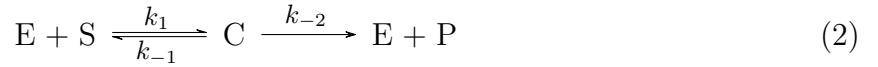Here, we are going to outline the mathematical steps to derive a solution for a kinetic problem. Here, we consider a part of a signalling cascade as our problem. The reactions in this mechanism are as following:

$$E_i + X \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} E \tag{1}$$

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C \xrightarrow{k_{-2}} E + P \tag{2}$$

where k_a, k_{-a}, k_1, k_{-1} and k_{-2} are the rate constants for individual steps in each reactions. X is also subject to degradation with rate constants k_d:

$$\xrightarrow{k_x} X \xrightarrow{k_d} \tag{3}$$
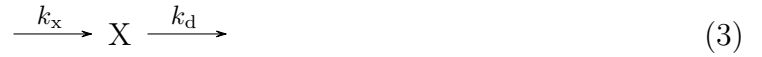
where k_x is the rate of production of X.

The goal is to obtain the mean first passage time for p (the number of molecules of P) reaching a particular level p_m and the standard deviation of this quantity.

As a first step toward solving this problem, we derive the chemical master equation (CME) for this model reactions. To get the CME, we need to make some assumptions. We assume that the amount of X (X_0) and S (S_0) is much greater than the the total amount of enzyme (E_0). We suppose that the the production and degradation of X are fast (faster than the other reactions) and also the rate constants $(k_x$ and $k_d)$ are such that X accumulates to a high level, much higher than E_0. In this conditions,the level of X molecules will reach a steady-state.

Thus, we have the following mass conversation equations:

$$s + p + c = S_0$$

$$e_i + e + c = E_0$$

$$x + e + c = X_0$$

where s, p, c, e_i, e and x denote integer values that the random variables $S(t)$, $P(t)$, $C(t)$, $E_i(t)$, $E(t)$ and $X(t)$ representing the number of molecules of each reactant at time t can take respectively.

The conservation equations enable us to describe the state of the system by just three parameters. Here, I take e, p and c.

So the CME for this reactions is

$$\frac{dP_{e,p,c}}{dt} = \kappa_a(e_i + 1)(x + 1)P_{e-1,p,c}$$
$$+\kappa_{-a}(e + 1)P_{e+1,p,c}$$
$$+\kappa_1(e + 1)(s + 1)P_{e+1,p,c-1}$$
$$+\kappa_{-1}(c + 1)P_{e-1,p,c+1}$$
$$+\kappa_{-2}(c + 1)P_{e-1,p-1,c+1}$$
$$+\kappa_x P_{e,p,c}$$
$$+\kappa_d(x + 1)P_{e,p,c}$$
$$-P_{e,p,c}[\kappa_a(e_i)(x) + \kappa_{-a}(e) + \kappa_1$$
$$(e)(s) + \kappa_{-1}(c) + \kappa_{-2}(c) + \kappa_x + \kappa_d(x)].$$

$$(4)$$

where all rate constants are corresponding stochastic ones.

From the Assumptions and conservation equations ,mentioned above, we can Assume that

$$e_i = E_0 - e - c$$

$$s = S_0$$

$$x = X_0$$

Now we write the chemical master equation 4 based on these assumptions:

$$\frac{dP_{e,p,c}}{dt} = \kappa_a(E_0 - e - c + 1)(X_0 + 1)P_{e-1,p,c}$$
$$+\kappa_{-a}(e + 1)P_{e+1,p,c}$$
$$+\kappa_1(e + 1)(S_0 + 1)P_{e+1,p,c-1}$$
$$+\kappa_{-1}(c + 1)P_{e-1,p,c+1}$$
$$+\kappa_{-2}(c + 1)P_{e-1,p-1,c+1}$$
$$+\kappa_x P_{e,p,c}$$
$$+\kappa_d(X_0 + 1)P_{e,p,c}$$
$$-P_{e,p,c}[\kappa_a(E_0 - e - c)(X_0) + \kappa_{-a}(e) + \kappa_1(e)(S_0)$$
$$+\kappa_{-1}(c) + \kappa_{-2}(c) + \kappa_x + \kappa_d(x)].$$

$$(5)$$

The next step is introducing the joint generating function

$$F(u, v, w, t) = \sum_{E=0}^{E_0} \sum_{p=0}^{S_0} \sum_{c=0}^{E_0} u^e v^p w^c P_{s,p,x}. \tag{6}$$

Multiplying (5) by $u^e v^p w^c$ and summing over possible values of s, p and x will give us the partial differential equation for the generating function F(u,v,w,t).

$$\frac{dF(u, v, w, t)}{dt} = f(u, v, w, \frac{dF}{du}, \frac{dF}{dw}, \frac{dF}{du}) \tag{7}$$

We can solve the resultant PDE by using the method of characteristic. It seems that this method is an appropriate one for dealing with this kind of PDEs. However, making approximations for solving this pde is an essential.

Now, we can obtain the distribution for the number of each component of the reaction. Thus, we just need to put $u = 1$ and $w = 1$ in the joint generating function: generating function will be just a function of v $(F(v, t))$ or it just describes the distribution for the number of

P molecules. We can also get the mean and the variance easily from the generating function.

By expanding $F(v,t)$ in v, and using (6), we can obtain the distribution for the number of P molecules $(P(p,t))$.

The next step is deriving the 'propagator' probability $P_{p|p'}(t)$, which is the probability of having p number of P molecules at time t given p' molecules initially. We can get that from the generating function since we have this relationship between $F(v,t)$ and $P_{p|p'}(t)$

$$F(v,t) = \sum_p P_{p|p'}(t) v^p$$

Using $P_{p|p'}(t)$ and $P(p,t)$, we can obtain the distribution for the first passage time for p reaching a particular level p_m $(f_{p_m}(t))$ since we have

$$P(p_m,t) = \int_0^t dt' f_{p_m}(t') P_{p_m|p_m}(t-t')$$

This integral is a Volterra integral equation of the first kind and can be solved numerically.

Finally, we can get the mean and the variance for the distribution for the first passage time. They can be obtained using the definition of mean and variance

$$<p_m> = \sum_{p_m} p_m f_{p_m}(t)$$

$$\sigma^2 = <p_m^2> - <p_m>^2$$