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# High Gain Observer for Backstepping Control of a MRI-guided Therapeutic Microrobot in Blood Vessels

Laurent Arcese, Ali Cherry, Matthieu Fruchard, Antoine Ferreira

**Abstract**— This paper reports modeling, control and observation of a microsized polymer aggregate of magnetic particles inside an artery, using a MRI device for supplying propulsion in order to achieve targeted chemotherapy. Non-newtonian behaviour of blood is taken into account, as well as wall effects and interactions, resulting in a highly nonlinear model. A backstepping approach is synthesized to ensure Lyapunov stability along a pre-planned trajectory inherited from the model, with robustness concerns.

This paper reports modeling and control of a microsized polymer aggregate of magnetic particles inside an artery, using a MRI device for supplying propulsion in order to achieve targeted chemotherapy. Non-newtonian behaviour of blood is taken into account, as well as wall effects and interactions, resulting in a highly nonlinear model. A backstepping approach is synthesized to ensure Lyapunov stability along a pre-planned trajectory inherited from the model, with robustness concerns.

## I. INTRODUCTION

Minimally invasive cancer therapy is currently an active research area since related techniques can both reach remote places without operating and reduce drug or radiation dose. Thereby, they result in lessened medical side effects and a better therapeutic efficiency and safety. Among these approaches, cathetered embolization, focused ultrasound or radiotherapy [12] are commonly used, though restricted to accessible places or limited by the non ability to target precisely tumor cells. These drawbacks can be avoided by targeted chemotherapy, which relies on a selective delivery using either drugs linked to antibodies specific for tumor-associated antigens [16], or drugs carried by autonomous untethered microrobots controlled so as to reach the tumor. However, it proves difficult to embed actuators sufficiently powerful to propel such robots in the cardiovascular system, especially when swimming against the blood flow. Most of swimming approaches consequently rely upon magnetic fields to wirelessly transmit power to the microrobot [5], [8], [1].

A recent magnetic actuation, particularly well-suited for medical purposes, has been provided by Martel [14]. The authors improve the classical bead pulling through the use of the gradients coils of clinical MRI devices to provide propelling power. On top of that, the relevance

of using clinical MRI devices is twofold: they are widely spread in hospitals, and their imaging ability yields fine observation of the robot's position in the cardiovascular system. The control and imaging multiplexing has already been experimented in [17].

As the smallest capillaries are under a dozen micrometers large, the size of the robot should not exceed 100 nanometers [4] to avoid embolization hazards and to drive the drugs as close as possible to the tumor. However, forces induced by clinical MRI coils are not strong enough to steer nanorobots in larger vessels. Besides, hydrodynamics wall effects show that a partial vessel occlusion by the robot results in an optimal ratio between the robot's and the vessel's radii [14], [20]. A natural way of overcoming the MRI limitations is thus to make the radius of the robot decrease as it enters smaller vessels, e.g. with a microrobot made of a degradable polymer binded aggregate of magnetic particles.

We first define a precise forces balance (Section II), which includes wall effects (parabolic profile of blood flow, pulsatile arterial walls and effect of the ratio of robot's on vessel's radii), wall interactions (Van der Waals and electrostatic forces) and non-Newtonian behaviour of blood. Although this forces balance results in a highly nonlinear model (even if considering the sole hydrodynamics forces), the great majority of related literature, to our knowledge, synthesizes control laws using linear tools. Besides, there is no consideration about observation issues. Hence, instabilities or sensitivity to noise or to unmodeled dynamics, reported for instance in [17] with a PID controller, could have been expected. We show that a backstepping control approach (Section III), designed for this specific non linear model, improves the quality and robustness of the tracking along a reference trajectory. As the MRI imager only measures the robot's position, we develop a high gain observer (Section IV) to rebuild the microrobot's velocity, which is required to implement the control law. In Section V, simulation experiments illustrate the benefits of using this controller-observer pair in an arteriole with minor bifurcations. In particular, the high gain observer, designed so as to ensure robustness to noise measurement, greatly smoothen the output and in turn improves the overall tracking efficiency. Finally, conclusion and prospects are discussed in the last section.

