Numerical Simulation on Behaviour of Magnetic Beads in Magnetic Filter for Medical Protein Screening System using High Gradient Magnetic Separation

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Abstract. Recently, Antibody drugs are attracting attention in the medical field. Antibody using immune function has high efficacy and side effects are relatively few, so it is expected to become the mainstream of future medicine. Indispensable technologies for development of antibody drugs are continuous, large amount and high-speed separation of medical protein. Therefore, we have proposed superconducting high gradient magnetic separation (HGMS) system for medical protein. If HGMS system using superconducting magnet is realized, processing time of separation can be greatly shortened. In the previous studies, it was possible to separate 200 nm magnetic beads suspended in pure water, with the result that the capture ratio was 97.8% and the collection ratio was 94.1%. However, depending on the type of the suspension, the clogging of the magnetic filter and the phenomenon that the magnetic nano-beads are not trapped have been confirmed. Therefore, in this study, the magnetic force of the magnetic filter is evaluated by electromagnetic fluid and particle tracing analysis considering the behaviour of the magnetic beads two-dimensionally in the magnetic filter.

1. Introduction
The antibody is a type of immune, which mainly present in blood and body fluids, recognizing and destroying viruses invaded the body as antigens. Antibody drugs are expected to have less side effects, achieve high and long efficacy in the body, thus reducing the number of dosing drugs. Therefore, the development of new antibody drugs has been actively carried out all over the worldwide. The global market scale is estimated to grow 10 times in the next 10 years [1]. On the other hand, as a disadvantage, it can be mentioned that the current antibody drugs are very expensive. Regarding this problem, continuous, large amount and high-speed separation by improvement of producing technology leads to reduction of production cost in the industry.

We have been conducting research on development of high gradient magnetic separation (HGMS) system using magnetic beads for antibody screening [2-6]. In this system, by applying a high magnetic field to the magnetic filter by the superconducting magnet, a high gradient of magnetic field and magnetic force is generated around the magnetic wire. In previous studies, the prototype HGMS system using superconducting magnets was constructed [4-6]. The dimensions of the system cabinet were 517 mm wide × 617 mm deep × 1000 mm high. The cabinet must be small as it is a tabletop type. The superconducting magnet was set in the middle of the cabinet, and the room temperature bore had a 30-mm diameter. The magnetic filter was inserted in a 20-mm inner diameter tube set in the middle of the room temperature bore of the magnet. The cooling system was a Gifford-McMahon (GM) cryocooler.
with a cooling capacity of 6 W at 55 K and cooled via conduction. The operating temperature was 4.2 K. A resonance circuit was added to the HGMS system in order to improve the recovery of nanobeads [6]. The filter was demagnetized in the AC magnetic field by the resonance circuit to make good use of the superconducting magnet of HGMS. It was possible to separate 200-nm magnetic beads suspended in pure water, with the result that the capture ratio was 97.8% and the collection ratio was 94.1% [4]. However, depending on the type of the suspension, the clogging of the magnetic filter and the phenomenon that the magnetic nano-beads are not trapped have been confirmed. Therefore, in this study, we carried out numerical analysis to investigate the behaviour of magnetic beads around the magnetic filter and develop the magnetic filter with wire diameter, aperture, and stack interval as variables.

2. High gradient magnetic separation
At present, in the separation of medical proteins such as magnetic separation and affinity chromatography, affinity beads are mainly used as carriers. Affinity beads specifically and reversibly adsorb certain biomolecules. There are two types of affinity beads. One is nonmagnetic beads for chromatography and centrifugation and the other is magnetic beads for magnetic separation. Chromatography and centrifugal separation are difficult for continuous operation and require long time for separation, so it is unsuitable for high-speed, large-amount, and continuous separation. For beads of the same total mass, if the size is reduced to 1/10, the number of beads is $10^3$ times, and the probability of attaching antibodies can be dramatically increased. However, the force caused by mass is small with downsizing the beads. On the other hand, magnetic force for even substances of small mass can be large in a high magnetic field and high gradient magnetic field. The magnetic force, $F_{mag}$, is the following expression when the external magnetic field is sufficiently large.

$$F_{mag} = V_p (M_s \cdot \nabla) H$$

where $V_p$, and $M_s$ are the volume, saturation magnetization of the magnetic beads, respectively. $H$ is the magnitude of the magnetic field. Therefore, we have proposed a high gradient magnetic separation (HGMS) using a small superconducting magnet [2]. In case of using this small superconducting magnet, the magnetic field can be up to 2 - 4 T, thereby a high magnetic-field gradient and large magnetic force can be generated.

