1 Setup of a Simulation

A few words about how to setup simulation experiments. If we consider the reaction

\[ A + B \leftrightarrow C \]

as an example, we need to specify reaction rates, \( k_1, k_2 \) for the forward and backward reactions. We need also to specify the initial condition, i.e., \( a(0), b(0), c(0) \). An equilibrium solution satisfies,

\[ k_2 c^* = k_1 a^* b^* = k_1 (\alpha - c^*)(\beta - c^*) \]

In complex problems it may be quite difficult to compute the equilibrium value, and instead of specifying \( k_1, k_2 \) we can specify the equilibrium values, \( a^*, b^*, c^* \). In this case \( k_1, k_2 \) are not arbitrary, they satisfy,

\[ \frac{k_1}{k_2} = \frac{c^*}{a^* b^*}. \]

2 Estimating Fluctuations

A simulation of one of the basic reactions we have described so far, show that regardless of the initial conditions the solution reaches equilibrium around which it fluctuates. The fluctuation is very important in biology, and we will analyze it in more details in this section. We will demonstrate the analysis on a very simple equation

\[ A \leftrightarrow X \] (1)

Our goal here to to start with the master equation and derive from it an approximation, called the Fokker-Planck equation, which we can solve approximately, getting accurate enough estimates for the level of fluctuations in terms of the different parameters in the problem, such as molecular abundance and reaction rates. As before we identify a conserved quantity and simplify the master equation to include less variables. Here \( a(t) + x(t) = \alpha \), where \( \alpha = a(0) + x(0) \) The transition probabilities are

\[ P(x \to x - 1) = k_2 \Delta t x + O(\Delta t^2) \]
\[ P(x \to x + 1) = k_1 \Delta t a + O(\Delta t^2) = k_1 (\alpha - x) \Delta t + O(\Delta t^2) \]
\[ P(x \to x) = 1 - \Delta t k - 1(\alpha - x) - k_2 x \Delta t + O(\Delta t^2) \] (2)
Notice that if the system is in a vicinity of a value $\tilde{x}$ such that $\Delta t k_2 \tilde{x} < \Delta k_1 (\alpha - x)$, then the system is more likely to go toward smaller values of $x$. On the contrary, if $\Delta t k_2 \tilde{x} > \Delta k_1 (\alpha - x)$, the system will go toward larger values of $x$. This follows from the above transiting probabilities.

The value $x^*$ satisfying

$$k_2 x^* = k_1 (\alpha - x^*)$$

defines a point where the system is likely to go up or down with equal probabilities. This is the mean value of $x$, also predicted by the ODE for this reaction. We introduce some notation to simplify the analysis, and also to make it more general.

$$P(x \rightarrow x + 1) = \Delta t^+(x)$$
$$P(x \rightarrow x - 1) = \Delta t^-(x)$$

(3)

The master equation is rewritten as

$$P(x, t + \Delta t) = t^-(x + 1)P(x + 1, t) + t^+(x - 1)P(x - 1) + (1 - t^-(x) - t^+(x))P(x, t)$$

(4)

Letting $t \rightarrow 0$ we obtain a differential equation

$$\frac{\partial P}{\partial t} = [t^-(x + 1)P(x + 1) - t^-(x)P(x)] + [t^+(x - 1)P(x - 1) - t^+(x)P(x)]$$

(5)

At equilibrium we have

$$t^-(x + 1)P(x + 1) - t^-(x)P(x) + t^+(x - 1)P(x - 1) - t^+(x)P(x) = 0$$

(6)

This equation is hard to solve, and we will approximate it using a differential equation that is easier to handle. Recall that in one of the first lectures we discussed Taylor theorem and used it to construct difference equations approximating first and second derivatives. We will use it here to derive a differential equation. We have derived,

$$\frac{1}{\Delta x} [P(x + \Delta x, t) - P(x - \Delta x, t)] \approx \frac{\partial P}{\partial x}$$
$$\frac{1}{\Delta x^2} [P(x + \Delta x, t) - 2P(x, t) + P(x - \Delta x, t)] \approx \frac{\partial^2 P}{\partial x^2}$$

