BMT-72106, INTRACELLULAR DIFFUSION MODEL

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ABSTRACT

Diffusion is random movement of molecules but has a net direction toward regions of lower concentration in order to reach an equilibrium.[1] There can be simple passive diffusion occuring when small molecules pass through the lipid bilayer of a cell membrane while another kind of diffusion, facilitated diffusion occurs depending on carrier proteins imbedded in the membrane to allow specific substances to pass through only. Intuitively, the rate of diffusion is affected by properties of cell, the diffusing molecule, and the surrounding solution. To have a deeper insight of its process in molecular, we consider it from microscopic point of view, simulating the molecule as a random walker with the diffusion coefficient according to Stokes-Einstein equation and then through simulation of the ligand-enzyme binding system, we are able to see the dynamics of the ligand during the diffusion among the surrounded enzymes.

1. INTRODUCTION

Diffusion in molecular scale can be described as a random walk process[2]The mean-square diffusion distance or displacement of a molecule in two dimensions after time t can be calculated from equation $< x^2 >= 4Dt$
where x^2 is the mean-square diffusion distance and D is the diffusion coefficient. For a small molecule (under 1 kDa) the diffusion coefficient at body temperature is around $5 * 10^{10} m^2/s$. The most well known equation to relate the molecular size and diffusion coefficient is the Stokes-Einstein equation: $D = \frac{k_B T}{6\pi * \eta * R}$,
where k_B is Boltzmanns constant, T is the absolute temperature, η is the dynamic viscosity and R is the radius of the molecule. This equation works quite well for large spherical molecules. Diffusion is usually described as "net movement" in biological study.[3] Although the diffusion is analogue to the random walk process, for an individual atoms, ions or molecules move "randomly", this motion is actually the result of "collisions" with other ions. Because such movement of a substance within a mixture is governed by kinetic energy related to temperature, pressure and etc., some related phenomenone of the diffusion on cellular scale can also be detected in daily life. For instance, the soak of ankle into the water, oxygen breath in and carbon-dioxide comes out and etc. In the cellular scale, the diffusion through barriers is also one interesting example. Some small molecules can cross small membrane pore while other membranes only allow certain types of molecules crossing over. Memberane's selectively permeability is thus studied as the subject of much current research along with membrane function. Interestingly, because membranes are thin structures (mentioned also in the instruction with D being around $5 * 10^{10} m^2/s$), the diffusion distance is also really small making the molcule transportation in short distance only usually. Thinking on time scale, the diffusion distance is proportion to the diffusion coefficient. If the diffusion distance is overlarge, than the time will also be very large if the diffusion coefficient is not changed. Thus, the passive diffusion (just diffusion only) enables molecules to move over micron-length scales within seconds.And the transport of molecules in lager cells becomes a problem which makes passive diffusion alone insufficient to deliver proteins from nucleus at one end of the cell to the other end. Even in smaller cells, diffusion is not fast enough to enable the necessary movement of large assemblies. To overcome the limitations of passive diffusion and to be able to target specific proteins to particular regions, cells use chemical energy to actively move molecules and other large structures through the cytoplasm, a process called active transport. Accordingly, back to macro understanding, such process, active transport is also used to move ions across a membrane against a concentration gradient consuming energy. Thus, the advantage of the diffusion is that it does not need to cost energy while moving or transporting and it takes place based on concentration gradient. Some transfer of energy happens using diffusion process. For instance, the transfer of energy through ATP. However, it is not able to transfer against concentration gradient and it cannot make the transport in large distance. As in the Stokes-Einstein, the diffusion coefficient increases with the Tamperature increases which is more related to the kinetice property of molcule according to the drift velocity. The force under isothermal contains the diffusion force which is directly related to temperatue because in atomic scale, the atom can only move by substituting place with another atom. Substitutional lattice diffusion is often

contingent upon the availability of point vacancies throughout the crystal lattice. Diffusing particles migrate from point vacancy to point vacancy by the rapid, essentially random jumping. The vacancy is changed with temperature. ————

2. SIMULATION OF LIGAND ENZYME BINDING

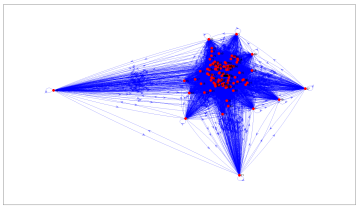

Fig. 1. transition matrix state

One typical way to study the Random walker is to use the markov chain transition matrix. The total states are calculated with iteration of each step's possibility. Here, we have 6 evenly possible choice for each iteration and thus basically for each transition element its either 0 or 1/6 and it is a large sparse matrix because our ligand (walker) can are set to move one nm each step.

