PROJECT ACRONYM

**CUPIDO**

PROJECT TITLE

**Cardio Ultraefficient nanoParticles for Inhalation of Drug prOducts**

# Deliverable 4.4

# Extended model, describing relationship between FeCaPs and deposition site when exposed to an external magnetic field

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# Table of Revisions

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| 1 | 21/01/2018 | Document preparation | Alexandra K. Diem and Kristian Valen-Sendstad |
| 2 | 22/01/2018 | Document revision | Daniele Catalucci |
| 3 | 30/01/2018 | Document revision | IPR Team |
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# 1. Executive summary

This WP is devoted to computational modeling and simulation of cardiac biophysical phenomena, which is of critical relevance for accelerating the translatability and use of CaP toward human biomedical research. In particular, the use of simulations will allow refining experimental studies and better bridging of small to large animal research and eventually to humans. In this WP, simulation of electromagnetic fields will be performed to assess the effect on heart tissues (task 4.1). In addition, computer simulations will predict blood flow and the resulting distribution of CaPs and FeCaPs in/through the cardiovascular system and evaluate the effects of forces from an electromagnetic field on FeCaPs distribution.

SIM will model the cardiac perfusion for CaP deposition prediction taking the whole heart into account, *i.e.* multi-scale modeling spanning orders of magnitude from millimeters to nanometers. Blood flow modeling through the rest of the cardiovascular system will be based on reduced order modeling (1D) coupled with algebraic deposition models. SIM will then couple the 1D model with a 3D model of the flow in the coronary arteries (left anterior descending/left circumflex arteries) and a multi-scale poromechanical formulation at the (sub-) capillary level. In addition, SIM will use a coupling between the fluid and CaPs, which will be described with an advection-diffusion-reaction equation to study passive transport through the vascular network accounting for various physico-chemical parameters developed in sub-task 4.2.1. The models will be implemented in the finite element method library FEniCS in combination with SIM open-source flow framework. BET will provide SIM with input from WP3, which are subject-specific DICOM images that will be segmented using the Vascular Modeling Toolkit provided in both rodents and swine, together with biopsy nanoparticle deposition studies to parametize deposition models. This work will create an iterative platform with WP1 and 3, helping to optimize CaP for idealized delivery, and to suggest specific experimental studies to reduce the number of animals required to adequately test the nanoparticle concept.

**Key deliverable achievements**:

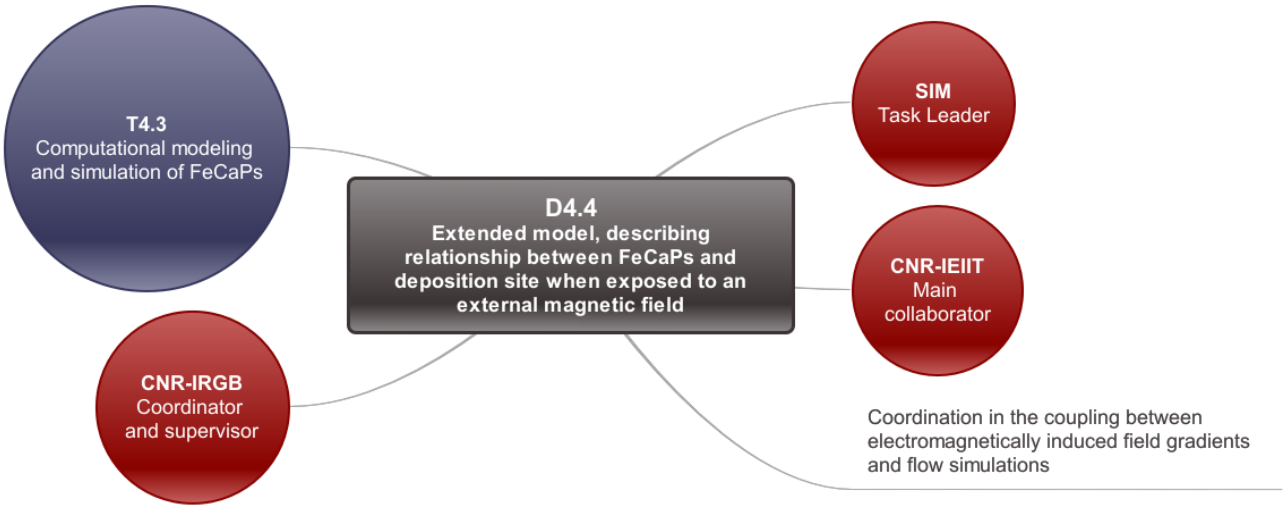
1) Accounting for electromagnetic field (gradients) in the in the finite element method library FEniCS in combination with SIM open-source flow framework.

