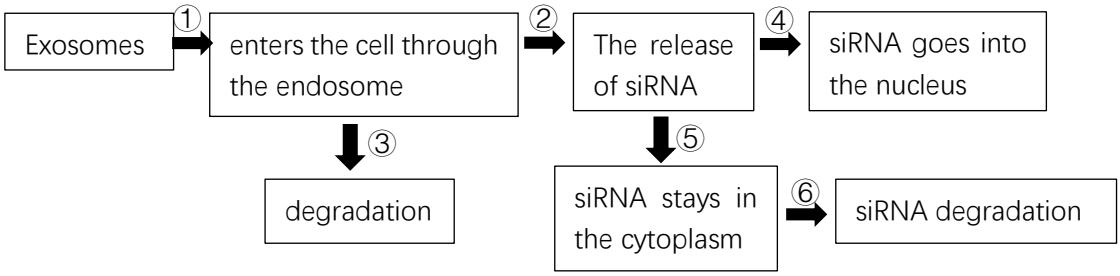
Modeling of exosome-mediated siRNA entry into cells

Background:

In our project, siRNA transmission in vivo is mediated by exosomes. Exosomes are derived from polyvesicles formed by the entrapment of intracellular lysosome particles and released into the extracellular matrix after the fusion of the extracellular membrane with the cell membrane. Various cells in human body can secrete exosomes. During the process of exosomes carrying siRNA into cells, the degradation of lysosomes and siRNA would cause the loss of siRNA. In order to evaluate the loss quantitatively, we simulated the process.

Modeling:

1. Process



2. Internalization

   Because exosomes and liposomes have similar properties, most of the constants are borrowed from liposome models. In previous models, there were up to 9, 000 liposomes that were said to be delivered to cells. And according to our measurement, the concentration of siRNA in a liposome can reach 104.The liposome enters the cell as an intra - somatic form. We hypothesize that liposomes could reach the cells at the instant they are added to the medium, we can assume that there are 9,000 molecule servers to deal with the liposomes simultaneously in the process of internalization. The time distribution is an exponential distribution with the parameter μ1 and we generate 9000 random numbers from this distribution to describe the time.

3. Next steps

   For a step, if the value of a given constant satisfies $0<\mu<1$, it can be interpreted as the probability that the molecular server processes a molecule in one second.Therefore, if there are n molecules, the probability of processing at least one molecule in one second is:

$$p_n = 1 - (1-\mu)^n$$

   There are already N molecules, but the probability Pn(1) that only one molecule is processed within a certain time interval is:

$$p_{n(1)} = n\mu\,(1-\mu)^{n-1}$$

   If we consider a shorter interval (1 ms for example), μ would be scaled down to μ'. This constant satisfies $n\mu' \leqslant 1$ and $(1-\mu')n \approx 1$. Then the probability $P(n1) \approx n\mu'$. So we choose exactly 1 ms as the interval, all the kinetic constant shrinking by one thousand times.

   For steps where the molecule can go in one of two directions, the probability p of the