$E[K] = \tau(I + T + T^2 + \cdots) * ones$
$= \tau(I-T)^{-1} * ones$ Here, for calculating in a more accurate way, instead of using 3D independent grids for each dimension as 1D separately, I convert the 3D coordinates into one matrix with index mapping them back to the coordinate. It can be seen that the mean steps being stationary with large enzyme numbers is less than 100. The total states is the expectancy of the total number of the transition states which lead to their final state. In our simulation, for enzymes less than 1250, the required steps are more than thousand (maximum being 5170 and thus not calculated here. For enzymes larger than 1250, the result is less than 100.

As we can see in the figure, the blue line shows the simulation which we got the largest steps more than 7000 for finding the enzymes which occurs at around with 250 enzymes while the lowest required steps converge to less than 50 after enzymes more than 1250. In contrary, the mean steps required is around 4250 with 1 enzyme and the converged status occurs with more than 1500 enzymes in the grids. But it started to reach the final state(ligand managing to find the enyme) faster with enzyme numbers being 750. Generally, one thing is sure is that with the enzymes increasing, the steps required to find the enzyme is decreasing. And ofcourse, there is always the inormal situation. Here, for some simulations, the ligand keeps the same with the enzymes changing.

stepsenzymes.PNG

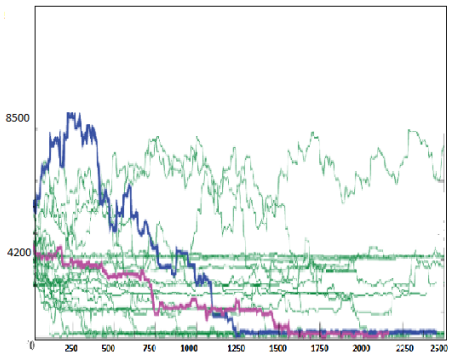

Fig. 2. MC steps vs enzyme numbers

3. FURTHER EXPLORATIONS

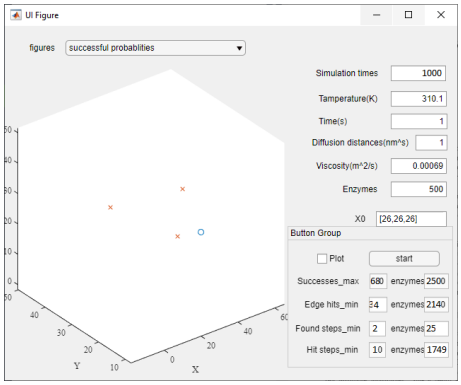

Fig. 3. Application used.

The application used here is programmed in MATLAB. The simulation times is defautly set as 1, temperature as body temperature, time as 1 second and diffustion distance as $1nm^2$. The viscosity is $0.00069m^2/s$. The enzymes is from 1 to the set number and the initial coordinates ins $X0 = [26, 26, 26]$. As the move of the ligand is shown in the Random walker figure, it will stopped with three conditions:

1)steps larger than set
2)ligand hits the edges
3)ligand finds the enzymes

The maximum successes numbers is 680 which can be found wih enzyme number being 2500 and the minimum hits edge numbers is actually 340 when enzymes number is 2140. When the enzyme number is 25, we reach the minimum found steps which is 2. And with the enzyme numbers being 1749, we got the minimum hit edge steps which is 10. Since there is outliers, the meaan vale of the success steps

which is the average steps is what we are more interested in and the maximum steps for finding the enzymes is also important because it is the upperboundary which shows us the proper lest enzyme numbers.

4. SUMMARY

In summary, we can see that the diffusion behavior of the ligand is highly related to the number of the enzymes. As the diffusion disances is in nm scale, the steps required to find the enzyme is large than thousand if there are less than 1250 enzymes. However, it reduces with the number of enzymes increases. If the number of enzymes is more than 1500. The average steps finding the enzyme successfully goes around 80 times smaller.Thus, the diffusion of the ligand is with higher rate if it is in the with the enzymes with higher concentration. Of course, because the diffusion coefficient is dependent on temperature, viscosity and diffusion distance, if we want to let ligand find the enzymes more easily, we can also rise the temperature. ——————————

REFERENCES

[1]1999 M. Beals, L. Gross, S. Harrell
[2] John Kuriyan. The Molecules of Life: Physical and Chemical Principles.
[3]Asmussen, S. R. (2003). "Markov Chains". Applied Probability and Queues. Stochastic Modelling and Applied Probability