A Cooperative Molecular Communication for Targeted Drug Delivery

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Abstract. The lack of actively targeted nanoparticles and a low drug concentration in lesions are two of the main problems in drug delivery. This paper proposes a cooperative molecular communication system for drug delivery, electromagnetic control in the lead with bacteria followers. The leading particle is consisted by two function: could be controlled by electromagnetic field, and release attractant molecules. This cooperative scheme provides actively targeted ability by electromagnetic control, furthermore it expands the impact range of chemotactic substances to improve the chemotactic efficiency. To approach the specific position, this paper proposes electromagnetic field to control the nanoparticles, while bacteria could search the larger concentration positions and get closer to the leading particles. This paper develops mathematical modelling for the proposed model, as well as the self-adapted concentration gradient field searching algorithm. Finally, this paper performs biologically realistic simulation experiments to evaluate the performance of the proposed model.

Keywords: Molecular communication · Cooperative communication · Targeted drug delivery

1 Introduction

The possibility of engineering nanoparticles that selectively detect and delivery to the cancer cells has been developed for last a few decades. However, [1] revealed that a median of 0.7% of the injected dose (ID) of the nanoparticles reached the tumor, and delivery efficiency has not well improved. If we improve delivery efficiencies, the injection volume of drug encapsulation strategy for nanoparticles would decrease. Biodegradable semiconductor materials [2] combined with bio-inspired molecular communications (MC) [3,4], will find important applications in controllable drug delivery. More important, the process

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of targeted drug delivery process can be viewed as a molecular communication system that uses principles beyond classical electromagnetism [3]. An engineered transmitter releases nanoparticle into a fluid propagation medium. These drug nanoparticles are regarded as information carrier; thus, the concentration of nanoparticles is encoded as message. The propagation of particles is divided into passive (e.g., diffusion) or active (e.g., with molecular motors) transport mechanism. The reception process donates that particles eventually received at a selectively receiver (e.g., ligand-based receptors), where messages are decoded. Under this framework of MC, it delivers drug messages (healing actions) from the transmitter location (injection site) to the receiver location (targeted site).

In [6], magnetism-sensitive molecules are used as the information carrier, which can be controlled to some extent by an external field and observed and monitored in real-time with existing imaging technology, the corresponding MC scheme is named touchable communication (TouchCom). However, only a few numbers of particles can be controlled by external electromagnetic filed. In [5], they proposed a leader-follower-based MC, follower bio-nanomachines move according to the attractant gradient established by leader bio-nanomachines. We follow part of the idea leader-and- follower in [5]. As different from [5], the followers are bacteria and the leading particle is the in the motion by external electromagnetic filed.

Cooperative Communication is a technology used relay nodes multi-user environment and the multiple-input multiple-output system to increase the communication capacity this is proposed by [7]. Here we define the source node for the leading particle, the relay nodes denotes that be released by leading particle as attractant molecules to enhance the efficiency .In the drug delivery application, various methods could be considered in precise delivering the drugs, the chemotaxis model has been created by [8–10], the electromagnetic model for the molecular is also had been established by [8] and other models such as the hydrogen-bonding based electronic transmission system created by [11]. However, their models are hardly ever mentioned and tested the cooperative communication system. Cooperative molecular communication system could be the effective MIMO system for high capacity transmitting too. While we are putting quantitative concentration particles in an environment, the particles could attract the bacteria in damaged tissue or the bacteria already included the drugs and around the attractant. As result, the position with larger concentration would attract more bacteria than the position with less concentration so the number of bacteria around the destination is much larger than with no attraction source. Based on the it we propose a model which explicating the chemotaxis to enhance the efficiency of the molecular communication system.

Inside the human body, there're innumerable cross of vessels and to get to the precise position of destination there's an effective navigating system by controlling the electromagnetic field. The whole system is proposed by [6], the TouchCom devices and testing show the practicability of this model. So, we assume that there's a kind of particle is the derivative of an organic molecule and bacteria could be attracted by it. And it should be merged by the metal ion so

the electromagnetic devices could control the positions, velocity and accelerate of the source particle. While it's getting closer to the destination, the leading particle will release attractant molecules. During its route, the bacteria injected before will randomly act, when the attractant molecules' concentration reached the bacteria's minimum sensing band, the bacteria they attracted would try to get closer to the attractant. And then the bacteria follow the particles to the destination. Here we show the Fig. 1 to reveal the details of our model.

