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Feasibility of Orthogonal Taguchi Arrays for Determining Parameter Trends in MDT

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Abstract: Huge parameter studies are usually conducted to optimize and characterize systems for steering magnetic nanoparticles in magnetic drug targeting (MDT). Thus, many simulations or measurements are needed to determine the system which is time-consuming and expensive. To overcome this problem, this paper investigates the feasibility of using orthogonal arrays according to Taguchi's method for determining parameter trends in MDT. These trends can then be used to further optimize the appropriate parameters. By doing so, parameters typically varied in the literature were changed in three levels in a simulation and measurement scenario. In these scenarios, using orthogonal Taguchi arrays reduced the number of analyzed parameter combinations from 243 to 9. Overall, the results reveal that the relative importance of the parameters was correctly identified in the simulation and measurement scenario. The trends of the parameters showed some outliers due to single dominant parameters or correlations among them. However, this is normal for the analysis with orthogonal Taguchi arrays. Thus, it can be concluded that using orthogonal Taguchi arrays to optimize and characterize steering systems in MDT dramatically reduces the optimization time.

Keywords: magnetic drug targeting, MDT, magnetic nanoparticles, orthogonal arrays, SPIONs, Taguchi method.

1 Introduction

Magnetic drug targeting (MDT) is an innovative therapeutic approach to enable local cancer treatment and is a well-established research topic [1]. This therapy uses special magnetic nanoparticles, called superparamagnetic iron-oxide nanoparticles (SPIONs), that are characterised by a high magnetic susceptibility χ_m with no remanence [2], as carriers for the cancer drug. Since these SPIONs are magnetic, they can be guided through the cardiovascular system to the tumor region using external magnetic fields. In doing so, it has already been proven in animal studies [3] that MDT allows a highly efficient therapy with low side effects, as most anticancer drugs

are limited to the tumor region [1]. However, to the best of the authors' knowledge, MDT is not clinically certified and there is still a lot of research work to be done.

Especially, the design of suitable steering magnets is an open research question [4]. To optimize the steering magnets, or generally to evaluate the influence of various parameters on particle steering, many publications conduct extensive parameter studies [5–7]. Here, one parameter is usually varied, and all others are kept constant. Therefore, many simulations or measurements are necessary, which is time-consuming and, thus, expensive. As other disciplines, such as chemistry or manufacturing, also face this problem, there are special statistical methods for evaluating parameter trends in a reduced number of experiments [8]. However, to the best of the authors' knowledge, such methods have not been used in MDT so far. Thus, this paper examines in simulations and measurements the feasibility of such statistical methods for the reduction of experiments in MDT with orthogonal arrays according to Taguchi, as this is an efficient way of evaluating the tendencies of individual parameters.

2 Fundamentals

2.1 Taguchi Method

The reduction in complexity of the Taguchi method is based on orthogonal arrays [9], a matrix in which each possible pair of parameters occurs an equal number of times in each pair of columns [8]. The orthogonal array used in this paper is depicted in Table 1. Here, p_i corresponds to the evaluated parameter, and Q_i is the experiment's result [9]. In this paper, five different parameters with three levels, high (2), middle (1), and low (0) are investigated. Thus, a total of $3^5 = 243$ com-

Tab. 1: Orthogonal Taguchi-Array L_9 with each 3 levels for 5 parameters. 0 corresponds to a low, 1 to a middle and 2 to a high value, respectively [9].

Experiment	p_1	p_2	p_3	p_4	p_5	Result
1	0	0	0	0	0	Q_1
2	0	0	2	2	1	Q_2
3	0	2	0	2	2	Q_3
4	1	1	2	0	2	Q_4
5	1	2	1	0	1	Q_5
6	1	2	2	1	0	Q_6
7	2	0	1	1	2	Q_7
8	2	1	0	1	1	Q_8
9	2	1	1	2	0	Q_9

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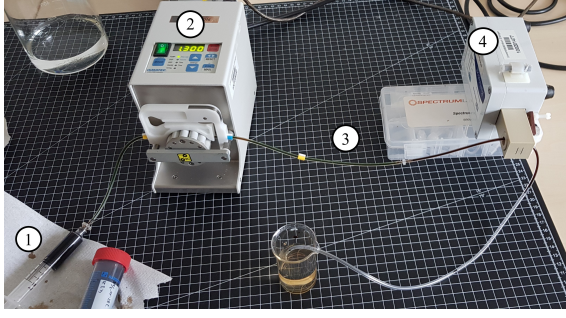


Fig. 1: Measurement setup consisting of (1) syringe with SPIONs, (2) peristaltic pump for providing the velocity flow, (3) positioning of the magnetic arrays, (4) susceptometer for evaluating the amount of passed SPIONs [11].

binations would have to be examined in a conventional investigation. Moreover, in the case of measurements, the same parameter set should be analyzed several times to obtain a meaningful result. However, using the orthogonal array according to Taguchi, only nine experiments are necessary to determine the trends of the parameters.