## II. MODELING: FORCES BALANCE

The purpose of this section is to present a 2D state space model of a ferromagnetic microrobot of radius  $r$  immersed

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in blood vessel. The model encompasses the different forces that affect the robot's motion as well as its interaction with the vessel wall. The translational and rotational motions of the robot are expressed by:

$$\begin{cases} m \frac{d\vec{v}}{dt} = \vec{F}_m + \vec{F}_d + \vec{W}_a + \vec{F}_c + \vec{F}_{vdw} + \vec{F}_{elec} \\ J \frac{d\vec{\omega}}{dt} = \vec{T}_m + \vec{T}_d + \vec{M}_c \end{cases} \quad (1)$$

where  $\vec{v}$  and  $\vec{\omega}$  are, respectively, the translational and rotational velocity of the robot,  $m$  and  $J$  its mass and moment of inertia.  $\vec{F}_m$ ,  $\vec{F}_d$ ,  $\vec{W}_a$ ,  $\vec{F}_c$ ,  $\vec{F}_{vdw}$  and  $\vec{F}_{elec}$  respectively denote the magnetic force produced by the MRI gradient coils, blood hydrodynamic drag force, apparent weight, the robot-to-wall contact force, the Van der Waals force and the electrostatic force.  $\vec{T}_m$ ,  $\vec{T}_d$  and  $\vec{M}_c$  denote respectively the magnetic torque, hydrodynamic drag torque and the robot-to-wall contact moment.

In the rest of this paper, we assume that the orientation of the robot does not change due to the magnetic torque which tends to align the magnetization of the robot along the external field.  $\vec{T}_d$  and  $\vec{M}_c$  are much smaller order than  $\vec{T}_m$ .

To determine whether statistical mechanics or continuum mechanics formulations of fluid dynamics should be used, we refer to the dimensionless Knudsen number  $K_n = \frac{k_b T}{P \pi r^3 2^{5/2}}$ , where  $T$ ,  $k_b$  and  $P$  respectively denote temperature, the Boltzmann constant and pressure. In our case, the low value  $K_n \approx 10^{-13}$  ( $\ll 10^{-3}$ ) ensures that the robot is large enough to neglect the effect of Brownian motion: the robot's motion is subjected to generic Navier-Stokes equations.

#### A. Magnetic force

The gradient coils of the MRI system provide magnetic gradients which produce a magnetic force  $F_m$  on the robot:

$$\vec{F}_m = \tau_m \mu_0 V (\vec{M} \cdot \nabla) \vec{H} \quad (2)$$

where  $V$  is the robot's total volume,  $\tau_m = \frac{V_m}{V}$  with  $V_m$  the ferromagnetic volume,  $\vec{M}$  is the magnetization of the material,  $\mu_0$  is the permeability of free space,  $\vec{H}$  is the external magnetic field and  $\nabla$  is the gradient operator.

#### B. Hydrodynamic drag force

The hydrodynamic drag force  $\vec{F}_d$  exerting on a spherical body in an infinite extent of fluid is expressed as:

$$\vec{F}_d = -\frac{1}{2} \rho_f (\vec{v} - \vec{v}_f)_\infty^2 A C_{d_\infty} \quad (3)$$

where  $\vec{v} - \vec{v}_f$  denotes the relative velocity of the robot with respect to the fluid,  $A$  is the frontal area of the core and  $\rho_f$  is the density of the fluid.  $C_{d_\infty}$  is the drag coefficient, a dimensionless quantity used to quantify the drag or resistance of an object in a fluid.  $C_{d_\infty}$  is a function of the Reynolds number  $Re_\infty = \frac{2r\rho_f|\vec{v}-\vec{v}_f|_\infty}{\eta}$ ; its expression for a spherical body in laminar flow is given by [21]:

$$C_{d_\infty} = \frac{24}{Re_\infty} + \frac{6}{1 + \sqrt{Re_\infty}} + 0.4$$

1) *Non-Newtonian fluid*: In case of blood, which exhibits a non-newtonian behavior, the fluid's viscosity  $\eta$  is a function of vessel diameter  $d$  (in micron) and hematocrit rate  $h_d$  according to the following empirical relations [15]:

$$\eta = \frac{\eta_{plasma} d^2}{(d-1.1)^2} \left[ 1 + \frac{(\eta_{0.45} - 1) d^2}{(d-1.1)^2} \frac{(1-h_d)^c - 1}{(1-0.45)^c - 1} \right]$$