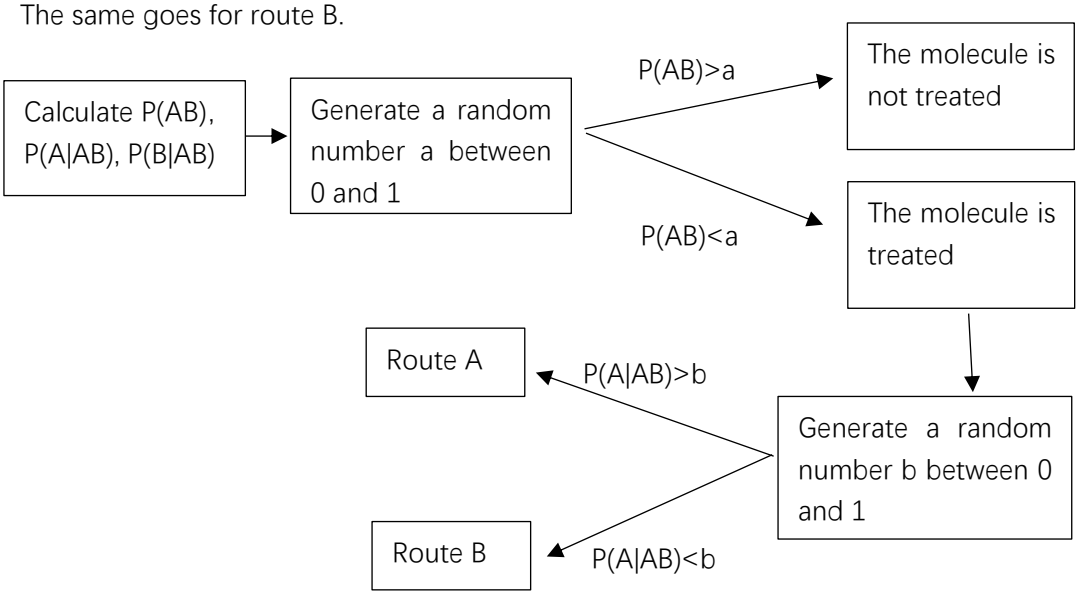
liposome/plasmid going in either direction is equal to:

$$p(AB) = p_A(1 - p_B) + p_B(1 - p_A)$$

So the probability of the molecule going the A route is:

$$p(A|AB) = \frac{p_A - p_A p_B}{p_A + p_B - 2p_A p_B}$$

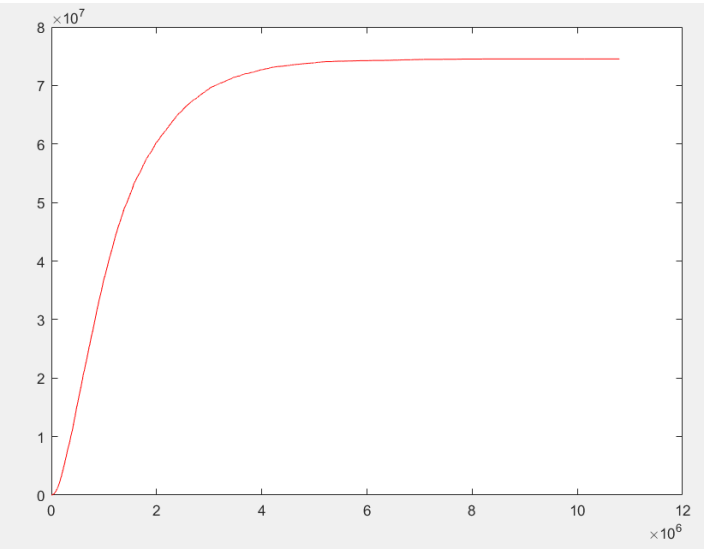
The same goes for route B.



If the molecule only have one way to go, then we only go to the step of determining the magnitude of a and P(AB).

4. Result

According to the simulation results, we mapped the changes of the number of siRNA molecules in the cytoplasm over time within three hours.It can be seen that the siRNA molecules in the cytoplasm reach saturation quickly and remain stable for three hours. There are 8×10^7 molecules of siRNA that function in the cytoplasm.



Reaction constants of each step:

	Value	Source
①	1.4	[1]
②	1.7×10^{-4}	[1]
③	8.3×10^{-5}	[2]
④	5×10^{-5}	[1]
⑤	3.5×10^{-3}	[1]
⑥	3.3×10^{-5}	[2]

1. Martin, T. M., Wysocki, B. J., Wysocki, T. A., & Pannier, A. K. (2015). Identifying intracellular pdna losses from a model of nonviral gene delivery. IEEE Trans Nanobioscience, 14(4), 455.
2. Wysocki, B. J., Martin, T. M., Wysocki, T. A., & Pannier, A. K. (2013). Modeling nonviral gene delivery as a macro-to-nano communication system. Nano Communication Networks, 4(1), 14-22.