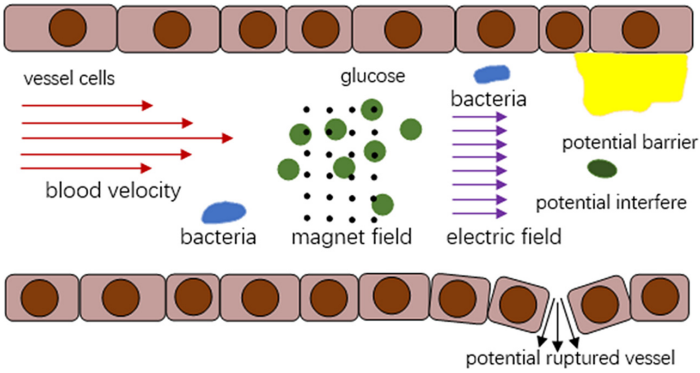

Fig. 1. The illustration of cooperative molecular system.

The paper is organized as follows. In Section, we present the architecture of proposed cooperative molecular communication system included bacteria followers and electromagnetic field controlled leading particles. In Section, we will propose the mathematical model for this section. In section, we evaluate the efficiency of this cooperative MC system by simulation results.

2 Section Basic Model

Now let's assume that there's a kind of particle is benefit to the bacteria's living so if the bacteria contact with larger concentration position than it possessed then the bacteria would try to get closer to this position. With the standard concentration distribution function let's set an upper concentration limit for the bacteria so when the increase of concentration is greater than it, the bacteria would get to the largest concentration position. Based on these we create an simulate environment, Fig. 2 shows a typical concentration distribution in human vessel and Fig. 3 shows the actually mathematical model of the concentration distribution function. So, in the local area the distribution of the concentration could be considered as:

$$C = \frac{M}{(4D\pi t)^{\frac{3}{2}}} e^{\frac{-\left(x^2+y^2\right)}{4Dt}} \tag{1}$$

According to [12,13], the parameter D is the diffusion coefficient of the molecule, the M is numbers of attractant released by relay node in a period time. As the time t is becoming infinite the concentration is becoming uniformed in the local area. However, this circumstance is not permitted because there's no difference for the bacteria, so we set a limited time TB for the bacteria to find the particle's position. If it doesn't find it in the limited time, we consider it would not find the particle forever and record zero for it.

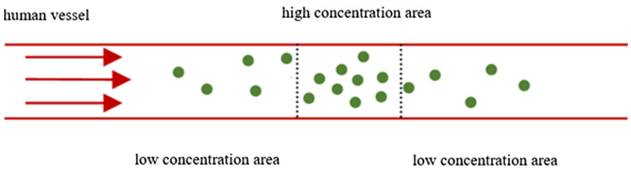

Fig. 2. A circumstance in human vessel while the injected area's concentration is greater than the area does not inject the particles.

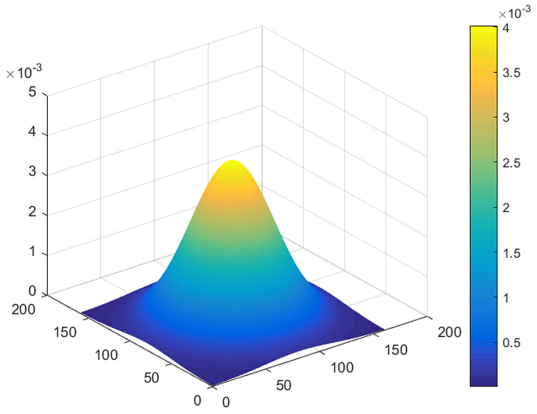

Fig. 3. A typically mathematical model of concentration distribution.