with parameters  $\eta_{plasma}$  and  $\eta_{0.45}$  denoting respectively the plasma's viscosity and the relative apparent blood viscosity for a fixed discharge hematocrit of 0.45, given by:

$$\eta_{0.45} = 6 e^{-0.085d} + 3.2 - 2.44 e^{-0.06d^{0.645}}$$

The shape of the viscosity dependance on hematocrit is:

$$c = \frac{10^{11}}{d^{12}} - (0.8 + e^{-0.075d}) \left( \frac{d^{12}}{d^{12} + 10^{11}} \right)$$

2) *Wall effects*: For endovascular applications, influence of the vessel walls on the velocity of the robot has to be taken into account. In general, this wall effect is expressed as a ratio between the terminal relative velocity of the robot  $(\vec{v} - \vec{v}_f)_t$  and its velocity  $(\vec{v} - \vec{v}_f)_\infty$  in an infinite extent of fluid [11]:

$$\frac{|\vec{v} - \vec{v}_f|_t}{|\vec{v} - \vec{v}_f|_\infty} = \frac{1 - \lambda^{\alpha_0}}{1 + \left(\frac{\lambda}{\lambda_0}\right)^{\alpha_0}} \quad (4)$$

with ratio  $\lambda = 2r/D$  and  $D$  denoting the vessel diameter (in meter). Parameters  $\alpha_0$  and  $\lambda_0$  are functions of Reynolds number, but are commonly set to 1.5 and 0.29, respectively.

Thus, equation (3) is corrected as follows:

$$\vec{F}_d = -\frac{1}{2} \rho_f \left[ \left( \frac{1 + \left(\frac{\lambda}{\lambda_0}\right)^{\alpha_0}}{1 - \lambda^{\alpha_0}} \right) (\vec{v} - \vec{v}_f)_t \right]^2 A C_{d_t} \quad (5)$$

Wall effects on the fluid in the vessel traditionally result in a parabolic profile of blood flow (see Figure 1). Besides, to fully take into account pulsatile flow caused by heart pumping in arteries, one has to consider a periodic deformation of the vessel's diameter  $D(t)$  synchronized with  $v_f(t)$ .

#### C. Apparent weight

In addition to the magnetic and hydrodynamic forces, apparent weight (combined action of weight and buoyancy) is acting on the spherical robot:

$$\vec{W}_a = V(\rho - \rho_f) \vec{g} \quad (6)$$

where  $\rho = \tau_m \rho_m + (1 - \tau_m) \rho_{poly}$  with  $\rho_m$  and  $\rho_{poly}$  the magnetic material's and polymer's densities.

#### D. Contact force

The normal and tangential interaction between the robot and the wall are assumed to be expressed by a Voigt model with the spring constant  $K$  and the decay coefficient of dashpot  $b$ , as shown in Figure 2, where the indexes  $\vec{n}$  and  $\vec{t}$  indicate respectively the normal and tangential normalized vectors.

