VPH-NoE
Exemplar Project Proposal

Project title: POP (from PDE to ODE and back)
An integration tool for multiscale simulation

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Estimated costs:
The estimated cost for a postdoc to be employed in the PI Institution will be 4000 Euro per person-month, for a period of 12 months.

Current funding for the project:
All the core technology involved has been developed in the following previous projects:
- FIRB Research Project funded by MIUR (Ministero dell'Istruzione, Università e Ricerca Italiana) on Interdisciplinary Laboratory of Bioinformatics Technologies (LITBIO) 2005-2010. `http://www.litbio.org`.
- Strategic Project funded by MIUR on Oncology over Internet Methodologies, Models, Techniques and Tools, per information extraction and retrieval (O2I). 2002-2005.

We have recently established a collaboration to apply this core technology to the VPH modelling problems with the Rizzoli Institute (IOR), based on internal funding.
The EP grant would give us the possibility to generalise the work and deliver a tool useful to the vast majority of VPH projects.

Letter of the Head of the School of Science and Technology:
It is attached to the end of this document.

Letter of Prof. Rod Hose, on behalf of USFD and UPS teams (VPH-NoE Core Members), supporting POP project:
It is attached at the end of to this document.

Project Summary

The **POP** (From PDE to ODE and back) project addresses the challenge of efficiently integrating some well-known heterogeneous Ordinary Differential Equation (ODE)- and Partial Differential Equation (PDE)-based simulation tools pertaining to the Virtual Physiological Human (VPH) ToolKit domain. The main objectives of the **POP** project are to enable the integration of PDE models, typically used to describe physiological or pathological processes at the organ or tissue scale, with ODE models commonly used to model biochemical, metabolic, cellular processes at a lower dimensional scales and to increase the computational simulation efficiency.

The integration solution proposed in **POP** will be realized by a suitable architecture and specific technologies in order to be automatic, transparent, scalable and based on a plug-and-play type interface and to import models specified in widely used modelling languages (ML). The proposed solution will be based on Web Service technologies and scripting languages to interface with the other ToolKit components and will support both SBML and CellML model specification.

Contents

1 Project description **2**
- 1.1 Motivations . . . 3
- 1.2 Architecture and Technologies . . . 4
- 1.3 A case study: Integrating MCM and CudaODE . . . 5
- 1.4 Proposed Contributions for the VPH ToolKit . . . 7
- 1.5 Potential Biomedical Implication . . . 7
- 1.6 Milestones and Deliverables . . . 8

2 The List of Publications of the Team **9**

1 Project description

This section is devoted to describe the main objectives of the project, motivations, technology and a case study. The **POP** (From PDE to ODE and back) project addresses the challenge of efficiently integrating some well-known heterogeneous Ordinary Differential Equation (ODE)- and Partial Differential Equation (PDE)-based simulation tools pertaining to the Virtual Physiological Human (VPH) ToolKit domain.

The main objectives of the **POP** project are:

- enable the integration of PDE models, typically used to describe physiological or pathological processes at the organ or tissue scale, with ODE models commonly used to model biochemical, metabolic, cellular processes at a lower dimensional scales;
- increasing the computational simulation efficiency: if we consider that every cell of the PDE model is to be associated to an ODE model, the coupled solution requires a very efficient scheme in order to be sustainedble, for real-world problem sizes.

The integration solution proposed in **POP** will be realized by a suitable architecture and specific technologies in order to:

- be automatic, transparent, scalable and based on a plug-and-play type interface: The proposed solution will use Web Service technologies and scripting languages to interface with the other components.

- import models specified in widely used modelling languages, such as SBML or CellML , at run time: The POP Service WSDL interface will support both SBML [1] and CellML [2] model specification, while the plugging scripts on the client (tool) side will provide also well-defined conversion functions between the involved formats.

1.1 Motivations

Modelling and simulation of biological systems is becoming more and more important both in clinical use and in basic research. Many of the models used to describe such systems have comparable resolution regimes and work on different spatial and temporal scales.