2) Implementation of Darcy's equations.

3) Accounting for a heterogeneous and highly anisotropic medium by including statistical cardiac fiber orientation obtained from magnetic resonance image acquisitions.

## 2. Cooperation between participants

There has been multiple Skype meeting between CNR-IEIIT (Milan) and SIM to coordinate the coupling between electromagnetically induced field gradients and flow simulations. In addition to that, CNR-IEIIT (Genoa) has been included several times to plan laboratory experiments and purchase of relevant equipment. The coordinator has also been involved occasionally. We have also had multiple email exchanges and the cooperation and communication has been satisfactory.



## 3. Accounting for electromagnetic field (gradients) in the in the finite element method library FEniCS in combination with SIM open-source flow framework

Oasis is a high-level/high-performance finite element Navier–Stokes solver written from scratch inPython using building blocks from the FEniCS project (fenicsproject.org). The solver is unstructured and targets large-scale applications in complex geometries on massively parallel clusters. Oasis utilizes MPI and interfaces, through FEniCS, to the linear algebra backend PETSc. Oasis advocates a high-level, programmable user interface through the creation of highly flexible Python modules for new problems. Through the high-level Python interface the user is placed in complete control of every aspect of the solver. A version of the solver, that is using piecewise linear elements for both velocity and pressure, is shown to reproduce very well the classical, spectral, turbulent channel simulations of Moser et al. (1999). The computational speed is strongly dominated by the iterative solvers provided by the linear algebra backend, which is arguably the best performance any similar implicit solver using PETSc may hope for. Higher order accuracy is also demonstrated and new solvers may be easily added within the same framework. Figure 1 shows a snapshot of an idealized turbulent channel flow. Exposure to an electromagnetic field is not shown due to the preliminary nature of the WP; patient-specific electromagnetic fields will be tested at a later point.

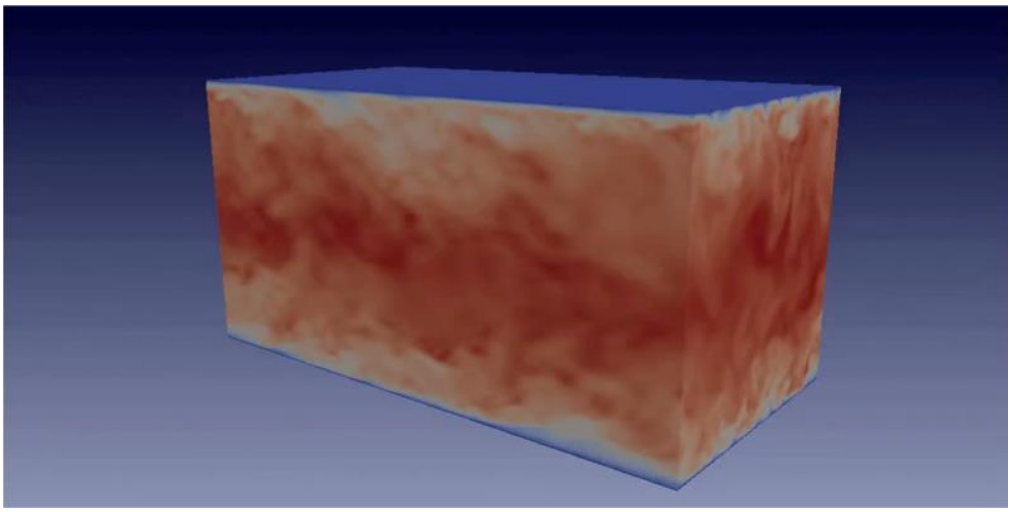


Figure 1. Example of the performance of the Navier-stokes solver Oasis that showed excellent performance and accuracy versus state-of-the-art benchmarks.

## 4. Implementation of Darcy's equations and accounting for a heterogeneous and highly anisotropic medium by including statistical cardiac fiber orientation obtained from magnetic resonance image acquisitions

Blood is delivered to the myocardium via a dense intramural network of blood vessels, consisting of both small arteries and capillaries. Because of the large number of individual small blood vessels, it is neither feasible nor useful to model flow through each individual blood vessel. Instead, we model perfusion in the myocardium as a porous medium using Darcy's law in the standard fashion. Darcy's law relates the macroscopic flow rate through the medium u to the fluid pressure p via the permeability parameter K:

$$u = -K\nabla p.$$

Additionally, the fluid is considered to be incompressible.