While the particles have injected in the vessel, we consider they could release and dissolve themselves stably into ionic state and both the particles and the bacteria would keep relative static in the blood flow. The ionic particles carry electron so electromagnetic field could control the ionic particles' direction and velocity. In limited time the particles keep themselves united and only release a small part of themselves into the plasma so there's a definite concentration difference between local position and bacteria's position. To control the particles' position precisely, it's considerable to calculate the exactly results of the

electromagnetic field's direction and amplitude. The following functions describe the details it.

$$F = k\frac{q_1 q_2}{d^2} = \frac{q_1 q_2}{4\pi\varepsilon d^2}$$

$$k = \frac{1}{4\pi\varepsilon} \tag{2}$$

The upper parameter q1 and q2 are the electrons, the parameter d is the distance between electrons. The is the plasma permittivity and we consider it as a constant in our model. With the effect of the electric force the particles acquire an extra accelerate from it. If the electric field is uniformed, we can equal (2) to following equation.

$$\boldsymbol{F} = q\boldsymbol{E} \tag{3}$$

The parameter E is a constant amplify field and the parameter q is particle's charged quantity. To change the direction of the particles an extra magnetic field is needed in our model. Here is the calculate about the magnetic field.

Consider the magnetic field strength H is:

$$H = \frac{1}{4\pi\mu}\frac{qr}{r^3} \tag{4}$$

And then if we ignore the magnetization intensity M in plasma, the magnetic induction intensity B could be equalled as:

$$B = \frac{H}{\mu} \tag{5}$$

For the particle in uniform magnetic field, it would under the force caused by magnetic field.

$$\boldsymbol{F} = q\boldsymbol{B}\boldsymbol{v} \tag{6}$$

The upper parameter r is the vector between two magnetic particles, parameter is permeability of plasma. And the F is the Lorentz force. However, in our model we only consider the uniform magnetic field for ideal environment. The fluid drag should be considered in this model but according the Stokes law and conclusion in [14], the particle at relative static could ignore the fluid drag caused by plasma. Based on these, when a single particle is affected by the Lorentz force, it would turn its direction, we calculate it as following function.

$$x = x + \frac{q\boldsymbol{B}\boldsymbol{v}t}{m}\cos\omega t$$

$$y = y + \frac{q\boldsymbol{B}\boldsymbol{v}t}{m}\sin\omega t \tag{7}$$

Parameter v is the velocity of the particle and the parameter is the angular velocity of Lorentz force. The should be constant when the velocity of the particle is constant.

3 Section III. Model's Efficiency

The drug's delivery efficiency generally depends on two parameters which are delayed time and the capacity of it can carried. In this model we put a few bacteria in the testing environment. Both of them are randomly act if they don't receive enough concentration of the particles, they would continue their random actions or they would follow the particles to the destination. Based on this and Sect. 1, we test some circumstances and get an approximate result about the efficiency of this model.

3.1 Part 1 the Static Environment

While the particle putted in the environment, we assume that there are a few bacteria are searching for it. As the Fig. 4, this is the range we set to the environment the bacteria would randomly search and act during the limited time TB. For the bacteria in top right area we set it's the standard group and the lower left group as the control group which parameters are different from the standard group. And the Fig. 5 shows the time costed by the bacteria to reach the border area of the particle. As it shows, the standard one cost less time but in low efficiency state compared with the control group. The control group we changed its slower velocity, larger volume and the larger upper limit of the concentration than the standard group. Although the time is delayed, the efficiency is much more than the standard group.

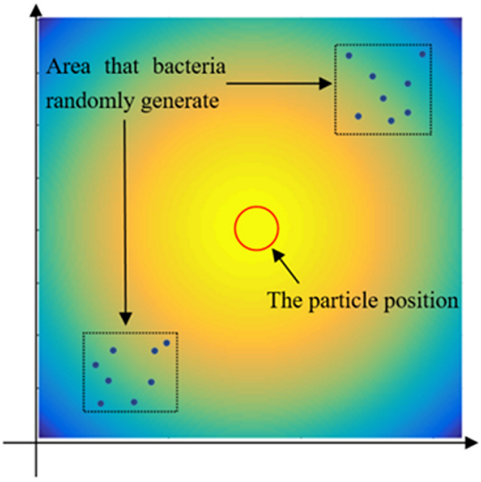

Fig. 4. The bacteria's distribution and the initial setting of testing model.