Figure 1 shows a schematic diagram of the superconducting HGMS system. The magnetic filter was inserted in a tube set in the middle of the room temperature bore of the magnet. HGMS systems can be divided into three major parts: pre-treatment part, magnetic separation part and post-processing part. In the pre-treatment part, the antibody in the suspension specifically attaches with an affinity substance. In the magnetic separation part, a high magnetic field is generated by the superconducting magnet and a high magnetic field gradient is generated around the magnetic filter, so the magnetic force acts on the
magnetic beads attaching antibodies. As a result, the magnetic beads are adsorbed by the magnetic filter. Then, the magnetic field is reduced to zero. In the post-processing part, the magnetic filter is demagnetized by a resonance circuit using a superconducting magnet in the HGMS. Next, the tube and filter are flushed with a solution, and then the nano-beads are recovered.

3. Numerical Analysis of behaviour of the magnetic beads around the magnetic filter

3.1. Analysis conditions
In order to investigate the behaviour of the magnetic beads around the magnetic filter in HGMS system using COMSOL as the parameter of wire diameter \(d\), aperture \(A\), stack interval \(H\), and number of stack filters as shown in Figure 2. In this study, the two-dimensional simulation was applied for the fundamental behaviour of magnetic beads. The aperture ratio, \(\varepsilon\), is determined by the diameter and the aperture as following expression.

\[
\varepsilon = \left(\frac{A}{A + d}\right)^2 \times 100
\]

where \(A\) is aperture, \(d\) is wire diameter. Table 1 lists the specifications of the magnetic filter in this simulation. The size of the magnetic filter is assumed to be commercially available from Kansai Wire Netting Co., Ltd. Currently, many of the filters for magnetic separation are S43000 because of high chemical resistance and strength. In the analysis model, a magnetic filter was arranged, and a periodic boundary condition was set for the black thick line in Figure 2.

| Wire diameter \(d\) (µm) | Aperture \(A\) (µm) | Aperture ratio \(\varepsilon\) (%) |
|--------------------------|-------------------|-----------------------------|
| 30                       | 34                | 28.22                       |
| 30                       | 48                | 37.87                       |
| 30                       | 72                | 49.83                       |
| 40                       | 45                | 28.03                       |
| 40                       | 75                | 42.53                       |
| 40                       | 101               | 51.31                       |
| 50                       | 52                | 25.99                       |
| 50                       | 77                | 36.76                       |
| 50                       | 104               | 45.61                       |
| 60                       | 67                | 27.83                       |
| 60                       | 84                | 34.03                       |
| 60                       | 121               | 44.69                       |
| 70                       | 84                | 29.75                       |
| 70                       | 111               | 37.61                       |
| 70                       | 142               | 44.86                       |

Figure 2. Schematic diagram of analysis model.

3.2. Electromagnetic field analysis
The electromagnetic field analysis was carried out in order to evaluate the magnetic force around the wire for the analysis model as shown in Figure 2. A uniform magnetic field of 3 T was applied to calculate the distribution of the magnetic force in various wire structure. Figure 3 shows the distribution of magnetic force in various magnetic wire structures. The strongest magnetic force is generated for the wire with cross section of circular, and the range of magnetic force is wider as well. From the above, it is considered that the circular cross-section magnetic wire used for magnetic separation is optimal. Figure 4 shows a vector map of the magnetic force generated around the magnetic wire. As seen in Figure 4, an attractive force is generated around the upper part of the magnetic wire. On the other hand,
repulsive force is generated at the side of the magnetic wire, which is considered to greatly affect the behaviour of the magnetic beads.

![Figure 3. Distribution of magnetic force around the magnetic wire with cross section of (a) Circular shape, (b) quadrate shape, and (c) rhomboid shape.](image1)

![Figure 4. Vector map of magnetic force around the magnetic wire with cross sectional of circular shape.](image2)

3.3. Fluid dynamics Analysis

The fluid analysis was carried out using the model as shown in Figure 2. In this simulation, the viscosity of fluids is $1.1 \times 10^{-3}$ Pa s, and fluid velocity at inlet is 5.0 mm/s, and temperature is 293.15 K. Figure 5 shows the velocity distributions of fluid for the filter with wire diameter of 30 µm and various aperture. As seen in Figure 5, because the fluid flows so as to avoid an obstacle, and the flow velocity becomes the maximum at the side of the magnetic wires in this simulation, and the flow velocity decreases in the upper and lower parts of the magnetic wire.

![Figure 5. Distribution of flow velocity around the magnetic wire (d=30 µm) with an aperture ratio of (a) ε = 28.22%, (b) ε = 37.87%, and (c) ε = 49.83%.](image3)