$$\nabla \cdot u = 0.$$

Note that this does not mean that the porous medium as a whole is incompressible – the solid matrix will be considered an elastic medium. When modeling the myocardium it is important to take directionality of fibers and blood vessels into account. This can be achieved by implementing K as an inhomogeneous tensor to reflect varying permeabilities in varying directions. We have implemented a test case using the permeability tensor:

$$K = k(x,y)I,$$

where I is the identity matrix and

$$k(x,y) = \max\left\{\exp\left[-\left(\frac{y-\frac{1}{2}-0.1\sin(10x)}{0.1}\right)^2\right], 0.01\right\}$$

In a 3D Cartesian coordinate system this results in an inhomogeneous permeability, displaying a sinusoidal wave in the xy-plane. The boundary condition p = 1 – x is applied in the xy-plane. Figure 2 demonstrates the result of this test case and demonstrates the feasibility of using Darcy's law to model inhomogeneous porosity in the myocardium.

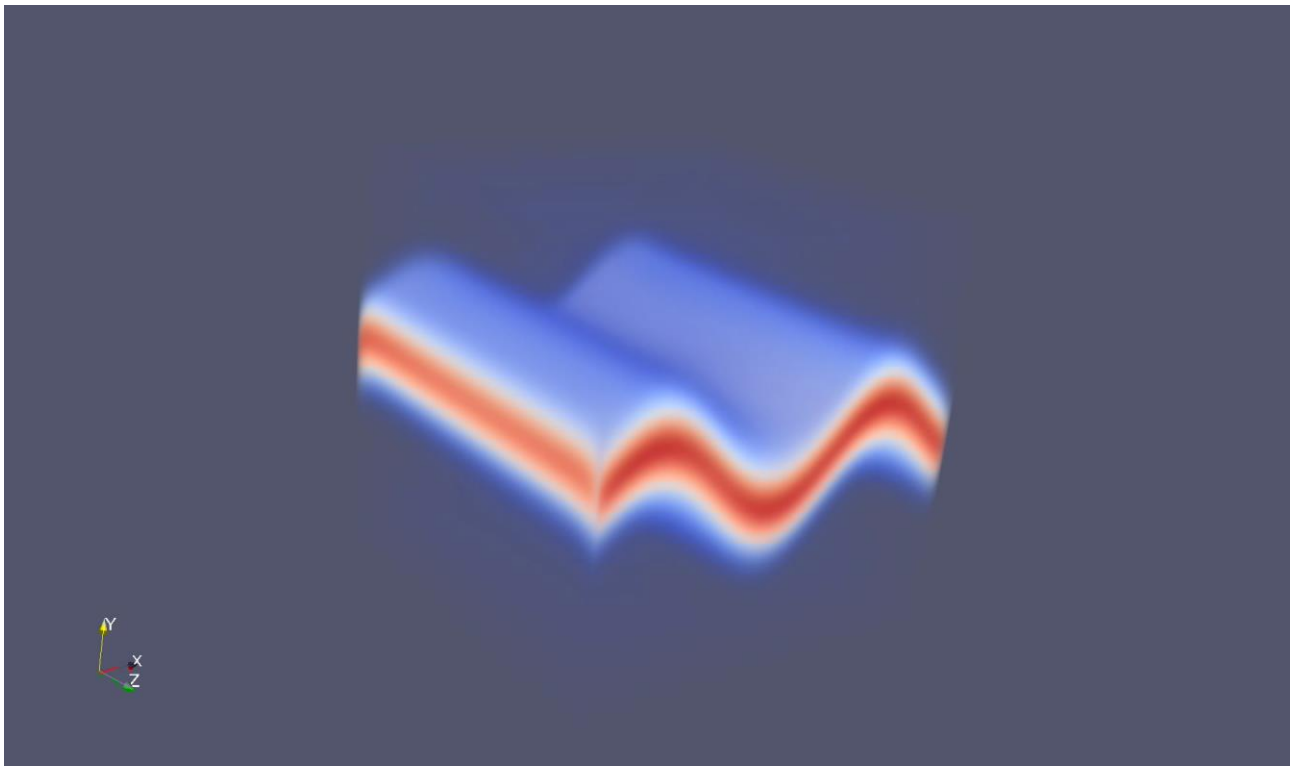



Figure 2. FENICS results of the implementation of Darcy's equation exposed to a pressure gradient and variable permeability tensor.

## 5. Conclusions

The deliverables D4.4 is well on track, and the work-in-progress is good. After just 6 months of work, all main building blocks are in place. Next steps will be related to couple them together, i.e., Navier-Stokes with multi-compartmental Darcy, both with and without an electromagnetic field in animal-specific models.