2.2 Evaluation of Parameter Trends

To determine the parameter trends, in the first step, the mean value Q_{mean} of the experimental results Q_i is calculated [10]

$$Q_{\text{mean}} = \frac{1}{N} \sum_{i=1}^N Q_i, \quad (1)$$

where N corresponds to the number of all experiments. Thus, in this paper $N = 9$ (compare Table 1). Based on this, the influence $Q_{p_j=k_L}$ on the overall result can be derived by [10]

$$Q_{p_j=k_L} = \frac{1}{N_{p_j=k_L}} \sum_{i=1}^{N_{p_j=k_L}} (Q_i |_{p_j=k_L} - Q_{\text{mean}}). \quad (2)$$

Here, p_j is again the investigated parameter, and k_L is the corresponding level (high, middle, low). $Q_i |_{p_j=k_L}$ is the result at which a parameter p_j has the level k_L and $N_{p_j=k_L}$ represents the number of results Q_i at which p_j was set to k_L [10]. Thus, in this paper $N_{p_j=k_L} = 3$. Based on Eq. 2 for every parameter p_j and every level k_L , the parameter trend can be determined.

Another interesting aspect is the relative importance of the individual parameters, which indicates how relevant a certain parameter is to the result. This can be identified using the sum-of-squares approach (SoS) [10]. The result of the SoS SS_{p_j} for the respective parameter p_j is obtained by [10]

$$SS_{p_j} = \sum_{k_L} N_{p_j=k_L} \cdot Q_{p_j=k_L}^2. \quad (3)$$

Finally, the total sum SS_{total} of the results of the SoS SS_{p_j} is required, for which they are summed up [10]:

$$SS_{\text{total}} = \sum_j SS_{p_j}. \quad (4)$$

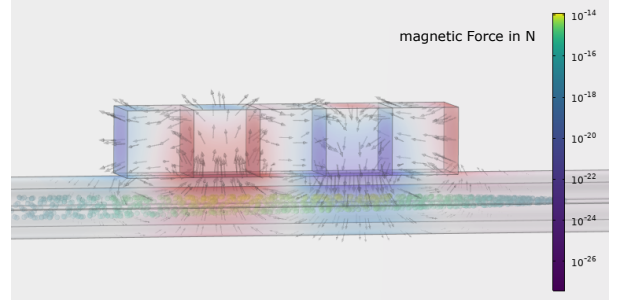


Fig. 2: Exemplary SPION pulse influenced by the Halbach array at $t = 50$ s. The color of the particles corresponds to the magnetic force toward the magnetic array.

Using Eq. 3 and Eq. 4, the relative importance of the individual parameters p_j can finally be derived from the quotient $SS_{p_j} / SS_{\text{total}}$ [10].

3 Methods and Evaluations

To generalize the work, a typical simulation and measurement scenario was analyzed. Both were conducted and evaluated similarly to our previously published work [11]. A photo of the measurement setup with all components is depicted in Figure 1. An overview of the fixed parameters of the simulation and measurement setup can be found in Table 2.

3.1 Simulation Model

The simulations of the particle steering were conducted in a 3D particle-based model using COMSOL Multiphysics® 6.1. As a steering system, different Halbach arrays with five, seven, and nine permanent magnets (PMs) made of NdFeB were chosen, as Halbach arrays are commonly used in MDT since they provide the strongest magnetic field and force [5]. The simulation model consists of a straight tube with deionized (DI) water surrounded by an air-filled cuboid. The air space is terminated with a perfectly matched layer. The simulation geometry with propagating SPIONs is shown in Figure 2. The numerical studies for all the experiments shown in Table 1 were carried out and the number of captured SPIONs N_c was extracted as experiment result Q_i . Each simulation analyzed one SPION pulse in a time-dependent study with a time step of $t = 0.1$ s for 400 s. The SPIONs were released at $t = 0$ s and N_c was determined at $t = 400$ s. For simplicity, particle-particle interaction was neglected.

Tab. 2: Overview of the fixed parameters for the simulation and measurement setup.

