}}} dt_{\text{dec}} \right) - \frac{1}{\nu^2} \\
&= \nu \left(0 + \frac{2}{\nu^3} \right) - \frac{1}{\nu^2} = \frac{1}{\nu^2}
\end{aligned}$$

2 Question 2: Diffusion

2.1 Free Diffusion in an Infinite System

To verify whether equation 4 is the solution of equation 5, only need to substitute equation 4 back to equation 5.

$$q(x,t) = \sqrt{\frac{1}{4\pi Dt}}\, e^{-\frac{(x-\frac{L}{2})^2}{4Dt}} \tag{4}$$

$$\frac{\partial q(x,t)}{\partial t} = D\frac{\partial^2 q(x,t)}{\partial x^2} \tag{5}$$

Set $A(t) = \sqrt{\frac{1}{4\pi Dt}}$, $B(t) = e^{-\frac{(x-\frac{L}{2})^2}{4Dt}}$ and $A'(t) = -\frac{1}{4\sqrt{\pi D} t^{\frac{3}{2}}}$, $B'(t) = \frac{\left(-\frac{L}{2}+x\right)^2 e^{-\frac{\left(-\frac{L}{2}+x\right)^2}{4Dt}}}{4Dt^2}$

$$\frac{\partial q(x,t)}{\partial t} = A'(t) \cdot B(t) + B'(t) \cdot A(t) = -\frac{1}{4\sqrt{\pi D} t^{\frac{3}{2}}} \cdot e^{-\frac{(x-\frac{L}{2})^2}{4Dt}} + \frac{\left(-\frac{L}{2}+x\right)^2 e^{-\frac{\left(-\frac{L}{2}+x\right)^2}{4Dt}}}{4Dt^2} \cdot \sqrt{\frac{1}{4\pi Dt}}$$

$$\frac{\partial q}{\partial t} = -\frac{B(t)}{4\sqrt{\pi D} t^{\frac{3}{2}}} + \frac{(x-\frac{L}{2})^2 B(t)}{8\sqrt{\pi} D^{\frac{3}{2}} t^{\frac{5}{2}}} = \left(\frac{(2x-L)^2 - 8Dt}{16Dt^2} \right) \cdot \frac{B(t)}{\sqrt{4\pi Dt}}$$

Set $C(x) = e^{-\frac{(x-\frac{L}{2})^2}{4Dt}}$, $C'(x) = \frac{(L-2x)C(x)}{4Dt}$, $E = \sqrt{\frac{1}{4\pi Dt}}$

$$\frac{\partial q(x,t)}{\partial x} = E \cdot C'(x), \quad \frac{\partial^2 q(x,t)}{\partial x^2} = \frac{\partial}{\partial x}\left[\frac{E}{4Dt} \cdot (L-2x) \cdot C(x)\right] = \frac{E}{4Dt} \cdot \frac{\partial}{\partial x}[(L-2x) \cdot C(x)]$$

$$\frac{\partial}{\partial x}[(L-2x) \cdot C(x)] = L \cdot C'(x) - 2\frac{\partial}{\partial x}[x \cdot C(x)], \quad \frac{\partial}{\partial x}[x \cdot C(x)] = C(x) + xC'(x)$$

$$\begin{aligned}
\frac{\partial^2 q(x,t)}{\partial x^2} &= \frac{E}{4Dt} \cdot [L \cdot C'(x) - 2 \cdot C(x) - 2x \cdot C'(x)] = \frac{E}{4Dt}[(L-2x)C'(x) - 2C(x)] \\
&= \frac{E}{4Dt}\left[\frac{(L-2x)^2 C(x)}{4Dt} - 2C(x)\right] = \frac{E}{4Dt}\left[\frac{(L-2x)^2}{4Dt} - 2\right] \cdot C(x) \\
&= \frac{E}{4Dt}\left[\frac{(L-2x)^2 - 8Dt}{4Dt}\right] \cdot C(x) = \frac{(L-2x)^2 - 8Dt}{16D^2t^2} \cdot \frac{C(x)}{\sqrt{4\pi Dt}}
\end{aligned}$$

$\because C(x) = B(t)$ (They are the same fucntion, just fix different variable)

$$\therefore \frac{(L-2x)^2 - 8Dt}{16D^2t^2} \cdot \frac{C(x)}{\sqrt{4\pi Dt}} = D \cdot \frac{(2x-L)^2 - 8Dt}{16Dt^2} \cdot \frac{B(t)}{\sqrt{4\pi Dt}}$$

$$\frac{\partial q(x,t)}{\partial t} = D\frac{\partial^2 q(x,t)}{\partial x^2}$$

2.2 Find $Q^\infty(t)$

$Q^\infty(t)$ is the probability that the position of the protein outside the region$(0 < x < L)$. Therefore, $Q^\infty(t) = \int_{-\infty}^{0} q(x,t)dx + \int_{L}^{+\infty} q(x,t)dx$.

