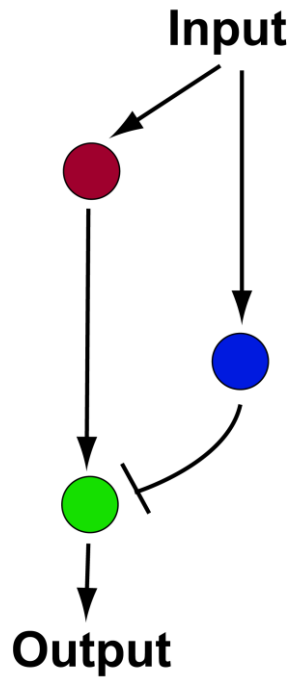


Modeling Molecular Processes-1

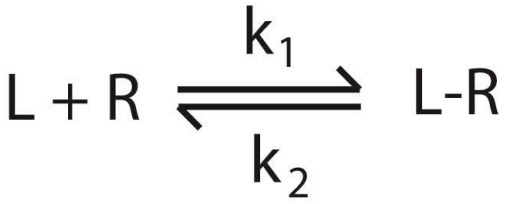
Mathematical formulations for elementary molecular processes

Ordinary Differential Equations (ODEs) representing rate of change of concentration of molecules

These equations are often based on Law of Mass Action

Some time multiple steps are clubbed together to create one elementary process and is represented by one ODE

Ligand Binding



Forward rate $= k_1.[L][R]$

Reverse rate $= k_2[L-R]$

$$\frac{d[L-R]}{dt} = k_1.[L][R] - k_2[L-R]$$

$$\frac{d[R]}{dt} = -k_1.[L][R] + k_2[L-R]$$

$$\frac{d[L]}{dt} = -k_1.[L][R] + k_2[L-R]$$

Ligand Binding

$$L + R \underset{k_2}{\overset{k_1}{\rightleftharpoons}} L\text{-}R$$

At steady state, $\frac{d[L-R]}{dt} = 0$

$$\therefore \quad k_1.[L][R] - k_2[L-R] = 0$$

$$\Rightarrow k_1.[L][R] = k_2[L-R]$$

$$\frac{k_1}{k_2} = \frac{[L-R]}{[L][R]} = K_{eq}$$

Affinity of the ligand is usually represented by Dissociation Constant, K_d

$$K_d = \frac{1}{K_{eq}} = \frac{k_2}{k_1} = \frac{[L][R]}{[L-R]}$$

Unit of k_1: 1/M.sec

Unit of k_2: 1/sec

Unit of K_d: M

Simulating Ligand Binding

$$\frac{d[R]}{dt} = -k_1.[L][R] + k_2[L-R]$$

$$\frac{d[L]}{dt} = -k_1.[L][R] + k_2[L-R]$$

$$\frac{d[L-R]}{dt} = k_1.[L][R] - k_2[L-R]$$

Assume total ligand and total receptor remain constant

Represent free R and free L in terms of LR

$$[L] = [L]_T - [L-R]$$

$$[R] = [R]_T - [L-R]$$

Reduced and make non-redundant ODE:

$$\frac{d[L-R]}{dt} = k_1.[L][R] - k_2[L-R]$$

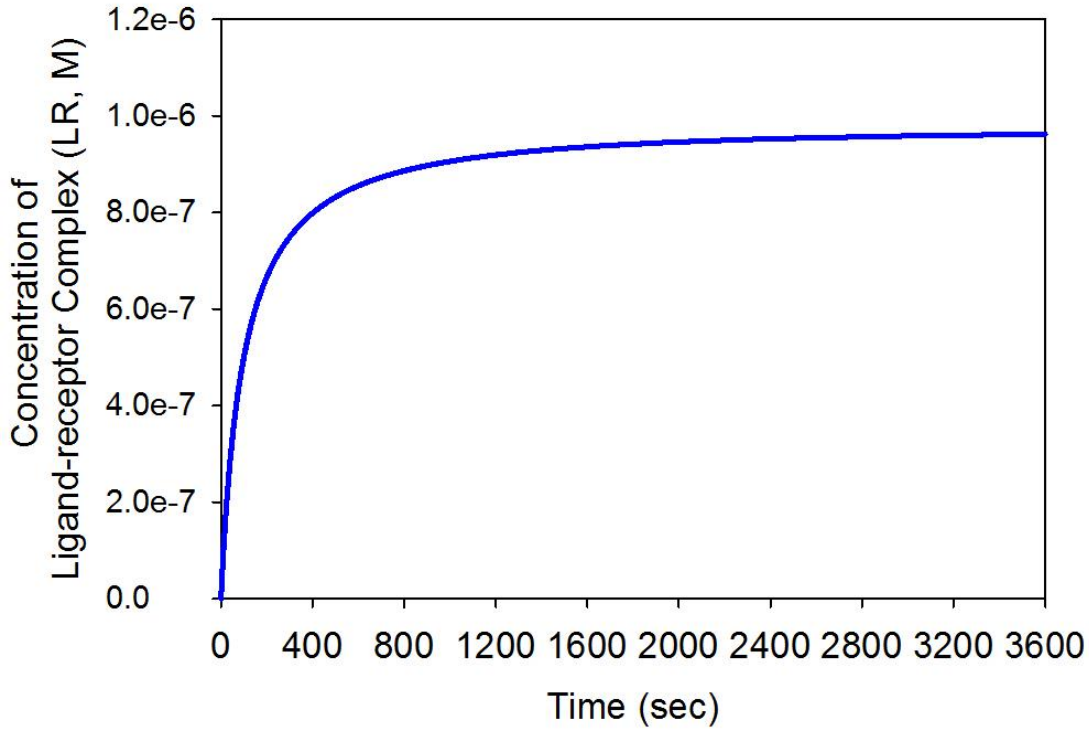
$$\Rightarrow \frac{d[L-R]}{dt} = k_1.([L]_T - [L-R]).([R]_T - [L-R]) - k_2[L-R]$$

Simulating Ligand Binding

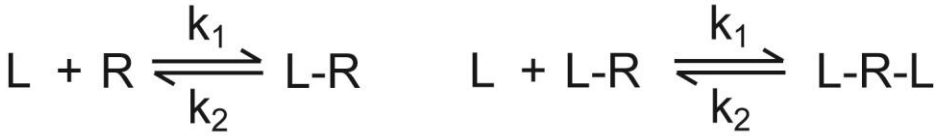
JSim code

```
math receptor_ligand
{ realDomain t;
        t.min = 0;t.delta = 0.1;t.max = 3600;

  //Define dependent variable
         real LR(t);

  //Define parameters
         real k1 = 10^(4); //1/M.sec
         real k2 = 10^(-5); //1/sec
         real LT = 10^(-6); // M
         real RT = 10^(-6); // M


  // Initial value
        when (t = t.min){LR =0;}

  // ODEs
          LR:t =  k1*(LT-LR)*(RT-LR) - k2*LR;
}
```

Simulating Ligand Binding



Ligand Binding to Bi-valent Receptor



$$\frac{d[L-R]}{dt} = 2.k_1.[L][R] - k_2[L-R] - k_1.[L][L-R] + 2.k_2[L-R-L]$$

$$\frac{d[L-R-L]}{dt} = k_1.[L][L-R] - 2.k_2[L-R-L]$$

Use conservation of ligand and receptor

$$[R]_T = [R] + [L-R] + [L-R-L]$$

$$[L]_T = [L] + [L-R] + 2.[L-R-L]$$

Production and degradation

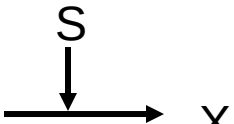
Constitutive production

$$\frac{d[x]}{dt} = k_s$$

Constitutive degradation

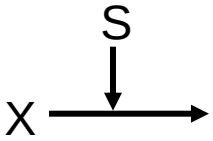
$$\frac{d[x]}{dt} = -k_d[x]$$

Induced production



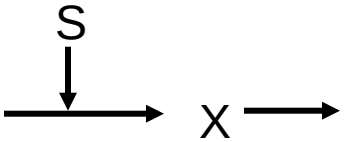
$$\frac{d[x]}{dt} = k_s.S$$

Induced degradation



$$\frac{d[x]}{dt} = -k_d.S.[x]$$

Combined production and degradation:



$$\frac{d[x]}{dt} = k_s.S - k_d[x]$$

Key points:

1. ODEs are formulated for elementary processes representing rate of change in concentrations of molecules.
2. Such ODEs are often based on Law of Mass Action
3. Often multiple steps are clubbed and considered as a single step
4. It is better to keep the ODEs as simple as possible based on assumptions and existing knowledge of the system
5. Number of variables can be reduced by considering conservation.
6. Ligand-receptor binding can be modeled using Law of Mass Action
7. Be careful of possible ways of the process and stoichiometry of reaction