Diffusion and Interaction between ion Ca$^{2+}$ and ion Gd$^{3+}$ in a Model Synapse: A Monte Carlo Study

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Abstract. Gadolinium (Gd$^{3+}$) is a commonly used in MRI. The role of Gd$^{3+}$ as contrast agent greatly helps to improve the quality of an image and Gadolinium entrance in a body through a diffusion process after administration. Diffusion process takes place from outside pre-synapse to inside pre-synapse through Ca$^{2+}$ channels. This process causes a delay of Ca$^{2+}$ in passing Ca$^{2+}$ channels to pre-synapse. This study aims to determine equilibrium concentration of Ca$^{2+}$ and Gd$^{3+}$ so that Ca$^{2+}$ can pass Ca$^{2+}$ channels. To address the effect of Gd$^{3+}$ concentration around Ca$^{2+}$ channels, we developed a Monte Carlo simulation on Ca diffusion and interaction with Gd. We find Gd$^{3+}$ concentration in a certain threshold can be potential as a blocker Ca$^{2+}$ diffuse entrance into pre-synapse. In another hand, an amount of Ca$^{2+}$ channels and pre-synapse terminal to continuing diffusion of vesicles to clef was important. And the trapping Gd$^{3+}$ in pre-synapse effects in diffusion delays also. These simulations identify characteristics of the interaction between Ca$^{2+}$ and Gd$^{3+}$ in Ca channels which entrance into pre-synapse through diffusion process depend on concentration with each other.

Key words: Monte Carlo Cell, Synapse, Diffusion, Contras Agents

1. Introduction

Gadolinium is chemical substances which it popularly used in magnetic resonance imaging as contrast media. The first gadolinium-based contrast agent (GBCA) available for clinical was in 1988 [1]. When Gadolinium injected into the body of the patient will be enhanced between pathological and normal anatomical structures facilitated the detection and assessment of the disease and improves the quality of the MRI images [1,2]. Behind the advantages of Gadolinium as a contrast agent, it has minor disadvantages especially for the patient with kidney disorders and has a potent blocking Calcium channel.

In 1982, G. W Bourne and J.M. Trifaro [3] found that Gadolinium ion a potent inhibitor of catecholamine and the possibility of an inhibition by Gd$^{3+}$ of the Ca$^{2+}$ mediated effects. Specifically, Gd$^{3+}$ had a parallel shift to the right of the Ca$^{2+}$ concentration [3H]noradrenaline output relationship suggesting a competitive antagonism between Ca$^{2+}$ and Gd$^{3+}$. The presence of Gd$^{3+}$ a potent block both N-type and non-N-type current of Ca Channel and in a complex fashion also [4]. A subsequent study [5], the block by Gd$^{3+}$ follows one prediction of this model, the reciprocal of the open time was a linear function of the blocking ion concentration which gadolinium ions produce some distinct kinds
of block ion channels in Xenopus oocytes i.e. a concentration-dependent reduction in channel open, in open current, and reversible inhibition of channel opening.

Diffusion is one important mechanism in daily life especial in our body. Many substances in our body transported from one part to another part by the diffusion mechanism. Likewise, many substances injected in our body distributed by diffusion including Gadolinium. This mechanism is important to explore the functions of gadolinium with respect to the effect of Gd\(^{3+}\) in the body. One of a disadvantage Gd\(^{3+}\) is block Ca channel in a synapse. Consequently, transport substance in a body disturbed. Using this information, this study wanted to know the mechanism of Gadolinium in our body especially interaction between Gadolinium (Gd\(^{3+}\)) and Calcium (Ca\(^{2+}\)) and interaction each other in a synapse. This question is addressed using Monte Carlo simulation of the synapse which consist of a part which one are presynaptic and postsynaptic. The simulation is carried out using a variety number of Gd\(^{3+}\) and Ca\(^{2+}\). The result indicated the ratio between Gd\(^{3+}\) and Ca\(^{2+}\) can be used to determine the speed blocking of Ca channel.

2. Methods
Monte Carlo Cell simulation was carried out using MCell 3.3 running on desktop computer 3.40 GHz Intel Core i7 (Windows 7). Visualization of the synapse (pre-synapse and post-synapse) and movies was made with the output of MCell using blender 2.76 which add-on with Cellblender 1.0. (www.mcell.org).