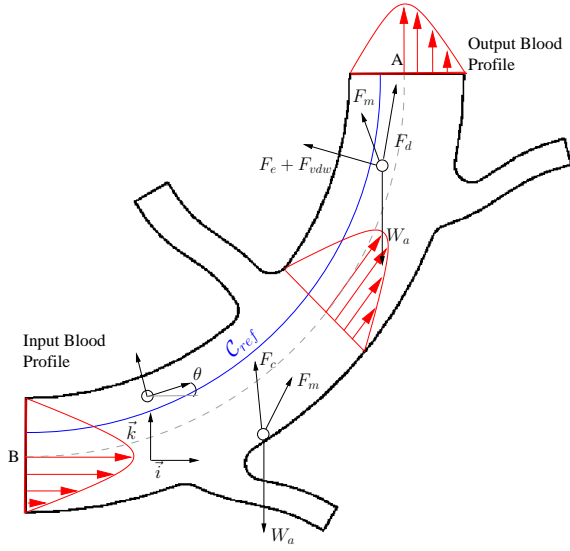


Fig. 1. Scheme of a blood vessel with minor bifurcations

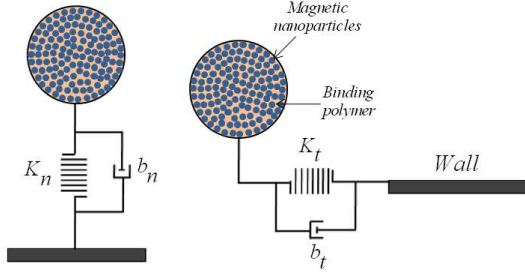


Fig. 2. Model of contact forces: robot-to-wall

The normal component of the contact force  $\vec{F}_{cn}$  acting on the robot is given by the sum of a non-linear elastic component and a linear viscous damping: [18]:

$$\vec{F}_{cn} = (K_n \delta^{3/2} + b_n \dot{\delta}) \vec{n} \quad (7)$$

where  $\delta$  is the elastic deformation of the wall at the contact point and  $\vec{n}$  is the normal unit vector pointing from the robot to the contact surface. The stiffness  $K_n$  can be calculated by Hertzian contact theory [19] as follows:

$$K_n = \frac{\frac{4\sqrt{r}}{3}}{\frac{1-\sigma_p^2}{E_p} + \frac{1-\sigma_w^2}{E_w}}$$

where  $E_p$  and  $E_w$  are the Young's modulus of robot and wall, and  $\sigma_p$ ,  $\sigma_w$  are respectively the Poisson's ratios of robot and wall. The damping coefficient  $b_n$  is deduced from  $K_n$  using  $b_n = 2\sqrt{mK_n}$ .

The tangential component of the contact force takes part when the robot is rotating or in case of oblique collision with the wall:

$$\vec{F}_{ct} = (K_t \zeta + b_t \dot{\zeta}) \vec{t} \quad (8)$$

where  $\zeta$  is the displacement in the tangential direction and  $\vec{t}$  is the tangential unit vector. The stiffness  $K_t$  and damping

coefficient  $b_t$  are given by:

$$K_t = \frac{8\sqrt{r}G_p}{2-\sigma_p} \delta^{1/2}, \quad b_t = 2\sqrt{mK_t}$$

where  $G_p$  is the shear modulus related to the Young's modulus  $E_p$  and Poisson ratio  $\sigma_p$ , i.e.  $G_p = \frac{E_p}{2(1+\sigma_p)}$ .

### E. Van der Waals and electrostatic forces

When the robot and the wall are not in contact, they interact each other through Van der Waals and electrostatic forces. These two interaction forces have different dominant regimes. In fact, when the robot is close to the wall, Van der Waals force is dominant. As the robot move away from the wall, the Van der Waals force rapidly decrease and the electrostatic force becomes dominant.

The Van der Waals potential between the robot and the wall is given by [9]:

$$\vec{V}_{vdw} = -\frac{A_h}{6} \left( \frac{1}{h} + \frac{1}{2+h} + \ln \frac{h}{2+h} \right) \vec{n} \quad (9)$$

where  $A_h$  is the Hamaker constant and  $h$  is the distance between robot and wall. Then, the Van der Waals interaction force is given by differentiating (9)  $\vec{F}_{vdw} = -\nabla \vec{V}_{vdw}$ . The electrostatic force between the robot and the wall considered as an uncharged surface is given by [6]:

$$\vec{F}_{elec} = \frac{q^2}{4\pi\epsilon\epsilon_0(r+h)^2} \vec{n} \quad (10)$$

with  $q$  the robot charge,  $\epsilon$  the dielectric density of the medium in which the interaction occurs and  $\epsilon_0$  the vacuum permittivity.

[7] gives the expression of the maximum allowable charge  $Q = 30 \times (100r)^{-0.3}$  for a spherical body of radius  $r$ .