Continuum-based models are widely used to describe and simulate biological systems at different scales. From a modelling point of view, *Partial Differential Equations* (PDE) are typically associated to larger dimensional scales (e.g., organ and tissue), where spatial information has to be explicitly described and related to time for faithfully describing the system evolution. On the other hand, *Ordinary Differential Equations* (ODE) are typically associated to smaller scales (e.g., cell, molecule), when it is sufficient to describe the evolution over time but not across space. In some cases PDEs and ODEs models can also co-exist at the same scale (e.g., when different aspects of the same system at the same resolution are taken into account, with and without explicit spatial information).

The development of biomedical research in directions defined by the Physiome, systems biology, and more recently the Virtual Physiological Human (VPH) have made these multiscale scenarios where PDEs models are coupled with ODEs models more and more important. In particular, it is quite common in the VPH context to have an organ or tissue-scale model, based on PDE (finite element, finite volumes, etc.) with millions of cells, and to have a single ODE model that describe some process at an underlying scale (bone remodelling, blood clotting, calcium propagation) that must be solve with a different sent of inputs for each of the PDE cells. This scenario poses two ICT compelling cases:

- The first is that the PDE and the ODE models are generated, and solved using totally different software solutions, that have not been conceived to be interoperable one with the other, if this coupling was not considered initially in their design (as in the case of the link between Auckland CMISS and CellML). In all other cases, one ends up with the PDE and the ODE implemented in totally separated software systems.

- The second problem is scalability: if the PDE has 100 million cells, in theory we should solve 100 million times the ODE model for each solution step. Since this is not currently possible, we resort to tricks such as separated sampling grids, with different resolutions for the two-coupled models. But each of these tricks has drawbacks, and in principle they should be avoided all together, if possible.

[1] Hucka M, et al. The systems biology markup language (SBML): a medium for representation and exchange of biochemical network models. Bioinformatics. 2003 Mar 1;19(4):524-31.

[2] Lloyd CM, Halstead MD, Nielsen PF. CellML: its future, present and past. Prog Biophys Mol Biol. 2004 Jun-Jul; 85(2-3):433-50.

1.2 Architecture and Technologies

The **POP** integration solution acts on two different layers:

- "physical", where the integration is provided at application level;

- "logical", where the integration is provided at model level.

Physical layer. The physical layer, presented schematically in Fig. 1, fully exploits the Web Service paradigm. The core of **POP** is a Web Service (**POP** Service), which can be automatically invoked by PDE-based tools through a well-defined WSDL interface. The WSDL template requires, as input, the specification of both ODE model and data characterizing the simulation to run in (eventually specific and parallel) ODE-based tools. A separation between model and data is expected for those simulations requiring a computation on a large amount of data. PDE- and ODE-based tools are interfaced to **POP** Service simply by scripts running at the client side. The clear separation between invocation stubs (at the client side) and logic of integration (at the service side) makes the **POP** integration solution being scalable, non-invasive and characterized by an easy plug-and play procedure (even if for others modelling software systems which have not been yet taken into account). POP plug-in (and/or scripts) will be freely downloadable by "real users". The POP framework will be open-source, downloadable, distributed under on open license. This feature, clearly, encourage other tools to making use of POP.