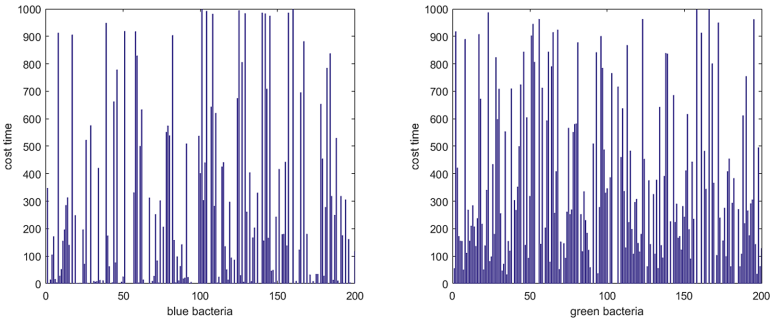

Fig. 5. The different bacteria's timing cost to the static particle. The left figure is the blue bacteria we set in the top right position and it's small but less upper concentration limit. And the right figure is the green bacteria we set in the lower left position. The X-axis is the number of the bacteria we test and the Y-axis is the time that the bacteria cost to reach the position. (Color figure online)

3.2 Part 2 Dynamic Model

For the dynamic model we are adding the electromagnetic control for the particle and the bacteria keep the same state as the part 1 model. The electromagnetic field we set is not based on the realistic model so we have to convert it by the equation (4,6). For the better simulation, this model we use the gradient field searching algorithm proposed by [15,16] for the bacteria to search the largest concentration.

$$\nabla f(x,y) = \frac{\partial f}{\partial x} e_x + \frac{\partial f}{\partial y} e_y \tag{8}$$

Equation 8 is the gradient descent function and it's usually used for optimization and searching. However, our model is not continuous and derivable so we set a minimum unit in our simulation model.

We assume that the bacteria are disturbed between the top right and the lower left areas and the electromagnetic field we are going to limit the particle's velocity. So, we can ignore the other affections to the particle. Also, we have to set the mass and the charge in an appropriate range for the particle or it would performance badly. Here the Fig. 6 is the model and Fig. 7 shows the results of testing.

The gradient field searching algorithm is originally used in neural networks and reinforcement learning. Its basic objective is finding the fastest descent of the field. So, the gradient field searching algorithm is commonly used. Here we present the pseudo code of algorithm designing. Our model is based on the MATLAB so we set the parameter CELL_NEXT_STEP as the differential step in the model. While the bacteria are searching the gradient, we can set it run the function with multiple steps and so this could be more effective and precise.

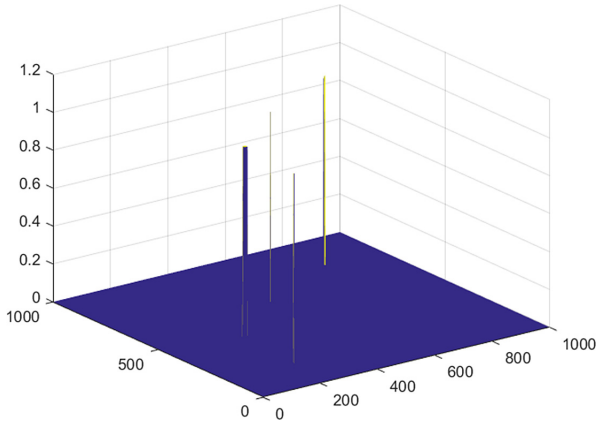

Fig. 6. The environment of our model the central one is the origin location of the particle and the others are the bacteria's location and the particle's present location.