## III. MODELING: OPTIMAL TRAJECTORY

Previous forces balance gives us sufficient informations to plan an optimal trajectory. At least two cases A and B, shown on the Figure 1, should be taken into account. In the first one, the robot is in a vertical vessel and the magnetic force  $\vec{F}_m$  should counter both contributions of the robot's apparent weight  $\vec{W}_a$  and the drag force  $\vec{F}_d$  when blood is flowing back (Curve A of Figure 3). The drag force decreases when the robot approaches the wall due to the parabolic profile of velocity. Thus the reference trajectory should be as near as possible to wall. In the second case, the robot is in a horizontal vessel and the magnetic force should counter contributions of the robot's apparent weight, electrostatic and Van der Waals forces,  $\vec{F}_{elec}$  and  $\vec{F}_{vdw}$  (Curve B of Figure 3). This case shows that near the wall,  $\vec{F}_{elec}$  and  $\vec{F}_{vdw}$ , which point to the wall, are dominant and the magnetic force is no more sufficient to counter it. Nevertheless there is an optimal position where the sum of the two forces compensates perfectly the robot's weight. Moreover, the curve A shows that at this point, the magnetic force exceeds the drag force. From these observations, we define an optimal path as an arc passing through the point C.

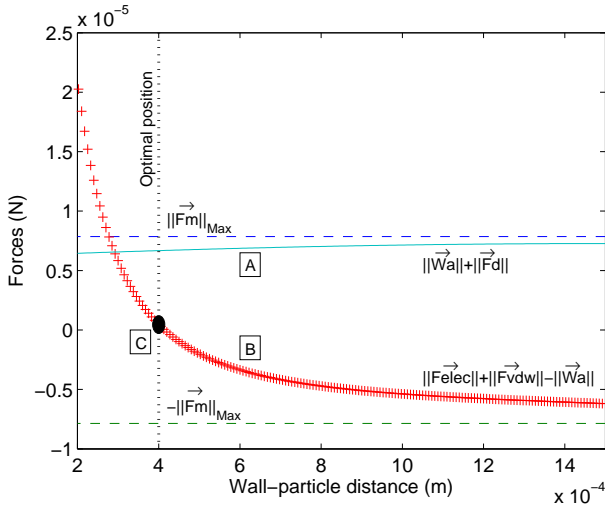


Fig. 3. Forces balances in vertical (A) and horizontal (B) artery

#### IV. MODELING: STATE SPACE REPRESENTATION

Let  $(x, z)$  denote the position of the robot in the vessel with respect to a given frame  $\mathcal{F}(O, \vec{i}, \vec{k})$ . The state model is established from differential equation (1) defining the robot's dynamic behavior, projected on  $\vec{i}$  and  $\vec{k}$  axes:

$$\begin{cases} m\ddot{x} = F_{m_x} + F_{d_x} + F_{c_{n_x}} + F_{c_{t_x}} + F_{v_{d_w_x}} \\ m\ddot{z} = F_{m_z} + F_{d_z} + W_a + F_{c_{n_z}} + F_{c_{t_z}} + F_{v_{d_w_z}} \end{cases} \quad (11)$$

where indexes  $x$  (respectively  $z$ ) denote projections on  $\vec{i}$  ( $\vec{k}$ ).

Let  $x_1, x_2, x_3, x_4$  denote respectively the particle's position and velocity along  $\vec{i}$  axis, and the position and velocity along  $\vec{k}$  axis. Assuming that positions  $x_1$  and  $x_3$  can be measured thanks to the MRI imaging system, let  $y$  denote the state's measure. Using expressions of forces given by (2), (5), (6), (7), (8), (10) and Van der Waals interaction derived from potential (9), and adequate projection of local frame along the geometry of the vessel<sup>1</sup>, system (11) can be written in the form:

$$(\mathcal{S}) \begin{cases} \dot{x}_1 = x_2 \\ \dot{x}_2 = f_2(x_1, x_2, x_3, x_4) + au_1 \\ \dot{x}_3 = x_4 \\ \dot{x}_4 = f_4(x_1, x_2, x_3, x_4) + au_2 \\ y = \begin{pmatrix} x_1 \\ x_3 \end{pmatrix} \end{cases} \quad (12)$$

where control inputs  $u_1 = \nabla B_x$  and  $u_2 = \nabla B_z$  are the magnetic gradients, parameter  $a = \frac{\tau_m M}{\rho}$ , and  $f_i$  are very highly nonlinear functions of the full state.

#### V. CONTROL APPROACH

In this section, we present a control design for Lyapunov-stabilizing trajectories for system  $(\mathcal{S})$ . Since determination of Lyapunov functions is generically a challenging issue, it is preferable to use Lyapunov control functions in a backstepping control approach [13], [10]. Since this design

<sup>1</sup>The drag force is not linearly distributed between  $\vec{i}$  and  $\vec{k}$  axis.