Category	Value	Label
PM	$5 \times 5 \times 5$ mm	size of single PM
	10^6 A/m	magnetization
vessel	30 cm	length of the tube
	2200 kg/m ³	mass density
SPIONs	25 nm	radius of one particle
	10	rel. permeability

3.2 Measurement Setup

In the measurements, the detected susceptibility χ_m was analyzed. Five measurements were conducted for every scenario defined in Table 1, and the mean value was derived. As in [11], the standard deviation was two to three powers of ten smaller than the mean value (including all outliers). A photo of the measurement setup is shown in Figure 1. The velocity flow with DI water was generated in tubes from Ismatec® Tygon ST using a peristaltic pump. The SPIONs were continuously injected as in a typical MDT treatment [3, 5]. During the entire measurements, it was ensured that the tube did not sag. χ_m was detected using a commercial Barington® MS3 susceptometer, calibrated according to its manual. As the SPIONs are injected continuously, the measured χ_m saturates over time. Thus, $\chi_{m,max}$ is chosen for Q_i . The SPIONs, consisting of magnetite (Fe_3O_4), were provided by the Section for Experimental Oncology and Nanomedicine of the University Hospital in Erlangen. They have a diameter of 50 nm and are synthesized in clusters with approx. 66 SPIONs per cluster and approx. $4.34 \cdot 10^{13}$ clusters per milliliter for a particle concentration of 3.75 mg Fe/ml [12].

3.3 Investigated Parameters

Steering SPIONs in MDT is challenging, as its success depends on many multiphysical properties like e. g. the velocity flow, the SPIONs' properties, and the magnetic field gradient [5–7, 12]. In the parameter study, the aim was to consider parameters from all different physical domains. Table 3 summarizes the chosen parameters and their levels. As in a particle-based model the particle concentration cannot be changed in COMSOL, the number of considered SPIONs was varied. Furthermore, Table 4 shows an overview of the used tubes.

4 Results and Discussion

4.1 Simulation Results

As Figure 2 shows, the SPION pulse is moved by the velocity flow along the tube. The Halbach array captures SPIONs underneath it. The number of captured SPIONs N_c is evaluated, and the studied parameter influences are depicted in Figure 3a and Table 5. The velocity flow, which is decisive for how long the SPIONs are under the array, has the highest influence on N_c . The slower the velocity, the stronger the resulting mag-

Tab. 4: Overview of the used tubes from Ismatec® Tygon ST.

Tube	Inner diameter	Wall thickness
0	1.52 mm	0.84 mm
1	1.75 mm	0.75 mm
2	2.79 mm	0.90 mm

netic force and the higher N_c , as shown in [5]. For the same reason, the length of the Halbach array has an impact. Moreover, the inner diameter of the tube influences the velocity, as it was defined in ml/min. Thus, the velocity is slower for a larger tube diameter. However, the importance of the number of simulated SPIONs and the distance between the tube end and Halbach array are small. In additional individual parameter studies, no impact of these parameters has been found.

4.2 Measurement Results

In the measurements, the SPIONs were sent continuously, and χ_m was evaluated as Q_i . The results of the trend study can be found in Figure 3b and Table 6. In contrast to the simulation results, the inner diameter of the tube (p_4), followed by the particle concentration (p_3), has the biggest impact. The reason for this is that χ_m increases linearly with the particle concentration [12]. For thicker tubes, the amount of SPIONs in the susceptometer's detection area is larger. Thus, as can be seen in Figure 3b, with increasing values of p_3 and p_4 , Q_i increases, too. The influence of the other parameters, in contrast, is much smaller. This is reasonable, as e. g. the velocity flow hardly changes the continuous propagation of the SPIONs. In comparative additional studies where only the velocity flow and the distance between the susceptometer and Halbach array were varied, no impact of both parameters was detected. By only varying the number of PMs in the Halbach array, χ_m decreased from $2.80 \cdot 10^{-3}$ for five PMs to $2.70 \cdot 10^{-3}$ for nine PMs. This trend is also visible in Figure 3b.

4.3 Discussion of Taguchi's Method

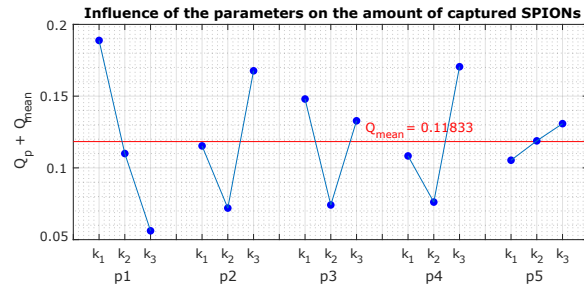
Overall, the simulation and measurement results depicted in Figure 3, Table 5, and Table 6 show the trends of the investigated parameters quite well. However, the main disadvantage of the Taguchi method is that no correlations between the parameters become apparent in the experimental results. This is particularly troublesome when two parameters act antagonistically against each other or are mutually exclusive. However, such behavior has not been observed in the analysis of this

Tab. 3: Values for the levels in the simulations and measurements.