3.4. Electromagnetic-fluid-particle tracing coupled analysis

Electromagnetic-fluid-particle tracing coupled analysis was conducted using the analysis model as shown in Figure 2. Analysis conditions are the same in subsections 3.2 and 3.3 applying a uniform magnetic field of 3 T and flowing water from the inlet. The mass, diameter and relative permeability of bead is $1.0 \times 10^{-5}$ ng, 100 nm, and 1.05, respectively. These values supposed the beads manufactured by Tamagawa Seiki Co., Ltd with a saturation magnetization of 0.3 T. Figure 6 shows the particle trajectories when the inlet velocity of 5.0 mm/s in a single layer with a diameter of 30 µm. As seen in
Figure 6, the magnetic beads are adsorbed by the magnetic force generated on the upper part of the magnetic wire, and due to the influence of the repulsive force generated on the side of the magnetic wire, it is not adsorbed at the lower part of the magnetic wire. Figure 7 shows the change of the capture ratio for the various diameter in a single layer. When diameter is smaller, the capture ratio is higher. Furthermore, when aperture ratio ($\varepsilon$) is high, the capture ratio tends to decrease. However, considering the clogging of magnetic beads in previous studies, it is necessary to properly use filter size depending on the size and concentration of magnetic beads. Figure 8 shows the change in the capture ratio for the various stack interval ($H$) of 2-layers filter with the inlet velocity of 5.0 mm/s. It is difficult to grasp the trend since the movement of the fluid changes complicatedly depending on the stack interval and aperture. In the case of $d = 30 \mu m$, it is more efficient to select the aperture of filter rather than interval of stack in order to increase the capture ratio of beads.

Figure 9 shows the capture ratio of beads for various number of stack filters in the case of $v = 5$ mm/s and $H = 100 \mu m$. As seen in Figure 9, when the number of stack filters is taken as a variable under the condition of $d = 70 \mu m$, $H = 100 \mu m$, and $v = 5.0$ mm/s, about 80% of the magnetic beads flowing through the suspension are caught up to the 2nd layer. As a result, it is highly possibility to occurs the clogging in 1st and 2nd layers at $v = 5.0$ mm/s, therefore it is desirable to increase the flow velocity and the number of stack filters with the low concentration of beads in suspension.

4. Conclusion
In this study, the magnetic force of the magnetic filter is evaluated by electromagnetic fluid and particle tracing analysis considering the behaviour of the magnetic beads two-dimensionally in the magnetic filter. The filter with the diameter of 30 $\mu m$ and the aperture ratio of 28.22% captures the magnetic beads most efficiently. However, in the case of 10-layers filter, the capture ratio achieves about 90% even if high aperture ratio which means low capture ratio, so in consideration of the clogging of beads, the diameter of 30 $\mu m$ and aperture ratio of 49.83% is optimal. Currently, we confirmed that the capture ratio greatly fluctuates when the inflow velocity is changed. And, it can be expected to improve the treatment time of capturing beads. In order to accurately evaluate the phenomenon in a real system, we are conducting a three-dimensional electromagnetic-fluid-particle coupled analysis using a commercial magnetic mesh filter.

![Figure 6. The trajectory of magnetic beads around the magnetic wire (d=30 $\mu m$) with an aperture ratio of (a) $\varepsilon=28.22\%$, (b) $\varepsilon=37.87\%$, and (c) $\varepsilon=49.83\%$.](image-url)
Figure 7. Capture ratio of beads for various wire diameter in single-layer filter.

(a) $d = 30 \, \mu m$

(b) $d = 70 \, \mu m$

Figure 8. Capture ratio of beads for various stack interval in 2-layers filter with $v = 5.0 \, mm/s$.

(a) $d = 30 \, \mu m$

(b) $d = 70 \, \mu m$

Figure 9. Capture ratio of beads for various number of stack filters with $v = 5 \, mm/s$ and $H = 100 \, \mu m$.

References

[1] https://www.visiongain.com/Report/1445/Next-Generation- Antibody-Therapies-Market-Forecast-2015-2025
[2] Ueda H, Agatsuma K, Kajikawa K, Furuse M, Fuchino S and Ishiyama A 2009 Design and Test of Filter of High Gradient Magnetic Separation System for Trapping Immunoglobulin in Serum IEEE Trans. Appl. Supercond. 19 2157-2161

[3] Ueda H, Agatsuma K, Fuchino S, Imura T, Furuse M, Kajikawa K, Ishiyama A, Koizumi T and Miyake S 2010 Improvement in High Gradient Magnetic Separation System for Trapping Immunoglobulin in Serum IEEE Trans. Appl. Supercond. 20 949-952

[4] Ueda H, Agatsuma K, Furuse M, Fuchino S, Kajikawa K, Kamioka Y, Iitsuka T and Nakamura S 2014 Performance of Filters in Medical Protein Separation System Using Superconducting Magnet IEEE Trans. Appl. Supercond. 24 3700405

[5] Fuchino S, Furuse M, Agatsuma K, Kamioka Y, Iitsuka T, Nakamura S, Ueda H and Kajikawa K 2014 Development of Superconducting High Gradient Magnetic Separation System for Medical Protein Separation IEEE Trans. Appl. Supercond. 24 4400204

[6] Kajikawa K, Ueda H, Kamioka Y, Agatsuma K, Fuchino S, Furuse M, Iitsuka T and Nakamura S 2014 Development of Degaussing System of Magnetic Filters for High Gradient Magnetic Separation to Improve Recovery Ratio of Trapped Magnetic Nanobeads IEEE Trans. Appl. Supercond. 24 4400305