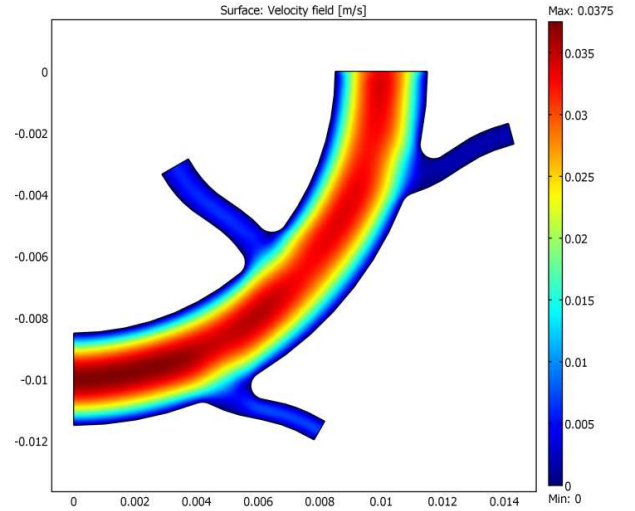


Fig. 4. Consol results : Velocity profile in a blood vessel with minor bifurcations

requires a triangular form for the control system, we propose the following change of coordinates:

$$\begin{cases} X = \begin{pmatrix} x_1 \\ x_3 \end{pmatrix}; \quad Y = \begin{pmatrix} x_2 \\ x_4 \end{pmatrix}; \quad U = \begin{pmatrix} u_1 \\ u_2 \end{pmatrix} \end{cases} \quad (13)$$

Thus, we obtain a new system in a triangular form:

$$(\mathcal{S}') \begin{cases} \dot{X} = Y \\ \dot{Y} = F(X, Y) + U \\ y = X \end{cases} \quad (14)$$

Denoting  $X_{ref}$ ,  $\dot{X}_{ref}$  and  $\ddot{X}_{ref}$  respectively the desired reference trajectory, velocity and acceleration, the control law for system  $(\mathcal{S}')$  can be expressed as [3]:

$$U = \ddot{X}_{ref} + (k_1 + k_2)\dot{X}_{ref} + (1 + k_1 k_2)X_{ref} - (1 + k_1 k_2)X - (k_1 + k_2)Y - F(X, Y) \quad (15)$$

where  $k_1$  and  $k_2$  are the strictly positive backstepping gains.

#### VI. SIMULATIONS

The robot is made of  $\tau_m = 80\%$  NdFeB particles which has a combination of very high remanence and coercivity, and 20% of binding polymer. Simulations are performed by taking into account the limitations of a clinical MRI system. In order not to exceed the capacity of existing MRI systems, the applied control law (15) is now corrected as  $\frac{u_i}{k(t)}$ , with  $k(t) = \max\left\{1, \frac{u_i}{u_{i,max}}\right\}$ .

A pulsatile flow is included by imposing a time-varying velocity. As a first approximation of a physiological pulse, we use a time-sinusoidal profile with spatial parabolic form. In the case of artery, such an approximation leads to:

$$v_f(t) = 0.035(1 + 1.15 \sin 2\pi t) \times \left[1 - \left(\frac{D/2 - h}{r}\right)^2\right]$$

Our studies assume the presence of minor bifurcations (see Figure 1). This geometry leads to only slight change