2.3 Multiply Choise Question

Option 1 is the correct one. Since if one protein is outside of the axon, it means it must have reached $x = L$ or $x = 0$. However, if one protein, has reached the $x = L$ or $x = 0$, it is not necessarily outside the axon. Since one protein may have reached the $x = L$ or $x = 0$ and then diffused back into the axon.

2.4 Using simulation to estimate PDF

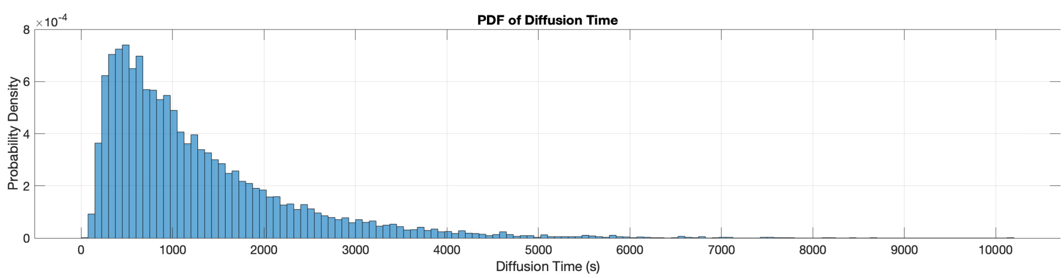


Figure 2: PDF for Diffusion Time

The code that generates this figure can be found in the appendix.

2.5 Calculate $\langle T_{diff} \rangle$ and VAR$(T_{\mathbf{diff}})$

$\langle T_{diff} \rangle$ and $Var(T_{diff})$ is calculated by the simulation data generated in the last section. The $\langle T_{diff} \rangle$ is equal to 1261, and VAR(T_{diff}) is equal to 1069503.4.

3 Question 3: Comparing decay and diffusion

3.1 ν for $\langle T_{dec} \rangle = \langle T_{diff} \rangle$

$\langle T_{dec} \rangle$ is already calculated in question 1.4, that is $\langle T_{dec} \rangle = \frac{1}{\nu}$. $\langle T_{diff} \rangle$ is also calculated in question 2.5, which is $\langle T_{diff} \rangle = 1261$. If ν for $\langle T_{dec} \rangle = \langle T_{diff} \rangle$, then $\frac{1}{\nu} = 1261$. $\nu = \frac{1}{1261}$. Since $p(t_{dec})$ is already calculated, substitute $\nu = \frac{1}{1261}$ can get a PDF which is demonstrated by blue line in figure 3, and the distribution of diffusion is calculated from data generated from section 2.4, and estimate the PDF distribution by function `ksdensity`.

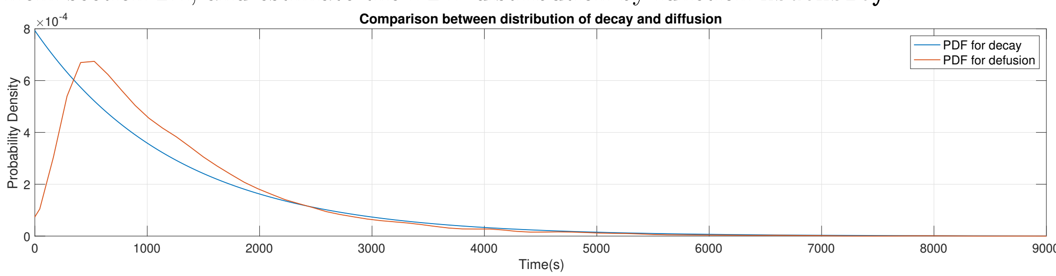


Figure 3: Comparison between the distribution of decay and diffusion

The $\mathrm{VAR}(T_{\mathrm{dec}})$ can also be calculated, assuming $\langle T_{dec} \rangle = \langle T_{diff} \rangle$, and $\nu = \frac{1}{1261}$. $\mathrm{VAR}(T_{\mathrm{dec}}) = \frac{1}{\nu^2}$, calculated in section 1.4, and it is equal to $1261^2 = 1590121$. It is bigger than $\mathrm{VAR}(T_{\mathrm{diff}})$, which is calculated in section 2.5, it is equal to 1069503.4.