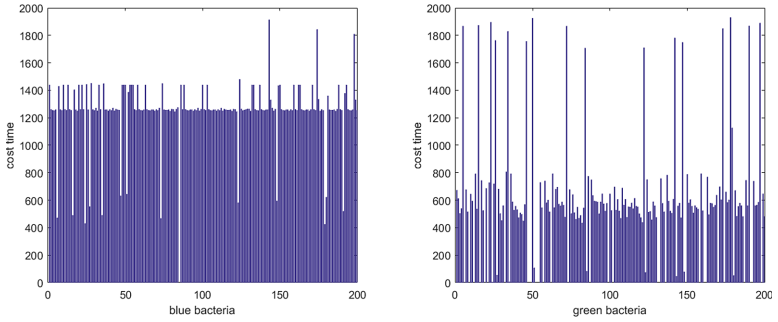

Fig. 7. The result of dynamic model the left one is blue bacteria which received constant electromagnetic controlling and its efficiency is higher than green one. And the right figure is green bacteria. Although it cost less time but without the algorithm and controlling the efficiency of green bacteria is far less than blue one. (Color figure online)

4 Section Simulation Result

In this section, we will show the results of our testing models. We would test the models in different aspects such as the expected delayed time, the variance of delayed time and the efficiency. The expected time and the variance could be counted as the following equation:

$$E(x) = \frac{1}{n}\sum_{i=1}^{n} x_i$$

$$D(x)^2 = \frac{1}{n}\sum_{i=1}^{n} (x_i - \bar{x})^2 \tag{9}$$

```
Function GFSA(Upper_Limit) is:
    While(Current_Concentration < Upper_Limit)
        CELL_TEMP(1) = CELL_LOC1_SEARCH;
        CELL_TEMP(2) = CELL_LOC2_SEARCH;
        CELL_TEMP(3) = CELL_LOC3_SEARCH;
            ……
        CELL_TEMP(n-1) = CELL_LOCn-1_SEARCH;
        CELL_TEMP(n) = CELL_LOCn_SEARCH;
        Current_Concentration = max(CELL_TEMP);
        CELL_NEXT_STEP = max(LOC);
    End
RETURN CELL_NEXT_STEP;
```

Fig. 8. The pseudo code.

However, there're a few results are zero in Figs. 5 and 7 because the bacteria are missing the target while in the limited time for them to search the particle so we have to count it as 1000 to imply the Eq. 9. The following sheet is the result (Fig. 8).

	Static Model 1	Static Model 2	Dynamic Model 1	Dynamic Model 2
Expectation	470.41	471.73	1254.85	702.24
Variance	168746.28	115353.75	46504.93	163065.94

(10)

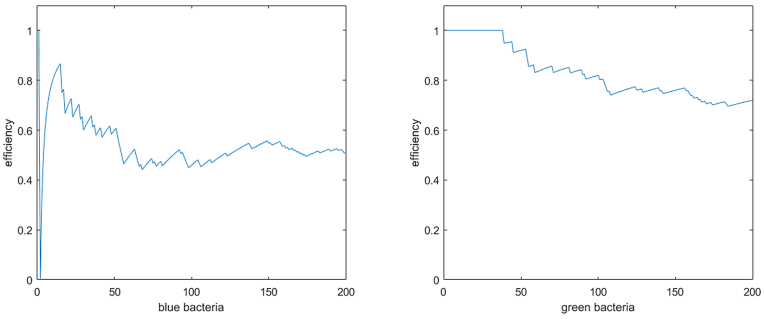

Fig. 9. The efficiency of the static models. It's exactly that the green bacteria performance more stable than the blue one. And the variance is less than blue one. (Color figure online)

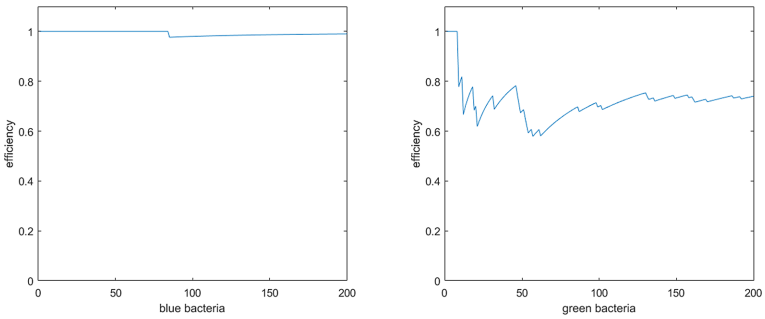

Fig. 10. The efficiency of the dynamic models. The standard group used the electromagnetic control and the performance the most stable than others while the control group is randomly act to search the dynamic particle.