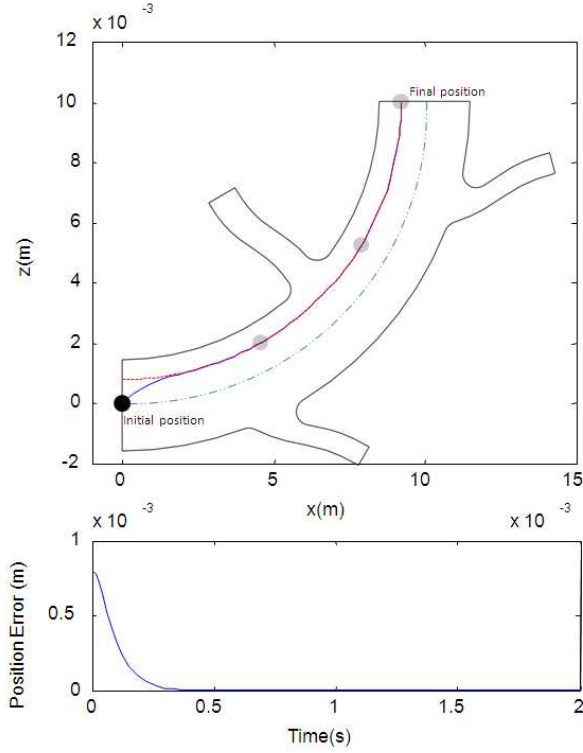


Fig. 5. XZ trajectory : reference trajectory (red dotted) and real trajectory (blue solid line)

in the velocity's profile and amplitude (see Figure 4). The developed controller must be sufficiently robust to compensate this effect which could be considered as a disturbance. Major bifurcations will require a further study of velocity's field profile.

The purpose of the control is to ensure a null error between desired and a pre-planned trajectory. In the following, the performances and stability of the controller with respect to noise measurement, parameters variations and uncertainties are illustrated by two simulations, whose parameters are given in Table I. A first simulation is led so as to pinpoint robustness to model errors, and the second one to study sensitivity to output noise.

Simulation of Figures 5, 6 is performed by assuming that the blood's viscosity and permittivity are affected by uncertainties of 100% of their nominal values and the vessel's diameter by uncertainties of 10%. This simulation shows that after a transient phase, the position tracking performance is robust enough to model's error (subfigure of Figure 5). Despite these uncertainties, Figure 6 shows that the control inputs don't reach saturation. This is due to the choice of an optimal reference trajectory deduced from the analysis of Section III.

In a second simulation (Figures 7 and 8), we assume a white gaussian noise is applied on the position measurement. This noise is about 10% of the measured signal. Figure 7 illustrate that the controller is quite stable despite the noise, and does not even reach saturations (Figure 8). Nevertheless,

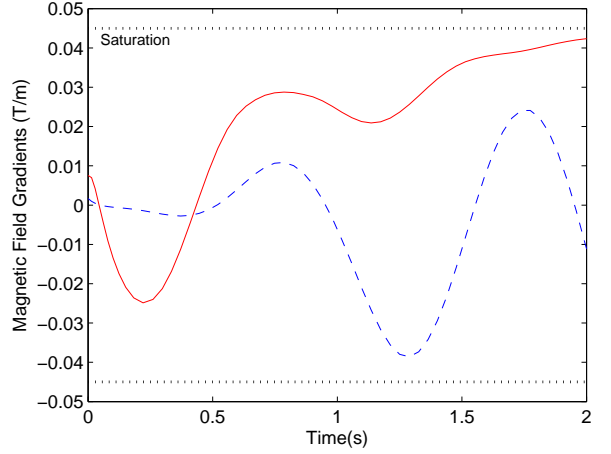


Fig. 6. Control input : magnetic field gradients on  $\vec{i}$ -axis (dotted) and on  $\vec{k}$ -axis (solid line)

TABLE I  
SIMULATIONS DATA

|                            |                 |                               |
|----------------------------|-----------------|-------------------------------|
| Plasma's viscosity         | $\eta_{plasma}$ | $5 \times 10^{-3} [Pa.s]$     |
| Blood's density            | $\rho_f$        | $1060 [kg.m^{-3}]$            |
| Robot's density            | $\rho_m$        | $8000 [kg.m^{-3}]$            |
| Robot's radius             | $r$             | $300 [\mu m]$                 |
| Vessel's diameter          | $D$             | $3 [mm]$                      |
| Polymer's density          | $\rho_{poly}$   | $1500 [kg.m^{-3}]$            |
| Ferromagnetic ratio        | $\tau_m$        | 0.8                           |
| Magnetization              | $M$             | $1.95 \times 10^6 [A.m^{-1}]$ |
| Hematocrit                 | $h_d$           | 0.45                          |
| Robot's Young's modulus    | $E_p$           | $10^9 [Pa]$                   |
| Wall's Young's modulus     | $E_w$           | $0.75 \times 10^6 [Pa]$       |
| Robot's Poisson's ratio    | $\sigma_p$      | 0.27                          |
| Wall's Poisson's ratio     | $\sigma_w$      | 0.30                          |
| Hamaker constant           | $A_h$           | $4 \times 10^{-19} [J]$       |
| Blood's dielectric density | $\epsilon$      | $77 [C^2.N^{-1}.m^{-2}]$      |
| Initial condition on $x$   | $x_0$           | $(0, 0, 0, 0)^T$              |
| Inputs saturations         | $u_{i,max}$     | $45 [mT.m^{-1}]$              |
| Controller gains           | $k_1$           | 15                            |
|                            | $k_2$           | 30                            |