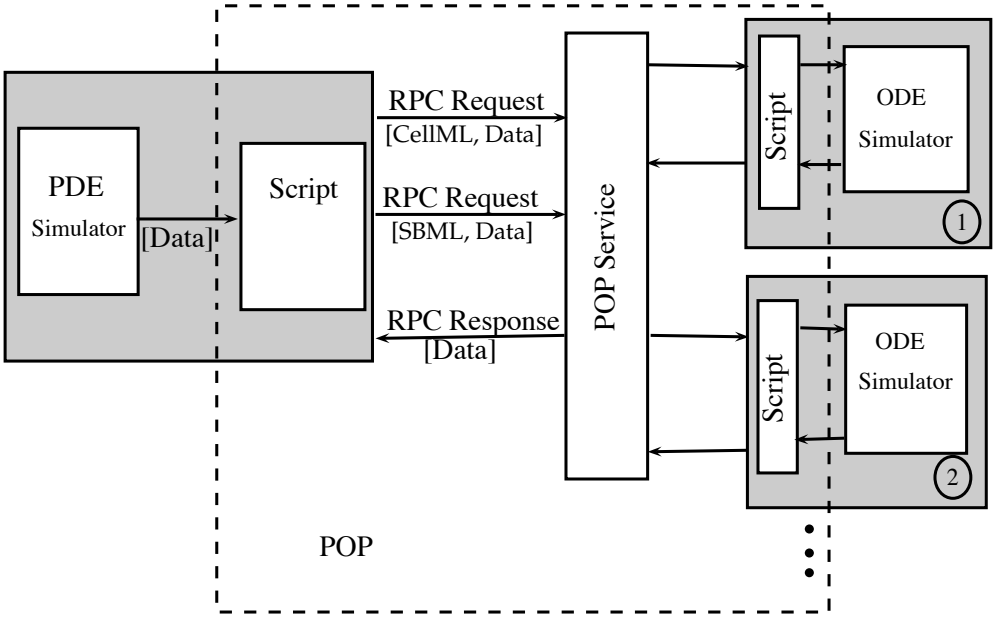

Figure 1: POP Framework.

The WSDL template includes invocation patterns of the form:

$1 \rightarrow n$ in the case the PDE model factorization produces n different ODE models, each of which has to be calculated and simulated on its dataset;

$1 \rightarrow 1$ in the case the PDE model factorization produces one ODE model, to iteratively calculate and simulate on gigabytes of data (as described in Fig. 2).

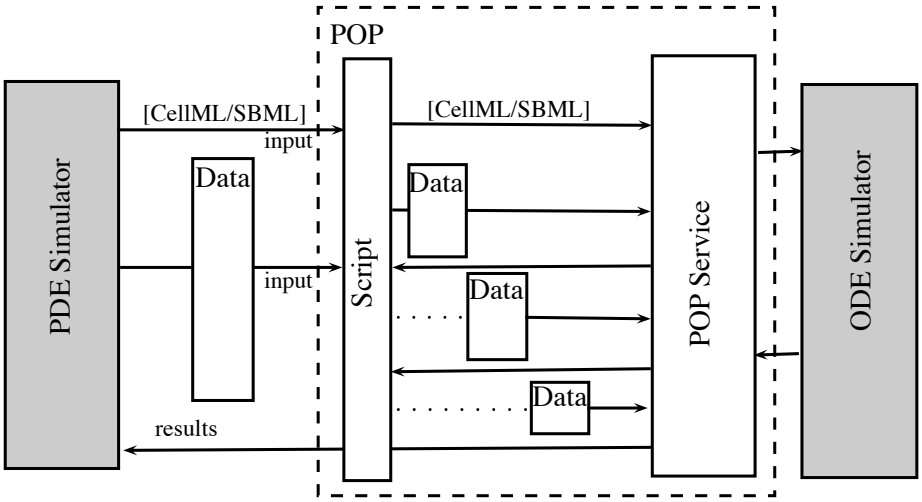

Figure 2: $1 \rightarrow 1$ communication protocol template

As a consequence, suitable communication protocols are defined in order to coordinate the service negotiation as well as the correct data flow. Well-known orchestration and conversation standards as WS-BPEL [3] and WS-CDL [4] are exploited at this aim.

Logical layer. Scripts provided by **POP** are engineered to support the export of ODE models both in CellML and SBML, two widely accepted modelling language (ML) standards for sharing biochemical or physological models. It is well-known that CellML and SBML have different emphasis: SBML is designed to represent biochemical reaction, while CellML has a somehow broader scope, to represent mathematical models of biological and physiological systems and to include information about model structure, mathematics and metadata by leveraging existing XML based standards (e.g., MathML). However, the two standards can work together by means of well-defined conversion mappings from CellML to SBML and back. POP returns, on-demand, an XML output to allow operating in a chain by also utilising preexisting components..

1.3 A case study: Integrating MCM and CudaODE

The *Meshless Cell Method* (MCM) [5] is a numerical method to solve filed problem such as linear elasticity, developed by the university of Trieste and by the Istituto Ortopedico Rizzoli. This method presents various advantages over the most common finite element method, but the most important in the VPH context, is that an MCM model can be initialised directly by a regular 3D lattice, typical of medical imaging.