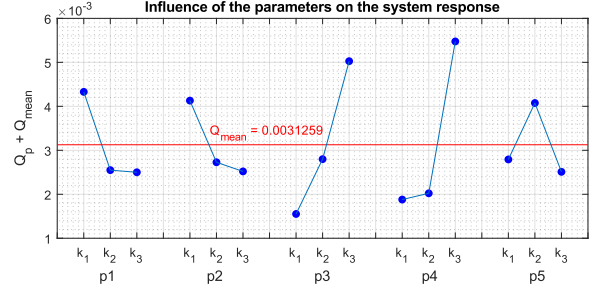
No.	Parameter	0	1	2
p_1	velocity flow [ml/min]	0.5	1.0	2.0
p_2	number of magnets	5	7	9
$p_{3,sim}$	number of particles	500	1000	2000
$p_{3,meas}$	particle concentration [mg Fe/ml]	1.88	3.75	7.50
p_4	inner diameter tube [mm]	1.52	1.75	2.79
$p_{5,sim}$	distance tube end ↔ array [cm]	5	10	20
$p_{5,meas}$	distance suscept. ↔ array [cm]	5	10	20

Tab. 5: Influences of the parameters in the simulations.

Parameter	Sum of Squares (SoS)	Importance SS_{p_i}/SS_{total}
velocity flow	0.0267	42 %
number of magnets	0.0138	21 %
number of particles	0.0091	14 %
inner diameter tube	0.0138	21 %
distance suscept. ↔ array	$9.765 \cdot 10^{-4}$	2 %
total	0.0644	100 %



(a) Influence in simulations.



(b) Influence in measurements.

Fig. 3: Influences of the parameters according to Taguchi; p_1 := velocity flow, p_2 := number of magnets, p_3 := number of particles (sim.) or particle concentration (means.), p_4 := inner diameter tube, and p_5 := distance between eval. location and Halbach array.

paper. Nevertheless, if a single parameter clearly dominates, the tendencies of the other parameters can be distorted. This can be seen, for example, in the level k_2 of the parameter p_4 : In general, it is expected that Q_i increases with increasing diameter. However, Q is lower for k_2 than for k_1 . The reason can be found in the design of the experiments (compare Table 1): $p_4 = 1$ is always paired with a high value for p_1 , which reduces Q . Hence, the trend of $p_4 = 1$ is lower. In the measurements, Q_2 was much higher than the other results, as $p_3 = 2$ and $p_4 = 2$ were combined. Such single outliers increase the importance of other parameters. Therefore, e. g. p_5 has a higher importance in Table 6 than in Table 5.

In summary, it can be concluded that for the investigated simulation and measurement scenario, the importance of the parameters was correctly identified in Table 5 and 6. The trends in Figure 3, however, have to be interpreted with care, as single dominant parameters can falsify the trends.

5 Conclusion

The influence of different multiphysical parameters for a typical simulation and measurement scenario in magnetic drug targeting (MDT) was investigated using orthogonal Taguchi arrays. The parameters were chosen to cover parameters typically varied in the literature [5–7]. Thereby, the number of combinations was reduced from 243 to 9 for the investigated scenarios, which decreases time and costs significantly. The results correctly identified the importance of all parameters, and apart from some outliers, the parameter trends were accurate, too. It is expected that this also holds true for other parameters such as varying sizes of SPIONs. Therefore, using orthogonal Taguchi arrays seems promising to save time and effort while optimizing magnetic steering systems in MDT.

Tab. 6: Influences of the parameters in the measurements.

Parameter	Sum of Squares (SoS)	Importance SS_{p_i}/SS_{total}
velocity flow	$0.652 \cdot 10^{-5}$	11 %
number of magnets	$0.460 \cdot 10^{-5}$	8 %
particle concentration	$1.859 \cdot 10^{-5}$	32 %
inner diameter tube	$2.486 \cdot 10^{-5}$	42 %
distance suscept. $\leftrightarrow$ array	$0.418 \cdot 10^{-5}$	7 %
total	$5.875 \cdot 10^{-5}$	100 %

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