Predictable Therapeutic Microswarm Dispersion for Targeted Drug Delivery Application

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INTRODUCTION

The magnetic nanoparticles (MNPs) based micro-nanorobots are emerging drug carriers. Controllability by an external magnetic field is the major advantage of these drug carriers. However, they are facing several challenges including controllability of the individual motion of MNPs under a global magnetic field. The microswarm control where collective MNPs were guided by a magnetic field was proposed as a solution [1]. Steering the MNPs as a microswarm to the targeted region has many advantages which include increasing the delivered drug to the site, preserving the healthy organs from drug penetration, and decreasing the negative side effects.

In recent studies, particle swarms were guided using a rotating/oscillating magnetic field [2], [3]. A simulation platform for steering the aggregated MNPs based on the gradient field was developed [4]. Despite studies on the separation, no computational platform for predicting changes in particle dispersion under different magnetic field conditions has been introduced. After reaching the position of interest, the aggregates also had to be separated to ensure successful drug delivery.

In this study using mathematical modelling, a separation platform has been developed. More details on the mathematical model used here can be found in [5]. The paper is divided into two sections. First, the accuracy of the simulation platform is discussed and then the effective parameters have been studied.

MODELLING ROTATING MAGNETIC FIELD

In this study, the magnetic field strength (MFS) is considered in two directions (Fig. 1). The coefficient of variation of the MFS is defined as follows:

$$\begin{cases} f_x+f_y=1 \\ f_x=0,\ \ 0\le t<T_1 \quad ; \quad f_x=1,\ \ T_1\le t\le T_2 \end{cases} \tag{1}$$

where f_x and f_y are the coefficients of variation in directions x and y.

The applied magnetic field is described with three parameters: the coefficient of variation $\vec{f}=(f_x, f_y, 0)$, the frequency of the magnetic field $1/T_2$ and the period ratio $\alpha=T_2/T_1$ (Fig. 1-a).

MODEL VERIFICATION

The simulation results are compared to experiments in [6]. This simulation uses 1000 particles with a radius of 125 nm. The applied field has a frequency of 10 Hz with a frequency ratio of 2. Considering the particles' size, the Brownian force is assumed to be zero. For describing the change of particle's location in a specific time, two user-defined geometrical parameters were introduced (details can be found in [5]). These parameters are dispersion and the ideal percentage of dispersion changes (IPDC). Dispersion is a parameter that shows the average distance of particles from the gravity center of the whole particles. IPDC illustrates the difference between the dispersion at the determined time and the ideal dispersion of the particles. The ideal dispersion is the minimum concentration of particles. The ideal dispersion is a function of the number, diameter, and coefficient of elasticity of the particles. Fig. 1 offers a diagram of the IPDC with respect to time for both the simulation and experimental results. As shown in the diagram, both the simulation and experimental results follow the same trend of deceleration before settling down after 10 s. The final ideal percentage of dispersion change (IPDC) is inclined to 62% and 58% for the experimental and the simulation results (error =9.7—the difference between experimental and simulation results).

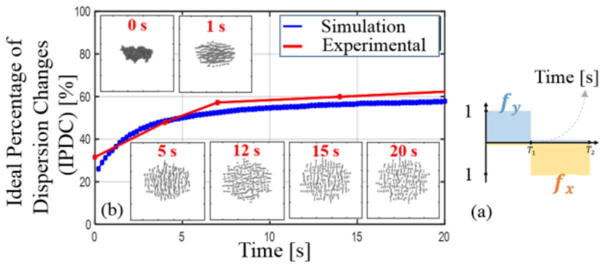

Fig. 1 (a) Schematic of the change of the variation coefficient over time. (b) The IPDC and the particles' position per time.

RESULTS

To evaluate the effect of the number of MNPs, we perform three simulations with 500, 1000 and 1500 particles number. Fig. 2-a presents these results. The particle radius and simulation time are equal to 125 nm and 35 s, respectively, for all cases. The applied magnetic field has a frequency and MFS of 10 Hz and 10 mT with a period ratio of 2. The results show that the IPDC changes over time are independent of the number of MNPs, and the trends of the diagrams are similar in all cases. To better describe the process of changing the results, we introduced two terms: the final IPDC and the stability time. The final IPDC indicates the ultimate limit

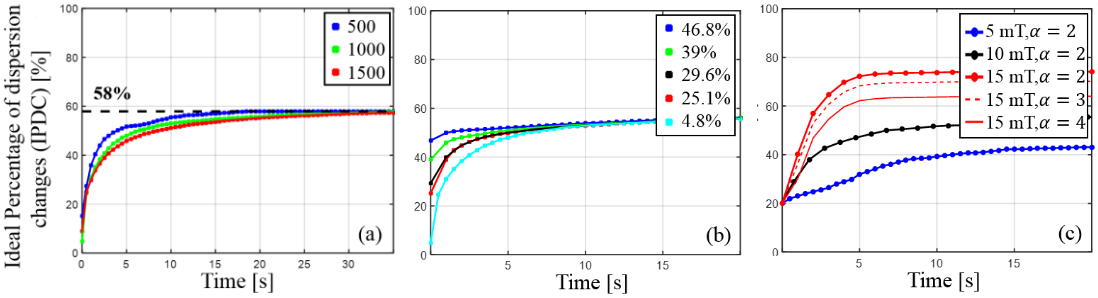

Fig. 2 (a)-(c) The diagram of the effect of the particle number, initial dispersion, MFS and the period ratio on IPDC changes over time.

of the dispersion changes, and when the particles reach their final IPDC, the particles' dispersion value stabilises itself, and the magnetic field becomes inert. The stability time determines the duration of the applied magnetic field by which the dispersion changes stabilise. After that time, the imposed field no longer affects the particles as, in time, the particles become so distanced and dipole force decreases ($F_{dip_{ij}} \propto 1/\hat{r}_{ij}{}^{4}$). The results of Fig. 2-a show that when the other effective parameters are the same, the final IPDC and the stability time are independent of the number of particles.