So, according the result, we can find the dynamic model 1 cost the longest time but most stable than others (Fisg. 9 and 10).

As the efficiency, we define that the more zeroes in the result the less efficiency this system is. Based on this we have the following figures reveal the efficiency of whole system.

5 Conclusion

In this paper, we propose using the cooperative molecular communication to improve the efficiency of drug delivery. And while in testing, it shows that our simulation model uses the electromagnetic field to control the position of attractant and the gradient field searching algorithm for the bacteria to effectively act and search the particle is performing well in this ideal model. However, in many people's vessels there're many potential problems like the hyperlipemia and the hyperglycemia could hamper the blood flow and causing the turbo in the vessel. So, in future of our simulation we have to add more features to this model and establish the GUI for it.

References

1. Wilhelm, S., et al.: Analysis of nanoparticle delivery to tumours. Nat. Rev. Mater. **1**(5) (2016)
2. Hwang, S.W., et al.: Materials for bioresorbable radio frequency electronics. Adv. Mater. **25**, 3526–3531 (2013)
3. Akyildiz, I.F., Jornet, J.M., Pierobon, M.: Nanonetworks: a new frontier in communications. Commun. ACMs **54**, 84–89 (2011)
4. Chahibi, Y., Akyildiz, I.F.: Molecular communication noise and capacity analysis for particulate drug delivery systems. IEEE Trans. Commun. **62**(11), 3891–3903 (2014)

5. Nakano, T., et al.: Performance evaluation of leader-follower-based mobile molecular communication networks for target detection applications. IEEE Trans. Commun. **65**(2), 663–676 (2017)
6. Chen, Y., Kosmas, P., Anwar, P.S., Huang, L.: A touch-communication framework for drug delivery based on a transient microbot system. IEEE Trans. Nanobiosci. **14**(4), 397–408 (2015)
7. Nosratinia, A., Hunter, T.E., Hedayat, A.: Cooperative communication in wireless networks. IEEE Commun. Mag. **42**(10), 74–80 (2004)
8. Taheri, M.H., Mohammadpourfard, M., Sadaghiani, A.K., Kosar, A.: Wettability alterations and magnetic field effects on the nucleation of magnetic nanofluids: A molecular dynamics simulation. J. Mol. Liq. **260**, 209–220 (2018)
9. Shao, J., Xuan, M., Zhang, H., Lin, X., Wu, Z., He, Q.: Chemotaxis-guided hybrid neutrophil micromotors for targeted drug transport. Angew. Chemie **129**(42), 13115–13119 (2017)
10. Lo, C., Bhardwaj, K., Marculescu, R.: Towards cell-based therapeutics: a bio-inspired autonomous drug delivery system. Nano Commun. Netw. **12**, 25–33 (2017)
11. Yang, Y., Zheng, Q., Yan, Y., Liu, Y., Shao, H.: The enhanced electronic communication in ferrocenemethanol molecular cluster based on intermolecular hydrogen-bonding. Chin. Chem. Lett. **29**(1), 179–182 (2018)
12. Yang, L., Mao, Y., Liu, Q., et al.: High-efficiency target detection scheme through relay nodes in chemotactic-based molecular communication. In: 2018 IEEE International Conference on Sensing, Communication and Networking (SECON Workshops), pp. 1–4. IEEE (2018)
13. Lin, L., Wu, Q., Liu, F., et al.: Mutual information and maximum achievable rate for mobile molecular communication systems. IEEE Trans. Nanobiosci. **17**(4), 507–517 (2018)
14. Safaei, S., Archereau, A.Y.M., Hendy, S.C., et al.: Molecular dynamics simulations of Janus nanoparticles in a fluid flow. Soft Matter **15**(33), 6742–6752 (2019)
15. Møller, M.F.: A scaled conjugate gradient algorithm for fast supervised learning. Neural Netw. **6**(4), 525–533 (1993)
16. Baird III, L.C., Moore, A.W.: Gradient descent for general reinforcement learning. In: Advances in Neural Information Processing Systems, pp. 968–974 (1999)