(7)
In the master equation above we have functions evaluated at \(x + 1\), \(x - 1\), and \(x\). We will use Taylor for the products \(t^+(x \pm 1)P(x \pm 1)\), giving

\[
t^+ (x - 1)P(x - 1, t) \approx t^+(x)P(x, t) - \frac{\partial}{\partial x}t^+(x)P(x) + \frac{1}{2} \frac{\partial^2}{\partial x^2}t^+(x)P(x)
\]

\[
t^- (x + 1)P(x + 1, t) \approx t^-(x)P(x, t) + \frac{\partial}{\partial x}t^-(x)P(x) + \frac{1}{2} \frac{\partial^2}{\partial x^2}t^-(x)P(x)
\]

Substituting these in the differential master equation we get,

\[
\frac{\partial P}{\partial t} = -\frac{\partial}{\partial x}[t^+(x) - t^-(x)]P(x, t) + \frac{1}{2} \frac{\partial^2}{\partial x^2}[t^+(x) + t^-(x)]P(x, t)
\]

We introduce the following coefficients,

\[
V(x) = t^+(x) - t^-(x) \quad D(x) = t^+(x) + t^-(x)
\]

and write the Fokker-Planck equation as

\[
\frac{\partial P}{\partial t} + \frac{\partial}{\partial x}V(x)P(x, t) = \frac{1}{2} \frac{\partial^2}{\partial x^2}D(x)P(x, t)
\]

In our example

\[
t^+(x) = k_2(\alpha - x) \quad t^-(x) = k_1 x
\]

and

\[
V(x) = -(k_1 + k_2)x + k_2\alpha \quad D(x) = k_2\alpha + (k_1 - k_2)x
\]

To obtain an approximation for \(P(x, t)\) at equilibrium. We denote by \(x^*\) the equilibrium value, \(V(x^*) = 0\), \(x^* = \frac{k_2}{k_1 + k_2}\). We write \(V(x)\) as,

\[
V(x) = -(k_1 + k_2)(x - \frac{k_2}{k_1 + k_2}) \equiv -\gamma(x - x^*)
\]

\[
D(x) = k_2\alpha + (k_1 - k_2)x^* + (k_1 - k_2)(x - x^*) = D^* + (k_1 - k_2)(x - x^*)
\]

An approximation to the equilibrium solution is given by

\[
\frac{\partial}{\partial x}[-\gamma(x - x^*)P_{eq}] = \frac{1}{2} \frac{\partial}{\partial x}D^* P_{eq}
\]

Integrating once and using the fact that \(P\) vanishes at infinity,

\[ -2(x - x^*)\gamma P_{eq} = \frac{\partial}{\partial x}D^* P_{eq} \]
or
\[
\frac{1}{P_{eq}} \frac{\partial P_{eq}}{\partial x} = -\frac{2\gamma}{D^*} (x - x^*)
\]

Integrating once more we have
\[
\log P_{eq} = -\frac{\gamma}{D^*} (x - x^*)^2 + c_0
\]
or the more familiar form,
\[
P_{eq} = \frac{1}{Z} e^{-\frac{\gamma}{D^*} (x - x^*)^2}
\]
where $Z$ is a normalization constant. From this we conclude that the trajectories of our system fluctuate around the mean $x^*$, and the size of the fluctuations is roughly $\sqrt{\frac{D^*}{\gamma}}$. In our case this means fluctuation of
\[
\sqrt{\frac{k_2 \alpha + (k_1 - k_2) x^*}{k_1 + k_2}} = \sqrt{x^* (1 + \frac{k_1 - k_2}{k_1 + k_2})} = \sqrt{x^*} \frac{2}{1 + \frac{k_2}{k_1}}
\]