The MCM is similar, although less popular, to the Lattice Boltzmann methods that are used in Compute Fluid Dynamics, in the sense that they also can be initialised directly with the medical imaging grid, avoiding massive pre-processing steps. The major drawback of these lattice methods is that the number of cells involved is usually very large, in the range 10^6 to 10^8. Because of this the coupling of MCM models that represent the bone tissue biomechanics, with ODE models to represent bone remodelling adaptation that occurs at the Bone Multicellular Unit (BMU) level is

[3] Web Services Business Process Execution Language), `http://www.oasis-open.org/committees/wsbpel/`

[4] Web Services Choreography Description Language), `http://www.w3.org/TR/ws-cdl-10/`

[5] Taddei F, Pani M, Zovatto L, Tonti E, Viceconti M. A new meshless approach for subject-specific strain prediction in long bones: Evaluation of accuracy. Clin Biomech (Bristol, Avon). 2008 Nov; 23(9):1192-9.

currently impossible, if not with complex multi-resolution tricks that drastically reduce the efficacy of the multiscale approach.

Cuda-ODE (see Fig. 3) is a tool for massive parallel computations exploiting CUDA [6], a general-purpose parallel computing architecture relying on nVidia graphics processing units (GPUs).

The MCM-CudaODE integration follows the $1 \rightarrow 1$ template. During a simulation, MCM needs to calculate a large number of ODEs, based on the same mathematical model, on different data. CudaODE takes in input the ODE model in CellML (namely, in MathML) e the data in a matrix format, where each row corresponds to values for a specific ODE.

CudaODE creates an internal computational model based on Cellular Open Resource [7] (COR), suitable for CUDA; once both thread number and memory device have been configured, all ODEs are computed at the same time on the input matrix.

Very often the amount of ODEs may overcome the Core CUDA computational power; in such a case, data are partitioned and elaborated by means of a sequence of separate invocations. The whole conversation is tuned by a simple BPEL orchestration protocol described as follows:

1. Service request and protocol negotiation (depending on the amount of data and the service availability);
2. Sending ODE model;
3. Sending data (in one or more steps) in a matrix format.
4. Receiving results.

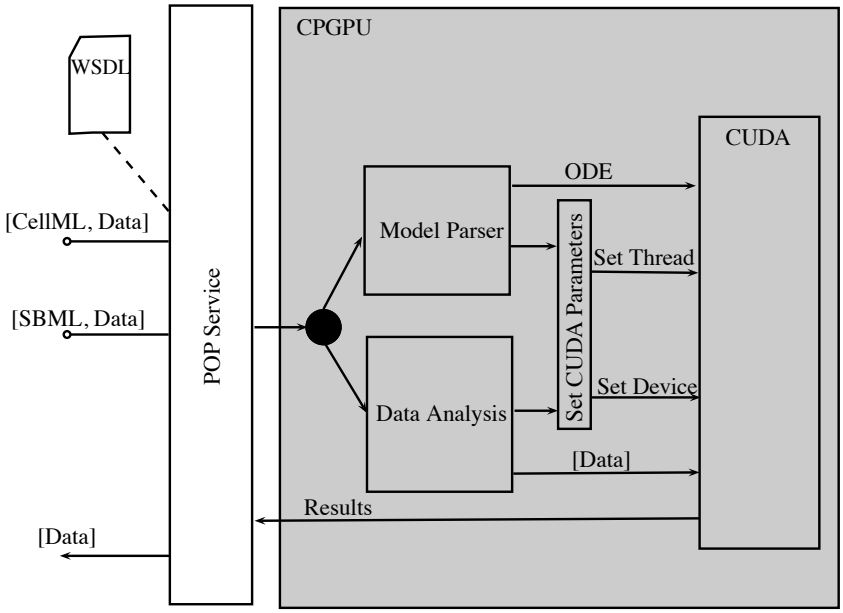

Figure 3: CudaODE.

[6] CUDA,ComputeUnifiedDeviceArchitecture, `http://www.nvidia.co.uk/object/cuda_what_is_uk.html`

[7] A.Garny,P.Kohl,andD.Noble.Cellularopenresource(cor):apubliccellmlbasedenvironment for modeling biological function. I. J. Bifurcation and Chaos, 13(12):35793590, 2003.

1.4 Proposed Contributions for the VPH ToolKit

What we propose is to package the POP system in a free and open-source general purpose sorftware tool, that can be used in principle to couple *any* PDE modelling enviroment with any ODE modelling environment, both with a $1 \rightarrow n$ and $1 \rightarrow 1$ coupling, and to deploy it onto low-cost HPC architectures such as GPGPU systems, in order to obtain a direct multiscale PDE/ODE solution even on PDE problems with millions of cells is an acceptable time scale.