Fig. 2-b depicts the results of the simulations, which reveal that under any initial dispersion value, the IPDC converges to the same value. In all cases, the diameters of all particles are equal to 250 nm. Other parameters, such as the number of MNPs, frequency, MFS and period ratio, are set to equal 1000, 10 Hz, 10 mT and 2, respectively. All cases showed acceptable stability for the dispersion time. In Fig. 2-b, where the $IPDC_{t=0}$=46.8 %, the IPDC changes begin to slow, and the value of the IPDC becomes almost stable after 1s, but where the $IPDC_{t=0}$=4.8 %, the elapsed time required for the IPDC to reach the constant value of 57.2% is approximately 7 s.

Fig. 2-c illustrates the effects of the MFS and the period ratio on the dispersion stability time and the final IPDC when the MNPs number, diameter and frequency are equal to 1000, 250 nm and 10 Hz. The results reveal that the larger the MFS, the less stable the dispersion of particles in time. When the MFS is equal to 15 mT, the dispersion stabilises in 5 s, and the IPDC reaches 74.5%. When the MFS is equal to 10 mT and 5 mT, however, the dispersion stabilises itself after 7 s and 10 s, respectively, with IPDC values of 57.6% and 42.3%. Therefore, the stronger the magnetic field becomes, the sooner the dispersion process stabilises, and the higher the final IPDC tendency's value reaches. The dipole force is responsible for this phenomenon. Three cases are used to study the effect of the period ratio (Fig. 2-c). In all cases, the MFS is equal to 15 mT, and three-period ratios, namely, 2, 3 and 4, are used. The results demonstrate that a decrease in the period ratio is directly related to a simultaneous increase in the value of the IPDC. In these simulations, the slope of the curve is similar, and the stability time is equal to 5 s. However, the cases have different final IPDC values; for the period ratios of 2, 3 and 4, the value of the IPDC reaches 74.5%, 70.1% and 63%, respectively. Therefore, we conclude that the dispersion stability time is independent of the period ratio and only affects the final IPDC's value.

DISCUSSION AND CONCLUSION

In this study, we demonstrate a numerical platform that has the ability to predict the separation of the microswarms under the oscillating magnetic field. A study of the effective parameters shows that independent of any environmental, geometric and process conditions, the dispersion changes are slow, and the dispersion becomes stable after 20 s. In addition, the value of the final dispersion of MNPs is related to the MFS value, period ratio, and particle diameter. The results showed that at a very high and very low frequency, microswarm dispersion does not have high scattering and the final scattering changes are very small. In general, the introduced platform can be useful for predicting the dispersion of the particles under different magnetic conditions. The platform can be used to predict recently introduced therapeutic microswarms.

REFERENCES

[1] H. Xie et al., “Reconfigurable magnetic microrobot swarm: Multimode transformation, locomotion, and manipulation,” Science Robotics, vol. 4, no. 28, pp. 1–15, 2019, doi: 10.1126/scirobotics.aav8006.

[2] A. K. Hoshiar, S. D. Javan, T. Le, M. R. H. Yazdi, and J. Yoon, “Studies on Aggregated Nanoparticles Steering during Deep Brain Membrane Crossing,” Nanomaterial, vol. 11, no.10, pp. 1–16, 2021.

[3] A. K. Hoshiar, T. A. Le, P. Valdastri, and J. Yoon, “Swarm of magnetic nanoparticles steering in multi-bifurcation vessels under fluid flow,” Journal of Micro-Bio Robotics, 2020, doi: 10.1007/s12213-020-00127-2.

[4] P. Vartholomeos and C. Mavroidis, “In Silico Studies of Magnetic Microparticle Aggregations in Fluid Environments for MRI-Guided Drug Delivery,” IEEE Transactions on Biomedical Engineering, vol. 59, no. 11, pp. 3028–3038, Nov. 2012, doi: 10.1109/TBME.2012.2213340.

[5] K. Abolfathi, M. R. H. Yazdi, and A. K. Hoshiar, “Studies of Different Swarm Modes for the MNPs under the Rotating Magnetic Field,” IEEE Transactions on Nanotechnology, vol. 19, pp. 849–855, 2020, doi:10.1109/TNANO.2020.3041798.

[6] B. Wang, K. F. Chan, J. Yu, Q. Wang, and L. Yang, “Reconfigurable Swarms of Ferromagnetic Colloids for Enhanced Local Hyperthermia,” Advanced Functional Material, vol. 1705701, pp. 1–12, 2018, doi: 10.1002/adfm.201705701.