The model illustrated in Fig. 1.a represents a sketch of a synapse which consisting of two part a presynaptic and postsynaptic where two kinds ions Gd\(^{3+}\) and Ca\(^{2+}\) around presynaptic. Figure 1.b was a model synapse design with blender 2.76 consist of the presynaptic is on top with volume 0.02 \(\mu\text{m}^3\) and surface area 1.85 \(\mu\text{m}^2\) and the postsynaptic is below with volume 0.21 \(\mu\text{m}^3\) and surface area 2.07 \(\mu\text{m}^2\). Ca\(^{2+}\) competes with Gd\(^{3+}\) to diffuse into presynaptic. Ca\(^{2+}\) diffusion goes into synapses through Ca channel that on a surface of presynaptic. The presynaptic model has 23 Ca channel with 500 ions as buffer distributed randomly. Gd\(^{3+}\) diffusion outside presynaptic and attach at ions buffer as blocking the channel. Depend on time amount of Gd\(^{3+}\) totally blocking Ca channel which affect to a speed of Ca\(^{2+}\) diffusion. Physically, Gd\(^{3+}\) has the same crystallographic radius as Ca\(^{2+}\) [6] which Gd\(^{3+}\) has an ionic radius (0.938 Å) and Ca\(^{2+}\) has the ionic radius (0.99 Å) [5].

![Figure 1](image1.png)

**Figure 1.** The model synapse consisting a presynaptic and a postsynaptic (a) synapse model with ion Gd\(^{3+}\) and Ca\(^{2+}\) which Gd\(^{3+}\) blocking Ca channel of Ca\(^{2+}\) base on Neuroscience [7], (b) synapse model used in the MCell simulator.
This study used a two kinds diffusion process. The first process describes diffusion Gd$^{3+}$ to Ca channel and finally attach to Ca channel with forward rate constant $f_w$. The second process in the same time with the previous process, Ca$^{2+}$ diffusion into presynaptic through Ca channel with forward rate constant $f_w$ and backward constant $b_w$. The simulation was carried out using a set of standard parameters values (Table 1) and a time step of $1 \times 10^{-6}$ s was used for simulation with a standard parameter.

**Table 1. Standard values of the parameters used in the simulations**

| Parameter                     | Standard value                  |
|-------------------------------|---------------------------------|
| Forward rate                  | $3 \times 10^8$ cm$^2$s$^{-1}$  |
| Backward rate                 | $2 \times 10^7$ s$^{-1}$        |
| Diffusion coefficient Ca$^{2+}$| $6 \times 10^{-6}$ cm$^3$s$^{-1}$[8][9] |
| Diffusion coefficient Gd$^{3+}$| $1 \times 10^{-6}$ cm$^2$s$^{-1}$ |
| Diffusion coefficient buffer  | $0$ cm$^2$s$^{-1}$              |
| Ca Channel density            | $10^{-4}$ µm$^2$ [10]           |

3. Results and Discussion

**Blocking Ca Channel**

Calcium and Gadolinium diffusion can be described mathematically using a combination of Fick’s second law of diffusion. Diffusion through or attach on Ca channel of a presynaptic alike diffusion to N disk-like absorbers on the surface of a presynaptic which shape of a presynaptic base on a sphere. In this study, standard Ca channel density around a $10^{-4}$ µm$^2$ distribute into 23 channel (Table 1) and compared five simulations with different random number seeds for ratio 1:19 for Gd$^{3+}$ of Ca$^{2+}$ and found $t_{50} = 11.9 \pm 0.2$ ms (mean $\pm$ SD).

Fig. 2 shows how the number of Ca$^{2+}$ diffused from outside presynaptic (black line) into presynaptic (red line) through Ca channel with ratio 1:9 for Gd$^{3+}$ of Ca$^{2+}$. Ca$^{2+}$ declines quickly in the first $5.00 \times 10^{-3}$ s, then decline more gradually and reaches a steady state from 0.20 s which half-saturation occurs at $t_{50} = 6.95 \times 10^{-3}$ s. Moreover, the second part of the Fig. 2 was diffusion of Gd$^{3+}$ attaches on Ca channel become a block of Ca$^{2+}$. Ga$^{3+}$ decline gradually from an initial state and at $7.50 \times 10^{-2}$ blocking 66.8% of total area Ca channel and $t_{50} = 2.19 \times 10^{-2}$ s. In short, Ca$^{2+}$ diffused perfectly until steady state condition before Gd$^{3+}$ totally block Ca channel, indeed $t_{50}$ of Gd$^{3+}$ block Ca channel longer than $t_{50}$ of Ca$^{2+}$ diffused.