The web service architecture, and the presence of plug-in adapters, make possible to re-use the POP system to couple whatever two solvers with a very moderate effort.

In addition, the native support of CellML and SBML, the two most popular mark-up languages to describe ODE models in biomedical research will immediately open to the PDE modellers the large collections of ODE models stored in the cellml.org and BioModels databases.

Once FieldML will be released, a simple adapter will make possible to support the same neutral mechanism also for the PDE side. Until then, however, the use of the adapters plug-ins will make relatively painless the integration of POP with popular FEM and CFD environments, such as Ansys, Abaqus, CFx, Fluent, etc.

1.5 Potential Biomedical Implication

The integration MCM-CudaODE is quite exemplificative to understand potential biomedical implications of **POP**. The proposed solution has been already exploited for simulating *bone remodelling* [1], [8], a typical multiscale phenomenon 4 where macroscopic behaviour and microstructure strongly influence each other[9]. The major consideration behind the tool coupling, from a numerical and modelling point of view, are that the functional adaptation of bone tissue to its mechanical environment can be studied by considering the internal stress and/or strain states of singular Bone Multicellular Units (BMU). Hence, the integration MCM-CudaODE mainly realizes a parallelization of *global* simulations of the bone tissue behaviour in terms of *local* simulation of each BMU behaviour.

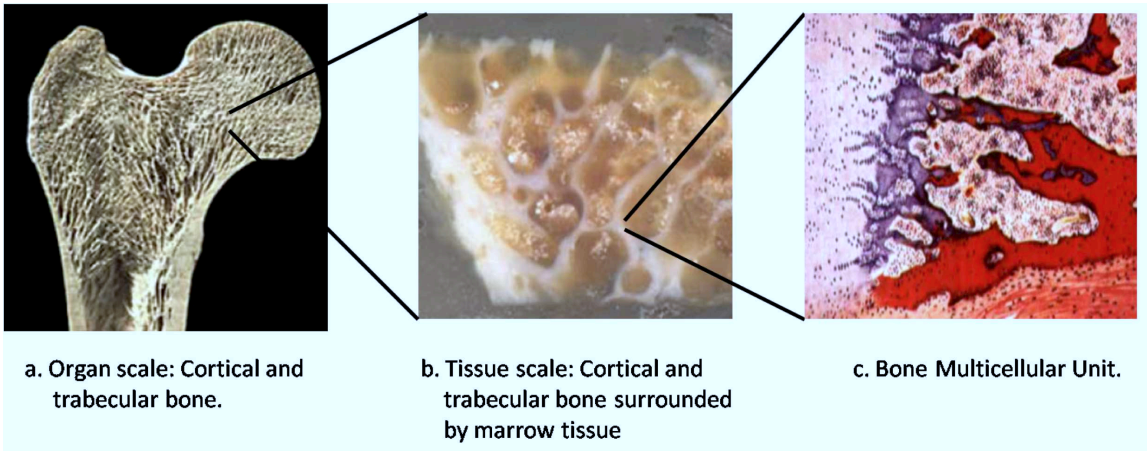

Figure 4: Multiscale view of a human femur.

[8] Sanz-Herrera JA, Garca-Aznar JM, Doblar M. On scaffold designing for bone regeneration: A computational multiscale approach. Acta Biomater. 2009 Jan;5(1):219-29. Epub 2008 Aug 5.

[9] For a more detailed description of the process, see Unicam References [3, 2]

In detail, MCM discretises bone tissue as a 3D lattice of cells (BMUs) of $20-100$ microns. A cell has eight nodes, each with a density value; when a cell is on the surface of bone tissue, density has at least one node below a well-established mineralization threshold.

When applied to the 3D lattice, MCM analysis evaluates by a PDE the stress field on each cell, so defining the loading conditions operating on it. Then, MCM invokes CudaODE sending a common ODE model, representing the functional adaptation of a generic BMU, and a matrix of data, where each row contains the actual parameters on which the functional adaptation of the associated BMU has to been computed. CudaODE elaborates the output (local BMU density changes, corresponding to local formation and adaptation of trabeculae at the tissue level), and sent back the resulting data matrix to MCM. Changes of cell density values starts again the MCM computation at the tissue level, because the deformations depend on the density at each point, creating an iterative coupling of the tissue model with the cell one.

