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Many particle magnetic dipole–dipole and hydrodynamic interactions in magnetizable stent assisted magnetic drug targeting

P.J. Cregg [a,*], Kieran Murphy [a], Adil Mardinoglu [a], Adriele Prina-Mello [b,*]

[a] SEAM Centre, Materials Characterisation and Processing Group, Waterford Institute of Technology, Waterford, Ireland
[b] CRANN and School of Physics, Trinity College, Dublin 2, Ireland

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ABSTRACT

The implant assisted magnetic targeted drug delivery system of Avilés, Ebner and Ritter is considered both experimentally (*in vitro*) and theoretically. The results of a 2D mathematical model are compared with 3D experimental results for a magnetizable wire stent. In this experiment a ferromagnetic, coiled wire stent is implanted to aid collection of particles which consist of single domain magnetic nanoparticles (radius ≈ 10 nm). In order to model the agglomeration of particles known to occur in this system, the magnetic dipole–dipole and hydrodynamic interactions for multiple particles are included. Simulations based on this mathematical model were performed using open source C++ code. Different initial positions are considered and the system performance is assessed in terms of collection efficiency. The results of this model show closer agreement with the measured *in vitro* experimental results and with the literature. The implications in nanotechnology and nanomedicine are based on the prediction of the particle efficiency, in conjunction with the magnetizable stent, for targeted drug delivery.

1. Introduction

The development of more effective drug treatment methodologies is an area of much research. In most drug delivery systems much of any drug administered to patients does not reach its target site. The aim of the drug targeting is to decrease the amount of drug delivered to healthy tissue, while maintaining the therapeutic action at the desired site. One such approach is magnetic drug targeting (MDT). For instance magnetic particles can be employed as carriers in a cancer treatment, thereby avoiding the side effects of conventional chemotherapy [1,2]. MDT typically uses an external magnetic field source to capture and retain magnetic drug carrier particles (MDCPs) at a specific site after being injected into the body. Studies have shown that MDT is a relatively safe and effective methodology for targeting drugs to a specific site in the body [3–5]. However, there are some significant limitations of MDT. One limitation associated with MDT is the gradient problem, that is the magnetic force requires a magnetic field gradient. Specifically it can be difficult using external magnets only to target areas deep within the body, without targeting the surface more strongly [6]. To overcome this problem several authors [7–16] have proposed implanting ferromagnetic materials such as wires, seeds and stents within the body. Of the various IA-MTD implants suggested by Ebner, Ritter and co-workers [9–16], we consider a magnetizable stent as the implant, with MDCPs containing magnetic single domain nanoparticles. Previously, by considering high gradient magnetic separation, Mikkelsen et al. [17] have included both the hydrodynamic and dipole–dipole interactions for the case of low magnetic fields. Also, Mehasni et al. have considered the effect of magnetic dipole–dipole interaction on the performance of high gradient magnetic separation systems [18]. Some of the present authors have previously considered the effect of the interactions for two MDCPs on the agglomeration of the MDCPs [19]. Here, we calculate the effect of interactions of many particles on the collection efficiency of the system leading to the agglomeration of particles. Avilés et al. [14] compared the (non-interacting) particle model of this stent system with *in vitro* experimental arrangement using a ferromagnetic stent made in the shape of a coil. Their results indicated that at low fluid velocity more particles were collected than predicted. Furthermore, they suggested that particle agglomeration (due to interparticle interactions) might explain this. With this in mind, we have further developed their mathematical model to include both dipole–dipole and hydrodynamic interactions between many MDCPs. These theoretical results are presented here and are compared with the experimental results of Avilés et al. [14] and new *in vitro* experiments. Simulations are performed using OpenFOAM a finite volume simulation C++ library.

2. Experimental setup

In this experiment ferromagnetic particles with diameter of 0.86 μm containing 45.8 wt% magnetite are used as the MDCPs

* Corresponding authors.
E-mail addresses: pjcregg@wit.ie (P.J. Cregg), prinamea@tcd.ie (A. Prina-Mello).

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(Polysciences Europe GmbH). Stainless steel (SS) 430 (California Fine Wire Co.) is taken as the wire material for the stent with a 62.5 μm radius following Avilés et al. [14]. The stent is prepared by looping a length of wire, L, into a 2 cm long coil having a 0.04 cm radius containing 10 loops, N_l, with 0.2 cm between each loop. Between use, each stent wire is cleaned by a 30 minute sonication in ethanol. A set of 15 identical coil stents are made and cleaned for the full MDT experimental testing.

The stent is firmly positioned within a borosilicate glass capillary tube by interference adhesion against the inner surface of the tube (radius of 0.04 cm). Controlled thickness capillary tubing is used to maximize the contrast between stent and glass curvature for real time video imaging and particle detection. Furthermore, this is also eliminates any turbulence caused by the irregular glass surface roughness. In this experiment we use a capillary glass tube (0.04 cm radius) and particle size proportionally similar to Avilés et al. [14].