it's clear that the system is sensitive to noise. We can expect that this drawback effect can be reduced using an observer. In addition to estimate some parameters like blood's velocity (assumed to be known in this paper), an observer will tend to smooth the output signals.

## VII. CONCLUSION

In this paper, we have presented a highly nonlinear model for a MRI guided microrobot in blood vessels. This model takes into account the non-newtonian behavior of blood, as well as wall effects and interactions. It makes it possible to hence deduce an optimal trajectory. Besides, we have developed a nonlinear control law based on the backstepping approach. Parameters uncertainties and noise effects have been illustrated by simulations. It appears that the system is robust to uncertain physiological parameters, but proved quite sensitive to output noise, though remains stable.

As stated in Section VI, system robustness to noise can be improved by implementing a high gain observer based on

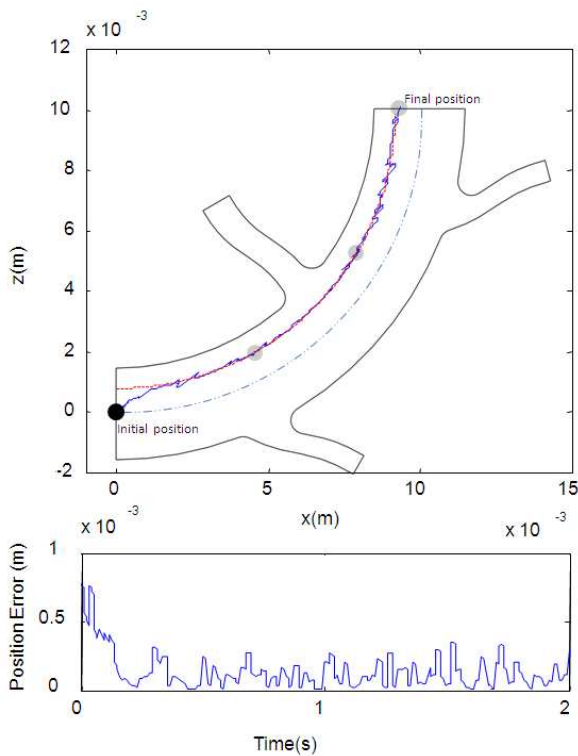


Fig. 7. XZ trajectory : reference trajectory (red dotted) and real trajectory (blue solid line)

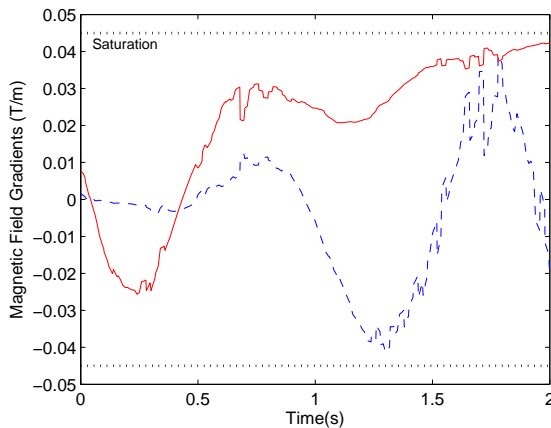


Fig. 8. Control input : magnetic field gradients on  $\vec{i}$ -axis (dotted) and on  $\vec{k}$ -axis (solid line)

[3] but fitted for this more complete and complex model. We are also working on estimating the blood's velocity and frequency, assumed to be known at the moment, using Kazantis-Kravaris Luenberger observers [2]. Additionally, the modeling of impact of major bifurcations on the blood's velocity profile is underway.

## VIII. ACKNOWLEDGMENTS

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