The process described here for the tissue-BMU coupling in bone remodelling prediction, can be generalised to a number of problems including all those involving cellular adaptation of tissues in relation to field properties (strain, temperature, electric stimuli, etc.). In addition to the Istituto Ortopedico Rizzoli and their bone application, we are discussing with Prof. Frangi at UPF, and Prof. Hose at USFD about the possibility to apply the POP approach also to vascular, and neurovascular problems (clotting, stenosis, etc.).

It should be noted that while the usefulness of the POP system become obvious in lattice-oriented PDE solver such as MCM or LBM, nothing prevents to use coupled with other PDE includes finite element, finite volume, or finite differences models.

1.6 Milestones and Deliverables

The following diagram shows 5, in yellow, the six tasks that represent the project milestones and, in green, the project deliverables associated to each task. The red ones are sub-task.

Task-1 The Requirements Analysis task consists in studying the state of the art of VPH ToolKit: tools. methods, services and related technologies. [Unicam]

Task-2 The Design task consists in identifying and functionally describing every system components. [Unicam, IOR]

Task-3 The Development and Testing Task implies:

- the development and testing of the POP integrator component [Unicam]
- the development and testing of the CUDA/ODE simulator component [Unicam, IOR]

This task gives rise to the first two deliverables.

Task-4 Integration Deployment task will take into account the integration of components by providing to possibly partners the suitable interface (the script). This task gives rise to the third deliverable, the integrated POP Tool. [Unicam, IOR, USFD, UPF and possibly others NoE-VPH members]

Task-5 Testing and validation of the proposed demonstrator task will allow to tune the usability of the POP tool. [Unicam, IOR, USFD, UPF and possibly others NoE-VPH members]

Task-6 Documentation task will provide the user manual including set-up instructions and examples of the POP tool. This task gives rise to a fourth deliverable: the POP manual. [Unicam]

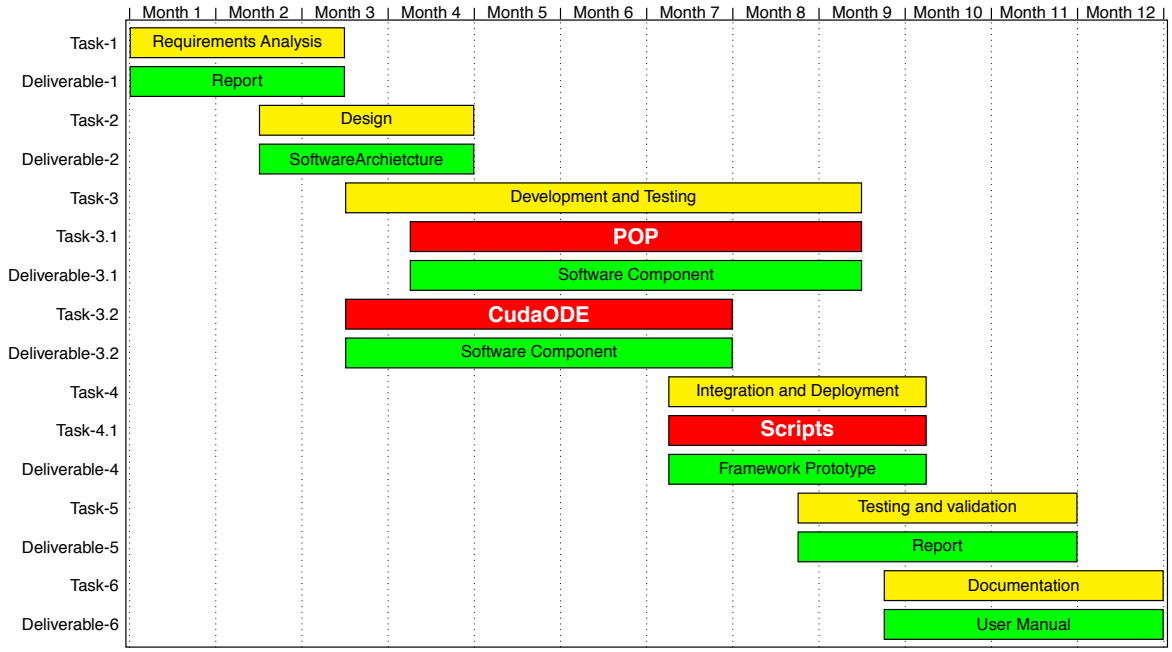

Figure 5: Gantt Diagram.