$\therefore \mathrm{VAR}(T_{\mathrm{dec}}) > \mathrm{VAR}(T_{\mathrm{diff}})$

3.2 Short Times Event

If $\langle T_{dec} \rangle = \langle T_{diff} \rangle = 1261$, then $\frac{1}{10}\langle T_{dec} \rangle = \frac{1}{10}\langle T_{diff} \rangle = 126.1$. Based on figure 3, $p(126.1) > q(126.1)$. It means if there is an event happened, it is more possible this event is a decay than diffusion out of the main body.

This can be explained by the physics behind decay and diffusion. Decay can happen instantly, therefore, it has an exponential decay of the probability against time. However, it normally takes some for a protein to diffuse to somewhere, thus, diffusion has a positively skewed distribution. This explained why in a short time, a event happened it is more possible because of decay rather than diffusion.

3.3 Decay occurs before Diffuse outside

The probability of decay event happened before protein diffuse outside of the axon is about 0.54, this result is calculated by taking the mean of multiple simulation results. (more detailed code is shown in the appendix)

3.4 $\langle T_{diff,new} \rangle$ and $\langle T_{diff,new} \rangle$

If considering only decay events that happen before diffusion out of the axon, the new $\langle T_{dec} \rangle$ will smaller than original $\langle T_{dec} \rangle$, and if only considering the diffusion events that happen before decay, new $\langle T_{diff} \rangle$ is also smaller than original $\langle T_{diff} \rangle$. This result is generated by multiply `Matlab` simulation(detailed code is in the appendix).

A Matlab Code

```
clc
clear all

%% Parameters
L = 1; % Length of axon in mm
D = 1e-4; % Diffusion coefficient in mm^2/s
delta_t = 1; % Time step in seconds
num_trajectories = 10000; % Number of trajectories to simulate



% Preallocation
diffusion_times = zeros(num_trajectories, 1);


%% q2.4
% Simulation
for i = 1:num_trajectories
    x = L/2; % Initial position of the protein
    while x > 0 && x < L
        delta_x = sqrt(2 * D * delta_t) * randn;
        x = x + delta_x;
        diffusion_times(i) = diffusion_times(i) + delta_t;
    end
end

edges = 0:75:max(diffusion_times);
% Histogram of diffusion times
histogram(diffusion_times,edges, 'Normalization', 'pdf');
title('PDF of Diffusion Times');
xlabel('Diffusion Time (s)');
ylabel('Probability Density');
grid on;


%% q2.5

mean_diff = mean(diffusion_times);
var_diff = var(diffusion_times);

%% q3.1

v = 1/mean_diff;

figure(2)

% Define the function
```

```
p = @(t) v * exp(-v * t);

% Plot the function over a specified range of t
% For example, from t = 0 to 10000 seconds
t_range = linspace(0, 10000, 10000);
plot(t_range, p(t_range),"LineWidth",1,'DisplayName','PDF for
    decay');

hold on

[f, xi] = ksdensity(diffusion_times);

plot(xi,f,'LineWidth',1,'DisplayName','PDF for defusion')

% Add labels and title
xlabel('Time(s)');
ylabel('Probability Density');
title('Comparison between distribution of decay and diffusion'
    );
grid on;
xlim([0, 9000])
legend




%% q3.3

t_dec = -log(rand(num_trajectories,1))./ v;
faster = t_dec < diffusion_times;
prob = sum(faster)/num_trajectories;


%% q3.4
new_diff = [];
new_dec = [];
for i = 1:num_trajectories
    if t_dec(i) > diffusion_times(i)%%diff before dec
        new_diff = [new_diff diffusion_times(i)];
    end
    if t_dec(i) < diffusion_times(i)%%dec before diff
        new_dec = [new_dec t_dec(i)];
    end
end

new_mean_dec = sum(new_dec)/length(new_dec);
new_mean_diff = sum(new_diff)/length(new_diff);
```