The experimental setup is shown in Fig. 1. It consists of a capillary glass tube with a regularly spaced coil stent, an equally spaced pair of single NdFeB permanent magnets (in opposition), connected by tygon tubing to a 2.5 ml syringe where one end is connected to a high precision syringe pump to supply the suspension of MDCPs and the other end is connected to a collection system for collection efficiency measurements. The setup also comprises an inverted microscope connected to a CCD camera for high resolution imaging (QI Micropublisher, USA) and video acquisition. Magnetic field strength is measured by a Hall probe gaussmeter (Lake Shore, USA). The particle, pre- and post-wash buffer solution where precisely injected by using 2.5 ml syringes connected to a high precision syringe pump system and software where it is possible to control injection direction, volume injected, flow rate in relation to the fluid solution injected (Nemesys system, Cetoni Gmbh, Germany). For each solution injected the total concentration is measured, pre- and post-experiment, by flow cytometry technique (Accuri, C6 Flow Cytometer and CFlow plus software, UK). Thus, each experiment had the same initial volume of solution.

Microscopy imaging is carried out using an Olympus microscope (Olympus, Japan) connected to a QI micropublisher camera driven by ImagePro software (Media Cybernetics, UK). Real-time streaming is carried out using Debut software (NCH Software, USA).

An homogeneous particle solution is prepared with the use of full cell culture media (RPMI, Gibco, UK) with the addition of 5% bovine serum albumin (BSA) to make up to a similar viscosity. The concentration of the MDCP solution used here is 4×10^{10} per liter, a lower concentration than that used in the experiment of Avilés et al. [14]. There the concentration was 50 mg/liter which corresponds to 11.2×10^{10} per liter. These concentrations are calculated from the mass of one MDCP. In both concentrations the particles agglomerated and they create clusters. In this study, we use lower concentration of MDCP due to the higher magnetite load single MDCP containing 45.8 wt% magnetite whereas Avilés et al. [14] uses MDCP containing 25 wt% magnetite. To model the behavior of the MDCPs, we use smaller number of the MDCPs for lower concentration to match the experimental setup of Avilés et al. [14].

Once the MDT system is set up, control runs are carried out, with and without magnetic field to calibrate the system and monitor the particle trajectory and agglomeration in the absence of the stent.

The coil stent is then inserted into the tube and two homogeneous magnetic field strengths $\mu_0 H_0 = 0.15$ T and $\mu_0 H_0 = 0.60$ T are applied for different fluid velocities ranging between 0.58 cm/s and 52.6 cm/s. Once the magnetic field is applied the MDCPs were seen to agglomerate and create clusters. Different flow rates were chosen similar to those Avilés et al. [14]. For $\mu_0 H_0 = 0.15$ T magnetic field strength 0.05, 0.1, 0.2, 0.4, 1.0 cm/s injection velocities and for $\mu_0 H_0 = 0.60$ T magnetic field strength 0.2, 0.4, 1.0, 2.0, 4.5 cm/s injection velocities were used.

The amount of the MDCPs collected by the stent is measured by the differential between the MDCP concentration in the collection tube and the known initial particle concentration. Both solutions are measured by flow cytometry in triplicate counts.

After each particle solution injection the magnetic gradient was removed to demagnetize the superparamagnetic particles and to account for the mechanically bound particle residuals (always $< 1\%$ of the overall injected volume).

3. Outline of model

In order to effectively model this system, the 3D geometry of the stent and tube is reduced to 2D slice through the center of the tube (See Fig. 2). Thus the coiled stent is modeled as a series of circular cross sections of an infinite wire with radius of R_{wire} located at the upper and lower boundaries of the walls. At each wall the wires are separated by a distance, h, between their centers, and the upper and lower sections are offset by $h/2$ as shown in Fig. 2. It should be noted that physically this

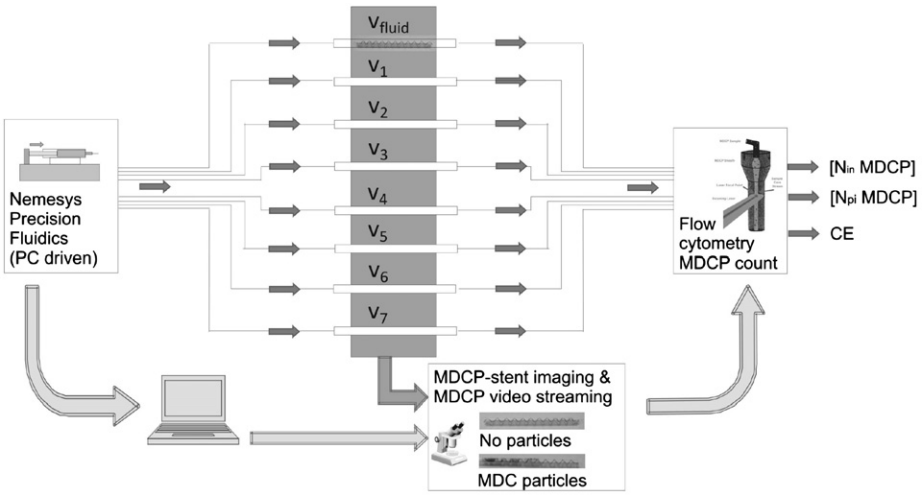

Fig. 1. Schematic diagram of the *in vitro* experimental setup used to study a stent-based IA-MDT system.