2 The List of Publications of the Team

Unicam partner

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[2] **Cacciagrano, D. and Corradini, F. and Merelli**. Bone remodelling: a complex automata-based model running in BioShape. In *ACRI 2010: Proc. of The Ninth International Conference on Cellular Automata for Research and Industry*.

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[5] **N. Cannata, F. Corradini, E. Merelli**. Multiagent modelling and simulation of carbohydrate oxidation. *International Journal of Modelling, Identification and Control (IJMIC)* 3(1), 2008

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[7] E. Bartocci, **F. Corradini, E. Merelli**, and L. Scortichini. BioWMS: a web-based Workflow Management System for bioinformatics. *BMC Bioinformatics*, 8(Suppl 1), 2007.

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[9] **F. Corradini**, L. Mariani, and **E. Merelli**. An agent-based approach to tool integration. *Journal of Software Tools Technology Transfer*, 6(3):231-244, November 2004.

IOR partner

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[2] L. Cristofolini, F. Taddei, M. Baleani, F. Baruffaldi, S. Stea, and **Viceconti, M.** Multiscale investigation of the functional properties of the human femur. *Philos Transact A Math Phys Eng Sci*, 366(1879):3319–3341, 2008.

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[4] P. Hunter, P. Coveney, B. de Bono, V. Diaz, J. Fenner, A. Frangi, P. Harris, R. Hose, P. Kohl, P. Lawford, K. McCormack, M. Mendes, S. Omholt, A. Quarteroni, J. Skr, J. Tegner, S. Randall, Thomas, I. Tollis, I. Tsamardinos, J. van Beek, and **Viceconti, M.** A vision and strategy for the virtual physiological human in 2010 and beyond. *Philos Transact A Math Phys Eng Sci.*, 368:2595–2614, 2010.

[5] E. Schileo, F. Taddei, L. Cristofolini, and **Viceconti, M.** Subject-specific finite element models implementing a maximum principal strain criterion are able to estimate failure risk and fracture location on human femurs tested in vitro. *Journal Biomech.*, 41(2):356–367, 2008.

[6] E. Schileo, F. Taddei, A. Malandrino, L. Cristofolini, and **Viceconti, M.** Subject-specific finite element models can accurately predict strain levels in long bones. *Journal Biomech.*, 40(13):2982–2989, 2007.

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[9] **Viceconti, M.** and P. Kohl. The virtual physiological human: computer simulation for integrative biomedicine i. *Philos Transact A Math Phys Eng Sci.*, 368:2591–4, 2010.

UNIVERSITY OF CAMERINO

Letter of Support from the Head of the School of Science and Technology

The School of Science and Technology of the University of Camerino, which is General Member of VPH-NoE, will give the usual levels of support and access to necessary space and facilities to the post-doc that will be enrolled by the funds following the proposal entitled " From PDE to ODE and back (POP)" under the scientific responsability of Emanuela Merelli.

Camerino, May 12th 2010

The Dean

Prof. Roberto Ballini

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14 May 2010

Reference: DRH/MB

To whom it may concern

The computing paradigm proposed in this project is clearly of significant interest to the VPH community. We have many applications in which we solve continuum problems represented as partial differential equations but in which local chemical or biological reactions interact with the mechanics. Often there are changes in constitutive equations associated with these processes. One example is the representation of clotting in a haemodynamics simulation (Harrison et al, J Biomechanics, 40 (13) 3023-3028; 2007, Narracott et al, J Artif Organs (8) 56–62; 2005). The medical physics team at USFD is keen to work together with UPF to provide a model of this type as an exemplar to be executed in the proposed simulation environment. The specific model chosen for this implementation will depend on the availability of personnel in the two institutions to interact with the POP during its twelve month execution period.

Yours faithfully

Professor Rod Hose
Professor of Computational Biomechanics