**Figure 2.** Result simulation of MCell ratio Gd$^{3+}$ and Ca$^{2+}$ 1:9. Ca$^{2+}$ diffused from outside presynaptic into presynaptic through Ca channel and $t_{50}$ Ca$^{2+}$ faster than $t_{50}$ Gd$^{3+}$ blocking Ca Channel.
Effect of Gd$^{3+}$

Fig. 3 shows the relation between the logarithms of the Ca$^{2+}$ number and output of Ca$^{2+}$ number. In this study, a number of Ca$^{2+}$ increase from 500 to 5000 in the absent as well as presence of Gd$^{3+}$ and complementary to this, number Gd$^{3+}$ was 500. The presence of Gd$^{3+}$ makes diffusion of Ca$^{2+}$ disturbed because wide of Ca channel be smaller. Thus, there was a shift to the right side of the Ca$^{2+}$ output of absent Gd$^{3+}$ in the presence of Gd$^{3+}$. The result of the simulation suggested the possibility of an inhibitor by Gd$^{3+}$ of Ca$^{2+}$ mediated effect and competitive antagonism between Ca$^{2+}$ and Gd$^{3+}$.

The increased of Gd$^{3+}$ in synapse had the effect at wide a shift between absent and a presence of Gd$^{3+}$. It has been shown that the presence of Gd$^{3+}$ had a disadvantage in an excessive number because it can because delays transport Ca$^{2+}$ diffuse into presynaptic.

![Figure 3](image3.png)

**Figure 3.** Effect of Gd$^{3+}$ attached to Ca Channel and blocking diffusion of Ca$^{2+}$ at 0.01 s. In the figure, black line was absence Gd$^{3+}$ and red line was presence Gd$^{3+}$ in Ca$^{2+}$ which Ca$^{2+}$ increase stepwise.

Speed of Blocking

Fig. 4 summarizes the result of simulation Gd$^{3+}$ block of Ca$^{2+}$ diffused into presynaptic. As synapse gets more, Ca$^{2+}$ collide each other Ca$^{2+}$ and Gd$^{3+}$ as elastic collisions. Furthermore, Ca$^{2+}$ diffused into presynaptic through Ca channel suddenly collide with ions buffer. In contrast, Gd$^{3+}$ inelastic collision with buffer ions and produce a blocking buffer on Ca channel. It is apparent that increasing number of Gd$^{3+}$ in synapse had an effect at speed blocking Ca$^{2+}$ pass Ca channel.

![Figure 4](image4.png)

**Figure 4.** Result of simulation dependent time of Gd$^{3+}$ blocking Ca channel at variety ratio Gd$^{3+}$ and Ca$^{2+}$ (a) all range time (0-0.075s), (b) blocking Ca channel stepwise 20%
The variation ratio $Gd^{3+}$ and $Ca^{2+}$ from lower to the higher number of $Gd^{3+}$ shows a result that higher number of $Gd^{3+}$ has the higher speed for blocking. Fig. 4.a shows a relation between times and numbers of ion $Gd^{3+}$ blocking Ca channel. In the lowest and a second lowest ratio of $Gd^{3+}$: $Ca^{2+}$ (1:19) and (1:9), all $Ca^{2+}$ successfully diffused into presynaptic and reach steady state before all $Gd^{3+}$ blocked Ca channel. The ratio of $Gd^{3+}$: $Ca^{2+}$ (2:8) until (5:5) more than enough was able to block all of Ca channel albeit with different duration. The increasing number of $Gd^{3+}$ resulted in the duration of totally blocking of Ca channel shorter. On the other hand, the relation between blocking area in percent and time shows at Fig. 4.b. The higher the percentage of $Gd^{3+}$ to $Ca^{2+}$ affects the speed closing Ca channel and at the low and high $Gd^{3+}$ gave exponential function relation to every doubling area blocking come up linear function.

Thus, the results at Fig. 4 possible to calculation amount of $Gd^{3+}$ to injection getting the best image in MRI treatment.

4. Conclusion
Monte Carlo successfully simulated interaction between $Ca^{2+}$ and $Gd^{3+}$ which antagonism of $Ca^{2+}$ by $Gd^{3+}$ and $Gd^{3+}$ as blocker diffusion process in synapse. The result of this investigation provides a framework for determining how specific ratio between $Gd^{3+}$ and $Ca^{2+}$ so that diffusion still happen but $Gd^{3+}$ can give another advantage. The speed of diffusion $Ca^{2+}$ into presynaptic and speed of $Gd^{3+}$ blocking of Ca channel depends on ratio between $Ca^{2+}$ and $Gd^{3+}$. The higher number of $Gd^{3+}$, then an impact on the speed blocking Ca channel increase.

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